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SYNTHESIS OF TETRASUBSTITUTED BICYCLO[3.2.1]OCTENES AS POTENTIAL INHIBITORS OF INFLUENZA VIRUS SIALIDASE

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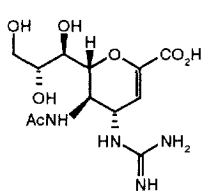
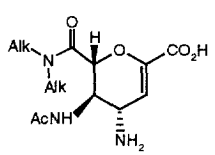
Abstract: Several racemic bicyclo[3.2.1]octene derivatives have been synthesised and evaluated as inhibitors of influenza virus sialidases. The 5-acetamido-bicyclo[3.2.1]octenol **4** showed modest activity against influenza A and B virus sialidases.

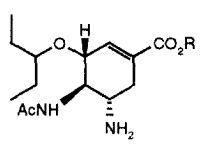
Influenza sialidase plays a crucial role in the life cycle of the influenza virus, and its inhibition has potential for both the prophylaxis and treatment of influenza infections.[1] Zanamivir **1** is a potent and selective inhibitor of both influenza A and B virus sialidases and is currently undergoing clinical evaluation.[2] Since the discovery of zanamavir, attention has focussed on the search for inhibitors with modified physicochemical properties which could make them more suitable for systemic delivery. Recently, we reported a series of more lipophilic carboxamides **2** in which we had retained the dihydropyran template of zanamivir but replaced the 6-glycerol sidechain with a carboxamide group and the guanidine by an amino group. These analogues showed excellent inhibitory activity, particularly against influenza A virus sialidase.[3,4] We also showed that the glycerol sidechain could be replaced by heterocyclic rings giving inhibitors with promising activity.[5] In an accompanying paper, we have reported the replacement of the glycerol sidechain with ketone and ether groups.[6]



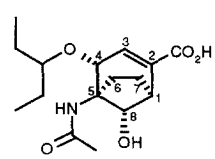
zanamivir **1**



carboxamide **2**



3 a) R = Et GS4104
b) R = H GS4071



4

Other workers have focussed on replacement of the dihydropyran ring with alternative scaffolds. Biocryst and Gilead have reported weak inhibitors based on an aromatic nucleus.[7,8] Workers from Gilead have replaced the dihydropyran ring of zanamivir with a cyclohexene ring and replaced the

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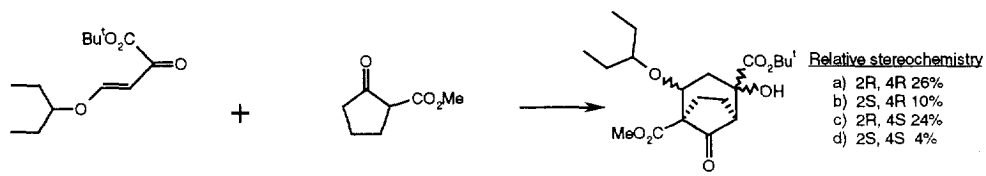
glycerol sidechain with a lipophilic ether. This led to the discovery of GS4104 **3a**, a prodrug which is orally active in both the mouse and ferret models and currently undergoing clinical evaluation.[9-11]

As part of the continuing search for novel scaffolds on which to mimic the geometry of the sialidase transition state, we have prepared analogues derived from the bicyclo[3.2.1]octene template **4.** Our initial molecular modelling suggested that this bicyclo[3.2.1]octene template should closely mimic the transition state geometry of zanamivir in the neuraminidase active site, and adopt a similar conformation to GS4071 **3b**. Furthermore, the introduction of the bridge would give increased lipophilicity to the molecule.

Our synthetic strategy was designed to construct the bicyclo[3.2.1]octane ring system containing four functional groups in a single stage. Progress to the target molecule **4** would then be a matter of functional group interconversion. For these initial studies, we opted for a hydroxy substituent at the C-8 position, which although not optimal would act as a good prototype for this strategy.

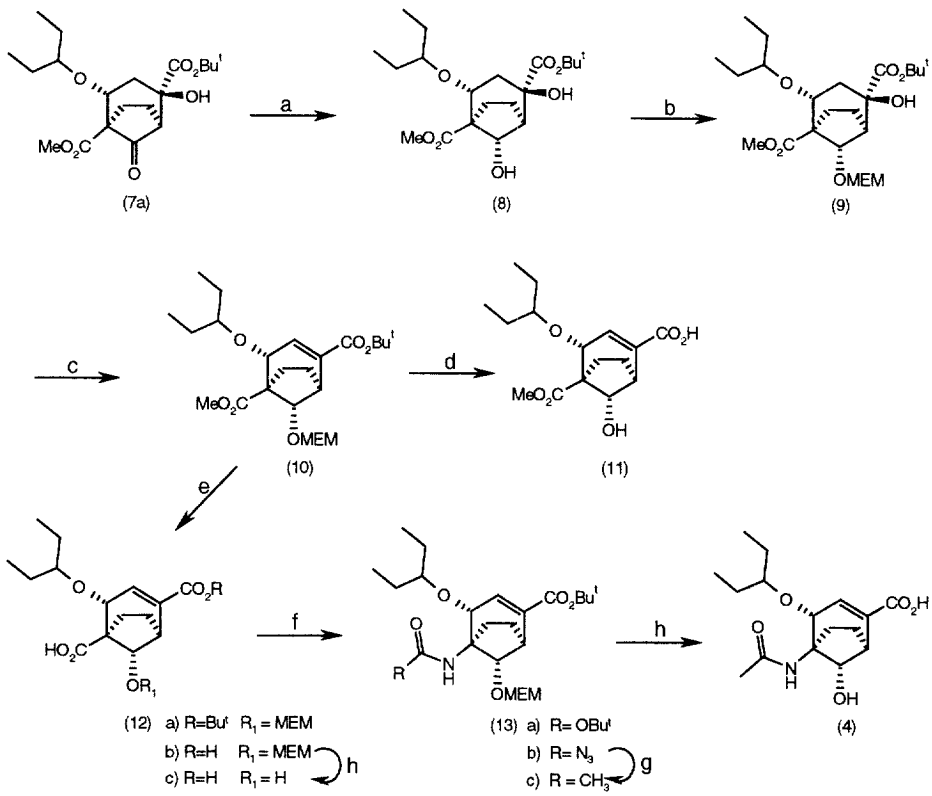
Synthesis of Racemic Bicyclo[3.2.1]octenes

The [3.2.1]bicyclic nucleus was constructed from the readily available ester **6** using an extension of the method of Rodrigues *et al*[12]. This method involves a base promoted Michael addition followed by an intramolecular aldol reaction and is typified by the reaction between methyl 2-oxocyclopentanecarboxylate and crotonaldehyde.[12] In his work, Rodrigues used an aldehyde as the aldol component. We envisaged that the carbonyl group of an α-keto-β,γ–unsaturated ester might also undergo this reaction and at the same time introduce carboxyl functionality. The required α–keto-β,γ–unsaturated ester **5** was prepared[13] in 29% yield by reaction of 3-pentyl vinyl ether[14] with t-butyl oxalyl chloride.[15] Reaction of the α–keto-β,γ–unsaturated ester **5** with methyl 2-oxocyclopentanecarboxylate **6** in a mixture of N,N-dimethylpropylene urea and dichloromethane with DBU as base gave the product **7** as a racemic mixture of four diastereoisomers (**7a-d**)[16] in 66% yield. The individual diastereoisomers were separated by a combination of column chromatography and preparative hplc. Each diastereoisomer was isolated as mixture of enantiomers and no attempt was made to resolve these enantiomers.



(5) (6) (7)

For ease of synthesis, the racemic compound **7a** which had the required relative stereochemistry at the 4 and 5-positions was carried through to the next stage. Reduction of **7a** with sodium triacetoxyborohydride in tetrahydrofuran was directed[17] by the neighbouring β-hydroxy group and gave the hydroxy derivative **8**, stereospecifically in 90% yield.



Reagents and conditions: a) $NaBH(OAc)_3$, CH_3CO_2H, THF, b) $ClCH_2OCH_2CH_2OCH_3$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, c) SO_2Cl_2, pyridine, CH_2Cl_2, d) CF_3CO_2H, e) LiI, collidine, N_2 f) $(PhO)_2PON_3$, Et_3N, Dioxan, t-BuOH, g) i) NaOH, dioxan, H_2O ii) Ac_2O, pyridine, DMAP, h) CF_3CO_2H.

Selective protection of the 8-hydroxyl group was accomplished using 2-methoxyethoxymethyl chloride and diisopropylethylamine in dichloromethane at 40° for 48hr giving the product **9** in 90% yield. Elimination of the 2-hydroxyl group was achieved[10] using sulphuryl chloride and pyridine in dichloromethane to give the alkene **10** in 49% yield. Deprotection of **10** with trifluoroacetic acid gave a quantitative yield of the carboxylic acid **11**. Selective deprotection of **10** with lithium iodide in

collidine at 110° under a nitrogen stream gave the mono acid **12a** in 47% yield together with 27% recovered starting material and 25% of the diacid **12b**.

The mono acid **12a** was heated under reflux with diphenylphosphoryl azide and triethylamine in t-butanol in an effort to effect a modified Curtius reaction.[18] However, under these conditions, the desired product **13a** was only produced in trace amounts, the major product (41%) being the carbamoyl azide **13b**. Presumably, this product arises because of the hindered nature of the intermediate isocyanate.

Hydrolysis of the carbamoyl azide **13b** using sodium hydroxide in aqueous dioxan, followed by acetylation with acetic anhydride in pyridine gave the acetamide **13c**. Final deprotection with trifluoroacetic acid gave the target acetamide **4.**

Biological Results

Table 1 shows the inhibitory activity[19] of the compounds against influenza A and B sialidases, with 2-deoxy-2,3-didehydro-N-acetylneuraminic acid (Neu5Ac2en) included for comparison.

Table 1 Sialidase Inhibitory Activities

Compound	Flu A $IC_{50}(\mu M)$	Flu B $IC_{50}(\mu M)$
11	99	83
12c	>670	>670
4	80	340
Neu5Ac2en	2.8	3.0

The target molecule **4** and the methyl ester analogue **11** were weak inhibitors of influenza A and B sialidases, being 10 to 100 fold less active than Neu5Ac2en. The carboxylic acid analogue **12c** was devoid of activity.

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16. ^{1}H NMR data for the racemic diastereoisomers were obtained in $CDCl_3$ at 250MHz :-

(7a) δ 4.41 (1H, t, J = 8, 8Hz, CH), 3.78 (3H, s, CO_2Me), 3.33 (1H, m, CH), 3.19 (1H, s, OH), 2.57-2.25 (3H, m, 3 x CH), 2.15 (2H, d, J = 8Hz, CH_2), 2.06-1.81 (2H, m, 2 x CH), 1.50 (9H, s, t-Bu), 1.50-1.35 (4H, m, 2 x CH_2), 0.86 (3H, t, CH_3), 0.78 (3H, t, CH_3).

(7b) δ 4.43 (1H, dd, J = 10.5, 6Hz, CH), 3.78 (3H, s, CO_2Me), 3.31 (1H, m, CH), 3.25 (1H, s, OH) 2.45 (1H, dt, J = 13, 13, 5Hz, CH) 2.37-2.07 (4H, m, 4 x CH), 2.00-1.82 (2H, m, 2 x CH), 1.50 (9H, s, t-Bu), 1.50-1.35 (4H, m, 2 x CH_2), 0.87 (3H, t, CH_3), 0.78 (3H, t, CH_3).

(7c) δ 4.51 (1H, dd, J = 3.5, 2Hz, CH), 4.07 (1H, br s, OH), 3.78 (3H, s, CO_2Me), 3.55 (1H, m, CH) 2.78 (1H, br d, J = 6.5Hz, CH), 2.47 (1H, dd, 15, 3.5Hz, CH), 2.25-1.70 (5H, m, 5 x CH), 1.48 (9H, s, t-Bu), 1.50-1.30 (4H, m, 2 x CH_2) 0.83 (3H, t, CH_3) 0.80 (3H, t, CH_3).

(7d) δ 4. 18 (1H, dd, J = 4, 2Hz, CH) 3.76 (3H, s, CO_2Me), 3.45 (1H, m, CH), 2.94, (1H, br s, OH), 2.69 (1H, br d, J = 6Hz, CH) 2.44 (1H, dt, J = 15, 2, 2Hz, CH), 2.25-1.80 (5H, m, 5 x CH), 1.47 (9H, s, t-Bu), 1.55-1.20 (4H, m, 2 x CH_2) 0.82 (3H, t, CH_3) 0.78 (3H, t, CH_3).

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19. Inhibition of influenza sialidase was determined in a fluorimetric assay by measuring the ability of compounds to inhibit the hydrolysis of 2'-(4-methylumbelliferyl)-α-D-N-acetylneuraminic acid by whole virus (A/Aichi N2 or B Victoria) grown in hen eggs. The IC_{50} value quoted is the concentration of inhibitor required to reduce the enzymic activity in this preparation by 50%.

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