

# Biexponential Decomposition of a Neuraminidase Inhibitor Prodrug (GS-4104) in Aqueous Solution

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**Purpose.** To examine the degradation kinetics and identify the degradation products of a neuraminidase inhibitor prodrug, GS-4104.

**Methods.** Degradation was studied as a function of pH and temperature using a stability-indicating RP-HPLC assay. Degradation products were isolated by RP-HPLC and identified by NMR. Specific rate constants were calculated based on a scheme defined by product(s) analysis.

**Results.** Three distinct degradation products were observed in the pH region studied (pH 2–8): isomer I, GS-4071, and isomer II. Isomer I resulted from the N, N-migration of the acetyl group. GS-4071 was formed by the hydrolysis of the ethyl ester. Both GS-4071 and isomer I degraded further to isomer II by N, N-acyl migration and ester hydrolysis, respectively. The N, N-acyl migration reaction was characterized using two dimensional heteronuclear multiple bond correlation (HMBC) NMR. The decomposition kinetics of GS-4104 follow a biexponential decay at pH 2–7. The degradation kinetics of GS-4104 at pH 4.0, 70°C were independent of the initial GS-4104 concentration. **Conclusions.** The degradation profile indicates that development of solution or solid dosage form of GS-4104 with adequate shelf-life stability at room temperature is feasible.

**KEY WORDS:** neuraminidase inhibitor; biexponential kinetics; GS-4104; N, N-acyl migration; heteronuclear multiple bond correlation NMR.

## INTRODUCTION

The antiviral agent (3*R*, 4*R*, 5*S*)-3-(1-ethylpropyloxy)-4-acetamido-5-amino-1-cyclohexene-1-carboxylic acid (GS-4071) is a potent transition state inhibitor of viral neuraminidase and has demonstrated potent *in vitro* and *in vivo* antiviral activity against influenza viruses in pre-clinical studies (1,2). However, the oral bioavailability of GS-4071 was less than 5% in rats (1). The ethyl ester prodrug, GS-4104 (Figure 1), is considerably more hydrophobic (log *P* = 0.36) than GS-4071 (log *P* = –2.1) and the bioavailability of GS-4071 after administration of GS-4104 in various animal species was 30–60% (1,3). The *in vitro* neuraminidase assay revealed that GS-4104 is a relatively poor inhibitor of viral neuraminidase (IC<sub>50</sub> ~ 100 nM) as compared to the parent compound GS-4071 (IC<sub>50</sub> = 2 nM) (3). The prodrug GS-4104 undergoes esterase-mediated metabolism to regenerate GS-4071 *in vivo* (2,3).

Currently, GS-4104 is in development for the treatment and prevention of influenza. As part of the pharmaceutical development program for GS-4104, we have investigated its chemical stability. In the present study, we have identified the

degradation products and described the aqueous solution degradation pathways for GS-4104. The degradation scheme involves a rapid intramolecular equilibration followed by hydrolysis.

## MATERIALS AND METHODS

The amorphous hydrochloride salt of GS-4104 was synthesized by the Organic Chemistry and Process Chemistry Departments, Gilead Sciences, Inc. All salts and solvents were either reagent or HPLC grade and used as received. In-house deionized water was used for buffer and mobile phase preparations.

## Instrumentation

pH measurements were made on a pH meter (a Radiometer PHM84) equipped with an combination electrode (Sensorex SG900C). Potency assays were performed using a HPLC system (Spectra-Physics) equipped with a solvent delivery system (Model P4000), a detector (Model UV2000), a Model Autosampler (AS3000), and Beckman PeakPro software for data acquisition with a Chromlink Module.

The <sup>1</sup>H NMR spectra and <sup>1</sup>H-<sup>1</sup>H and <sup>13</sup>C-<sup>1</sup>H correlated 2D-NMR spectra of all degradation products in deuterium oxide were recorded on a spectrometer (Varian Unity Plus 500 FT-NMR) operating at 500 MHz for collecting <sup>1</sup>H-NMR data and at 125 MHz for collecting <sup>13</sup>C-NMR data. The <sup>1</sup>H-<sup>1</sup>H correlated 2D-NMR spectra were obtained from correlation spectroscopy (COSY), and <sup>13</sup>C-<sup>1</sup>H correlated 2D-NMR spectra were obtained from heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond correlation (HMBC, optimized for 8 Hz coupling) experiments.

## Dissociation Constant (pK<sub>a</sub>)

The dissociation constant of GS-4104 was measured by a potentiometric titration method at 25°C and 70°C. Deionized water was first boiled vigorously for 5 minutes, the flask sealed with a stopper and cooled to room temperature. GS-4104 was used without drying. A solution of GS-4104 (10 mM) was prepared and kept at 25°C and 70°C in the CO<sub>2</sub> free deionized water and titrated with 0.1 N HCl or 0.1 N NaOH.

## Kinetics

A series of buffers were prepared for evaluation of the solution stability studies. The total buffer concentration was 100 mM, and total ionic strength was adjusted to 0.30 M with KCl. The pH 2.0 and 3.0 buffers were prepared from H<sub>3</sub>PO<sub>4</sub> and KH<sub>2</sub>PO<sub>4</sub>. The pH 4.0 and 5.0 buffers were prepared from CH<sub>3</sub>COOH and CH<sub>3</sub>COOK. The pH 6.0, 7.0 and 8.0 buffers were prepared from KH<sub>2</sub>PO<sub>4</sub> and K<sub>2</sub>HPO<sub>4</sub>. The pH of the buffer solutions were measured at recorded at 70°C.

The solution stability of GS-4104 (~200 μg/mL, 5.7 × 10<sup>–4</sup> M) was studied in the pH range of 2.0–8.0. Solution stability samples were stored in a 70°C stability chamber (Baxter Scientific Products, Constant Temperature Oven DK-63). Two individual samples were analyzed at specific time point by a stability-indicating HPLC method. The specific first order rate constants (k<sub>1</sub>, k<sub>–1</sub>, k<sub>2</sub>, k<sub>3</sub>) were initially estimated at a given pH condition by an independent regression analysis of each phase of the biexponential decay curve. The values for k<sub>4</sub> and k<sub>–4</sub>

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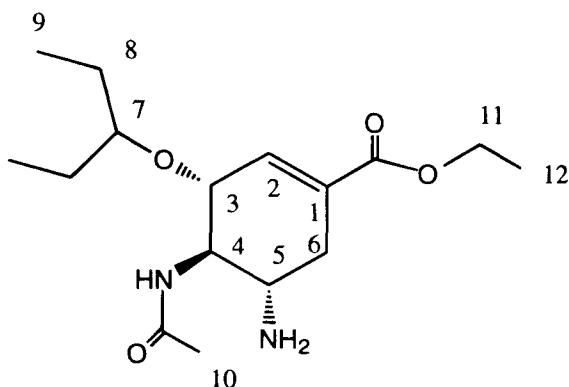


Fig. 1. GS-4104: Ethyl-(3R,4R,5S)-3-(1-ethylpropyloxy)-4-acetamido-5-amino-1-cyclohexene-1-carboxylate.

were assumed to be similar to  $k_1$  and  $k_{-1}$ . The obtained rate constants were used to fit the product time curves using the commercial software program "ithink" (version 2.1, High Performance System Inc.).

The effect of concentration on degradation of GS-4104 was evaluated at 200  $\mu\text{g/mL}$  and 2.5  $\text{mg/mL}$ . The solution stability of GS-4104 at 2.5  $\text{mg/mL}$  was examined in a pH 4.0, 130 mM acetate buffer at 70°C. Samples were withdrawn periodically and analyzed by HPLC.

#### Stability Indicating HPLC Method

All analyses of GS-4104 and its degradation products were carried out by a reverse phase HPLC method using a modular system described in the instrumentation section. The HPLC method employed a Prodigy ODS-2  $\text{C}_{18}$ , 5 $\mu$ , 4.6  $\times$  150 mm, Phenomenex column. Elutions were performed at ambient temperature using mixtures of mobile phases consisting of 50 mM sodium acetate in (A) 7.5% acetonitrile/92.5%  $\text{H}_2\text{O}$  v/v and in (B) 60% acetonitrile/40%  $\text{H}_2\text{O}$  v/v. The flow rate was set at 1.5 mL/min with UV detection at 220 nm. The mobile phase was initially set at 100% mobile phase A followed by a 15 min linear gradient to 100% mobile phase B and 5 min of re-equilibration. The elution times of GS-4104, isomer I, GS-4071, and isomer II were 9.8, 10.7, 4.2, and 3.6 minutes, respectively.

#### HPLC Method for Isolation of Degradation Products

The HPLC method for the purification of isomer I employed a Prodigy ODS-2,  $\text{C}_{18}$ , 5 $\mu$ , 4.6  $\times$  250 mm, column (Phenomenex) at ambient temperature with a mobile phase consisting of 35% acetonitrile in 50 mM ammonium acetate. The flow rate was maintained at 1.5 mL/min, and 100  $\mu\text{L}$  aliquots were injected into the chromatograph. The eluents were monitored at 220 nm and collected from 5.1–6.5 min. The same chromatographic conditions were employed for the purification of isomer II and GS-4071, except the mobile phase consisted of 7.5% acetonitrile in 50 mM ammonium acetate. The eluent was collected from 5.3–6.1 min for isomer II and 11–13 min for GS-4071. The collected eluents were freeze dried twice to remove the excess amount of ammonium acetate salt.

## RESULTS AND DISCUSSION

### Dissociation Constant ( $\text{pK}_a$ )

The primary amine group is the only ionizable moiety on GS-4104. The  $\text{pK}_a$  values determined by potentiometric titration with one equivalent of HCl at 25°C and 70°C were 7.7 and 6.6, respectively. The  $\text{pK}_a$  value of GS-4104 is significantly lower than a typical  $\text{pK}_a$  value of 10.8 (25°C) for primary aliphatic amines (4). The  $\beta$ -substituted amide group is partially responsible for lowering the  $\text{pK}_a$  of primary amine for GS-4104 (4).

### Characterization of Degradation Products

Three distinct degradation products were observed in the pH region studied (pH 2–8): isomer I, GS-4071, and isomer II. These degradation products were purified by HPLC using a reverse phase column. The structures of these degradation products were identified by NMR. All proton and carbon signals were assigned by correlation spectroscopy (COSY) and heteronuclear multiple quantum coherence (HMQC) experiments. Table 1 summarizes the  $^1\text{H}$  spectral assignment for GS-4104 and its degradation products. The structure of the degradation products were elucidated based on the proton signals and heteronuclear multiple bond correlation coupling (HMBC) between the amide carbonyl carbon and the adjacent ring hydrogen.

For isomer I, all signals in  $^1\text{H}$ -NMR are intact compared to GS-4104, however, the HMBC spectrum showed three-bond coupling between the amide carbonyl carbon (175 ppm) and the C-5 proton (4.05 ppm). This is consistent with isomer I being the N, N-acyl migrated product of GS-4104. The  $^1\text{H}$ -NMR spectra for GS-4104 and GS-4071 exhibited similar patterns, except the signals corresponding to the ethyl moiety are absent for GS-4071. The HMBC spectrum for GS-4071 exhibited the coupling between the amide carbonyl carbon (175.4 ppm) and the C-4 proton (4.16 ppm), indicating that GS-4071 is the free acid resulting from the ester hydrolysis of GS-4104. The  $^1\text{H}$ -NMR spectrum of isomer II also lacks ethyl signals. The HMBC spectrum for isomer II revealed coupling between the amide carbonyl carbon (175.6 ppm) and the C-5 proton (4.39 ppm). Therefore, isomer II was assigned as an

Table 1.  $^1\text{H}$  Spectral Assignment for GS-4104 and Its Degradation Products

| Assignment                 | $^1\text{H}$ chemical shift in ppm |           |           |           |
|----------------------------|------------------------------------|-----------|-----------|-----------|
|                            | GS-4104                            | Isomer I  | GS-4071   | Isomer II |
| CH at C-2                  | 6.93                               | 6.93      | 6.62      | 6.64      |
| CH at C-3                  | 4.42                               | 4.18      | 4.38      | 4.54      |
| CH at C-4                  | 4.14                               | 2.99      | 4.16      | 3.38      |
| CH at C-5                  | 3.68                               | 4.05      | 3.67      | 4.39      |
| $\text{CH}_a$ at C-6       | 3.05                               | 2.77      | 3.00      | 2.81      |
| $\text{CH}_b$ at C-6       | 2.61                               | 2.31      | 2.59      | 2.48      |
| CH at C-7                  | 3.63                               | 3.68      | 3.65      | 3.72      |
| $\text{CH}_2$ at C-8 (4 H) | 1.52-1.69                          | 1.69-1.61 | 1.67-1.57 | 1.74-1.65 |
| $\text{CH}_3$ at C-9 (6 H) | 0.953                              | 1.00      | 1.0 -0.95 | 1.02      |
| $\text{CH}_3$ at C-10      | 2.15                               | 2.13      | 2.19      | 2.16      |
| O- $\text{CH}_2$ at C-11   | 4.35                               | 4.32      | NA        | NA        |
| $\text{CH}_3$ at C-12      | 1.36                               | 1.37      | NA        | NA        |

N, N-acyl migration isomer of GS-4071. The mass spectra data were also consistent with the structural assignments based on the NMR data for all the degradation products.

### Degradation Pathways

Figure 2 depicts the proposed degradation pathways for GS-4104. GS-4071 was formed by the direct hydrolysis of the ethyl ester. Isomer I resulted from the N, N-migration of the acetyl group. Both GS-4071 and isomer I degraded further to isomer II by N, N-acyl migration and ester hydrolysis, respectively. Incubation of a purified sample of isomer I at pH 6.0 at 70°C leads to the formation of GS-4104, GS-4071, and isomer II, indicating that the N, N-acyl migration is reversible. Isomer II degrades at pH 6.0, 70°C to yield exclusively GS-4071. Quantitation was performed by comparison of peak areas of GS-4104 and its degradation products with external GS-4104 standards. The molar absorptivity of isomer I was assumed to be similar to GS-4104, and the experimentally determined correction factor of 1.6 was used to account for the difference in the molar absorptivity of GS-4071 and isomer II relative to GS-4104. Mass balance for the degradation products of GS-4104 was obtained in the pH region of 2–8.

### Degradation Kinetics

The degradation kinetics of GS-4104 were studied in aqueous solution at constant ionic strength (0.30 M) over the pH range of 2–8. The semilogarithmic plots of GS-4104 concentration versus time were biphasic in the pH range of 2–7 (Figure 3), indicating that the disappearance of GS-4104 is controlled by two distinct rate determining processes. The rate equations derived from the reaction scheme in Figure 2 are shown below,

$$\frac{d[\text{GS-4104}]}{dt} = k_{-1} [\text{Isomer I}] - k_1 [\text{GS-4104}] - k_2 [\text{GS-4104}] \quad (1)$$

$$\frac{d[\text{Isomer I}]}{dt} = k_1 [\text{GS-4104}] - k_3 [\text{Isomer I}] - k_{-1} [\text{Isomer I}] \quad (2)$$

$$\frac{d[\text{GS-4071}]}{dt} = k_2 [\text{GS-4104}] + k_{-4} [\text{Isomer II}] - k_4 [\text{GS-4071}] \quad (3)$$

$$\frac{d[\text{Isomer II}]}{dt} = k_3 [\text{Isomer I}] + k_4 [\text{GS-4071}] - k_{-4} [\text{Isomer II}] \quad (4)$$

The solution to the differential equation describing the molar quantities of GS-4104 as a function of time is shown in equation 5:

$$[\text{GS-4104}]_t = \{[\text{GS-4104}]_0(k_{-1} + k_3 - a)/(b - a)\} \exp(-a t) + \{[\text{GS-4104}]_0(k_{-1} + k_3 - b)/(b - a)\} \times \exp(-b t) \quad (5)$$

where  $a + b = -(k_1 + k_{-1} + k_2 + k_3)$ ,  $ab = k_1k_3 + k_2k_3$ ,  $[\text{GS-4104}]_0$  is the initial concentration of GS-4104,  $k_1$  and  $k_{-1}$  are the rate constants for the N, N-acyl migration of GS-4104 and isomer I, and  $k_2$  and  $k_3$  are the pseudo-first order rate constants for the ester hydrolysis of GS-4104 and isomer I (Figure 2). The rate constants  $k_4$  and  $k_{-4}$  do not influence the degradation kinetics of GS-4104 but govern the equilibrium distribution between GS-4071 and Isomer II.

As predicted by equation 5, the decomposition kinetics of GS-4104 followed a biexponential decay (Figure 3). The initial phase is governed by the rate of N, N-acyl migration and the secondary phase is controlled by the rate of ester hydrolysis.

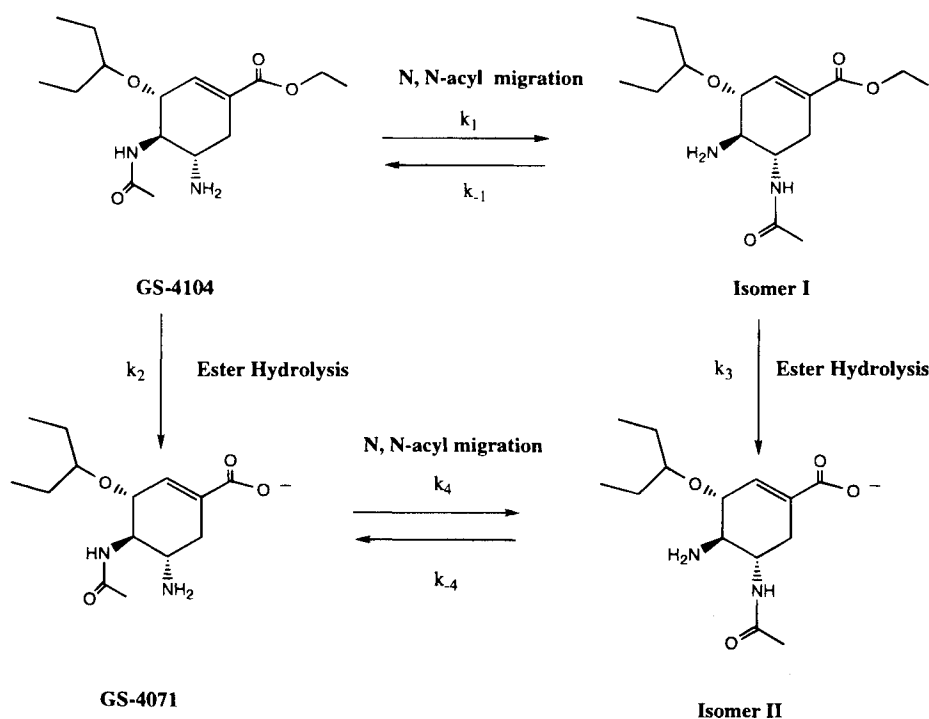


Fig. 2. Degradation pathways for GS-4104.

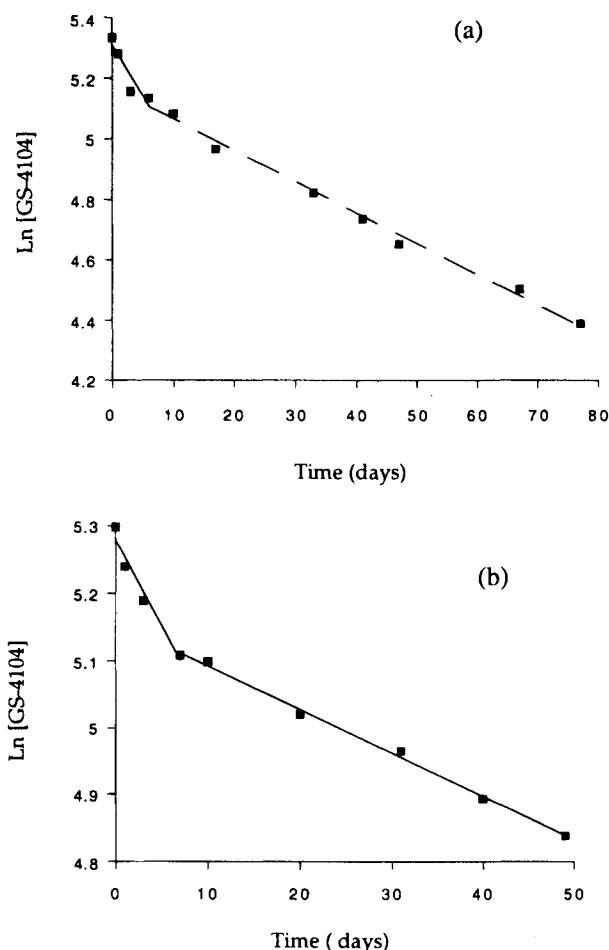


Fig. 3. A degradation curve of GS-4104 at 70°C a): pH 5.0 and b): pH 3.0.

Pseudo-first order kinetics were only observed at pH 8.0, where the rate of ester hydrolysis is sufficiently high to dominate the observed kinetics.

The specific first order rate constants ( $k_1$ ,  $k_{-1}$ ,  $k_2$ ,  $k_3$ ) were initially estimated at a given pH condition by separately curve fitting each phase of the biexponential decay (Table 2). These estimated rate constants were used to simulate the concentration time profiles for all the reaction species (Figure 4). A good correlation was observed between the simulated curves and the experimental values. For instance, when the simulated concentrations were plotted against the experimental data for GS-4104

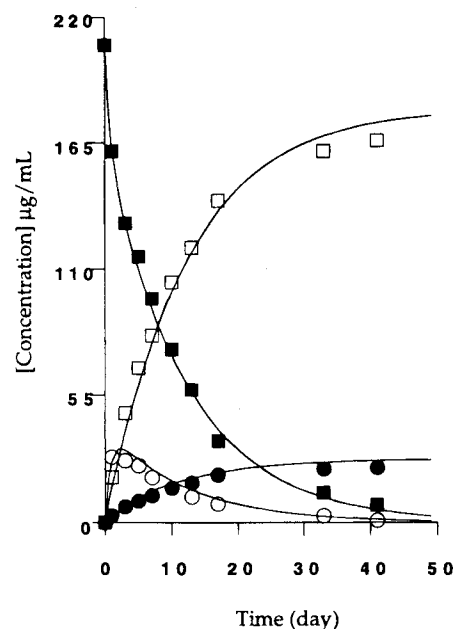


Fig. 4. Product distribution curves of GS-4104 at 70°C in a pH 6.0 phosphate buffer: (■) GS-4104; (□) GS-4071; (○) Isomer I, (●) Isomer II). Dashed lines are simulated data according to the mechanism shown in Figure 2.

and its degradation products at various pH conditions, the  $r^2$  values were  $> 0.985$ . The degradation kinetics of GS-4104 at pH 4.0, 70°C were independent of the initial GS-4104 concentration from 200 µg/mL to 2.5 mg/mL (data not shown).

The pH-rate profiles for each of the apparent degradation rate constants for GS-4104 ( $k_1$ ,  $k_{-1}$ ,  $k_2$ ) at 70°C are illustrated in Figure 5. The role of buffer catalysis has not been evaluated in these studies and, thus, the reported rate constants have not been corrected for buffer concentrations. Plots for  $k_1$ ,  $k_{-1}$  and  $k_2$  are all V-shapes with the minimum reactivity at pH 4.0. The plot for  $k_2$  is linear at pH values above and below pH 4.0. The slopes are approximately equal to unity, indicating both specific acid and base catalysis. The pH-rate profile for  $k_2$  can be described by the following equation:

$$k_2 = k_{2H^+} [H^+] + k_{2OH^-} [OH^-]$$

where  $k_{2H^+}$  and  $k_{2OH^-}$  are the rate constants for hydrogen ion and hydroxide-ion catalysis, respectively. The rate of ester hydrolysis is independent of the ionization state of the primary amine group. In addition, the values of the rate constants for ester hydrolysis for GS-4104 and isomer I ( $k_2$  and  $k_3$ ) are similar (Table 2).

The specific rate constants for the N, N-acyl migration reaction of GS-4104 ( $k_1$  and  $k_{-1}$ ) exhibit a less pronounced pH dependency with the slopes of approximately 0.5. Similar types of base- and acid-catalyzed intramolecular acyl migrations have been observed in acylated diamines (5,6). The reaction mechanism appears to be an intramolecular rearrangement involving nucleophilic attack of a nitrogen lone pair on the amide carbonyl group leading to the formation of the tetrahedral intermediate. This mechanism has also been suggested by other investigators for the analogous rearrangement of S-acylisothiureas and isomides (7). Rate constants,  $k_1$  and  $k_{-1}$  obeyed the Arrhenius

Table 2. First Order Rate Constants for the Degradation of GS-4104 at 70°C

| pH  | $k_1(\text{hr}^{-1}) \cdot 10^3$ | $k_{-1}(\text{hr}^{-1}) \cdot 10^3$ | $k_2(\text{hr}^{-1}) \cdot 10^3$ | $k_3(\text{hr}^{-1}) \cdot 10^3$ |
|-----|----------------------------------|-------------------------------------|----------------------------------|----------------------------------|
| 2.0 | 4.0                              | 26.0                                | 1.78                             | 1.78                             |
| 3.0 | 2.0                              | 13.3                                | 0.28                             | 0.28                             |
| 4.0 | 1.0                              | 6.8                                 | 0.05                             | 0.05                             |
| 5.0 | 4.0                              | 20.0                                | 0.43                             | 0.43                             |
| 6.0 | 8.3                              | 33.0                                | 3.4                              | 3.4                              |
| 7.0 | 50.0                             | 150                                 | 18.5                             | 18.5                             |
| 8.0 | 70.0                             | 700                                 | 78.0                             | 78.0                             |

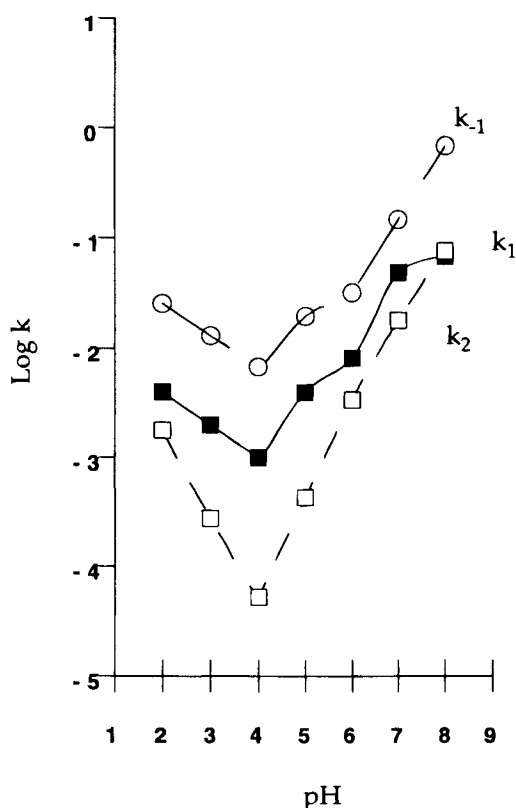


Fig. 5. Plots of the pH-rate profiles for the isomerization ( $k_1$  and  $k_{-1}$ ) and ester hydrolysis ( $k_2$ ) of GS-4104 at 70°C.

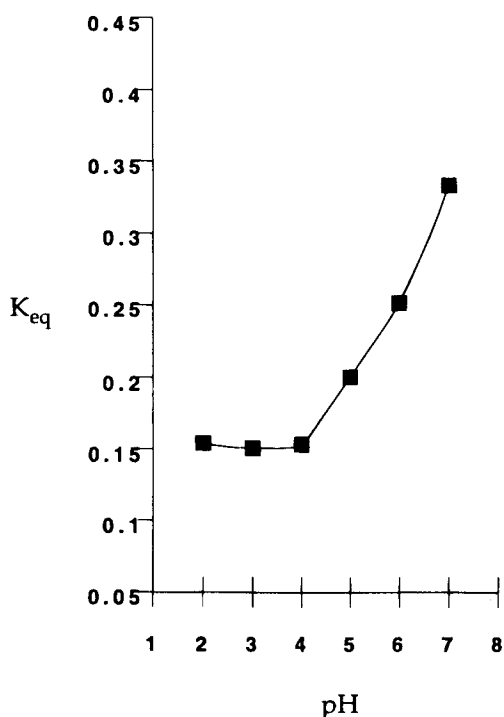


Fig. 6. A plot of pH-dependency of  $K_{eq}$  for the equilibrium isomerization of GS-4104 and isomer I.

equation at pH 4.0 (60, 70, 82, and 90°C). The calculated values for the observed activation energies of  $k_1$  and  $k_{-1}$  were 29.1 and 26.9 Kcal/mole, respectively. The large observed activation energies are consistent with the conformationally strained *trans* acyl migration in a six-membered carbocyclic system (8).

Figure 6 depicts the pH-dependency of the equilibrium constant,  $K_{eq}$  ( $k_1/k_{-1}$ ), for the isomerization of GS-4104 to isomer I. The value of  $K_{eq}$  represents the extent of isomerization of GS-4104 to isomer I at a given pH and temperature. The values of  $K_{eq}$  suggest that GS-4104 is the thermodynamically more stable isomer within the pH range studied. The  $K_{eq}$  is independent of pH at pH values below 4.0 and appears to linearly increase with increasing pH in the range of 4.0 to 7.0.

In summary, the degradation kinetics of GS-4104 were examined in a dilute aqueous solution. Two degradation pathways were identified for GS-4104: N, N-migration of the acetyl group (yielding isomer I) and the ethyl ester hydrolysis (yielding GS-4071). The degradation kinetics of GS-4104 follow a biexponential decay at pH 2.0–7.0. The pH-rate profiles of GS-4104 demonstrate that the drug is relatively stable in the pH range 2.0–8.0 and has maximal stability at pH 4.0. The extrapolated rate constants at 25°C for N,N-acyl migration and ester hydrolysis indicate that development of solution or solid dosage form of GS-4104 with adequate shelf-life stability at room temperature is feasible.

## REFERENCES

1. C. U. Kim, W. Lew, M. A. Williams, L. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, W. Li, L. Tai, P. Escarpe, K. C. Cundy, E. J. Eisenberg, S. Lacy, R. W. Sidwell, R. C. Stevens, and W. G. Laver. New potent, orally active neuraminidase inhibitor as anti-influenza agents: *in vitro* and *in vivo* activity of GS-4071 and analogues. 36th ICAAC, New Orleans, Louisiana, September, 1996.
2. C. U. Kim, W. Lew, M. A. Williams, H. Liu, L. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, L. Tai, W. G. Laver, and R. C. Stevens. Influenza neuraminidase inhibitors possessing a novel hydrophobic interaction in the enzyme active site: design, synthesis, and structural analysis of carbocyclic sialic acid analogues with potent anti-influenza activity. *J. Am. Chem. Soc.* **119**:681–690 (1997).
3. W. Li, P. A. Escarpe, E. J. Eisenberg, K. C. Cundy, C. Sweet, K. J. Jakeman, J. Merson, W. Lew, M. Williams, L. Zhang, C. U. Kim, N. Bischofberger, M. S. Chen, and D. B. Mendel. Identification of GS-4104 as an orally bioavailable prodrug of the influenza virus neuraminidase inhibitor GS-4071. *Antimicrob. Agents Chemother.* **42**:647–653 (1998).
4. D. D. Perrin, Boyd Dempsey, and E. P. Serjeant, "pKa prediction for organic acids and bases," Chapman and Hall, London, 1981.
5. L. V. Pavlova and F. Y. Rachinskii. Rearrangements connected with the migration of acyl and certain other groups. *Russian Chem. Rev.* **37**:587–602 (1968).
6. B. Fernandez, I. Perillo, and S. Lamdan. Alkaline hydrolysis of 1,2,3-trisubstituted cyclic amidinium salts. Kinetic study of N,N' acyl migration in alkaline solution in an ethylenediamine derivative. *J. Chem. Soc. Perkin II* 545–550 (1978).
7. R. F. Pratt and T. C. Bruce. Reactions of s-acylisothioureas. II. Effects of structure and stereochemistry on the rates of hydrolysis, thiol elimination, and S to N acyl migration in acyclic systems. *J. Am. Chem. Soc.* **94**:2823–2837 (1972).
8. S. K. Chung and Y. T. Chang. Base-catalyzed acyl migrations in myo-inositol dibenzoates. *J. Chem. Soc. Chem. Commun.* 13–14 (1995).