Supplementary material (ESI) for Organic & Biomolecular Chemistry

Electronic Supplementary Material

Synthesis and Photochemical Properties of Photoactivated Antitumor Prodrugs Releasing 5-Fluorouracil

Zhouen Zhang, Hiroshi Hatta, Takeo Ito and Sei-ichi Nishimoto*

Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Katsura Campus, Nishikyo-ku, Kyoto 615-8510, Japan

E-mail:nishimot@scl.kyoto-u.ac.jp

Supporting Information

1. Synthesis of photoprodrugs 1 and 2

1-(2'-Nitrobenzyl) -5-fluorouracil (1)

Photoactivated 5-FU prodrugs **1**-**2** were synthesized using a similar method for preparation of 1-(2'-oxocycloalkyl)-5-fluorouracils reported previously.[1] 5-Fluorouracil was reacted with hexamethyldilazane to produce 5-fluoro-2,4-di(trimethylsilyloxy)primidine (**5**).[1,2] Intermediate compound **5** (1.37 g, 5.0 mmol) was refluxed for 4 hrs with 2-nitrobenzyl bromide (1.3 g, 6.0 mmol) in dry acetonitrile (5 ml) under nitrogen in the dark. After cooled to room temperature, the resulting solution was treated by methanol (7 ml) for 30 min and then evaporated in vacuum. The residue was purified by column chromatography (1:1 *v/v* hexane-ethyl acetate) to give compound **1** (300 mg, 23%) as pale powder: R_f 0.3 (1:1 *v/v* hexane-ethyl acetate); δ_H (400 MHz, DMSO-d_6) 5.16 (s, 2 H, CH_2), 7.37 (d, J = 7.8 Hz, 1 H, 6'-H), 7.58

(dd, J = 7.8, 7.8 Hz, 1 H, 4'-H), 7.73 (dd, J = 7.8, 7.8 Hz, 1 H, 5'-H), 8.12 (d, J = 7.3 Hz, 2 H, 3'-H and 6 -H), 11.93 (d, J = 4.8 Hz, 1 H, NH); δ_C (100 MHz, DMSO-d_6) 48.3 (CH_2), 124.9 (C-3'), 127.9 (C-4'), 128.6 (C-6'), 129.8 (d, J = 34.0 Hz, C-6), 131.7 (C-5'), 134.2 (C-1'), 139.9 (d, J = 229.7 Hz, C-5), 147.4 (C-2'), 149.7 (C-2), 157.4 (d, J = 26.5 Hz, C-4). FAB-HRMS (positive mode, glycerol matrix) *m/z* 266.0586 [MH^+], $C_{11}H_9FN_3O_4$ requires 266.0577.

1 -(2'-Nitro-4'-carboxybenzyl) -5-fluorouracil (2)

According to similar procedure as in **1**, compound **2** was prepared from intermediate compound **5** (0.86g, 3.2 mmol) and 4-bromomethyl-3-nitrobenzoic acid (1.0 g, 3.8mmol) to give pale yellow powder (197 mg, 20 %): R_f 0.3 (1 : 3 : 0.004 v/v methanol-ethyl acetate-acetic acid); δ_H (300 MHz, DMSO-d_6) 5.15 (s, 2 H, CH_2), 7.44 (d, J = 8.0 Hz, 1 H, 5'-H), 8.05 (d, J = 6.6 Hz, 1 H, 6-H), 8.12 (d, J = 8.0 Hz, 1 H, 6'-H), 8.45(s, 1 H, 2'-H), 11.89 (s, 1 H, NH); δ_C (75 MHz, DMSO-d_6) 48.6 (CH_2), 125.5 (C-2'), 128.7 (C-5'), 129.9 (d, J = 34.2 Hz, C-6), 131.6 (C-1'), 134.3 (C-6'), 136.3 (C-4'), 140.2 (d, J = 230.4 Hz, C-5), 147.5 (C-3'), 149.9 (C-2), 157.6 (d, J = 25.5 Hz, C-4), 165.3 (COOH). FAB-HRMS (positive mode, NBA matrix): *m/z* 310.0472 [MH^+], $C_{12}H_9FN_3O_6$ requires 310.0472.

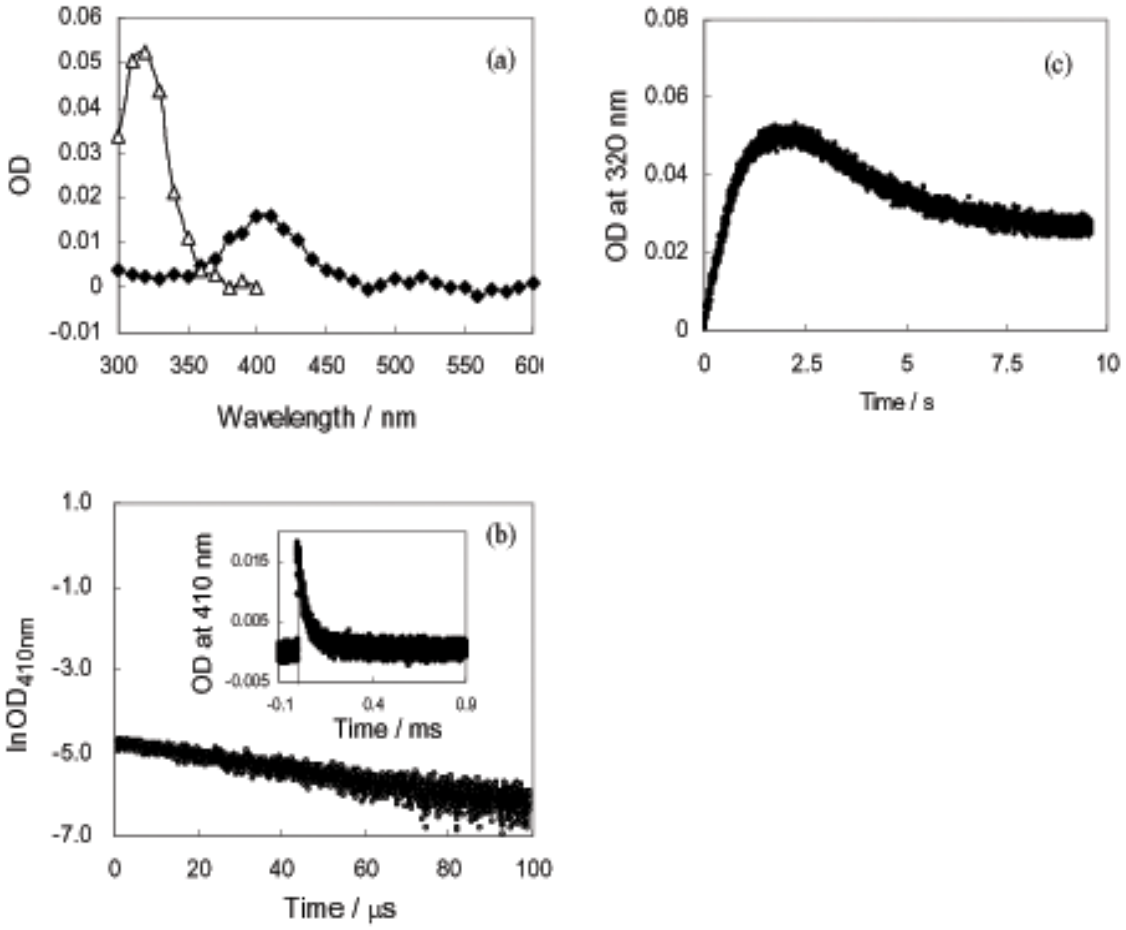

Fig. S1 Nanosecond LFP of prodrug **1** (0.1 mM) in Ar-saturated acetonitrile solution: (a) Transient absorption spectra observed at (Δ)1.0 μs and (♦) 2 s after 266-nm LFP; (b) The first-order kinetic plot of $lnOD_{410nm}$ against time for the decay of transient absorption at 410 nm. The inset displays decay of the transient absorbance at λ_{max} = 410 nm; (c) Growth and decay of the transient absorbance at λ_{max} = 320 nm.

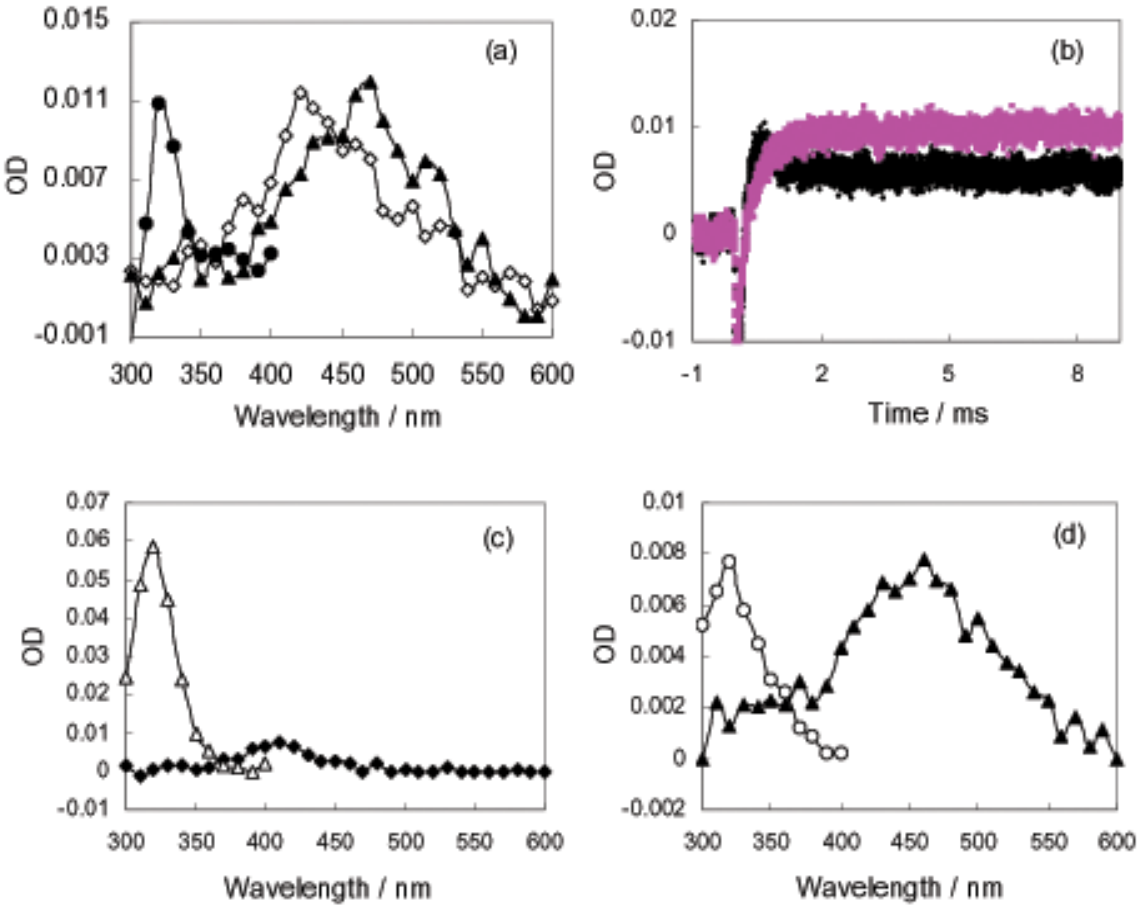

Fig. S2 (a) Transient absorption spectra observed at (◊)1.0 μs, (▲) 3.0 μs and (●) 2.2 s after LFP of 0.1 mM prodrug **1** in Ar-saturated acetonitrile-H_2O (2:1 *v/v*) solution; (b) transient absorbance observed at λ_{max} = 410 nm (black curve) and λ_{max} = 460 nm (red curve). (c) Transient absorption spectra observed at (♦)1.6 μs and (Δ) 2.3 s after LFP of 0.1 mM prodrug **1** in Ar-saturated acetonitrile-H_2O (2:1 *v/v*) solution, at pH 2.5. (d) Transient absorption spectra observed at (▲)1.0 μs and (○) 2.0 s after LFP of 0.1 mM prodrug **1** in Ar-saturated acetonitrile-H_2O (2:1 *v/v*) solution, at pH 7.5.

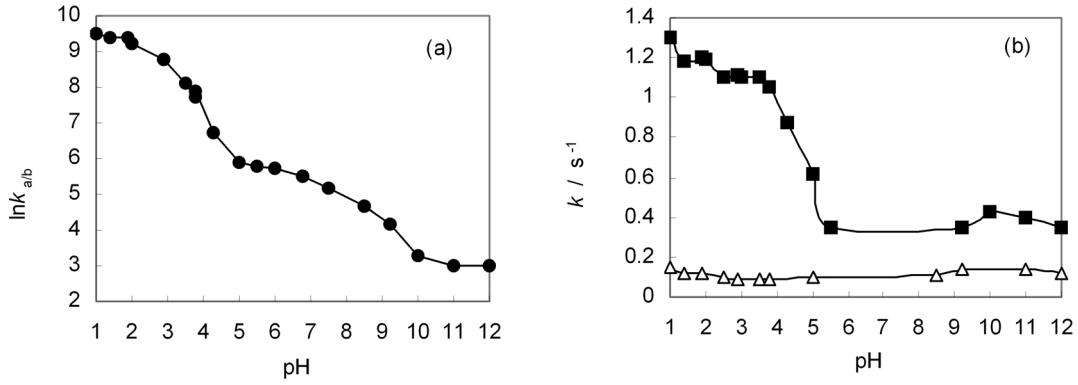

Fig. S3 (a) pH-rate profile for decay of the intermediate **A**; (b) pH-rate profiles for the (■) growth and (Δ) decay of the intermediate **C**.

References:

1. M. Mori, H. Hatta and S. Nishimoto, *J. Org. Chem*., 2000, **65**, 4641-4647.
2. R. Duschinsky, E. Fells and T. F. Gabriel, *United States Patent*. 1967, 3354160.