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Synthesis and Antitumor Activity of 5-Fluoro-4-(furfurylideneaminooxy)hexahydro-2,6-dioxo-5-pyrimidinecarboxylates

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A series of 5-fluoro-*t*-4-[(*Z*)- and (*E*)-furfurylideneaminooxy]hexahydro-2,6-dioxo-*r*-5-pyrimidinecarboxylates (**6** and **7**) was prepared by treatment of the corresponding 4-acetoxyhexahydropyrimidinecarboxylates **5** with (*Z*)- and (*E*)-furfuraldoximes (**10** and **11**), respectively, and tested for antitumor activity against murine colon carcinoma 26. The oxime ether **7c** (TAC-788) showed antitumor activity against various murine tumors.

Keywords——5-fluorohexahydro-2,6-dioxo-5-pyrimidinecarboxylate; furfuraldoxime; nitrone; substitution; stereoisomer; antitumor activity; 5-fluorouracil; TAC-788; colon carcinoma 26

Although 5-fluorouracil (5-FU, **1**)[1] and its masked compounds, 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur, **2**)[2] and 1-hexylcarbamoyl-5-fluorouracil (carmofur, **3**),[3] are clinically used in the treatment of cancer, efforts have been made to develop more effective 5-FU derivatives with fewer side effects and more potent antitumor activity.[4]

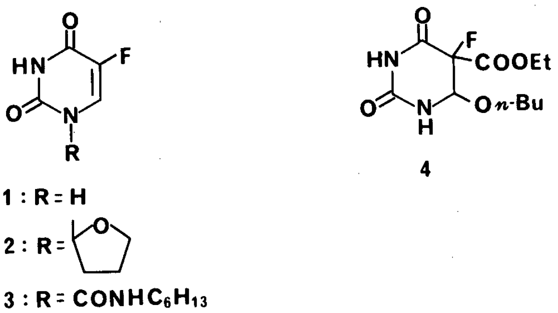


Chart 1

Recently, Miyashita *et al.* reported the synthesis of a novel class of 5-FU masked compounds, 4-substituted-5-fluorohexahydro-2,6-dioxo-5-pyrimidinecarboxylates.[5] Among these, ethyl 4-butoxy-5-fluorohexahydro-2,6-dioxo-5-pyrimidinecarboxylate (TAC-278, **4**) was investigated clinically and showed moderate antitumor activity against human carcinoma.[6]

In the course of our studies on this series of compounds, 4-alkylideneaminooxy analogs[5] were found to be more effective than the 4-alkoxy ones against murine solid tumors.[7] However, only a few derivatives having a monosubstituted methyleneaminooxy group at the 4-position have been prepared.[5] These facts prompted us to synthesize monosubstituted methyleneaminooxy analogs of this series and to evaluate their antitumor activity and pharmacodynamics in an attempt to find more effective compounds than **4** and other 5-FU derivatives including tegafur and carmofur.

The present paper deals with the synthesis and evaluation of the antitumor activity of 5-fluoro-*t*-4-[(*Z*)- and (*E*)-furfurylideneaminooxy]hexahydro-2,6-dioxo-*r*-5-pyrimidinecarboxylates (**6** and **7**), which show potent antitumor activity against murine tumors.

Chemistry

When ethyl 4-acetoxy-5-fluorohexahydro-5-pyrimidinecarboxylate (**5a**) was treated with (*Z*)-furfuraldoxime (**10a**) in acetone–pyridine at room temperature, according to the procedure reported by Miyashita *et al.*,[5] a mixture of the nitrone **9a** (36%) and the (*Z*)-oxime ether **6a** (16%) resulted. Similar treatment of isobutyl 4-acetoxy-5-fluorohexahydro-5-pyrimidinecarboxylate (**5c**) with **10a** also afforded a mixture of **9b** (19%) and **6c** (21%).

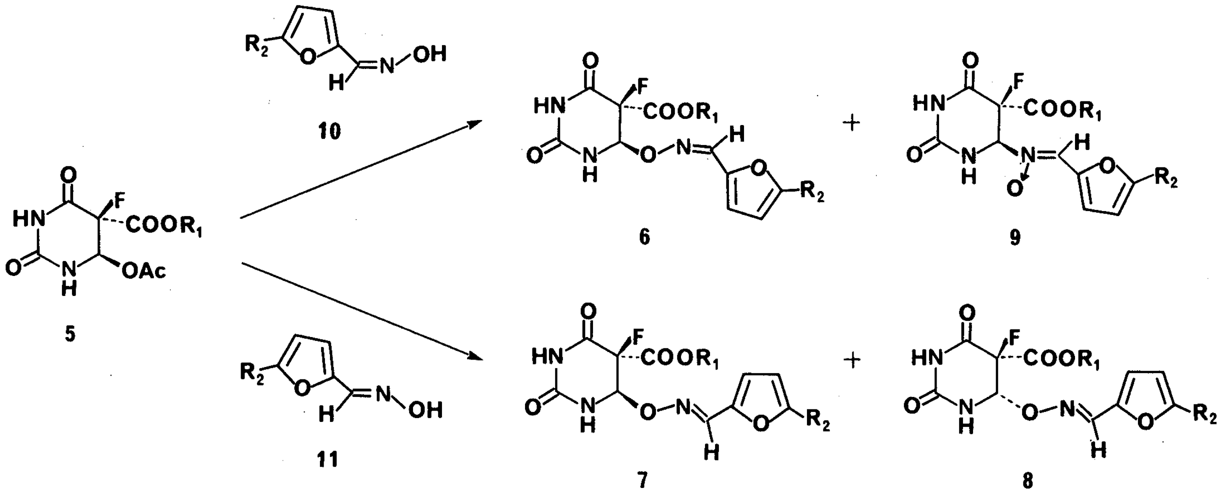


Chart 2

The reaction of (*Z*)-benzaldoxime[8] and **10a**[9] with alkyl halides yields the kinetically favored nitrones almost exclusively. However, in the present reaction, the substitution products **6a** and **6c** were also obtained even though the yields were low. This stimulated us to examine the possibility that the nitrones **9** are intermediates in the present substitution reaction by treating **9b** with **10a** and (*E*)-furfuraldoxime (**11a**). Treatment of **9b** with **10a** and **11a** in acetone–pyridine at 60 °C gave **6c** and the (*E*)-oxime ether **7c** in 57% and 55% yields, respectively. These results clearly indicate that **9b** proceeds *via* the elimination–addition mechanism through the intermediate A[5] under these conditions, giving the thermodynamically stable addition products **6c** and **7c** (Chart 3). Moreover, the present elimination reaction might proceed in a similar fashion to the olefin-forming elimination of nitrones possessing electron-withdrawing groups.[10]

Thus, heating of the acetates **5** with **10a** and (*Z*)-5-methylfurfuraldoxime (**10b**) in acetone–pyridine at 60 °C afforded the corresponding **6** in moderate yields except for **6b** (Table I).

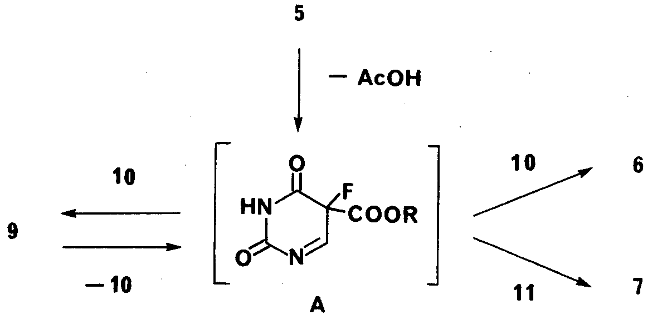
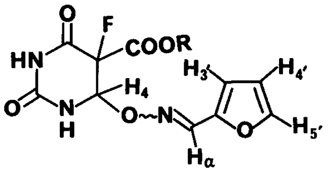


Chart 3

Table I. Yields and Physical Properties

Compd.	R_1	R_2	mp (°C) (Recryst. solv.)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
6a	Et	H	152—153	40	$C_{12}H_{12}FN_3O_6$	46.01	3.86	13.42
			(AcOEt–hexane)			(46.06	3.86	13.46)
6b	iso-Pr	H	131—134	24	$C_{13}H_{14}FN_3O_6$	47.71	4.31	12.84
			(AcOEt–hexane)			(47.69	4.48	12.71)
6c	iso-Bu	H	159—160	40	$C_{14}H_{16}FN_3O_6$	49.27	4.73	12.31
			(AcOEt–hexane)			(49.00	4.74	12.24)
6d	Et	Me	163—164	57	$C_{13}H_{14}FN_3O_6$	47.71	4.31	12.84
			(AcOEt–hexane)			(47.81	4.27	12.85)
7a	Et	H	189—190	52	$C_{12}H_{12}FN_3O_6$	46.01	3.86	13.42
			(EtOH)			(46.17	3.69	13.55)
7b	iso-Pr	H	198—199	62	$C_{13}H_{14}FN_3O_6$	47.71	4.31	12.84
			(MeOH–H_2O)			(47.59	4.23	12.65)
7c	iso-Bu	H	167—168	66	$C_{14}H_{16}FN_3O_6$	49.27	4.73	12.31
			(AcOEt–hexane)			(49.36	4.94	12.42)
7d	Et	Me	181—182	51	$C_{13}H_{14}FN_3O_6$	47.71	4.31	12.84
			(EtOH)			(47.81	4.27	12.85)

Table II. ^{1}H-NMR Data



6—8

Compd.	H-4	H-α	H-3′	H-4′	H-5′
6a	5.67	7.83	7.03	6.88	7.87
	(dd, J=5 and 1 Hz)	(s)	(d, J=4 Hz)	(dd, J=4 and 2 Hz)	(d, J=2 Hz)
6b	5.55	7.81	7.01	6.67	7.85
	(dd, J=5 and 1 Hz)	(s)	(d, J=4 Hz)	(dd, J=4 and 1 Hz)	(d, J=1 Hz)
6c	5.66	7.83	7.05	6.70	7.88
	(dd, J=5 and 2 Hz)	(s)	(d, J=4 Hz)	(dd, J=4 and 2 Hz)	(d, J=2 Hz)
6d	5.60	7.70	6.90	6.30	—
	(dd, J=5 and 1 Hz)	(s)	(d, J=4 Hz)	(d, J=4 Hz)	—
7a	5.57	8.27	6.85	6.60	7.82
	(dd, J=5 and 1 Hz)	(s)	(d, J=4 Hz)	(dd, J=4 and 2 Hz)	(d, J=2 Hz)
7b	5.48	8.25	6.83	6.58	7.80
	(dd, J=5 and 1 Hz)	(s)	(d, J=4 Hz)	(dd, J=4 and 1 Hz)	(d, J=1 Hz)
7c	5.60	8.23	6.87	6.61	7.83
	(dd, J=5 and 1 Hz)	(s)	(d, J=3 Hz)	(dd, J=3 and 2 Hz)	(d, J=2 Hz)
7d	5.52	8.13	6.72	6.22	—
	(dd, J=5 and 1.5 Hz)	(s)	(d, J=4 Hz)	(d, J=4 Hz)	—
8	5.71	8.15	6.86	6.59	7.81
	(dd, J=11 and 2 Hz)	(s)	(d, J=4 Hz)	(dd, J=4 and 2 Hz)	(d, J=2 Hz)

Substitution reactions of the acetates **5** with **11a** and (*E*)-5-methylfurfuraldoxime (**11b**) were carried out in pyridine in the presence of triethylamine at room temperature to give the corresponding **7** in moderate yields (Chart 2 and Table I). In this reaction, it seems to be

Table III. Antitumor Activities of **6** and **7** against Murine Colon Carcinoma 26[a]

Compd.	Dose (mmol/kg/d)	$T/C^{b)}$ (%)	Compd.	Dose (mmol/kg/d)	$T/C^{b)}$ (%)
6a	0.25	28	**7c** (TAC-788)	0.25	22
	0.5	1		0.5	1
	1	1		1	0
6b	0.25	60	**7d**	0.25	54
	0.5	3		0.5	12
	1	1		1	2
6c	0.25	19	**1** (5-FU)	0.25	30
	0.5	0		0.5	Toxic[c]
	1	0		1	NT[d]
6d	0.25	18	**2** (tegafur)	0.25	85
	0.5	1		0.5	64
	1	1		1	2
7a	0.25	55	**3** (carmofur)	0.25	55
	0.5	6		0.5	7
	1	1		1	1
7b	0.25	62	**4** (TAC-278)	0.25	90
	0.5	18		0.5	76
	1	6		1	51

a) A tumor fragment (2 mm^3) was implanted subcutaneously in CDF$_1$ female mice, and the drugs were administered orally once daily for 7 d starting 24 h after the tumor was transplanted. *b*) The T/C% values were calculated on the basis of the average tumor weight of the treated animals (5 mice/group) relative to that of the control animals (20 mice) on the 10th day. *c*) All mice died of drug toxicity. *d*) Not tested.

Table IV. Antitumor Activity of **7c** against Murine Lewis Lung Carcinoma, MethA Sarcoma and L1210 Leukemia[a]

Tumor	Compd.	Dose (mmol/kg):	T/C (%)[b] 0.2	0.3	0.4	0.5	0.6
Lewis lung	**7c**		63	18	8	NT	NT
	3		61	25	20	NT	NT
MethA	**7c**		NT	36	32	24	24
	3		NT	45	32	32	19
L1210	**7c**		NT	134	159	168	195
	3		NT	117	141	154	161

a) A tumor fragment (2 mm^3) and 1×10^6 cells were implanted subcutaneously (for Lewis lung and MethA) in BDF$_1$ and BALB/c female mice, respectively, and tumor cells (1×10^5 cells of L1210) were implanted intraperitoneally in BDF$_1$ female mice. The drugs were administered orally once daily for 7 d (for Lewis lung and MethA) or for 9 d (for L1210) starting 24 h after the tumor was transplanted. *b*) The T/C% values were calculated on the basis of the average tumor weight on the 10th day (for Lewis lung and MethA) or the mean survival time (for L1210) of the treated animals (5 mice/group) relative to that of the control animals (20 mice). NT: not tested.

necessary to add triethylamine to the reaction mixture for the reaction to proceed smoothly.

Further, isobutyl 5-fluoro-*c*-4-[(*E*)-furfurylideneaminooxy]hexahydro-*r*-5-pyrimidinecarboxylate (**8**) was isolated from the reaction mixture of the acetate **5c** with **11a** by preparative high-performance liquid chromatography (p-HPLC).[11]

The stereochemistry of **6**, **7** and **8** was determined as follows. In the proton magnetic resonance (^{1}H-NMR) spectra, signals due to the H-4 proton of **6** and **7**, coupled with an NH proton and a fluorine atom, appeared in the region of δ 5.58—5.67 as a double doublet which changed to a doublet having the coupling constant $J=1$—2 Hz when D_2O was added, whereas the corresponding signal of **8** at δ 5.71 exhibited the coupling constant $J=11$ Hz on similar treatment (Table II). These results demonstrate that both **6** and **7** have a *trans* relationship and **8** has a *cis* one between the H-4 proton and the fluorine atom at the 5-position.[12] Further, in the ^{1}H-NMR spectra of **6**, signals due to protons at the α-position and the furan ring showed absorption patterns similar to those of **10**, whereas the corresponding signals of **7** and **8** were similar to those of **11** on direct comparison.

These results clearly indicate that **6** and **7** are 5-fluoro-*t*-4-[(*Z*)- and (*E*)-furfurylideneaminooxy]hexahydro-*r*-5-pyrimidinecarboxylates, respectively, and **8** is 5-fluoro-*c*-4-[(*E*)-furfurylideneaminooxy]hexahydro-*r*-5-pyrimidinecarboxylate.

Biological Results

Preliminary *in vivo* screening of the (*Z*)- and (*E*)-oxime ethers **6** and **7** was carried out against the colon carcinoma 26 system. The results, together with those for 5-FU, tegafur, carmofur and TAC-278 as positive controls, are summarized in Table III. Compounds **6** and **7** have potent antitumor activities comparable to that of carmofur and superior to those of tegafur and TAC-278. No significant difference in antitumor activity was observed between the (*Z*)- and (*E*)-isomers when the carbon number of the ester group at the 5-position was changed.

Among these compounds, **7c** (TAC-788) appears to be the most promising antitumor agent as a pro-drug of 5-FU on the basis of its favorable pharmacodynamic properties and potent antitumor activity against various murine tumors (Table IV), and it is now undergoing clinical studies.

Experimental

All melting points were determined on a Yanagimoto hot plate apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer. Tetramethylsilane and dimethyl sulfoxide (DMSO)-d_6 were used as the internal standard and the solvent, respectively, unless otherwise specified. Chemical shifts are expressed in δ (ppm) values. The following abbreviations are used: s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, and m = multiplet. Mass spectrum (MS) was recorded on a JEOL JMS-01SC spectrometer. Column chromatography was carried out with Kieselgel 60 Art. 7734 (Merck). p-HPLC was carried out on a Toyo Soda (Tokyo, Japan) automatic preparative liquid chromatograph, model HLC-827, with a built-in ultraviolet (UV) spectrophotometer (254 nm), recorder and fraction collector.

Preparation of Materials——Isopropyl and isobutyl 4-acetoxy-5-fluorohexahydro-2,6-dioxo-5-pyrimidinecarboxylates (**5b** and **5c**) were prepared from isopropyl and isobutyl 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylates[13] according to the literature.[5] **5b**: mp 126—128 °C (crude). ^{1}H-NMR: 1.25 (6H, t, $J=6$ Hz), 2.09 (3H, s), 5.07 (1H, m), 6.08 (1H, dd, $J=1$, 6 Hz), 9.07 (1H, m), 11.63 (1H, s). **5c**: mp 176—177 °C (crude). ^{1}H-NMR: 0.84 (6H, d, $J=6$ Hz), 1.90 (1H, m), 2.07 (3H, s), 4.02 (2H, d, $J=6$ Hz), 6.15 (1H, dd, $J=2$, 6 Hz), 9.13 (1H, m), 11.33 (1H, s). (*Z*)- and (*E*)-Furfuraldoximes (**10a** and **11a**) were prepared according to the modified procedure.[14] (*Z*)- and (*E*)-5-Methylfurfuraldoximes (**10b** and **11b**) were prepared according to the literature.[15]

5-Fluoro-*t*-4-[(*Z*)-furfurylideneaminooxy]hexahydro-*r*-5-pyrimidinecarboxylates (6a—d). General Procedure——A solution of **5** (0.5 mol) and **11** (0.6 mol) in acetone–pyridine (1 : 2, 450 ml) was stirred at 60 °C for 15 h. The acetone was evaporated off under reduced pressure, and the residual oil was poured into ice-water (3 l). The precipitate was collected by filtration and washed with H_2O (250 ml × 2). Recrystsllization from the solvent gave **6** (Tables I and II).

Reaction of Ethyl and Isobutyl 4-Acetoxy-5-fluorohexahydro-5-pyrimidinecarboxylates (5a and 5c) with (*Z*)-Furfuraldoxime (10a)——a) Reaction of **5a**: A solution of **5a**[5] (26.2 g, 0.1 mol) and **10a** (13.3 g, 0.12 mol) in acetone–pyridine (1 : 2, 60 ml) was stirred at room temperature for 73 h. The solvent was evaporated off, H_2O (150 ml) was added to the residue and the mixture was stirred. The viscous solid which precipitated was collected by filtration and washed with H_2O. The solid was added to AcOEt (50 ml) and the mixture was stirred at room temperature for 5 min. The precipitate was collected by filtration and washed with AcOEt–hexane (2 : 1, 100 ml) to give **9a** (11.27 g, 36%), mp 136—137 °C (crude). *Anal.* Calcd for $C_{12}H_{12}FN_3O_6$: C, 46.01; H, 3.86; N, 13.42. Found: C, 46.00; H, 3.82; N, 13.22. ^{1}H-NMR δ: 1.23 (3H, t, $J=7$ Hz), 4.31 (2H, q, $J=7$ Hz), 6.02 (1H, dd, $J=1$, 4 Hz), 6.67 (1H, m), 7.60 (1H, d, $J=4$ Hz), 7.88 (1H, d, $J=2$ Hz), 8.30 (1H, m), 11.01 (1H, s). The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (250 g) with AcOEt–hexane (1 : 1) to afford **6a** (5.0 g, 16%).

b) Reaction of **5c**: Treatment of **5c** (1.95 g, 6.7 mmol) with **10a** (1.11 g, 10 mmol) in the manner described above gave **6c** (455 mg, 21%) and **9b** (399 mg, 19%), mp 162—164 °C (crude). *Anal.* Calcd for $C_{14}H_{16}FN_3O_6$: C, 49.27; H, 4.73; N, 12.31. Found: C, 49.00; H, 4.77; N, 12.25. ^{1}H-NMR δ: 0.90 (6H, d, $J=7$ Hz), 1.73—2.17 (1H, m), 4.11 (2H, d, $J=6$ Hz), 6.07 (1H, dd, $J=1$, 5 Hz), 6.71 (1H, m), 7.65 (1H, d, $J=4$ Hz), 7.90 (1H, d, $J=2$ Hz), 8.35 (1H, s), 8.87 (1H, m), 11.09 (1H, s).

Reaction of *N*-Furfurylidene-*N*-(5-fluoro-5-isobutoxycarbonylhexahydropyrimidin-4-yl)amine *N*-Oxide (9b) with (*Z*)- and (*E*)-Furfuraldoximes (10a and 11a)——a) Reaction with **10a**: A solution of **9b** (341 mg, 1 mmol) and **10a** (133 mg, 1.2 mmol) in acetone–pyridine (1 : 2, 3 ml) was heated with stirring at 60 °C for 15 h. The solvent was evaporated off under reduced pressure, and the residue was purified by column chromatography on silica gel (15 g) with AcOEt–hexane (1 : 4) to give **6c** (193 mg, 57%).

b) Reaction with **11a**: A solution of **9b** (341 mg, 1 mmol) and **11a** (133 mg, 1.2 mmol) in acetone–pyridine (1 : 2, 3 ml) was stirred at room temperature for 51 h. The solvent was evaporated off under reduced pressure, and the residue was treated as described above, giving **7c** (188 mg, 55%).

5-Fluoro-*t*-4-[(*E*)-furfurylideneaminooxy]hexahydro-*r*-5-pyrimidinecarboxylates (7a—d). General Procedure—— A solution of **5** (30 mmol), **11** (30 mmol) and dry triethylamine (30 mmol) in dry pyridine (15 ml) was stirred at room temperature for 20 h. The solvent was evaporated off under reduced pressure, and the residue was extracted with AcOEt (100 ml × 2). The organic layer was washed with H_2O (50 ml × 2) and dried (Na_2SO_4). Removal of the solvent under reduced pressure and recrystallization of the residue from the solvent afforded **7** (Tables I and II).

Isolation of Isobutyl 5-Fluoro-*c*-4-[(*E*)-furfurylideneaminooxy]hexahydro-*r*-5-pyrimidinecarboxylate (8)——The filtrate after recrystallization of **7c** was collected and concentrated under reduced pressure. The residue was fractionated by column chromatography on silica gel with $CHCl_3$–acetone (5 : 1). The fractions containing **8** were collected and concentrated under reduced pressure. The residue was subjected to p-HPLC on a YMC-S30 column and eluted with MeOH–H_2O (50 : 55). The MeOH was evaporated off under reduced pressure, and the residual solution was lyophilized to give **8** (Table II), mp 158—160 °C. MS m/z: 341 (M^+), $C_{14}H_{16}FN_3O_6$.

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