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Studies of Antitumor-Active 5-Fluorouracil Derivatives. I. Synthesis of *N*-Phthalidyl 5-Fluorouracil Derivatives

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Several 5-fluorouracil derivatives in which the phthalidyl (1,3-dihydro-3-oxoisobenzofuran-1-yl) group, appropriately substituted on its benzene ring, is substituted at the *N*(1)- or *N*(3)-position or at both positions were synthesized, and their antitumor activities were evaluated. Among these compounds, 1-(1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-fluorouracil (**3a**, 590-S) was shown to be markedly active against several experimental tumor systems. Several methods for a simple and efficient large-scale preparation of **3a** were examined. The large-scale preparation of **3a** was effected most efficiently by the condensation of 5-fluorouracil with the quaternary ammonium salt of 3-bromophthalide in the presence of a base. The synthesis of (+)- and (−)-**3a** is also described.

Keywords——antitumor agent; prodrug; 1-(1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-fluorouracil; *N*-phthalidyl-5-fluorouracil; selective *N*-substitution; quaternary ammonium salt; 590-S

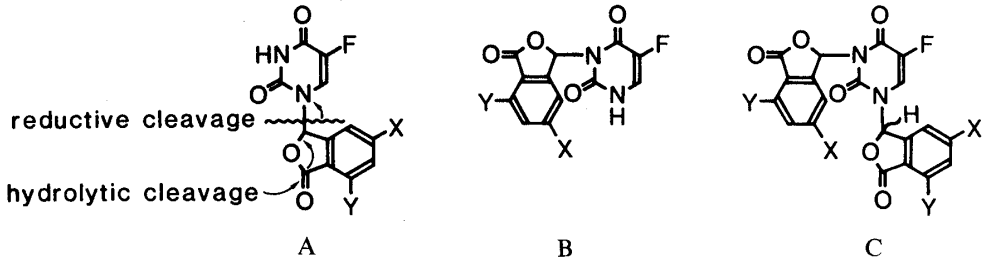
5-Fluorouracil (5-FU), an analogue of uracil which inhibits thymidylate synthetase, has been widely used clinically as an antitumor agent (especially against solid tumors) for more than two decades since it was synthesized by Duschinsky *et al.* in 1957[1] and its antitumor activity was demonstrated by Heidelberger *et al.* in the same year.[2] However, its clinical usefulness is often limited because of its severe toxic side effects which cause gastrointestinal disorders when the drug is orally administered at the effective dose.

Efforts have been made to synthesize novel prodrug derivatives of 5-FU possessing a broader spectrum of antitumor activity with lesser toxic side effects than the parent compound.[3a-z,α,β] 1-(Tetrahydrofuran-2-yl)-5-FU (Tegafur)[3a] and 1-hexylcarbamoyl-5-FU (Carmofur)[4] possess several distinct advantages over the parent compound and have been marketed in Japan as orally active antitumor chemotherapeutic agents. As these derivatives still have several disadvantages such as poor tumor affinity, a low blood concentration of 5-FU (which is the active metabolite), and side effects due to other metabolites, we conducted extensive studies to find novel prodrug derivatives of 5-FU superior to both of these compounds.

The nature of the chemical bond between 5-FU and the substituent used as a pro-moiety[5] seems to be an important characteristic of the prodrug. The bond should have reasonable stability but should also decompose appropriately in the biological environment. The phthalidyl group, which has been applied to talampicillin, a prodrug of the penicillin antibiotic ampicillin,[6a,b] is interesting as a pro-moiety from several points of view when its derivatives, having an appropriate substituent on the benzene ring, are substituted either at the *N*(1)- or the *N*(3)-position of 5-FU or at both the *N*(1)- and *N*(3)-positions, as shown in Chart 1. The rate of hydrolytic cleavage of phthalidyl derivatives by esterase can be controlled by the nature of the substituent, X and Y, on the aromatic ring of phthalide, and moreover reductive regeneration of 5-FU might be possible, as 5-FU is substituted at the benzylic position of phthalides and tumors with an ischemic zone are considered to have an enhanced

ability to reduce a variety of substrates.[7)]

This report describes the syntheses of several 5-FU derivatives in which the phthalidyl group, appropriately substituted on its benzene ring, is substituted at the *N*(1)- or the *N*(3)-position or at both positions.

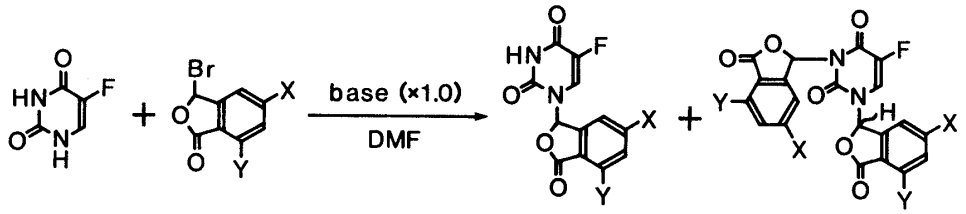


A B C

Chart 1

Synthesis of *N*(1)-Phthalidyl-5-FU Derivatives

Selective alkylation or acylation of 5-FU at the *N*(1)-position is not an easy process.[8a-d)] Simple alkylation of 5-FU with 3-bromophthalide derivatives **2a**—**g** in the presence of a base gave a mixture of *N*(1)-monophthalidyl derivatives **3a**—**g** and *N*(1),*N*(3)-diphthalidyl derivatives **4a**—**g**. As shown in Table I, the product ratio of *N*(1),*N*(3)-diphthalidyl derivatives **4** seems to decrease when the substituent X or Y is electron-withdrawing.



1 **2** **3** **4**

Chart 2

TABLE I. Yields of **3** and **4**

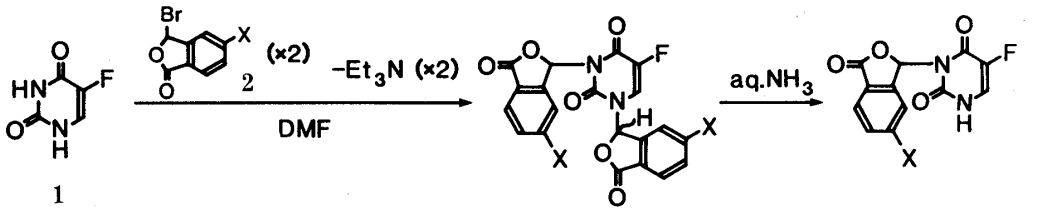
	X	Y	Yield (%) **3**	**4**
a	H	H	28	32
b	CN	H	54	4
c	CO_2Et	H	60	11
d	CO_2Bu^t	H	60	9
e	CO_2POM[a)]	H	40	10
f	H	CO_2Et	55	11
g	H	CO_2Bu^t	44	15

a) POM: pivaloyloxymethyl.

Synthesis of *N*(1), *N*(3)-Diphthalidyl-5-FU Derivatives and *N*(3)-Phthalidyl-5-FU Derivatives

Reaction of 5-FU with 2 mol eq of 3-bromophthalide derivatives and base gave almost quantitative yields of the *N*(1),*N*(3)-diphthalidyl-5-FU derivatives **4a**, **b** and **4h**, **i** as diastereomeric mixtures. Treatment of **4a**, **b** with aqueous ammonia gave the *N*(3)-monophthalidyl derivatives **5a**, **b**, but this method to obtain *N*(3)-monophthalidyl derivatives is not satisfactory as 2 eq of expensive 3-bromophthalide derivatives are needed.

Thus, we tried using an appropriate protecting group which could be easily removed



4a: X=H (82%)
4b: X=CN (51%)
4h: X=OCH_3 (51%)
4i: X=$OSiMe_2Bu^t$ (47%)

5a: X=H (48%)
5b: X=CN (42%)

Chart 3

under mild reductive or oxidative conditions to selectively obtain *N*(1)- or *N*(3)-phthalidyl-5-FU derivatives.

N(1)-Alkylation of 5-FU

The 2,2,2-trichloroethoxycarbonyl or 4-methoxybenzyl protecting group was introduced at the *N*(3)-position of 5-FU. Treatment of 5-FU with 2 mol eq of 2,2,2-trichloroethyl chloroformate and triethylamine gave 1,3-bis(2,2,2-trichloroethoxycarbonyl)-5-FU (**6**). Hydrolysis of **6** with aqueous 30% hydrogen peroxide in the presence of a catalytic amount of sodium hydroxide gave 3-(2,2,2-trichloroethoxycarbonyl)-5-FU (**9a**) in good overall yield. 1-(Methoxycarbonyl)-, 1-(ethoxycarbonyl)- and 1-(2,2,2-trichloroethoxycarbonyl)-5-FU (**7a**—**c**), obtained by treatment of 5-FU with 1 eq of methyl-, ethyl- or 2,2,2-trichloroethyl chloroformate and triethylamine, were allowed to react further with 4-methoxybenzyl bromide in the presence of triethylamine to obtain the corresponding 1-(methoxycarbonyl)-, 1-(ethoxycarbonyl)- and 1-(2,2,2-trichloroethoxycarbonyl)-3-(4-methoxybenzyl)-5-FU (**8a**—**c**). Removal of the methoxycarbonyl, ethoxycarbonyl and 2,2,2-trichloroethoxycarbonyl groups of **8a**—**c** with 30% aqueous hydrogen peroxide and a catalytic amount of sodium

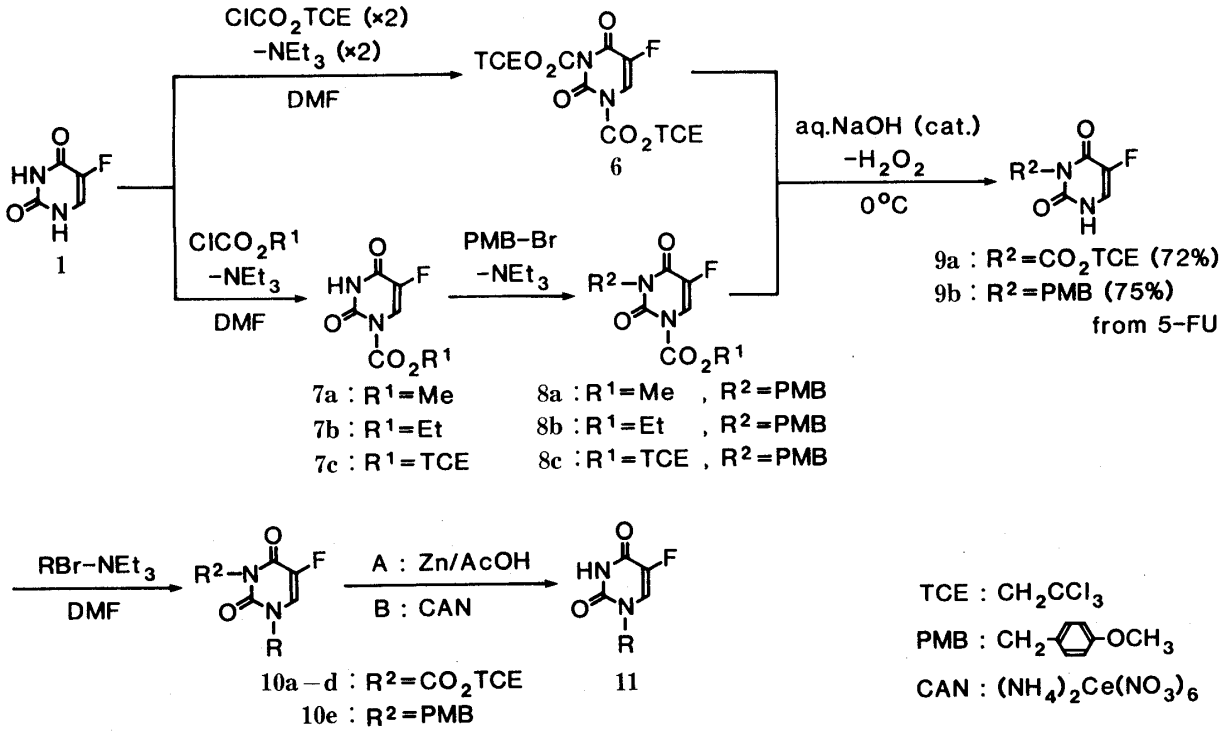
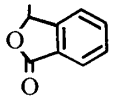
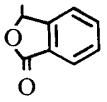
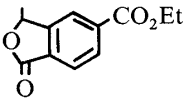
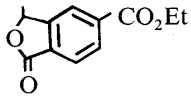
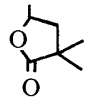
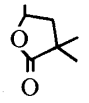
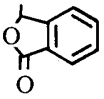
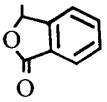


Chart 4

TABLE II

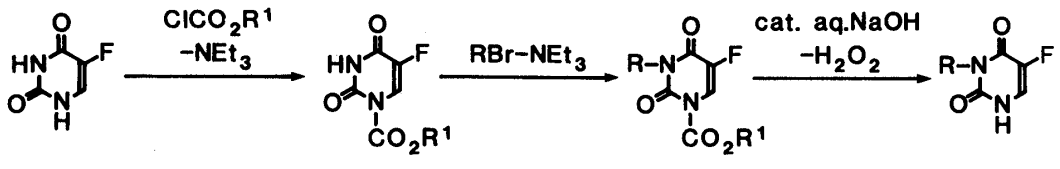
Yields of **10** from **9a** or **9b**				Yields of **3** or **11** from **10**		
Compound	R^2	R	Yield (%)	Compound	R	Yield (%)
10a	$CO_2TCE^{a)}$	$-CH_2Ph$	96	**11a**	$-CH_2Ph$	92
10b	CO_2TCE		69	**3a**		88
10c	CO_2TCE		84	**3c**		100
10d	CO_2TCE		54	**11b**		85
10e	$PMB^{a)}$		93	**3a**		63

a) TCE: trichloroethyl. PMB = *p*-methoxybenzyl.

hydroxide gave 3-(4-methoxybenzyl)-5-FU (**9b**). The *N*(3)-protected 5-FU derivative **9a** or **9b** was alkylated with various halides in the presence of triethylamine and gave **10a—e** in almost quantitative yield. Reductive deprotection of the 2,2,2-trichloroethoxycarbonyl group of **10a—d** with zinc in acetic acid or oxidative deprotection of the 4-methoxybenzyl group of **10e** with ceric ammonium nitrate[9] gave the corresponding *N*(1)-substituted 5-FU derivatives **11a**, **b**, **3a** and **3c**, as shown in Table II.

N(3)-Alkylation of 5-FU

Derivatives of 5-FU protected at the *N*(1)-position with a methoxycarbonyl-, ethoxycarbonyl- or 2,2,2-trichloroethoxycarbonyl group, **7a—c**, were easily obtained by treatment of 5-FU with 1 mol eq of the corresponding chloroformate and triethylamine. These products were alkylated with various halides to obtain **8a**, **d—k**. Smooth deprotection of the *N*(1)-acyl group of **8a**, **d—k** was effected under mild conditions by treatment with aqueous 30% hydrogen peroxide in the presence of a catalytic amount of sodium hydroxide at low temperature or by reduction with zinc in acetic acid in the case of the 2,2,2-trichloroethoxycarbonyl protecting group. The *N*(3)-substituted 5-FU derivatives thus obtained are listed in Table III.



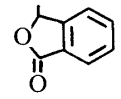
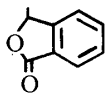
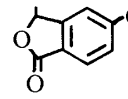
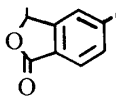
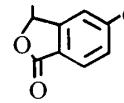
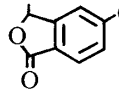
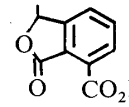
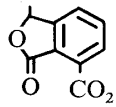
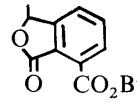
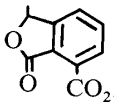
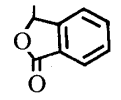
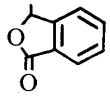
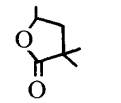
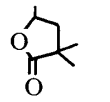
1 **7a—c** **8a, d—k** **5, 9**

R^1 = Me, Et, TCE

Chart 5

The antitumor activity of phthalidyl-5-FU derivatives in which the phthalidyl group is substituted at the *N*(1)-, or the *N*(3)-position or at both the *N*(1), and *N*(3)-positions was tested primarily against L-1210 leukemia in BDF_1 mice and in some cases against P 388 leukemia

TABLE III

Yields of **8** from **7a—c**				Yields of **5** or **9** from **8**		
Compound	R^1	R	Yield (%)	Compound	R	Yield (%)
8a	Me	$-CH_2-C_6H_4-OCH_3$	—	**9b**	$-CH_2-C_6H_4-OCH_3$	75[a]
8d	Me		—	**5a**		50[a]
8e	Et		77	**5c**		91
8f	Et		65	**5d**		76
8g	Et		65	**5f**		81
8h	Et		47	**5g**		73
8i	TCE	$-CH_2Ph$	—	**9c**	$-CH_2Ph$	84[a]
8j	TCE		85	**5a**		85
8k	TCE		69	**9d**		94

a) Overall yields from **7a** or **7c**.

TABLE IV. Hydrolysis of 1-Phthalidyl-5-FU Derivative (**3a—d, j** and **k**) in Phosphate Buffer and Mouse Plasma, and Their Antitumor Activities

	3:X	$\tau_{1/2}$ (min)		ILS_{max} (%) L-1210	Total dose (mg/kg) (*i.p.–p.o.*)
		Phosphate buffer pH = 7.5 (at 37 °C, c = 10^{-5} M/l)	Mouse plasma pH = 7.6 (at 37 °C, c = 10^{-3} M/l)		
b	CN	77	30	48	(2000)
c	CO_2Et	201	—	70	(3000)
d	CO_2Bu^t	188	—	58	(3000)
j	CO_2H	703	—	72	(2000)
k	CO_2Na	—	—	60	(1000)
a	H (590-S)	790	350	50	(2000)

ILS = increase of life span.

and B 16 melanoma in BDF_1 mice, Ehrlich carcinoma, Sarcoma 180 and Shionogi carcinoma 42 in DS mice, and Walker carcino sarcoma 256 and Yoshida sarcoma in Wistar rat. The results, which will be reported elsewhere,[10] showed that in general, *N*(1)-phthalidyl derivatives had favorable antitumor activity with lower toxicity than the corresponding *N*(3)- or *N*(1), *N*(3)-diphthalidyl derivatives. To evaluate the effectiveness of the synthesized derivatives

as orally acceptable prodrugs of 5-FU, their stability in the gastric tract or blood must be considered. Hydrolysis studies in phosphate buffer at pH 7.5 and in mouse plasma at pH 7.6 were carried out with some of the *N*(1)-phthalidyl-5-FU derivatives which showed favorable antitumor activity, and the results are summarized in Table IV. Consideration of the stability and antitumor effect *in vivo* led us to conclude that **3a** and **3j**, which have high stability and also good antitumor activity, would be good candidates for further study.

An intensive study by Nitta *et al.*[11] showed that 1-(1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (**3a**) was markedly active against several experimental tumor systems such as L-1210 leukemia, L5178Y lymphoma, Gardner lymphoma 6C3HED-OG, Sarcoma 180, Meth A fibrosarcoma, and NH 138 hepatoma in mice, with low toxicity. Thus **3a** was selected for clinical trial and given the code number 590-S. At this stage, we tried to find a simple and efficient method for large-scale preparation of **3a**, as a large quantity would be needed for preclinical studies.

Synthesis of 1-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-5-FU (3a)

Method A——5-Fluoro-2,4-dimethoxypyrimidine (**13a**), 5-fluoro-2,4-diethoxypyrimidine (**13b**)[12] or 5-fluoro-2,4-bis(trimethylsilyloxy)pyrimidine (**13c**)[13] was allowed to react with 3-chlorophthalide (**12a**) or 3-bromophthalide (**2a**) with or without solvent and catalyst at a relatively high temperature. The resulting 1-phthalidyl-5-FU derivatives **14a**—**c**, were treated with acid to obtain **3a**. As shown in Table V, use of 3-bromophthalide generally gave the product in better yield at a relatively low temperature. Use of a catalyst such as stannic chloride or trimethylsilyl trifluoromethanesulfonate[14] allowed the reaction temperature to be lowered by about 50 to 60 °C and improved the yield. In the case of the reaction between **13c** and **12a** in the presence of stannic chloride catalyst, solvents could be conveniently used and dichloroethane was found to be superior to acetonitrile or toluene. The insufficient yield obtained in the case of the reaction of **13a** with **2a** was probably due to a side reaction of **13a** with the methyl bromide produced during the reaction.

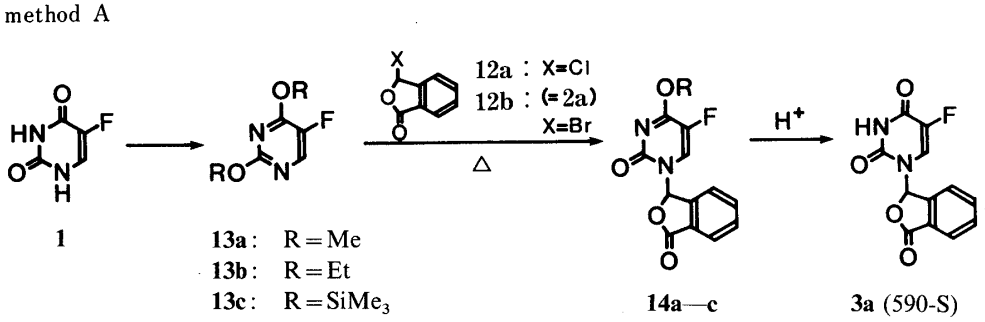


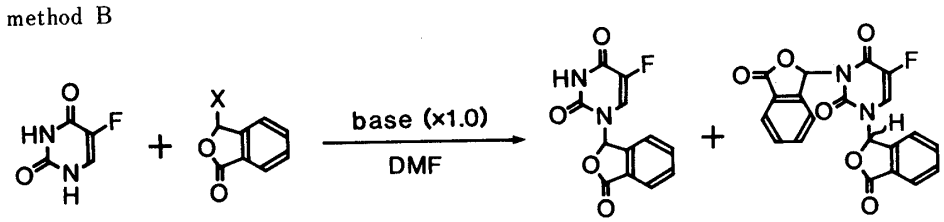
Chart 6

Method B——Clearly the direct alkylation of 5-FU with 3-bromophthalide is the simplest method but as described before, the formation of 1,3-diphthalidyl-5-FU (**4a**) could not be avoided. We thought that the leaving group at the 3-position of phthalide might affect the product ratio in the alkylation of 5-FU, as a tendency for the yield of the *N*(1)-monosubstituted product to increase was observed when the reactivity of the 3-bromide of the phthalides was decreased by an electron-withdrawing substituent on its benzene ring. Thus, we used 3-chlorophthalide (**12a**), which is a weaker alkylating agent than the corresponding bromo analogue. As expected, this reagent gave an almost quantitative yield of **3a** in the reaction with 5-FU in the presence of triethylamine or potassium carbonate and the formation of **4a** was negligible (Table VI). When the substituent at the 3-position of phthalide was trifluoroacetoxy or methanesulfonyloxy, a significant difference in product ratio was observed depending upon the nature of the base used. With potassium carbonate, the major

TABLE V. Yields of **3a** by Method A

Substrate		Reaction conditions				Yield (%)
13:R	**12**:X	Catalyst	Solvent	Temp. (°C)	Time (h)	**3a**
CH_3	Cl	—	—	125—135	1	48
CH_3	Cl	$SnCl_4$	—	60—70	1	43
CH_3	Br	—	—	90—100	1	69
C_2H_5	Cl	—	—	155—165	3	27
C_2H_5	Cl	$SnCl_4$	—	100—110	1	41
C_2H_5	Br	—	—	100	1.5	94
Me_3Si	Cl	—	—	140—160	3	60
Me_3Si	Cl	$SnCl_4$	—	90—100	1	87
Me_3Si	Cl	$SnCl_4$	$ClCH_2CH_2Cl$	Reflux	2	87
Me_3Si	Cl	$SnCl_4$	CH_3CN	Reflux	2	60
Me_3Si	Cl	$(CH_3)_3SiOSO_2CF_3$	—	115—125	5	27
Me_3Si	Br	—	—	110—130	3	86
Me_3Si	Br	$SnCl_4$	—	60—80	2	90
Me_3Si	Br	$(CH_3)_3SiOSO_2CF_3$	—	60—80	7	84

reaction products were phthalaldehydic acid and 5-FU, whose formation was probably due to attack on the trifluoroacetoxycarbonyl or methanesulfonyl functions by the anion of 5-FU. When triethylamine was used as the base, **3a** was produced in acceptable yields with both substituents at the 3-position of phthalide. In the latter case, quaternary *N*,*N*,*N*-triethyl-*N*-phthalidylammmonium salts seemed to be involved as intermediates.



1 **12a**: X=Cl **3a** **4a**
12b (=**2a**): X=Br
12c: X=CF_3CO_2
12d: X=CH_3SO_3

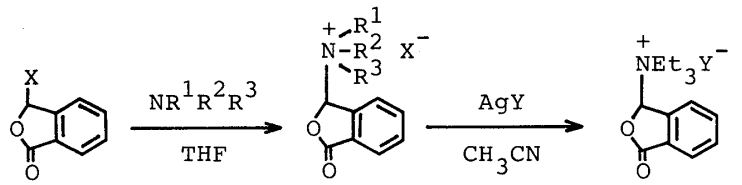
Chart 7

TABLE VI. Yields of **3a** by Method B

12	Reaction conditions		Yield (%)	
X	Base	Time (h)	**3a**	**4a**
Br	Et_3N	1	28	32
Cl	Et_3N	15	87	—
Cl	Et_3N	15	82[b]	—
Cl	K_2CO_3	2	91	—
Cl	K_2CO_3	2	92[b]	—
CF_3CO_2	Et_3N	15	83	—
CF_3CO_2	K_2CO_3	15	—[a]	—
CH_3SO_3	Et_3N	15	62	—
CH_3SO_3	K_2CO_3	15	30[a]	—

a) 5-FU and phthalaldehydic acid were recovered. *b*) In DMSO.

TABLE VII. Preparation of *N,N,N*-Trialkyl-*N*-phthalidylquaternary Ammonium Salts (**15a—h**)



12a: X=Cl
2a: X=Br

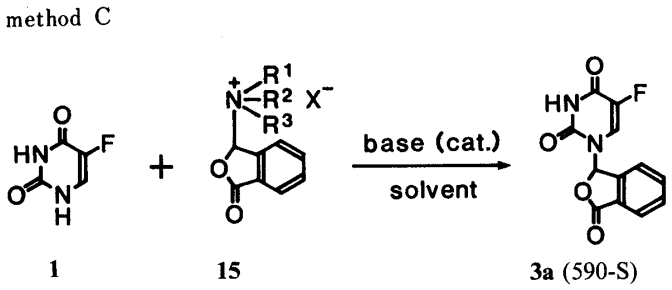
15a—e **15f—h**

15	$NR^1R^2R^3$	X	Yield (%)
a	Et_3N	Cl	24
b	Et_3N	Br	88
c	MeN O	Cl	52
d	MeN O	Br	83
e	EtN O	Br	72

15	Y	Yield (%)
f	$OCOCF_3$	95
g	OSO_2Me	95
h	OSO_2-C$_6$H$_4$-Me	95

Method C——In view of our observations with method B, we decided to study the synthesis and reactivity of some quaternary ammonium bases. 3-Chlorophthalide or 3-bromophthalide was treated with triethylamine, *N*-methylmorpholine or *N*-ethylmorpholine and the corresponding quaternary salts **15a—e** were obtained. Other quaternary salts **15f—h** were obtained from the reaction of *N,N,N*-triethyl-*N*-phthalidylammonium bromide (**15b**) with silver trifluoroacetate, silver methanesulfonate and silver *p*-toluenesulfonate in acetonitrile (Table VII).

These quaternary salts were allowed to react with 5-FU in the presence of a base such as triethylamine, *N*-methylmorpholine or potassium carbonate in dimethylsulfoxide (DMSO) or dimethylformamide (DMF), and **3a** was obtained in almost quantitative yield (Table VIII). Scarcely any formation of **4a** was observed.



1 **15** **3a** (590-S)

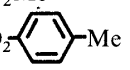
Chart 8

The reaction of 3-bromophthalide and triethylamine in DMF gave a quaternary ammonium salt, which, when allow to react *in situ* with 5-FU in the presence of potassium carbonate, gave an almost quantitative yield of **3a**. This procedure seems to be the most convenient and efficient method presently known for producing **3a**.

Synthesis of (+)- and (−)-Isomers of 1-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-5-FU (3a)

Like the α- and β-isomers in nucleosides and 1-(tetrahydrofuran-2-yl)-5-FU, 1-(1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (**3a**) has one asymmetric carbon at the 3-position of

TABLE VIII. Yields of **3a** by Method C

15	$NR_1R^2R^3$	X	Base	Solvent	Yield (%) **3a**
a	Et_3N	Cl	Et_3N	DMSO	95
b	Et_3N	Br	Et_3N	DMF	93
f	Et_3N	$OCOCF_3$	Et_3N	DMF	95
g	Et_3N	OSO_2Me	Et_3N	DMF	95
h	Et_3N		Et_3N	DMF	96
c		Cl		DMF	66
d		Br		DMSO	61
d		Br	K_2CO_3	DMSO	94

the phthalide ring and exists as two isomers. To examine the possible differences in susceptibility to esterase hydrolysis and in antitumor activity between the (+)- and (−)-isomers, we tried to synthesize them.

As **3a** was found to be a stronger acid than 1-(tetrahydrofuran-2-yl)-5-FU, judging from its pK_a value in aqueous acetonitrile,[15] we first tried optical resolution *via* the formation of its diastereomeric salts with optically active alkaloids such as brucine and cinchonidine; similar procedures had been effective for the resolution of 1-(tetrahydrofuran-2-yl)-5-FU.[3e] Unfortunately, salt formation was unsuccessful probably due to the poor solubility of **3a** itself compared to the corresponding salts with alkaloids. Next, we tried to resolve 1-(6-carboxy-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (**3j**), prepared by hydrolysis of **3d** with trifluoroacetic acid, in a similar way, and to convert the resolved isomers of **3j** to the corresponding optically active (+)- and (−)-isomers of **3a**.

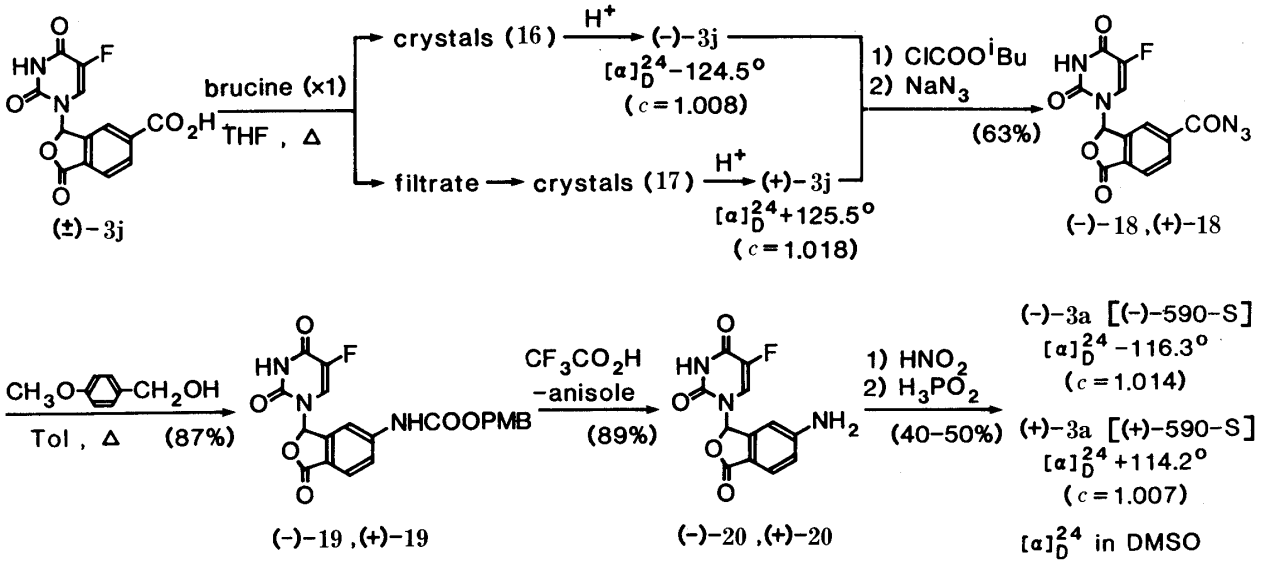


Chart 9. Synthesis of (+)- and (−)-Isomers of **3a**

Heating **3j** with brucine in tetrahydrofuran (THF) gave crystals of **16**, which upon filtration and acidification gave (−)-**3j** in almost quantitative yield. Evaporation of the filtrate gave **17**, which upon treatment with acid gave (+)-**3j**. Isomers (−)-**3j** and (+)-**3j** were

separately derived to the corresponding (−)-**3a** and (+)-**3a** as follows. Treatment of **3j** with isobutyl chloroformate and triethylamine, and subsequently with lithium azide or sodium azide, gave the acid azide derivative **18**. Refluxing of **18** with 4-methoxybenzyl alcohol in toluene gave the 4-methoxybenzyloxy carbamate derivative **19**. Treatment of **19** with trifluoroacetic acid and anisole gave the corresponding amine **20**. Diazotization of **20** with nitrous acid followed by reduction of the diazonium salts with hypophosphorous acid gave **3a**. The optical purities of the synthesized (−)-**3a** and (+)-**3a** were estimated by measuring the nuclear magnetic resonance (NMR) spectra of the *N*(3)-4-bromobenzyl derivatives of (+)-**3a** and (±)-**3a** in $CDCl_3$ in the presence of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium (III) derivative [Eu(hfc)$_3$]. The data indicated that more than 99% optical purity had been obtained. No significant differences between these isomers were observed in any of the relevant properties such as the rate of hydrolytic cleavage by esterase and antitumor activity *in vivo*.

Experimental

Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere using dry solvents under anhydrous conditions, with anhydrous $MgSO_4$ as a drying agent for the extracts. The organic solvents were removed under reduced pressure with a rotary evaporator. Medium-pressure column chromatographies on Merck "Lobar" columns pre-packed with LiChroprep Si 60: size A (240—10 mm, 40—63 μm), size B (310—25 mm, 40—63 μm) and size C (440—37 mm, 63—125 μm) were carried out to separate and purify the products. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Hitachi 260-10 spectrophotometer, ultraviolet (UV) spectra with a Hitachi EPS-3T spectrophotometer and NMR spectra with a Varian EM-390, T-60A or XL-200 spectrometer. No attempts were made to maximize the yields.

1-(6-Cyano-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (3b)——1-Bromo-6-cyano-1,3-dihydro-3-oxoisobenzofuran (**2b**), prepared by photobromination of 6-cyano-1,3-dihydro-3-oxoisobenzofuran (5.0 g, 31 mmol) with *N*-bromosuccinimide (9.0 g, 50 mmol) in a CCl_4–benzene (1 : 1) mixture (300 ml), was reacted with 4.0 g (31 mmol) of 5-FU in 40 ml of DMF in the presence of 4.3 ml (31 mmol) of Et_3N at 0—3 °C for 15 h. The crystalline product was filtered off and washed with a small amount of cold DMF and water to obtain 3.8 g of crude **3b**. The filtrate and washings were combined and the products were isolated by extraction with AcOEt–MeCN (1 : 1) mixture. The organic layer was washed with water, dried and evaporated. Separation of the residue by column silica gel chromatography using benzene–AcOEt (2 : 1) mixture as an eluent gave an additional 1.2 g of crude **3b**. Recrystallization of the combined product from MeOH gave 4.81 g (54%) of **3b**, mp 269—271 °C. IR (KBr): 1674, 1687, 1714, 1734, 1779, 2240 cm^{-1}. UV (EtOH) nm (ε): 240.5 (10700), 247.5 (10700). NMR (DMSO-d_6) δ: 7.50 (1H, s), 7.74 (1H, d, J=7 Hz), 8.04 (2H, s), 8.28 (1H, s), 12.0 (1H, br). *Anal.* Calcd for $C_{13}H_6FN_3O_4$: C, 54.37; H, 2.11; F, 6.61; N, 14.63. Found: C, 54.46; H, 2.37; N, 14.62; F. 6.48. From the less polar fraction, 0.5 g (3.6%) of **4b** was obtained as a diastereomeric mixture.

1,3-Bis(1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (4a)——Et_3N (9.6 ml, 68 mmol) was added to an ice-cooled mixture of 4.02 g (31 mmol) of 5-FU and 14.5 g (68 mmol) of 1-bromo-1,3-dihydro-3-oxoisobenzofuran in 60 ml of DMF. The mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. $Et_3N \cdot HBr$ was removed by filtration and washed with a small amount of cold DMF. The filtrate was evaporated and the residue was crystallized from CH_2Cl_2–ether to obtain 9.9 g (82%) of **4a** as a diastereomeric mixture. A portion of this product was separated by column silica gel chromatography using a benzene–AcOEt (2 : 1) mixture as an eluent to obtain two diastereomers of **4a**. A-isomer (eluted as a less polar fraction): mp 259—261 °C (from CH_2Cl_2–ether). IR (KBr): 1658, 1698, 1736, 1785 cm^{-1}. UV (EtOH) nm (ε): 228.5 (14100), 271 (6800). NMR (DMSO-d_6) δ: 7.4—8.3 (11H, m). *Anal.* Calcd for $C_{20}H_{11}FN_2O_6$: C, 60.92; H, 2.81; N, 7.11. Found: C, 60.79; H, 2.66; N, 6.97. B-isomer (eluted as a polar fraction): mp 251—254 °C (from CH_2Cl_2–ether). IR (KBr): 1690, 1738, 1776 cm^{-1}. UV (EtOH) nm (ε): 228.5 (21000), 270 (10000). NMR (DMSO-d_6) δ: 7.4—8.3 (11H, m). *Anal.* Found: C, 60.59; H, 2.63; N, 7.09.

3-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-5-FU (5a)——A mixture of a solution of 1.5 g (3.8 mmol) of the diastereomeric mixture of **4a** in 6 ml of pyridine, 0.75 ml of 28% aq. NH_4OH and 30 ml of EtOH was stirred at 60 °C for 4.5 h, then cooled. The solvents were evaporated off. The crystalline product obtained on addition of $CHCl_3$ was filtered off and washed with $CHCl_3$. Recrystallization from MeOH yielded 671 mg (48%) of **5a**, mp 231—234 and 256—262 °C. IR (KBr): 1667, 1736, 1788 cm^{-1}. UV (EtOH) nm (ε): 227.5 (11100), 275 (7500). NMR (DMSO-d_6) δ: 3.0—6.5 (1H, br), 7.35—8.05 (4H, m), 7.76 (1H, s), 7.88 (1H, d, J=6 Hz). *Anal.* Calcd for $C_{12}H_7FN_2O_4$: C, 54.97; H, 2.69; F; 7.24; N, 10.69. Found: C, 55.31; H, 2.66; F, 7.17; N, 10.59.

The other *N*(1)-phthalidyl-, *N*(3)-phthalidyl- and *N*(1),*N*(3)-diphthalidyl-5-FU-derivatives with the physical

properties listed below were obtained by similar procedures.

1-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-5-FU (3a)——mp 298—300 °C (DMSO–MeOH). IR (KBr): 1607, 1670, 1685, 1717, 1800 cm^{-1}. UV (EtOH) nm (ε): 228 (14450), 264 (9680). NMR (DMF-d_7) δ: 7.66 (1H, s), 7.76 (1H, d, J=7 Hz), 7.85—8.05 (4H, m). *Anal.* Calcd for $C_{12}H_7FN_2O_4$: C, 54.97; H, 2.69; F, 7.25; N, 10.69. Found: C, 55.08; H, 2.68; F, 7.16; N, 10.65.

1-(6-Ethoxycarbonyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (3c)——mp 241—242 °C (acetone–ether). IR (Nujol): 1662, 1712, 1778 cm^{-1}. UV (EtOH) nm (ε): 242.5 (14300). NMR (acetone-d_6) δ: 1.37 (3H, t, J=8 Hz), 4.40 (2H, q, J=8 Hz), 7.47 (1H, d, J=6 Hz), 7.62 (1H, s), 7.87—8.12 (1H, m), 8.17—8.47 (2H, m). *Anal.* Calcd for $C_{15}H_{11}FN_2O_6$: C, 53.90; H, 3.32; F. 5.68; N, 8.38. Found: C, 53.77; H, 3.46; F, 5.45; N, 8.11.

1-[6-(*tert*-Butoxycarbonyl)-1,3-dihydro-3-oxoisobenzofuran-1-yl]-5-FU (3d)——mp 218—220 °C (AcOEt–ether). IR (Nujol): 1662, 1712, 1778 cm^{-1}. UV (EtOH) nm (ε): 241.5 (11300). NMR (DMSO-d_6) δ: 1.57 (9H, s), 3.37 (1H, br), 7.48 (1H, s), 7.72 (1H, d, J=7 Hz), 7.86—8.33 (3H, m). *Anal.* Calcd for $C_{17}H_{15}FN_2O_6$: C, 56.35; H, 4.17; F. 5.24; N, 7.73. Found: C, 56.19; H, 4.20; F, 5.13; N, 7.54.

1-(1,3)-Dihydro-3-oxo-6-pivaloyloxymethoxycarbonylisobenzofuran-1-yl)-5-FU (3e)——mp 219—221 °C (acetone–ether). IR (Nujol): 1663, 1720, 1783 cm^{-1}. UV (EtOH) nm (ε): 242.5 (20100). NMR ($CDCl_3$) δ: 1.19 (9H, s), 6.05 (2H, s), 7.63 (1H, d, J=7 Hz), 7.70 (1H, s), 8.09 (1H, d, J=8 Hz), 8.39 (1H, dd, J=1.5, 8 Hz), 8.47 (1H, d, J=1.5 Hz). *Anal.* Calcd for $C_{19}H_{17}FN_2O_8$: C, 54.29; H, 4.08; F, 4.52; N, 6.67. Found: C, 54.12; H, 4.09; F, 4.42; N, 6.63.

1-(4-Ethoxycarbonyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (3f)——mp 230—232 °C (acetone–ether). IR (Nujol): 1670, 1720, 1788 cm^{-1}. UV (EtOH) nm (ε): 238.5 (sh) (11200), 263.5 (8800). NMR (acetone-d_6) δ: 1.38 (3H, t, J=7 Hz), 2.25—4.15 (1H, br), 4.39 (2H, q, J=7 Hz), 7.55 (1H, d, J=8 Hz), 7.60 (1H, s), 7.74—8.09 (3H, m). *Anal.* Calcd for $C_{15}H_{11}FN_2O_6$: C, 53.90; H, 3.32; F, 5.68; N, 8.38. Found: C, 53.46; H, 3.31; F, 5.58; N, 8.19.

1-[4-(*tert*-Butoxycarbonyl)-1,3-dihydro-3-oxoisobenzofuran-1-yl]-5-FU (3g)——mp 188—191 °C (acetone–ether). IR (Nujol): 1669, 1713, 1800 cm^{-1}. UV (EtOH) nm (ε): 237 (sh) (13700), 263.5 (10500). NMR (acetone-d_6) δ: 1.62 (9H, s), 7.59 (1H, d, J=6 Hz), 7.66 (1H, s), 7.84—8.28 (3H, m). *Anal.* Calcd for $C_{17}H_{15}FN_2O_6$: C, 56.35; H, 4.17; F, 5.24; N, 7.73. Found: C, 56.19; H, 4.20; F, 5.13; N, 7.54.

1,3-Bis(6-cyano-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (4b)——mp 200—215 °C (AcOEt–EtOH, as a diastereomeric mixture). IR (KBr): 1685, 1740, 1792 cm^{-1}. UV (EtOH) nm (ε): 240.5 (16700), 248 (15800). NMR (DMSO-d_6) δ: 7.35—8.55 (9H, m).

1,3-Bis(6-ethoxycarbonyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (4c)——Amorphous powder. IR ($CHCl_3$): 1705, 1725, 1796 cm^{-1}. NMR (acetone-d_6) δ: 1.39 (6H, t, J=7 Hz), 4.43 (4H, q, J=7 Hz), 7.6—8.6 (9H, m).

1,3-Bis[6-(*tert*-butoxycarbonyl)-1,3-dihydro-3-oxoisobenzofuran-1-yl]-5-FU (4d)——Amorphous powder. IR ($CHCl_3$): 1704, 1740, 1792 cm^{-1}. NMR (acetone-d_6) δ: 1.61 (18H, s), 7.64 (1H, d, J=7 Hz), 7.70 (1H, s), 7.9—8.5 (7H, m).

1,3-Bis(1,3-dihydro-3-oxo-6-pivaloyloxymethoxycarbonylisobenzofuran-1-yl)-5-FU (4e)——Amorphous powder. IR ($CHCl_3$): 1704, 1746, 1798 cm^{-1}. NMR ($CDCl_3$) δ: 1.04 (18H, s), 5.96 (4H, s), 6.77 (1H, d, J=5 Hz), 7.8—9.0 (8H, m).

1,3-Bis(4-ethoxycarbonyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (4f)——Amorphous powder. IR ($CHCl_3$): 1700, 1724, 1798 cm^{-1}. NMR ($CDCl_3$) δ: 1.40 (6H, t, J=7 Hz), 4.23 (4H, q, J=7 Hz), 6.83 (1H, d, J=5 Hz), 6.32 (1H, s), 7.5—8.1 (7H, m).

1,3-Bis[4-(*tert*-butoxycarbonyl)-1,3-dihydro-3-oxoisobenzofuran-1-yl]-5-FU (4g)——Amorphous powder. IR ($CHCl_3$): 1700, 1796 cm^{-1}. NMR ($CDCl_3$) δ: 1.63 (18H, s), 6.77 (1H, d, J=5 Hz), 7.2—8.1 (8H, m).

1,3-Bis(6-methoxy-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (4h)——A-Isomer (eluted as a less polar fraction), mp 248—250 °C (ether). IR (KBr): 1660, 1722, 1773 cm^{-1}. NMR (DMSO-d_6) δ: 3.88 (6H, s), 7.0—8.1 (9H, m). *Anal.* Calcd for $C_{22}H_{15}FN_2O_8 \cdot 1/2H_2O$: C, 57.02; H, 3.48; F, 4.10; N, 6.04. Found: C, 57.39; H, 3.40; F, 4.12; N, 5.79. B-Isomer (eluted as a polar fraction), mp 165—168 °C (ether). IR (KBr): 1680, 1737, 1777 cm^{-1}. UV (EtOH) nm (ε): 261 (16400). NMR ($CDCl_3$) δ: 3.84 (6H, s), 6.7—7.9 (9H, m). *Anal.* Found: C, 57.15; H, 3.55; F, 3.98; N, 5.86.

1,3-Bis[6-(*tert*-butyldimethysilyloxy)-1,3-dihydro-3-oxoisobenzofuran-1-yl]-5-FU (4i)——Amorphous powder. IR ($CHCl_3$): 1688, 1700, 1740, 1784 cm^{-1}. NMR ($CDCl_3$) δ: 0.28 (12H, s), 1.0 (18H, s), 6.6—8.0 (9H, m).

3-(6-Cyano-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (5b)——mp 277—281 °C (MeOH). IR (KBr): 1660, 1725, 1794, 2225 cm^{-1}. UV (EtOH) nm (ε): 240.5 (18300), 248.8 (17600). NMR (DMSO-d_6) δ: 4.0 (1H, br), 7.84 (1H, s), 7.92 (1H, d, J=6 Hz), 8.08 (2H, s), 8.30 (1H, s). *Anal.* Calcd for $C_{13}H_6FN_3O_4$: C, 54.37; H, 2.11; F, 6.61; N, 14.63. Found: C, 54.57; H, 2.56; F, 6.28; N, 14.31.

3-(2,2,2-Trichloroethoxycarbonyl)-5-FU (9a)——An ice-cooled solution of 5 g (38.4 mmol) of 5-FU in 50 ml of DMF was treated with 13.8 ml (98.8 mmol) of Et_3N and 13.6 ml (99 mmol) of 2,2,2-trichloroethyl chloroformate. After the mixture had reacted for 2 h with ice cooling, it was poured into ice-cooled 2 N aq. HCl and the product was isolated by AcOEt extraction. The AcOEt layer was washed with water, dried and evaporated. The crude 1,3-bis(2,2,2-trichloroethoxycarbonyl)-5-FU (**6**) thus obtained was dissolved in a mixture of 100 ml of CH_2Cl_2 and 50 ml of MeOH and allowed to react with 10 ml of 30% aq. H_2O_2 (88 mmol) and 0.1 ml of 6 N aq. NaOH at 0—3 °C for 30 min. The reaction mixture was poured into ice-cooled 2 N aq. HCl and the product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with 5% aq. $Na_2S_2O_3$ and water, dried and evaporated. Recrystallization of

the residue from ether yielded 10.31 g (88%) of **9a**, mp 146—149 °C. IR ($CHCl_3$): 1681, 1696, 1741, 1802 cm^{-1}. NMR (acetone-d_6) δ: 4.78 (1H, br), 5.18 (2H, s), 7.70 (1H, d, J=6 Hz). *Anal.* Calcd for $C_7H_4Cl_3FN_2O_4$: C, 27.52; H, 1.32; F, 6.21; N, 9.17. Found: C, 27.67; H, 1.49; F, 6.21; N, 9.08.

3-(4-Methoxybenzyl)-5-FU (9b). General Procedure for Synthesis of *N*(3)-Substituted 5-FU Derivatives——An ice-cooled solution of 13 g (0.1 mol) of 5-FU and 13.9 ml (0.1 mol) of Et_3N in 260 ml of DMF was treated with 7.73 ml (0.1 mol) of methyl chloroformate, and the mixture was stirred at 0—3 °C for 3 h. Subsequently, 20.85 ml (0.15 mol) of Et_3N and 30.16 g (0.15 mol) of 4-methoxybenzyl bromide were added. After the reaction had proceeded at 0—3 °C for 3 h and at room temperature for 15 h, the mixture was poured into ice water and the product was isolated by AcOEt extraction. The AcOEt layer was washed with water, dried and evaporated. The crude 3-(4-methoxybenzyl)-1-methoxycarbonyl-5-FU (**8a**), thus obtained was dissolved in a mixture of 50 ml of CH_2Cl_2 and 50 ml of MeOH and allowed to react with 11.3 ml (0.11 mol) of 30% aq. H_2O_2 and 0.2 ml of 6 N aq. NaOH at 0—3 °C for 1 h. The reaction mixture was poured into ice-cooled 2 N aq. HCl and the product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with water, dried and evaporated. Recrystallization of the residue from ether yielded 17.0 g (68%) of **9b**, mp 161—162 °C. IR (Nujol): 1650, 1715 cm^{-1}. NMR (DMSO-d_6) δ: 3.74 (3H, s), 4.91 (2H, s), 6.87 (2H, d, J=9 Hz), 7.26 (2H, d, J=9 Hz), 7.83 (1H, d, J=6 Hz). *Anal.* Calcd for $C_{12}H_{11}FN_2O_3$: C, 57.60; H, 4.43; F, 7.59; N, 11.20. Found: C, 57.44; H, 4.34; F, 7.48; N, 11.29.

General Procedure for Synthesis of *N*(1)-Substituted 5-FU Derivatives——Synthesis of **3c**: A mixture of 3.54 g (11.75 mmol) of **9a**, 3.35 g (11.75 mmol) of 1-bromo-6-ethoxycarbonyl-1,3-dihydro-3-oxoisobenzofuran and 1.64 ml (11.75 mmol) of Et_3N in 36 ml of DMF was allowed to react at 0—3 °C for 15 h and the product was isolated by AcOEt extraction. The ACOEt layer was washed with water, dried and evaporated. The product was purified by column silica gel chromatography using benzene–AcOEt (4 : 1) mixture as an eluent. Recrystallization of the product from ether gave 5.0 g (84%) of 1-(6-ethoxycarbonyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)-3-(2,2,2-trichloroethoxycarbonyl)-5-FU (**10c**), mp 165—166 °C. IR ($CHCl_3$) 1720, 1751, 1803 cm^{-1}. NMR (acetone-d_6) δ: 1.18 (3H, t, J=7 Hz), 4.40 (2H, q, J=7 Hz), 5.21 (2H, s), 7.65 (1H, s), 7.70 (1H, d, J=6 Hz), 7.98 (1H, d, J=8 Hz), 8.30 (1H, dd, J=2, 8 Hz), 8.40 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{18}H_{12}Cl_3FN_2O_8$: C, 42.42; H, 2.37; F, 3.73; N, 5.50. Found: C, 42.54; H, 2.47; F, 3.64; N, 5.50. A mixture of 4.80 g (9.42 mmol) of **10c**, 14.1 g of AcOH and 15.4 g of Zn dust in 100 ml of CH_2Cl_2 was allowed to react with stirring at room temperature for 2 h, then filtered and washed with acetone. The solvent of the filtrate was evaporated off, and the product was isolated by acetone extraction. The product obtained by evaporation of the acetone was recrystallized from ether, giving 3.14 g (99%) of **3c**, mp 241—242 °C.

Synthesis of **3a**: A mixture of 15 g (60 mmol) of **9b**, 13.4 g (63 mmol) of 1-bromo-1,3-dihydro-3-oxoisobenzofuran and 8.35 ml (60 mmol) of Et_3N in 150 ml of DMF was reacted at room temperature for 15 h and the product was isolated by AcOEt extraction. The AcOEt layer was washed with water, dried and evaporated. Recrystallization of the residue from ether gave 21.32 g (93%) of 1-(1,3-dihydro-3-oxoisobenzofuran-1-yl)-3-(4-methoxybenzyl)-5-FU (**10e**), mp 163—164 °C. IR ($CHCl_3$): 1665, 1685, 1720, 1780 cm^{-1}. NMR ($CDCl_3$) δ: 3.77 (3H, s), 5.10 (2H, s), 6.55 (1H, d, J=6 Hz), 6.84 (2H, d, J=8 Hz), 7.45 (2H, d, J=8 Hz), 7.35—8.10 (5H, m). *Anal.* Calcd for $C_{20}H_{15}FN_2O_5$: C, 62.82; H, 3.95; F, 4.97; N, 7.33. Found: C, 62.59; H, 4.08; F, 4.94; N, 7.31. A mixture of 3.82 g (10 mmol) of **10e** and 14.5 g (28 mmol) of $Ce(NH_4)_2(NO_3)_6$ in 45 ml of acetonitrile and 5 ml of water was heated at 60 °C with stirring for 3 h. After cooling, the mixture was poured into water and the crystalline product was filtered off and washed with water. Recrystallization of the product from DMSO–MeOH gave 1.65 g (63%) of **3a**, mp 298—300 °C.

The same procedure was used to synthesize several derivatives, listed in Tables II and III, which had the following physical properties.

1-Benzyl-3-(2,2,2-trichloroethoxycarbonyl)-5-FU (10a)——mp 144—146 °C (*n*-hexane). IR ($CHCl_3$) 1690, 1730, 1800 cm^{-1}. NMR ($CDCl_3$) δ: 4.90 (2H, s), 5.00 (2H, s), 7.25 (1H, d, J=6 Hz), 7.38 (5H, s). *Anal.* Calcd for $C_{14}H_{10}Cl_3FN_2O_4$: C, 42.50; H, 2.55; N, 7.08. Found: C, 42.41; H, 2.70; N, 7.20.

1-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-3-(2,2,2-trichloroethoxycarbonyl)-5-FU (10b)——mp 190—191 °C (ether). IR ($CHCl_3$): 1700, 1740, 1795 cm^{-1}. NMR ($CDCl_3$) δ: 5.12 (2H, s), 6.80 (1H, d, J=6 Hz), 7.3—8.3 (5H, m). *Anal.* Calcd for $C_{15}H_8Cl_3FN_2O_6$: C, 41.17; H, 1.84; F, 4.34; N, 6.40. Found: C, 41.22; H, 1.91; F, 4.12; N, 6.59.

1-(4,4-Dimethyl-5-oxo-2,3,4,5-tetrahydrofuran-2-yl)-3-(2,2,2-trichloroethoxycarbonyl)-5-FU (10d)——mp 171—172 °C, (CH_2Cl_2–ether). IR ($CHCl_3$): 1690, 1730, 1795 cm^{-1}. NMR ($CDCl_3$) δ: 1.37 (3H, s), 1.39 (3H, s), 2.12 (1H, dd, J=13, 9 Hz), 2.65 (1H, dd, J=13, 6 Hz), 5.03 (2H, s), 6.50 (1H, dd, J=9, 6 Hz), 7.42 (1H, d, J=6 Hz). *Anal.* Calcd for $C_{13}H_{12}Cl_3FN_2O_6$: C, 37.39; H, 2.90; F, 4.55; N, 6.71. Found: C, 37.14; H, 3.18; F, 4.73; N, 6.81.

1-(4,4-Dimethyl-5-oxo-2,3,4,5-tetrahydrofuran-2-yl)-5-FU (11b)——mp 254—257 °C (acetone–water). IR (Nujol): 1665, 1705, 1795 cm^{-1}. NMR (acetone-d_6) δ: 1.33 (6H, s), 2.37—2.63 (2H, m), 6.43—6.80 (1H, m), 8.02 (1H, d, J=6 Hz). *Anal.* Calcd for $C_{10}H_{11}FN_2O_4$: C, 49.58; H, 4.57; F, 7.84; N, 11.56. Found: C, 49.57; H, 4.92; F, 7.47; N, 11.36.

1-Ethoxycarbonyl-3-(6-ethoxycarbonyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (8e)——mp 152—153 °C (CH_2Cl_2–MeOH). IR (Nujol): 1692, 1705, 1722, 1773 cm^{-1}. NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 1.42 (3H, t, J=7 Hz), 4.43 (2H, q, J=7 Hz), 4.47 (2H, q, J=7 Hz), 7.80—8.46 (5H, m). *Anal.* Calcd for $C_{18}H_{15}FN_2O_8$: C, 53.20; H,

3.72; F, 4.68; N, 6.89. Found: C, 53.00; H, 3.72; F, 4.53; N, 6.94.

3-[6-(*tert*-Butoxycarbonyl)-1,3-dihydro-3-oxoisobenzofuran-1-yl]-1-ethoxycarbonyl-5-FU (8f)——mp 181—183 °C (CH_2Cl_2–MeOH). IR (Nujol): 1689, 1708, 1783, 1800, 1810 cm^{-1}. NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 1.60 (9H, s), 4.47 (2H, q, J=7 Hz), 7.80—8.30 (5H, m). *Anal.* Calcd for $C_{20}H_{19}FN_2O_4$: C, 55.30; H, 4.41; F, 4.37; N, 6.45. Found: C, 55.18; H, 4.37; F, 4.27; N, 6.47.

1-Ethoxycarbonyl-3-(4-ethoxycarbonyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (8g)——Amorphous powder. IR ($CHCl_3$): 1712, 1770, 1799 cm^{-1}. NMR (acetone-d_6) δ: 1.20 (3H, t, J=7 Hz), 1.36 (3H, t, J=7 Hz), 4.47 (4H, q, J=7 Hz), 7.5—8.1 (4H, m), 8.13 (1H, d, J=6 Hz).

3-[4-(*tert*-Butoxycarbonyl)-1,3-dihydro-3-oxoisobenzofuran-1-yl]-1-ethoxycarbonyl-5-FU (8h)——mp 173—175 °C (acetone–ether). IR ($CHCl_3$): 1709, 1764, 1797 cm^{-1}. NMR (acetone-d_6) δ: 1.35 (3H, t, 7 Hz), 1.64 (9H, s), 4.40 (2H, q, J=7 Hz), 7.6—7.9 (4H, m), 8.22 (1H, d, J=7 Hz). *Anal.* Calcd for $C_{20}H_{19}FN_2O_8$: C, 55.30; H, 4.41; F, 4.37; N, 6.45. Found: C, 55.17; H, 4.34; F, 4.34; N, 6.40.

3-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-1-(2,2,2-trichloroethoxycarbonyl)-5-FU (8j)——Amorphous powder. IR ($CHCl_3$) 1712, 1770, 1782, 1818 cm^{-1}. NMR ($CDCl_3$) δ: 4.97 (2H, s), 7.1—8.2 (5H, m), 8.05 (1H, d, J=6 Hz).

3-(4,4-Dimethyl-5-oxo-2,3,4,5-tetrahydrofuran-2-yl)-1-(2,2,2-trichloroethoxycarbonyl)-5-FU (8k)——mp 146—147 °C (ether–*n*-hexane). IR ($CHCl_3$): 1680, 1705, 1770, 1810 cm^{-1}. NMR ($CDCl_3$) δ: 1.35 (3H, s), 1.43 (3H, s), 2.37—2.63 (2H, m), 4.97 (2H, s), 6.93 (1H, dd, J=9, 7 Hz), 8.00 (1H, d, J=6 Hz). *Anal.* Calcd for $C_{13}H_{12}Cl_3FN_2O_6$: C, 37.39; H, 2.90; F, 4.55; N, 6.71. Found: C, 37.47; H, 3.11; F, 4.58; N, 6.69.

3-(6-Ethoxycarbonyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (5c)——mp 232—233 °C (MeCN–MeOH). IR (Nujol): 1692, 1736, 1770 cm^{-1}. NMR (acetone-d_6) δ: 1.34 (3H, t, J=7 Hz), 4.38 (2H, q, J=7 Hz), 7.73 (1H, d, J=6 Hz), 7.90 (1H, s), 7.96 (1H, d, J=8 Hz), 8.24 (1H, d, J=8 Hz), 8.28 (1H, s). *Anal.* Calcd for $C_{15}H_{11}FN_2O_6$: C, 53.90; H, 3.32; F, 5.68; N, 8.38. Found: C, 53.65; H, 3.48; F, 5.53; N, 8.46.

3-[6-(*tert*-Butoxycarbonyl)-1,3-dihydro-3-oxoisobenzofuran-1-yl]-5-FU (5d)——mp 194—197 °C (MeCN–MeOH). IR (Nujol): 1671, 1714, 1745, 1789 cm^{-1}. NMR (acetone-d_6) δ: 1.55 (9H, s), 7.73 (1H, d, J=6 Hz), 7.88 (1H, s), 7.93 (1H, d, J=8 Hz), 8.18 (1H, d, J=8 Hz), 8.26 (1H, s). *Anal.* Calcd for $C_{17}H_{15}FN_2O_6 \cdot 1/2H_2O$: C, 55.01; H, 4.35; F, 5.12; N, 7.55. Found: C, 55.04; H, 4.08; F, 5.31; N, 7.65.

3-(4-Ethoxycarbonyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (5f)——mp 232—235 °C (acetone–ether). IR (KBr): 1671, 1714, 1736, 1771 cm^{-1}. NMR (acetone-d_6) δ: 1.42 (3H, t, J=7 Hz), 4.46 (2H, q, J=7 Hz), 7.7—8.1 (5H, m). *Anal.* Calcd for $C_{15}H_{11}FN_2O_6$: C, 53.90; H, 3.32; F, 5.68; N, 8.38. Found: C, 53.87; H, 3.46; F, 5.42; N, 8.15.

3-[4-(*tert*-Butoxycarbonyl)-1,3-dihydro-3-oxoisobenzofuran-1-yl]-5-FU (5g)——mp 187—188 °C (acetone–ether). IR (KBr): 1661, 1717, 1743, 1787 cm^{-1}. NMR (acetone-d_6) δ: 1.63 (9H, s), 7.7—8.0 (5H, m). *Anal.* Calcd for $C_{17}H_{15}FN_2O_6$: C, 56.35; H, 4.17; F, 5.24; N, 7.73. Found: C, 56.53; H, 4.42; F, 5.03; N, 7.55.

3-(4,4-Dimethyl-5-oxo-2,3,4,5-tetrahydrofuran-2-yl)-5-FU (9d)——mp 194—195 °C (acetone–ether). IR (Nujol): 1660, 1720, 1760 cm^{-1}. NMR (acetone-d_6) δ: 1.37 (3H, s), 1.40 (3H, s), 2.47—2.77 (2H, m), 6.80—7.17 (1H, m), 7.73 (1H, d, J=6 Hz). *Anal.* Calcd for $C_{10}H_{11}FN_2O_4$: C, 49.58; H, 4.57; F, 7.84; N, 11.56. Found: C, 49.07; H, 4.59; F, 8.17; N, 11.20.

Synthesis of 1-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-5-FU (3a, 590-S)——Method A: (a) A mixture of 1.86 g (10 mmol) of 2,4-diethoxy-5-fluoropyrimidine (**13b**) and 2.13 g (10 mmol) of **2a** was heated with stirring at 100 °C for 1.5 h. After cooling of the reaction mixture, 4 ml of DMSO and 1 ml of conc. aq. HCl were added, and the resulting mixture was stirred at 100 °C for 15 min. The mixture was poured into water and the crystalline precipitate was collected by filtration, washed with water and methanol, and dried, yielding 2.08 g (94%) of **3a**.

(b) A mixture of 5.49 g (20 mmol) of 5-fluoro-2,4-bis(trimethylsilyloxy)pyrimidine (**13c**) and 4.26 g (20 mmol) of **2a** was made homogeneous by heating at 60 °C, then 0.46 ml (4 mmol) of $SnCl_4$ was added and the whole was stirred at 60—80 °C for 2 h. After cooling, it was poured into 20 ml of MeOH and the mixture was stirred at room temperature for 15 min. The crystalline precipitate was collected by filtration, washed with water and MeOH, and dried, giving 4.74 g (90%) of **3a**.

Method B: A mixture of 26 g (0.2 mol) of 5-FU, 33.8 g (0.2 mol) of 1-chloro-1,3-dihydro-3-oxoisobenzofuran (**12a**) and 27.6 g (0.2 mol) of K_2CO_3 in 390 ml of DMF was allowed to react with stirring at room temperature for 1 h and then poured into 2 l of ice water containing 200 ml of 1 N aq. HCl. The crystalline precipitate was collected by filtration, washed with water and MeOH, and dried, giving 47.6 g (91%) of **3a**.

Method C: A mixture of 8.52 g (40 mmol) of **2a** and 27.87 ml (200 mmol) of Et_3N in 85 ml of THF was allowed to react at room temperature for 4 d. The crystalline precipitate was collected by filtration and washed with CH_2Cl_2, giving 11.04 g (88%) of *N*-(1,3-dihydro-3-oxoisobenzofuran-1-yl)-*N*,*N*,*N*,-triethyl ammonium bromide (**15b**), mp 173—177 °C. IR (Nujol): 1800 cm^{-1}. NMR (DMSO-d_6) δ: 1.25 (9H, t, J=8 Hz), 3.58 (6H, q, J=8 Hz), 7.16 (1H, s), 7.80—8.23 (4H, m). *Anal.* Calcd for $C_{14}H_{20}BrNO_2$: C, 53.51; H, 6.42; N, 4.46. Found: C, 53.48; H, 6.43; N, 4.51. A mixture of 1.3 g (10 mmol) of 5-FU, 3.14 g (10 mmol) of **15b** and 0.14 ml (1 mmol) of Et_3N in 26 ml of DMF was allowed to react with stirring at room temperature for 15 h, and then poured into 260 ml of ice-water containing 5 ml of 2 N aq. HCl. The crystalline precipitate was collected by filtration, washed with water and MeOH, and dried, giving 2.44 g (93%) of **3a**.

The physical properties of the ammonium salts listed in Table VII are as follows.

***N*-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-*N,N,N*-triethyl Ammonium Chloride (15a)**——mp 179—181 °C. IR (Nujol): 1785 cm^{-1}. NMR (DMSO-d_6) δ: 1.24 (9H, t, J=8.5 Hz), 3.59 (6H, q, J=8.5 Hz), 7.23 (1H, s), 7.80—8.27 (4H, m). *Anal.* Calcd for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; N, 5.19. Found: C, 62.57; H, 7.66; N, 5.35.

4-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-4-methyl Morpholinium Chloride (15c)——mp 209—210 °C. IR (Nujol): 1790 cm^{-1}. NMR (DMSO-d_6) δ: 3.03 (3H, s), 3.7—4.2 (8H, m), 7.43 (1H, s), 7.9—8.25 (4H, m). *Anal.* Calcd for $C_{13}H_{16}ClNO_3$: C, 57.89; H, 5.98; N, 5.19. Found: C, 57.75; H, 6.02; N, 5.29.

4-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-4-methyl Morpholinium Bromide (15d)——mp 198—200 °C. IR (Nujol): 1796 cm^{-1}. NMR (DMSO-d_6) δ: 3.03 (3H, s), 3.4—4.2 (8H, m), 7.33 (1H, s), 7.8—8.3 (4H, m). *Anal.* Calcd for $C_{13}H_{16}BrNO_3$: C, 49.69; H, 5.13; N, 4.46. Found: C, 49.47; H, 5.11; N, 4.55.

4-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-4-ethyl Morpholinium Bromide (15e)——mp 165—166 °C. IR (Nujol): 1790 cm^{-1}. NMR (DMSO-d_6) δ: 1.21 (3H, t, J=7 Hz), 3.5—4.2 (10H, m), 7.30 (1H, s), 7.83—8.30 (4H, m). *Anal.* Calcd for $C_{14}H_{18}BrNO_3$: C, 51.23; H, 5.52; N, 4.27. Found: C, 50.88; H, 5.65; N, 4.40.

***N*-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-*N,N,N*-triethyl Ammonium Trifluoroacetate (15f)**——Wax. IR ($CHCl_3$): 1677, 1803 cm^{-1}. NMR (DMSO-d_6) δ: 1.23 (9H, t, J=8 Hz), 3.56 (6H, q, J=8 Hz), 7.07 (1H, s), 7.80—8.27 (4H, m).

***N*-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-*N,N,N*-triethyl Ammonium Methanesulfonate (15g)**——Wax. IR ($CHCl_3$): 1803 cm^{-1}. NMR (DMSO-d_6) δ: 1.23 (9H, t, J=8 Hz), 2.30 (3H, s), 3.55 (6H, q, J=8 Hz), 7.03 (1H, s), 7.80—8.25 (4H, m).

***N*-(1,3-Dihydro-3-oxoisobenzofuran-1-yl)-*N,N,N*-triethyl Ammonium *p*-Toluenesulfonate (15h)**——Wax. IR ($CHCl_3$): 1800 cm^{-1}. NMR (DMSO-d_6) δ: 1.22 (9H, t, J=8 Hz), 2.27 (3H, s), 3.53 (6H, q, J=8 Hz), 7.00 (1H, s), 7.10 (2H, d, J=8 Hz), 7.50 (2H, d, J=8 Hz), 7.80—8.23 (4H, m).

Optical Resolution of 1-(6-Carboxy-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU (3j)——Synthesis of **3j**: A mixture of 43.5 g (120 mmol) of **3d** and 200 ml of CF_3COOH in 100 ml of CH_2Cl_2 was allowed to react at room temperature for 2 h, then the solvent and excess reagent were evaporated off. The residue was triturated with CH_2Cl_2 and the crystalline product, obtained by filtration, was washed with CH_2Cl_2 and ether, giving 36.3 g (98.8%) of **3j**. A portion of the product was recrystallized from acetone–ether, mp 297—300 °C. IR (Nujol): 1666, 1722, 1760 cm^{-1}. UV (EtOH) nm (ε): 243.5 (8500). NMR (DMSO-d_6) δ: 7.55 (1H, s), 7.78 (1H, d, J=7 Hz), 8.03 (1H, d, J=8 Hz), 8.26 (1H, d, J=8 Hz), 8.33 (1H, s). *Anal.* Calcd for $C_{13}H_7FN_2O_6 \cdot 1/2H_2O$: C, 49.53; H, 2.56; F, 6.03; N, 8.89. Found: C, 49.41; H, 2.69; F, 5.98; N, 8.86.

Formation of Diastereomers with Brucine: A mixture of 51.8 g (169 mmol) of **3j** and 66.7 g (169 mmol) of anhydrous brucine in 420 ml of THF was heated under reflux and the crystals produced were collected by filtration while the mixture was hot. Washing of the crystals with THF followed by recrystallization from THF gave 53.98 g (91.1%) of a pure diastereomer **16**; mp 277—278 °C. $[\alpha]_D^{24}$ −98.6° (c=1.008, DMSO). *Anal.* Calcd for $C_{36}H_{33}FN_4O_{10}$: C, 61.71; H, 4.75; F, 2.71; N, 8.00. Found: C, 61.44; H, 4.79; F, 2.58; N, 7.64. Concentration of the mother liquor gave a solid, which was recrystallized from THF–ether to yield 52.76 g (89.0%) of the other pure diastereomer **17**, mp 216—220 °C. $[\alpha]_D^{24}$ +18.0° (c=1.010, DMSO). *Anal.* Calcd for $C_{36}H_{33}FN_4O_{10} \cdot H_2O$: C, 60.17; H, 4.91; F, 2.64; N, 7.80. Found: C, 59.91; H, 4.93; F, 2.38; N, 7.51.

Recovery of (−)- and (+)-Isomers of **3j** from the Diastereomers: When 53.98 g (77 mmol) of **16** in 2 N aq. HCl was stirred at room temperature for 1 h, a solid precipitated. This solid was collected by filtration, washed with water, and recrystallized from THF, yielding 22.3 g (94.6%) of the (−)-isomer of **3j**, mp 287—288 °C. $[\alpha]_D^{24}$ −124.5° (c=1.008, DMSO). *Anal.* Calcd for $C_{13}H_7FN_2O_6 \cdot H_2O$: C, 48.15; H, 2.80; F 5.86; N, 8.64. Found: C, 47.95; H, 2.93; F, 5.93; N, 8.62. The same treatment of 52.76 g of **17** gave 21.7 g (94.2%) of the (+)-isomer of **3j**, mp 289—291 °C. $[\alpha]_D^{24}$ +125.5° (c=1.018, DMSO). *Anal.* Calcd for $C_{13}H_7FN_2O_6 \cdot H_2O$: C, 48.15; H, 2.80; F, 5.86; N, 8.64. Found: C, 47.76; H, 2.95; F, 5.93; N, 8.51.

Conversion of (+)-3j to (+)-3a——(+)-1-(6-Azidocarbonyl-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU [(+)-**18**]: First, 8.56 ml (67 mmol) of isobutyl chloroformate and 9.40 ml (67 mmol) of Et_3N were added dropwise to a cooled solution of 20.6 g (67 mmol) of (+)-**3j** in 210 ml of DMF at −40 °C, and the mixture was stirred at −30 °C for 30 min. Next, 3.30 g (67 mmol) of lithium azide was added and the mixture was stirred at 0—3 °C for 1 h, then poured into ice water. The product was isolated by AcOEt extraction, and the AcOEt layer was washed with water, dried and evaporated. As recovery of the unreacted (+)-**3j** could not be avoided, the residue was subjected to the same reaction procedure again and the almost pure acid azide derivative (+)-**18** was obtained. IR (Nujol): 1670, 1700, 1785, 2135 cm^{-1}. NMR (acetone-d_6) δ: 7.57 (1H, d, J=7H), 7.70 (1H, s), 8.10 (1H, d, J=8 Hz), 8.37 (1H, d, J=8H), 8.47 (1H, s).

(+)-1-[6-(4-Methoxybenzyloxycarbonyl)-1,3-dihydro-3-oxoisobenzofuran-1-yl]-5-FU [(+)-**19**]: The crude (+)-**18** obtained in the above reaction and 13.8 g (100 mmol) of 4-methoxybenzyl alcohol in 60 ml of toluene were stirred under reflux for 3 h. The crystals which precipitated on cooling were obtained by filtration and recrystallized from THF–ether, giving 24.18 g [81.4% from (+)-**3j**] of (+)-**19**, mp 148—153 and 204—206 °C. $[\alpha]_D^{25}$ +132.7° (c=1.012, DMSO). IR (Nujol): 1662, 1687, 1696, 1738, 1750, 1761, 1797 cm^{-1}. NMR (acetone-d_6) δ: 3.80 (3H, s), 5.13 (2H, s), 6.92 (2H, d, J=9 Hz), 7.37 (2H, d, J=9 Hz), 7.39 (1H, d, J=7 Hz), 7.60 (1H, s), 7.75 (1H, d, J=8 Hz), 7.88 (1H, d, J=8 Hz), 8.06 (1H, s). *Anal.* Calcd for $C_{21}H_{16}FN_3O_4$: C, 57.14; H, 3.65; F, 4.30; N, 9.52. Found: C, 56.89; H, 3.72; F,

4.14; N, 9.52.

(+)-1-(6-Amino-1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU [(+)-**20**]: A mixture of 14.9 g (33.8 mmol) of (+)-**19**, 38 ml of anisole, and 150 ml of trifluoroacetic acid in 150 ml of CH_2Cl_2 was allowed to react at room temperature for 30 min, then the excess reagents and solvent were evaporated off under reduced pressure. Trituration of the residue with petroleum ether gave a crystalline solid which was collected by filtration. It was washed with ether and dried to give 8.58 g (92%) of (+)-**20**, mp 282—285 °C. $[\alpha]_D^{25}$ +236.8° (c=1.013, DMSO). IR (Nujol): 1612, 1658, 1710, 1754, 3370, 3490 cm^{-1}. NMR (DMSO-d_6) δ: 7.43 (1H, s), 7.62 (1H, d, J=8 Hz), 7.64 (1H, d, J=7 Hz), 7.95 (1H, d, J=8 Hz). *Anal.* Calcd for $C_{12}H_8FN_3O_4$: C, 51.99; H, 2.91; F, 6.85; N, 15.16. Found: C, 51.66; H, 3.12; F, 7.19; N, 14.99.

(+)-**3a** [(+)-590-S]: A solution of 1.89 g (27.4 mmol) of $NaNO_2$ in 7 ml of water was added dropwise to a cooled solution of 7.59 g (27.4 mmol) of (+)-**20** in 39.2 ml of conc. aq. HCl and 20 ml of water at 0 °C, and the mixture was stirred for another 30 min. Then, 28.5 ml of 50% aq. H_3PO_2 solution was added and the mixture was stirred at 0—3 °C for 1 h. The crystals which precipitated when the reaction mixture was poured into water were collected by filtration, washed with water and MeOH, and dried. Recrystallization of the crystals from DMSO–MeOH gave 6.17 g (86%) of (+)-**3a**, mp 298 °C. $[\alpha]_D^{23}$ +114.2° (c=1.006, DMSO). *Anal.* Calcd for $C_{12}H_7FN_2O_4$: C, 54.92; H, 2.69; F, 7.25; N, 10.69. Found: C, 54.76; H, 2.87; F, 7.30; N, 10.78.

By the same procedures as described above, (−)-**3j** was converted to (−)-**3a**.

(−)-**19**: mp 211—213 °C. $[\alpha]_D^{25}$ −128.5° (c=1.012, DMSO). *Anal.* Calcd for C, 57.14; H, 3.65; F, 4.30. N, 9.52. Found: C, 57.26; H, 3.75; F, 4.17; N, 9.30.

(−)-**20**: mp 277—279 °C. $[\alpha]_D^{25}$ −232.6° (c=1.000, DMSO). *Anal.* Calcd for C, 51.99; H, 2.91; F, 6.85; N, 15.16. Found: C, 51.74; H, 3.21; F, 6.88; N, 14.91.

(−)-**3a**: mp 298 °C. $[\alpha]_D^{23.5}$ −113.4° (c=1.018, DMSO). *Anal.* Calcd for C, 54.97; H, 2.69; F, 7.25; N, 10.69. Found: C, 54.92; H, 2.88; F, 7.39; N, 10.77.

Estimation of Optical Purity of (+)- and (−)-3a by ^{1}H-NMR Spectral Measurement Using a Chiral Shift Reagent——Samples of (±)- and (+)-**3a** were converted to the corresponding (±)- and (+)-3-(4-bromobenzyl)-1-(1,3-dihydro-3-oxoisobenzofuran-1-yl)-5-FU [(±)-**21** and (+)-**21**], and their ^{1}H-NMR spectra were measured wtih a 200 MHz instrument in $CDCl_3$ in the presence of Eu(hfc)$_3$ at a molecular ratio of 1.55 or 1.45.

(±)-**21**: NMR [$CDCl_3$, Eu(hfc)$_3$/(±)-**21**=1.55] δ: 5.99 (1H, d, J=14 Hz) and 6.34 (1H, d, J=14 Hz) [–C<u>H</u>$_2$–C_6H_4–Br of (−)-**21**], 6.06 (1H, d, J=14 Hz) and 6.09 (1H, d, J=14 Hz) [–C<u>H</u>$_2$–C_6H_4–Br of (+)-**21**], 7.04 [1H, d, J=6 Hz, (6)-<u>H</u> of (+) and (−)-**21**], 7.12—8.2 (8H, m, aromatic-<u>H</u>), 8.88 [1H, s, =C<u>H</u>–OCO of (−)-**21**], 8.92 [1H, s, =C<u>H</u>–OCO of (+)-**21**].

(+)-**21**: mp 203—204 °C (CH_2Cl_2–MeOH). $[\alpha]_D^{25}$ +60.6° (c=1.005, DMSO). IR (Nujol): 1660, 1688, 1760, 1808 cm^{-1}. NMR [$CDCl_3$, Eu(hfc)$_3$/(+)-**21**=1.45] δ: 6.04 (1H, d, J=14 Hz) and 6.08 (1H, d, J=14 Hz) (–C<u>H</u>$_2$–C_6H_4–Br), 7.03 (1H, d, J=6 Hz, (6)-<u>H</u>), 7.24—8.18 (8H, m, aromatic-<u>H</u>), 8.94 (1H, s, =C<u>H</u>–OCO). *Anal.* Calcd for $C_{19}H_{12}BrFN_2O_4$: C, 52.92; H, 2.81; F, 4.41; N, 6.50. Found: C, 52.78; H, 2.96; F, 4.27; N, 6.47.

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