Synthesis and Antitumor Activities of Prodrugs of Benzoylphenylureas

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Received April 14, 1993

Various benzoylphenylurea derivatives were synthesized as candidate prodrugs and their antitumor activities were examined *in vivo* against P388 leukemia. All of the prodrugs were soluble in most organic solvents and showed good antitumor activities against P388 leukemia cells in mice when dosed intraperitoneally or orally.

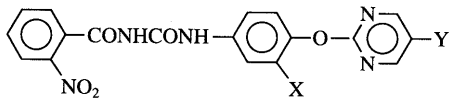
Keywords benzoylphenylurea; antitumor agent; prodrug; *N*-[4-(2-pyrimidinyloxy)phenyl]carbamoyl-2-nitrobenzimidate; *N*-acyl-*N'*-(2-nitrobenzoyl)-*N*-[4-(2-pyrimidinyloxy)phenyl]urea

In a previous paper,[1] we reported the synthesis and antitumor activities of novel benzoylphenylurea derivatives, and one of them, *N*-[4-(5-bromo-2-pyrimidinyloxy)-3-chlorophenyl]-*N'*-(2-nitrobenzoyl)urea (**1**) (coded HO-221: Table I), is presently under development for possible clinical use as an antitumor agent. HO-221 shows significant antitumor activities against various tumor models by oral administration, and is especially effective against solid tumor models.[2] Furthermore, HO-221 is free from cross-resistance to any known antitumor agents.[3] Its mode of action is reported to be the inhibition of DNA polymerase.[4] However, HO-221 is almost insoluble in water and most organic solvents. Therefore, HO-221 has the disadvantage of being difficult to formulate, and its bioavailability is relatively low. To overcome this problem, we have been seeking derivatives of HO-221 which might have higher solubility in various organic solvents. In order to increase the bioavailability of benzoylphenylureas, we planned to synthesize prodrugs of benzoylphenylureas by means of the conversion of the acylurea moieties of benzoylphenylureas (**1**, **2**, **3**, **4**, **5**) (Table I). In this paper, we describe the synthesis and antitumor activities of some lipid-soluble derivatives of benzoylphenylureas.

Synthesis First, we synthesized benzoylphenylureas bearing on the nitrogen position a substituent such as acyl, substituted mercapto or phosphinothioyl, by the method shown in Chart 1. Thus, treatment of 4-pyrimidinyloxyanilines with various chlorides in the presence of triethylamine gave *N*-substituted 4-pyrimidinyloxyanilines. The desired *N*-substituted benzoylphenylureas were obtained by the reaction of the anilines with 2-nitrobenzoyl isocyanate.

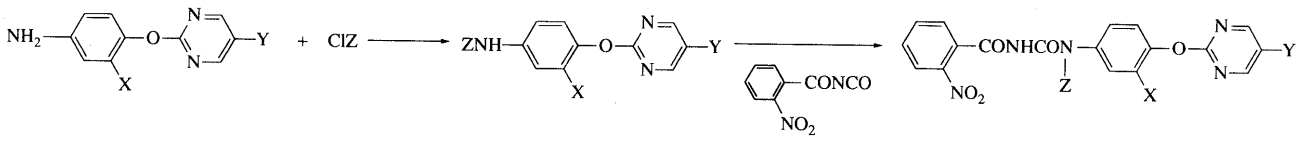
Secondly, we synthesized *N*-phenylcarbamoylbenzimidates by treating 2-nitrobenzimidate with 4-pyrimidinyloxyphenyl isocyanates (Chart 2).[5] One of the intermediates, 4-pyrimidinyloxyphenyl isocyanates, was obtained by the reaction of 4-pyrimidinyloxyanilines with trichloromethyl chloroformate. Another intermediate, 2-nitrobenzimide, was prepared by the reaction of 2-nitrobenzamide with super acid esters such as isopro-

TABLE I. Structures and Antitumor Activities of Benzoylphenylureas



Compd. No.	X	Y	Antitumor activity			
			i.p.[a]		*p.o.*[b]	
			Dose (mg/kg)	*T/C* (%)	Dose (mg/kg)	*T/C* (%)
1 (HO-221)	Cl	Br	12.5	173	400	210
2	CH_3	Cl	3.125	153	25	205
3	CH_3	Br	3.125	163	25	204
4	CF_3	Cl	3.125	160	6.25	237
5	CF_3	Br	3.125	153	6.25	186

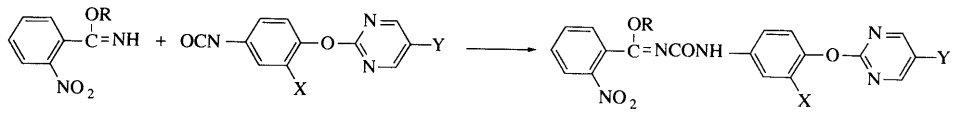
a) Intraperitoneal injection. *b*) *Per os* (oral) administration.



X : Cl, CH_3, CF_3 Y : Cl, Br Z : SR, SCO_2R, $SN(R^1)CO_2R^2$, $SN(R^1)SO_2R^2$, COR, $P(S)(OC_2H_5)_2$

R, R^1, R^2 : alkyl, alkenyl, phenyl

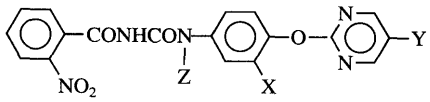
Chart 1



X : Cl, CH_3, CF_3 Y : Cl, Br R : alkyl

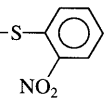
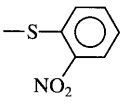
Chart 2

TABLE II. Structures and Antitumor Activities of *N*-Substituted Benzoylphenylureas



Compd. No.	X	Y	Z	mp (°C)	^{1}H-NMR δ (ppm)	Antitumor activity			
						i.p.[c]		*p.o.*[d]	
						Dose[e] (mg/kg)	*T/C* (%)	Dose[e] (mg/kg)	*T/C* (%)
6[a]	Cl	Br	$-COCH_3$	130—135	2.07 (3H, s), 7.00—8.33 (7H, m), 8.52 (2H, s), 12.10 (1H, s)	NT		50	160
7[a]	CH_3	Cl	$-COC_2H_5$	96—101	1.06 (3H, t, J=7 Hz), 2.12 (3H, s), 2.22 (2H, q, J=7 Hz), 6.93—8.23 (7H, m), 8.38 (2H, s), 12.16 (1H, s)	50 25	236 162	25	180
8[a]	CH_3	Cl	$-COC_3H_7(n)$	Amorphous	0.67—1.88 (5H, m), 2.00—2.44 (5H, m), 6.86—8.30 (7H, m), 8.42 (2H, s), 12.29 (1H, s)	NT		50	256
9[a]	CH_3	Cl	$-COC_4H_9(n)$	Amorphous	0.58—1.90 (7H, m), 2.02—2.40 (5H, m), 6.89—8.30 (7H, m), 8.41 (2H, s), 12.31 (1H, s)	NT		50 25	233 155
10[a]	CH_3	Cl	$-COC_5H_{11}(n)$	Amorphous	0.81—1.86 (9H, m), 2.00—2.36 (5H, m), 6.87—8.25 (7H, m), 8.41 (2H, s), 12.28 (1H, s)	NT		50 25	293 155
11[a]	CH_3	Cl	$-COC_6H_{13}(n)$	Amorphous	0.63—1.87 (11H, m), 2.00—2.40 (5H, m), 6.86—8.30 (7H, m), 8.42 (2H, s), 12.29 (1H, s)	NT		25	164
12[a]	CH_3	Br	$-COC_3H_7(n)$	Amorphous	0.68—1.90 (5H, m), 2.01—2.35 (5H, m), 6.86—8.30 (7H, m), 8.52 (2H, s), 12.30 (1H, s)	NT		50	287
13[a]	CH_3	Br	$-COC_4H_9(n)$	Amorphous	0.65—1.82 (7H, m), 2.00—2.33 (5H, m), 6.80—8.26 (7H, m), 8.48 (2H, s), 12.23 (1H, s)	NT		25 12.5	238 199
14[a]	CH_3	Br	$-COC_5H_{11}(n)$	Amorphous	0.65—1.88 (9H, m), 2.01—2.38 (5H, m), 6.87—8.32 (7H, m), 8.51 (2H, s), 12.28 (1H, s)	NT		25	190
15[a]	CH_3	Br	$-COC_6H_{13}(n)$	Amorphous	0.62—1.83 (11H, m), 2.01—2.42 (5H, m), 6.85—8.29 (7H, m), 8.50 (2H, s), 12.27 (1H, s)	NT		25	224
16[a]	CH_3	Br	$-COC_7H_{15}(n)$	57—61	0.62—1.93 (13H, m), 2.00—2.38 (5H, m), 6.86—8.28 (7H, m), 8.46 (2H, s), 12.21 (1H, s)	NT		25	189
17[a]	CH_3	Br	$-COC_{10}H_{21}(n)$	Amorphous	0.70—1.78 (19H, m), 2.01—2.33 (5H, m), 6.83—8.31 (7H, m), 8.48 (2H, s), 12.22 (1H, s)	NT		100 50	236 155
18[a]	CH_3	Br	$-COC_{11}H_{23}(n)$	Amorphous	0.69—1.89 (21H, m), 2.01—2.37 (5H, m), 6.83—8.29 (7H, m), 8.48 (2H, s), 12.28 (1H, s)	NT		100	261
19[a]	CH_3	Br	$-COCH=CH_2$	Amorphous	2.11 (3H, s), 5.50—8.23 (10H, m), 8.46 (2H, s), 12.25 (1H, s)	NT		25	176
20[a]	Cl	Br	$-S-N(C_3H_7(n))-CO_2CH(CH_3)_2$	Amorphous	0.73 (3H, t, J=7 Hz), 1.20—1.80 (8H, m), 3.37 (2H, br t, J=7 Hz), 4.68—5.32 (1H, m), 7.10—8.22 (7H, m), 8.43 (2H, s), 11.54 (1H, s)	12.5	243	3.125	193
21[a]	Cl	Br	$-S-N(C_8H_{17}(n))-CO_2CH_3$	Amorphous	0.80—1.67 (15H, m), 3.39 (2H, br t, J=7 Hz), 3.94 (3H, s), 7.16—8.33 (7H, m), 8.48 (2H, s), 11.35 (1H, s)	NT		50	142
22[a]	Cl	Br	$-S-N(CH_3)-CO_2C_8H_{17}(n)$	Amorphous	0.70—1.95 (15H, m), 3.18 (3H, s), 4.28 (2H, t, J=6 Hz), 7.12—8.31 (7H, m), 8.49 (2H, s), 11.40 (1H, s)	NT		50 25	221 150
23[a]	Cl	Br	$-S-N(CH_3)-CO_2Ph$	Amorphous	3.35 (3H, s), 7.03—8.27 (12H, m), 8.48 (2H, s), 10.98 (1H, s)	NT		12.5	131
24[a]	CH_3	Cl	$-S-N(CH_3)-CO_2CH_3$	83—88	2.07 (3H, s), 3.15 (3H, s), 3.88 (3H, s), 6.99—8.30 (7H, m), 8.38 (2H, s), 11.09 (1H, s)	NT		25	228
25[a]	CH_3	Cl	$-S-N(CH_3)-CO_2CH(CH_3)_2$	Amorphous	1.36 (6H, d, J=6 Hz), 2.12 (3H, s), 3.15 (3H, s), 4.70—5.40 (1H, m), 6.97—8.32 (7H, m), 8.40 (2H, s), 11.26 (1H, s)	12.5 6.25	165 124	12.5 6.25	205 142

TABLE II. (continued)

Compd. No.	X	Y	Z	mp (°C)	^{1}H-NMR δ (ppm)	Antitumor activity			
						i.p.[c]		*p.o.*[d]	
						Dose[e] (mg/kg)	*T/C* (%)	Dose[e] (mg/kg)	*T/C* (%)
26[a]	CH_3	Cl	$-S-N(C_3H_7(n))-CO_2CH(CH_3)_2$	67—70	0.72 (3H, t, J=7 Hz), 1.18—1.79 (8H, m), 2.11 (3H, s), 3.37 (2H, t, J=7 Hz), 4.74—5.41 (1H, m), 6.97—8.31 (7H, m), 8.41 (2H, s), 11.50 (1H, s)	NT		12.5 6.25	260 141
27[a]	CF_3	Cl	$-S-N(CH_3)-CO_2CH(CH_3)_2$	86—92	1.37 (6H, d, J=6 Hz), 3.17 (3H, s), 4.80—5.42 (1H, m), 7.80—8.32 (7H, m), 8.44 (2H, s), 11.48 (1H, s)	6.25	171	6.25 3.125	282 137
28[a]	CH_3	Cl	$-S-N(C_2H_5)-SO_2CH_3$	Amorphous	1.07 (3H, t, J=7 Hz), 2.14 (3H, s), 3.11 (3H, s), 3.46 (2H, q, J=7 Hz), 6.97—8.30 (7H, m), 8.42 (2H, s), 10.22 (1H, s)	6.25	158	12.5 6.25	153 142
29[a]	Cl	Br	$-SC_4H_9(n)$	Amorphous	0.74—1.97 (7H, m), 2.92 (2H, t, J=7 Hz), 7.07—8.38 (7H, m), 8.51 (2H, s), 9.77 (1H, s)	NT		50 25	248 145
30[a]	Cl	Br	$-SC_{10}H_{21}(n)$	Oil	0.82—1.97 (19H, m), 2.89 (2H, br t, J=7 Hz), 7.00—8.30 (7H, m), 8.46 (2H, s), 9.76 (1H, s)	NT		100 50	258 134
31[a]	CH_3	Br	$-SC_{10}H_{21}(n)$	Amorphous	0.61—1.83 (19H, m), 2.11 (3H, s), 2.90 (2H, br t, J=7 Hz), 6.94—8.30 (7H, m), 8.47 (2H, s), 9.64 (1H, s)	NT		6.25	132
32[a]	CH_3	Br	–SPh	Amorphous	2.08 (3H, s), 6.89—8.37 (12H, m), 8.50 (2H, s), 9.52 (1H, s)	NT		12.5 6.25	224 132
33[b]	Cl	Br		Amorphous	7.26—8.68 (11H, m), 8.80 (2H, s), 10.27 (1H, s)	NT		12.5 6.25	184 163
34[a]	CH_3	Cl	–SPh	Amorphous	2.05 (3H, s), 6.77—8.31 (11H, m), 8.38 (2H, s), 9.59 (1H, s)	NT		25	247
35[b]	CH_3	Cl		171—174	2.05 (3H, s), 6.97—8.56 (11H, m), 8.71 (2H, s), 11.15 (1H, s)	NT		50 25	222 199
36[a]	Cl	Br	$-SCO_2CH_3$	103—107	3.93 (3H, s), 7.13—8.40 (7H, m), 8.58 (2H, s), 9.02 (1H, s)	12.5	174	25 12.5	189 139
37[a]	CH_3	Cl	$-SCO_2CH_3$	Amorphous	2.19 (3H, s), 3.96 (3H, s), 7.00—8.70 (10H, m)	12.5 6.25	190 128	6.25	131
38[a]	CH_3	Br	$-P(=S)-(OC_2H_5)_2$	Amorphous	1.18 (6H, t, J=7 Hz), 2.16 (3H, s), 3.70—4.47 (4H, m), 7.02—8.30 (7H, m), 8.48 (2H, s), 8.90 (1H, s)	NT		50	190

a) ^{1}H-NMR spectra were measured in $CDCl_3$. *b*) ^{1}H-NMR spectra were measured in DMSO-d_6. *c*) Intraperitoneal injection. *d*) *Per os* (oral) administration. *e*) When two values are listed, the upper one is the optimum dose at which the highest *T/C* value among the tested doses was obtained, and the lower one is the minimum dose at which the *T/C* value was 125% or more. When the optimum dose was equal to the minimum dose, only one value is listed. NT: not tested.

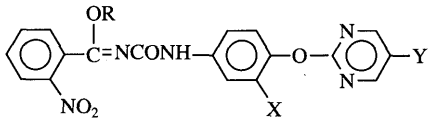
pyl fluorosulfonate[6] or triethyloxonium tetrafluoroborate.

The structural assignment was carried out by ^{1}H-nuclear magnetic resonance (^{1}H-NMR) and elemental analysis. Although the *N*-substituted benzoylphenylureas were pure, they did not crystallize readily, and they were obtained in amorphous forms in many cases. In order to predict the bioavailabilities of *N*-substituted benzoylphenylureas and *N*-phenylcarbamoylbenzimidates, the solubilities of these compounds in ethyl acetate were measured. For example, the solubilities of compounds **13** and **49** were 15% and 49%, respectively. On the other hand, the solubility of compound **3**, the parent compound of prodrugs **13** and **49**, was 0.53%.

Antitumor Activities The structures, melting points, ^{1}H-NMR spectral data and antitumor activities of *N*-substituted benzoylphenylureas **6**—**38**, and those of *N*-phenylcarbamoylbenzimidates **39**—**54** are summarized in Tables II and III, respectively. Since we hoped to find an oral antitumor agent, antitumor activities of compounds **6**—**54** were examined by oral administration. As we reported in the previous paper,[1] it is difficult to determine the intrinsic maximum *T/C* value for these compounds. Therefore, antitumor activities were compared by considering the dose level which gave the highest *T/C* value, among those tested.

Among *N*-acylbenzoylphenylureas (**6**—**19**), compounds bearing longer acyl groups (**17**, **18**) show apparently lower antitumor activities than compound **13**, which has a valeryl group. A wide variety of *N*-(substituted mercapto)benzoylphenylureas (**20**—**37**) and *N*-benzoyl-*N'*-phenyl-*N'*-thiophosphonourea (**38**) show high antitumor activities. As with *N*-acylbenzoylphenylureas, compounds bearing longer alkyl groups (**21**, **22**, **30**) show lower activities than compounds bearing propyl, isopropyl or butyl groups (**20**, **29**). Similarly it was found from

TABLE III. Structures and Antitumor Activities of *N*-Phenylcarbamoylbenzimidates



Compd. No.	X	Y	R	mp (°C)	^{1}H-NMR δ (ppm)	Antitumor activity			
						i.p.[c]		*p.o.*[d]	
						Dose[e] (mg/kg)	*T/C* (%)	Dose[e] (mg/kg)	*T/C* (%)
39[a]	Cl	Br	CH_3	153—155	3.98 (3H, s), 7.16—8.25 (8H, m), 8.50 (2H, s)	NT		200	186
40[b]	Cl	Br	C_2H_5	183—184	1.40 (3H, t, J=8 Hz), 4.42 (2H, q, J=8 Hz), 6.92 (1H, d, J=9 Hz), 7.27—8.20 (7H, m), 8.42 (2H, s)	25	205	200 100	150 138
41[b]	Cl	Br	iso-C_3H_7	81—85	1.37 (6H, d, J=8 Hz), 4.85—5.65 (1H, m), 6.85—8.16 (8H, m), 8.43 (2H, s)	100 50	253 147	400 200	265 173
42[b]	Cl	Br	*sec*-C_5H_{11}	63—65	0.76—1.84 (10H, m), 4.95—5.44 (1H, m), 6.88—8.22 (8H, m), 8.46 (2H, s)	NT		200 100	243 195
43[b]	Cl	Br	*n*-$C_{10}H_{21}$	92—93	0.88—1.92 (19H, m), 4.28 (2H, t, J=6 Hz), 6.88—8.25 (8H, m), 8.46 (2H, s)	100	143	400	154
44[a]	CH_3	Cl	C_2H_5	145—146	1.34 (3H, t, J=7 Hz), 2.04 (3H, s), 4.36 (2H, q, J=7 Hz), 6.73—8.17 (8H, m), 8.33 (2H, s)	NT		25 12.5	198 132
45[a]	CH_3	Br	CH_3	79—81	2.02 (3H, s), 3.91 (3H, s), 6.69—8.12 (8H, m), 8.38 (2H, s)	100 50	247 135	100 50	200 185
46[b]	CH_3	Br	C_2H_5	103—104	1.36 (3H, t, J=7 Hz), 2.03 (3H, s), 4.36 (2H, q, J=7 Hz), 6.66—8.20 (8H, m), 8.36 (2H, s)	6.25	205	25 12.5	235 154
47[b]	CH_3	Br	iso-C_3H_7	71—74	1.38 (6H, d, J=7 Hz), 2.06 (3H, s), 4.99—5.70 (1H, m), 6.77—8.28 (8H, m), 8.48 (2H, s)	6.25	159	50 25	218 135
48[b]	CH_3	Br	*n*-C_5H_{11}	Amorphous	0.79—1.91 (9H, m), 2.06 (3H, s), 4.30 (2H, t, J=6 Hz), 6.72—8.18 (8H, m), 8.39 (2H, s)	12.5	199	12.5 6.25	205 129
49[a]	CH_3	Br	*sec*-C_5H_{11}	54—58	0.73—1.93 (10H, m), 2.07 (3H, s), 4.73—5.46 (1H, m), 6.87—8.34 (8H, m), 8.60 (2H, s)	50 25	294 159	200 100	312 247
50[b]	CH_3	Br	*n*-$C_{10}H_{21}$	75—76	0.72—1.80 (19H, m), 2.02 (3H, s), 4.20 (2H, t, J=6 Hz), 6.71—8.22 (8H, m), 8.37 (2H, s)	25	154	100 50	199 169
51[a]	CF_3	Cl	CH_3	68—69	3.98 (3H, s), 7.00—8.22 (8H, m), 8.34 (3H, s)	25 12.5	263 161	50 25	274 132
52[a]	CF_3	Br	CH_3	83—85	3.98 (3H, s), 6.95—8.30 (8H, m), 8.48 (2H, s)	12.5	145	50 25	296 197
53[b]	CF_3	Br	C_2H_5	82—84	1.40 (3H, t, J=7 Hz), 4.38 (2H, q, J=7 Hz), 6.84—8.20 (8H, m), 8.38 (2H, s)	6.25	189	12.5 6.25	342 275
54[b]	CH_3	Br	iso-C_3H_7	70—73	1.20 (3H, d, J=6 Hz), 5.01—5.62 (1H, m), 6.87—8.23 (8H, m), 8.48 (2H, s)	6.25	159	25 12.5	256 136

a) ^{1}H-NMR spectra were measured in $CDCl_3$. *b*) ^{1}H-NMR spectra were measured in CCl_4. *c*) Intraperitoneal injection. *d*) *Per os* (oral) administration. *e*) When two values are listed, the upper one is the optimum dose at which the highest *T/C* value among the tested doses was obtained, and the lower one is the minimum dose at which the *T/C* value was 125% or more. When the optimum dose was equal to the minimum dose, only one value is listed. NT: not tested.

comparison of a set of compounds which have the same substituents X and Y, that the decyl benzimidates (**43**, **50**) show lower activities than ethyl, isopropyl or pentyl benzimidates (**40**, **41**, **46**, **47**, **48**). As for branched-chain alkyl benzimidates, the activity of **49** was lower than that of **48**, which is straight-chain alkyl benzimidate. Furthermore, comparison of **45** with **46** indicated that the activity of methyl benzimidate was inferior to that of ethyl benzimidate.

The above results suggest that compounds bearing a longer alkyl group in the prodrug moiety show lower antitumor activity. This may be because those compounds can not easily regenerate the parent compound *in vivo*. This is also the case for branched-chain alkyl benzimidates. However, the compounds bearing a methyl group as the protective group show lower antitumor activities. It is considered that these lower activities result from the lower absorption rates of these compounds.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX400 or JEOL JNM-PMX60$_{SI}$ spectrometer with tetramethylsilane as an internal standard, and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Examples of Preparation of *N*-Substituted Benzoylphenylureas. 1) *N*-[4-(5-Chloro-2-pyrimidinyloxy)-3-methylphenyl]-*N'*-(2-nitrobenzoyl)-*N*-valerylurea (9) Valeryl chloride (1.12 ml, 9.4 mmol) was added dropwise to a solution of 4-(5-chloro-2-pyrimidinyloxy)-3-methylaniline (2.0 g, 8.5 mmol) and triethylamine (1.3 ml, 9.3 mmol) in tetrahydrofuran (THF) (20 ml) at 0 °C. The mixture was stirred at room temperature for 40 min. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with saturated brine, dried over Na_2SO_4 and evaporated to yield *N*-[4-(5-chloro-2-pyrimidinyloxy)-3-methylphenyl]valeramide (2.6 g, 96%), mp 146—150 °C.

A mixture of *N*-[4-(5-chloro-2-pyrimidinyloxy)-3-methylphenyl]-valeramide (2.0 g, 6.3 mmol), 2-nitrobenzoyl isocyanate (2.43 g, 12.6 mmol) and THF (40 ml) was heated under reflux for 2.5 h. The solvent was evaporated off under reduced pressure, and the residue was purified

by column chromatography on silica gel (hexane : EtOAc = 7 : 3) to give **9** (1.65 g, 52%) as a white amorphous solid. *Anal.* Calcd for $C_{24}H_{22}ClN_5O_6$: C, 56.31; H, 4.33; N, 13.68. Found: C, 56.53; H, 4.28; N, 13.48. ^{1}H-NMR ($CDCl_3$) δ: 0.58—1.90 (7H, m), 2.02—2.40 (5H, m), 6.89—8.30 (7H, m), 8.41 (2H, s), 12.31 (1H, s).

2) Methyl 4-[4-(5-Bromo-2-pyrimidinyloxy)-3-chlorophenyl]-7-(2-nitrophenyl)-2-octyl-5,7-dioxo-3-thia-2,4,6-triazaheptanoate (21) A solution of methyl *N*-chlorosulfenyl-*N*-octylcarbamate (3.0 g, 11.8 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a solution of 4-(5-bromo-2-pyrimidinyloxy)-3-chloroaniline (3.0 g, 10.0 mmol) and triethylamine (1.52 ml, 10.9 mmol) in CH_2Cl_2 (30 ml) at 0 °C. The mixture was stirred at room temperature for 3 h, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 4 : 1) to give methyl *N*-[4-(5-bromo-2-pyrimidinyloxy)-3-chlorophenyl]aminothio-*N*-octylcarbamate (4.0 g, 77%) as an oil.

2-Nitrobenzoyl isocyanate (1.77 g, 9.2 mmol) was added dropwise to a solution of methyl *N*-[4-(5-bromo-2-pyrimidinyloxy)-3-chlorophenyl]-aminothio-*N*-octylcarbamate (4.0 g, 7.7 mmol) in 1,2-dichloroethane. The mixture was stirred at room temperature for 1.5 h, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 4 : 1) to give **21** (2.65 g, 48%) as a white amorphous solid. *Anal.* Calcd for $C_{28}H_{30}BrClN_6O_7S$: C, 47.37; H, 4.26; N, 11.84. Found: C, 47.41; H, 4.23; N, 12.10. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.67 (15H, m), 3.39 (2H, br t, J = 7 Hz), 3.94 (3H, s), 7.16—8.33 (7H, m), 8.48 (2H, s), 11.35 (1H, s).

3) Diethyl *N*-[4-(5-Bromo-2-pyrimidinyloxy)-3-methylphenyl]-*N*-(2-nitrobenzoylcarbamoyl)amidothiophosphate (38) A solution of butyl lithium (0.70 g, 10.9 mmol) in hexane (7.4 ml) was added dropwise to a solution of 4-(5-bromo-2-pyrimidinyloxy)-3-methylaniline (3.0 g, 10.7 mmol) in THF (30 ml) with stirring at −78 °C. Stirring was continued at −78 °C for 15 min, then a solution of *O,O*-diethyl phosphorochloridothionate (2.22 g, 11.8 mmol) in THF (3 ml) was added dropwise to the reaction mixture. Stirring was further continued at room temperature for 2 h, and the mixture was poured into water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and purified by column chromatography on silica gel (hexane : EtOAc = 7 : 3) to give diethyl *N*-[4-(5-bromo-2-pyrimidinyloxy)-3-methylphenyl]amidothiophosphate (1.48 g, 32%) as an oil.

2-Nitrobenzoyl isocyanate (1.32 g, 6.9 mmol) was added dropwise to a solution of diethyl *N*-[4-(5-bromo-2-pyrimidinyloxy)-3-methylphenyl]-amidothiophosphate (1.48 g, 3.4 mmol) in THF. After being refluxed for 24 h, the mixture was poured into water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and purified by column chromatography on silica gel (hexane : EtOAc = 1 : 1) to give **38** (1.40 g, 66%) as a white amorphous solid. *Anal.* Calcd for $C_{23}H_{23}BrN_5O_7PS$: C, 44.24; H, 3.71; N, 11.22. Found: C, 44.47; H, 3.75; N, 10.96. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (6H, t, J = 7 Hz), 2.16 (3H, s), 3.70—4.47 (4H, m), 7.02—8.30 (7H, m), 8.48 (2H, s), 8.90 (1H, s).

Example of Preparation of *N*-Phenylcarbamoylbenzimidates. 1-Methylbutyl *N*-[4-(5-Bromo-2-pyrimidinyloxy)-3-methylphenyl]carbamoyl-2-nitrobenzimidate (49) 1-Pentene (30 ml) was added dropwise to FSO_3H (9.0 g, 90 mmol) at −78 °C. The mixture was stirred at −78 °C for 15 min, then CH_2Cl_2 (100 ml) precooled to −78 °C was added to it. Then 2-nitrobenzamide (15 g, 90 mmol) was added to the reaction mixture in one portion. The whole was stirred at room temperature for 12 h, then poured into a mixture of 1 N NaOH (250 ml) and CH_2Cl_2 (100 ml), which was cooled to 0 °C. The organic layer was washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 2 : 1) to give 1-methylbutyl 2-nitrobenzimidate (0.3 g, 1.4%) as an oil.

1-Methylbutyl 2-nitrobenzimidate (0.3 g, 1.3 mmol) was added dropwise to a solution of 4-(5-bromo-2-pyrimidinyloxy)-3-methylphenyl isocyanate (0.5 g, 1.6 mmol) in toluene (10 ml) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h and evaporated. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 2 : 1) to give **49** (0.35 g, 51%) as a white powder, mp 54—58 °C. *Anal.* Calcd for $C_{24}H_{24}BrN_5O_5$: C, 53.15; H, 4.46; N, 12.91. Found: C, 53.28; H, 4.28; N, 12.66. ^{1}H-NMR ($CDCl_3$) δ: 0.73—1.93 (10H, m), 2.07 (3H, s), 4.73—5.46 (1H, m), 6.87—8.34 (8H, m), 8.60 (2H, s).

Biological Testing Method Antitumor activity was tested by means of the protocols used for routine screening at the National Cancer Institute (Bethesda, Md.). P388 leukemia cells were intraperitoneally inoculated into BDF_1 mice in an amount of 1×10^6 cells/mouse. A test compound was intraperitoneally or orally administered to mice on days 1 and 4 after the inoculation. Groups of five mice per dose level of the test compound were used with one control group of five mice. The mice were observed for 30 d for survival or death. Antitumor activity of compounds was expressed as follows:

$$\frac{\text{median survival time of treated group}}{\text{median survival time of control}} \times 100\ (T/C)$$

Median survival times of the control group ranged from 9.2 to 10.8 d. Any sample with a T/C value that exceeded 125% was evaluated as antitumor-active.

Acknowledgments The authors are grateful to Mr. K. Fujikawa and Dr. T. Haga for their supervision and continued guidance throughout this work. They also thank Mr. H. Sugi for the biological assay.

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