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Synthesis and Antitumor Activity of Novel Benzophenone Derivatives

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Novel benzophenone derivatives were synthesized and screened for cytotoxic and antitumor activity. Friedel–Crafts condensation was employed to construct the benzophenone skeleton. Among the compounds synthesized, morpholino and thiomorpholino benzophenones 3a—d exhibited potent cytotoxic activity against P388 murine leukemia and PC-6 human lung carcinoma cells *in vitro*, and compounds 3a, 3c, and 3j, when administered intraperitoneally, showed significant antitumor activity against the malignant ascites caused by intraperitoneal inoculation of P388 cells in mice.

Key words benzophenone; cytotoxic activity; antitumor activity

In order to discover novel antitumor compounds with different pharmacophores from currently used antitumor drugs, and to develop them as antitumor agents with potent activity and low toxicity, 2500 compounds from our institute's chemical library were randomly screened for cytotoxic activity. It was found that certain benzophenone derivatives showed potent cytotoxic activity. Further modification of these benzophenone derivatives gave compounds with significant antitumor activity *in vivo*. Some (benzoylphenyl)piperidines have been reported to show activity as immunomodulators.[1,2] However, the antitumor activity of amino-substituted benzophenones and their potential as anti-cancer agents have not been investigated. In this report, we describe the synthesis and antitumor activity *in vitro* and *in vivo* of a series of novel amino-substituted benzophenones.

Chemistry

Benzophenone derivatives were prepared by Friedel–Crafts reaction of an acid chloride with suitably substituted benzenes in the presence of aluminum chloride. Thus, 2-chloro-5-nitrobenzoic acid (**1**) was treated with thionyl chloride and condensed with substituted benzenes to afford **2b**—**e**. Compounds **2b**—**e** and commercially available **2a** were treated with cyclic amines to give various aminonitrobenzophenones (**3a**—**k**). Reduction of the fluoro derivative (**3g**) with $NaBH_4$ gave the nitrobenzhydrol (**4**). Compound **3i** was heated with bromoethanol to afford **5**. Nitro derivatives (**3b**, **3f**—**h**, and **3k**) were reduced using tin(II) chloride hydrate to yield the corresponding amino derivatives (**6a**—**e**). The fluoro derivative (**6c**) was reduced by $NaBH_4$ to give the aminobenzhydrol (**7**). Several amide derivatives were also prepared in order to compare their antitumor activity with those of the corresponding benzophenones. Compound **1** was condensed with substituted anilines to give **8a**—**c**, which were treated with 1-methylpiperazine to afford **9a**—**c**. The piperidine derivative (**11**) was obtained from **1** *via* the carboxylic acid (**10**).

Biological Activity and Discussion

The cytotoxic activity of these compounds against P388 leukemia cells and PC-6 human lung carcinoma cells was investigated *in vitro*, and the GI_{50} (growth inhibition of 50%) values are shown in Table 1. 5-Fluorouracil (5-FU) was used as a reference compound. Nitrobenzophenone derivatives (**3a**—**k**) showed strong cytotoxic activity while the corresponding aminobenzophenones (**6a**—**e**) showed weak or no activity. The nitroalcohol **4** was one-tenth or less active as compared with the nitro ketone (**3g**). Amide derivatives (**9a**—**c**) were also only weakly active. Among the nitrobenzophenones (**3a**—**k**), the morpholino and thiomorpholino derivatives (**3a**—**d**) showed the highest activity. The nitro and carbonyl moieties in this skeleton are considered to be essential for cytotoxic activity. Nitrobenzophenone derivatives (**3a**—**f**, **j**—**k**), which showed strong cytotoxic activity *in vitro*, were tested against murine P388 leukemia by intraperitoneal administration. The ILS (increase in life span) and the BWLmax (maximum rate of body weight loss) values are shown in Table 2. Morpholino (**3a**), thiomorpholino (**3c**), and piperidino (**3j**) derivatives showed moderate effects, but **3b** was only slightly active, in spite of showing potent cytotoxic activity *in vitro*. Introduction of a chlorine substituent into **3a**, **3c**, and **3j** to give **3b**, **3d**, and **3k** respectively, reduced the survival-enhancing effect. The thiomorpholino derivative (**3c**) showed more than 30% ILS at all doses. However, **3c** was less active than 5-FU, and no correlation between *in vitro* cytotoxic activity and *in vivo* antitumor activity was observed. Compounds **3a**—**d** were confirmed to remain to a minor extent as residues in the peritoneal cavity by autopsy of the dead mice. It seems to be desirable to increase the water-solubility of these compounds. Further synthetic work aimed at structural modification is in progress to find compounds which show more potent *in vivo* antitumor activity than 5-FU.

Experimental

Melting points were determined on a Yanagimoto apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-30 or a 270-30 spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-40 or a JEOL JNM-FX90Q (90 MHz) instrument and the chemical shifts are given in δ values. Mass spectra (MS) were recorded on a JEOL JMS-01SG-2 or a JMS-D300 mass spectrometer. Elemental analyses were performed using a Perkin-Elmer 2400CHN instrument. Column chromatography was performed with silica gel 60 F 254 (70—230 mesh) (Merck). Sodium sulfate was employed as a drying agent.

2-Chloro-5-nitrobenzophenone Derivatives (2b—e). Illustrative Proce-

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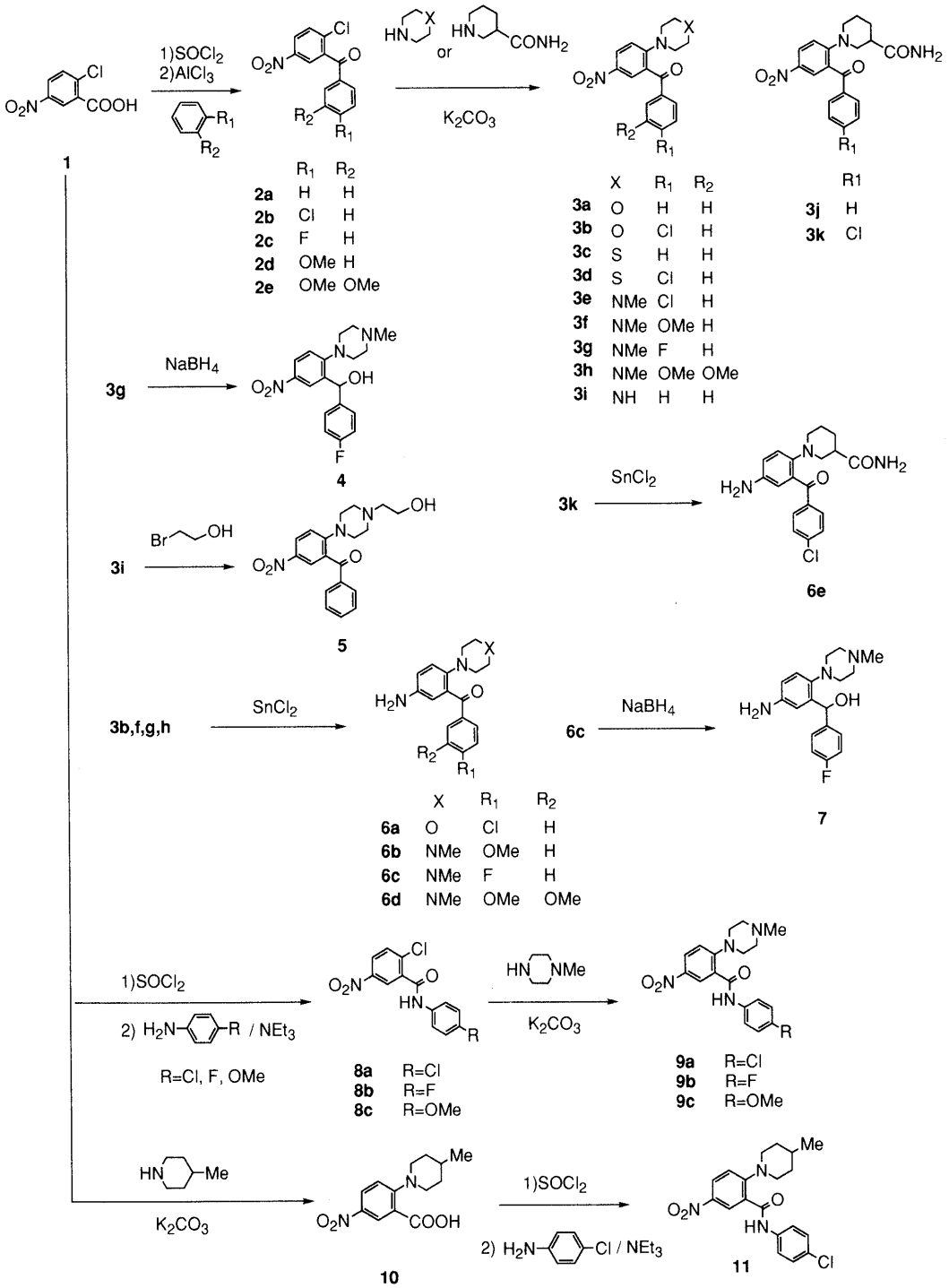

Chart 1

dure A mixture of 2-chloro-5-nitrobenzoic acid (**1**) (10 g, 50 mmol) and thionyl chloride (6.3 g, 53 mmol) was heated to reflux for 3 h. Removal of the solvent afforded a solid, to which were added appropriately substituted benzene derivatives (100 mmol) and aluminum chloride (7 g, 52 mmol). The resulting mixture was stirred overnight at room temperature, then poured onto ice and extracted with AcOEt. The organic layer was washed with 1 N NaOH and H_2O, dried, and evaporated *in vacuo* to give **2b**—**e**.

2b: (6.5 g, 44%), mp 96—97 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.1—7.4 (m, 2H, Ar-H), 7.7—8.0 (m, 2H, Ar-H), 7.99 (d, 1H, J=9 Hz, Ar-H), 8.48 (dd, 1H, J=9, 6 Hz, Ar-H), 8.53 (d, 1H, J=3 Hz, Ar-H).

2c: (10.3 g, 74%), mp 67—68 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.1—7.4 (m, 2H, Ar-H), 7.72 (d, 1H, J=9 Hz, Ar-H), 7.7—8.0 (m, 2H, Ar-H), 8.30 (d, 1H, J=3 Hz, Ar-H), 8.34 (dd, 1H, J=9, 3 Hz, Ar-H).

2d: (7.2 g, 83%), mp 71—76 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (s, 3H, OMe), 6.75 (d, 2H, J=12 Hz, Ar-H), 7.6—7.9 (m, 3H, Ar-H), 8.1—8.4 (m, 2H, Ar-H).

2e: (1.4 g, 12%), mp 143—145 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.0 (s, 6H, OMe), 6.90 (d, 1H, J=12 Hz, Ar-H), 7.1—7.3 (m, 1H, Ar-H), 7.6—7.8 (m, 2H, Ar-H), 8.3—8.4 (m, 2H, Ar-H).

Nitrobenzophenone Derivatives (3a—k). Illustrative Procedure A mixture of chloronitrobenzophenone (**2a**) (1.31 g, 5 mmol), anhydrous K_2CO_3 (0.69 g, 5 mmol), and morpholine (0.65 g, 7.5 mmol) in dimethylformamide (DMF) (13 ml) was stirred at 120 °C for 4 h. After removal of the solvent, the residue was diluted with $CHCl_3$. The organic layer was then washed, dried, and evaporated *in vacuo*, and the residue was recrystallized from EtOH to give **3a** as pale yellow prisms. Compounds **2b**—**e** were treated in the same manner as described above to give **3b**—**k**, respectively. The physical data for these compounds and the yields are shown in Table 3.

1-(4-Fluorophenyl)-1-[2-(4-methyl-1-piperazinyl)-5-nitrophenyl]methanol (4) Sodium borohydride was added in small portions over 1 h to a suspension of **3g** (3.43 g, 10 mmol) in isopropanol (45 ml) and the mixture was stirred at 80—90 °C until TLC indicated completion of the reaction.

Table 1. Cytotoxic Activity of Benzophenone, Benzyl Alcohol, and Benzamido Derivatives

Compd. No.	GI_{50} (ng/ml)[a]	
	P388	PC-6
3a	25.3	6.79
3b	16.8	1.26
3c	23	4.89
3d	23.1	3.76
3e	400	381
3f	294	107
3g	600	270
3h	940	379
3i	5540	4234
3j	242	<98
3k	615	268
4	7050	16400
5	3670	1206
6a	18000	6630
6b	35900	>50000
6c	42233	>50000
6d	>50000	>50000
6e	24400	10400
7	>50000	>50000
9a	11452	5998
9b	34100	30900
9c	25500	15800
11	16100	15200
5-FU	55	190

a) See Experimental.

Table 2. Antitumor Activity of Nitrobenzophenone Derivatives[a]

Compd. No.	ILS (%)[b] BWL_{max} (%) [day][c] Dose (mg/kg)				
	600×2	420×2	294×2	206×2	144×2
3a	35	27	29	35	ND
	8.1 [2]	6.4 [2]	6.5 [2]	2.7 [2]	
3b	6	4	6	4	ND
	1.2 [2]	1.9 [2]	2.9 [2]	0.9 [2]	
3c	36	36	36	30	ND
	7.9 [2]	6.8 [2]	5.5 [2]	4.4 [2]	
3d	18	24	18	18	ND
	4.6 [2]	7.0 [2]	5.9 [2]	4.5 [2]	
3e	22	15	14	9	7
	10.9 [2]	7.5 [2]	7.8 [2]	2.3 [2]	1.0 [2]
3f	24	22	15	13	ND
	5.7 [3]	2.7 [3]	<0	<0	
3j	36	29	10	13	ND
	<0	<0	<0	0.6 [3]	
3k	−9	−10	−11	−13	ND
	1.5 [2]	0.7 [2]	<0	<0	

ILS of 5-FU was 82% (100×2 mg/kg) or 73% (50×2 mg/kg). *a*) P388 tumor cells (1×10^6) were inoculated intraperitoneally (i.p.) (day 0). Nitrobenzophenone derivatives at the indicated doses were administered i.p. on days 1 and 5. *b*) See Experimental. *c*) Maximum rate of body weight loss (%), with numbers in parentheses denoting the day; <0 indicates no body weight loss. ND, not done.

Table 3. Physical Data for Benzophenone, Benzyl Alcohol, and Benzamido Derivatives

Compd.	Yield (%)	mp (°C)	^{1}H-NMR ($CDCl_3$)	IR (cm^{-1})	Formula	MS *m/z*	Analysis Calcd (Found)			
							C	H	N	Cl
3a	88	122—123	3.0—3.2 (m, 4H, $CH_2\times2$), 3.3—3.5 (m, 4H, $CH_2\times2$), 7.03 (d, 1H, J=10 Hz, Ar-H), 7.48 (t, 2H, J=8 Hz, Ar-H), 7.6—7.7 (m, 1H, Ar-H), 7.7—7.9 (m, 2H, Ar-H), 8.2—8.4 (m, 2H, Ar-H)	1660, 1600	$C_{17}H_{16}N_2O_4$	312 (M^+)	65.37 (65.27	5.16 5.21	8.97 8.84)	
3b	77	171—172	2.9—3.2 (m, 4H, $CH_2\times2$), 3.3—3.5 (m, 4H, $CH_2\times2$), 7.05 (d, 1H, J=9 Hz, Ar-H), 7.47 (d, 2H, J=9 Hz, Ar-H), 7.73 (t, 2H, J=9 Hz, Ar-H), 8.2—8.4 (m, 2H, Ar-H)	1658, 1600	$C_{17}H_{15}ClN_2O_4$	348 (M^++2) 346 (M^+)	58.89 (58.92	4.36 4.41	8.08 7.96	10.22 10.15)
3c	73	114—115	2.3—2.5 (m, 4H, $CH_2\times2$), 3.3—3.5 (m, 4H, $CH_2\times2$), 7.06 (d, 1H, J=8 Hz, Ar-H), 7.49 (t, 2H, J=8 Hz, Ar-H), 7.64 (d, 1H, J=8 Hz, Ar-H), 7.78 (d, 2H, J=8 Hz, Ar-H), 8.2—8.4 (m, 2H, Ar-H)	1652, 1600	$C_{17}H_{16}N_2O_3S$	328 (M^+)	62.18 (62.16	4.91 4.92	8.53 8.39)	
3d	81	141—143	2.3—2.5 (m, 4H, $CH_2\times2$), 3.3—3.5 (m, 4H, $CH_2\times2$), 7.07 (d, 1H, J=9 Hz, Ar-H), 7.46 (d, 2H, J=8 Hz, Ar-H), 7.72 (d, 2H, J=8 Hz, Ar-H), 8.25 (d, 1H, J=2 Hz, Ar-H), 8.30 (dd, 1H, J=9, 2 Hz, Ar-H)	1652, 1602	$C_{17}H_{15}ClN_2O_3S$	362 (M^+)	56.28 (56.25	4.17 4.25	7.72 7.58	9.77 9.88)
3e	56	159—161	2.16 (t, 4H, J=6 Hz, $CH_2\times2$), 2.20 (s, 3H, CH_3), 3.17 (t, 4H, J=6 Hz, $CH_2\times2$), 7.09 (d, 1H, J=12 Hz, Ar-H), 7.50 (d, 2H, J=10 Hz, Ar-H), 7.78 (d, 2H, J=10 Hz, Ar-H), 8.31 (s, 1H, Ar-H), 8.30—8.40 (m, 1H, Ar-H)	1656	$C_{18}H_{18}ClN_3O_3$	361 (M^++2) 359 (M^+)	60.08 (60.13	5.01 5.12	9.87 9.58	11.70 11.69)
3f	67	145—147	2.1—2.3 (m, 7H, CH_3, $CH_2\times2$), 3.21 (t, 4H, J=6 Hz, $CH_2\times2$), 3.93 (s, 3H, OCH_3), 6.99 (d, 2H, J=12 Hz, Ar-H), 7.04 (m, 1H, Ar-H), 7.83 (d, 2H, J=12 Hz, Ar-H), 8.27 (s, 1H, Ar-H), 8.29—8.31 (m, 1H, Ar-H)	1647	$C_{19}H_{21}N_3O_4$	355 (M^+)	64.22 (63.87	5.92 5.88	11.83 11.52)	
3g	67	147—149	2.1—2.3 (m, 7H, CH_3, $CH_2\times2$), 3.1—3.2 (m, 4H, $CH_2\times2$), 6.9—7.3 (m, 3H, Ar-H), 7.78 (dd, 2H, J=6, 3 Hz, Ar-H), 7.90 (s, 1H, Ar-H), 8.33 (dd, 1H, J=6, 3 Hz, Ar-H)	1656	$C_{18}H_{18}FN_3O_3$	343 (M^+)	62.97 (62.98	5.25 5.07	12.25 12.22)	
3h	73	140—142	2.1—2.3 (m, 7H, CH_3, $CH_2\times2$), 3.25 (br t, 4H, J=6 Hz, $CH_2\times2$), 3.94 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.8—7.5 (m, 4H, Ar-H), 8.2—8.3 (m, 2H, Ar-H)	1645	$C_{20}H_{23}N_3O_5$	385 (M^+)	62.30 (61.97	6.01 6.32	10.90 10.95)	
3i	91	139—140	1.46 (s, 1H, NH), 2.5—2.7 (m, 4H, $CH_2\times2$), 3.1—3.3 (m, 4H, $CH_2\times2$), 6.9—7.1 (m, 1H, Ar-H), 7.48 (t, 2H, J=8 Hz, Ar-H), 7.62 (t, 1H, J=8 Hz, Ar-H), 7.79 (d, 2H, J=8 Hz, Ar-H), 8.30 (s, 1H, Ar-H), 8.2—8.4 (m, 1H, Ar-H)	1656	$C_{17}H_{17}N_3O_3$	311 (M^+)	65.58 (65.61	5.50 5.52	13.50 13.26)	

Table 3. (continued)

Compd.	Yield (%)	mp (°C)	^{1}H-NMR ($CDCl_3$)	IR (cm^{-1})	Formula	MS *m/z*	Analysis Calcd (Found)			
							C	H	N	Cl
3j	93	143—145	1.2—2.3 (m, 5H, CH_2, CH×3), 2.8—3.5 (m, 4H, CH×4), 5.31, 5.90 (each br s, NH_2), 7.09 (d, 1H, J=9 Hz, Ar-H), 7.51 (t, 2H, J=8 Hz, Ar-H), 7.65 (t, 1H, J=8 Hz, Ar-H), 7.84 (dd, 2H, J=8, 2 Hz, Ar-H), 8.23 (d, 1H, J=2 Hz, Ar-H), 8.28 (dd, 1H, J=9, 2 Hz, Ar-H)	1670, 1650	$C_{19}H_{19}N_3O_4$	353 (M^+)	64.58 (64.21	5.42 5.40	11.89 11.75)	
3k	97	91—95	1.2—1.9 (m, 4H, CH_2×2), 2.0—2.2 (m, 1H, CH), 2.7—3.6 (m, 4H, CH_2×2), 5.87 (br s, 2H, NH_2), 7.09 (d, 1H, J=9 Hz, Ar-H), 7.46 (d, 2H, J=9 Hz, Ar-H), 7.77 (d, 2H, J=9 Hz, Ar-H), 8.2—8.3 (m, 2H, Ar-H)	1683, 1650	$C_{19}H_{18}ClN_3O_4$	389 (M^++2) 387 (M^+)	58.85 (58.72	4.68 4.80	9.14 9.27	10.84 10.76)
4	59	170—173	1.70 (br s, 1H, OH), 2.34 (s, 3H, CH_3), 2.4—2.6 (m, 4H, CH_2×2), 2.8—3.0 (m, 4H, CH_2×2), 6.09 (s, 1H, Ar-CH), 6.9—7.6 (m, 5H, Ar-H), 8.0—8.3 (m, 2H, Ar-H)	1590, 1518	$C_{18}H_{20}FN_3O_3$	345 (M^+)	62.60 (63.05	5.83 5.78	12.16 11.97)	
5	69	111—113	2.24 (br t, 4H, J=6 Hz, CH_2×2), 2.41 (t, 2H, J=5 Hz, CH_2), 3.17 (br t, 4H, J=6 Hz, CH_2×2), 3.55 (t, 2H, J=5 Hz, CH_2), 6.9—7.1 (m, 1H, Ar-H), 7.50 (t, 2H, J=8 Hz, Ar-H), 7.6—7.9 (m, 3H, Ar-H), 8.28 (s, 1H, Ar-H), 8.2—8.4 (m, 1H, Ar-H)	1650	$C_{19}H_{21}N_3O_4$	355 (M^+)	64.21 (64.17	5.96 5.93	11.83 11.61)	
6a	79	174—176	2.74 (t, 4H, J=4 Hz, CH_2×2), 3.28 (t, 4H, J=4Hz, CH_2×2), 3.6—3.9 (br s, 2H, NH_2), 6.73 (d, 1H, J=3 Hz, Ar-H), 6.81 (dd, 1H, J=8, 3 Hz, Ar-H), 6.98 (d, 1H, J=8 Hz, Ar-H), 7.38 (d, 2H, J=8 Hz, Ar-H), 7.69 (d, 2H, J=8 Hz, Ar-H)	1641	$C_{17}H_{17}ClN_2O_2$	318 (M^++2) 316 (M^+)	64.56 (64.17	5.38 5.40	8.86 8.89	11.24 10.72)
6b	48	137—141	2.0—2.2 (m, 4H, CH_2×2), 2.13 (s, 3H, CH_3), 2.84 (br t, 4H, J=6 Hz, CH_2×2), 3.62 (br s, 2H, NH_2), 3.90 (s, OCH_3), 6.72 (d, 1H, J=3 Hz, Ar-H), 6.80 (dd, 1H, J=10, 3 Hz, Ar-H), 6.91 (d, 2H, J=12 Hz, Ar-H), 7.00 (d, 1H, J=10 Hz, Ar-H), 7.78 (d, 2H, J=12 Hz, Ar-H)	1638	$C_{19}H_{23}N_3O_2$	325 (M^+)	70.15 (70.19	7.08 7.17	12.92 12.78)	
6c	75	161—163	1.9—2.7 (m, 7H, CH_3, CH_2×2), 2.66 (br t, 4H, J=6 Hz, CH_2×2), 3.55 (br s, 2H, NH_2), 6.6—7.2 (m, 5H, Ar-H), 7.5—7.7 (m, 2H, Ar-H)	1650	$C_{18}H_{20}FN_3O$	313 (M^+)	68.88 (69.01	6.76 6.39	13.38 13.42)	
6d	31	180—183[a]	2.1—2.2 (m, 7H, CH_2×2, CH_3), 2.85 (br t, 4H, J=6 Hz, CH_2×2), 3.60 (br s, 2H, NH_2), 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.6—7.0 (m, 3H, Ar-H), 7.25—7.35 (m, 2H, Ar-H), 7.41 (d, 1H, J=10 Hz, Ar-H)	1640	$C_{20}H_{25}N_3O_3$	355 (M^+)	67.57 (67.03	7.09 6.67	11.82 11.66)	
6e	34	172—176	1.3—1.8 (m, 4H, CH_2×2), 2.15 (br t, 1H, CH), 2.6—2.8 (m, 2H, CH_2), 2.97 (br s, 2H, CH_2), 3.70 (br s, 2H, NH_2), 5.55 (br s, 2H, NH_2), 6.61 (d, 1H, J=3 Hz, Ar-H), 6.77 (dd, 1H, J=8, 3 Hz, Ar-H), 7.01 (d, 1H, J=8 Hz, Ar-H), 7.39 (d, 2H, J=8 Hz, Ar-H), 7.72 (d, 2H, J=8 Hz, Ar-H)	1659	$C_{19}H_{20}ClN_3O_2$ ·2HCl·EtOH	359 (M^++2) 357 (M^+)	52.85 (52.12	5.92 5.81	8.81 8.73	22.30 22.28)
7	61	198—200	1.75 (br s, 1H, OH), 2.31 (s, 3H, CH_3), 2.4—2.8 (m, 8H, CH_2×4), 3.60 (br s, 2H, NH_2), 5.75 (br s, 1H, Ar-CH), 6.37 (d, 1H, J=3 Hz, Ar-H), 6.57 (dd, 1H, J=9, 3 Hz, Ar-H), 6.8—7.5 (m, 5H, Ar-H)	1614	$C_{18}H_{22}FN_3O$	315 (M^+)	68.55 (68.61	7.03 7.12	13.32 13.20)	
9a	97	150—153	2.38 (s, 3H, CH_3), 2.5—2.7 (m, 4H, CH_2×2), 3.0—3.4 (m, 4H, CH_2×2), 7.32 (d, 1H, J=9 Hz, Ar-H), 7.34 (d, 2H, J=9 Hz, Ar-H), 7.70 (d, 2H, J=9 Hz, Ar-H), 8.28 (dd, 1H, J=9, 3 Hz, Ar-H), 8.90 (d, 1H, J=3 Hz, Ar-H)	1676	$C_{18}H_{19}ClN_4O_3$	376 (M^++2) 374 (M^+)	57.66 (57.61	5.11 5.42	14.95 14.99	9.46 9.57)
9b	87	141—143[a]	2.39 (s, 3H, CH_3), 2.5—2.8 (m, 4H, CH_2×2), 3.1—3.4 (m, 4H, CH_2×2), 7.0—7.2 (m, 2H, Ar-H), 7.32 (d, 1H, J=9 Hz, Ar-H), 7.6—7.8 (m, 2H, Ar-H), 8.29 (dd, 1H, J=9, 3 Hz, Ar-H), 8.93 (d, 1H, J=3 Hz, Ar-H), 10.65 (br s, 1H, NH)	1668, 1611	$C_{18}H_{19}FN_4O_3$	358 (M^+)	60.32 (60.13	5.30 5.55	15.65 15.84)	
9c	82	126—129	2.37 (s, 3H, CH_3), 2.5—2.8 (m, 4H, CH_2×2), 3.1—3.3 (m, 4H, CH_2×2), 3.82 (s, 3H, OCH_3), 6.91 (d, 2H, J=9 Hz, Ar-H), 7.26 (d, 1H, J=9 Hz, Ar-H), 7.65 (d, 2H, J=9 Hz, Ar-H), 8.25 (dd, 1H, J=9, 3 Hz, Ar-H), 8.90 (d, 1H, J=3 Hz, Ar-H), 10.47 (br s, 1H, NH)	1668	$C_{19}H_{22}N_4O_4$	370 (M^+)	61.61 (61.37	5.99 6.08	15.12 15.05)	
11	95	170—171	1.04 (d, 3H, J=7 Hz, CH_3), 1.3—1.8 (m, 3H, CH_2, CH), 1.8—2.1 (m, 2H, CH_2), 2.8—3.0 (m, 2H, CH_2), 3.2—3.5 (m, 2H, CH_2), 7.32 (d, 1H, J=9 Hz, Ar-H), 7.36 (d, 2H, J=9 Hz, Ar-H), 7.68 (d, 2H, J=9 Hz, Ar-H), 8.28 (dd, 1H, J=9, 3 Hz, Ar-H), 8.99 (d, 1H, J=3 Hz, Ar-H), 11.10 (br s, 1H, NH)	1674, 1602	$C_{19}H_{20}ClN_3O_3$	373 (M^+)	61.04 (60.99	5.39 5.64	11.24 11.26)	

a) Decomposition.

The reaction mixture was then cooled, and poured into ice water. The resulting precipitate was collected and washed with H_2O. The crude product was chromatographed on silica gel ($CHCl_3$–MeOH, 95 : 5) and recrystallized from EtOH to afford **4** (2.05 g, 59%) as a pale yellow powder (Table 3).

5-Nitro-2-[4-(2-hydroxyethyl)-1-piperazinyl]benzophenone (5) A mixture of **3i** (2.2 g, 7 mmol), 2-bromoethanol (1.75 g, 14 mmol), and anhydrous Na_2CO_3 (2.22 g, 21 mmol) in xylene (4 ml) was stirred at 100 °C for 1 h. The reaction mixture was diluted with $CHCl_3$ and washed with H_2O, then the organic solution was dried and evaporated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$–EtOH, 49 : 1) to afford **5** (1.72 g, 69.2%) as yellow crystals (Table 3).

Aminobenzophenone Derivatives (6a—e). Illustrative Procedure A mixture of tin(II) chloride dihydrate (26 g, 114 mmol) and **3b** (2.7 g, 7.7 mmol) in EtOH (200 ml) was refluxed for 20 min. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with 10 N NaOH and brine, then dried, and the solvent was removed *in vacuo*. The residue was recrystallized from AcOEt to give **6a** (1.93 g, 79%). Compounds **3f—h** and **3k** were treated in the same manner to give **6b—e**, respectively (Table 3).

1-[5-Amino-2-(4-methyl-1-piperazinyl)phenyl]-1-(4-fluorophenyl)-methanol (7) Compound **6c** was treated in the same manner as described for the preparation of **4** to give **7** (Table 3).

Nitrobenzamido Derivatives (9a—c). Illustrative Procedure A mixture of **1** (10 g, 50 mmol) and thionyl chloride (6.3 g, 53 mmol) was heated to reflux for 3 h. After removal of the solvent, CH_2Cl_2 (30 ml) was added to the residual solid, and the resulting solution was added slowly to a solution of *p*-chloroaniline (6.4 g, 50 mmol) and triethylamine (13.9 ml, 100 mmol) in CH_2Cl_2 (30 ml). The reaction mixture was stirred overnight at room temperature. After removal of the solvent, the residue was dissolved in $CHCl_3$ and the resulting organic layer was washed with H_2O, 1 N HCl, H_2O, saturated $NaHCO_3$ solution and H_2O, dried, and evaporated *in vacuo*. The residue was recrystallized from EtOH to give **8a** (12.2 g). Compounds **8b** and **8c** were obtained by the same procedure as described for **8a**.

8a: (78%), mp 184—186 °C. ^{1}H-NMR (DMSO) δ: 3.31 (s, 1H, NH), 7.41 (d, 2H, J=10 Hz, Ar-H), 7.75 (d, 2H, J=10 Hz, Ar-H), 7.87 (d, 1H, J=10 Hz, Ar-H), 8.34 (dd, 1 H, J=10, 3 Hz, Ar-H), 8.46 (d, 1H, J=3 Hz, Ar-H).

8b: (84%), mp 167—169 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.09 (d, 2H, J=9 Hz, Ar-H), 7.60 (dd, 2H, J=9, 5 Hz, Ar-H), 7.65 (d, 1H, J=9 Hz, Ar-H), 7.97 (br s, 1H, NH), 8.26 (dd, 1H, J=9, 3 Hz, Ar-H), 8.59 (d, 1H, J=3 Hz, Ar-H).

8c: (71%), mp 151—153 °C. ^{1}H-NMR (DMSO) δ: 3.76 (s, 3H, OMe), 6.8—7.0 (m, 2H, Ar-H), 7.5—7.7 (m, 2H, Ar-H), 7.82 (d, 1H, J=9 Hz, Ar-H), 8.21—8.41 (m, 2H, Ar-H), 10.45 (br s, 1H, NH).

A mixture of **8a** (10.5 g, 33 mmol), 1-methylpiperazine (4.2 g, 42 mmol), and anhydrous K_2CO_3 (5.1 g, 37 mmol) in DMF (30 ml) was stirred at 100 °C for 5 h. The reaction mixture was poured into ice-water, and the precipitate was collected and recrystallized from EtOH to afford **9a** (12.2 g, 97%) as yellow prisms. Compounds **9b** and **9c** were obtained by the same procedure as described for **9a** (Table 3).

***N*-(4-Chlorophenyl)-2-(4-methyl-1-piperidinyl)-5-nitrobenzamide (11)** A mixture of **1** (11.1 g, 55 mmol), 4-methylpiperidine (7.4 g, 75 mmol), and anhydrous K_2CO_3 (18.8 g, 95 mmol) in EtOH (120 ml) was refluxed for 60 h. The reaction mixture was poured into 1 N HCl (300 ml) with stirring, and the precipitate was collected and washed with H_2O to afford **10** (12.6 g, 87%) as yellow prisms, mp 162—163 °C. IR (KBr): 1659 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (d, 3H, J=5 Hz, CH_3), 7.66 (d, 1H, J=9 Hz, Ar-H), 8.43 (dd, 1H, J=9, 3 Hz, Ar-H), 9.07 (d, 1H, J=3 Hz, Ar-H).

A mixture of **10** (10.5 g, 40 mmol) and thionyl chloride (15 ml, 200 mmol) in CH_2Cl_2 (80 ml) was stirred at room temperature for 3 h. After removal of the solvent, CH_2Cl_2 (30 ml) was added to the residue, and the resulting solution was added slowly to a solution of *p*-chloroaniline (5.10 g, 40 mmol) and triethylamine (20 ml, 200 mmol) in CH_2Cl_2 (50 ml). The reaction mixture was stirred at room temperature for 3 h, then washed with 1 N HCl, H_2O, saturated $NaHCO_3$ solution and H_2O. The organic layer was dried and evaporated, and the residue was recrystallized from EtOH to give **11** (14.2 g, 95%) as yellow prisms (Table 3).

***In Vitro* Cytotoxicity** To examine the direct growth-inhibitory effects of test compounds against P388 murine leukemia cells and PC-6 human lung carcinoma cells, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed and the concentration giving a growth inhibition of 50% (GI_{50}) was calculated according to a published procedure.[3]

Evaluation of Therapeutic Effect *in Vivo* P388 cells (1×10^6) were inoculated intraperitoneally (i.p.) into CDF1 mice (6 mice per group) on day 0. Compounds were suspended in BTC salt solution (0.9% benzyl alcohol, 0.4% Tween 80, 0.5% carboxymethyl cellulose, 0.9% NaCl) and given i.p. on days 1 and 5. The ILS was calculated using the following formula: ILS (%) = [(median survival time of treated group)/(median survival time of control goup) − 1] × 100. To evaluate the intensity of the side effects of compounds, the rate of body weight loss (BWL) was utilized as a parameter of toxicity. BWL was calculated using the formula: BWL = (1 − BWn/BWs) × 100 (%), where BWn and BWs represent the mean body weights of mice on day n and on the day of initial administration, respectively. The maximum value of BWL was designated as BWLmax, and BWLmax less than zero indicates no body weight loss.

References

1) Georgiev V. St, *TIPS*, **9**, 446—451 (1988).
2) Bellamy F. D., Chazan J. B., Dodey P., Dutartre P., Ou K., Pascal M., Robin J., *J. Med. Chem.*, **34**, 1545—1552 (1991).
3) Mitsui I., Kumazawa E., Hirota Y., Aonuma M., Sugimori M., Ohsuki S., Uoto K., Ejima A., Terasawa H., Sato K., *Jpn. J. Cancer Res.*, **86**, 776—782 (1995).