Synthesis and Antitumor Activity of Novel Pyrimidinyl Pyrazole Derivatives. II.[1] Optimization of the Phenylpiperazine Moiety of 1-[5-Methyl-1-(2-pyrimidinyl)-4-pyrazolyl]-3-phenylpiperazinyl-1-*trans*-propenes

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A series of novel 3-substituted-1-[5-methyl-1-(2-pyrimidinyl)-4-pyrazolyl]-1-*trans*-propenes in order to improve the *in vitro* and *in vivo* activity of our prototype 3-[4-(3-chlorophenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-pyrazolyl]-1-*trans*-propene (2) were synthesized and evaluated by assays of growth inhibition against several tumor cell lines *in vitro* and antitumor activity against some tumor models when dosed both intraperitoneally and orally *in vivo*. Compounds 7a and 7e, the 3,5-difluorophenyl and 3,5-dichlorophenyl analogues of 2, respectively, showed significantly more potent cytotoxicity than 2 *in vitro* and potent antitumor activities without causing decrease of body temperature related to side effects.

Key words cytotoxic activity; antitumor activity; pyrazole; structure–activity relationship

In the previous paper,[1] we reported the synthesis and antitumor activity of novel pyrimidinyl pyrazole derivatives. These derivatives were found as new antiproliferative agents through random screening using our laboratory's chemical library. One of them, 3-[4-(3-chlorophenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-pyrazolyl]-1-*trans*-propene (**2**), showed significant antitumor activity against several tumor models by both intraperitoneal injection and oral administration. Furthermore, **2** was free from the cross-resistance to some currently used antitumor agents such as vincristine (VCR) and adriamycin (ADM). These pyrazole derivatives, however, tended to cause undesirable effects, *e.g.*, muscle relaxation and decrease of body temperature without body weight loss, because these compounds had previously been prepared as tranquilizers or antihypertensive agents. To overcome these problems, we have been seeking derivatives of **1** that might furthermore increase the antitumor activity while decreasing the side effects. As a first step in the structural modification of this scaffold, we focused on the phenylpiperazine moiety, namely, the introduction of some substituents on the phenyl ring and replacement of the phenylpiperazinyl group with some piperidinyl groups. We describe here the synthesis and structure–activity relationships (SARs) with regard to *in vitro* cytotoxic activity and *in vivo* antitumor activity of these pyrazole derivatives.

Chemistry

The synthesis of the derivatives bearing a substituted phenylpiperazine moiety was carried out *via* the route shown in Chart 1. The new substituted piperazines **4a**—**d** were prepared from aniline derivatives **3a**—**d** and bis(2-chloroethyl)amine hydrochloride. Mannich reaction of 4-acetyl-5-methyl-1-pyrimidinylpyrazole (**5**)[1] with modified piperazines **4a**—**d** or **4e**—**i**[2] gave **6a**—**i**, respectively. 1-Propanone derivatives **6j**—**l** were prepared according to the reported procedure.[3] Compounds **6a**—**l** were reduced with sodium borohydride to give the corresponding alcohols, which were dehydrated by *p*-toluenesulfonic acid (*p*-TsOH) to afford 1-*trans*-propene derivatives **7a**—**l**. Catalytic hydrogenation of **6i** over Pd/C with acetic anhydride gave the 3-acetylaminophenyl derivative **8**. Compound **9** was obtained from **8** by the same procedure as described for **7a**—**l** from **6a**—**l**. Carbamoylphenyl derivative **10** was prepared from **7c** by hydrolysis of the cyano group with hydrochloride.

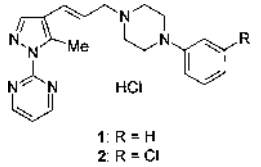

Fig. 1

We also developed a new, efficient synthetic method to construct this scaffold by employing reductive amination instead of Mannich reaction, because Mannich reaction of hydroxyphenylpiperazine **15** with **5** did not progress (Chart 2). Bromination of **5** with Br_2 and treatment with cesium acetate (CsOAc) gave **11**. Compound **11** was hydrolyzed with aqueous NaOH to give the α-hydroxyketone, followed by reduction with sodium borohydride, and then oxidative cleavage of the 1,2-diol with sodium periodate to give the aldehyde **12**. According to the Mukaiyama protocol,[4] the carbon–carbon bond formation of **12** with allyl bromide was performed using metallic tin, followed by protection of the secondary alcohol with triethylsilyl chloride to give **13**. Oxidation of **13** with osmium tetraoxide (OsO_4), followed by oxidative cleavage of the 1,2-diol with sodium periodate gave the aldehyde **14**. The above method demonstrated the synthesis of the key intermediate **14** in 40% overall yield through 9 steps from **5**. The reductive amination of **15** with **14** by treatment with $NaBH_3CN$ in acetic acid (AcOH)/EtOH gave the corresponding adduct, followed by deprotection and simultaneous dehydration with *p*-TsOH to afford the 1-*trans*-propene derivative **16**.

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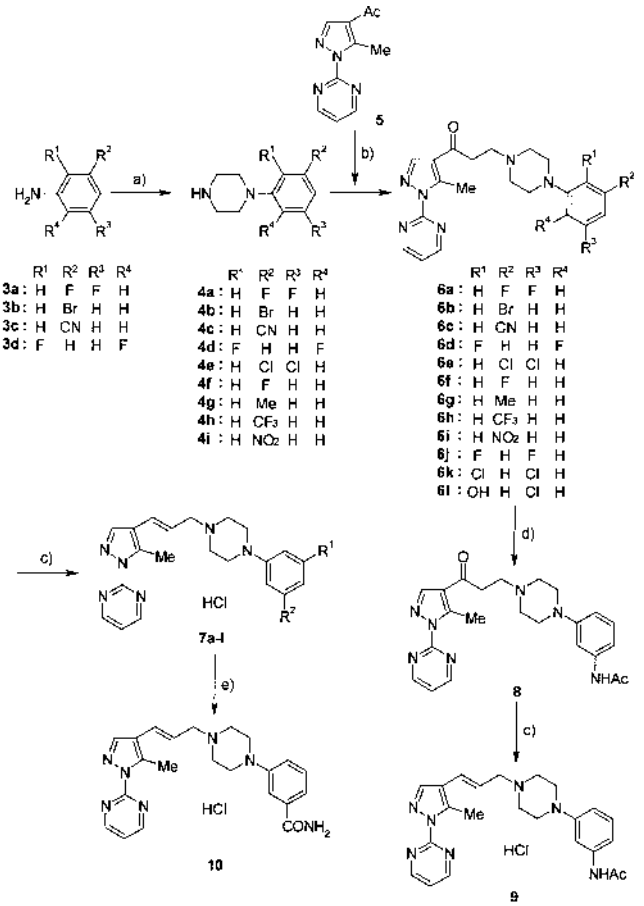
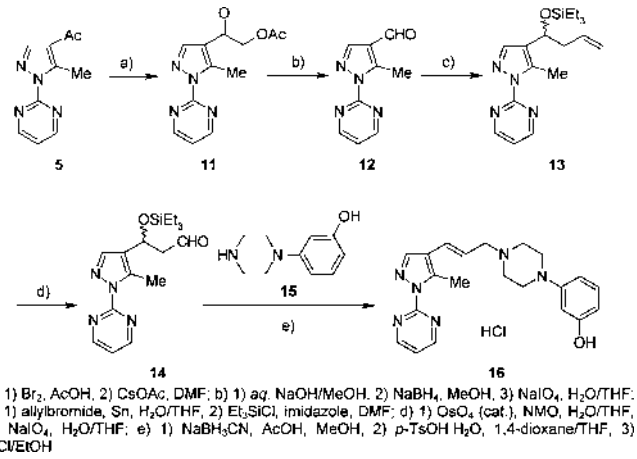


a) bis(2-chloroethyl)amine, K_2CO_3, *n*-BuOH; b) (HCHO)*n*, HCl, EtOH; c) 1) $NaBH_4$, EtOH/THF, 2) *p*-TsOH·H_2O, 1,4-dioxane. THF, 3) HCl/EtOH; d) H_2/Pd-C, Ac_2O, AcOH; e) 1) *c*-HCl. 2) HCl/EtOH

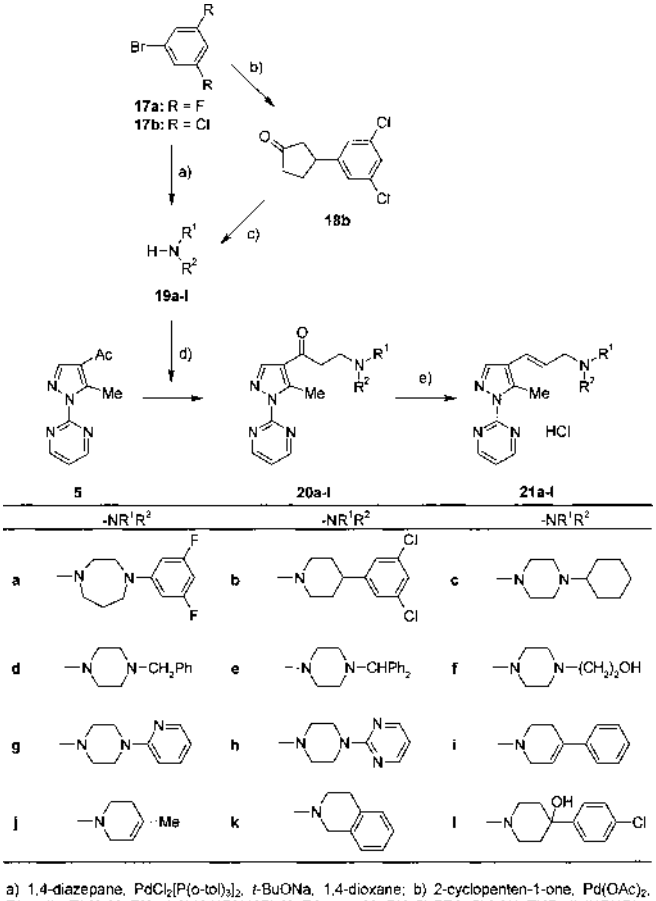
Chart 1



a) 1) Br_2, AcOH, 2) CsOAc, DMF; b) 1) *aq.* NaOH/MeOH. 2) $NaBH_4$, MeOH, 3) $NaIO_4$, H_2O/THF; c) 1) allylbromide, Sn, H_2O/THF, 2) Et_3SiCl, imidazole, DMF; d) 1) OsO_4 (cat.), NMO, H_2O/THF, 2) $NaIO_4$, H_2O/THF; e) 1) $NaBH_3CN$, AcOH, MeOH, 2) *p*-TsOH H_2O, 1,4-dioxane/THF, 3) HCl/EtOH

Chart 2

Furthermore, some derivatives **21a**—**l** with other variations as modifications of the piperazine or phenyl group were synthesized *via* the route shown in Chart 3. Compound **19a** was prepared *via* a palladium(II)-catalyzed aromatic amination reaction[5] with 1-bromo-3,5-difluorobenzene (**17a**) and the unprotected 1,4-diazepane. 1-Bromo-3,5-dichlorobenzene (**17b**) was converted to **18b** through a palladium-catalyzed cross-coupling reaction[6] with 2-cyclopentene-1-one in the presence of the phosphine ligand. Compound **18b** was



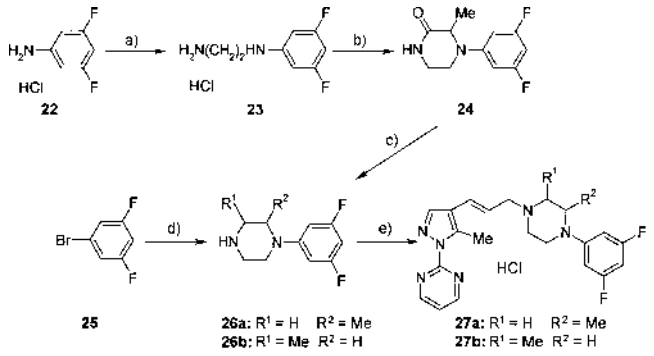
a) 1,4-diazepane, $PdCl_2[P(o\text{-tol})_3]_2$, *t*-BuONa, 1,4-dioxane; b) 2-cyclopenten-1-one, $Pd(OAc)_2$, $P(o\text{-tol})_3$, Et_3N, MeCN; c) 1) H_2NOH·HCl, NaOAc, *aq.* MeOH, 2) PPA, 3) LAH, THF; d) (HCHO)*n*, HCl, EtOH; e) 1) $NaBH_4$, EtOH/THF, 2) *p*-TsOH H_2O, 1,4-dioxane/THF, 3) HCl/EtOH.

Chart 3

treated with hydroxylamine to afford the imine, followed by the rearrangement with polyphosphoric acid and reduction with lithium aluminum hydride (LAH) to construct the 4-phenylpiperidine skeleton **19b**. Mannich reaction of **5** with **19a**—**f** gave **20a**—**f**. Compounds **20g**—**l** were prepared according to the reported procedure.[3] 1-*trans*-Propene derivatives **21a**—**l** were obtained from **20a**—**l** by the same procedure as described in Chart 1.

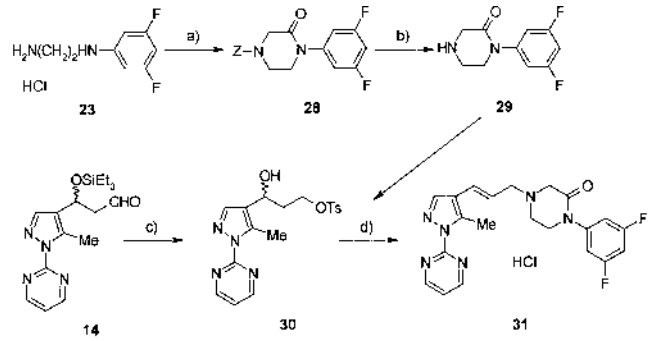
Modification of the piperazine moiety was carried out *via* the routes shown in Charts 4 and 5. Aminoethylation of **22** with 2-oxazolidinone as an aziridine equivalent[7] afforded the desired *N*-phenylethylenediamine (**23**). 2-Piperazinone **24** was prepared from **23** in two steps (2-chloropropanoyl chloride, Et_3N, CH_2Cl_2, then K_2CO_3, *tert*-BuOH), and the following reduction of the amide with LAH afforded **26a**. Compound **26b** was prepared *via* a palladium(II)-catalyzed aromatic amination reaction with the unprotected 2-methylpiperazine.[5] Compounds **27a** and **27b** were obtained from **26a** and **26b**, respectively, by the sequence of reactions described in Chart 2, because Mannich reaction with **5** did not progress (Chart 4).

The synthetic route to **31**, which was not prepared from **29** by either Mannich reaction with **5** or reductive amination with **14**, is shown in Chart 5. The *N*-phenylethylenediamine (**23**) was protected with benzyl chloroformate (ZCl), then treated with 2-bromoacethyl bromide followed by construction of the piperazinone with K_2CO_3 to afford the protected 2-piperazinone **28**. Deprotection of the Z group of **28** by hy-



a) 1,3-oxazolidin-2-one; b) 1) 2-chloropropanoyl chloride, Et_3N, CH_2Cl_2, 2) K_2CO_3, *t*-BuOH; c) LAH, THF; d) 2-methylpiperazine, $PdCl_2[P(o\text{-tol})_3]_2$, *t*-BuONa, 1,4-dioxane; e) 1) **14**, $NaBH_3CN$, AcOH, MeOH, 2) *p*-TsOH·H_2O, 1,4-dioxane/THF, 3) HCl/EtOH.

Chart 4



a) 1) ZCl, Et_3N, THF, 2) 2-bromoacetyl bromide, *aq.* NaOH, AcOEt, 3) K_2CO_3, DMF; b) H_2, Pd/C, 1,4-dioxane/EtOH; c) 1) $NaBH_4$, MeOH, 2) TsCl, pyridine; d) 1) K_2CO_3, MeCN, 2) *p*-TsOH · H_2O, 1,4-dioxane/THF, 3) HCl/EtOH.

Chart 5

drogenation over Pd/C provided **29**. The aldehyde **14** was reduced with $NaBH_4$ to give the corresponding primary alcohol, which was tosylated to afford the deprotected compound **30**. Alkylation of **29** with **30** by treatment with K_2CO_3 in MeCN gave the corresponding adduct, followed by dehydration with *p*-TsOH to afford the 1-*trans*-propene derivative **31**.

Biological Activity and Discussion

The *in vitro* cytotoxic activity of these compounds was measured by using the human lung cancer cell lines PC-6 and PC-12, and the concentrations producing a 50% growth inhibitory effect (GI_{50}) are listed in Table 1. Compounds **1**, **2**, and 5-fluorouracil (5-FU) were used as reference compounds, because **1** and **2** are orally available and the administration route is the same as that of 5-FU. Among a series of phenylpiperazinyl derivatives, **7a**, **e**, **f**, **j**, and **l** having a fluorine or chlorine atom at the 3 or 5 position of benzene showed the highest *in vitro* cytotoxic activity, while the corresponding compounds **7b** with a bromine atom at the 3 position and **7d** with fluorine atoms at other positions of benzene showed moderate or weak activity. The activity of the corresponding compounds **7c**, **g**—**i** bearing CN, Me, CF_3, and NO_2 at the same position of the phenyl ring was moderate or weak. The hydroxy derivative **16** increased the activity compared to that of the non-substituted compound **1**. The activity of the 3-methylphenyl compound **7g** and the 3-trifluoromethylphenyl compound **7h** was the same as that of the non-substituted phenylpiperazinyl derivative **1**. Introduction

Table 1. Cytotoxic Activity of Pyrimidinyl Pyrazole Derivatives

Compd. No.	GI_{50} (ng/ml)[a]	
	PC-6	PC-12
1	153	1020
2	34	208
7a	6.4	63
7b	57	376
7c	36	139
7d	113	568
7e	6.3	205
7f	7.8	45
7g	117	574
7h	175	951
7i	48	411
7j	2.6	16
7k	14	67
7l	6.9	52
9	>1000	>1000
10	>1000	>1000
16	41	240
21a	>1000	>1000
21b	527	>1000
21c	>1000	>1000
21d	>1000	>1000
21e	>1000	>1000
21f	>1000	>1000
21g	869	>1000
21h	>1000	>1000
21i	201	>1000
21j	>1000	>1000
21k	>1000	>1000
21l	>1000	>1000
27a	23	358
27b	23	104
31	>1000	>1000
VCR	0.3	33
5-FU	460	30

PC-6, PC-12: Human non-small cell lung cancer cell lines. *a*) See Experimental.

of a bulky group to the 3 position of the phenyl ring caused a decrease of cytotoxic activity (**9**, **10**). Strong cytotoxic activity was observed when the phenyl ring possessed a halogen atom at the 3 position. The order of *in vitro* potency was halogen atom>hydroxy group>alkyl group. In the series of compounds **21a**—**l** in Chart 3, only **21i** bearing the tetrahydropyridinyl group showed almost the same activity as the non-substituted phenylpiperazine **1** against PC-6. The other compounds showed very weak or no activity. Introduction of a methyl group to the piperazine caused a decrease of cytotoxic activity (**27a**, **b**), and the piperazinone derivative **31** was not active. The phenylpiperazine moiety in this scaffold was considered to be essential for cytotoxic activity.

Compounds **7a**, **e**, **f**, **j**, **k**, and **l**, which showed strong cytotoxic activity *in vitro*, were evaluated in the *in vivo* assay by employing murine fibrosarcoma Meth A as a solid tumor model. 5-FU was used as the reference compound. As shown in Table 2, compounds **7a**, **e**, **j**—**l** showed significantly potent antitumor activity by intraperitoneal injection compared to that of 5-FU. Among them, compounds **7a** and **7e** did not cause muscle relaxation or decrease of body temperature though these side effects were observed in prototypes **1** and **2** at the level of each maximum tolerated dose (MTD) in spite of same antitumor activity. Introduction of fluorine or chlorine atom at the 3 and 5 positions of benzene caused a de-

Table 2. Antitumor Activity of Pyrimidinyl Pyrazole Derivatives against Murine Fibrosarcoma Meth A[a)]

Compd. No.	Antitumor Activity[b)]							
	i.p.				*p.o.*			
	Dose (mg/kg)	IR (%)	BWLmax[c)] (%)	D/U[d)]	Dose (mg/kg)	IR (%)	BWLmax (%)	D/U
7a	7.4×5	63***	<0	0/7	12.5×5	86***	7.5	0/7
	5.1×5	31**	<0	0/7	10.5×5	82***	2.4	0/7
7e	80.0×5	56***	14.1	0/7	140.0×5	81***	10.1	0/7
	60.0×5	31**	5.6	0/7	98.0×5	77***	10.3	0/7
7f	28.0×5	60***	10.9	2/7				
	19.6×5	24*	<0	0/7				
7j	5.8×5	52***	7.4	0/7				
	4.6×5	31	<0	0/7				
7k	38.4×5	57***	1.6	0/7				
	30.7×5	40***	4.1	0/7				
7l	210.0×5	71***	6.8	0/7				
	147.0×5	37***	1.1	0/7				
5-FU	40.0×5	66	27.0	6/7	60.0×5	80	25.4	3/7
	20.0×5	26	9.2	0/7	40.0×5	40**	14.5	0/7

IR and BWLmax of VCR were 9.0% and 17.3% (1.6 mg/kg, i.v.), respectively. IRs of **2** were 62% (43×5 mg/kg, i.p.) and 88% (60×5 mg/kg, *p.o.*).[1)] *a*) Murine fibrosarcoma Meth A cells (1×10^6 cells/0.1 ml/head) were implanted into the right flank of BALB/C mice (day 0). Pyrimidinylpyrazole derivatives at the indicated doses were administered intraperitoneally (i.p.) or per os (oral) administration (*p.o.*) on days 7—11 consecutively. *b*) See Experimental. *c*) Rate of body weight loss. *d*) Number of mice that died of toxicity/number of mice used. ***$p<0.001$, **$p<0.01$, *$p<0.05$ *vs.* the control group.

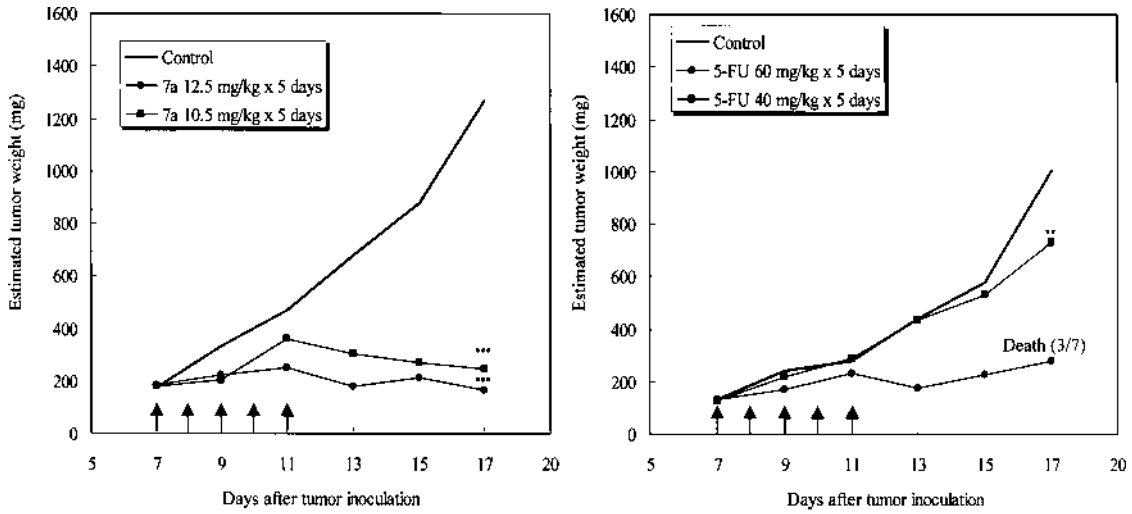


Fig. 2. Tumor Growth Inhibition Curves of **7a** and 5-FU

***$p<0.001$, **$p<0.01$ *vs.* the control group.

crease of side effects. When administered orally, compounds **7a** and **7e** exhibited a potent effect with respective inhibition rate (IR) values of 86% and 81% at the MTDs, while 5-FU and VCR showed weak activity with IR values of 40% and 9.0% at the MTDs. The tumor growth inhibition curves of **7a** and 5-FU are shown in Fig. 2. Furthermore, compounds **7a** and **7e** were tested in the *in vivo* assay against murine P388 leukemia by intraperitoneal injection or oral administration. As shown in Table 3, the antitumor activity of **7a** and **7e** by oral administration was the same as that of **2** and superior to that of 5-FU, although the effect of **7e** was moderate when administered intraperitoneally. The optimal dose of **7e** was about 10 times higher than that of **7a**, even though these compounds exhibited almost the same cytotoxic activity *in vitro*. Therefore, the oral absorption rate of these two compounds in rats was evaluated using the intestinal loop method.[6)] As a result, compound **7a** displayed quite a high absorption rate of 87.2%, while that of **7e** was 6.2%. It is interesting to note that only difference between a fluoride atom and chloride atom on the phenyl ring dramatically affected the oral absorbability.

Compounds **7a** and **7e** were selected for further evaluation against several multi-drug resistant (MDR) cell lines, PC-6/VCR and PC-6/ADM. These two cell lines have been reported to overexpress P-glycoprotein.[7)] As shown in Table 4, VCR and ADM showed high cross resistance rates of 400 against PC-6/VCR and 22 against PC-6/ADM, respectively. Compounds **7a** and **7e** did not show cross-resistance as indicated by their equal rates of 0.9 against PC-6/VCR and 1.3 against PC-6/ADM.

In conclusion, the study on structural modifications of the phenylpiperazine moiety in this scaffold **1** has resulted in the

Table 3. Therapeutic Effect of **7a** and **7e** on Mice Bearing P388 Murine Leukemia[a)]

Compd. No.	Survival[b)]					
	i.p.			*p.o.*		
	Dose (mg/kg)	ILS (%)[c)]	D/U[d)]	Dose (mg/kg)	ILS (%)	D/U
7a		NT		10×5	135**	0/6
		NT		7×5	93**	0/6
7e	200×2	48**	0/6	160×5	120**	0/6
	100×2	33**	0/6	140×5	118**	0/6
5-FU	100×2	74**	0/6	60×5	52**	0/6
	50×2	61**	0/6			

ILSs of **2** were 69% (77×2 mg/kg, i.p.) and 127% (60×5 mg/kg, *p.o.*). *a*) P388 tumor cells (1×10^6) were inoculated into CDF1 mice i.p. (day 0). Pyrimidinylpyrazole derivatives at the indicated doses were administrated i.p. on days 1 and 5 or *p.o.* on days 1—5, respectively. *b*) See Experimental. *c*) Increase in lifespane. *d*) Number of mice that died of toxicity/number of mice used. NT: Not tested. $^{**}p<0.01$ *vs.* the control group.

Table 4. *In Vitro* Cytotoxicity against Multi-Drug Resistant Cell Lines[a)]

Compd. No.	GI_{50} ng/ml (Rate[b)])				
	PC-6	PC-6/VCR		PC-6/ADM	
7a	6.4	5.8	(0.9)	8.3	(1.3)
7e	6.3	5.7	(0.9)	8.1	(1.3)
VCR	0.3	120	(400)	—	
ADM	14	—		308	(22)

a) See Experimental. *b*) (GI_{50} value against VCR or ADM-resistant cell line)/(GI_{50} value against PC-6 cell line).

discovery of 3,5-difluorophenyl and 3,5-dichlorophenyl compounds, **7a** and **7e**, that displayed potent antitumor activity in mice without causing a decrease of body temperature, compared with that caused by **2**, on both intraperitoneal injection and oral administration. Furthermore, although the leading compound **2** in this scaffold caused muscle relaxation and crouching at MTD in mice, these visible symptoms were not observed for compound **7a**. Mechanism of action for the cytotoxic activity of this scaffold was reported to be inhibition of tubulin polymerization.[8)] Further work with **7a** to investigate the inhibitory activity and the binding site on tubulin will be described elsewhere.

Experimental

Melting points were determined on a Yanaco MP-500D apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JEOL JIR-5300 or Horiba FT-720 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-EX400 (400 MHz) instrument, and the chemical shifts are given in δ values. Mass spectra (MS) were recorded on a JEOL JMS-HX110 or a JMS-AX505W mass spectrometer. Elemental analyses were performed with a Perkin-Elmer Series II CHNS/O 2400 instrument. Column chromatography was performed with silica gel 60 F 254 (70—230 mesh) (Merck). Sodium sulfate was employed as a drying agent.

1-(3,5-Difluorophenyl)piperazine Hydrochloride (4a) A mixture of 3,5-difluoroaniline (**3a**) (10 g, 77 mmol) and bis(2-chloroethyl)amine hydrochloride (13.7 g, 77 mmol) in *n*-BuOH (120 ml) was refluxed for 48 h. Anhydrous sodium carbonate (10.6 g, 77 mmol) was added to the mixture. After being stirred for 24 h, the reaction mixture was cooled, and the precipitate obtained was filtered. The precipitate was suspended with water and extracted with $CHCl_3$. The organic phase was washed with water, dried, and evaporated *in vacuo*. Et_2O and 1 N HCl/EtOH (2.5 ml) were added to the residue, and the precipitate obtained was filtered to give **4a** (12.6 g) as a white powder. Compounds **3b**—**d** were treated in the same manner as described above to give **4b**—**d**, respectively.

4a: Yield 74%, a white powder. ^{1}H-NMR (DMSO-d_6) δ: 6.70 (1H, d, J=9 Hz), 6.56 (2H, t, J=9 Hz), 3.5—3.4 (4H, m), 3.2—3.1 (4H, m).

4b: Yield 72%, a white powder. ^{1}H-NMR ($CDCl_3$) δ: 7.10 (1H, t, J=8 Hz), 7.03 (1H, t, J=2 Hz), 6.95 (1H, ddd, J=8, 2, 1 Hz), 6.83 (1H, dd, J=8, 2 Hz), 3.3—3.1 (4H, m), 3.1—2.9 (4H, m).

4c: Yield 37%, a white powder. ^{1}H-NMR ($CDCl_3$) δ: 7.32 (1H, dd, J=9, 7 Hz), 7.2—7.0 (3H, m), 3.3—3.1 (4H, m), 3.1—2.9 (4H, m).

4d: Yield 10%, a white powder. ^{1}H-NMR ($CDCl_3$) δ: 7.2—7.1 (1H, m), 6.96 (2H, t, J=9 Hz), 3.4—3.5 (4H, m), 3.4—3.3 (4H, m).

3-[4-(3,5-Difluorophenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-propanone (6a) Paraformaldehyde (650 mg, 22 mmol) and a solution of 1 N HCl/EtOH (5.0 ml) were added to a mixture of **4a** (1.1 g, 5.0 mmol) and **5**[1)] (1.0 g, 5.0 mmol) in EtOH (85 ml), and the mixture was heated to reflux for 4 d. The mixture was diluted with $CHCl_3$, successively washed with saturated aqueous $NaHCO_3$ and brine, and then dried. Evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column ($CHCl_3$/MeOH=50/1) to give **6a** (129 mg, 6%) as a yellow caramel. Compounds **4b**—**i** were treated in the same manner as described above to give **6b**—**i**, respectively. The physical data for these compounds and yields are shown in Table 5.

3-[4-(3,5-Difluorophenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-*trans*-propene Hydrochloride (7a) Sodium borohydride (50 mg, 1.3 mmol) was added in small portions to a solution of **6a** (103 mg, 0.25 mmol) in anhydrous EtOH (10 ml) and THF (10 ml) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with a solution of 1 N HCl/EtOH. The mixture was diluted with $CHCl_3$, successively washed with saturated aqueous $NaHCO_3$ and brine, and dried. Evaporation of the solvents afforded the corresponding secondary alcohol. Next, *p*-TsOH·H_2O (68 mg, 0.38 mmol) was added to a solution of the above product in anhydrous 1,4-dioxane (10 ml) and THF (10 ml), and the mixture was heated to reflux for 40 min. The reaction mixture was diluted with $CHCl_3$, successively washed with saturated aqueous $NaHCO_3$ and brine, and dried. After removal of the solvents, the crude mixture was chromatographed on a silica gel column ($CHCl_3$/MeOH=50/1) to afford the propene. An appropriate volume of a solution of 1 N HCl/EtOH was added to a solution of the propene in a small amount of EtOH, and the solvent was removed. The residue was recrystallized from EtOH to give **7a** (39 mg, 35%) as a white powder. Compounds **6b**—**l** were treated in the same manner as described above to give **7b**—**l**, respectively. The physical data for these compounds and yields are shown in Table 6.

3-[4-(3-Acetylamino)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-propanone (8) Compound **6i** (404 mg, 1.0 mmol) and acetic anhydride (113 μl) were dissolved in AcOH (22 ml) and hydrogenated over 10% Pd/C (110 mg) for 24 h at room temperature. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to afford the crude mixture, which was chromatographed on a silica gel column ($CHCl_3$/MeOH=100/3) to give **8** (277 mg, 63%) as a yellow caramel. The physical data for **8** are shown in Table 5.

3-[4-(3-Acetylamino)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-*trans*-propene Hydrochloride (9) Synthesis of **9** was performed as described for the synthesis of **7a**. Compound **9** was obtained from **8** in 53% yield as a white powder. The physical data for **9** are shown in Table 6.

3-[4-(3-Carbamoylphenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-*trans*-propene Hydrochloride (10) Compound **7c** (88 mg, 0.2 mmol) was dissolved in conc. HCl (0.5 ml), and the mixture was stirred for 62 h at room temperature. The reaction mixture was diluted

Table 5. Physical Data for Propanone Derivatives

Compd. No.	Yield (%)	^{1}H-NMR ($CDCl_3$) δ
6a	6	9.01 (2H, d, J=5 Hz), 8.42 (1H, s), 7.67 (1H, t, J=5 Hz), 6.77 (2H, d, J=10 Hz), 6.58 (1H, t, J=9 Hz), 4.0—3.9 (2H, m), 3.7—3.6 (2H, m), 3.5—3.4 (4H, m), 3.2—3.1 (4H, m), 2.82 (3H, s)
6b	40	8.86 (2H, d, J=5 Hz), 8.15 (1H, s), 7.35 (1H, t, J=5 Hz), 7.10 (1H, t, J=8 Hz), 7.03 (1H, t, J=2 Hz), 6.95 (1H, ddd, J=8, 2, 1 Hz), 6.83 (1H, dd, J=8, 2 Hz), 3.21 (4H, t, J=5 Hz), 3.09 (2H, t, J=7 Hz), 3.00 (3H, s), 2.88 (2H, t, J=7 Hz), 2.67 (4H, t, J=5 Hz)
6c	39	9.01 (2H, d, J=5 Hz), 8.43 (1H, s), 7.66 (1H, t, J=5 Hz), 7.47 (1H, d, J=2 Hz), 7.45 (1H, t, J=8 Hz), 7.37 (1H, dd, J=8, 2 Hz), 7.26 (1H, d, J=8 Hz), 4.0—3.9 (2H, m), 3.7—3.6 (2H, m), 3.4—3.4 (4H, m), 3.3—3.1 (4H, m), 2.82 (3H, s)
6d	57	9.01 (2H, d, J=5 Hz), 8.42 (1H, s), 7.67 (1H, t, J=5 Hz), 7.2—7.1 (1H, m), 7.09 (2H, t, J=9 Hz), 3.6—3.5 (6H, m), 3.4—3.3 (4H, m), 3.3—3.2 (2H, m), 2.82 (3H, s)
6e	61	8.36 (1H, s), 7.6—7.5 (3H, m), 7.08 (2H, s), 6.96 (1H, s), 4.0—3.9 (2H, m), 3.6—3.5 (2H, m), 3.5—3.4 (4H, m), 3.3—3.1 (4H, m), 2.54 (3H, s)
6f	16	8.86 (2H, d, J=5 Hz), 8.15 (1H, s), 7.34 (1H, t, J=5 Hz), 7.18 (1H, dd, J=15, 8 Hz), 6.67 (1H, d, J=8 Hz), 6.5—6.4 (1H, m), 6.4—6.3 (1H, m), 3.2—3.1 (4H, m), 3.09 (2H, t, J=7 Hz), 3.00 (3H, s), 2.88 (2H, t, J=7 Hz), 2.66 (4H, m)
6g	31	8.86 (2H, d, J=5 Hz), 8.15 (1H, s), 7.34 (1H, t, J=5 Hz), 7.15 (1H, t, J=8 Hz), 6.75 (1H, s), 6.74 (1H, d, J=8 Hz), 6.68 (1H, d, J=8 Hz), 3.21 (4H, t, J=5 Hz), 3.10 (2H, t, J=7 Hz), 3.00 (3H, s), 2.89 (2H, t, J=7 Hz), 2.68 (4H, t, J=5 Hz), 2.32 (3H, s)
6h	35	8.86 (2H, d, J=4 Hz), 8.15 (1H, s), 7.4—7.3 (2H, m), 7.2—7.0 (3H, m), 3.26 (4H, t, J=5 Hz), 3.10 (2H, t, J=7 Hz), 3.00 (3H, s), 2.90 (2H, t, J=7 Hz), 2.69 (4H, t, J=5 Hz)
6i	59	9.01 (2H, d, J=5 Hz), 8.42 (1H, s), 7.68 (1H, dt, J=8, 2 Hz), 7.79 (1H, t, J=2 Hz), 7.66 (1H, t, J=5 Hz), 7.54 (1H, t, J=8 Hz), 7.51 (1H, dt, J=8, 2 Hz), 4.1—4.0 (2H, m), 3.8—3.6 (2H, m), 3.6—3.5 (4H, m), 3.3—3.2 (4H, m), 2.82 (3H, s)
8	63	8.86 (2H, d, J=5 Hz), 8.14 (1H, s), 7.35 (1H, t, J=5 Hz), 7.3—6.6 (4H, m), 3.3—3.1 (4H, m), 3.10 (2H, t, J=7 Hz), 3.00 (3H, s), 2.89 (2H, t, J=7 Hz), 2.7—2.6 (4H, m), 2.16 (3H, s)
20a	10	8.86 (2H, d, J=5 Hz), 8.12 (1H, s), 7.35 (1H, t, J=5 Hz), 6.55 (1H, m), 6.51 (1H, m), 6.27 (1H, m), 3.6—3.4 (4H, m), 3.1—2.9 (4H, m), 2.98 (3H, s), 2.8—2.7 (2H, m), 2.7—2.6 (2H, m), 2.0—1.9 (2H, m)
20b	9	8.86 (2H, d, J=5 Hz), 8.15 (1H, s), 7.34 (1H, t, J=5 Hz), 7.20 (1H, t, J=2 Hz), 7.11 (2H, d, J=2 Hz), 3.1—3.0 (2H, m), 2.99 (3H, s), 2.9—2.8 (2H, m), 2.8—2.7 (2H, m), 2.5—2.4 (1H, m), 2.15 (1H, dd, J=14, 7 Hz), 2.0—1.8 (4H, m), 1.40 (1H, dt, J=11, 7 Hz)
20c	18	8.86 (2H, d, J=5 Hz), 8.13 (1H, s), 7.35 (1H, t, J=5 Hz), 3.06 (2H, t, J=7 Hz), 2.99 (3H, s), 2.83 (2H, t, J=7 Hz), 2.7—2.4 (8H, m), 2.4—2.1 (1H, m), 2.0—1.7 (4H, m), 1.7—1.5 (2H, m), 1.3—1.0 (4H, m)
20d	32	9.00 (2H, d, J=5 Hz), 8.36 (1H, s), 7.66 (1H, t, J=5 Hz), 7.7—7.4 (5H, m), 3.8—3.2 (14H, m), 2.80 (3H, s)
20e	35	9.00 (2H, d, J=5 Hz), 8.38 (1H, s), 7.66 (1H, t, J=5 Hz), 7.5—7.2 (10H, m), 4.49 (1H, s), 3.6—3.1 (12H, m), 2.80 (3H, s)
20f	28	8.86 (2H, d, J=5 Hz), 8.13 (1H, s), 7.35 (1H, t, J=5 Hz), 3.62 (2H, t, J=5 Hz), 3.05 (2H, t, J=8 Hz), 2.99 (3H, s), 2.83 (2H, t, J=8 Hz), 2.55 (2H, t, J=6 Hz), 2.7—2.4 (9H, m)

with ice-water, alkalized with $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was washed with brine and dried. After removal of the solvent, the crude residue was chromatographed on a silica gel column ($CHCl_3$/MeOH=100/3) to afford the propene. An appropriate volume of a solution of 1 N HCl/EtOH was added to a solution of the propene in a small amount of EtOH, and the solvent was removed. The residue was recrystallized from EtOH to give **10** (50 mg, 54%) as a white powder. The physical data for **10** are shown in Table 6.

2-[5-Methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-2-oxoethyl Acetate (11) Bromine (0.5 ml) was added to a solution of **5** (2.0 g, 9.86 mmol) in AcOH (50 ml), and the mixture was stirred at 70 °C for 1.5 h. The reaction mixture was diluted with AcOEt, washed with saturated aqueous $NaHCO_3$ and brine, and dried. Evaporation of the solvents afforded the crude mixture, which was recrystallized from EtOH to give the bromoethanone (2.8 g, quantitative yield) as colorless needles: ^{1}H-NMR ($CDCl_3$) δ: 8.88 (2H, d, J=5 Hz), 8.16 (1H, s), 7.37 (1H, t, J=5 Hz), 4.29 (2H, s), 3.01 (3H, s).

Cesium acetate (2.0 g, 10.42 mmol) was added to a solution of the bromoethanone (0.97 g, 3.45 mmol) in *N*,*N*-dimethylformamide (DMF, 10 ml) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with AcOEt, washed with brine, and dried. Evaporation of the solvents afforded **11** (0.86 g, quantitative yield) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 8.87 (2H, d, J=5 Hz), 8.11 (1H, s), 7.37 (1H, t, J=5 Hz), 5.13 (2H, s), 3.01 (3H, s), 2.24 (3H, s).

5-Methyl-1-(2-pyrimidinyl)-1*H*-pyrazole-4-carbaldehyde (12) One normal aqueous NaOH (6.0 ml) was added to a solution of **11** (0.8 g, 3.22 mmol) in MeOH (20 ml), and the mixture was stirred at room temperature for 20 min. After removal of the solvents, the crude mixture was chromatographed on a silica gel column ($CHCl_3$/MeOH=30/1) to afford the primary alcohol (0.8 g, quantitative yield) as a white caramel: ^{1}H-NMR ($CDCl_3$) δ: 8.88 (2H, d, J=5 Hz), 8.06 (1H, s), 7.38 (1H, t, J=5 Hz), 4.70 (2H, s), 3.05 (3H, s), 2.5—2.4 (1H, m).

Sodium borohydride (0.3 mg) was added to a solution of the primary alcohol (0.81 g, 3.69 mmol) in EtOH (20 ml) and tetrahydrofuran (THF, 10 ml) at 0 °C, and the mixture was stirred at the same temperature for 20 min. The reaction mixture was quenched with a solution of 1 N HCl/EtOH, and the solvents were removed to afford the diol. Next, sodium periodate (4.0 g) was added to a solution of the above product in THF (15 ml) and water (3.0 ml), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with AcOEt, washed with brine, and dried. After removal of the solvents, the residue was chromatographed on a silica gel column ($CHCl_3$/AcOEt=2/1) to give **12** (0.52 g, 75%) as a white caramel: ^{1}H-NMR ($CDCl_3$) δ: 10.05 (1H, s), 8.87 (2H, d, J=5 Hz), 8.17 (1H, s), 7.35 (1H, t, J=5 Hz), 3.01 (3H, s).

2-[5-Methyl-4-[1-[(triethylsilyl)oxy]-3-butenyl]-1-1*H*-pyrazolyl]pyrimidine (13) Allyl bromide (0.16 ml, 0.6 mmol) and metallic tin (70 mg) were added to a solution of **12** (94 mg, 0.5 mmol) in THF (2.5 ml) and water (2.5 ml), and the mixture was sonicated for 1 h in an ultrasonic cleaning bath (Pasolina USC-1). The reaction mixture was carefully quenched with 1 N aqueous HCl (2.0 ml) at 0 °C, diluted with $CHCl_3$/MeOH (95/5), washed with brine, and dried. After removal of the solvents, the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH=98/2) to give the alcohol (112 mg, 97%) as a colorless amorphous solid: ^{1}H-NMR ($CDCl_3$) δ: 8.77 (2H, d, J=5 Hz), 7.77 (1H, s), 7.22 (1H, t, J=5 Hz), 5.8—5.7 (1H, m), 5.3—5.2 (1H, m), 5.2—5.2 (1H, m), 4.76 (1H, dd, J=8, 6 Hz), 2.68 (3H, s), 2.7—2.4 (2H, m).

Imidazole (100 mg, 1.46 mmol) and chlorotetraethylsilane (2.45 ml, 1.46 mmol) were added successively to a solution of the alcohol (112 mg, 0.49 mmol) in anhydrous DMF (3.0 ml) at 0 °C, and the mixture was stirred for 12 h. Water (10 ml) was added to the mixture, and the whole was extracted with AcOEt. The organic layer was washed with brine and dried. After removal of the solvents, the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH=99/1) to afford **13** (170 mg, quantitative yield) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 8.77 (2H, d, J=5 Hz), 7.74 (1H, s), 7.19 (1H, t, J=5 Hz), 5.8—5.7 (1H, m), 5.1—5.0 (2H, m), 4.72 (1H, t, J=8 Hz), 2.65 (3H, s), 2.6—2.5 (1H, m), 2.5—2.3 (1H, m), 0.90 (9H, t, J=8 Hz), 0.55 (6H, m).

3-[5-Methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-3-[(triethylsilyl)oxy]-propanal (14) 4-Methylmorpholine *N*-oxide (NMO, 1.08 g, 9.22 mmol)

Table 6. Physical Data for Pyrimizinylpyrazole Derivatives

Compd. No.	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_6) δ	IR (cm^{-1})	Formula	FAB/MS (m/z)	*Anal.* Calcd (Found)		
							C	H	N
7a	35	189—193	8.92 (2H, d, J=5 Hz), 8.08 (1H, s), 7.54 (1H, t, J=5 Hz), 6.81 (1H, d, J=16 Hz), 6.76 (2H, d, J=9 Hz), 6.58 (1H, t, J=9 Hz), 6.21 (1H, dt, J=9 Hz),16, 7 Hz), 4.0—3.9 (4H, m), 3.6—3.5 (2H, m), 3.2—3.0 (4H, m), 2.62 (3H, s)	3048, 1660, 1576, 1400	$C_{21}H_{22}F_2N_6$ ·1.0 HCl ·1.0 H_2O	397 (M^++H)	55.94 (55.61	5.59 5.57	18.63 18.42)
7b	41	209—211	8.92 (2H, d, J=5 Hz), 8.08 (1H, s), 7.53 (1H, t, J=5 Hz), 7.20 (1H, t, J=8 Hz), 7.19 (1H, d, J=8 Hz), 7.01 (2H, dd, J=8, 2 Hz), 6.82 (1H, d, J=16 Hz), 6.23 (1H, dt, J=16, 8 Hz), 4.0—3.8 (4H, m), 3.6—3.5 (2H, m), 3.2—3.0 (4H, m), 2.62 (3H, s)	1660, 1592, 1566, 1430	$C_{21}H_{23}BrN_6$ ·1.0 HCl ·0.5 H_2O	439 (M^++H)	52.03 (51.83	5.20 5.26	17.33 17.26)
7c	50	215—225	8.92 (2H, d, J=5 Hz), 8.08 (1H, s), 7.54 (1H, t, J=5 Hz), 7.5—7.4 (2H, m), 7.39 (1H, d, J=8 Hz), 7.25 (1H, d, J=7 Hz), 6.82 (1H, d, J=16 Hz), 6.23 (1H, dt, J=16, 8 Hz), 4.1—3.9 (4H, m), 3.6—3.5 (2H, m), 3.3—3.0 (4H, m), 2.62 (3H, s)	2224, 1602, 1576, 1474	$C_{22}H_{23}N_7$ ·1.0 HCl	386 (M^++H)	62.63 (62.36	5.73 5.79	23.23 22.98)
7d	56	221—224	8.92 (2H, d, J=5 Hz), 8.09 (1H, s), 7.53 (1H, t, J=5 Hz), 7.2—7.1 (1H, m), 7.08 (2H, t, J=9 Hz), 6.83 (1H, d, J=16 Hz), 6.22 (1H, dt, J=16, 8 Hz), 4.0—3.9 (2H, m), 3.6—3.5 (4H, m), 3.4—3.3 (2H, m), 3.2—3.1 (2H, m), 2.63 (3H, s)	2468, 1576, 1474, 1000	$C_{21}H_{22}F_2N_6$ ·1.0 HCl ·1.0 H_2O	397 (M^++H)	55.94 (55.87	5.59 5.55	18.63 18.62)
7e	25	209—212	8.92 (2H, d, J=5 Hz), 8.08 (1H, s), 7.53 (1H, t, J=5 Hz), 7.05 (2H, s), 6.95 (1H, s), 6.81 (1H, d, J=16 Hz), 6.21 (1H, dt, J=16, 8 Hz), 4.0—3.9 (4H, m), 3.6—3.5 (2H, m), 3.2—3.0 (4H, m), 2.62 (3H, s)	2932, 1586, 1432, 1400	$C_{21}H_{22}Cl_2N_6$ ·1.0 HCl ·1.0 H_2O	428[b] (M^+)	52.13 (52.07	5.21 5.19	17.36 17.03)
7f	28	193—197	8.92 (2H, d, J=5 Hz), 8.08 (1H, s), 7.54 (1H, t, J=5 Hz), 7.28 (1H, t, J=8 Hz), 7.26 (1H, t, J=8 Hz), 6.83 (1H, d, J=16 Hz), 6.8—6.7 (1H, m), 6.6—6.5 (1H, m), 6.23 (1H, dt, J=16 Hz, 7 Hz), 3.9—3.8 (4H, m), 3.54 (2H, d, J=7 Hz), 3.1—3.0 (4H, m), 2.62 (3H, s)	1658, 1578, 1472, 1402	$C_{21}H_{23}FN_6$ ·1.0 HCl ·0.5 H_2O	379 (M^++H)	59.50 (59.40	5.94 5.97	19.82 19.77)
7g	35	200—202	8.92 (2H, d, J=5 Hz), 8.08 (1H, s), 7.53 (1H, t, J=5 Hz), 7.14 (1H, t, J=8 Hz), 6.83 (1H, d, J=8 Hz), 6.82 (1H, s), 6.80 (1H, d, J=16 Hz), 6.69 (1H, d, J=8 Hz), 6.23 (1H, dt, J=16, 7 Hz), 4.0—3.9 (2H, m), 3.9—3.7 (2H, m), 3.7—3.5 (2H, m), 3.3—3.0 (4H, m), 2.63 (3H, s), 2.27 (3H, s)	1660, 1606, 1496, 1432	$C_{22}H_{26}N_6$ ·1.1 HCl ·1.0 H_2O	375 (M^++H)	61.08 (60.82	6.78 6.74	19.43 19.36)
7h	23	196—201	8.91 (2H, d, J=5 Hz), 8.07 (1H, s), 7.52 (1H, t, J=5 Hz), 7.47 (1H, t, J=8 Hz), 7.28 (1H, d, J=8 Hz), 7.26 (1H, s), 7.15 (1H, d, J=8 Hz), 6.83 (1H, d, J=16 Hz), 6.24 (1H, dt, J=16, 8 Hz), 4.1—3.9 (4H, m), 3.7—3.5 (2H, m), 3.3—3.1 (4H, m), 2.65 (3H, s)	1660, 1576, 1474, 1432	$C_{22}H_{23}F_3N_6$ ·1.1 HCl ·1.2 H_2O	429 (M^++H)	54.31 (54.38	5.47 5.38	17.27 17.09)
7i	33	180—192	8.92 (2H, d, J=5 Hz), 8.09 (1H, s), 7.76 (1H, s), 7.67 (1H, d, J=8 Hz), 7.54 (1H, t, J=8 Hz), 7.54 (1H, t, J=5 Hz), 7.48 (1H, d, J=8 Hz), 6.82 (1H, d, J=16 Hz), 6.23 (1H, dt, J=16, 8 Hz), 4.1—3.9 (4H, m), 3.4—3.2 (2H, m), 3.3—3.1 (4H, m), 2.63 (3H, s)	1744, 1616, 1524, 1430	$C_{21}H_{23}N_7O_2$ ·1.0 HCl ·2.0 H_2O	406 (M^++H)	52.77 (52.74	5.90 5.82	20.51 20.69)
7j	33	209—212	8.92 (2H, d, J=5 Hz), 8.09 (1H, s), 7.54 (1H, t, J=5 Hz), 7.22 (1H, ddd, J=12, 9, 5 Hz), 7.00 (1H, ddd, J=10, 7, 3 Hz), 6.9—6.8 (1H, m), 6.82 (1H, d, J=16 Hz), 6.22 (1H, dt, J=16, 8 Hz), 4.0—3.9 (2H, m), 3.6—3.5 (4H, m), 3.3—3.1 (4H, m), 2.63 (3H, s)	2468, 1580, 1434, 1244	$C_{21}H_{22}F_2N_6$ ·1.0 HCl ·1.0 H_2O	397 (M^++H)	55.94 (55.74	5.59 5.54	18.63 18.60)
7k	67	210—215	8.92 (2H, d, J=5 Hz), 8.10 (1H, s), 7.54 (1H, t, J=5 Hz), 7.49 (1H, d, J=8 Hz), 7.27 (1H, s), 7.18 (1H, d, J=8 Hz), 6.83 (1H, d, J=16 Hz), 6.22 (1H, dt, J=16, 8 Hz), 4.0—3.9 (2H, m), 3.7—3.4 (4H, m), 3.3—3.1 (4H, m), 2.63 (3H, s)	2844, 1576, 1438, 1366	$C_{21}H_{22}Cl_2N_6$ ·1.1 HCl ·1.0 H_2O	429 (M^++H)	51.74 (52.18	5.17 5.15	17.24 17.26)
7l	52	210—220	8.92 (2H, d, J=5 Hz), 8.09 (1H, s), 7.54 (1H, t, J=5 Hz), 7.0—6.8 (4H, m), 6.23 (1H, dt, J=16, 8 Hz), 4.0—3.9 (2H, m), 3.7—3.5 (4H, m), 3.3—3.2 (2H, m), 3.1—2.9 (2H, m), 2.63 (3H, s)	3052, 2844, 1734, 1594	$C_{21}H_{23}ClN_6O$ ·1.0 HCl ·0.2 H_2O	411 (M^++H)	55.93 (55.91	5.45 5.51	18.63 18.05)
9	10	200—220	8.86 (2H, d, J=5 Hz), 8.07 (1H, s), 7.44 (1H, d, J=2 Hz), 7.43 (1H, t, J=5 Hz), 7.22 (1H, t, J=8 Hz), 6.98 (1H, d, J=8 Hz), 6.92 (1H, d, J=16 Hz), 6.77 (1H, dd, J=8, 2 Hz), 6.22 (1H, dt, J=16, 8 Hz), 4.01 (2H, d, J=7 Hz), 3.85 (2H, d, J=12 Hz), 3.69 (2H, d, J=12 Hz), 3.28 (2H, t, J=12 Hz), 3.13 (2H, t, J=12 Hz), 2.76 (3H, s), 2.12 (3H, s)	2592, 1656, 1578, 1500	$C_{23}H_{27}N_7O$ ·1.0 HCl ·0.5 H_2O	418 (M^++H)	59.67 (60.08	6.31 6.24	21.28 20.80)
10	53	140—146	8.92 (2H, d, J=5 Hz), 8.08 (1H, s), 7.53 (1H, t, J=5 Hz), 7.48 (1H, s), 7.38 (1H, d, J=8 Hz), 7.33 (1H, t, J=8 Hz), 7.16 (1H, d, J=8 Hz), 6.84 (1H, d, J=16 Hz), 6.24 (1H, dt, J=16, 8 Hz), 4.0—3.8 (4H, m), 3.7—3.5 (2H, m), 3.3—3.1 (4H, m), 2.63 (3H, s)	2592, 1664, 1576, 1430	$C_{22}H_{25}N_7O$ ·1.3 HCl ·1.7 H_2O	404 (M^++H)	54.88 (54.67	6.22 6.50	20.36 20.08)
16	25	188—195	8.91 (2H, d, J=4 Hz), 8.07 (1H, s), 7.53 (1H, t, J=4 Hz), 7.03 (1H, t, J=8 Hz), 6.83 (1H, d, J=16 Hz), 6.42 (1H, d, J=8 Hz), 6.38 (1H, s), 6.31 (1H, d, J=8 Hz), 6.23 (1H, dt, J=16, 7 Hz), 4.0—3.9 (2H, m), 3.8—3.7 (2H, m), 3.6—3.5 (2H, m), 3.2—3.0 (4H, m), 2.63 (3H, s)	3140, 2464, 1574, 1436	$C_{21}H_{24}N_6O$ ·1.5 HCl ·0.5 H_2O ·1.0 EtOH	377 (M^++H)	56.65 (56.78	6.44 6.18	17.33 17.26)

Table 6. Continued

Compd. No.	Yield (%)	mp (°C)	^{1}H-NMR (DMSO-d_6) δ	IR (cm^{-1})	Formula	FAB/MS (m/z)	*Anal.* Calcd (Found)		
							C	H	N
21a	19	130—140	8.78 (2H, d, J=5 Hz), 7.88 (1H, s), 7.21 (1H, t, J=5 Hz), 6.6—6.5 (1H, m), 6.5—6.4 (1H, m), 6.37 (1H, d, J=16 Hz), 6.29 (1H, dt, J=13, 2 Hz), 6.08 (1H, dt, J=16, 7 Hz), 3.6—3.5 (2H, m), 3.5—3.4 (2H, m), 3.29 (2H, d, J=7 Hz), 2.8—2.7 (2H, m), 2.69 (3H, s), 2.6—2.5 (2H, m), 2.0—1.9 (2H, m)	2960, 1658, 1564, 1398	$C_{22}H_{24}F_2N_6$ ·1.0 HCl ·2.2 H_2O	410 (M^++H)	54.31 (54.47	6.09 6.11	17.27 16.98)
21b	53	109—121	8.91 (2H, d, J=5 Hz), 8.07 (1H, s), 7.5—7.3 (3H, m), 7.29 (2H, d, J=2 Hz), 6.68 (1H, d, J=16 Hz), 6.25 (1H, dt, J=16, 7 Hz), 4.0—3.8 (2H, m), 3.8—3.3 (2H, m), 3.3—2.8 (2H, m), 2.81 (3H, s), 2.2—1.8 (3H, m), 1.7—1.5 (1H, m)	1472, 1398, 1208, 1094	$C_{22}H_{23}Cl_2N_5$ ·1.0 HCl ·2.0 H_2O	428 (M^++H)	52.76 (52.58	5.63 5.63	13.98 14.30)
21c	23	202—237	8.91 (2H, d, J=5 Hz), 8.03 (1H, s), 7.53 (1H, t, J=5 Hz), 6.87 (1H, d, J=15 Hz), 6.15 (1H, dt, J=15, 7 Hz), 4.0—3.8 (1H, m), 3.8—3.6 (2H, m), 3.6—3.2 (8H, m), 2.81 (3H, s), 2.2—2.0 (2H, m), 1.9—1.7 (2H, m), 1.7—1.5 (1H, m), 1.5—1.4 (2H, m), 1.4—1.2 (2H, m), 1.2—1.0 (1H, m)	2936, 1662, 1574, 1472	$C_{21}H_{30}N_6$ ·2.0 HCl ·1.0 H_2O	367 (M^++H)	55.14 (55.91	7.49 7.79	18.37 17.79)
21d	29	197—201	8.91 (2H, d, J=5 Hz), 8.03 (1H, s), 7.53 (1H, t, J=5 Hz), 7.4—7.3 (5H, m), 6.85 (1H, d, J=16 Hz), 6.15 (1H, dt, J=16, 8 Hz), 4.0—3.2 (12H, m), 2.62 (3H, s)	2936, 1572, 1442, 1404	$C_{22}H_{26}N_6$ ·1.5 HCl ·1.2 H_2O	375 (M^++H)	58.62 (58.53	6.69 6.30	18.64 18.65)
21e	15	202—205	8.91 (2H, d, J=5 Hz), 8.04 (1H, s), 7.53 (1H, t, J=5 Hz), 7.4—7.1 (10H, m), 6.82 (1H, d, J=16 Hz), 6.15 (1H, dt, J=16, 8 Hz), 4.38 (1H, s), 3.8—3.4 (10H, m), 2.60 (3H, s)	2988, 1574, 1434, 922	$C_{28}H_{30}N_6$ ·2.0 HCl	451 (M^++H)	64.24 (64.09	6.16 6.11	16.05 15.99)
21f	48	—[a]	8.77 (2H, d, J=5 Hz), 7.71 (1H, s), 7.20 (1H, t, J=5 Hz), 6.98 (1H, d, J=16 Hz), 6.05 (1H, dt, J=16, 8 Hz), 4.87 (2H, d, J=8 Hz), 4.40 (2H, t, J=6 Hz), 3.41 (2H, t, J=7 Hz), 3.33 (2H, t, J=7 Hz), 2.67 (3H, s), 2.54 (2H, t, J=5 Hz), 2.6—2.4 (5H, m)	3620, 1432, 1296, 1120	$C_{17}H_{24}N_6O$ ·2.0 HCl ·2.0 EtOH	329 (M^++H)	51.11 (50.88	7.76 7.57	17.03 16.99)
21g	18	218—224	8.91 (2H, d, J=5 Hz), 8.16 (1H, d, J=5 Hz), 8.08 (1H, s), 7.53 (1H, t, J=5 Hz), 7.07 (1H, d, J=5 Hz), 6.82 (1H, d, J=16 Hz), 6.81 (2H, t, J=5 Hz), 6.21 (1H, dt, J=16, 7 Hz), 4.4—4.3 (2H, m), 4.0—3.9 (2H, m), 3.6—3.5 (2H, m), 3.3—3.2 (2H, m), 3.1—3.0 (2H, m), 2.62 (3H, s)	2988, 1638, 1574, 1396	$C_{20}H_{23}N_7$ ·2.0 HCl ·0.5 H_2O	361[b] (M^+)	54.18 (54.04	5.91 6.03	22.00 21.55)
21h	15	130—140	8.92 (2H, d, J=5 Hz), 8.45 (2H, d, J=5 Hz), 8.07 (1H, s), 7.54 (1H, t, J=5 Hz), 6.80 (1H, d, J=17 Hz), 6.77 (1H, t, J=5 Hz), 6.21 (1H, dt, J=17, 8 Hz), 4.8—4.7 (2H, m), 4.0—3.9 (2H, m), 3.6—3.5 (2H, m), 3.5—3.3 (2H, m), 3.2—3.0 (2H, m), 2.61 (3H, s)	1624, 1582, 1474, 1430	$C_{19}H_{22}N_8$ ·1.1 HCl ·2.5 H_2O	363 (M^++H)	50.99 (51.28	6.33 6.11	25.04 25.33)
21i	24	112—114	8.92 (2H, d, J=5 Hz), 8.07 (1H, s), 7.53 (1H, t, J=5 Hz), 7.50 (2H, d, J=7 Hz), 7.40 (2H, t, J=7 Hz), 7.33 (1H, t, J=7 Hz), 6.86 (1H, d, J=16 Hz), 6.26 (1H, dt, J=16, 8 Hz), 6.22 (1H, br s), 4.1—3.9 (2H, m), 3.9—3.7 (2H, m), 3.7—3.6 (1H, m), 3.2—3.1 (1H, m), 3.0—2.8 (1H, m), 2.9—2.7 (1H, m), 2.63 (3H, s)	2432, 1566, 1496, 1470	$C_{22}H_{23}N_5$ ·1.9 HCl ·2.0 H_2O	357[b] (M^+)	57.10 (57.19	6.29 6.18	15.13 15.16)
21j	66	225—230	8.92 (2H, d, J=5 Hz), 8.05 (1H, s), 7.54 (1H, t, J=5 Hz), 6.81 (1H, d, J=15 Hz), 6.20 (1H, dt, J=15, 7 Hz), 5.43 (1H, s), 4.0—3.0 (6H, m), 2.61 (3H, s), 2.6—2.1 (2H, m), 1.73 (3H, s)	2928, 1662, 1472, 1430	$C_{17}H_{21}N_5$ ·1.0 HCl ·0.1 H_2O	295[b] (M^+)	61.20 (61.28	6.71 6.82	20.99 20.78)
21k	24	200—220	8.93 (2H, d, J=5 Hz), 8.07 (1H, s), 7.54 (1H, t, J=5 Hz), 7.4—7.2 (4H, m), 6.87 (1H, d, J=15 Hz), 6.29 (1H, dt, J=15, 7 Hz), 4.7—4.2 (2H, m), 4.2—3.0 (6H, m), 2.63 (3H, s)	2932, 1574, 1472, 1430	$C_{20}H_{21}N_5$ ·1.1 HCl ·0.5 H_2O	331[b] (M^+)	63.13 (63.09	6.12 6.36	18.41 17.90)
21l	38	230—235	8.93 (2H, d, J=5 Hz), 8.09 (1H, s), 7.54 (1H, t, J=5 Hz), 7.49 (2H, d, J=8 Hz), 7.44 (2H, d, J=8 Hz), 6.85 (1H, d, J=15 Hz), 6.25 (1H, dt, J=15, 7 Hz), 5.60 (1H, s), 4.0—3.8 (2H, m), 3.6—3.2 (4H, m), 2.62 (3H, s), 2.5—2.3 (2H, m), 2.0—1.8 (2H, m)	2936, 1662, 1576, 1476	$C_{22}H_{24}ClN_5O$ ·1.5 HCl	393 (M^++H)	58.90 (58.99	5.73 5.66	15.61 15.54)
27a	53	130—140	8.78 (2H, d, J=5 Hz), 7.90 (1H, s), 7.21 (1H, t, J=5 Hz), 6.42 (1H, d, J=16.0 Hz), 6.33 (2H, dd, J=11, 2 Hz), 6.2—6.1 (1H, m), 6.08 (1H, dt, J=16, 7 Hz), 4.0—3.8 (1H, m), 3.3—3.1 (4H, m), 2.97 (1H, d, J=11 Hz), 2.83 (1H, d, J=11 Hz), 2.70 (3H, s), 2.37 (1H, dd, J=11, 4 Hz), 2.23 (1H, td, J=11, 4 Hz), 1.19 (3H, d, J=6 Hz)	2932, 1574, 1472, 1430	$C_{22}H_{24}F_2N_6$ ·1.0 HCl ·1.6 H_2O	411 (M^++H)	55.54 (55.72	5.97 6.11	17.66 17.34)
27b	36	127—133	8.78 (2H, d, J=5 Hz), 7.90 (1H, s), 7.21 (1H, t, J=5 Hz), 6.42 (1H, d, J=16.0 Hz), 6.4—6.3 (2H, m), 6.3—6.2 (1H, m), 6.11 (1H, ddd, J=16, 8, 6 Hz), 3.7—3.6 (1H, m), 3.5—3.4 (2H, m), 3.1—2.9 (3H, m), 2.70 (3H, s), 2.7—2.5 m), 7.21 (3H, d, J=6 Hz)	2932, 1630, 1432, 1198	$C_{22}H_{24}F_2N_6$ ·1.0 HCl	411 (M^++H)	54.71 (54.93	6.05 5.84	17.40 17.19)
31	51	185—191	8.78 (2H, d, J=5 Hz), 7.90 (1H, s), 7.22 (1H, t, J=5 Hz), 6.93 (2H, dd, J=8, 2 Hz), 6.7—6.6 (1H, m), 6.46 (1H, d, J=16.0 Hz), 6.66 (1H, dt, J=16, 7 Hz), 3.72 (2H, t, J=5 Hz), 3.39 (2H, s), 3.27 (2H, d, J=7 Hz), 2.90 (2H, t, J=5 Hz), 2.71 (3H, s)	1682, 1602, 1574, 1478	$C_{21}H_{20}F_2N_6O$ ·1.0 HCl ·1.0 H_2O	411 (M^++H)	54.25 (54.55	4.99 4.92	18.08 17.93)

a) Amorphous solid. *b*) FDMS.

and a catalytic amount of osmium tetraoxide were added to a solution of **13** (1.59 g, 4.61 mmol) in THF (20 ml) and water (5 ml), and the mixture was stirred at room temperature for 24 h. A suspension of sodium periodate (4.93 g, 23.1 mmol) in water (20 ml) was added to the above mixture at room temperature, and the mixture was stirred at the same temperature for 2 h. The mixture was diluted with $CHCl_3$, washed with brine, and dried. After removal of the solvents, the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH=99/1) to give **14** (0.91 g, 57%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 9.81 (1H, t, J=2 Hz), 8.78 (2H, d, J=5 Hz), 7.77 (1H, s), 7.22 (1H, t, J=5 Hz), 5.27 (1H, dd, J=8, 5 Hz), 2.97 (1H, ddd, J=16, 8, 2 Hz), 2.73 (3H, s), 2.7—2.6 (1H, m), 0.89 (9H, t, J=8 Hz), 0.5—0.4 (6H, m).

3-[4-(3-Hydroxyphenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-*trans*-propene Hydrochloride (16) AcOH (220 μl, 3.88 mmol) and sodium cyanoborohydride (305 mg, 4.85 mmol) were added successively to a solution of **14** (336 mg, 0.970 mmol) and **15** (864 mg, 4.85 mmol) in MeOH (170 ml), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$ and brine, and dried. Evaporation of the solvents afforded the corresponding adduct. Next, a solution of 1 N HCl/EtOH (10 ml) was added to a solution of the above product in EtOH (10 ml), and the mixture was stirred at room temperature for 17 h. After removal of the solvents, the crude mixture was dissolved in THF (15 ml) and 1,4-dioxane (15 ml). *p*-TsOH·H_2O (275 mg, 1.45 mmol) was added to a solution of the crude mixture in anhydrous 1,4-dioxane (5 ml) and THF (5 ml), and the mixture was heated to reflux for 2 h. The reaction mixture was diluted with $CHCl_3$, successively washed with saturated aqueous $NaHCO_3$ and brine, and dried. After removal of the solvents, the crude mixture was chromatographed on a silica gel column ($CHCl_3$/MeOH=50/3) to afford the propene. An appropriate volume of a solution of 1 N HCl/EtOH was added to a solution of the propene in a small amount of EtOH, and the solvent was removed. The residue was recrystallized from EtOH to give **16** (113 mg, 25%) as a white powder. The physical data for **16** are shown in Table 6.

3-(3,5-Dichlorophenyl)cyclopentanone (18b) 2-Cyclopentenone (2.2 g, 27 mmol), palladium(II) acetate (940 mg), tris(2-methylphenyl)phosphine (112 mg), and Et_3N (4.3 ml, 31 mmol) were added to a solution of 1-bromo-3,5-dichlorobenzene (**17b**, 5.9 g, 26 mmol) in CH_3CN (8.0 ml), and the mixture was heated to reflux for 3 weeks. The reaction mixture was diluted with $CHCl_3$, washed with 1 N HCl and brine, and dried. After removal of the solvents, the crude mixture was chromatographed on a silica gel column ($CHCl_3$) to afford **18b** (1.13 g, 19%) as a colorless clear oil: ^{1}H-NMR ($CDCl_3$) δ: 7.26 (1H, t, J=2 Hz), 7.14 (2H, d, J=2 Hz), 3.38 (1H, ddt, J=14, 11, 7 Hz), 2.67 (1H, dd, J=14, 7 Hz), 2.4—2.3 (2H, m), 2.6—2.4 (2H, m), 1.97 (1H, dt, J=11, 7 Hz).

1-(3,5-Difluorophenyl)-1,4-diazepane (19a) 1,4-Diazepane (2.0 g, 20.7 mmol), dichlorobis(tri-*o*-tolylphosphine)palladium (122 mg, 0.155 mmol), and sodium *tert*-butoxide (695 mg, 7.23 mmol) were added to a solution of 1-bromo-3,5-difluorobenzene (**17a**, 1.0 g, 5.18 mmol) in toluene (25 ml), and the mixture was stirred at 100 °C for 13 h. The reaction mixture was washed with water and brine, and dried. After removal of the solvents, the crude mixture was chromatographed on a silica gel column ($CHCl_3$/MeOH=9/1) to afford **19a** (346 mg, 32%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 6.5—6.4 (1H, m), 6.51 (1H, dt, J=8, 2 Hz), 6.28 (1H, dt, J=13, 2 Hz), 3.6—3.5 (4H, m), 3.02 (2H, t, J=5 Hz), 2.84 (2H, t, J=5 Hz), 2.0—1.9 (2H, m).

4-(3,5-Difluorophenyl)piperidine (19b) Sodium acetate (1.3 g) and hydroxylamine hydrochloride (0.68 g, 9.9 mmol) were added to a solution of **18b** (1.13 g, 5.0 mmol) in MeOH (20 ml) and water (10 ml), and the mixture was heated to reflux for 2 h. The reaction mixture was diluted with $CHCl_3$, washed with water and brine, and dried. Removal of the solvents afforded the corresponding oxime. To this residue was added polyphosphoric acid (10 g), and the mixture was stirred at 80 °C for 2 h. The reaction mixture was diluted with ice-water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was washed with brine and dried. After removal of the solvents, the crude mixture was chromatographed on a silica gel column ($CHCl_3$/AcOEt=1/1) to afford the mixture of 4-(3,5-dichlorophenyl)-2-piperidinone and 5-(3,5-dichlorophenyl)-2-piperidinone (800 mg, 66%) as a red caramel. The ratio of 4-(3,5-dichlorophenyl)-2-piperidinone and the isomer was about 1 : 1 based on the NMR spectrum. This mixture was used in the next reaction without further purification: FAB-MS m/z 244 (M^++H).

A solution of the mixture of the above 2-piperidinones (800 mg, 3.3 mmol) in THF (20 ml) was added to a suspension of LAH (370 mg, 9.7 mmol) in THF (40 ml) at 0 °C, and the mixture was heated to reflux for 5 h. The reaction mixture was carefully quenched with AcOEt, and the whole was filtered through a Celite pad. The filtrate was concentrated to afford the mixture of **19b** and 3-(3,5-dichlorophenyl)piperidine (800 mg, quantitative yield as the mixture) as a pale red oil. This mixture was used in the next Mannich reaction without further purification: FAB-MS m/z 228 (M^++H).

3-[4-(3,5-Difluorophenyl)-1-(1,4-diazepanyl)]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-propanone (20a) Synthesis of **20a**—**f** from **19a**—**f** was performed as described for the synthesis of **6a**. The physical data for **20a**—**f** are shown in Table 5.

3-[4-(3,5-Dichlorophenyl)-1-piperidinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-*trans*-propene Hydrochloride (21a) Synthesis of **21a**—**l** from **20a**—**l** was performed as described for the synthesis of **7a**. The physical data for **21a**—**l** are shown in Table 6.

***N*^{1}-(3,5-Difluorophenyl)-1,2-ethanediamine Hydrochloride (23)** The mixture of 3,5-difluoroaniline hydrochloride (**22**, 10.6 g, 64 mmol) and 1,3-oxazolidin-2-one (5.6 g, 64 mmol) was stirred at 170 °C for 4 d. The reaction mixture was cooled, and the precipitate obtained was filtered. The precipitate was recrystallized from Et_2O to give **23** (13.7 g, quantitative yield) as a pale red powder: ^{1}H-NMR ($CDCl_3$) δ: 6.45 (2H, d, J=9 Hz), 6.35 (1H, t, J=9 Hz), 4.30 (2H, t, J=8 Hz), 3.72 (3H, br s), 3.55 (2H, t, J=8 Hz).

4-(3,5-Difluorophenyl)-3-methyl-2-piperazinone (24) Et_3N (15 ml) and 2-chloropropanoyl chloride (3.0 ml, 30.9 mmol) were successively added dropwise to a solution of **23** (2.6 g, 15.1 mmol) in CH_2Cl_2 (10 ml) at 0 °C, and the mixture was stirred at the same temperature for 20 min. The reaction mixture was diluted with $CHCl_3$, washed with 10% aqueous NaOH and brine, and dried. Removal of the solvents afforded the corresponding amide. Next, K_2CO_3 (3.0 g) was added to a solution of the above product in EtOH (50 ml), and the mixture was heated to reflux for 41 h. The mixture was diluted with $CHCl_3$, washed with 10% aqueous NaOH and brine, and dried. After removal of the solvents, the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH=40/1) to give **24** (1.2 g, 35%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 6.45 (2H, d, J=9 Hz), 6.34 (1H, t, J=9 Hz), 4.0—3.9 (2H, m), 3.8—3.5 (3H, m), 1.34 (3H, d, J=6.8 Hz).

1-(3,5-Difluorophenyl)-2-methylpiperazine (26a) A solution of **24** (400 mg, 1.8 mmol) in THF (20 ml) was added to a suspension of LAH (200 mg, 5.3 mmol) in THF (20 ml), and the mixture was stirred at room temperature for 5 h. The reaction mixture was carefully quenched with AcOEt, and the whole was filtered through a Celite pad. The filtrate was washed with brine, and dried. After removal of the solvents, the crude mixture was chromatographed on a silica gel column ($CHCl_3$/MeOH=20/1) to afford **26a** (60 mg, 32%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 6.46 (2H, d, J=9 Hz), 6.38 (1H, t, J=9 Hz), 4.30 (1H, br s), 4.0—3.7 (1H, m), 3.7—3.6 (2H, m), 3.6—3.5 (3H, m), 2.78 (1H, dd, J=12, 3 Hz), 2.46 (1H, dd, J=12, 9 Hz), 1.18 (3H, d, J=7 Hz).

1-(3,5-Difluorophenyl)-3-methylpiperazine (26b) 2-Methylpiperazine (623 mg, 6.22 mmol) was treated in the same manner as for **19a** to give **26b** (346 mg, 32%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 6.3—6.2 (2H, m), 6.24 (1H, tt, J=9, 2 Hz), 3.4—3.3 (2H, m), 3.1—3.0 (1H, m), 2.98 (1H, dt, J=12, 3 Hz), 2.9—2.8 (1H, m), 2.75 (1H, dt, J=12, 3 Hz), 2.39 (1H, dd, J=12, 10 Hz),1.14 (3H, d, J=6 Hz).

3-[4-(3,5-Difluorophenyl)-3-methyl-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-*trans*-propene Hydrochloride (27a) Compounds **26a** and **26b** were treated in the same manner as described above to give **27a** and **27b**, respectively. The physical data for these compounds and yields are shown in Table 6.

Benzyl 4-(3,5-Difluorophenyl)-3-oxo-1-piperazinecarboxylate (28) Et_3N (1.20 ml, 8.57 mmol) and ZCl (0.665 ml, 3.9 mmol) were successively added dropwise to a solution of **23** (813 mg, 3.9 mmol) in anhydrous THF (10 ml) at 0 °C, and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with $CHCl_3$, washed with brine, and dried. After removal of the solvents, the crude mixture (800 mg) was dissolved in AcOEt (7.5 ml). 2-Bromoactyl bromide (0.71 ml, 8.22 mmol) and a solution of NaOH (411 mg, 10.3 mmol) were added successively to the above solution at 0 °C, and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with $CHCl_3$, washed with brine, and dried. Removal of the solvents afforded the corresponding amide (1.1 g). Next, K_2CO_3 (1.07 g, 7.73 mmol) was added to a solution of the above product in DMF (6 ml), and the mixture was stirred at room temperature for 48 h. The mixture was diluted with $CHCl_3$, washed with brine, and dried. After removal of the solvents, the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH=50/1) to give **28** (800 mg, 59%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 7.5—7.2 (5H, m), 7.0—6.8 (1H, m), 6.8—6.7 (1H, m), 5.19 (2H, s), 4.33 (2H, s), 4.0—3.8 (2H, m), 3.8—3.6 (2H, m).

1-(3,5-Difluorophenyl)-2-piperazinone (29) Compound **28** (800 mg, 2.31 mmol) was dissolved in EtOH (40 ml) and hydrogenated over 10%

Pd/C (250 mg) for 10 min at room temperature. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to afford the crude mixture, which was chromatographed on a silica gel column ($CHCl_3$/MeOH=30/1) to give **29** (326 mg, 67%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 7.0—6.8 (2H, m), 6.8—6.6 (2H, m), 3.70 (2H, s), 3.68 (2H, t, J=5 Hz), 3.23 (2H, t, J=5 Hz).

3-Hydroxy-3-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]propyl-4-methyl-benzenesulfonate (30) Sodium borohydride (38 mg, 1.0 mmol) was added to a solution of **14** (328 mg, 0.95 mmol) in MeOH (4.0 ml) at 0 °C, and the mixture was stirred at the same temperature for 1 h. A solution of 1 N HCl/EtOH (1.0 ml) and water (20 ml) was successively added to the reaction mixture, and the whole was extracted with $CHCl_3$. The organic layer was dried and then evaporated *in vacuo* to afford the primary alcohol (296 mg). Next, *p*-toluenesulfonyl chloride (361 mg, 1.84 mmol) was added to a solution of the above product in pyridine (3.0 ml) at 0 °C, and the mixture was stirred at the same temperature for 24 h. The mixture was diluted with $CHCl_3$, washed with brine, and dried. After removal of the solvents, the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH=95/5) to give the tosylate, which was kept in a refrigerator overnight to afford **30** (350 mg, 74%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 8.79 (1H, d, J=5 Hz), 7.80 (2H, d, J=8 Hz), 7.70 (1H, s), 7.35 (2H, d, J=8 Hz), 7.24 (1H, t, J=5 Hz), 4.88 (1H, dd, J=5, 9 Hz), 4.4—4.3 (1H, m), 4.2—4.1 (1H, m), 2.66 (3H, s), 2.44 (3H, s), 2.2—2.1 (1H, m), 2.1—2.0 (1H, m).

3-[4-(3,5-Difluorophenyl)-3-oxo-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-propene Hydrochloride (31) Compound **29** (33 mg, 0.15 mmol) and K_2CO_3 (11 mg) were added to a solution of **30** (30 mg, 0.077 mmol) in CH_3CN (1 ml) and THF (10 ml), and the mixture was stirred at 60 °C for 30 min. The reaction mixture was diluted with $CHCl_3$, washed with brine, and then dried. Evaporation of the solvents afforded the corresponding adduct. Next, *p*-TsOH·H_2O (50 mg, 0.263 mmol) was added to a solution of the above product in anhydrous 1,4-dioxane (3 ml) and THF (3 ml), and the mixture was heated to reflux for 40 min. The reaction mixture was diluted with $CHCl_3$, successively washed with saturated aqueous $NaHCO_3$ and brine, and dried. After removal of the solvents, the crude mixture was chromatographed on a silica gel column ($CHCl_3$/MeOH=98/2) to afford the propene. An appropriate volume of a solution of 1 N HCl/EtOH was added to a solution of the propene in a small amount of EtOH, and the solvent was removed. The residue was recrystallized from EtOH to give **31** (14 mg, 51%) as a white powder. The physical data and yields are shown in Table 6.

***In Vitro* Cytotoxicity** To examine the direct growth-inhibitory effects of the test compounds against PC-6 and PC-12 human non-small cell lung cancer cell lines and resistant cell lines (PC-6/VCR and PC-6/ADM), 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.[9]

Evaluation of Therapeutic Effect *in Vivo* P388 cells (1×10^6) were inoculated 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 administered i.p. or *p.o.* on days 1 and 5, or days 1—5 consecutively. The increase in life span (ILS) was calculated by the following formula: ILS (%)=[(median survival time of treated group)/(median survival time of control group)−1]×100. Meth A murine fibrosarcoma cells (1×10^6) were implanted into the right flank of BALB/c mice (day 0). Compounds were administered *p.o.* on days 7—11 consecutively. Tumor weights were measured on day 17. The tumor growth-inhibition rate (IR) was calculated by the formula: IR (%)=(1−TWt/TWc)×100 (%), where TWt represents the mean of tumor weight of a treated group, and TWc represents that of the control group. To evaluate the intensity of the side effects of compounds, the rate of body weight loss (BWL) was utilized as a parameter of toxicity. The maximum value of BWL was designated as BWLmax, and a BWLmax of less than zero indicates no body weight loss.

References and Notes

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