Synthesis and Antitumor Activity of Novel Pyrimidinyl Pyrazole Derivatives. III.[1,2] Synthesis and Antitumor Activity of 3-Phenylpiperazinyl-1-*trans*-propenes

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A series of novel 3-[4-phenyl-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-pyrazolyl]-1-*trans*-propenes and related compounds were synthesized and evaluated by their cytotoxic activity against several tumor cell lines *in vitro* and *in vivo* antitumor activity against some tumor models when administered both intraperitoneally and orally. Compounds with the 3-chloropyridin-2-yl group (9g) and the 3-fluoro-5-substituted phenylpiperazinyl group (29b, c, and e) showed significantly potent cytotoxicity by *in vitro* testing. Among them, the 3-cyano-5-fluorophenyl derivative (29b) exhibited potent antitumor activity against several tumor cells including human carcinoma without causing undesirable effects in mice.

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

In previous papers, we reported novel pyrimidinyl pyrazole derivatives (Fig. 1) that showed *in vitro* and *in vivo* antitumor activity. These compounds were also found to inhibit tubulin polymerization as a mechanism of their action in cells.[1,2] To investigate the possibilities for modification of this scaffold, we divided the moieties into five parts from A to E as shown in Fig. 1. So far, it has been reported that the length of the three carbon chain on moiety C and the existence of piperazine on moiety D are important for the activity. In an effort to improve the activity, we replaced the pyrimidine and pyrazole moieties of A and B with some heteroaryl moieties and introduced various substituents to the phenyl ring of moiety E. We describe here the modification of moieties A, B, and E and the antitumor activities of the resulting compounds.

Chemistry

Syntheses of the 1-arylpyrazolyl compounds (**9a**—**k**) were carried out *via* the route shown in Chart 1. The hydrazine derivatives (**5a**—**j**)[3—7] were subjected to the construction of a pyrazole ring with ethoxymethyleneacetylacetone[8] to provide the 4-acetyl-1-heteroarylpyrazoles (**6a**—**j**). Phenylpyrazole derivative (**6k**) was prepared by following the reported

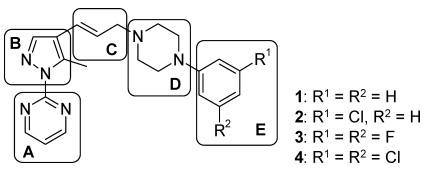
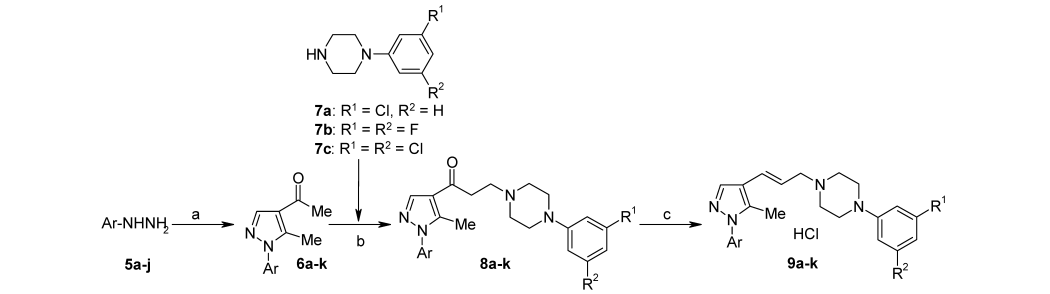
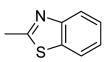
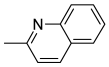
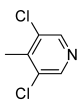
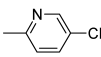


Fig. 1



	-Ar	R^1	R^2		-Ar	R^1	R^2		-Ar	R^1	R^2		-Ar	R^1	R^2
a		Cl	H	**b**		Cl	H	**c**		Cl	H	**d**		Cl	H
e		Cl	H	**f**		Cl	H	**g**		F	F	**h**		F	F
i		F	F	**j**		F	F	**k**		Cl	Cl				

a) ethoxymethyleneacethylacetone, EtOH, b) (HCHO)*n*, HCl, EtOH, c) 1) $NaBH_4$, EtOH/THF, 2) *p*-TsOH·H_2O, 1,4-dioxane, THF, 3) HCl/EtOH.

Chart 1

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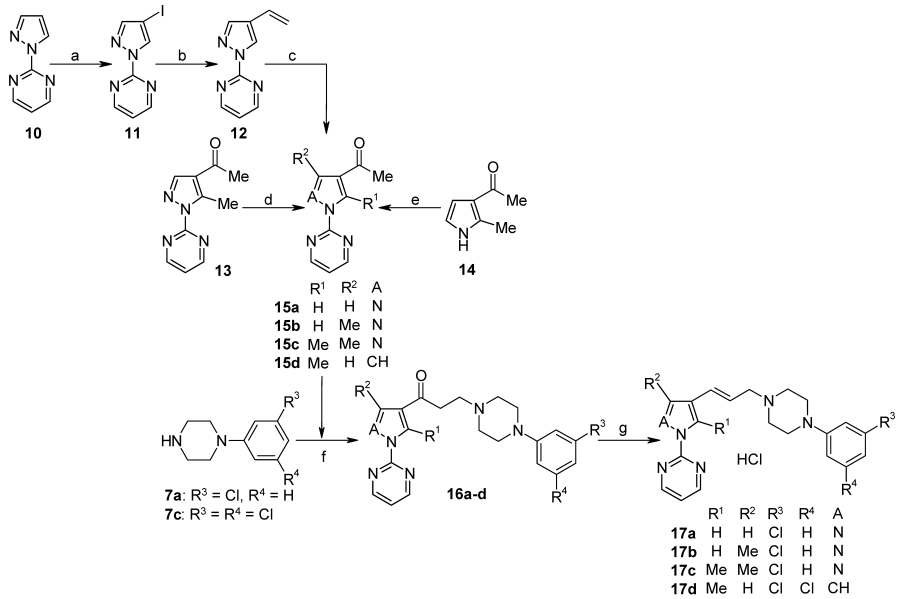
procedure.[9,10] Mannich reaction of pyrazoles (**6a**—**k**) with 1-(3-chlorophenyl)piperazine (**7a**), 1-(3,5-difluorophenyl)-piperazine (**7b**), or 1-(3,5-dichlorophenyl)piperazine (**7c**) gave **8a**—**k**, respectively. Compounds (**8a**—**k**) were reduced with sodium borohydride to give the corresponding alcohols, which were dehydrated by *p*-toluenesulfonic acid (*p*-TsOH) to afford 1-*trans*-propene derivatives **9a**—**k**.

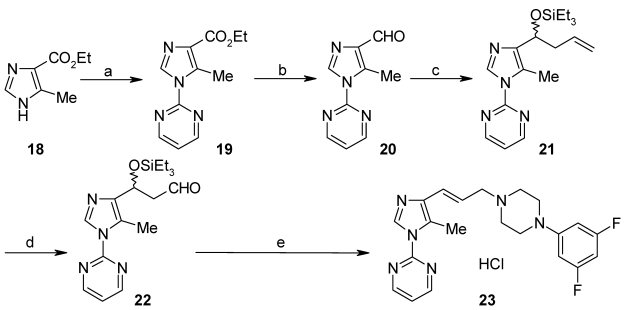
Modification of the pyrazole moiety was carried out *via* the route shown in Charts 2 and 3. Compound (**11**), which was prepared by iodination of 2-(1-pyrazolyl)pyrimidine (**10**)[11] with periodic acid, afforded **12** through a palladium-catalyzed cross-coupling reaction with vinyltributylstannum in the presence of lithium chloride.[12] Compound (**12**) was treated with sulfuric acid and then oxidized with manganese (IV) oxide to afford 5-demethylpyrazole (**15a**). Migration of the pyrimidinyl group of **13**[1,2] to the 2-position from the 1-position on the pyrazole ring was carried out by using diethyl carbonate and sodium hydride to produce 3-methylpyrazole (**15b**). Dimethylpyrazole (**15c**) was prepared following the reported procedure.[13] To investigate the possibility of replacing the pyrazole ring with a pyrrole ring, 1-(2-methyl-1*H*-pyrrol-3-yl)ethanone (**14**)[14,15] was reacted with 2-chloropyrimidine to afford 2-methylpyrrole (**15d**). The derivatives bearing a pyrazole ring (**17a**—**c**) and a pyrrole ring (**17d**) were obtained from the 4-acetylpyrazole derivatives (**15a**—**c**) and the pyrrole derivative (**15d**) with modified piperazines (**7a**) and (**7c**) *via* the Mannich reaction and dehydration, respectively (Chart 2).

Furthermore, the imidazole derivative (**23**) having a nitrogen atom at 3-position of the pyrazole ring was also prepared by the procedure to construct this scaffold by employing reductive amination instead of the Mannich reaction (Chart 3). Ethyl 4-methyl-5-imidazolecarboxylate (**18**) was condensed with 2-chloropyrimidine to afford pyrimidinylimidazole (**19**). Reduction of **19** with diisobutylaluminum hydride (DIBAL) gave aldehyde (**20**). The carbon–carbon bond formation of **20** with allyl bromide was performed with metallic stannum,[16] followed by protection of the secondary alcohol with triethylsilyl chloride to give **21**. Oxidation of **21** with osmium tetraoxide (OsO_4) and simultaneous oxidative cleavage of the 1,2-diol with sodium periodate gave aldehyde (**22**). The reductive amination of **22** with **7b** by treatment with



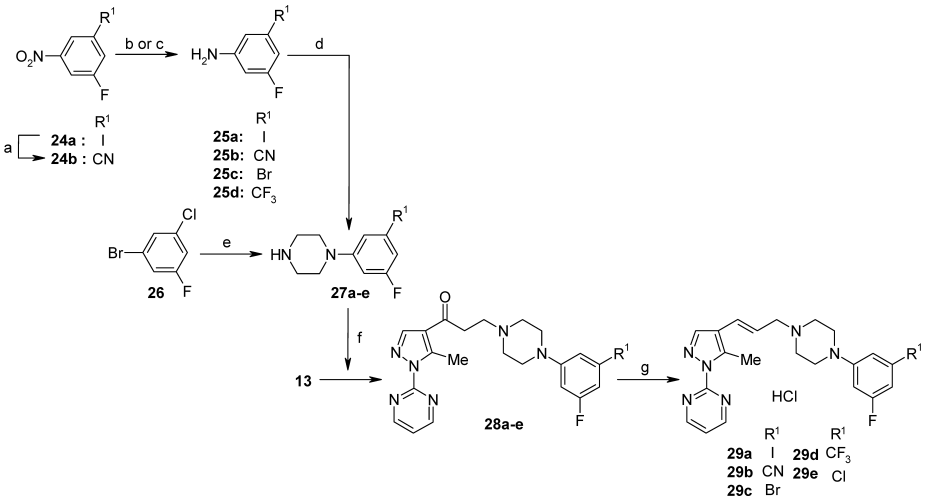
a) HIO_4, I_2, H_2SO_4-AcOH, b) vinyltributylstannum, $(Ph_3P)_4Pd$, LiCl, 1,4-dioxane, c) 1) cH_2SO_4, 2) MnO_4, 1,4-dioxane, d) $(EtO)_2CO$, NaH, PhMe, e) 2-chloropyrimidine, KOH, DMSO, f) $(HCHO)n$, HCl, EtOH, g) 1) $NaBH_4$, EtOH/THF, 2) *p*-TsOH·H_2O, 1,4-Dioxane, THF, 3) HCl/EtOH.

Chart 2



a) 2-chloropyrimidine, K_2CO_3, DMF, b) DIBAL, THF/CH_2Cl_2, 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) **7b**, $NaBH_3CN$, AcOH, MeOH, 2) HCl/EtOH.

Chart 3



a) CuCN, DMF, b) $SnCl_2 \cdot 2\,H_2O$, EtOH, c) H_2/Pd-C, EtOH, d) bis(chloroethyl)amine, K_2CO_3, *n*-BuOH, e) piperazine, $PdCl_2[P(o\text{-}tol)_3]_2$, *t*-BuONa, 1,4-dioxane, f) (HCHO)*n*, HCl, EtOH, g) 1) $NaBH_4$, EtOH/THF, 2) *p*-TsOH·H_2O, 1,4-dioxane, THF, 3) HCl/EtOH.

Chart 4

sodium cyanoborohydride in acetic acid (AcOH)/EtOH gave the corresponding adduct, followed by deprotection and simultaneous dehydration with hydrochloride to afford the 1-*trans*-propene derivative (**23**).

On the other hand, some 3,5-disubstituted phenylpiperazine derivatives were synthesized *via* the route shown in Chart 4, because 3,5-disubstitution of phenylpiperazine enhanced activity. As for the introduction of cyanide, 1-fluoro-3-iode-5-nitrobenzene (**24a**) was reacted with copper(I) cyanide to afford 1-cyano-3-fluoro-5-nitrobenzene (**24b**). After reduction of the nitro group of compounds (**24a**, **b**), the anilines (**25a**—**d**) were treated with bis(2-chloroethyl)amine hydrochloride and potassium carbonate to give the phenylpiperazines (**27a**—**d**). Compound (**27e**) was prepared *via* a palladium(II)-catalyzed aromatic amination reaction[17] of 1-bromo-3-chloro-5-fluorobenzene (**26**) with piperazine. Mannich reaction of **13** with 3,5-disubstituted phenylpiperazines (**27a**—**e**) gave **28a**—**e**, respectively. Propene derivatives (**29a**—**e**) were obtained from **28a**—**e** by the same procedure as described in Chart 1.

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 (**2**—**4**), VCR, and 5-fluorouracil (5-FU) were used as reference compounds.

Among a series of 1-arylpyrazole derivatives (**9a**—**f**) bearing the 3-chlorophenylpiperazine moiety, the pyridine derivatives (**9a**, **b**), and the pyrazine derivative (**9c**) showed weak activity, while the other compounds (**9d**—**f**) were not active. On the other hand, in a series of 1-arylpyrazole compounds (**9g**—**j**) bearing the 3,5-difluorophenylpiperazine moiety, the 3-chloropyridin-2-yl derivative (**9g**) showed similar activity and potency to that of the corresponding pyrimidin-2-yl derivative (**3**). The activities of compounds (**9h**—**j**) bearing a 3-chloropyridin-4-yl, 3,5-dichloropyridin-4-yl, and 5-chloropyridin-2-yl moiety, respectively, were moderate or inactive. The phenylpyrazole compound (**9k**) had decreased activity compared with that of the pyrimidinylpyrazole compound (**4**). The pyrimidin-2-yl part and the 3-chloropyridin-2-yl part on moiety A are important for potent activity, because all the other derivatives showed decreased *in vitro* activity compared with the corresponding pyrimidine derivatives.

As for the modification of moiety B, compound (**17c**) having methyl groups at both 3- and 5-positions of pyrazole showed weak *in vitro* cytotoxic activity, while the corresponding compounds (**17a**) without methyl group and (**17b**) with a methyl group at 3-position of pyrazole were not ac-

Table 1. Cytotoxic Activity of 1-*trans*-Propene Derivatives

Compd. No.	GI_{50} (ng/ml)[a]	
	PC-6	PC-12
9a	306	NT[b]
9b	127	589
9c	113	583
9d	>1000	>1000
9e	>1000	>1000
9f	>1000	>1000
9g	8.8	35
9h	31	109
9i	>1000	>1000
9j	57	358
9k	455	>1000
17a	>1000	>1000
17b	>1000	>1000
17c	461	>1000
17d	691	>1000
23	>1000	>1000
29a	104	667
29b	4.8	27
29c	5.4	75
29d	40	370
29e	2.5	22
2	34	208
3	6.4	63
4	6.3	205
VCR	0.3	33
5-FU	460	30

PC-6, PC-12: Human non-small cell lung cancer cell lines. *a*) See Experimental. *b*) NT: not tested.

tive. The fact that compounds (**2**) and (**17c**) retained the cytotoxic activity, while no activity was observed with **17a** and **b**, indicates that a methyl group at 5-position of pyrazole plays a critical role for showing cytotoxic activity. Replacement of the pyrazole ring with the pyrrole or imidazole ring caused a decrease of cytotoxic activity (**17d**, **23**), even though these compounds had a methyl group at the same position. It seemed to be very difficult to retain *in vitro* activity by changing the structure of moiety B.

In the series of 3-fluoro-5-substituted phenyl derivatives (**29a**—**e**) listed in Chart 4, compounds (**29b**, **e**) which bear a cyano or a chloro group at the same position of the phenyl ring, showed slightly enhanced activity compared with the corresponding 3,5-difluorophenyl derivative (**3**) against PC-6 and PC-12. The 3-bromo-5-fluorophenyl derivative (**29c**) showed almost the same activity as **3**, but the iodo substituent at 3-position dramatically decreased the *in vitro* activity (**29a**). The activity of the corresponding compound (**29d**) bearing the trifluoromethyl group at the same position of the phenyl ring was moderate.

Compounds (**9g**), (**29b**), (**29c**), and (**29e**), which showed strong *in vitro* cytotoxic activity, were tested in the *in vivo* assay against murine fibrosarcoma Meth A as a solid tumor model by intraperitoneal injection or oral administration. 5-FU was used as a reference compound.

As shown in Table 2, all compounds exhibited more potent antitumor activity at the maximum tolerated dose (MTD) than that (26%) of 5-FU by intraperitoneal injection. Particularly, compound (**29b**) exhibited potent effect with the respective inhibition rate (IR) value of 75% at the MTD, the antitumor activity of **29b** was superior to those of **2** and **3** when administered intraperitoneally. The effect of **9g**, **29c**, and **29e**, however, was moderate in spite of showing activity almost equal to the *in vitro* cytotoxic activity of **29b**. These compounds also did not cause a decrease of body temperature as the side effect at the level of each MTD. Furthermore, muscle relaxation and crouching posture were not observed for these compounds at the MTD in mice, although the lead compound (**2**) in this scaffold caused these visible symptoms. The tumor growth inhibition curves of **29b** and 5-FU are shown in Fig. 2.

When administered orally, the effects of these compounds

Table 2. Antitumor Activity of 1-*trans*-Propene 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
9g	35.0×5	47*	<0	0/7	60.0×5	89***	15.0	1/7
	28.0×5	34*	<0	0/7	35.0×5	55**	<0	0/7
29b	10.0×5	75***	14.2	0/7	10.0×5	86***	12.3	0/7
	7.0×5	58**	1.2	0/7	7.0×5	72**	2.0	0/7
29c	60.0×5	43**	2.0	0/7				
29e	20.0×5	51**	1.6	0/7	30.0×5	81***	3.5	0/7
	14.0×5	43**	<0	0/7	20.0×5	57**	<0	0/7
5-FU[1,2)]	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

Inhibition rate (IR) of VCR; 9.0% (1.6 mg/kg, i.v.), **2**; 62% (43×5 mg/kg, i.p.) and 88% (60×5 mg/kg, *p.o.*), **3**; 63% (7.4×5 mg/kg, i.p.) and 86% (12.5×5 mg/kg, *p.o.*).[1,2)] *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 (BML). *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.

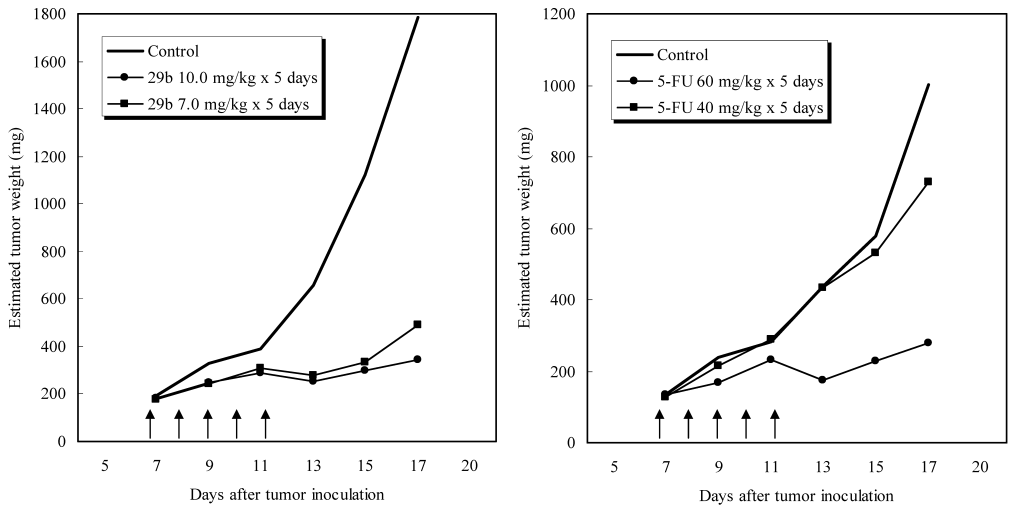


Fig. 2. Tumor Growth Inhibition Curves of **29b** and 5-FU[1)] against Meth A

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). Compound **29b** and 5-FU at the indicated doses were administered orally on days 7—11, consecutively.

Table 3. Antitumor Effect of **3** and **29b** on Human Carcinoma in Nude Mice[a)]

	Antitumor activity[b)]											
	29b				**3**				VCR			
	Dose (mg/kg)	IR (%)	BWLmax[c)] (%)	D/U[d)]	Dose (mg/kg)	IR (%)	BWLmax[c)] (%)	D/U[d)]	Dose (mg/kg)	IR (%)	BWLmax[c)] (%)	D/U[d)]
PC-12	8.0×8	70***	1.0	0/5	10.0×8	68***	3.1	0/6	1.6×1	−10	17.2	0/6
PC-14	8.0×8	38*	2.8	0/6	10.0×8	53**	7.8	0/6	1.6×1	53**	15.8	0/6

a) Human non-small cell lung cancer PC-12 and PC-14 blocks were inoculated s.c. into BALB/cAnNCrj-nu mice (day 0). Compounds **29b** and **3** at the indicated doses were administered *per os* (oral) administration (*p.o.*) from day 11 or 14. VCR was administrated i.v. on day 11 or 14, once. *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.

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

Compd. No.	GI_{50} (ng/ml) PC-6	Rate[c)]				
		PC-6/VCR29-9	PC-6/ADM2-1	PC-6/Tax1-1	PC-6/CDDP2-7	PC-6/FU26-23
29b	4.8	0.97	1.63	1.34	2.17	1.87
VCR	0.101	842	691	398	2.58	1.60
ADM	12.6	27.9	18.7	8.65	1.02	0.46
Taxol	0.31	580	365	299	1.08	1.02
Cisplatin	203	0.54	1.17	0.66	28.6	0.11
5-FU	420	0.85	1.09	0.78	0.72	24.8

a) See Experimental. *b*) PC-6/VCR29-9, PC-6/ADM2-1 and PC-6/Tax1-1 overexpress P-glycoprotein. PC-6/CDDP2-7 overexpresses GSH (glutathione) and GSSG. Mechanism of 5-FU resistance in the PC-6/FU26-23 cell line is unknown. *c*) (GI_{50} value against drug-resistant cell line)/(GI_{50} value against PC-6 cell line).

were superior to that by intraperitoneal injection (Table 2). Compounds (**29b**) and (**29e**) showed potent antitumor activity with the respective IR values of 86% and 81% at the MTD. The effects of **29b** and **29e** by oral administration were superior to that (40%) of 5-FU and the same as that of **2** and **3**, although the effect of **9g** was moderate at the MTD (IR=55%). The oral absorption rates of compounds (**9g**) and (**29e**) were evaluated by the intestinal loop method.[18)] As a result, both compounds displayed high oral absorption rates of 99.8% (**9g**) and 99.9% (**29e**) compared with 87.2% of **3** and 6.2%[1)] of **4**. A fluoride atom of the phenyl ring on moiety A was considered to be essential for good oral absorption.

Furthermore, the antitumor activity of **29b** was evaluated for oral administration by employing human lung carcinoma PC-12 and PC-14 in nude mice. As shown in Table 3, compound **29b** exhibited significantly potent antitumor activity against PC-12 with a respective IR value of 70% at the MTD compared with that of vincristine (VCR) by intravenous injection, and the effect was almost equal to that of **3**. The tumor growth inhibition curves of **29b** and **3** are shown in Fig. 3. While the antitumor activity of **29b** against PC-14 was weak at the MTD (IR=38%), compound **3** and VCR showed more potent activity with IR values of 53% at the MTDs compared with that of **29b**.

Consequently, compound (**29b**) was selected for further evaluation against various drug-resistant cell lines.[19)] As shown in Table 4, compound (**29b**) did not show cross-resistance as indicated by the almost equal rates against all drug-resistant cell lines, while all reference drugs drastically decreased the *in vitro* activity against each drug resistant cell. Compound (**29b**) possessed high activity against solid tumors that were insensitive to some chemotherapeutic drugs.

Physico-chemical properties of compound (**29b**) were compared with those of compounds (**2**—**4**) (Table 5). Water solubility of both monohalogenated and dihalogenated compounds (**2**—**4**) were low at pH=6.8, whereas the appropriate amount could be dissolved at pH=1.1 because of the existence of piperazine. Especially, the dihalogenated compounds (**3**, **4**) showed poor water solubility compared with the monohalogenated compound (**2**). The logarithm of the distribution coefficient (LogD) of compound (**29b**) in *n*-octanol/water system was 2.9 while those of the mono and dihalogenated compounds (**2**—**4**) were more than 3.5 at pH=6.8. Introduction of a cyano group on the phenyl ring improved water solubility.

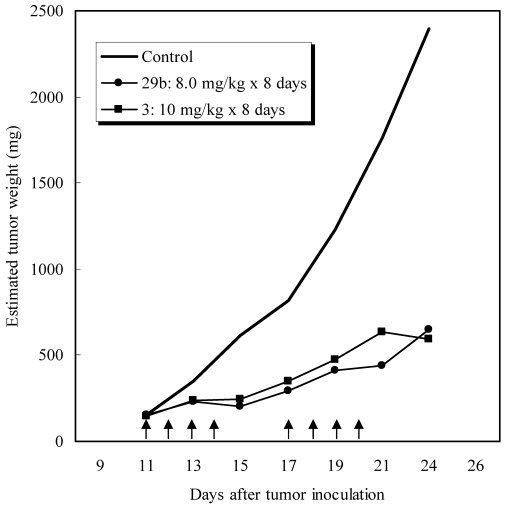


Fig. 3. Tumor Growth Inhibition Curves of **29b** and **3** against PC-12

Human non-small cell lung cancer PC-12 block was inoculated s.c. into BALB/cAnNCrj-nu mice (day 0). Compounds **29b** and **3** at the indicated doses were administered orally on days 11—14 and 17—20, consecutively.

Table 5. Physico-chemical Properties of 1-*trans*-Propene Derivatives

Compd. No.	Water solubility (μg/ml)		LogD[a] (pH=6.8)
	pH=1.1	pH=6.8	
2	86.0	16.9	>3.7
3	244.2	5.1	>3.6
4	77.7	1.6	>3.5
29b	307.1	107.4	2.9

a) The logarithm of the distribution coefficient (LogD) of compounds in *n*-octanol/water system.

In conclusion, the study on structural modifications of moieties A, B, and E in this scaffold **1** has resulted in the discovery of the 3-chloropyridin-2-yl compound (**9g**) and the 3-fluoro-5-substituted phenyl derivatives (**29b**, **c**, **e**), which showed strong *in vitro* cytotoxic activity. Among them, compound (**29b**) displayed potent antitumor activity in mice without causing undesirable effects by means of both intraperitoneal injection and oral administration. The mechanism of action for the cytotoxic activity of this scaffold was reported to be inhibition of tubulin polymerization.[20,21] Therefore, the tubulin polymerization inhibitory activity of **29b** was evaluated. As a result, compound (**29b**) displayed inhibition concentration values (IC_{50}) of 53 μM, suggesting that inhibition of tubulin polymerization contributes to expression of the activity. Further work to improve the activity and the mechanism of action in cells 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.

4-Acetyl-5-methyl-1-(2-pyridyl)pyrazole (6a) A mixture of pyridin-2-ylhydrazine (3.3 g, 30 mmol) and ethoxymethyleneacetylacetone[8] (4.7 g, 30 mmol) in EtOH (40 ml) was stirred at 70 °C for 1 h. The reaction mixture was cooled, and the precipitate obtained was filtered to give **6a** (4.6 g, 74%) as a pale yellow powder. Compounds **5b**—**k** were treated in the same manner as described above to give **6b**—**k**, respectively.

6a: Yield 74%, a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 2.51 (3H, s), 2.92 (3H, s), 7.32 (1H, t, J=5 Hz), 7.80 (1H, d, J=8 Hz), 7.88 (1H, t, J=8 Hz), 8.02 (1H, s), 8.53 (1H, d, J=5 Hz).

6b: Yield 90%, a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 2.51 (3H, s), 2.72 (3H, s), 7.46 (2H, d, J=6 Hz), 8.06 (1H, s), 8.78 (2H, d, J=6 Hz).

6c: Yield 55%, a colorless powder. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 2.95 (3H, s), 8.06 (1H, s), 8.47 (1H, dd, J=3, 2 Hz), 8.59 (1H, d, J=3 Hz), 9.23 (1H, d, J=2 Hz).

6d: Yield 64%, a red amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 2.51 (3H, s), 2.66 (3H, s), 7.77 (1H, br s), 8.24 (2H, br s).

6e: Yield 82%, a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 3.18 (3H, s), 7.40 (1H, t, J=8 Hz), 7.50 (1H, t, J=8 Hz), 7.86 (1H, d, J=8 Hz), 7.96 (1H, d, J=8 Hz), 8.03 (1H, s).

6f: Yield 63%, a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, s), 3.10 (3H, s), 7.60 (1H, t, J=7 Hz), 7.77 (1H, t, J=8 Hz), 7.88 (1H, d, J=8 Hz), 8.02 (1H, d, J=9 Hz), 8.06 (1H, s), 8.07 (1H, d, J=6 Hz), 8.32 (1H, d, J=7 Hz).

6g: Yield 65%, a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s), 2.52 (3H, s), 7.47 (1H, dd, J=8, 5 Hz), 7.97 (1H, dd, J=8, 2 Hz), 8.08 (1H, s), 8.56 (1H, dd, J=5, 2 Hz).

6h: Yield 74%, a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s), 2.52 (3H, s), 7.37 (1H, d, J=5 Hz), 8.08 (1H, s), 8.70 (1H, d, J=5 Hz), 8.84 (1H, s).

6i: Yield 28%, a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.53 (3H, s), 8.14 (1H, s), 8.7—8.8 (3H, m).

6j: Yield 64%, a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 2.97 (3H, s), 8.10 (1H, s), 8.79 (2H, s).

3-[4-(3-Chlorophenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyridyl)-4-1*H*-pyrazolyl]-1-propanone (8a) Paraformaldehyde (1.4 g, 46 mmol) and a solution of 1 N HCl/EtOH (11 ml) were added to a mixture of **6a** (2.3 g, 11 mmol) and **7a**[1,2] (2.6 g, 11 mmol) in EtOH (200 ml), and the mixture was heated to reflux for 2 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 **8a** (2.3 g, 50%) as a yellow amorphous solid. Compounds **6b**—**k** and **7a**—**c** were treated in the same manner as described above to give **8b**—**k**, respectively. The physical data for these compounds and yields are shown in Table 6.

3-[4-(3-Chlorophenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyridyl)-4-1*H*-pyrazolyl]-1-*trans*-propene Hydrochloride (9a) Sodium borohydride (0.55 g, 15 mmol) was added in small portions to a solution of **8a** (1.3 mg, 2.9 mmol) in anhydrous EtOH (70 ml) and THF (70 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 (0.83 g, 4.4 mmol) was added to a solution of the above product in anhydrous 1,4-dioxane (50 ml) and THF (50 ml), and the mixture was heated to reflux for 3.5 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=50/1) 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 **9a** (0.89 g, 70%) as a pale yellow powder. Compounds **8b**—**k** were treated in the same manner as described above to give **9b**—**k**, respectively. The physical data for these compounds and yields are shown in Table 7.

4-Iodo-1-(2-pyrimidinyl)pyrazole (11) Periodic acid (2.1 g), iodine (4.5 g), water (10 ml), and sulfuric acid (1.5 ml) were successively added to a solution of **10**[11] (6.2 g, 42 mmol) in acetic acid (51 ml), and the mixture was stirred at 65 °C for 2.5 h. The solvents were evaporated *in vacuo*, and water (90 ml) and $NaHCO_3$ (5.2 g) were added to the residue. The resulting precipitates were collected by filtration to give **11** (8.4 g, 73%) as a pale yellow solid: ^{1}H-NMR ($CDCl_3$) δ: 7.25 (1H, t, J=5 Hz), 7.83 (1H, s), 8.68 (1H, s), 8.76 (2H, d, J=5 Hz).

1-(2-Pyrimidinyl)-4-vinylpyrazole (12) 2,6-Di-*tert*-butyl-4-methylphenol (50 mg) was added to a mixture of **11** (2.0 g, 7.5 mmol), vinyltributylstannum (2.4 ml, 8.0 mmol), lithium chloride (1.0 g, 23 mmol), and tetrakis(triphenylphosphine)palladium (0) (0.18 g, 0.16 mmol) in 1,4-dioxane (38 ml), and the mixture was heated to reflux for 4 h. 10% Aqueous KF (20 ml) was added to the reaction mixture, and the mixture was stirred for 8 h at room temperature. The resulting precipitates were removed by filtration. The filtrate was diluted with AcOEt, and the solution was successively washed with water and brine, and then dried. Filtration and evaporation of the solvent afforded the crude mixture, which was chromatographed on a silica gel column (AcOEt/hexane=3/1) to give **12** (0.87 g, 68%) as a pale brown solid: ^{1}H-NMR ($CDCl_3$) δ: 5.24 (1H, dd, J=11, 1 Hz), 5.64 (1H, dd, J=18, 1 Hz), 6.61 (1H, dd, J=18, 11 Hz), 7.20 (1H, t, J=5 Hz), 7.94 (1H, s), 8.55 (1H, s), 8.74 (2H, d, J=5 Hz).

4-Acetyl-1-(2-pyrimidinyl)pyrazole (15a) Compound **12** (0.50 g, 2.9 mmol) was added to 35% aqueous sulfuric acid (15 ml), and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with ice-water and alkalized with $NaHCO_3$, and the whole was extracted with $CHCl_3$/MeOH (9/1). The organic layer was washed with brine and dried. After filtration and evaporation of the solvents, the crude mixture was chromatographed on a silica gel column (AcOEt/hexane=3/1) to afford the corresponding alcohol (0.12 g, 22%): ^{1}H-NMR ($CDCl_3$) δ: 1.58 (3H, d, J=7 Hz), 5.00 (1H, q, J=7 Hz), 7.21 (1H, t, J=5 Hz), 8.53 (1H, s), 7.93 (1H, s), 8.74 (2H, d, J=5 Hz).

The mixture of the above alcohol (0.12 g, 0.64 mmol) and manganese (IV) oxide (0.80 g, 9.2 mmol) was stirred for 12 h at room temperature. The reaction mixture was diluted with AcOEt, and the whole was filtered through a Celite pad. Removal of the solvent afforded **15a** (0.11 g, 92%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ: 2.54 (3H, s), 7.33 (1H, t, J=5 Hz), 8.22 (1H, s), 8.81 (2H, d, J=5 Hz), 9.09 (1H, s).

Table 6. Physical Data for Propanone Derivatives

Compd. No.	Yield (%)	^{1}H-NMR ($CDCl_3$) δ
8a	50	2.84 (3H, s), 3.1—3.3 (4H, m), 4—3.6 (4H, m), 3.6—3.7 (2H, m), 3.9—4.0 (2H, m), 6.88 (1H, d, *J*=8 Hz), 6.98 (1H, d, *J*=8 Hz), 7.08 (1H, s), 7.27 (1H, t, *J*=8 Hz), 7.51 (1H, t, *J*=5 Hz), 8.4 (1H, d, *J*=8 Hz), 8.08 (1H, t, *J*=8 Hz), 8.40 (1H, s), 8.58 (1H, d, *J*=5 Hz)
8b	31	2.73 (3H, s), 3.1—3.3 (4H, m), 3.5—4.0 (8H, m), 6.88 (1H, dd, *J*=8, 2 Hz), 6.99 (1H, dd, *J*=8, 2 Hz), 7.08 (1H, s), 7.27 (1H, t, *J*=8 Hz), 7.88 (2H, d, *J*=6 Hz), 8.52 (1H, s), 8.87 (2H, d, *J*=6 Hz)
8c	79	2.85 (3H, s), 3.1—3.4 (6H, m), 3.5—3.7 (4H, m), 3.8—4.0 (2H, m), 6.87 (1H, dd, *J*=8, 2 Hz), 6.98 (1H, dd, *J*=8, 2 Hz), 7.08 (1H, t, *J*=2 Hz), 7.27 (1H, dt, *J*=8, 2 Hz), 8.50 (1H, s), 8.66 (1H, dd, *J*=3, 2 Hz), 8.76 (1H, d, *J*=3 Hz), 9.16 (2H, d, *J*=2 Hz)
8d	14	2.53 (3H, s), 3.0—3.2 (4H, m), 3.2—3.4 (4H, m), 3.5—3.6 (2H, m), 3.6—3.8 (2H, m), 6.88 (2H, d, *J*=8 Hz), 6.98 (2H, d, *J*=8 Hz), 7.08 (1H, s), 7.27 (1H, t, *J*=8 Hz), 7.75 (1H, d, *J*=4 Hz), 8.25 (1H, d, *J*=4 Hz)
8e	37	2.67 (4H, t, *J*=5 Hz), 2.89 (2H, t, *J*=7 Hz), 3.08 (2H, t, *J*=7 Hz), 3.19 (3H, s), 3.22 (4H, t, *J*=5 Hz), 6.80 (2H, dt, *J*=8, 2 Hz), 6.88 (1H, t, *J*=2 Hz), 7.16 (1H, t, *J*=8 Hz), 7.41 (1H, t, *J*=8 Hz), 7.51 (1H, t, *J*=8 Hz), 8.87 (1H, d, *J*=8 Hz), 7.96 (1H, d, *J*=8 Hz), 8.09 (1H, s)
8f	49	3.04 (3H, s), 3.1—3.3 (4H, m), 3.5—3.6 (4H, m), 3.6—3.7 (2H, m), 3.9—4.0 (2H, m), 6.88 (1H, d, *J*=8 Hz), 7.00 (1H, d, *J*=8 Hz), 7.09 (1H, s), 7.27 (1H, t, *J*=8 Hz), 7.70 (1H, t, *J*=8 Hz), 7.87 (1H, t, *J*=8 Hz), 8.04 (1H, d, *J*=8 Hz), 8.06 (1H, d, *J*=9 Hz), 8.10 (1H, d, *J*=8 Hz), 8.49 (1H, s), 8.64 (1H, d, *J*=9 Hz)
8g	53	2.51 (3H, s), 2.66 (4H, t, *J*=5 Hz), 2.89 (2H, t, *J*=7 Hz), 3.08 (2H, t, *J*=7 Hz), 3.21 (4H, t, *J*=5 Hz), 6.3—6.4 (1H, m), 6.4—6.5 (2 H, m), 7.48 (1H, dd, *J*=8, 5 Hz), 7.97 (1H, dd, *J*=8, 2 Hz), 8.12 (1H, s), 8.56 (1H, dd, *J*=5, 2 Hz)
8h	36	2.47 (3H, s), 2.67 (4H, t, *J*=5 Hz), 2.90 (2H, t, *J*=7 Hz), 3.09 (2H, t, *J*=7 Hz), 3.22 (4H, t, *J*=5 Hz), 6.25 (1H, tt, *J*=9, 2 Hz), 6.36 (2H, dd, *J*=9, 2 Hz), 7.37 (1H, d, *J*=5 Hz), 8.13 (1H, s), 8.70 (1H, d, *J*=5 Hz), 8.84 (1H, s)
8i	24	2.37 (3H, s), 3.2—3.3 (4H, m), 3.5—3.6 (4H, m), 3.6—3.7 (2H, m), 3.9—4.1 (2H, m), 6.5—6.6 (1H, m), 6.7—6.8 (2H, m), 8.51 (1H, s), 8.99 (2H, s)
8j	24	2.84 (3H, s), 3.1—3.3 (4H, m), 3.3—3.6 (4H, m), 3.6—3.7 (2H, m), 3.9—4.1 (2H, m), 6.5—6.6 (1H, m), 6.74 (2H, d, *J*=9 Hz), 7.89 (1H, d, *J*=9 Hz), 8.19 (1H, dd, *J*=9, 3 Hz), 8.42 (1H, s), 8.63 (1H, d, *J*=3 Hz)
8k	62	2.54 (3H, s), 3.1—3.3 (4H, m), 3.4—3.5 (4H, m), 3.5—3.7 (2H, m), 3.9—4.1 (2H, m), 6.96 (1H, s), 7.08 (2H, s), 7.5—7.6 (5H, m), 8.36 (1H, s)
16a	58	2.67 (4H, t, *J*=5 Hz), 2.90 (2H, t, *J*=7 Hz), 3.10 (2H, t, *J*=7 Hz), 3.21 (4H, t, *J*=5 Hz), 6.7—6.8 (2H, m), 6.87 (1H, t, *J*=2 Hz), 7.16 (1H, t, *J*=8 Hz), 7.33 (1H, t, *J*=5 Hz), 8.24 (1H, s), 8.81 (2H, d, *J*=5 Hz), 9.13 (1H, s)
16b	36	2.63 (3H, s), 2.67 (4H, t, *J*=5 Hz), 2.89 (2H, t, *J*=7 Hz), 3.08 (2H, t, *J*=7 Hz), 3.21 (4H, t, *J*=5 Hz), 6.79 (2H, dt, *J*=8, 2 Hz), 6.87 (1H, t, *J*=2 Hz), 7.16 (1H, t, *J*=8 Hz), 7.28 (1H, t, *J*=5 Hz), 8.78 (2H, d, *J*=5 Hz), 9.08 (1H, s)
16c	32	2.58 (2H, t, *J*=5 Hz), 2.61 (3H, s), 2.66 (2H, t, *J*=5 Hz), 2.8—3.0 (1H, m), 2.91 (3H, s), 3.06 (1H, t, *J*=7 Hz), 3.1—3.3 (4H, m), 6.78 (1H, d, *J*=8 Hz), 6.81 (1H, d, *J*=8 Hz), 6.87 (1H, s), 7.16 (1H, t, *J*=8 Hz), 7.30 (1H, t, *J*=5 Hz), 8.84 (2H, d, *J*=5 Hz)
16d	48	2.88 (3H, s), 3.2—3.3 (4H, t, *J*=5 Hz), 3.4—3.5 (4H, m), 3.6—3.7 (2H, m), 4.0—4.1 (2H, m), 6.85 (1H, d, *J*=3 Hz), 6.94 (1H, s), 7.06 (2H, s), 7.52 (1H, t, *J*=5 Hz), 7.60 (1H, d, *J*=3 Hz), 8.91 (2H, d, *J*=5 Hz)
28a	26	2.83 (3H, s), 3.1—3.2 (4H, m), 3.5—3.6 (4H, m), 3.6—3.7 (2H, m), 3.9—4.0 (2H, m), 6.91 (1H, d, *J*=12 Hz), 7.02 (1H, d, *J*=8 Hz), 7.1—7.2 (1H, m), 7.66 (1H, t, *J*=5 Hz), 8.41 (1H, s), 9.00 (2H, d, *J*=5 Hz), 10.1—10.2 (1H, m)
28b	20	2.83 (3H, s), 3.1—3.3 (4H, m), 3.4—3.6 (4H, m), 3.65 (2H, d, *J*=11 Hz), 4.07 (2H, d, *J*=13 Hz), 7.1—7.2 (1H, m), 7.26 (1H, dt, *J*=13, 2 Hz), 7.3—7.4 (1H, m), 7.66 (1H, t, *J*=5 Hz), 8.42 (1H, s), 9.00 (2H, d, *J*=5 Hz), 10.7—10.8 (1H, m)
28c	32	2.5—2.6 (4H, m), 2.99 (3H, s), 3.0—3.2 (2H, t, *J*=7 Hz), 3.5—3.8 (4H, m), 6.55 (1H, dt, *J*=9, 2 Hz), 6.8—6.9 (2H, m), 7.39 (1H, t, *J*=5 Hz), 8.32 (1H, s), 8.88 (2H, d, *J*=5 Hz)
28d	30	2.6—2.7 (4H, m), 2.89 (2H, t, *J*=7 Hz), 3.00 (3H, s), 3.09 (2H, t, *J*=7 Hz), 3.2—3.3 (4H, m), 6.7—6.8 (1H, m), 6.8—6.9 (1H, m), 6.88 (1H, s), 7.35 (1H, t, *J*=5 Hz), 8.15 (1H, s), 8.86 (2H, d, *J*=5 Hz)
28e	32	2.6—2.6 (4H, m), 2.88 (2H, t, *J*=7 Hz), 3.00 (3H, s), 3.08 (2H, t, *J*=7 Hz), 3.2—3.3 (2H, m), 6.46 (1H, dt, *J*=12, 2 Hz), 6.53 (1H, dt, *J*=8, 2 Hz), 6.64 (1H, s), 7.35 (1H, t, *J*=5 Hz), 8.14 (1H, s), 8.86 (2H, d, *J*=5 Hz)

4-Acetyl-3-methyl-1-(2-pyrimidinyl)pyrazole (15b) The mixture of **13**[1,2] (0.40 g, 2.0 mmol), diethyl carbonate (0.40 ml), and NaH (0.16 g of 60% in mineral oil, 4.0 mmol) in toluene (180 ml) was heated to reflux for 3 h. The reaction mixture was poured into 10% hydrochloric acid, and the whole was extracted with AcOEt. The organic layer was washed with brine and dried. After filtration and evaporation of the solvents, the residue was recrystallized from ether to give **15b** (0.31 g, 78%) as a colorless powder: ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 2.63 (3H, s), 7.28 (1H, t, *J*=5 Hz), 8.78 (2H, d, *J*=5 Hz), 9.02 (1H, s).

3-Acetyl-2-methyl-1-(2-pyrimidinyl)pyrrole (15d) Compound **14**[14,15] (0.92 g, 7.5 mmol) was added to a suspension of KOH (2.0 g, 30 mmol) in DMSO (15 ml), and the reaction mixture was stirred at room temperature for 1 h. 2-Chloropyrimidine (1.0 g, 9.0 mmol) was added to the above reaction mixture, and the mixture was stirred for 20 h at room temperature. The reaction mixture was diluted with ice-water and the whole was extracted with AcOEt. The organic layer was washed with brine and dried. After filtration and evaporation of the solvents, the crude mixture was chromatographed on a silica gel column (hexane/AcOEt=2/1) to afford **15d** (1.2 g, 80%) as a colorless powder: ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s), 2.96 (3H, s), 6.62 (1H, d, *J*=3 Hz), 7.20 (1H, t, *J*=5 Hz), 7.58 (1H, d, *J*=3 Hz), 8.73 (2H, d, *J*=5 Hz).

3-[4-(3-Chlorophenyl)-1-piperazinyl]-1-[1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-propanone (16a) Mannich reaction of **16a**—**d** from **15a**—**d** with **7a**, **c** was performed as described for the synthesis of **8a**. The physical data for **16a**—**d** are shown in Table 6.

3-[4-(3-Chlorophenyl)-1-piperazinyl]-1-[1-(2-pyrimidinyl)-4-1*H*-pyrazolyl]-1-propene Hydrochloride (17a) Synthesis of **17a**—**d** from **16a**—**d** was performed as described for the synthesis of **9a**. The physical data for **17a**—**d** are shown in Table 7.

4-Ethoxycarbonyl-5-methyl-1-(2-pyrimidinyl)imidazole (19) The mixture of ethyl 4-methyl-5-imidazolecarboxylate (**18**, 20 g, 0.13 mmol), K_2CO_3 (18 g, 0.13 mol), and 2-chloropyrimidine (15 g, 0.13 mmol) in DMF (132 ml) was stirred at 100 °C for 6 h. 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=98/2) to give **19** (22 g, 73%) as a brown amorphous solid: ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, *J*=7 Hz), 2.93 (3H, s), 4.41 (2H, q, *J*=7 Hz), 7.31 (1H, t, *J*=5 Hz), 8.50 (1H, s), 8.77 (2H, d, *J*=5 Hz).

4-Formyl-5-methyl-1-(2-pyrimidinyl)imidazole (20) A solution of DIBAL (31 ml of a 1.0 M solution in hexane, 31 mmol) was added dropwise to a solution of **19** (4.7 g, 20 mmol) in anhydrous CH_2Cl_2 (50 ml) and THF (50 ml) at −78 °C, and the mixture was stirred for 2.5 h at −78 °C. The reaction mixture was poured into 1 N aqueous hydrochloric acid, and the whole was extracted with $CHCl_3$. The organic layer was washed with brine and dried. After filtration and evaporation of the solvents, the residue was crystallized from ether to give **20** (3.0 g, 80%) as a colorless powder: ^{1}H-NMR ($CDCl_3$) δ: 2.99 (3H, s), 7.34 (1H, t, *J*=5 Hz), 8.57 (1H, s), 8.79 (2H, d, *J*=5 Hz), 10.08 (1H, s).

2-[5-Methyl-4-[1-[(triethylsilyl)oxy]-3-butenyl]-1-1*H*-imidazolyl]-

Table 7. Physical Data for Pyrimidinylpyrazole 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
9a	70	199—204	2.66 (3H, s), 3.2—3.1 (4H, m), 3.6—3.5 (2H, m), 4.0—3.9 (4H, m), 6.19 (1H, dt, J=16, 7 Hz), 6.82 (1H, d, J=16 Hz), 6.87 (1H, dd, J=8, 2 Hz), 6.97 (1H, dd, J=8, 2 Hz), 7.05 (1H, s), 7.26 (1H, t, J=8Hz), 7.39 (1H, dd, J=5, 2 Hz), 7.83 (1H, d, J=8 Hz), 8.00 (1H, t, J=8 Hz), 8.04 (1H, s), 8.50 (1H, d, J=5 Hz)	1594 1474 1442 1119	$C_{22}H_{24}ClN_5$ 1.0HCl 0.5H_2O	394[a] 396 (M^+)	60.14 (60.76	5.97 5.98	15.94 15.92)
9b	67	195—200	2.60 (3H, s), 3.1—3.0 (4H, m), 3.5—3.4 (2H, m), 4.1—3.9 (4H, m), 6.27 (1H, dt, J=16, 8 Hz), 6.84 (1H, d, J=16 Hz), 6.88 (1H, t, J=8 Hz), 6.97 (1H, d, J=8 Hz), 7.06 (1H, s), 7.27 (1H, d, J=8 Hz), 8.01 (2H, d, J=6 Hz), 8.23 (1H, s), 8.86 (2H, d, J=6 Hz)	2316 1630 1600 1378	$C_{22}H_{24}ClN_5$ 2.0HCl 0.75H_2O	395 397 (M+H)	55.00 (55.36	5.77 5.94	14.57 14.21)
9c	13	197—199	2.66 (3H, s), 3.2—3.0 (2H, m), 3.4—3.2 (6H, m), 4.0—3.8 (2H, m), 6.24 (1H, dt, J=16, 7 Hz), 6.83 (2H, d, J=16 Hz), 6.87 (1H, dd, J=8, 2 Hz), 6.96 (1H, dd, J=8, 2 Hz), 7.05 (1H, t, J=2 Hz), 7.26 (1H, dt, J=8, 2 Hz), 8.14 (1H, s), 8.57 (1H, dd, J=3, 2 Hz), 8.63 (1H, d, J=3 Hz), 9.14 (2H, d, J=2 Hz)	1514 1432 1352 1296	$C_{21}H_{23}ClN_6$ 1.0HCl 0.5H_2O	395 397 (M+H)	57.28 (57.25	5.71 5.74	19.01 18.80)
9d	90	180—182	2.60 (3H, s), 3.2—3.1 (2H, m), 3.3—3.2 (4H, m), 3.6—3.4 (4H, m), 3.8—3.6 (2H, m), 6.32 (1H, dt, J=16, 8 Hz), 6.82 (1H, d, J=16 Hz), 6.85 (2H, d, J=8 Hz), 6.95 (2H, d, J=8 Hz), 7.03 (1H, s), 7.23 (1H, t, J=8 Hz), 7.74 (1H, d, J=3 Hz), 8.27 (1H, d, J=3 Hz)	1610 1574 1507 1454	$C_{20}H_{22}ClN_5S$ 1.0HCl 1.5H_2O 1.0EtOH	400 402 (M+H)	51.86 (51.69	6.33 6.44	13.75 13.47)
9e	91	206—210	2.84 (3H, s), 3.2—3.1 (4H, m), 3.6—3.5 (2H, m), 4.0—3.9 (4H, m), 6.29 (1H, dt, J=16, 8 Hz), 6.86 (1H, d, J=16 Hz), 6.88 (1H, d, J=8 Hz), 6.97 (1H, d, J=8 Hz), 7.06 (1H, s), 7.27 (1H, t, J=8 Hz), 7.43 (1H, t, J=8 Hz), 7.53 (1H, t, J=8 Hz), 7.92 (1H, d, J=8 Hz), 8.08 (1H, d, J=8 Hz), 8.24 (1H, s)	1660 1628 1592 1446	$C_{24}H_{24}ClN_5S$ 1.0HCl 0.2H_2O	450 452 (M+H)	58.82 (58.72	5.22 5.17	14.29 14.11)
9f	82	209—211	2.85 (3H, s), 3.3—3.1 (4H, m), 3.6—3.5 (2H, m), 4.0—3.9 (4H, m), 6.24 (1H, dt, J=16, 8 Hz), 6.87 (1H, d, J=16 Hz), 6.88 (1H, d, J=8 Hz), 6.97 (1H, d, J=8 Hz), 7.07 (1H, s), 7.27 (1H, t, J=8 Hz), 7.63 (1H, t, J=8 Hz), 7.82 (1H, t, J=8 Hz), 7.99 (1H, d, J=8 Hz), 8.05 (1H, d, J=8 Hz), 8.09 (1H, d, J=9 Hz), 8.16 (1H, s), 8.55 (1H, d, J=9 Hz)	1632 1598 1504 1480	$C_{26}H_{26}ClN_5$ 1.0HCl 1.0H_2O	444 446 (M+H)	62.64 (62.78	5.86 5.75	14.05 14.10)
9g	55	209—215	2.22 (3H, s), 3.0—3.3 (4H, m), 3.5—3.6 (2H, m), 3.8—4.0 (4H, m), 6.16 (1H, dt, J=16, 7 Hz), 6.57 (1H, t, J=9 Hz), 6.73 (2H, d, J=9 Hz), 6.78 (1H, d, J=16 Hz), 7.67 (1H, dd, J=5, 8 Hz), 8.00 (1H, s), 8.27 (1H, dd, J=8, 2 Hz), 8.60 (1H, dd, J=5, 2 Hz), 10.8—10.9 (1H, m)	1664 1586 1486 1116	$C_{22}H_{22}F_2ClN_5$ 1.0HCl	430 432 (M+H)	56.66 (56.84	4.96 5.01	15.00 14.80)
9h	33	120—124	2.21 (3H, s), 3.0—3.1 (2H, m), 3.2—3.3 (2H, m), 3.5—3.6 (2H, m), 3.9—4.0 (4H, m), 6.18 (1H, dt, J=16, 7 Hz), 6.57 (1H, t, J=9 Hz), 6.73 (2H, d, J=9 Hz), 6.79 (1H, d, J=16 Hz), 7.66 (1H, d, J=5 Hz), 8.05 (1H, s), 8.75 (1H, d, J=5 Hz), 8.93 (1H, s), 11.1—11.2 (1H, m)	1625 1500 1392 1114	$C_{22}H_{22}ClF_2N_5$ 1.0HCl 2.4H_2O	430 432 (M+H)	51.85 (51.98	5.50 5.23	13.74 13.77)
9i	35	195—207	2.15 (3H, s), 3.0—3.2 (4H, m), 3.5—3.6 (2H, m), 3.8—4.0 (4H, m), 6.18 (1H, dt, J=16, 7 Hz), 6.56 (1H, t, J=9 Hz), 6.72 (2H, d, J=9 Hz), 6.79 (1H, d, J=16 Hz), 8.12 (1H, s), 8.95 (2H, s), 10.5—10.6 (1H, m)	2968 2660 1628 1492	$C_{22}H_{21}Cl_2F_2N_5$ 1.0HCl 2.5H_2O	464 466 (M+H)	48.41 (48.72	4.99 5.06	12.83 12.60)
9j	79	191—200	2.64 (3H, s), 3.0—3.2 (4H, m), 3.4—3.6 (2H, m), 3.8—4.0 (4H, m), 6.19 (1H, dt, J=16, 7 Hz), 6.56 (1H, t, J=9 Hz), 6.72 (2H, d, J=9 Hz), 6.80 (1H, d, J=16 Hz), 7.87 (1H, d, J=9 Hz), 8.07 (1H, s), 8.11 (1H, dd, J=9, 3 Hz), 8.55 (1H, d, J=3 Hz), 10.6—10.7 (1H, m)	2924 1626 1480 1400	$C_{22}H_{22}ClF_2N_5$ 1.0HCl 0.25H_2O	430 432 (M+H)	56.12 (56.37	5.03 5.04	14.87 14.63)
9k	94	207—210	2.36 (3H, s), 3.0—3.2 (4H, m), 3.4—3.6 (2H, m), 3.9—4.0 (4H, m), 6.12 (1H, dt, J=16, 7 Hz), 6.78 (1H, d, J=16 Hz), 6.97 (1H, s), 7.06 (2H, s), 7.4—7.6 (5H, m), 7.95 (1H, s)	2847 1590 1504 1398	$C_{23}H_{24}Cl_2N_4$ 1.0HCl 0.25H_2O	429 431 (M+H)	58.99 (59.25	5.49 5.49	11.96 11.80)

Table 7. (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
17a	42	126—130	2.66 (4H, t, J=5 Hz), 3.20 (1H, d, J=7 Hz), 3.24 (4H, t, J=5 Hz), 6.18 (1H, dt, J=16, 7 Hz), 6.48 (1H, d, J=16 Hz), 6.7—6.8 (2H, m), 6.88 (1H, t, J=2 Hz), 7.16 (1H, t, J=8 Hz), 7.21 (1H, t, J=5 Hz), 7.92 (1H, s), 8.53 (1H, s), 8.75 (2H, d, J=5 Hz)	1660 1590 1574 1480	$C_{20}H_{21}ClN_6$ 2.0HCl 0.75H_2O 0.5EtOH	381 383 (M+H)	51.44 (51.53	5.65 5.74	17.14 16.84)
17b	49	144—149	2.38 (3H, s), 3.0—3.2 (4H, m), 3.55 (2H, d, J=7 Hz), 3.9—4.0 (4H, m), 6.30 (1H, dt, J=16, 7 Hz), 6.78 (1H, d, J=16 Hz), 6.88 (1H, dd, J=8, 2 Hz), 6.98 (1H, dd, J=8, 2 Hz), 7.0—7.1 (1H, m), 7.28 (1H, t, J=8 Hz), 7.47 (1H, t, J=5 Hz), 8.86 (2H, d, J=5 Hz), 8.87 (1H, s), 10.8—10.9 (1H, m)	1664 1594 1572 1378	$C_{21}H_{23}ClN_6$ 1.8HCl 0.75H_2O	395 397 (M+H)	53.21 (53.25	5.57 5.40	17.73 17.84)
17c	9	210—214	2.38 (3H, s), 2.63 (3H, s), 3.0—3.3 (4H, m), 3.5—3.6 (2H, m), 3.8—4.0 (4H, m), 6.07 (1H, dt, J=16, 8 Hz), 6.82 (1H, d, J=16 Hz), 6.87 (1H, dd, J=8, 1 Hz), 6.96 (1H, dd, J=8, 2 Hz), 7.05 (1H, dd, J=2, 1 Hz), 7.26 (1H, t, J=8 Hz), 7.49 (1H, t, J=5 Hz), 8.89 (2H, d, J=5 Hz)	1660 1596 1572 1398	$C_{22}H_{25}ClN_6$ 1.0HCl 0.5H_2O	410 412 (M+H)	58.15 (58.47	5.99 5.97	18.49) 17.94)
17d	37	207—213	2.65 (3H, s), 3.0—3.3 (4H, m), 3.4—3.6 (2H, m), 3.9—4.1 (4H, m), 6.00 (1H, dt, J=16 Hz), 6.54 (1H, t, J=2 Hz), 6.88 (1H, d, J=16 Hz), 6.95 (1H, d, J=3 Hz), 7.02 (2H, d, J=2 Hz), 7.38 (1H, t, J=5 Hz), 7.67 (1H, d, J=3 Hz), 8.81 (2H, d, J=5 Hz), 10.6—10.8 (1H, br s)	1650 1577 1554 1504	$C_{22}H_{23}Cl_2N_5$ 1.0HCl 0.25H_2O	428 430 (M+H)	56.30 (56.22	5.26 5.28	14.92 14.96)
23	27	132—136	2.64 (3H, s), 3.3—3.0 (6H, m), 4.1—4.0 (4H, m), 6.52 (1H, dt, J=16, 7 Hz), 6.6—6.5 (1H, m), 6.7—6.6 (2H, m), 6.95 (1H, d, J=16 Hz), 7.61 (1H, t, J=5 Hz), 8.95 (2H, d, J=5 Hz), 9.01 (1H, s), 11.27 (1H, br s)	1627 1535 1452 1199	$C_{21}H_{22}F_2N_6$ 2.0HCl 2.5H_2O	397 (M+H)	49.03 (48.87	5.68 5.66	16.34 16.46)
29a	46	205—211	2.63 (3H, s), 3.0—3.2 (4H, m), 3.5—3.6 (2H, m), 3.9—4.0 (4H, m), 6.21 (1H, dt, J=16, 7 Hz), 6.81 (1H, d, J=16 Hz), 6.89 (1H, d, J=13 Hz), 7.02 (1H, d, J=8 Hz), 7.17 (1H, s), 7.52 (1H, t, J=5 Hz), 8.08 (1H, s), 8.91 (2H, d, J=5 Hz), 10.5—10.6 (1H, m)	3096 2452 1570 1340	$C_{21}H_{22}FIN_6$ 1.0HCl 2.4H_2O	505 (M+H)	43.19 (42.98	4.80 5.11	14.39 14.46)
29b	22	210—212	2.63 (3H, s), 3.0—3.3 (4H, m), 3.5—3.6 (2H, m), 3.9—4.0 (2H, m), 4.0—4.1 (2H, m), 6.22 (1H, dt, J=16, 7 Hz), 6.81 (1H, d, J=16 Hz), 7.16 (1H, d, J=7 Hz), 7.24 (1H, d, J=13 Hz), 7.34 (1H, s), 7.53 (1H, t, J=5 Hz), 8.08 (1H, s), 8.92 (2H, d, J=5 Hz), 10.7—10.8 (1H, m)	2928 2456 1660 1574	$C_{22}H_{22}FN_7$ 1.0HCl 2.0H_2O	404 (M+H)	55.52 (55.57	5.72 5.50	20.06 20.63)
29c	29	197—200	2.63 (3H, s), 3.0—3.2 (4H, m), 3.5—3.6 (2H, m), 3.9—4.0 (4H, m), 6.21 (1H, dt, J=16, 7 Hz), 6.63 (1H, t, J=8 Hz), 6.81 (1H, d, J=16 Hz), 6.9—7.0 (2H, m), 7.03 (1H, s), 7.53 (1H, t, J=5 Hz), 8.09 (1H, s), 8.91 (2H, d, J=5 Hz), 10.3—10.4 (1H, m)	1606 1574 1434 1400	$C_{21}H_{22}N_6BrF$ 1.0HCl 0.75H_2O	457 459 (M+H)	49.72 (49.78	4.87 4.84	16.57 16.28)
29d	41	180—182	2.63 (3H, s), 3.0—3.3 (4H, m), 3.5—3.6 (2H, m), 3.9—4.0 (2H, m), 4.0—4.1 (2H, m), 6.21 (1H, dt, J=16, 7 Hz), 6.82 (1H, d, J=16 Hz), 6.9—7.0 (1H, m), 7.1—7.2 (2H, m), 7.53 (1H, t, J=5 Hz), 8.09 (1H, s), 8.92 (2H, d, J=5 Hz), 10.4—10.5 (1H, m)	2848 1660 1602 1434	$C_{22}H_{22}F_4N_6$ 1.0HCl 1.75H_2O	447 (M+H)	51.37 (51.43	5.19 4.89	16.34 16.16)
29e	52	200—203	2.63 (3H, s), 3.0—3.3 (4H, m), 3.5—3.6 (2H, m), 3.9—4.0 (4H, m), 6.22 (1H, dt, J=16, 7 Hz), 6.7—6.8 (1H, m), 6.81 (1H, d, J=16 Hz), 6.8—6.9 (1H, m), 6.91 (1H, s), 7.53 (1H, t, J=5 Hz), 8.08 (1H, s), 8.91 (2H, d, J=5 Hz), 10.7—10.8 (1H, m)	2924 2528 1610 1432	$C_{21}H_{22}ClFN_6$ 1.0HCl 1.5H_2O	413 (M+H)	52.95 (52.90	5.50 5.33	17.64 17.40)

a) FDMS.

pyrimidine (21) Allyl bromide (4.9 ml, 57 mmol) and metallic tin (2.2 g, 19 mmol) were added to a solution of **20** (3.0 g, 16 mmol) in THF (50 ml) and water (50 ml), and the mixture was sonicated for 2.5 h in an ultrasonic cleaning bath (Pasolina USC-1). The reaction mixture was carefully quenched with 1 N aqueous HCl (200 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 (2.8 g, 77%) as a colorless amorphous solid: ^{1}H-NMR ($CDCl_3$) δ: 2.5—2.8 (2H, m), 2.59 (3H, s), 4.75 (1H, dd, J=13, 7 Hz), 5.09 (1H, dd, J=10, 1 Hz), 5.16 (1H, dd, J=16, 1 Hz), 5.83 (1H, ddt, J=16, 10, 7 Hz), 7.21 (1H, t, J=5 Hz), 8.51 (1H, s), 8.71 (2H, d, J=5 Hz).

Imidazole (1.5 g, 22 mmol) and chlorotetraethylsilane (3.7 ml, 22 mmol) were added successively to a solution of the above alcohol (1.7 g, 7.3 mmol) in anhydrous DMF (10 ml) at 0 °C, and the mixture was stirred for 3.5 h at room temperature. Water (30 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** (2.9 g, quantitative yield) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 0.5—0.6 (6H, m), 0.8—1.0 (9H, m), 2.5—2.7 (2H, m), 2.62 (3H, s),4.79 (1H, t, J=7 Hz), 4.99 (1H, dt, J=10 Hz), 5.06 (1H, d, J=17 Hz), 5.79 (1H, ddt, J=17, 10, 7 Hz), 7.19 (1H, t, J=5 Hz), 8.46 (1H, s), 8.70 (2H, d, J=5 Hz).

3-[5-Methyl-1-(2-pyrimidinyl)-4-1*H*-imidazolyl]-3-[(triethylsilyl)oxy]propanal (22) 4-Methylmorpholine *N*-oxide (NMO, 1.3 g, 11 mmol) and a catalytic amount of osmium tetraoxide were added to a solution of **21** (1.9 g, 5.6 mmol) in THF (25 ml) and water (3.0 ml), and the mixture was stirred at room temperature for 4 h. A suspension of sodium periodate (5.9 g, 28 mmol) in water (25 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 **22** (0.23 g, 12%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 0.5—0.6 (6H, m), 0.9—1.0 (9H, m), 2.64 (3H, s), 2.87 (1H, ddd, J=16, 5, 2 Hz), 3.07 (1H, ddd, J=16, 8, 2 Hz), 5.31 (1H, dd, J=8, 5 Hz), 7.22 (1H, t, J=5 Hz), 8.48 (1H, s), 8.71 (2H, d, J=5 Hz), 9.86 (1H, t, J=2 Hz).

3-[4-(3,5-Difluorophenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-1*H*-imidazolyl]-1-*trans*-propene Hydrochloride (23) AcOH (15 μl, 1.3 mmol) and sodium cyanoborohydride (82 mg, 1.3 mmol) were added successively to a solution of **22** (89 mg, 0.26 mmol) and **7b** (0.25 g, 1.3 mmol) in EtOH (10 ml), and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with $CHCl_3$, 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=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 **23** (28 mg, 27%) as a colorless powder. The physical data for **23** are shown in Table 7.

1-Cyano-3-fluoro-5-nitrobenzene (24b) CuCN (5.0 g, 56 mmol) was added to a solution of 1-fluoro-3-iodo-5-nitrobenzene (**24a**, 15 g, 56 mmol) in DMF (120 ml), and the mixture was heated to reflux for 3 h. The mixture was diluted with ether, successively washed with 1 N aqueous HCl, water, and brine, and then dried. Evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column (hexane/AcOEt=50/3) to give **24b** (8.0 g, 86%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 7.73 (1H, dd, J=7, 2 Hz), 8.21 (1H, dt, J=8, 2 Hz), 8.3—8.4 (1H, m).

3-Fluoro-5-iodoaniline (25a) The suspension of 1-fluoro-3-iodo-5-nitrobenzene (**24a**, 2.0 g, 7.5 mmol) and $SnCl_2 \cdot 2H_2O$ (6.0 g, 26 mmol) in EtOH (30 ml) was heated to reflux for 1.5 h. After removal of the solvent, the crude mixture was diluted with ether, washed with 4 N aqueous NaOH and brine, and dried. Evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column (hexane/AcOEt=9/1) to give **25a** (8.0 g, 86%) as an orange oil: ^{1}H-NMR ($CDCl_3$) δ: 3.7—3.8 (2H, m), 6.32 (1H, dt, J=11, 2Hz), 6.7—6.9 (1H, m), 6.9—7.0 (1H, m).

3-Cyano-5-fluoroaniline (25b) Compound **24b** (14 g, 85 mmol) was dissolved in EtOH (850 ml) and hydrogenated with 10% Pd/C (5.0 g) under H_2 atmosphere for 2 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 (hexane/AcOEt=4/1) to give **25b** (8.5 g, 74%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 4.0—4.1 (2H, m), 6.56 (1H, dt, J=10, 2 Hz), 6.6—6.7 (2H, m).

1-(3-Fluoro-5-iodophenyl)piperazine (27a) A mixture of **25a** (1.4 g, 6.0 mmol) and bis(2-chloroethyl)amine hydrochloride (1.1 g, 6.1 mmol) in *n*-BuOH (15 ml) was refluxed for 45 h. Anhydrous sodium carbonate (0.83 g, 6.0 mmol) was added to the mixture. After being stirred for 26 h, the reaction mixture was diluted with $CHCl_3$, successively washed with 1 N aqueous NaOH, water, and brine, and then dried. Evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column ($CHCl_3$/MeOH=20/1) to give **27a** (0.53 g, 28%) as an orange oil. Compounds **25b**—**d** were treated in the same manner as described above to give **27b**—**d**, respectively.

27a: Yield 28%, an orange oil. ^{1}H-NMR ($CDCl_3$) δ: 3.0—3.1 (4H, m), 3.1—3.2 (4H, m), 6.52 (1H, dd, J=12, 2 Hz), 6.87 (1H, dd, J=7, 2 Hz), 6.9—7.0 (1H, m).

27b: Yield 23%, a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 3.0—3.1 (4H, m), 3.1—3.2 (4H, m), 6.75 (1H, d, J=2 Hz), 6.7—6.8 (1H, m), 6.9—7.0 (1H, m).

27c: Yield 19%, a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 3.00 (4H, dd, J=5, 3 Hz), 3.14 (4H, dd, J=5, 3 Hz), 6.50 (1H, dt, J=12, 2 Hz), 6.68 (1H, dt, J=8, 2 Hz), 6.79 (1H, s).

27d: Yield 30%, a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 3.0—3.1 (4H, m), 3.2—3.3 (4H, m), 6.71 (1H, dd, J=12, 2 Hz), 6.74 (1H, dd, J=10, 2 Hz), 6.8—6.9 (1H, m).

1-(3-Chloro-5-fluorophenyl)piperazine (27e) Piperazine (25 g, 0.29 mol), dichlorobis(tri-*o*-tolylphosphine)palladium (1.7 g, 2.2 mmol), and sodium *tert*-butoxide (9.6 g, 0.10 mol) were added to a solution of 1-bromo-3-chloro-5-fluorobenzene (**26**, 15 g, 72 mmol) in toluene (350 ml), and the mixture was stirred at 100 °C for 38 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=93/7) to afford **27e** (5.7 g, 37%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ: 2.8—3.2 (4H, m), 3.0—3.3 (4H, m), 6.46 (1H, dt, J=12, 2 Hz), 6.53 (1H, dt, J=8, 2 Hz), 6.6—6.7 (1H, m).

3-[4-(3-Fluoro-5-iodophenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-(1*H*)-pyrazolyl]-1-propanone (28a) Synthesis of **28a**—**e** from **27a**—**e** with **13** was performed as described for the synthesis of **8a**. The physical data for **28a**—**e** are shown in Table 6.

3-[4-(3-Fluoro-5-iodophenyl)-1-piperazinyl]-1-[5-methyl-1-(2-pyrimidinyl)-4-(1*H*)-pyrazolyl]-1-*trans*-propene Hydrochloride (29a) Synthesis of **29a**—**e** from **28a**—**e** was performed as described for the synthesis of **9a**. The physical data for **29a**—**e** are shown in Table 7.

***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,[19] 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.[22]

Evaluation of Therapeutic Effect *in Vivo* 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. Human non-small cell lung cancer PC-12 and PC-14 blocks were inoculated s.c. into BALB/cAnNCrj-nu mice (day 0). Compounds at the indicated doses were administered *per os* (oral) administration (*p.o.*) on days 11—14 and 17—20, or on days 14—17 and 21—24. VCR was administrated i.v. on day 11 or 14, once. The tumor growth-inhibition rate (IR) was calculated by the formula: IR (%)=(1−TWt/TWc)×100 (%), where TWt represents the mean tumor weight of a treated group, and TWc represents that of the control group. To evaluate the intensity of the side effects of the 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.

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