Synthesis and Antitumor Activity of Fused Quinoline Derivatives. IV.[1a-d] Novel 11-Aminoindolo[3,2-*b*]quinolines

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Indolo[3,2-*b*]quinoline derivatives (1) having various amine moieties were prepared and their antitumor activities against P388 leukemia in mice were evaluated, for the purpose of gaining an insight into the role of the amine moiety in the antitumor activity and searching for an effective amine moiety. Introduction of a methylene group between the phenyl group and amino or methanesulfonamido group resulted in decrease or loss of activity.

Key words indolo[3,2-*b*]quinoline; synthesis; antitumor activity; structure–activity relationship; quinone diimine

We have previously synthesized novel fused tri- and tetracyclic quinoline derivatives having an amine moiety as a side chain.[1a-d] This work led to the development of an indolo[3,2-*b*]quinoline derivative (**1**, Fig. 1), having an *N*-[3-(*N*,*N*-dimethylamino)propyl]amino or *N*-[2-methoxy-4-(methanesulfonamido)phenyl]amino group at the 11 position, which has potent antitumor activity.

The present investigation was focused on the development of indoloquinoline derivatives with more an effective amine moiety than the *N*-[2-methoxy-4-[(methanesulfonamido)phenyl]]amino group. Furthermore, we attempted to clarify the role of the amine in the antitumor activity. This paper describes the synthesis, antitumor activity, and structure–activity relationship of novel indolo[3,2-*b*]-quinoline derivatives (**1**) having various amine moieties at the 11 position of the chromophore.

Synthesis As shown in Table 1, indolo[3,2-*b*]quinoline derivatives (**1**) were prepared by coupling reaction of 11-chloroindolo[3,2-*b*]quinoline (**2**)[2] with various amines (**3**). In the case of oily **3**, heating of **2** and excess amine (**3b, c**) readily gave **1b, c** (method A). However, in the preparation of **1g, j, n—q, y** by heating of **2** with 1 or 2 eq of crystalline amine (**3g, j, n—q, y**) in 2-ethoxyethanol, the reaction was very sluggish. The addition of a few drops of concentrated hydrochloric acid to the reaction mixture was effective for accelerating the reaction to give **1g, j, n—q, y** (method B). Hydrochloric acid may increase the electrophilicity of the carbon atom at the 11 position by protonation of the nitrogen atom at the 5 position.

Compound **1d** was obtained by methanesulfonylation of **1c** (Chart 1). Compound **1f** was synthesized *via* **1e** starting from **1c** according to the method used for the synthesis of cimetidine[3] (Chart 1). Compound **1i** was obtained by catalytic hydrogenation on palladium-carbon (Pd/C) of **1g**, followed by methanesulfonylation. In the preparation of **1m** starting from **1j**, several attempts to reduce the nitro group of **1j** to an amino group by using catalytic hydrogenation on Pd/C, tin with hydrochloric acid, or zinc with acetic acid failed and resulted in the formation of the debenzylated compound (**1k**). However, treatment of **1j** with $NaBH_4$[4] in the presence of $NiCl_2$ successfully afforded **1l**, which was derived to the desired product **1m** by methanesulfonylation (Chart 1).

Compounds **1s—x**, which are congeners in which the

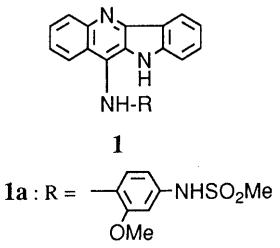
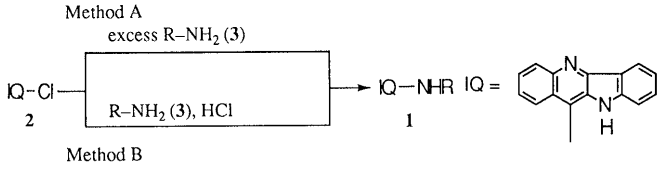
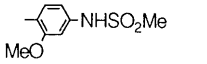
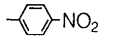
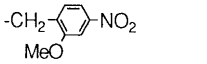
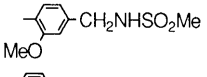
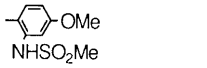
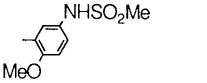
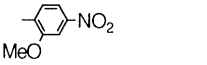


Fig. 1. Indoloquinoline Derivative

Table 1. Coupling Reaction of 11-Chloroindoloquinoline (**2**) with Amines (**3**)



Compd. No.	Amine (3) R	Method	Indoloquinoline (1)
3a		B	1a
3b	-$(CH_2)_3NMe_2$	A	1b
3c	-$(CH_2)_3NH_2$	A	1c
3g		B	1g
3j		B	1j
3n		B	1n
3o		B	1o
3p		B	1p
3q		B	1q

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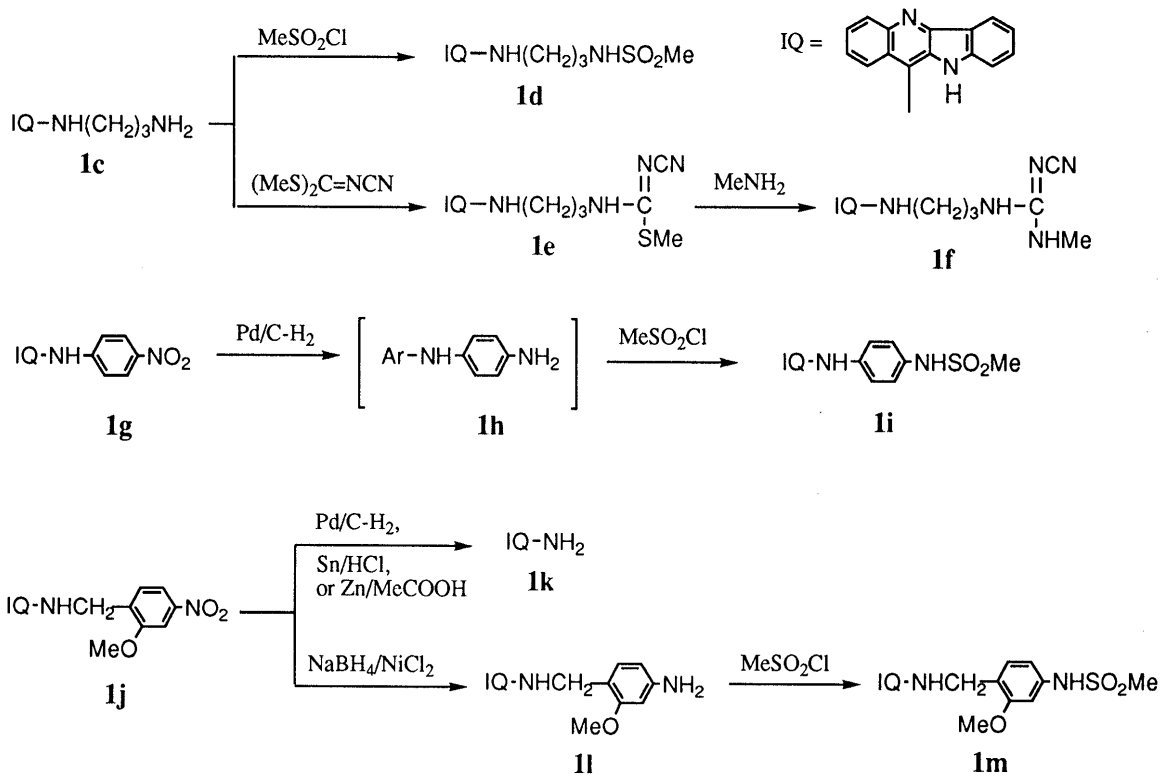


Chart 1

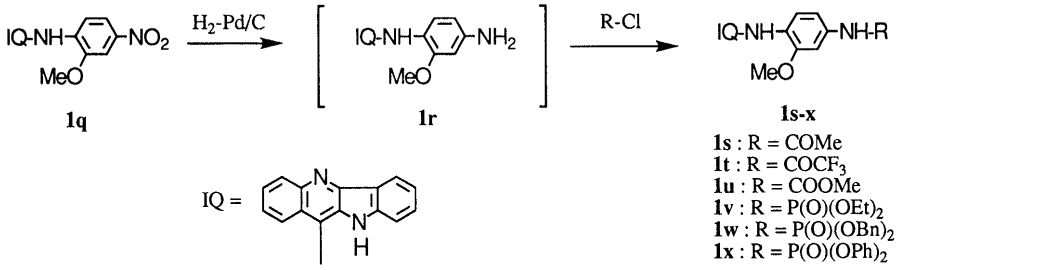


Chart 2

methanesulfonamido group of **1a** is replaced by various acylamino groups, were prepared by acylation of the amino derivative (**1r**) prepared from the nitro derivative (**1q**) (Chart 2). Introduction of acetyl, trifluoroacetyl, methoxycarbonyl, and dialkylphosphoryl groups onto the amino group of **1q** gave the corresponding derivatives (**1s—x**).

In the preparation of some indolo[3,2-*b*]quinoline derivatives (**1j, n—p**), various amines (**3j, n—p**), which were unknown in the literature, were synthesized by the routes shown in Chart 3. The amine (**3j**), having a methylene group between the benzene ring and amino group, was prepared by selective reduction of the amido group of **6j** while keeping the coexisting nitro group intact, by using borane methylsulfide complex (BMS).[5] The amine (**3n**), having a methylene group between the benzene ring and methanesulfonamido group, was prepared *via* **5n**, which was through synthesized to apply the selective reduction of **4n**. Compounds **3o** and **3p** were prepared by using an acetyl group as a protecting group of for the amino group.

Antitumor Activities and Discussion

The novel indolo[3,2-*b*]quinolines (**1**) listed in Table 2 were tested for antitumor activity against leukemia P388 in mice (Table 2).

Derivatives having an aliphatic amino moiety were not effective. Compound **1b** having a basic amino group (like nitracrine), compound **1d** having methanesulfonamide group (like **1a**), and compound **1f** having a weakly acidic imino group (like cimetidine) were inactive. The methoxy group in the anilino group was important for the antitumor activity. Compound **1i** exhibited lower activity than **1a**. Activity seems to require an anilino group binding directly to the methanesulfonamido group at the 4 position. Compound **1j**, in which a methylene group is inserted between the amino group and benzene ring of **1a**, exhibited no activity and compound **1n**, in which a methylene group is inserted between the benzene ring and methanesulfonamide group, exhibited low activity. Compounds **1o, p** having methoxy and methansulfonamide groups at different positions from those of **1a** were inactive. Replacement of the methanesulfonamide with other groups was possible with retention of activity. Compounds **1s, t** having a carboxamido group, compound **1u** having a carbamate group, and compounds **1v—x** having phosphoramide exhibited potent activity. Consequently, we conclude that an essential structure of amine moiety for the appearance

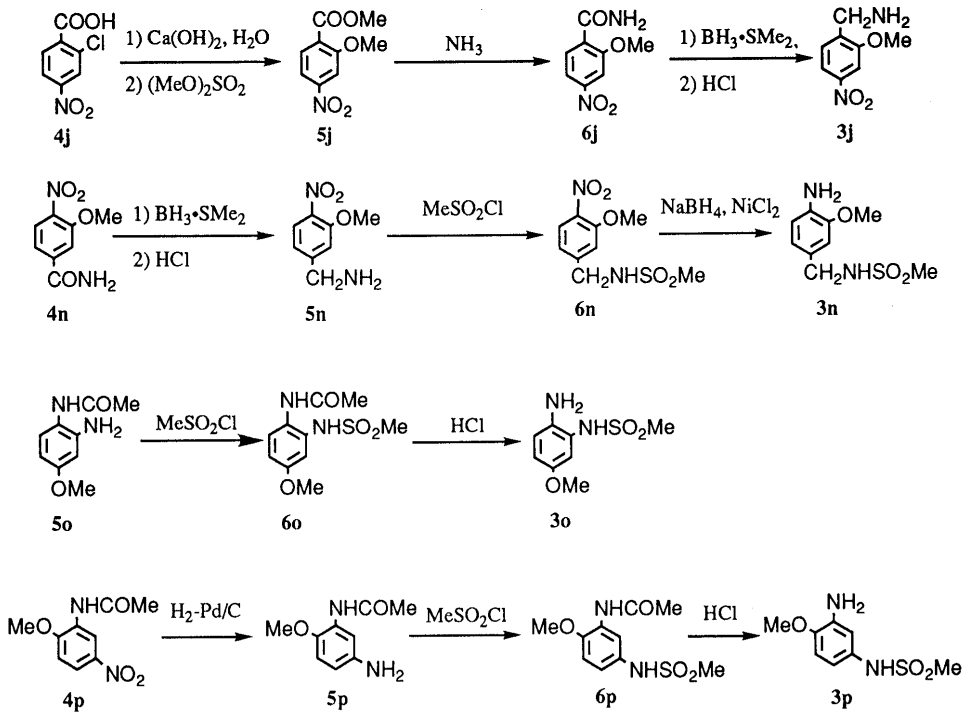
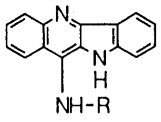
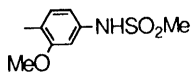
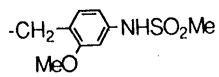
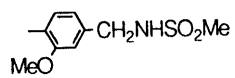
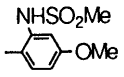


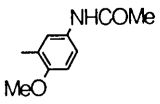
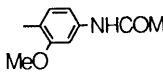
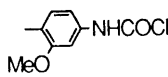
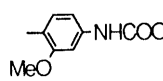
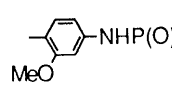
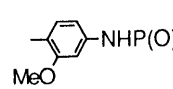
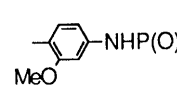
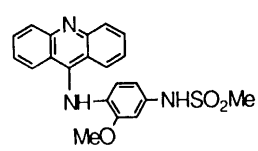
Chart 3

Table 2. Antitumor Activity of Indoloquinoline (**1**)

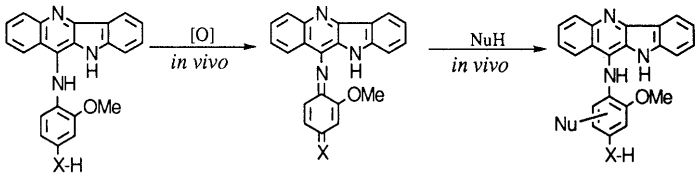


1

Compd.	R	Antitumor act. P388 in mice Dose, mg/kg ip.[a]	% (T/C)[b]
1a		12.5	203
		6.3	300
		3.1	172
1b	$-(CH_2)_3NMe_2$	Inactive[c]	
1d	$-(CH_2)_3NHSO_2Me$	Inactive	
1f	$-(CH_2)_3NHC(NHMe)=NCN$	Inactive	
1i		50	213
		25	172
		12.5	168
1j		Inactive	
1n		50	96
		25	118
		12.5	137
1o		Inactive	

Compd.	R	Antitumor act. P388 in mice Dose, mg/kg ip.	% (T/C)
1p		Inactive	
1s		200	76
		100	240
		50	260
1t		50	237
		25	175
		12.5	139
1u		50	221
		25	266
		12.5	288
1v		50	326
		25	200
		12.5	169
1w		50	330
		25	198
		12.5	154
1x		50	153
		25	154
		12.5	150
AMSA		40	223
		20	198
		10	174

a) The dose listed was given once a day at days 1 and 5. *b*) T/C > 120%, active. *c*) Dose: 400 mg/kg.



1a : X = NSO_2Me
1s-x : X = N-acyl

Quinone Diimine

Chart 4

of antitumor activity is an anilino group having an NH group at the 4 position.

The results of the structure–activity relationship study on the amine moiety of indoloquinoline derivatives were not essentially different from those obtained by Denny and co-workers in the amsacrine (AMSA) studies.[6a,b] In particular, our finding of antitumor activity of compounds **1j, n** supports Denny's suggestion concerning with the role of the amine moiety in the antitumor activity.[6b] We consider that the effective metabolites of the antitumor-active derivatives of this series would be the compounds having a quinone diimine formed from **1a, s—x** by oxidation *in vivo*; they would undergo 1,4-addition with a nucleophile *in vivo* (Chart 4).

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. Mass spectra (MS) were recorded on a VG-70SE spectrometer. ^{1}H-NMR spectra were run on a Hitachi R-1500 (60 MHz) or a Varian VXR-500 (500 MHz) spectrometer. Merck silica gel 60 (230—400 mesh) was employed for column chromatography.

11-(3-*N*,*N*-Dimethylaminopropyl)amino-10*H*-indolo[3,2-*b*]quinoline (1b) A mixture of 11-chloro-10*H*-indolo[3,2-*b*]quinoline[2] (**2**, 800 mg, 3.2 mmol) and 3-*N*,*N*-dimethylpropanediamine (**3b**, 10 ml) was heated at reflux for 24 h. The mixture was poured into ice water, and the resulting precipitates were collected by filtration and recrystallized from $CHCl_3$ to give 1.0 g (100%) of **1b** as yellow crystals, mp 195—197 °C. IR (Nujol) cm^{-1}: 3360, 3320. ^{1}H-NMR ($CDCl_3$) δ: 1.58—2.08 (2H, m, $CH_2C\underline{H}_2CH_2NMe_2$), 2.35 (each 3H, s, $C\underline{H}_3 \times 2$), 2.46—2.87 (2H, m, $CH_2CH_2C\underline{H}_2NMe_2$), 3.60—3.98 (2H, m, $C\underline{H}_2CH_2CH_2NMe_2$), 7.01—7.71 (5H, m, Ar-H), 7.71—8.60 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 319 $[(M+1)^+]$. *Anal.* Calcd for $C_{20}H_{22}N_4$: C, 75.44; H, 6.96; N, 17.60. Found: C, 75.48; H, 7.21; N, 17.31.

11-(3-Aminopropyl)amino-10*H*-indolo[3,2-*b*]qulinoline (1c) A mixture of **2** (300 mg, 1.2 mmol), 1,3-propanediamine (0.5 ml, 6 mmol), and 1 drop of concentrated HCl was heated at reflux in 2-ethoxyethanol (3 ml) for 15 h. The mixture was poured into ice water, then made basic with a 10% KOH solution and extracted with CH_2Cl_2. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. After removal of the solvent, the residue was washed with petroleum ether to give 350 mg (100%) of **1c** as yellow crystals, mp 129—131 °C. ^{1}H-NMR ($CDCl_3$ and 3 drops of DMSO-d_6) δ: 1.70—2.25 (2H, m, $CH_2C\underline{H}_2CH_2NMe_2$), 2.77—3.09 (2H, m, $CH_2CH_2C\underline{H}_2NMe_2$), 3.77—4.12 (2H, m, $C\underline{H}_2CH_2CH_2NMe_2$), 5.05 (3H, br, $N\underline{H}_2$, N<u>H</u>), 7.03—7.72 (5H, m, Ar-H), 7.94—8.49 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 291 $[(M+1)^+]$. *Anal.* Calcd for $C_{18}H_{18}N_4$: C, 74.46; H, 6.25; N, 19.30. Found: C, 74.48; H, 6.21; N, 19.31.

11-(2-Methoxy-4-nitrobenzyl)amino-10*H*-indolo[3,2-*b*]quinoline (1j) (General Procedure) A mixture of **2** (720 mg, 3 mmol) and the hydrochloride of **3j** (650 mg, 3 mmol) was heated at reflux in 2-ethoxyethanol (10 ml) for 5 h. The resulting precipitates were collected by filtration, dissolved in a saturated $KHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. The solvent was removed to give 460 mg (40%) of **1j** as yellow crystals, mp 266—270 °C (dec.). IR (Nujol) cm^{-1}: 3400. ^{1}H-NMR ($CDCl_3$) δ: 3.59 (3H, s, $OC\underline{H}_3$), 4.74—4.97 (2H, m, $C\underline{H}_2$), 7.13—7.63 (9H, m, Ar-H), 7.93—8.45 (4H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 399 $[(M+1)^+]$. *Anal.* Calcd for $C_{23}H_{18}N_4O_3$: C, 69.34; H, 4.55; N, 14.06. Found: C, 69.12; H, 4.38; N, 14.27.

11-(4-Nitrophenyl)amino-10*H*-indolo[3,2-*b*]quinoline (1g) Free base **1g**, yellow crystals, mp 211—213 °C (dec.). ^{1}H-NMR (CF_3COOD) δ: 6.83 (2H, d, J=9 Hz, 2′-H, 6′-H), 7.23—8.55 (10H, m, Ar-H). *Anal.* Calcd for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81. Found: C, 71.37; H, 4.06; N, 15.66.

***N*-[4-(10*H*-Indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxybenzyl]-methanesulfonamide (1n)** Free base **1n**, yellow crystals, mp 186—189 °C. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6 + D_2O) δ: 2.79 (3H, s, $SO_2C\underline{H}_3$), 3.91 (3H, s, $OC\underline{H}_3$), 4.08 (2H, s, $C\underline{H}_2$), 6.01—7.90 (8H, m, Ar-H), 7.90—8.52 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 447 $[(M+1)^+]$. *Anal.* Calcd for $C_{24}H_{22}N_4O_3S$: C, 64.56; H, 4.97; N, 12.55. Found: C, 64.30; H, 4.92; N, 12.70.

***N*-[2-(10*H*-Indolo[3,2-*b*]quinolon-11-yl)amino-5-methoxyphenyl]-methanesulfonamide (1o)** Free base **1o**, yellow crystals, mp 180 °C (dec.). ^{1}H-NMR (DMSO-d_6 + D_2O) δ: 3.13 (3H, s, $SO_2C\underline{H}_3$), 3.82 (3H, s, $OC\underline{H}_3$), 6.77 (1H, d, J=2 Hz, 6′-H), 7.12—7.80 (7H, m, Ar-H), 8.13—8.61 (3H, m, Ar-H). *Anal.* Calcd for $C_{23}H_{20}N_4O_3S$: C, 63.87; H, 4.66; N, 12.95. Found: C, 63.83; H, 4.91; N, 13.01.

***N*-[3-(10*H*-Indolo[3,2-*b*]quinolon-11-yl)amino-4-methoxyphenyl]-methanesulfonamide (1p)** Free base **1p**, yellow crystals, mp 300 °C (dec.). IR (Nujol) cm^{-1}: 3420, 3390. ^{1}H-NMR (CF_3COOD) δ: 3.28 (3H, s, $SO_2C\underline{H}_3$), 4.04 (3H, s, $OC\underline{H}_3$), 7.24—7.63 (7H, m, Ar-H), 7.75—8.57 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 433 $[(M+1)^+]$. *Anal.* Calcd for $C_{23}H_{20}N_4O_3S$: C, 63.87; H, 4.66; N, 12.95. Found: C, 63.83; H, 5.11; N, 12.01.

11-*N*-(2-Methoxy-4-nitrophenyl)amino-10*H*-indolo[3,2-*b*]quinoline (1q) Free base **1q**, yellow crystals, mp 276—277 °C. IR (Nujol) cm^{-1}: 3390, 3340. ^{1}H-NMR (CF_3COOD) δ: 4.21 (3H, s, $OC\underline{H}_3$), 7.02—8.53 (11H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 385 $[(M+1)^+]$. *Anal.* Calcd for $C_{22}H_{16}N_4O_3$: C, 68.74; H, 4.20; N, 14.58. Found: C, 68.73; H, 4.17; N, 14.20.

***N*-[3-[(10*H*-Indolo[3,2-*b*]quinolin-11-yl)amino]propyl]methanesulfonamide (1d)** Methanesulfonyl chloride (0.3 ml, 3.9 mmol) was added dropwise to a solution of **1c** (1.0 g, 3.5 mmol) in dry pyridine (5 ml) at 0 °C. The mixture was stirred for 1 h at room temperature, poured into ice water, made basic with a saturated $KHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from EtOH to give 900 mg (70%) of **1d** as yellow crystals, mp 217—218 °C. IR (Nujol) cm^{-1}: 3340. ^{1}H-NMR (pyridine-d_5 + D_2O) δ: 1.90—2.35 (2H, m, $CH_2C\underline{H}_2CH_2NMe_2$), 3.02 (3H, s, $SO_2C\underline{H}_3$), 3.46 (2H, t, J=7 Hz, $CH_2CH_2C\underline{H}_2NMe_2$), 4.25 (2H, t, J=7 Hz, $C\underline{H}_2CH_2CH_2NMe_2$), 6.55 (2H, br, $N\underline{H} \times 2$), 7.50—8.15 (5H, m, Ar-H), 8.25—9.43 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 369 $[(M+1)^+]$. *Anal.* Calcd for $C_{19}H_{20}N_4O_2S$: C, 61.94; H, 5.47; N, 15.21. Found: C, 61.95; H, 5.43; N, 15.22.

[1-[3-[(10*H*-indolo[3,2-*b*]quinolin-11-yl)amino]propyl]-2-methylthioisoureido]carbonitrile (1e) Dimethyl *N*-cyanodithioiminocarbonate (1.1 g, 6.7 mmol) was added dropwise to a solution of **1c** (1.30 g, 6.7 mmol) in EtOH (3 ml). The mixture was stirred at room temperature for 12 h. The resulting precipitates were collected by filtration and recrystallized from EtOH to give 820 mg (46%) of **1e** as yellow crystals, mp 194—196 °C. IR (Nujol) cm^{-1}: 3270, 2190. ^{1}H-NMR ($CDCl_3$ and 3 drops of DMSO-d_6) δ: 1.83—2.47 (2H, m, $CH_2C\underline{H}_2CH_2NMe_2$), 2.70—3.69 (2H, m, $CH_2CH_2C\underline{H}_2NMe_2$), 3.60 (3H, s, $SC\underline{H}_3$), 3.91—4.42 (2H, m, $C\underline{H}_2CH_2CH_2NMe_2$), 7.30—8.09 (5H, m, Ar-H), 8.10—8.83 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 389 $[(M+1)^+]$. *Anal.* Calcd for $C_{21}H_{20}N_6S$: C, 64.93; H, 5.19; N, 21.63. Found: C, 64.86; H, 5.32; N, 21.40.

[1-[3-[(10*H*-indolo[3,2-*b*]quinolin-11-yl)-amino]propyl]-3-methyl-2-guanidido]carbonitrile (1f) A mixture of **1e** (450 mg, 1.2 mmol) and 40%

$MeNH_2$ methanolic solution (10 ml) was stirred at 0 °C for 12 h. After removal of MeOH, the residue was recrystallized from CH_3CN to give 410 mg (93%) of **1f** as yellow crystals, mp 155—160 °C. IR (Nujol) cm^{-1}: 3410, 3280, 2170. ^{1}H-NMR (pyridine-d_5 : D_2O = 1 : 1) δ: 1.54—2.07 (2H, m, $CH_2CH_2CH_2NMe_2$), 2.64 (3H, s, NCH_3), 3.06—3.62 (2H, m, $CH_2CH_2CH_2NMe_2$), 3.64—3.94 (2H, m, $CH_2CH_2CH_2NMe_2$), 6.87—7.57 (5H, m, Ar-H), 7.98—8.80 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 372 [(M+1)$^+$]. *Anal.* Calcd for $C_{21}H_{21}N_7$: C, 67.91; H, 5.70; N, 26.40. Found: C, 68.06; H, 5.32; N, 26.20.

***N*-[4-(10*H*-Indolo[3,2-*b*]quinolin-11-yl)aminophenyl]methansulfonamide (1i)** A mixture of **1g** (490 mg, 1.4 mmol), MeOH (30 ml), and THF (20 ml) was hydrogenated over 10% Pd/C (10%, 500 mg) at atmospheric pressure. The catalyst was removed by filtration and the solvent was evaporated off to give **1h**, which was used in the next reaction without further purification. Methanesulfonyl chloride (0.22 ml, 2.8 mmol) was added dropwise at −15 °C for 30 min to a mixture of the above precipitate, 4-*N*,*N*-dimethylaminopyridine (DMAP, 650 mg, 5.2 mmol), and *N*,*N*-dimethylformamide (DMF). The reaction mixture was poured into ice water, and then extracted with AcOEt. The AcOEt layer was washed with water, dried, and evaporated *in vacuo*. Recrystallization of the residue from Et_2O gave **1i** (340 mg, 61%), mp 213—214 °C. IR (Nujol) cm^{-1}: 3280. ^{1}H-NMR ($CDCl_3$ and 3 drops of D_2O) δ: 2.90 (3H, s, SO_2CH_3), 6.58—8.56 (12H, m, Ar-H), 9.10 (1H, br, NH), 10.05 (1H, br, NH). FAB-MS (positive ion mode) *m/z*: 403 [(M+1)$^+$]. *Anal.* Calcd for $C_{22}H_{18}N_4O_2S$: C, 65.66; H, 4.51; N, 13.92. Found: C, 65.42; H, 4.23; N, 13.94.

11-Amino-10*H*-indolo[3,2-*b*]quinoline (1k) A mixture of **1j** (460 mg, 1.2 mmol) and AcOH (15 ml) was hydrogenated over 10% Pd/C at atmospheric pressure. The catalyst was removed by filtration and the solvent was evaporated off to give 205 mg (100%) of **1k** as red crystals. ^{1}H-NMR (DMSO-d_6) δ: 7.27—7.74 (5H, m, Ar-H), 7.74—8.70 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 234 [(M+1)$^+$].

11-(4-Amino-2-methoxybenzyl)amino-10*H*-indolo[3,2-*b*]quinoline (1l) A mixture of **1j** (460 mg, 1.2 mmol), $NiCl_2$ (0.57 g, 2.4 mmol), $NaBH_4$ (0.18 g, 0.48 mmol), and MeOH (20 ml) was stirred at room temperature for 2 h. The mixture was made acidic with a 10% HCl solution, then made basic with a 28% NH_3 aqueous solution and extracted with AcOEt. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. The solvent was removed to give 190 mg (42%) of **1l**, which was used in the next reaction without further purification.

***N*-[4-[(10*H*-Indolo[3,2-*b*]quinolin-11-yl)amino]methyl]-3-methoxyphenyl]methanesulfonanilide (1m)** Methanesulfonyl chloride (0.08 ml, 1.0 mmol) was added dropwise to a solution of **1l** (250 mg, 0.7 mmol) in dry pyridine (4 ml) at 0 °C. The mixture was stirred at room temperature for 1.5 h, then poured into ice water and extracted with AcOEt. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel with a mixture of AcOEt and hexane (2 : 1) to give 150 mg (50%) of **1m** as yellow crystals, mp 186—189 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.79 (3H, s, SO_2CH_3), 3.91 (3H, s, OCH_3), 4.08 (2H, s, CH_2), 6.01—7.90 (8H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 447 [(M+1)$^+$]. *Anal.* Calcd for $C_{24}H_{22}N_4O_3S$: C, 64.56; H, 4.97; N, 12.55. Found: C, 64.30; H, 4.92; N, 12.60.

***N*-[4-(10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]-acetamide (1s) (General Procedure)** A mixture of **1q** (900 mg, 2.34 mmol), tetrahydrofuran (THF) (25 ml), and MeOH (25 ml) was hydrogenated over 10% Pd/C at atmospheric pressure. The catalyst was removed by filtration under an argon atmosphere, and the solvent was evaporated off to give crude 11-(4-amino-2-methoxyphenyl)amino-10*H*-indolo[3,2-*b*]quinoline (**1r**). Acetyl chloride (0.22 ml, 3.0 mmol) was added dropwise to a solution of **1r** and DMAP (650 mg, 5.2 mmol) in pyridine (10 ml) at −15 °C. The reaction mixture was stirred at room temperature for 30 min, then poured into ice water, made basic with a 10% KOH solution and extracted with AcOEt. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from Et_2O to give 850 mg (92%) of yellow crystals, mp 171—173 °C. IR (Nujol) cm^{-1}: 1660. ^{1}H-NMR (CF_3COOD) δ: 2.36 (3H, s, $COCH_3$), 3.87 (3H, s, OCH_3), 7.14—8.54 (14H, m, Ar-H). EI-MS (positive ion mode) *m/z*: 396 (M^+). *Anal.* Calcd for $C_{24}H_{20}N_4O_2$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.52; H, 3.83; N, 14.94.

***N*-[4-(10*H*-Indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]trifluoroacetamide (1t)** Yellow crystals, mp 174—175 °C. IR (Nujol) cm^{-1}: 1660. ^{1}H-NMR (CF_3COOD) δ: 3.97 (3H, s, OCH_3), 7.19—8.56 (11H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 451 [(M+1)$^+$]. *Anal.* Calcd for $C_{24}H_{17}F_3N_4O_2$: C, 64.00; H, 3.80; N, 12.65. Found: C, 64.22; H, 3.83; N, 12.24.

Methyl *N*-[4-(10*H*-Indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]carbamate (1u) Yellow crystals, mp 178—180 °C. IR (Nujol) cm^{-1}: 3390, 1710. ^{1}H-NMR (DMSO-d_6) δ: 3.71, 3.75 (each 3H, each s, $OCH_3 \times 2$), 6.85—7.10 (2H, m, Ar-H), 7.10—8.02 (6H, m, Ar-H), 8.02—8.72 (3H, m, Ar-H), 9.72 (1H, br, NH), 11.03 (1H, br, NH). EI-MS *m/z*: 380 (M^+ − 32). *Anal.* Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.92; H, 4.83; N, 13.44.

Diethyl [*N*-[4-(10*H*-Indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]amido]phosphate (1v) Yellow crystals, mp 254—256 °C (dec.). IR (Nujol) cm^{-1}: 3200.^{1}H-NMR (CF_3COOD) δ: 1.45 (6H, t, J=7 Hz, $CH_3 \times 2$), 3.98 (3H, s, OCH_3), 4.23—4.79 (4H, m, $CH_2 \times 2$), 6.82—8.70 (11H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 491 [(M+1)$^+$]. *Anal.* Calcd for $C_{26}H_{27}N_4O_4P$: C, 63.67; H, 5.55; N, 11.42. Found: C, 63.72; H, 5.26; N, 11.49.

Dibenzyl [*N*-[4-(10*H*-Indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]amido]phosphate (1w) Yellow crystals, mp 160—165 °C (dec.). IR (Nujol) cm^{-1}: 3200. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (3H, s, OCH_3), 5.16 (each 2H, d, J=8 Hz, $CH_2 \times 2$), 6.40—7.61 (8H, m, Ar-H), 7.30 (10H, s, Ar-H). FAB-MS (positive ion mode) *m/z*: 615 [(M+1)$^+$]. *Anal.* Calcd for $C_{36}H_{31}N_4O_4P$: C, 70.35; H, 5.08; N, 9.12. Found: C, 70.56; H, 5.04; N, 9.34.

Diphenyl *N*-[4-*N*-(10*H*-Indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]phosphoramidate (1x) Yellow crystals, mp 160—165 °C (dec.). IR (Nujol) cm^{-1}: 3200. ^{1}H-NMR ($CDCl_3$) δ: 3.80 (3H, s, OCH_3), 6.11—7.73 (18H, m, Ar-H), 7.73—8.69 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 587 [(M+1)$^+$]. *Anal.* Calcd for $C_{34}H_{27}N_4O_4P$: C, 69.62; H, 4.64; N, 9.55. Found: C, 69.45; H, 4.87; N, 9.84.

Methyl 2-Methoxy-4-nitrobenzoate (5j) A mixture of 2-chloro-4-nitrobenzoic acid (**4j**, 25 g, 0.13 mol), $Ca(OH)_2$ (20 g, 0.27 mol), $Cu(Ac)_2$ (4.8 g, 39 mmol), and water (30 ml) was heated for 7 h at 160 °C in an autoclave. The reaction mixture was made acidic with a 10% HCl solution, and the resulting precipitates were collected by filtration and dissolved in AcOEt. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. The solvent was evaporated off to give 12.6 g of crude 2-hydroxy-4-nitrobenzoic acid. Tetrabutylammonium bromide (500 mg, 1.0 mmol) and dimethyl sulfate (1.20 ml, 1.3 mmol) were added to a mixture of the above product (2 g, 11.2 mmol), a 20% NaOH solution (40 ml), and CH_2Cl_2 (30 ml) and the whole was stirred at room temperature for 10 h, poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with a 10% H_2SO_4 solution and a saturated NaCl solution, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel with a mixture of AcOEt and hexane (1 : 1), and recrystallized from Et_2O to give 1.8 g (82%) of **5j** as colorless crystals, mp 76—78 °C. IR (Nujol) cm^{-1}: 1740. ^{1}H-NMR ($CDCl_3$) δ: 3.89, 3.95 (each 3H, each s, $OCH_3 \times 2$), 7.60—7.88 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 212 [(M+1)$^+$]. *Anal.* Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.12; H, 4.38; N, 6.87.

2-Methoxy-4-nitrobenzamide (6j) A mixture of **5j** (12 g, 57 mmol), a 28% NH_3 aqueous solution (250 ml), and MeOH (250 ml) was stirred at room temperature for 10 h. The mixture was poured into water and made acidic with a 10% HCl solution. After removal of MeOH, the resulting precipitates were collected by filtration and washed with Et_2O to give 10 g (95%) of **6j** as colorless crystals, mp 255—256 °C. IR (Nujol) cm^{-1}: 3450, 3160, 1670. ^{1}H-NMR ($CDCl_3$ and 3 drops of DMSO-d_6) δ: 4.01 (3H, s, OCH_3), 7.85—8.16 (3H, m, Ar-H). FAB-MS (positive ion mode) *m/z*: 197 [(M+1)$^+$]. *Anal.* Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.36; H, 3.99; N, 14.05.

2-Methoxy-4-nitrobenzylamine (3j) BMS (13.5 ml, 0.14 mmol) was added dropwise to a solution of **6j** (10.8 g, 55 mmol) in dry THF (110 ml) at 0 °C. The mixture was stirred for 30 min at room temperature, then heated at reflux for 8 h. MeOH (20 ml) was added dropwise to the mixture at 0 °C and the whole was stirred at room temperature for 12 h. After the introduction of a stream of HCl, the mixture was heated at reflux for 1 h and then cooled to 0 °C. The resulting precipitates were collected by filtraion and recrystallized from Et_2O to give 9.2 g (77%) of the hydrochloride of **3j**. Free base **3j**, colorless crystals. IR (Nujol) cm^{-1}: 3390, 3200. ^{1}H-NMR ($CDCl_3$ and 3 drops of DMSO-d_6) δ: 4.01 (3H, s, OCH_3), 7.60 (1H, d, J=8 Hz, 6-H, Ar-H), 7.72—8.04 (2H, m, Ar-H). *Anal.* Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.72; H, 3.99; N, 15.47.

3-Methoxy-4-nitrobenzylamine (5n) BMS (4.2 ml, 36 mmol) was added dropwise to a solution of 3-methoxy-4-nitrobenzamide[7] (**4n**, 3.5 g, 18 mmol) in dry THF (50 ml) at 0 °C. The reaction mixture was stirred for 30 min, then was heated at reflux for 6 h. MeOH (7 ml) was added dropwise to the mixture and the whole was stirred at room temperature for 12 h. After introduction of a stream of HCl, the mixture was heated at reflux for 1 h and then cooled to 0 °C. The resulting precipitates were collected by filtration to give 2.4 g (62%) of the hydrochloride of **5n**. Free base **5n**, yellow oil, IR (Neat) cm^{-1}: 3400. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (2H, br, NH), 3.90 (3H, s, OCH_3), 4.03 (2H, s, CH_2), 6.93—7.30 (2H, m, Ar-H), 7.76 (1H, d, J=8 Hz, 5-H, Ar-H). *Anal.* Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.52; H, 5.38; N, 15.47.

***N*-(3-Methoxy-4-nitro)benzylmethanesulfonamide (6n)** Methanesulfonyl chloride (1.8 ml, 12 mmol) was added dropwise to a solution of **5n** (1.8 g, 10 mmol) in dry pyridine (10 ml) at 0 °C. The mixture was stirred at room temperature for 1 h, the mixture was poured into ice water, made acidic with a 10% HCl solution and extracted with AcOEt. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. The solvent was removed to give 2.5 g (87%) of **6n** as yellow crystals. IR (Nujol) cm^{-1}: 3320. ^{1}H-NMR ($CDCl_3$ and 3 drops of DMSO-d_6) δ: 2.90 (3H, s, SO_2CH_3), 3.91 (3H, s, OCH_3), 4.29 (2H, d, J=7 Hz, CH_2), 6.54 (1H, br, NH), 6.98 (1H, dd, J=2 Hz, 8 Hz, 6-H), 7.16 (1H, d, J=2 Hz, 2-H), 7.78 (1H, d, J=8 Hz, 5-H). *Anal.* Calcd for $C_9H_{12}N_2O_5S$: C, 41.53; H, 4.65; N, 10.76. Found: C, 41.72; H, 4.48; N, 10.87.

***N*-(3-Methoxy-4-amino)benzylmethanesulfonamide (3n)** $NaBH_4$ (1.5 g, 24 mmol) was added to a mixture of **6n** (1.8 g, 7 mmol), $NiCl_2$ (3.0 g, 12 mmol), and MeOH (30 ml) at 0 °C. The whole was stirred at room temperature for 30 min. After removal of MeOH, the reaction mixture was made acidic with a 10% HCl solution. It was then made basic with a 28% NH_3 aqueous solution and extracted with AcOEt. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel with AcOEt to give 1.5 g (100%) of **3n** as yellow crystals. IR (Neat) cm^{-1}: 3470, 3375, 3300. ^{1}H-NMR ($CDCl_3$) δ: 2.72 (3H, s, SO_2CH_3), 3.72 (3H, s, OCH_3), 4.07 (2H, d, J=6 Hz, CH_2), 5.54 (1H, t, J=6 Hz, NH), 6.35—6.80 (3H, m, Ar-H). *Anal.* Calcd for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13; N, 12.16. Found: C, 46.72; H, 6.38; N, 12.37.

***N*-(2-Methanesulfonamido-4-methoxyphenyl)acetamide (6o)** Methanesulfonyl chloride (2 ml, 24 mmol) was added dropwise to a solution of *N*-(2-amino-4-methoxyphenyl)acetamide[8] (**5o**, 4.0 g, 22 mmol) in dry pyridine (30 ml) at 0 °C. The mixture was stirred at room temperature for 1.5 h, made acidic with a 10% HCl solution and extracted with AcOEt. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from EtOH to give 2.6 g (46%) of **6o** as red crystals, mp 135—137 °C. IR (Nujol) cm^{-1}: 3325, 3200, 1650. ^{1}H-NMR ($CDCl_3$ and 3 drops of DMSO-d_6) δ: 2.15 (3H, s, $COCH_3$), 2.89 (3H, s, SO_2CH_3), 3.76 (3H, s, OCH_3), 6.75 (1H, dd, J=3, 9 Hz, 5-H), 7.00 (1H, d, J=3 Hz, 3-H), 7.40 (1H, d, J=9 Hz, 6-H), 8.51 (1H, br, NH), 9.10 (1H, br, NH). FAB-MS (positive ion mode) m/z: 259 $[(M+1)^+]$. *Anal.* Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.85. Found: C, 46.22; H, 5.38; N, 10.87.

***N*-(2-Amino-5-methoxyphenyl)methanesulfonamide (3o)** A mixture of **6o**[6] (2.5 g, 10 mmol) and a 10% HCl solution (10 ml) was heated at reflux in EtOH (20 ml) for 3 h. After removal of the solvent, the resulting precipitates were collected by filtration to give 2.4 g (100%) of the hydrochloride of **3o**. Free base **3o**, yellow crystals, mp 90—91 °C. IR (Nujol) cm^{-1}: 3425, 3340, 3125. ^{1}H-NMR (DMSO-d_6) δ: 3.02 (3H, s, SO_2CH_3), 3.80 (3H, s, OCH_3), 6.72—7.54 (3H, m, Ar-H), 8.10 (3H, br, NH and NH_2). FAB-MS (positive ion mode) m/z: 217 $[(M+1)^+]$. *Anal.* Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found: C, 44.12; H, 5.38; N, 12.87.

***N*-(5-Amino-2-methoxyphenyl)acetamide (5p)** A mixture of *N*-(2-methoxy-5-nitrophenyl)acetamide[9] (**4p**, 6.3 g, 30 mmol) and MeOH (300 ml) was hydrogenated over 10% Pd/C at atmospheric pressure. The catalyst was removed by filtration and the solvent was evaporated to give 5.3 g (97%) of **5p**, colorless crystals, mp 95—96 °C. IR (Nujol) cm^{-1}: 3450, 3340, 3250, 1670. FAB-MS (positive ion mode) m/z: 181 $[(M+1)^+]$. *Anal.* Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.12; H, 5.48; N, 15.77.

***N*-(5-Methanesulfonamido-2-methoxy)phenylacetamide (6p)** Methanesulfonyl chloride (1.9 ml, 24 mmol) was added dropwise to a solution of **5p** (4.0 g, 22 mmol) in dry pyridine (20 ml) at −15 °C. The mixture was stirred at room temperature for 1.5 h and poured into a 10% KOH solution. The basic solution was washed with Et_2O and made acidic with a 10% HCl solution. The resulting precipitates were collected by filtration and washed with water to give 4.6 g (81%) of **6p**, yellow crystals, mp 254—255 °C. IR (Nujol) cm^{-1}: 3400, 3110, 1670. FAB-MS (positive ion mode) m/z: 259 $[(M+1)^+]$. *Anal.* Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.85. Found: C, 46.72; H, 5.38; N, 10.87.

***N*-(3-Amino-4-methoxyphenyl)methanesulfonamide (3p)** A mixture of **6p** (4.0 g, 16 mmol) and a 10% HCl solution (10 ml) was heated at reflux in EtOH (40 ml) for 2 h. After removal of the solvent, the resulting precipitates were collected by filtration to give 3.7 g (97%) of the hydrochloride of **3p**. Free base **3p**, white crystals, mp 74—75 °C. IR (Nujol) cm^{-1}: 3500, 3400, 3250. FAB-MS (positive ion mode) m/z: 217 $[(M+1)^+]$. *Anal.* Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found: C, 44.22; H, 5.38; N, 12.87.

Antitumor Activity Assays and evaluation of antitumor activities were carried out according to the methods described previously.[1a,b]

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