Synthesis and Antitumor Activity of Fused Quinoline Derivatives. V.[1a-d] Methylindolo[3,2-*b*]quinolines

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Indolo[3,2-*b*]quinoline derivatives (1b—i) with a methyl group at each possible position have been synthesized. The 1-methyl (1b) and 9-methyl (1i) derivatives were inactive, but the 3-methyl (1d), 4-methyl (1e), and 6-methyl (1f) derivatives exhibited high treatment/control (T/C) value and cure rates against leukemia P388 in mice. These results indicated that modification of indolo[3,2-*b*]quinoline derivatives at 3, 4, and 6 positions may be useful approach for lead optimization.

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

We have developed indolo[3,2-*b*]quinoline derivatives as candidate anticancer drugs (Fig. 1; **1a**),[1a] and now the focus of our study has turned to lead optimization.[1b-d] One approach to lead optimization is to find the positions at which a variety of functional groups can be substituted on the lead compound without decreasing its activity. In this paper, we describe the synthesis and antitumor activity of indolo[3,2-*b*]quinolines with a methyl group at each possible position.

Synthesis The methylindolo[3,2-*b*]quinoline derivatives (**1b—i**) were synthesized by using a modification of the method of Gorlitzer and Weber,[2] as shown in Chart 1.

As starting materials, methylanthranilic acids (**2b—e**) were converted to the corresponding methyl-2-(chloroacetamido)benzoic acids (**3b—e**) by reaction with chloroacetyl chloride at reflux in dry benzene. The amination of **3b—e** with aniline (**4a**) afforded methyl-2-(*N*-phenylamino)acetamidobenzoic acids (**5b—e**). 2-[*N*-(Methylphenylamino)acetamido]benzoic acids (**5f, g, i**) were prepared by the amination of 2-(chloroacetamido)benzoic acid (**3a**)[1a] with the corresponding toluidine (**4f, g, i**). Cyclization of these acids (**5b—g, i**) by heating with polyphosphoric acid (PPA) gave the corresponding methylindolo[3,2-*b*]quinolones (**6b—i**), which were converted to chlorides (**7b—i**) by treatment with phosphorus oxychloride ($POCl_3$). Among the chlorides, 2-[*N*-(3-methylphenylamino)acetamido]benzoic acid (**4f**) gave a mixture of 11-chloro-6-methyl- (**7f**) and 11-chloro-8-methyl-

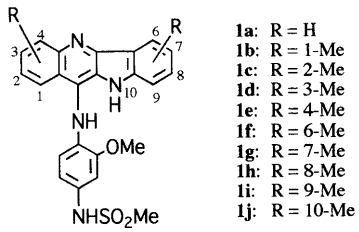

Fig. 1

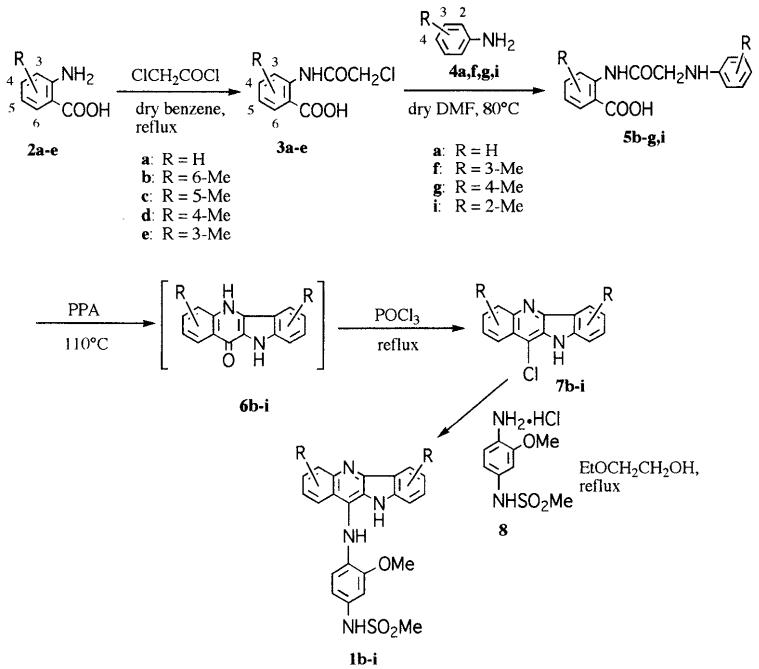

Chart 1

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Table 1. Antitumor Activities of Methylindolo[3,2-*b*]quinolines (**1a—j**)

Compound		Antitumor activity against in P388		
No.	R	Dose (mg/kg)[a]	T/C (%)[b]	Cure[c]
1a	H	50	68	
		25	111	
		12.5	203	2/6
		6.3	300	3/6
		3.1	177	
1b	1-Me	Inactive		
1c	2-Me	50	126	
		25	110	
		12.5	106	
1d	3-Me	50	332	4/6
		25	222	
		12.5	196	
1e	4-Me	50	305	4/6
		25	235	1/6
		12.5	198	
1f	6-Me	50	269	
		25	288	2/6
		12.5	240	2/6
1g	7-Me	50	115	
		25	192	
		12.5	189	
1h	8-Me	50	75	
		25	77	
		12.5	153	
		6.3	234	
		3.1	173	
1i	9-Me	Inactive		
1j	10-Me	Inactive		

a) The dose was given twice, on days 1 and 5. *b*) T/C > 120%, active. *c*) The cure rates were observed at day 30.

10*H*-indolo[3,2-*b*]quinoline (**7h**), which were easily separated by column chromatography on silical gel. In the ^{1}H-NMR spectra of **7f** and **7h**, differences were observed in the number of the protons which showed signals at lower field than 8 ppm among the aromatic protons. In our previous study, we found that the protons at the 1, 4, 6 positions on the indolo[3,2-*b*]quinoline ring were observed at lower field than 8 ppm. Based on these findings, we determined the structures of **7f** (δ: 8.06—8.44 ppm, 2H) and **7h** (δ: 8.02—8.44 ppm, 3H). The final products (**1b—i**) were obtained by heating the corresponding chlorides (**7b—i**) with *N*-(4-amino-3-methoxyphenyl)methanesulfonamide hydrochloride (**8**)[3] at reflux in 2-ethoxyethanol.

Antitumor Activities and Discussion Antitumor activities of these compounds **1a—j** were examined against leukemia P388 in mice (Table 1).

The methyl indoloquinoline derivatives (**1a—i**) exhibited extremely different activities. The 1-methyl (**1b**), 2-methyl (**1c**), 9-methyl (**1i**), and 10-methyl (**1j**) derivatives, which have the methyl group close to an amino moiety, were inactive or very weakly active. In our previous work, it was found that **1j** had no intercalating ability and that the carbon atom of the methyl group of **1j** was disturbed the coplanarity of the indoloquinoline ring.[1a,4] The result obtained from the molecular calculation for **1b** was similar to that **1j** and suggests that loss of the activity of **1b** is a consequence of loss of the intercalating ability. Other derivatives (**1d—h**) exhibited high potency. The 3-methyl (**1d**), 4-methyl (**1e**), and 6-methyl (**1f**) derivatives possessed more potent antitumor activities in terms of both treatment/control (T/C) value and cure rate at higher doses than that of the lead compound (**1a**). These results indicate that introduction of a methyl group at the 3, 4, or 6 position of the indoloquinoline ring decreases the toxicity of the lead compound at high doses, and that functionalization at these positions will be favorable for lead optimization of the indoloquinoline derivative.

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-200 (200 MHz) spectrometer. Merck Silica gel 60 (230—400 mesh) was employed for column chromatography.

2-(Chloroacetamido)-6-methylbenzoic Acid (3b) (General Procedure) Chloroacetyl chloride (7.36 ml, 92.5 mmol) was added dropwise to a solution of 2-amino-6-methylbenzoic acid[5] (**2b**, 7.00 g, 46.3 mmol) in dry benzene (70 ml). The reaction mixture was heated at reflux for 0.5 h, then the solvent was removed. The resulting residue was poured into ice water, and the precipitates were collected by filtration and washed with water to give **3b** (9.67 g, 92%), mp 145—146 °C. IR (KBr): 3300—2550, 1700, 1675 cm^{-1}. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 2.39 (3H, s), 4.33 (2H, s), 7.10 (1H, d, J=7 Hz), 7.36 (1H, dd, J=8, 7 Hz), 7.70 (1H, d, J=8 Hz), 10.16 (1H, br), 13.40 (1H, br). *Anal.* Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.85; H, 4.47; N, 6.14.

2-(Chloroacetamido)-5-methylbenzoic Acid (**3c**): mp 201—203 °C. IR (Nujol): 3700—3200, 1690, 1660 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.31 (3H, s), 4.18 (2H, s), 7.31 (1H, dd, J=9, 2 Hz), 7.85 (1H, d, J=2 Hz), 8.70 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 53.02; H, 4.24; N, 6.55.

2-(Chloroacetamido)-4-methylbenzoic Acid (**3d**): mp 208—209 °C. IR (Nujol): 3250, 1690, 1660 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.40 (3H, s), 4.15 (2H, s), 6.88 (1H, dd, J=7, 2 Hz), 7.93 (1H, d, J=7 Hz), 8.46 (1H, J=2 Hz), 11.58 (1H, br), 12.19 (1H, br). *Anal.* Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.65; H, 4.56; N, 6.16.

2-(Chloroacetamido)-3-methylbenzoic Acid (**3e**): mp 198—199 °C. IR (Nujol): 3250, 3500—2450, 1690, 1660 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.29 (3H, s), 4.19 (2H, s), 7.18—7.51 (2H, m), 7.90 (1H, dd, J=8, 2 Hz), 9.18 (1H, br), 10.01 (1H, br). *Anal.* Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.63; H, 4.23; N, 6.24.

6-Methyl-2-[(*N*-phenylamino)acetamido]benzoic Acid (5b) (General Procedure) A mixture of **3b** (9.00 g, 39.5 mmol) and distilled aniline (7.92 ml, 86.9 mmol) in dry *N*,*N*-dimethylformamide (DMF, 9 ml) was heated at 80 °C for 2 h. The reaction mixture was poured into ice water and made basic with 10% aqueous NaOH. The aqueous layer was washed with AcOEt, made basic with 20% aqueous H_2SO_4, and extracted with AcOEt. The AcOEt layer was washed with water and saturated NaCl solution, dried, and evaporated *in vacuo* to give **5b** (6.87 g, 61%), mp 185—187 °C (AcOEt and hexane). IR (KBr): 3400, 3300, 3130—2925, 1725, 1670 cm^{-1}. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 2.36 (3H, s), 3.80 (2H, s), 6.54—6.68 (3H, m), 6.93—7.46 (5H, m), 8.09 (1H, d, J=7.6 Hz), 10.35 (1H, br). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.34; H, 5.77; N, 9.55.

5-Methyl-2-[*N*-(phenylamino)acetamido]benzoic Acid (**5c**): mp 171—174 °C. IR (Nujol): 3400, 3250, 3500—2500, 1660 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.29 (3H, s), 3.83 (2H, s), 6.45—6.80 (3H, m), 6.91—7.47 (4H, m), 7.79 (1H, d, J=2 Hz), 8.64 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.46; H, 5.36; N, 10.00.

4-Methyl-2-[*N*-(phenylamino)acetamido]benzoic Acid (**5d**): mp 173—174 °C. IR (Nujol): 3400, 3250, 3250, 1670 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.39 (3H, s), 3.86 (2H, s), 6.36—7.27 (7H, m), 7.84 (1H, d, J=7 Hz), 8.55 (1H, d, J=2 Hz), 12.26 (1H, br). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.56; H, 5.46; N, 9.46.

3-Methyl-2-[*N*-(phenylamino)acetamido]benzoic Acid (**5e**): mp 156—158 °C. IR (Nujol): 3500, 3250, 1700 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.25 (3H, s), 3.85—4.10 (2H, m), 6.59—6.90 (3H, m), 7.01—7.52 (6H, m), 9.88 (1H, br). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.69; H, 5.71; N, 9.56.

2-[*N*-(3-Methylphenylamino)acetamido]benzoic Acid (**5f**): mp 164—166 °C. IR (Nujol): 3500, 3250, 1690 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.21 (3H, s), 3.85 (2H, s), 6.31—6.63 (3H, m), 6.84—7.31 (2H, m), 7.43—7.71 (1H, m), 7.99 (1H, dd, J=8, 2 Hz), 8.78 (1H, dd, J=8, 2 Hz), 12.08 (1H, br). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.68; H, 5.70; N, 9.86.

2-[*N*-(4-Methylphenylamino)acetamido]benzoic Acid (**5g**): mp 162—165 °C. IR (Nujol): 3400, 3240, 3300—2500, 1665 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.19 (3H, s), 3.88 (2H, s), 6.13—6.72 (4H, m), 6.81—7.25 (3H, m), 7.34—7.68 (1H, m), 8.00 (1H, dd, J=9, 2 Hz), 8.78 (1H, dd, J=9, 2 Hz), 12.22 (1H, br). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.54; H, 5.68; N, 9.72.

2-[*N*-(2-Methylphenylamino)acetamido]benzoic Acid (**5i**): mp 142—144 °C. IR (Nujol): 3400, 3250, 3350—2400, 1670 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.30 (3H, s), 4.00 (2H, s), 6.40—6.92 (4H, m), 6.95—7.33 (3H, m), 7.38—7.77 (1H, m), 8.08 (1H, dd, J=8, 2 Hz), 8.83 (1H, dd, J=8, 2 Hz), 12.11 (1H, br). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.69; H, 5.79; N, 9.86.

11-Chloro-1-methyl-10*H*-indolo[3,2-*b*]quinoline (7b) (General Procedure) Compound **5b** (6.00 g, 21.1 mmol) was added portionwise to polyphosphoric acid (PPA, 250 g) at 110 °C and the mixture was heated with mechanical stirring at 110 °C for 1.5 h. The reaction mixture was poured into ice water and made basic with KOH. The resulting precipitates were collected, washed with water, and dried to give 1-methyl-10*H*-indolo[3,2-*b*]quinolin-11-one (**6b**, about 7.00 g).

A mixture of the above crude product and $POCl_3$ (70 ml) was heated at reflux for 1.5 h. The excess $POCl_3$ was removed and the residue was poured into ice water. The precipitates were collected by filtration and washed with water. A mixture of the precipitates, CH_3CN (5 ml), and saturated aqueous $KHCO_3$ was stirred at room temperature for 3 h. The mixture was filtered and the precipitates were washed with water. The precipitates were purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 1) to give **7b** (2.56 g, 45%), mp 263—264 °C (dec.). IR (KBr): 3170—3000 cm^{-1}. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 3.09 (3H, s), 7.28—7.72 (5H, m), 8.16 (1H, dd, J=8, 2 Hz), 8.37 (1H, d, J=8 Hz), 11.61 (1H, br). FAB-MS (positive ion mode) m/z: 267 [(M + 1)$^+$], 269 [(M + 1)$^+$ + 2]. *Anal.* Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 71.83; H, 4.51; N, 10.14.

11-Chloro-2-methyl-10*H*-indolo[3,2-*b*]quinoline (**7c**): mp 221—223 °C. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 2.68 (3H, s), 7.10—7.69 (4H, m), 7.85—8.54 (3H, m), 11.65 (1H, br). FAB-MS (positive ion mode) m/z: 267 [(M + 1)$^+$], 269 [(M + 1)$^+$ + 2]. *Anal.* Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.36; H, 4.19; N, 10.54.

11-Chloro-3-methyl-10*H*-indolo[3,2-*b*]quinoline (**7d**): mp 207—209 °C. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.50 (3H, s), 7.00—7.57 (4H, m), 7.87—8.46 (3H, m). FAB-MS (positive ion mode) m/z: 267 [(M + 1)$^+$], 269 [(M + 1)$^+$ + 2]. *Anal.* Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.17; H, 4.44; N, 10.63.

11-Chloro-4-methyl-10*H*-indolo[3,2-*b*]quinoline (**7e**): mp 216—218 °C. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.94 (3H, s), 7.12—7.72 (5H, m), 7.98—8.50 (2H, m), 11.41 (1H, br). FAB-MS (positive ion mode) m/z: 267 [(M + 1)$^+$], 269 [(M + 1)$^+$ + 2]. *Anal.* Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.45; H, 4.16; N, 10.57.

11-Chloro-6-methyl-10*H*-indolo[3,2-*b*]quinoline (**7f**): This compound was separated by column chromatography of a mixture of **7f** and **7h** obtained from **5f**, mp 213—214 °C. ^{1}H-NMR (60 MHz, MeOH-d_4) δ: 3.11 (3H, s), 6.91—7.85 (5H, m), 8.06—8.44 (2H, m), 9.58 (1H, br). EI-MS m/z: 266 (M$^+$), 268 (M$^+$ + 2). *Anal.* Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.36; H, 4.52; N, 10.29.

11-Chloro-7-methyl-10*H*-indolo[3,2-*b*]quinoline (**7g**): mp 210—212 °C. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.44 (3H, s), 6.90—7.27 (2H, m), 7.45—7.80 (2H, m), 7.97—8.35 (3H, m). FAB-MS (positive ion mode) m/z: 267 [(M + 1)$^+$], 269 [(M + 1)$^+$ + 2]. *Anal.* Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.22; H, 4.39; N, 10.43.

11-Chloro-8-methyl-10*H*-indolo[3,2-*b*]quinoline (**7h**): This compound was separated by column chromatography from a mixture of **7f** and **7h** obtained from **5f**, mp 213—215 °C. ^{1}H-NMR (MeOH-d_4) δ: 2.50 (3H, s), 7.17—7.85 (4H, m), 8.02—8.44 (3H, m), 11.36 (1H, br). EI-MS m/z: 266 (M$^+$), 268 (M$^+$ + 2). *Anal.* Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.36; H, 4.16; N, 10.55.

11-Chloro-9-methyl-10*H*-indolo[3,2-*b*]quinoline (**7i**): mp 162—163 °C. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 2.62 (3H, s), 6.99—7.88 (4H, m), 8.09—8.49 (3H, m), 10.91 (1H, br). FAB-MS (positive ion mode) m/z: 267 [(M + 1)$^+$], 269 [(M + 1)$^+$ + 2]. *Anal.* Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.17; H, 4.17; N, 10.59.

***N*-[4-(1-Methyl-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (1b) (General Procedure)** A solution of **7b** (500 mg, 1.87 mmol) and *N*-(4-amino-3-methoxyphenyl)methanesulfonamide hydrochloride[3] (567 mg, 2.24 mmol) in 2-ethoxyethanol (6.0 ml) was heated at reflux for 3 h. The reaction mixture was poured into ice water and made basic with saturated aqueous $KHCO_3$. MeOH (2 ml) was added and the whole was stirred at room temperature for 2 h, then filtered and washed with water. The precipitates were purified by column chromatography (SiO_2, AcOEt : hexane = 1 : 2) to give **1b** (0.345 g, 41%), mp 204—206 °C (dec.). IR (KBr) 3470—3420, 3210 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 2.76 (3H, s), 2.87 (3H, s), 3.95 (3H, s), 5.86 (1H, d, J=8.4 Hz), 6.49 (1H, dd, J=8.4, 2.0 Hz), 6.95 (1H, d, J=2.0 Hz), 7.20—7.29 (2H, m), 7.43—7.56 (3H, m), 7.66 (1H, br), 8.07 (1H, d, J=8.4 Hz), 8.31 (1H, d, J=7.8 Hz), 9.16 (1H, br), 10.92 (1H, br). FAB-MS (positive ion mode) m/z: 447 [(M + 1)$^+$]. *Anal.* Calcd for $C_{24}H_{22}N_4O_3S \cdot 0.2H_2O$: C, 64.04; H, 5.02; N, 12.45. Found: C, 64.25; H, 4.93; N, 12.08.

N-[4-(2-Methyl-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (**1c**): Free base **1c**: mp 253—255 °C. IR (Nujol) 3380, 3330 cm^{-1}. ^{1}H-NMR (60 MHz, CF_3COOD) δ: 2.53 (3H, s), 3.36 (3H, s), 3.85 (3H, s), 7.05—7.69 (7H, m), 7.86—8.50 (3H, m). 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, 64.50; H, 4.90; N, 12.50.

N-[4-(3-Methyl-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (**1d**): Free base **1d**: mp 231—234 °C. IR (Nujol) 3450, 3310 cm^{-1}. ^{1}H-NMR (60 MHz, DMSO-d_6 + $CDCl_3$ + D_2O) δ: 2.48 (3H, s), 2.86 (3H, s), 3.95 (3H, s), 6.31 (1H, d, J=8 Hz), 6.51—6.76 (1H, m), 6.96—7.58 (5H, m), 7.76—8.16 (2H, m), 8.29—8.51 (1H, m). 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, 64.49; H, 4.95; N, 12.55.

N-[4-(4-Methyl-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (**1e**): Free base **1e**: mp 235—237 °C. IR (Nujol) 3300 cm^{-1}. ^{1}H-NMR (60 MHz, DMSO-d_6 + $CDCl_3$) δ: 2.99 (3H, s), 3.15 (3H, s), 3.69 (3H, s), 6.99—7.22 (2H, m), 7.35—8.02 (7H, m), 8.62—8.91 (1H, m), 9.19 (1H, br), 10.40 (1H, br). EI-MS m/z: 446 (M$^+$).

N-[4-[(6-Methyl-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (**1f**): Free base **1f**: mp 204—206 °C. IR (Nujol): 3400 cm^{-1}. ^{1}H-NMR (60 MHz, CF_3COOD) δ: 3.06 (3H, s), 3.33 (3H, s), 3.93 (3H, s), 7.09—7.56 (5H, m), 7.59—8.64 (5H, m). EI-MS m/z: 446 (M$^+$). *Anal.* Calcd for $C_{24}H_{22}N_4O_3S$: C, 64.56; H, 4.97; N, 12.55. Found: C, 64.85; H, 5.01; N, 12.79.

N-[4-[(7-Methyl-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (**1g**): Free base **1g**: mp 218—220 °C. IR (Nujol): 3270 cm^{-1}. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 2.50 (3H, s), 3.35 (3H, s), 4.01 (3H, s), 7.02—8.45 (10H, m). EI-MS m/z: 446 (M$^+$).

N-[4-[(8-Methyl-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (**1h**): Free base **1h**: mp 243—245 °C. IR (Nujol): 3300 cm^{-1}. ^{1}H-NMR (60 MHz, CF_3COOD) δ: 2.50 (3H, s), 3.09 (3H, s), 3.60 (3H, s), 6.89—7.31 (7H, m), 8.07—8.57 (3H, m), 9.87 (1H, br), 10.31 (1H, br). EI-MS m/z: 446 (M$^+$). *Anal.* Calcd for $C_{24}H_{22}N_4O_3S$: C, 64.56; H, 4.97; N, 12.55. Found: C, 64.81; H, 4.93; N, 12.68.

N-[4-[(9-Methyl-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (**1i**): Free base **1i**: mp 203—205 °C. IR (Nujol): 3300 cm^{-1}. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 2.46 (3H, s), 3.08 (3H, s), 3.77 (3H, s), 6.81—7.90 (7H, m), 7.98—8.92 (3H, m), 9.72 (1H, br). 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, 64.43; H, 4.96; N, 12.59.

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

References and Notes

1) *a*) Yamato M., Takeuchi Y., Chang M-r., Hashigaki K., Tsuruo T., Tashiro T., Tsukagoshi S., *Chem. Pharm. Bull.*, **38**, 3048—3052 (1990); *b*) Yamato M., Takeuchi Y., Chang M-r., Hashigaki K., *ibid.*, **40**, 528—530 (1992); *c*) Takeuchi Y., Chang M-r., Hashigaki K., Tashiro T., Tsuruo T., Tsukagoshi S., Yamato M., *ibid.*, **40**, 1481—1485 (1992); *d*) Takeuchi Y., Oda T., Chang M-r., Harada K., Hashigaki K., Yamato M., *ibid.*, **45**, 406—411 (1997).
2) Gorlitzer K., Weber J., *Arch. Pharm.*, **314**, 852—861 (1981).
3) Cain B. F., Atwell J., Denny W. A., *J. Med. Chem.*, **18**, 1110—1117 (1975).
4) Yamato M., Takeuchi Y., Hashigaki K., Ikeda Y., Chang M-r., Takeuchi K., Matsushima M., Tsuruo T., Tashiro T., Tsukagoshi S., Yamashita Y., *J. Med. Chem.*, **32**, 1295—1300 (1989).
5) Mayer F., Schulze M., *Chem. Ber.*, **58**, 1465—1469 (1925).