Synthesis and Antitumor Activity of Fused Quinoline Derivatives. III.[1,2] Novel *N*-Glycosylamino-indolo[3,2-*b*]quinolines

Yasuo TAKEUCHI,[a] Ming-rong CHANG,[a] Kuniko HASHIGAKI,[a] Tazuko TASHIRO,[b] Takashi TSURUO,[b] Shigeru TSUKAGOSHI,[b] and Masatoshi YAMATO*,[a]

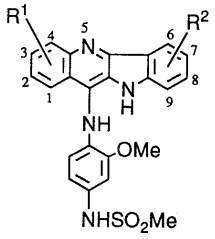
Faculty of Pharmaceutical Sciences, Okayama University,[a] Tsushimanaka 1–1–1, Okayama 700, Japan and Cancer Chemotherapy Center,[b] Kamiikebukuro 1–37–1, Toshima-ku, Tokyo 170, Japan. *Received November 8, 1991*

Novel indolo[3,2-*b*]quinolines (1b—k), having a nitro, amino, acetamido, methanesulfonamido, or glycosylamino group at the 2, 7, or 8-position, were prepared and their antitumor activities against P388 leukemia in mice were examined. The 7-galactopyranosylamino derivative (1g) showed the most potent activity (optimal dose = 25 mg/kg, T/C > 333%, cure rate 5/6).

Keywords indolo[3,2-*b*]quinoline; glycosylation; antitumor activity; P388 leukemia

We previously studied structure–activity relationships for the antitumor activity of novel fused tri- and tetracyclic quinolines with various side chains.[1] These studies led to the development of an indoloquinoline derivative (Fig. 1, **1a**) having an *N*-[4-(methanesulfonamido)-2-methoxyphenyl]amino group as a side chain, which has a remarkably potent antitumor activity against leukemia P388 in mice.[2] These studies also showed that variations of the chromophore in size, planarity, linearity, or electronic charge (including various kinds of hetero atoms) could lead to dramatic changes in their antitumor activities due to their differentiating intercalative abilities.

As a continuation of this study, we previously communicated the synthesis and antitumor activity of 7-(*N*-glycosylamino)indolo[3,2-*b*]quinolines.[3] In this paper, involving the details of the previous results, we describe the effects of the introduction of various substituents into the chromophore moiety of **1a** on their antitumor activities. Compounds with nitro (**1b**), amino (**1c**), acetamido (**1d**), and methanesulfonamido (**1e**) groups at the 7-position of the chromophore moiety of **1a** were synthesized. 7-Glucopyranosylamino (**1f**), 7-galactopyranosylamino (**1g**), 7-arabinopyranosylamino (**1h**), and 7-(2-deoxyribofuranosyl)amino (**1i**) derivatives were also synthesized with the expectation of improved solubility or bioavailability.[4] Compounds **1j** and **1k** having a galactopyranosylamino group at the 8 or 2 position, regioisomers of **1g**, were prepared in order to examine whether or not the antitumor activity varies with the change of the substituted position of the galactopyranosylamino group.



1a: $R^1 = R^2 = H$
1b: $R^1 = H$, $R^2 = 7\text{-}NO_2$
1c: $R^1 = H$, $R^2 = 7\text{-}NH_2$
1d: $R^1 = H$, $R^2 = 7\text{-}NHCOMe$
1e: $R^1 = H$, $R^2 = 7\text{-}NHSO_2Me$
1f: $R^1 = H$, $R^2 = 7\text{-}NH\text{-}glucopyranosyl$
1g: $R^1 = H$, $R^2 = 7\text{-}NH\text{-}galactopyranosyl$
1h: $R^1 = H$, $R^2 = 7\text{-}NH\text{-}arabinopyranosyl$
1i: $R^1 = H$, $R^2 = 7\text{-}NH\text{-}2\text{-}deoxyribofuranosyl$
1j: $R^1 = H$, $R^2 = 8\text{-}NH\text{-}galactopyranosyl$
1k: $R^1 = 2\text{-}NH\text{-}galactopyranosyl$, $R^2 = H$

Fig. 1

Synthesis The compounds 7-nitro (**1b**), 7-amino (**1c**), 7-acetamido (**1d**), and 7-methanesulfonamido (**1e**) indolo[3,2-*b*]quinoline derivatives were successfully prepared starting with 11-chloro-10*H*-indolo[3,2-*b*]quinoline (**2**, Chart 1). Namely, nitration of **2**[5] with concentrated nitric acid ($d = 1.51$) in acetic acid afforded 7-nitro derivative (**3**) with regioselectivity.[6] The structure of **3** was confirmed by the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum in which the signal peak due to the proton at the 6-position appeared at the lower field ($\delta = 9.00$ ppm) than that of **2** owing to the deshielding effect of the nitro group at the 7-position. Refluxing a mixture of **3** and *N*-(4-amino-2-methoxyphenyl)methanesulfonamide hydrochloride (**4**)[7] in 2-ethoxyethanol gave **1b**. Compound **1b**

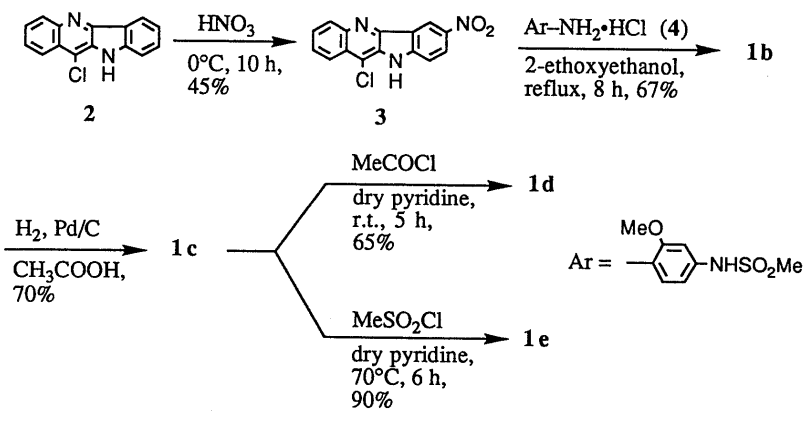


Chart 1

was converted to the amino derivative (**1c**) by catalytic hydrogenation on palladium carbon. The acetamido (**1d**) or methanesulfonamido (**1e**) derivative was obtained by treatment of **1c** with acetyl chloride or methanesulfonyl chloride, respectively.

In the preparation of glycosylamino derivatives, we selected glucopyranose, galactopyranose, arabinopyranose, and 2-deoxyribofuranose as typical sugars. The 7-glucopyranosylamino (**1f**), 7-galactopyranosylamino (**1g**), and 7-arabinopyranosylamino (**1h**) derivatives were prepared by the reaction of **1c** with the corresponding per-(*O*-acetylated)glycosyl bromide[8-10] followed by deacetylation with ammonia in methanol, respectively. On the other hand, the 7-(2-deoxyribofuranosyl)amino derivative (**1i**) was prepared by the reaction of **1c** with 3,5-di-*O*-benzyl-2-deoxyribofuranosyl bromide[11] followed by catalytic debenzylation on palladium carbon in a hydrogen atmosphere. The structures of these compounds (**1f—h**) were identified based on the spectral data of their corresponding peracetylated derivatives which were again derived from **1f—h**. Thus, the relative configuration of the 1 and 2 positions of the glycosyl moiety of the *O*-acetyl derivative of **1g** was assigned to be *trans* based on the large coupling constant value ($J=8$ Hz) in its ^{1}H-NMR spectrum. The relative configuration of the *O*-acetyl derivatives **1f**, **1h**, and **1i**, however, could not be assigned on the basis of their coupling constants.

The regioisomers of **1g**, 8-galactopyranosylamino (**1j**) and 2-galactopyranosylamino (**1k**) derivatives were prepared as shown in Chart 2. Compound **1j** was prepared starting from 2-(chloroacetamido)benzoic acid (**5**). Compound **5** was converted to acetamidobenzoic acid **7** by the reaction of **5** with aniline **6**,[12] which was cyclized to give indoloquinolinone **8** by heating with polyphosphoric acid (PPA). Compound **8** was converted to the 11-bromo derivative (**9**) and then reacted with **4** to give the 8-amino derivative (**10**). Compound **1j** was prepared by the reaction of **10** with 2,3,5,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide[9] followed by deacetylation with ammonia in methanol. Compound **1k** was synthesized starting with methyl 2-amino-5-nitrobenzoate (**11**).[13] Acetylation of **11** with chloroacetyl chloride successfully gave compound **12**. The reaction of **12** with aniline followed by hydrogenation gave the amino derivative (**14**). Compound **14** was tosylated and hydrolyzed with 10% potassium hydrogen carbonate solution to give **16**. Compound **16** was converted to **1k** by the same procedure as used in the preparation of **1j**.

Antitumor Activities These indoloquinoline derivatives (**1b—k**) were evaluated for antitumor activities against P388 leukemia in mice (Table I). Introduction of a nitro group at the 7-position of lead compound **1a** resulted in a remarkable decrease in the antitumor activity, but the amino derivative (**1c**) was found to be a more potent active compound than **1b**. The effect of introduction of a glycosylamino group on the activity remarkably varied with the kind of sugar and substituted position on the

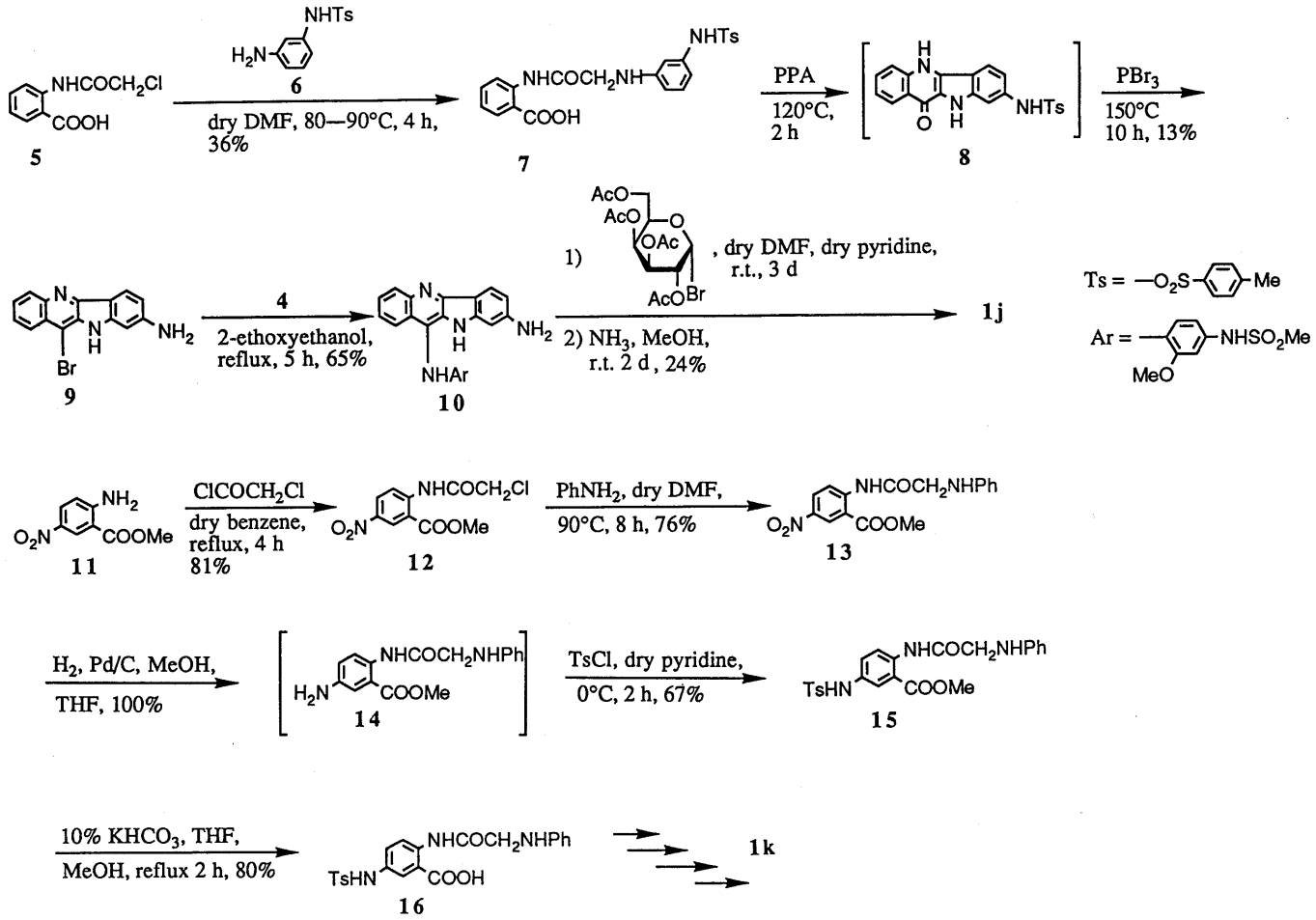
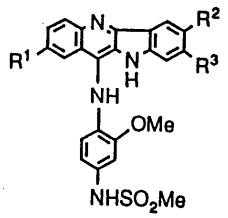
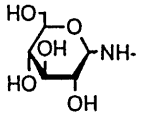
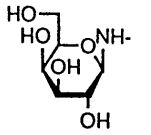
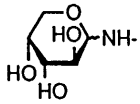
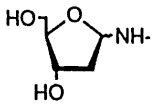
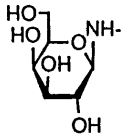
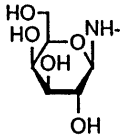


Chart 2

TABLE I. Antitumor Activities of Indolo[3,2-*b*]quinolines



Compound				Antitumor act.		
No.	R^1	R^2	R^3	Dose (mg/kg)[a]	T/C (%)[b]	Cure[c]
1a	H	H	H	50	68	
				25	111	
				12.5	203	2/6
				6.25	300	3/6
				3.13	177	
1b	H	NO_2	H	50	70	
				25	131	
				12.5	164	1/6
				6.25	136	
				3.13	123	
1c	H	NH_2	H	50	242	1/6
				25	200	
				12.5	171	
1d	H	NHCOMe	H	50	184	
				25	174	
				12.5	135	
1e	H	$NHSO_2Me$	H	50	143	
				25	114	
				12.5	126	
1f	H		H	50	90	
				25	145	
				12.5	213	2/6
1g	H		H	50	>333	5/6
				25	>333	5/6
				12.5	268	1/6
1h	H		H	50	119	
				25	>332	4/6
				12.5	290	
1i	H		H	50	185	
				25	140	
				12.5	114	
1j		H	H	50	216	
				25	164	
				12.5	185	
1k	H	H		50	173	
				25	147	
				12.5	120	

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

chromophore moiety. It was especially noted that the 7-galactopyranosylamino (**1g**) and 7-arabinopyranosylamino (**1h**) derivatives exhibited remarkably excellent activities compared to the other compounds including the lead compound **1a**. The activities of 2-galactopyranosylamino (**1k**) and 8-galactopyranosylamino (**1j**) derivatives, regioisomers of **1g**, were weak.

The improved antitumor activity of **1g** and **1h** may be explained by the introduction of the glycosyl moiety at the 7-position which resulted in an increase in solubility and bioavailability.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken on a Hitachi R-24 spectrometer at 60 MHz with Me_4Si as an internal standard. Electron ionization mass spectra (EI-MS) and fast atom bombardment mass spectra (FAB-MS) were recorded on a VG-70SE spectrometer. Infrared (IR) absorption spectra were recorded on a JASCO A-102 spectrometer.

11-Chloro-7-nitro-10*H*-indolo[3,2-*b*]quinoline (3) Nitric acid (50 ml, d=1.51) was added dropwise to a mixture of 11-chloro-10*H*-indolo-[3,2-*b*]quinoline (**2**, 2.52 g, 10 mmol) and glacial acetic acid (30 ml) at 0 °C and the reaction mixture was stirred at room temperature for 10 h. After the mixture was poured into ice water, the resulting precipitates were collected and then washed with a saturated $KHCO_3$ solution and recrystallized from a mixture of tetrahydrofuran (THF) and MeOH to give 2.51 g (84%) of **3** as yellow crystals, mp 262—264 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.76—8.64 (5H, m), 8.65—8.84 (1H, m), 9.00 (1H, s, 6-H), 11.59 (1H, br, NH). EI-MS m/z: 299 (M^++2), 297 (M^+). *Anal.* Calcd for $C_{15}H_8ClN_3O_2$: C, 60.52; H, 2.71; N, 14.11. Found: C, 60.35; H, 2.95; N, 14.38.

***N*-[3-Methoxy-4-(7-nitro-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-phenyl]methanesulfonamide (1b)** A mixture of **3** (5.80 g, 20 mmol) and *N*-(4-amino-2-methoxyphenyl)methanesulfonamide hydrochloride (**4**, 5.20 g, 24 mmol) was heated at reflux in 2-ethoxyethanol (50 ml) for 8 h. The resulting precipitates were collected and recrystallized from a mixture of dimethylformamide (DMF) and MeOH to give 6.4 g (67%) of the hydrochloride of **1b** as yellow crystals. Free base **1b**: mp 234—236 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.00 (3H, s, SO_2CH_3), 3.64 (3H, s, OCH_3), 6.78—8.32 (7H, m), 8.51—9.10 (2H, m), 9.18—9.48 (1H, m), 10.30, 11.15 (2H, each br, NH×2). EI-MS m/z: 477 (M^+). *Anal.* Calcd for $C_{23}H_{19}N_5O_5S$: C, 57.85; H, 4.01; N, 14.67. Found: C, 57.63; H, 3.84; N, 14.52.

***N*-[4-(7-Amino-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (1c)** A solution of **1b** (2 g, 4.2 mmol) in glacial acetic acid (150 ml) was hydrogenated over 10% Pd–carbon (500 mg) at atmospheric pressure for 48 h. The catalyst was removed by filtration and the solvent was removed to give 1.36 g (72%) of the acetate of **1c**. Free base **1c**, mp 210—212 °C (dec.). IR (Nujol): 3460, 3370, 3280 cm^{-1}. ^{1}H-NMR (CF_3COOD) δ: 3.33 (3H, s, SO_2CH_3), 3.96 (3H, s, OCH_3), 7.00—8.61 (10H, m). FAB-MS (positive ion mode) m/z: 448 [$(M+1)^+$]. *Anal.* Calcd for $C_{23}H_{21}N_5O_3S$: C, 61.73; H, 4.73; N, 15.65. Found: C, 61.93; H, 4.49; N, 15.77.

***N*-[4-(7-Acetamido-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (1d)** Acetyl chloride (0.3 ml, 1.05 mmol) was added to a solution of **1c** (500 mg, 1.1 mmol) in dry pyridine (10 ml). The reaction mixture was stirred at room temperature for 5 h. After the mixture was poured into ice water, the resulting precipitates were collected and then washed with water and recrystallized from a mixture of THF and MeOH to give 470 mg (65%) of **1d** as yellow crystals, mp 223—226 °C (dec.). IR (Nujol): 1680 cm^{-1}. ^{1}H-NMR (CF_3COOD) δ: 2.08 (3H, s, $COCH_3$), 3.28 (3H, s, SO_2CH_3), 3.80 (3H, s, OCH_3), 6.84—8.51 (11H, m). FAB-MS (positive ion mode) m/z: 490 [$(M+1)^+$]. *Anal.* Calcd for $C_{25}H_{23}N_5O_4S$: C, 61.34; H, 4.74; N, 14.31. Found: C, 61.20; H, 4.56; N, 14.32.

***N*-[4-(7-Methanesulfonamido-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (1e)** Methanesulfonyl chloride (1.3 ml, 1.05 mmol) was added dropwise to a solution of **1c** (500 mg, 1.1 mmol) in dry pyridine (10 ml) at 0 °C. The reaction mixture was heated at 70 °C for 6 h. After the mixture was poured into ice water, the resulting precipitates were collected and recrystallized from a mixture of THF and MeOH to give 520 mg (90%) of **1e** as yellow crystals, mp 251—255 °C (dec.). ^{1}H-NMR (CF_3COOD) δ: 2.91, 3.30 (each 3H, each s, SO_2CH_3×2), 3.82 (3H, s, OCH_3), 7.01—7.17 (3H, m), 7.22—7.90 (5H, m), 7.94—8.51 (3H, m). FAB-MS (positive ion mode) m/z: 526 [$(M+1)^+$]. *Anal.* Calcd for $C_{24}H_{23}N_5O_5S_2$: C, 54.84; H, 4.41; N, 13.33. Found: C, 54.88; H, 4.12; N, 13.14.

2,3,4,6-*O*-Tetraacetate of *N*-[4-[7-(Glucopyranosyl)amino-10*H*-indolo-[3,2-*b*]quinolin-11-yl]amino-3-methoxyphenyl]methanesulfonamide (1f) A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[8] (450 mg,

0.8 mmol), dry pyridine (1 ml, 12 mmol), and dry DMF (10 ml) was stirred at room temperature for 12 h under an argon atmosphere, then **1c** (440 mg, 1 mmol) was added. The reaction mixture was stirred at room temperature for 1 d, then poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with water and a saturated $KHCO_3$ solution, and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was chromatographed on neutral alumina with a mixture of CH_2Cl_2 and hexane (1 : 1) to give 230 mg (30%) of tetraacetate of **1f** as yellow crystals, mp 172—178 °C (dec.). IR (Nujol): 1760, 1740 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.05, 2.08, 2.11, 2.14 (each 3H, each s, $COCH_3 \times 4$), 2.96 (3H, s, SO_2CH_3), 4.04 (3H, s, OCH_3), 3.79—4.64 (3H, m, 5″-H and CH_2), 5.11—5.39 (3H, m, 2″-H, 3″-H, and 4″-H), 5.78—5.99 (1H, m, 1″-H), 6.27—6.90 (3H, m), 7.00—7.99 (9H, m), 8.09—8.74 (3H, m). *Anal.* Calcd for $C_{37}H_{43}N_5O_{12}S$: C, 56.84; H, 5.54; N, 8.96. Found: C, 56.60; H, 5.33; N, 8.71.

***N*-[4-[7-(Glucopyranosyl)amino-10*H*-indolo[3,2-*b*]quinolin-11-yl]-amino-3-methoxyphenyl]methanesulfonamide (1f)** A mixture of 2,3,4,6-*O*-tetraacetate of **1f** (110 mg, 0.14 mmol), a 37% aqueous NH_3 solution (20 ml), and MeOH (100 ml) was bubbled with NH_3 gas at room temperature for 2 d. After MeOH and water were removed under reduced pressure, the resulting precipitates were collected and then washed with water and recrystallized from MeOH to give 75 mg (87%) of **1f** as yellow crystals, mp 201—205 °C (dec.). IR (Nujol): 3540—2700 cm^{-1}. ^{1}H-NMR (MeOH-d_4 + DMSO-d_6) δ: 2.96 (3H, s, SO_2CH_3), 3.72—3.81 (3H, m, 5″-H and 6″-H_2), 4.04 (3H, s, OCH_3), 4.33—4.72 (3H, m, 2″-H, 3″-H, and 4″-H), 5.00—5.32 (1H, m, 1″-H), 6.35—6.83 (2H, m), 7.01—7.73 (5H, m), 7.94—8.62 (3H, m). FAB-MS (positive ion mode) *m/z*: 610 $[(M+1)^+]$. *Anal.* Calcd for $C_{29}H_{31}N_5O_8S$: C, 57.13; H, 5.13; N, 11.49. Found: C, 57.35; H, 5.24; N, 11.71.

***N*-[4-[7-(β-Galactopyranosyl)amino-10*H*-indolo[3,2-*b*]quinolin-11-yl]amino-3-methoxyphenyl]methanesulfonamide (1g)** A mixture of 2,-3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide[9] (450 mg, 0.8 mmol), dry pyridine (1 ml, 12 mmol), and dry DMF (10 ml) was stirred at room temperature for 12 h under an argon atmosphere, then **1c** (440 mg, 1 mmol) was added. The reaction mixture was stirred at room temperature for 3 d, then poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with water and a saturated $KHCO_3$ solution, and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was dissolved in a mixture of MeOH (100 ml) and a 37% aqueous NH_3 solution (20 ml). The reaction mixture was bubbled with NH_3 gas at 0 °C over a 5 h period and stirred at room temperature for 3 d. After MeOH and water were removed under reduced pressure, the resulting precipitates were collected and then washed with water and recrystallized from MeOH to give 140 mg (30%) of **1g** as yellow crystals, mp 181—185 °C (dec.). FAB-MS (positive ion mode) *m/z*: 610 $[(M+1)^+]$. *Anal.* Calcd for $C_{29}H_{31}N_5O_8S$: C, 57.13; H, 5.13; N, 11.49. Found: C, 56.98; H, 5.12; N, 11.29. 2,3,4,6-*O*-Tetraacetate of **1g**: mp 193—196 °C (dec.). $[\alpha]_D^{15}$ −24° (c=0.1, MeOH). IR (Nujol): 3600, 3360, 1760, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$: DMSO-d_6 : D_2O = 10 : 1 : 1) δ: 1.96, 2.01, 2.08, 2.14 (each 3H, each s, $COCH_3$), 2.89 (3H, s, SO_2CH_3), 4.00 (3H, s, OCH_3), 3.81—4.26 (3H, m, 5″-H and 6″-H_2), 5.12—5.49 (3H, m, 2″-H, 3″-H, and 4″-H), 5.60 (1H, d, J=8 Hz, 1″-H), 6.30 (1H, d, J=8 Hz, 5′-H), 6.63 (1H, dd, J=2, 8 Hz, 6′-H), 6.88—7.75 (5H, m), 7.93—8.55 (3H, m).

***N*-[4-[7-(Arabinopyranosyl)amino-10*H*-indolo[3,2-*b*]quinolin-11-yl]-amino-3-methoxyphenyl]methanesulfonamide (1h)** A mixture of 2,3,4-tri-*O*-acetyl-α-arabinopyranosyl bromide[10] (560 mg, 1.5 mmol), dry pyridine (2 ml, 24 mmol), and dry DMF (20 ml) was stirred at room temperature for 12 h under an argon atmosphere, then **1c** (360 mg, 0.75 mmol) was added. The reaction mixture was stirred at room temperature for 1 d, then poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with water and a saturated $KHCO_3$ solution, and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was dissolved in a mixture of MeOH (100 ml) and a 37% aqueous NH_3 solution (20 ml). The reaction mixture was bubbled with NH_3 gas at 0 °C over a 5 h period and stirred at room temperature for 3 d. After MeOH and water were removed under reduced pressure, the resulting precipitates were collected and then washed with water and recrystallized from MeOH to give 120 mg (25%) of **1h** as yellow crystals, mp 202—204 °C (dec.). FAB-MS (positive ion mode) *m/z*: 580 $[(M+1)^+]$. *Anal.* Calcd for $C_{28}H_{29}N_5O_7S$: C, 58.02; H, 5.04; N, 12.08. Found: C, 57.99; H, 4.99; N, 12.36. 2,3,4-*O*-Triacetate of **1h**: mp 193—195 °C (dec.). IR (Nujol): 3600, 3380, 1760, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$: DMSO-d_6 : D_2O = 10 : 1 : 1) δ: 1.99, 2.06, 2.10 (each 3H, each s, $COCH_3 \times 3$), 2.86 (3H, s, SO_2CH_3), 3.93 (3H, s, OCH_3), 3.76—4.37 (3H, m, 4″-H and 5″-H_2), 5.01—5.37 (2H, m, 2″-H and 3″-H), 5.50—5.68 (1H, m, 1″-H), 6.01—6.50 (2H, m), 6.87—6.99 (1H, m), 7.04—7.66 (4H, m), 7.94—8.41 (3H, m).

***N*-[4-[7-(Deoxyribofuranosyl)amino-10*H*-indolo[3,2-*b*]quinolin-11-yl]-amino-3-methoxyphenyl]methanesulfonamide (1i)** A mixture of 3,5-di-*O*-benzyl-α-deoxyribofuranosyl bromide[11] (450 mg, 0.8 mmol), dry pyridine (1 ml, 12 mmol) and dry DMF (10 ml) was stirred at room temperature for 48 h under an argon atmosphere, then **1c** (440 mg, 1 mmol) was added. The reaction mixture was stirred at room temperature for 4 d, then poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with water and a saturated $KHCO_3$ solution, and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was chromatographed on neutral alumina with a mixture of CH_2Cl_2 and hexane (1 : 2) to give 510 mg of crude *N*-[4-[7-(3,5-di-*O*-benzyldeoxyribofuranosyl)amino-10*H*-indolo[3,2-*b*]quinolin-11-yl]amino-3-methoxyphenyl]-methanesulfonamide.

A solution of the above product (510 mg) in MeOH (50 ml) was hydrogenated over 10% Pd–carbon at atmospheric pressure for 6 d. The catalyst was removed by filtration and the solvent was removed to give 180 mg (32%) of **1i** as yellow crystals, mp 171—175 °C (dec.). IR (Nujol): 3700—3200, 3400, 3280 cm^{-1}. ^{1}H-NMR (DMSO-d_6 + MeOH-d_6) δ: 1.69—1.98 (2H, m, 2″-H_2), 2.93 (3H, s, SO_2CH_3), 3.37—3.67 (4H, m, 3″-H, 4″-H, and 5″-H_2), 3.93 (3H, s, OCH_3), 5.00—5.22 (1H, m, 1″-H), 6.24—6.80 (2H, m), 6.99—7.13 (1H, m), 7.20—7.81 (4H, m), 8.02—8.53 (3H, m). FAB-MS (positive ion mode) *m/z*: 564 $[(M+1)^+]$. *Anal.* Calcd for $C_{28}H_{29}N_5O_6S$: C, 59.66; H, 5.19; N, 12.43. Found: C, 59.68; H, 5.10; N, 12.41.

2-[*N*-[3-(4-Toluenesulfonamido)phenylamino]acetamido]benzoic Acid (7) A mixture of 2-(chloroacetamido)benzoic acid[5] (**5**, 4.4 g, 20 mmol), *N*-(3-aminophenyl)-4-toluenesulfonamide[12] (**6**, 10.5 g, 40 mmol), and dry DMF (5 ml) was heated at 80—90 °C for 4 h. The mixture was poured into ice water and the aqueous mixture was extracted with AcOEt. The organic layer was washed with water and a saturated $KHCO_3$ solution, and dried over $MgSO_4$. After the solvent was removed, the residue was chromatographed on silica gel with a mixture of AcOEt, hexane, and aceitc acid (1 : 4 : 0.01) to give 4 g (36%) of **7** as yellow crystals, mp 250—252 °C. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 2.29 (3H, s, CH_3), 3.97 (2H, s, CH_2), 6.30—7.27 (6H, m), 7.37—7.87 (2H, m), 8.05 (1H, dd, J=8, 2 Hz, 6-H), 8.79 (1H, dd, J=8, 2 Hz, 2-H), 12.57 (1H, br, COOH). *Anal.* Calcd for $C_{22}H_{19}N_3O_5S$: C, 60.40; H, 4.38; N, 9.61. Found: C, 60.21; H, 4.12; N, 9.65.

8-Amino-11-bromo-10*H*-indolo[3,2-*b*]quinoline (9) A mixture of **7** (2.2 g, 5 mmol) and PPA (50 g) was heated with a mechanical stirrer at 120 °C for 2 h. The reaction mixture was poured into ice water and the aqueous mixture was made basic with a saturated $KHCO_3$ solution. The resulting precipitates were collected and then washed with water and dried to give 1.8 g of crude 8-(4-toluenesulfonamido)-10*H*-indolo[3,2-*b*]-quinolin-11-one (**8**).

A mixture of the above product **8** and PBr_3 (20 ml) was heated at 150 °C for 10 h. After the excess PBr_3 was removed, the residue was made basic with a 10% $KHCO_3$ solution. The resulting precipitates were collected and dissolved in $CHCl_3$. The organic layer was washed with a saturated $KHCO_3$ solution and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on alumina with a mixture of AcOEt and hexane (2 : 1) to give 200 mg (13%) of **9** as yellow crystals, mp 211—214 °C. IR (Nujol): 3410, 3300 cm^{-1}. ^{1}H-NMR (CF_3COOD) δ: 7.84—8.52 (5H, m), 8.68—8.97 (2H, m). FAB-MS (positive ion mode): 314 $[(M+1)^+ + 2]$, 312 $[(M+1)^+]$. *Anal.* Calcd for $C_{15}H_{10}BrN_3$: C, 57.71; H, 3.23; N, 13.46. Found: C, 58.00; H, 3.43; N, 13.26.

***N*-[4-(8-Amino-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (10)** A mixture of **9** (100 mg, 0.3 mmol) and **4** (100 mg, 0.4 mmol) was heated at reflux in 2-ethoxyethanol (5 ml) for 5 h. The resulting precipitates were collected and were added to make them basic with a saturated $KHCO_3$ solution. The resulting precipitates were collected to give 87 mg (65%) of **10** as yellow crystals, mp 215—217 °C (dec.). IR (Nujol): 3400, 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 2.91 (3H, s, SO_2CH_3), 3.98 (3H, s, OCH_3), 6.30 (1H, d, J=9 Hz), 6.54 (1H, d, J=2 Hz), 6.87—7.78 (6H, m), 7.92—8.55 (3H, m). FAB-MS (positive ion mode) *m/z*: 448 $[(M+1)^+]$. *Anal.* Calcd for $C_{23}H_{21}N_5O_3S$: C, 61.73; H, 4.73; N, 15.65. Found: C, 61.55; H, 4.96; N, 15.57.

***N*-[4-[8-(β-Galactopyranosyl)amino-10*H*-indolo[3,2-*b*]quinolin-11-yl]-amino-3-methoxyphenyl]methanesulfonamide (1j)** A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide[9] (1.4 g, 2.4 mmol), dry pyridine (1 ml, 12 mmol), and dry DMF (10 ml) was stirred at room temperature for 12 h under an argon atmosphere, then **10** (1.34 g, 3 mmol) was added. Stirring of the reaction mixture continued at room temperature for 3 d. The mixture was poured into ice water and the aqueous mixture was extracted with CH_2Cl_2. The organic layer was washed with water and

a saturated $KHCO_3$ solution, and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was chromatographed on alumina with CH_2Cl_2 to give 680 mg of a yellow product. The above product was dissolved in a mixture of MeOH (100 ml) and a 37% aqueous NH_3 solution (20 ml). The reaction mixture was bubbled with NH_3 gas at 0 °C over a 5 h period and stirred at room temperature for 2 d. After MeOH and water were removed under reduced pressure, the resulting precipitates were collected and then washed with water and recrystallized from MeOH to give 140 mg (24%) of **1j** as yellow crystals, mp 114—117 °C (dec.). $[\alpha]_D^{15}$ −32° (c=0.1, MeOH). EI-MS m/z: 609 (M^+). *Anal.* Calcd for $C_{29}H_{31}N_5O_8S$: C, 57.13; H, 5.13; N, 11.49. Found: C, 57.05; H, 5.37; N, 11.26. 2,3,4,6-*O*-Tetraacetate of **1j**: mp 193—195 °C (dec.). ^{1}H-NMR ($CDCl_3$: DMSO-d_6 : D_2O = 10 : 1 : 1) δ: 2.00, 2.02, 2.10, 2.14 (each 3H, each s, $COCH_3$ × 4), 2.89 (3H, s, SO_2CH_3), 3.97 (3H, s, OCH_3), 3.81—4.23 (3H, m, 5″-H and 6″-H_2), 5.12—5.55 (3H, m, 2″-H, 3″-H, and 4″-H), 5.67 (1H, d, J=8 Hz, 1″-H), 6.34 (1H, d, J=9 Hz, 5′-H), 6.64 (1H, dd, J=2, 8 Hz, 6′-H), 6.93—7.81 (5H, m), 7.96—8.72 (3H, m).

Methyl 2-Chloroacetamido-5-nitrobenzoate (12) Chloroacetyl chloride (1.20 ml, 11 mmol) was added dropwise to a solution of methyl 2-amino-5-nitrobenzoate[13] (**11**, 1.96 g, 10 mmol) in dry benzene (20 ml). The reaction mixture was heated at reflux for 20 min. The benzene was removed and the residue was recrystallized from benzene to give 2.0 g (81%) of **12** as grey crystals, mp 151—152 °C. ^{1}H-NMR (CF_3COOD) δ: 4.20 (3H, s, OCH_3), 4.49 (2H, s, CH_2), 8.52 (1H, dd, J=9, 3 Hz, 4-H), 8.96 (1H, d, J=9 Hz, 6-H), 9.12 (1H, d, J=3 Hz, 3-H). *Anal.* Calcd for $C_{10}H_9ClN_2O_5$: C, 44.05; H, 3.33; N, 10.27. Found: C, 44.25; H, 3.59; N, 10.00.

Methyl 5-Nitro-2-[(*N*-phenylamino)acetamido]benzoate (13) A mixture of **12** (540 mg, 2 mmol), distilled aniline (1 ml, 4 mmol), and dry DMF (5 ml) was heated at 90 °C for 8 h. The reaction mixture was poured into ice water and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with a saturated $KHCO_3$ 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 500 mg (76%) of **13** as white crystals, mp 123—125 °C. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 3.82 (3H, s, OCH_3), 3.92 (2H, s, CH_2), 6.55—6.84 (3H, m), 6.92—7.32 (2H, m), 8.33 (1H, dd, J=9, 3 Hz, 4-H), 8.80 (1H, d, J=3 Hz, 6-H), 8.98 (1H, d, J=9 Hz, 3-H), 12.02 (1H, br, NH). *Anal.* Calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76. found: C, 58.33; H, 4.84; N, 12.51.

Methyl 2-[(*N*-Phenylamino)acetamido]-5-(4-toluenesulfonamido)benzoate (15) A mixture of **13** (490 mg, 1.5 mmol), THF (50 ml) and MeOH (50 ml) was hydrogenated over 10% Pd–carbon (100 mg) at atmospheric pressure for 2 d. The catalyst was removed by filtration and the solvent was removed to give 470 mg (100%) of methyl 5-amino-2-[(*N*-phenylamino)acetamido]benzoate (**14**) as yellow crystals.

A mixture of the above product, 4-toluenesulfonyl chloride (430 mg, 2.3 mmol), and dry pyridine (5 ml) was stirred at room temperature for 10 h. The reaction mixture was poured into ice water, and the resulting precipitates were collected and recrystallized from MeOH to give 450 mg (67%) of **15** as white crystals, mp 213—216 °C. IR (Nujol): 3420, 3220, 1700, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 2.35 (3H, s, CH_3), 3.68 (3H, s, OCH_3), 3.80 (2H, s, CH_2Cl), 6.47—6.82 (3H, m), 6.95—7.46 (7H, m), 7.52—7.87 (3H, m), 8.56 (1H, d, J=9 Hz, 3-H), 10.00 (1H, br, NH). *Anal.* Calcd for $C_{23}H_{21}N_3O_5S$: C, 61.18; H, 4.69; N, 9.31. Found: C, 61.50; H, 5.68; N, 8.30.

2-[(*N*-Phenylamino)acetamido]-5-(4-toluenesulfonamido)benzoic Acid (16) A mixture of **15** (190 mg, 0.4 mmol), a 10% $KHCO_3$ solution (5 ml), THF (5 ml), and MeOH (5 ml) was heated at reflux for 3 h. The reaction mixture was neutralized with a 10% HCl solution and the solvents were removed to give 150 mg (80%) of **16** as yellow crystals, mp 181—183 °C. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 2.33 (3H, s, CH_3), 3.82 (2H, s, CH_2Cl), 6.43—6.77 (3H, m), 6.89—7.44 (7H, m), 7.51—7.90 (3H, m), 8.55 (1H, d, J=9 Hz, 3-H). *Anal.* Calcd for $C_{22}H_{19}N_3O_5S$: C, 60.40; H, 4.38; N, 9.61. Found: C, 60.19; H, 4.67; N, 9.40.

2-Amino-11-bromo-10*H*-indolo[3,2-*b*]quinoline (18) A mixture of **16** (2.2 g, 48 mmol) and PPA (50 g) was heated with a mechanical stirrer at 120—130 °C for 2 h. The reaction mixture was poured into ice water and the aqueous mixture was made basic with a saturated $KHCO_3$ solution. The resulting precipitates were collected, washed with water, and dried to give 1.8 g (88%) of 2-(4-toluenesulfonamido)-10*H*-indolo[3,2-*b*]quinoline (**17**).

A mixture of **17** (1 g, 2.5 mmol) and PBr_3 (20 ml) was heated at 150 °C for 10 h. After the excess PBr_3 was removed *in vacuo*, the residue was made basic with a 10% $KHCO_3$ solution. The resulting precipitates were collected and dissolved in $CHCl_3$. The organic layer was washed with a saturated $KHCO_3$ solution and dried over $MgSO_4$. The residue was chromatographed on alumina with a mixture of AcOEt and hexane (2 : 1) to give 80 mg (10%) of **18** as yellow crystals, mp 252—254 °C. IR (Nujol): 3450, 3260 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 7.25—7.80 (4H, m), 7.88—8.37 (3H, m), 11.45 (1H, br, NH). FAB-MS (positive ion mode) m/z: 314 [$(M+1)^+$ + 2], 312 [$(M+1)^+$]. *Anal.* Calcd for $C_{15}H_{10}BrN_3$: C, 57.71; H, 3.23; N, 13.46. Found: C, 57.54; H, 3.12; N, 13.65.

***N*-[4-(2-Amino-10*H*-indolo[3,2-*b*]quinolin-11-yl)amino-3-methoxyphenyl]methanesulfonamide (19)** A mixture of **18** (1.03 g, 3 mmol) and **4** (1 g, 4 mmol) was heated at reflux in 2-ethoxyethanol (5 ml) for 5 h. The resulting precipitates were collected and added to a saturated $KHCO_3$ solution. The resulting precipitates were collected to give 940 mg (70%) of **19** as yellow crystals, mp 206—208 °C. IR (Nujol): 3510, 3420, 3280 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 2.91 (3H, s, SO_2CH_3), 4.01 (3H, s, OCH_3), 6.36 (1H, d, J=8 Hz, 6′-H), 6.62 (1H, d, J=3 Hz, 3′-H), 6.74—7.81 (5H, m), 7.91—8.60 (3H, m), 10.67 (1H, br, NH). FAB-MS (positive ion mode) m/z: 448 [$(M+1)^+$]. *Anal.* Calcd for $C_{23}H_{21}N_5O_3S$: C, 61.73; H, 4.73; N, 15.65. Found: C, 61.54; H, 4.52; N, 15.65.

***N*-[4-[2-(β-Galactopyranosyl)amino-10*H*-indolo[3,2-*b*]quinolin-11-yl]-amino-3-methoxyphenyl]methanesulfonamide (1k)** A mixture of **18** (1.4 g, 2.4 mmol), dry pyridine (1 ml, 12 mmol), and dry DMF (10 ml) was stirred at room temperature for 12 h under an argon atmosphere, then 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide[9] (1.34 g, 3 mmol) was added. Stirring of the reaction mixture continued at room temperature for 24 h, then the mixture was poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with water and a saturated $KHCO_3$ solution, and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was chromatographed on alumina with CH_2Cl_2 to give a yellow product. This product was dissolved in a mixture of MeOH (100 ml) and a 37% aqueous NH_3 solution (20 ml). The reaction mixture was bubbled with a NH_3 gas at 0 °C over a 5 h period and stirred at room temperature for 4 d. After MeOH and water were removed under reduced pressure, the resulting precipitates were collected and washed with water to give a solid. Recrystallization of this solid from MeOH gave 140 mg (30%) of **1k** as yellow crystals, mp 190—193 °C (dec.). $[\alpha]_D^{15}$ −15° (c=0.1, MeOH). ^{1}H-NMR ($CDCl_3$: DMSO-d_6 : D_2O = 10 : 1 : 1) δ: 2.94 (3H, s, SO_2CH_3), 3.72—3.81 (3H, m, 5″-H and 6″-H_2), 4.02 (3H, s, OCH_3), 4.33—4.72 (3H, m, 2″-H, 3″-H, and 4″-H), 5.09 (1H, d, J=6 Hz, 1″-H), 6.43 (1H, d, J=8 Hz, 5′-H), 6.58—6.83 (1H, m), 7.01—7.74 (5H, m), 7.94—8.62 (3H, m). FAB-MS (positive ion mode) m/z: 611 [$(M+1)^+$]. *Anal.* Calcd for $C_{29}H_{31}N_5O_8S$: C, 57.13; H, 5.13; N, 11.49. Found: C, 57.05; H, 5.37; N, 11.24.

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

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