SYNTHESIS AND ANTITUMOR ACTIVITY OF 7-(*N*-GLYCOSYLAMINO)-INDOLO[3,2-*b*]QUINOLINES

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Novel indolo[3,2-*b*]quinolines (**1d-g**), introduced at the 7-position with an *N*-glycosylamino group, were prepared and their antitumor activities against leukemia P388 in mice were examined. The *N*-Galactopyranosylamino derivative (**1e**) was a much more potent anti-leukemia compound (optimal dose = 25 mg/kg, T/C > 333%, cure 5/6) than lead compound **1a**.

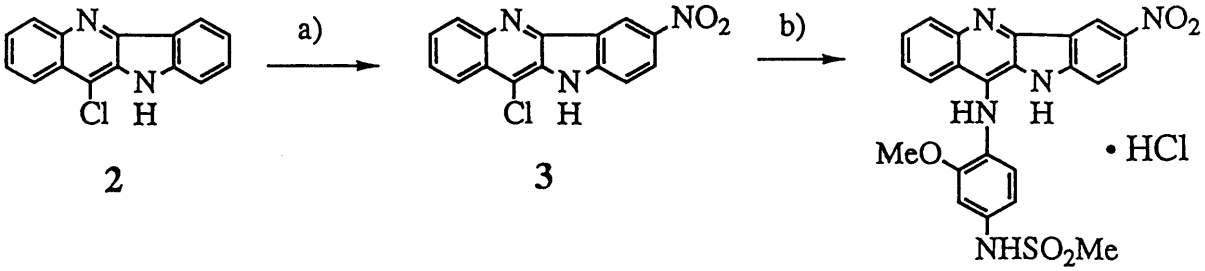
KEYWORDS indolo[3,2-*b*]quinoline; glycosylation; antitumor activity; intercalation; P388 leukemia

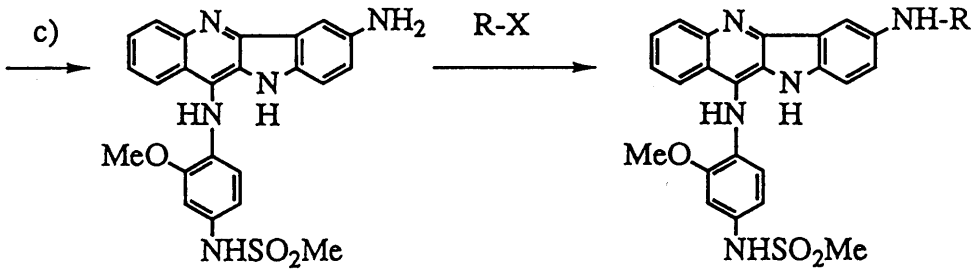
We have designed and synthesized novel fused tri- and tetra-cyclic quinolines with various side chains, aiming to develop a new-intercalative antitumor-active compound.[1,2] Among the compounds previously prepared, indoloquinoline derivative (**1a**)containing an *N*-{2-methoxy-4-[(methylsulfonyl)amino]phenyl}-amino group as a side chain shows the most potent activity against leukemia P388 in mice. In earlier studies, of the structure-activity relationship of this series, the slight structural modification of the chromophore moiety lead to dramatic changes in the compound's intercalative ability and in the antitumor activity. Searching for more effective indoloquinoline derivatives, we have synthesized a new type of **1a** containing a glycosylamino group on the chromophore. Glycosylation of a drug generally increases its bioavailability, its penetrability into target cells, and its biological activity.[3] This paper describes the synthesis and antitumor activity of 7-(*N*-glycosylamino)indolo[3,2-*b*]quinoline derivatives (**1d-g**).

The aglycon moiety, 7-aminoindolo[3,2-*b*]quinoline derivative (**1c**), was synthesized from an 11-chloro derivative[4] (**2**) through three steps as shown in Chart 1. Nitration of **2** with nitric acid in acetic acid afforded regioselectively 11-chloro-7-nitroindolo[3,2-*b*]quinoline (**3**) in 85% yield. Refluxing **3** with *N*-(4-amino-2-methoxyphenyl)methanesulfamide hydrochloride[5] in 2-ethoxyethanol gave **1b** in 65% yield. Compound **1b**, on hydrogenation over 10% Pd/C, gave **1c** in 78% yield.

As a glycosyl moiety, we selected the glucopyranosyl, galactopyranosyl, arabinopyranosyl, and deoxyribofuranosyl groups. The typical procedure of the glycosylation of **1c** is as follows: A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide[6] (560 mg, 1.5 mmol), dry DMF (30 ml), and dry pyridine (2 ml) was stirred at room temperature for 12 h under an argon atomosphere, to which **1c** (360 mg, 0.75 mmol) was added. After stirring at the same temperature for 1 day, the reaction mixture was worked up

in the usual way. The crude *O*-acetyl product was hydrolyzed with a saturated NH_3 in MeOH-H_2O (5:1) at room temperature for 3 days. A standard work-up and subsequent purification by recrystallization from MeOH gave **1e** in a 30% yield as a green crystal. After compounds **1d-f** were again converted to the corresponding *O*-acetyl derivatives, their structures were identified based on their spectral data. Thus, the relative configuration of the 1" and 2" carbons of the glycosylamino group in the *O*-acetyl derivatives of **1d** or **1e**[7] was assigned to the *trans* based on their large coupling constant, $J_{1",2"} \approx 8$ Hz, in their ^{1}H-NMR spectra. However, the relative configuration of the *O*-acetyl derivatives of **1f** and **1g** could not be assigned on the basis of their coupling constants.



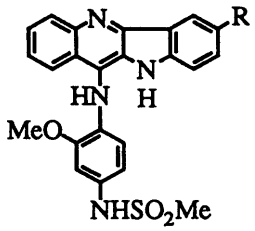


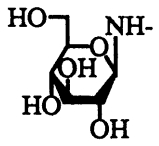
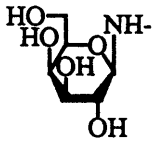
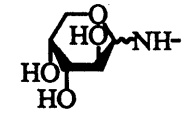
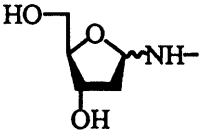
1d: R= glucopyranosyl
1e: R= galactopyranosyl
1f: R= arabinopyranosyl
1g: R= deoxyribofuranosyl

a) HNO_3 (*d*=1.42), r.t., 12 h; b) *N*-(4-Amino-2-methoxyphenyl)methanesulfonamide hydrochloride, $EtOCH_2CH_2OH$, reflux, 8 h; c) H_2, Pd-C, AcOH, r.t.

These 7-(*N*-glycosylamino)indolo[3,2-*b*]quinolines (**1d-g**) and their related compounds (**1a-c**) were evaluated against leukemia P388 in mice (Table I). Apparently, the introduction of a glycosyl group into the chromophore of lead compound **1a** greatly increased its antitumor potency. In this series, 7-(*N*-galactopyranosylamino)indolo[3,2-*b*]quinoline (**1e**) was the most potent antitumor compound [optimal dose = 25 mg, T/C > 333%, cure 5/6 (at day 30)] against P388.

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



Compd. No.	R	Dose (mg/kg)[a]	T/C (%)[b]	Cure[c]
1a	H	12.5	203	2/6
		6.25	300	3/6
		3.13	177	
1b	NO_2	50	70	
		25	131	
		12.5	164	1/6
1c	NH_2	50	242	1/6
		25	200	
		12.5	171	
1d		50	90	
		25	145	
		12.5	213	2/6
1e		50	>333	5/6
		25	>333	5/6
		12.5	268	1/6
1f		50	119	
		25	>332	4/6
		12.5	290	
1g		50	185	
		25	140	
		12.5	114	

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.

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7) *O*-Tetraacetate of **1e**; mp 193—195°C (decomp.). IR (Nujol): 3600, 3380, 1760, 1740 cm^{-1}. ^1H-NMR (60 MHz, $CDCl_3$: 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—4.36 (3H, m, 5"H and CH_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), 6.74 (1H, dd, J = 2 and 8 Hz, 6'H), 6.88—7.75 (5H, m), 7.93—8.55 (3H, m).

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