

SYNTHESIS OF 7-SUBSTITUTED INDOLO[3,2-*b*]-QUINOLINE DERIVATIVES

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Abstract---Indolo[3,2-*b*]quinoline derivatives (**7b-j**) having the substituent, such as a nitro, amino, methyl, halogen, methoxy, or hydroxy group were prepared by three methods.

We have been studying structure-activity relationships of fused tri- and tetracyclic quinoline derivatives, aiming to develop a new DNA intercalative antitumor agent. In the earliest time, we have prepared tetrahydro analogues (**2,3**) of amsacrine (**1**),¹ a DNA intercalative anticancer agent, as shown in Figure 1.²

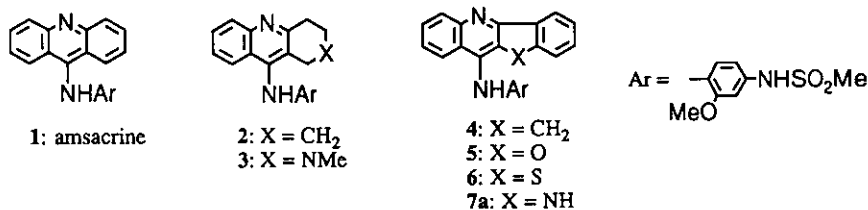
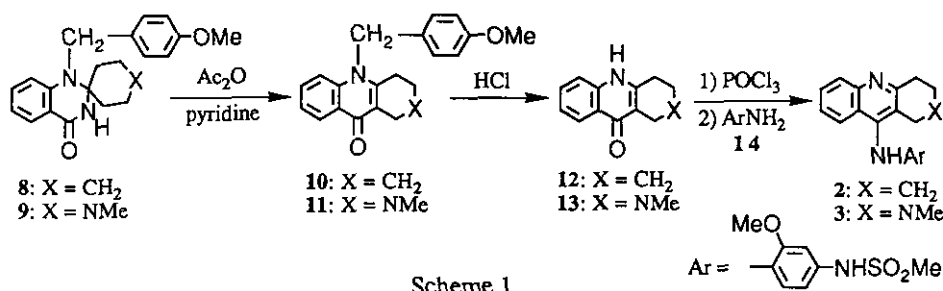


Figure 1

In this synthesis, fused quinolinones (**10,11**) have been prepared by the use of rearrangement reaction of spiro(1,2,3,4-tetrahydroquinazolin)-4-ones (**8,9**) with acetic anhydride and pyridine (Scheme 1). The resulting compounds (**2,3**) are inactive because

the chromophore, tetrahydroacridine ring, can not intercalate with DNA due to non-planarity of their ring systems. These findings led us to search a candidate of new intercalative chromophore. We have developed antitumor-active fused tetracyclic quinolines,³ such as indeno[1,2-*b*]- (4), benzofuro[3,2-*b*]- (5), benzothieno[3,2-*b*]- (6), and indolo[3,2-*b*]- (7a) quinolines having the same side chain of amsacrine (Figure 1). Among these compounds, the indolo[3,2-*b*]quinoline (7a) exhibits the most potent activity and has a broad antitumor spectrum.⁴ We have then selected 7a as a lead compound for further molecular-modification study.



This communication describes the syntheses of indolo[3,2-*b*]quinoline derivatives (7b-j) having various kinds of substituents at 7-position of the chromophore of 7a (Figure 2). Three synthetic methods shown in Schemes 2-5 were selectively used according to the kind of substituents at 7-position.

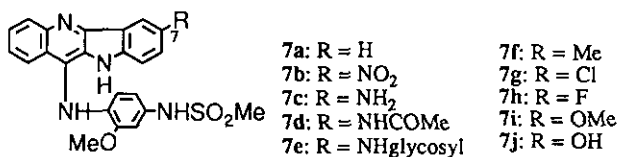
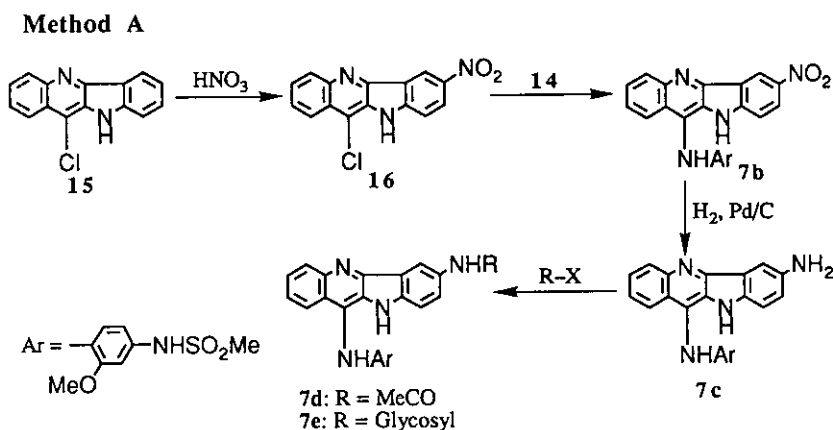


Figure 2

The 7-nitro (**7b**), 7-amino (**7c**), 7-acetamido (**7d**), and 7-glycosylamino (**7e**) congeners were prepared by the method A *via* the nitration of 11-chloro-10*H*-indolo[3,2-*b*]quinoline (**15**) (Scheme 2). The synthetic methods and antitumor activities of these compounds were previously communicated.⁵

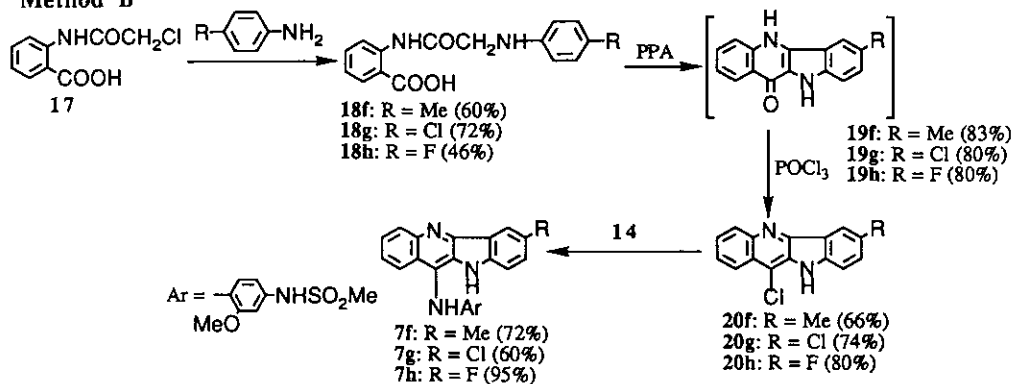


Scheme 2

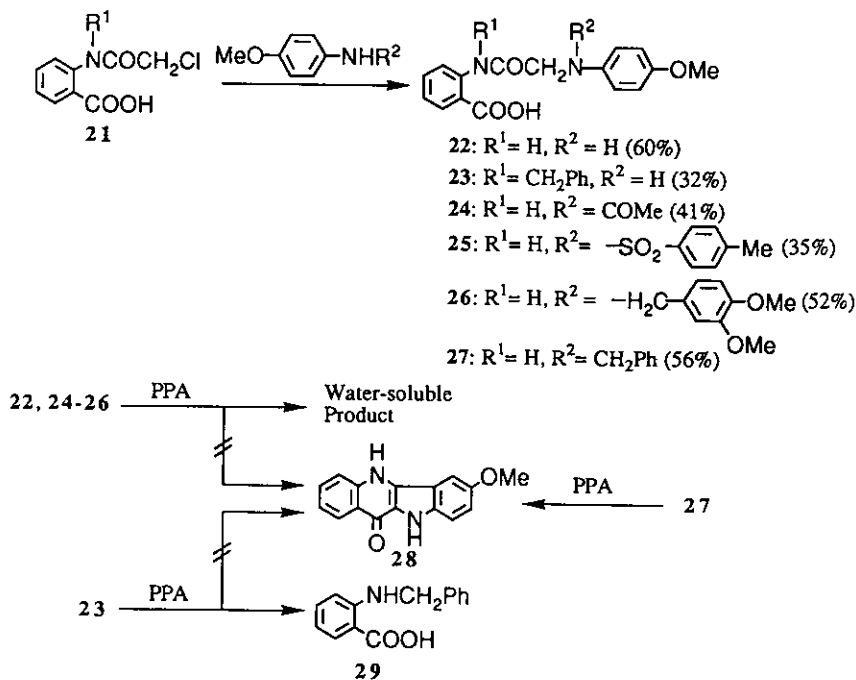
The 7-methyl (**7f**), 7-chloro (**7g**), and 7-fluoro (**7h**) congeners were synthesized by the method B (Scheme 3). The 2-[[*N*-(4-methylphenyl)amino]acetamido]- (**18f**), 2-[[*N*-(4-chlorophenyl)amino]acetamido]- (**18g**), and 2-[[*N*-(4-fluorophenyl)amino]acetamido]-benzoic acids (**18h**) were prepared by the reaction of 2-chloroacetamidobenzoic acid (**17**)⁶ with the corresponding aniline derivatives, respectively. Cyclization of these acids (**18f-h**) by heating with polyphosphoric acid (PPA) afforded the corresponding indolo[3,2-*b*]quinolones (**19f-h**), which were converted to the indoloquinolyl chlorides (**20f-h**) by the treatment with phosphorous trichloride (POCl₃). The final products (**7f-h**) were obtained by heating **20f-h** with *N*-(4-amino-3-methoxy)phenylmethanesulfonamide (**14**),¹ respectively.

Preparation of the 7-methoxy (**7i**) and 7-hydroxy (**7j**) congeners were attempted. At first, cyclization of 2-[[*N*-(4-methoxyphenyl)amino]acetamido]benzoic acid (**22**) to 7-methoxy-5*H*,10*H*-indolo[3,2-*b*]quinolin-11-one (**28**) was attempted according to the method B for the preparation of **19** by heating with PPA. However, the desired **28** could not be obtained

Method B



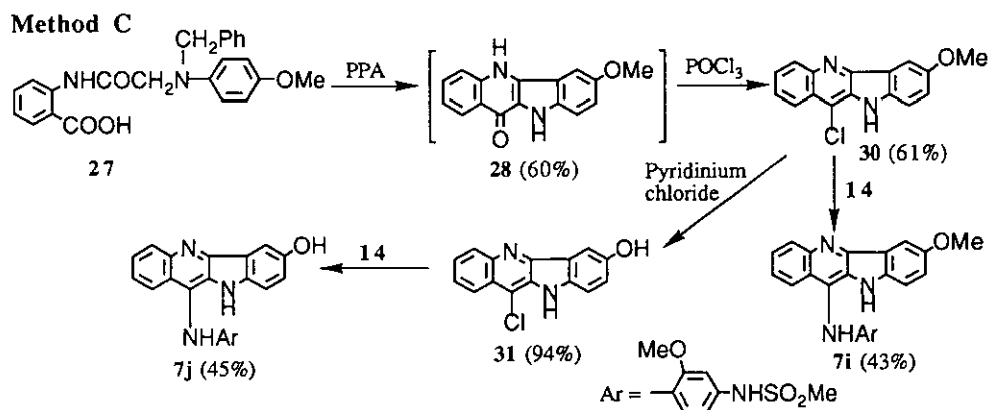
Scheme 3



Scheme 4

at all, and the reaction product was inassignable because of freely soluble compound in water. Therefore, 2- $\{N$ -benzyl- $[N$ -(4-methoxyphenylamino)acetamido]benzoic acid (23), which corresponds to the N -protected derivative at the nitrogen atom of the acetamido moiety of 22 with a benzyl group, was prepared and heated with PPA. However, only N -benzylanthanilic acid (29) was isolated and 28 could not be obtained. Next, N -acetyl (24), N -tosyl (25), N -(3,4-dimethoxy)benzyl (26), and N -benzyl (27) derivatives, which correspond to the N -protected derivatives at the nitrogen atom of the anilino moiety of 22, were prepared and their cyclization to 28 were examined. Only when N -benzyl derivative (27) was heated with PPA, the desired 28 was obtained in 60% yield. All other derivatives (24-26) were changed into freely water-soluble products (Scheme 4).

The 7-methoxy (7i) and 7-hydroxy (7j) congeners were prepared from 28 by the method C (Scheme 5). The 7-methoxy congener (7i) was prepared by the chlorination of 28 followed by amination according to the method A for the preparation of 7a. The 7-hydroxy congener (7j) was synthesized *via* 7-hydroxy-11-chloro derivative (31) prepared by demethylation of 7-methoxy-11-chloro derivative (30) with pyridinium chloride.



Scheme 5

In this series of compounds, 7-glycosylamino (**7e**), 7-methoxy (**7i**), and 7-hydroxy (**7j**) congeners were found to be more potent antitumor-active than the lead compound (**7a**).

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