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

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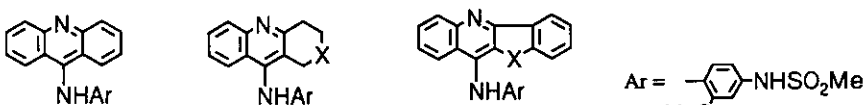
Abstract---Indolo[3,2-*b*]quinoline derivatives (**7b–j**) having the substituent, such as a nitro, amino, methyl, halogen, methoxy, or hydroxy group were prepared by three methods.

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 eariest time, we have prepared tetrahydro analogues (**2**,**3**) of amsacrine (**1**),[1] a DNA intercalative anticancer agent, as shown in Figure 1.[2]



1: amsacrine

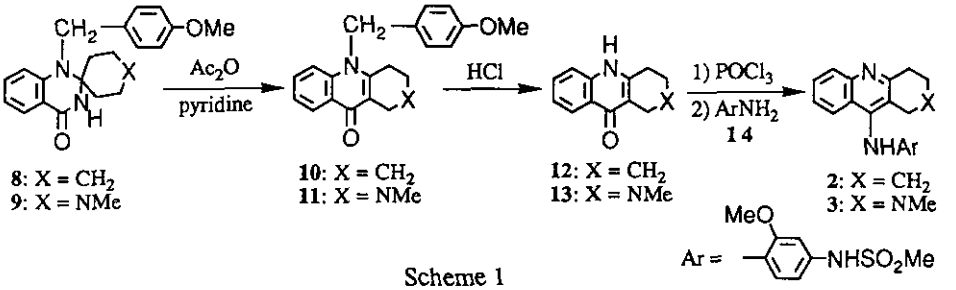
2: X = CH_2
3: X = NMe

4: X = CH_2
5: X = O
6: X = S
7a: X = NH

Figure 1

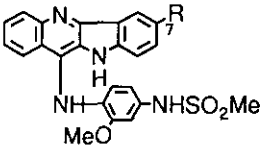
In this synthesis, fused quinolinones (**10**,**11**) have been prepared by the use of rearrangement reaction of spiro(1,2,3,4-tetrahydroquinazolin)-4-ones (**8**,**9**) with acetic anhydride and pyridine (Scheme 1). The resulting compounds (**2**,**3**) are inactive because

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.



Scheme 1

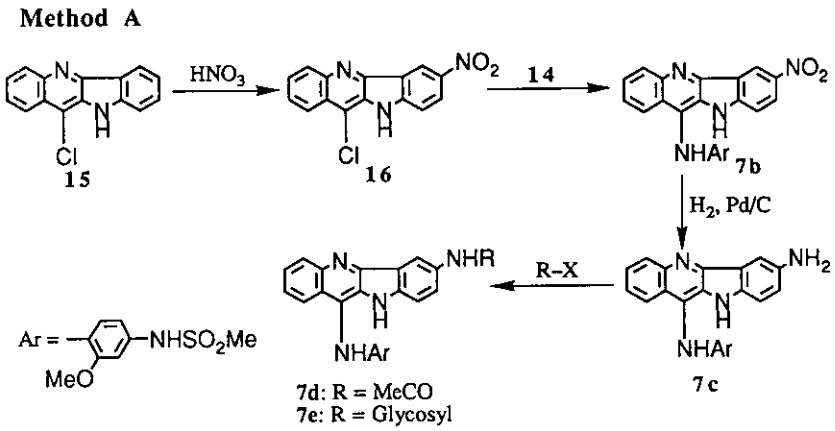
This communication describes the syntheses of indolo[3,2-*b*]quinoline derivatives (**7b-j**) having various kinds of substituents at 7-position of the chromophore of **7a** (Figure 2). Three synthetic methods shown in Schemes 2-5 were selectively used according to the kind of substituents at 7-position.



7a: R = H
7b: R = NO_2
7c: R = NH_2
7d: R = NHCOMe
7e: R = NHglycosyl
7f: R = Me
7g: R = Cl
7h: R = F
7i: R = OMe
7j: R = OH

Figure 2

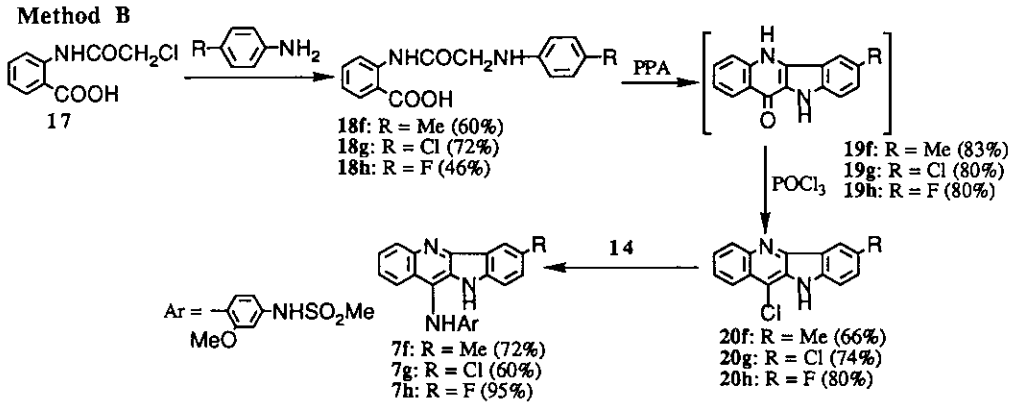
The 7-nitro (**7b**), 7-amino (**7c**), 7-acetamido (**7d**), and 7-glycosylamino (**7e**) congeners were prepared by the method A *via* the nitration of 11-chloro-10*H*-indolo[3,2-*b*]quinoline (**15**) (Scheme 2). The synthetic methods and antitumor activities of these compounds were previously communicated.[5]



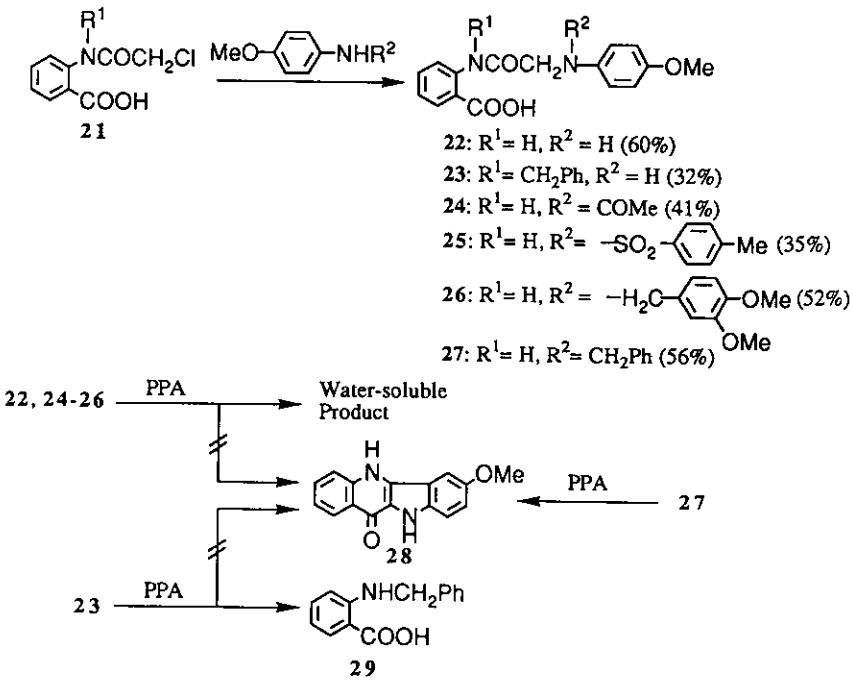
Scheme 2

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 ($POCl_3$). 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



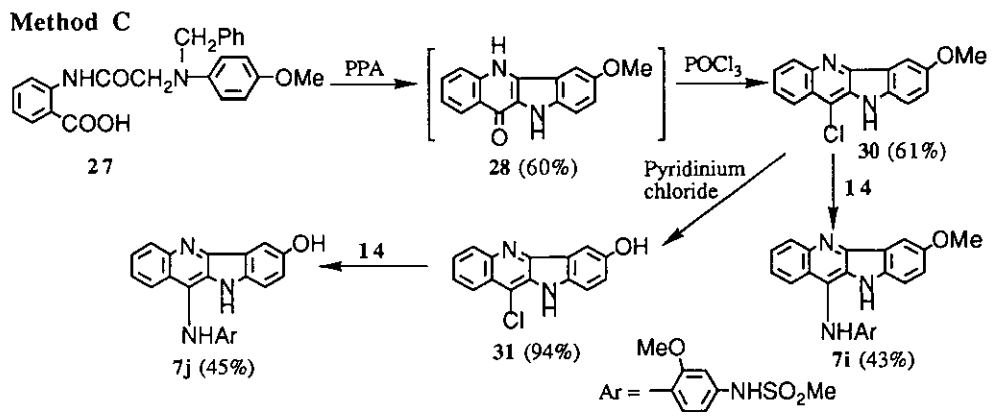
Scheme 3



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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