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Synthesis of a Bis-pyrrolo-quinone Structure Analogue to Wakayin

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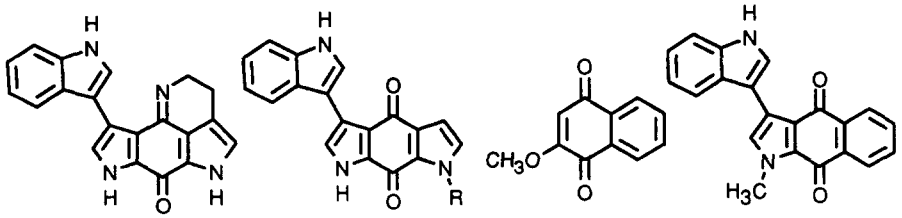
Abstract : The addition of different amines to indole-4,7-quinone is studied. The application of this reaction with indolyl-2-oxoethylamine lead to the preparation of an analogue of wakayin **2.**

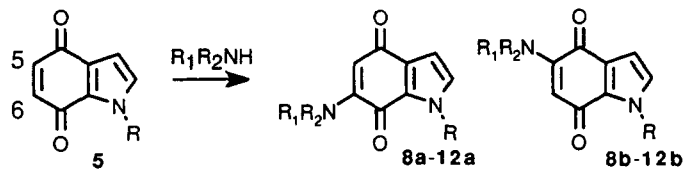
Wakayin **1** isolated from *Ascidian clavelina* [1], shows biological activities such as inhibition of topoisomerases I and II[2]. Untillnow no synthesis of this structure is reported and we planned to obtain the bispyrroloquinone structure **2** substituted with an indole moiety in position 3. Zhang[3] described an approach of structure **4** by the reaction of methoxyquinoline-dione **3** with N-methyltryptamine and subsequent cyclisation by using DDQ in acetic acid (scheme 1).



1 **2** **3** **4** **Scheme 1**

In this work, we wanted first to study the regiochemistry of the addition of different amines to indole-4,7-quinone **5** and then the cyclisation to obtain the bis-indolequinone structure **2.**

In a previous study[4], we have shown that the regiochemistry of the hetero-Diels-Alder reaction with crotonaldehyde dimethylhydrazone and **5**[5] was dependent upon the substitution of the nitrogen atom. With an electron-withdrawing substituent on the nitrogen atom of the indole-4,7-quinone (R = SO_2-Ph-Me), the addition of benzylamine gave the 6-isomer[6] whereas with a hydrogen[6] or a methyl group[7], the 5-isomer was the major product (scheme 2).



5 **8a-12a** **8b-12b** **Scheme 2**

In our hands, with these conditions (quinone/amine : 1/1, solvent : benzene, room temperature or reflux[6]), the amines were formed in low yields.

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We observed that the yields were improved if the the ratio quinone/nucleophile was 1/5 and if an alcoholic solution of the quinone was added slowly (10 ml/h) to the amine in ethanol at room temperature (Table).

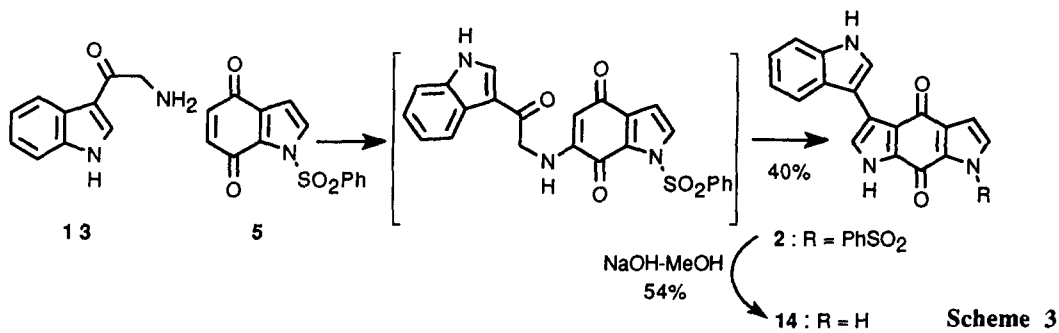
Table

aminoquinones 8-12	nucleophile	yield (%)	8a-12a/8b-12b*
8 : $R_1 = R_2 = H$	NaN_3	58	**8a/8b** = 75/25
9 : R_1=$PhCH_2CH_2$-, R_2=H	phenylethylamine	85	**9a/9b**= 70/30
10 : R_1=R_2=benzyle	dibenzylamine	77	**10a/10b** = 70/30
11 : R_1=indol-3-yl-ethyl, R_2= H	tryptamine	59	**11a/11b** = 90/10
12 : R_1=indol-3-yl-ethyl, R_2=benzyl	N-benzyltryptamine	63	**12a/12b** = 85/15

* : with **8**, **11** and **12** the ratio of regioisomers was calculated after chromatographic purification (silica gel); **9** and **10** were submitted to hydrolysis (MeOH-NaOH) and then the ratio of the deprotected regioisomers was calculated after separation by column chromatography.

The cyclisation of the tryptamine derivatives **11** and **12** with DDQ[3] did not give the expected products. However, we succeeded by using the oxo-tryptamine **13**. This product was prepared from the N-Boc-tryptamine which was oxidized by the Yonemitsu procedure[8] and deprotected with trifluoroacetic acid.

Very slow addition of indole-quinone **5** to the alcoholic solution of **13** (5 equivalents) gave **2** (only one isomer), which was purified by column chromatography and obtained as yellow cristals. This compound was hydrolyzed into **14**. The regiochemistry was determined by ^1H-^{13}C NMR-correlations (HSQC and HMBC).



13 5 **Scheme 3**

The application of this reaction to the total synthesis of wakayin is in progress.

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5- **5** was synthesized from 4,7-dimethoxyindole (see: Showalter, H. D. H.; Pohlmann, G. *Org. Proc. Intern.*, **1992**, *24*, 484); 4,7-dimethoxyindole was sulfonylated and then oxidized by using CAN.

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9- Compound **5** : Mp : 266-267°C; IR : ν (cm^{-1}): 3310, 3221, 2925, 1650, 1641, 1425. ^1H-NMR (500 MHz, CD_3OD) δ (ppm): 8.25 (1H, m, CH),7.97 (1H, s, CH), 7.95 (1H, s, CH), 7.40 (1H, m, CH), 7.20 (2H, m, CH), 6.90 (1H, d, J=3 Hz, CH), 6.60 (1H, d, J=3Hz, CH). ^{13}C-NMR (125 MHz, CD_3OD) δ (ppm): 179.7, 173.4, 138.0, 137.6, 134.8, 134.7, 129.3, 126.1, 126.0, 125.9, 124.0, 123.1, 122.3, 121.3, 117.1, 112.4, 108.3.