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First efficient synthesis of novel oxophenyl-arcyriaflavin analogs

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Abstract—New oxophenylarcyriaflavins were synthesized in a few efficient steps. The key steps involved at first a palladium cross-coupling between the 3-bromo-4-(1*H*-indol-3-yl)1-methylpyrrole-2,5-dione and the 2-formylphenylboronic acid or a methyl 2-trialkylstannylbenzoate, followed by an intramolecular acylation in a C-2 indolic position. All the sequence was carried out without any indolic protective group.

Indolocarbazole derivatives are a family of natural or synthetic products commonly exemplified by the Rebeccamycin **I**, a weak inhibitor of topoisomerase I.[1] In order to develop selective kinase inhibitors, interacting with the ATP binding site of the enzymes, modifications of the indolocarbazole moiety appeared as a valid alternative to the synthesis of glycosylated compounds. Indeed, recent developments in this domain confirmed the inhibition of Cyclin dependent kinases (CDK) by indolocarbazole aglycones such as arcyriaflavin A **II** or several (het)aryl carbazoles in a nanomolar range.[2]

In addition, the use of indene versus indole generated the CEP-7055 **III**, a strong inhibitor of VEGF-R2 (KDR kinase), which is a candidate for clinical trials in the antiangiogenic area (Fig. 1).[3]

For our own part, we demonstrated that one of the two indoles could be replaced by a naphthyl (compounds **IV**) or a phenyl group (compounds **V**).[4,5] In addition, a few studies reported bis-indolic compounds, which contained a seven-membered ring but, so far, no significant activities have been reported. For instance, derivatives such as homoarcyriaflavin,[6] arcyriacyanin A,[7] and the marine alkaloid caulersine, were recently described and synthesized (Fig. 2).[8–10]

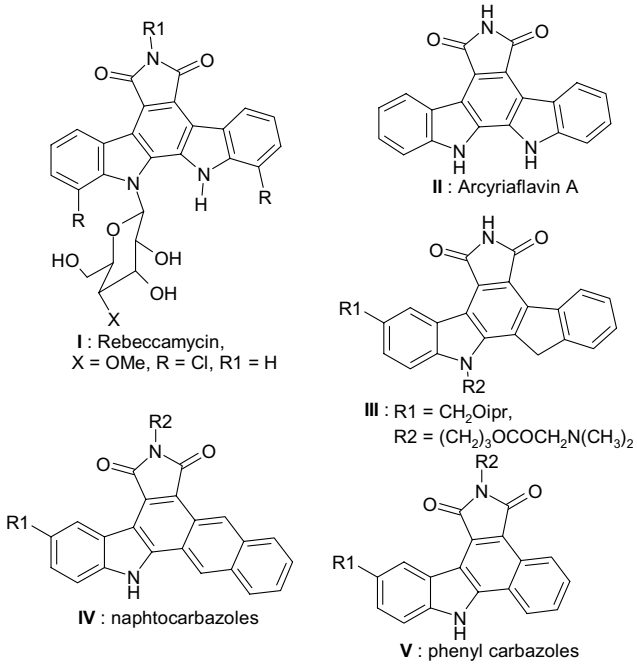

Figure 1. Most representative indolocarbazole derivatives.

Here we report the design and synthesis of new hybrid derivatives **5** and **11**. They contained an indole as **I**–**V**, a seven-membered ring related to **VIII** and a phenyl group like **V**. The central cycloheptatrienone moiety was coupled with a maleimide or a maleic anhydride. The resulting original structures were obtained applying

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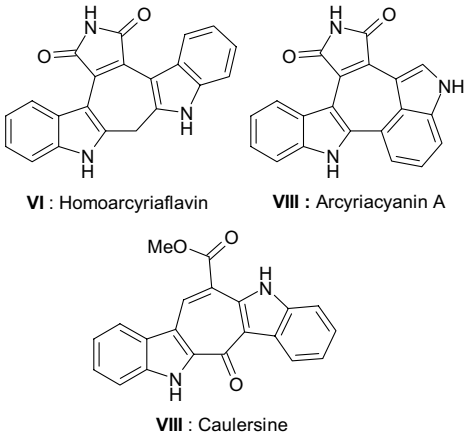


Figure 2. Bisindolyl compounds containing a central seven-membered ring.

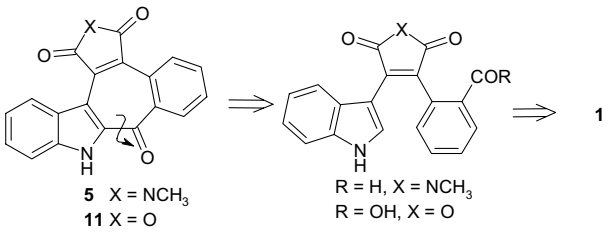


Figure 3. Retrosynthetic scheme.

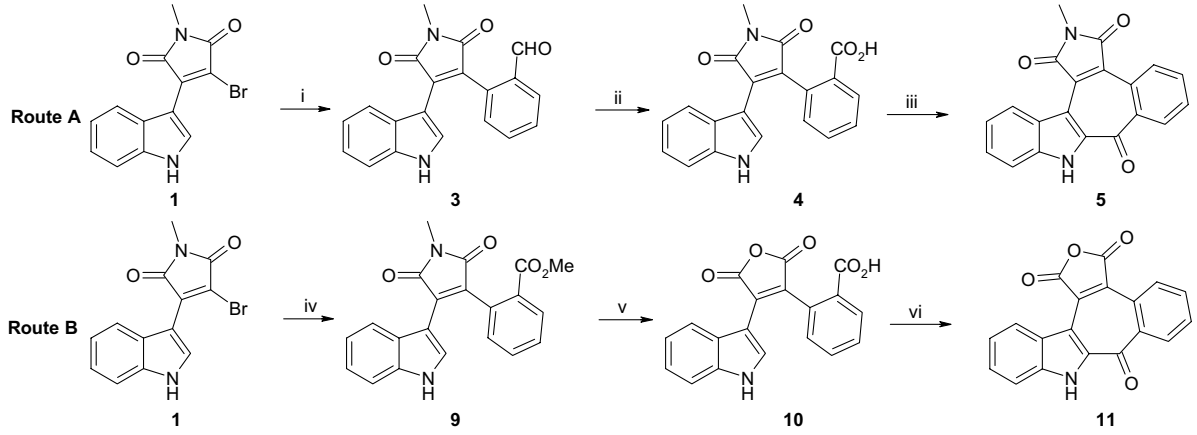
the retrosynthetic scheme shown in Figure 3, in a few steps from 3-bromo-4-(1*H*-indol-3-yl)-1-methylpyrrole-2,5-dione **1**[10,11] and involved as key steps (i) a cross-coupling palladium catalyzed reaction, (ii) an oxidation, and (iii) an intramolecular cyclization in the C-2 indolic position.

First reaction (route A) involved the preparation of **1**, which was classically obtained from indole and 2,3-dibromomaleimide in the presence of LiHMDS in THF in a fair good yield.[11] A palladium cross-coupling Suzuki type reaction (Table 1) between **1** and the commercially available 2-formylphenylboronic acid **2** (1.1 equiv) led to **3**. According to our previous work using the 2-methoxynaphthalene boronic acid,[5] we carried out the reaction in presence of K_2CO_3 (1.8 equiv) in a refluxing mixture of dioxane/water 85/15 using $Pd(OAc)_2$ as a catalyst (entry 1). The reaction afforded the desired compound **3** in 30% yield after 13 h. Increasing the reaction time was unfruitful and led to the degradation of the mixture proving the low stability of **3**, certainly due to the presence of the free nitrogen atom in aqueous basic conditions. Decreasing the reaction time to 8 h led to **3** in only 26%. Fortunately, the reaction with 1.5 equiv of boronic acid led after 6 h to the desired compound **3** in 72% yield. This result was higher than the one obtained in the naphthalenic studies (55%)[5] (Scheme 1).

The next step was aimed at generating a C-2 indolic carbonyl function. The literature reported several useful

Table 1. Conditions of the palladium catalyzed reactions. All the reactions were carried out at reflux

Entry	Reagents	Catalyst (equiv)	Additive (equiv)	Solvent	Reaction time (h)	Product (yield, %)
1	**1** (1 equiv), **2** (1.1 equiv)	$Pd(OAc)_2$ (0.1)	K_2CO_3 (1.8)	Dioxane/water 85/15	(a) 13 (b) 8	**3** (30) **3** (26)
2	**1** (1 equiv), **2** (1.5 equiv)	$Pd(OAc)_2$ (0.1)	K_2CO_3 (1.8)	Dioxane/water 85/15	6	**3** (72)
3	**6**	$Pd(PPh_3)_4$ (0.1)	Sn_2Bu_6 (1.2)	Toluene	23	**7** (47)
4	**6**	Pd $(PPh_3)_4$ (0.1)	Sn_2Me_6 (1.2)	Toluene	2	**8** (97)
5	**1** (1 equiv), **7** (1.2 equiv)	$PdCl_2(PPh_3)_2$ (0.2)	CuI (0.1)	Dioxane	8	**9** (12)
6	**1** (1 equiv), **7** (1.5 equiv)	$PdCl_2(PPh_3)_2$ (0.2)	CuI (0.1)	Dioxane	6	**9** (74)
7	**1** (1 equiv), **8** (1.5 equiv)	$PdCl_2(PPh_3)_2$ (0.2)	CuI (0.1)	Dioxane	5	**9** (70)



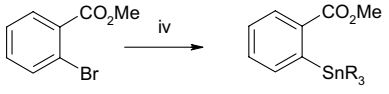
Scheme 1. Reagents and conditions: (i) 2-formylphenylboronic acid **2** (1.5 equiv), $Pd(OAc)_2$ (0.1 equiv), K_2CO_3 (1.8 equiv), dioxane/water 85/15, rflx., 6 h, 72%; (ii) NH_2SO_3H (8.1 equiv), $NaClO_2$ (2.2 equiv), dioxane/water, 6 °C, 1 min, 81%; (iii) $BF_3{\cdot}Et_2O$ (40 equiv), DCE, rflx., 6 h, 89%; (iv) from **7** (1.5 equiv), $PdCl_2(PPh_3)_2$ (0.2 equiv), CuI (0.1 equiv), dioxane, rflx., 6 h, 74%, from **8** idem, 5 h, 70%; (v) aq KOH (45%, 60 equiv), acetone, rt, 20 h then HCl concn to pH = 1, rt, 3 days, 98%; (vi) see (iii), 20 h, 70%.

methods in the absence of a nitrogen indolic protective group. These implied the use of carboxylic acids, and the formation of an acylium ion by Friedel–Crafts related reactions. So we oxidized the aldehyde function of **3** into a carboxylic acid with an aqueous solution of sodium chlorite (2.2 equiv) and sulfamic acid (8.1 equiv) between 7 and 10 °C.[12] After only 1 min the starting material completely disappeared and the reaction afforded the desired carboxylic acid **4** in 57% yield. If the reaction was performed at 6 °C by accurate control of the temperature during the oxidant addition, the acid **4** was obtained in 81% yield. An increase of the time to 5 min led only to degradation. Numerous variations indicated that these conditions were extremely efficient, but extremely time and concentration sensitive.

Following route A, the ring closure leading to the central seven-membered cycle was the next goal. As described in the literature, we chose to perform it through an electrophilic cyclization. Common reagents for such a reaction were $AlCl_3$ or phosphoric reactants such as PPSE.[13–15] Milder conditions involved the use of an anhydride in presence of $BF_3{\cdot}Et_2O$.[16–18] For our own part, we carried out the reaction in the presence of a large excess of $BF_3{\cdot}Et_2O$ as a Lewis acid in refluxing DCE without any pre-activation of the carboxylic acid function.[16–18] After 12 h, compound **5** was isolated in 66% yield along with numerous nonidentified by-products. The yield could be increased to 89% by lowering the reaction time to 5 h 30 min. After completion of the reaction, an aqueous treatment and extractions led directly to pure **5**. To our knowledge, it is the first example of such an acylation using $BF_3{\cdot}Et_2O$ without an indolic protection.

Considering that the Suzuki reaction and the highly sensitive oxidation to access compound **4** were limiting steps to scale up the synthesis, route B was designed. The 2-tributylstannyl and trimethylstannyl derivatives **7** and **8** were reported as efficient reagents in such a strategy.[19,20] Starting from the methyl-2-bromo benzoate **6**, compound **7** could be prepared using $Pd(PPh_3)_4$ as a catalyst. Unfortunately, the yield was limited to 41% after 21 h using a low amount of palladium catalyst (0.008 equiv). Surprisingly, increasing the amount of catalyst to 0.1 equiv did not decrease the reaction time. After 23 h, the yield of compound **5** was slightly increased to 47% (Scheme 2, entry 3).

In order to enhance the yield, we decided to explore some other conditions by slight step by step modifications. So we used $PdCl_2(PPh_3)_2$ as a catalyst, in the presence or absence of LiCl in refluxing THF or dioxane



6 **7** R = Bu
8 R = Me

Scheme 2. Reagents and conditions: for **7**: $Pd(PPh_3)_4$ (0.1 equiv), Sn_2Bu_6 (1.2 equiv), tol., rflx., 23 h, 47%, for **8** Sn_2Me_6 (1.2 equiv), 2 h, 97%.

with no significant results. The same reaction was carried out using hexamethylditin (in spite of its greater toxicity). Indeed, whereas the use of Sn_2Bu_6 proved to be quite ineffective, Nicolaou reported the achieving of 71% yield shifting from Bu to Me.[20] In our hand, after a reaction time of 2 h, compound **8** was obtained in 97% yield (entry 4).

The Stille procedure between the bromo compound **1** and the stannylated derivative **7** (1.2 equiv) was performed with $PdCl_2(PPh_3)_2$ as a catalyst in refluxing dioxane in the presence of CuI. After 8 h only 12% of the desired compound **9** was obtained (entry 5). Increasing the amount of **7** to 1.5 equiv reduced the reaction time to 6 h and the yield increased to 74%. Under similar conditions, the trimethyltin derivative **8** led to the same product **9** after 5 h in 70% yield (entries 6 and 7). The ester was saponified using aqueous KOH in acetone at room temperature during 5 h. Then, the acidification step led, after 12 additional hours, to the maleic compound **10** in 98% yield without any difficulty. The intramolecular cyclization corresponding to the final step was performed with $BF_3{\cdot}Et_2O$ during 20 h to afford the second targeted analog **11** in 70% yield. During the course of this cyclization, no side reaction was observed in spite of the presence of the anhydride function.

In this paper we described two different ways to obtain the *N*-methylmaleimide compound **5** and the anhydride **11** in three steps from compound **1**. Route A, which included a Suzuki reaction led to **5** in 52% overall yield.[21] Route B involving a Stille reaction afforded the anhydride **11** in 51% global yield. The two routes were quite similar but way B implied the preparation of a trimethyltin derivative by an additional step. The biological evaluation of **5** and **11** as kinase inhibitors are being currently performed. Further investigations to explore the reactivity of the maleimide and anhydride functions and a generalization of the synthetic sequence to substituted indoles are already in progress and will be reported in due course.

Acknowledgements

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21. *Synthesis of* **5**: To a solution of acid **4** (745 mg, 2.15 mmol) in dichloroethane (120 mL), $BF_3{\cdot}Et_2O$ (11 mL, 86.6 mmol) was added dropwise. The mixture was refluxed for 5 h 30 min before quenching with iced water (100 mL). CH_2Cl_2 (100 mL) was added and the aqueous layer was extracted three times with CH_2Cl_2 (60 mL). The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$ (120 mL) then with water (3×120 mL). After drying over Na_2SO_4, the solvents were removed under reduced pressure. The orange solid was washed with a slight amount of cold MeOH to give **5** (626 mg, 89%) : mp 230–233 °C (dec). IR (KBr, cm^{-1}) ν 3272 (NH), 1768, 1703, 1388, 750. ^1H NMR (DMSO-d_6, 250 MHz) δ (ppm) 2.98 (s, 3H), 7.27 (t, 1H, $J = 7.4$ Hz), 7.47 (t, 1H, $J = 7.4$ Hz), 7.63 (d, 1H, $J = 8.2$ Hz), 7.71–7.86 (m, 2H), 8.30 (d, 1H, $J = 8.0$ Hz), 8.63 (d, 1H, $J = 8.3$ Hz), 8.70 (d, 1H, $J = 8.1$ Hz), 13.09 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ (ppm) 24.1 (CH_3), 111.3 (Cq), 112.8 (CH), 121.8 (CH), 123.8 (Cq), 125.0 (CH), 126.4 (CH), 126.9 (CH), 128.1 (Cq), 129.3 (CH), 130.2 (CH + Cq), 130.9 (CH), 131.7 (Cq), 137.1 (Cq), 138.0 (Cq), 141.1 (Cq), 168.9 (C=O), 170.1 (C=O), 179.8 (C=O). HRMS-ESI 328.0848 calcd for $C_{20}H_{12}N_2O_3$, found 328.0855 ($M^{+\cdot}$).