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Synthesis and biological evaluation of novel benzodioxinocarbazoles (BDCZs) as potential anticancer agents

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ABSTRACT

We report the efficient synthesis and biological evaluation of new benzodioxinoindolocarbazoles heterocycles (BDCZs) designed as potential anticancer agents. Indolic substitution and maleimide variations were performed to design a new library of BDCZs and their cytotoxicity were evaluated on two representative cancer cell lines. Several derivatives have shown a marked cytotoxicity with IC_{50} values in the nanomolar range. Results are reported in this Letter.

The indolocarbazole alkaloids are a family of natural products isolated from marine invertebrates and cultures of diverse microorganisms.[1] Rebeccamycin (Fig. 1), an important member of this family, is potent inhibitor of topoisomerase I. Its biological activities have made it a high profile lead compound for the development of anticancer drugs,[2] and several analogues (i.e., NB-506 and J-107088 or edotecarin) have entered clinical trials.[3]

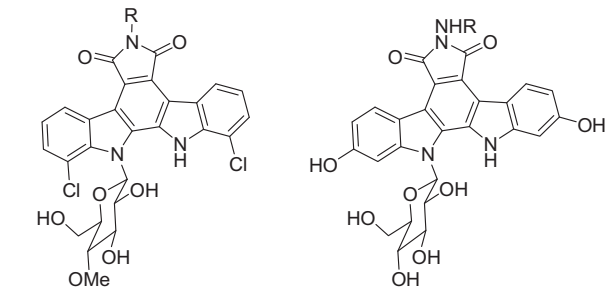
A number of research groups, including ours, have sought to synthesize various simplified derivatives (Fig. 2), lacking the sugar moiety to obtain strong protein kinase inhibitors and/or in vitro cytotoxic agents.[4] In order to develop such selective series, bioisosteric replacement of one indole ring by another heteroaryl moiety appears indeed to be a valid alternative compared to the restrictive synthesis of glycosylated compounds.[5]

On the background of these findings, we describe herein the preparation of new potential anticancer lead compounds bearing an original benzodioxinocarbazole moiety.[4f] For the establishment of primary structure–activity relationships of these new functionalized carbazoles, cell studies were performed.

We endeavored to prepare original benzodioxino-pyrrolocarbazoles (BDCZs) **V** (Fig. 3) using a general synthetic route that relied on a photochemically induced 6π-electrocyclization as a key step.[4a,d,6] The synthetic strategy is also based on a Stille Pd(0)-catalyzed cross-coupling reaction starting from intermediate **VII** and 2-trialkylstannylbenzodioxine.

Structural variations were performed on the indolic part, for fine-tuning developments and for establishing structure–activity relationships. Electron rich and acceptor/donor hydrogen bond groups were used. In addition, to induce a selective cytotoxic activity and to increase water solubility of our new heterocyclic scaffold, we though to introduce a dimethylaminoalkyl chain onto the maleimide moiety.[4e–i]

The synthesis began with the construction of the upper side of the molecule via a Stille palladium cross-coupling reaction[7]



Rebeccamycin R = H
NSC 655 649 R = $(CH_2)_2N(C_2H_5)_2$

NB-506 R = CHO
J-107088 R = $CH(CH_2OH)_2$

Figure 1.

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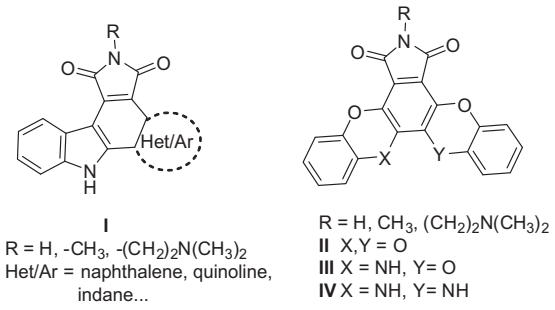


Figure 2. Examples of indolocarbazoles bioisosteres **I**–**IV**.

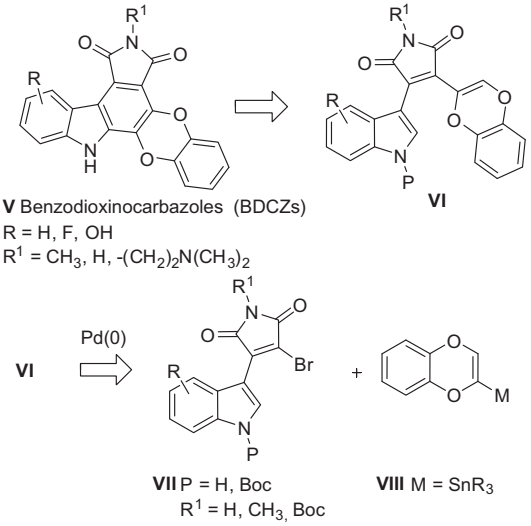


Figure 3. General synthetic scheme.

(Table 1) to afford in fair to good yields desired compounds **16–27**. Reactions were performed starting from 2-trimethylstannyl-benzodioxine and indolo-derivatives **1–15**[8] in the presence of $Pd(PPh_3)_4$ and CuI in dioxane at 65 °C or 100 °C. The palladium cross-coupling reaction could be conducted with *N*-Me, *N*-Boc or *N*-H maleimide and Boc protected or unprotected indolyl compounds. Indole could be functionalized by electro-donor or -withdrawing groups. For benzyloxy derivatives (entries 5–8, 12–15) best yields were obtained after protection of the indolyl nitrogen with a Boc group.[8]

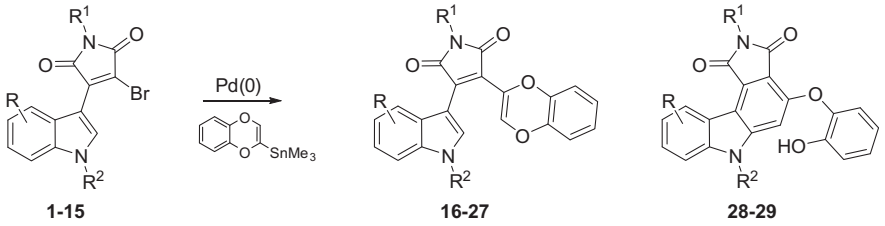
It is worth noting that ring-opened phenols **28** or **29** were isolated as separable by-products starting from **7** or **8**, respectively. As previously demonstrated, these phenolic derivatives result from the ring opening of the benzodioxane moiety obtained via a spontaneous [4+2] cycloaddition/ring opening sequence.[9]

Next, our attention turned to study the key cyclization step. Good results were obtained by performing a photochemical induced 6π-electrocyclization (Table 2). This key step was accomplished by submitting coupled derivatives **16–27** to irradiation (UV 500 W DEMA-lamp) and led to the attempted BDCZs **30–40**.[10] The reaction was conducted in the presence of an excess of diiodine in order to induce a further spontaneous aromatization.

Starting from unprotected derivatives **17–19** or **23–25**, the reaction led respectively to carbazoles **31–33** or **36–38** isolated as the sole products in moderate yields (entries 2–4, 7–9). With Boc derivatives (entries 1, 5, 6, 10, 11), both processes of β-elimination and of aromatization concomitantly occurred which afforded a separable mixture of attempted BDCZS and phenolic derivatives **41–45**. It is noteworthy that the Boc protective group of the indolyl nitrogen survives to the experimental conditions whereas the maleimide Boc protection is cleaved (entries 10 and 11).

To fully prepare our derivatives for biological assays and to enhance their solubility, additional reactions were next performed (Table 3). Maleimide substitution was carried out by heating the starting carbazoles **31–35** in the presence of *N*,*N*-dimethylethylenediamine (entries 1–5).[11] The transimidification process led to

Table 1
Stille palladium cross-coupling procedure[a]



Entry	Compound	R	R^1	R^2	Time	CuI (mol %)	Products[b] (yields %)
1	**1**	H	CH_3	Boc	1 h	20	**16**[c] (82%)
2	**2**	H	CH_3	H	1 h 45 min	20	**17** (79%)
3	**3**	5-F	CH_3	H	1 h 40 min	10	**18** (81%)
4	**4**	6-F	CH_3	H	45 min	10	**19** (82%)
5	**5**	5-OBn	CH_3	H	1 h	20	Degradation
6	**6**	6-OBn	CH_3	H	50 min	10	**20** (64%)
7	**7**	5-OBn	CH_3	Boc	50 min	20	**21** (76%), **28** (20%)
8	**8**	6-OBn	CH_3	Boc	30 min	10	**22** (84%), **29** (16%)
9	**9**	H	H	H	2 h	10	**23** (76%)
10	**10**	5-F	H	H	2 h40	10	**24** (82%)
11	**11**	6-F	H	H	1 h50	10	**25** (85%)
12	**12**	5-OBn	H	H	1 h	10	Degradation
13	**13**	6-OBn	H	H	1 h	10	Degradation
14	**14**	5-OBn	Boc	Boc	1 h10	10	**26** (69%)
15	**15**	6-OBn	Boc	Boc	2 h	10	**27** (65%)

[a] Reagents and conditions: (a) $PdCl_2(PPh_3)_2$ 10 mol %, CuI 10 or 20 mol %, dioxane 65 °C.
[b] Yields are indicated as isolated products.
[c] The reaction was conducted at 100 °C.