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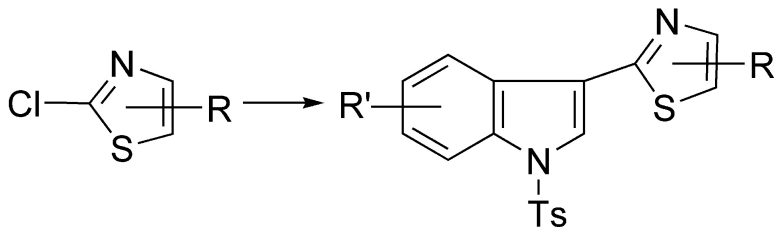

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Reports

Solution-Phase Synthesis of a Thiazoyl-Substituted Indolyl Library via Suzuki Cross-Coupling

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Introduction

The application of parallel synthesis to generate combinatorial libraries as an efficient means of creating pharmaceutical "drug-like leads" has gained considerable interest.[1,2] By accelerating the synthesis and screening of an ever larger number of synthetic analogues, combinatorial chemistry has greatly impacted the drug discovery process.[3] Despite this success, compounds originating from natural sources still play a major role in drug therapy. One of the topics of current combinatorial chemistry is to design small molecule libraries based on natural products as templates.[4]

Camalexins (**1a**−**1c**), which was produced as phytoalexins in the leaves of *Camelina sativa* (Cruciferae) in response to infection by the fungus *Alternaria brassicae*, was elucidated to be (3′-indolyl)-2-thiazoles.[5] The naturally occurring BE 10988 (**2**), an inhibitor of topoisomerase, was shown to be a thiazole-substituted indolequinone.[6] Several syntheses of analogues of these two natural products were introduced, from a Grignard reaction of substituted indoles and 2-bromothiazole,[7] with a Hantzsch reaction as the key step,[8] or by photocyclization of substituted (indol-1-yl)thioureas.[9] The thiazole and benzothiazole derivatives of indole have been found to exhibit antimicrobial[7] and cytotoxic activities.[8] Our efforts for the synthesis and biological activity studies of bis(indolyl)thiazoles also developed new antitumor agents.[10] Biaryl bond construction using the Suzuki reaction is attractive because both solution-[11] and solid-phase[12] reaction conditions are documented. The boric acid byproducts of the Suzuki coupling process are essentially nontoxic, which is of particular importance in library synthesis. In our efforts to search for novel antitumor agents, we have synthesized bisindole alkaloids utilizing Suzuki coupling as the key step.[13] As a part of our ongoing study in building libraries for pharmaceutical drug discovery,[14] we designed some analogues of camalexins mainly by introducing diversities in the thiazole moiety. Herein, we report a solution-phase synthesis of a thiazoyl-substituted indolyl library using Suzuki cross-

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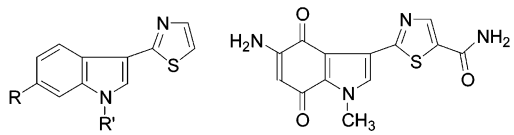
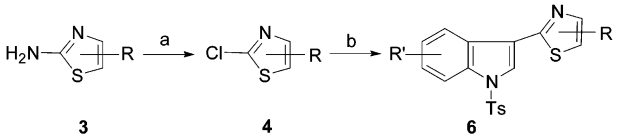


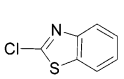
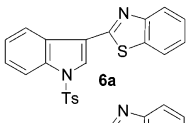
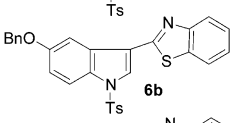
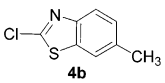
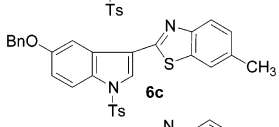
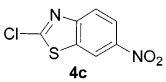
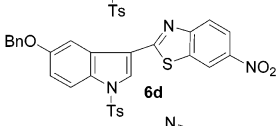
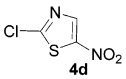
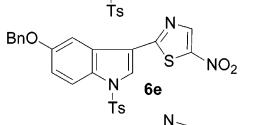
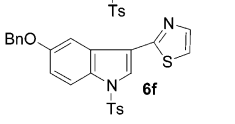
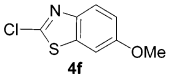
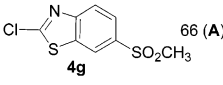
Figure 1. Structures of naturally occurring camalexins and BE 10988.

Scheme 1[a]



[a] Reagents and conditions: (a) method A: (1) $NaNO_2$, $CuSO_4$, concentrated HCl; (2) CuCl, concentrated HCl; method B: *t*-BuONO, $CuCl_2$, CH_3CN; (b) **5**, $Pd(PPh_3)_4$, 2 M aq. Na_2CO_3, MeOH/benzene (1/4), 80 °C.

Table 1. Preparation of 2-Chlorothiazoles and Synthesis of (Indolyl)Thiazoyl via Suzuki Cross-Coupling

entry	2-chlorothiazole **4**	Yield (%)[a] (method)[b]	Indolyl thiazole **6**	Yield (%)[d]
1	 **4a**	—— [c]	 **6a**	87
2	**4a**	—— [c]	 **6b**	84
3	 **4b**	53 (**A**)	 **6c**	52
4	 **4c**	52 (**B**)	 **6d**	90
5	 **4d**	77 (**B**)	 **6e**	92
6	 **4e**	—— [c]	 **6f**	85
7	 **4f**	91 (**B**)	No Reaction	
8	 **4g**	66 (**A**)	No Reaction	

[a] Isolated yields for preparation of **4** from **3**. [b] The method used for preparation of 2-chlorothiazole (Scheme 1). [c] The 2-chlorothiazoles were from commercial sources. [d] Isolated yields for synthesis of **6** via Suzuki cross-coupling.

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coupling between diverse 2-chlorothiazoles (**4a**−**4g**) and *N*-tosyl-3-indolylboronic acids (**5a**−**5b**).

Results and Discussion

A 2-chlorothiazoyl sublibrary was prepared[14b] before the target library construction could begin. The 2-chlorothiazoles, except for the commercially available **4a** and **4e**, were prepared from the corresponding 2-aminothiazoles by Sandmeyer reactions (method A) or by using the *tert*-butyl nitrite-cupric chloride reagent system (method B).[15] The latter procedure not only utilized a solvent (acetonitrile) which dissolves the starting aminothiazoles **3** but also eliminated the hydrogen-substituted byproduct, resulting in higher yields of the desired products **4** (Scheme 1, Table 1).

With the thiazoyl sublibrary in hand, we next turned our attention to the elaboration of 2-(3′-indolyl)thiazoyl library using Suzuki cross-coupling (Scheme 1). Relative to aryl bromide or iodide, the reactivity of aryl chloride in this reaction has proven to be much lower. A model reaction of **4a** (in 1 mmol scale) with *N*-tosyl-3-indolylboronic acid (**5a**) gave **6a** in a yield of 87% (Table 1, entry 1), which established the efficacy of the proposed coupling process. A benzyloxy group was introduced into the indole core, which might facilitate a possibly necessary solid-phase synthesis. Thus, 5-benzyloxy-*N*-tosyl-3-indolylboronic acid (**5b**) was subjected to the Suzuki reactions with the constructed 2-chlorothiazoyl sublibrary in the presence of a catalytic $Pd(PPh_3)_4$ and with 2 M aqueous solution of Na_2CO_3 as the base. The cross-couplings proceeded smoothly in good-to-excellent yield (Table 1, entries 2−6) unless the thiazole substrate was an electron-rich benzothiazole 2-chloride (entries 7−8).

In summary, we have designed an exploratory library based on natural products by introducing diversities into the thiazole moiety, and have employed Suzuki cross-coupling in the synthesis of the library in good-to-excellent yields. This library is now being evaluated for biological activity and the details will be reported in due course. Our further study in building (indolyl)thiazoyl libraries for pharmaceutical drug discovery will be decided upon the evaluation.

Supporting Information Available. Experimental procedures and analytical data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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