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Synthesis of diketopiperazine-based carboline homodimers and in vitro growth inhibition of human carcinomas

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ABSTRACT

Starting from D- or L-tryptophan, we have synthesized and characterized six compounds **2.29**–**2.31a** and **b** that belong to a class of nitrogen heterocycles: the carboline-based homodimers. Each individual homodimer features a 1,3-*trans* relationship on each side of the central diketopiperazine core, but differs in absolute stereochemistry and also in substitution on the 4′ and 4″ oxygens (–Bn, $-CH_3$, or –H). The in vitro cytotoxicity of the six compounds was evaluated by measuring the growth inhibition in NCI–H520 and PC-3 human carcinoma cells. Phenol **2.30a** inhibited cancer cell growth approximately three times better than its enantiomer **2.30b** and possessed a GI_{50} comparable to the clinically used agent etoposide in both cell lines. We have concluded that both the stereochemistry imparted by L-tryptophan and the presence of hydroxy substituents at the 4′ and 4″ positions are necessary to generate cytotoxic properties in the homodimer class. We are now employing **2.30a** as a new lead compound in our efforts to discover improved indole-based cancer chemotherapeutics.

Interest in the synthesis of novel indole-based heterocycles has increased in recent years due to the prevalence of indoles in biologically-active natural products such as the fumitremorgin class[1,2] and the significance of the indole moiety in clinical chemotherapeutics like ellipticine.[3,4] As Danishefsky,[5] Corey,[6] Boger,[7] Cook,[8] Joullié[9] and others[10] have independently demonstrated, indoles can be easily incorporated into a complex target molecule by starting from the amino acid tryptophan (Trp). While pursuing a program to synthesize β-carboline derivatives from D- or L-Trp–OMe using the Pictet–Spengler reaction,[11] we serendipitously discovered a new class of cytotoxic carboline analogs that are similar in structure to ellipticine,[3,12] azatoxin,[13] gypsetin,[5] the tryprostatins,[14] and other[15] heterocycles. This group of bivalent, nitrogen-rich heterocycles, which we identify as the carboline homodimer class, contains several characteristic structural features: (1) seven consecutive fused rings (2) a central diketopiperazine (DKP) core, and (3) indole rings that cap each end (Fig. 1). Although each homodimer retains a 1,3-*trans* relationship on each side of the central DKP ring, the six homodimers also differ by their absolute configuration at C_{7a}/C_{15a} and C_{14}/C_6, and by their substitution at the 4′ and 4″ phenol oxygen (Scheme 1).

We synthesized three enantiomeric pairs of the homodimers: **2.29a** and **b** (R = –Bn); **2.30a** and **b** (R = –H); or **2.31a** and **b**

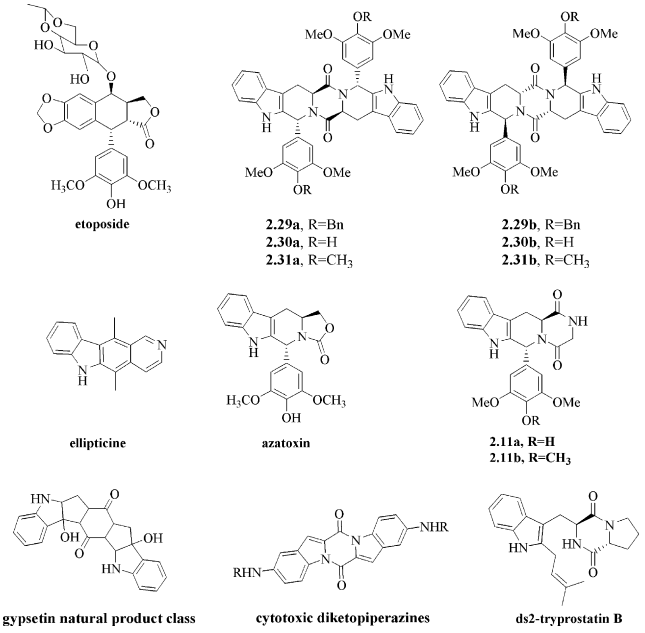

Figure 1. Structures of carboline homodimers, etoposide, and structurally-related nitrogen heterocycles.

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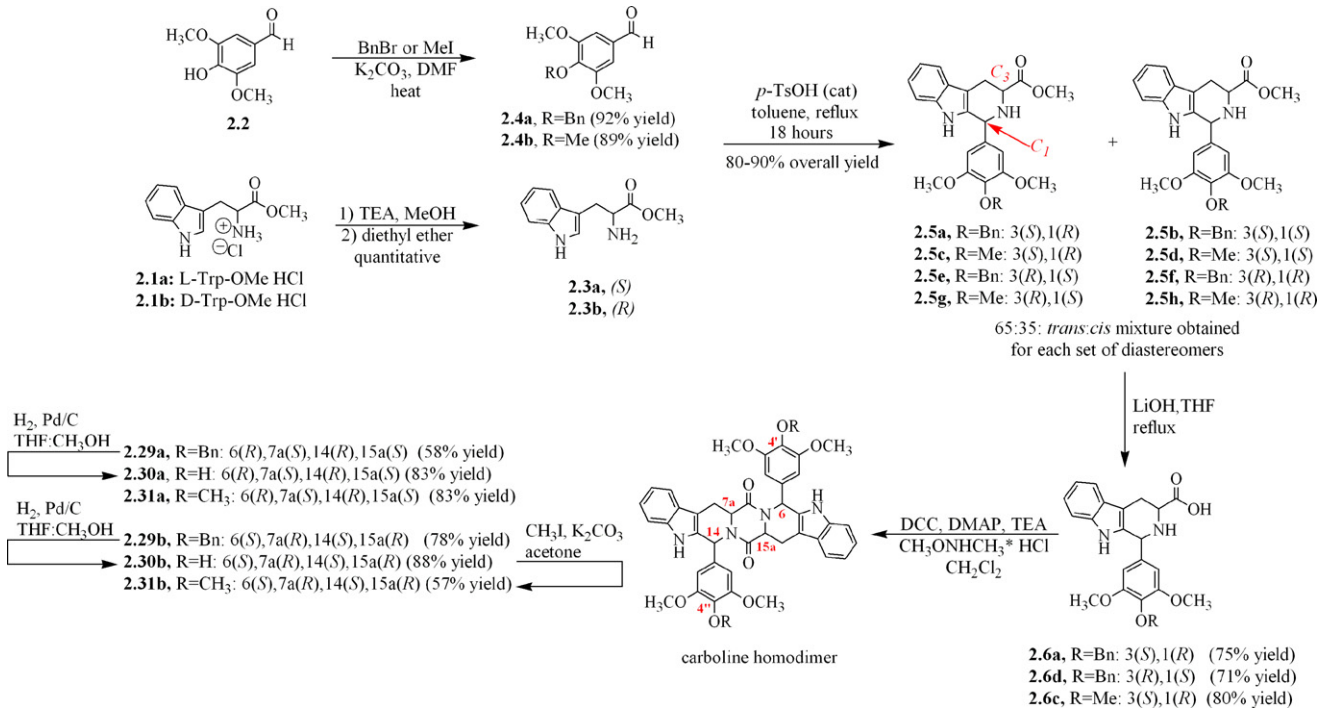
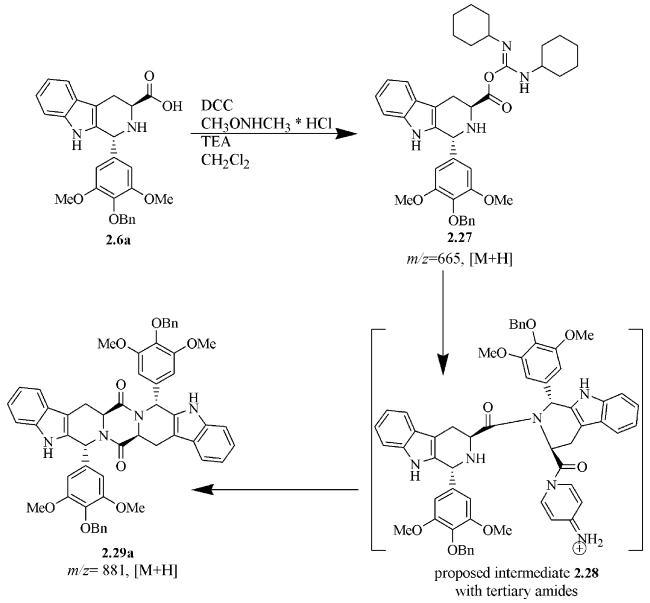


Scheme 1. Synthetic approach to synthesize carboline homodimers **2.29**–**2.31a** and **b**.

(R = –CH_3) as indicated in Scheme 1.[16] The key *trans*-1,3-disubstituted β-carboline synthons **2.5a**, **c**, **e**, and **g** were accessed via a Pictet–Spengler condensation in good yields,[17] and were subsequently saponified to their respective carboline-based carboxylic acids **2.6a**, **c**, and **d** using LiOH in THF.[11] *Trans*-carboline acid **2.6a** was then treated with *N*,*O*-dimethylhydroxylamine hydrochloride, DCC, and TEA in CH_2Cl_2 with the goal of synthesizing the Weinreb amide.[18] After this reaction was complete, the two products observed on thin-layer chromatography (TLC) were isolated using silica gel column chromatography in approximately a 1:1 ratio. Subsequent spectroscopic analysis revealed that the less polar product (R_f = 0.69; 9:1:$CHCl_3$/acetone) was in fact the DCC-based carboline intermediate **2.27** (Scheme 2), while the more polar spot (R_f = 0.58) was a 2,5-DKP-based dimer of our carboline core **2.29a**. Although 2,5-DKPs are well-documented products of α-amino acid coupling,[15a,16a,19] we were surprised and intrigued by our result; no DKP products were isolated when the reagent PyBop was used to couple **2.6a** with various amino acids during previous experiments.[11] Overall, and as detailed in Scheme 2, we think that **2.29a** resulted from attack of a second carboline molecule on the activated DCC intermediate **2.27** and that the ring closure was facilitated by populating accessible conformations of the two tertiary amides present in **2.28**.[20] Furthermore, to hasten the rate of our reaction and improve the homodimer yield we added *N*,*N*-dimethylaminopyridine (DMAP), a well known acylation catalyst. This simple change promoted complete conversion of starting material, improved our yield of sister compound **2.29b** to 78% and shortened our reaction time to 5 h.



Scheme 2. Proposed intermediates in the formation of the carboline homodimers.

With three pairs of homodimer enantiomers in hand, we next evaluated the compounds' abilities to inhibit the growth of lung (NCI–H520) and prostate (PC-3) human cancer cells as a measure of cytotoxicity. Two of the six dimers screened exhibited double-digit micromolar cytotoxicity (Tables 1 and 2). Phenol **2.30a** possessed a GI_{50} of 21.5 and 21.9 μM in lung and prostate lines, respectively, which was in the same range as the GI_{50} for etoposide and ds_2–Tps B (Fig. 1; Tables 1 and 2).[14c] Enantiomer **2.30b** was approximately three times less active in the same cell line (Table 2). Because phenol **2.30a** contains the same *trans* relationship and absolute stereochemistry as the azatoxin and etoposide cores, we were not surprised by its antiproliferative activity.

Table 1
In vitro GI_{50} data for homodimers **2.30a** and **b** against human carcinomas

Compound	NCI–H520[a]	PC-3[a]
Etoposide	13.5	12.5
Ds_2–Tps B	11.9	12.3
2.30a	21.5 (±1.1)	21.9 (±3.1)
2.30b	61.5 (±1.6)	55.3 (±1.0)

[a] GI_{50} is defined as the drug concentration required to inhibit 50% of cell growth.