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Synthesis and Biological Evaluation of Manzamine Analogues

Jeffrey D. Winkler,* Allyn T. Londregan, Justin R. Ragains, and Mark T. Hamann*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104, and Department of Pharmacognosy, University of Mississippi, University, Mississppi 38677

winkler@sas.upenn.edu

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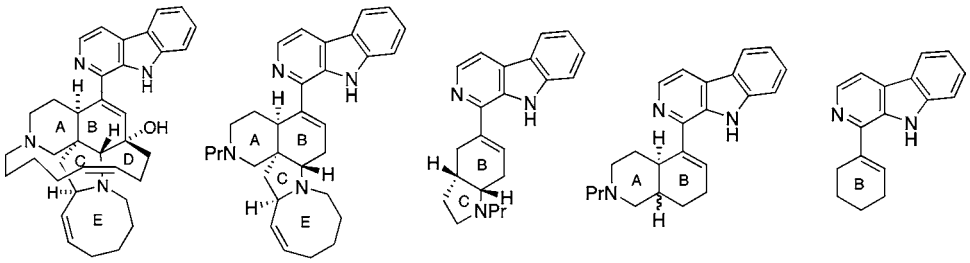
ABSTRACT



The synthesis and biological evaluation of a series of analogues of manzamine A, representing partial structures of the pentacyclic ABCDE diamine core, is described. All new compounds were screened against *Plasmodium falciparum* and demonstrated attenuated antimalarial activity relative to that of manzamine A.

Malaria is a disease that affects 300−500 million people each year and results annually in 1−2 million deaths, mostly among children. Structurally and functionally novel antimalarial agents with new mechanisms of action are needed as monotherapeutic agents and for use in combined chemotherapy with other presently available drugs. The urgent need for new and effective antimalarials escalates as *Plasmodium falciparum* and other human malaria parasite species have developed resistance to most of the commercially available antimalarials.[1] The manzamine alkaloids represent important lead structures for the development of antiinfectives. Manzamine A and related structures are highly potent, orally bioavailable[2] antimalarial agents that are more effective than most currently available therapeutics, i.e., chloroquine and artemisinin. In addition, some of the manzamine class have also demonstrated activity against the AIDS-opportunistic infectious diseases including tuberculosis and toxoplasmosis.

The isolated yield of **1** from its natural source, the Okinawan sponge *Haliclona* sp.**,** was originally reported to be 0.026% from wet sponge. The paucity of **1** from the natural source, coupled with the length of the total syntheses reported from our laboratory and by Martin,[3,4] prompted us to examine the biological activity of simplified structures based on **1**. We report herein the design, synthesis, and preliminary biological evaluation of a series of analogues of the pentacyclic ABCDE diamine core of manzamine A (Figure 1). The ca. 400-fold dimunition in activity against *P. faciparum* for the non-β-carboline-containing manzamine congener ircinol A (**2**)[5] prompted us to leave the β-carboline heterocycle intact in all new analogues.

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(2) Sayed, El; Kelly, M.; Kara, U.; Ang, K.; Katsuyama, I.; Dunbar, D.; Khan, A.; Hamann, M. *J. Am. Chem. Soc.* **2001**, *123*, 1804−1808.

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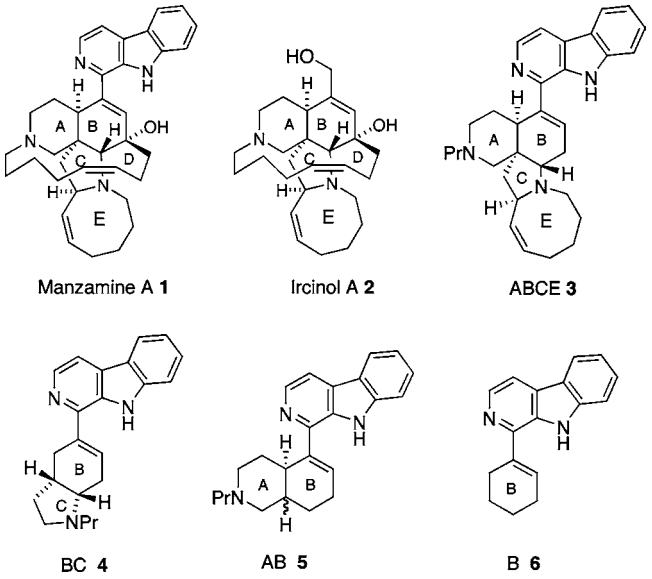
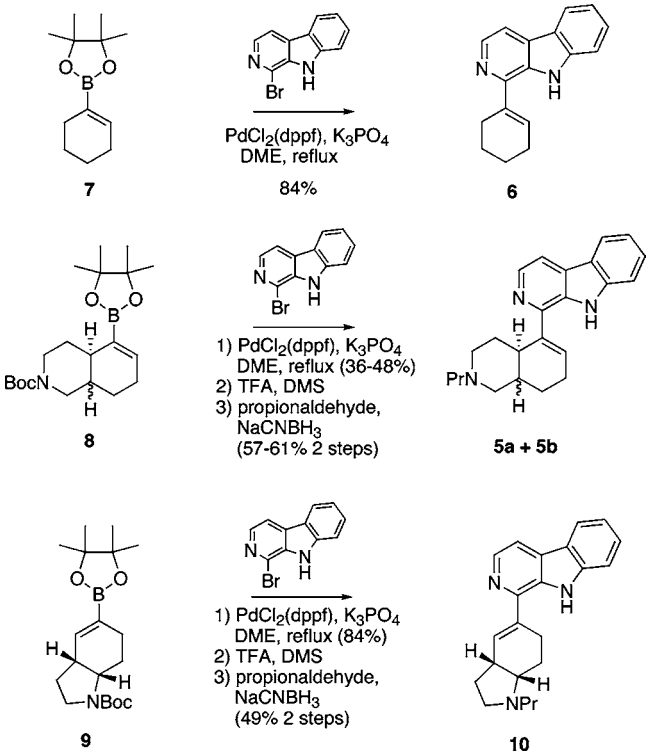


Figure 1. Analogues targeted for synthesis.

We prepared the B ring analogue **6** via Suzuki coupling of known boronic ester[6] **7** and 1-bromo-β-carboline.[7] The corresponding AB and BC ring analogues **5** and **4**, respectively, could be constructed in a similar manner via the Suzuki coupling of the appropriate BC and AB boronic esters[8,9] with 1-bromo-β-carboline (Scheme 1). We note that the $\Delta^{9,10}$ alkene in β-carboline **10** (manzamine numbering), which results from the regiochemistry of enolization of the ketone precursor, is regioisomeric with the $\Delta^{10,11}$ B-ring alkene in **1**. Completion of the synthesis of *cis*-AB **5a**, *trans*-AB **5b** and iso-BC **10** analogues was achieved by Boc deprotection of the Suzuki adducts and reductive alkylation of the resulting secondary amines with propionaldehyde.

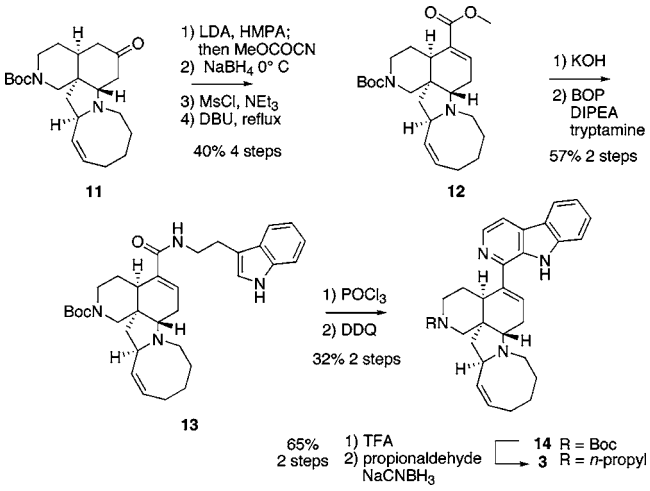
The preparation of the ABCE analogue **3** is based on our total synthesis of **1**[3] and proceeds through the tetracyclic ketone **11**[10] (Scheme 2). Regioselective conversion of **11** to unsaturated ester **12** was effected via carboxylation of the enolate derived from **11** to give the corresponding β-

Scheme 1. B, BC, and AB Ring Syntheses[a]



[a] For the preparation of **8** and **9**, see footnotes 8 and 9.

Scheme 2. ABCE Synthesis



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(8) The AB boronic esters were synthesized starting from commercially available 5-hydroxyisoquinoline. Hydrogenation of 5-hydroxyisoquinoline (Adams catalyst, HOAc, H_2SO_4) followed by Boc-protection of the crude amine afforded a mixture of diastereomeric alcohols (48%). The *cis*- and *trans*-alcohols were separated chromatographically and then oxidized with Dess−Martin reagent to the corresponding *cis*- and *trans*-fused ketones (71 and 55%, respectively). The separated ketones were then converted to the corresponding enol triflates (KHMDS, Comins' reagent) to afford 68 and 72% yields of the *cis*- and *trans*-enol triflates corresponding to **8**, respectively. The enol triflates were then converted to the corresponding boronic esters using the method of Miyaura[7] (bis-pinacolatodiboron, $PdCl_2(PPh_3)_2$, PPh_3, PhMe) to afford 91 and 78% yields of the *cis*- and *trans*-boronic esters **8a** and **8b**, respectively.

(9) The BC boronic ester **9** was synthesized starting from commercially available 5-hydroxyindole, which was hydrogenated (Rh/Al_2O_3), followed by Boc protection of the resulting crude amine (48% overall yield). The resulting epimeric alcohols were oxidized with Dess−Martin reagent to afford the corresponding *cis*-fused ketone as a single diastereomer (74−99%). The ketone was then treated with KH at room temperature followed by the addition of Comins' reagent (72%) to afford the $\Delta^{9,10}$ (manzamine numbering) enol triflate, which is iomeric with the $\Delta^{10,11}$ alkene regiochemistry in the B ring of manzamine A (72% yield). Attempts to generate the ($\Delta^{10,11}$) enol triflate under kinetic conditions resulted in the formation of inseparable mixtures of regioisomeric enol triflates. Conversion of the iso-BC enol triflate to boronic ester **9** was achieved via the aforementioned method of Miyaura.

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ketoester, followed by ketone reduction and β-elimination of the derived mesylate. Coupling of the carboxylic acid derived from **12** with tryptamine in the presence of BOP (Castro's reagent) led to the formation of amide **13**. Bischler−Napieralski cyclization of **13** followed by DDQ-mediated dehydrogenation afforded the Boc-protected ABCE analogue **14**. Boc deprotection followed by reductive alkylation with propionaldehyde afforded the ABCE tetracycle **3**. The B, AB (cis and trans), iso-BC, and ABCE analogues were then screened for activity against the W2 and D6 (chloroquine-resistant) clones of *P. falciparum* (Table 1). Two features of these data are striking: (1) the relatively narrow range of differences in biological activity among the new monocyclic (B), bicyclic (AB and BC), and tetracyclic (ABCE) analogues (ca. 10^1) and (2) the significantly attenuated activity of all new analogues relative to manzamine A (ca. 10^3). These results suggest that partial structures of manzamine A may not serve as useful leads for the development of new anti-infectives.

Table 1. Evaluation of Analogues Against *P. falciparum*

compound	W2 clone IC_{50} (ng/mL)	D6 clone IC_{50} (ng/mL)
manzamine A (**1**)	13.5	25.0
B (**6**)	5550	3510
iso BC (**10**)	4190	920
cis AB (**5a**)	1270	930
trans AB (**5b**)	2770	1020
ABCE (**14**)	520	270

One of us has recently described the isolation of manzamine A and related substances in significantly higher yield than originally reported, making **1** a viable starting material for the development of new chemotherapeutic agents.[11] Studies directed toward the development of new malaria chemotherapy lead structures via functionalization of manzamine A are currently underway in our laboratory, and our results will be reported in due course.

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Supporting Information Available: Experimental procedures and ^{1}H NMR, ^{13}C NMR, and FT-IR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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