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Novel One-Pot Total Syntheses of Deoxyvasicinone, Mackinazolinone, Isaindigotone, and Their Derivatives Promoted by Microwave Irradiation

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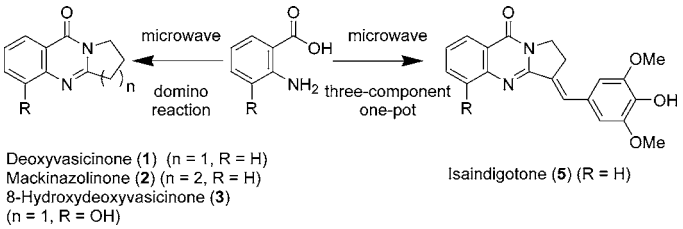
ABSTRACT



Total syntheses of deoxyvasicinone (1), mackinazolinone (2), and 8-hydroxydeoxyvasicinone (3) via novel microwave-assisted domino reactions, as well as a novel three-component one-pot total synthesis of isaindigotone (5) promoted by microwave irradiation, are reported. The efficient reaction process enabled us to rapidly access related natural product derivatives and to identify a new class of cytotoxic agents.

Quinazolinone alkaloids are a class of natural products that display a variety of biological activities.[1] Among them, pyrrolo[2,1-*b*]quinazoline alkaloids such as deoxyvasicinone (**1**),[2] 8-hydroxydeoxyvasicinone (**3**),[3] vasicinone (**4**),[4] and isaindigotone (**5**)[5,6] exhibit antiinflammatory, antimicrobial, and antidepressant activities (Figure 1). The related alkaloid mackinazolinone (**2**) possesses a broad spectrum of pharmacological activities.[7] Luotonin A (**6**) is a pyrroloquinazolinoquinoline alkaloid with cytotoxic activity against the

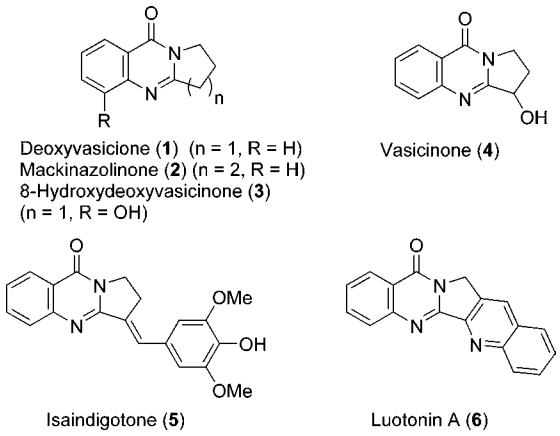


Figure 1. Structures of the pyrrolo[2,1-*b*]quinazoline and the related alkaloids.

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murine leukemia P-388 cell line (IC_{50} 1.8 μg/mL)[8] and has been shown to stabilize the human topoisomerase I−DNA covalent binary complex in the same fashion as the antitumor alkaloid camptothecin and its analogues. [9]

A number of methods have been reported for the synthesis of deoxyvasicinone (**1**). These include carbonylation catalyzed by palladium,[10] transition-metal-catalyzed reductive N-heterocyclization,[11] coupling of *O*-methylbutyrolactim with anthranilic acid,[12] cycloaddition of anthranilic acid iminoketene to a methyl butyrolactam (via sulfonamide anhydride),[13] intramolecular aza-Wittig reactions using PPh_3 and PBu_3,[14] the cycloaddition of anthranilamide with succinic anhydrides,[15] and solvent-free microwave-assisted reactions between isatoic anhydride and pyrrolidone.[16] Some of these methods are also applicable for the synthesis of mackinazolinone (**2**). In addition, isaindigotone (**5**) has been synthesized in six steps from commercially available starting materials.[17]

We recently reported a highly efficient, microwave-assisted, three-component, one-pot reaction for the synthesis of various 2,3-disubstituted quinazolin-4-ones from readily available starting materials.[18] On the basis of this methodology, we successfully achieved a three-component one-pot total synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione cores and their natural product alkaloids.[19] As a continuation of our studies, the unique structures and biological activities of the vasicinone family of natural products elicited our interest in pyrrolo[2,1-*b*]quinazoline and related alkaloids as targets for the total synthesis and natural product-templated library synthesis. In addition, we envisioned that development of *efficient and concise* methods for the total synthesis of these chemotypes, which overcome the drawbacks of the existing methods in terms of simplicity and versatility, would provide a practical entry into natural product-templated libraries suited for our broad-based phenotypic screens.[20] Herein, we describe novel total syntheses of **1**, **2**, and **3** via microwave-assisted domino reactions,[21] as well as a novel total synthesis of **5** via a three-component one-pot reaction promoted by microwave irradiation.[22] Further, the new methods have a sufficiently broad chemistry scope, enabling access to various derivatives of these natural products by employing an economical, one-pot reaction process that requires only one reagent, one protecting group, and one solvent for complete syntheses from readily available anthranilic acids, Boc-amino acids, and benzaldehydes.

Retrosynthetic strategies are depicted in Figure 2. Within the context of the domino concept, **1** and **2** could be formed via transannular cyclization of intermediate cyclic-diamide **10**. The diamide **10** may be prepared via ring expansion of the intermediate benzoxazinone **9b**, which could be accessed in situ from Boc-benzoxazinone **9a**, which in turn should be generated in situ from readily available anthranilic acid (**7a**) and Boc-amino acids (**8**). In addition, we also envisioned that isaindigotone (**5**) could be synthesized through a condensation reaction of **1** with the aldehyde **11a** via a three-component one-pot reaction process. All of these transformations would be carried out under microwave conditions.

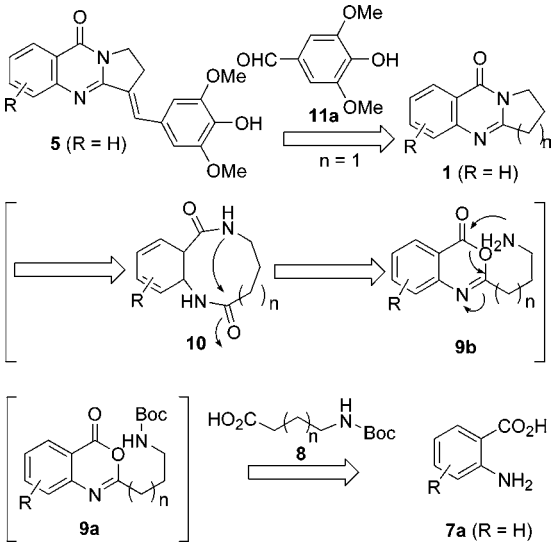

Figure 2. Retrosynthetic strategy of **1** and **5**.

Empirical validation of our design started from the synthesis of **1** by employing our "standard" microwave conditions.[18,19] Reaction of anthranilic acid (**7a**) (1.0 equiv) with 4-(*tert*-butoxycarbonylamino)butyric acid (**8a**) (1.0 equiv) in the presence of $P(OPh)_3$ (1.2 equiv) in pyridine under microwave irradiation at 150 °C for 10 min generated

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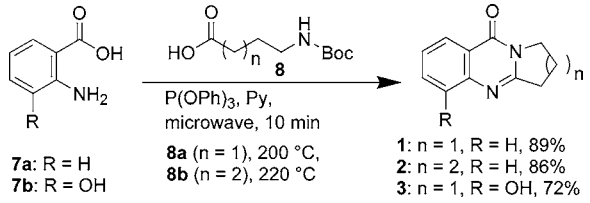
only the Boc-benzoxazinone intermediate **9a** (R = H, *n* = 1, Figure 2). However, microwave irradiation of the original reaction mixture at 200 °C for 10 min (Scheme 1) triggered

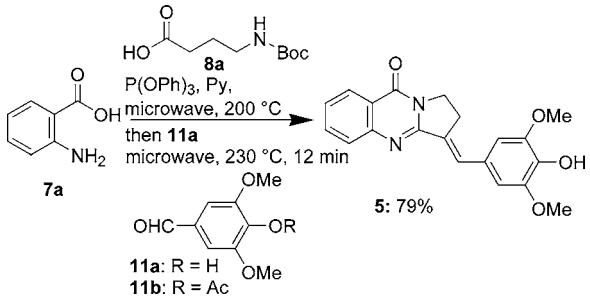
Scheme 1



the reactions in a domino process wherein Boc-benzoxazinone formation, deprotection, cyclization, and dehydration (i.e., **9a** to **9b** to **10** to **1**, in Figure 2), resulting in assembly of the desired product **1** in 89% yield. Additionally, reaction of anthranilic acid (**7a**) (1.0 equiv) with 5-(*tert*-butoxycarbonylamino)pentanoic acid (**8b**) (1.0 equiv) in the presence of $P(OPh)_3$ (1.2 equiv) in pyridine under microwave irradiation at 220 °C for 10 min afforded **2** in 86% yield. The higher temperature employed for the reaction indicates that the formation of the six-membered ring via the same domino process is more difficult than that of the five-membered ring. Notably, 8-hydroxy-deoxyvasicinone (**3**), which bears a free OH group on the phenyl ring could also be synthesized in 72% yield when the 1:1 ratio of **7b** and **8a** was subjected to the microwave irradiation at 200 °C for 10 min in the presence of $P(OPh)_3$ (1.2 equiv) in pyridine without protection of the OH group in **7b**. Moreover, since **1** has previously been employed in the synthesis of vasicinone (**4**)[23] and luotonin A (**6**),[24] the synthesis of **1** thus constitutes formal syntheses of both **4** and **6**.

With an efficient route to **1**, **2**, and **3** developed, the total synthesis of isaindigotone (**5**) was then investigated with **1** as a key intermediate (Scheme 2). The synthesis of **5** has

Scheme 2



previously been achieved in two steps in 64% yield from **1**, first by condensation of **1** with a large excess (7 equiv) of

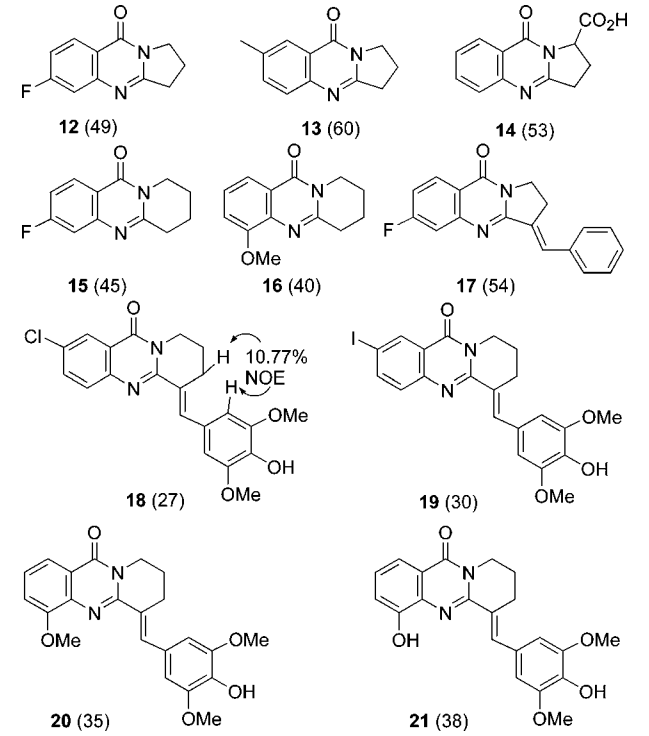


Figure 3. Derivatives of quinazoline qlkaloids **1**, **2**, **3**, and **5**. The numbers in parentheses are the isolated yields (%) via high-throughput HPLC purification (not optimized).

4-acetoxy-3,5-dimethoxybenzaldehyde (**11b**) refluxed in acetic anhydride for 1 day, followed by hydrolysis of the acyl group.[11] Therefore, we initially attempted to carry out the condensation reaction of **1** with **11b** under basic conditions with pyridine as the solvent to simplify the process by not exchanging the solvent from pyridine to acetic anhydride prior to the condensation reaction and to avoid the workup to remove excess **11b** and its side products. The condensation reaction in pyridine did occur smoothly under microwave irradiation at 230 °C. Next, we tried to further simplify the reaction process by removing the deprotection step through the use of **11a** rather than **11b**. Gratifyingly, the desired product **5** was formed under microwave irradiation.

Under the final optimized microwave conditions, reaction of anthranilic acid (**7a**) (1.0 equiv) with 4-(*tert*-butoxycarbonylamino)butyric acid (**8a**) (1.0 equiv) in the presence of $P(OPh)_3$ (1.2 equiv) in pyridine at 200 °C for 10 min, followed by addition of 4-hydroxy-3,5-dimethoxybenzaldehyde (**11a**) (1.2 equiv) and microwave irradiation at 230 °C for 12 min, afforded isaindigotone (**5**) in 79% yield. It is noteworthy that only one protecting group (Boc), one reagent ($P(OPh)_3$), and one solvent (pyridine) were used during the entire synthesis, greatly simplifying the reaction process.

A cursory evaluation of the scope of our approach was conducted in the preparation of the natural product derivatives summarized in Figure 3 using conditions established for the syntheses of **1**, **2**, **3**, and **5**. Purification of the products was evaluated using standard in-house high-throughput

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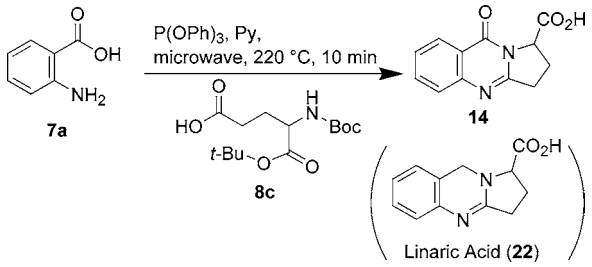
HPLC methods, which provided moderate to good recoveries.[25] The results show that anthranilic acids **7** containing both electron-donating (products **13**, **16**, and **20**) and electron-withdrawing (products **12**, **15**, and **17**−**19**) substituents are tolerated under the reaction conditions. The condensation reactions between six-membered C-ring derivatives and the benzaldehydes also worked smoothly (products **18**−**21**).[26] Notably, the deoxyvasicinone derivative **14** (Figure 3, Scheme 3), a quinazolinone analogue of the newly isolated

Scheme 3



natural product linaric acid (**22**),[27] could be synthesized in one step by reacting anthranilic acid (**7a**) (1.0 equiv) with 2-*tert*-butoxycarbonylamino-pentanedioic acid 1-*tert*-butyl ester (**8c**) (1.0 equiv) in the presence of $P(OPh)_3$ (1.2 equiv) and in situ saponification of the *tert*-butyl ester under the microwave irradiation at 220 °C in pyridine for 10 min.

Compounds **12**−**21** along with natural products **1**, **2**, **3**, and **5** were screened against six cancer cell lines in an MTS cell proliferation assay (Table 1). Surprisingly, while isaindigotone (**5**) did not show any cytotoxic or cytostatic activity, compounds **20** and **21** containing the pyrido[2,1-*b*]quinazoline core structure showed promising cytotoxic activity,

(25) Recovery using standard high-throughput HPLC methods is usually lower than that by purification on flash column chromatography for these specific compounds.

(26) Six-membered C-ring derivatives (**18**−**21**) were assigned as *E* configuration on the basis of the NOE analysis (see **18** in Figure 3).

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Table 1. Cytotoxic Activity of **20** and **21** Using a Cell Proliferation Assay (IC_{50} in μM)

	cell line					
compd	A549	NCI−H460	HT29	DU-145	MDA-MB-231	SF-268
20	0.7	0.3	18.6	0.5	1.3	0.8
21	5.5	1.4	>20	3.1	7.7	4.8

which is an unprecedented feature of these types of molecules. Notably, this class of compounds is a hybrid chemical series of mackinazolinone (**2**) and isaindigotone (**5**) structures, yet neither parent species (**2** or **5**) exhibits cytotoxic activity. These unusual results open new opportunities for the discovery of novel anticancer agents from privileged structure-based quinazolinone natural product-templated libraries.

In summary, we have devised novel total syntheses of deoxyvasicinone (**1**), mackinazolinone (**2**), and 8-hydroxydeoxyvasicinone (**3**) via microwave-assisted domino reactions, as well as a total synthesis of the related natural product isaindigotone (**5**), via a three-component one-pot reaction from readily available starting materials using microwave technology. The synthetic approach uses only one reagent, one protecting group, and one solvent. The efficiency and versatility of the method enabled us to quickly access natural product derivatives and thus identify a novel class of cytotoxic agents. Further application of this methodology to the total synthesis of other natural products and to the construction of natural product-templated libraries for phenotypic screening will be described in due course.

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Supporting Information Available: Experimental procedure and spectral data for compounds **1**, **2**, **3**, **5**, and **12**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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