CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201000237

Synthesis and Biological Activities of Azalamellarins

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Abstract: The synthesis of azalamellarins, a new series of lactam analogues of biologically active lamellarins, was achieved using Cu^{I}-mediated and microwave-assisted $C-N_{amide}$ bond formation. Seventeen azalamellarins, including *N*-allylazalamellarins and *N*-propylazalamellarins χ-D, L-N, and J-dehydro J, were synthesized and evaluated for their cytotoxicity against the cancer cell lines HuCCA-1, A-549, HepG2, and MOLT-3. The results showed that certain azalamellarins exhibited good activities in the micromolar IC_{50} value range (IC_{50} = the drug concentration that causes 50% of cell-growth inhibition after 72 h of continuous exposure to the test molecule), comparable to their parent lamellarin analogue.

Keywords: antitumor agents · azalamellarins · microwave-assisted reactions · lactams · lactones

Introduction

Lamellarins are compounds of marine origin that display a wide range of biological activities including topoisomerase I (top1) and kinase inhibition as well as cytotoxic activities in a range of cancer cell cultures. As such, they are currently reported to be in development as potential anticancer agents.[1] As a novel, potent inhibitor of DNA top1, lamellarin D (LAM-D) (**1**) also displays potent cytotoxic activities against multidrug-resistant tumor cell lines and is highly cytotoxic to prostate-cancer cell lines.[2] Recently our group reported the synthesis[3] and structure–activity relationship (SAR) study of 25 lamellarin derivatives based on a 6*H*-[1]benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolinone pentacyclic planar chromophore.[4] Although several lamellarin derivatives show potent anticancer potency in vitro, they suffer from several drawbacks that result from relatively low aqueous solubility and the relatively labile nature of the lactone ring under basic conditions. Therefore, a number of analogues of lamellarin have been synthesized with the aim of improving their inhibitory potencies as well as other desirable physicochemical properties.[5] Among the modifications that were investigated to achieve these goals were the replacement of the lactone moiety with the lactam moiety, which produced the desired azalamellarin D (**2**) to potentially increase the solubility and stability.

Lactams occur in a wide range of synthetic and natural product derivatives, many of which have potential uses as pharmacologically active compounds.[6] This useful pharmacophore has attracted much interest specifically for its use as an antitumor and anticancer agent.[7] Oxynitidine (**3**), a benzo[*c*]phenanthridine alkaloid from Xanthoxylum (Rutaceae), has been investigated as a potential antitumor and antiviral agent (Scheme 1).[8] Pancratistatin (**4**), a highly oxygenated phenanthridone, shows a high level of in vivo cancer-cell-growth inhibitory activity and antiviral activity.[9] Indenoisoquinoline (NSC 314622) (**5**) acts as a novel non-camptothecin topoisomerase I (top1) inhibitor that is cytotoxic in cancer cell cultures and is under development as a potential anticancer agent.[10]

Previous methods of forming C–N bonds have been reported extensively.[11] The Buchwald–Hartwig amination is a popular method in modern organocopper chemistry to form various C–N bonds.[12] Indeed, copper-mediated cross-coupling reactions to form aryl C–N bonds have been studied under microwave conditions between arylboronic acids and pyrazinones.[13]

The target phenanthridin-6-one,[14] which consists of a δ-lactam in the center of the structure, has attracted attention owing to its presence in natural products and ability to un-

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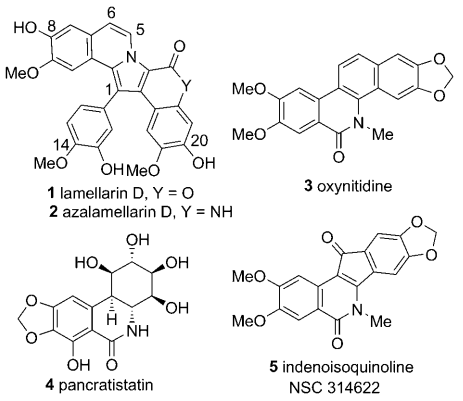
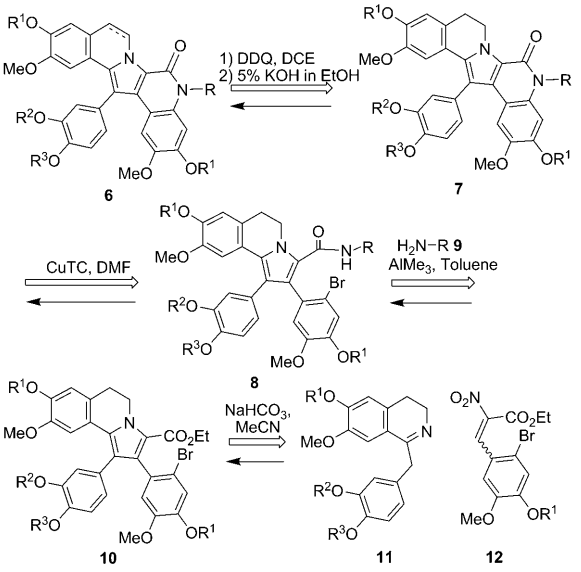
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201000237.



Scheme 1. Lamellarin D (**1**), azalamellarin D (**2**), and biologically active compounds **3**–**5** that contain aromatic lactam.

dergo further transformations (Scheme 1). Accordingly, we made an effort to develop the method for forming C_{aryl}–N_{amide} bonds among phenanthridin-6-one derivatives and successfully applied it to the synthesis of azalamellarins, lactam analogues of lamellarins, as shown in Scheme 2. The intramolecular cross-coupling consists of an Ullmann-type



Scheme 2. Retrosynthetic plan of azalamellarin synthesis.

reaction induced by a copper(I)thiophene-2-carboxylate (CuTC),[15] and is facilitated by microwave irradiation for milder conditions and faster reaction times.[16]

Results and Discussion

Model Study in the Synthesis of Azalamellarin

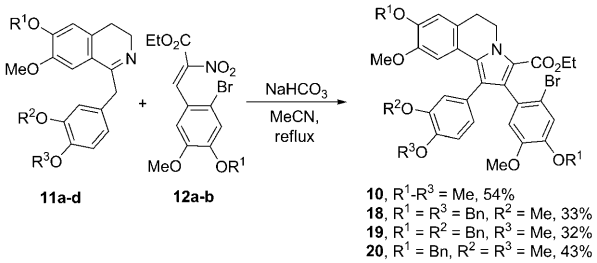
Aminolysis[17] of the 2-halobiarylcarboxylates **13**[16] with available amines **9a–d** was studied to reduce the sequence from the ester to the amides into one step. The amide formation under microwave (MW) irradiation using trimethylaluminum in toluene as solvent at 100 °C gave the 2-halobiarylcarboxamides **14a–d** in moderate to good yields. With various amides **14** in hand, the Cu^I-mediated and MW-assisted $C–N_{amide}$ bond formation was studied. The phenanthridin-6-one derivatives **15a–d** were obtained in moderate to excellent yields (27 to 96%) under mild conditions with a temperature of 200 °C in DMF (Table 1). Copper-mediated lactamization reactions allow for milder conditions and a faster reaction time, compared to classical heating during the synthesis of the O-analogue lactone.[16]

Having successfully developed a method for the synthesis of phenanthridin-6-one derivatives **15**, and with the desire to study the effect of substitution patterns on the SAR, we then applied the above approach to the synthesis of azalamellarin model **17**. The tandem Michael-addition/ring-closure (Mi–RC) Grob-type condensation of benzyldihydroisoquinoline **11a** and α-nitrocinnamate **12a** using $NaHCO_3$ in acetonitrile heated at reflux gave ethyl-1-aryl-2-(2-bromoaryl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**10**) in moderate yield (54%; Scheme 3). The key step involves the Mi–RC of the imines **11** and mixture of *cis*/*trans* nitrocinnamate derivatives **12**.[3c] Ethyl-1-aryl-2-(2-bromoaryl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylates **18** to **20** were also synthesized using Mi–RC chemistry and were used further in the synthesis of six pairs of *N*-allyl and *N*-propylazalamellarin χ-D, L-N, and J-dehydro J analogues, which are synthetic analogues that mimic natural lamellarins.

The aminolysis[17] of compound **10** with various amines **9a–d** was studied using trimethylaluminum (2 M $AlMe_3$) in toluene as solvent at 100 °C to give 1,2-biarylpyrroloisoquinoline-3-carboxamide derivatives **16a–d** in good yields (76 to 94%) (Table 2, entries 1 to 4). The Cu^I-mediated and

Abstract in Thai:

การศึกษาการสร้างพันธะคาร์บอนและไนโตรเจนของวงเลคแทม โดยปฏิกิริยาการใช้เกลือโลหะทองแดงและพลังงานไมโครเวฟ สามารถสร้างวงฟีแนนทรีดีนและสารต้นแบบเอซาลาเมลลาริน ซึ่งนำไปสู่การพัฒนาต่อยอดการสังเคราะห์สารอนุพันธ์ของลาเมลลาริน เพื่อให้มีความเสถียรและมีการละลายในตัวกลางของการทดสอบความเป็นพิษต่อเซลล์มะเร็งได้ดีขึ้น งานวิจัยประสพความสำเร็จในการสังเคราะห์สารอนุพันธ์เอซาลาเมลลาริน *χ-D, L-N* และ *J-dehydro J* ทั้งชนิดไม่มีและมีหมู่เอริล ไพรพิลบนไนโตรเจนของวงเลคแทม สารอนุพันธ์เอซาลาเมลลารินที่สังเคราะห์ได้ แสดงฤทธิ์ความเป็นพิษต่อเซลล์มะเร็ง *HuCCA-1, A-549, HepG2* และ *MOLT-3* ในระดับไมโครโมลาร์เมื่อเปรียบเทียบกับอนุพันธ์ของลาเมลลารินต้นแบบ โดยเฉพาะสารเอซาลาเมลลาริน *D* **(2)** แสดงฤทธิ์ความเป็นพิษต่อเซลล์มะเร็ง *HepG2* ได้ดีในระดับเดียวกับลาเมลลาริน *D* **(1)** ซึ่งเป็นสารต้นแบบจากธรรมชาติ



Scheme 3. Synthesis of compounds **10** and **18**–**20**.

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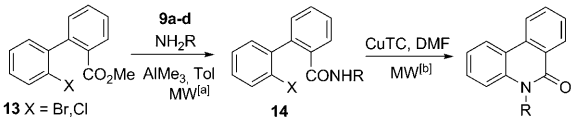
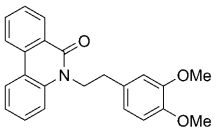
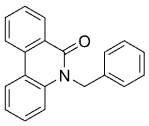
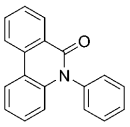
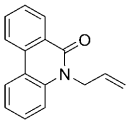
Table 1. Synthesis of phenanthridin-6-ones **15** using Cu^{I}-mediated and MW-assisted C_{aryl}–N_{amide} coupling.



Entry	Products	X	Amidation yield [%] **14**[a]	Lactamization yield [%] **15**[b]
1	**15a** 	Br	**14a**, 96	**15a**, 37
2		Cl	**14b**, 93	**15a**, 72
3	**15b** 	Br	**14c**, 84	**15b**, 62
4		Cl	**14d**, 86	**15b**, 72
5	**15c** 	Br	**14e**, 82	**15c**, 96
6		Cl	**14f**, 85	**15c**, 55
7	**15d** 	Br	**14g**, 38[c]	**15d**, 31
8		Cl	**14h**, 41[d]	**15d**, 27

[a] Amidation conditions: ester (1 equiv), amine (1.2 equiv), $AlMe_3$ (1 equiv), toluene, MW 100 W, 100 °C, 100 psi, 5 min. [b] Lactamization: CuTC (0.5 equiv), DMF, MW 200–250 W, 200 °C, 38–100 psi, 10–60 min. [c] Recovered starting material 61 % yield. [d] Recovered starting material 57 % yield.

MW-assisted C–N_{amide} bond formation was then studied under mild conditions with a temperature of 200 °C in DMF to yield azalamellarins **17a–d** in good to excellent yields (74 to 98 %).

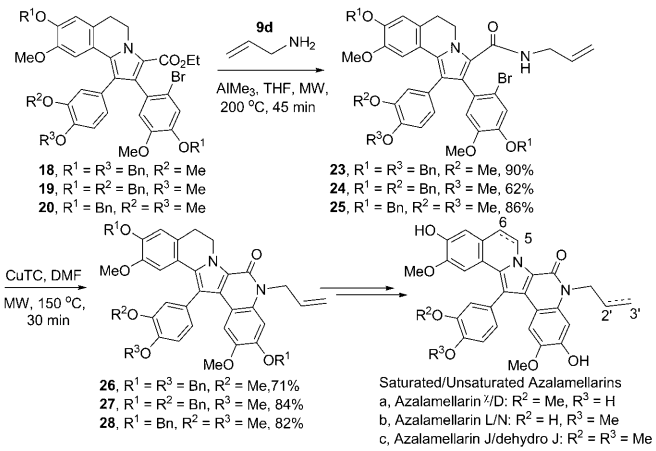
Synthesis of Benzyl-Protected Azalamellarins 26–28

We then turned our attention to the synthesis and cytotoxic evaluation of azalamellarin analogues of χ-D, L-N, and J-dehydro J, which are mimics of natural lamellarins. The effective methodology of the synthesis of azalamellarins **17a–d** was used as the key step, including the use of solid support for the debenzylation step and the oxidation step of C5–C6-saturated azalamellarins to unsaturated azalamellarins. The reaction of dihydroisoquinolines **11b–d** and α-nitrocinnamate **12b** in the presence of $NaHCO_3$ and acetonitrile heated at reflux overnight gave the protected form of compounds **18–20** in moderate yields (32–43 %; Scheme 3). Amidation of the carboxylates was conducted under microwave irradiation at 200 °C using $AlMe_3$ in toluene, as previously reported, to generate carboxamide derivatives. However, substitution of the benzyl groups on the periphery significantly lowered the yields. Increasing the equivalent amount of amine **9a**, $AlMe_3$, temperature, and reaction time gave disappointing yields (Table 3, entries 1 to 4). We then modified the amidation conditions to improve the yield. THF was found to be the most effective solvent and, when combined with an increase in amine to 4–5 equiv and $AlMe_3$ to 2.0–2.4 equiv, led to much improved yields (Table 3, entries 5 to 7).

From the above-mentioned improved amidation conditions, the reaction of carboxylates **18–20** with 5.0 equiv amine **9d** in the presence of 2.0 equiv $AlMe_3$ in THF gave carboxamides **23–25** in moderate to good yields. The Cu^{I}-mediated and MW-assisted C–N_{amide} bond formation of carboxamides **23–25** were performed in DMF under mild condition with a temperature of 150 °C in order to affect the lactamization. These conditions gave benzyl-protected azalamellarins **26–28** in good yields (Scheme 4).

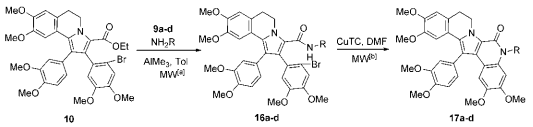
Synthesis of Azalamellarins χ-D, L-N, and J-dehydro J

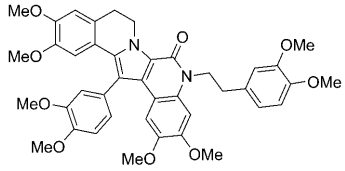
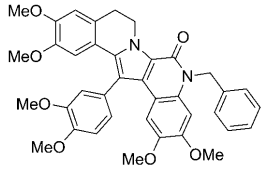
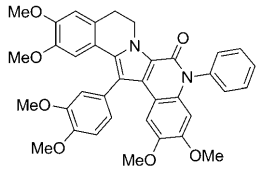
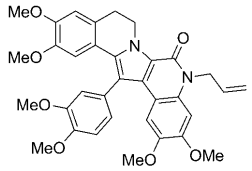
We next turned to the debenzylation step that leads to saturated *N*-allylazalamellarins **29–31** and saturated *N*-propylazalamellarins **33–35**, respectively, depending on the methodology. A hydrogenolysis route was used for both cleavage of benzyl group and reduction at the C2′–C3′ position to yield *N*-propylazalamellarins **33–35** in good yields, whereas the saturated *N*-allylazalamellarins **29–31** were obtained from the application of solid-support debenzylation as shown in Scheme 5.[18] This reaction was performed initially for the polydebenzylation of the complex molecules by using *p*TsOH immobilized on silica (PTS–Si)



Scheme 4. Synthesis of saturated *N*-allylazalamellarins **26–28**.

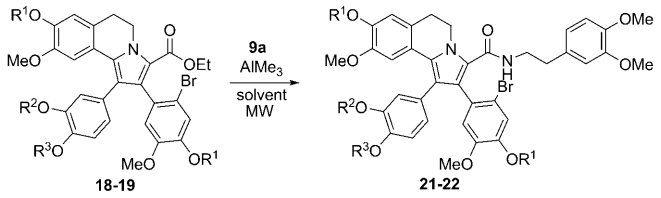
Table 2. Synthesis of azalamellarins **17** using Cu^{I}-mediated and MW-assisted C_{aryl}–N_{amide} coupling.



Entry	Products	Amidation yield [%] **16**[a]	Lactamization yield [%] **17**[b]
1	**17a** 	**16a**, 76[c]	**17a**, 90
2	**17b** 	**16b**, 89	**17b**, 98
3	**17c** 	**16c**, 94	**17c**, 60[d]
4	**17d** 	**16d**, 80	**17d**, 74

[a] Amidation conditions: ester (1 equiv), amine (1.2 equiv), $AlMe_3$ (1 equiv), toluene, MW 100 W, 100 °C, 100 psi, 5 min. [b] Lactamization: CuTC (0.5 equiv), DMF, MW 200–250 W, 200 °C, 38–100 psi, 10–60 min. [c] $AlMe_3$ (1 equiv), toluene, 300 W, 250 °C, 100 psi, 20–40 min. [d] 300 W, 250 °C, 100 psi, 60 min, recovered starting material 24% yield.

Table 3. Conditions for the MW-assisted amidation of ethyl dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate derivatives.



Entry	Ester[a]	Solvent[c]	**9a** [equiv]	$AlMe_3$ [equiv]	*T* [°C]	*t* [min]	Product yield [%]
1	**19**	toluene	1.1	2.0	250	60	**22**, 15
2	**19**	toluene	1.5	2.4	300	60	**22**, 2
3	**19**	toluene	1.8	2.8	250	90	**22**, 8
4	**19**	toluene	3.0	3.0	250	60	**22**, 7
5	**19**	THF	4.0	2.4	100	20	**22**, 60
6	**18**	THF	5.0	2.4	100	20	**21**, 77
7	**18**[b]	THF	4.0	2.0	100	40	**21**, 75

[a] Reaction scale is 0.1 mmol. [b] Reaction scale is 1.0 mmol. [c] MW power 300 W for toluene and 100 W for THF.

in toluene and a minute amount of methanol under a constant temperature of 80 °C. After filtration, *N*-allylazalamellarins **29**–**31** were purified and obtained in moderate yields. The main side product was characterized as monobenzyl-substituted diarylmethane **32** of benzyl-cation product in a tiny quantity that was supported by NMR spectroscopic data (see the Supporting Information).

With the C5–C6-saturated precursors in hand, we next investigated the preparation of the unsaturated form. Both *N*-allylazalamellarins and *N*-propylazalamellarins were investigated in the same manner and involved three steps as shown in Schemes 6 and 7. Treatment of saturated azalamellarins with acetyl chloride in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine in dichloromethane at room temperature furnished acetates **36**–**41**. To elaborate the C5–C6 moiety, the introduction of the double bond was achieved by using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dichloroethane heated at reflux overnight to yield the desired products **42**–**47** in high yields. Finally, the acetyl groups were hydrolyzed under basic conditions to give the final products, unsaturated azalamellarins **48**–**53**.

In addition, the *N*-unsubstituted azalamellarin D (**2**) was also studied to determine the SAR associated with the side chain. Azalamellarin D (**2**) was prepared by means of deallylation of *N*-allylazalamellarin **26** by using [ClRh(PPh_3)$_3$] and OsO_4 with $NaIO_4$ for isomerization and oxidation,[19] respectively, to yield tribenzyl azalamellarin **54**, which was further debenzylated by hydrogenolysis to cleave the benzyl groups (Scheme 8). After acetylation with acetic anhydride, followed by oxidation using DDQ, which utilized the same conditions as *N*-allyl and *N*-propylazalamellarins, the azalamellarin D triace-

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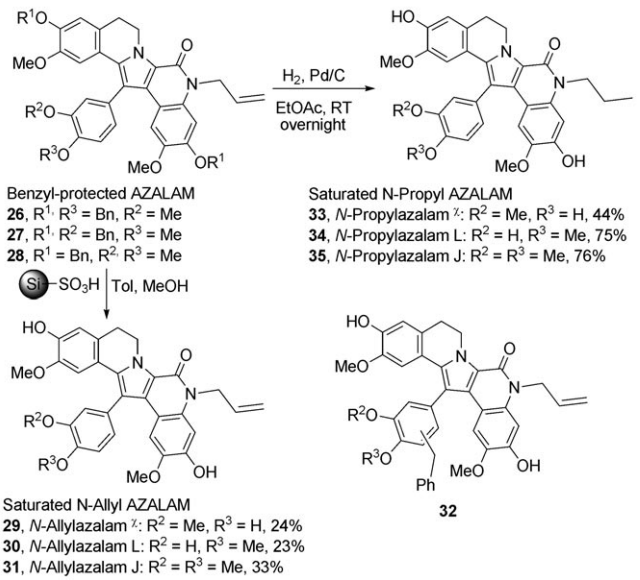
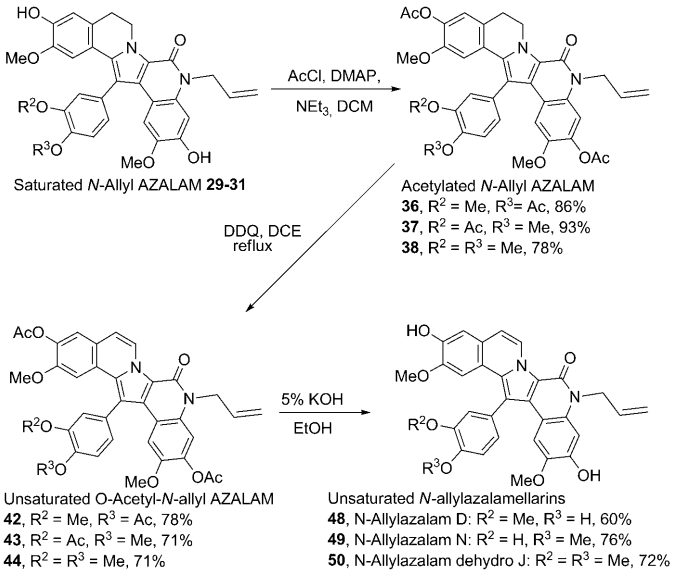


Scheme 5. Synthesis of saturated *N*-allylazalamellarins χ, L, and J (**29**–**31**) and *N*-propylazalamellarins χ, L, and J (**33**–**35**).



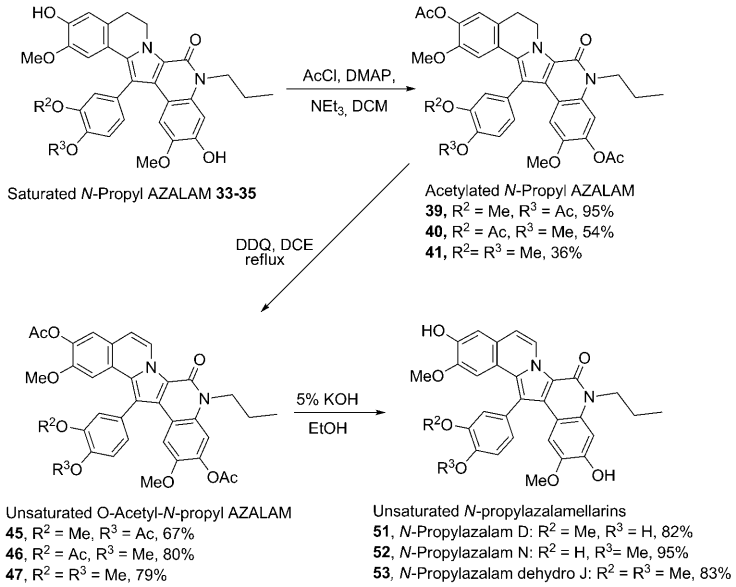
Scheme 6. Synthesis of unsaturated *N*-allylazalmellarins D, N, and dehydro J (**48**–**50**)

tate **55** was obtained. Basic hydrolysis yielded azalamellarin D (**2**) in 4% overall yield from azalamellarin **18**.

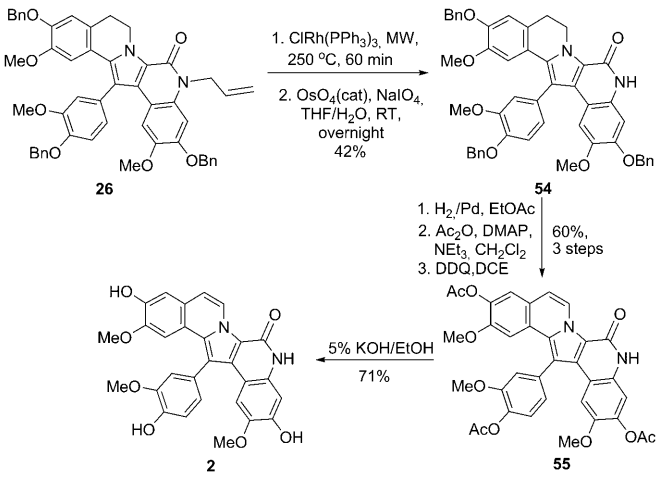
Biological Activity of Azalamellarins 17a–d and Their Corresponding Carboxamides 16a–d

To examine the effect of the *N*-aryl/alkyl side chain of synthetic azalamellarins, a panel of four human tumor cell lines was used to evaluate the cytotoxic potential of azalamellarins **17a**–**d** and their corresponding carboxamides **16a**–**d**; the cell lines were HuCCA-1 cholangiocarcinoma, A549 lung carcinoma, HepG2 hepatoblastoma, MOLT-3 T-lymphoblast (acute lymphoblastic leukemia). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide (XTT) assays were used to estimate IC_{50} values, that is, the drug concentration that causes 50% of cell-growth inhibition after 72 h of continuous exposure to the test molecule. The results obtained are shown in Table 4.

We found that azalamellarins with hexamethoxyl groups have significantly increased solubility in DMSO compared with lamellarin G trimethyl ether, which is the core lactone structure of this class but is insoluble in DMSO. Azalamellarins **17a**–**b** and **17d** as well as carboxamide analogues **16a**–**d**, except *N*-phenylazalamellarin **17c**, are soluble in DMSO. Interestingly, *N*-allylazalamellarin **17d** showed cytotoxicity in a lower micromolar IC_{50} range (3.435 μM) against the HepG2 hepatoblastoma. The open lactam ring of this azalamellarin, *N*-allylcarboxamide **16d**, gave lower cytotoxicity by an order of magnitude (38.51 μM). The other side chains of lactams and carboxamides resulted in either a considerable decrease or no observed potency. This study provided crucial information about the importance of the lactam moiety to significantly increase the solubility of lamellarin derivatives in the biological medium. The *N*-allylamine was used as a side chain for



Scheme 7. Synthesis of unsaturated *N*-propylazalmellarins D, N, and dehydro J (**51**–**53**)



Scheme 8. Synthesis of azalamellarin D (**2**).

Table 4. Biological activities of azalamellarins **17a–d** and their corresponding carboxamides **16a–d** in MTT and XTT assays.[a]

Entry	Compound	IC_{50} [μM]			
		HuCCA-1[c,g]	A549[d,g]	HepG2[e,g]	MOLT-3[f,h]
1	**16a**	inactive	inactive	inactive	11.98
2	**16b**	inactive	inactive	inactive	6.40
3	**16c**	inactive	inactive	inactive	5.11
4	**16d**	inactive	75.51	38.51	12.55
5	**17a**	inactive	inactive	inactive	0.21
6	**17b**	inactive	inactive	inactive	1.37
7	**17c**[b]	N/A	N/A	N/A	N/A
8	**17d**	34.35	42.94	3.435	2.85
9	doxorubicin	0.52	0.43	ND	ND
10	etoposide	ND	ND	27.18	0.017

[a] Soluble in DMSO (10 mg mL^{-1}). [b] Insoluble in DMSO. [c] HuCCA-1: Cholangiocarcinoma. [d] A549: Lung carcinoma. [e] HepG2: Hepatoblastoma. [f] MOLT-3: T-lymphoblast (acute lymphoblastic leukemia). [g] MTT assay. [h] XTT assay. N/A = Not available owing to the insolubility of the compounds in DMSO. ND = Not determined.

the synthesis of the subsequent azalamellarin analogues, as discussed in the preceding sections.

Biological Activity of Saturated and Unsaturated *N*-Allyl and *N*-Propylazalamellarins χ-D, L-N, and J-dehydro J

The importance of the lactam in the cytotoxic activities of azalamellarins was studied by comparing the IC_{50} of six pairs of azalamellarins and azalamellarin D (**2**), each of which contains exactly the same substituents and differs only in the side chain of *N*-lactam. Thirteen azalamellarins, both saturated and unsaturated *N*-allyl and *N*-propylazalamellarins χ-D, L-N, J-dehydro J, and azalamellarin D were evaluated for their cytotoxicity using MTT and XTT assays depending on the cell-line types. Although the cytotoxicities of azalamellarins were only comparable to the native lactone structure of lamellarins, we found the tendency of the selective activity of azalamellarins that was effective against HepG2 cell line. The presence of allyl and propyl side chains of azalamellarins showed a significant decrease in the biological activities compared to their native lactone structure of lamellarins. Most synthetic azalamellarins exhibited better cytotoxic activities than the positive control etoposide in HepG2 cell line at micromolar levels of IC_{50} as shown in Table 5.

Without any side chains, azalamellarin D (**2**) was more cytotoxic than its *N*-allyl/propyl side-chain analogues among a panel of four human tumor cell lines (Table 5, entry 6) and gave results that were as good as its equivalent lactone core, lamellarin D (Table 5, entry 7).

Conclusion

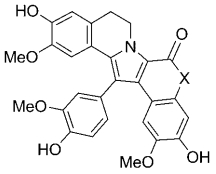
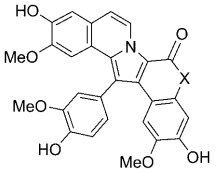
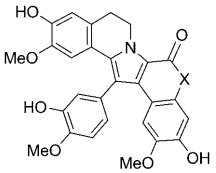
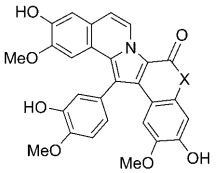
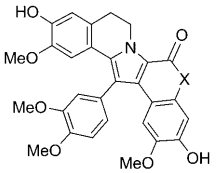
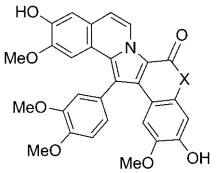
In conclusion, we have achieved the synthesis of azalamellarin D (**2**) and its derivatives by means of a copper(I)-mediated and microwave-assisted C–N_{amide} bond formation process. The method we have developed and reported here should be applicable to the synthesis of other lactam systems in natural products and synthetic compounds. Interestingly, this study reveals for the first time a significant contribution from the change of a lactone to a lactam moiety, which in turn significantly increases the aqueous solubility of the corresponding lamellarin lactam derivatives in the biological medium. Azalamellarin D (**2**) exhibited good activities in the micromolar IC_{50} value range, comparable to its parent lamellarin D (**1**). The presence of allyl and propyl side chains on the lactam nitrogen of the azalamellarins resulted in either a considerable decrease or no observed potency. This is the first report of a structure–activity relationship at this position, since previous studies have focused on lamellarin D and its derivatives, which possess a hydrogen atom at C7, a C5=C6 double bond, C8 and C20 hydroxy groups, as well as a lactone moiety. This SAR study has helped to delineate the important structural elements in the lactone–lactam skeleton that contribute to cytotoxicity. Information from our synthetic work and SAR studies is critical to improve our understanding of the structural requirements for good anticancer activity and to help us more efficiently design new molecules to probe SAR further.

Experimental Section

General Methods

Microwave reactions were performed with a CEM Discover instrument. Melting points were determined with an electrochemical melting-point apparatus and reported without correction. ^{1}H NMR spectra were re-

Table 5. Biological activities of synthetic azalamellarins and their natural lamellarins in MTT and XTT assays.[a]

Entry	Structure	Compound	IC_{50} [μM]			
			HuCCA-1[b]	A549[b]	HepG2[b]	MOLT-3[c]
1		azalam **29**; X = *N*-allyl	31.4	20.3	8.64	3.09
2		azalam **33**; X = *N*-*n*Pr	19.35	19.35	8.85	2.30
3		lam χ X = O	4.0	8.3	0.95	0.48
4		azalam **48**; X = *N*-allyl	19.50	7.06	4.70	1.28
5		azalam **51**; X = *N*-*n*Pr	inactive	inactive	inactive	0.425
6		azalam D **2**; X = NH	0.12	0.74	0.13	0.03
7		lam D **1**; X = O	0.078	0.085	0.28	0.0049
8		azalam **30**; X = *N*-allyl	7.68	7.46	4.07	3.53
9		azalam **34**; X = *N*-*n*Pr	56.2	49.76	10.93	3.58
10		lam L; X = O	inactive	2.99	1.75	0.66
11		azalam **49**; X = *N*-allyl	7.43	6.50	6.50	2.60
12		azalam **52**; X = *N*-*n*Pr	18.5	8.75	5.55	1.55
13		lam N; X = O	inactive	inactive	0.27	0.011
14		azalam **31**; X = *N*-allyl	66.7	17.1	10.5	2.24
15		azalam **35**; X = *N*-*n*Pr	23.4	11.68	9.0	1.49
16		lam J; X = O	inactive	inactive	inactive	0.388
17		azalam **50**; X = *N*-allyl	inactive	inactive	inactive	2.00
18		azalam **53**; X = *N*-*n*Pr	10.82	5.86	5.7	0.577
19		dehydrolam J; X = O	0.22	0.3	0.34	0.0064
20		doxorubicin	0.52	0.75	0.60	ND
21		etoposide	ND	ND	28.9	0.027

[a] Soluble in DMSO (10 mg mL^{-1}). [b] MTT assay. [c] XTT assay. HuCCA-1 = Cholangiocarcinoma. A549 = Lung carcinoma. HepG2 = Hepatoblastoma. MOLT-3 = T-lymphoblast (acute lymphoblastic leukemia). ND = Not determined.

corded with 200 MHz and 400 MHz instruments at 200 and at 400 MHz, respectively; ^{13}C NMR spectra were recorded with 200 and 400 MHz instruments at 50 and at 100 MHz, respectively. FTIR spectra were record with a universal ATR (UATR) accessory. Low-resolution mass spectra were obtained with an LC–MS instrument using electron-impact ionization (EI). High-resolution mass spectra were obtained with a MicroTOF instrument using atmospheric pressure chemical ionization (APCI) in positive or negative mode. Column chromatography was carried out using aluminum oxide (100–125 mesh) or Merck silica gel (70–230 mesh). Thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were carried out on silica gel. All reagents were purified and dried according to the standard procedures.

*General Procedure for the Preparation of Dihydropyrrolo[2,1-a]*isoquinoline Carboxylates (**18–20**)

A mixture of benzyldihydroisoquinoline **11** (1.5 equiv), nitrocinnamate **12** (1 equiv), and $NaHCO_3$ (1.5 equiv) in acetonitrile (15 mL) was heated to reflux for 16 h. After being allowed to cool to RT, water and EtOAc were added. The two layers were separated, and the aqueous phase was extracted with EtOAc (3×). The combined organic layers were washed once with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product, which was further purified by column chromatography on silica (30% EtOAc/hexanes) to furnish the desired products in moderate yield (32–43%):

*Compound **18***

Employing the general procedure for the synthesis of pyrrolo[2,1-*a*]isoquinoline carboxylate with benzyldihydroisoquinoline **11b** (4.85 g,

9.83 mmol) and nitrocinnamate **12b** (2.86 g, 6.55 mmol) in acetonitrile (50 mL) gave **18** as a yellow sticky gum (1.68 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 0.86 (t, $^3J_{H,H}$ = 7.1 Hz, 3H; CH_3), 2.88–3.10 (m, 2H; CH_2), 3.23 (s, 3H; CH_3), 3.63 (s, 3H; CH_3), 3.65 (s, 3H; CH_3), 3.92–4.1 (m, 2H; CH_2), 4.33 (m, 1H; CH*H*), 4.88 (m, 1H; C*H*H), 5.10 (d, $^2J_{H,H}$ = 2.4 Hz, 2H; CH_2), 5.13 (s, 4H; $2CH_2$), 6.55 (s, 1H; CH), 6.71–6.75 (m, 5H; 5CH), 7.04 (s, 1H; CH), 7.28–7.44 ppm (m, 15H; 15CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 13.6, 28.9, 42.7, 55.2, 55.8, 56.0, 59.7, 70.6, 70.9, 71.0, 108.9, 113.2, 113.5, 114.3, 115.0, 115.6, 116.9, 118.6, 121.3, 121.4, 122.8, 125.5, 127.0, 127.2, 127.3, 127.8, 127.9, 128.0, 128.2, 128.5, 128.6, 130.4, 130.8, 131.6, 136.5, 136.9, 137.2, 146.5, 147.1, 147.2, 147.8, 148.1, 149.2, 161.5 ppm; IR (UATR): $\tilde{\nu}_{max}$ = 1739 (C=O), 1251 (C–O), 1211 cm^{-1} (C–N); EIMS: *m*/*z* (%): 881 (31) [*M*+2H$^+$], 879 (32) [*M*$^+$], 789 (43), 712 (15), 698 (17), 91 (100); HRMS (FAB): *m*/*z*: calcd for $C_{51}H_{47}BrNO_8$: 880.2480; found: 880.2458.

Compound ***19***

Employing the general procedure for the synthesis of pyrrolo[2,1-*a*]isoquinoline carboxylate with benzyldihydroisoquinoline **11c** (2.49 g, 5.05 mmol) and nitrocinnamate **12b** (1.47 g, 3.37 mmol) in acetonitrile (25 mL) gave **19** as a yellow sticky gum (0.84 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 0.86 (t, $^3J_{H,H}$ = 7.1 Hz, 3H; CH_3), 2.98 (m, 2H; CH_2), 3.32 (s, 3H; CH_3), 3.62 (s, 3H; CH_3), 3.82 (s, 3H; CH_3), 4.02 (m, 2H; CH_2), 4.37 (m, 1H; CH*H*), 4.87(m, 1H; C*H*H), 4.90 (s, 2H; CH_2), 5.08 (d, $^2J_{H,H}$ = 3.7 Hz, 2H; CH_2), 5.14 (s, 2H; CH_2), 6.55 (s, 1H; CH), 6.65 (s, 1H; CH), 6.74 (s, 1H; CH), 6.76–6.81 (m, 3H; 3CH), 7.03 (s, 1H; CH), 7.24–7.44 ppm (m, 15H; 15CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 13.6, 28.8, 42.7, 55.2, 55.9 (2C), 59.6, 70.8, 70.9, 71.0, 108.9, 111.4, 113.1, 115.0, 115.5, 116.3, 116.9, 118.5, 121.2, 121.3, 123.5, 125.5, 127.2, (4C), 127.3 (2C), 127.7 (2C), 127.8 (2C), 127.9 (2C), 128.4 (2C), 128.5 (4C), 130.3, 130.9, 131.5, 136.4, 136.9, 147.1, 147.2, 147.8, 148.0, 148.3, 161.5 ppm; IR (UATR): $\tilde{\nu}_{max}$ = 1739 cm^{-1} (C=O); EIMS: *m*/*z* (%): 881 (0) [*M*+2H$^+$], 879 (0) [*M*$^+$], 698 (13), 91 (100); HRMS (FAB): *m*/*z*: calcd for $C_{51}H_{47}BrNO_8$: 880.2480; found: 880.2456.

Compound ***20***

Employing the general procedure for the synthesis of pyrrolo[2,1-*a*]isoquinoline carboxylate with benzyldihydroisoquinoline **11d** (2.54 g, 6.1 mmol) and nitrostyrene **12b** (1.78 g, 4.07 mmol) in acetonitrile (25 mL) gave **20** as a yellow sticky gum (1.40 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 0.87 (t, $^3J_{H,H}$ = 7.1 Hz, 3H; CH_3), 2.92–3.10 (m, 2H; CH_2), 3.37 (s, 3H; CH_3), 3.65 (s, 3H; CH_3), 3.65 (s, 3H; CH_3), 3.84 (s, 3H; CH_3), 3.93–4.11 (m, 2H; CH_2), 4.39 (m, 1H; CH*H*), 4.89 (m, 1H; C*H*H), 5.10 (d, $^2J_{H,H}$ = 2.5 Hz, 2H; CH_2), 5.15 (s, 2H; CH_2), 6.57 (s, 1H; CH), 6.74 (d, $^4J_{H,H}$ = 2.2 Hz, 1H; CH), 6.75 (s, 2H; 2CH), 6.75 (d, $^3J_{H,H}$ = 8.6 Hz, 1H; CH), 6.81 (dd, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 1.6 Hz, 1H; CH), 7.03 (s, 1H; CH), 7.29–7.45 ppm (m, 10H; 10CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 13.6, 28.9, 42.7, 55.3, 55.7, 55.8, 56.0, 59.7, 71.0 (2C), 109.0, 110.7, 113.2, 113.9, 115.0, 115.6, 116.9, 118.6, 121.3, 121.4, 122.9 (2C), 125.6, 127.2 (2C), 127.3 (2C), 127.7, 127.9, 128.0, 128.6 (3C), 130.4, 130.9, 131.6, 136.5, 136.9, 147.1, 147.2, 147.6, 147.9, 148.1, 148.5, 161.5 ppm; IR (UATR): $\tilde{\nu}_{max}$ = 1687 (C=O), 1251 (C–O), 1212 cm^{-1} (C–N); EIMS: *m*/*z* (%): 805 (58) [*M*+2H$^+$], 803 (61) [*M*$^+$], 725 (32), 713 (84), 622 (4), 91 (36); HRMS (FAB): *m*/*z*: calcd for $C_{45}H_{43}BrNO_8$: 804.2167; found: 804.2158

*General Procedure for Preparation of Dihydropyrrolo[2,1-a]*isoquinoline Carboxamides **23–25**

In a 10 mL microwave vessel, a mixture of ester **18**–**20** (1 equiv), amine **9d** (5 equiv), and trimethylaluminum (2 M $AlMe_3$ in toluene, 2.4 equiv) in THF (1 mL) was sealed and heated in a microwave reactor to 150 °C for 60 min (100 W, 120 psi). The reaction was quenched with water and extracted with CH_2Cl_2. The combined organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product, which was further purified by column chromatography on silica (30% EtOAc/hexanes) to furnish the desired products as a yellow sticky gum (62–90%):

Compound ***23***

Employing the general procedure with ester **18** (87.6 mg, 0.1 mmol), allyl amine **9d** (28.5 mg, 0.5 mmol), and $AlMe_3$ (0.12 mL) in THF (1 mL) (60 min, 150 °C, 300 W, 100 psi) gave product **23** as a yellow sticky gum (80.1 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.89–3.07 (m, 2H; CH_2), 3.23 (s, 3H; CH_3), 3.66 (s, 6H; $2CH_3$), 3.78–3.82 (m, 2H; CH_2), 4.39 (m, 1H; CH*H*), 4.84–4.93 (m, 3H; 2C*H*H), 5.10 (d, $^2J_{H,H}$ = 2.0 Hz, 2H; CH_2), 5.12(s, 4H; $2CH_2$), 5.55–5.65 (m, 2H; NH, CH), 6.66 (s, 1H; CH), 6.68 (s, 1H; CH), 6.72–6.74 (m, 4H; 4CH), 7.09 (s, 1H; CH) 7.28–7.43 ppm (m, 15H; 15CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 29.0, 41.5, 43.0, 55.2, 55.8, 56.1, 70.7, 71.0, 71.2, 108.7, 113.3, 113.6, 114.2, 115.5, 115.7, 115.8, 117.4, 120.7, 121.5, 121.7, 122.8, 125.5, 126.4, 127.0, 127.2, 127.4, 127.8, 127.8, 128.2, 128.4, 128.5 (2C), 128.6, 129.3, 133.8, 136.1, 137.0, 137.1, 146.5, 146.9, 147.8, 148.3, 149.0, 149.2, 161.6 ppm; IR (UATR): $\tilde{\nu}_{max}$ = 3423 (N–H), 1640 cm^{-1} (C=O); EIMS: *m*/*z* (%): 892 (0) [*M*+2H$^+$], 890 (0) [*M*$^+$], 802 (25), 711 (29), 631 (28), 541 (24), 91 (100); HRMS (FAB): *m*/*z*: calcd for $C_{52}H_{48}BrN_2O_7$: 891.2639; found: 891.2665.

Compound ***24***

Employing the general procedure with ester **19** (93.6 mg, 0.1 mmol), allyl amine **9b** (30.2 mg, 0.53 mmol), and $AlMe_3$ (0.12 mL) in THF (1 mL) (60 min, 150 °C, 300 W, 100 psi) gave product **24** as yellow sticky gum (55.0 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.90–3.07 (m, 2H; CH_2), 3.32 (s, 3H; CH_3), 3.65 (s, 3H; CH_3), 3.79 (m, 2H; CH_2), 3.83 (s, 3H; CH_3), 4.40 (m, 1H; CH*H*), 4.84–4.93 (m, 1H; C*H*H), 4.91 (d, $^2J_{H,H}$ = 1.6 Hz, 2H; CH_2), 4.91 (s, 2H; CH_2), 5.08 (d, $^2J_{H,H}$ = 3.8 Hz, 2H; CH_2), 5.14 (s, 2H; CH_2), 5.53–5.65 (m, 2H; CH, NH), 6.62 (s, 1H; CH), 6.65 (s, 1H; CH), 6.73 (s, 1H; CH), 6.78 (m, 3H; 3CH), 7.08 (s, 1H; CH), 7.23–7.46 ppm (m, 15H; 15CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 29.0, 41.5, 43.0, 55.2, 55.9, 56.1, 70.8, 70.9, 71.1, 108.7, 111.5, 113.2, 115.4, 115.7, 115.8, 116.1, 117.3, 120.7, 121.5, 121.6, 123.5, 125.5 (2C), 126.4, 127.2 (3C), 127.4 (2C), 127.8 (2C), 127.9 (2C), 128.2 (2C), 128.4 (2C), 128.6 (4C), 129.4, 133.9, 136.1, 136.9, 137.0, 146.9, 147.8, 148.3, 148.9, 161.6 ppm, 1C not observed; IR (UATR): $\tilde{\nu}_{max}$ = 3420 (N–H), 1695 cm^{-1} (C=O); EIMS: *m*/*z* (%): 892 (0) [*M*+2H$^+$], 890 (0) [*M*$^+$], 564 (23), 179 (31), 91 (100); HRMS (FAB): *m*/*z*: calcd for $C_{52}H_{48}BrN_2O_7$: 891.26; found: 891.2632.

Compound ***25***

Employing the general procedure with ester **20** (195.0 mg, 0.24 mmol), allyl amine **9b** (68.9 mg, 1.21 mmol), and $AlMe_3$ (0.29 mL) in THF (1 mL) (60 min, 150 °C, 300 W, 100 psi) gave product **25** as a yellow sticky gum (168.0 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.91–3.08 (m, 2H; CH_2), 3.37 (s, 3H; CH_3), 3.66 (s, 3H; CH_3), 3.67 (s, 3H; CH_3), 3.80 (m, 2H; CH_2), 3.83 (s, 3H; CH_3), 4.41 (m, 1H; CH*H*), 4.85–4.93 (m, 3H; CH_2, C*H*H), 5.10 (d, $^2J_{H,H}$ = 1.9 Hz, 2H; CH_2), 5.14 (s, 2H; CH_2), 5.55–5.66 (m, 2H; CH, NH), 6.68 (s, 1H; CH), 6.73–6.81 (m, 5H; 5CH), 7.09 (s, 1H; CH), 7.29–7.47 ppm (m, 10H; 10CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 29.0, 41.5, 43.0 (2C), 55.3, 55.7, 55.8, 56.1, 71.0 (2C), 108.8, 110.8, 113.3, 113.7, 115.4, 115.7, 115.8, 117.4, 120.8, 121.5, 121.7, 122.9, 125.6, 126.4, 127.2 (2C), 127.4 (2C), 127.9 (2C), 128.2 (2C), 128.5 (2C), 128.6 (2C), 129.3, 133.8, 136.0, 137.0, 147.0, 147.6, 147.8, 148.2, 148.5, 148.9 ppm; IR (UATR): $\tilde{\nu}_{max}$ = 3416 (N–H), 1695 cm^{-1} (C=O); EIMS: *m*/*z* (%): 816 (0) [*M*+2H$^+$], 814 (3) [*M*$^+$], 576 (4), 91 (100); HRMS (FAB): *m*/*z*: calcd for $C_{46}H_{44}BrN_2O_7$: 815.2326; found: 815.2343.

*General Lactamization Procedure (**26–28**)*

In a 10 mL microwave vessel, a mixture of dihydropyrrolo[2,1-*a*]isoquinoline carboxamides **23**–**25** (1 equiv) and CuTC (2.8 equiv) in DMF (1–2 mL) was sealed and heated in a microwave reactor to 150 °C for 30 min (200 W, 100 psi). The reaction was monitored by means of TLC until completion. The reaction was filtered on silica gel and concentrated under reduced pressure to yield a yellow-brown oil. The crude product was then purified by column chromatography on silica (30% EtOAc/hexanes) to furnish the desired products (71–84%):

Compound ***26***

Employing the general procedure with amide **23** (348.2 mg, 0.4 mmol) and CuTC (209.5 mg, 1.1 mmol) in DMF (2 mL) (30 min, 150 °C, 200 W, 100 psi) gave product **26** as a yellow sticky gum (225.0 mg, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 3.01$ (t, $^3J_{H,H} = 7.2$ Hz, 2H; CH_2), 3.28 (s, 3H; CH_3), 3.34 (s, 3H; CH_3), 3.87 (s, 3H; CH_3), 4.86–5.04 (m, 4H; $2CH_2$), 4.96 (dd, $^3J_{H,H} = 17.5$ Hz, $^2J_{H,H} = 1.0$ Hz, 1H; CH*H*), 5.08 (dd, $^3J_{H,H} = 10.5$ Hz, $^2J_{H,H} = 1.0$ Hz, 1H; C*H*H), 5.14 (s, 2H; CH_2), 5.19 (s, 2H; CH_2), 5.27 (s, 2H; CH_2), 5.80–5.90 (m, 1H; CH), 6.70 (s, 1H; CH), 6.74 (s, 1H; CH), 6.79 (s, 1H; CH), 6.89 (s, 1H; CH), 7.02–7.09 (m, 3H; 3CH), 7.27–7.49 ppm (m, 15H; 15CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 28.9$, 29.7, 42.3, 44.3, 55.1, 55.2, 56.2, 70.9 (2C), 71.4, 102.7, 105.7, 108.9, 112.4, 113.3, 114.1, 114.6, 114.7, 116.4, 118.8, 121.2, 123.6, 125.5, 126.5, 127.0, 127.1, 127.2, 127.9, 128.0, 128.6 (2C), 128.7, 129.9, 130.3, 132.4, 133.6, 136.8, 137.0, 144.9, 146.8, 147.4, 147.5, 147.9, 150.4, 155.5 ppm; IR (UATR): $\tilde{\nu}_{max} = 1636$ (C=O), 1212, 1180 cm^{-1} (C–N); EIMS: *m/z* (%): 810 (8) [M^+], 630 (35), 629 (9); HRMS (FAB): *m/z*: calcd for $C_{52}H_{47}N_2O_7$: 811.3378; found: 811.3406.

Compound ***27***

Employing the general procedure with amide **24** (50.1 mg, 0.06 mmol) and CuTC (29.9 mg, 0.16 mmol) in DMF (2 mL) (30 min, 150 °C, 200 W, 100 psi) gave product **27** as a yellow sticky gum (38.1 mg, 84 %). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 3.01$ (t, $^3J_{H,H} = 6.7$ Hz, 2H; CH_2), 3.34 (s, 3H; CH_3), 3.40 (s, 3H; CH_3), 3.95 (s, 3H; CH_3), 4.86–5.01 (m, 4H; $2CH_2$), 4.92 (d, $^3J_{H,H} = 17.2$ Hz, 1H; CH*H*), 5.09 (d, $^3J_{H,H} = 10.5$ Hz, 1H; C*H*H), 5.12 (d, $^2J_{H,H} = 2.6$ Hz, 2H; CH_2), 5.15 (s, 2H; CH_2), 5.20 (s, 2H; CH_2), 5.81–5.90 (m, 1H; CH), 6.64 (s, 1H; CH), 6.74 (s, 1H; CH), 6.79 (s, 1H; CH), 6.89 (s, 1H; CH), 7.11 (s, 1H; CH), 7.12 (d, $^3J_{H,H} = 6.1$ Hz, 1H; CH), 7.13 (d, $^3J_{H,H} = 6.4$ Hz, 1H; CH), 7.21–7.44 ppm (m, 15H; 15CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 29.0$, 42.3, 44.3, 55.1, 55.2, 56.4, 70.9 (2C), 71.4, 102.7, 105.8, 108.9, 112.5, 112.6, 113.2, 114.0, 116.5, 116.8, 118.8, 121.2, 124.2, 125.5, 126.4, 127.1 (2C), 127.2 (2C), 127.4 (2C), 127.9 (2C), 128.0 (2C), 128.5 (2C), 128.6 (4C), 129.3, 130.3, 132.4, 133.7, 136.4, 136.9, 144.9, 146.8, 147.5, 147.8, 148.9, 149.3, 155.5 ppm; IR (UATR): $\tilde{\nu}_{max} = 1635$ cm^{-1} (C=O); EIMS: *m/z* (%): 810 (0.87) [M^+], 720 (10), 629 (12), 91 (100); HRMS (FAB): *m/z*: calcd for $C_{52}H_{47}N_2O_7$: 811.3378; found: 811.3398.

Compound ***28***

Employing the general procedure with amide **25** (609.8 mg, 0.75 mmol) and CuTC (199.4 mg, 1.05 mmol), in DMF (2 mL) (30 min, 150 °C, 200 W, 100 psi) gave product **28** as a brown sticky gum (451.4 mg, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 3.03$ (t, $^3J_{H,H} = 6.6$ Hz, 2H; CH_2), 3.37 (s, 3H; CH_3), 3.44 (s, 3H; CH_3), 3.86 (s, 3H; CH_3), 3.96 (s, 3H; CH_3), 4.87 (d, $^3J_{H,H} = 2.37$ Hz, 2H; CH_2), 4.95 (m, 3H; CH_2, CH*H*), 5.09 (dd, $^3J_{H,H} = 10.5$ Hz, $^2J_{H,H} = 1.0$ Hz, 1H; C*H*H), 5.14 (s, 2H; CH_2), 5.19 (s, 2H; CH_2), 5.81–5.90 (m, 1H; CH), 6.73 (s, 1H; CH), 6.76 (s, 1H; CH), 6.80 (s, 1H; CH), 6.93 (s, 1H; CH), 7.08 (d, $^4J_{H,H} = 1.5$ Hz, 1H; CH), 7.10 (s, 1H; CH), 7.13 (dd, $^3J_{H,H} = 8.1$ Hz, $^4J_{H,H} = 1.8$ Hz, 1H; CH), 7.28–7.43 ppm (m, 10H; 10CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 29.0$, 42.3, 44.3, 55.2 (2C), 56.1, 56.2, 70.9, 71.4, 102.7, 105.8, 108.9, 112.0 (2C), 113.3, 114.1, 114.2, 116.5, 118.8, 121.2, 123.8, 125.5, 126.5, 127.1 (2C), 127.2 (2C), 127.9 (3C), 128.6 (4C), 129.4, 130.4, 132.4 (2C), 133.7, 136.8, 145.0, 146.8, 147.5, 147.9, 148.6, 149.8 ppm; IR (UATR): $\tilde{\nu}_{max} = 1636$ cm^{-1} (C=O); EIMS: *m/z* (%): 735 (10) [M+H$^+$], 644 (46), 553 (39), 91 (51); HRMS (FAB): *m/z*: calcd for $C_{46}H_{43}N_2O_7$: 735.3065; found: 735.3037.

Compound ***54***

$[ClRh(PPh_3)_3]$ (10 mol %) was added to a solution of lactam **26** (1 equiv) in dry toluene (40 mL mmol^{-1} of starting material). The resulting mixture was heated at reflux for 14 h, cooled to room temperature, concentrated, and passed through a short plug of Celite (3 % MeOH/CH_2Cl_2) to generate a crude product as a brown viscous oil that was used for the next reaction without further purification. The crude product in THF (10 mL mmol^{-1} of starting material) was added to OsO_4 followed by a solution of $NaIO_4$ in H_2O (10 mL mmol^{-1} of starting material). The reaction mixture was heated to 80 °C and monitored with TLC. At that time, the reaction was cooled to room temperature, diluted with H_2O, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product, which was further purified by preparative thin-layer chromatography (PTLC) to give the desired product **54** as a brown oil (162.7 mg, 42 %). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 3.03$ (br t, 2H; CH_2), 3.29 (s, 3H; CH_3), 3.35 (s, 3H; CH_3), 3.87 (s, 3H; CH_3), 4.85–5.00 (m, 2H; CH_2), 5.15 (d, $^2J_{H,H} = 8.0$ Hz, 2H; CH_2), 5.27 (s, 2H; CH_2), 5.30 (s, 2H; CH_2), 6.72 (s, 1H; CH), 6.75 (s, 1H; CH), 6.76 (s, 1H; CH), 6.76 (s, 1H; CH), 7.04 (d, $^3J_{H,H} = 8.07$ Hz, 1H; CH), 7.07 (s, 1H; CH), 7.08 (d, $^3J_{H,H} = 7.8$ Hz, 1H; CH), 7.39 (m, 15H; 15CH), 9.68 ppm (s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 28.9$, 42.4, 55.2, 55.3, 56.2, 70.9 (2C), 71.0, 101.1, 105.3, 108.9, 111.3, 113.4, 114.6, 114.7, 116.9, 118.7, 119.0, 121.1, 123.6, 126.3, 127.0 (2C), 127.2 (2C), 127.3 (2C), 128.0 (2C), 128.6 (3C), 128.7 (2C), 129.2, 129.6, 136.8, 137.0, 147.4, 148.0, 150.4, 156.1 ppm, 5C not observed; IR (UATR): $\tilde{\nu}_{max} = 3355$ (N–H), 1651 (C=O), 1214 cm^{-1} (C–N); EIMS: *m/z* (%): 770 (2) [M^+], 680 (6), 91 (100); HRMS (FAB): *m/z*: calcd for $C_{49}H_{43}N_2O_7$:771.3065; found: 771.3088.

Compound ***55***

A solution of lactam **54** (1 equiv) in EtOAc was placed in a high-pressure Parr apparatus at room temperature. Palladium on activated charcoal (ca. 100 mg) was added to this solution. The resulting mixture was hydrogenated (75 psi) until all starting material was consumed (normally 15 h) as indicated by TLC. The mixture was then filtered through a plug of Celite and concentrated under reduced pressure to give a gray solid. The obtained gray solid (1 equiv) was then treated with Et_3N (4.5 equiv), DMAP (1 equiv), and acetic anhydride (4.5 equiv) in CH_2Cl_2 (25 mL mmol^{-1} of starting material) at 0 °C. The resulting mixture was stirred at room temperature and monitored with TLC until completion. The reaction was quenched with water and extracted with CH_2Cl_2. The combined organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product, which was further oxidized using DDQ (2.5 equiv) in dichloroethane (100 mL mmol^{-1} of starting material) while heating to reflux for 16 h. After being allowed to cool to RT, water and CH_2Cl_2 were added. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product, which was further purified by column chromatography on silica (1 % MeOH/CH_2Cl_2) to furnish the desired product **55** as pale yellow solid (45.1 mg, 60 %). M.p. 281 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 2.34$ (s, 3H; CH_3), 2.35 (s, 3H; CH_3), 2.38 (s, 3H; CH_3), 3.45 (s, 3H; CH_3), 3.45 (s, 3H; CH_3), 3.84 (s, 3H; CH_3), 6.94 (d, $^3J_{H,H} = 7.5$ Hz, 1H; CH), 6.96 (s, 1H; CH), 7.01 (s, 1H; CH), 7.21 (s, 1H; CH), 7.25 (d, $^3J_{H,H} = 6.4$ Hz, 1H; CH), 7.25 (s, 1H; CH), 7.29 (d, $^3J_{H,H} = 5.9$ Hz, 1H; CH), 7.36 (s, 1H; CH), 9.49 ppm (d, $^3J_{H,H} = 7.4$ Hz, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 20.6$ (3C), 55.5 (2C), 56.2, 195.0, 106.4 (2C), 110.4, 111.2, 111.8, 114.0, 115.3, 115.6, 120.5,123.4, 123.5, 123.8, 123.9, 127.6, 129.5, 131.6, 135.4, 139.6, 140.0, 140.1, 146.6, 150.5, 152.3, 156.1, 168.9, 169.2 ppm (2C); IR (UATR): $\tilde{\nu}_{max} = 3442$ (N–H), 1765 (C=O), 1648 cm^{-1} (C=O); EIMS: *m/z* (%): 624 (35) [M^+], 582 (69), 540 (100), 498 (56), 43 (29); HRMS (FAB): *m/z*: calcd for $C_{39}H_{29}N_2O_{10}$:625.1817; found: 625.1838.

Compound ***2***

Compound **55** (42 mg, 0.067 mmol) was dissolved by 5 % KOH/EtOH solution (KOH 1 equiv). The resulting mixture was stirred at room temperature and monitored with TLC until completion. The reaction was acidify with 2N HCl until reaching pH 7 and extracted with EtOAc. The combined organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give desired product **2** as a pale green solid (23.7 mg, 71 %). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): $\delta = 3.33$ (s, 3H; CH_3), 3.36 (s, 3H; CH_3), 3.75 (s, 3H; CH_3), 6.79 (s, 1H; CH), 6.88 (s, 1H; CH), 6.99 (dd, $^3J_{H,H} = 7.5$, 1.9 Hz, 1H; CH), 7.00 (d, $^3J_{H,H} = 7.1$ Hz, 1H; CH), 7.08 (d, $^3J_{H,H} = 8.0$ Hz, 1H; CH), 7.11 (s, 1H; CH), 7.12 (s, 1H; CH), 7.12 (s, 1H; CH), 9.36 (d, $^3J_{H,H} = 7.2$ Hz, 1H; CH), 9.27 (s, 1H; OH), 9.49 (s, 1H; OH), 9.71 (s, 1H; OH), 11.3 ppm (s, 1H; NH); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): $\delta = 54.9$,

55.2, 56.4, 102.7, 105.9, 106.3, 109.0, 110.5, 110.8, 112.0, 112.4, 115.6, 116.8, 118.2, 123.0, 124.3, 124.4, 127.3, 128.3, 131.8, 131.8, 143.8, 146.9, 147.5, 147.8, 148.4, 149.1, 155.8 ppm; IR (UATR): $\tilde{\nu}_{max}$ = 3356 (N–H), 1605 cm^{-1} (C=O); EIMS: *m*/*z* (%): 499 (29) [$M+H^+$], 498 (100) [M^+], 95 (12); HRMS (FAB): *m*/*z*: calcd for $C_{28}H_{23}N_2O_7$: 499.1500; found: 499.1506.

Cytotoxicity Test[4]

All azalamellarins were dissolved in DMSO and tested for their cytotoxic activities against HuCCA-1, A-549, HepG2, and MOLT-3 cancer cell lines. The cells suspended in the corresponding culture medium were inoculated in 96-well microtiter plates (Corning Inc., NY, USA) at a density of 10000–20000 cells per well, and incubated at 37 °C in a humidified atmosphere of 95% air and 5% CO_2. After 24 h, an equal volume of additional medium that contained either the serial dilutions of the test compounds, positive control (etoposide), or negative control (DMSO) was added to the desired final concentrations, and the microtiter plates were further incubated for an additional 48 h. The number of surviving cells in each well was determined using either MTT assay (for adherent cells) or XTT assay (for suspended cells) to determine the IC_{50}, which is defined as the concentration that inhibits cell growth by 50% (relative to negative control) after 48 h of continuous exposure to each test compound. Within each experiment, determinations were done in triplicate, and each compound was tested in at least two separate experiments. Any experiments with a variation greater than 10% were excluded from the analysis. The results are expressed as the mean IC_{50} value; standard deviations are omitted for visual clarity.

Acknowledgements

Financial support from the Thailand Research Fund (TRF; RMU4980048 for N.T), the award of the Royal Golden Jubilee Scholarship (PHD/0028/2552 for S.B.), and from NSF-REU research fellowship (CHE-0453126 for C.J.B. and C.W.) are gratefully acknowledged. The Center of Excellence on Environmental Health, Toxicology and Management of Chemicals (ETM) is gratefully acknowledged. The authors are thankful to Dr. Poonsakdi Ploypradith and Ms. Supattra Karnkra for providing lamellarin derivatives. Special thanks go to Ms. Pagamas Intachote (Laboratory of Immunology) and Ms. Busakorn Saimanee (Integrated Research Unit) Chulabhorn Research Institute for conducting the cytotoxicity assays.

[1] a) C. Ballot, J. Kluza, A. Martoriati, U. Nyman, P. Formstecher, B. Joseph, C. Bailly, P. Marchetti, *Mol. Cancer Ther.* **2009**, *8*, 3307–3317; b) M. A. Gallego, C. Ballot, J. Kluza, N. Hajji, A. Martoriati, L. Castéra, C. Cuevas, P. Formstecher, B. Joseph, G. Kroemer, C. Bailly, P. Marchetti, *Oncogene* **2008**, *27*, 1981–1992; c) D. Pla, F. Albericio, M. Alvarez, *Anticancer Agents Med. Chem.* **2008**, *8*, 746–760; d) E. Marco, W. Laine, C. Tardy, A. Lansiaux, M. Iwao, F. Ishibashi, C. Bailly, F. Gago, *J. Med. Chem.* **2005**, *48*, 3796–3807; e) C. Bailly, *Curr. Med. Chem. Anticancer Agents* **2004**, *4*, 363–378.

[2] a) D. Pla, A. Marchal, C. A. Olsen, A. Francesh, C. Cuevas, F. Albericio, M. Alvarez, *J. Med. Chem.* **2006**, *49*, 3257–3268; b) J. Kluza, M. A. Gallego, A. Loyenz, J. C. Beauvillian, J. M. Sousa-Faro, C. Cuevas, P. Marchetti, C. Bailly, *Cancer Res.* **2006**, *66*, 3177–3187; c) M. Vanhuyse, J. Kluza, C. Tardy, G. Otero, C. Cuevas, C. Bailly, A. Lansiaux, *Cancer Lett.* **2005**, *221*, 165–175; d) M. Facompré, C. Tardy, C. Bal-Mahieu, P. Colson, C. Peres, I. Manzanares, C. Cuevas, C. Bailly, *Cancer Res.* **2003**, *63*, 7392–7399.

[3] a) P. Ploypradith, T. Petchmanee, P. Sahakitpichan, N. D. Litvinas, S. Ruchirawat, *J. Org. Chem.* **2006**, *71*, 9440–9448; b) P. Ploypradith, R. K. Kagan, S. Ruchirawat, *J. Org. Chem.* **2005**, *70*, 5119–5125; c) P. Ploypradith, C. Mahidol, P. Sahakitpichan, S. Wongbundit, S. Ruchirawat, *Angew. Chem.* **2004**, *116*, 884–886; *Angew. Chem. Int. Ed.* **2004**, *43*, 866–868; d) P. Ploypradith, W. Jinaglueng, C. Pavaro, S. Ruchirawat, *Tetrahedron Lett.* **2003**, *44*, 1363–1366; e) S. Ruchirawat, T. Mutarapat, *Tetrahedron Lett.* **2001**, *42*, 1205–1208.

[4] M. Chittchang, P. Butsomboon, S. Ruchirawat, P. Ploypradith, *ChemMedChem* **2009**, *4*, 457–465.

[5] For recent works, see: a) M. Chittchang, M. Paul Gleeson, P. Ploypradith, S. Ruchirawat, *Eur. J. Med. Chem.* **2010**, *45*, 2165–2172; b) L. Shen, X. Yang, B. Yang, Q. He, Y. Hu, *Eur. J. Med. Chem.* **2010**, *45*, 11–18; c) T. Ohta, T. Fukuda, F. Ishibashi, M. Iwao, *J. Org. Chem.* **2009**, *74*, 8143–8153; d) D. Pla, M. Martí, J. Farrera-Sinfreu, D. Pulido, A. Francesch, P. Calvo, C. Cuevas, M. Royo, R. Aligué, F. Albericio, M. Alvarez, *Bioconjugate Chem.* **2009**, *20*, 1112–1121; e) D. Pla, A. Francesch, P. Calvo, C. Cuevas, R. Aligué, F. Albericio, M. Alvarez, *Bioconjugate Chem.* **2009**, *20*, 1100–1111; f) J. C. Liermann, T. Opatz, *J. Org. Chem.* **2008**, *73*, 4526–4531; and references therein.

[6] C. Barberis, T. D. Gordon, C. Thomas, X. Zhang, K. P. Cusack, *Tetrahedron Lett.* **2005**, *46*, 8877–8880.

[7] D. Strumberg, Y. Pommier, K. Paull, M. Jayaraman, P. Nagafuji, M. Cushman, *J. Med. Chem.* **1999**, *42*, 446–457.

[8] For isolation and activities, see: a) M. Hesse, *Alkaloids* (Eds: P. M. Wallimann, M. V. Kisakürek), Wiley-VCH, Zürich, **2002**; b) D. Li, B. Zhao, S. P. Sim, T. K. Li, A. Liu, L. F. Liu, E. LaVoie, *J. Bioorg. Med. Chem.* **2003**, *11*, 521–528; c) M. E. Wall, M. C. Wani, H. Taylor, *J. Nat. Prod.* **1987**, *50*, 1095–1099; d) F. R. Stermitz, J. P. Gillespie, L. G. Amoros, R. Romero, T. A. Stermitz, K. A. Larson, S. Earl, J. E. Ogg, *J. Med. Chem.* **1975**, *18*, 708–713; For the synthesis, see: e) T. N. Le, S. G. Gang, W.-J. Cho, *J. Org. Chem.* **2004**, *69*, 2768–2772; f) T. N. Le, W.-J. Cho, *Chem. Pharm. Bull.* **2006**, *54*, 476–480.

[9] For isolation, see: a) G. R. Pettit, V. Gaddamidi; G. M. Cragg, *J. Nat. Prod.* **1984**, *47*, 1018–1020, G. M. Cragg, D. L. Herald, Y. Sagawa, *J. Chem. Soc. Chem. Commun.* **1984**, 1693–1694; b) G. R. Pettit, V. Gaddamidi; G. M. Cragg, *J. Nat. Prod.* **1984**, *47*, 1018–1020. For activities, see: c) G. R. Pettit, V. Gaddamidi, D. L. Herald, S. B. Singh, G. M. Cragg, J. M. Schmidt, F. E. Boettner, M. Williams, Y. Sagawa, *J. Nat. Prod.* **1986**, *49*, 995–1002; d) B. Gabrielsen, T. P. Monath, J. W. Huggins, D. F. Kevauver, G. R. Petti, G. Groszek, M. Holingshead, J. J. Kirsi, W. M. Shannon, E. M. Schubert, J. DaRe, B. Ugarkar, M. A. Ussery, M. J. Phelan, *J. Nat. Prod.* **1992**, *55*, 1569–1581. For the first synthesis, see: e) S. Danishefsky, J. Y. Lee, *J. Am. Chem. Soc.* **1989**, *111*, 4829–4837.

[10] a) X. Xiao, A. Morrell, P. E. Fanwick, M. Cushman, *Tetrahedron* **2006**, *62*, 9705–9712; b) A. Ioanoviciu, S. Antony, Y. Pommoer, B. L. Staker, L. Stewart, M. Cushman, *J. Med. Chem.* **2005**, *48*, 4803–4814; and references therein.

[11] For the selected publications on Cu^I-catalyzed C–N bond formations, see: a) E. Sperotto, J. G. de Vries, G. P. M. van Klink, G. van Koten, *Tetrahedron Lett.* **2007**, *48*, 7366–7370; b) R. Martín, R. Rodríguez, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 7237–7240; *Angew. Chem. Int. Ed.* **2006**, *45*, 7079–7082; c) H. Zhang, Q. Cai, D. Ma, *J. Org. Chem.* **2005**, *70*, 5164–5173; d) T. Hu, C. Li, *Org. Lett.* **2005**, *7*, 2035–2038; e) H.-J. Cristau, P.-P. Cellier, J.-F. Spinder, M. Taillefer, *Chem. Eur. J.* **2004**, *10*, 5607–5622; f) J. C. Antilla, J. M. Baskin, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 5578–5587; g) T. Jin, S. Kamijo, Y. Yamamoto, *Eur. J. Org. Chem.* **2004**, 3789–3791; h) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 793–796; i) F. Y. Kwong, A. Klapars, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 581–584; j) K. Yamada, T. Kubo, H. Tokuyama, T. Fukuyama, *Synlett* **2002**, 0231–0234; k) M. Wolter, A. Klapars, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3803–3805; l) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729; m) J. C. Antilla, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 2077–2079; n) R. Gujadhur, D. Venkataraman, J. T. Kintigh, *Tetrahedron Lett.* **2001**, *42*, 4791–4793; o) P. Y. S. Lam, G. Vincent, C. G. Clark, S. Deudon, P. K. Jadhav, *Tetrahedron Lett.* **2001**, *42*, 3415–3418.

[12] Buchwald–Hartwig amination, see: a) J. P. Wolfe, S. L. Buchwald, *Org. Synth.* **2004**, *10*, 423; b) H. Christensen, S. Kiil, K. Dam-Johansen, O. Nielsen, M. B. Sommer, *Org. Process Res. Dev.* **2006**, *10*, 762–769.

[13] B. K. Singh, P. Appukkuttan, S. Claerhout, V. S. Parmar, E. Van der Eycken, *Org. Lett.* **2006**, *8*, 1863–1866.

[14] For phenanthridin-6-ones, see: a) R. Ferraccioli, D. Carenzi, E. Motti, M. Catellani, *J. Am. Chem. Soc.* **2006**, *128*, 722–723; b) T. Harayama, T. Akiyama, Y. Nakano, H. Nishioka, H. Abe, Y. Takeuchi, *Chem. Pharm. Bull.* **2002**, *50*, 519–522; c) S. Caddick, W. Kofie, *Tetrahedron Lett.* **2002**, *43*, 9347–9350; d) J. A. Murphy, F. Rasheed, S. Gastaldi, T. Ravishanker, N. Lewis, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1549–1558; e) R. A. Abramovitch, Q. Shi, *Heterocycles* **1994**, *37*, 1463–1466; f) C. Lampard, J. A. Murphy, F. Rasheed, N. Lewis, M. B. Hursthouse, D. E. Hibbs, *Tetrahedron Lett.* **1994**, *35*, 8675–8678; g) W. B. Motherwell, A. M. K. Pennell, *J. Chem. Soc. Chem. Commun.* **1991**, 877–879; h) K. C. Majumdar, S. K. Chattopadhyay, A. K. Gupta, *Indian J. Chem. Sect. B* **1990**, *29*, 1138–1140; i) I. Datta, T. K. Das, S. Ghosh, *Tetrahedron* **1990**, *46*, 6821–6830; j) J. J. Eisch, C. A. Kovacs, P. Chobe, *J. Org. Chem.* **1989**, *54*, 1275–1284; k) H. Togo, O. Kikuchi, *Heterocycles* **1989**, *28*, 373–381; l) H. Togo, O. Kikuchi, *Tetrahedron Lett.* **1988**, *29*, 4133–4134; m) A. Albini, E. Fasani, V. Frattini, *J. Chem. Soc. Perkin Trans. 1* **1988**, 235–240; n) D. Ostović, R. M. G. Roberts, M. Kreevoy, *J. Am. Chem. Soc.* **1983**, *105*, 7629–7631; o) J. Grimshaw, D. Mannus, *J. Chem. Soc. Perkin Trans. 1* **1977**, 2456; p) A. R. Forrester, M. Gill, E. M. Johansson, C. J. Meyer, R. H. Thomson, *Tetrahedron Lett.* **1977**, *18*, 3601–3604; q) D. R. Eckroth, T. H. Kinstle, D. O. De La Cruz, J. K. Sparacino, *J. Org. Chem.* **1971**, *36*, 3619–3621; r) G. J. Heiszwolf, H. Kloosterziel, *Chem. Commun.* **1966**, 767–768; s) D. H. Hey, T. M. Moynehan, *J. Chem. Soc.* **1959**, 1563–1572.

[15] For selected publications on CuTC, see: a) L. S. Liebeskind, J. Srogl, *Org. Lett.* **2002**, *4*, 979–981; b) C. L. Kusturin, L. S. Liebeskind, W. L. Neumann, *Org. Lett.* **2002**, *4*, 983–985; c) C. Savarin, L. S. Liebeskind, *Org. Lett.* **2001**, *3*, 91–93; d) C. Savarin, L. S. Liebeskind, *Org. Lett.* **2001**, *3*, 2149–2152; e) R. Shen, J. A. Porco, *Org. Lett.* **2000**, *2*, 1333–1336; f) L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* **2000**, *122*, 11260–11261; g) J. Srogl, L. S. Liebeskind, *Org. Lett.* **2000**, *2*, 3229–3231; h) S. Zhang, D. Zhang, L. S. Liebeskind, *J. Org. Chem.* **1997**, *62*, 2312–2313; i) G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.

[16] N. Thasana, R. Worayuthakarn, P. Kradanrat, E. Hohn, L. Young, S. Ruchirawat, *J. Org. Chem.* **2007**, *72*, 9379–9382; and references therein.

[17] a) J. A. Marshall, G. P. Luke, *Synlett* **1992**, 1007–1008; b) D. Glynn, D. Bernier, S. Woodward, *Tetrahedron Lett.* **2008**, *49*, 5687–5688.

[18] K. Tangdenpaisal, S, Sualek, S. Ruchirawat, P. Ploypradith, *Tetrahedron* **2009**, *65*, 4316–4325.

[19] P. Wipf, C. R. Hopkins, *J. Org. Chem.* **2001**, *66*, 3133–3139.

Received: March 30, 2010
Published online: August 2, 2010

