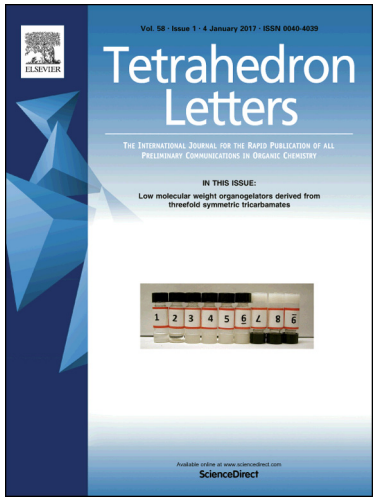

Synthesis of bengamide E analogues and their cytotoxic activity

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Synthesis of bengamide E analogues and their cytotoxic activity

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ABSTRACT

A series of bengamide E analogues were prepared from the corresponding polyketide chain and amino acids *via* amide coupling reactions. Opening of the polyketide chain lactone ring with α-aminolactams was successfully achieved under microwave irradiation in the presence of sodium 2-ethyl hexanoate. A cytotoxic activity evaluation against a panel of cancer cell lines (KB, HepG-2, Lu-1, MCF-7, HL-60 and Hela) indicated that the 2'*R* analogues were generally more cytotoxic than the 2'*S* analogues. Additionally, several analogues exhibited selective inhibition against various cancer cell lines: compounds **32a** and **32b** selectively inhibited MCF-7 cells, while **33b** and **35b** were more sensitive toward Lu-1 and HepG-2, respectively. Notably, some of the synthetic analogues possess cytotoxic activities with IC_{50} values less than 1 μM.

1. Introduction

Marine sponges of the family Jaspidae have proven to be an important source of bioactive secondary metabolites. The sponge-derived bengamides, first reported in 1986,[1] have a unique molecular structure and were found to possess a broad spectrum of biological activities such as antitumor, antibiotic, and anthelmintic properties.[2a-d] The structural modification of bengamides has focused mainly on altering the different stereocenters of the polyketide side-chain;[3a-e] the substituent located at the terminal olefinic position;[4a-c] or modification of the caprolactam unit.[5a-c] These modifications have led to the obtainment of more potent bengamide derivatives. Modification by replacement of isopropyl by *tert*-butyl at the terminal of the polyketide chain has proven successful and simplified the synthesis of analogues. Also, the presence of *tert*-butyl instead of isopropyl in the structures of bengamide analogues makes these structures more stable by avoiding olefin isomerization. A bengamide analogue, LAF389 (Fig. 1) with *tert*-butyl at the terminal polyketide side-chain,[6] has been used in a clinical trial. However, poor pharmacokinetic properties and unclear side effects, which appeared early in the trial, have prevented its further development.[7] This prompted the search for new bengamide derivatives.

Herein, we report the synthesis of a series of bengamide analogues with replacement of isopropyl at terminal polyketide chain by the *tert*-butyl group, and modification of the caprolactam ring including changes of ring size and stereochemistry at C-2' of the lactam units. Additionally, cytotoxic activity evaluation of the synthetic bengamide analogues was also reported.

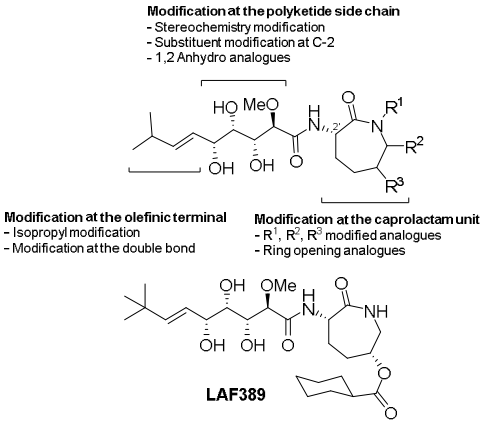

Figure 1. Reported structural modification of bengamides

2. Result and Discussion

In the first steps, lactams **3a-b**, **4a-b** were synthesized from the corresponding enantiomeric amino acids. Several methods for the synthesis of α-amino-lactams from amino acids have been reported,[8a-c] however, it was evident that these involved the use of expensive reagents such as Me_3SiCl and $(Me_3Si)_2NH$, or

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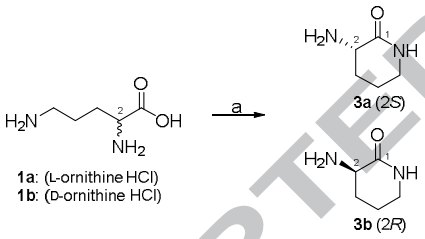
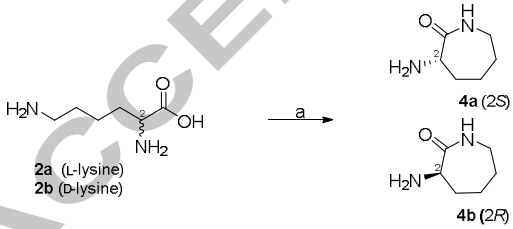
needed to be performed under high pressure, at high temperature and with long reaction times. In this work, the α-amino-lactams were synthesized under microwave irradiation (Scheme 1, 2). Compounds **4a** and **4b** were obtained in 79% and 82% yield under microwave irradiation (284 W) for 60 min in ethylene glycol from L-lysine and D-lysine, respectively. Since, D- and L-ornithines were commercially available in the monohydrochloride salt forms, addition of a base to the reaction mixture would be required. In the first attempt, pyridine was used for the cyclization reaction of D-ornithine monohydrochloride under microwave irradiation (284 W) for 60 min in ethylene glycol to give compound **3b** in moderate yield (55%). A higher yield (78%) was obtained when aqueous $NaHCO_3$ (10%) was used instead of pyridine. Applying the same procedure, compound **3a** was synthesized from L-ornithine monohydrochloride in 66% yield.

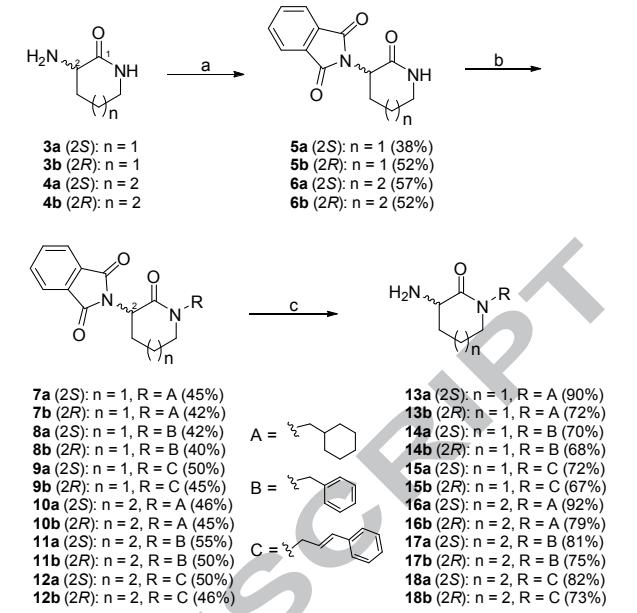
The primary amino groups of aminolactams **3a**-**b**, **4a**-**b** were protected using phthalic anhydride which was achieved under microwave irradiation (Scheme 3). It was found that these reactions conducted under conventional heating at 110 °C required much longer times. For example (data not shown), treatment of **4a** with phthalic anhydride in acetic acid in the presence of 4Å molecular sieves at 110 °C for 15 h, afforded **6a** in 41% yield, while compound **6a** was obtained in 57% yield when the reaction was irradiated (284 W) for 60 min. With microwave irradiation, compounds **5a**-**b** and **6b** were prepared in 38–52% yield from the corresponding aminolactams **3a**-**b** and **4b** (Scheme 3). The protected compounds **5a**-**b**, **6a**-**b** were then reacted with alkylbromides in the presence of K_2CO_3, KOH and KI, to obtain the corresponding amino-protected *N*-alkylaminolactams **7a**-**b**–**12a**-**b**. Hydrazine mediated phthalimide deprotection of **7a**-**b**–**12a**-**b** gave compounds **13a**-**b**–**18a**-**b**, respectively.



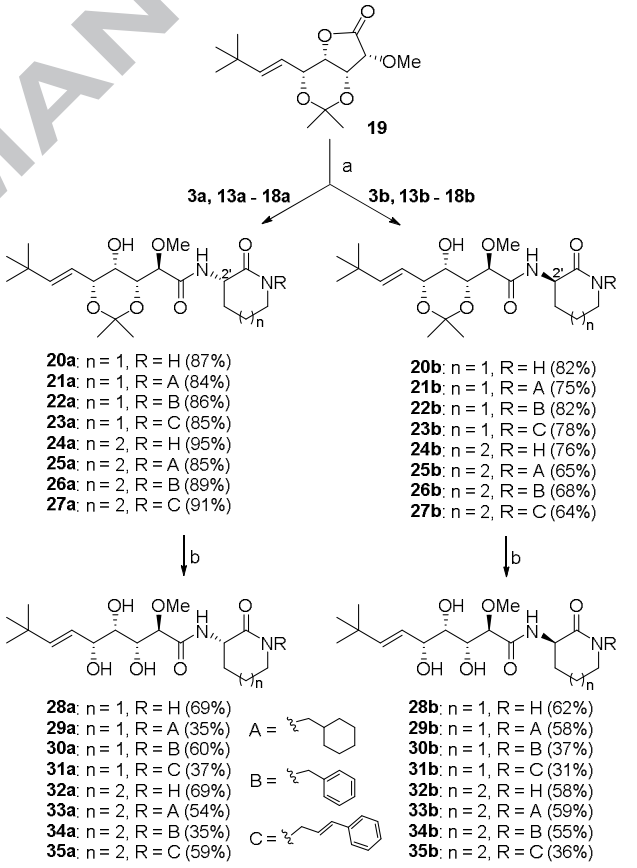
Scheme 1. Reagents and conditions: (a) aq. $NaHCO_3$ (10%), MW (284 W), 60 min; **3a** (78%), **3b** (72%).



Scheme 2 Reagents and conditions: (a) Ethylene glycol, MW (284 W), 60 min; **4a** (79%), **4b** (82%).



Scheme 3. Reagents and conditions: a) phthalic anhydride, acetic acid, MS 4Å, MW (284 W), 1 h; b) bromomethylcyclohexane, benzyl bromide or cinnamyl bromide, K_2CO_3, KOH, KI, DMSO, 0 to 60 °C, 23 h; c) aq. hydrazine (35%), acetonitrile, rt, 2 h.

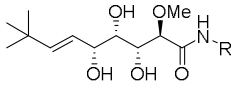


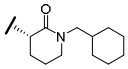
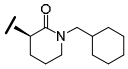
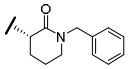
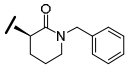
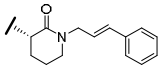
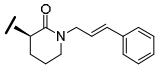
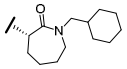
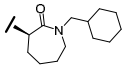
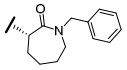
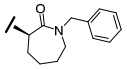
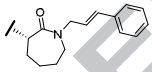
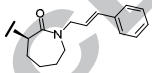
Scheme 4. Reagents and conditions: (a) *N*-alkylaminolactams, **13a**-**b** – **18a**-**b**, sodium 2-ethyl hexanoate, THF, MW (100 W) 60 min; (b) TFA, H_2O, THF, 0 °C, 1 h.

With polyketide **19** which was prepared according to the literature method,[6,9] and the *N*-alkylaminolactams in hand, the amide coupling reaction was achieved by treatment of **19** with *N*-alkylaminolactams **3a**-**b**, **4a**-**b**, **13a**-**b**–**18a**-**b** under microwave irradiation (100 W) to afford the desired coupling compounds **20a**-**b**–**27a**-**b** (Scheme 4). It was found that the coupling reaction

of polyketide **19** with aminolactams without microwave assistance took much longer (15-20 h).[6] Finally, acetonide deprotection with TFA in THF at 0 °C afforded the corresponding bengamide analogues **28a-b–35a-b**.

Table 1. Cytotoxicity of compounds **28a-b – 35a-b** (IC_{50}: μM)



Compound	R	KB	HepG-2	Lu-1	MCF-7	HL-60	Hela
28a		22.1	>50	13.8	>50	>50	>50
28b		11.1	22.0	2.6	>50	>50	>50
29a		8.2	11.8	12.7	20.1	>50	>50
29b		2.4	6.6	2.6	8.8	>50	>50
30a		2.9	11.3	7.5	17.8	55.8	39.7
30b		4.4	12.0	2.7	20.4	29.0	19.7
31a		2.3	6.6	5.8	4.3	36.8	36.8
31b		1.7	2.4	2.3	15.1	21.5	16.1
32a		22.0	22.8	4.3	1.5	>50	>50
32b		1.1	1.2	0.6	0.2	5.4	2.3
33a		11.8	>50	17.1	>50	>50	>50
33b		0.4	1.0	0.3	10.4	19.5	39.1
34a		5.7	4.8	7.7	32.5	45.6	41.5
34b		1.0	1.9	1.1	8.6	10.6	16.2
35a		1.9	1.5	23.6	4.9	13.4	26.9
35b		1.1	0.4	25.1	2.7	8.9	9.5
Ellipticine		0.3	0.4	0.3	0.6	0.5	0.4

All synthetic derivatives were evaluated for their cytotoxicity against a panel of cancer cell lines, KB (mouth epidermal carcinoma cells), HepG2 (human liver hepatocellular carcinoma cells), LU (human lung adenocarcinoma cells), MCF7 (human breast cancer cells), HL-60 (human promyelocytic leukemia cells), and Hela (human cervical carcinoma cells). Cytotoxicity comparison of the tested compounds revealed that, the 2'*R* series were generally more cytotoxic than the corresponding 2'*S*-epimer which possessed similar C-2' configuration as the natural bengamides. These synthetic analogues were found to be less active against HL-60 and Hela cell lines in comparison with the other tested cell lines (KB, HepG-2, Lu-1 and MCF-7).) Additionally, the cytotoxicity data (Table 1) indicated that several compounds exhibited selective inhibition against some cancer cell lines: compounds **32a** and **32b** selectively inhibited MCF-7 cells, while **33b** and **35b** were more sensitive toward Lu-1 and HepG-2, respectively. Additionally, compounds **32b**, **33b** and **35b** possessed cytotoxic activities with IC_{50} values less than 1 μM against several cancer cell lines.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedures and NMR spectra for the synthetic bengamide E derivatives) associated with this article can be found, in the online version, at http://

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Highlights

- Bengamide analogues were prepared *via* amide coupling reactions under MW irradiation
- The 2'*R* analogues were generally more cytotoxic than the 2'*S* analogues
- Some of the synthetic analogues had cytotoxicities with IC_{50} values less than 1 μM

Graphical Abstract

Synthesis of bengamide E analogues and their cytotoxic activity

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