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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.

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.

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 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 (Schemes 1 and 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

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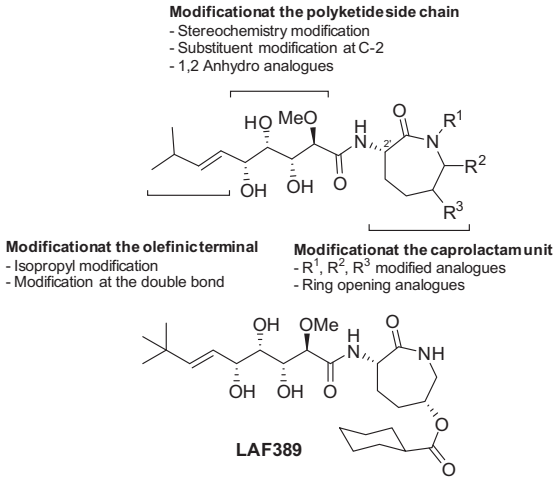
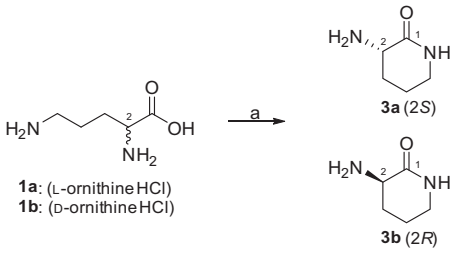
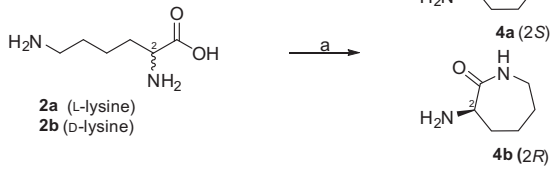


Fig. 1. Reported structural modification of bengamides.



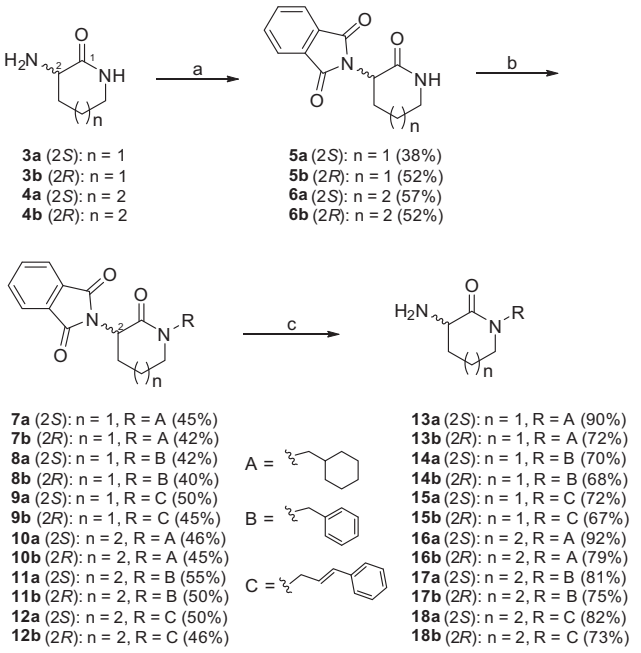
Scheme 1. Reagents and conditions: (a) aq. $NaHCO_3$ (10%), MW (284 W), 60 min; **3a** (78%), **3b** (72%).



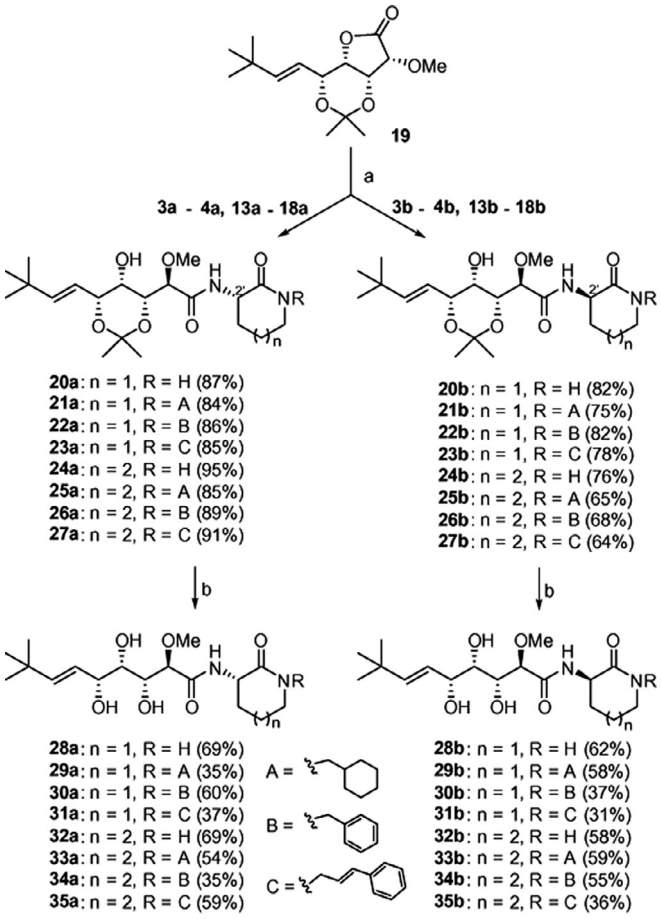
Scheme 2. Reagents and conditions: (a) Ethylene glycol, MW (284 W), 60 min; **4a** (79%), **4b** (82%).

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



Scheme 4. Reagents and conditions: (a) *N*-alkylaminolactams, **3a–b, 4a–b, 13a–b–18a–b**, sodium 2-ethyl hexanoate, THF, MW (100 W) 60 min; (b) TFA, H_2O, THF, 0 °C, 1 h.