Bioorganic & Medicinal Chemistry Letters 24 (2014) 5216–5218

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis of new bioisosteric hemiasterlin analogues with extremely high cytotoxicity

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ARTICLE INFO

Article history:
Received 3 September 2014
Revised 22 September 2014
Accepted 24 September 2014
Available online 2 October 2014

Keywords:
Tripeptides
Hemiasterlin
Unnatural hemiasterlin
Cytotoxicity

ABSTRACT

In this Letter, the synthesis and the evaluation of the cytotoxicity of new hemiasterlin analogues were reported. The indole moiety was replaced respectively by benzofurane, naphthalene and 4-bromobenzene groups. Most of these derivatives possess strong cytotoxic activity on two human tumour cell lines (KB and Hep-G_2), and some analogues showed comparable cytotoxic activity to that observed for paclitaxel and ellipticine, against KB and Hep-G_2 cancer cell lines.

Approximately 3.2 million new cases of cancer and 1.7 million deaths from cancer occurred in Europe in 2008 and the medical costs associated with cancer in 2010 were projected to reach $124.6 billion in the US. The increasing costs of cancer care illustrate the crucial need to advance our scientific knowledge to improve cancer treatments and reduce costs.[1] In the 1950s, scientists discovered two plant-derived antileukemic agents, vinblastine and vincristine, and isolated podophyllotoxin. These discoveries prompted the National Cancer Institute (NCI) and the US Department of Agriculture to start the systematic collection and screening of plants for antitumor activity. Finally, the list of natural product used as cancer therapeutics is impressive (Vinca alkaloids, anthracycline antitumor antibiotics, camptothecins, epothilones, podophyllotoxins, rapamycin mTOR inhibitors, taxanes, etc.).

Hemiasterlin (**1**), a natural tripeptide isolated from marine sponges, is a potent antimitotic agent acting by inhibition of microtubule depolymerization. The observed antimitotic activity was found to be due to the binding of **1** to the vinca-peptide site in tubulin.[2,3] The synthetic related analogue HTI-286 (**2**) displayed especially potent cytotoxicity against paclitaxel (Taxol™) resistant cancer cell lines in vitro and in vivo and is currently in clinical trials (Fig. 1).[3b]

There are several reports on the preparation of new hemiasterlin derivatives in which the indole aromatic ring moiety A was replaced by other aromatic systems.[4,5] Nevertheless, and in spite of the substantial efforts accomplished during the last decade, only few hemiasterlin analogues as **3a** and **3b** were reported with promising cytotoxicity activities.[6–8] Recently, we synthesized new hemiasterlin analogues in which the α,α-dimethylbenzylic group and amino NHMe moiety were replaced respectively by a α,β-unsaturated aryl and an amide NHAc group leading to the suppression of one chiral center. Among our prepared compounds, the two analogues **4a** and **4b** showed a comparable cytotoxicity activity to paclitaxel and ellipticine against KB cancer cell lines (Fig. 1).[9]

As a part of our ongoing work, we will continue to focus on the new biological active hemiasterlin analogues. For this purpose, we investigated the synthesis and the cytotoxicity of new hemiasterlin derivatives in which the indole moiety was replaced by various aryl groups as bioisosteric moieties.[10] These new compounds will be prepared by classical peptide coupling approach between the racemic carboxylic acid fragments A **8a–c** (Scheme 1) and enantiopure dipeptide **10** (Scheme 2).[9]

The preparation of the carboxylic acids **8a–c** is depicted in Scheme 1. Azalactones **5a–c**, prepared as previously reported from common aldehydes,[9,11] were first hydrolyzed under classical reaction conditions to lead to **6a–c** and then converted into α,α-dimethylketocarboxylic acids **7a–c**. The last step of this preparation, aiming to obtain **8a–c**, consists then to convert the ketone into methylamine via a reductive amination reaction. The reduction

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http://dx.doi.org/10.1016/j.bmcl.2014.09.065
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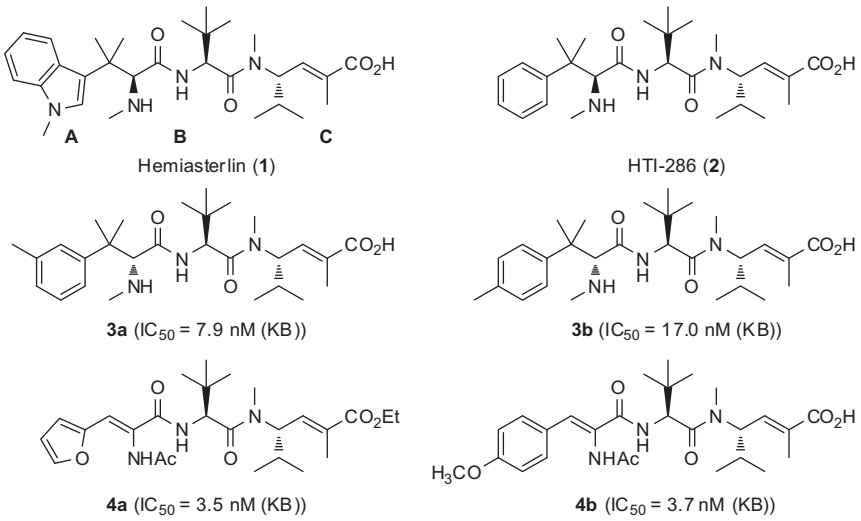
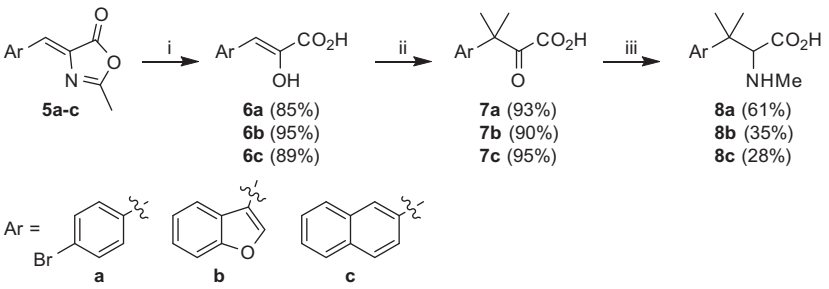
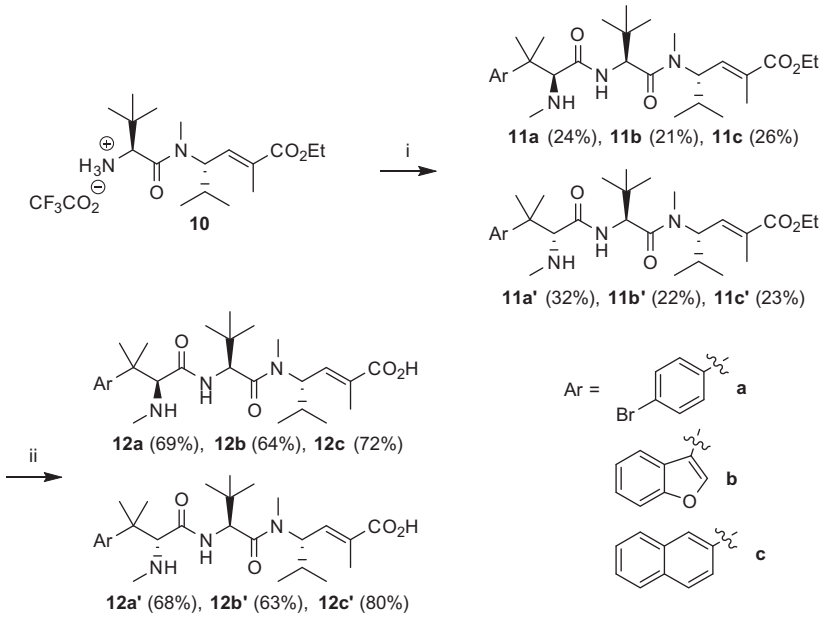


Figure 1. Structures of hemiasterlin derivatives and HTI analogues.



Scheme 1. Reagents and conditions (i) (1) 1.6 equiv NaOH (1 N), 85 °C, 1 h, (2) HCl (5 N) then HCl (12 N), 4 h, 120 °C. (ii) 3 equiv NaOH, 3.0 equiv MeI, THF, rt, 48 h (iii) 3.5 equiv $MeNH_2$, THF, rt, 1 h then 1.5 equiv BH_3 pyridine, 50 °C, 4 h.



Scheme 2. Reagents and conditions (i) 1.1 equiv **8a**–**c**, 1.2 equiv PyBOP, 2.5 equiv DIEA, DMF, rt, 18 h. (ii) 10.0 equiv LiOH, MeOH/H_2O (3:1), rt, 10 h.

of the imines formed in situ by condensation of **7a**–**c** with methylamine was only possible by treatment with the borane-pyridine complex.[4b] The expected products were isolated with moderate yields (Scheme 1).

The first analogues of hemiasterlin (**12** and **12′**) were obtained in two steps after peptide coupling of **8a**–**c** with **10**, separation of the diastereoisomers and saponification of the ethyl ester function (Scheme 2). The peptide coupling reaction was accomplished with

Table 1
Cytotoxicity evaluation[a]

Entry	Compound	IC_{50} (μM)			
		KB	Hep-G_2	LU	MCF_7
1	**11a**	0.012	0.006	32.5	148.7
2	**11a′**	0.172	0.010	66.9	>269.0
3	**11b**	0.013	0.011	54.9	>269.0
4	**11b′**	0.76	0.73	>269.0	>269.0
5	**11c**	0.013	0.013	132.2	>269.0
6	**11c′**	0.181	0.144	25.5	133.2
7	**12a**	0.0017	0.0018	>269.0	>269.0
8	**12a′**	0.011	0.013	>269	>269.0
9	**12b**	0.0017	0.0019	193.4	>269.0
10	**12b′**	0.043	0.037	42.3	>269.0
11	**12c**	0.0019	0.0019	>269.0	>269.0
12	**12c′**	0.014	0.034	205.0	>269.0
13[b]	Ellipticine	1.26	1.26	1.8	2.1
14[b]	Paclitaxel	3.9	0.19	—	—

[a] MTT cellular assay, 3 d exposure (more details in Supplement material).
[b] IC_{50} in nM.

PyBOP in the presence of an excess of base to lead to the stereochemically pure **11** and **11′** after separation by column chromatography on silica gel of both diastereoisomers. The saponification of esters was then carried out using lithium hydroxide solution to give **12a–c** and **12a′–c′** in moderate to good yields (Scheme 2).

According to the literature[7,12] we assigned the stereochemistry of the diastereoisomers as *S*,*S*,*S* for compounds **11a–c** and *R*,*S*,*S* for **11a′-c′**.

All final compounds were evaluated in vitro for their cytotoxic activity against four human cell lines (KB, Hep-G_2, LU and MCF_7) and the results were summarized in Table 1 (the most significative results are indicated in bold). Most of analogues of hemiasterlin prepared during this work possess a potent cytotoxicity against KB and Hep-G_2 and some of them showed comparable activities to ellipticine and paclitaxel. As noticed in the literature[7] the absolute configuration of the chiral center C14 plays an essential role in the cytotoxicity. Indeed, the *R*,*S*,*S*-diastereoisomers **11a′–c′** and **12a′–c′** presented an IC_{50} ten to fifteen time weaker than the *S*,*S*,*S*-diastereoisomers **11a–c** and **12a–c**.

In conclusion, preparation of new modified hemiasterlin derivatives was achieved in which the indol moiety were replaced by a naphthalene, benzofurane and 4-bromobenzene groups. This approach served to produce mixture of two separable diastereoisomers in which the carbon atom C14 can be either *R* or *S*. Most of these new analogues of hemiasterlin possess strong cytotoxic activities comparable to ellipticine and paclitaxel on two human tumor cell lines (KB and Hep-G_2). As it has been previously demonstrated that the hemiasterlin analogues act as tubulin polymerization inhibitors[6a] we are henceforth engaged in more detailed biological studies for compounds **12a–c** and the results will be reported in due course.

Acknowledgments

This work was financially supported in part by scientific research and technological development project (code: ĐT.NCCB-ĐHUD.2011-G/07).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.09.065.

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