Tetrahedron Letters 59 (2018) 3202–3205

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis and cytotoxicity screening of derivatives of the simplified ecteinascidin pentacyclic skeleton as anticancer agents

Ju Guo [a,*], Yang Yang [a], Nan Wang [b], Zhanzhu Liu [b,*]

[a] Key Laboratory for Green Chemical Process of Ministry of Education, Wuhan Institute of Technology, Wuhan 430205, PR China
[b] State Key Laboratory of Bioactive Substances and Functions of Natural Medicines, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, PR China

ARTICLE INFO

Article history:
Received 22 April 2018
Revised 7 July 2018
Accepted 9 July 2018
Available online 10 July 2018

Keywords:
Ecteinascidin pentacyclic skeleton
Synthesis
Cytotoxicity
Structure-activity relationship

ABSTRACT

A series of new ecteinascidin pentacyclic-derived compounds bearing aryl carboxylic amide side chains at C-22 have been designed and synthesized. The cytotoxicity evaluation confirmed their potent antitumor activity by use of eight different cell lines. Studies on the structure-activity relationship of them showed that the chemical structure of C-22 pendants have great effects on the tumor-killing activity. Notably, Compounds **6**, **7** and **8** with benzo[*b*]thiophene-2-carboxamide pendants exhibited excellent broad-spectrum antitumor activity with the low IC_{50} values of 10^{-7} M.

Introduction

Cancers are seriously threatening human health and increasing the social burdens, due to their high morbidity and mortality. Although a lot of antitumor medicines and therapeutic strategies have been developed and applied in clinic nowadays, cancers still cannot be thoroughly cured except early resection, which can be ascribed to the extreme mechanism complexity. It should be pointed out that chemical therapies remain one of the most important treatment methods. In this context, mountains of efforts have been devoted to the discovery of antitumor lead compounds. To this end, the isolation and structure derivatizations of natural products are still playing indispensable roles in the search for lead compounds [1–3]. Of the current tens of thousands of natural products, the large family of tetrahydroisoquinoline alkaloids (THIQs) have attracted extensive attentions from medical chemists around the world, due to their promising antitumor activity. Since the first isolation of THIQ compound AYB-1206 from *Streptomyces lusitanus* by Canadian scientist Kluepfel in 1974 [4], more than 60 members of this family have been reported [5]. Especially, as an outstanding member of THIQ family, Ecteinascidin 743(ET-743) (Fig. 1) has been commercialized in the European Union for the treatment of soft tissue tumors [6]. Inspired by the prominent antitumor activity of THIQ compounds, synthetic chemists have paid considerable efforts to their total synthesis and structural modifications over the past decade. Many unique synthetic strategies to access these THIQs have been designed and realized [7–15]. However, due to their high structural complexity, the current synthetic routes for THIQs are generally lengthy and the overall yields are low, which greatly hampers their derivatizations and slows the paces to be developed into medicines. Therefore, chemical modifications of available THIQ compounds seem to be a more practical strategy in the development of THIQ-derived tumor-killing drugs.

In 1999, Corey et al. discovered a structurally similar THIQ compound Phthalascidin 650 (Pt-650) (Fig. 2), which exhibited comparable antitumor activity with ET-743. Encouraged by this, chemists and biologists began to turn their research focus on the isolation and synthesis of structural analogs of THIQs [10–15]. A noteworthy case is Zalypsis (Fig. 2), which, as an ET-743 analogue developed by the Spanish company Pharma, has entered the clinical phase II trials [13–15].

As a continual interest in THIQs, we have paid considerable efforts to the studies on their synthesis and structure-activity relationship (SAR) in the past years [16–24]. In our previous studies, we identified a promising precursor compound **1**(Fig. 3), which demonstrated strong antitumor activity. After some preliminary studies on its SAR, it was found that the pendants attached to C-22 show significant effect on the antitumor activity and selectivity of the compound, which greatly inspire us to make more derivatizations at C-22.

Inspired by our previous reaserch [25] and the structure of Zalypsis, we synthesized a series of novel ecteinascidin-skeleton compounds and studied their SAR of the aryl moiety of 3-aryl

* Corresponding authors.
E-mail addresses: guoju1984@163.com (J. Guo), liuzhanzhu@imm.ac.cn (Z. Liu).

https://doi.org/10.1016/j.tetlet.2018.07.027
0040-4039/

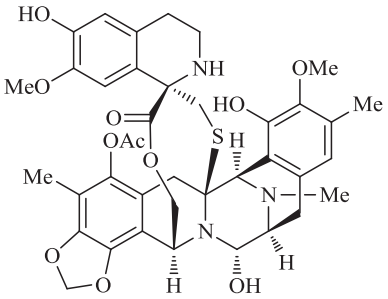

Fig. 1. Structure of ET-743.

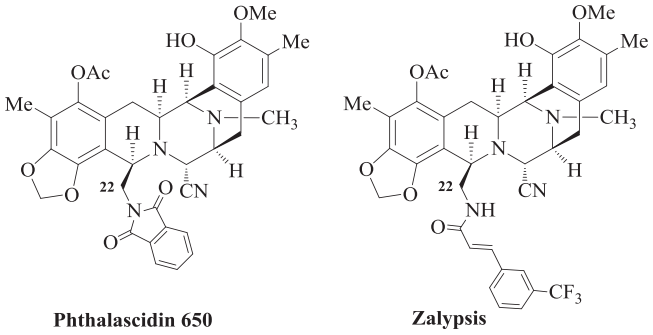

Fig. 2. Structure of Phthalascidin650 and Zalypsis.

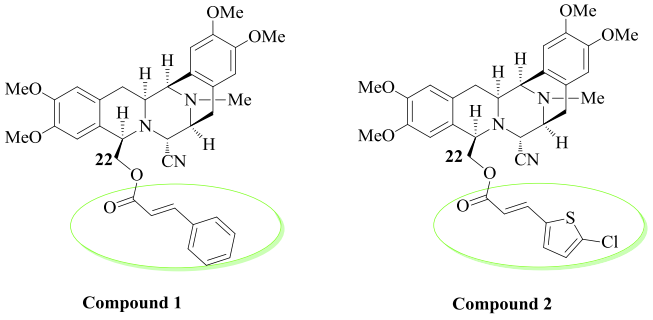

Fig. 3. Structure of lead compound **1** and Compound **2**.

acrylic amide at C-22. It was found that compound **2** with a 3-thiophenyl acrylic amide side chain exhibited broad and potent cytotoxic activity, and that the change of C-22 side chain would significantly decrease the antitumor activity. Herein, encouraged by these results and in continual interest in drug design and discovery, we report the design, synthesis and evaluation of novel ecteinascidin derivatives with different aryl carboxylic amide moieties at C-22, as anticancer agents. In this paper, we synthesized twenty-four simplified tetrahydroisoquinoline analogues in 13 steps employing the synthetic route we had built previously (Scheme 1) [20]. For products **6**–**29**, A series of aryl amide groups with various electron-donating (CH_3-, CH_3O- and *t*-Bu-) or electron-withdrawing (F-, Cl-, Br- and CF_3-) substituents were installed at C-22. Due to the high importance of the presence of conjugated aryl amide side chains at C-22 [26–28], we did not extend to target products containing benzyl or aliphatic groups. All the analogues were evaluated for their in vitro cytotoxicity against HCT-8, BEL-7402, Ketr3, A549, MCF-7, BGC-823, HELA, and KB human tumor cell lines.

Results and discussion

Chemistry

Compound **3** was synthesized from L-dopa through a multi-step stereospecific synthetic route we had built previously. Under Mitsunobu reaction conditions, compound **4** was obtained in high yield. The removal of the phthalimide group of **4** in the presence of N_2H_4-H_2O provided precursor 5, which was acylated with various aromatic carboxylic acids to afford the corresponding target amides **6**–**29** (Scheme 1). All the structures of the compounds were confirmed by ^{1}H NMR, [13]C NMR, and FAB-MS.

Cytotoxicity assay

Compound **6**–**29** were respectively tested in vitro against eight different cell lines, including HCT-8 (human colon cancer cell line), BEL-7402 (human hepatic carcinoma cell line), BGC-823 (human gastric adenocarcinoma cell line), A549 (human lung adenocarcinoma epithelial cell line), HELA (human Cervical cancer cell line), KB (human Nasopharyngeal cancer cell line), Ketr3 (human kidney cancer cell line), and MCF-7 (human breast cancer cell line).

As shown in Table 1, most of the compounds exhibited considerable cytotoxicities to these eight cell lines. Notably, compounds **6**, **7**, **8**, **14**, **25** and **29** showed selective inhibition against the five tumor cell lines of HCT-8, Bel-7402, Ketr3, MCF-7 and BGC-823 with the IC_{50} values at the level of 10^{-7} M regardless of the structural changes at C-22.

Meanwhile, compounds **6**, **7**, **8**, **14**, **19**, **25** and **29** showed higher cytotoxicity against tumor cell lines of KB with the IC_{50} values at the level of 10^{-7} M. On the other hand, compounds **6**, **7**, **8**, **9**, **10**, **11**, **12**, **14**, **16**, **19**, **26** and **29** showed higher cytotoxicity against tumor cell lines of HELA than the other compounds. It was found that compounds **6**, **7** and **8** also showed strong antitumor activity toward the human lung adenocarcinoma epithelial cell line A549 with the IC_{50} values at the level of 10^{-7} M. Notably, the pendants at C-22 of compound **6**, **7** and **8** has a common benzo[*b*]thiophene-2-carboxamide core, suggesting its importance on the antitumor activity. On the other hand, the substituent effects on the antitumor activity at the aromatic ring of the C-22 pendants could be observed. For example, compound **9** showed stronger cytotoxicity against the five tumor cell lines of Bel-7402, Ketr3, MCF-7, BGC-823, HELA than compounds **10** and **11**; compound **16** also showed higher cytotoxicity against the six tumor cell lines of HCT-8, Bel-7402, Ketr3, MCF-7, BGC-823, HELA when compared with compound **18**. In addition, the number of the same kind of substituents is also informative on the tumor-killing activity. For example, compound **28** with three methoxy groups on the benzene ring showed higher cytotoxicity against tumor cell lines of Ketr3, A549 and MCF-7 than compound **27** with two methoxy groups at C-22. It could be concluded that the tumor-killing activity of the obtained compounds is closely related with the chemical structures of C-22 pendants, which is also consistent with the previous research [25].