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Efficient synthesis and cytotoxicity of novel microtubule-stabilizing agent ceratamine A analogues

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ABSTRACT

An efficient synthesis of microtubule-stabilizing agent ceratamine A analogues is described. The key step is the application of either reductive Heck reaction or Heck reaction to construct the imidazo[4,5-*d*] azepine core. Thirteen novel analogues of ceratamine A were synthesized and evaluated for their *in vitro* cytotoxicity against five human cancer cell lines (HCT-116, HepG2, BGC-823, A549 and A2780). It was the first report about the systematic structural modification and SARs study of ceratamine A. The results demonstrated that bulky substituents at C-14 and C-16 could enhance the cytotoxicy and modification at N-7 was crucial for high potency. Especially compound **1f** bearing methyl group at C-14 and C-16, and compound **1k** bearing benzyl group on N-7, showed better cytotoxicy than ceratamine A against A549.
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1. Introduction

As one of the critical components of the cytoskeleton, microtubules have a substantial effect on mitosis and cell division. Antimitotic activity can be achieved through disrupting microtubule dynamics, such as promoting or preventing tubulin polymerization.[1] Generally, highly proliferating cells such as cancer cells suffer most.[2] In view of the successful clinical utility of paclitaxel and docetaxel, a large amount of microtubule-stabilizing agents have been synthesized by structural modification from natural products.[3] Nevertheless, the drug resistance, due to the overexpression of P-glycoprotein and the tubulin genes' mutation, has claimed the demand for additional microtubule perturbers with novel structures and binding sites.[4]

Ceratamine A, (Fig. 1) a novel heterocylic alkaloid, which was isolated from marine sponge *Pseudoceratina* sp. collected in Papua New Guinea, displays effective antimitotic activity by promoting tubulin polymerization. The mechanistic studies illuminated that ceratamine A did not bind the same site at microtubules as paclitaxel.[5] Although, ceratamine A is not as potent as many traditional tubulin stabilizers (like paclitaxel or discodermolide), its unique features have caused great interest.[5] Ceratamine A is structually simple and is the only nonchiral molecule among all natural microtubule stabilizers. It is also argued that the utility of microtubule-stabilizing agents with the ability of brain penetration might be another useful therapeutic way to treat taupathies, like Alzheimer's disease. Notably, the relatively simple structure of ceratamine A might be beneficial to cross the blood-brain barrier.[6] The above advantages make ceratamine A a promising lead compound.

So far, there have been two reports on the total synthesis of ceratamine A, including our group.[7] In addition, Andersen's group synthesized a few ceratamine A analogues (Fig. 1) and found that the coumpound which was introduced of methyl group on both C-14 and C-16 as well as on N at C-2 showed better antimitotic activity than ceratamine A.[8] Recently, experiments of metabolism *in vitro* were conducted to evaluate the pharmacokinetics of ceratamine A. The result revealed that demethylation had easily happened on N-7, which would decrease the antimitotic activity.[9] However, further structural modification and structural-activity relationships of ceratamine A have not been reported due to the limitation of synthetic routes.

In this paper, we have established an efficient route for the synthesis of ceratamine A analogues. A total of thirteen ceratamine A derivatives were synthesized through modifying the side chain and the substituents on N-7 as depicted in Fig. 2 and evaluated against five cancer cell lines (HCT-116, HepG2, BGC-823, A549 and

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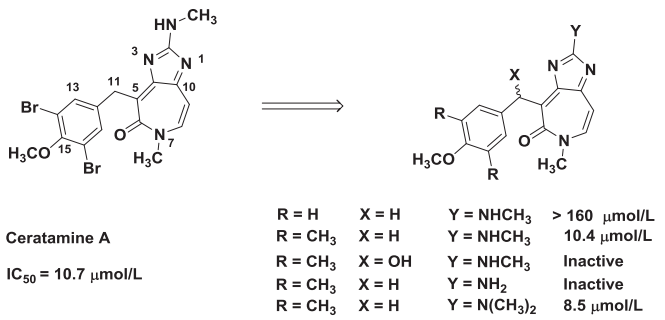


Fig. 1. Chemical structure and antimitotic activity of ceratamine A and synthesized analogues by Andersen's group.[8]

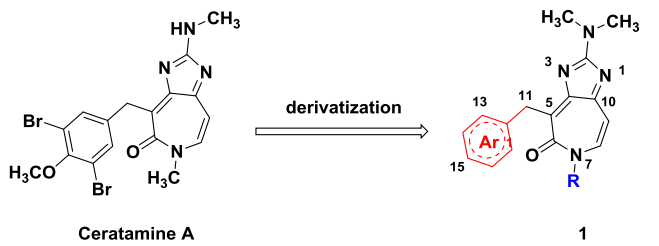


Fig. 2. Structural modification of ceratamine A.

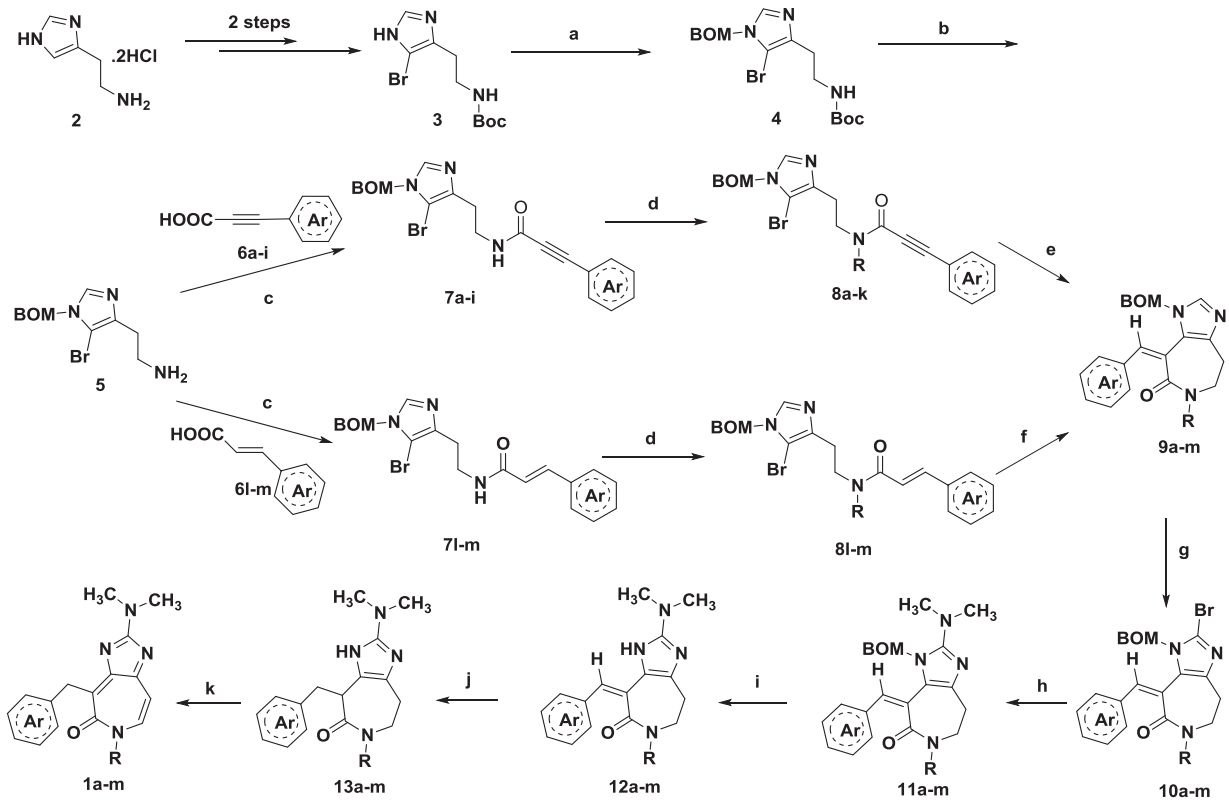
A2780) *in vitro*. The aim of our work is to investigate the SARs of ceratamine A on anticancer activity and find better analogue of ceratamine A.

2. Results and discussion

Inspired by the building of 3-benzazepine framework through reductive Heck reaction,[10,11] we envisioned that Heck cyclization could be used in the construction of imidazo[4,5-*d*]azepine ring. The entire synthetic route is demonstrated in Scheme 1. *N*-(*tert*-Butyloxycarbonyl)-5-bromohistamine **3** was easily synthesized from commercially available histamine dihydrochloride **2**.[12] The BOM-protected imidazole **4** was prepared by treatment of compound **3** with BOMCl and NEt_3 in THF. Deprotection of compound **4** with CF_3COOH cleanly gave compound **5** in gram scale. Treatment of phenylpropiolic acids **6a-i** generated by Sonogashira reaction[13] with amine **5** afforded compounds **7a-i** in satisfied yields. Then, alkylation of the crude products of **7a-i** with NaH afforded amides **8a-k**. Compounds **9a-k** were then successfully prepared through reductive Heck reaction.[10] The configuration of the double bond was identified by NOE effect of compound **9a** (see the Supplementary data). However, compounds **9a-k** were contaminated by the debrominated byproducts and finally purified by column chromatography.[14] To solve the problem, ordinary Heck reaction was applied for the synthesis of compounds **9l-m**, starting from amine **5** and cinnamic acids.[15] We found that amides **8l-m** were converted to the products **9l-m** smoothly with obviously fewer debrominated byproducts.

It is reported that the methylene protons signals of 7-membered ring often broadened or even disappeared in the ^{1}H NMR spectra due to the flipping of 7-membered lactam ring.[10,16] This phenomina were also observed in our experiment and the structures of compounds **9a-m** were confirmed by variable-temperature ^{1}H NMR (see the Supplementary data).

Reaction of **9a-m** with NBS afforded compounds **10a-m**, which



Scheme 1. Reagents and conditions: (a) BOMCl, THF, r.t., overnight, 85%; (b) CF_3COOH, CH_2Cl_2, r.t., 4 h, 92%; (c) acid, EDCI, DMAP, CH_2Cl_2, r.t., 30 h; (d) RX, NaH, DMF, r.t., overnight.; (e) $Pd(PPh_3)_4$, HCOONa, DMF/H_2O(3:1), 100 °C, 6 h; (f) $Pd(PPh_3)_4$, Methyl dicyclohexylamine, DMF, 120 °C, 20 h; (g) NBS, THF, 0 °C, 30 h; (h) aq. $HNMe_2$, sealed tube, 120 °C,20 h; (i) $AlCl_3$, DCM, r.t., 1 h; (j) PtO_2, H_2, EtOH, r.t.,5 h; (k) IBX, Py., DMSO, 36 °C, 1 h.

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