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Synthesis of macrocycles containing 1,3,4-oxadiazole and pyridine moieties

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ABSTRACT

A series of peptide-like 25–28 membered macrocycles containing 1,3,4-oxadiazoles and pyridines bearing a chiral center scaffold have been synthesized by using known coupling reagents and common protecting groups. The yield of the purified macrocycles was poor on an average, yet it seems to be independent of amino acid substitution or stereochemistry. These macrocycles represent a new class of structures for further development and for future application in high-throughput screening against a variety of biological targets.

Medium and large-sized ring compounds have always been considered by medicinal chemists as a stand-alone class of molecules, not only due to their interesting physico-chemical and biological properties, but also due to the challenge of their synthesis.[1] Natural products contain a wide variety of conformationally constrained, macrocyclic, peptide based rings that present both as backbone and side chain pharmacophoric groups for interacting with biological targets.[2] Such biologically active compounds are generally used by plants and animals in chemical warfare in order to gain an advantage against competitors or assaults.[3] Peptide based macrocycles from marine sources continue to be investigated for their biological activity,[3,4] as are similar compounds from plants.[5]

Medicinal chemists have long used macrocyclization as a tool in drug discovery. A classic illustration of this technique was the discovery of potent cyclic peptide somatostatin mimics three decades ago.[6,7] The method of cyclization since then developed into a general paradigm in peptidomimetic drug design that has been widely used in the discovery of biologically-active compounds for studying the cell.[8] Indeed, there are both natural product and synthetic macrocyclic peptides with known anticancer use or potential[9] thereby illustrating their functional similarity.

Several research groups have reported the synthesis of macrocyclic peptides containing heterocyclic amino acids.[10–13] In addition to the potency and selectivity gained by macrocyclization of peptides, cyclic peptides also resist proteolytic degradation and other metabolisms.

In view of the above aspects of cyclization of peptides, we report the synthesis and characterization of peptide-like macrocyclic compounds that contain oxadiazoles and pyridine, thereby yielding a unique compound class from macrocyclic natural products and known paradigms in drug discovery. The final compounds are 25–28 membered macrocycles with variations in stereochemistry and amino acid side chains. Indeed, macrocycles are underrepresented in screening libraries due in part to their synthetic challenge[14,15] and some biologically active compounds as shown in Figure 1.

It is important to note that these macrocycles represent a new class of compounds. Their features mimic those of known bioactive natural products, and we anticipate that such compounds would have reasonable pharmacokinetic properties. The presence of intrinsic points of diversity allows for the introduction of additional pharmacophores into the periphery, which has been selected by comparing known drugs and natural products.

The synthetic plan for the macrocyclic construction is summarized in Scheme 1. The core intermediate **7** was prepared from methyl 5-(4-aminophenyl)pyridine-3-carboxylate **6** by reacting with 4-carboxybenzaldehyde under reductive amination conditions.[16] Introduction of pinacolborane moiety by Miyaura–Ishiyama protocol afforded **4** in good yield.[17] Boronate **4** was coupled with commercially available amino protected bromo compound **2** under Suzuki coupling conditions to afford pyridine biphenyl **5** in 81%.[18] Deprotection of *tert*-butyl carbamate in acidic media gave **6** in good yield.

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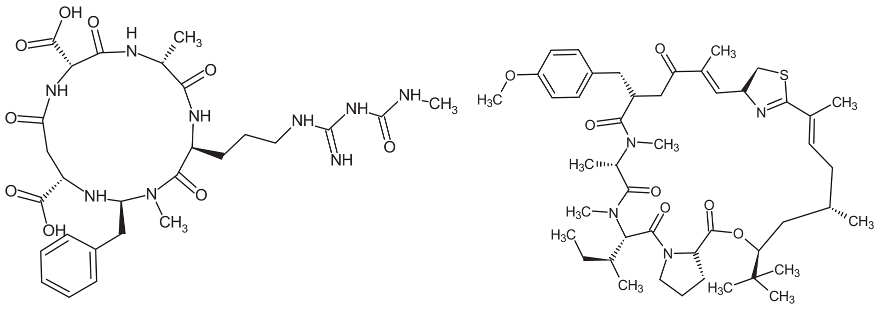
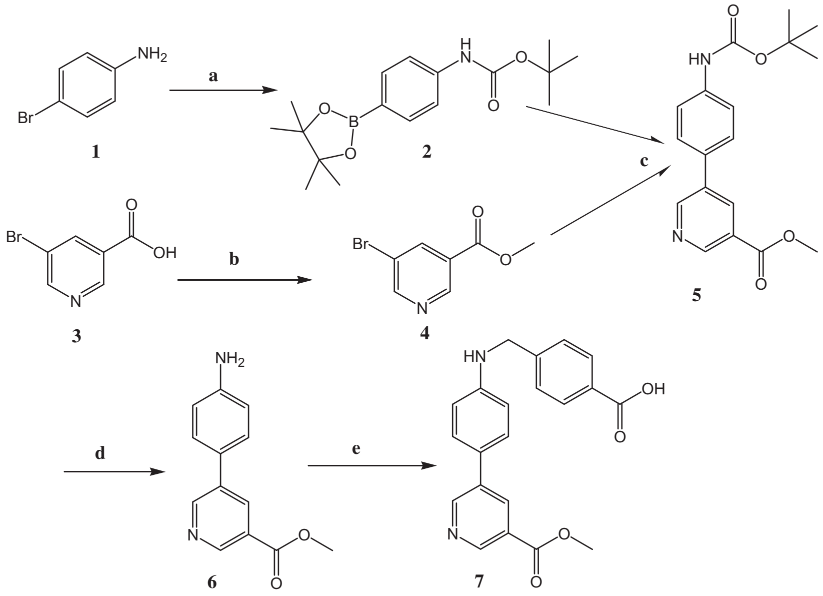


Argifin (E)-Dehydroapratoxin A 6

Figure 1. Bioactive macrocycles.



Scheme 1. Reagents and conditions: (a) (i) di*tert*-butylcarbamate (1.5 equiv), TEA (triethylamine) (3 equiv), THF, 80 °C, 8 h; (ii) bis(pinacolate)diboron (1.5 equiv), $PdCl_2(dppf)$ (0.05 equiv), KOAc, dioxane–H_2O, 90 °C, 16 h (b) thionyl chloride (4 equiv), MeOH, 80 °C, 4 h; (c) bis(triphenylphosphine) palladium(II) chloride, Na_2CO_3, DMF–H_2O (9:1), 10 h; (d) dioxane in HCl (4 M), rt, 2 h; (e) 4-carboxybenzaldehyde (1.5 equiv), acetic acid (5 equiv), sodium triacetoxyborohydride (3 equiv), DMF–THF, rt, 16 h.

The second challenge in the present synthetic method was the preparation of oxadiazole intermediates. The synthesis was achieved from commercially available amino acids as outlined in Scheme 2. The treatment of amino acids with thionyl chloride in the presence of methanol gave the substituted amino acid ester products in good yield. Subsequent protection of amino group with di*tert*-butyl carbamate provided compounds **8–11** in 80–92% yield. The intermediate thus obtained was treated with hydrazine monohydrate at reflux temperature to afford the substituted hydrazides (**12–15**) in excellent yield. The hydrazides were reacted with substituted isothiocyanate to form thiourea intermediates and subsequently the resulting reaction mixture was treated with EDC·HCl at reflux temperature to afford the oxadiazole[19,20] products (**16–19**) in one-pot. Further the deprotection *tert*-butyl carbamate or reduction of nitro group gave the corresponding amines (**20–23**) in 92–97% overall yield (Table 1).

All reactions were carried out under inert atmosphere. The crude reaction products were purified by column chromatography.

The fragments **20–23** were easily synthesized by a known method. Then, condensation between amines and carboxylic acid **7** as described in the Schemes 1 and 2 in the presence of EDC·HCl and HOBT[21] to afford corresponding amide derivatives in 60–80% overall yield. Removal of *tert*-butyl carbamate protecting groups with a solution of 4 M HCl in dioxane produced primary amines/reduction of nitro group using Pd/C (10%) in DMSO at room temperature gave amines. Then, hydrolysis of ester with LiOH/H_2O gave the corresponding free carboxylic acids in 85–94% excellent yield.

The amine **20** synthesized (as shown in Scheme 2) was coupled with an acid **7** to afford the amide derivatives **24** in good yield. Hydrolysis of ester under basic medium gave the acid intermediate **25** in excellent yield. Hydrogenation of nitro group of **25** gave the amine **26** in 85%. The critical macrocyclization was achieved after optimization of the conditions.[22] The optimum conditions presented in Table 2, entry 5, result in the cyclized compound in 65% yield. The same macrocyclization conditions was used for the synthesis of **39**.

The synthetic route has been simplified by using a common intermediate and, in addition to this, alternative conditions were developed for the synthesis of amine derivatives. To overcome the solubility problem of compound **25**, DMSO and methanol mixture have been used as solvents but the removal of DMSO from the mixture posed a major problem. Similarly to overcome the solubility issue of other two compounds such as **31** and **35**, the synthetic stratagies were changed. The nitro groups at the oxadiazoles were reduced to amine derivatives by protecting the other side amino