Tetrahedron 74 (2018) 962–969

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis and evaluation of simplified functionalized bongkrekic acid analogs

Satoshi Fujita [a], Masaki Suyama [a], Kenji Matsumoto [e], Atsushi Yamamoto [b], Takenori Yamamoto [c, d], Yuka Hiroshima [c], Takayuki Iwata [e], Arihiro Kano [e], Yasuo Shinohara [c, d, **], Mitsuru Shindo [e, *]

[a] Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, 6-1, Kasuga-koen, Kasuga, 816-8580, Japan
[b] Faculty of Pharmaceutical Sciences, Suzuka University of Medical Science, Minamitamagakicho-3500, Suzuka, Mie, 513-8670, Japan
[c] Institute for Genome Research, Tokushima University, Kuramotocho-3, Tokushima, 770-8503, Japan
[d] Graduate School of Pharmaceutical Sciences, Tokushima University, Shomachi-1, Tokushima, 770-8505, Japan
[e] Institute for Materials Chemistry and Engineering, Kyushu University, 6-1, Kasuga-koen, Kasuga 816-8580, Japan

ARTICLE INFO

Article history:
Received 1 December 2017
Received in revised form
5 January 2018
Accepted 9 January 2018
Available online 11 January 2018

Keywords:
Bongkrekic acid
Adenine nucleotide translocator
Mitochondria
Inhibitor
ATP

ABSTRACT

Bongkrekic acid (BKA) is a strong inhibitor of adenine nucleotide translocase (ANT), inducing inhibition of adenosine triphosphate synthesis. We designed and synthesized simplified benzene-ring-containing BKA analogs. The key reaction is the one-pot double Sonogashira reaction, which forms the main skeleton. The analogs were efficiently synthesized in 8–10 longest linear sequence steps. This synthetic method can be applied for the preparation of other analogs having different combinations of carbon chain lengths. Furthermore, the allyloxy group on the benzene ring can be easily replaced by other functional groups. Our preliminary biological evaluation based on mitochondrial inhibitory effects revealed the high potency of the analogs bearing the same carbon chain length as that of BKA. In particular, the prefunctionalized analogs are potential ANT inhibitors.

1. Introduction

Bongkrekic acid (BKA), isolated from *Burkholderia gladioli* pathovar *cocovenenans*,[1] is a strong inhibitor of adenine nucleotide translocase (ANT) in the mitochondrial inner membrane on the matrix side,[2] inhibiting adenosine triphosphate (ATP) synthesis and suppressing mitochondria-dependent apoptosis (Fig. 1). Recently, a cancer cell-specific death effect was also found.[3] BKA has, therefore, become an important biological tool for research into the function of mitochondria, the mechanism of apoptosis, and new antitumor drugs. However, because of its limited availability,[4] the efficient chemical synthesis of BKA is required. Thus, we have developed an efficient total synthesis of BKA in a pure form[5]; however, even this method requires more than 30 steps, and this may lead to hesitation in the synthesis of BKA on a large scale. Because of this supply issue, we have been developing BKA analogs by simplifying its structure based on structure–activity relationship studies, which indicate that tricarboxylic acids are essential moieties for bioactivity.[5a] We have also synthesized highly simplified analogs (e.g., **1**) with apoptosis-suppressing activity,[6] as well as inhibitory activity for mitochondrial ATP synthesis.[7] Notably, the carbon chain length connecting the carboxylic acids, is very important for the inhibitory activity. However, if functional groups are introduced into the simplified analogs to prepare molecular probes or more potent analogs having additional functions, the simple alkane chain is inconvenient. Furthermore, because the conformation of **1** is highly flexible, it is challenging to obtain conformational information to determine the pharmacophore. Herein, we report the design and synthesis of simplified BKA analogs bearing a benzene-ring-containing carbon chain, and the evaluation of their ANT inhibitory activity.

* Corresponding author. Institute for Materials Chemistry and Engineering, Kyushu University, 6-1, Kasuga-koen, Kasuga 816-8580, Japan.
** Corresponding author. Institute for Genome Research, Tokushima University, Kuramotocho-3, Tokushima, 770-8503, Japan.
E-mail address: shindo@cm.kyushu-u.ac.jp (M. Shindo).

https://doi.org/10.1016/j.tet.2018.01.018
0040-4020/

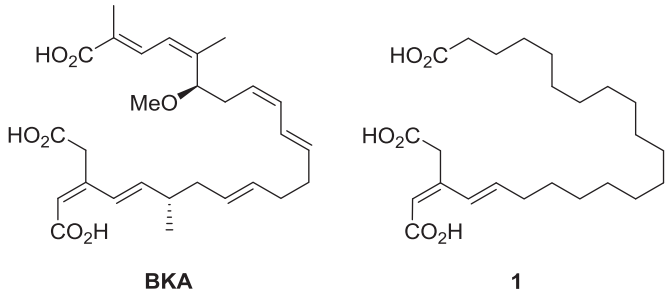


Fig. 1. BKA and the simplified analog **1**.

2. Results

BKA is expected to have a folded conformation induced by intramolecular hydrogen bond(s).[8] We, thus, designed a tricarboxylic acid (**2**) that contains a benzene ring in the carbon chain of **1** (Fig. 2). We anticipated that the *meta*-disubstitution would be more appropriate rather than *para*-substitution to obtain a more rigid folded structure.[9] Furthermore, the permeability of the cell membrane would be improved owing to higher lipophilicity by the aromatic ring. If the benzene ring is pre-functionalized, additional functions can be easily introduced into the BKA analogs, as shown in **2**. Based on this concept, we decided to synthesize compound **3**, which has the same total carbon number (24) including the benzene ring as analog **1**, and compound **4**, which contains the same (24) carbon chain length, as depicted by the bold line in **4**.

2.1. Synthesis of *3* and *4*

Compound **3** was synthesized as shown in Scheme 1. The double Sonogashira coupling of 1-bromo-3-iodobenzene (**7**) with hept-6-yn-1-ol (**8**)[10] and, subsequently, with 5-TBSO-pentyne (**10a**), afforded **11a** in good yield. After complete hydrogenation with a PtO_2 catalyst, the resulting **12a** was oxidized with Dess–Martin periodinane to give the corresponding aldehyde, which was subjected to borylalkenylation by $CrCl_2$ (Takai reaction)[11] to provide alkenylborane **14a**. Suzuki-Miyaura coupling of **14a** with iodoalkene **15**,[5a] followed by desilylation, furnished **16a** in good yield. Finally, Jones oxidation of the diol moiety of **16a**, followed by deprotection with acid, provided **3**. In the same manner, **4** was synthesized using **10b** as a starting alkyne by the same protocol, except for the final deprotection, which proceeded partially during oxidation.

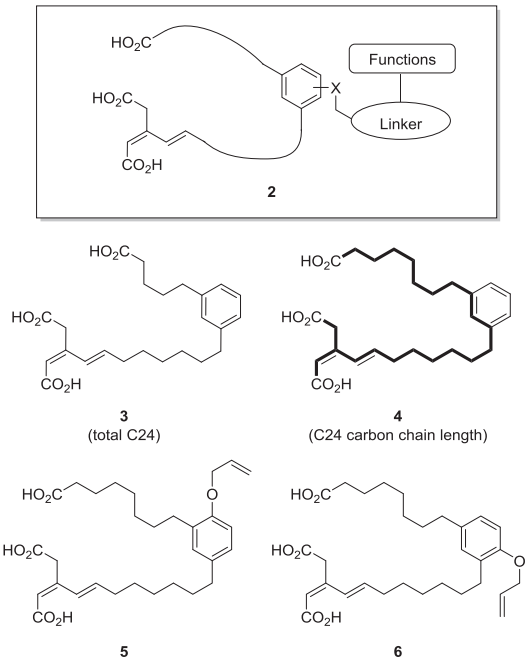
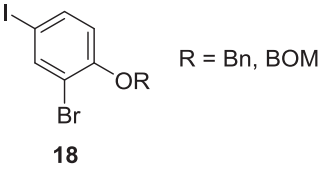


Fig. 2. BKA analogs synthesized in the present study.

2.2. Synthesis of *5* (1st generation synthesis)

We then designed allyloxy analogs of **4**, **5**, and **6** because the preliminary evaluation of the ANT-inhibitory effects suggests that **4** was more active than **3**. Furthermore, an allyloxy group can be easily converted into other functionality. The initial attempts on the double Sonogashira reactions of Bn- and BOM-protected 2-bromo-4-iodophenol **18** failed because the reactivity of the 2-bromo group on **18** was too low for the second Sonogashira coupling.



Next, BOM-protected 2,4-diiodophenol **19** was subjected to the Sonogashira coupling; however, this resulted in moderate yield with poor selectivity. This product **21** was sufficiently reactive for the Sonogashira coupling with alkyne **22**. After hydrogenation with a Pd/C catalyst, the selective deprotection of the BOM group was carefully examined. After the screening of the reagents and reaction conditions, we found that treatment with *B*-bromocatecholborane[12] at −78 °C gave a relatively high yield of the deprotected **25a** and the doubly deprotected **25b**. After separation, **25b** was subjected to selective *O*-allylation to give **26**. Following the procedure in the previous section, **5** was synthesized from **26** in six steps (Scheme 2).

2.3. Synthesis of *6* (2nd generation)

Although **6** could be synthesized using the same protocol as that of **5**, we tried to improve the synthesis, due to low efficiency of several steps (double Sonogashira coupling and deprotection of BOM). We suspected that the BOM group was not an appropriate protecting group and should be re-examined. As a protecting group for phenol, an acetyl group was found to be much better than BOM and Bn[13] because the double Sonogashira coupling was highly selective without detection of minor isomers (Scheme 3). The one-pot double coupling reaction (from **31** to **33**) was also successfully completed in 72% yield. Presumably, the BOM group acts as a directing group for Pd inducing ortho selectivity[14] and, thus, the coupling reaction at *C-2* competitively proceeded with that at C-4. On the other hand, an acetoxy group seemed to be worse directing group than the ether-type protecting groups, partly because of the plausible dominant conformations (A, B > C, D in Fig. 3).

With the double coupling product in hand, **33** was converted into **36** in four steps in the same manner as described above (Scheme 4). Although the deprotection of the acetate in **36** by methanolysis or hydrolysis did not give the desired product, phenol acetate-selective aminolysis with pyrrolidine successfully afforded **38** in good yield after *O*-allylation.[15] Finally, the synthesis of **6** was achieved after the same transformation of **28**.