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Structure–activity-relationship studies on dihydrofuran-fused perhydrophenanthrenes as an anti-Alzheimer's disease agent

Kenji Sugimoto [a], Kosuke Tamura [a], Chihiro Tohda [b], Naoki Toyooka [c], Hideo Nemoto [d], Yuji Matsuya [a,*]

[a] Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan
[b] Institute of Natural Medicine, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan
[c] Graduate School of Science and Engineering, University of Toyama, 3190 Gofuku, Toyama 930-8555, Japan
[d] Lead Chemical Co. Ltd, 77-3 Himata, Toyama 930-0192, Japan

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ABSTRACT

As an extended study on development of anti-Alzheimer's disease agent, we newly synthesized various dihydrofuran-fused perhydrophenanthrenes via *o*-quinodimethane chemistry. This study revealed that the introduction of carbon side-chain on 8-position or removal of the acetal moiety on 3-position arose a cytotoxicity on rat cortical neurons. On the other hand, the ethereal or thio-ethereal substituent on 8-position enhanced the elongation effect on Aβ-damaged neurons. The necessity of the cyano group on 10b position was also proved in this structure–activity-relationship study.

1. Introduction

Naturally occurring furan-fused polycyclic compounds have been known to possess unique biological activities and interesting structural frameworks. Pentacyclic polyketides halenaquinone,[1] halenaquinol,[2] and xestoquinone,[3] which were isolated from marine sponges, were found to exhibit anti-microbial activity, protein–tyrosine kinase inhibitory activity, or cardiotonic activity. Furthermore, halenaquinol sulfate[4] was revealed to show selective inhibitory activity and anticipated as an anti-virus agent. Motivated by such hopeful biological activities, synthetic chemists established their total syntheses via efficient construction of the pentacyclic core. Harada and co-workers achieved total synthesis of (−)-haleaquinone and (+)-xestoquinone starting from Wieland–Miescher ketone.[5] Shibasaki and co-workers reported asymmetric syntheses of halenaquinol and haleaqinone featured by stereoselective construction of quaternary stereogenic center with asymmetric intramolecular Heck reaction.[6] In the synthesis of xestoquinone, palladium-catalyzed asymmetric polyene cyclization[7] or Diels–Alder reaction between isobenzofuran derivative and chiral dienophile[8] were utilized for formation of polycyclic core. Since our group was also interested in the relationship between the polycyclic furan systems and biological activities, we originally established concise construction of dihydrofuran-fused perhydropenanthrenes via a tandem electrocyclization reaction of benzocyclobutenes based on *o*-quinodimethane chemistry[9] and fortunately could find some congeners having fascinating activities[9c–i] such as anti-virus acitivities against HVJ or various influenza viruses,[9c–g] and significant inducer of apoptosis on tumor cell (Fig. 1).[9h] Developing a continuous assay of these derivatives (**DF-1**–**10**), recently we could reveal the phenolic congeners **DF-3** and **DF-8**–**10** possess dendritic extension activities in amyloid β (Aβ)-damaged neurons for the first time and especially 9-hydroxyl derivatives **DF-8** and **DF-10** were found to show more potent activities.[9i] This means that the brain function damaged by Alzheimer's disease can be recovered with these congeners to return to a normal memory, making a clear distinction between the symptomatic treatments with cholinesterase inhibitors. The therapeutic potential of these derivatives prompted us to extend further structure–activity-relationship studies on various furan-fused perhydrophenanthrenes, on which the 9-hydroxyl group was fixed, utilizing tandem electrocyclization reaction of corresponding benzocyclobutenes and finally we could reveal the importance of hetero atom on 8-position, acetal functionality on 3-position, and cyano group on 10b-position. Herein we will report the detail of this SAR studies.

2. Results and discussion

2.1. Chemistry

2.1.1. Derivatives possessing carbon substituent on 8-position

For late-stage derivatizations by palladium-catalyzed coupling reaction, we prepared 8-iodo congener **7** as a key intermediate

* Corresponding author. Tel.: +81 76 434 7530; fax: +81 76 434 5047.
E-mail address: matsuya@pha.u-toyama.ac.jp (Y. Matsuya).

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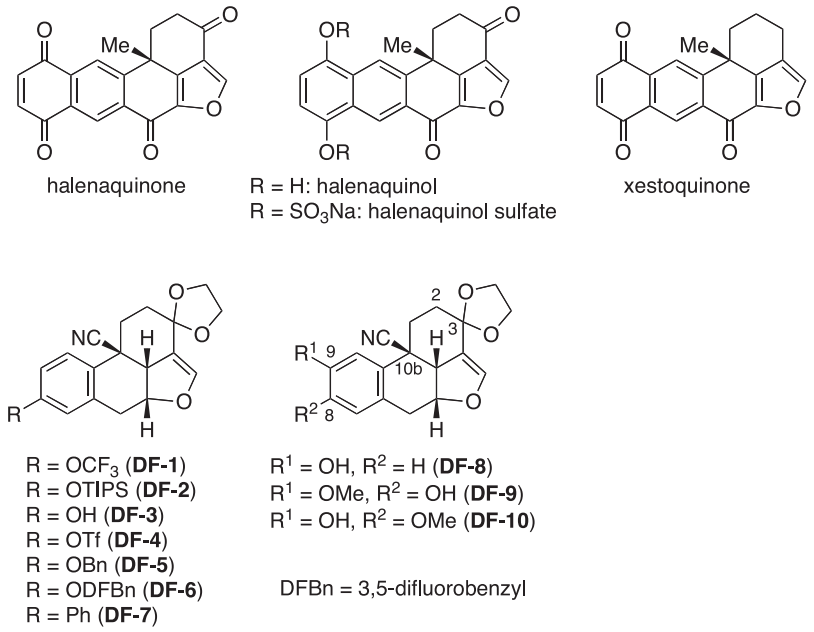
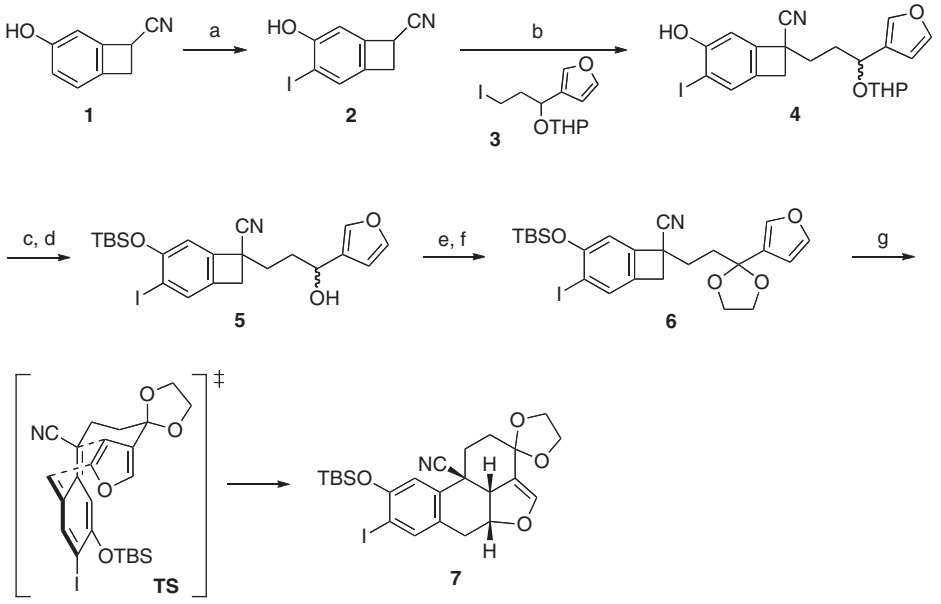


Figure 1. Natural and artificial furan-fused polycyclic compounds.

(Scheme 1). Readily available cyanobenzocyclobutene **1**[10] was iodinated with NIS under acidic condition followed by alkylation of dianion generated from resultant **2** afforded substituted benzocyclobutene **4**. Protection of phenolic hydroxyl group by TBS and acidic ethanolysis of THP ether gave secondary alcohol **5**. Oxidation and acetalization set up the tandem electrocyclization precursor **6**. Pivotal dihydrofuran-fused perhydrophenanthrene **7** could be furnished as a single diastereomer in refluxing *o*-dichlorobenzene via an exclusive *endo* transition state **TS**.

As shown in Scheme 2, aryl iodides **5** and **7** were transformed into DFs via palladium-catalyzed coupling reactions. **DF-11** was obtained by cleavage of silyl ether on **7**. Sonogashira coupling reaction of **7** with TMS–acetylene or 3-butyn-1-ol followed by the addition of TBAF afforded corresponding 8-acetylenyl derivatives **DF-12** or **DF-13**, respectively. **DF-11** was further transformed into **DF-14** by Suzuki–Miyaura coupling with phenylboronic acid. On the other hand, 8-(1-undecenyl) derivative **DF-15** was produced by Heck reaction between **DF-11** and 1-undecene. Additionally, 2,3-dehydro derivatives **DF-16**–**18** were synthesized via **8**, which was the product of one-pot tandem electrocyclization–dehydration reaction from benzocyclobutene **5** via intermediate **A**.[9c] Aryl iodide **8** was transformed into 8-ethynyl derivative **DF-16** via Sonogashira coupling-desilylation sequence. After desilylation of **8**, hydroxybutynyl side chain was introduced by Sonogashira coupling reaction to give **DF-17**. Suzuki–Miyaura coupling between **9** and phenylboronic acid afforded 9-phenyl substituted congener **DF-18**.

On the other hand, 8-H derivatives were synthesized from known benzocyclobutene **10**, for the purpose of comparison of



Scheme 1. Reagents and conditions: (a) NIS, TsOH, CH_2Cl_2, rt, 1.5 h, 90%; (b) LDA (2 equiv), THF, −78 °C; **3**, −78 °C to rt, 2 h, 74%; (c) TBSCl, imidazole, DMF, 0 °C to rt, 6 h, quant.; (d) PPTS, EtOH, reflux, 3 h, 86%; (e) PDC, MS 4A, CH_2Cl_2, rt, 3 h, 74%; (f) ethylene glycol, TsOH, benzene, reflux, 22 h, quant.; (g) *o*-dichlorobenzene, reflux, 2 h, 82%.