Bioorganic & Medicinal Chemistry Letters 26 (2016) 283–287

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

The synthesis and BK channel-opening activity of *N*-acylaminoalkyloxime derivatives of dehydroabietic acid

Yong-Mei Cui [a,*], Xin-Lan Liu [a], Wen-Ming Zhang [a], Hai-Xia Lin [a], Tomohiko Ohwada [b,*], Katsutoshi Ido [c], Kohei Sawada [c]

[a] Department of Chemistry, Innovative Drug Research Center, College of Sciences, Shanghai University, Shanghai 200444, China
[b] Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan
[c] Tsukuba Research Laboratories, Eisai Co. Ltd, Ibaraki 300-2635, Japan

ARTICLE INFO

Article history:
Received 6 September 2015
Revised 25 November 2015
Accepted 11 December 2015
Available online 12 December 2015

Keywords:
BK channels
Openers
Oxime
Dehydroabietic acid

ABSTRACT

A series of *N*-acylaminoalkyloxime derivatives of dehydroabietic acid were synthesized and evaluated for BK channel-opening activities in an assay system of CHO-K1 cells expressing hBKα channels. The structure-activity relationship study revealed that a non-covalent interaction between the S atom of the 2-thiophene and the carbonyl O atom may contribute to conformation restriction for interaction with the ion channel. This research could guide the design and synthesis of novel abietane-based BK channel opener.

Large-conductance calcium-activated K^+ channels (also called maxi-K or BK channels) characteristically respond to two distinct physiological stimuli, that is, changes in membrane voltage and in cytosolic Ca^{2+} concentration, and may couple with other ion channels (such as Ca^{2+} ion channels,[1,2] chloride channel,[3] TRPC channels[4]) to serve as a negative feedback pathway controlling ionic homeostasis, cell excitability, and neuron activity.[5] BK channels consist of channel-forming α-subunits and accessory β-subunits (β_1–β_4) arranged in tetramers,[6] having a voltage sensor and pore as the membrane-spanning domain and having a cytosolic domain containing metal-binding sites. Recently published studies on electron cryomicroscopy (cryo-EM)[7] and X-ray crystallographic structure analysis[8] of the BK channel have provided the first glimpse into the assembly of the quaternary structure of this massive channel protein, corroborating the close interactions among these domains during channel gating that were suggested by the previous functional studies.[9] Recent cloning studies have revealed the presence of multiple splice variants of α-subunits[10–12] and multiple subtypes of β-subunits (β_1, β_2/β_3 and β_4).[13] Thus, there is a large diversity of BK channels, which may be specific to tissues and organs. The BK channels are expressed in a number of organ systems, such as smooth muscle cells, skeletal muscle cells, neuronal cells, and secretory epithelial cells,[10] and they have important physiological roles in modulating muscle contraction or neurotransmitter release and hormone secretion.[14]

The physiological role and widespread distribution of BK channels suggest that agents that open these channels could have profound impacts on diseases such as ischemic stroke, epilepsy, asthma, and bladder overactivity.[15] During the past few years, various classes of BK channel openers as well as their chemistry and pharmacology have been described.[16–19] Well-characterized BK channel openers not only are expected to have therapeutic potential, but also should be of assistance in understanding the function, structure and role of BK channels.

Our previous study showed that the dehydroabietic acid (DHAA, **1**, Fig. 1) structure provides a template for chemical modulators of BK channels.[20] By introducing an oxime ether chain in position 7 of the dehydroabietane skeleton, we obtained compounds such as CYM04 with BK channel-opening activity comparable to that of NS1619 and its mechanism of action has been studied.[21–23] While several interaction models[23]of chemical openers with BK channels have been proposed, binding site and binding mode of chemical openers are still unrevealed. Most probable binding sites may be present in the transmembrane helices (TM) constituting the channel pore (such as TM5 (S5) and TM6 (S6)),[24] however, the intracellular domain such as S6-RCK1 linker has been proposed as a binding site of CYM04.[23] In this context, shape and contiguity of hydrophobic moiety of the chemical BK channel openers are

* Corresponding authors.
E-mail addresses: ymcui@shu.edu.cn (Y.-M. Cui), ohwada@mol.f.u-tokyo.ac.jp (T. Ohwada).

http://dx.doi.org/10.1016/j.bmcl.2015.12.038
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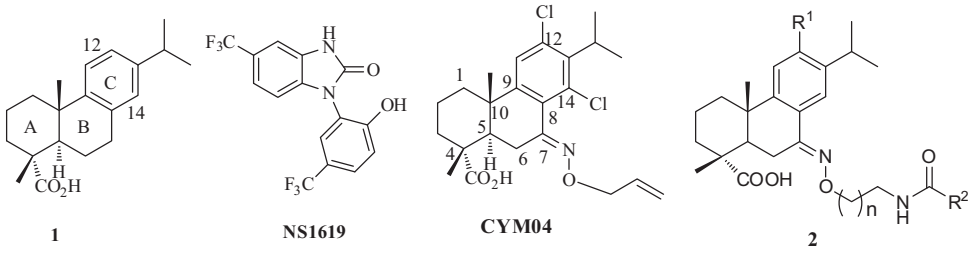
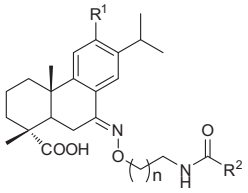
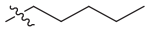
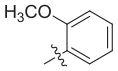
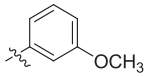
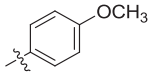
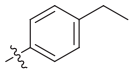
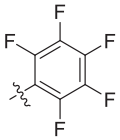
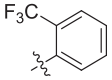
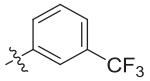
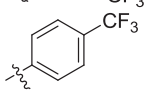


1 NS1619 CYM04 2

Figure 1. The structures of dehydroabietic acid (**1**), NS 1619, CYM04 and **2**.

Table 1
Structure and BKα-opening properties of dehydroabietate derivatives



Compound	R^1	*n*	R^2	Ionic current in the presence of test compound (30 μM) as % of control current (*n* = 8)
Buffer	—	—	—	104.0 ± 2.6
NS1619	—	—	—	267.5 ± 45.0
CYM04	—	—	—	287.5 ± 65.8
7a	Br	1	—	98.6 ± 15.0
9a	Br	1	CH_3	139.5 ± 26.3
9b	Br	1		141.8 ± 17.8
9c	Br	1		146.4 ± 13.8
9d	Br	1		148.8 ± 32.4
9e	Br	1		121.4 ± 19.6
9f	Br	1		101.2 ± 4.7
9g	Br	1		90.4 ± 3.6
9h	Br	1		102.4 ± 11.0
9i	Br	1		68.0 ± 3.6
9j	Br	1		118.0 ± 40.0
9k	Br	1		136.4 ± 33.3
9l	Br	1		123.0 ± 13.8
9m	Br	1		112.7 ± 5.0
9n	Br	1		107.0 ± 7.9
9o	Br	1		151.3 ± 20.4