ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett
Letter

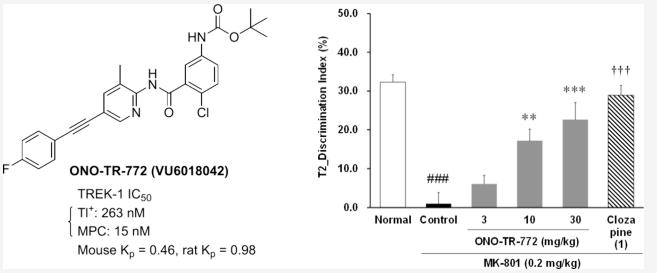
Discovery of ONO-TR-772 (VU6018042): A Highly Selective and CNS Penetrant TREK Inhibitor *in Vivo* Tool Compound

Motoyuki Tanaka, Takahiro Mori, Gakuji Hashimoto, Katsukuni Mitsui, Akihiro Kishi, Elizabeth S. Childress, Sean R. Bollinger, Trevor C. Chopko, Thomas M. Bridges, Douglas G. Stafford, Zhonping Huang, Mark A. Wolf, Darren W. Engers, Jerod S. Denton, Haruto Kurata,* and Craig W. Lindsley*

Cite This: *ACS Med. Chem. Lett.* 2025, 16, 896−901
Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Herein we describe our continuing work on the K_2P family of potassium ion channels with the chemical optimization of a selective and CNS penetrant series of TREK inhibitors, culminating in the discovery of ONO-TR-772 (VU6018042). From an HTS hit harboring a benzyl ether linker, SAR proved intractable until an acetylene linker was identified as an isosteric replacement. Robust SAR was then observed, and a key fluorination to enhance PK and CNS penetration provided ONO-TR-772 (VU6018042), a potent (TREK-1 IC_{50} = 15 nM), selective (>10 μM versus other K_2P channels except TREK-2), and CNS penetrant (rat K_p = 0.98) TREK inhibitor. ONO-TR-772 (VU6018042) demonstrated robust efficacy in an MK-801 challenge NOR paradigm, with an MED of 10 mg/kg.



KEYWORDS: *TWIK-related K+ channel (TREK), two-pore domain potassium channel (K_2P), Novel object recognition (NOR), cognition, ion channel*

Potassium (K^+) channels represent a major thrust of drug development activities targeting both shaker type voltage-gated (K_v) and inward rectifier (K_{ir}) channels.[1−6] Far less explored is the third family, the two pore domain (K_2P) family of potassium channels, consisting of 15 K_2P subtypes, within six distinct subfamilies: tandem of P domains in a weakly inward rectifying potassium channel (TWIK), TWIK related K^+ channels (TREK), TASK (TWIK related acid-sensitive K^+ channels), TWIK related ALkaline pH-activated K^+ channels (TALK), tandem pore domain halothane inhibited K^+ channels (THIK), and TWIK related spinal cord K^+ channel (TRESK).[1−6] Our first priority was to develop potent and selective *in vivo* tool compounds to modulate TREK-1. TREK-1 is highly expressed in the central and peripheral nervous systems, and modulation of these channels are proposed to play key roles in multiple CNS and peripheral disorders; unfortunately, a deeper understanding of the therapeutic potential of TREK-1 has been hampered by a lack of small molecule tools.[1−12]

Recently (Figure 1), we disclosed ONO-2920632 (**1**, VU6011887),[13] a highly selective and CNS penetrant TREK-2 preferring activator (structurally distinct from BL-1249 (**2**)[14,15]), with potential for nonopiate pain management. Attention now turned to the development of TREK inhibitors for the potential treatment of cognitive deficits, as numerous studies implicate TREK-1.[7−12] For example, inhibition of

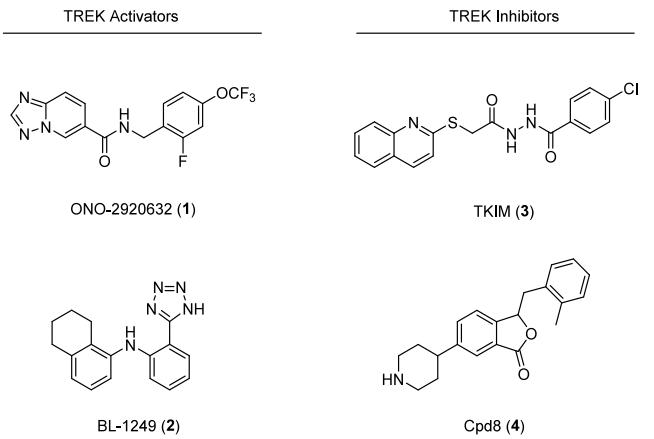
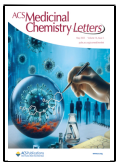


Figure 1. Structures of reported TREK-1 and TREK-2 activators **1** and **2**, and the more recently developed TREK-1 inhibitors **3** and **4**.

Received: April 11, 2025
Revised: April 24, 2025
Accepted: April 25, 2025
Published: April 28, 2025



https://doi.org/10.1021/acsmedchemlett.5c00215
ACS Med. Chem. Lett. 2025, 16, 896−901

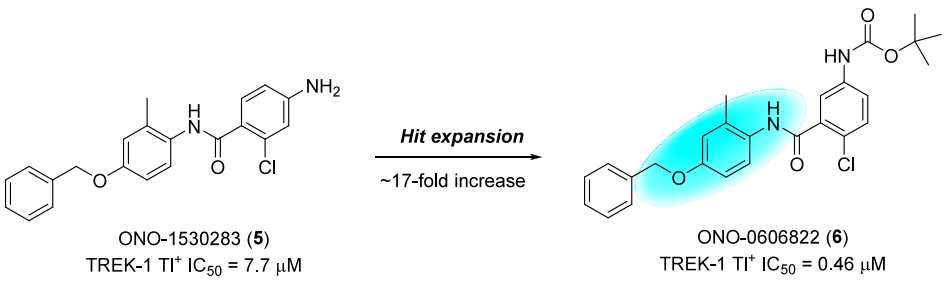
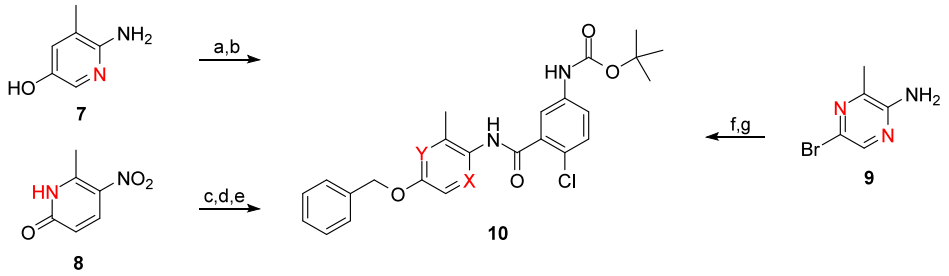


Figure 2. Structures of the HTS hit **5**, and a rapid hit expansion exercise improved potency ~17-fold to afford submicromolar TREK-1 lead **6**.

Scheme 1. Synthesis of Heteroaryl Analogues 10[a]



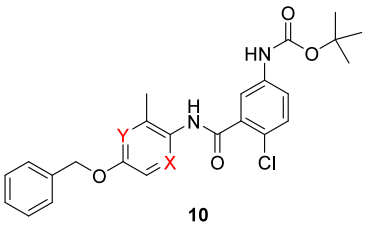
[a]Reagents and conditions: (a) BnBr, Cs_2CO_3, DMF, rt, 12%; (b) 5-(*tert*-butoxycarbonylamino)-2-chlorobenzoic acid, DIEA, DMF, HBTU, rt to 60 °C, 18%; (c) BnOH, DIAD, PPh_3, THF, rt, 24%; (d) Fe, NH_4Cl, THF, H_2O, 75 °C, 87%; (e) 5-(*tert*-butoxycarbonylamino)-2-chlorobenzoic acid, DIEA, DCM, T_3P, rt, 42%; (f) BnOH, NaH, 0−120 °C, 34%; (g) 5-(*tert*-butoxycarbonylamino)-2-chlorobenzoic acid, DIEA, DCM, T_3P, rt, 26%.

TREK-1 protects mice from cognitive impairment induced by anesthesia,[7] and TREK-1 gene expression is increased in the hippocampus of schizophrenic patients relative to normal controls.[16] Likewise, inhibition of TREK-2 is required for the neurotensin-mediated facilitation of spatial learning, and TREK-2 expression is increased in the cortex and hippocampus of several CNS pathologies.[17,18] Taken together, these data argue for the need to pharmacologically validate the role of TREK-1 and TREK-2 inhibition in preclinical rodent cognition models. Yet, the tools to do so are limited to peptides such as spadin,[19] weak (IC_{50}s 2 to >10 μM) off-target small molecule inhibitors such as fluoxetine,[20] atypical antipsychotics,[21] antihypertensives,[22] and antiarrhythmic drugs.[23] A state-dependent TREK-1 inhibitor, TKIM (**3**), has been reported with an IC_{50} of 2.96 μM[24] as well as more recently the CNS-penetrant isobenzofuran-1(3*H*)-one derivative, Cpd8 (**4**) (TREK-1 IC_{50} of 810 nM), which displayed selectivity versus TREK-2 and neuroprotective effects *in vitro* and *in vivo*.[25] In this letter, we describe our efforts toward the development of a potent, selective, and CNS penetrant TREK inhibitor derived from a weak HTS hit.

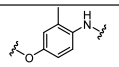
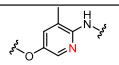
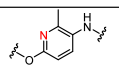
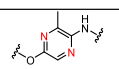
A high throughput screen employing a functional TREK-1 thallium (Tl^+) flux assay identified (Figure 2) ONO-1530283 (**5**) as a weak TREK-1 inhibitor (IC_{50} = 7.7 μM). A hit expansion exercise increased TREK-1 potency ~17-fold (IC_{50} = 0.46 μM) to afford ONO-0606822 (**6**), the lead for the program despite superhepatic rodent clearance and high clogP (5.2). Moreover, we were concerned about the latent quinone moiety in **6**; thus, the initial aim of the optimization was to remove the latent quinone by the addition of heteroatoms to the phenyl core while also reducing lipophilicity.

Scheme 1 highlights the routes to access key heteroaryl congeners **10** of TREK inhibitor lead **6**. For both pyridine isomers and the pyrazine analogue, commercial starting materials **7**−**9** underwent either alkylation reactions or a Mitsunobu reaction to install the benzyl ether moiety, followed by nitro reduction, in the case of **8**, and a polyphosphonic anhydride (T_3P) coupling with 5-(*tert*-butoxycarbonylamino)-2-chlorobenzoic acid to provide amide analogues **10**. TREK-1 inhibitory data is shown in Table 1; while the SAR was without texture, clogPs did decrease by almost a log (~4.4), but both *in vitro* and *in vivo* clearance in rat remained suprahepatic (CL_p > 100 mL/min/kg). The *N*-Boc moiety proved to be, surprisingly, not responsible for the poor PK. However, these data prompted the team to modify the core for subsequent optimization to the pyridine congener **10a**.

Table 1. TREK-1 Inhibitory Activity and Lipophilicity of Analogues 10



10

Compound		h TREK-1 Tl^+ IC_{50} (μM)	cLogP	ChromatoLogD
6		0.46	5.2	4.9
10a		0.56	4.9	4.4
10b		0.85	4.9	5.0
10c		0.56	4.4	4.8

https://doi.org/10.1021/acsmedchemlett.5c00215
ACS Med. Chem. Lett. 2025, 16, 896−901

From previous work in our laboratories,[26] we found that an acetylene was a productive bioisosteric replacement for a benzyl ether moiety, and we applied this tactic to both **10a** and **10c** (Figure 3) modifying Scheme 1 to replace the alkylation

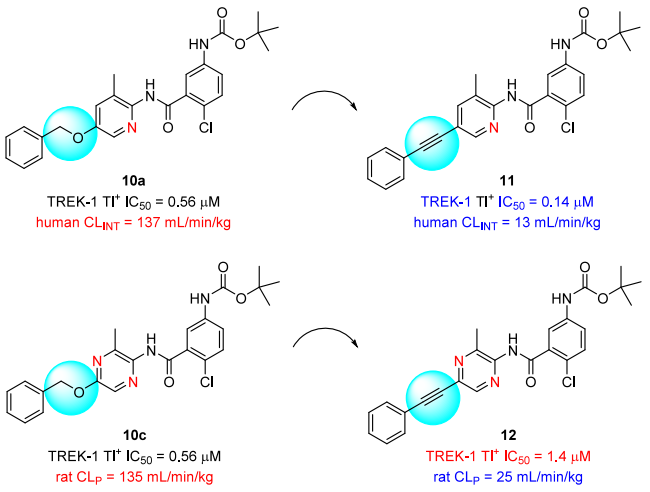
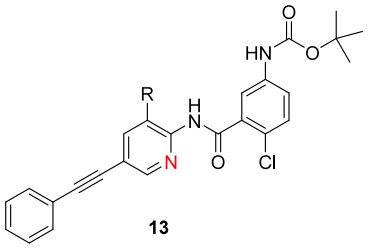


Figure 3. Impact of replacement of the benzyl ether with an acetylene moiety on both TREK-1 potency and *in vitro* and *in vivo* clearance.

step with a Sonogashira coupling (see Supporting Information for full details) to provide **11** and **12**. In the case of **10a**, the acetylenic variant **11** displayed an ~ 4-fold increase in TREK-1 potency (IC_{50} = 0.14 μM) and lowered human microsomal intrinsic clearance 10-fold (h CL_{INT} = 13 mL/min/kg). Interestingly, TREK-1 potency diminished in the pyrazine matched pairs **10c** (IC_{50} = 0.56 μM) and **12** (IC_{50} = 1.4 μM), but *in vivo* rat clearance improved dramatically with installation of the acetylene (**10c**: suprahepatic CL_p= 135 mL/min/kg; **12**: CL_p = 25 mL/min/kg). Therefore, **11** became the new lead, and we elected to explore 2-position substituents on the pyridine core in analogues **13** (Table 2) as well as substituents on the distal phenyl ring pendant to the acetylene, as in derivatives **14** (Table 3).

In the 3-positon on the pyridine core (Table 2), a fluoro congener **13a** was equipotent to the parent methyl **6** and displayed similar or better microsomal stability and a little higher protein binding profiles. TREK-1 potency eroded as

Table 2. TREK-1 Inhibitory Activity and *in Vitro* DMPK Profiles of Analogues 13

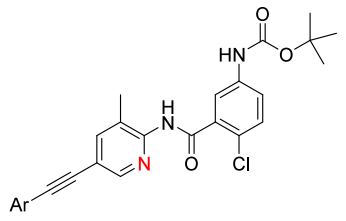


13

compd	R	h TREK-1 Tl+ IC_{50} (μM)	LMS CL_{INT} human/mouse (mL/min/kg)	PPB human/mouse (%)
11	Me	0.14	13/34	99.5/98.7
13a	F	0.11	10/6	99.8/98.9
13b	Cl	0.43	ND[a]	ND/>99.9
13c	OMe	0.91	ND	ND

[a]ND = not determined.

Table 3. TREK-1 Inhibitory Activity and *in Vitro* DMPK Profiles of Analogues 13[a]



14

Compound	Ar	h TREK-1 Tl+ IC_{50} (μM)	LMS CL_{INT} human/mouse (mL/min/kg)	PPB human/mouse (%)
11		0.14	13/34	99.5/98.7
14a		0.54	13/13	ND
14b		0.21	20/40	>99.9/>99.9
14c		0.26	7.5/13	99.4/98.4
14d		0.61	27/78	ND

[a]ND = not determined.

either a chlorine atom (**13b**, IC_{50} = 0.43 μM) was introduced or an electron-donating methoxy group (**13c**, IC_{50} = 0.91 μM). While the introduction of substituents to the distal phenyl ring of the acetylene moiety had no impact on TREK-1 potency (Table 3), a 4-F phenyl congener **14c** possessed improved microsomal stability (human CL_{INT} = 7.5 mL/min/kg, mouse CL_{INT} = 13 mL/min/kg). Thus, all efforts shifted toward a more detailed evaluation of **14c** (ONO-TR-772).

Up to this point in the program, SAR was guided by a thallium flux TREK-1 assay, it was now time to evaluate broader K_2P and ion channel activity for **14c**. Gratifyingly, **14c** proved to be >67-fold selective over other K_2P channels (TASK-3, TRESK, TWIK-2, TRAAK, TASK-1, TASK-2). Only TREK-2 was shown to be equipotent with TREK-1 in the profiling electrophysiological assays. In human manual patch clamp (MPC), **14c** was a potent TREK-1 inhibitor (IC_{50} = 15 nM), and therefore, more accurately described as a dual TREK-1/2 inhibitor. As mouse would be the species used in our cognition PD assay, we evaluated **14c** in mouse MPC, and it was a potent TREK-1 inhibitor (IC_{50} = 67 nM). Prior to performing cognition studies, we needed to assess broader ancillary pharmacology to ensure we would be evaluating selective TREK-1/2 inhibition. When gauged against a cardiovascular (CV) ion channel panel, **14c** was similarly highly selective (<50% at 10 μM versus: $Ca_v1.2$, HNC4, $K_{ir}2.1$, $K_v1.5$, $K_v4.3$, KCNQ1, $Na_v1.5$ and hERG). The only activity >50% at 10 μM was Kir2.2 (52%). The clean ion channel pharmacology profile prompted the team to collect a broader ancillary pharmacology profile across GPCRs, ion channels and transporters in the Eurofins lead profiling screen. Here, **14c** showed >50% inhibition at 10 μM for only four of 68 targets: A_3 (84%, K_i = 0.48 μM), Calcium L-type/benzothiazepine (56%, K_i = 2.6 μM), Calcium L-type/dihydropyridine (76%, K_i = 0.54 μM) and sodium channel, site 2 (84%, K_i = 0.65 μM).

https://doi.org/10.1021/acsmedchemlett.5c00215
ACS Med. Chem. Lett. 2025, 16, 896−901

Weak activity at these targets would not obscure our proof-of-concept studies in rodent cognition models, so **14c** advanced into DMPK profiling.

In liver microsomes, CL_{INT} for **14c** was low across all species (h, r, m: 7.5, 29, and 13 mL/min/kg); however, the lipophilic nature of **14c** (clogP = 5.53) led to high plasma protein binding (h, r, m: 99.4%, 99.9% and 98.4%), brain homogenate binding (r, m: >99.9% and 99.4%) and low aqueous solubility (<5 μM). In a rat IV:PBL PK cassette study, **14c** demonstrated a good IVIVC with low clearance (CL_p = 21.2 mL/min/kg), high volume of distribution (6.7 L/kg) long half-life ($t_{1/2}$ = 6.78 h) and a K_p of 0.98. In a 10 mg/kg PO mouse PBL study, **14c** displayed a K_p of 0.44, highlighting excellent CNS exposure in both mouse and rat; however, due to the high brain homogenate binding (driven by the lipophilic nature of **14c**), a $K_{p,uu}$ could not be accurately ascertained. From the 10 mg/kg PO CD-1 male mouse study with **14c**, C_{max} total brain concentrations achieved 252 nM (T_{max} = 4 h, AUC 2269 h*nM), which we felt was too low to proceed with a novel object recognition (NOR) cognition assay. Switching to an IP route of administration (10 mg/kg) increased total brain exposure (C_{max} of 888 nM, 5.3 nM unbound based on mouse brain homogenate binding, T_{max} = 4 h, AUC 12,261 h*nM). Based on the lipophilicity of **14c**, we assumed the unbound brain level was a low estimate, so we elected to proceed with the NOR study at doses of 3, 10, and 30 mg/kg IP. Since the brain T_{max} was at 4 h, **14c** or the clozapine positive control was dosed IP to male CD-1 mice 3.5 h prior to the MK-801 (0.2 mg/kg IP) challenge, and then the discrimination index was assessed (Figure 4). As expected, MK-801 induced a significant cognitive deficit,[27] which was dose dependently reversed by **14c**, with a minimum effective dose (MED) at 10 mg/kg and

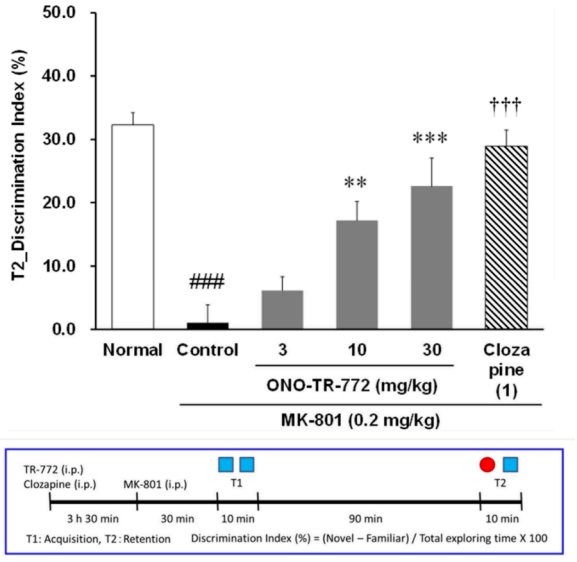


Figure 4. Effect of **14c** (ONO-TR-772/VU6018042) in the MK-801 challenged novel object recognition task. **14c** dose-dependently enhanced recognition memory in male CD-1 mice after challenged with MK-801. Pretreatment with 3, 10, and 30 mg/kg **14c** IP 3.5 h prior to MK-801 treatment and exposure to identical objects significantly enhanced recognition memory assessed 90 min later. Minimum effective dose (MED) is 10 mg/kg. N = 15/group of male CD-1 mice. # $p < 0.05$, ###, $p < 0.001$ vs normal (t test), **$p < 0.01$; ***$p < 0.001$ vs vehicle (Dunnett posthoc test). †††, $p < 0.001$ vehicle group (t test).

comparative efficacy at 30 mg/kg to the internal control clozapine (1 mg/kg IP). Thus, selective inhibition of TREK-1/2 was shown, for the first time, to be efficacious in the NOR paradigm and suggests therapeutic relevance for TREK-1 and or TREK-1/2 inhibition to treat cognitive disorders.

In parallel with the *in vivo* POC work, efforts were being made to find alternatives for the privileged *N*-Boc moiety, which contributed to the high lipophilicity and structural concern. Only one viable replacement emerged, a cyclopropyl amide (Figure 5), as shown in **15a** (TREK-1 IC_{50} = 0.18 μM)

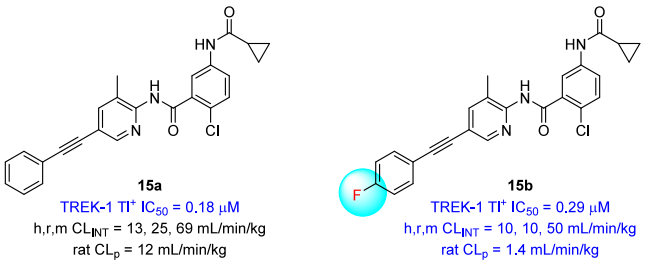


Figure 5. Cyclopropyl amides are viable replacements for the *N*-Boc moiety. Introduction of the 4-F phenyl moiety reduces *in vivo* rat clearance almost 10-fold.

and **15b** (TREK-1 IC_{50} = 0.29 μM). In these matched pairs, the impact of the 4-F phenyl moiety was profound on both *in vitro* and *in vivo* clearance (10-fold reduction in *in vivo* rat CL_p); however, both analogues still possessed high plasma protein binding (>99.7%) and no improvement on aqueous solubility. Further optimization on this series is required to improve fraction unbound, solubility and reduce lipophilicity. Therefore, **14c** ONO-TR-772 (VU60108042) stands as a valuable rodent *in vivo* tool compound to explore selective inhibition of TREK-1 and TREK-2.

In summary, we have developed a potent, selective, and CNS penetrant TREK inhibitor **14c** (ONO-TR-772, VU6018042) that provided proof of concept for pro-cognitive efficacy in an MK-801 challenge NOR paradigm with an MED of 10 mg/kg IP. While a valuable *in vivo* probe for the community, further efforts are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.5c00215.

Additional experimental details, methods for the synthesis and characterization of all compounds (^{1}H NMR, ^{13}C NMR, 2-D NMR, HRMS), *in vitro* and *in vivo* DMPK protocols and supplemental figures (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Craig W. Lindsley − *Warren Center for Neuroscience Drug Discovery, Vanderbilt University, Nashville, Tennessee 37232, United States; Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, United States;* orcid.org/0000-0003-0168-1445; Email: craig.lindsley@vanderbilt.edu

Haruto Kurata − *Drug Discovery Chemistry, Ono Pharmaceutical Co., Ltd, Mishima, Osaka 618-8585, Japan;*

https://doi.org/10.1021/acsmedchemlett.5c00215
ACS Med. Chem. Lett. 2025, 16, 896−901

orcid.org/0000-0002-9009-3428; Email: h.kurata@ono-pharma.com

Authors

Motoyuki Tanaka − *Drug Discovery Chemistry, Ono Pharmaceutical Co., Ltd, Mishima, Osaka 618-8585, Japan*
Takahiro Mori − *Research Center of Neurology, Ono Pharmaceutical Co., Ltd, Mishima, Osaka 618-8585, Japan*
Gakuji Hashimoto − *Research Center of Neurology, Ono Pharmaceutical Co., Ltd, Mishima, Osaka 618-8585, Japan*
Katsukuni Mitsui − *Research Center of Neurology, Ono Pharmaceutical Co., Ltd, Mishima, Osaka 618-8585, Japan*
Akihiro Kishi − *Research Center of Neurology, Ono Pharmaceutical Co., Ltd, Mishima, Osaka 618-8585, Japan*
Elizabeth S. Childress − *Warren Center for Neuroscience Drug Discovery, Vanderbilt University, Nashville, Tennessee 37232, United States; Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, United States*
Sean R. Bollinger − *Warren Center for Neuroscience Drug Discovery, Vanderbilt University, Nashville, Tennessee 37232, United States; Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, United States*
Trevor C. Chopko − *Warren Center for Neuroscience Drug Discovery, Vanderbilt University, Nashville, Tennessee 37232, United States; Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, United States*
Thomas M. Bridges − *Warren Center for Neuroscience Drug Discovery, Vanderbilt University, Nashville, Tennessee 37232, United States; Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, United States*
Douglas G. Stafford − *Curia Global, Inc., Albany, New York 12203, United States*
Zhonping Huang − *Curia Global, Inc., Albany, New York 12203, United States*
Mark A. Wolf − *Curia Global, Inc., Albany, New York 12203, United States*
Darren W. Engers − *Warren Center for Neuroscience Drug Discovery, Vanderbilt University, Nashville, Tennessee 37232, United States; Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, United States*
Jerod S. Denton − *Warren Center for Neuroscience Drug Discovery, Vanderbilt University, Nashville, Tennessee 37232, United States; Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, United States; Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee 37232, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmedchemlett.5c00215

Author Contributions

C.W.L., H.K., J.S.D., D.W.E., J.W. and T.M.B. oversaw the medicinal chemistry, target selection and interpreted biological/DMPK data. C.W.L. wrote the manuscript. M.T., E.S.C., S.R.B., T.C.C., D.S., Z.H. and M.W. performed chemical synthesis. T.M. and J.SD performed and analyzed *in vitro* pharmacology assays. G.H., K.M. and A.K. performed *in vivo* behavior pharmacology assays. T.M.B. and W.N. performed *in vitro* and *in vivo* DMPK studies. All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): While we abandoned the patent application for the compounds described in this manuscript, Vanderbilt and Ono hold patents on other TREK inhibitors.

■ ACKNOWLEDGMENTS

We thank William K. Warren, Jr. and the William K. Warren Foundation for support of our programs and endowing both the Warren Center for Neuroscience Drug Discovery and the William K. Warren, Jr. Chair in Medicine (C.W.L.).

■ ABBREVIATIONS

TREK, TWIK RElated K^+ channels; MED, minimum effective dose; PK, pharmacokinetics; PBL, plasma:brain level study; NOR, novel object recognition

■ REFERENCES

(1) Patel, A. J.; Honore, E. Properties and modulation of mammalian 2P domain K+channels. *Trends Neurosci* **2001**, *24* (6), 339−346.
(2) Fink, M.; Duprat, F.; Lesage, F.; Reyes, R.; Romey, G.; Heurteaux, C.; Lazdunski, M. Cloning, functional expression and brain localization of a novel unconventional outward rectifier K+ channel. *EMBO J.* **1996**, *15* (24), 6854−6862.
(3) Honore, E. The neuronal background K2P channels: focus on TREK1. *Nat. Rev. Neurosci* **2007**, *8* (4), 251−261.
(4) Avalos Prado, P.; Chassot, A. A.; Landra-Willm, A.; Sandoz, G. Regulation of two-pore-domain potassium TREK channels and their involvement in pain perception and migraine. *Neurosci. Lett.* **2022**, *773*, 136494.
(5) Feliciangeli, S.; Chatelain, F. C.; Bichet, D.; Lesage, F. The family of K2P channels: salient structural and functional properties. *J. Physiol.* **2015**, *593*, 2587−2603.
(6) Medhurst, A. D.; Rennie, G.; Chapman, C. G.; Meadows, H.; Duckworth, M. D.; Kelsell, R. E.; Gloger, I. I.; Pangalos, M. N. Distribution analysis of human two pore domain potassium channels in tissues of the central nervous system and periphery. *Brain Res. Mol. Brain Res.* **2001**, *86*, 101−114.
(7) Cai, Y.; Peng, Z.; Guo, H.; Wang, F.; Zeng, Y. TREK-1 pathway mediates isoflurane-induced memory impairment in middle-aged mice. *Neurobiol. Learn. Mem.* **2017**, *145*, 199−204.
(8) Francis-Oliveira, J.; Higa, G. S. V.; Viana, F. J. C.; Cruvinel, E.; Carlos-Lima, E.; Borges, F. d. S.; Zampieri, T. T.; Rebello, F. P.; Ulrich, H.; De Pasquale, R. TREK-1 inhibition promotes synaptic plasticity in the prelimbic cortex. *Exp. Neurol.* **2024**, *373*, 114652.
(9) Tong, L.; Cai, M.; Huang, Y.; Zhang, H.; Su, B.; Li, Z.; Dong, H. Activation of K(2)P channel-TREK1 mediates the neuroprotection induced by sevoflurane preconditioning. *Br. J. Anaesth.* **2014**, *113*, 157−167.
(10) Hervieu, G. J.; Cluderay, J. E.; Gray, C. W.; Green, P. J.; Ranson, J. L.; Randall, A. D.; Meadows, H. J. Distribution and expression of TREK-1, a two-pore-domain potassium channel in the adult rat CNS. *Neuroscience* **2001**, *103*, 899−919.
(11) Mathie, A.; Veale, E. L. Therapeutic potential of neuronal two-pore domain potassium-channel modulators. *Curr. Opin. Investig. Drugs* **2007**, *8*, 555−562.
(12) Honore, E. The neuronal background K2P channels: focus on TREK1. *Nat. Rev. Neurosci* **2007**, *8* (4), 251−261.
(13) Yashiro, K.; Iwaki, Y.; Urata, H.; Kokubo, M.; Mori, T.; Sekioka, Y.; Isami, K.; Kato, J.; Wieting, J.; McGowan, K. M.; Bridges, T. M.; Boutaud, O.; Engers, D. W.; Denton, J. S.; Kurata, H.; Lindsley, C. W. Discovery of ONO-2920632 (VU6011887): A highly selective and CNS penetrant TREK-2 (TWIK-Related K+ Channel 2)

preferring activator *in vivo* tool compound'. *ACS Chem. Neurosci.* **2025**, *16*, 960−967.
(14) Pope, L.; Arrigoni, C.; Lou, H.; Bryant, C.; Gallardo-Godoy, A.; Renslo, A. R.; Minor, D. L., Jr. Protein and Chemical Determinants of BL-1249 Action and Selectivity for K_{2P} Channels. *ACS Chem. Neurosci.* **2018**, *9*, 3153−3165.
(15) Iwaki, Y.; Yashiro, K.; Kokubo, M.; Mori, T.; Wieting, J. M. N.; McGowan, K. M.; Bridges, T. M.; Engers, D. W.; Denton, J. S.; Kurata, H.; Lindsley, C. W. Towards a TREK-1/2 (TWIK-Related K+ Channel 1 and 2) dual activator tool compound: Multi-dimensional optimization of BL-1249. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1601−1604.
(16) Benes, F. M. Amygdalocortical circuitry in schizophrenia: From circuits to molecules. *Neuropsychopharmacology* **2010**, *35*, 239−257.
(17) Xiao, Z.; Cilz, N. I.; Kurada, L.; Hu, B.; Yang, C.; Wada, E.; Combs, C. K.; Porter, J. E.; Lesage, F.; Lei, S. Activation of neurotensin receptor 1 facilitates neuronal excitability and spatial learning and memory in the entorhinal cortex: Beneficial actions in an Alzheimer's Disease model. *J. Neurosci.* **2014**, *34*, 7027−7042.
(18) Li, Z.-B.; Zhang, H.-X.; Li, L.-L.; Wang, X.-L. Enhanced expressions of arachidonic acid-sensitive tandem-pore domain potassium channels in rat experimental acute cerebral ischemia. *Biochem. Biophys. Res. Commun.* **2005**, *327*, 1163−1169.
(19) Pietri, M.; Djillani, A.; Mazella, J.; Borsotto, M.; Heurteaux, C. First evidence of protective effects on stroke recovery and post-stroke depression induced by sortilin-derived peptides. *Neuropharmacology* **2019**, *158*, 107715.
(20) Kennard, L. E.; Chumbley, J. R.; Ranatunga, K. M.; Armstrong, S. J.; Veale, E. L.; Mathie, A. Inhibition of the human two-pore domain potassium channel, TREK-1, by fluoxetine and its metabolite norfluoxetine. *Br. J. Pharmacol.* **2005**, *144*, 821−829.
(21) Thummler, S.; Duprat, F.; Lazdunski, M. Antipsychotics inhibit TREK but not TRAAK channels. *Biochem. Biophys. Res. Commun.* **2007**, *354* (1), 284−289.
(22) Liu, H.; Enyeart, J. A.; Enyeart, J. J. Potent inhibition of native TREK-1 K+ channels by selected dihydropyridine Ca2+ channel antagonists. *J. Pharmacol Exp Ther* **2007**, *323*, 39−48.
(23) Schmidt, C.; Wiedmann, F.; Schweizer, P. A.; Becker, R.; Katus, H. A.; Thomas, D. Class I antiarrhythmic drugs inhibit human cardiac two-pore-domain K(+) (K2 (2)p) channels. *Eur. J. Pharmacol.* **2013**, *721*, 237−248.
(24) Ma, Y.; Luo, Q.; Fu, J.; Che, Y.; Guo, F.; Mei, L.; Zhang, Q.; Li, Y.; Yang, H. Discovery of an inhibitor for the TREK-1 channel targeting an intermediate transition state of channel gating. *J. Med. Chem.* **2020**, *63*, 10972−10983.
(25) Liu, K.; Ji, Y.; Xie, Y.; Wang, C.; Zhou, J.; Wei, Z.; Wang, X.; Zheng, X.; Cen, Y.; Zhang, F.; Xu, B. Discovery of Isobenzofuran-1(3*H*)-one derivative as selective TREK-1 Inhibitors with in vitro and in vivo neuroprotective effects. *J. Med. Chem.* **2025**, *68*, 5804−5823.
(26) Bartolome-Nebreda, J. M.; Conde-Ceide, S.; Delgado, F.; Iturrino, L.; Pastor, J.; Pena, M. A.; Trabanco, A. A.; Tresadern, G.; Wassvik, C. M.; Stauffer, S. R.; Jadhav, S.; Gogi, K.; Vinson, P. N.; Noetzel, M. J.; Days, E.; Weaver, C. D.; Lindsley, C. W.; Niswender, C. M.; Jones, C. K.; Conn, P. J.; Rombouts, F.; Lavreysen, H.; Macdonald, G. J.; Mackie, C.; Steckler, T. Dihydrothiazolopyridone derivatives as a novel family of positive allosteric modulators of the mGlu5 receptor. *J. Med. Chem.* **2013**, *56*, 7243−7259.
(27) Van der Staay, F. J.; Rutten, K.; Erb, C.; Blokland, A. Effects of the cognition impairer MK-801 on learning and memory in mice and rats. *Behavioural Brain Research* **2011**, *220*, 215−229.

https://doi.org/10.1021/acsmedchemlett.5c00215
ACS Med. Chem. Lett. 2025, 16, 896−901