Bioorganic & Medicinal Chemistry Letters 19 (2009) 783–787

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Spiro-piperidine azetidinones as potent TRPV1 antagonists

Dong Xiao [a,*], Anandan Palani [a], Robert Aslanian [a], Brian A. McKittrick [a], Andrew T. McPhail [b], Craig C. Correll [c], P. Tara Phelps [c], John C. Anthes [c], Diane Rindgen [d]

[a] Chemical Research Department, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA
[b] Department of Chemistry, P.M. Gross Chemical Laboratory, Duke University, Durham, NC 27708, USA
[c] Neurobiology Research Department, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA
[d] Exploratory Drug Metabolism, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

ARTICLE INFO

Article history:
Received 2 October 2008
Revised 3 December 2008
Accepted 4 December 2008
Available online 10 December 2008

Keywords:
TRPV1
Spiro-azetidinone stability

ABSTRACT

A series of *spiro*-piperidine azetidinone were synthesized and evaluated as potential TRPV1 antagonists. An important issue of plasma stability was investigated and resolved. Further focused SAR study lead to the discovery of a potent antagonist with good oral pharmacokinetic profile in rat.

Transient receptor potential V1 (TRPV1) is a membrane-bound, non-selective, transient receptor potential cation channel. TRPV1 is expressed throughout the nervous system but is predominantly expressed in nociceptive C- and Aδ-fibers. Data from TRPV1 knock-out mice and pharmacological evaluation of developed TRPV1 antagonists has demonstrated that TRPV1 is intimately involved in inflammatory hyperalgesia and detection of noxious stimuli. Therefore, TRPV1 receptor antagonists may have value in treating pain, cough and bladder dysfunction.[1] Due to its therapeutic potential, this area of research has attracted intensive interest from a broad range of academic and industrial research organizations. Recently, several companies have disclosed their medicinal chemistry efforts on TRPV1 antagonists[2] and several compounds have entered the clinic.[3]

Our exploratory program for TRPV1 antagonists started with an in-house screening lead **1**, a racemic mixture exhibiting moderate activity.[4] Our initial goal of this study was to confirm the lead, establish the absolute configuration and determine if the TRPV1 activity resided solely in one of the enantiomers (Fig. 1).

The chemistry used in synthesizing compound **1** was adopted from earlier work in β-lactam chemistry[5] and is shown in Scheme 1. The enolate of ester **2** was treated with *N*-phenylbenzaldimine to afford a lactam, which was separated by chiral HPLC chromatography to enantiomer **3a** and **3b** in a 1:1 ratio. To elucidate the absolute stereochemistry, **3a** was deprotected and treated with (*R*) or (*S*) camphorsulfonyl chloride. As it turned out, only the crystal of

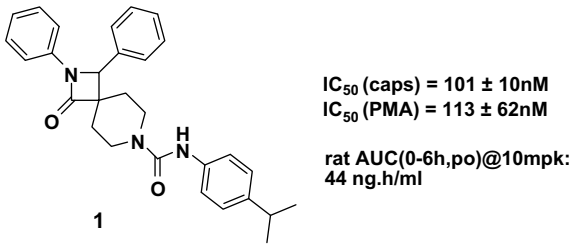


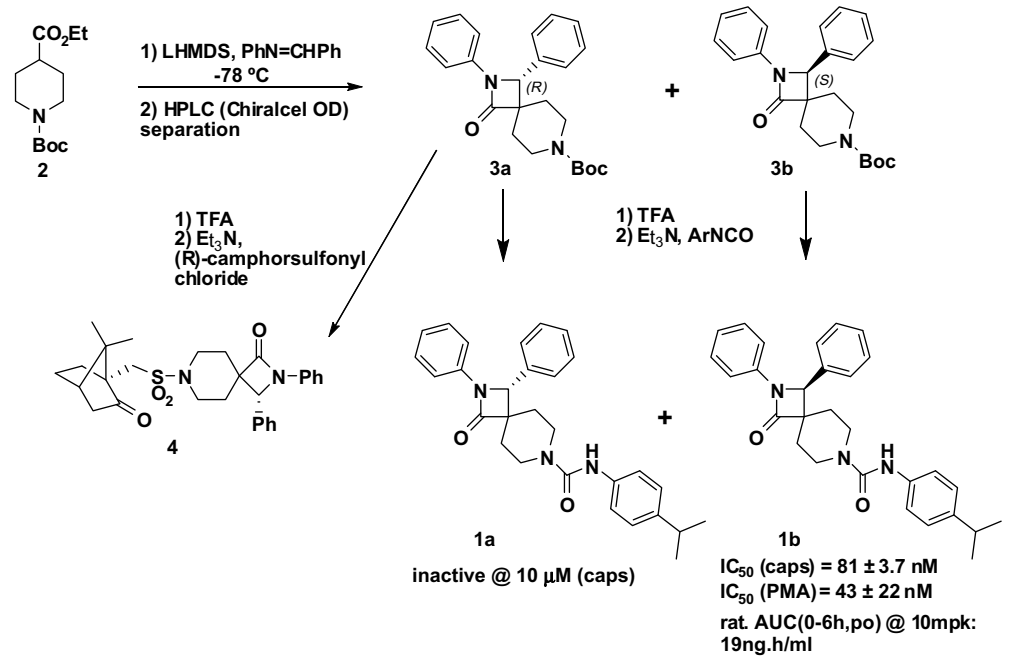
Figure 1.

(*R*) sulfonamide **4** was suitable for X-ray crystallography,[6] which established the absolute stereochemistry of **3a** as the (*R*) configuration. Subsequently, both **3a** and **3b** were converted separately to enantiomerically pure **1a** and **1b**. Between the two enantiomers only **1b** was active. Therefore the active compound **1b** had the (*S*) configuration. As expected compound **1b** was more potent than **1**, however, the AUC in a rat pharmacokinetic (PK) study[7] using oral administration was consistently very low.

After confirmation of the potency and establishment of the absolute stereochemistry of **1b**, the low rat oral pharmacokinetics was addressed. It was suspected that the *spiro*-piperidine azetidinone core structure may not be stable in plasma under physiological pH. It is known that attaching certain strained ring structures to a β-lactam (such as in penicillins **5**) could make the amide carbonyl more susceptible to nucleophilic attack.[8a] On the other hand, the monocyclic β-lactam core like that found in the commercial drug ezetimibe (**6**)[8b] was not considered to be labile under physiological conditions. To evaluate the stability issue, we synthesized

* Corresponding author. Tel.: +1 908 740 4484.
E-mail address: dong.xiao@spcorp.com (D. Xiao).

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.12.024



Scheme 1.

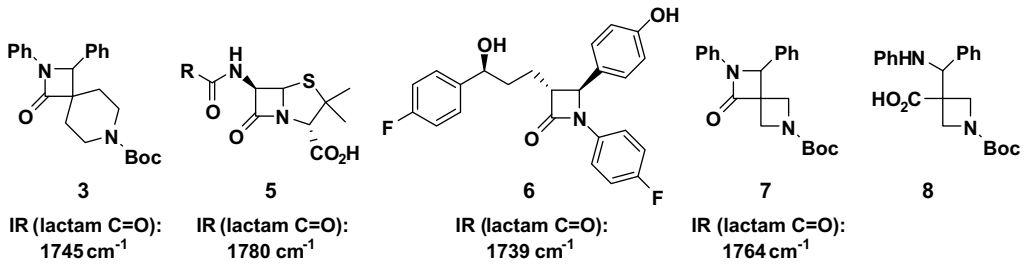


Figure 2.

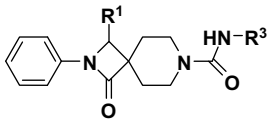
a strained analog **7** as a control to **3**. The carbonyl stretches in the IR spectra of **3** and **7** were determined and compared with the corresponding stretch of penicillins and ezetimibe, since the carbonyl stretch is a well-known measurement of strain in four-membered rings. As expected, the more strained **7** showed a similar carbonyl stretch to the penicillins (1764 cm^{-1} vs 1780 cm^{-1}), while the less strained **3** resembled ezetimibe (1745 cm^{-1} vs 1739 cm^{-1}). Subsequently, the stability was further investigated by treating both **3** and **7** in pH 7.4 buffer spiked with 0.1 M NaSMe and methyl amine to mimic plasma conditions. Compound **7** quickly degraded to the corresponding amino acid **8** in 2 h, whereas the less strained compound **3** under identical conditions remained intact for 24 h, monitored by LC–MS. This finding suggested that the low plasma level of **1b** may not be attributed to the stability of the *spiro*-piperidine-β-lactam core (Fig. 2).

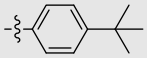
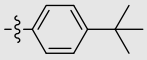
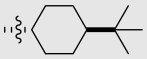
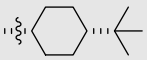
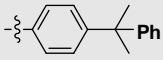
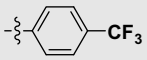
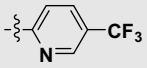
After confirming the stability of **3** in pH 7.4 buffer, we decided to investigate the SAR to achieve the following objectives: (1) develop a modular synthetic approach to address the SAR of major structural components, (2) improve potency to the single digit nM range and (3) address the inadequate PK profile.

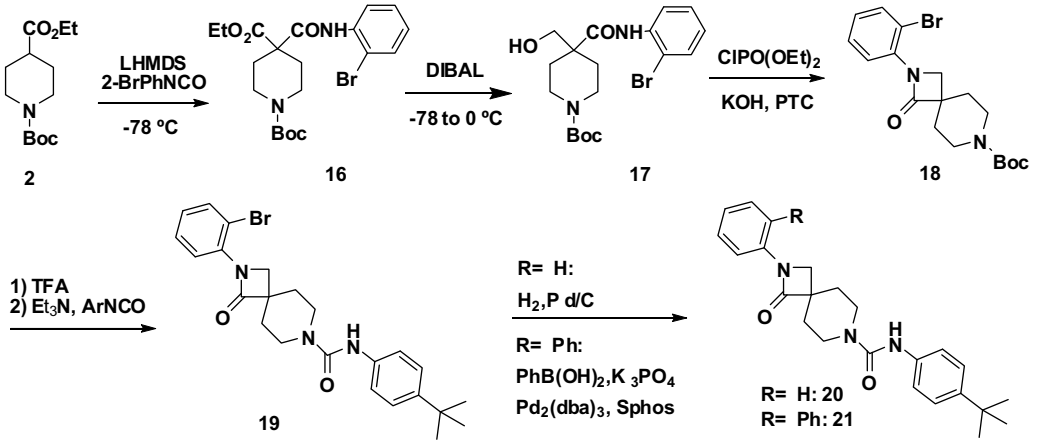
With readily available chiral intermediate **3b** in hand, the SAR of the piperidine urea was investigated first. Based on earlier literature of urea type TRPV1 antagonists,[2t] a limited set of analogs were synthesized using an analogous route to Scheme 1. As shown in Table 1, the (*S*) enantiomer of *tert*-butyl analog **9** displayed low nanomolar potency, while the (*R*) enantiomer **10** was much less active. Despite the increase in potency, the plasma level of **9** was not improved. Changing the urea from *tert*-butylphenyl to *tert*-butylcyclohexyl afforded a pair of diastereomers **11** and **12**. The *trans*-isomer **11**, while retaining some TRPV1 activity, showed no plasma levels in a rat PK study. Additional analogs revealed an improvement in PK when a *p*-trifluoromethylphenyl urea was introduced to replace the *tert*-butyl analog, for example, **14**. However, the potency of analogs **13–15** decreased substantially.

At this time we decided to shift our medicinal chemistry efforts to other regions of the molecule. One of the initiatives was directed at the β-lactam chiral center. Having that center present in targets increased the synthetic complexity and required more resources and longer timelines to conduct research. We therefore sought to eliminate the chiral center either by removing the C-linked phenyl or by transposing it to the *ortho*-position of the *N*-aryl phenyl group. This was the only position the C-linked phenyl can be accommodated, which renders the molecule achiral. The chemistry is shown in Scheme 2. Condensation of the enolate of **2** with 2-bromophenylisocyanate afforded compound **16**. Subsequent reduction of the ester with DIBAL provided compound **17**. Cyclization of **17** under phase-transfer conditions[9] provided lactam **18**, which was converted to urea **19** using standard procedures. Manipulation of the bromide functionality gave rise to targets **20** and **21**.

Table 1



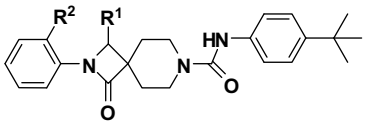
Entry	R^1	R^3	IC_{50} (caps) (nM)	IC_{50} (PMA) (nM)	rat AUC (0–6 h, po) at 10 mpk ng h/ml
9	(*S*)-Ph		9.4 ± 1.2	12 ± 1.5	49
10	(*R*)-Ph		8.5% at 10 μM	ND	ND
11	(*S*)-Ph		49 ± 3.8	32 ± 3.1	0
12	(*S*)-Ph		528 ± 64	232 ± 28	ND
13	(*S*)-Ph		226 ± 53	ND	ND
14	(±)-Ph		85 ± 20	103 ± 60	1658
15	(±)-Ph		205 ± 38	318 ± 38	ND



Scheme 2.

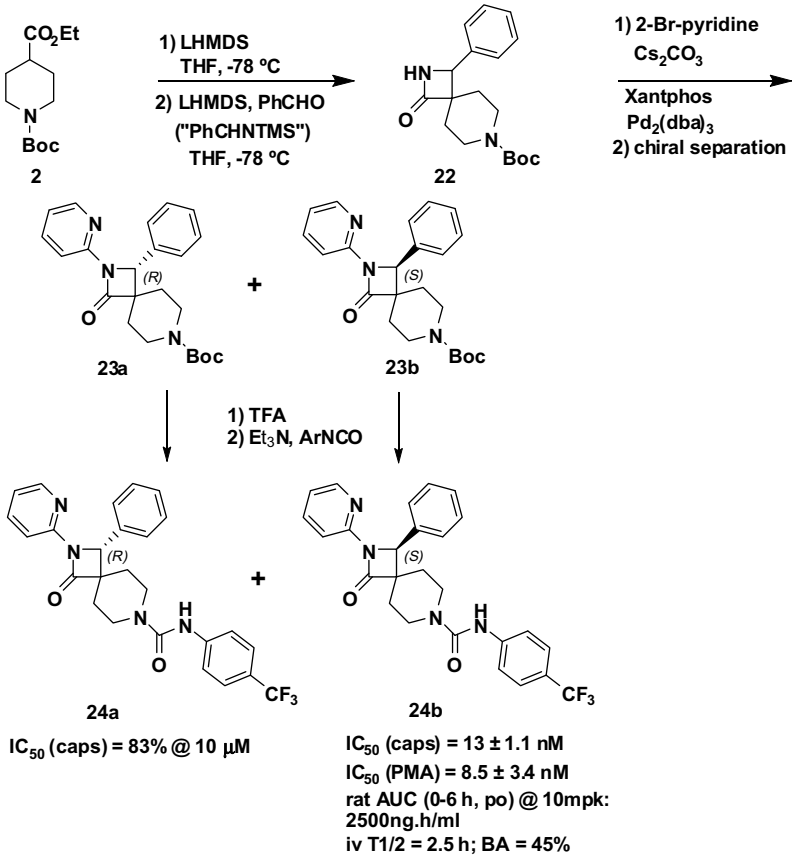
The *des*-phenyl analog **20** showed a large decrease in activity compared to **9**. Additionally, the phenyl transposed analog **21** was much less active. Retrospectively, when the X-ray structure of **4** was re-examined, it revealed a phenyl–phenyl edge to face conformation[6] that was not possible for **21** (Table 2).

Table 2



Entry	R^1	R^2	IC_{50} (caps) (nM)	IC_{50} (PMA) (nM)
9	(*R*)-Ph	H	9.4 ± 1.2	12 ± 1.5
20	H	H	80 ± 6.2	59 ± 4
21	H	Ph	73% at 10 μM	ND

Unable to simplify the structure by eliminating the β-lactam chiral center, we shifted the SAR investigation to the lactam *N*-aryl moiety. Since electron-deficient heterocycles may be used to replace the *N*-phenyl group to slow down metabolism by oxidative enzymes, the 2-pyridyl group was introduced. We reasoned that the 2-pyridyl isomer would be less prone to oxidation than the 3- or 4-substituted analogs due to sterics. This group would also lower the Clog*P* and increase aqueous solubility.[10] We would retain the *p*-trifloromethylphenyl as the piperidine urea, since it provides much desired PK improvement. The synthesis of the proposed targets is shown in Scheme 3. Once again, the enolate of **2** was treated with pre-formed N-TMS-benzaldimine, which afforded unsubstituted lactam **22**. A palladium catalyzed arylation reaction[11] provided the *N*-pyridyl lactam, which was separated to two enantiomers **23a** and **23b**. The absolute configurations were assigned in analogy to the phenyl analogs. Further elaboration furnished targets **24a** and **24b**.



Scheme 3.

The pyridyl analog **24b** turned out to be potent with equal activity in the capsaicin and PMA assays. When this compound was tested in the rat PK assay, a much improved exposure was achieved with desirable duration. This compound **24b** represents an advanced lead with good potency and oral bioavailability in rat and is suitable for further in-depth optimization.

In summary, a screening lead **1** was confirmed and preliminary medicinal chemistry was investigated. During this study, we established the absolute stereochemistry of the β-lactam and demonstrated the importance of a properly substituted phenyl group. We also confirmed the stability of the center *spiro*-piperidine-β-lactam core at physiological pH in the presence of thio and amino nucleophiles. With a minimum number of analogs, a potent analog **24b** with good rat PK profile was discovered. In addition, three synthetic routes were developed, which lay down a solid foundation for further optimization efforts.

Acknowledgments

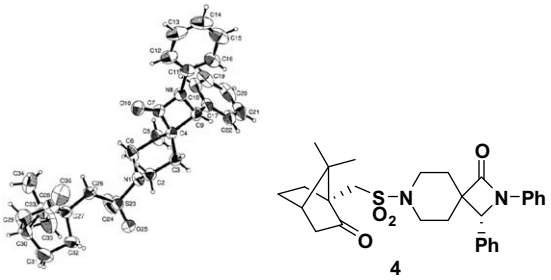
We thank Drs. John J. Piwinski and John C. Hunter for supporting this research program and Dr. Duane Burnett for helpful discussions.

References and notes

1. For recent reviews (a) McLeod, R. L.; Correll, C. C.; Jia, Y.; Anthes, J. C. *Lung* **2008**, *186*, S59; (b) Gunthorpe, M. J.; Szallasi, A. *Curr. Pharm. Des.* **2008**, *14*, 32; (c) Vasudevan, A.; Kort, M. E. *Annu. Rep. Med. Chem.* **2007**, *42*, 81; (d) Westaway, S. M. *J. Med. Chem.* **2007**, *50*, 2589; (e) Correll, C. C.; Palani, A. *Expert Opin. Ther. Patents* **2006**, *16*, 783; (f) Kyle, D. J.; Tafesse, L. *Expert Opin. Ther. Patents* **2006**, *16*, 977; (g) Roberts, L. A.; Connor, M. *Recent Patents CNS Drug Discov.* **2006**, *1*, 65.
2. For recent example (a) Brown, B. S.; Keddy, R.; Zheng, G. Z.; Schmidt, R. G.; Koenig, J. R.; McDonald, H. A.; Bianchi, B. R.; Honore, P.; Jarvis, M. F.; Surowy, C. S.; Polakowski, J. S.; Marsh, K. C.; Faltynek, C. R.; Lee, C.-H. *Bioorg. Med. Chem.* **2008**, *16*, 8516; (b) Blum, C. A.; Zheng, X.; Brielmann, H.; Hodgetts, K. J.; Bakthavatchalam, R.; Chandrasekhar, J.; Krause, J. E.; Cortright, D.; Matson, D.; Crandall, M.; Ngo, C. K.; Fung, L.; Day, M.; Kershaw, M.; De Lombaert, S.; Chenard, B. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4573; (c) Cheung, W. S.; Calvo, R. R.; Tounge, B. A.; Zhang, S.-P.; Stone, D. R.; Brandt, M. R.; Hutchinson, T.; Flores, C. M.; Player, M. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4569; (d) Tamayo, N.; Liao, H.; Stec, M. M.; Wang, X.; Chakrabarti, P.; Retz, D.; Doherty, E. M.; Surapaneni, S.; Tamir, R.; Bannon, A. W.; Gavva, N. R.; Norman, M. H. *J. Med. Chem.* **2008**, *51*, 2744; (e) Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Surowy, C. S.; Honore, P.; Marsh, K. C.; Hannick, S. M.; McDonald, H. A.; Wetter, J. M.; Sullivan, J. P.; Jarvis, M. F.; Faltynek, C. R.; Lee, C.-H. *J. Med. Chem.* **2008**, *51*, 392; (f) Ryu, H.; Jin, M.-K.; Kim, S. Y.; Choi, H.-K.; Kang, S.-U.; Kang, D. W.; Lee, J.; Pearce, L. V.; Pavlyukovets, V. A.; Morgan, M. A.; Tran, R.; Toth, A.; Lundberg, D. J.; Blumberg, P. M. *J. Med. Chem.* **2008**, *51*, 57; (g) Shishido, Y.; Jinno, M.; Ikeda, T.; Ito, F.; Sudo, M.; Makita, N.; Ohta, A.; Iki-Taki, A.; Ohmi, T.; Kanai, Y.; Tamura, T.; Shimojo, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1072; (h) Norman, M. H.; Zhu, J.; Fotsch, C.; Bo, Y.; Chen, N.; Chakrabarti, P.; Doherty, E. M.; Gavva, N. R.; Nishimura, N.; Nixey, T.; Ognyanov, V. I.; Rzasa, R. M.; Stec, M.; Surapaneni, S.; Tamir, R.; Viswanadhan, V. N.; Treanor, J. J. S. *J. Med. Chem.* **2007**, *50*, 3497; (i) Drizin, I.; Gomtayan, A.; Bayburt, E. K.; Schmidt, R. G.; Zheng, G. Z.; Perner, R. J.; DiDomenico, S.; Koenig, J. R.; Turner, S. C.; Jinkerson, T. K.; Brown, B. S.; Keddy, R. G.; McDonald, H. A.; Honore, P.; Wismer, C. T.; Marsh, K. C.; Wetter, J. M.; Polakowski, J. S.; Segreti, J. A.; Jarvis, M. F.; Faltynek, C. R.; Lee, C.-H. *Bioorg. Med. Chem.* **2006**, *14*, 4740; (j) Ognyanov, V. I.; Balan, C.; Bannon, A. W.; Bo, Y.; Dominguez, C.; Fotsch, C.; Gore, V. K.; Klionsky, L.; Ma, V. V.; Qian, Y.-X.; Tamir, R.; Wang, X.; Xi, N.; Xu, S.; Zhu, D.; Gavva, N. R.; Treanor, J. J. S.; Norman, M. H. *J. Med. Chem.* **2006**, *49*, 3719; (k) Fletcher, S. R.; McIver, E.; Lewis, S.; Burkamp, F.; Leech, C.; Mason, G.; Boyce, S.; Morrison, D.; Richards, G.; Sutton, K.; Jones, A. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2872; (l) Bonache, M. A.; Garcia-Martinez, C.; Garcia de Diego, L.; Carreno, C.; Perez de Vega, M. J.; Garcia-Lopez, M. T.; Ferrer-Montiel, A.; Gonzalez-Muniz, R. *ChemMedChem* **2006**, *1*, 429; (m) Xi, N.; Bo, Y.; Doherty, E. M.; Fotsch, C.; Gavva, N. R.; Han, N.; Hungate, R. W.; Klionsky, L.; Liu, Q.; Tamir, R.; Xu, S.; Treanor, J. J. S.; Norman, M. H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5211; (n) Suh, Y.-G.; Lee, Y.-S.; Min, K.-H.; Park, O.-H.; Kim, J.-K.; Seung, H.-S.; Seo, S.-Y.; Lee, B.-Y.; Nam, Y.-H.; Lee, K.-O.; Kim, H.-D.; Park, H.-G.; Lee, J.; Oh, U.; Lim, J.-O.; Kang, S.-U.; Kil, M.-J.; Koo, J.-Y.; Shin, S. S.; Joo, Y.-H.; Kim, J. K.; Jeong, Y.-S.; Kim, S.-Y.; Park, Y.-H. *J. Med. Chem.* **2005**, *48*, 5823; (o) Lee, J.; Jin, M.-K.; Kang, S.-U.; Kim, S. Y.; Lee, J.; Shin, M.; Hwang, J.; Cho, S.; Choi, Y.-S.; Choi, H.-K.; Kim, S.-E.; Suh, Y.-G.; Lee, Y.-S.; Kim, Y.-H.; Ha, H.-J.; Toth, A.; Pearce, L. V.; Tran, R.; Szabo, T.; Welter, J. D.; Lundberg, D. J.; Wang, Y.; Lazar, J.; Pavlyukovets, V. A.; Morgan, M. A.; Blumberg, P. M. *Bioorg. Med. Chem. Lett.*

2005, *15*, 4143; (p) Lee, J.; Kang, S.-U.; Kil, M.-J.; Shin, M.; Lim, J.-O.; Choi, H.-K.; Jin, M.-K.; Kim, S. Y.; Kim, S.-E.; Lee, Y.-S.; Min, K.-H.; Kim, Y.-H.; Ha, H.-J.; Tran, R.; Welter, J. D.; Wang, Y.; Szabo, T.; Pearce, L. V.; Lundberg, D. J.; Toth, A.; Pavlyukovets, V. A.; Morgan, M. A.; Blumberg, P. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4136; (q) Shao, B.; Huang, J.; Sun, Q.; Valenzano, K. J.; Schmid, L.; Nolan, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 719; (r) Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Zheng, G. Z.; Perner, R. J.; Didomenico, S.; Koenig, J. R.; Turner, S.; Jinkerson, T.; Drizin, I.; Hannick, S. M.; Macri, B. S.; McDonald, H. A.; Honore, P.; Wismer, C. T.; Marsh, K. C.; Wetter, J.; Stewart, K. D.; Oie, T.; Jarvis, M. F.; Surowy, C. S.; Faltynek, C. R.; Lee, C. H. *J. Med. Chem.* **2005**, *48*, 744; (s) Doherty, E. M.; Fotsch, C.; Bo, Y.; Chakrabarti, P. P.; Chen, N.; Gavva, N.; Han, N.; Kelly, M. G.; Kincaid, J.; Klionsky, L.; Liu, Q.; Ognyanov, V. I.; Tamir, R.; Wang, X.; Zhu, J.; Norman, M. H. *J. Med. Chem.* **2005**, *48*, 71; (t) Swanson, D. M.; Dubin, A. E.; Shah, C.; Nasser, N.; Chang, L.; Dax, S. L.; Jetter, M.; Breitenbucher, J. G.; Liu, C.; Mazur, C.; Lord, B.; Gonzales, L.; Hoey, K.; Rizzolio, M.; Bogenstaetter, M.; Codd, E. E.; Lee, D. H.; Zhang, S.-P.; Chaplan, S. R.; Carruthers, N. I. *J. Med. Chem.* **2005**, *48*, 1857. and references cited therein.

3. Szallasi, A.; Cortwright, D. A.; Blum, C. A.; Eid, S. R. *Nat. Rev. Drug Discov.* **2007**, *6*, 357.
4. TRPV1 assay: TRPV1 activity was determined via FLIPR assay at 37 °C using a stably transfected HEK293 cell line. All compounds used in these studies were dissolved in dimethyl sulfoxide (DMSO) and vehicle alone (DMSO) was used as a control. In all experiments, DMSO concentration was kept below 0.2% final. All compounds were characterized by their ability to inhibit 2 modes of TRPV1 activation: (1) small molecule induced activation via the addition of capsaicin (caps), and (2) phosphorylation-mediated activation of TRPV1 through activation of PKC via the addition of phorbol myristate acetate (PMA). Calculation of EC_{50} and IC_{50} values were determined using GraphPad Prism v3.02 (GraphPad Software, Inc.). Data presented is the average of at least three separate determinations. All values are given in nM and SEM given for each compound except for the less potent compounds, for which only % inhibition are reported. Full experimental details: Correll, C. C.; Phelps, P. T.; Anthes, J. C.; Egan, R. W.; Umland, S.; Greenfeder, S. *Neurosci. Lett.* **2004**, *370*, 55.
5. Aslanian, R. G.; Chan, T.-Y.; Harris, J. M.; McKittrick, B. A.; Neustadt, B. R.; Palani, A.; Priestley, T.; Smith, E. M.; Stamford, A. W.; Vaccaro, H. M.; Xiao, D. Preparation of spirocyclic azetidinone derivatives and therapeutic applications thereof PCT Int. Appl. 2008, WO 2008033465 A1.
6. The X-ray coordinates of compound **4** has been deposited with Cambridge Crystallographic Data Centre for small molecules (CCDC) as CCDC 708149. The ORTEP diagram of **4** (40% probability ellipsoids) is shown below:



4

7. The rat PK assay was run at 10 mpk using oral dosing with 20% HPBCD as vehicle. AUC was determined from 0 to 6 hours. For lead compound **24b**, an additional iv dosing was performed. Reference: Cox, K. A.; Dunn-Meynell, K.; Korfmacher, W. A.; Broske, L.; Nomeir, A. A.; Lin, C. C.; Cayen, M. N.; Barr, W. H. *Drug Discov. Today* **1999**, *4*, 232.
8. For a discussion on the influence of bicyclic structure on susceptibility of nucleophilic attack towards lactam carbonyls in drug design: (a) Smith, P. W.; Whittington, A. R.; Cobley, K. N.; Jaxa-Chamiec, A.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, *1*, 21; (b) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R.; Yumube, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1988**, *41*, 973.
9. (a) Thiruvengadam, T. K.; Tann, C. H.; Lee, J.; McAllister, T. L.; Sudhakar, A. US patent 1994, 5306817.; (b) Wu, G.; Tormos, W. *J. Org. Chem.* **1997**, *62*, 6412.
10. The values of CLog*P* and solubility of **9** and its pyridyl analog **24b** calculated by ACDLABS 11.0 (© Advanced Chemistry Development, Inc., Toronto, Canada) are shown below: **9**: CLog*P*: 5.11; solubility at pH 7: 9.4×10^{-8} mol/L **24b**: CLog*P*: 4.48; solubility at pH 7: 3.0×10^{-7} mol/L.
11. Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101.