Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 5825–5830
Bioorganic & Medicinal Chemistry Letters

Structure–activity relationship (SAR) investigations of substituted imidazole analogs as TRPV1 antagonists

Vijay K. Gore,[a,*] Vu V. Ma,[a] Rami Tamir,[b] Narender R. Gavva,[b] James J. S. Treanor[b] and Mark H. Norman[a]

[a]*Chemistry Research & Discovery, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, USA*
[b]*Department of Neuroscience, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, USA*

Received 29 May 2007; revised 19 August 2007; accepted 21 August 2007
Available online 25 August 2007

Abstract—A novel series of 4,5-biarylimidazoles as TRPV1 antagonists were designed based on the previously reported 4,6-disubstituted benzimidazole series. The analogs were evaluated for their ability to block capsaicin- or acid-induced calcium influx in TRPV1-expressing CHO cells. These studies led to the identification of a highly potent and orally bioavailable TRPV1 antagonist, imidazole **33**.

Vanilloid receptor-1 (VR1 or TRPV1) is a member of the transient receptor potential (TRP) family of ion channels.[1] This highly Ca^{2+} permeable receptor is predominantly expressed in peripheral sensory neurons that are involved in nociception and neurogenic inflammation.[2] TRPV1 is activated by endogenous ligands such as anandamide and lipoxygenase metabolites.[3,4] It is also activated by a variety of stimuli such as heat and acid, and exogenous chemical stimuli such as capsaicin (the pungent component found in chili peppers). TRPV1 activation with agonists is known to have analgesic effects because it leads to desensitization of sensory neurons, making them less sensitive to painful stimuli. However, prolonged use of such agonists (e.g., topical muscle pain relievers containing capsaicin as the active component) is associated with side effects such as burning sensation, irritation, and neurotoxicity due to continuous influx of Ca^{2+} ions into the cells.[5] TRPV1 receptor antagonists on the other hand inhibit the activation of the primary sensory neurons and therefore may have fewer side effects than TRPV1 agonists.[6] This hypothesis is also supported by the observation that thermal hyperalgesia is reduced in inflammatory pain models in knockout mice lacking the TRPV1 gene.[7]

In our work toward the discovery of new analgesic agents, we recently reported the synthesis and SAR studies of a series of 2-(4-pyridin-2-ylpiperazin-1-yl)-1*H*-benzo-[*d*]imidazoles as potent TRPV1 antagonists (exemplified by compound **1**).[8] During the course of this work we identified a hydrophobic binding pocket in the TRPV1 receptor which could be accessed from the C-4 position of the benzimidazole ring. We found that significant enhancements in TRPV1 potency could be obtained by the addition of hydrophobic groups in this C-4 position. As an alternative way to gain entry into this binding pocket we designed a series of novel trisubstituted imidazole analogs (e.g., compound **2**). In this series, the imidazole ring would be shifted slightly (compared to the 4-substituted benzimidazole ring) to position the aromatic substituents at C-4 and C-5 in the optimal region of the space. Superposition of the molecules in this way suggested that the 4,5-biaryl-substituted imidazole **2** would overlap well with the 4,6-disubstituted benzimidazole analog **1** (Fig. 1).

To test this hypothesis we prepared imidazole **2** and evaluated its ability to inhibit the TRPV1 receptor. We found that compound **2** and hence the 4,5-disubstituted-imidazole group could serve as an alternative to the C-4-substituted benzimidazole scaffold (**1**). Herein, we describe the synthesis and biological activity of a series of 4,5-biaryl-substituted imidazoles of type **2** as a novel class of TRPV1 antagonists.

Keywords: VRI; TRPV1; Vanilloid receptor-1; Biaryl imidazoles; TRPV1 antagonists.
* Corresponding author. Tel.: +1 805 447 4823; fax: +1 805 480 1337; e-mail: vgore@amgen.com

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.08.044

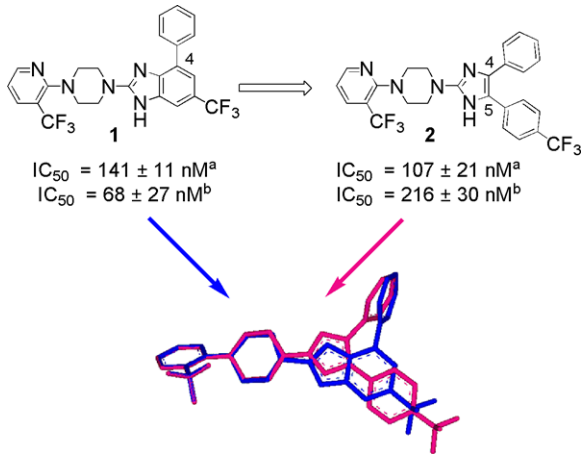
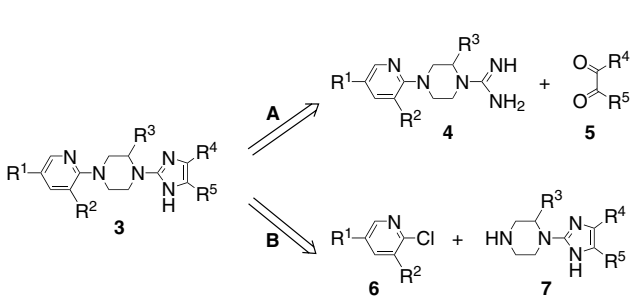


Figure 1. Superimposition of compounds **1** (blue) and **2** (red). [a]Inhibition of capsaicin-mediated $^{45}Ca^{2+}$ influx in CHO cells expressing rat TRPV1 receptor. [b]Inhibition of acid-mediated (pH 5) $^{45}Ca^{2+}$ influx in CHO cells expressing rat TRPV1 receptor.

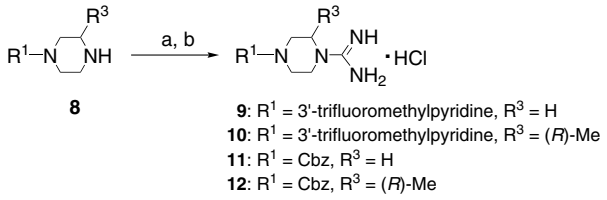
For the purposes of our study, we utilized the rat TRPV1 channel recombinantly expressed in Chinese hamster ovary (CHO) cells. The compound's ability to inhibit both the capsaicin- and acid-mediated influx of $^{45}Ca^{2+}$ was examined. Our goal was to improve potency and pharmacokinetic properties over compound **2** as well as to gain better understanding of the pharmacophores required for TRPV1 activity in this novel series.

The majority of compounds required for our SAR study were prepared by one of two general routes (methods A and B, Scheme 1). In method A, 4,5-biarylimidazoles **3** were obtained by coupling piperazinyl-guanidines **4** with 1,2-biarylethane-1,2-diones **5** in the presence of Hunig's base followed by hydrogenolysis.[9] In method B, the final products **3** were obtained by coupling chloro-pyridine derivatives (**6**) with 2-piperazinyl-4,5-biarylimidazoles (**7**) by heating under microwave-assisted conditions in the presence of base.

The requisite piperazinyl-guanidines (**9**–**12**) were synthesized in a two-step sequence as shown in Scheme 2. Treatment of various piperazines (**8**) with 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea in the presence of a mercury(II) salt promoter and triethylamine as the base resulted in formation of the bis-Boc-protected guanidines, which, upon deprotection using 4 N HCl in dioxane, yielded the free guanidines (**9**–**12**).[10]



Scheme 1. Retrosynthesis of 4,5-biarylimidazoles (**3**).



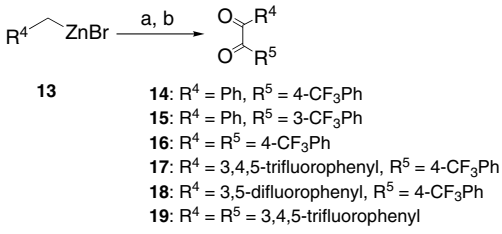
Scheme 2. Synthesis of guanidines **9**–**12**. Reagents and conditions: (a) 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea, Et_3N, $HgCl_2$, CH_2Cl_2, room temperature, 12 h; (b) 4 N HCl, 1,4-dioxane, room temperature, 8 h, 60% (over two steps).

Scheme 3 details the syntheses of the intermediate 1,2-biarylethane-1,2-diones. Biarylethane-diones (**14**–**19**) were obtained in good yields by Cu(I)-mediated cross-coupling of various substituted benzoyl chlorides with the appropriately substituted benzylzinc(II) bromides, followed by treatment with *n*-bromosuccinimide (NBS).[11,12]

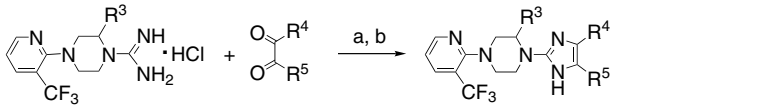
General method A was followed for synthesis of the 4,5-biarylimidazoles **2** and **21**–**27** as shown in Scheme 4. The reaction of biaryl-diones **14**–**19** and commercially available propane-1,2-dione **20** with guanidines **9** and **10** in presence of Hunig's base followed by catalytic hydrogenation provided the final products **2** and **21**–**27**.

Guanidines **11** and **12** were reacted with the diones **14** and **17** in presence of Hunig's base, followed by hydrogenolysis to yield the intermediates **28**–**30** (Scheme 5). These intermediates were elaborated using method B described earlier to synthesize the final products **31**–**33**. Accordingly, compounds **28**–**30** were coupled with SEM-protected (2,3-dichloropyridin-5-yl)methanol under microwave-assisted conditions, followed by treatment with trifluoroacetic acid to yield the final products **31**–**33** (Scheme 5).

The analog without a substituent at the C-4 position of the imidazole ring (i.e., compound **37**) was synthesized as shown in Scheme 6. Amino-aryl-ethanone hydrochloride **34** was converted to the corresponding 4-substituted-1*H*-imidazol-2(3*H*)-one **35**.[13] The imidazolone was treated with phosphorus oxychloride followed by protection with a SEM-group to yield the N-1-protected 2-chloroimidazole **36**. This intermediate was subjected to Pd-mediated amination[14] reaction conditions with 1-(3-(trifluoromethyl)pyridin-2-yl)piperazine followed

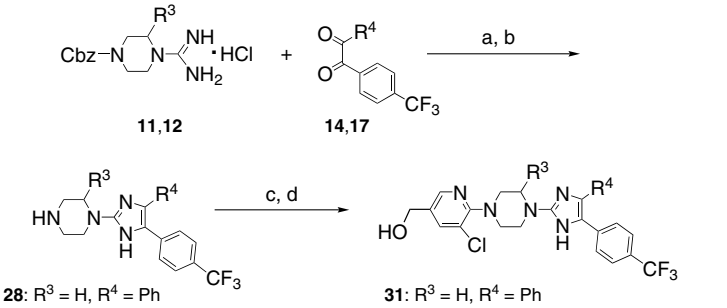


Scheme 3. Synthesis of 1,2-biarylethane-1,2-diones **14**–**19**. Reagents and conditions: (a) benzoyl chloride, THF, LiBr, CuCN, −25 °C to room temperature, 16 h; (b) NBS, DMSO, 65 °C, 4 h, 35% (over two steps).



2: R^3 = H, R^4 = Ph, R^5 = 4-CF_3Ph
21: R^3 = H, R^4 = Ph, R^5 = 3-CF_3Ph
22: R^3 = H, R^4 = R^5 = 4-CF_3Ph
23: R^3 = H, R^4 = 3,4,5-trifluorophenyl, R^5 = 4-CF_3Ph
24: R^3 = H, R^4 = 3,5-difluorophenyl, R^5 = 4-CF_3Ph
25: R^3 = H, R^4 = R^5 = 3,4,5-trifluorophenyl
26: R^3 = (*R*)-Me, R^4 = Ph, R^5 = 4-CF_3Ph
27: R^3 = H, R^4 = Me, R^5 = 4-CF_3Ph

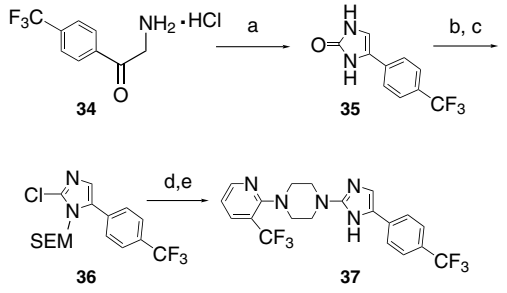
Scheme 4. Synthesis of compounds **2** and **21**–**27**. Reagents and conditions: (a) **14**–**19**, MeOH, DIPEA, room temperature, 8 h; (b) MeOH, 10% Pd/C, H_2, room temperature, 12 h, 30% (over two steps).



28: R^3 = H, R^4 = Ph
29: R^3 = (*R*)-Me, R^4 = Ph
30: R^3 = (*R*)-Me, R^4 = 3,4,5-trifluorophenyl

31: R^3 = H, R^4 = Ph
32: R^3 = (*R*)-Me, R^4 = Ph
33: R^3 = (*R*)-Me, R^4 = 3,4,5-trifluorophenyl

Scheme 5. Synthesis of compounds **31**–**33**. Reagents and conditions: (a) **14** or **17**, EtOH, DIPEA, room temperature, 5 h; (b) EtOH, 20% $Pd(OH)_2$/C, H_2, room temperature, 6 h, 40% (over two steps); (c) 2,3-dichloro-5-(((2-(trimethylsilyl)ethoxy)methoxy)methyl)pyridine, NMP, $NaHCO_3$, Microwave, 190 °C, 0.5 h, 65–70%; (d) TFA, room temperature, 2 h, 65%.



Scheme 6. Synthesis of compound **37**. Reagents and conditions: (a) KOCN, H_2O, 80 °C, 4 h, 85%; (b) $POCl_3$, 110 °C, 12 h, 90%; (c) $ClCH_2OCH_2CH_2SiMe_3$ (SEM-Cl), DIPEA, CH_2Cl_2, 12 h, 90%; (d) 1-(3-(trifluoromethyl)pyridin-2-yl)piperazine, $Pd(dba)_3$, 2-(di-*tert*-butylphosphino)biphenyl, NaO^{t}Bu, microwave, 150 °C, 10 min, 15%; (e) TFA, CH_2Cl_2, room temperature, 5 h, 70%.

by deprotection using trifluoroacetic acid to obtain analog **37**.

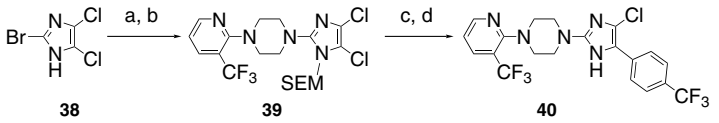
The 5-chloro substituted analog **40** was synthesized in four steps starting from 2-bromo-4,5-dichloro-1*H*-imidazole as shown in Scheme 7. Bromo-imidazole **38** was treated with SEM-Cl followed by treatment with 1-(3-(trifluoromethyl)pyridin-2-yl)piperazine under microwave-assisted conditions to yield intermediate **39**. Intermediate **39** was subjected to Suzuki coupling with (4-trifluoromethyl)phenylboronic acid followed by deprotection using trifluoroacetic acid to obtain analog **40**.

Scheme 8 shows the preparation of ester analog **43**. Methyl 1*H*-imidazole-4-carboxylate (**41**) was subjected to bromination conditions followed by protection with a SEM-group. Subsequent treatment with 1-(3-(trifluoromethyl)pyridin-2-yl)piperazine under microwave-assisted conditions provided intermediate **42**. Intermediate **42** was subjected to deprotection using trifluoroacetic acid followed by Suzuki coupling with (4-trifluoromethyl)phenylboronic acid to obtain ester analog **43**.

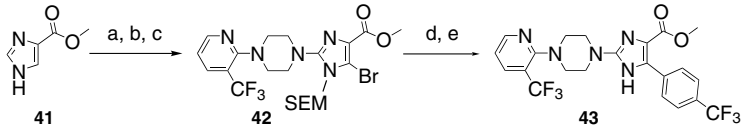
The syntheses of the final four amide derivatives **45**–**48** are shown in Scheme 9. The Suzuki coupling of **42** with 4-(trifluoromethyl)phenylboronic acid followed by hydrolysis with LiOH provided carboxylic acid **44**. Compound **44** was condensed with various amines[15] under peptide coupling conditions in presence of BOP reagent and the intermediates were deprotected using trifluoroacetic acid to obtain amide analogs **45**–**48**.

The compounds were tested for their ability to block the capsaicin- or acid-induced (pH 5) uptake of $^{45}Ca^{2+}$ in CHO cells expressing rat TRPV1. Functional activity is reported as IC_{50} (nM) and represents the average of at least two independent experiments with three replicates at each concentration.

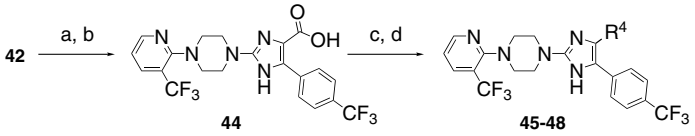
We first examined the substitutions of the imidazole ring (R^4 and R^5, Tables 1 and 2). The imidazole analog **2** had an IC_{50} value of 107 nM in the capsaicin-mediated



Scheme 7. Synthesis of compound **40**. Reagents and conditions: (a) $ClCH_2OCH_2CH_2SiMe_3$, NaH, THF, 0.5 h, 65%; (b) 1-(3-(trifluoromethyl)pyridin-2-yl)piperazine, microwave, 130 °C, 15 min, 6%; (c) (4-trifluoromethyl)phenylboronic acid, $PdCl_2(PPh_3)_2$, Na_2CO_3, DME/H_2O/EtOH (7:3:2), microwave, 130 °C, 1 h; (d) TFA, CH_2Cl_2, room temperature, 1 h, 3% (over two steps).

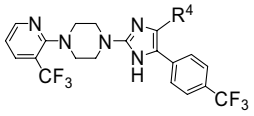


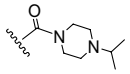
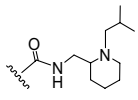
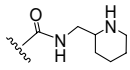
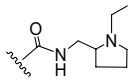
Scheme 8. Synthesis of compound **43**. Reagents and conditions: (a) Br_2, AcOH, 12 h, room temperature, 15%; (b) $ClCH_2OCH_2CH_2SiMe_3$, NaH, THF, 12 h, 90%; (c) 1-(3-(trifluoromethyl)pyridin-2-yl)piperazine, microwave, 130 °C, 15 min, 55%; (d) TFA, room temperature, 1 h, 75%; (e) (4-trifluoromethyl)phenylboronic acid, $PdCl_2(PPh_3)_2$, Na_2CO_3, DME/H_2O/EtOH (7:3:2), microwave, 130 °C, 1 h, 15%.



Scheme 9. Synthesis of compounds **45–48**. Reagents and conditions: (a) (4-trifluoromethyl)phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane, microwave, 130 °C, 15 min, 85%; (b) LiOH, THF/H_2O (5:1), 0 °C to room temperature, 16 h, 55%; (c) Amine, BOP, DIPEA, CH_2Cl_2, room temperature, 48 h; (d) TFA, room temperature, 1 h, 16% (over two steps).

Table 1. Structures and assay results of analogs **2**, **37**, **27**, **40** and **43**, and **45–48**



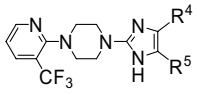
Compound	R^4	rTRPVI (Cap)[a] IC_{50} ± SEM (nM)	rTRPVI (pH 5)[a] IC_{50} ± SEM (nM)
2	Ph	107 ± 21	216 ± 30
37	H	861 ± 74	>4000
27	Me	628 ± 71	>4000
40	Cl	160 ± 28	>4000
43	COOMe	1170 ± 1650	180 ± 32
45		700 ± 308	1000 ± 84
46		1900 ± 700	>4000
47		2950 ± 72	>4000
48		4100 ± 1100	3300 ± 1200

[a] The inhibition assays were carried out in rat TRPV1 channel expressed in CHO cells. Results are the average of at least two independent experiments with three replicates at each concentration.

assay and 216 nM in the acid-mediated assay. Removal of the phenyl group from the imidazole ring resulted in compound **37**, which had weaker potency in the capsaicin-mediated assay (IC_{50} = 861 nM) compared to compound **2**, and was inactive in the acid-mediated assay (Table 1). This result indicated that 4,5-disubstitution of the imidazole ring was essential for activity in both cell assays. Next, we tested compounds **27**, **40**, and **43** containing smaller groups such as methyl, chlorine, and methyl ester at the C-4 position, respectively. All three analogs were moderately active in the capsaicin-mediated assay; however the methyl ester **43** was the only analog that showed activity in both cell assays. These data suggested that larger substitutents were preferred at the C-4 position of the imidazole ring and could provide potency enhancement in both assays. Therefore, we utilized methyl ester **43** to prepare amide analogs **45–48** (Table 1). Basic amines such as piperazine, piperidine, and pyrrolidine were introduced in an attempt to improve the solubility properties. Unfortunately, all four amides **45–48** demonstrated weak activity in both capsaicin and acid-mediated cell assays.

Because the amide modifications did not provide any potency enhancement, we explored various 4,5-biaryl modifications on the imidazole ring (Table 2). Accordingly, replacement of the *p*-(trifluoromethyl)phenyl group of compound **2** with the corresponding meta-substituted analog (**21**) maintained potency in the acid-mediated assay but was 10- to 12-fold weaker in the capsaicin-mediated assay (Table 2). These results suggested that an aryl substitution with *p*-(trifluoromethyl)phenyl group was optimal for activity, therefore we retained it as the R^5 substituent and investigated additional substitutions on the R^4 position of the imidazole ring. Compounds **22–24** were tested for functional activity and analog **23** with the 3,4,5-trifluorophenyl substitution

Table 2. Structures and assay results of analogs **2** and **21–25**



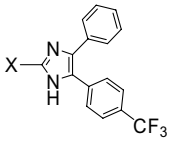
Compound	R^4	R^5	rTRPVI (Cap)[a] IC_{50} ± SEM (nM)	rTRPVI (pH 5)[a] IC_{50} ± SEM (nM)
2	Ph	4-CF_3Ph	107 ± 21	216 ± 30
21	Ph	3-CF_3Ph	1235 ± 265	165 ± 17
22	4-CF_3Ph	4-CF_3Ph	573 ± 31	146 ± 84
23	3,4,5-Trifluoro-Ph	4-CF_3Ph	7 ± 2	20 ± 3
24	3,5-Difluoro-Ph	4-CF_3Ph	35 ± 4	85 ± 10
25	3,4,5-Trifluoro-Ph	3,4,5-Trifluoro-Ph	44 ± 4	32 ± 3

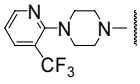
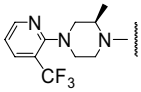
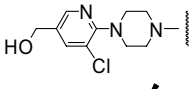
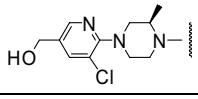
[a] The inhibition assays were carried out in rat TRPV1 channel expressed in CHO cells. Results are the average of at least two independent experiments with three replicates at each concentration.

showed a 15-fold enhancement in potency in the capsaicin-mediated assay and a 10-fold improvement in the acid-mediated assay as compared to compound **2**. However, compound **25** with the 4,5-bis(3,4,5-trifluorophenyl) substitution on the imidazole ring did not show further improvement in the cell potency. These data indicated that the 4,5-biaryl substitution in analog **23** was the optimal combination of substituents in this series.

In the next phase of our investigation, we explored the effects of modifications on the pyridyl-piperazine moiety of compound **2** (Table 3). Based on our SAR understanding of the benzimidazole series we introduced the (*R*)-2-methylpiperazine and the 3′-chloro-5′-hydroxymethyl pyridine ring modifications in this new series. Accordingly, compounds **26** and **31**, formed by introduction of the (*R*)-2-methylpiperazine and 3′-chloro-5′-hydroxymethyl pyridine, respectively, were tested in the cell assays. Each of these modifications individually did not provide the potency enhancement in the cell assays; however, when we introduced these two modifications in the same molecule, the resulting analog **32** showed a 4- to 5-fold improvement in potency in both assays (Table 3). This finding was consistent with observations in our previously reported benzimidazole work.[8]

Table 3. Structures and assay results of analogs **2**, **26**, **31**, and **32**



Compound	X	rTRPVI (Cap)[a] IC_{50} ± SEM (nM)	rTRPVI (pH 5)[a] IC_{50} ± SEM (nM)
2		107 ± 21	216 ± 30
26		117 ± 5	341 ± 29
31		90 ± 19	160± 22
32		26 ± 3	29 ± 2

[a] The inhibition assays were carried out in rat TRPV1 channel expressed in CHO cells. Results are the average of at least two independent experiments with three replicates at each concentration.

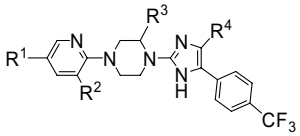
In the final phase of this investigation we evaluated the effect of combining the structural features of the two most potent analogs (compounds **23** and **32**). For example, we retained the 4,5-biarylimidazole substitution from **23** and combined it with the pyridyl-piperazine unit from **32** (Table 4). This hybrid analog (**33**) was more potent in both the capsaicin-mediated and acid-mediated cell assays compared to analogs **23** or **32**.

Because of their excellent in vitro potencies, we studied compounds **23** and **33** in more detail. The pharmacokinetic (PK) profiles with intravenous (iv) dosing in Sprague–Dawley rats for compounds **23**, **33**, and the initial hit **2**, are shown in Table 5. A high rate of clearance (CL) was observed for compound **2** (10.0 L/h/kg) following iv dosing; however, compounds **23** and **33** exhibited relatively low rates of clearance (1.9 and 0.8 L/h/kg, respectively). Although the rate of clearance for compound **23** was lower than that for compound **2**, the volume of distribution was also lower (V_{ss} = 1.7 L/kg), consequently no improvement in half-life relative to compound **2** was observed. In contrast, compound **33** demonstrated low clearance (0.8 L/h/kg), combined with a high volume of distribution (5.4 L/kg), resulting in an overall increase in half-life over compound **2** (6.3 vs 2.3 h).

The results from PK studies in rats dosed orally (po) with suspensions of compounds **2**, **23**, and **33** are summarized in Table 6. While the oral bioavailability of compounds **2** and **23** was low (F_{oral} = 6% and 3%, respectively), compound **33** was well absorbed with a bioavailability of 40%. The maximum plasma concentration (C_{max}) following po dose for compound **33** was 347 ng/mL at 4.7 h, which was significant improvement over compounds **2** (C_{max} = 13 ng/mL at 1.3 h) and **23** (C_{max} = 17 ng/mL at 1.0 h).

In conclusion, through SAR studies based on compound **2**, we identified a novel class of imidazole analogs as

Table 4. Structures and assay results of analogs **23**, **32**, and **33**



Compound	R^1	R^2	R^3	R^4	rTRPVI (Cap)[a] IC_{50} ± SEM (nM)	rTRPVI (pH 5)[a] IC_{50} ± SEM (nM)
23	H	CF_3	H	3,4,5-Trifluoro	7 ± 2	20 ± 3
32	CH_2OH	Cl	(*R*)-Me	Ph	26 ± 3	29 ± 2
33	CH_2OH	Cl	(*R*)-Me	3,4,5-Trifluoro	1 ± 0.4	4 ± 0.4

[a] The inhibition assays were carried out in rat TRPV1 channel expressed in CHO cells. Results are the average of atleast two independent experiments with three replicates at each concentration.

Table 5. Mean pharmacokinetic parameters following intravenous dose[a] in Sprague–Dawley rats[b] of compounds **2**, **23**, and **33**

Compound	AUC_{0-inf} (ng h/mL)	CL (L/h/kg)	$t_{1/2}$ (h)	V_{ss} (L/kg)
2	105	10.0	2.3	5.0
23	529	1.9	1.9	1.7
33	1233	0.8	6.3	5.4

[a] Dosed at 1 mg/kg as a solution in DMSO.
[b] $n = 3$ animals per study.

Table 6. Mean pharmacokinetic parameters following oral dose[a] in Sprague–Dawley rats[b] of compounds **2**, **23**, and **33**

Compound	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-inf} (ng h/mL)	Bioavailability *F*(%)
2	13	1.3	30	6
23	17	1.0	80	3
33[c]	347	4.7	2456	40

[a] Dosed at 5 mg/kg as a suspension in 5% Tween 80 in Oraplus.
[b] $n = 2$ animals per study.
[c] $n = 3$ animals per study.

potent and orally bioavailable TRPV1 antagonists. Discovery of analogs **23** and **33** supported our hypothesis that the 4,5-biarylimidazole core could serve as an alternative to the previously disclosed benzimidazole core.[8] We were able to achieve 100-fold improvement in the capsaicin-mediated assay and 50-fold improvement in the acid-mediated cell assay compared to the initial compound **2**. In addition, we found that 3′-chloro-5′-hydroxymethylpyridine substitution on the (*R*)-2-methylpiperazine ring resulted in the most potent analog **33**, which also had a significantly improved pharmacokinetic profile over compounds **2** and **23**.

Acknowledgments

We thank our colleagues Vellarkad N. Viswanadhan, Sekhar Surapaneni, Annette Bak, and their co-workers in the molecular structure, PKDM, and pharmaceutics departments, respectively. We also acknowledge Randy Hungate, Paul J. Reider, H. Christian Fibiger, and Jean-Claude Louis for their support.

References and notes

1. Vanilloid receptor-1 is referred to as TRPV1 in this report according to the recently adopted nomenclature: Montell, C.; Birnbaumer, L.; Flockerzi, V.; Bindels, R. J.; Bruford, E. A.; Caterina, M. J.; Clapham, D. E.; Harteneck, C.; Heler, S.; Julius, D.; Kojima, I.; Mori, Y.; Penner, R.; Prawitt, D.; Scharenberg, A. M.; Schultz, G.; Shimizu, N.; Zhu, M. X. *Mol. Cell* **2002**, *9*, 229.
2. Nagy, I.; Santha, P.; Jancso, G.; Urban, L. *Eur. J. Pharmacol.* **2004**, *500*, 351.
3. Smart, D.; Gunthrope, M. J.; Jerman, J. C.; Nasir, S.; Gray, J.; Muir, A. I.; Chambers, J. K.; Randal, A. D.; Davis, J. B. *Br. J. Pharm.* **2000**, *129*, 227.
4. Hwang, S. W.; Cho, H.; Kwak, J.; Lee, S.-Y.; Kang, C.-J.; Jung, J.; Cho, S.; Min, K. H.; Suh, Y.-G.; Kim, D.; Oh, U. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 6155.
5. Caterina, M. J.; Julius, D. *Annu. Rev. Neurosci.* **2001**, *24*, 487.
6. (a) Szallasi, A.; Appendino, G. *J. Med. Chem.* **2004**, *47*, 2717; (b) Valenzano, K. J.; Sun, Q. *Curr. Med. Chem.* **2004**, *11*, 3185; (c) Rami, H. K.; Gunthorpe, M. J. *Drug Discov. Today: Ther. Strateg.* **2004**, *97*, 1; (d) Lopez-Rodriguez, M. L.; Viso, A.; Ortega-Gutierrez, S. *Mini Rev. Med. Chem.* **2003**, *733*, 3.
7. (a) Caterina, M. J.; Leffler, A.; Malmberg, A. B.; Martin, W. J.; Trafton, J.; Petersen-Zeitz, K. R.; Koltzenburg, M.; Basbaum, A. I.; Julius, D. *Science* **2000**, *288*, 306; (b) Davis, J. B.; Gray, J.; Gunthrope, M. J.; Hatcher, J. P.; Davey, P. T.; Overend, P.; Harries, M. H.; Latcham, J.; Clapham, C.; Atkinson, K.; Hughes, S. A.; Rance, K.; Grau, E.; Harper, A. J.; Pugh, P. L.; Rogers, D. C.; Bingham, S.; Randall, A.; Sheardown, S. A. *Nature* **2000**, *405*, 183.
8. Ognyanov, V. I.; Chenera, B.; Bannon, A. W.; Bo, Y.; Dominguez, C.; Fotsch, C.; Gore, V. K.; Klionsky, L.; Ma, V. V.; Qian, Y.; Tamir, R.; Wang, X.; Xi, N.; Xu, S.; Zhu, D.; Gavva, N.; Treanor, J. J. S.; Norman, M. H. *J. Med. Chem.* **2006**, *49*, 3719.
9. Nishimura, T.; Kitajima, K. *J. Org. Chem.* **1979**, *44*, 818.
10. Batey, R. A.; Ramsden, P. D.; Powell, D. A. *J. Org. Chem.* **2003**, *68*, 2300.
11. (a) Rieke, R. D.; Wehmeyer, R. M.; Zhu, L. *J. Org. Chem.* **1991**, *56*, 1445; (b) Rieke, R. D.; Hanson, M. V.; Brown, J. D. *J. Org. Chem.* **1996**, *61*, 2726.
12. Izawa, Y.; Tatsugi, J. *Syn. Comm.* **1998**, *28*, 859.
13. Ertan, M.; Dalkara, S.; Calis, U. *Arzneim.-Forsch./Drug Res.* **1992**, *42*, 592.
14. Buchwald, S. L.; Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. *J. Org. Chem.* **2000**, *65*, 1158.
15. Balan, C.; Bo, Y.; Dominguez, C.; Fotsch, C.; Gore, V. K.; Ma, V. V.; Norman, M. H.; Ognyanov, V. I.; Qian, Y.; Wang, X.; Xi, N.; Xu, S. Benzimidazole derivatives and their use as vanilloid receptor ligands. WO 04035549-A1, 2004.