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4-(2-Pyridyl)piperazine-1-benzimidazoles as potent TRPV1 antagonists

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Abstract—A series of 4-(2-pyridyl)piperazine-1-benzimidazole analogues based on compound **1** was synthesized and evaluated for TRPV1 antagonist activity in capsaicin-induced (CAP) and pH 5.5-induced (pH) FLIPR assays in a human TRPV1-expressing HEK293 cell line. Potent TRPV1 antagonists were identified through SAR studies. From these studies, several antagonists were found, with IC_{50} values ranging from 32 nM to ~5000 nM. Among these, **11** [IC_{50} = 90 nM (CAP) and 104 nM (pH)] was further evaluated and found to be orally available in rats ($F\%$ = 19.7).

The ability of capsaicin (CAP) (Fig. 1), the pungent ingredient of hot chili peppers, and related 'vanilloid' analogs of CAP such as resiniferatoxin (RTX), to activate mammalian nociceptors and cause pain has been known for some time.[1,2] The mechanism of action is now known to be the result of the gating of a highly Ca^{2+}-permeable, nonselective cation channel, the transient receptor potential TRPV1 vanilloid receptor, originally known as the VR1 receptor.[3] The results of knockout studies in rodents lacking the TRPV1 gene[4,5] and recent pre-clinical data using TRPV1 antagonists[6] clearly point to the potential of developing therapeutics based on the antagonism of the receptor for treatment of both inflammatory and neuropathic pain.

In addition to capsazepine (CPZ) (Fig. 1), a competitive TRPV1 antagonist that has been well characterized,[7] several classes of potent synthetic antagonists have been published recently.[8–12] Some of the representative structures are shown in Figure 1.

In this paper, we report for the first time a series of 4-(2-pyridyl)piperazine-1-benzimidazoles as potent TRPV1 antagonists. Our work was initiated with compound **1** (Fig. 1),[12] a potent and orally bioavailable TRPV1 antagonist (IC_{50} value: 35 nM, $F\%$ = 15). To further expand on the SAR, we designed analogs with isostere replacements of the urea moiety. One such transformation is depicted in Figure 2. By incorporation of the urea with the benzene moiety, we designed novel benzimidazole analogs. The synthetic route for such compounds is described in Scheme 1. The synthesis of compounds in the benzimidazole series started with commercially available phenenediamine **3**. Treatment of **3** with DCI in refluxing THF gave urea **4**, which was then converted to intermediate 2-chlorobenzimidazole **5**. Dichloropyridine **6** was treated with piperazine **7** at 80 °C to give compound **8**. The coupling between **5** and **8** was accomplished at high temperature. A mixture of **5** and **8** in *p*-xylene was heated in a sealed tube at 145 °C for 3 days to give the desired products **9**–**21**.

All final compounds were purified to >97%. The purity of the compounds was determined by RP-HPLC and correct molecular weight was confirmed by mass spectrometry (LC/MS with an electrospray sample inlet system).[13] Structures were further confirmed by ^1H NMR spectroscopy.[14]

The compounds were evaluated for TRPV1 antagonist activity based on their ability to block CAP-induced activation or low pH-induced activation of the human TRPV1 channel in a HEK293 cell line. The tests were carried out measuring CAP- or pH-mediated calcium

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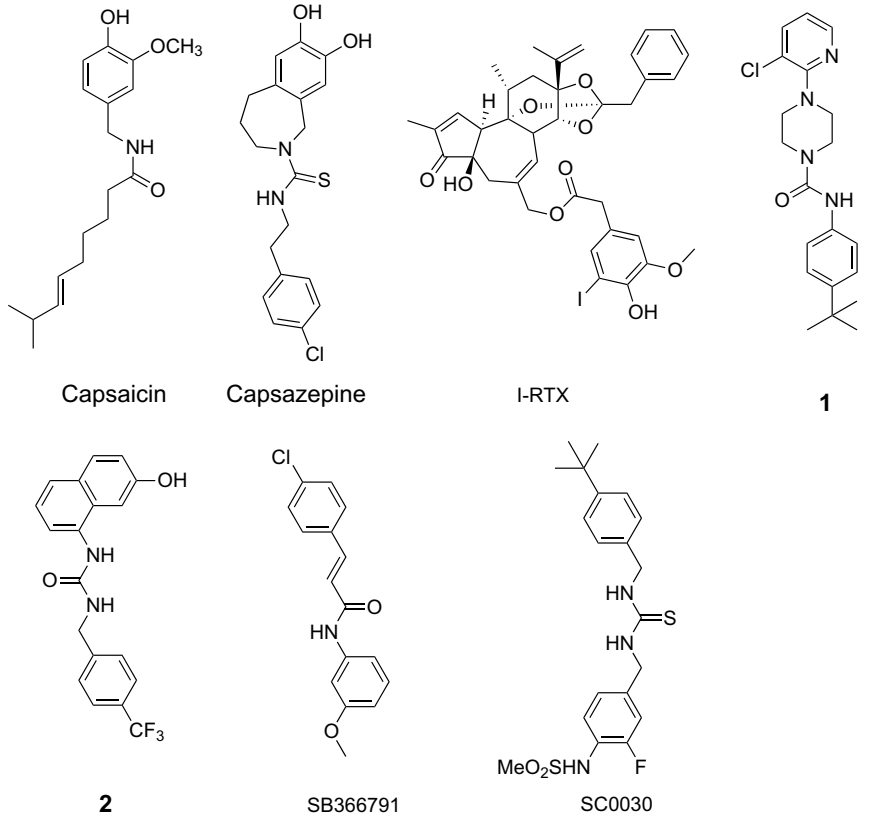


Figure 1. Structures of capsaicin, capsazepine, and other known TRPV1 antagonists.

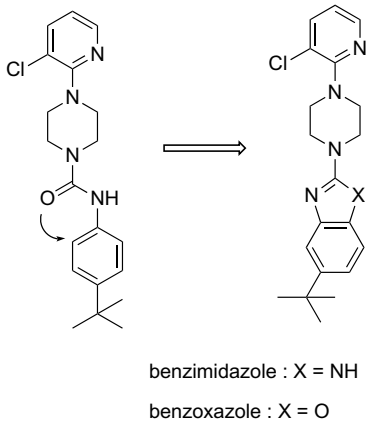
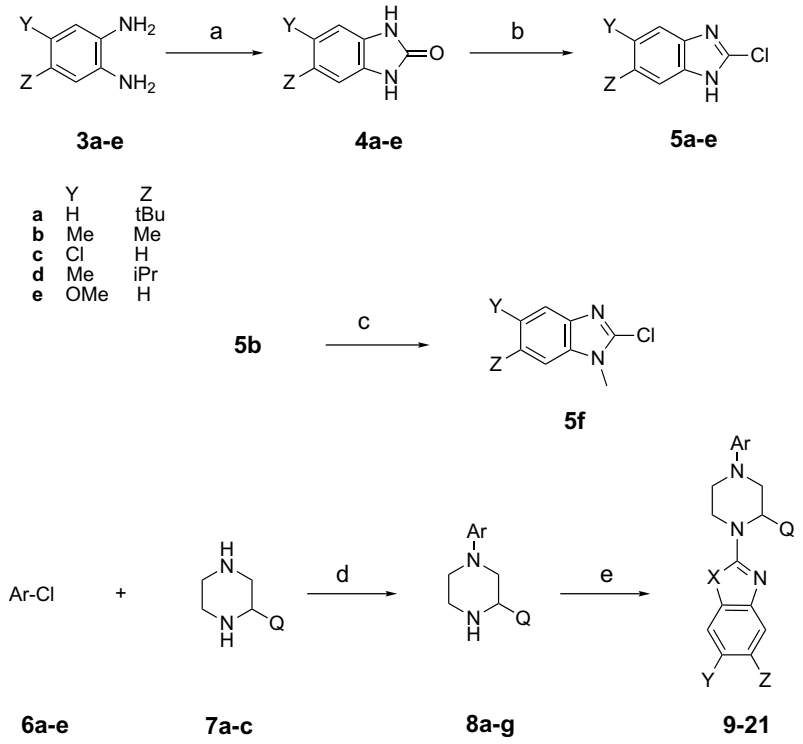


Figure 2. Design of benzimidazoles and benzoxazoles from **1**.

influx with a fluorometric imaging plate reader (FLIPR), in which either 100 nM CAP or pH 5.5 were used as agonists for the respective assays.

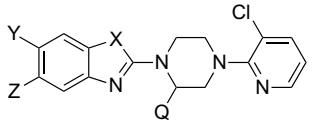
The benzimidazole series attracted further attention when the first member of this series, compound **9** proved to be active in the human CAP assay but moderate in human pH assay (Table 1). We investigated the effect of introducing an asymmetric center into the piperazine ring by utilizing the commercially available 2-(*R*)-methyl piperazine (**7b**) and 2-(*S*)-methyl piperazine (**7c**), in the synthesis of target molecules. As shown in Table 1, the presence of the asymmetric center in the middle piperazine ring plays an important role for the potency of the compounds. If the methyl in the piperazine is in the same configuration as in **7b**, the potencies of the resulting compounds were enhanced; that is, **11** ($IC_{50} = 90 \pm 28$ nM) and **13** ($IC_{50} = 113 \pm 42$ nM) were more potent than **9** ($IC_{50} = 136 \pm 29$ nM), and **10** ($IC_{50} = 726 \pm 99$ nM), respectively. The effect of enhancement on potency by the (*R*)-methyl is even more obvious in human pH assay, where **11** ($IC_{50} = 104 \pm 41$ nM) is 16-fold more potent than **9** ($IC_{50} = 1688 \pm 344$ nM). However, if the methyl in the piperazine is in the configuration as in **7c**, the potencies of the resulting compounds were diminished; that is, **12** and **14** were much less potent than **9** and **10**, respectively.

We then investigated the effect of subsequent change of the substitution on the benzene ring of the benzimidazole. When **9**, the first member of the series was designed, we intentionally retained the *t*-butyl group of **1** because of its importance uncovered in the urea series.[12] We suspect that substitution on the benzene ring of the benzimidazole series might also play a critical role in potency. As anticipated, when *t*-butyl was replaced with chlorine, the potency of **15** was decreased about threefold compared to **11**. When replaced with methoxy group, the potency of **16** decreased further, about fivefold compared to **11**. We further probed additional substitution patterns on the benzene ring with compounds **10**, **13**, **14**. It was found that disubstitution on the benzene ring



Scheme 1. Reagents and conditions: (a) CDI, THF, reflux, 4 h. (b) $POCl_3$, DBU, reflux. (c) NaH, DMF, MeI. (d) DIEA, acetonitrile, reflux. (e) **5**, *p*-xylene, 145 °C.

Table 1. Variation of substitution on the benzene ring and piperazine ring



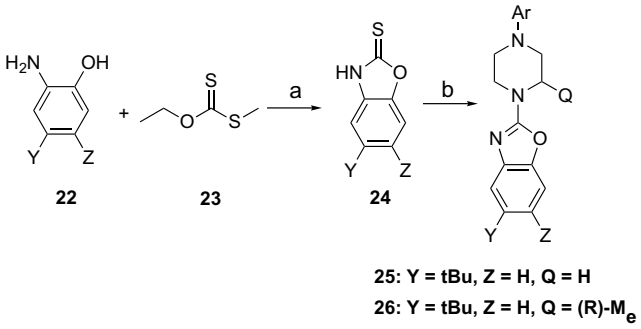
No.	X	Y	Z	Q	IC_{50} (nM) human CAP	IC_{50} (nM) human pH
9	NH	*t*-Bu	H	H	136 ± 29	1688 ± 344
10	NH	Me	Me	H	726 ± 99	>25,000
11	NH	*t*-Bu	H	(*R*) Me	90.4 ± 28.1	104 ± 41
12	NH	*t*-Bu	H	(*S*) Me	948 ± 222	3608 ± 988
13	NH	Me	Me	(*R*) Me	113 ± 42	10,000 ± 2442
14	NH	Me	Me	(*S*) Me	5773 ± 2803	>25,000
15	NH	Cl	H	(*R*) Me	325 ± 116	—
16	NH	OMe	H	(*R*) Me	665 ± 226	—
17	N-Me	Me	Me	H	5447 ± 2059	>25,000
18	N-Me	Me	Me	(*R*) Me	3128 ± 1671	—
25	O	H	*t*-Bu	H	2143 ± 952	>10,000
26	O	H	*t*-Bu	(*R*) Me	305 ± 92	1409 ± 767

IC_{50} values are the mean ± SEM of at least three determinations.

was tolerated as demonstrated, but a decrease in potency was observed. The potency for **10** is approximately sixfold less than **9**. Once again, we observed the significant influence of an asymmetric center in the piperazine ring on potency. In the human CAP assay, compound **13** (IC_{50} = 113 ± 42 nM), with (*R*)-methyl configuration as **7b**, is equipotent to **11** (IC_{50} = 90.4 ± 28.1 nM), sixfold more potent than **10** (IC_{50} = 726 ± 99 nM), and almost 50-fold more potent than its enantiomer **14** (IC_{50} = 5773 ± 2803 nM). In general, appropriate substitution on the benzene ring of the benzimidazole seems required in this series to maintain potency.[15]

We further investigated the importance of the NH of the benzimidazole in determining the potency of the compounds. It was found that in the CAP assay the potency of **17** (IC_{50} = 5447 ± 2059 nM) was reduced almost eightfold compared to **10** (IC_{50} = 726 ± 99 nM). Note that the introduction of a (*R*)-methyl group on the piperazine ring (**18**) that benefits other members of the series does not compensate the detrimental effect of the N-methylation; **18** (IC_{50} = 3128 ± 1671 nM) is about 27-fold less potent than **13** (IC_{50} = 113 ± 42 nM).

To further illustrate the importance of the NH in benzimidazole, we replaced it with an oxygen atom to

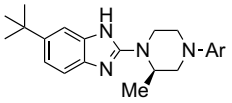


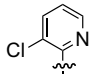
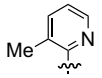
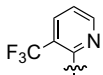
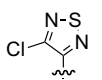
Scheme 2. Reagents and conditions: (a) ethanol, reflux. (b) **8**, *p*-xylene, 145 °C.

generate benzoxazoles (Fig. 2). The synthesis of corresponding benzoxazoles is shown in Scheme 2. It started with commercially available aminophenols **22**. Treatment of **22** with O-ethyl-S-methyl dithiocarbonate **23** at reflux in ethanol gave **24**, which was used without purification in the following step. As in the benzimidazole series, the desired benzoxazoles **25** and **26** were obtained when the mixture of **24** and **8** was heated at high temperature. It was found that the potency of **25** was significantly decreased, 15-fold compared to **9**. With the beneficial configuration of (*R*)-methyl group in the piperazine, the potency of **26** (IC_{50} = 305 ± 92 nM) in the CAP assay was recovered compared to **25** (IC_{50} = 2143 ± 952 nM), but was still much less active than **11** (IC_{50} = 90 ± 28 nM).

It is known that changes in the hetero aromatic ring can also influence the potency of compounds.[12] With that in mind, we also investigated a few different hetero aromatic moieties that are known to maintain or improve potency in other series (Table 2). When the chloropyridine in **11** (IC_{50} = 90.4 ± 28.1 nM) was replaced with a methyl pyridine in **19** (IC_{50} = 70.4 ± 19.1 nM), the potency in the CAP assay increased slightly. The potency increased threefold when a trifluoromethylpyridine was used for **20** (IC_{50} = 32.4 ± 9.0 nM). It would appear that

Table 2. Variation of aromatic ring



No.	Ar	IC_{50} (nM) human CAP	IC_{50} (nM) human pH
11		90.4 ± 28.1	104 ± 41
19		70.4 ± 19.1	597 ± 150
20		32.4 ± 9.0	1778 ± 672
21		776 ± 255	>10,000

IC_{50} values are the mean ± SEM of at least three determinations.

Table 3. PK parameters of compound **11** following single 3 mg/kg iv and 30 mg/kg oral dose

Vd	6.87 L/kg
CL	8.02 L/h/kg
$t_{1/2}$	0.59 h
F%	19.7

electronic factors play a role in the increased potency for **20**. Finally a chloro thiadiazole was introduced for **21**, and this significantly reduced potency, about sevenfold. In contrast to that observed in the human CAP assay, all replacements of the original chloropyridine resulted in a decrease in potency in the human pH assay.

Within this series, **11** was selected for in vivo pharmacokinetic (PK) study in rat. The in vivo profile of **11** is summarized in Table 3. The PK study was designed to estimate systemic drug exposure following a single 3 mg/kg iv and 30 mg/kg oral administration to rats. Following iv administration, compound **11** showed a moderate terminal half life ($t_{1/2}$ = 0.6 h), due to its relatively rapid clearance (CL = 8.0 L/h/kg). Following oral administration of 30 mg/kg, compound **11** was slowly absorbed (T_{max} = 3 h, C_{max} = 300 ng/mL). More importantly, the oral dosing confirmed that **11** was orally bioavailable (F% = 19.7), similar to lead **1** (F% = 15).

In summary, we have prepared a series of TRPV1 antagonists based on the lead compound **1**. The SAR studies uncovered some important factors for the design of potent TRPV1 antagonists in the benzimidazole series. In addition, we have identified a compound from this series, **11**, that is orally available in rats.

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References and notes

1. Szallasi, A.; Blumberg, P. M. *Pharmacol. Rev.* **1999**, *51*, 159.
2. Caterina, M. J.; Julius, D. *Annu. Rev. Neurosci.* **2001**, *24*, 487.
3. Montell, C.; Bringbaumer, L.; Flockerzi, V. *Cell* **2002**, *108*, 595.
4. Davis, J.; Gray, J.; Gunthorpe, M.; Hatcher, J.; Davey, P.; Overend, P.; Harries, M.; Latchman, J.; Clapham, C.; Atkinson, K.; Hughes, S.; Rance, K.; Grau, E.; Harper, A.; Pugh, P.; Rogers, D.; Bingham, S.; Randall, A.; Sheardown, S. *Nature* **2000**, *405*, 183.
5. Caterina, M. A.; Malmberg, A.; Martin, W.; Trafton, J.; Petersen-Zeitz, K.; Koltzenburg, M.; Basbuam, A.; Julius, D. *Science* **2000**, *288*, 306.
6. Pomonis, J.; Harrison, J.; Mark, L.; Bristol, D.; Valenzano, K.; Walker, K. *J. Pharmacol. Exp. Ther.* **2003**, *306*, 387.
7. Walpole, C. S. J.; Bevan, S.; Bovermann, G.; Boelsterli, J. J.; Breckenridge, R.; Davis, J. W.; Hughes, G. A.; James,

I.; Oberer, L.; Wunter, J.; Wrigglesworth, R. *J. Med. Chem.* **1994**, *37*, 1942.
8. Gunthorpe, M.; Rami, H.; Jerman, J.; Smart, D.; Gill, C.; Soffin, E.; Hannan, S.; Lappin, S.; Egerton, J.; Smith, G.; Worby, A.; Howett, L.; Owen, D.; Nasir, S.; Davies, C.; Thompson, M.; Wyman, P.; Randall, A.; Davis, J. *Neuropharmacology* **2004**, *46*, 133.
9. Seabrook, G.; Sutton, K.; Jarolimek, W.; Hollingworth, G.; Teague, S.; Webb, J.; Clark, N.; Boyce, S.; Kerby, J.; Ali, Z.; Chou, M.; Middleton, R.; Kaczorowski, G.; Jones, A. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 1052.
10. Suh, Y.; Lee, Y.; Min, K.; Park, O.; Seung, H.; Kim, H.; Park, H.; Choi, J.; Lee, J.; Kang, S.; Oh, U.; Koo, J.; Joo, Y.; Kim, S.; Kim, J.; Park, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4389.
11. McDonnell, M.; Zhang, S.; Nasser, N.; Dubin, A.; Dax, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 531.
12. Sun, Q.; Tafesse, L.; Islam, K.; Zhou, X.; Victory, S.; Zhang, C.; Hachicha, M.; Schmid, L.; Patel, A.; Rotshteyn, Y.; Valenzano, K.; Kyle, D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3611.
13. LC–MS was performed on an Agilent Series 1100 MSD instrument with an electrospray sample inlet system. HPLC profile generated on an Eclipse XDB-C18 rapid resolution 4.6 × 50 mm column with a gradient of 85:15 to 10:90 of 0.1% TFA/acetonitrile with 0.1% TFA and UV detection at 260 nm.
14. NMR and MS data for compounds in Table 1 and Table 2. Compound **9**: ^{1}H NMR (400 MHz): (CD_3OD) δ 8.21 (dd, 1H, J = 1.6, 4.8 Hz), 7.77 (dd, 1H, J = 1.6, 7.6 Hz), 7.34 (d, 1H, J = 2 Hz), 7.21 (dd, 1H, J = 0.4, 8.4 Hz), 7.14 (dd, 1H, J = 2, 8.4 Hz), 7.01 (dd, 1H, J = 4.8, 7.6 Hz), 3.70 (m, 4H), 3.49 (m, 4H), 1.37 (s, 9H). MS: 370.2 (MH^+). Compound **10**: (CD_3OD) δ 8.25 (dd, 1H, J = 1.6, 4.8 Hz), 7.82 (dd, 1H, J = 1.6, 8 Hz), 7.06 (dd, 1H, J = 4.8, 7.6 Hz), 3.82 (m, 4H), 3.58 (m, 4H), 2.38 (s, 6H). MS: 342.1 (MH^+). Compound **11**: (CD_3OD) δ 8.22 (dd, 1H, J = 1.6, 4.8 Hz), 7.78 (dd, 1H, J = 1.6, 7.6 Hz), 7.33 (dd, 1H, J = 0.8, 2 Hz), 7.19 (dd, 1H, J = 0.8, 8.4 Hz), 7.12 (dd, 1H, J = 1.6, 8.4 Hz), 7.02 (dd, 1H, J = 4, 8 Hz), 4.37 (m, 1H), 3.84 (m, 3H), 3.58 (m, 1H), 3.20 (dd, 1H, J = 4, 12 Hz), 3.08 (dt, 1H, J = 3.2, 12 Hz), 1.45 (d, 3H, J = 6.4 Hz), 1.37 (s, 9H). MS: 384 (M^+). Compound **12**: (CD_3OD) δ 8.22 (dd, 1H, J = 1.6, 4.8 Hz), 7.78 (dd, 1H, J = 1.6, 7.6 Hz), 7.34 (d, 1H, J = 1.6 Hz), 7.20 (d, 1H, J = 8.4 Hz), 7.13 (dd, 1H, J = 2, 8.4 Hz), 7.02 (dd, 1H, J = 4.8, 8 Hz), 4.36 (m, 1H), 3.85 (m, 3H), 3.60 (dt, 1H, J = 2.8, 12 Hz), 3.20 (dd, 1H, J = 4, 12 Hz), 3.08 (dt, 1H, J = 3.2, 13 Hz), 1.45 (d, 3H, J = 6.4 Hz), 1.37 (s, 9H). MS: 384 (M^+). Compound **13**: (CD_3OD) δ 8.25 (dd, 1H, J = 1.6, 4.8 Hz), 7.82 (dd, 1H, J = 2, 8 Hz), 7.07 (dd, 1H, J = 4.4, 8 Hz), 4.30 (m, 1H), 3.90 (m, 4H), 3.26 (dd, 1H, J = 1.6, 13 Hz), 3.17 (m, 1H), 2.38 (s, 6H), 1.59 (d, 3H, J = 6.8 Hz). MS: 356.1 (MH^+). Compound **14**: (CD_3OD) δ 8.25 (dd, 1H, J = 1.2, 4.4 Hz), 7.81 (dd, 1H, J = 1.6, 7.6 Hz), 7.07 (dd, 1H, J = 4.8, 7.6 Hz), 4.31 (m, 1H), 3.88 (m, 4H), 3.26 (dd, 1H, J = 3.6, 13 Hz), 3.16 (m, 1H), 2.38 (s, 6H), 1.59 (d, 3H, J = 6.4 Hz). MS: 356.1 (MH^+). Compound **15**: (CD_3OD) δ 8.21 (dd, 1H, J = 1.6, 4.8 Hz), 7.78 (dd, 1H, J = 1.6, 7.6 Hz), 7.24 (s, 1H), 7.20 (d, 1H,J = 8 Hz), 7.02 (dd, 1H, J = 4.8, 8 Hz), 7.01 (d, 1H, J = 8 Hz), 4.36 (m, 1H), 3.86 (m, 3H), 3.62 (dt, 1H, J = 3.2, 12 Hz), 3.18 (dd, 1H, J = 2.8, 13 Hz), 3.07 (dt, 1H, J = 3.2, 13 Hz), 1.46 (d, 3H, J = 6.8 Hz). MS: 362.1 (MH^+). Compound **16**: (CD_3OD) δ 8.24 (dd, 1H, J = 1.8, 4.8 Hz), 7.80 (dd, 1H, J = 1.8, 7.9 Hz), 4.31 (m, 1H), 3.91 (m, 2H), 3.80 (dt, 1H, J = 3.5, 12 Hz), 3.25 (dd, 1H, J = 3.2, 12 Hz), 3.15 (dt, 1H, J = 4.0, 12 Hz), 1.56 (d, 3H, J = 6.6 Hz). MS: 358.1 (MH^+). Compound **17**: (CD_3OD) δ 8.23 (dd, 1H, J = 1.6, 4.8 Hz), 7.78 (dd, 1h, J = 2, 8 Hz), 7.27 (br s, 1H), 7.14 (br s, 1H), 7.02 (dd, 1H, J = 4.8, 7.6 Hz), 3.69 (s, 3H), 3.56 (m, 4H), 3.45 (m, 4H), 2.39 (s, 3H), 2.35 (s, 3H). MS: 356.1 (MH^+). Compound **18**: ($CDCl_3$) δ 8.14 (dd, 1H, J = 1.6, 4.8 Hz), 7.54 (dd, 1H, J = 1.6, 8 Hz), 7.36 (s, 1H), 6.96 (s, 1H), 6.80 (dd, 1H, J = 4.8, 8 Hz), 3.70 (m, 1H), 3.55 (m, 2H), 3.33 (m, 3H), 3.15 (m, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 1.18 (s, 3H), 1.09 (d, 3H, J = 6.4 Hz). MS: 370 (MH^+). Compound **19**: ($CDCl_3$) δ 8.17 (d, 1H, J = 4.8 Hz), 7.44 (d, 1H, J = 7.6 Hz), 7.42 (s, 1H), 7.27 (d, 1H, J = 8.4 Hz), 7.13 (d, 1H, J = 8.4 Hz), 6.91 (dd, 1H, J = 4.8, 7.2 Hz), 4.42 (m, 1H), 3.97 (d, 1H, J = 12 Hz), 3.62 (dt, 1H, J = 3.2, 12 Hz), 3.47 (d, 1H, J = 12 Hz), 3.33 (d, 1H, J = 13 Hz), 3.18 (dd, 1H, J = 3.2, 12 Hz), 3.06 (dt, 1H, J = 2.8, 12 Hz), 2.32 (s, 3H), 1.45 (d, 3H, J = 6.8 Hz), 1.33 (s, 9H). MS: 364.2 (MH^+). Compound **20**: ($CDCl_3$) δ 8.49(d, 1H, J = 4.8 Hz), 7.93 (dd, 1H, J = 1.6, 8.0 Hz), 7.42 (s, 1H), 7.26 (d, 1H, J = 8.4 Hz), 7.14 (dd, 1H, J = 1.6, 8.4 Hz), 7.08 (dd, 1H, J = 4.8, 8.0 Hz), 4.37 (m, 1H), 3.89 (d, 1H, J = 12 Hz), 3.64 (dt, 1H, J = 3.2, 12 Hz), 3.56 (d, 1H, J = 13 Hz), 3.45 (d, 1H, J = 13 Hz), 3.37 (dd, 1H, J = 3.6, 12 Hz), 3.17 (dt, 1H, J = 3.2, 12 Hz), 1.39 (d, 3H, J = 6.8 Hz), 1.35 (s, 9H). MS: 418.2 (MH^+). Compound **21**: (CD_3OD) δ 7.34 (s, 1H), 7.20 (d, 1H, J = 8.4 Hz), 7.13 (dd, 1H, J = 1.6, 8.4 Hz),4.38 (m, 1H), 4.05 (br d, 2H, J = 12 Hz), 3.90 (br d, 1H, J = 13 Hz), 3.58 (dt, 1H, J = 3.6, 12 Hz), 3.27 (dd, 1H, J = 3.6, 12 Hz), 3.20 (dt, 1H, J = 3.6, 12 Hz), 1.43 (d, 3H, J = 6.4 Hz), 1.37 (s, 9H). MS: 391.1 (MH^+). Compound **25**: ($CDCl_3$) δ 8.23 (dd, 1H, J = 1.6, 4.8 Hz), 7.65 (dd, 1H, J = 2, 7.6 Hz), 7.46 (d, 1H, J = 1.6 Hz), 7.20 (dd, 1H, J = 0.4, 8.4 Hz), 7.10 (dd, 1H, J = 2, 8.4 Hz), 6.91 (dd, 1H, J = 5.2, 7.6 Hz), 3.88 (m, 4H), 3.50 (m, 4H), 1.37 (s, 9H). MS: 371.1 (MH^+). Compound **26**: ($CDCl_3$) δ 8.23 (dd, 1H, J = 1.6, 4.8 Hz), 7.65 (dd, 1H, J = 2, 7.6 Hz), 7.47 (d, 1H, J = 2 Hz), 7.20 (d, 1H, J = 8.4 Hz), 7.10 (dd, 1H, J = 2, 8.4 Hz), 6.91 (dd, 1H, J = 4.8, 8 Hz), 4.60 (m, 1H), 4.60 (d, 1H, J = 13 Hz), 3.84 (m, 2H), 3.67 (dt, 1H, J = 3.6, 13 Hz), 3.17 (dd, 1H, J = 4, 12 Hz), 3.08 (dt, 1H, J = 3.2, 12 Hz), 1.52 (d, 3H, J = 6.8 Hz), 1.37 (s, 9H). MS: 385.2 (MH^+).
15. Unpublished results indicated that if there is no substitution on the benzene ring the resulting benzimidazoles are inactive toward the TRPV1 receptor.