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Graphical Abstract

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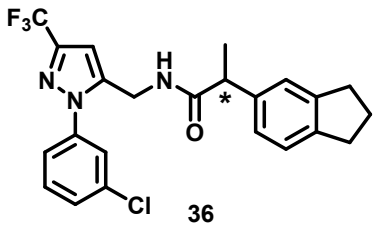

36

	36
In vitro	
CAP (f)K_i	4.1 nM (hTRPV1)
	13.4 nM (mTRPV1)
low pH	weak
heat (45 °C)	weak
Formalin Model	
ED_{50} (1st phase)	0.19 mg/kg
ED_{50} (2nd phase)	0.067 mg/kg
1 mg/kg in 2nd phase	100% MPE

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Discovery of Indane Propanamides as Potent and Selective TRPV1 Antagonists

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ABSTRACT

A series of indane-type acetamide and propanamide analogues were investigated as TRPV1 antagonists. The analysis of structure-activity relationship indicated that indane A-region analogues exhibited better antagonism than did the corresponding 2,3-dihydrobenzofuran and 1,3-benzodioxole surrogates. Among them, antagonist **36** exhibited potent and selective antagonism toward capsaicin for *h*TRPV1 and *m*TRPV1. Further, *in vivo* studies indicated that antagonist **36** showed excellent analgesic activity in both phases of the formalin mouse pain model and inhibited the pain behavior completely at a dose of 1 mg/kg in the 2nd phase.

The transient receptor potential vanilloid 1 (TRPV1), expressed in primary sensory neurons, is a molecular integrator of nociceptive stimuli. It is activated by multiple activators such as noxious heat, low pH, endogenous endovanilloids and natural vanilloids such as capsaicin.[4-7] While TRPV1 represents a promising therapeutic target for the treatment of neuropathic pain and a wide range of other conditions in which C-fiber sensory neurons are involved,[1-3] the extensive efforts directed at the development of potent TRPV1 antagonists[8] have so far yielded no clinical candidates which have advanced to Phase 3 trials. The main obstacle has been mechanism-associated side effects such as hyperthermia or loss of sensitivity to thermal pain. Recent reports indicate that different modes of TRPV1 activation are differentially associated with the pattern of response at the whole animal level, suggesting that ligands with selective modes of antagonism would be of particular interest for avoidance of such side effects.[3,9]

On the basis of the three pharmacophoric regions previously designated for capsaicin, we have investigated an extensive series of 2-(3-fluoro-4-methylsulfonamidophenyl)propanamides as human TRPV1 antagonists (**Figure 1**).[10-21] Among them, antagonists **1** and **2**, the two prototypes of our antagonist, displayed excellent antagonistic activity against multiple activators including capsaicin, *N*-arachidonoyl dopamine (NADA), low pH and heat (45 °C). The antagonism was stereospecific to the *S*-configuration in the propanamide B-region regardless of the C-region. Consistent with the *in vitro* mechanism of action, the compounds antagonized capsaicin-induced hypothermia in mice and demonstrated strong antiallodynic activity in neuropathic pain models. The basis for this high potency was shown by molecular docking studies using our established *h*TRPV1 homology model,[10] indicating that the 6-trifluoromethyl and 2-(4-methylpiperidinyl) groups in the C-region of **1** and the 1-(3-chlorophenyl) and 3-trifluoromethyl groups in the C-region of **2**, respectively, provided the two hydrophobic interactions with the receptor that have been identified as critical for potent antagonism.[10-14]

The analysis of the structure activity relationships (SAR) of the prototype antagonists has focused on the C-region. In the pyridine C-region of **1**, a variety of functional groups including the amino, oxy, thio, alkyl, aryl and sulfonamido groups[10-15] were incorporated at the 2-position, the trifluoromethyl group at the 6 position was substituted with the t-butyl group[16] and the pyridine core was modified by its isomers[17] or replaced by phenyl.[18] In the pyrazole C-region of **2**, 3-trifluoromethyl and 3-chlorophenyl groups were also modified with t-butyl and 3-substituted phenyl groups, respectively.[19] In addition, the SAR of the B-region propanamide group was explored by the substitution with α-substituted acetamide[20] and urea[21] surrogates.

As part of our continuing effort to discover TRPV1 antagonists as clinical candidates for neuropathic pain, we now

have which either acetamide or propanamide was employed as the B-region and a variety of pyridine and pyrazole derivatives previously studied were explored as the C-region (**Figure 1**). In this study, we describe the syntheses of a series of indane, 2,3-dihydrobenzofuran and 1,3-benzodioxole derivatives and characterize their antagonism toward activation of *h*TRPV1 by capsaicin. With the most potent antagonist in the series, we further characterize in detail its *in vitro* activities and evaluate its analgesic activity in the formalin pain model.

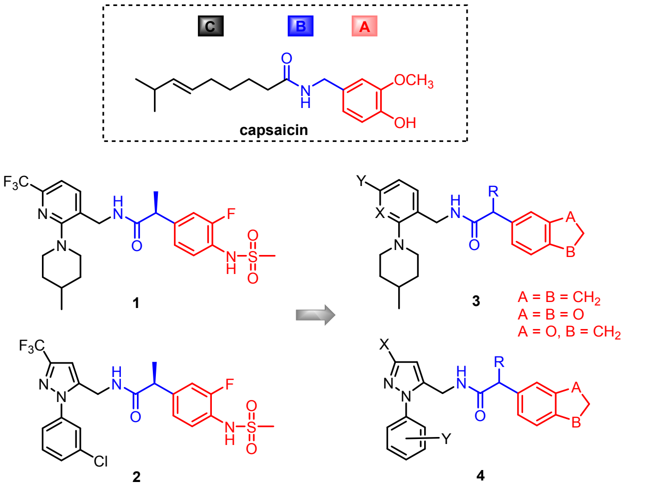
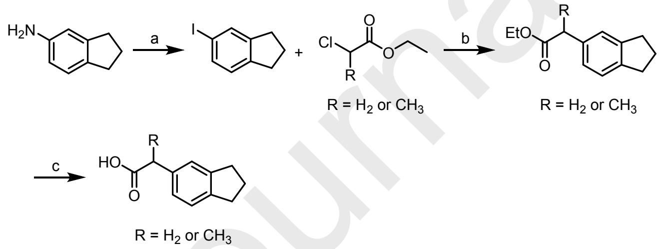
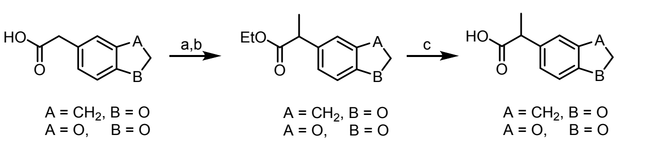


Figure 1. Design of the indane-type A-region analogues

For the synthesis of indane analogues, commercially available 5-aminoindane was converted to 5-iodoindane by the Sandmeyer reaction using sodium nitrite in dilute hydrogen chloride. The Ni-catalyzed cross coupling reaction[22] of 5-iodoindane with either ethyl 2-chloroacetate or ethyl 2-chloropropanoate provided ethyl 2-indanylacetate or ethyl 2-indanylpropanoate which was hydrolyzed to the corresponding acid, respectively (**Scheme 1**).



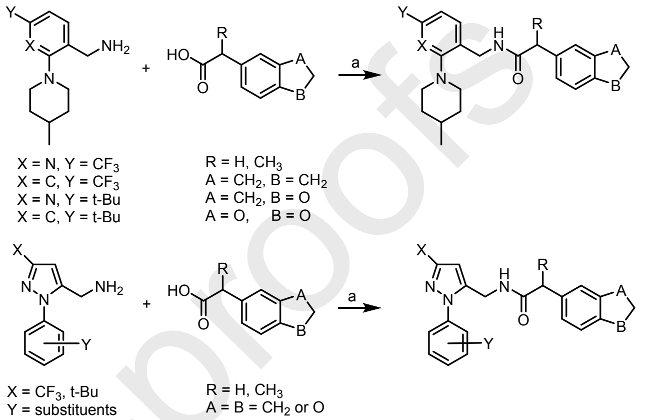
Scheme 1. Synthesis of indane A-region analogues
Reagents and conditions: (a) $NaNO_2$, KI, HCl, H_2O, 0-5 ℃, 2 h, 60%; (b) Mn, $NiBr_2$bipy, CF_3CO_2H, DMF, 50 ℃, 15 h, 30-42%; (c) LiOH, THF:H_2O = 1:1, r.t., 15 h, 83-94%.



Scheme 2. Syntheses of 2,3-dihydrobenzofuran and 1,3-benzodioxole A-region analogues
Reagents and conditions: (a) H_2SO_4, EtOH, reflux, 15 h, 80-89%; (b) NaH, CH_3I, DMF, 0 °C, 1 h, 70-75%; (c) LiOH·H_2O, THF/H_2O (1:1), r.t., 15 h, 90-95%.

1,3-benzodioxole propionate analogues, commercially available dihydrobenzofuran-5-yl acetic acid or benzodioxol-5-yl acetic acid was protected as the corresponding ethyl ester, respectively. The α-methylation of the esters with methyl iodide followed by hydrolysis provided the corresponding propionic acids, respectively (**Scheme 2**).

The prepared acetic/propionic acids corresponding to A/B regions were coupled with the C-region amines previously reported, including pyridine[10,16], phenyl[18], and pyrazole[19] cores using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to provide the final compounds, respectively.

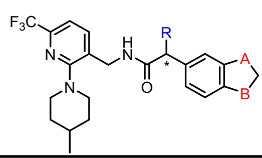


Scheme 3. The synthesis of final compounds
Reagents and conditions: (a) EDC, HOBt, NEt_3, CH_3CN, r.t, 5-15 h, 85-92%.

The *in vitro* assay for TRPV1 antagonism was performed using a fluorometric imaging plate reader (FLIPR) with *h*TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells.[10] The activity of the synthesized compounds was measured by inhibition of TRPV1 activation by capsaicin (100 nM) and expressed as binding affinity ($K_{i(\mathrm{CAP})}$). The results are summarized in **Tables 1-5**.

First, we investigated the antagonistic activities of the six scaffolds of the indan-5-yl, dihydrobenzofuran-5-yl, 1,3-benzodioxol-5-yl acetamide and propanamide. For comparison, the scaffolds were fixed with the same prototype C-region, the 6-trifluoromethyl-2-(4-methylpiperidinyl)pyridin-3-yl group (**Table 1**). Among the representatives studied (**5-10**), indan-5-yl acetamide (**5**) and 1,3-benzo-1,3-dioxol-5-yl acetamide (**9**) exhibited promising antagonism with $K_{i(\mathrm{CAP})}$ = 13.3 and 15.9 nM, respectively.

Table 1. The SAR of the A- and B-regions

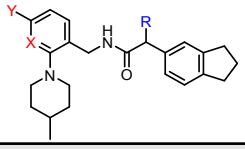


	R	A	B	$K_{i(\mathrm{CAP})}$ (nM)[a]
5	H	CH_2	CH_2	13.3
6	CH_3	CH_2	CH_2	57.4
7	H	CH_2	O	20.5
8	CH_3	CH_2	O	29.7
9	H	O	O	15.9
10	CH_3	O	O	43.8

[a] Values from triplicate experiments

and 1,3-benzodioxole A-region scaffolds. For the SAR of the pyridine C-region, we examined 6-t-butyl pyridine and 6-CF_3/t-butyl phenyl C-region analogues (**11-16**) of the indan-5-yl and 1,3-benzodioxol-5-yl acetamide and propanamide scaffolds (**Tables 2** and **3**). The SAR analysis indicated that, in the indane A-region, only the 6-CF_3 phenyl analogue of indan-5-yl acetamide (**11**) displayed comparable antagonism to that of **5** and, in the 1,3-benzodioxole A-region, any modification of the pyridine did not improve antagonistic activity compared to **9**.

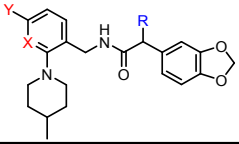
Table 2. The SAR of the pyridine C-region of the indane A-region scaffold



	R	X	Y	$K_{i(CAP)}$ (nM)[a]
5	H	N	CF_3	13.3
11	H	C	CF_3	12.0
12	H	N	t-Bu	39.9
13	H	C	t-Bu	46.5
6	CH_3	N	CF_3	57.4
14	CH_3	C	CF_3	96.4
15	CH_3	N	t-Bu	44.0
16	CH_3	C	t-Bu	61.7

[a] Values from triplicate experiments

Table 3. The SAR of the pyridine C-region of the 1,3-benzodioxole A-region scaffold



	R	X	Y	$K_{i(CAP)}$ (nM)[a]
9	H	N	CF_3	15.9
17	H	C	CF_3	32.4
18	H	N	t-Bu	50.5
19	H	C	t-Bu	22.7
10	CH_3	N	CF_3	43.8
20	CH_3	C	CF_3	17.3
21	CH_3	N	t-Bu	31.4
22	CH_3	C	t-Bu	37.2

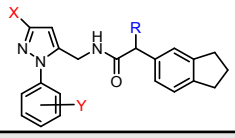
[a] Values from triplicate experiments

Next, we investigated the SAR of the pyrazole C-region of the indan-5-yl and 1,3-benzodioxol-5-yl acetamide and propanamide scaffolds. Previously, we demonstrated that 3-CF_3 and 3-t-butyl pyrazole derivatives provided the most potent antagonism among a series of pyrazole C-region derivatives.[19] Therefore, a series of 1-phenyl 3-CF_3/t-butyl pyrazole analogues were explored as the C-region in the indane and benzodioxole A-region analogues (**Tables 4** and **5**).

The SAR analysis of the pyrazole C-region indicated that (1) the 3-substituted phenyl displayed better antagonism than did the corresponding 4-substituted phenyl group at the 1-position. Among them, the 3-chlorophenyl group appeared to be optimal

thyl pyrazoles exhibited full antagonism, 3-t-butylpyrazoles shifted the activity to partial antagonism. (3) The indane A-region analogues displayed better antagonism than did the corresponding 1,3-benzodioxole A-region surrogates.

Table 4. The SAR of the pyrazole C-region of the indane A-region scaffold



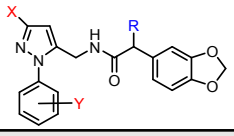
	R	X	Y	$K_{i(CAP)}$ (nM)[a]
23	H	CF_3	3-Cl	5.2
24	H	CF_3	4-F	24
25	H	CF_3	4-Cl	37.8
26	H	t-Bu	3-F	11.2
27	H	t-Bu	3-Cl	2.9
28	H	t-Bu	3-CF_3	7.1
29	H	t-Bu	4-F	49.9
30	H	t-Bu	4-Cl	11.1
31	H	t-Bu	4-CF_3	78.6
32	H	t-Bu	3,4-F_2	12.8
33	H	t-Bu	3-Cl,4-F	7.5
34	H	t-Bu	3,5-Cl_2	15.7
35	CH_3	CF_3	3-F	pAG
36	CH_3	CF_3	3-Cl	4.1
37	CH_3	CF_3	3-CF_3	7.5
38	CH_3	CF_3	4-Cl	45
39	CH_3	CF_3	4-CF_3	51.3
40	CH_3	CF_3	4-OCH_3	WE
41	CH_3	CF_3	4-OCF_3	51.6
42	CH_3	CF_3	3,4-F_2	30.5
43	CH_3	CF_3	3-Cl,4-F	14.7
44	CH_3	CF_3	3,4-Me_2	11.3
45	CH_3	t-Bu	H	pAG
46	CH_3	t-Bu	3-F	pAG
47	CH_3	t-Bu	3-Cl	pAG
48	CH_3	t-Bu	3-CF_3	pAG
49	CH_3	t-Bu	4-F	pAG
50	CH_3	t-Bu	4-Cl	AG
51	CH_3	t-Bu	4-CF_3	62.4
52	CH_3	t-Bu	4-OCH_3	WE
53	CH_3	t-Bu	4-OCF_3	65.9
54	CH_3	t-Bu	3,4-F_2	AG
55	CH_3	t-Bu	3-Cl,4-F	pAG
56	CH_3	t-Bu	3,5-Cl_2	AG

[a] Values from triplicate experiments

Detailed *in vitro* activities of **36**, the most potent antagonist in this series, were investigated for antagonism toward different *h*TRPV1 activators as well as for antagonism against capsaicin in the case of *m*TRPV1. In contrast to the excellent antagonism of *h*TRPV1 activation by capsaicin ($K_{i(CAP)}$ = 4.1 nM), compound **36** exhibited weak antagonism toward low pH (5% inhibition at 10 μM) and heat (45 °C) (15% inhibition at 2.5 μM). As with *h*TRPV1, antagonist **36** also proved to be a highly potent

anta and
with $K_{i(CAP)}$ = 13.4 nM.

Table 5. The SAR of the pyrazole C-region of the 1,3-benzodioxole A-region scaffold



	R	X	Y	$K_{i(CAP)}$ (nM)[a]
57	H	CF_3	3-Cl	28.3
58	H	CF_3	4-F	WE
59	H	CF_3	4-Cl	53.9
60	H	t-Bu	3-F	38.6
61	H	t-Bu	3-Cl	9.2
62	H	t-Bu	3-CF_3	12.2
63	H	t-Bu	4-F	pAG
64	H	t-Bu	4-CF_3	63.2
65	H	t-Bu	4-OCH_3	WE
66	H	t-Bu	4-OCF_3	WE
67	H	t-Bu	3,4-F_2	25.8
68	H	t-Bu	3-Cl,4-F	10.7
69	H	t-Bu	3,5-Cl_2	71
70	CH_3	CF_3	3-F	17.5
71	CH_3	CF_3	3-Cl	11.2
72	CH_3	CF_3	3-CF_3	5.8
73	CH_3	CF_3	4-CF_3	42.5
74	CH_3	CF_3	4-OCF_3	WE
75	CH_3	CF_3	3-Cl,4-F	7.5
76	CH_3	t-Bu	3-Cl	pAG
77	CH_3	t-Bu	4-F	pAG

[a] Values from triplicate experiments

To evaluate the *in vivo* activity of antagonist **36**, we examined its antinociceptive activity in the formalin mouse model.[23] Administration of **36** by intraperitoneal injection demonstrated excellent analgesic activity in both the 1st and 2nd phase in a dose-dependent manner, providing an ED_{50} of 0.19 mg/kg in the 1st phase and 0.067 mg/kg in the 2nd phase, respectively (**Figure 2**). In addition, at a dose of 1 mg/kg, compound **36** was able to inhibit the pain behavior completely in the 2nd phase showing 100% maximal possible effect (%MPE).

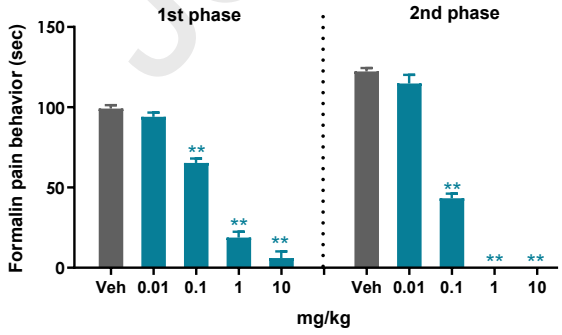


Figure 2. Analgesic activity of **36** in the formalin pain model by i.p. injection

1,3-benzodioxole A-region analogues of potent antagonists **1** and **2** were investigated. Either acetamide or propanamide was employed as the B-region and various pyridine and pyrazole derivatives previously studied were explored in the C-region. The analysis of SAR indicated that the indane A-region scaffold showed better antagonism than did the corresponding 2,3-dihydrobenzofuran and 1,3-benzodioxole scaffolds. The most potent antagonist **36** exhibited potent and selective antagonism toward capsaicin but weak antagonism to low pH and elevated temperature for *h*TRPV1. It also displayed highly potent antagonism to capsaicin for *m*TRPV1. Further *in vivo* studies indicated that antagonist **36** showed excellent analgesic activity in the formalin mouse pain model in both the 1st and 2nd phases and inhibited the pain behavior completely at a dose of 1 mg/kg in the 2nd phase.

Acknowledgments

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