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Chain-branched 1,3-dibenzylthioureas as vanilloid receptor 1 antagonists

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Abstract—A series of chain-branched 1,3-dibenzylthiourea derivatives were synthesized, and tested their antagonist activity against vanilloid receptor 1. Chain-branching led to a significant change in the mode of action and the potency. (*R*)-Methyl or ethyl-branched 1,3-dibenzylthiourea derivatives showed the most potent antagonist activity up to the IC_{50} value of 0.05 μM which is 10-fold more potent than capsazepine.
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Among the several therapeutic approaches for the treatment of pain, main are the modulation of opioid receptors and cyclooxygenase.[1] However, these approaches have undesirable side effects associated with their uses,[2] and this has prompted a search for mechanistically different analgesic agents.[1] In this context, vanilloid receptor 1 (VR1) is at present one of the attractive targets for the discovery of novel analgesics.[3] VR1 is a ligand-gated nonselective cation channel activated by capsaicin. By acting on VR1, capsaicin excites and then desensitizes a subset of primary neurons involved in nociception, neurogenic inflammation, and a variety of local regulatory functions.[4]

Despite the concentrated works on VR1 agonists including capsaicin, their excitatory side effects such as pungency and hypothermia responses could not be separated from the antinociceptive properties.[5] Since the discovery of capsazepine as a first competitive VR1 antagonist,[6] the possibility of VR1 antagonist as an ideal analgesic has been suggested carefully, and followed by the continued efforts to discover the novel antagonists.[7–9]

From our previous work,[8] we found that chain-branching of the acyclic thiocarbamates led to a significant change in the mode of action on VR1, thereby converting the agonist binding mode into the antagonist one. But still, there is a need to develop the more potent VR1 antagonists. As far as we know, thiourea is the most powerful functionality found in VR1 modulators such as SDZ249482 (**2**), capsazepine, MK056 (**3**), and SC0030 (**4**).[9] In line with the previous result, this work was initiated when the thiourea **5**, the methyl-branched form of the strong agonist **1**, was discovered as a VR1 antagonist from our preliminary study. Thus we set about to explore the SAR of chain-branched 1,3-dibenzylthioureas as VR1 antagonist (Fig. 1).

The synthetic routes to various alkyl-branched 1,3-dibenzylthiourea analogues are outlined in Schemes 1–4. The optically active methyl-branched 1,3-dibenzylthioureas (**6–11**, **17–19** and **21**) were chosen as the first targets in order to clarify the stereo effect of the stereogenic center and the substituent effect on the phenyl ring. Scheme 1 shows one-step conversion of the commercially available chiral amines into the corresponding thioureas (**6–11**) using 4-*tert*-butylbenzyl-isothiocyanate in basic conditions.

Scheme 2 depicts the synthesis of the methyl-branched 1,3-dibenzylthioureas having acetamide or methanesulfonamide functionality. The commercially available chiral compound **12** was protected with di-*tert*-butyldi-

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carbonate to give the *N*-Boc^t **13**. Compound **13** was then reduced to the amine **14** by catalytic hydrogenation. The acetylation or mesylation of the amine **14** with acetic anhydride or methanesulfonic anhydride, followed by deprotection of *t*-Boc group with trifluoroacetic acid gave the amine **16**. Compound **16** was then condensed with 4-*tert*-butylbenzylisothiocyanate to furnish the desired compound **17**, **18**, and **19,** respectively. Deprotection of compound **14** with trifluoroacetic acid gave the diamine **20**, which is condensed with 4-*tert*-butylbenzylisothiocyanate to afford compound **21**.

As shown in Scheme 3, a series of the racemic alkyl-branched methanesulfonamide derivatives **26**–**30** were also synthesized in order to gauge the effect of the R on the antagonist activity against VR1. Friedel–Crafts acylation of the methanesulfonamide **22**, followed by reductive amination via oxime **24** afforded the amine **25**.

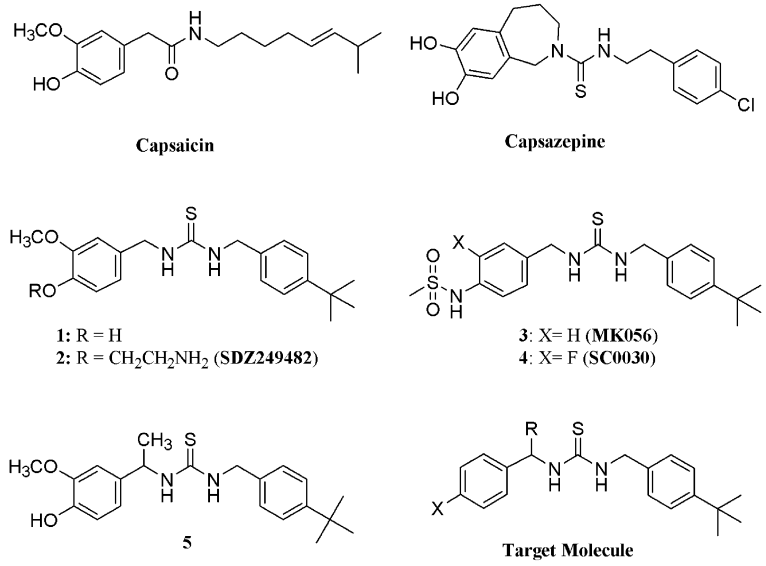
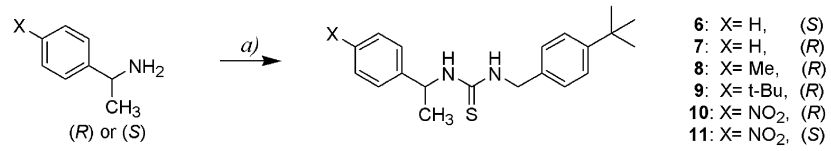
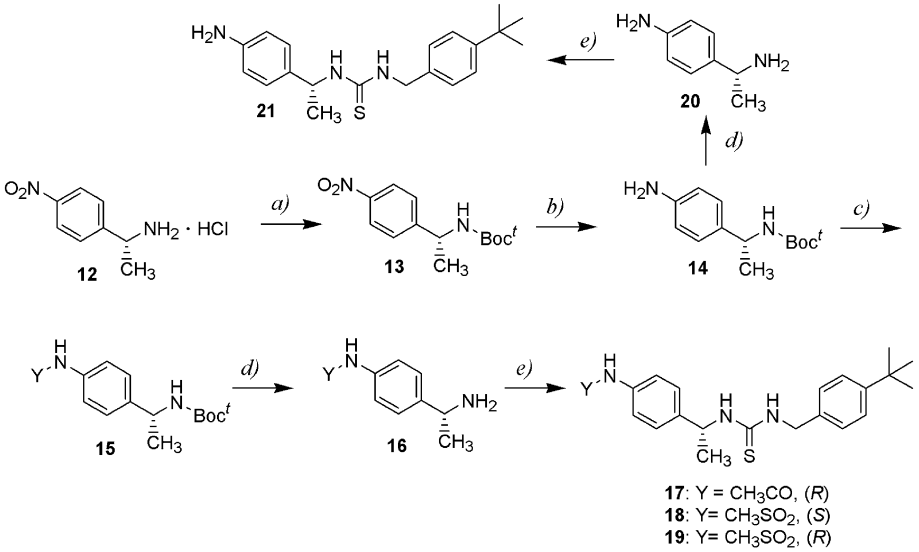


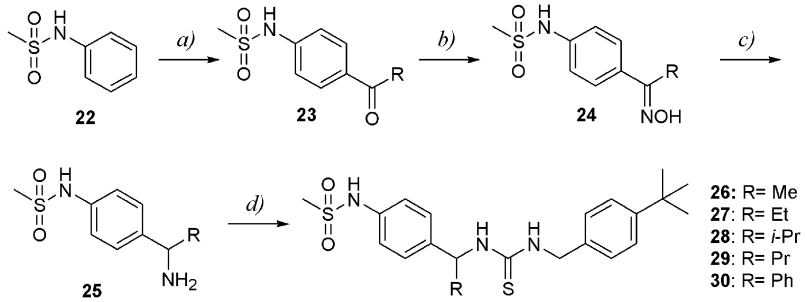
Figure 1. Structures of capsaicin, capsazepine, and 1,3-dibenzylthiourea analogues.



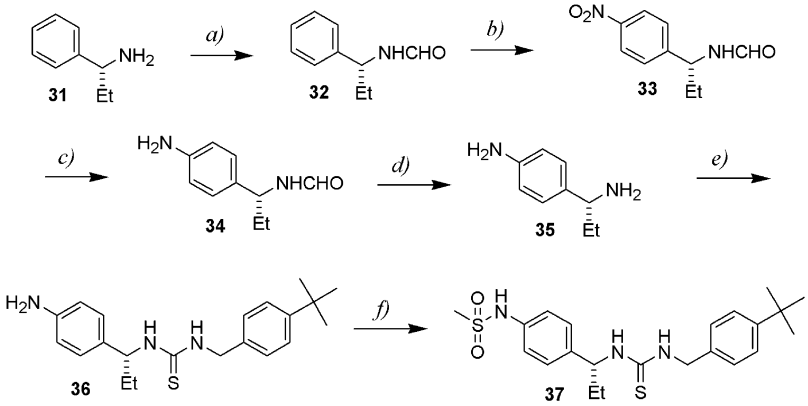
Scheme 1. Reagents and conditions: (a) 4-*tert*-butylbenzylisothiocyanate, triethylamine, CH_2Cl_2, 84–99%.



Scheme 2. Reagents and conditions: (a) di-*tert*-butyldicarbonate, aqueous $NaHCO_3$-CH_2Cl_2, 94%, (b) H_2, Pd-C, MeOH, 95%, (c) acetic anhydride, or methanesulfonic anhydride, pyridine, CH_2Cl_2, (d) CF_3CO_2H, (e) 4-*tert*-butylbenzylisothiocyanate, triethylamine, CH_2Cl_2, 86% (2 steps).



Scheme 3. Reagents and conditions: (a) $(RCO)_2O$, $AlCl_3$, $ClCH_2CH_2Cl$, 35–50%; (b) NH_2OH, HCl, AcONa, 73–94%, (c) H_2, Pd/C, MeOH, 75–95%, (d) 4-*tert*-butylbenzylisothiocyanate, THF, 59–87%.



Scheme 4. Reagents and conditions: (a) formic acid, acetic anhydride, 96%, (b) HNO_3, H_2SO_4, −20 °C, 58%. (c) H_2, Pd/C, MeOH, 88%, (d) 1N-KOH, MeOH, reflux, 77%, (e) 4-*tert*-butylbenzylisothiocyanate, THF, 71%, (f) $(CH_3SO_2)_2O$, pyridine, CH_2Cl_2, −40 °C, 91%.

Compound **25** was then condensed with 4-*tert*-butylbenzylisothiocyanate to furnish the desired compounds **26–30**, respectively.

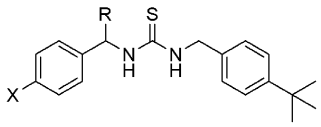
The ethyl-branched (*R*)-isomer **37** was prepared through the route described in Scheme 4. The synthesis started with the commercially available (*R*)-(+)-1-phenylpropylamine (**31**, ChiPros™, 98% ee). Compound **31** was formylated with HCO_2H and acetic anhydride, followed by nitration to afford compound **33**. Hydrogenation of compound **33** with H_2 on Pd/C, followed by deprotection with KOH gave the diamine **35**. Chemoselective formation of the thiourea **36** was successively achieved by treatment of the diamine **35** with 4-*tert*-butylbenzylisothiocyanate at −40 °C. Mesylation of **36** with methanesulfonic anhydride furnished the thiourea **37**.

The biological activities of the 1,3-dibenzylthioureas were evaluated as both agonists and antagonists in the $^{45}Ca^{2+}$-influx assay using the neonatal rat cultured spinal sensory neurons by the method described in the literature.[10] The results are summarized in Table 1.

Stereochemistry of the chiral center is critical. *R*-enantiomers are uniformly more potent than the *S*-enantiomers. The eudismic ratios are ranged from 5 to 50. The substitution on the phenyl ring of 1,3-dibenzylthiourea compounds had a dramatic effect on the potency and selectivity. As we have reported previously,[9] 4-substitution by the methanesulfonamide group changed receptor binding from the agonist mode to the antagonist mode. Until now, this was the only way for the 1,3-dibenzylthiourea compounds to exert the antagonism. Here, however, we found the interesting cases that, if being chain-branched, the 1,3-dibenzylthioureas could retain the antagonist activity even without methanesulfonamide functionality. Most of alkyl-branched compounds in this study possessed the antagonist activity ranged from the IC_{50} value of 25 μM to 0.05 μM. Even without polar substituents on the phenyl ring, compounds **6**, **7**, **8** and **9** showed the antagonist activity. In particular, compound **8** having methyl group on 4-position of phenyl ring showed the comparable antagonist activity as capsazepine did. In view of a general trend that polar substitution on phenyl ring is the primary requisite for receptor binding, this is an unusual phenomenon. Chain-branching appears to be the most important factor for the antagonist activity. Compound **19** having methanesulfonamide group was one of the most potent analogues (IC_{50} = 0.05 μM) found from our SAR studies. This compound is approximately 10-fold more potent than capsazepine. Consistent with the previous result,[9] methanesulfonamide group was found to be the best functionality for 4-position on the phenyl ring.

Having optimized the 4-position of phenyl ring, attention was turned to explore the appropriate alkyl group to maximize the chain-branching effect. At first, we prepared compounds **26–30** into the racemic form for convenience. The examination of the effect of R revealed that the smaller groups showed the better

Table 1. $^{45}Ca^{2+}$-Influx activity of the alkyl-branched 1,3-dibenzylthiourea derivatives



No.	X	R	Absolute configuration	$^{45}Ca^{2+}$ influx activity (μM)[a]	
				Agonist (EC_{50})	Antagonist (IC_{50})
6	H	Me	*S*	>100	25.5
7	H	Me	*R*	>100	4.96
8	CH_3	Me		>100	0.40
9	Bu^t	Me	*R*	>100	3.49
10	NO_2	Me	*R*	>100	0.58
11	NO_2	Me	*S*	>100	14.7
21	NH_2	Me	*R*	>100	3.30
17	CH_3CONH	Me	*R*	>100	3.60
18	CH_3SO_2NH	Me	*S*	>100	1.47
19	CH_3SO_2NH	Me	*R*	>100	0.05
26	CH_3SO_2NH	Me	*Racemate*	>100	0.15
27	CH_3SO_2NH	Et	*Racemate*	>100	0.36
28	CH_3SO_2NH	*i*-Pr	*Racemate*	>100	3.24
29	CH_3SO_2NH	Pr	*Racemate*	>100	1.49
30	CH_3SO_2NH	Phenyl	*Racemate*	>100	16.7
37	CH_3SO_2NH	Et	*R*	>100	0.05
3 (MK056)	CH_3SO_2NH	H	—	>100	0.11
Capsazepine				>100	0.60

[a] EC_{50} (the concentration of derivatives necessary to produce 50% of the maximal response) and IC_{50} values (the concentration of derivatives necessary to reduce to 0.5 μM capsaicin by 50%) were estimated with at least 3 replicates at each concentration. Each compound was tested in two independent experiments. Antagonist data were fitted with a sigmoid function.

antagonist activity than the bulkier ones. The racemic methyl-branched analogue **26** had similar activity compared to the ethyl analogue **27**, whereas the *i*-propyl, propyl, and phenyl analogues **28**–**30** showed weak VR1 antagonist activities. Further investigation of chiral ethyl analogue revealed that (*R*)-ethyl analogue **37** was as potent as (*R*)-methyl analogue **19** with the IC_{50} value of 0.05 μM, suggesting that ethyl group appeared to be the maximum size permitted for R group. Compounds **19** and **37** were also 2-fold more potent as chain-branched 1,3-dibenzylureas compared to non-branched analogue MK056 (**3**), indicating that chain-branching is not detrimental, but beneficial to the potency in the present cases.

In summary, a series of chain-branched 1,3-dibenzylthiourea derivatives were synthesized, and tested their antagonist activity against VR1. The most notable fact is that the agonist could be changed into the antagonist simply by introducing an alkyl chain at the benzylic position of 1,3-dibenzylthioureas. (*R*)-Methyl or ethyl-branched dibenzylthiourea derivatives (**19**, **37**) showed the most potent antagonist activity up to the IC_{50} value of 0.05 μM which is 10-fold more potent than capsazepine. The chain-branching method described here appears to be a promising strategy for the development of a novel antagonist.

Acknowledgements

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