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Chain-Branched Acyclic Phenethylthiocarbamates as Vanilloid Receptor Antagonists

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Abstract—A series of acyclic phenethylthiocarbamate derivatives have been synthesized, and their antagonist effect against vanilloid receptor tested. Chain branching led to a significant change in antagonist activity of the parent molecule. Ethyl-branched **1e** showed a 6.3 μM of IC_{50} value in $^{45}Ca^{2+}$-influx assay.

Capsaicin and its vanilloid analogues have been extensively studied for the development of novel analgesics with entirely different mechanism either from opioids or NSAIDs. By acting on vanilloid receptor (VR1), capsaicin excites and then desensitizes a subset of primary neurons involved in nociception, neurogenic inflammation, and a variety of local regulatory functions.[1] Due to this unique biological activity, VR1 is at present one of the most attractive targets for the treatment of pain.[2] Resiniferatoxin,[3] olvanil,[4] SDZ-249482,[5] and KR-25018[6] are well-known potent VR1 agonists developed to date. However, despite the concentrated effort on agonists, they have been exposed to the side effects such as pungency and/or hypothermia responses.[7] In this context, the possibility of VR1 antagonist as an ideal analgesic has been suggested carefully, and followed by some efforts to discover the novel antagonists in the last decade.[8] In 1994, capsazepine has been developed by Sandoz group as a first competitive VR1 antagonist,[9] however, the utility of capsazepine is limited by its moderate in vivo activity and nonspecificity.[10]

Coupled with the recent cloning of VR1,[11] the renewed interest on VR antagonist prompts us to examine the structural modification of capsazepine. The noticeable difference between the agonist and the antagonist is in their binding mode on VR1. In contrast to the agonist's coplanar conformation, the antagonists are known to have an orthogonal conformation between the vanilloid aromatic ring (A region) and the amide/thiourea bond (B region).[7a]

Our basic strategy for structural modification is to seek the chain-branched acyclic compounds deviated from coplanar conformation with minimal structural disturbance from cyclic capsazepine. Due to their flexibility, acyclic compounds are often better than the corresponding rigid cyclic ones to achieve the pharmacophoric conformation. However, all of the acyclic vanilloid compounds known to date act as receptor agonists. In this sense, the development of acyclic vanilloid compounds with antagonist activity looks like a very difficult task to be achieved, but if possible, is of importance in this research field. Here, we examined the chain branching method as a solution for the above-mentioned two incompatible facts. Chain branching often interferes with receptor binding by steric effect, thereby reducing the potency or altering the pharmacological profiles of the ligand. It is anticipated that chain branching may destabilize the agonist binding mode (conformation) of acyclic vanilloid compounds for steric reason, thereby

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leading to more favorable conformation for antagonist binding mode. As shown in Figure 1, a series of compounds **1a–s** were designed as the first targets for preparation.

A series of the thiocarbamate compounds with a systemic variation of the alkyl groups have been synthesized in order to gauge the effect of the R_1 on the antagonist activity of these compounds against VR1 receptor. The thiocarbamates **1b**, and **1d–k** were prepared from 3-methoxy-4-hydroxycinamaldehyde (**2**) in five steps as shown in Scheme 1. Protection of phenolic OH with the TBS group, followed by addition of Grignard reagent afforded the corresponding allylic alcohol **4** in good yield. Catalytic hydrogenation of **4** on Pd/C gave the saturated alcohol **5**. After forming the alkoxide with NaH in THF, **5** was treated with phenethylisothiocyanate to give the corresponding thiocarbamate **6**. Deprotection of the TBS group with TBAF gave the desired compounds **1b** and **1d–k**, respectively. Compounds **1a** and **1c** were also prepared in similar ways with different starting material such as 4-hydroxy-3-methoxyphenylacetone and 4-(4′-hydroxy-3′-methoxyphenyl)butan-2-one.

The biological activities of the thiocarbamate **1a–k** 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.[12] The results are summarized in Table 1. As expected, the antagonist activities of the compounds **1a–k** are strongly influenced by chain length. Optimal carbon chain length between A and B region was found to be propyl. Further examination of the effect of R_1 reveals that the smaller groups showed better antagonist activity than the bulkier one. The methyl (**1b**) and ethyl (**1e**) derivatives had IC_{50} values ranging from 6.3 to 9.9 μM. When R_1 is hydrogen, however, activity is reduced greatly. This implies the important contribution of R_1 branching for antagonist activity. Moderate activities were also observed for phenethyl derivatives (**1i**, **1j**). Thus, compound **1e** with ethyl group and optimal propyl chain was chosen as a lead for next SAR study.

It is well known that modification of B-region both in capsaicin and capsazepine has a great influence on their

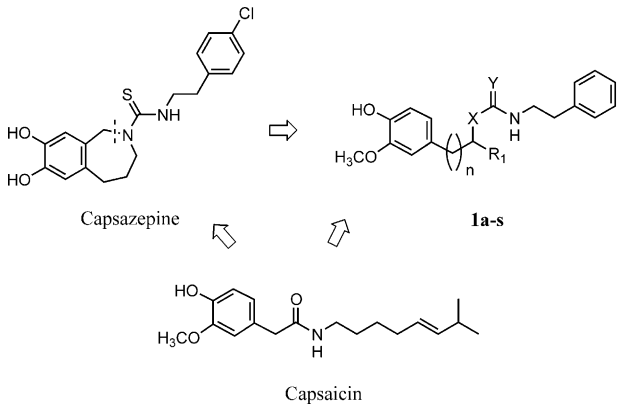
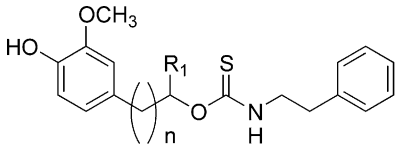


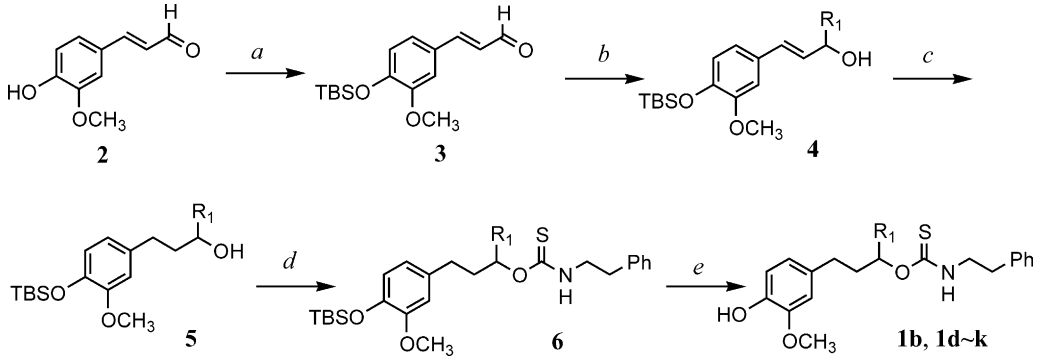
Figure 1. Structures of capsaicin, capsazepine and target molecules **1a–s**.

Table 1. $^{45}Ca^{2+}$-influx activity of the phenethylthiocarbamate derivatives

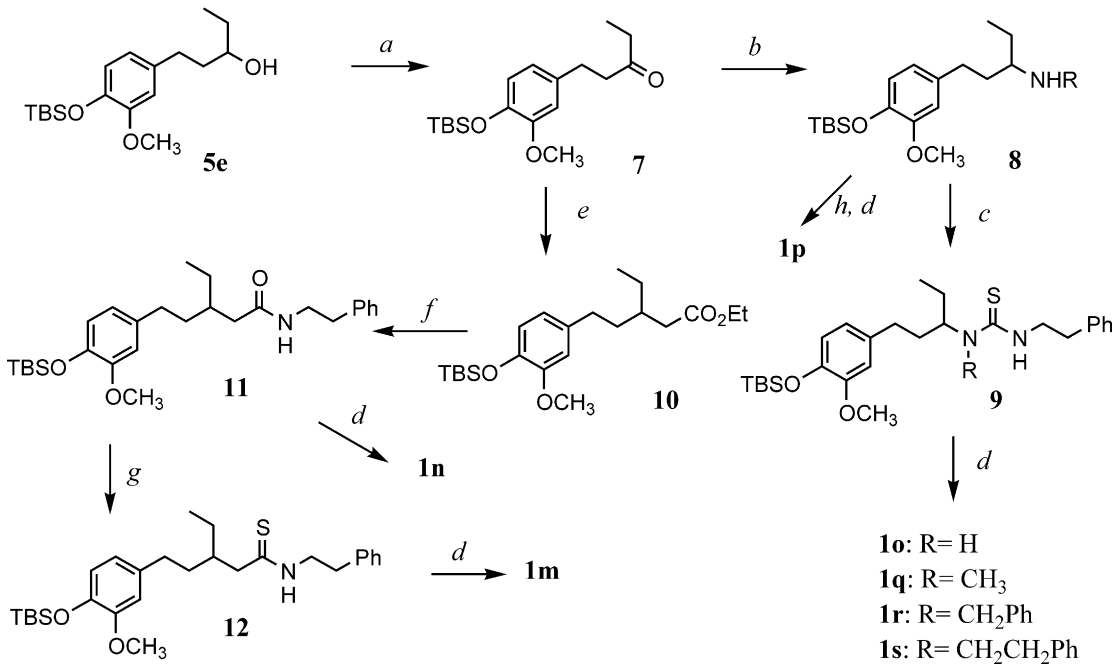


Compd	*n*	R_1	$^{45}Ca^{2+}$ influx activity (μM)[a]	
			Agonist (EC_{50})	Antagonist (IC_{50})
1a	1	Methyl	>100	>30
1b	2	Methyl	>100	9.9
1c	3	Methyl	>100	>30
1d	2	H	>100	>30
1e	2	Ethyl	>100	6.3
1f	2	Propyl	>100	27.9
1g	2	Phenyl	>100	>30
1h	2	Benzyl	>100	25
1i	2	Phenethyl	>100	19.2
1j	2	2-(4-Trifluoromethylphenyl)ethyl	>100	10.7
1k	2	Phenylpropyl	>100	>30
Capsazepine		—	>100	0.6

[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.



Scheme 1. Reagents and conditions: (a) NaH, THF; then TBSCl, 99%; (b) R_1MgBr, THF, 80–99%; (c) H_2, Pd/C, MeOH, 80–100%; (d) NaH, R_2NCS, THF, 75–95%; (e) TBAF, THF, 90–99%.



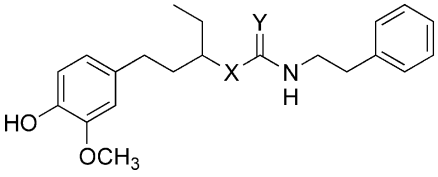
Scheme 2. Reagents and conditions: (a) PCC, CH_2Cl_2, 98%; (b) RNH_2; H_2, Pd/C 40∼85%; (c) $PhCH_2CH_2NCS$, toluene, reflux, 45–85%; (d) TBAF, THF, 75–95%; (e) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 58%; H_2, Pd/C, 81%; (f) $PhCH_2CH_2NH_2$, Me_3Al, CH_2Cl_2, 98%; (g) Lawesson's reagent, toluene, 80 °C, 47%; (h) phenethylamine, diethyl dicarbonate, DMAP, CH_2Cl_2, 21%.

agonist or antagonist activity. At the present time, thiourea has its most potent functionality for the B-region. Thus, we studied the SAR of B-region modification. Carbamate, thiocarbamate, amide, thioamide, urea, and thiourea analogues were prepared according to Scheme 2. Alcohol **5e** was oxidized with PCC to give the ketone **7** in 98% yield. Reductive amination of **7** followed by deprotection gave **1o**, **1p**, **1q** and **1r**, respectively. Horner–Worthward–Emmons olefination of **7** with triethyl phosphonoacetate, followed by catalytic hydrogenation afforded ester **10** in 47% yield. Direct amide formation from ester was achieved with trimethylaluminium and phenethylamine to afford **11** in 98% yield. Treatment of **11** with Lawesson's reagent in toluene at 80 °C gave the thioamide **12** in 47% yield. Subsequent deprotection of TBS group from **11** and **12** with TBAF gave **1n** and **1m**, respectively.

As shown in Table 2, amide **1n** and thioamide **1m** were found to be inactive, which implies that hetero atom is needed at X position for activity. Carbamate **1l** and urea **1p** are less reactive than the corresponding thiocarbamate **1e** and thiourea **1o**, indicating that sulfur is better than oxygen at the Y position. In comparison of IC_{50} values of the alkyl thiourea derivatives (**1o**, **1q**–**s**) turned out that *N*-alkylation was not fruitful way to increase the antagonist activity of the thiourea **1o**. At the present time, thiocarbamate is the best functionality for this new scaffold.

In summary, a series of chain-branched acyclic phenethylthiocarbamate derivatives have been synthesized, and their antagonist effect against vanilloid receptor tested. Ethyl-branched phenethylthiocarbamate **1e** showed 6.3 μM of IC_{50} value. Although the potency is still lower than that of capsazepine at this stage, the most important thing is that the first acyclic vanilloid compounds with antagonist activity are prepared by chain branching method. In addition, the chain branching method presented here appears to be a promising strategy for the development of novel antagonists.

Table 2. $^{45}Ca^{2+}$-Influx activity of the ethyl branched vanilloid derivatives



Compd	X	Y	$^{45}Ca^{2+}$ influx activity (μM)	
			Agonist (EC_{50})	Antagonist (IC_{50})
1e	O	S	>100	6.3
1l	O	O	>100	>30
1m	CH_2	S	>100	>30
1n	CH_2	O	>100	>30
1o	NH	S	>100	28.5
1p	NH	O	>100	>30
1q	NCH_3	S	>100	27.2
1r	NCH_2Ph	S	>100	20.9
1s	NCH_2CH_2Ph	S	>100	>30
Capsazepine		—	>100	0.6

Acknowledgements

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