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Halogenation of 4-hydroxy-3-methoxybenzyl thiourea TRPV1 agonists showed enhanced antagonism to capsaicin

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Abstract—Selected potent TRPV1 agonists (**1**–**6**) have been modified by 5- or 6-halogenation on the aromatic A-region to analyze their effects on potency and efficacy (agonism versus antagonism). The halogenation caused enhanced functional antagonism at TRPV1 compared to the corresponding prototype agonists. The analysis of SAR indicated that the antagonism was enhanced as the size of the halogen increased (I > Br > Cl) and when the 6-position was halogenated. Compounds **23c** and **31b** were found to be potent full antagonists with K_i (as functional antagonist) = 23.1 and 30.3 nM in rTRPV1/CHO system, respectively.

TRPV1 is a member of the transient receptor potential (TRP) superfamily;[1] the TRP family proteins form non-voltage activated cation channels and share a structural characteristic of six transmembrane segments.[2,3] TRPV1 functions as a molecular integrator of nociceptive stimuli expressed predominantly on unmyelinated pain-sensing nerve fibers (C-fibers) and small Aδ fibers in the dorsal root, trigeminal, and nodose ganglia. It is activated by protons,[4] heat,[5] endogenous substances such as anandamide[6] and lipoxygenase products,[7] by vanilloids such as capsaicin (CAP)[8] and resiniferatoxin (RTX),[9] or indirectly by bradykinin.[10] Since TRPV1 is a non-selective cation channel with high Ca^{2+} permeability, its activation by these agents leads to an increase in intracellular Ca^{2+} that results in excitation of the primary sensory neurons (Fig. 1).

The receptor activation can be blocked either by desensitization subsequent to agonist exposure or by direct antagonism. Both strategies would have considerable therapeutic utility targeting inflammatory and neuropathic pain, cystitis, and bladder hyperreflexia. TRPV1 antagonists have attracted much attention so far as promising drug candidates to inhibit the transmission of painful signals from the periphery to the CNS and to block other pathological states associated with this receptor. A therapeutic advantage of TRPV1 antagonism over agonism is that it lacks the initial excitatory effect preceding the desensitization. The initial acute pain associated with capsaicin treatment has proven to be the limiting toxicity. A further advantage of antagonists is that their effects are readily reversible (Fig. 2).

Previously, we have demonstrated that so-called simplified RTX analogues, *N*-(3-pivaloyloxy-2-benzylpropyl)-*N*′-(4-hydroxy-3-methoxybenzyl)thioureas (**1** and **2**),[11] *N*-[2-pivaloyloxy-1-(phenethyl)ethyl]-*N*′-(4-hydroxy-3-methoxybenzyl)thioureas (**3** and **4**),[12] and *N*-[2-pivaloyloxy-1-(4-*t*-butylbenzyl)ethyl]-*N*′-(4-hydroxy-3-methoxybenzyl)thiourea (**5**),[12] possess potent TRPV1 agonism with high affinity, having a range of K_i (binding) = 6.35–56 nM and EC_{50} (agonism) = 1.97–21.5 nM in rat TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells and excellent analgesic activities. *N*-(4-*t*-Butylbenzyl)-*N*′-(4-hydroxy-3-methoxybenzyl) thiourea (**6**) also proved to be a highly potent agonist by the Novartis group[13] and by us.[14] Interestingly, we have found that isosteric replacement of the phenolic hydrox-

Keywords: TRPV1 agonist; TRPV1 antagonist; Halogenation; Resiniferatoxin; Capsaicinoid.
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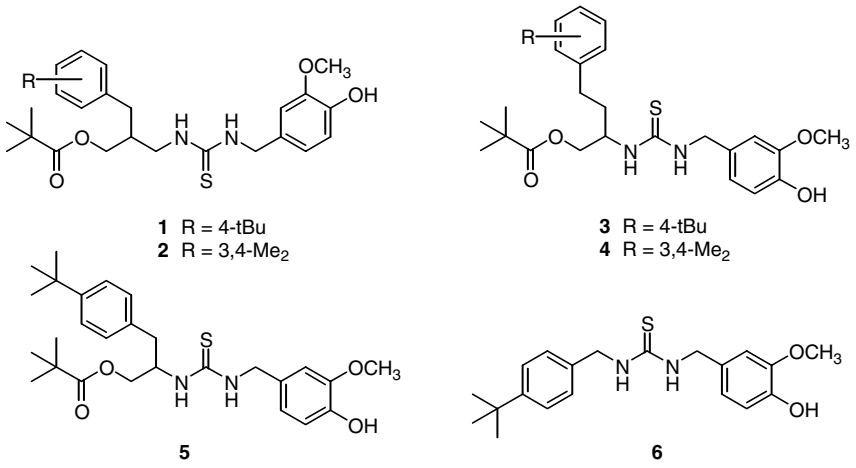


Figure 1.

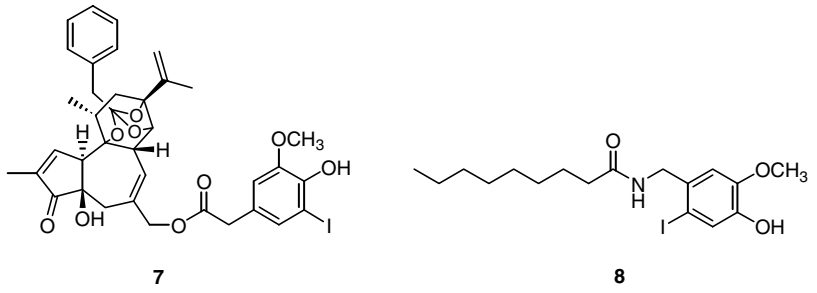
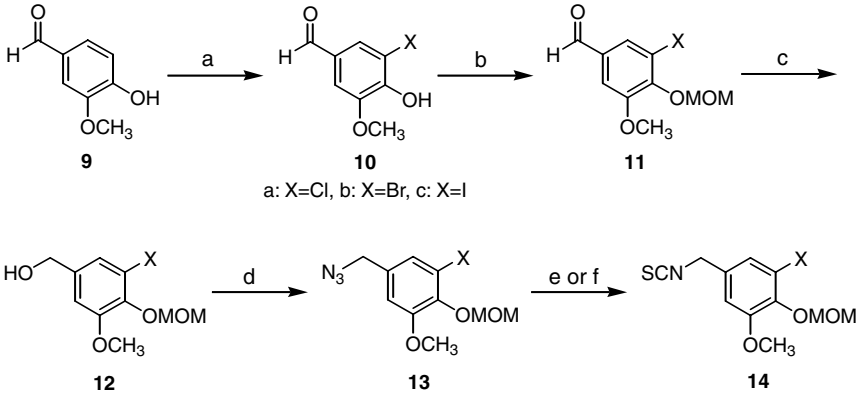


Figure 2.

yl group in lead agonists with the methylsulfonamido group provided a series of antagonists effective against the action of capsaicin. Among them, the 3-fluoro-4-methylsulfonylamino analogue of the A-region in agonists **2** and **6** showed excellent antagonism with values of K_i (ant) = 7.8 and 9.16 nM, respectively.[14,15]

Recently it was reported that the halogenation of the aromatic A-ring of agonists also shifted the agonism of the ligands toward antagonism. Two leading examples are 5-iodoresiniferatoxin (**7**)[16] and 6-iodononivamide (**8**),[17] iodinated products of the agonists RTX and nonivamide, which showed potent antagonism with a K_i = 5.8 nM in the rTRPV1/HEK293 system and an IC_{50} = 10 nM in the hTRPV1/HEK293 system, respectively. The result prompted us to investigate how the halogenation on the aromatic A-region of our potent agonists modulates their functional activity.

In the present study, we describe the syntheses, receptor activities, and the analysis of structure–activity relationships of 5- and 6-halogenated analogues of our lead agonists (**1**–**6**).



Scheme 1. Reagents and conditions: (a) NCS, NaH, THF, 78% for X = Cl; Br_2, CH_2Cl_2, 91% for X = Br; H_3BO_3, 1 N NaOH, KI, I_2, H_2O, 50% for X = I; (b) MOMCl, DBU, DMF, 75% for X = Cl; MOMCl, NEt_3, CH_2Cl_2, 92% for X = Br, 91% for X = I; (c) $NaBH_4$, LiCl, THF–EtOH, 93–99%; (d) DPPA, DBU, toluene, 90–99%; (e) CS_2, PPh_3, THF, 83% for X = Cl; (f) i—PPh_3, H_2O, THF, 71–96%; ii—TDI, NEt_3, DMF, 50% for X = Br, 46% for X = I.