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Silicon switch approach in TRPV1 antagonist MK-056 and its analogues

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ABSTRACT

In searching for opportunities to exploit the benefits of silicon in TRPV1 research, we tried to investigate the pharmacological effects of sila-substitution (C/Si exchange) of *tert*-butyl group in the MK-056 series. Compound **13a**, with a 4-positioned trimethylsilanyl group on the B ring in place of *tert*-butyl group, exhibited the most potent antagonist activity with IC_{50} values of 0.15 μM, which is almost equipotent with that of MK-056. This is the first example that *tert*-butyl group on MK-056 series can be replaced to the other substituent without loss of activity.

1. Introduction

Silicon and carbon are members of group IV of Periodic Table of the Element and share some similarities in several aspects. Due to these similarities, in general, the silicon-substituted derivatives share the same pharmacological mode of action as the corresponding carbon analogues. However, these two elements also have some subtle differences in molecular size, shape, electronegativity, and lipophilicity. These differences can lead to marked alterations in the physicochemical and biological properties of silicon-containing analogues.[1] Thus, incorporation of silicon into biologically pre-validated drug scaffolds represents an excellent tetrahedral isostere of carbon. This silicon switch approach for safe marketed drugs is cost-effective and of lower developmental risk because known drugs have recognized pharmacology and toxicity profiles, proven safety in humans, and established manufacturing and formulation methods.[2]

Recently, we have reported the synthesis and biological evaluation of 1,3-dibenzylthioureas as novel TRPV1 antagonist (Fig. 1).[3] TRPV1 is a ligand-gated nonselective cation channel vanilloid receptor 1 (VR1) with high Ca^{2+} permeability,[4] emerging as a novel target for the treatment of pain.[5] Based on the premise that direct blockage of TRPV1 by its antagonists could be a promising way of silencing pain signaling pathways,[6] extensive works have been done to develop new TRPV1 antagonists during the past decade.[7] We have also reported the dibenzylthiourea analogues including MK-056 (**1**),[3a] SC-0030 (**2**),[3b] and ATC-120 (**3**),[3c] which exhibit highly potent competitive TRPV1 antagonist effects, as well as their structure–activity relationship (SAR).[8] From the SAR study, it revealed that 4-*tert*-butyl group of MK-056 derivatives is essential for potency. All attempts to replace *tert*-butyl groups of MK-056 series to other alkyl groups resulted in weakening their potencies.[9]

In searching for opportunities to exploit the benefits of silicon in TRPV1 (transient receptor potential vanilloid subfamily 1) research, we tried silicon switch approach to search for new TRPV1 antagonist that have beneficial pharmacodynamic or pharmacokinetic properties and novel IP position. In this context, we decided to investigate the pharmacological effects of sila-substitution (C/Si exchange) of *tert*-butyl group in the MK-056 series.

2. Results and discussion

2.1. Chemistry

Trimethylsilanyl, ethyldimethylsilanyl, and triethylsilanyl groups were chosen as bioisosteres of *t*-butyl group. MK-056 (**1**), SC-0030 (**2**) and ATC-120 (**3**) were also chosen as reference compounds in order to clarify the sila-substitution effect. It is because that these three compounds represent the most important scaffolds in 1,3-dibenzylthioureas with high antagonist activity. Thus, target compounds in this study were the trialkylsilanyl derivatives of MK-056 (**1**), SC-0030 (**2**) and ATC-120 (**3**). These targets were synthesized via the route outlined in Schemes 1 and 2. 4-Trialkyls-

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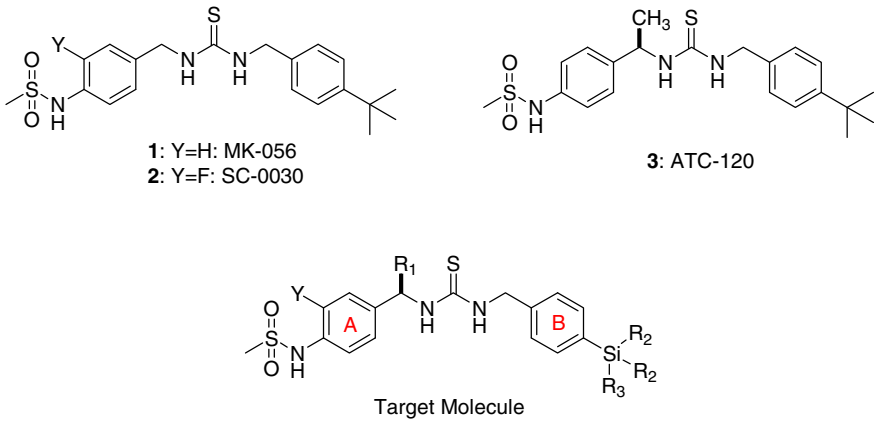
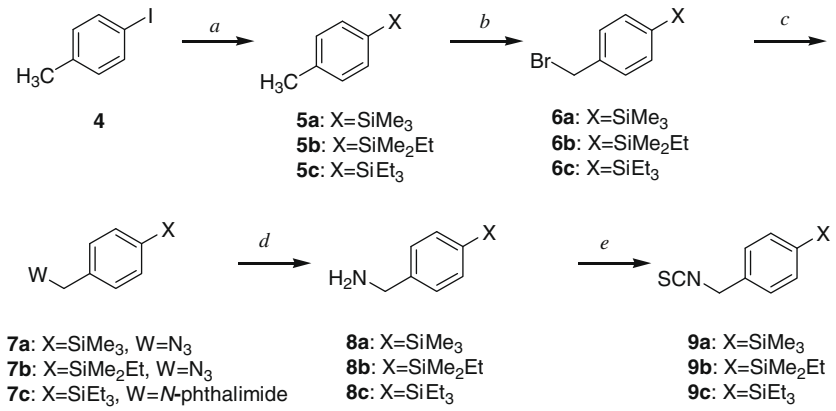
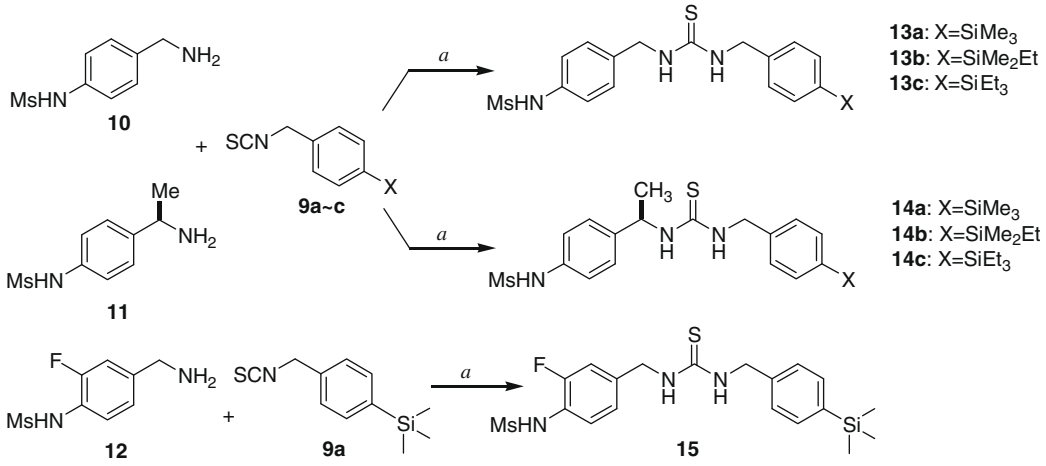


Figure 1. Structures of 1,3-dibenzylthioureas.



Scheme 1. Reagents and conditions: (a) *t*-BuLi, THF, −78 °C, then R_3SiCl, 59–73%; (b) NBS, AIBN, CCl_4, reflux; (c) NaN_3, CH_3CN, reflux, 37–76% (two steps)/or phthalimide, Cs_2CO_3, acetone, reflux, 35% (two steps); (d) H_2, Pd on carbon/or $SnCl_2$, EtOH/or NH_2NH_2, ethanol, 98–100%; (e) 1,1-thiocarbonyl di-2(1*H*)-pyridone, DCM, 43–80%.



Scheme 2. Reagents and conditions: (a) Triethylamine, DCM, rt, 46–74%.

ilanylbenzylisothiocyanates were synthesized via the route outlined in Scheme 1. Halogen-metal exchange of 4-iodotoluene (**4**) by *t*-butyllithium, followed by quenching with three kinds of chlorotrialkylsilanes gave the corresponding 4-trialkylsilanyltoluenes **5a–c**.[10] 4-Trialkylsilanyltoluenes **5a–c** were treated with *N*-bromosuccinimide in CCl_4 in the presence of AIBN under reflux to give the corresponding benzyl bromides **6a–c**.[11] Nucleophilic substitution of benzyl bromide **6a–c** to azide **7a–b** or *N*-phthalimide **7c**, followed by reduction or hydrolysis gave the corresponding benzylamines **8a–c**.[12] Treatment of benzylamines **8a–c** with 1,1-thiocarbonyl di-2(1*H*)-pyridone gave the corresponding 4-trialkylsilanylbenzylisothiocyanates **9a–c**. The requisite 4-methanesulfonamidobenzylamines **10–12** were prepared according to the previously reported method.[3c,8,13] Finally, 4-methanesulfo-

namidobenzylamines **10**–**12** were treated with the appropriate 4-trialkylsilanylbenzylisothiocyanates **9a**–**c** and triethylamine in dry dichloromethane to give the compounds trialkysilanyl-1,3-dibenzylthioureas **13**–**15** as target compounds.

2.2. Biological evaluation

The synthesized silicon-substituted 1,3-dibenzylthioureas **13a**–**c**, **14a**–**c** and **15** were tested for their antagonist activities on TRPV1 by $^{45}Ca^{2+}$-influx assay using neonatal rat cultured spinal sensory neurons.[14] The results are summarized in Table 1. MK-056 (**1**), SC-0030 (**2**), and ATC-120 (**3**) were used as reference compounds. Among the three trialkylsilanyl analogues of MK-056, not unexpectedly, the most potent is trimethylsilanyl analogue **13a**, and the worst is triethylsilanyl analogue **13c**. As shown in Table 1, compound **13a**, with a 4-positioned trimethylsilanyl group on the B ring in place of *tert*-butyl group, exhibited the most potent antagonist activity with IC_{50} values of 0.15 μM, which is almost equipotent with that of MK-056. This is the first example that *tert*-butyl group on MK-056 series can be replaced to the other substituent without loss of activity. However, replacing *tert*-butyl group with dimethylethylsilanyl group, compound **13b** showed a drastic loss of activities. Small difference made by one methyl group in **13b** led to the drop in potency by one order of magnitude in comparison with **13a**. This result is consistent with previous results that 4-positioned *tert*-butyl group on the B ring is very reluctant to permit chemical modification.[8] Substitution at 4-position on the B ring with a triethylsilanyl group, **13c**, was not tolerated and showed a 20-fold decrease in antagonist activity compared to **13a**, indicating that increasing bulk at the 4-position on the B ring beyond a trimethylsilanyl was detrimental for receptor binding. Next, we also investigated the sila-substitution effect of SC-0030 (**2**) and ATC-120 (**3**) analogues. The similar trend was observed in ATC-120 series (**14a**–**c**), indicating that trimethylsilanyl group is the best bioisostere of *tert*-butyl group. While **13a** was equipotent with that of parent MK-056, **14a** and **15** were about fourfold less potent than parent carbon compounds (**2**, **3**), but retaining the antagonist activities with IC_{50} values in the range of submicromole. As mentioned above, one of the goals for silicon switch is to search for new TRPV1 antagonist having beneficial pharmacodynamic or pharmacokinetic properties and novel IP position. Compound **13a** comes closest to achieving this goal in that its IC_{50} values are very near that of MK-056.

3. Conclusion

In summary, we have designed and synthesized a series of silicon analogues of the MK-056 by silicon switch approach to search for new TRPV1 antagonist. The synthesized seven silicon-substituted 1,3-dibenzylthioureas **13a**–**c**, **14a**–**c** and **15** were tested for their antagonist activities on TRPV1 by $^{45}Ca^{2+}$-influx assay using neonatal rat cultured spinal sensory neurons. Compound **13a**, with a 4-positioned trimethylsilanyl group on the B ring in place of *tert*-butyl group, exhibited the most potent antagonist activity with IC_{50} values of 0.15 μM, which is almost equipotent with that of MK-056. This is the first example that *tert*-butyl group on MK-056 series can be replaced to the other substituent without loss of activity. The results emphasize the great potential of the carbon/silicon switch strategy for drug design.

4. Experimental section

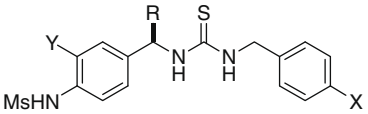
4.1. General method

The melting points were obtained using Büchi 535 melting point apparatus and were uncorrected. Optical rotations were measured on a JASCO DIP 1000 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Inova 400 spectrometer and the chemical shifts are reported as values in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. The infrared spectra (IR) were recorded on a JASCO FT/IR-430 spectrophotometer. Low resolution mass spectra were obtained on VG Trio-2 GC–MS. High resolution mass spectra were obtained on a JEOL JMS-AX 505wA and JEOL JMS-HX/HX 110A spectrometer. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel glass plates ($60F_{254}$). Column chromatography was performed using the forced flow of indicated solvent on Merck Kieselgel 60 (230–400 mesh). Unless otherwise noted, the materials were obtained from commercially available sources and were used without further purification. THF was freshly distiled from sodium benzophenone ketyl under an argon atmosphere. Benzene, DCM, DMF, triethylamine (TEA) and toluene were freshly distiled under a nitrogen atmosphere with calcium hydride.

4.1.1. Trimethyl *p*-tolyl silane (5a)

To a solution of 4-iodotoluene (**4**, 700 mg, 3.21 mmol) in anhydrous THF (16 mL, 0.2 M) was added dropwise *tert*-BuLi (1.7 M

Table 1
$^{45}Ca^{2+}$-Uptake inhibition by MK-056 analogues



Compound	X	R	Y	$^{45}Ca^{2+}$ influx activity[a] (μM)	
				Agonist (EC_{50})	Antagonist (IC_{50})
13a	Trimethylsilanyl	H	H	>100	0.15
13b	Ethyldimethylsilanyl	H	H	>100	1.20
13c	Triethylsilanyl	H	H	>100	3.10
1 (MK-056)	*tert*-Butyl	H	H	>100	0.11
14a	Trimethylsilanyl	Me	H	>100	0.21
14b	Ethyldimethylsilanyl	Me	H	>100	0.67
14c	Triethylsilanyl	Me	H	>100	1.50
3 (ATC-120)	*tert*-Butyl	Me	H	>100	0.05
15	Trimethylsilanyl	H	F	>100	0.16
2 (SC-0030)	*tert*-Butyl	H	F	>100	0.04

[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 the response to 0.5 μM capsaicin by 50%) were estimated with at least three replicates at each concentration. Each compound was tested in two independent experiments. Antagonist data were fitted with a sigmoidal function.

solution in hexane, 3.77 mL, 6.42 mmol) at −78 °C. The mixture was stirred for 20 min at −78 °C, and chlorotrimethylsilane (698 μL, 6.42 mmol) was added. After being stirred for an hour at the same temperature, the reaction mixture was quenched with aqueous NH_4Cl and diluted with ethyl acetate (30 mL). The layers were separated, and the aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane) to afford the title compound **5a** as a colourless liquid (359 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 2H, J = 8.0 Hz), 7.12 (d, 2H, J = 8.0 Hz), 2.29 (s, 3H), 0.19(s, 9H); IR (NaCl, neat) cm^{-1} 3011, 2995, 1247, 1106.

4.1.2. Ethyldimethyl(*p*-tolyl)silane (5b)

By the same procedure described above, the product was obtained from **4** as syrup in 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 2H, J = 8.0 Hz), 7.16 (d, 2H, J = 8.0 Hz), 2.34 (s, 3H), 0.94 (t, 3H, J = 8.0 Hz), 0.70 (q, 2H, J = 8.0 Hz), 0.22 (s, 6H); IR (NaCl, neat) cm^{-1} 3011, 2954.

4.1.3. Triethyl (*p*-tolyl)silane (5c)

By the same procedure described above, the product was obtained from **4** as syrup in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, 2H, J = 7.6 Hz), 7.25 (d, 2H, J = 7.6 Hz), 2.42 (s, 3H), 1.05 (t, 9H, J = 7.6 Hz), 0.87 (q, 6H, J = 7.6 Hz); IR (NaCl, neat) cm^{-1} 3011, 2954.

4.1.4. (4-Bromomethylphenyl)trimethylsilane (6a)

To a solution of *p*-tolyl trimethylsilane (**5a**, 359.0 mg, 2.18 mmol) in carbon tetrachloride (22 mL, 0.1 M) were added *N*-bromosuccinimde (427.7 mg, 2.40 mmol) and AIBN (5 mg) at room temperature. The reaction mixture was stirred at refluxing temperature for 2 h and then cooled to room temperature. *n*-Hexane (30 mL) was added to the solution, and the resulting turbid suspension was filtered through a pad of Celite to obtain the filtrate as a transparent liquid. The filter cake was rinsed twice with hexane (20 mL). The combined filtrates were concentrated in vacuo to afford the title compound (582 mg, 110%) as yellow oil. This crude product was directly used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 2H, J = 8.0 Hz), 7.33 (d, 2H, J = 8.0 Hz), 4.46 (s, 2H), 0.23 (s, 9H); IR (NaCl, neat) cm^{-1} 3015, 2955, 1393, 1248.

4.1.5. (4-Bromomethylphenyl)ethyldimethylsilane (6b)

By the same procedure described above, the crude product was obtained from **5b** as syrup. This crude product was directly used for the next step without further purification. R_f = 0.62 (silica gel, *n*-hexane).

4.1.6. (4-Bromomethylphenyl)triethylsilane (6c)

By the same procedure described above, the crude product was obtained from **5c** as syrup. This crude product was directly used for the next step without further purification. R_f = 0.42 (silica gel, *n*-hexane).

4.1.7. (4-Azidomethylphenyl)trimethylsilane (7a)

To a solution of the crude bromide **6a** (582 mg) in acetonitrile (22 mL) were added sodium azide (233.4 mg, 3.59 mmol) in one portion at room temperature. The reaction mixture was stirred at refluxing temperature for 2 h and then cooled to room temperature. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane) to afford the title compound **7a** as colourless liquid (181 mg, 37%, two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz), 4.31 (s, 2H), 0.25(s, 9H); IR (NaCl, neat) cm^{-1} 3018, 2956, 2099.

4.1.8. (4-Azidomethylphenyl)ethyldimethylsilane (7b)

By the same procedure described above, the product was obtained from **6b** as syrup in 76% yield (two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 2H, J = 7.6 Hz), 7.22 (d, 2H, J = 7.6 Hz), 4.25 (s, 2H), 0.87 (t, 3H, J = 8.0 Hz), 0.86 (s, 3H), 0.65 (q, 2H, J = 8.0 Hz), 0.17 (s, 3H); IR (NaCl, neat) cm^{-1} 3422, 2955, 2099.

4.1.9. 2-(4-Triethylsilanylbenzyl)isoindole-1,3-dione (7c)

To a solution of the crude bromide **6c** (155.0 mg, 0.55 mmol) in acetone (11 mL) were added phthalimide (96.4 mg, 0.66 mmol) and cesium carbonate (213.5 mg, 0.66 mmol) at room temperature. The reaction mixture was stirred at refluxing temperature for 12 h, and then cooled to room temperature. The reaction mixture was concentrated in vacuo, and then diluted with ethyl acetate (30 mL). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the title compound **7c** as solid (67.4 mg, 35%, two steps). Mp, 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, 2H, J = 3.2, 5.6 Hz), 7.53 (dd, 2H, J = 3.2, 5.6 Hz), 7.26 (d, 2H, J = 8.0 Hz), 7.22 (d, 2H, J = 8.0 Hz), 4.68 (s, 2H), 0.75 (t, 9H, J = 8.0 Hz), 0.58 (q, 6H, J = 8.0 Hz); IR (KBr) cm^{-1} 2951, 2909, 1713.

4.1.10. 4-Trimethylsilanylbenzylamine (8a)

To a stirred solution of benzyl azide **7a** (180.8 mg, 0.88 mmol) in methanol (10 mL) was added 10% Pd/C (36.0 mg, 20 wt% of starting material). The solution was stirred under H_2 balloon condition for 1 h at room temperature. The reaction mixture was filtered through a pad of Celite and concentrated in vacuo to afford benzylamine **8a** as syrup (153.5 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.25 (m, 2H), 3.42 (s, 2H), 0.19 (s, 9H); IR (NaCl, neat) cm^{-1} 3352, 3017, 2954.

4.1.11. 4-(Ethyldimethylsilanyl)benzylamine (8b)

To a solution of the azide **7b** (313.1 mg, 1.43 mmol) in ethanol (15 mL) was added $SnCl_2$ (813.4 mg, 4.29 mmol) at room temperature. After being stirred at room temperature for 5 h, the reaction mixture was concentrated in vacuo, and then diluted with ethyl acetate (50 mL). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the title compound **8b** as syrup (276.0 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2H, J = 8.0 Hz), 7.41 (d, 2H, J = 8.0 Hz), 4.08 (s, 2H), 0.90 (t, 3H, J = 7.6 Hz), 0.72 (q, 2H, J = 8.0 Hz), 0.22 (s, 6H); IR (NaCl, neat) cm^{-1} 3378, 3017, 2955.

4.1.12. 4-Triethylsilanylbenzylamine (8c)

To a solution of the phthalimide **7c** (30 mg, 0.085 mmol) in ethanol (6 mL) were added hydrazine (5.13 mg, 0.1 mmol) at room temperature. The reaction mixture was stirred at refluxing temperature for 12 h and then cooled to room temperature. The reaction mixture was concentrated in vacuo, and then diluted with ethyl acetate (30 mL). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the title compound **8c** as syrup (19 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 2H, J = 7.6 Hz), 7.23 (d, 2H, J = 7.6 Hz), 3.91 (s, 2H), 0.89 (t, 9H, J = 7.6 Hz), 0.71 (q, 6H, J = 7.6 Hz); IR (NaCl, neat) cm^{-1} 3374, 3299, 3011, 2955.

4.1.13. (4-Isothiocyanatomethylphenyl)trimethylsilane (9a)

To a solution of the benzylamine **8a** (153.5 mg, 0.86 mmol) in dichloromethane (17 mL) was added 1,1-thiocarbonyl di-2(1*H*)-pyridone (219.0 mg, 0.94 mmol) in one portion at room temperature. After being stirred for 12 h at the same temperature, the reaction mixture was quenched with H_2O (5 mL) and diluted with

dichloromethane (30 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane) to afford the title compound **9a** as colourless solid (152.4 mg, 80%). Mp, 69–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, J = 8.2 Hz), 7.23 (d, 2H, J = 8.2 Hz), 4.69 (s, 2H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 134.6, 133.9, 126.1, 48.6, −1.2; IR (KBr) cm^{-1} 2954, 2927, 2180, 2112; MS (EI) *m*/*z* (relative intensity) 221 (M^+, 100), 206 (100), 191 (50), 174 (100)); HRMS (EI) calcd for $C_{11}H_{15}NSSi$ (M^+) 221.0694, found 221.0692.

4.1.14. Ethyl(4-isothiocyanatomethylphenyl)dimethylsilane (9b)

By the same procedure described above, the product was obtained from **8b** as syrup in 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 2H, J = 7.6 Hz), 7.21 (d, 2H, J = 7.6 Hz), 4.61 (s, 2H), 0.86 (t, 3H, J = 7.6 Hz) 0.65 (q, 2H, J = 7.6 Hz), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 134.6, 134.2, 126.0, 48.6, 7.3, 7.2, −3.6; IR (KBr) cm^{-1} 3018, 2954, 2175, 2092; MS (EI) *m*/*z* (relative intensity) 235 (M^+, 8), 206 (48), 177 (25), 147 (36), 83 (100); HRMS (EI) calcd for $C_{12}H_{17}NSSi$ (M^+) 235.0851, found 235.0848.

4.1.15. Triethyl(4-isothiocyanatomethylphenyl)silane (9c)

By the same procedure described above, the product was obtained from **8c** as oil in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, 2H, J = 7.6 Hz), 7.25 (d, 2H, J = 7.6 Hz), 4.66 (s, 2H), 0.92 (t, 9H, J = 7.6 Hz) 0.75 (q, 6H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.0, 134.8, 126.2, 48.8, 7.5, 3.5; IR (NaCl, neat) cm^{-1} 2953, 2910, 2092, 1633, 1105; MS (EI) *m*/*z* (relative intensity) 263 (M^+, 100), 235 (100), 177 (100), 147 (100), 86 (100); HRMS (EI) calcd for $C_{14}H_{21}NSSi$ (M^+) 263.1164, found 263.1164.

4.1.16. *N*-{4-[3-(4-Trimethylsilanylbenzyl)thioureidomethyl]-phenyl}methanesulfonamide (13a)

To a solution of the *N*-(4-aminomethylphenyl)methanesulfonamide (**10**, 44.4 mg, 0.22 mmol) in dichloromethane (5 mL) were added isothiocyanate **9a** (44.6 mg, 0.20 mmol) and triethylamine (89 mg, 0.66 mmol) at room temperature. After being stirred for 12 h at room temperature, the reaction mixture was quenched with H_2O (1 mL) and diluted with dichloromethane (30 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; 17% ethyl acetate in *n*-hexane) to afford the title compound **13a** as liquid (39.4 mg, 46%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (d, 2H, J = 8.0 Hz), 7.24 (d, 2H, J = 8.0 Hz), 7.23 (d, 2H, J = 8.4 Hz), 7.16 (d, 2H, J = 8.4 Hz), 4.77 (s, 2H), 4.66 (s, 2H), 2.87 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 182.9, 138.7, 136.7, 134.4, 133.0, 128.2, 126.6, 120.2, 47.8, 47.2, 38.5, −1.5; (NaCl, neat) cm^{-1} 3299, 3063, 2952, 1573, 1158; LRMS (FAB^+) *m*/*z* (rel intensity) 422 [100, (M+H)], 342 (17), 239 (39), 199 (24), 184 (100); HRMS (FAB^+) calcd for $C_{19}H_{28}N_3O_2S_2Si$ (M+H) 422.1392, found 422.1398.

4.1.17. *N*-{4-[3-(4-Ethyldimethylsilanylbenzyl)thioureidomethyl]phenyl}methanesulfonamide (13b)

By the same procedure described above, the product was obtained from **10** and **9b** as solid in 74% yield. Mp 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 2H, J = 8.0 Hz), 7.37 (br s, 1H), 7.20 (d, 2H, J = 8.0 Hz), 7.13 (d, 2H, J = 8.0 Hz), 7.08 (d, 2H, J = 8.0 Hz), 6.47 (br s, 2H), 4.57 (s, 4H), 2.88 (s, 3H), 0.89 (t, 3H, J = 8.0 Hz), 0.67 (q, 2H, J = 8.0 Hz), 0.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 140.7, 139.2, 136.2, 134.3, 134.1, 128.8, 126.8, 121.1, 47.7, 39.3, 7.3, 7.2, −3.5; IR (KBr) cm^{-1} 3356, 3068, 2924, 1613, 1326; LRMS (FAB^+) *m*/*z* (rel intensity) 436 [59, (M+H)], 253 (26), 184 (100); HRMS (FAB^+) calcd for $C_{20}H_{30}N_3O_2S_2Si$ (M+H) 436.1549, found 436.1545.

4.1.18. *N*-{4-[3-(4-Triethylsilanylbenzyl)thioureidomethyl]-phenyl}methanesulfonamide (13c)

By the same procedure described above, the product was obtained from **10** and **9c** as solid in 60% yield. Mp 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 2H, J = 8.0 Hz), 7.41 (br s, 1H), 7.23 (d, 2H, J = 8.0 Hz), 7.17 (d, 2H, J = 8.4 Hz), 7.11 (d, 2H, J = 8.4 Hz), 6.50 (br s, 2H), 4.60 (s, 4H), 2.91 (s, 3H), 0.93 (t, 9H, J = 7.6 Hz), 0.76 (q, 6H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 137.4, 137.0, 136.2, 134.7, 134.2, 128.8, 126.7, 121.0, 48.3, 47.8, 39.4, 7.3, 3.2; IR (KBr) cm^{-1} 3363, 3263, 3066, 2953, 2873, 1152; LRMS (FAB^+) *m*/*z* (rel intensity) 464 [84, (M+H)], 384 (14), 281 (37), 220 (37), 184 (100); HRMS (FAB^+) calcd for $C_{22}H_{34}N_3O_2S_2Si$ (M+H) 464.1862, found 464.1865.

4.1.19. *(R)*-*N*-(4-{1-[3-(4-Trimethylsilanylbenzyl)thioureido]-ethyl}phenyl)methanesulfonamide (14a)

By the same procedure described above, the product was obtained from *N*-[4-[(1*R*)-1-aminoethyl]phenyl]methanesulfonamide (**11**) and **9a** as solid in 61% yield. Mp 96–98 °C; $[\alpha]_D^{20}$ −10.18 (*c* 2.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.41 (d, 2H, J = 8.0 Hz), 7.17 (d, 2H, J = 8.4 Hz), 7.13 (d, 2H, J = 8.4 Hz), 7.09 (d, 2H, J = 6.8 Hz), 5.01 (br s, 1H), 4.58 (s, 2H), 2.92 (s, 3H), 1.42 (d, 3H, J = 6.8 Hz), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 139.7, 137.8, 136.5, 134.0, 127.4, 126.8, 121.5, 53.6, 48.7, 39.6, 23.2, −0.92; IR (KBr) cm^{-1} 3351, 3262, 3024, 2955, 1544, 1325; LRMS (FAB^+) *m*/*z* (rel intensity) 436 [11, (M+H)], 281 (11), 198 (37), 147 (70), 73 (100); HRMS (FAB^+) calcd for $C_{20}H_{30}N_3O_2S_2Si$ (M+H) 436.1549, found 436.1554.

4.1.20. *(R)*-*N*-[4-(1-{3-[4-(Ethyldimethylsilanyl)benzyl]thioureido}ethyl)phenyl]methanesulfonamide (14b)

By the same procedure described above, the product was obtained from **11** and **9b** as solid in 70% yield. Mp 85–87 °C; $[\alpha]_D^{20}$ −8.35 (*c* 2.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.40 (d, 2H, J = 7.6 Hz), 7.17 (d, 2H, J = 8.0 Hz), 7.13 (d, 2H, J = 7.6 Hz), 7.08 (d, 2H, J = 7.6 Hz), 5.00 (br s, 1H), 4.57 (s, 2H), 2.93 (s, 3H), 1.42 (d, 3H, J = 7.0 Hz), 0.89 (t, 3H, J = 7.6 Hz), 0.66 (q, 2H, J = 7.0 Hz), 0.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 139.6, 139.3, 137.6, 136.5, 134.3, 127.4, 126.8, 121.5, 53.5, 48.8, 39.6, 23.2, 7.6, 7.5, −3.3; IR (KBr) cm^{-1} 3350, 3026, 2955, 1613, 1324; LRMS (FAB^+) *m*/*z* (rel intensity) 450 [20, (M+H)], 370 (6), 253 (23), 198 (100); HRMS (FAB^+) calcd for $C_{21}H_{32}N_3O_2S_2Si$ (M+H) 450.1705, found 450.1716.

4.1.21. *(R)*-*N*-(4-{1-[3-(4-Triethylsilanylbenzyl)thioureido]-ethyl}phenyl)methanesulfonamide (14c)

By the same procedure described above, the product was obtained from **11** and **9c** as solid in 72% yield. Mp 89–91 °C; $[\alpha]_D^{20}$ −10.29 (*c* 2.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.39 (d, 2H, J = 7.6 Hz), 7.18 (d, 2H, J = 8.4 Hz), 7.14 (d, 2H, J = 8.4 Hz), 7.10 (d, 2H, J = 6.8 Hz), 5.10 (br s, 1H), 4.58 (s, 2H), 2.93 (s, 3H), 1.42 (d, 3H, J = 6.8 Hz), 0.90 (d, 9H, J = 8.0 Hz), 0.73 (q, 6H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 139.8, 137.6, 137.2, 136.5, 134.0, 127.4, 126.8, 121.5, 53.6, 48.7, 39.6, 23.2, −0.92; IR (KBr) cm^{-1} 3356, 3262, 3025, 2953, 1542, 1325; LRMS (FAB^+) *m*/*z* (rel intensity) 478 [19, (M+H)], 281 (29), 220 (20), 198 (100); HRMS (FAB^+) calcd for $C_{23}H_{36}N_3O_2S_2Si$ (M+H) 478.2018, found 478.2023.

4.1.22. *N*-{2-Fluoro-4-[3-(4-trimethylsilanylbenzyl)thioureidomethyl]phenyl}methanesulfonamide (15)

By the same procedure described above, the product was obtained from **12** and **9a** as solid in 72% yield. Mp 70–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 2H, J = 8.0 Hz), 7.32 (d, 2H, J = 8.0 Hz), 7.22 (d, 2H, J = 8.0 Hz), 6.97 (br s, 1H), 6.94 (m, 2H), 4.61 (s, 2H), 4.55 (s, 2H), 2.91 (s, 3H), 0.21 (s, 9H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 182.3, 155.7, 153.2, 140.1, 137.3, 133.7, 126.7, 124.4, 123.7, 123.4, 114.8, 48.1, 47.2, 39.8, −1.2; IR (KBr) cm^{-1} 3360, 3260, 3025, 2955, 1331, 1157; LRMS (FAB^+) *m/z* (rel intensity) 440 [100, (M+H)], 360 (17), 202 (43), 163 (68); HRMS (FAB^+) calcd for $C_{19}H_{27}FN_3O_2S_2Si$ (M+H) 440.1298, found 440.1296.

4.2. Culture of DRG neurons

DRG neurons were prepared from neonatal Sprague–Dawley rats. DRGs of all spinal levels were dissected aseptically and collected. Ganglia were incubated sequentially for 30 min at 37 °C in 200 U/mL collagenase and 2.5 mg/mL trypsin. The digestion was halted by an addition of an equal volume of DME/F12 medium supplemented with 10% horse serum. The ganglia were then triturated through a fire-polished Pasteur pipet, filtered through nylon membrane, and spun down. Dissociated cells were plated onto Terasaki plates previously coated with 10 μg/mL poly-D-ornithine at a density of 1500–1700 neurons/well. The cells were then cultured for 3 days in DME/F12 medium containing 1.2 g/L sodium bicarbonate, 15 mM HEPES, 50 mg/L gentamycin, and 10% horse serum, diluted 1:1 with identical medium conditioned by C6 glioma cells (2 days on a confluent monolayer) in a humidified atmosphere at 37 °C containing 5% CO_2. Medium was supplemented with 200 ng/mL nerve growth factor. Cytosine arabinoside (100 μM) was added for the first 2 days to kill dividing nonneuronal cells.

4.2.1. $^{45}Ca^{2+}$ Uptake assays

Terasaki plates containing DRG neurons grown for 3 days were equilibrated with four washes of HEPES (10 mM, pH 7.4)-buffered calcium- and magnesium-free Hank's balanced salt solution. The solution in each well was removed from the individual wells. For antagonistic studies, medium (10 μL) containing 10 μCi/mL $^{45}Ca^{2+}$ and 0.5 M capsaicin together with the test concentration of the compound was added to each well. The neurons were incubated at room temperature for 10 min, and then the Terasaki plates were washed six times in HEPES (10 mM, pH 7.4)-buffered calcium and magnesium-free Hank's balanced salt solution and dried in an oven. Sodium dodecyl sulfate (0.3%, 10 μL) was then added to dissolve the cells and extract the $^{45}Ca^{2+}$. The contents of each well were transferred to scintillation vials and counted in 3 mL of aquasol-2 scintillant. Antagonist activities of test compounds were given as IC_{50} (the concentration of the compound necessary to reduce the response to 0.5 μM capsaicin by 50%). The IC_{50} values were estimated at least three replicates at each concentrated. Each compound was tested at least in two independent experiments.

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