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N-[4-(Methylsulfonylamino)benzyl]thiourea analogues as vanilloid receptor antagonists: analysis of structure–activity relationships for the 'C-Region'

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Abstract—We recently reported that *N*-(4-*t*-butylbenzyl)-*N*′-[4-(methylsulfonylamino)benzyl] thiourea (**2**) was a high affinity antagonist of the vanilloid receptor with a binding affinity of $K_i = 63$ nM and an antagonism of $K_i = 53.9$ nM in rat VR1 heterologously expressed in Chinese hamster ovary (CHO) cells (*Mol. Pharmacol.* **2002**, *62*, 947–956). In an effort to further improve binding affinity and antagonistic potency, we have modified the C-region of the lead 4-*t*-butylbenzyl group with diverse surrogates, such as araalkyl, alkyl, 4-alkynylbenzyl, indanyl, 3,3-diarylpropyl, 4-alkoxybenzyl, 4-substituted piperazine and piperidine. The lipophilic surrogates, arylalkyl and alkyl, conferred modest decreases in binding affinities and antagonistic potencies; the groups having heteroatoms resulted in dramatic decreases. Our findings indicate that 4-t-butylbenzyl is one of the most favorable groups for high receptor binding and potent antagonism to VR1 in this structural series.

1. Introduction

The vanilloid receptor VR1[1] is a ligand-gated non-selective cation channel present on polymodal nociceptors, which is activated by protons,[2] heat,[3] natural ligands such as capsaicin (CAP),[4] resiniferatoxin (RTX),[5] and endogenous substances such as anandamide[6] and the lipoxygenase product 12-HPETE.[7] VR1 has been cloned from dorsal root ganglia (DRG) of the rat[8] and from the human,[9] and is structurally a member of the transient receptor potential (TRP) family of channel proteins,[10] oligomerizing as a tetramer.[11] The vanilloid receptor is expressed predominantly on unmyelinated pain-sensing nerve fibers (C-fibers) and small Aδ, fibers in the dorsal root, trigeminal, and nodose ganglia. Since the activation of the vanilloid receptor triggers cation influx resulting in excitation of primary sensory neurons, action potentials, and ultimately the central perception of pain, the blocking of pain-producing activators by VR1 antagonists has been considered as a promising strategy to inhibit the transmission of painful signals from the periphery to the CNS. Proof of principle for this approach has been provided with VR1 antagonists such as capsazepine, iodo-RTX, urea compounds and *N*-[4-(methylsulfonylamino)benzyl]thiourea compounds.

Capsazepine, the first competitive antagonist,[12] has only modest potency and is somewhat non-specific, also antagonizing voltage sensitive calcium channels[13] and the nicotinic cholinergic receptor[14] in rat. In vitro, capsazepine has been shown not only to inhibit capsaicin-mediated responses in rat,[15,16] mouse[17] and guinea pig,[18] but also low pH mediated activation of human or guinea pig but not rat VR1.[19,20] 5-Iodo-RTX, prepared semi-synthetically from RTX by iodination, was reported to display potent antagonism in rat and human VR1.[21,22] More recently, several series of synthetic urea compounds have been described as VR1 antagonists[23–26] and, in particular, BCTC was characterized in vitro and in vivo as a potent, orally-effective, VR1 selective antagonist.[25,26] Potential therapeutic applica-

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tions of these antagonists include chronic pain, such as that associated with diabetic neuropathy, post-herpetic neuralgia, arthritis and cluster headache, urologic problems including detrusor hyperreflexia and bladder hypersensitivity, and pruritus.[1]

Vanilloid receptor ligands such as capsaicin have been divided into three structural regions, the A-, B- and C-regions,[4] as shown in Figure 1. Recently, we discovered that isosteric replacement of the phenolic OH group in the A-region of potent agonists by an alkylsulfonylamido group was able to maintain their strong affinities while modifying their activities from agonism to antagonism.[27–29] The acid dissociation constant of the NH group in alkylsulfonamides is close to that of the phenolic OH group. Its effectiveness as a bioisostere in this setting implies that the NH portion of the alkylsulfonamide hydrogen bonds with the receptor site by aligning itself in a manner closely approximating the phenolic OH group with respect to both bond distances and bond angles. Structure activity analysis of alkylsulfonamides indicated that the methylsulfonamido group was optimal for maximal binding and antagonism.[29] Consequently, the isosteric replacement of the phenolic OH group in the potent agonists *N*-(4-*t*-butylbenzyl)-*N*′-(4-hydroxy-3-methoxybenzyl)thioureas (**1,** $K_i = 58.6$ nM, agonism $EC_{50} = 2.55$ nM)[30] and *N*-(3-acyloxy-2-benzylpropyl)-N′-(4-hydroxy-3-methoxybenzyl)thioureas (**3,** $K_i = 17.4$ nM, agonism $EC_{50} = 1.97$ nM)[31] with the methylsulfonamido group led to the corresponding potent antagonists, **2** ($K_i = 63$ nM, antagonism $K_i = 53.9$ nM)[27] and **4** ($K_i = 29.3$ nM, antagonism $K_i = 67$ nM),[29] with high binding affinities, respectively (Fig. 1).

As a continuation of our effort to optimize the receptor binding affinity and antagonistic potency of the lead antagonists, we have investigated the structure–activity relationships in the C-region of *N*-(4-*t*-butylbenzyl)-*N*′-[4-(methylsulfonylamino)benzyl]thiourea (**2**), in which the *N*-[4-(methylsulfonylamino)benzyl]thiourea group, corresponding to the crucial antagonistic pharmacophore, was fixed as the A- and B-regions and the C-region was substituted with other appropriate hydrophobic groups utilized for analysis of capsaicinoid SAR. In this paper, we describe the synthesis, in vitro characterization using CHO cells heterologously expressing rat VR1, and structure relationship analysis of a series of *N*-4-(methylsulfonylamino)benzyl thiourea analogues.

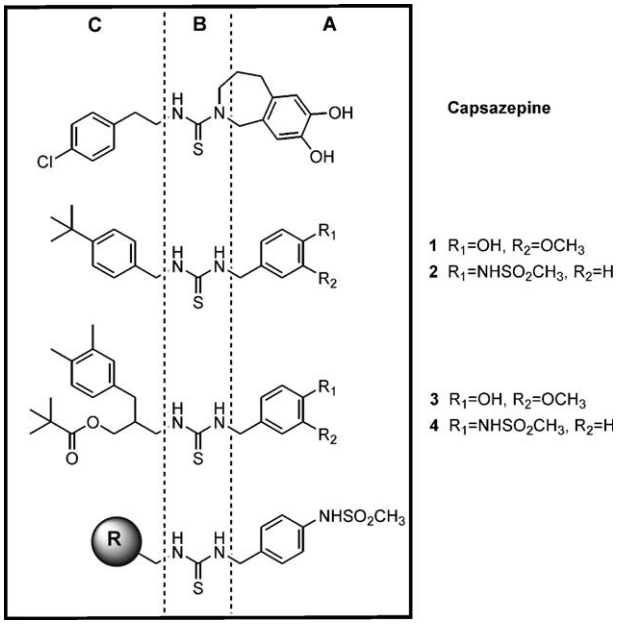
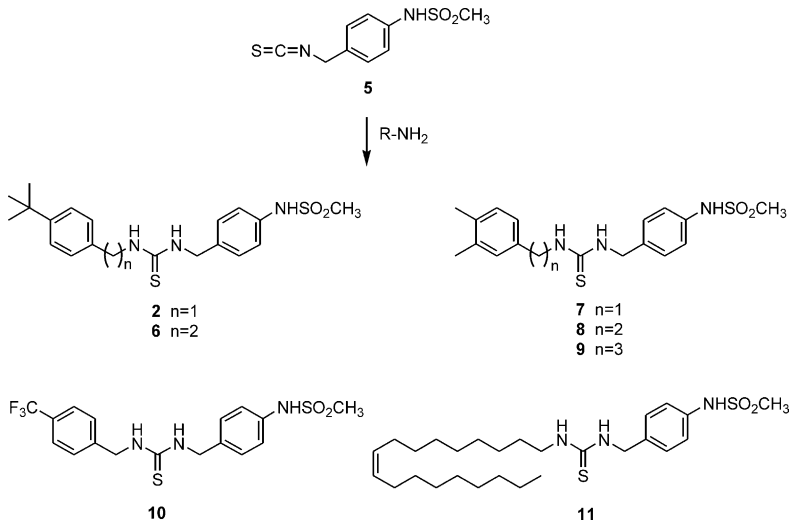


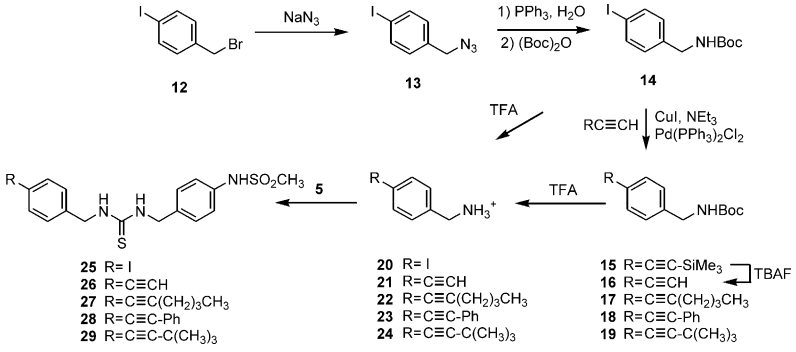
Figure 1.

2. Chemistry

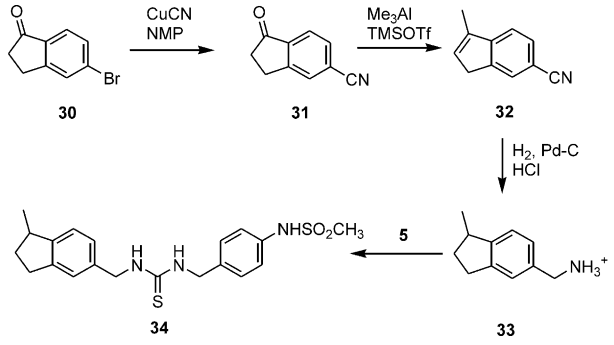
The syntheses of *N*-[4-(methylsulfonylamino)benzyl] thiourea analogues were achieved by the general coupling methods between 4-(methylsulfonylamino)benzyl isothiocyanate (**5**)[29] and the corresponding amines. As shown in Scheme 1, arylalkyl amines, such as 3,4-dimethylphenylmethyl, ethyl, and propyl amines, 4-*t*-butylphenylmethyl, ethyl amines and 4-trifluoromethylbenzyl, and oleyl amine were coupled with isothiocyanate (**5**) to afford the corresponding thioureas **2**, **6**–**11**, respectively. The syntheses of *N*-(4-alkynylbenzyl) thiourea analogues were outlined in Scheme 2. 4-Iodobenzyl bromide (**12**) was converted into *N*-Boc 4-iodobenzyl amine (**14**) in 3 steps. Palladium-catalyzed coupling of **14** with several alkynes followed by *N*-Boc deprotection under acidic conditions provided 4-alkynylbenzyl amines (**20**–**24**), which underwent the general coupling to provide thioureas **25**–**29**. The synthesis of the *N*-(1-methylindan-5-yl)methyl thiourea analogue was shown in Scheme 3. 5-Bromo indanone (**30**) was converted into the corresponding cyanide (**31**) with copper cyanide. The ketone of **31** was methylated and subsequently eliminated to provide 3-methylindene (**32**). Nitrile reduction of **32** followed by the general coupling afforded thiourea **34**. The syntheses of *N*-(3-phenyl-3-arylpropyl) thiourea analogues was represented in Scheme 4. The coupling of cinnamamide (**35**) with several iodobenzenes by the Heck reaction[32] produced 3-phenyl-3-aryl-2-propenamides (**36**–**38**, respectively). The 2-propenamides were reduced to the corresponding propyl amines (**43**–**45**), which, along with commercially available 3,3-diphenylpropyl amine (**42**), underwent the general coupling to afford thioureas **46**–**47**, respectively. The syntheses of *N*-(4-alkoxybenzyl) thiourea analogues were outlined in Scheme 5. 4-Cyanophenol (**50**) was alkylated with several halides to produce 4-alkoxybenzonitriles (**51**–**53**, respectively). Nitrile reduction of **51**–**53** followed by the general coupling produced thioureas **57**–**59**, respectively. *N*-piperazinyl thiourea analogues (**61**, **63**, **65**) were prepared starting from 4-phenyl (**60**), 4-benzyl (**62**), and 4-benzhydryl (**65**) piperazines, respectively, by following the general coupling method as shown in Scheme 6. The syntheses of *N*-piperidinyl thiourea analogues was shown in Schemes 7 and 8. The reaction of N-Boc ethyl isonipecotate (**69**) with phenyl Grignard and subsequent elimination provided 4-diphenylmethylene piperidine (**71**), which was hydrogenated to give 4-benzhydryl piperidine (**73**). Reductive amination of *tert*-butyl-4-oxo-1-piperidinecarboxylate (**75**) with 4-isopropylaniline and 3,4-dimethylaniline followed by *N*-alkylation with 3,4-dimethyl benzyl chloride and 4-bromo-2-



Scheme 1.



Scheme 2.



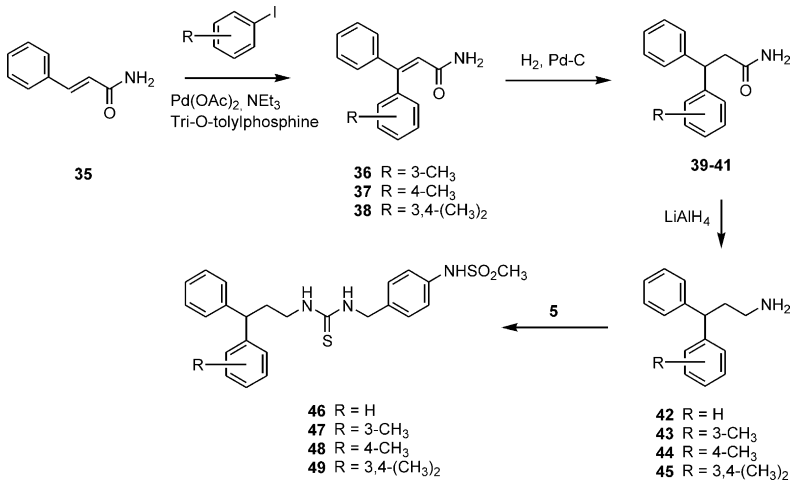
Scheme 3.

methyl-2-butene produced the correponding four 4-dialkylamino piperidines (**78**–**81**). The coupling of the prepared piperidines with isothiocyanate (**5**) afforded N-(4-substituted piperidinyl) thioureas (**72**, **74**, **86**–**89**, respectively).

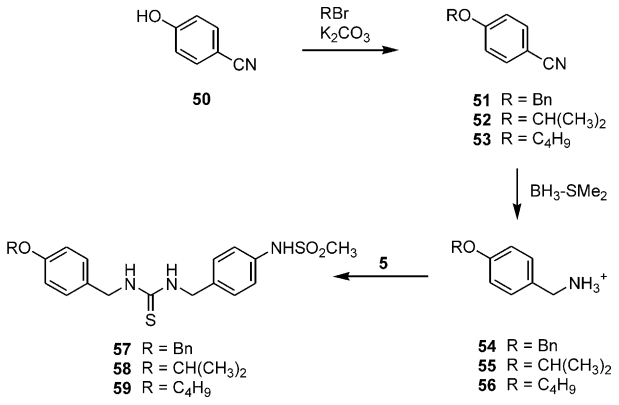
3. Results and discussion

The potencies and activities as agonists and antagonists of the synthesized VR1 ligands were assessed in vitro by a $^{45}Ca^{2+}$ uptake assay, which was carried out using rat VR1 heterologously expressed in Chinese hamster ovary cells (CHO/VR1 cells) as previously described.[29] The in vitro antagonistic potencies of the compounds were evaluated by measuring antagonism of the $^{45}Ca^{2+}$ uptake induced by 50 nM capsaicin and expressed as the $K_i \pm$SEM, respectively, correcting for competition by capsaicin. All compounds were also evaluated as agonists. Potencies as agonists were expressed as $EC_{50} \pm$SEM, and absolute levels of $^{45}Ca^{2+}$ uptake were compared with that induced by a maximally effective concentration of capsaicin in this system, namely 300 nM. Receptor binding affinities were assessed in terms of the ability of the compounds to compete for specific binding of [^{3}H]RTX in the CHO/VR1 system and were expressed as the $K_i \pm$SEM. All values represent the mean of at least three experiments. Determinations of lack of effect represent the results of 1 or 2 experiments. The results are summarized in Table 1.

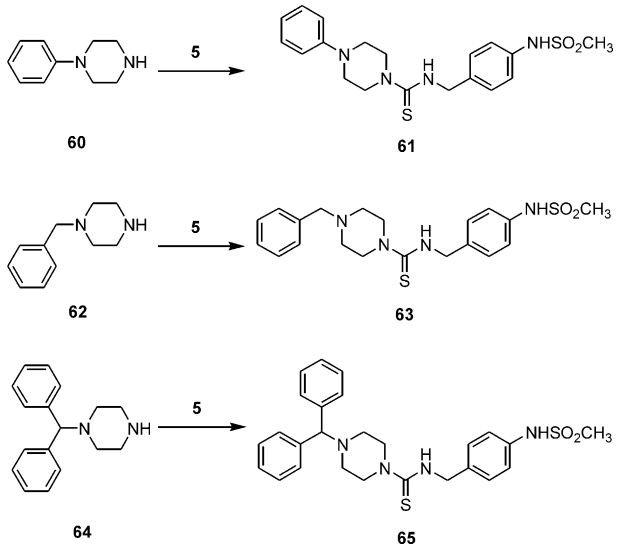
One-carbon elongation of 4-t-butylbenzyl in the parent antagonist (**2**), providing *N*-(4-*t*-butylphenylethyl) thiourea (**6**), led to reduced potencies both in binding affinity with a $K_i = 1260$ nM (20-fold) and in antagonism with an $K_i = 242$ nM (4.5-fold). Since the 3,4-dimethylphenylpropyl group is utilized as the C-region of DA-5018, a capsaicinoid agonist currently under clinical trials, 3,4-dimethylphenyl derivatives (**7**–**9**) were also investigated and proved less potent than the corresponding *t*-butylphenyl analogues. Their antagonism decreased inversely as the carbon length of the linker



Scheme 4.



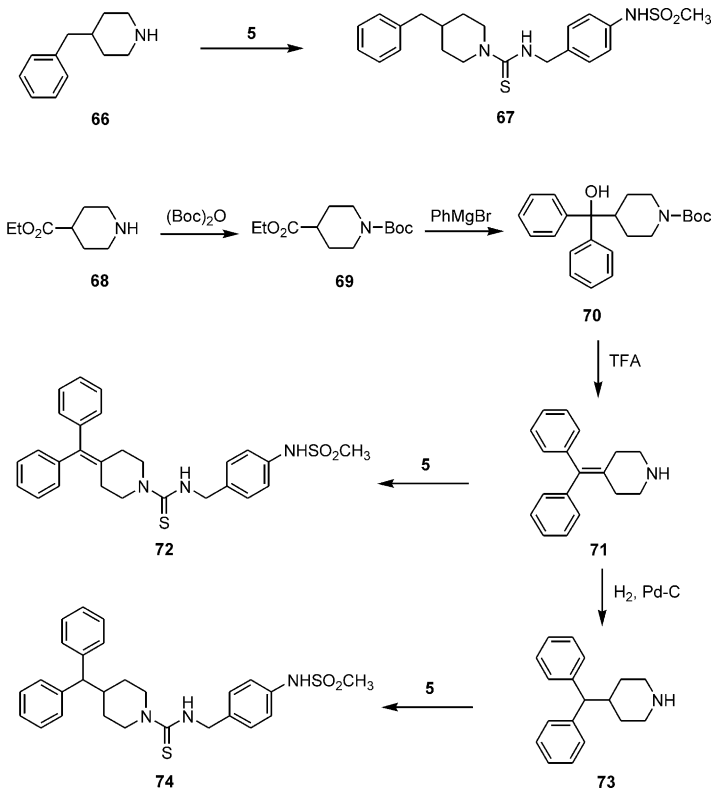
Scheme 5.



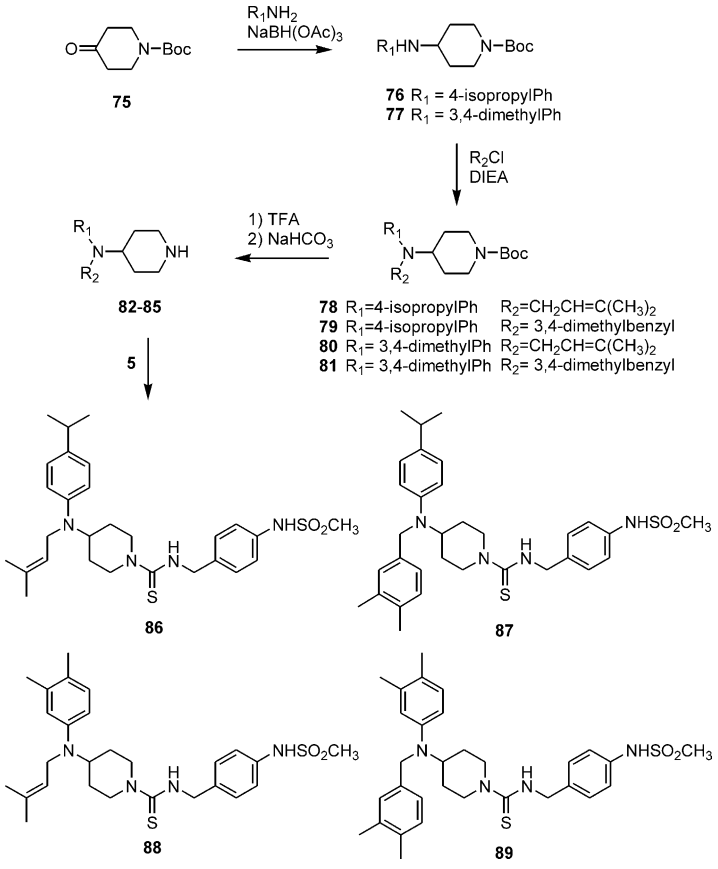
Scheme 6.

increased. The result from these arylalkyl analogues suggested that a short and compact lipophilic group, rather than an extended group, appeared to be preferred as a C-region for better binding ability and antagonism. Replacement of the 4-*t*-butyl group in **2** with a trifluoromethyl group produced compound **10** with modestly reduced potency for binding [$K_i = 678$ nM (11-fold)] and for antagonism [$K_i = 308$ nM (6-fold)]. The N-oleyl analogue (**11**), derived from olvanil, exhibited dramatic loss in binding affinity and antagonism. This finding confirmed that a linear-type group as a C-region was not an appropriate candidate for VR1 antagonism, at least as determined in our assay system. Isosteric substitutions of the 4-*t*-butyl group in **2** were investigated with iodo and several alkyne derivatives, such as ethynyl (**26**), hexynyl (**27**), 2-phenylethynyl (**28**), and 2-*t*-butylethynyl (**29**). The 4-iodo analogue (**25**) showed significantly reduced binding affinity (ca. 30-fold) and antagonistic potency (6-fold) compared to the parent compound. Furthermore, it showed partial agonism. Polarized groups, such as the iodo and trifluoromethyl groups, did not appear to be appropriate surrogates of the 4-*t*-butyl group for binding and antagonism to VR1. The alkyne analogues (**26**–**29**) displayed no antagonism and very weak binding affinities, except for **29,** which had moderate activity. As a conformationally constrained analogue of the 4-*t*-butylphenyl group, the *N*-(1-methylindan-5-yl) analogue (**34**) was examined and displayed modestly reduced potency in binding affinity with a $K_i = 359$ nM (6-fold) and unaltered potency in antagonism with an $EC_{50} = 65.8$ nM. We also investigated *N*-(3,3-diarylpropyl) analogues as replacements for the C-region because these groups provided excellent analgesic activities although their in vitro results were not available.[33] However, their potencies did not exceed that of the lead compound (**1**), and displayed moderately reduced potencies both in binding affinities (6-fold in **46**, 4-fold in **47**, 1.5-fold in **48** and 2-fold in **49**) and antagonism (4-fold in **46**, 10-fold in **47**, 2.5-fold in **48** and 7-fold in **49**). Interestingly, their activity at the receptor was susceptible to minor modification on the benzene ring. Whereas the 4-methylphenyl analogue (**48**) showed full antagonism with antagonistic potency 2-fold weaker than parent, the 3-methylphenyl analogue (**47**) was a partial antagonist with 10-fold weaker potency. The sensitivity of the agonistic/antagonistic character to small variations was also observed in the SAR of capsazepine surrogates.[34]

Resiniferatoxin (RTX) is an ultrapotent capsaicin analogue with a binding potency approximately 4 orders of



Scheme 7.



Scheme 8.

Table 1. Potencies of vanilloid ligands for binding to rat VR1 and for inducing calcium influx in CHO/VR1 cells

	K_i (nM) Binding affinity	EC_{50} (nM) Agonism	K_i (nM) Antagonism
Capsazepine	1300 (±150)	NE[a]	520 (±12)
2	63 (±10)	NE	53.9 (±8.7)
6	1260 (±310)	NE	242 (±78)
7	3120 (±120)	Weak[b]	630 (±120)
8	2090 (±570)	NE	770 (±190)
9	4000 (±1200)	Weak[b]	NE
10	678 (±92)	NE	308 (±94)
11	8200 (±2800)	NE	12400 (±3900)
25	2100 (±460)	Weak[b]	329 (±82)
26	8300 (±1900)	NE	NE
27	>10,000	NE	NE
28	>10,000	NE	NE
29	1650 (±400)	NE	419 (±53)
34	359 (±61)	NE	65.8 (±5.7)
46	390 (±170)	NE	204 (±57)
47	256 (±67)	1460 (±380)	530 (±330)
48	99 (±29)	NE	135 (±16)
49	137 (±28)	NE	360 (±100)
57	>10,000	>4000	NE
58	6000 (±940)	Weak[b]	NE
59	>10,000	NE	NE
61	>10,000	NE	6100 (±2100)
63	2066 (±91)	NE	NE
65	3700(±890)	NE	NE
67	7300 (±1400)	NE	NE
72	>10,000	NE	NE
74	>10,000	NE	NE
86	2000(±590)	NE	NE
87	>10,000	NE	NE
88	1900 (±360)	Weak[b]	weak
89	>10,000	NE	NE

[a] NE: not effective at 10 or 30 μM.
[b] Only fractional calcium uptake compared to 300 nM capsaicin (**6**, 15%; **9**, 48%; **25**, 22%; **58**, 15%; **88**: 20%).

magnitude greater than that of capsaicin.[35] The comparison of their structures powerfully argued that a more complex pharmacophore of the C-region than that of capsaicin could confer a marked enhancement in potency. Based in part on previously published structure–activity relationship studies on RTX,[36] we have proposed four functional groups, 4-hydroxy-3-methoxyphenyl, C_{20}-ester, C_3-keto, and orthophenyl, as principal pharmacophores for interaction with the capsaicin binding site of VR1. The orthophenyl group would reside in the hydrophobic pocket occupied by the fatty chain in the capsaicinoid. Interestingly, there are three oxygens next to the orthophenyl group and they may establish some polar interactions with the receptor. Recently, Appendino et al. observed that 12-hydroxy (ricinoleyl vanillamide, rinvanil) and 12-acetoxy (ricinoleyl vanillamide 12-acetate) analogues of olvanil showed increased efficacy without greatly altered potency compared to olvanil.[37] From that observation, they proposed that polar elements might be present within the apolar pocket accommodating the acyl residue of capsaicin. However, this polar element would not establish a hydrogen bond with the hydroxy of rinvanil, as evidenced by the observation that its activity was significantly increased by acetylation. These findings prompted us to explore lipophilic groups containing heteroatoms capable of interacting with polar elements in the C-region binding site of the receptor. The 4-*t*-butylbenzyl group on the lead antagonist (**2**) was substituted with 4-alkoxybenzyl groups such as 4-(benzyloxy)benzyl, 4-(isopropoxy)benzyl and 4-butoxybenzyl to provide **57**–**59**, respectively. The *N*-(4-benzyloxy)benzyl analogue (**57**) showed great reduction in binding affinity and agonism (with very low potency) rather than antagonism. Although the isopropoxy group of **58** has a similar size compared to *t*-butyl, the binding potency of **58** was reduced 100-fold compared to the parent compound. This result suggested that the oxygen atom of the isopropoxy group might cause repulsive bumping with hydrophobic groups in the binding site of the receptor, resulting in the dramatic loss in binding affinity. Appropriate position of the polar group in the C-region is clearly important; the polar group was located remote from the A,B-region in 12-hydroxy and 12-acetoxy olvanil, both which showed potent agonism.[37] The 4-butoxybenzyl analogue (**59**) displayed no detectable binding affinity or agonism/antagonism in this assay.

Nitrogen containing polar groups were also incorporated into the C-region. Several 4-substituted piperizine and piperidine derivatives were investigated as surrogates of the 4-t-butylbenzyl group. The 4-phenyl (**61**), 4-benzyl (**63**) and 4-diphenylmethyl (**65**) piperazine analogues exhibited very weak binding affinities and lack of agonism/antagonism. Similarly, 4-benzyl (**67**), 4-diphenylmethylene (**72**) and 4-diphenylmethyl (**74**) piperidine also showed almost complete loss of affinities for binding and agonism/antagonism. It is noteworthy that the

4-nitrogen of piperazine provided rather favorable binding because piperazine **63** and **65** had better binding affinities than the corresponding piperidine analogues **67** and **74**, respectively. Finally, 4-disubstituted amino piperidine analogues (**86–89**) were prepared as structural combinations of 4-substituted piperazine and 4-alkylpiperidine. However, none of these analogues displayed any significant agonism/antagonism and the 3-methyl-2-butenylamino piperidine analogues (**86**, **88**) showed only weak binding affinity.

In conclusion, on the basis of the recent discovery of *N*-(4-*t*-butylbenzyl)-*N*′-[4-(methylsulfonylamino)benzyl] thiourea (**2**) as a potent vanilloid receptor antagonist, the structure–activity relationships of the C-region were investigated on the template of *N*-[4-(methylsulfonylamino)benzyl]thiourea, fixed as A and B-regions. Diverse surrogates including araalkyl, alkyl, 4-alkynylbenzyl, indanyl, 3,3-diarylpropyl, 4-alkoxybenzyl, 4-substituted piperazine and piperidine were substituted for the 4-*t*-butylbenzyl group of **2** in an effort to optimize antagonism. However, none of synthesized compounds showed any significant improvement in binding affinity and antagonistic potency compared to **2**. We conclude that the 4-*t*-butylbenzyl group is so far one of most favorable groups for receptor binding and antagonism as was similarly found in a series of capsaicinoid agonists.

4. Experimental

4.1. General method

All chemical reagents were commercially available. Melting points were determined on a Melting Point Büchi B-540 apparatus and are uncorrected. Silica gel column chromatography was performed on silica gel 60, 230-400 mesh, Merck. Proton NMR spectra were recorded on a JEOL JNM-LA 300 at 300 MHz. Chemical shifts are reported in ppm units with Me_4Si as a reference standard. Mass spectra were recorded on a VG Trio-2 GC-MS. Combustion analyses were performed on an EA 1110 Automatic Elemental Analyzer, CE Instruments, and were within 0.4% of the calculated values unless otherwise noted.

4.2. General procedure for thiourea synthesis

4.2.1. Method A. A solution of amine (1 mmol) was treated with 4-(methylsulfonylamino)benzyl isothiocyanate (1 mmol, 242 mg) in CH_2Cl_2 (10 mL), stirred overnight at room temperature and then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes as eluant.

4.2.2. Method B. A solution of amine salt (1 mmol) in DMF (5 mL) was treated with triethylamine (0.2 mL, 1.5 mmol) and 4-(methylsulfonylamino)benzyl isothiocyanate (242 mg, 1 mmol), and stirred overnight at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes as eluant.

4.2.3. *N*-(4-*tert*-Butylphenylethyl)-*N*′-[-4-(methylsulfonylamino)benzyl]thiourea (6). Compound **6** was prepared by following the general procedure for thiourea synthesis (Method A) in 93% yield.: white solid, mp = 58 °C; ^{1}H NMR ($CDCl_3$) δ 7.33 (d, 2H, J = 8.3 Hz), 7.27 (d, 2H, J = 8.3 Hz), 7.18 (d, 2H, J = 8.3 Hz), 7.10 (d, 2H, J = 8.3 Hz), 6.32 (s, 1H, $NHSO_2$), 5.70 (bs, 1H, NHCS), 5.60 (bs, 1H, NHCS), 4.56 (bs, 2H, $NHCH_2Ar$), 3.72 (bs, 2H, $NHCH_2CH_2Ar$), 3.01 (s, 3H, SO_2CH_3), 2.86 (t, 2H, J = 6.8 Hz, $NHCH_2CH_2Ar$), 1.31 (s, 9H, $C(CH_3)_3$); MS (FAB) m/z 420 (MH^+). Anal. calcd for $C_{21}H_{29}N_3O_2S_2$: C, 60.11; H, 6.97; N, 10.01; S, 15.28. Found: C, 60.39; H, 7.00; N, 9.97; S, 15.24.

4.2.4. *N*-(3,4-Dimethylbenzyl)-*N*′-[-4-(methylsulfonylamino)benzyl]thiourea (7). Compound **7** was prepared by following the general procedure for thiourea synthesis (Method A) in 94% yield: white solid, mp = 110 °C; ^{1}H NMR ($CDCl_3$) δ 6.97–7.25 (m, 7H), 6.68 (s, 1H, $NHSO_2$), 6.20 (bs, 1H, NHCS), 6.01 (bs, 1H, NHCS), 4.65 (d, 2H, J = 5.4 Hz, $NHCH_2$), 4.51 (d, 2H, J = 5.2 Hz, $NHCH_2$), 3.00 (s, 3H, SO_2CH_3), 2.15–2.30 (m, 6H, 2×CH_3); MS (FAB) m/z 378 (MH^+). Anal. calcd for $C_{18}H_{23}N_3O_2S_2$: C, 57.27; H, 6.14; N, 11.13; S, 16.99. Found: C, 57.49; H, 6.16; N, 11.09; S, 16.91.

4.2.5. *N*-(3,4-Dimethylphenylethyl)-*N*′-[-4-(methylsulfonylamino)benzyl]thiourea (8). Compound **8** was prepared by following the general procedure for thiourea synthesis (Method A) in 92% yield: white solid, mp = 134 °C; ^{1}H NMR ($CDCl_3$) δ 7.14–7.25 (m, 4H), 6.85–7.05 (m, 3H), 6.68 (s, 1H, $NHSO_2$), 5.90 (bs, 1H, NHCS), 5.80 (bs, 1H, NHCS), 4.55 (bs, 2H, $NHCH_2Ar$), 3.66 (bs, 2H, $NHCH_2CH_2Ar$), 3.00 (s, 3H, SO_2CH_3), 2.93 (t, 1H, J = 7 Hz, $NHCH_2CH_2Ar$), 2.82 (t, 1H, J = 7 Hz, $NHCH_2CH_2Ar$), 2.2–2.3 (m, 6H, 2×CH_3); MS (FAB) m/z 392 (MH^+). Anal. calcd for $C_{19}H_{25}N_3O_2S_2$: C, 58.28; H, 6.44; N, 10.73; S, 16.38. Found: C, 58.52; H, 6.47; N, 10.70; S, 16.32.

4.2.6. *N*-(3,4-Dimethylphenylpropyl)-*N*′-[-4-(methylsulfonylamino)benzyl]thiourea (9). Compound **9** was prepared by following the general procedure for thiourea synthesis (Method A) in 94% yield: white solid, mp = 125–127 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (d, 2H, J = 8.3 Hz, 2H), 7.19 (d, 2H, J = 8.3 Hz, 2H), 6.85–7.05 (m, 3H), 6.80 (s, 1H, $NHSO_2$), 5.91 (bs, 2H, 2×NHCS), 4.56 (bs, 2H, $NHCH_2Ar$), 3.38 (bs, 2H, $NHCH_2CH_2CH_2Ar$), 2.99 (s, 3H, SO_2CH_3), 2.59 (t, 2H, J = 7.3 Hz, $NHCH_2CH_2CH_2Ar$), 2.20 (d, 6H, 2×CH_3), 1.90 (m, 2H, $NHCH_2CH_2CH_2Ar$); MS (FAB) m/z 406 (MH^+). Anal. calcd for $C_{20}H_{27}N_3O_2S_2$: C, 59.23; H, 6.71; N, 10.36; S, 15.81. Found: C, 59.48; H, 6.74; N, 10.31; S, 15.76.

4.2.7. *N*-(4-Trifluoromethylbenzyl)-*N*′-[-4-(methylsulfonylamino)benzyl]thiourea (10). Compound **10** was pre-

pared by following the general procedure for thiourea synthesis (Method A) in 90% yield: white solid, mp = 154 °C; ^{1}H NMR (DMSO-d_6) δ 9.66 (s, 1H, $NHSO_2$), 8.03 (bs, 2H, NHCS), 7.67 (d, 2H, J = 8.0 Hz), 7.45 (d, 2H, J = 7.8 Hz), 7.23 (d, 2H, J = 7.8 Hz), 7.15 (d, 2H, J = 8.0 Hz), 4.76 (bs, 2H, $NHCH_2$), 4.61 (bs, 2H, $NHCH_2$), 2.94 (s, 3H, SO_2CH_3); MS (FAB) m/z 418 (MH^+). Anal. calcd for $C_{17}H_{18}F_3N_3O_2S_2$: C, 48.91; H, 4.35; N, 10.07; S, 15.36. Found: C, 49.25; H, 4.38; N, 10.03; S, 15.31.

4.2.8. *N*-Oleyl-*N*′-[-4-(methylsulfonylamino)benzyl]-thiourea (11). Compound **11** was prepared by following the general procedure for thiourea synthesis (Method A) in 88% yield: white solid, mp = 133 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, 2H, J = 8.3 Hz), 7.20 (d, 2H, J = 8.3 Hz), 6.53 (s, 1H, $NHSO_2$), 5.85 (bs, 1H, NHCS), 5.34 (m, 2H, CH = CH), 4.71 (bs, 2H, $NHCH_2$), 3.32 (bs, 2H, $NHCH_2CH_2$), 3.02 (s, 3H, SO_2CH_3), 2.00 (m, 4H, $CH_2CH=CHCH_2$), 1.56 (m, 2H, $NHCH_2CH_2$), 1.25–1.3 (m, 22H), 0.88 (t, 3H, CH_3); MS (FAB) m/z 510 (MH^+). Anal. calcd for $C_{27}H_{47}N_3O_2S_2$: C, 63.61; H, 9.29; N, 8.24; S, 12.58. Found: C, 63.90; H, 9.33; N, 8.20; S, 12.54.

4.2.9. 4-Iodobenzyl azide (13). A solution of 4-iodobenzyl bromide (**12**) (1.485 g, 5 mmol) in DMF (5 mL) was treated with sodium azide (0.975 g, 15 mmol) and stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:10) as eluant to afford **13** (1.282 g, 99%) as a white solid: mp = 36 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 2H, J = 8.3 Hz), 7.06 (d, 2H, J = 8.3 Hz), 4.29 (s, 2H, CH_2).

4.2.10. *tert*-Butyl *N*-(4-iodobenzyl)carbamate (14). A solution of **13** (1.036 g, 4 mmol) in THF (25 mL) was treated with triphenylphosphine (1.5 g, 4 mmol) and H_2O (0.36 g, 20 mmol). After being stirred overnight at room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in THF (40 mL) and treated with triethylamine (1.115 mL, 8 mmol) and di-*tert*-butyl dicarbonate (1.746 mL, 8 mmol). After being stirred at room temperature for 3 h, the reaction mixture was diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:3) as eluant to afford **14** (1.146 g, 86%) as a white solid: mp = 91 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2H, J = 8.3 Hz), 7.03 (d, 2H, J = 8.3 Hz), 4.85 (bs, 1H, NH), 4.25 (d, 2H, J = 5.8 Hz, CH_2), 1.45 (s, 9H, $C(CH_3)_3$).

4.2.11. *tert*-Butyl *N*-{4-[2-(trimethylsilyl)ethynyl]benzyl}-carbamate (15). A solution of **14** (666 mg, 2 mmol) in THF (20 mL) was treated with (trimethylsilyl)acetylene (0.34 mL, 2.4 mmol), triethylamine (0.557 mL, 4 mmol), copper(I) iodide (38 mg, 0.2 mmol) and dichlorobis (triphenylphosphine)palladium (I) (70 mg, 0.1 mmol), and stirred at room temperature for 3 h. The reaction mixture was diluted with ether, filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:10) to afford **15** (721 mg, 99%) as a yellow solid: mp = 95 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 2H, J = 8.0 Hz), 7.18 (d, 2H, J = 8.0 Hz), 4.79 (bs, 1H, NH), 4.28 (d, 2H, J = 5.1 Hz, CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 0.23 (s, 9H, $Si(CH_3)_3$).

4.2.12. *tert*-Butyl *N*-(4-ethynylbenzyl)carbamate (16). A solution of **15** (530 mg, 1.75 mmol) in THF (10 mL) was treated with tetrabutylammonium fluoride (1.0 M, 3.5 mL, 3.5 mmol) and stirred at room temperature for 1 h. After evaporation, the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:5) as eluant to afford **16** (430 mg, 100%) as a white solid: mp = 82 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 2H, J = 8.3 Hz), 7.23 (d, 2H, J = 8.3 Hz), 4.85 (bs, 1H, NH), 4.31 (d, 2H, J = 5.6 Hz, CH_2), 3.06 (s, 1H, CH≡C), 1.46 (s, 9H, $C(CH_3)_3$).

4.2.13. *tert*-Butyl *N*-[4-(1-hexynyl)benzyl]carbamate (17). Compound **17** was prepared from 1-hexyne by following the procedure described for the synthesis of **15** in 98% yield: yellow solid, mp = 62 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, 2H, J = 8.3 Hz), 7.19 (d, 2H, J = 8.3 Hz), 4.81 (bs, 1H, NH), 4.29 (d, 2H, J = 5.9 Hz, CH_2NH), 2.40 (t, 2H, J = 7.1 Hz, $C=CCH_2$), 1.45-1.65 (m, 4H, CH_2CH_2), 1.46 (s, 9H, $C(CH_3)_3$), 0.95 (t, 2H, J = 7.3 Hz, CH_3).

4.2.14. *tert*-Butyl *N*-[4-(2-phenylethynyl)benzyl]carbamate (18). Compound **18** was prepared from phenylacetylene by following the procedure described for the synthesis of **15** in 98% yield: yellow solid, mp = 136 °C; ^{1}H NMR ($CDCl_3$) δ 7.45–7.55 (m, 4H), 7.3–7.38 (m, 3H), 7.27 (d, 2H, J = 8.3 Hz), 4.84 (bs, 1H, NH), 4.33 (d, 2H, J = 5.6 Hz, CH_2NH), 1.47 (s, 9H, $C(CH_3)_3$).

4.2.15. *tert*-Butyl *N*-[4-(3,3-dimethyl-1-butynyl)benzyl]-carbamate (19). Compound **19** was prepared from *tert*-butylacetylene by following the procedure described for the synthesis of **15** in 99% yield: yellow solid, mp = 103 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 2H, J = 8.3 Hz), 7.18 (d, 2H, J = 8.3 Hz), 4.79 (bs, 1H, NH), 4.28 (d, 2H, J = 5.6 Hz, CH_2NH), 1.45 (s, 9H, $C(CH_3)_3$), 1.31 (s, 9H, $C\equiv CC(CH_3)_3$).

4.2.16. 4-Iodobenzyl amine trifluoroacetate (20). A cooled solution of **14** (333 mg, 1 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with trifluoroacetic acid (1 mL). After being stirred at room temperature for 1 h, the reaction mixture was evaporated. The residue was diluted with EtOAc and concentrated in vacuo several times to afford **20** (330 mg, 95%) as white solid, which was used for the next coupling with further purification: mp = 164 °C; ^{1}H NMR (acetone-d_6) δ 7.76 (d, 2H, J = 8.3 Hz), 7.32 (d, 2H, J = 8.3 Hz), 4.98 (s, 2H, CH_2).

4.2.17. 4-Ethynylbenzyl amine trifluoroacetate (21). Compound **21** was prepared from **16** by following the

procedure described for the synthesis of **20** in 98% yield.: white solid, mp = 182 °C; ^{1}H NMR (acetone-d_6) δ 7.50 (s, 4H), 5.03 (s, 2H, CH_2), 3.69 (s, 1H, CH≡C).

4.2.18. 4-(1-Hexynyl)benzyl amine trifluoroacetate (22). Compound **22** was prepared from **17** by following the procedure described for the synthesis of **20** in 98% yield: red solid, mp = 160 °C; ^{1}H NMR (DMSO-d_6) δ 8.20 (bs, 3H, NH_3^+), 7.41 (m, 4H), 4.02 (d, 2H, $CH_2NH_3^+$), 2.42 (t, 2H, J = 6.8 Hz, C≡CCH_2), 1.35–1.55 (m, 4H, CH_2CH_2), 0.90 (t, 2H, J = 7.1 Hz, CH_3).

4.2.19. 4-(2-Phenylethynyl)benzyl amine trifluoroacetate (23). Compound **23** was prepared from **18** by following the procedure described for the synthesis of **20** in 88% yield.: red solid, mp = 185 °C; ^{1}H NMR (DMSO-d_6) δ 8.17 (bs, 3H, NH_3), 7.4–7.65 (m, 9H), 4.08 (bs, 2H, $CH_2NH_3^+$).

4.2.20. 4-(3,3-Dimethyl-1-butynyl)benzyl amine trifluoroacetate (24). Compound **24** was prepared from **19** by following the procedure described for the synthesis of **20** in 97% yield: brown solid, mp = 180 °C; ^{1}H NMR (DMSO-d_6) δ 8.00 (bs, 3H, NH_3), 7.36 (d, 2H, J = 7.3 Hz), 7.21 (d, 2H, J = 7.3 Hz), 3.89 (bs, 2H, $CH_2NH_3^+$), 1.29 (s, 9H, C≡C$C(CH_3)_3$).

4.2.21. *N*-(4-Iodobenzyl)-*N′*-[4-(methylsulfonylamino)-benzyl]thiourea (25). Compound **25** was prepared by following the general procedure for thiourea synthesis (Method B) in 73% yield: white solid, mp = 186 °C; ^{1}H NMR (acetone-d_6) δ 8.52 (bs, 1H, NH), 7.68 (d, 2H, J = 8.2 Hz), 7.46 (bs, 1H, NH), 7.30 (m, 4H), 7.15 (d, 2H, J = 8.0 Hz), 4.78 (m, 4H, $CH_2NHCSNHCH_2$), 2.96 (s, 3H, SO_2CH_3); IR (KBr) 3229, 1543, 1321, 1146 cm^{-1}; MS (FAB) m/z 476 (MH^+). Anal. calcd for $C_{16}H_{18}IN_3O_2S_2$: C, 40.43; H, 3.82; N, 8.84; S, 13.49. Found: C, 40.62; H, 3.86; N, 8.80; S, 13.45.

4.2.22. *N*-(4-Ethynylbenzyl)-*N′*-[4-(methylsulfonylamino) benzyl]thiourea (26). Compound **26** was prepared by following the general procedure for thiourea synthesis (Method B) in 80% yield: white solid, mp = 158 °C; ^{1}H NMR (acetone-d_6) δ 7.54 (bs, 2H, NH), 7.2–7.5 (m, 8H), 4.84 (d, 2H, J = 4.9 Hz, $NHCH_2Ar$), 4.77 (d, 2H, J = 5.1 Hz, $NHCH_2Ar$), 3.30 (s, 1H, C≡CH), 2.93 (s, 3H, $NHSO_2CH_3$); IR (KBr) 2918, 1540, 1319, 1146 cm^{-1}; MS (FAB) m/z 374 (MH^+). Anal. calcd for $C_{18}H_{19}N_3O_2S_2$: C, 57.88; H, 5.13; N, 11.25; S, 17.17. Found: C, 57.59; H, 5.18; N, 11.20; S, 17.13.

4.2.23. *N*-[4-(1-Hexynyl)benzyl]-*N′*-[4-(methylsulfonylamino)benzyl]thiourea (27). Compound **27** was prepared by following the general procedure for thiourea synthesis (Method B) in 70% yield: white solid, mp = 161 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 2H, J = 8.0 Hz), 7.1–7.25 (m, 6H), 6.10 (bs, 1H, NH), 6.00 (bs, 1H, NH), 4.65 (d, 2H, J = 5.1 Hz, $NHCH_2Ar$), 4.61 (d, 2H, J = 4.9 Hz, $NHCH_2Ar$), 2.99 (s, 3H, SO_2CH_3), 2.41 (t, 2H, J = 6.8 Hz, C≡CCH_2), 1.4–1.7 (m, 4H, CH_2CH_2), 0.95 (t, 2H, CH_3); IR (KBr) 3436, 3239, 2931, 1634, 1553, 1323, 1147 cm^{-1}; MS (FAB) m/z 430 (MH^+). Anal. calcd for $C_{22}H_{27}N_3O_2S_2$: C, 61.51; H, 6.33; N, 9.78; S, 14.93. Found: C, 61.27; H, 6.36; N, 9.75; S, 14.98.

4.2.24. *N*-[4-(2-Phenylethynyl)benzyl]-*N′*-[4-(methylsulfonylamino)benzyl]thiourea (28). Compound **28** was prepared by following the general procedure for thiourea synthesis (Method B) in 82% yield: white solid, mp = 197 °C; ^{1}H NMR (acetone-d_6) δ 7.25–7.6 (m, 13H, Ar), 4.87 (d, 2H, J = 6.1 Hz, $NHCH_2Ar$), 4.79 (d, 2H, J = 5.9 Hz, $NHCH_2Ar$), 2.95 (s, 3H, $NHSO_2CH_3$); IR (KBr) 3435, 1627, 1550, 1324, 1136 cm^{-1}; MS (FAB) m/z 450 (MH^+). Anal. calcd for $C_{24}H_{23}N_3O_2S_2$: C, 64.12; H, 5.16; N, 9.35; S, 14.26. Found: C, 64.45; H, 5.13; N, 9.30; S,14.15.

4.2.25. *N*-[4-(3,3-Dimethyl-1-butynyl)benzyl]-*N′*-[4-(methylsulfonylamino)benzyl]thiourea (29). Compound **29** was prepared by following the general procedure for thiourea synthesis (Method B) in 88% yield: white solid, mp = 174 °C; ^{1}H NMR (acetone-d_6) δ 8.49 (bs, 1H, $NHSO_2$), 7.25–7.4 (m, 8H, Ar), 4.81 (d, 2H, J = 5.6 Hz, $NHCH_2Ar$), 4.78 (d, 2H, J = 5.6 Hz, $NHCH_2Ar$), 2.95 (s, 3H, $NHSO_2CH_3$), 1.29 (s, 9H, $C(CH_3)_3$); IR (KBr) 3434, 3270, 2927, 1541, 1510, 1319, 1145 cm^{-1}; MS (FAB) m/z 430 (MH^+). Anal. calcd for $C_{22}H_{27}N_3O_2S_2$: C, 61.51; H, 6.33; N, 9.78; S, 14.93. Found: C, 61.58; H, 6.31; N, 9.80; S, 14.90.

4.2.26. 5-Cyano-1-indanone (31). A solution of 5-bromo-1-indanone (**30**) (200 mg, 0.95 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was treated with copper cyanide (170 mg, 1.9 mmol) and heated at 140 °C for 20 h. After cooling, the mixture was directly purified by flash column chromatography on silica gel with EtOAc/hexanes (1:3) as eluant to afford **31** (158 mg, 76%) as a crystalline yellowish solid: mp = 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, J = 7.8 Hz, H-7), 7.81 (bs, 1H, H-4), 7.66 (dd, 1H, J = 7.8, 2 Hz, H-6), 3.22 (t, 2H, J = 5.8 Hz, H-3), 2.78 (m, 2H, H-2); IR (KBr) 2228 (CN), 1714 (C=O) cm^{-1}.

4.2.27. 6-Cyano-3-methyl-1H-indene (32). A cooled solution of **31** (100 mg, 0.64 mmol) in CH_2Cl_2 (2 mL) at 0 °C was treated with trimethyl aluminum (0.96 mL, 2 M in hexanes, 1.92 mmol) followed by trimethylsilyl trifluoromethanesulfonate (0.256 mL, 1.28 mmol) and stirred for 3 h at room temperature. The mixture was cooled, diluted with H_2O, and extracted with ether several times. The combined organic layer was concentrated and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:5) as eluant to afford **32** (87 mg, 88%) as a colorless oil.: ^{1}H NMR ($CDCl_3$) δ 7.69 (bs, 1H, H-7), 7.61 (dd, 1H, J = 7.8, 2 Hz, H-5), 7.38 (d, 1H, J = 7.8 Hz, H-4), 6.44 (m, 1H, H-2), 3.37 (m, 2H, H-1), 2.18 (m, 3H, CH_3).

4.2.28. (1-Methyl-indan-5-yl)methylamine hydrochloride (33). A suspension of **32** (80 mg, 0.515 mmol) and 10% palladium on carbon (40 mg) in MeOH (5 mL) was treated with concentrated hydrochloric acid (2 drops) and hydrogenated under a balloon of hydrogen overnight. The mixture was filtered through Celite and the filtrate was concentrated to afford **33** (94 mg, 92%) as a white solid, which was used for the next step after washing with ether several times: white solid, mp = 198–200 °C; ^{1}H NMR (CD_3OD) δ 7.2–7.3 (m, 3H, Ar), 4.05

(s, 2H, $CH_2NH_3^+$), 3.18 (m, 1H, H-1), 2.8–3.0 (m, 2H, H-3), 2.34 (m, 1H, H-2a), 1.60 (m, 1H, H-2b), 1.26 (d, 3H, $J = 6.8$ Hz, CH_3).

4.2.29. *N*-[(1-Methyl-indan-5-yl)methyl]-*N*′-[4-(methylsulfonylamino)benzyl]thiourea (34). Compound **34** was prepared by following the general procedure for thiourea synthesis (Method B) in 52% yield: white solid, mp = 69–71 °C; ^{1}H NMR ($CDCl_3$) δ 7.0–7.2 (m, 7H, Ar), 6.94 (bs, 1H, $NHSO_2$), 6.30 (bs, 1H, NH), 6.12 (bs, 1H, NH), 4.64 (d, 2H, $J = 5.1$ Hz, CH_2NH), 4.55 (d, 2H, $J = 5.0$ Hz, CH_2NH), 3.15 (m, 1H, H-1), 3.98 (s, 3H, SO_2CH_3), 2.7–2.9 (m, 2H, H-3), 2.30 (m, 1H, H-2a), 1.60 (m, 1H, H-2b), 1.26 (d, 3H, $J = 6.8$ Hz, CH_3); IR (KBr) 3359, 2954, 1556, 1327, 1152 cm^{-1}; MS (FAB) *m*/*z* 404 (MH^+). Anal. calcd for $C_{20}H_{25}N_3O_2S_2$: C, 59.52; H, 6.24; N, 10.41; S, 15.89. Found: C, 59.79; H, 6.28; N, 10.37; S, 15.84.

4.2.30. 3-(3-Methylphenyl)-3-phenyl-2-propenamide (36). A mixture of cinnamamide (1 g, 6.8 mmol), 3-iodotoluene (1.927 g, 8.84 mmol), triethylamine (1.24 mL, 8.84 mmol), palladium(II) acetate (15 mg, 0.07 mmol) and tri-*O*-tolylphosphine (83 mg, 0.27 mmol) in 1,2-dichlorobenzene (15 mL) was heated at 120 °C for 20 h. The reaction mixture was diluted with water and extracted with EtOAc several times. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (2:1) as eluant to afford **36** (1.614 g, 90%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.1–7.5 (m, 9H, Ar), 6.38 (s, 1H, C = CH), 5.17 (bs, 1H, NH_2), 5.00 (bs, 1H, NH_2), 2.35 (s, 3H, CH_3).

4.2.31. 3-(4-Methylphenyl)-3-phenyl-2-propenamide (37). Compound **37** was prepared from 4-iodotoluene by following the procedure described for the synthesis of **36** in 98% yield: white solid; ^{1}H NMR ($CDCl_3$) δ 7.0–7.5 (m, 9H, Ar), 6.38 (s, 1H, C = CH), 5.26 (bs, 1H, NH_2), 5.04 (bs, 1H, NH_2), 2.32 (s, 3H, CH_3).

4.2.32. 3-(3,4-Dimethylphenyl)-3-phenyl-2-propenamide (38). Compound **38** was prepared from 4-iodo-o-xylene by following the procedure described for the synthesis of **36** in 98% yield: white solid; ^{1}H NMR ($CDCl_3$) δ 7.0–7.5 (m, 8H, Ar), 6.37 (s, 1H, C = CH), 5.23 (bs, 1H, NH_2), 5.01 (bs, 1H, NH_2), 2.26 (s, 3H, CH_3), 2.22 (s, 3H, CH_3).

4.2.33. 3-(3-Methylphenyl)-3-phenyl-2-propanamide (39). A suspension of **36** (1.186 g, 5 mmol) and 5% palladium on carbon (100 mg) in MeOH (20 mL) was hydrogenated under a balloon of hydrogen for 16 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo to afford **39** (1.16 g, 97%) as a white solid, which was used for the next step without further purification.: ^{1}H NMR ($CDCl_3$) δ 6.95–7.4 (m, 9H, Ar), 5.18 (bs, 2H, NH_2), 4.51 (t, 1H, $J = 7.8$ Hz, CH), 2.94 (d, 2H, $J = 7.8$ Hz, CH_2), 2.30 (s, 3H, CH_3).

4.2.34. 3-(4-Methylphenyl)-3-phenyl-2-propanamide (40). Compound **40** was prepared from **37** by following the procedure described for the synthesis of **39** in 98% yield: yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.95–7.4 (m, 9H, Ar), 5.79 (bs, 1H, NH_2), 5.49 (bs, 1H, NH_2), 4.47 (t, 1H, $J = 7.8$ Hz, CH), 2.88 (d, 2H, $J = 7.8$ Hz, CH_2), 2.27 (s, 3H, CH_3).

4.2.35. 3-(3,4-Dimethylphenyl)-3-phenyl-2-propanamide (41). Compound **41** was prepared from **38** by following the procedure described for the synthesis of **39** in 99% yield: white solid; ^{1}H NMR ($CDCl_3$) δ 6.95–7.3 (m, 8H, Ar), 5.66 (bs, 1H, NH_2), 5.45 (bs, 1H, NH_2), 4.45 (t, 1H, $J = 7.8$ Hz, CH), 2.90 (d, 2H, $J = 7.8$ Hz, CH_2), 2.19 (s, 6H, $2\times CH_3$).

4.2.36. 3-(3-Methylphenyl)-3-phenyl-2-propylamine (43). A cooled solution of lithium aluminium hydride (190 mg, 5 mmol) in THF (5 mL) at 0 °C was treated with a solution of **39** (478 mg, 2 mmol) in THF (5 mL) dropwise. After being refluxed for 4 h, the reaction mixture was cooled in ice-bath and treated by successive dropwise addition of H_2O (0.2 mL), 15% NaOH solution (0.4 mL), and H_2O (0.6 mL). After additional stirring for 30 min, the mixture was filtered by washing with EtOAc and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with CH_2Cl_2/MeOH (10:1) as eluant to afford **43** (347 mg, 77%) as a brown oil.: ^{1}H NMR ($CDCl_3$) δ 6.95–7.4 (m, 9H, Ar), 3.97 (t, 1H, $J = 7.8$ Hz, CH), 3.30 (bs, 2H, NH_2), 2.68 (t, 2H, $J = 6.8$ Hz, CH_2NH_2), 2.1–2.3 (s, 5H, $CHCH_2$ and CH_3).

4.2.37. 3-(4-Methylphenyl)-3-phenyl-2-propylamine (44). Compound **44** was prepared from **40** by following the procedure described for the synthesis of **43** in 89% yield: yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.95–7.4 (m, 9H, Ar), 3.97 (t, 1H, $J = 7.8$ Hz, CH), 3.10 (t, 2H, NH_2), 2.68 (t, 2H, $J = 6.8$ Hz, CH_2NH_2), 2.1–2.3 (s, 5H, $CHCH_2$ and CH_3).

4.2.38. 3-(3,4-Dimethylphenyl)-3-phenyl-2-propylamine (45). Compound **45** was prepared from **41** by following the procedure described for the synthesis of **43** in 91% yield: yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.95–7.3 (m, 8H, Ar), 3.94 (t, 1H, $J = 7.8$ Hz, CH), 2.65 (t, 2H, $J = 6.8$ Hz, CH_2NH_2), 2.1–2.2 (s, 8H, $CHCH_2$, $2\times CH_3$).

4.2.39. *N*-(3,3-Diphenylpropyl)-*N*′-[4-(methylsulfonylamino)benzyl]thiourea (46). Compound **46** was prepared by following the general procedure for thiourea synthesis (Method A) in 96% yield: white solid, mp = 77 °C; ^{1}H NMR (acetone-d_6) δ 8.37 (s, 1H, $NHSO_2$), 7.0–7.2 (m, 14H), 6.89 (bs, 2H, NHCS), 4.60 (d, 2H, $J = 5.6$ Hz, $NHCH_2Ar$), 3.90 (t, 1H, $J = 7.8$ Hz, Ph_2CH), 3.33 (m, 2H, CH_2CH_2NH), 2.82 (s, 3H, SO_2CH_3), 2.28 (m, 2H, CH_2CH_2NH); MS (FAB) *m*/*z* 454 (MH^+). Anal. calcd for $C_{24}H_{27}N_3O_2S_2$: C, 63.55; H, 6.00; N, 9.26; S, 14.14. Found: C, 63.68; H, 6.03; N, 9.23; S, 14.10.

4.2.40. *N*-[3-(3-Methylphenyl)-3-phenylpropyl]-*N*′-[4-(methylsulfonylamino)benzyl]thiourea (47). Compound **47** was prepared by following the general procedure for thiourea synthesis (Method A) in 97% yield: white solid, mp = 73 °C; ^{1}H NMR ($CDCl_3$) δ 7.0–7.35 (m, 13H), 6.05 (bs, 2H, NHCS), 4.48 (bs, 2H, $NHCH_2Ar$),

3.88 (t, 1H, $J=7.8$ Hz, Ar_2CH), 3.35 (bs, 2H, CH_2CH_2NH), 2.94 (s, 3H, SO_2CH_3), 2.25–2.3 (m, 5H, CH_2CH_2NH and CH_3); MS (FAB) m/z 468 (MH^+). Anal. calcd for $C_{25}H_{29}N_3O_2S_2$: C, 64.21; H, 6.25; N, 8.99; S, 13.71. Found: C, 64.48; H, 6.22; N, 8.97; S, 13.66.

4.2.41. *N*-[3-(4-Methylphenyl)-3-phenylpropyl]-*N′*-[4-(methylsulfonylamino)benzyl]thiourea (48). Compound **48** was prepared by following the general procedure for thiourea synthesis (Method A) in 95% yield: white solid, mp = 68 °C; ^{1}H NMR ($CDCl_3$) δ 7.0–7.35 (m, 13H), 6.04 (bs, 2H, NHCS), 4.48 (bs, 2H, $NHCH_2Ar$), 3.88 (t, 1H, $J=7.5$ Hz, Ar_2CH), 3.35 (bs, 2H, CH_2CH_2NH), 2.94 (s, 3H, SO_2CH_3), 2.25–2.30 (m, 2H, CH_2CH_2NH and CH_3); MS (FAB) m/z 468 (MH^+). Anal. calcd for $C_{25}H_{29}N_3O_2S_2$: C, 64.21; H, 6.25; N, 8.99; S, 13.71. Found: C, 64.40; H, 6.23; N, 8.95; S, 13.64.

4.2.42. *N*-[3-(3,4-dimethylphenyl)-3-phenylpropyl]-*N′*-[4-(methylsulfonylamino)benzyl]thiourea (49). Compound **49** was prepared by following the general procedure for thiourea synthesis (Method A)) in 96% yield: white solid, mp = 74 °C; ^{1}H NMR ($CDCl_3$) δ 7.15–7.3 (m, 9H), 6.9–7.05 (m, 3H), 5.96 (bs, 2H, NHCS), 4.47 (bs, 2H, $NHCH_2Ar$), 3.85 (t, 1H, $J=7.6$ Hz, Ar_2CH), 3.35 (bs, 2H, CH_2CH_2NH), 2.96 (s, 3H, SO_2CH_3), 2.31 (m, 2H, CH_2CH_2NH), 2.18 (d, 6H, $J=4.4$ Hz, $2\times CH_3$); MS (FAB) m/z 482 (MH^+). Anal. calcd for $C_{26}H_{31}N_3O_2S_2$: C, 64.83; H, 6.49; N, 8.72; S, 13.31. Found: C, 64.98; H, 6.46; N, 8.67; S, 13.29.

4.2.43. 4-Benzyloxybenzonitrile (51). A mixture of 4-cyanophenol (**50**) (0.6 g, 5 mmol), potassium carbonate (2.76 g, 20 mmol) and benzyl bromide (1.026 g, 6 mmol) in acetone (20 mL) was refluxed for 5 h and evaporated. The residue was diluted with CH_2Cl_2, washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with EtOAc/hexanes (2:1) as eluant to afford **51** (1.025 g, 98%) as a white solid.: ^{1}H NMR ($CDCl_3$) δ 7.57 (d, 2H, $J=8.3$ Hz, Ar), 7.3–7.45 (m, 5H, Ph), 7.01 (d, 2H, $J=8.3$ Hz, Ar), 5.11 (s, 2H, CH_2Ph).

4.2.44. 4-Isopropoxybenzonitrile (52). Compound **52** was prepared from 2-bromopropane by following the procedure described for the synthesis of **51** in 84% yield: white solid; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 2H, $J=8.3$ Hz, Ar), 6.91 (d, 2H, $J=8.3$ Hz, Ar), 4.62 (m, 1H, $CH(CH_3)_2$), 1.36 (d, 6H, $J=5.8$ Hz, $CH(CH_3)_2$).

4.2.45. 4-Butoxybenzonitrile (53). Compound **53** was prepared from butyl bromide by following the procedure described for the synthesis of **51** in 85% yield: white solid; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 2H, $J=8.3$ Hz, Ar), 6.94 (d, 2H, $J=8.3$ Hz, Ar), 4.00 (t, 2H, $J=6.6$ Hz, OCH_2), 1.78 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 0.98 (t, 3H, $J=7.3$ Hz, CH_3).

4.2.46. 4-Benzyloxybenzylamine hydrochloride (54). A mixture of **51** (418 mg, 2 mmol) in THF (10 mL) was treated with borane methylsulfide (2.0 M in THF, 1.1 mL, 2.2 mmol) and refluxed for 3 h. The reaction mixture was cooled, treated with hydrochloric acid in dioxane, and concentrated in vacuo. The residue was triturated with ether and precipitated solid was filtered to afford **54** (388 mg, 78%) as a white solid, which was used in next step without any further purification: ^{1}H NMR (DMSO-d_6) δ 8.29 (bs, 2H, NH_3^+), 7.3–7.5 (m, 7H, Ar), 7.02 (d, 2H, $J=8.5$ Hz, Ar), 6.53 (s, 1H, NH_3^+), 5.12 (s, 2H, $PhCH_2O$), 3.92 (s, 2H, $CH_2NH_3^+$).

4.2.47. 4-Isopropoxybenzylamine hydrochloride (55). Compound **55** was prepared from **52** by following the procedure described for the synthesis of **54** in 55% yield: white solid; ^{1}H NMR (DMSO-d_6) δ 8.14 (bs, 2H, NH_3^+), 7.36 (d, 2H, $J=8.3$ Hz, Ar), 6.93 (d, 2H, $J=8.3$ Hz, Ar), 4.62 (m, 1H, $CH(CH_3)_2$), 3.91 (s, 2H, $CH_2NH_3^+$), 1.24 (d, 6H, $J=5.8$ Hz, $CH(CH_3)_2$).

4.2.48. 4-Butoxybenzylamine hydrochloride (56). Compound **56** was prepared from **53** by following the procedure described for the synthesis of **54** in 77% yield: white solid; ^{1}H NMR (DMSO-d_6) δ 8.21 (bs, 2H, NH_3^+), 7.37 (d, 2H, $J=8.3$ Hz, Ar), 6.94 (d, 2H, $J=8.3$ Hz, Ar), 3.9–4.0 (m, 4H, OCH_2 and $CH_2NH_3^+$), 1.66 (m, 2H, CH_2), 1.42 (m, 2H, CH_2), 0.91 (t, 3H, $J=7.3$ Hz, CH_3).

4.2.49. *N*-[4-(Benzyloxy)benzyl]-*N′*-[4-(methylsulfonylamino)benzyl]thiourea (57). Compound **57** was prepared by following the general procedure for thiourea synthesis (Method B) in 72% yield.: white solid, mp = 181 °C; ^{1}H NMR (acetone-d_6) δ 7.25–7.4 (m, 11H), 6.95 (d, 2H, $J=8.7$ Hz), 5.10 (s, 2H, OCH_2Ph), 4.77 (d, 2H, $J=5.3$ Hz, $NHCH_2Ar$), 4.71 (d, 2H, $J=5.4$ Hz, $NHCH_2Ar$), 2.95 (s, 3H, $NHSO_2CH_3$); IR (KBr) 3435, 1552, 1138 cm^{-1}.

MS (FAB) m/z 456 (MH^+). Anal. calcd for $C_{23}H_{25}N_3O_3S_2$: C, 60.63; H, 5.53; N, 9.22; S, 14.08. Found: C, 60.45; H, 5.56; N, 9.17; S, 13.99.

4.2.50. *N*-(4-Isopropoxybenzyl)-*N′*-[4-(methylsulfonylamino)benzyl]thiourea (58). Compound **58** was prepared by following the general procedure for thiourea synthesis (Method B) in 70% yield: white solid, mp = 143 °C; ^{1}H NMR (acetone-d_6) δ 7.25–7.35 (m, 6H), 6.85 (d, 2H, $J=8.5$ Hz), 4.78 (d, 2H, $J=4.6$ Hz, $NHCH_2Ar$), 4.70 (d, 2H, $J=5.3$ Hz, $NHCH_2Ar$), 4.58 (m, 1H, $OCH(CH_3)_2$), 2.95 (s, 3H, $NHSO_2CH_3$), 1.26 (d, 6H, $J=6.1$ Hz, $CH(CH_3)_2$).

IR (KBr) 3428, 1551, 1138 cm^{-1}; MS (FAB) m/z 408 (MH^+). Anal. calcd for $C_{19}H_{25}N_3O_3S_2$: C, 55.99; H, 6.18; N, 10.31; S, 15.74. Found: C, 55.69; H, 6.18; N, 10.26; S, 15.82.

4.2.51. *N*-(4-Butoxybenzyl)-*N′*-[4-(methylsulfonylamino)-benzyl]thiourea (59). Compound **59** was prepared by following the general procedure for thiourea synthesis (Method B) in 76% yield: white solid, mp = 167 °C; ^{1}H NMR (acetone-d_6) δ 7.25–7.35 (m, 6H), 6.85 (d, 2H, $J=8.5$ Hz), 4.76 (d, 2H, $J=4.6$ Hz, $NHCH_2Ar$), 4.71 (d, 2H, $J=5.3$ Hz, $NHCH_2Ar$), 3.96 (t, 2H, $J=6.3$ Hz, OCH_2), 2.95 (s, 3H, $NHSO_2CH_3$), 1.72 (m, 2H, OCH_2CH_2), 1.48 (m, 2H, CH_2CH_3), 0.95 (t, 3H, CH_3); IR (KBr) 3432, 1551, 1139 cm^{-1}; MS (FAB) m/z 422 (MH^+). Anal. calcd for $C_{20}H_{27}N_3O_3S_2$: C, 56.98; H, 6.46; N, 9.97; S, 15.21. Found: C, 56.84; H, 6.48; N, 9.92; S, 15.20.

4.2.52. *N*-(4-Phenylpiperazinyl)-*N*′-[4-(methylsulfonylamino)benzyl]thiourea (61). Compound **61** was prepared by following the general procedure for thiourea synthesis (Method A) in 92% yield: white solid, mp = 171 °C; ^{1}H NMR (DMSO-d_6) δ 9.58 (bs, 1H, $NHSO_2$), 8.28 (t, 1H, J = 5.1 Hz, $NHCH_2$), 7.2–7.3 (m, 4H, Ph), 7.14 (d, 2H, J = 8.0 Hz), 6.94 (d, 2H, J = 8.0 Hz), 6.77 (t, 1H, J = 7.3 Hz), 4.75 (d, 2H, J = 5.1 Hz, $NHCH_2$), 3.96 (m, 4H, H-2,6), 3.18 (m, 4H, H-3,5), 2.94 (s, 3H, SO_2CH_3); IR (KBr) 3400, 2917, 1384, 1151, 668 cm^{-1}; MS (FAB) m/z 405 (MH^+). Anal. calcd for $C_{19}H_{24}N_4O_2S_2$: C, 56.41; H, 5.98; N, 13.85; S, 15.85. Found: C, 56.61; H, 5.95; N, 13.89; S, 15.79.

4.2.53. *N*-(4-Benzylpiperazinyl)-*N*′-[4-(methylsulfonylamino)benzyl]thiourea (63). Compound **63** was prepared by following the general procedure for thiourea synthesis (Method A) in 92% yield: white solid, mp = 124–126 °C; ^{1}H NMR ($CDCl_3$) δ 7.15–7.4 (m, 9H, Ar), 6.45 (bs, 1H, $NHSO_2$), 5.65 (bt, 1H, $NHCH_2$), 4.87 (d, 2H, J = 5.1 Hz, $NHCH_2$), 3.83 (t, 4H, J = 5.1 Hz, H-2,6), 3.54 (s, 2H, $PhCH_2N$), 3.01 (s, 3H, SO_2CH_3), 2.50 (t, 4H, J = 5.1 Hz, H-3,5); MS (FAB) m/z 419 (MH^+). Anal. calcd for $C_{20}H_{26}N_4O_2S_2$: C, 57.39; H, 6.26; N, 13.39; S, 15.32. Found: C, 57.21; H, 6.22; N, 13.34; S, 15.28.

4.2.54. 1-Benzhydrylpiperazine (64). To a solution of benzhydrol (1 g, 5.43 mmol) in CH_2Cl_2 (10 mL) was slowly added thionyl chloride (0.48 mL, 6.51 mmol). The mixture was stirred for 2 h at room temperature and then concentrated in vacuo. The residue was dissolved in acetonitrile (10 mL) and then piperazine (2.3 g, 27.15 mmol) was added. After being stirred overnight at 70 °C, the mixture was concentrated and partitioned into CH_2Cl_2-1N NaOH. The organic phase was collected, dried over $MgSO_4$, filtered and the filtrate was concentrated to afford **64** (1.1 g, 80%) as a yellow solid, which was washed with ether and then used for the next coupling: white solid, mp = 54–57 °C; ^{1}H NMR ($CDCl_3$) δ 7.05–7.5 (m, 10H, 2×Ph), 4.17 (s, 1H, Ph_2CHN), 2.78 (t, 4H, J = 4.9 Hz, H-2,6), 2.30 (bs, 4H, H-3,5).

4.2.55. *N*-(4-Benzhydrylpiperazinyl)-*N*′-[4-(methylsulfonylamino)benzyl]thiourea (65). Compound **65** was prepared by following the general procedure for thiourea synthesis (Method A) in 98% yield: white solid, mp = 87–89 °C; ^{1}H NMR ($CDCl_3$) δ 7.05–7.4 (m, 14H, Ar), 5.89 (t, 1H, J = 5.1 Hz, $NHCH_2$), 4.80 (d, 2H, J = 5.1 Hz, $NHCH_2$), 4.22 (s, 1H, Ph_2CHN), 3.78 (m, 4H, H-2,6), 2.92 (s, 3H, SO_2CH_3), 2.41 (m, 4H, H-3,5); IR (KBr) 3391, 1538, 1323, 1151, 750 cm^{-1}; MS (FAB) m/z 495 (MH^+). Anal. calcd for $C_{26}H_{30}N_4O_2S_2$: C, 63.13; H, 6.11; N, 11.33; S, 12.96. Found: C, 62.98; H, 6.10; N, 11.28; S, 12.89.

4.2.56. *N*-(4-Benzylpiperidyl)-*N*′-[4-(methylsulfonylamino)benzyl]thiourea (67). Compound **67** was prepared by following the general procedure for thiourea synthesis (Method A) in 92% yield.: white solid, mp = 162–164 °C; ^{1}H NMR ($CDCl_3$) δ 7.1–7.4 (m, 9H, Ar), 5.64 (bt, 1H, $NHCH_2$), 4.86 (d, 2H, J = 5.1 Hz, $NHCH_2$), 4.59 (d, 2H, J = 12.7 Hz, H-2,6(eq)), 3.02 (s, 3H, SO_2CH_3), 2.96 (m, 2H, H-2,6(ax)), 2.56 (d, 2H, J = 6.8 Hz, $PhCH_2$), 1.84 (m, 1H, H-4), 1.72 (m, 2H, H-3,5(eq)), 1.26 (m, 2H, H-3,5(ax)); MS (FAB) m/z 418 (MH^+). Anal. calcd for $C_{21}H_{27}N_4O_2S_2$: C, 60.40; H, 6.52; N, 10.06; S, 15.36. Found: C, 60.57; H, 6.50; N, 10.00; S, 15.30.

4.2.57. *N*-(*tert*-Butoxycarbonyl) ethyl 4-piperidinecarboxylate (69). A mixture of ethyl isonipecotate (0.677 g, 3 mmol), di-*tert*-butyl dicarbonate (0.786 g, 3.6 mmol) and Na_2CO_3 (0.636 g, 6 mmol) was refluxed in H_2O/THF (10:4 mL) for 1 h. The reaction mixture was then cooled and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:1) as eluant to afford **69** (0.741 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.14 (q, 2H, J = 7.3 Hz, $CO_2CH_2CH_3$), 4.02 (bd, 2H, J = 11.5 Hz, H-2,6(eq)), 2.83 (bt, 2H, J = 11.5 Hz, H-2,6(ax)), 2.43 (m, 1H, H-4), 1.82–1.92 (m, 2H, H-3,5(eq)), 1.55–167 (m, 2H, H-3,5(ax)), 1.46 (s, 9H, $C(CH_3)_3$), 1.26 (t, 3H, J = 7.3 Hz, $CO_2CH_2CH_3$).

4.2.58. *N*-(*tert*-Butoxycarbonyl) 4-[hydroxy(diphenyl)methyl]piperidine (70). A cooled solution of **69** (0.741 g, 2.88 mg) in benzene at 0 °C was treated dropwise with phenyl magnesium bromide (1 M in THF, 8.84 mL, 8.64 mmol) over 10 min and stirred for 1 h at room temperature. The reaction mixture was quenched with aqueous NH_4Cl solution and extracted with ether several times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to afford **70** (0.847 g, 80%) as a white solid. mp = 192–194 °C; ^{1}H NMR ($CDCl_3$) δ 7.15–7.5 (m, 10H, 2×Ph), 4.12 (bs, 2H, H-2,6(eq)), 2.83 (t, 2H, J = 12.2 Hz, H-2,6(ax)), 2.55 (m, 1H, H-4), 2.12 (s, 1H, OH), 1.2–1.55 (m, 4H, H-3,5), 1.42 (s, 9H, $C(CH_3)_3$); MS (FAB) m/z 368 (MH^+).

4.2.59. 4-(Diphenylmethylene)piperidine (71). A mixture of **70** (0.856 g, 2.33 mmol) and trifluoroacetic acid (8 mL) in CH_2Cl_2 (8 mL) was stirred for 16 h at room temperature and then concentrated. The residue was diluted with 1 N NaOH solution and extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford **71** (0.574 g, 98%) as a white solid. mp = 77–78 °C; ^{1}H NMR ($CDCl_3$) δ 7.1–7.3 (m, 10H, 2×Ph), 2.91 (t, 4H, J = 5.6 Hz, H-2,6), 2.33 (t, 4H, J = 5.6 Hz, H-3,5), 2.21 (bs, 1H, NH).

4.2.60. *N*-[4-(Diphenylmethylene)piperidinyl]-*N*′-[4-(methylsulfonylamino)benzyl]thiourea (72). Compound **72** was prepared by following the general procedure for thiourea synthesis (Method A) in 98% yield: white solid, mp = 92–95 °C; ^{1}H NMR ($CDCl_3$) δ 7.1–7.35 (m, 14H, Ar), 6.71 (s, 1H, $NHSO_2$), 5.69 (t, 1H, J = 4.9 Hz, $NHCH_2$), 4.87 (d, 2H, J = 4.9 Hz, $NHCH_2$), 3.86 (t, 4H, J = 5.8 Hz, H-2,6), 2.99 (s, 3H, SO_2CH_3), 2.53 (t, 4H, J = 5.8 Hz, H-3,5); IR (KBr) 3268, 2917, 1614, 1537, 1324, 1152 cm^{-1}; MS (FAB) m/z 492 (MH^+). Anal. calcd for $C_{27}H_{29}N_3O_2S_2$: C, 65.96; H, 5.95; N, 8.55; S, 13.04. Found: C, 66.12; H, 5.91; N, 8.49; S, 12.98.

4.2.61. 4-Benzhydrylpiperidine (73). A suspension of **72** (0.57 g, 2.82 mmol) and 5% palladium on carbon (0.5 g) in MeOH (50 mL) was hydrogenated under a pressure of 40 psi for 30 h. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo to afford **73** as a colorless oil, which was used for the next step without further purification.: ^{1}H NMR ($CDCl_3$) δ 7.1–7.3 (m, 10H, 2×Ph), 3.48 (d, 1H, J = 11 Hz, $CHPh_2$), 2.84 (dd, 2H, H-2,6(eq)), 2.24 (s, 1H, NH), 2.07 (m, 1H, H-4), 1.89 (t, 2H, J = 11.7 Hz, H-2,6(ax)), 1.53 (t, 2H, J = 13.4 Hz, H-3,5(eq)), 1.25 (m, 2H, H-3,5(ax)).

4.2.62. *N*-(4-Benzhydrylpiperidinyl)-*N'*-[4-(methylsulfonylamino)benzyl]thiourea (74). Compound **74** was prepared by following the general procedure for thiourea synthesis (Method A) in 96% yield.: white solid, mp = 104–107 °C; ^{1}H NMR ($CDCl_3$) δ 7.1–7.35 (m, 14H, Ar), 6.67 (s, 1H, $NHSO_2$), 5.66 (t, 1H, J = 5.2 Hz, $NHCH_2$), 4.84 (d, 2H, J = 5.2 Hz, $NHCH_2$), 4.53 (d, 2H, J = 13.4 Hz, H-2,6(eq)), 3.48 (d, 1H, J = 11 Hz, Ph_2CH), 3.00 (m, 2H, H-2,6(ax)), 2.98 (s, 3H, SO_2CH_3), 2.40 (m, 1H, H-4), 1.62 (m, 2H, H-3,5(eq)), 1.24 (m, 2H, H-3,5(ax)); IR (KBr) 3398, 2917, 1539, 1322, 1151, 754 cm^{-1}; MS (FAB) m/z 494 (MH^+). Anal. calcd for $C_{27}H_{31}N_3O_2S_2$: C, 65.69; H, 6.33; N, 8.51; S, 12.99. Found: C, 65.88; H, 6.30; N, 8.48; S, 12.93.

4.2.63. *N*-(*tert*-Butoxycarbonyl) 4-(4-isopropylanilino) piperidine (76). A mixture of 4-isopropylaniline (0.15 mL, 1.1 mmol), *tert*-butyl-4-oxo-1-piperidinecarboxylate (**75**) (200 mg, 1 mmol) and 4 Å molecular sieve (400 mg) in CH_2Cl_2 (5 mL) was stirred for 30 min and then treated with $NaBH(OAc)_3$ (318 mg, 1.5 mmol). After being stirred for 2 h at room temperature, the reaction mixture was diluted with aqueous $NaHCO_3$ solution and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:2) as eluant to afford **14** (300 mg, 94%) as a white solid: mp = 100–101 °C; ^{1}H NMR ($CDCl_3$) δ 7.04 (d, 2H, J = 8.5 Hz, Ar), 6.55 (d, 2H, J = 8.5 Hz, Ar), 4.02 (bd, 2H, J = 10.2 Hz, H-2,6(eq)), 3.39 (bs, 2H, H-4 and NH), 2.92 (t, 2H, J = 11.5 Hz, H-2,6(ax)), 2.80 (m, 1H, $CHMe_2$), 2.02 (bd, 2H, J = 13.2 Hz, H-3,5(eq)), 1.46 (s, 9H, $C(CH_3)_3$), 1.32 (m, 2H, H-3,5(ax)), 1.20 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$).

4.2.64. *N*-(*tert*-Butoxycarbonyl) 4-(3,4-dimethylanilino)-piperidine (77). Compound **77** was prepared from 3,4-dimethylaniline by following the procedure described for the synthesis of **76** in 93% yield.: white solid, mp = 119 °C; ^{1}H NMR ($CDCl_3$) δ 6.93 (d, 1H, J = 7.8 Hz, Ar), 6.43 (d, 1H, J = 2.4 Hz, Ar), 6.38 (dd, 1H, J = 7.8, 2.4 Hz, Ar), 4.02 (bd, 2H, J = 10.2 Hz, H-2,6(eq)), 3.36 (m, 2H, H-4 and NH), 2.91 (t, 2H, J = 11.5 Hz, H-2,6(ax)), 2.16 (d, 6H, 2×CH_3), 2.02 (bd, 2H, J = 13.2 Hz, H-3,5(eq)), 1.46 (s, 9H, $C(CH_3)_3$), 1.2–1.45 (m, 2H, H-3,5(ax)).

4.2.65. *N*-(*tert*-Butoxycarbonyl) 4-[*N*-(4-isopropylphenyl)-*N*-(3-methyl-2-butenyl)amino]piperidine (78). A solution of **76** (318 mg, 1 mmol) and *N*,*N*-diisopropylethylamine (0.7 mL, 4 mmol) in THF (6 mL) was treated with 4-bromo-2-methyl-2-butene (0.23 mL, 2 mmol) and refluxed for 4 h. The mixture was evaporated, diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:5) as eluant to afford **78** (317 mg, 82%) as a white solid: mp = 107–108 °C; ^{1}H NMR ($CDCl_3$) δ 7.08 (d, 2H, J = 8.6 Hz, Ar), 6.68 (d, 2H, J = 8.6 Hz, Ar), 5.10 (m, 1H, >C=CH), 4.20 (bs, 2H, H-2,6(eq)), 3.76 (d, 2H, J = 5.1 Hz, >C=CCH_2N), 3.68 (m, 1H, H-4), 2.7-2.85 (m, 3H, H-2,6(ax) and $CHMe_2$), 1.78 (bd, 2H, J = 11.7 Hz, H-3,5(eq)), 1.68 (s, 6H, $(CH_3)_2C$=C), 1.56 (m, 2H, H-3,5(ax)), 1.47 (s, 9H, $C(CH_3)_3$), 1.21 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$).

4.2.66. *N*-(*tert*-Butoxycarbonyl) 4-[*N*-(3,4-dimethylbenzyl)-*N*-(4-isopropylphenyl)amino]piperidine (79). A solution of **76** (318 mg, 1 mmol) and N,N-diisopropylethylamine (0.87 mL, 5 mmol) in DMF (5 mL) was treated with 3,4-dimethylbenzyl chloride (0.43 mL, 3 mmol) and heated at 100 °C for 18 h. The mixture was diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:5) as eluant to afford **79** (375 mg, 86%) as a colorless oil.: ^{1}H NMR ($CDCl_3$) δ 7.0–7.08 (m, 5H, Ar), 6.66 (d, 2H, J = 8.8 Hz, Ar), 6.59 (d, 2H, J = 8.8 Hz, Ar), 4.33 (d, 2H, J = 12.7 Hz, NCH_2Ar), 4.19 (bs, 2H, H-2,6(eq)), 3.86 (m, 1H, H-4), 2.7–2.85 (m, 3H, H-2,6(ax) and $CHMe_2$), 2.2–2.3 (m, 6H, 2×CH_3), 1.84 (bd, 2H, J = 11 Hz, H-3,5(eq)), 1.5–1.6 (m, 2H, H-3,5(ax)), 1.44 (s, 9H, $C(CH_3)_3$), 1.19 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$).

4.2.67. *N*-(*tert*-Butoxycarbonyl) 4-[*N*-(3,4-dimethylphenyl)-*N*-(3-methyl-2-butenyl)amino]piperidine (80). Compound **80** was prepared from **77** by following the procedure described for the synthesis of **78** in 81% yield.: white solid, mp = 94–95 °C; ^{1}H NMR ($CDCl_3$) δ 6.96 (d, 1H, J = 7.8 Hz, Ar), 6.56 (d, 1H, J = 2.4 Hz, Ar), 6.50 (dd, 1H, J = 7.8, 2.4 Hz, Ar), 5.08 (m, 1H, >C=CH), 4.19 (bs, 2H, H-2,6(eq)), 3.74 (d, 2H, J = 4.9 Hz, >C=CCH_2N), 3.64 (m, 1H, H-4), 2.76 (t, 2H, J = 12.2 Hz, H-2,6(ax)), 2.18 (d, 6H, 2×CH_3), 1.78 (bd, 2H, J = 12.2 Hz, H-3,5(eq)), 1.68 (d, 6H, $(CH_3)_2C$=C), 1.55 (m, 2H, H-3,5(ax)), 1.46 (s, 9H, $C(CH_3)_3$).

4.2.68. *N*-(*tert*-Butoxycarbonyl) 4-[*N*-(3,4-dimethylbenzyl)-*N*-(3,4-dimethylphenyl)amino]piperidine (81). Compound **81** was prepared from **77** by following the procedure described for the synthesis of **79** in 91% yield: colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.9–7.1 (m, 4H, Ar), 6.4–6.6 (m, 2H, Ar), 4.32 (d, 2H, J = 12 Hz, NCH_2Ar), 4.20 (bs, 2H, H-2,6(eq)), 3.85 (m, 1H, H-4), 2.78 (t, 2H, J = 12.2 Hz, H-2,6(ax)), 2.15–2.3 (m, 12H, 4×CH_3), 1.81 (bd, 2H, J = 12.2 Hz, H-3,5(eq)), 1.55 (m, 2H, H-3,5(ax)), 1.42 (s, 9H, $C(CH_3)_3$).

4.2.69. 4-[*N*-(4-Isopropylphenyl)-*N*-(3-methyl-2-butenyl) amino]piperidine (82). A solution of **78** (318 mg, 1

mmol) in CH_2Cl_2 (12 mL) was treated with trifluoroacetic acid (3 mL) and stirred for 1 h at room temperature. The mixture was concentrated in vacuo, diluted with 1 N NaOH solution and extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (2:1) as eluant to afford **82** (223 mg, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.91 (bs, 1H, NH), 7.09 (d, 2H, J = 8.6 Hz, Ar), 6.69 (d, 2H, J = 8.6 Hz, Ar), 5.09 (m, 1H, >C=CH), 3.78 (d, 2H, J = 5.1 Hz, >C=CCH_2N), 3.70 (m, 1H, H-4), 3.38 (bd, 2H, H-2,6(eq)), 2.75–2.95 (m, 3H, H-2,6(ax) and $CHMe_2$), 1.8–1.95 (m, 4H, H-3,5), 1.68 (s, 6H, $(CH_3)_2$C=C), 1.21 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$).

4.2.70. 4-[*N*-(3,4-Dimethylbenzyl)-*N*-(4-isopropylphenyl) amino]piperidine (83). Compound **83** was prepared from **79** by following the procedure described for the synthesis of **82** in 92% yield: colorless oil; ^{1}H NMR ($CDCl_3$) δ 8.2 (bs, 1H, NH), 7.0–7.1 (m, 5H, Ar), 6.67 (d, 2H, J = 8.8 Hz, Ar), 6.58 (d, 2H, J = 8.8 Hz, Ar), 4.35 (d, 2H, J = 7.1 Hz, NCH_2Ar), 3.92 (m, 1H, H-4), 3.40 (d, 2H, J = 12.4 Hz, H-2,6(eq)), 2.94 (m, 2H, H-2,6(ax)), 2.80 (m, 1H, $CHMe_2$), 2.15–2.3 (m, 6H, 2×CH_3), 1.9–2.1 (m, 4H, H-3,5), 1.19 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$).

4.2.71. 4-[*N*-(3,4-Dimethylphenyl)-*N*-(3-methyl-2-butenyl) amino]piperidine (84). Compound **84** was prepared from **80** by following the procedure described for the synthesis of **82** in 96% yield: colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.96 (d, 1H, J = 7.8 Hz, Ar), 6.57 (d, 1H, J = 2.4 Hz, Ar), 6.50 (dd, 1H, J = 7.8, 2.4 Hz, Ar), 5.29 (bs, 1H, NH), 5.08 (m, 1H, >C=CH), 3.77 (d, 2H, J = 5.1 Hz, >C=CCH_2N), 3.64 (m, 1H, H-4), 3.27 (d, 2H, J = 12.2 Hz, H-2,6(eq)), 2.78 (bt, 2H, H-2,6(ax)), 2.18 (d, 6H, 2×CH_3), 1.7–1.9 (m, 4H, H-3,5), 1.68 (d, 6H, $(CH_3)_2$C=C).

4.2.72. 4-[*N*-(3,4-Dimethylbenzyl)-*N*-(3,4-dimethylphenyl) amino]piperidine (85). Compound **85** was prepared from **81** by following the procedure described for the synthesis of **82** in 92% yield.: colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.9–7.1 (m, 4H, Ar), 6.4–6.6 (m, 2H, Ar), 4.34 (d, 2H, J = 6.8 Hz, NCH_2Ar), 3.87 (m, 1H, H-4), 3.32 (b, 2H, J = 12.7 Hz, H-2,6(eq)), 2.87 (m, 2H, H-2,6(ax)), 2.1–2.3 (m, 12H, 4×CH_3), 1.8–2.0 (m, 4H, H-3,5).

4.2.73. *N*-{4-[*N*-(4-Isopropylphenyl)-*N*-(3-methyl-2-butenyl)amino]piperidinyl} - *N′* - [4 - (methylsulfonylamino)benzyl]thiourea (86). Compound **86** was prepared by following the general procedure for thiourea synthesis (Method A) in 95% yield: white solid, mp = 72–74 °C; ^{1}H NMR ($CDCl_3$) δ 7.33 (d, 2H, J = 8.5 Hz, Ar), 7.19 (d, 2H, J = 8.5 Hz, Ar), 7.08 (d, 2H, J = 8.8 Hz, Ar), 6.76 (bs, 1H, $NHSO_2$), 6.69 (d, 2H, J = 8.8 Hz, Ar), 5.78 (t, 1H, J = 4.9 Hz, $NHCH_2$), 5.07 (m, 1H, >C=CH), 4.86 (d, 2H, J = 4.9 Hz, $NHCH_2$), 4.72 (d, 2H, J = 13.4 Hz, H-2,6(eq)), 3.7–3.85 (m, 3H, C=CHCH_2N and H-4), 3.08 (t, 2H, J = 12.2 Hz, H-2,6(ax)), 3.00 (s, 3H, SO_2CH_3), 2.81 (m, 1H, $CHMe_2$), 1.89 (m, 2H, H-3,5(eq)), 1.6–1.75 (m, 8H, H-3,5(ax) and >$C(CH_3)_2$), 1.21 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$); IR (KBr) 3391, 2957, 1613, 1515, 1325, 1154 cm^{-1}; MS (FAB) m/z 529 (MH^+). Anal. calcd for $C_{28}H_{40}N_4O_2S_2$: C, 63.60; H, 7.62; N, 10.60; S, 12.13. Found: C, 63.78; H, 7.59; N, 10.56; S, 12.09.

4.2.74. *N*-{4-[*N*-(3,4-Dimethylbenzyl)-N-(4-isopropylphenyl)amino]piperidinyl} - *N′* - [4 - (methylsulfonylamino)benzyl]thiourea (87). Compound **87** was prepared by following the general procedure for thiourea synthesis (Method A) in 89% yield: white solid, mp = 105–108 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 2H, J = 8.5 Hz, Ar), 7.17 (d, 2H, J = 8.5 Hz, Ar), 6.95–7.15 (m, 3H, Ar), 6.68 (d, 2H, J = 8.8 Hz, Ar), 6.61 (d, 2H, J = 8.8 Hz, Ar), 6.47 (bs, 1H, $NHSO_2$), 5.64 (t, 1H, J = 4.6 Hz, $NHCH_2$), 4.83 (d, 2H, J = 4.6 Hz, $NHCH_2$), 4.70 (d, 2H, J = 12.9 Hz, H-2,6(eq)), 4.32 (d, 2H, J = 12.2 Hz, $ArCH_2N$), 4.00 (m, 1H, H-4), 3.09 (t, 2H, J = 12.7 Hz, H-2,6(ax)), 3.00 (s, 3H, SO_2CH_3), 2.80 (m, 1H, $CHMe_2$), 2.32 (s, 1H), 2.22 (s, 5H, 2×CH_3), 1.96 (m, 2H, H-3,5(eq)), 1.65 (m, 2H, H-3,5(ax)), 1.20 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$); IR (KBr) 3392, 2955, 1612, 1514, 1322, 1152, 753 cm^{-1}; MS (FAB) m/z 579 (MH^+). Anal. calcd for $C_{32}H_{42}N_4O_2S_2$: C, 66.40; H, 7.31; N, 9.68; S, 11.08. Found: C, 66.63; H, 7.28; N, 9.64; S, 11.02.

4.2.75. *N*-{4-[*N*-(3,4-Dimethylphenyl)-*N*-(3-methyl-2-butenyl)amino]piperidinyl}-*N′*-[4-(methylsulfonylamino)benzyl]thiourea (88). Compound **88** was prepared by following the general procedure for thiourea synthesis (Method A) in 93% yield: white solid, mp = 163–164 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 2H, J = 8.5 Hz, Ar), 7.19 (d, 2H, J = 8.5 Hz, Ar), 6.97 (m, 2H, Ar), 6.5–6.6 (m, 2H, Ar and $NHSO_2$), 5.78 (t, 1H, J = 4.9 Hz, $NHCH_2$), 5.05 (m, 1H, >C=CH), 4.86 (d, 2H, J = 4.9 Hz, $NHCH_2$), 4.71 (d, 2H, J = 13.4 Hz, H-2,6(eq)), 3.7–3.85 (m, 3H, C=CHCH_2N and H-4), 3.09 (t, 2H, J = 12.4 Hz, H-2,6(ax)), 3.01 (s, 3H, SO_2CH_3), 2.22 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 1.88 (m, 2H, H-3,5(eq)), 1.6–1.75 (m, 8H, H-3,5(ax) and $CH=C(CH_3)_2$); IR (KBr) 3391, 2918, 1612, 1510, 1324, 1152, 753 cm^{-1}; MS (FAB) m/z 515 (MH^+). Anal. calcd for $C_{27}H_{38}N_4O_2S_2$: C, 63.00; H, 7.44; N, 10.88; S, 12.46. Found: C, 63.25; H, 7.42; N, 10.85; S, 12.21.

4.2.76. *N*-{4-[*N*-(3,4-Dimethylbenzyl)-*N*-(3,4-dimethylphenyl)amino]piperidinyl} - *N′* - [4 - (methylsulfonylamino)-benzyl]thiourea (89). Compound **89** was prepared by following the general procedure for thiourea synthesis (Method A) in 92% yield: white solid, mp = 93–95 °C; ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 2H, J = 8.3 Hz, Ar), 7.16 (d, 2H, J = 8.3 Hz, Ar), 6.9–7.1 (m, 3H, Ar), 6.76 (s, 1H, Ar), 6.4–6.6 (m, 2H, Ar), 5.73 (t, 1H, J = 5.1 Hz, $NHCH_2$), 4.82 (d, 2H, J = 5.1 Hz, $NHCH_2$), 4.69 (d, 2H, J = 12.9 Hz, H-2,6(eq)), 4.30 (d, 2H, J = 10.2 Hz, $ArCH_2N<$), 3.98 (m, 1H, H-4), 3.08 (t, 2H, J = 13.2 Hz, H-2,6(ax)), 2.97 (s, 3H, SO_2CH_3), 2.22 (s, 5H, 2×CH_3), 2.18 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 1.94 (m, 2H, H-3,5(eq)), 1.50 (m, 2H, H-3,5(ax)); IR (KBr) 3392, 2919, 1612, 1509, 1322, 1152 cm^{-1}; MS (FAB) m/z 565 (MH^+). Anal. calcd for $C_{31}H_{40}N_4O_2S_2$: C, 65.92; H, 7.14; N, 9.92; S, 11.35. Found: C, 66.13; H, 7.11; N, 9.87; S, 11.30.

4.3. VR1 Binding assays and functional characterization for agonist/antagonist activity

The methods were described in previous reports.[29]

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