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N-4-*t*-Butylbenzyl 2-(4-methylsulfonylaminophenyl) propanamide TRPV1 antagonists: Structure–activity relationships in the A-region

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ABSTRACT

Structure–activity relationships for the A-region in a series of *N*-4-*t*-butylbenzyl 2-(4-methylsulfonylaminophenyl) propanamides as TRPV1 antagonists have been investigated. Among them, the 3-fluoro analogue **54** showed high binding affinity and potent antagonism for both rTRPV1 and hTRPV1 in CHO cells. Its stereospecific activity was demonstrated with marked selectivity for the (*S*)-configuration (**54*S*** versus **54*R***). A docking study of **54*S*** with our hTRPV1 homology model highlighted crucial hydrogen bonds between the ligand and the receptor contributing to its potency.

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1. Introduction

The transient receptor potential V1 (TRPV1) receptor[1] is a molecular integrator of nociceptive stimuli, including protons,[2] heat,[3] inflammatory mediators such as anandamide[4] and lipoxygenase products,[5] and vanilloids such as capsaicin (CAP)[6] and resiniferatoxin (RTX).[7] The receptor functions as a non-selective cation channel with high Ca^{2+} permeability and its activation leads to an increase in intracellular Ca^{2+} that results in excitation of primary sensory neurons and ultimately the central perception of pain.

TRPV1 antagonists are promising drug candidates. Therapeutic applications include inhibiting the transmission of nociceptive signaling from the periphery to the CNS as well as blocking other pathological states associated with this receptor. TRPV1 antagonists have thus emerged as novel and promising analgesic and antiinflammatory agents, particularly for chronic pain and inflammatory hyperalgesia.[8] The number of antagonists reported continues to increase and their clincal development has been extensively reviewed.[9–13]

Previously, we have reported that a series of *N*-4-(methylsulfonylaminobenzyl) thiourea analogues were effective antagonists of the action of capsaicin on rat TRPV1[14–17] (Fig. 1). A prototype antagonist (**1**) showed high binding affinity and potent antagonism (K_i = 63 nM and $K_{i(ant)}$ = 54 nM in rTRPV1/CHO).[14] We further found that 3-substitutents of the 4-(methylsulfonylamino)phenyl group in the A-region affected the extent of agonism/antagonism. Thus, the 3-fluoro derivative **2** (K_i = 53.5 nM, $K_{i(ant)}$ = 9.2 nM for rTRPV1/CHO) was a potent antagonist not only of capsaicin stimulation of rTRPV1 but also of stimulation by temperature and pH.[14,16] Conversely, the 3-methoxy derivative **3** showed a shift to partial agonism (K_i = 51 nM, 17% agonism and 84% antagonism for rTRPV1/CHO) while the binding affinity remained unaffected.[15]

In order to further optimize the antagonistic activities of *N*-4-(methylsulfonylaminobenzyl) thioureas and avoid the potential toxicity associated with the thiourea functionality, we explored the amide B-region surrogates of the above parent thiourea antagonists in a series of simplified RTX derivatives and concluded that the propanamide B-region surrogates showed stereospecific high binding affinities and potent antagonism.[18]

As a continuation of our effort to optimize the 4-methylsulfonamide TRPV1 antagonists, we have investigated a series of 2-(4-methylsulfonylaminophenyl) propanamide analogues as TRPV1 antago

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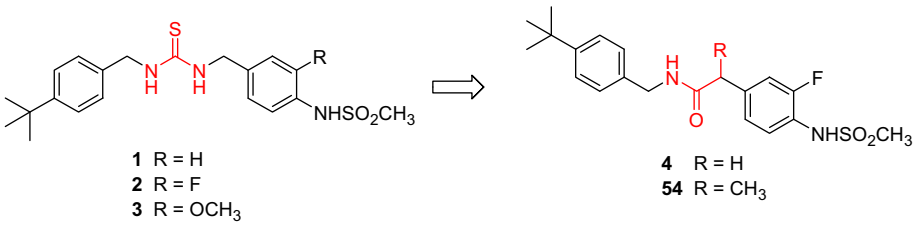


Figure 1. 4-(Methylsulfonylamino)phenyl TRPV1 antagonists

nists. In this Letter, we report the structure–activity relationships of the A-region in a series of *N*-4-*t*-butylbenzyl 2-(4-methylsulfonylaminophenyl) propanamide TRPV1 antagonists. Further biological characterization and molecular modeling of a key antagonist from this series will also be described.

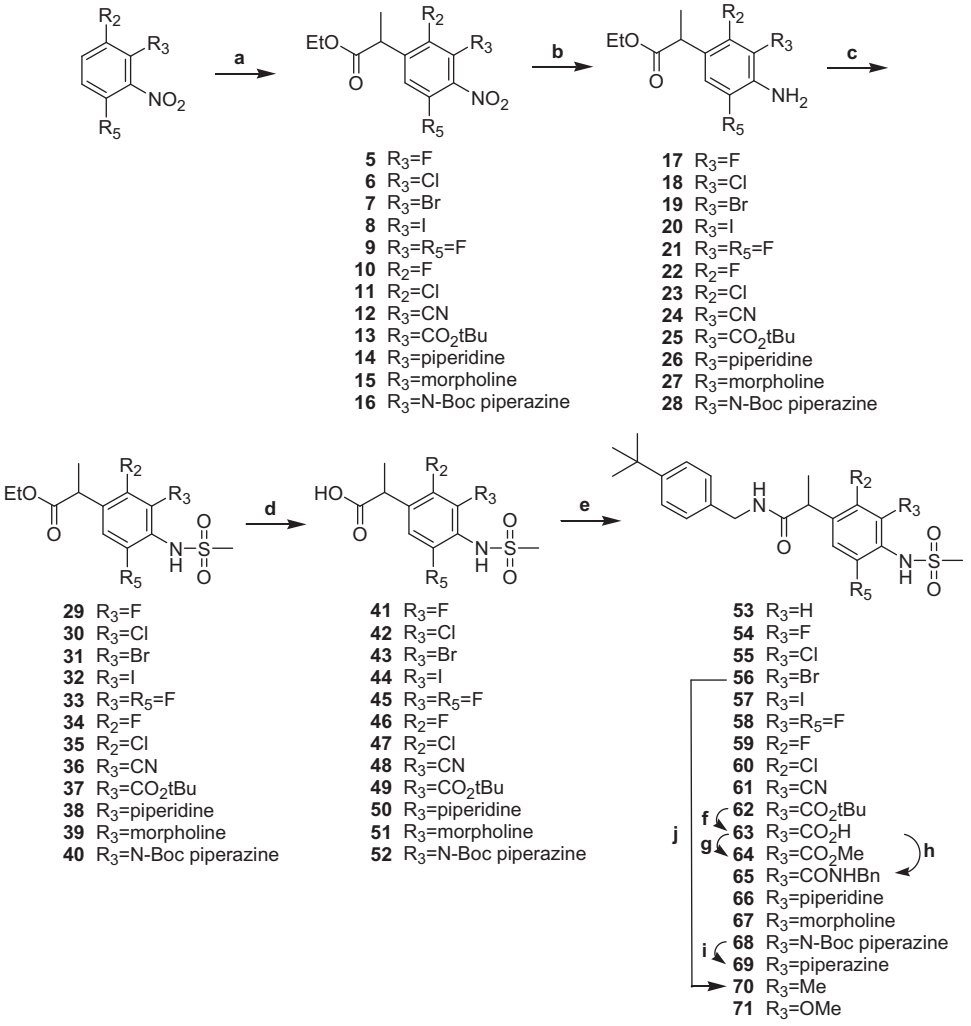
2. Result and discussion

2.1. Chemistry

The syntheses of substituted *N*-(4-*tert*-butylbenzyl)-2-[4-(methylsulfonylamino) phenyl] propionamide derivatives are represented in Scheme 1.

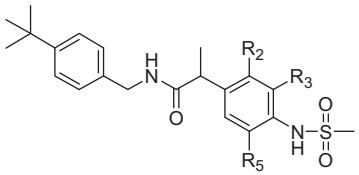
Ethyl 2-(4-nitrophenyl)propionates (**5–16**) were prepared from the corresponding 2-halonitrobenzenes by the reaction of Makosza's vicarious nucleophilic substitution.[19] The 4-nitro groups of **5–16** were reduced to amines **17–28** and then mesylated to give the corresponding 4-methylsulfonylamino compounds **29–40**, respectively. The esters of **29–40** were hydroyzed to afford the acids **41–52** and then coupled with 4-*t*-butylbenzylamine to provide the final propionamides.

The *t*-butyl ester **62** was hydrolyzed to acid **63** under acidic conditions and was converted to methyl ester **64** and benzyl amide **65**, respectively. The 3-piperazinyl **69** was obtained from **68** by acidic hydrolysis. 3-Methyl **70** was synthesized from 3-bromo **56** using tetramethyltin with palladium catalyst. The



Scheme 1. Reagents and conditions: (a) *t*-BuOK, ethyl 2-chloropropionate, DMF; (b) *Method A*: H_2, Pd-C, MeOH, *Method B*: Fe, AcOH; (c) MsCl, pyridine; (d) LiOH, H_2O–THF; (e) 4-*t*-butylbenzylamine, EDC, CH_2Cl_2; (f) CF_3CO_2H, CH_2Cl_2 (2:1); (g) TMS-diazomethane, MeOH; (h) $BnNH_2$, EDC, CH_2Cl_2; (i) CF_3CO_2H, CH_2Cl_2 (1:2); (j) $Sn(CH_3)_4$, $(PPh_3)_4Pd$, toluene.

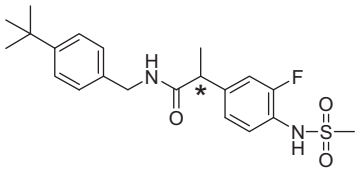
Table 1
rTRPV1 activities of *N*-(4-*tert*-butylbenzyl)-2-[4-(methylsulfonylamino)phenyl] propionamide ligands



	R_3	R_2	R_5	K_i (nM) binding affinity[c]	EC_{50} (nM) agonism[c]	K_i (nM) antagonism[c]
1				63.0	NE	54
2				53.5	NE	9.2
3				51.0	(17%)[a]	(84%)[b]
4				470 (±130)	NE	118 (±35)
53	H	H	H	106 (±34)	NE	17.5 (±1.6)
54	F	H	H	46.2 (±3.0)	NE	7.6 (±1.6)
55	Cl	H	H	30.7 (±7.4)	NE	29.5 (±8.5)
56	Br	H	H	7.4 (±1.5)	NE	25.0 (±7.4)
57	I	H	H	23.3 (±7.1)	NE	30.0 (±2.2)
58	F	H	F	19.9 (±6.1)	NE	7.4 (±2.1)
59	H	F	H	360 (±110)	NE	120 (±27)
60	H	Cl	H	1420 (±280)	NE	4500 (±1000)
61	CN	H	H	344 (±99)	NE	467 (±60)
62	CO_2tBu	H	H	6700 (±1200)	NE	(16%)[b]
63	CO_2H	H	H	NE	NE	NE
64	CO_2CH_3	H	H	1606 (±53)	NE	952 (±120)
65	CONHBn	H	H	3710 (±470)	NE	(23%)[b]
66		H	H	WE	NE	(37%)[b]
67		H	H	WE	NE	(34%)[b]
68		H	H	7000 (±1600)	NE	(13%)[b]
69		H	H	NE	NE	NE
70	CH_3	H	H	32.8 (±6.1)	NE	18.9 (±8.3)
71	OCH_3	H	H	540 (±130)	NE	232 (±71)

NE, no effect. WE, weak effect (quantitation of fractional agonism/antagonism is from 1 to 3 experiments).
[a] Only fractional calcium uptake compared with that induced by 300 nM capsaicin.
[b] Only fractional antagonism.
[c] Values represent mean ± SEM from three or more experiments.

Table 2
TRPV1 activities of the two chiral isomers of **54**



	rTRPV1		hTRPV1		
	K_i (nM) binding Affinity	K_i (nM) [CAP] antagonism	K_i (nM) binding affinity	K_i (nM) (CAP) antagonism	K_i (nM) (pH) antagonism
54	46.2 (±3.0)	7.6 (±1.6)	89 (±17)	5.1 (±1.2)	12.7 (±3.6)
54R	750 (±200)	186 (±29)	2590 (±390)	217 (±57)	440 (±41)
54S	24.4 (±0.82)	4.16 (±0.67)	15.8 (±4.4)	0.49 (±0.13)	8.3 (±1.6)

compounds **53** and **71** were prepared from the corresponding acids previously reported[18] by the coupling reaction.

The two enantiomers of **54**, ***54S*** and ***54R***, were synthesized from the corresponding optically pure acids, prepared by the resolution method using L-phenylalanol,[18] by the above coupling method.

2.2. Biological activity

The binding affinities and potencies as agonists/antagonists of the synthesized TRPV1 ligands were assessed in vitro by a binding competition assay with [^{3}H]RTX and by a functional $^{45}Ca^{2+}$ uptake assay using rat and human TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells, as previously described.[16] The results are summarized in Tables 1 and 2, together with the potencies of the previously reported thiourea antagonists **1–3**.[14–16]

We started by preparing and characterizing two amide B-region surrogates of the parent thiourea **2**. Whereas acetamide **4** showed a reduction in binding affinity and antagonism by an order of magnitude, the propanamide (α-methyl acetamide) **54** exhibited higher affinity (K_i = 46.2 nM) and more potent antagonism ($K_{i(ant)}$ = 7.6 nM) compared to **2**.

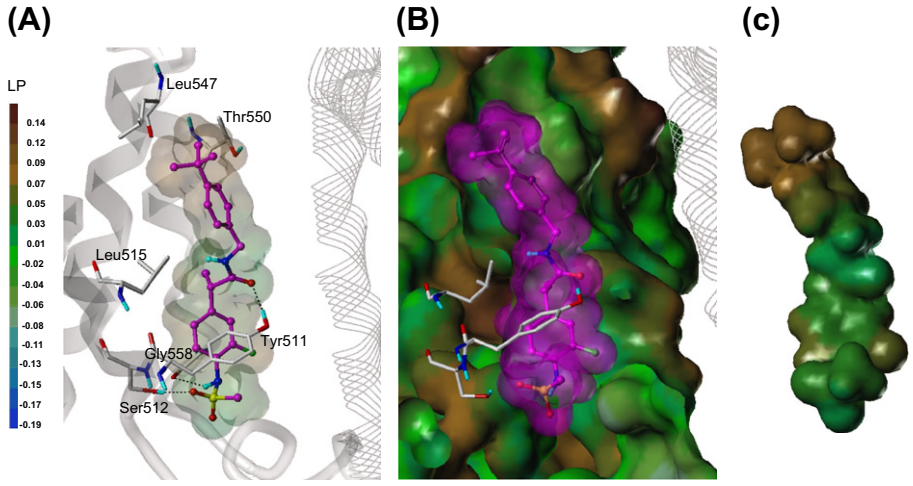


Figure 2. Predicted binding mode of **54*S*** in hTRPV1Homology model with surface representations. (A) Docked mode of **54*S***. The key interacting residues are marked and displayed as a capped-stick representation with carbon atoms in white. The helices are colored in gray and the helices of the neighboring monomer are displayed in a line ribbon representation. The ligand is depicted as a ball-and-stick with carbon atoms in magenta and its van der Waals surface is presented with lipophilic potential property (LP) which ranges from brown (highest lipophilic area) to blue (highest hydrophilic area). Hydrogen bonds are drawn in black dashed lines, and non-polar hydrogens are undisplayed for clarity. (B) Surface representations of the docked **54*S*** and hTRPV1. The Fast Connolly surface of hTRPV1 was generated by MOLCAD and colored by the lipophilic potential. For clarity, the surface of hTRPV1 is Z-clipped and that of the ligand is in its carbon color. (C) Van der Waals surface of **54*S*** colored by the lipophilic potential.

This result prompted us to investigate in detail the structure–activity relationships of the A-region 4-methylsulfonylaminophenyl group in the series while the B- and C-regions were fixed as the propanamide and the 4-*t*-butylbenzyl group, respectively.

The unsubstituted analogue **53** showed a two-fold reduction in the binding affinity and antagonism compared to **54**, indicating that the fluoro atom is crucial for activity. The replacement of fluoro in **54** with bulkier halogens, such as chloro (**55**), bromo (**56**) and iodo (**57**), led to an increase in binding affinity, but with a 4-fold reduction in their potencies as antagonists. The 3,5-difluoro substituted analogue **58** exhibited a two-fold enhancement in binding affinity and similar antagonism compared to **54**. On the other hand, the 2-halogen analogues, 2-fluoro (**59**) and 2-chloro (**60**), exhibited much reduced activities compared to the corresponding 3-halogen analogues **54** and **55**, probably due to a weaker electron-withdrawing effect toward the 4-sulfonamide in **59** and steric hinderance with the α-methyl in **60**.

As electron-withdrawing and hydrophilic groups, the cyano and carboxylate groups were introduced to the 3-position to provide **61–65**. Unfortunately, all of these compounds were found to be very weak or inactive antagonists.

As electron-donating groups, cyclic amines, methyl and methoxy groups were introduced to the 3-position. Whereas the 3-piperidinyl (**66**), morpholinyl (**67**), *N*-Boc piperazinyl (**68**) and piperazinyl analogues (**69**) showed marked loss of activity, the 3-methyl analogue (**70**) retained high potency in binding affinity and antagonism comparable with **54**. The 3-methoxy analogue (**71**) was intermediate, showing 10- to 30-fold reduced activity in binding affinity and antagonism.

The analysis of SAR indicated that electron withdrawing and lipophilic substituents at the 3-position appeared to be favorable for high binding and potent antagonism and the 3-fluoro substitution (**54**) was validated as the best for receptor antagonism.

For further exploration of the activity revealed by the racemate **54**, we prepared the two optically pure enantiomers of **54** and assessed their receptor binding and functional activities in rat and human (Table 2). Previously, our SAR investigation of the α-alkyl amide B-region in a series of simplified RTX analogues had indicated that the stereocenter at the α-position was crucial for determining the potencies, binding affinities, and antagonism, with the *S*-configuration of the α-alkyl demonstrating high receptor potency.[18] As anticipated, the receptor potencies revealed that the interaction of **54** was stereospecific. The (*S*)-isomer (**54*S***) proved to be the active isomer with a $K_{i(binding)}$ = 24.4 nM and a $K_{i(ant)}$ = 4.16 nM for rTRPV1, values which were ca. two-fold more potent than the respective values for **54**. The activity of **54*R***, in contrast, was 30- to 40-fold weaker.

The high potency of **54** was confirmed for human TRPV1. In hTRPV1, **54** showed similar potencies in binding affinity and antagonism compared to those in rTRPV1 with K_i = 89 nM, $K_{i(CAP)}$ = 5.1 nM and $K_{i(pH)}$ = 12.7 nM. The stereospecific activity of the active isomer (**54*S***) in binding affinity and functional antagonism was likewise observed with the hTRPV1, showing K_i = 15.8 nM, $K_{i(CAP)}$ = 0.49 nM and $K_{i(pH)}$ = 8.3 nM while **54*R*** again showed low potencies.

The further in vivo evaluation of **54** and **54*S*** will be presented elsewhere.

2.3. Molecular modeling

We have built the tetramer homology model of rat TRPV1 (rTRPV1) and performed the docking studies of the representative TRPV1 ligands.[20] The rat and human TRPV1 have more than 85% sequence identity, and only five residues in the ligand binding site are different. Using the rTRPV1 model, the human TRPV1 (hTRPV1) model was constructed and refined by energy minimization.

As shown in Figure 2, the binding site of hTRPV1 has a deep bottom hole, surrounded by Tyr511 and Ser512, and an upper hydrophobic region with Leu547. The docking study showed that the sulfonylaminobenzyl group (A-region) of **54*S*** occupied the deep bottom hole. An oxygen atom of the sulfonamide group appeared to form a hydrogen bond with Ser512 and its –NH could make a hydrogen bond with Gly558. In addition, the carbonyl group in the B-region participated in hydrogen bonding with Tyr511. Moreover, the highly hydrophobic 4-*t*-butylbenzyl group (C-region) extended nicely toward the upper hydrophobic region of the binding site and made a hydrophobic interaction with Leu547.

It appeared that the *S*-stereochemistry of α-methyl in the B-region contributes to proper positioning of the B- and C-regions toward the upper region in the binding site. Consequently, **54*S*** fully occupied the binding site with these important interactions and it could explain the high potency of **54*S***. This result is consis-

tent with our previous structure–activity relationship (SAR) studies of the B-region in a series of simplified RTX analogues in which the (*S*)-propanamide proved to be the active isomer.[18]

3. Conclusion

The structure–activity relationships of the A-region in a series of *N*-4-*t*-butylbenzyl 2-(4-methylsulfonylaminophenyl) propanamides as TRPV1 antagonists have been investigated. The analysis indicates that the 3-fluoro analogue **54** is validated as the best with high binding affinity and potent antagonism for both rTRPV1 and hTRPV1 in CHO cells. The two chiral isomers of **54** were synthesized and its (***S***)-configuration (**54*S***) was found to be the active one, showing approximately a two-fold enhancement in receptor activity compared to **54**, whereas the (***R***)-configuration showed marked loss of activity.

A docking study of **54*S*** with our hTRPV1 homology model indicates that the hydrophobic 4-*t*-butylbenzyl group (C-region) extended nicely toward the upper hydrophobic region of the binding site, making hydrophobic interactions with Leu547, while the 2-(3-fluoro-4-methylsulfonylaminophenyl) propanamide (A/B-regions) occupied the deep bottom hole, forming critical hydrogen bonds with Tyr511, Ser512 and Gly558 for high potency.

4. Experimental

4.1. Chemistry

4.1.1. General

All chemical reagents were commercially available. Melting points were determined on a melting point Buchi 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 and Bruker Analytik, DE/AVANCE Digital 400 at 400 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.

4.1.2. General procedure for alkylation

To a stirred solution of potassium *t*-butoxide (20 mmol) in DMF (20 mL) was added a mixture of nitrobenzene 4 (10 mmol) and ethyl 2-chloropropionate (10 mmol) at 0 °C dropwise. After being stirred for 10 min at 0 °C, the mixture was quenched with 1 N HCl solution, diluted with water and extracted with diethyl ether several times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:10) as eluant.

4.1.2.1. Ethyl 2-(3-fluoro-4-nitrophenyl)propionate (5). 68% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.02 (dd, 1H, *J* = 7.8, 8.0 Hz, H-5), 7.2–7.3 (m, 2H, H-2,6), 4.14 (m, 2H, $CO_2CH_2CH_3$), 3.78 (q, 1H, *J* = 7.1 Hz, $CHCH_3$), 1.52 (d, 3H, *J* = 7.1 Hz, $CHCH_3$), 1.22 (t, 3H, *J* = 7.08 Hz, $CO_2CH_2CH_3$).

4.1.2.2. Ethyl 2-(3-chloro-4-nitrophenyl)propionate (6). 64% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 1H, *J* = 8.4 Hz, H-5), 7.51 (d, 1H, *J* = 1.8 Hz, H-2), 7.36 (dd, 1H, *J* = 8.4, 1.8 Hz, H-6), 4.15 (m, 2H, $CO_2CH_2CH_3$), 3.77 (q, 1H, *J* = 7.2 Hz, $CHCH_3$), 1.53 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 1.24 (t, 3H, *J* = 7.08 Hz, $CO_2CH_2CH_3$).

4.1.2.3. Ethyl 2-(3-bromo-4-nitrophenyl)propionate (7). 52% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1H, *J* = 8.4 Hz, H-5), 7.69 (d, 1H, *J* = 2 Hz, H-2), 7.40 (dd, 1H, *J* = 8.4, 2 Hz, H-6), 4.15 (m, 2H, $CO_2CH_2CH_3$), 3.75 (q, 1H, *J* = 7.1 Hz, $CHCH_3$), 1.52 (d, 3H, *J* = 7.1 Hz, $CHCH_3$), 1.24 (t, 3H, *J* = 7.08 Hz, $CO_2CH_2CH_3$).

4.1.2.4. Ethyl 2-(3-iodo-4-nitrophenyl)propionate (8). 32% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1H, *J* = 2 Hz, H-2), 7.84 (d, 1H, *J* = 8.4 Hz, H-5), 7.43 (dd, 1H, *J* = 8.4, 2 Hz, H-6), 4.15 (m, 2H, $CO_2CH_2CH_3$), 3.72 (q, 1H, *J* = 7.1 Hz, $CHCH_3$), 1.52 (d, 3H, *J* = 7.1 Hz, $CHCH_3$), 1.24 (t, 3H, *J* = 7.08 Hz, $CO_2CH_2CH_3$).

4.1.2.5. Ethyl 2-(3,5-difluoro-4-nitrophenyl)propionate (9). 56% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.08 (br d, 2H), 4.16 (m, 2H, $CO_2CH_2CH_3$), 3.74 (q, 1H, *J* = 7.1 Hz, $CHCH_3$), 1.53 (d, 3H, *J* = 7.1 Hz, $CHCH_3$), 1.25 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.2.6. Ethyl 2-(2-fluoro-4-nitrophenyl)propionate (10). 36% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.03 (dd, 1H, *J* = 8.6, 2.2 Hz, H-3), 7.93 (dd, 1H, *J* = 9.5, 2.2 Hz, H-5), 7.52 (t, 1H, *J* = 8.3Hz, H-6), 4.17 (q, 2H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.08 (q, 1H, *J* = 7.1 Hz, $CHCH_3$), 1.55 (d, 3H, *J* = 7.1 Hz, $CHCH_3$), 1.23 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.2.7. Ethyl 2-(2-chloro-4-nitrophenyl)propionate (11). 28% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.26 (d, 1H, *J* = 2.4 Hz, H-3), 8.11 (dd, 1H, *J* = 8.6, 2.4 Hz, H-5), 7.55 (d, 1H, *J* = 8.6 Hz, H-6), 4.27 (q, 1H, *J* = 7.1 Hz, $CHCH_3$), 4.18 (m, 2H, $CO_2CH_2CH_3$), 1.55 (d, 3H, *J* = 7.1 Hz, $CHCH_3$), 1.23 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.2.8. Ethyl 2-(3-cyano-4-nitrophenyl)propionate (12). 20% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, 1H, *J* = 8.4 Hz, H-5), 7.87 (d, 1H, *J* = 2 Hz, H-2), 7.77 (dd, 1H, *J* = 8.4, 2 Hz, H-6), 4.17 (m, 2H, $CO_2CH_2CH_3$), 3.88 (q, 1H, *J* = 7.2 Hz, $CHCH_3$), 1.58 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 1.25 (t, 3H, *J* = 7.2 Hz, $CO_2CH_2CH_3$); IR (neat) 2236 (CN), 1731 (CO) cm^{-1}.

4.1.2.9. Ethyl 2-(3-*t*-butoxycarbonyl-4-nitrophenyl)propionate (13). 44% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 1H, *J* = 8.3Hz, H-5), 7.58 (d, 1H, *J* = 1.8 Hz, H-2), 7.49 (dd, 1H, *J* = 8.3, 1.8 Hz, H-6), 4.11 (m, 2H, $CO_2CH_2CH_3$), 3.78 (q, 1H, *J* = 7.2 Hz, $CHCH_3$), 1.53 (s, 9H, $C(CH_3)_3$), 1.50 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 1.19 (t, 3H, *J* = 7.08 Hz, $CO_2CH_2CH_3$).

4.1.2.10. Ethyl 2-(3-piperidino-4-nitrophenyl)propionate (14). Compound **14** prepared from **5b** by the condensation with piperidine. 93% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1H, *J* = 8.4 Hz, H-5), 7.02 (d, 1H, *J* = 1.8 Hz, H-2), 6.88 (dd, 1H, *J* = 8.4, 1.8 Hz, H-6), 4.14 (m, 2H, CO_2CH2CH_3), 3.69 (q, 1H, *J* = 7.1 Hz, $CHCH_3$), 3.02 (m, 4H, CH_2NCH_2), 1.65–1.75 (m, 4H), 1.60 (m, 2H), 1.49 (d, 3H, *J* = 7.1 Hz, $CHCH_3$), 1.23 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.2.11. Ethyl 2-(3-morpholino-4-nitrophenyl)propionate (15). Compound **15** prepared from **5b** by the condensation with morpholine. 58% yield, yellow oil, ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 1H, *J* = 8.4 Hz, H-5), 7.05 (d, 1H, *J* = 1.8 Hz, H-2), 7.00 (dd, 1H, *J* = 8.4, 1.8 Hz, H-6), 4.14 (m, 2H, $CO_2CH_2CH_3$), 3.85 (m, 4H, CH_2OCH_2), 3.72 (q, 1H, *J* = 7.1 Hz, $CHCH_3$), 3.07 (m, 4H, CH_2NCH_2), 1.51 (d, 3H, *J* = 7.1 Hz, $CHCH_3$), 1.23 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.2.12. Ethyl 2-(3-(*tert*-butoxycarbonyl)piperazino-4-nitrophenyl)propionate (16). Compound **16** prepared from **5b** by the condensation with *N*-(*tert*-butoxycarbonyl)piperazine. 48% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 1H, *J* = 8.4 Hz, H-5), 7.06 (d, 1H, *J* = 1.8 Hz, H-2), 7.00 (dd, 1H, *J* = 8.4, 1.8 Hz, H-6), 4.14 (m, 2H, $CO_2CH_2CH_3$), 3.72 (q, 1H, *J* = 7.1 Hz, $CHCH_3$), 3.12 (m, 8H, 2 × CH_2NCH_2), 1.50 (d, 3H, *J* = 7.1 Hz, $CHCH_3$), 1.49 (s, 9H, $C(CH_3)_3$), 1.23 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3. General procedure for nitro reduction

Method A: A suspension of nitro compound 5 (5 mmol) and 10% Pd–C (500 mg) in EtOH (30 mL) was hydrogenated under a balloon of hydrogen for 1 h and filtered through Celite. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:4) as eluant.

Method B: A suspension of nitro compound 5 (5 mmol) and activated iron (0.28 g, 5 mmol) in acetic acid (30 mL) was heated at 90 °C for 1 min. After being cooled at room temperature, the mixture was diluted with EtOH, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:4) as eluant.

4.1.3.1. Ethyl 2-(4-amino-3-fluorophenyl)propionate (17). *Method A:* 94% yield, a colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.96 (dd, 1H, J = 1.7, 11.9 Hz, H-2), 6.87 (dd, 1H, J = 1.7, 8.3Hz, H-6), 6.71 (dd, 1H, J = 8.3, 11.9 Hz, H-5), 4.11 (m, 2H, $CO_2CH_2CH_3$), 3.58 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.45 (br s, 2H, NH_2), 1.43 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.20 (t, 3H, J = 7.05 Hz, $CO_2CH_2CH_3$).

4.1.3.2. Ethyl 2-(4-amino-3-chlorophenyl)propionate (18). *Method B:* 88% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 1H, J = 2 Hz, H-2), 7.00 (dd, 1H, J = 2, 8.1 Hz, H-6), 6.71 (d, 1H, J = 8.1 Hz, H-5), 4.11 (m, 2H, $CO_2CH_2CH_3$), 4.00 (br s, 2H, NH_2), 3.56 (q, 1H, J = 7.1 Hz, $CHCH_3$), 1.44 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.21 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3.3. Ethyl 2-(4-amino-3-bromophenyl)propionate (19). *Method B:* 45% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 1H, J = 2 Hz, H-2), 7.05 (dd, 1H, J = 2, 8.2 Hz, H-6), 6.71 (d, 1H, J = 8.2 Hz, H-5), 4.11 (m, 2H, $CO_2CH_2CH_3$), 4.03 (br s, 2H, NH_2), 3.56 (q, 1H, J = 7.1 Hz, $CHCH_3$), 1.43 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.21 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3.4. Ethyl 2-(4-amino-3-iodophenyl)propionate (20). *Method B:* 34% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, 1H, J = 2 Hz, H-2), 7.08 (dd, 1H, J = 2, 8.3Hz, H-6), 6.69 (d, 1H, J = 8.3Hz, H-5), 4.12 (m, 2H, $CO_2CH_2CH_3$), 4.05 (br s, 2H, NH_2), 3.54 (q, 1H, J = 7.1 Hz, $CHCH_3$), 1.43 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.21 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3.5. Ethyl 2-(4-amino-3,5-difluorophenyl)propionate (21). *Method A:* 99% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.79 (ddd, 2H), 4.12 (m, 2H, $CO_2CH_2CH_3$), 3.68 (br s, 2H, NH_2), 3.56 (q, 1H, J = 7.1 Hz, $CHCH_3$), 1.43 (d, 3H, J = J = 7.1 Hz, $CHCH_3$), 1.22 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3.6. Ethyl 2-(4-amino-2-fluorophenyl)propionate (22). *Method A:* 96% yield, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.04 (t, 1H, J = 8.3Hz, H-6), 6.41 (dd, 1H, J = 8.2, 2.2 Hz, H-5), 6.35 (dd, 1H, J = 11.9, 2.2 Hz, H-3), 4.12 (m, 2H, $CO_2CH_2CH_3$), 3.87 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.64 (br s, 2H, NH_2), 1.43 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.20 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3.7. Ethyl 2-(4-amino-2-chlorophenyl)propionate (23). *Method A:* 97% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.08 (d, 1H, J = 8.4 Hz, H-6), 6.69 (d, 1H, J = 2.4 Hz, H-3), 6.55 (dd, 1H, J = 8.6, 2.4 Hz, H-5), 4.13 (m, 2H, $CO_2CH_2CH_3$), 4.07 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.69 (br s, 1H, NH_2), 1.43 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.21 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3.8. Ethyl 2-(4-amino-3-cyanophenyl)propionate (24). *Method A:* 42% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.25–7.35 (m, 2H, H-2 & H-6), 6.70 (d, 1H, J = 8.4 Hz, H-5), 4.36 (br s, 2H, NH_2), 4.12 (m, 2H, $CO_2CH_2CH_3$), 3.58 (q, 1H, J = 7.1 Hz, $CHCH_3$), 1.44 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.22 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3.9. Ethyl 2-[4-amino-3-(t-butoxycarbonyl)phenyl]propionate (25). *Method A:* 89% yield, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 1H, J = 2.2 Hz, H-2), 7.25 (dd, 1H, J = 2.2, 8.6 Hz, H-6), 6.65 (d, 1H, J = 8.6 Hz, H-5), 4.16 (m, 2H, $CO_2CH_2CH_3$), 5.70 (br s, 2H, NH_2), 3.63 (q, 1H, J = 7.1 Hz, $CHCH_3$), 1.62 (s, 9H, $C(CH_3)_3$), 1.48 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.26 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3.10. Ethyl 2-(4-amino-3-piperidinophenyl)propionate (26). *Method A:* 72% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.92 (d, 1H, J = 2 Hz, H-2), 6.84 (dd, 1H, J = 2, 8.1 Hz, H-6), 6.66 (d, 1H, J = 8.1 Hz, H-5), 4.10 (m, 2H, $CO_2CH_2CH_3$), 3.92 (br s, 2H, NH_2), 3.58 (q, 1H, J = 7.1 Hz, $CHCH_3$), 2.83 (m, 4H, CH_2NCH_2), 1.65–1.75 (m, 4H), 1.57 (m, 2H), 1.44 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.20 ^{1}H NMR(t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3.11. Ethyl 2-(4-amino-3-morpholinophenyl)propionate (27). *Method A:* 90% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.93 (d, 1H, J = 2 Hz, H-2), 6.89 (dd, 1H, J = 2, 8.3Hz, H-6), 6.69 (d, 1H, J = 8.3Hz, H-5), 4.10 (m, 2H, $CO_2CH_2CH_3$), 3.93 (br s, 2H, NH_2), 3.84 (m, 4H, CH_2OCH_2), 3.59 (q, 1H, J = 7.1 Hz, $CHCH_3$), 2.92 (m, 4H, CH_2NCH_2), 1.45 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.21 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.3.12. Ethyl 2-[4-amino-3-*N*-(*tert*-butoxycarbonyl)piperazinophenyl]propionate (28). *Method A:* 94% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.90 (d, 1H, J = 2 Hz, H-2), 6.88 (dd, 1H, J = 2, 8 Hz, H-6), 6.69 (d, 1H, J = 8 Hz, H-5), 4.10 (m, 2H, $CO_2CH_2CH_3$), 3.93 (br s, 2H, NH_2), 3.5–3.6 (m, 5H, $CHCH_3$ and $CH_2N(Boc)CH_2$), 2.86 (m, 4H, CH_2NCH_2), 1.4^{1}H NMR9 (s, 9H, $C(CH_3)_3$), 1.44 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.21 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4. General procedure for mesylation

A mixture of amine 6 (4 mmol) and methanesulfonyl chloride (6 mmol) in pyridine (10 mL) was stirred at 0 °C for 10 min. After aqueous workup, the residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:2) as eluant.

4.1.4.1. Ethyl 2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionate (29). 91% yield, white solid, mp = 81 °C; ^{1}H NMR ($CDCl_3$) δ 7.50 (t, 1H, J = 8.3Hz, H-5), 7.0–7.1 (m, 2H, H-2,6), 6.55 (br s, 1H, $NHSO_2$), 4.12 (m, 2H, $CO_2CH_2CH_3$), 3.68 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.02 (s, 3H, SO_2CH_3), 1.48 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.22 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.2. Ethyl 2-[3-chloro-4-(methylsulfonylamino)phenyl]propionate (30). 90% yield, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 1H, J = 8.4 Hz, H-5), 7.40 (d, 1H, J = 2 Hz, H-2), 7.25 (dd, 1H, J = 8.4, 2 Hz, H-6), 6.78 (br s, 1H, $NHSO_2$), 4.14 (m, 2H, $CO_2CH_2CH_3$), 3.67 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.02 (s, 3H, SO_2CH_3), 1.49 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.23 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.3. Ethyl 2-[3-bromo-4-(methylsulfonylamino)phenyl]propionate (31). 96% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 1H, J = 8.4 Hz, H-5), 7.55 (d, 1H, J = 2 Hz, H-2), 7.28 (dd, 1H, J = 8.4, 2 Hz, H-6), 6.76 (br s, 1H, $NHSO_2$), 4.13 (m, 2H, $CO_2CH_2CH_3$), 3.67 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.01 (s, 3H, SO_2CH_3), 1.49 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.23 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.4. Ethyl 2-[3-iodo-4-(methylsulfonylamino)phenyl]propionate (32). 95% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 1H, J = 2 Hz, H-2), 7.58 (d, 1H, J = 8.4 Hz, H-2), 7.32 (dd, 1H, J = 8.4, 2 Hz, H-6), 4.14 (m, 2H, $CO_2CH_2CH_3$), 3.65 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.01 (s, 3H, SO_2CH_3), 1.48 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.23 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.5. Ethyl 2-[3,5-difluoro-4-(methylsulfonylamino)phenyl]propionate (33). 95% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.05 (d, 2H, J = 8.4 Hz), 4.14 (m, 2H, $CO_2CH_2CH_3$), 3.71 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.47 (s, 3H, SO_2CH_3), 1.50 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.25 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.6. Ethyl 2-[2-fluoro-4-(methylsulfonylamino)phenyl]propionate (34). 92% yield, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.27 (t, 1H, J = 8.1 Hz, H-6), 7.02 (dd, 1H, J = 11, 2.2 Hz, H-3), 6.94 (dd, 1H, J = 8.4, 2.2 Hz, H-5), 4.16 (m, 2H, $CO_2CH_2CH_3$), 3.96 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.04 (s, 3H, SO_2CH_3), 1.49 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.23 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.7. Ethyl 2-[2-chloro-4-(methylsulfonylamino)phenyl]propionate (35). 89% yield, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 1H, J = 2.4 Hz, H-3), 7.28 (d, 1H, J = 8.4 Hz, H-6), 7.16 (dd, 1H, J = 8.6, 2.4 Hz, H-5), 4.1–4.2 (m, 3H, $CO_2CH_2CH_3$ and $CHCH_3$), 3.02 (s, 3H, SO_2CH_3), 1.48 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.24 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.8. Ethyl 2-[3-cyano-4-(methylsulfonylamino)phenyl]propionate (36). 98% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.55–7.7 (m, 3H), 4.15 (m, 2H, $CO_2CH_2CH_3$), 3.72 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.12 (s, 3H, SO_2CH_3), 1.51 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.24 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.9. Ethyl 2-[3-(t-butoxycarbonyl)-4-(methylsulfonylamino) phenyl]propionate (37). 99% yield, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, J = 2.2 Hz, H-2), 7.61 (d, 1H, J = 8.6 Hz, H-5), 7.43 (dd, 1H, J = 8.6, 2.2 Hz, H-6), 4.08 (m, 2H, $CO_2CH_2CH_3$), 3.66 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.00 (s, 3H, SO_2CH_3), 1.56 (s, 9H, $C(CH_3)_3$), 1.44 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.19 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.10. Ethyl 2-[3-piperidino-4-(methylsulfonylamino) phenyl]propionate (38). 96% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.79 (br s, 1H, $NHSO_2$), 7.45 (d, 1H, J = 8.4 Hz, H-5), 7.15 (d, 1H, J = 2 Hz, H-2), 7.07 (dd, 1H, J = 8.4, 2 Hz, H-6), 4.14 (m, 2H, $CO_2CH_2CH_3$), 3.64 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.04 (s, 3H, SO_2CH_3), 2.77 (m, 4H, CH_2NCH_2), 1.65–1.75 (m, 4H), 1.59 (m, 2H), 1.47 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.22 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.11. Ethyl 2-[3-morpholino-4-(methylsulfonylamino)phenyl]propionate (39). 92% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.72 (br s, 1H, $NHSO_2$), 7.46 (d, 1H, J = 8.4 Hz, H-5), 7.18 (d, 1H, J = 2 Hz, H-2), 7.13 (dd, 1H, J = 8.4, 2 Hz, H-6), 4.13 (m, 2H, $CO_2CH_2CH_3$), 3.86 (m, 4H, CH_2OCH_2), 3.66 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.08 (s, 3H, SO_2CH_3), 2.87 (m, 4H, CH_2NCH_2), 1.48 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.23 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.4.12. Ethyl 2-[3-*N*-(*tert*-butoxycarbonyl)piperazino-4-(methylsulfonylamino)phenyl] propionate (40). 99% yield, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.75 (br s, 1H, $NHSO_2$), 7.45 (d, 1H, J = 8.4 Hz, H-5), 7.15 (d, 1H, J = 2 Hz, H-2), 7.13 (dd, 1H, J = 8.4, 2 Hz, H-6), 4.13 (m, 2H, $CO_2CH_2CH_3$), 3.66 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.61 (m, 4H, $CH_2N(Boc)CH_2$), 3.09 (s, 3H, SO_2CH_3), 2.83 (m, 4H, CH_2NCH_2), 1.49 (s, 9H, $C(CH_3)_3$), 1.47 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.22 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$).

4.1.5. General procedure for hydrolysis

A solution of ester **7** (2 mmol) in H_2O and THF (1:2, 30 mL) was treated with lithium hydroxide (6 mmol) and stirred for 4 h at room temperature. The mixture was diluted with H_2O and CH_2Cl_2, acidified with 1 N HCl solution and extracted with CH_2Cl_2 several times. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was crystallized by diethyl ether and *n*-hexane.

4.1.5.1. 2-[3-Fluoro-4-(methylsulfonylamino)phenyl]propionic acid (41). 97% yield, white solid, mp = 120 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (t, 1H, J = 8.04 Hz, H-5), 7.1–7.15 (m, 2H, H-2,6), 6.60 (br s, 1H, $NHSO_2$), 3.73 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.03 (s, 3H, SO_2CH_3), 1.51 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.2. 2-[3-Chloro-4-(methylsulfonylamino)phenyl]propionic acid (42). 92% yield, pink solid, mp = 133–135 °C; ^{1}H NMR ($CDCl_3$) δ 10.19 (br s, 1H, CO_2H), 7.60 (d, 1H, J = 8.4 Hz, H-5), 7.41 (d, 1H, J = 1.8 Hz, H-2), 7.26 (dd, 1H, J = 8.4, 1.8 Hz, H-6), 6.91 (br s, 1H, $NHSO_2$), 3.72 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.02 (s, 3H, SO_2CH_3), 1.51 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.3. 2-[3-Bromo-4-(methylsulfonylamino)phenyl]propionic acid (43). 99% yield, white solid, mp = 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, 1H, J = 8.4 Hz, H-5), 7.56 (d, 1H, J = 2 Hz, H-2), 7.30 (dd, 1H, J = 8.4, 2 Hz, H-6), 6.76 (br s, 1H, $NHSO_2$), 3.72 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.02 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.4. 2-[3-Iodo-4-(methylsulfonylamino)phenyl]propionic acid (44). 99% yield, white solid, mp = 102–103 °C; ^{1}H NMR (CD_3OD) δ 7.88 (d, 1H, J = 1.8 Hz, H-2), 7.3–7.4 (m, 2H, H-5 and H-6), 3.52 (q, 1H, J = 7.1 Hz, $CHCH_3$), 2.97 (s, 3H, SO_2CH_3), 1.39 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.5. 2-[3,5-Difluoro-4-(methylsulfonylamino)phenyl]propionic acid (45). 92% yield, white solid, mp = 78–79 °C; ^{1}H NMR ($CDCl_3$) δ 7.00 (d, 2H, J = 8.4 Hz), 6.03 (br s, 1H, $NHSO_2$), 3.73 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.22 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.6. 2-[2-Fluoro-4-(methylsulfonylamino)phenyl]propionic acid (46). 86% yield, pink solid, mp = 134–136 °C; ^{1}H NMR ($CDCl_3$) δ 7.29 (t, 1H, J = 8.1 Hz, H-6), 7.02 (dd, 1H, J = 11, 2.2 Hz, H-3), 6.94 (dd, 1H, J = 8.4, 2.2 Hz, H-5), 6.82 (br s, 1H, $NHSO_2$), 4.02 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.05 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.7. 2-[2-Chloro-4-(methylsulfonylamino)phenyl]propionic acid (47). 84% yield, pink solid, mp = 188–190 °C; ^{1}H NMR (CD_3OD) δ 7.24 (d, 1H, J = 8.4 Hz, H-6), 7.21 (d, 1H, J = 2.4 Hz, H-3), 7.07 (dd, 1H, J = 8.6, 2.4 Hz, H-5), 4.02 (q, 1H, J = 7.1 Hz, $CHCH_3$), 2.88 (s, 3H, SO_2CH_3), 1.35 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.8. 2-[3-Cyano-4-(methylsulfonylamino)phenyl]propionic acid (48). 38% yield, white solid, mp = 108–111 °C; ^{1}H NMR (CD_3OD) δ 8.67 (d, 1H, J = 2.2 Hz, H-2), 8.60 (dd, 1H, J = 8.4, 2.2 Hz, H-6), 8.43 (d, 1H, J = 8.4 Hz, H-5), 5.98 (br s, 2H, NH_2), 4.64 (q, 1H, J = 7.1 Hz, $CHCH_3$), 4.05 (s, 3H, SO_2CH_3), 2.18 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.9. 2-[3-(*t*-Butoxycarbonyl)-4-(methylsulfonylamino)phenyl]propionic acid (49). 87% yield, yeollw solid, mp = 79–81 °C; ^{1}H NMR ($CDCl_3$) δ 10.53 (s, 1H, CO_2H), 7.87 (d, 1H, J = 2.2 Hz, H-2), 7.64 (d, 1H, J = 8.6 Hz, H-5), 7.46 (dd, 1H, J = 8.6, 2.2 Hz, H-6), 3.71 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.02 (s, 3H, SO_2CH_3), 1.57 (s, 9H, $C(CH_3)_3$), 1.48 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.10. 2-[3-Piperidino-4-(methylsulfonylamino)phenyl]propionic acid (50). 83% yield, white solid, mp = 152 °C; ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 1H, J = 8.4 Hz, H-5), 7.05–7.2 (m, 2H, H-2 and H-6), 3.69 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.06 (s, 3H, SO_2CH_3), 2.79 (m, 4H, CH_2NCH_2), 1.68–1.8 (m, 4H), 1.60 (m, 2H), 1.50 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.11. 2-[3-Morpholino-4-(methylsulfonylamino)phenyl]propionic acid (51). 93% yield, white solid, mp = 180 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, 1H, J = 8.4 Hz, H-5), 7.18 (d, 1H, J = 1.8 Hz, H-2), 7.15 (dd, 1H, J = 8.4, 1.8 Hz, H-6), 6.91 (br s, 1H, $NHSO_2$), 3.86 (m, 4H, CH_2OCH_2), 3.70 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.08 (s, 3H, SO_2CH_3), 2.86 (m, 4H, CH_2NCH_2), 1.51 (d, 3H, J = 7.1 Hz, $CHCH_3$).

4.1.5.12. 2-[3-(*N*-*tert*-Butoxycarbonyl)piperazino-4-(methylsulfonylamino)phenyl]propionic acid (52). 93% yield, white solid, mp = 139–142 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, 1H, J = 8.4 Hz, H-5), 7.12–7.16 (m, 2H, H-2 and H-6), 3.70 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.59 (m, 4H, $CH_2N(Boc)CH_2$), 3.08 (s, 3H, SO_2CH_3), 2.80 (m, 4H, CH_2NCH_2), 1.50 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.49 (s, 9H, C(C*H*$_3$)$_3$).

4.1.6. Generel procedure for coupling

A mixture of acid **8** (10 mmol), 4-*t*-butylbenzylamine (12 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (12 mmol) in CH_2Cl_2 (20 mL) was stirred for 12 h at room temperature. The reaction mixture was filtered off and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes as eluant.

4.1.6.1. *N*-(4-*tert*-Butylbenzyl)-2-[4-(methylsulfonylamino)phenyl]propionamide (53). Compound **53** prepared from the carboxylic acid previously reported by the general coupling procedure.

93% yield, white solid, mp = 77–79 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (dt, 2H), 7.27 (dt, 2H), 7.18 (dt, 2H), 7.11 (dt, 2H), 6.96 (br s, 1H, $NHSO_2$), 5.73 (br t, 1H, NH), 4.38 (ddd, 2H, $ArCH_2NH$), 3.55 (q, 1H, J = 7.1 Hz, C*H*CH_3), 2.98 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.29 (s, 9H, C(C*H*$_3$)$_3$); IR (KBr) 3277, 2963, 1649, 1512, 1464, 1333, 1228, 1153 cm^{-1}; MS (EI) *m/z* 388 (M^+); Anal. Calcd for $C_{21}H_{28}N_2O_3S$: C, 64.92; H, 7.26; N, 7.21. Found: C, 64.78; H, 7.24; N, 7.18.

4.1.6.2. *N*-(4-*tert*-Butylbenzyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (54). 78% yield, white solid, mp = 52–54 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 (t, 1H, J = 8.3Hz, H-5), 7.32 (br d, 2H, Ar), 7.1–7.2 (m, 4H, Ar), 6.73 (br s, 1H, $NHSO_2$), 5.83 (br t, 1H, NHCO), 4.36 (ddd of AB, 2H, $ArCH_2NH$), 3.52 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.00 (s, 3H, SO_2CH_3), 1.50 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.29 (s, 9H, C(C*H*$_3$)$_3$); IR (KBr) 3286, 2964, 1650, 1511, 1331, 1157, 1116 cm^{-1}; MS (FAB) *m/z* 407 (MH^+); Anal. Calcd for $C_{21}H_{27}FN_2O_3S$: C, 62.05; H, 6.69; N, 6.89. Found: C, 62.27; H, 6.67; N, 6.86.

4.1.6.3. *N*-(4-*tert*-Butylbenzyl)-2-[3-chloro-4-(methylsulfonylamino)phenyl]propionamide (55). 68% yield, white solid, mp = 126–129 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 1H, J = 8.2 Hz, H-5), 7.43 (d, 1H, J = 2 Hz, H-2), 7.34 (br d, 2H, Ar), 7.24 (dd, 1H, J = 8.2, 2 Hz, H-6), 7.14 (br d, 2H, Ar), 6.75 (br s, 1H, $NHSO_2$), 5.68 (br t, 1H, NHCO), 4.38 (ddd of AB, 2H, $ArCH_2NH$), 3.50 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.01 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.30 (s, 9H, C(C*H*$_3$)$_3$); IR (KBr) 3287, 2963, 1648, 1497, 1331, 1236, 1157 cm^{-1}; MS (FAB) *m/z* 423 (MH^+); Anal. Calcd for $C_{21}H_{27}ClN_2O_3S$: C, 59.63; H, 6.43; N, 8.38. Found: C, 59.47; H, 6.41; N, 8.40.

4.1.6.4. *N*-(4-*tert*-Butylbenzyl)-2-[3-bromo-4-(methylsulfonylamino)phenyl]propionamide (56). 76% yield, white solid, mp = 66–67 °C; ^{1}H NMR ($CDCl_3$) δ 7.55–7.6 (m, 2H, H-2 and H-5), 7.33 (d, 2H, J = 8.1 Hz, Ar), 7.27 (dd, 1H, J = 1.8, 8.6 Hz, H-6), 7.12 (d, 2H, J = 8.1 Hz, Ar), 6.80 (br s, 1H, $NHSO_2$), 5.91 (br t, 1H, NHCO), 4.36 (ddd of AB, 2H, $ArCH_2NH$), 3.50 (q, 1H, J = 7.1 Hz, C*H*CH_3), 2.98 (s, 3H, SO_2CH_3), 1.50 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.29 (s, 9H, C(C*H*$_3$)$_3$); IR (KBr) 3292, 2963, 1649, 1493, 1387, 1330, 1233, 1157, 1044 cm^{-1}; MS (FAB) *m/z* 467 (MH^+); Anal. Calcd for $C_{21}H_{27}BrN_2O_3S$: C, 53.96; H, 5.82; N, 5.99. Found: C, 53.67; H, 5.80; N, 5.97.

4.1.6.5. *N*-(4-*tert*-Butylbenzyl)-2-[3-iodo-4-(methylsulfonylamino)phenyl]propionamide (57). 75% yield, white solid, mp = 71 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, 1H, J = 2 Hz, H-2), 7.59 (d, 1H, J = 8.3Hz, H-5), 7.3–7.37 (m, 3H, Ar), 7.13 (d, 2H, J = 8.1 Hz, Ar), 6.60 (br s, 1H, $NHSO_2$), 5.67 (br t, 1H, NHCO), 4.39 (ddd of AB, 2H, $ArCH_2NH$), 3.48 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.01 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.30 (s, 9H, C(C*H*$_3$)$_3$); IR (KBr) 3299, 2963, 1649, 1539, 1486, 1385, 1329, 1231, 1115, 1036 cm^{-1}; MS (FAB) *m/z* 515 (MH^+); Anal. Calcd for $C_{21}H_{27}IN_2O_3S$: C, 49.03; H, 5.29; N, 5.45. Found: C, 49.33; H, 5.26; N, 5.43.

4.1.6.6. *N*-(4-*tert*-Butylbenzyl)-2-[3,5-difluoro-4-(methylsulfonylamino)phenyl]propionamide (58). 70% yield, white solid, mp = 80–81 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (dt, 2H), 7.15 (br d, 2H, Ar), 6.99 (dt, 2H, Ar), 6.16 (br s, 1H, $NHSO_2$), 5.76 (br t, 1H, NHCO), 4.38 (ddd of AB, 2H, J = 5.7, 14.5, 33.7 Hz, $ArCH_2NH$), 4.12 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.02 (s, 3H, SO_2CH_3), 1.50 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.30 (s, 9H, C(C*H*$_3$)$_3$); IR (KBr) 3376, 2962, 1653, 1511, 1454, 1331, 1231, 1155, 1023, 1155, 1023 cm^{-1}; MS (FAB) *m/z* 425 (MH^+); Anal. Calcd for $C_{21}H_{26}F_2N_2O_3S$: C, 59.42; H, 6.17; N, 6.60. Found: C, 59.20; H, 6.15; N, 6.63.

4.1.6.7. *N*-(4-*tert*-Butylbenzyl)-2-[2-fluoro-4-(methylsulfonylamino)phenyl]propionamide (59). 63% yield, white solid, mp = 111–113 °C; ^{1}H NMR ($CDCl_3$) δ 7.3–7.38 (m, 3H, H-6 and Ar), 7.28 (br s, 1H, $NHSO_2$), 7.15 (br d, 2H, Ar), 7.02 (dd, 1H, J = 11.4, 2.2 Hz, H-3), 6.87 (dd, 1H, J = 8.4, 2.2 Hz, H-5), 5.88 (br t, 1H, NHCO), 4.41 (ddd of AB, 2H, $ArCH_2NH$), 3.84 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.00 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.30 (s, 9H, C(C*H*$_3$)$_3$); IR (KBr) 3277, 2963, 1652, 1509, 1396, 1328, 1266, 1151, 1117 cm^{-1}; MS (FAB) *m/z* 407 (MH^+); Anal. Calcd for $C_{21}H_{27}FN_2O_3S$: C, 62.05; H, 6.69; N, 6.89. Found: C, 62.36; H, 6.66; N, 6.87.

4.1.6.8. *N*-(4-*tert*-Butylbenzyl)-2-[2-chloro-4-(methylsulfonylamino)phenyl]propionamide (60). 46% yield, white solid, mp = 134–136 °C; ^{1}H NMR ($CDCl_3$) δ 7.44 (d, 1H, J = 8.4 Hz, H-6), 7.34 (br d, 2H, Ar), 7.29 (d, 1H, J = 2.2 Hz, H-3), 7.15 (br d, 2H, Ar), 7.07 (dd, 1H, J = 8.4, 2.2 Hz, H-5), 5.88 (br t, 1H, NHCO), 4.40 (ddd of AB, 2H, $ArCH_2NH$), 3.84 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.00 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.30 (s, 9H, C(C*H*$_3$)$_3$); IR (KBr) 3286, 2963, 1650, 1608, 1494, 1376, 1324, 1154 cm^{-1}; MS (FAB) *m/z* 423 (MH^+); Anal. Calcd for $C_{21}H_{27}ClN_2O_3S$: C, 59.63; H, 6.43; N, 8.38. Found: C, 59.38; H, 6.41; N, 8.42.

4.1.6.9. *N*-(4-*tert*-Butylbenzyl)-2-[3-cyano-4-(methylsulfonylamino)phenyl]propionamide (61). 30% yield, white solid, mp = 102–105 °C; ^{1}H NMR ($CDCl_3$) δ 7.67 (d, 1H, J = 8.4 Hz, H-5), 7.63 (d, 1H, J = 1.8 Hz, H-2), 7.58 (dd, 1H, J = 8.4, 1.8 Hz, H-6), 7.35 (br d, 2H, Ar), 7.15 (br d, 2H, Ar), 5.73 (br t, 1H, NHCO), 4.38 (ddd of AB, 2H, $ArCH_2NH$), 3.51 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.11 (s, 3H, SO_2CH_3), 1.53 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.31 (s, 9H, C(C*H*$_3$)$_3$).

IR (KBr) 3285, 2963, 2231, 1649, 1501, 1404, 1334, 1157, 1114 cm^{-1}; MS (FAB) *m/z* 414 (MH^+); Anal. Calcd for $C_{22}H_{27}N_3O_3S$: C, 63.90; H, 6.58; N, 10.16. Found: C, 64.20; H, 6.56; N, 10.13.

4.1.6.10. *N*-(4-*tert*-Butylbenzyl)-2-[3-(t-butoxycarbonyl)-4-(methylsulfonylamino)phenyl]propionamide (62). 53% yield, white solid, mp = 75–77 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 1H, J = 2.2 Hz, H-2), 7.67 (d, 1H, J = 8.6 Hz, H-5), 7.50 (dd, 1H, J = 8.6, 2.2 Hz, H-6), 7.33 (br d, 2H, Ar), 7.13 (br d, 2H, Ar), 5.74 (br t, 1H, NHCO), 4.38 (ddd of AB, 2H, $ArCH_2NH$), 3.55 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.04 (s, 3H, SO_2CH_3), 1.60 (s, 9H, $CO_2C(CH_3)_3$), 1.53 (d, 3H, J = 7.1 Hz, CHC*H*$_3$), 1.30 (s, 9H, C(C*H*$_3$)$_3$); IR (KBr) 2966, 1678, 1500, 1395, 1330, 1253, 1153, 1089 cm^{-1}; MS (FAB) *m/z* 489 (MH^+); Anal. Calcd for $C_{26}H_{36}N_2O_5S$: C, 63.91; H, 7.43; N, 5.73. Found: C, 64.19; H, 7.41; N, 5.72.

4.1.6.11. *N*-(4-*tert*-Butylbenzyl)-2-[3-carboxyl-4-(methylsulfonylamino)phenyl]propionamide (63). Compound **63** prepared from **62** by acid hydrolysis. 74% yield, white solid, mp = 180–183 °C; ^{1}H NMR (CD_3OD) δ 8.45 (br t, 1H, NH), 8.12 (d, 1H, J = 2.2 Hz, H-2), 7.64 (d, 1H,

J = 8.6 Hz, H-5), 7.56 (dd, 1H, J = 8.6, 2.2 Hz, H-6), 7.30 (br d, 2H, Ar), 7.11 (br d, 2H, Ar), 4.29 (br s, 2H, $ArCH_2NH$), 3.69 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.04 (s, 3H, SO_2CH_3), 1.46 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.27 (s, 9H, $C(CH_3)_3$); IR (KBr) 3429, 2964, 1678, 1626, 1503, 1338, 1206, 1153 cm^{-1}; MS (EI) m/z 432 (M^+); Anal. Calcd for $C_{22}H_{28}N_2O_5S$: C, 61.09; H, 6.52; N, 6.48. Found: C, 61.28; H, 6.50; N, 6.46.

4.1.6.12. *N*-(4-*tert*-Butylbenzyl)-2-[3-(methoxycarbonyl)-4-(methylsulfonylamino)phenyl]propionamide (64). Compound **64** prepared from **63** by the diazomethane reaction. 79% yield, white solid, mp = 142–144 °C; ^1H NMR ($CDCl_3$) δ 10.38 (s, 1H, $NHSO_2$), 8.03 (d, 1H, J = 2.2 Hz, H-2), 7.70 (d, 1H, J = 8.6 Hz, H-5), 7.51 (dd, 1H, J = 8.6, 2.2 Hz, H-6), 7.33 (br d, 2H, Ar), 7.13 (br d, 2H, Ar), 5.69 (br t, 1H, NHCO), 4.38 (ddd of AB, 2H, $ArCH_2NH$), 3.94 (s, 3H, CO_2CH_3), 3.53 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.05 (s, 3H, SO_2CH_3), 1.54 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.30 (s, 9H, $C(CH_3)_3$); IR (KBr) 3296, 2961, 1688, 1608, 1503, 1398, 1332, 1258, 1156, 1088 cm^{-1}; MS (FAB) m/z 447 (MH^+); Anal. Calcd for $C_{23}H_{30}N_2O_5S$: C, 61.86; H, 6.77; N, 6.27. Found: C, 62.03; H, 6.79; N, 6.29.

4.1.6.13. *N*-(4-*tert*-Butylbenzyl)-2-[3-(benzylamino)carbonyl-4-(methylsulfonylamino)phenyl]propionamide (65). Compound **65** prepared from **63** by coupling with benzyl amine. 88% yield, white solid, mp = 79–81 °C; ^1H NMR ($CDCl_3$) δ 7.65 (d, 1H, J = 8.6 Hz, H-5), 7.61 (d, 1H, J = 2.2 Hz, H-2), 7.3–7.38 (m, 8H), 7.11 (br d, 2H, Ar), 5.84 (br t, 1H, NHCO), 4.60 (d, 2H, J = 5.88 Hz, $NHCH_2Ph$), 4.35 (ddd of AB, 2H, $ArCH_2NH$), 3.48 (q, 1H, J = 7.1 Hz, $CHCH_3$), 2.97 (s, 3H, SO_2CH_3), 1.50 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.29 (s, 9H, $C(CH_3)_3$); IR (KBr) 3303, 2963, 1644, 1537, 1333, 1267, 1152 cm^{-1}; MS (FAB) m/z 522 (MH^+); Anal. Calcd for $C_{29}H_{35}N_3O_4S$: C, 66.77; H, 6.76; N, 8.05. Found: C, 66.99; H, 6.78; N, 8.07.

4.1.6.14. *N*-(4-*tert*-Butylbenzyl)-2-[3-piperidino-4-(methylsulfonylamino)phenyl]propionamide (66). 86% yield, white solid, mp = 125 °C; ^1H NMR ($CDCl_3$) δ 7.78 (br s, 1H, $NHSO_2$), 7.45 (d, 1H, J = 8.4 Hz, H-5), 7.31 (br d, 2H, Ar), 7.15 (d, 1H, J = 2 Hz, H-2), 7.10 (br d, 2H, Ar), 7.05 (m, 1H, J = 8.4, 2 Hz, H-6), 5.59 (br t, 1H, NHCO), 4.38 (d of AB, 2H, J = 5.7 Hz, $ArCH_2NH$), 3.52 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.04 (s, 3H, SO_2CH_3), 2.75 (m, 4H, CH_2NCH_2), 1.65–1.75 (m, 4H), 1.6 (m, 2H), 1.52 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.29 (s, 9H, $C(CH_3)_3$); IR (KBr) 3290, 2937, 1648, 1501, 1335, 1242, 1157 cm^{-1}; MS (FAB) m/z 472 (MH^+); Anal. Calcd for $C_{26}H_{37}N_3O_3S$: C, 66.21; H, 7.91; N, 8.91. Found: C, 66.49; H, 7.94; N, 8.93.

4.1.6.15. *N*-(4-*tert*-Butylbenzyl)-2-[3-morpholino-4-(methylsulfonylamino)phenyl]propionamide (67). 84% yield, white solid, mp = 78 °C; ^1H NMR ($CDCl_3$) δ 7.69 (br s, 1H, $NHSO_2$), 7.46 (d, 1H, J = 8.2 Hz, H-5), 7.32 (br d, 2H, Ar), 7.18 (d, 1H, J = 1.8 Hz, H-2), 7.08–7.15 (m, 3H, H-6 and Ar), 5.63 (br t, 1H, NHCO), 4.38 (d of AB, 2H, J = 5.5 Hz, $ArCH_2NH$), 3.85 (m, 4H, CH_2OCH_2), 3.52 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.08 (s, 3H, SO_2CH_3), 2.84 (m, 4H, CH_2NCH_2), 1.52 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.29 (s, 9H, $C(CH_3)_3$); IR (KBr) 3293, 2962, 1650, 1505, 1455, 1333, 1156, 1115 cm^{-1}; MS (FAB) m/z 474 (MH^+); Anal. Calcd for $C_{25}H_{35}N_3O_4S$: C, 63.40; H, 7.45; N, 8.87. Found: C, 63.69; H, 7.47; N, 8.90.

4.1.6.16. *N*-(4-*tert*-Butylbenzyl)-2-[3-(*N*-*tert*-butoxycarbonyl)piperazino-4-(methylsulfonylamino)phenyl]propionamide (68). 88% yield, white solid, mp = 103 °C; ^1H NMR ($CDCl_3$) δ 7.66 (br s, 1H, $NHSO_2$), 7.46 (d, 1H, J = 8.2 Hz, H-5), 7.32 (br d, 2H, Ar), 7.15 (d, 1H, J = 1.8 Hz, H-2), 7.08–7.13 (m, 3H, H-6 and Ar), 5.60 (br t, 1H, NHCO), 4.38 (ddd of AB, 2H, $ArCH_2NH$), 3.58 (m, 4H, $CH_2N(Boc)CH_2$), 3.49 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.08 (s, 3H, SO_2CH_3), 2.79 (m, 4H, CH_2NCH_2), 1.55 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.49 (s, 9H, $C(CH_3)_3$), 1.30 (s, 9H, $C(CH_3)_3$); IR (KBr) 3294, 2965, 1690, 1502, 1366, 1333, 1245, 1160 cm^{-1}; MS (FAB) m/z 573 (MH^+); Anal. Calcd for $C_{30}H_{44}N_4O_5S$: C, 62.91; H, 7.74; N, 9.78. Found: C, 62.69; H, 7.77; N, 9.80.

4.1.6.17. *N*-(4-*tert*-Butylbenzyl)-2-[3-piperazino-4-(methylsulfonylamino)phenyl]propionamide (69). Compound **69** prepared from **9o** by acid hydrolysis. 96% yield, white solid, mp = 92 °C; ^1H NMR ($CDCl_3$) δ 7.46 (d, 1H, J = 8.3Hz, H-5), 7.32 (br d, 2H, Ar), 7.18 (d, 1H, J = 1.8 Hz, H-2), 7.08–7.13 (m, 3H, H-6 and Ar), 5.60 (br t, 1H, NHCO), 4.38 (d of AB, 2H, J = 5 Hz, $ArCH_2NH$), 3.52 (q, 1H, J = 7.1 Hz, $CHCH_3$), 3.06 (s, 3H, SO_2CH_3), 3.03 (m, 4H, CH_2NCH_2), 2.80 (m, 4H, CH_2NCH_2), 1.52 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.29 (s, 9H, $C(CH_3)_3$); IR (KBr) 3293, 2960, 1651, 1506, 1456, 1333, 1155 cm^{-1}; MS (FAB) m/z 473 (MH^+); Anal. Calcd for $C_{25}H_{36}N_4O_3S$: C, 63.53; H, 7.68; N, 11.85. Found: C, 63.77; H, 7.65; N, 11.83.

4.1.6.18. *N*-(4-*tert*-Butylbenzyl)-2-[3-methyl-4-(methylsulfonylamino)phenyl]propionamide (70). To a solution of **56** (110 mg, 0.27 mmol) and tetramethyl tin (72 mg, 0.4 mmol) in toluene (3 mL) was added tetrakis(triphenylphosphine)palladium (31 mg, 0.027 mmol, 0.1 equiv). The mixture was refluxed for 6 h under a dry N_2 atmosphere. The reaction mixture was cooled to ambient temperature, filtered through Celite and concentrated in vacuo. The residue was extracted with EtOAc several times. The combined organic layers were washed with saturated aqueous NaCl and dried over $MgSO_4$. Concentration in vacuo and subsequent purification by column chromatography (using EtOAc–hexane = 1:1) gave **9q** in 47% yield. white solid, mp = 72–74 °C; ^1H NMR ($CDCl_3$) 7.41–7.10 (m, 7H, Ar-H), 6.29 (br s, 1H, $NHSO_2$), 5.67 (br s, 1H, NHCO), 4.56–4.29 (m, 2H, $ArCH_2NH$), 3.52 (q, 1H, J = 6.39 Hz, $CHCH_3$), 3.01 (s, 3H, SO_2CH_3), 2.30 (s, 3H, $ArCH_3$), 1.52 (d, 3H, J = 7.14 Hz, $CHCH_3$), 1.30 (s. 9H, $C(CH_3)_3$); IR (KBr) 3285, 2953, 1650, 1501, 1488, 1321, 1156, 1024 cm^{-1}; MS (FAB) m/z 403 (MH^+); Anal. Calcd for $C_{22}H_{30}N_2O_3S$: C, 65.64; H, 7.51; N, 6.96. Found: C, 65.84; H, 7.53; N, 6.94.

4.1.6.19. *N*-(4-*tert*-Butylbenzyl)-2-[3-methoxy-4-(methylsulfonylamino)phenyl]propionamide (71). Compound **71** prepared from the carboxylic acid previously reported by the general coupling procedure.

83% yield, white solid, mp = 74–76 °C; ^1H NMR ($CDCl_3$) δ 7.1–7.5 (m, 5H), 6.85–6.9 (m, 2H), 6.75 (br s, 1H, $NHSO_2$), 5.75 (br t, 1H, NHCO), 4.39 (ddd of AB, 2H, $ArCH_2NH$), 3.85 (s, 3H, OCH_3), 3.54 (q, 1H, J = 7.1 Hz, $CHCH_3$), 2.94 (s, 3H, SO_2CH_3), 1.53 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.31 (s, 9H, $C(CH_3)_3$); IR (KBr) 3286, 2961, 1652, 1548, 1338, 1271, 1156, 1026 cm^{-1}; MS (FAB) m/z 419 (MH^+); Anal. Calcd for $C_{22}H_{30}N_2O_4S$: C, 63.13; H, 7.22; N, 6.69. Found: C, 63.36; H, 7.24; N, 6.67.

4.1.6.20. *N*-(4-*tert*-Butylbenzyl)-(2*S*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (54*S*). Compound **54*S*** prepared from the chiral (*S*)-carboxylic acid previously reported by the general coupling procedure. 98% yield, >98% ee, $[\alpha] = -15.5$ (c 0.5, $CHCl_3$). The spectra are identical to those of racemate **54**.

4.1.6.21. *N*-(4-*tert*-Butylbenzyl)-(2*R*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (54*R*). The compound was prepared by following the procedure described for the synthesis of **1–51**.

96% yield, >98% ee, $[\alpha]$ = +18.4 (c 0.5, $CHCl_3$). The spectra are identical to those of racemate **54**.

4.2. Molecular modeling

Based on our rat TRPV1 tetramer homology model, the human TRPV1 (hTRPV1) model[20] was constructed as a tetramer. In the binding site, five residues are different between rat and human, and they

were mutated as Ile514Met, Val518Leu, Val525Ala, Ser526Thr, and Met547Leu. Then, the side chains and backbone within 6 Å of the mutated residues were energy minimized using the Protein Composition Tool in SYBYL 8.1.1 (Tripos Int., St. Louis, MO, USA). The ligand structure was generated with Concord and energy minimized using the MMFF94s force field and MMFF94 charge until the rms of the Powell gradient was 0.05 kcal $mol^{-1}A^{-1}$ in SYBYL. The flexible docking study on the hTRPV1 model was performed using GOLD v.5.0.1 (Cambridge Crystallographic Data Centre, Cambridge, UK). It uses a genetic algorithm (GA) and allows for full ligand flexibility and partial protein flexibility. The binding site was defined as 8 Å around capsaicin which was extracted from the docking result in the rTRPV1 model and merged into the aligned hTRPV1 model. The side chains of the important six residues for ligand binding (i.e., Tyr511, Ser512, Leu515, Leu547, Thr550, and Asn551) were set to be flexible with 'crystal mode'. The default parameters were used with the GoldScore scoring function, and 30 docking runs per ligand were performed. All computation calculations were undertaken on an Intel® Xeon™ Quad-core 2.5 GHz workstation with Linux Cent OS release 5.5.

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