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2-(4-Methylsulfonylaminophenyl) propanamide TRPV1 antagonists: Structure–activity relationships in the B and C-regions

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Abstract

On the basis of the previous lead *N*-4-*t*-butylbenzyl 2-(3-fluoro-4-methylsulfonylaminophenyl) propanamide (**3**) as a potent TRPV1 antagonist, structure–activity relationships for the B (propanamide part) and C-region (4-*t*-butylbenzyl part) have been investigated for rTRPV1 in CHO cells. The B-region was modified with dimethyl, cyclopropyl and reverse amides and then the C-region was replaced with 4-substituted phenyl, aryl alkyl and diaryl alkyl derivatives. Among them, compound 50 showed high binding affinity with K_i = 21.5 nM, which was twofold more potent than **3** and compound **54** exhibited potent antagonism with $K_{i(ant)}$ = 8.0 nM comparable to **3**.

Keywords

TRPV1 antagonists; Analgesic; Capsaicin; Resiniferatoxin

1. Introduction

The transient receptor potential V1 (TRPV1) receptor[1] is a molecular integrator of nociceptive stimuli, functioning as a non-selective cation channel with high Ca^{2+} permeability. The receptor, located predominantly in primary sensory neurons, is activated by 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] Its activation leads to an increase in intracellular Ca^{2+}, which in turn causes excitation of the primary sensory neurons and ultimately the central perception of pain. Since TRPV1 antagonists inhibit the

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transmission of nociceptive signaling from the periphery to the CNS as well as block other pathological states associated with this receptor, they have been promising drug candidates as novel analgesic and antiinflammatory agents, particularly for chronic pain and inflammatory hyper-algesia.[8] The clinical development and therapeutic potentials of TRPV1 antagonists has been extensively reviewed.[9–13]

Previously, we have reported a prototype antagonist, *N*-(4-*t*-butylbenzyl)-*N*′−4-(3-fluoro-4-methylsulfonylaminobenzyl) thiourea (**1**),[14–17] in rat TRPV1/CHO (Fig. 1). The thiourea showed potent antagonism not only for capsaicin stimulation of rTRPV1 but also for stimulation by temperature and pH.[14,16] Further optimization in the B-region (thiourea part) provided the propanamide antagonist **3**, which exhibited higher binding affinity and more potent antagonism for both rTRPV1 and hTRPV1 in CHO cells compared to **1** (Fig. 1).[18] Its stereospecific activity was demonstrated with marked selectivity for the (*S*)-configuration (*S*-**3** vs. *R*-**3**); whereas the (*S*)-isomer was ca. twofold more potent than the racemate **3**, the (*R*)-isomer was 30- to 40-fold weaker. A docking study of *S*-**3** isomer with our hTRPV1 homology model identified crucial hydrogen bonds between the ligand and the receptor contributing to its stereospecific potency. A further advantage of the propanamide antagonists over the thiourea antagonists, such as **1**, is that the propanamide antagonists avoid the potential toxicity associated with the thiourea functionality.

As a continuation of our effort to optimize the 4-methylsulfonamide TRPV1 antagonists, we reported the structure–activity relationships for the A-region (4-methylsulfonylaminophenyl part) in a series of *N*-4-*t*-butylbenzyl 2-(4-methylsulfonylaminophenyl) propanamides as TRPV1 antagonists.[18] In this paper, we have investigated the structure–activity relationships of the B (propanamide part) and C-region (4-*t*-butylbenzyl part) in a series of 2-(3-fluoro-4-methylsulfonylaminophenyl) propanamide TRPV1 antagonists.

2. Result and discussion

2.1. Chemistry

The dimethyl and cyclopropyl amide analogues of **2–4** were synthesized from the corresponding acids, **5–7** and **11–13**,[19] by the coupling with 4-*t*-butylbenzyl amine to provide **8–10** and **14–16**, respectively (Scheme 1). The reverse amide analogues were prepared by the coupling of α-methyl benzylamine **17**[20] with the corresponding acids to give the final compounds **18–20** (Scheme 2). The syntheses of 2-(3-fluoro-4-methylsulfonylaminophenyl) propanamide analogues **22–60** were conducted by following the previous report.[18]

2.2. Biological activity

The binding affinities and potencies as agonists/antagonists of the synthesized TRPV1 ligands were assessed in vitro by a competitive binding assay with [^{3}H]RTX and by a functional $^{45}Ca^{2+}$ uptake assay using rat TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells, as previously described.[16] The results are summarized in Tables 1–4, together with the potencies of the previously reported parent antagonists **2–4**.[18]

For the modification of the propanamide B-region, the two α,α′-disubstituted analogues, the dimethyl (**8–10**) and cyclopropyl amides (**14–16**), have been investigated as TRPV1 ligands (Table 1). They all showed a dramatic loss in receptor activity compared to the corresponding α-methyl amides (propanamide) (**2–4**) regardless of the 3-substituents, indicating that an α-methyl in the B-region might constitute a principal pharmacophore by making a stereospecific interaction with the hydrophobic pocket of the receptor, as modeled previously.[19] As another B-region modification, the reversed amides, *N*-acyl α-methyl benzylamine (**18–20**), were explored (Table 2). Compound **18**, a reverse amide of **3**, exhibited a marked loss of activity compared to **3**. However, its one-carbon elongation analogue (**19**) improved the receptor activity and conformational restriction (**20**) provided further enhancement in activity, achieving a level only 2–3-fold less potent than parent **3**.

Previously, the structure–activity relations for the A-region in a series of 2-(4-methylsulfonylaminophenyl) propanamides were evaluated with the 4-*t*-butylbenzyl group as a fixed C-region. These studies identified the 2-(3-fluoro-4-methylsulfonylamino)phenyl propanamide moiety as the best A/B-regions with high binding affinity and potent antagonism. We therefore explored the extensive structure–activity relationships of the C-region with the above fixed A/B-region. The aryl alkyl and diaryl alkyl analogues of the C-region were represented in Tables 3 and 4, respectively.

The SAR of the C-region was started from the modification at the 4-position of the 4-*t*-butyl benzyl group. First, halogen groups, including 4-chloro (**22**), 4-bromo (**23**), 4-iodo (**24**) and 3,4-dichloro (**25**), were introduced as electron-withdrawing and lipophilic groups to replace the 4-*t*-butyl group of lead compound **3**. Although their receptor activities improved as the size of the halogen increased, the activity of the 4-iodo analogue (**24**) was still 10-fold less potent than that of the parent **3**. The 4-trifluoromethyl analogue (**26**) showed similar potency compared to the 4-chloro and 4-bromo analogues, reflecting their similar physicochemical properties. The 4-methoxy analogue (**27**), which placed an electron-donating group in the 4-position, exhibited a dramatic reduction in receptor potency. Next, various alkyl groups were incorporated into the 4-position. The activity increased with the size of 4-alkyl group up to the cyclopentyl group (**32**) but was then reduced in the cyclohexyl analogue (**33**). Interestingly, the 4-phenyl analogue (**34**) led to a dramatic loss in activity. The analysis indicated that the *t*-butyl group at the 4-position was best for potency, among the compounds examined, probably due to an optimal fit to the hydrophobic pocket.[19] Incorporation of the 2-bromo (**35**) and 2-cyano (**36**) groups into the 4-*t*-butylbenzyl did not affect the potency of the parent compound (**3**), suggesting that the 2-substituent was directed away from the binding pocket. Bicyclic analogues, naphthalene (**37**) and tetrahydronaphthalene (**38**), were found to be weak antagonists. One-carbon elongation of **3** to give **39** led a modest reduction in potency. The 3,4-dimethylphenylpropyl group, found in the previous clinical candidate DA-5018, was used as the C-region to provide **40**. Although it was found to be ca. 10-fold less potent than **3**, the stereospecific potency of the α-methyl group could be further confirmed with its two chiral compounds (**41**, **42**), in which the (*S*)-isomer (**42**) proved to be the active isomer with ca. twofold more potency than the racemate **40**. Conformational restriction of **40** to give **43** yielded little improvement in receptor potency. The 4-chlorophenylpropyl analogues, **44** and **45**, showed similar potencies compared to the

corresponding 3,4-dimethylphenyl analogues, **40** and **43**, respectively. The benzyloxy analogue (**46**) was found to a weak partial antagonist.

Next, a series of diphenylalkyl groups (**47–60**) as a C-region were investigated (Table 4).

The diphenylmethyl analogue (**47**) showed very weak binding affinity and partial antagonism. However, activity was enhanced as the number of carbons in the linker increased. The diphenylpropyl analogue (**49**) exhibited good binding affinity and antagonism. The modification of the propyl linker provided the three derivatives **50–52**; whereas the diphenylpropenyl analogue (**50**) showed several-fold enhanced potency, the diphenylcyclopropylmethyl (**51**) and the diphenylaminoethyl (**52**) analogues displayed a modest reduction in potency compared to **49**. The analysis indicated that the flat environment rather than a conformational restriction in the C-region was favorable for binding to the receptor. Compound **50** was found to have high affinity and potent antagonism with K_i = 21.5 nM and $K_{i(ant)}$ = 14.2 nM, which was twofold more potent in binding affinity and twofold less potent in antagonism compared to lead **3**. For further optimization from **49**, 4,4′-disubstituted diphenylpropyl (**53**, **55** and **58**) and diphenylpropenyl (**54**, **56** and **57**) analogues were explored, indicating that the substitutions did not affect the activity. They exhibited similar activities compared to the corresponding unsubstituted analogues, **49** and **50**. In particular, the (4,4′-dimethyl)diphenylpropenyl analogue (**54**) had potent antagonism with $K_{i(ant)}$ = 8.0 nM. The two diphenylcycloheptane analogues (**59**, **60**), as further conformationally constrained analogues of **50**, were prepared. However, they showed a 5–10-fold reduction in binding affinity and antagonism compared to **50**.

3. Conclusion

In order to further optimize the TRPV1 antagonism from the previous lead, *N*-4-*t*-butylbenzyl 2-(3-fluoro-4-methylsulfonylaminophenyl) propanamide (**3**), the structure activity relationships for the B and C-region have been investigated in detail. In the B-region, the propanamide was modified by dimethyl, cyclopropyl and reverse amides and in the C-region the 4-*t*-butylbenzyl was replaced with 4-substituted phenyl, aryl alkyl and diaryl alkyl derivatives. Among the compounds in the series, the diphenylpropenyl analogue (**50**) showed high binding affinity with K_i = 21.5 nM, which was twofold more potent than the lead **3**, and the (4,4′-dimethyl)diphenylpropenyl (**54**) analogue exhibited potent antagonism with $K_{i(ant)}$ = 8.0 nM comparable to **3** for rTRPV1 in the CHO cells.

4. Experimental

4.1. 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.

4.2. Generel procedure for coupling

A mixture of acid (10 mmol), amine (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.

4.2.1. *N*-(4-*tert*-Butylbenzyl)-2-[4-(methylsulfonylamino) phenyl]-2-methylpropionamide (8)—Yield 92%, white solid, mp = 141–143 °C, ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 2H, J = 8.5 Hz, Ar), 7.31 (d, 2H, J = 7.9 Hz, Ar), 7.18 (d, 2H, J = 8.5 Hz, Ar), 7.07 (d, 1H, J = 7.9 Hz, Ar), 6.40 (br s, 1H, $NHSO_2$), 5.46 (br t, 1H, NH), 4.36 (d, 1H, J = 5.7 Hz, $ArCH_2NH$), 3.00 (s, 3H, SO_2CH_3), 1.59 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.30 (s, 9H, $C(CH_3)_3$); IR (KBr) 2964, 1644, 1513, 1333, 1154 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, 7.49; N, 6.93.

4.2.2. *N*-(4-*tert*-Butylbenzyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]-2-methylpropionamide (9)—Yield 74%, white solid, mp = 48–51 °C, ^{1}H NMR ($CDCl_3$) δ 7.53 (t, 1H, J = 8.2 Hz, H-5), 7.33 (d, 2H, Ar), 7.14–7.2 (m, 2H, H-2 and H-6), 7.09 (d, 2H, Ar), 6.45 (br s, 1H, $NHSO_2$), 5.50 (br t, 1H, NH), 4.37 (d, 1H, J = 5.5 Hz, $ArCH_2NH$), 3.03 (s, 3H, SO_2CH_3), 1.58 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.30 (s, 9H, $C(CH_3)_3$); IR (KBr) 2964, 1648, 1512, 1333, 1272, 1158, 1121 cm^{-1}; MS (FAB) *m/z* 421 (MH^+); Anal. Calcd for $C_{22}H_{29}FN_2O_3S$: C, 62.83; H, 6.95; N, 6.66. Found: C, 62.60; H, 6.93; N, 6.64.

4.2.3. *N*-(4-*tert*-Butylbenzyl)-2-[3-methoxy-4-(methylsulfonylamino)phenyl]-2-methylpropionamide (10)—Yield 93%, white solid, mp = 54–56 °C, ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 1H, J = 8.2 Hz, H-5), 7.30 (d, 2H, Ar), 7.09 (d, 2H, Ar), 6.98 (dd, 1H, J = 1.8, 8.2 Hz, H-6), 6.83 (d, 1H, J = 1.8 Hz, H-2), 6.77 (br s, 1H, $NHSO_2$), 5.55 (br t, 1H, NH), 4.36 (d, 1H, J = 5.7 Hz, $ArCH_2NH$), 3.80 (s, 3H, OCH_3), 2.94 (s, 3H, SO_2CH_3), 1.59 (s, 6H, 2 × CH_3), 1.29 (s, 9H, $C(CH_3)_3$); IR (KBr) 3348, 2964, 1652, 1513, 1461, 1395, 1335, 1267, 1157, 1127, 1032 cm^{-1}; MS (FAB) *m/z* 433 (MH^+); Anal. Calcd for $C_{23}H_{32}N_2O_4S$: C, 63.86; H, 7.46; N, 6.48. Found: C, 63.60; H, 7.43; N, 6.45.

4.2.4. *N*-(4-*tert*-Butylbenzyl)-1-[4-(methylsulfonylamino) phenyl]cyclopropanecarboxamide (14)—Yield 90%, white solid, mp = 200–203 °C, ^{1}H NMR (DMSO-d_6) δ 9.75 (br s, 1H, NH), 4.15 (d, 2H, J = 6 Hz, $ArCH_2NH$), 2.98 (s, 3H, SO_2CH_3), 1.32 (dd, 2H, CH_2CCH_2), 1.25 (s, 9H, $C(CH_3)_3$), 0.94 (dd, 2H, CH_2CCH_2); IR (KBr) 2961, 1644, 1515, 1331, 1224, 1154 cm^{-1}; MS (FAB) *m/z* 401(MH^+); Anal. Calcd for $C_{22}H_{28}N_2O_3S$: C, 65.97; H, 7.05; N, 6.99. Found: C, 66.21; H, 7.08; N, 6.96.

4.2.5. *N*-(4-*tert*-Butylbenzyl)-1-[3-fluoro-4-(methylsulfonylamino)phenyl]cyclopropanecarboxamide (15)—Yield 75%, white

solid, mp = 56–58 °C, ^{1}H NMR ($CDCl_3$) δ 7.50 (br s, 1H, $NHSO_2$), 7.32 (br d, 2H, Ar), 7.05–7.2 (m, 5H, Ar), 5.84 (br t, 1H, NH), 4.36 (d, 2H, J = 5.7 Hz, ArCH_2NH), 3.33 (s, 3H, SO_2CH_3), 1.67 (dd, 2H, CH_2CCH_2), 1.29 (s, 9H, $C(CH_3)_3$), 1.15 (dd, 2H, CH_2CCH_2); IR (KBr) 2961, 1640, 1520, 1469, 1324, 1263, 1149 cm^{-1}; MS (FAB) *m/z* 441 ([M+Na]$^+$); Anal. Calcd for $C_{22}H_{27}FN_2O_3S$: C, 63.13; H, 6.50; N, 6.69. Found: C, 62.82; H, 6.47; N, 6.66.

4.2.6. *N*-(4-*tert*-Butylbenzyl)-1-[3-methoxy-4-(methylsulfonylamino)phenyl]cyclopropanecarboxamide (16)—Yield 82%, white solid, mp = 78–80 °C, ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 1H, J = 8.1 Hz, H-5), 7.31 (br d, 2H, Ar), 7.09 (br d, 2H, Ar), 7.03 (dd, 1H, J = 1.8, 8.1 Hz, H-6), 6.94 (d, 1H, J = 1.8 Hz, H-2), 6.80 (br s, 1H, $NHSO_2$), 5.67 (br t, 1H, NH), 4.36 (d, 2H, J = 5.85 Hz, ArCH_2NH), 3.86 (s, 3H, OCH_3), 2.97 (s, 3H, SO_2CH_3), 1.65 (dd, 2H, CH_2CCH_2), 1.29 (s, 9H, $C(CH_3)_3$), 1.06 (dd, 2H, CH_2CCH_2); IR (KBr) 2961, 1652, 1513, 1338, 1246, 1157, 1125, 1032 cm^{-1}; MS (FAB) *m/z* 431(MH^+), 453 ([M+Na]$^+$); Anal. Calcd for $C_{23}H_{30}N_2O_4S$: C, 64.16; H, 7.02; N, 6.51. Found: C, 63.91; H, 7.00; N, 6.48.

4.2.7. *N*-{1-[3-Fluoro-4-(methylsulfonylamino)phenyl]ethyl}−3-(4-*tert*-butylphenyl)acetamide (18)—Yield 36%, white solid, mp = 134–136 °C, ^{1}H NMR ($CDCl_3$) δ 7.48 (t, 1H, J = 8.8 Hz, H-5), 7.39 (br d, 2H, J = 8.3 Hz, Ar), 7.18 (br d, 2H, J = 8.3 Hz, Ar), 6.92–7.02 (m, 2H, Ar), 6.44 (br s, 1H, $NHSO_2$), 5.58 (d, 1H, J = 7.8 Hz, NH), 5.06 (m, 1H, C*H*CH_3), 3.56 (s, 2H, ArCH_2CO), 3.00 (s, 3H, SO_2CH_3), 1.37 (d, 3H, J = 7 Hz, CHC*H*$_3$), 1.33 (s, 9H, $C(CH_3)_3$); IR (KBr) 3279, 2963, 1648, 1513, 1331, 1156 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, 61.85; H, 6.67; N, 6.86.

4.2.8. *N*-{1-[3-Fluoro-4-(methylsulfonylamino)phenyl]ethyl}−3-(4-*tert*-butylphenyl) propanamide (19)—Yield 29%, white solid, mp = 152–154 °C, ^{1}H NMR ($CDCl_3$) δ 7.44 (t, 1H, J = 8 Hz, H-5), 7.31 (br d, 2H, J = 8.3 Hz, Ar), 7.11 (br d, 2H, J = 8.3 Hz, Ar), 6.95–7.02 (m, 2H, Ar), 6.82 (br s, 1H, $NHSO_2$), 5.72 (d, 1H, J = 7.1 Hz, NH), 5.02 (m, 1H, C*H*CH_3), 3.00 (s, 3H, SO_2CH_3), 2.93 (t, 2H, J = 7.1 Hz, CH_2Ar), 2.50 (m, 2H, CH_2CO), 1.34 (d, 3H, J = 7 Hz, CHC*H*$_3$), 1.30 (s, 9H, $C(CH_3)_3$); IR (KBr) 3274, 2963, 1647, 1513, 1452, 1332, 1157 cm^{-1}; MS (FAB) *m/z* 421 (MH^+); Anal. Calcd for $C_{22}H_{29}FN_2O_3S$: C, 62.83; H, 6.95; N, 6.66. Found: C, 62.62; H, 6.93; N, 6.64.

4.2.9. *N*-{1-[3-Fluoro-4-(methylsulfonylamino)phenyl]ethyl}−3-(4-*tert*-butylphenyl)-2-propenamide (20)—Yield 67%, white solid, mp = 154–156 °C, ^{1}H NMR ($CDCl_3$) δ 7.62 (d, 1H, J = 15.5 Hz, CH=), 7.52 (t, 1H, J = 8 Hz, H-5), 7.41 (dd, 4H, Ar), 7.12–7.18 (m, 2H, Ar), 6.54 (br s, 1H, $NHSO_2$), 6.37 (d, 1H, J = 15.5 Hz, =CH), 5.88 (d, 1H, J = 7.1 Hz, NH), 5.21 (m, 1H, C*H*CH_3), 3.02 (s, 3H, SO_2CH_3), 1.53 (d, 3H, J = 7 Hz, CHC*H*$_3$), 1.32 (s, 9H, $C(CH_3)_3$); IR (KBr) 3274, 2964, 1657, 1616, 1514, 1331, 1221, 1156 cm^{-1}; MS (FAB) *m/z* 419 (MH^+); Anal. Calcd for $C_{22}H_{27}FN_2O_3S$: C, 63.13; H, 6.50; N, 6.69. Found: C, 63.23; H, 6.52; N, 6.67.

4.2.10. *N*-(4-Chlorobenzyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (22)—Yield 98%, white solid, mp =

129–130 °C, ^{1}H NMR ($CDCl_3$) δ 7.53 (t, 1H, J = 8.3 Hz, H-5), 7.25–7.3 (m, 2H), 7.06–7.2 (m, 4H, Ar), 6.44 (br s, 1H, $NHSO_2$), 5.67 (br t, 1H, NHCO), 4.37 (ddd of AB, 2H, $ArCH_2NH$), 3.53 (q, 1H, J = 7.1 Hz, CH_3CH), 3.03 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, CH_3CH); IR (KBr) 3295, 1652, 1539, 1496, 1330, 1235, 1156, 1092 cm^{-1}; MS (FAB) m/z 385 [M-H]$^+$; Anal. Calcd for $C_{17}H_{18}ClFN_2O_3S$: C, 53.05; H, 4.71; N, 7.28. Found: C, 52.87; H, 4.70; N, 7.25.

4.2.11. *N*-(4-Bromo-benzyl)-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (23)—Yield 60%, white solid, mp = 172–174 °C, ^{1}H NMR (CD_3OD) δ 7.38–7.44 (m, 3H, Ar-H), 7.07–7.21 (m, 4H, Ar-H), 4.23 (s, 2H, $ArCH_2NH$), 3.64 (q, 1H, J = 7.2 Hz, CH_3CH), 2.96 (s, 3H, SO_2CH_3), 1.44 (d, 3H, J = 7.2 Hz, $CHCH_3$); IR (KBr) 3741, 3274, 1650, 1512, 1330, 1155, 973, 757, 616 cm^{-1}; MS (FAB) m/z 431 [M-H]$^+$; Anal. Calcd for $C_{17}H_{18}BrFN_2O_3S$: C, 47.56; H, 4.23; N, 6.53. Found: C, 47.43; H, 4.22; N, 6.51.

4.2.12. 2-(3-Fluoro-4-methanesulfonylamino-phenyl)-*N*-(4-iodo-benzyl)-propionamide (24)—Yield 60%, white solid, mp = 79–81 °C, ^{1}H NMR ($CDCl_3$) δ 7.62 (d, 2H, J = 8.4 Hz, Ar-H), 7.51 (dd,1H, J = 8.1,1.8 Hz, Ar-H), 7.16 (dd, 1H, J = 8.1, 1.8 Hz, Ar-H), 7.08 (d, 1H, J = 8.1 Hz, Ar-H), 6.94 (d, 2H, J = 8.4 Hz, Ar-H), 6.52 (br s, 1H, $NHSO_2$), 5.73 (br t, 1H, NHCO), 4.33 (d, 2H, J = 5.7 Hz, $ArCH_2NH$), 3.52 (q, 1H, J = 7.2 Hz, CH_3CH), 3.02 (s, 3H, $SOCH_3$), 1.51 (d, 3H, J = 7.2 Hz, $CHCH_3$); IR (KBr) 3739, 3293, 2922, 1642, 1511, 1332, 1153, 789 cm^{-1}; MS (FAB) m/z 477 [M-H]$^+$; Anal. Calcd for $C_{17}H_{18}FIN_2O_3S$: C, 42.87; H, 3.81; N, 5.88. Found: C, 42.66; H, 3.83; N, 5.86.

4.2.13. *N*-(3,4-Dichlorobenzyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (25)—Yield 76%, white solid, mp = 130–133 °C, ^{1}H NMR ($CDCl_3$) δ 7.53 (t, 1H, J = 8.3 Hz, H-5), 7.36 (d, 1H, Ar), 7.23 (d, 1H, Ar), 7.16 (dd, 1H, Ar), 7.10 (br d, 1H, Ar), 7.02 (dd, 1H, Ar), 6.51 (br s, 1H, $NHSO_2$), 5.76 (br t, 1H, NHCO), 4.36 (d of AB, 2H, $ArCH_2NH$), 3.54 (q, 1H, J = 7.1 Hz, CH_3CH), 3.03 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, CH_3CH); IR (KBr) 3738, 1647, 1512, 1459, 1325, 1153 cm^{-1}; MS (FAB) m/z 419 (MH^+); Anal. Calcd for $C_{17}H_{17}Cl_2FN_2O_3S$: C, 48.70; H, 4.09; N, 6.68. Found: C, 48.87; H, 4.11; N, 6.66.

4.2.14. *N*-(4-Trifluoromethylbenzyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (26)—Yield 81%, white solid, mp = 150–152 °C, ^{1}H NMR ($CDCl_3$) δ 7.5–7.6 (m, 3H, Ar), 7.26 (d, 2H, Ar), 7.05–7.2 (m, 2H, Ar), 5.86 (br t, 1H, NHCO), 4.46 (ddd of AB, 2H, $ArCH_2NH$) 3.56 (q, 1H, J = 7.1 Hz, CH_3CH), 3.02 (s, 3H, SO_2CH_3), 1.52 (d, 3H, J = 7.1 Hz, CH_3CH); IR (KBr) 3291, 1653, 1512, 1421, 1327, 1159, 1119, 1067, 1019 cm^{-1}; MS (FAB) m/z 419 (MH^+); Anal. Calcd for $C_{18}H_{18}F_4N_2O_3S$: C, 51.67; H, 4.34; N, 6.70. Found: C, 51.87; H, 4.32; N, 6.68.

4.2.15. *N*-(4-Methoxybenzyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (27)—Yield 96%, white solid, mp = 138 °C, ^{1}H NMR ($CDCl_3$) δ 7.48 (t, 1H, J = 8.3 Hz, H-5), 7.05–7.2 (m, 4H, Ar), 6.82 (d, 2H, Ar), 6.69 (br s, 1H, $NHSO_2$), 5.80 (br t, 1H, NHCO), 4.33 (ddd of AB, 2H, $ArCH_2NH$), 3.78 (s, 3H, OCH_3), 3.52 (q, 1H, J = 7.1 Hz, CH_3CH), 3.01 (s, 3H, SO_2CH_3), 1.51 (d, 3H, J = 7.1 Hz, CH_3CH); IR (KBr) 3315, 3206, 1642, 1510, 1455, 1322, 1246, 1155, 1033 cm^{-1};

MS (FAB) *m/z* 381 (MH^+); Anal. Calcd for $C_{18}H_{21}FN_2O_4S$: C, 56.83; H, 5.56; N, 7.36. Found: C, 56.61; H, 5.54; N, 7.33.

4.2.16. *N*-(4-Methylbenzyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (28)—Yield 96%, white solid, mp = 166 °C, ^{1}H NMR ($CDCl_3$) δ 7.51 (t, 1H, J = 8.3 Hz, H-5), 7.05–7.2 (m, 6H, Ar), 6.50 (br s, 1H, $NHSO_2$), 5.66 (br t, 1H, NHCO), 4.36 (ddd of AB, 2H, $ArCH_2NH$), 3.51 (q, 1H, J = 7.1 Hz, CH_3CH), 3.02 (s, 3H, SO_2CH_3), 2.32 (s, 3H, CH_3), 1.52 (d, 3H, J = 7.1 Hz, CH_3CH); IR (KBr) 3307, 3212, 1637, 1537, 1445, 1326, 1154 cm^{-1}; MS (FAB) *m/z* 365 (MH^+); Anal. Calcd for $C_{18}H_{21}FN_2O_3S$: C, 59.32; H, 5.81; N, 7.69. Found: C, 59.07; H, 5.79; N, 7.67.

4.2.17. *N*-(4-Isopropylbenzyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (29)—Yield 69%, white solid, mp = 137–139 °C, ^{1}H NMR ($CDCl_3$) δ 7.49 (t, 1H, J = 8.3 Hz, H-5), 7.05–7.2 (m, 6H, Ar), 6.70 (br s, 1H, $NHSO_2$), 5.80 (br t, 1H, NHCO), 4.36 (ddd of AB, 2H, $ArCH_2NH$), 3.52 (q, 1H, J = 7.1 Hz, CH_3CH), 3.00 (s, 3H, SO_2CH_3), 2.88 (m, 2H, $CH(CH_3)_2$), 1.51 (d, 3H, J = 7.1 Hz, CH_3CH), 1.22 (d, 6H, $CH(CH_3)_2$); IR (KBr) 3364, 2957, 1664, 1509, 1456, 1333, 1219, 1155 cm^{-1}; MS (FAB) *m/z* 393 (MH^+); Anal. Calcd for $C_{20}H_{25}FN_2O_3S$: C, 61.20; H, 6.42; N, 7.14. Found: C, 61.43; H, 6.40; N, 7.16.

4.2.18. *N*-(4-Cyclopropyl-benzyl)-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (30)—Yield 71%, white solid, mp = 115–117 °C, ^{1}H NMR (DMSO-d_6) δ 9.54 (s, 1H, NHCO), 8.46 (t, 1H, J = 5.7 Hz, Ar-H), 7.12–7.34 (m, 4H, Ar-H), 6.95–7.04 (m, 3H, Ar-H), 4. 17 (d, 2H, J = 5.7 Hz, $ArCH_2NH$), 3.67 (q, 1H, J = 7.2 Hz, CH_3CH), 3.00 (s, 3H, SO_2CH_3), 1.86 (m, 1H, cyclo-H), 1.33 (d, 3H, J = 7.2 Hz, $CHCH_3$), 0.89 (m, 2H, cyclo-H), 0.60 (m, 2H, cyclo-H); IR (KBr) 3289, 1650, 1600, 1512, 1331, 1156, 973 cm^{-1}; MS (FAB) *m/z* 391 (MH^+); Anal. Calcd for $C_{20}H_{23}FN_2O_3S$: C, 61.52; H, 5.94; N, 7.17. Found: C, 61.78; H, 5.92; N, 7.15.

4.2.19. *N*-(4-Cyclopent-2-enyl-benzyl)-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (31)—Yield 68%, white solid, mp = 125–127 °C, ^{1}H NMR ($CDCl_3$) δ 7.51 (t, 1H, J = 8.25 Hz, Ar), 7.12 (m, 6H, Ar), 6.45 (br s, 1H, NH), 5.93 (m, 1H, CH_2CH_2), 5.73 (m, 1H, CH_2CH_2), 5.64 (br s, 1H, NH), 4.39 (ddd, 2H, $ArCH_2NH$), 3.86 (m, 1H, cyclopentene), 3.50 (q, 1H, J = 7.14 Hz, $CHCH_3$), 3.02 (s, 1H, SO_2CH_3), 2.43 (m, 2H, cyclopentene), 1.68 (m, 2H, cyclopentene), 1.52 (d, 3H, J = 7.14 Hz, $CHCH_3$); IR (KBr) 3740, 3294, 1649, 1512, 1455, 1333, 1157, 973, 757, 616 cm^{-1}; MS (FAB) *m/z* 417 (MH^+); Anal. Calcd for $C_{22}H_{25}FN_2O_3S$: C, 63.44; H, 6.05; N, 6.73. Found: C, 63.24; H, 6.03; N, 6.71.

4.2.20. *N*-(4-Cyclopentyl-benzyl)-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (32)—Yield 74%, white solid, mp = 121–123 °C, ^{1}H NMR ($CDCl_3$) δ 7.51 (t, 1H, J = 8.32 Hz, Ar), 7.14 (m, 6H, Ar), 6.50 (br s, 1H, NH), 5.66 (br t, 1H, NH), 4.38 (ddd, 2H, $ArCH_2$), 3.50 (q, 1H, J = 7.14 Hz, $CHCH_3$), 3.02 (s, 1H, SO_2CH_3), 2.96 (m, 1H, cyclopentyl), 2.04 (m, 2H, cyclopentyl), 1.79 (m, 4H, cyclopentyl), 1.68 (m, 4H, cyclopentyl), 1.57 (d, 3H, J = 7.14 Hz, $CHCH_3$); IR (KBr) 3438, 3227, 2951, 1640,

1547, 1509, 1332, 1157, 1116, 983, 774 cm^{-1}; MS (FAB) *m/z* 419 (MH^+); Anal. Calcd for $C_{22}H_{27}FN_2O_3S$: C, 63.13; H, 6.50; N, 6.69. Found: C, 63.39; H, 6.52; N, 6.67.

4.2.21. *N*-(4-Cyclohexyl-benzyl)-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (33)—Yield 61%, white solid, mp = 72–74 °C, ^1H NMR ($CDCl_3$) δ 7.51 (dd, 1H, *J* = 8.1, 1.8 Hz, Ar-H), 7.08–7.20 (m, 6H, Ar-H), 5.63 (br t, 1H, NHCO), 4.38 (qd, 2H, *J* = 14.4, 5.4 Hz, $ArCH_2NH$), 3.50 (q, 1H, *J* = 7.2 Hz, CH_3CH), 3.02 (s, 3H, SO_2CH_3), 2.47 (m, 1H, cyclo-H), 1.72–1.84 (m, 4H, cyclo-H), 1.52 (d, 3H, *J* = 7.2 Hz, $CHCH_3$), 1.26–1.41 (m, 6H, cyclo-H); IR (KBr) 3290, 2925, 2851, 1650, 1511, 1449, 1332, 1157, 973 cm^{-1}; MS (FAB) *m/z* 433 (MH^+); Anal. Calcd for $C^{23}H^{29}FN^2O^3S$: C, 63.86; H, 6.76; N, 6.48. Found: C, 63.63; H, 6.78; N, 6.47.

4.2.22. *N*-(4-Biphenylmethyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (34)—Yield 78%, white solid, mp = 155–157 °C, ^1H NMR ($CDCl_3$) δ 7.1–7.58 (m, 12H, Ar), 6.45 (br s, 1H, $NHSO_2$), 5.71 (br t, 1H, NHCO), 4.45 (ddd, 2H, $ArCH_2NH$), 3.55 (q, 1H, *J* = 7.1 Hz, CH_3CH), 3.01 (s, 3H, SO_2CH_3), 1.54 (d, 3H, *J* = 7.1 Hz, CH_3CH); IR (KBr) 3430, 1647, 1530, 1405, 1324, 1152 cm^{-1}; MS (FAB) *m/z* 427 (MH^+); Anal. Calcd for $C_{23}H_{23}FN_2O_3S$: C, 64.77; H, 5.44; N, 6.57. Found: C, 64.51; H, 5.43; N, 6.53.

4.2.23. *N*-(2-Bromo-4-*tert*-butyl-benzyl)-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (35)—Yield 71%, white solid, mp = 138–140 °C, ^1H NMR ($CDCl_3$) δ 7.51–7.46 (m, 2H, Ar-H), 7.28–7.06 (m, 4H, Ar-H), 6.71 (br s, 1H, $NHSO^2$), 6.00 (br s, 1H, NHCO), 4.42 (m, 2H, $ArCH_2NH$), 3.54 (q, 1H, *J* = 7.14 Hz, CH_3CH), 3.02 (s, 3H, SO_2CH_3), 1.49 (d, 3H, *J* = 7.14 Hz, CH_3CH), 1.28 (s, 9H, $C(CH_3)_3$); IR (KBr) 3315, 2931, 1649, 1510, 1421, 1327, 1159, 1110, 927 cm^{-1}; MS (FAB) *m/z* 486 (MH^+); Anal. Calcd for $C_{21}H_{26}BrFN_2O_3S$: C, 51.96; H, 5.40; N, 5.77. Found: C, 51.76; H, 5.43; N, 5.74.

4.2.24. *N*-(4-*tert*-Butyl-2-cyano-benzyl)-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (36)—Yield 68%, white solid, mp = 129–131 °C, ^1H NMR ($CDCl_3$) δ 7.51 (m, 2H, Ar-H), 7.24 (m, 2H, Ar-H), 7.13 (dd, 1H, *J* = 11.37, 2.01 Hz, Ar-H), 7.07 (d, 1H, *J* = 7.43 Hz, Ar-H), 6.50 (br s, 1H, $NHSO_2$), 5.88 (br s, 1H, NHCO), 4.42 (m, 2H, $ArCH_2NH$), 3.52 (q, 1H, *J* = 7.14 Hz, CH_3CH), 3.02 (s, 3H, SO_2CH_3), 1.50 (d, 3H, *J* = 7.14 Hz, CH_3CH), 1.29 (s, 9H, $C(CH_3)_3$); IR (KBr) 3421, 2951, 2928, 2250, 1650, 1512, 1449, 1333, 1200, 1120, 981 cm^{-1}; MS (FAB) *m/z* 432 (MH^+); Anal. Calcd for $C_{22}H_{26}FN_3O_3S$: C, 61.23; H, 6.07; N, 9.74. Found: C, 61.00; H, 6.05; N, 9.72.

4.2.25. *N*-(1-Naphthylmethyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (37)—Yield 79%, white solid, mp = 159–161 °C, ^1H NMR ($CDCl_3$) δ 7.75–7.9 (m, 3H, Ar-H), 7.3–7.5 (m, 5H, Ar-H), 7.16 (dd, 1H, Ar-H), 7.04 (br d, 1H, Ar-H), 6.52 (br s, 1H, $NHSO_2$), 5.69 (br t, 1H, NHCO), 4.86 (ddd, 2H, $ArCH_2NH$), 3.49 (q, 1H, *J* = 7.1 Hz, CH_3CH), 2.96 (s, 3H, SO_2CH_3), 1.51 (d, 3H, *J* = 7.1 Hz, CH_3CH); IR (KBr) 3292, 1648, 1511, 1453, 1329, 1156 cm^{-1}; MS (FAB) *m/z* 401 (MH^+); Anal. Calcd for $C_{21}H_{21}FN_2O_3S$: C, 62.98; H, 5.29; N, 7.00. Found: C, 62.79; H, 5.27; N, 6.98.

4.2.26. *N*-(1,2,3,4-Tetrahydro-1-naphthalenyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (38)—Yield 73%, white solid, mp = 116–117 °C, ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 1H, Ar-H), 6.8–7.2 (m, 6H, Ar-H), 6.53 (br s, 1H, $NHSO_2$), 5.62 (br d, 1H, NHCO), 5.15 (m, 1H, C*H*NH), 3.51 (q, 1H, *J* = 7.14 Hz, CH_3CH), 3.00 (s, 3H, SO_2CH_3), 2.75 (m, 2H, cyclo-H), 1.7–1.9 (m, 4H, cyclo-H), 1.53 (d, 3H, *J* = 7.14 Hz, CH_3CH); IR (KBr) 3430, 3235, 1657, 1511, 1452, 1325, 1153 cm^{-1}; MS (FAB) *m/z* 391 (MH^+); Anal. Calcd for $C_{20}H_{23}FN_2O_3S$: C, 61.52; H, 5.94; N, 7.17. Found: C, 61.32; H, 5.91; N, 7.15.

4.2.27. *N*-[2-(4-*t*-Butylphenyl)ethyl]-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (39)—Yield 64%, white solid, mp = 124–126 °C, ^{1}H NMR ($CDCl_3$) δ 7.50 (t, 1H, *J* = 8.3 Hz, H-5), 7.29 (br d, 2H, Ar-H), 6.95–7.15 (m, 4H, Ar-H), 6.52 (br s, 1H, $NHSO_2$), 5.41 (br t, 1H, NHCO), 3.47 (m, 3H, CH_2NH and CH_3CH), 3.03 (s, 3H, SO_2CH_3), 2.72 (t, 2H, *J* = 6.8 Hz, CH_2Ar), 1.47 (d, 3H, *J* = 7.3 Hz, CH_3CH), 1.31 (s, 9H, $C(CH_3)_3$); IR (KBr) 3286, 2961, 1734, 1650, 1512, 1455, 1334, 1265, 1157 cm^{-1}; MS (FAB) *m/z* 421 (MH^+); Anal. Calcd for $C_{22}H_{29}FN_2O_3S$: C, 62.83; H, 6.95; N, 6.66. Found: C, 62.99; H, 6.98; N, 6.64.

4.2.28. *N*-[3-(3,4-Dimethylphenyl)propyl]-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (40)—Yield 95%, white solid, mp = 128–130 °C, ^{1}H NMR ($CDCl_3$) δ 7.50 (t, 1H, *J* = 8.3 Hz, H-5), 7.13 (dd, 1H, *J* = 1.95,11.2 Hz, H-2), 7.0–7.07 (m, 2H, Ar-H), 6.83–6.92 (m, 2H, Ar-H), 6.57 (br s, 1H, $NHSO_2$), 3.41 (q, 1H, *J* = 7.1 Hz, CHMe), 3.2–3.3 (m, 2H, CH_2NH), 3.01 (s, 3H, SO_2CH_3), 2.51 (t, 2H, *J* = 7.6 Hz, CH_2Ar), 2.22 (s, 6H, 2 × CH_3), 1.7–1.8 (m, 2H, CH_2), 1.45 (d, 3H, *J* = 7.1 Hz, $CHCH_3$); IR (KBr) 3294, 2931, 1648, 1509, 1449, 1331, 1157 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, 62.25; H, 6.67; N, 6.86.

4.2.29. *N*-[3-(3,4-Dimethylphenyl)propyl]-(2*R*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (41)—Yield 96%, white solid, mp = 128–130 °C, ^{1}H NMR ($CDCl_3$) δ 7.50 (t, 1H, *J* = 8.3 Hz, H-5), 7.13 (dd, 1H, *J* = 1.95, 11.2 Hz, H-2), 7.0–7.07 (m, 2H, Ar-H), 6.83–6.92 (m, 2H, Ar-H), 6.57 (br s, 1H, $NHSO_2$), 3.41 (q, 1H, *J* = 7.1 Hz, CHMe), 3.2–3.3 (m, 2H, CH_2NH), 3.01 (s, 3H, SO_2CH_3), 2.51 (t, 2H, *J* = 7.6 Hz, CH_2Ar), 2.22 (s, 6H, 2 × CH_3), 1.7–1.8 (m, 2H, CH_2), 1.45 (d, 3H, *J* = 7.1 Hz, $CHCH_3$); IR (KBr) 3294, 2931, 1648, 1509, 1449, 1331, 1157 cm^{-1}; MS (FAB) *m/z* 407 (MH^+); [α] −4.23 (c 0.25, $CHCl_3$); Anal. Calcd for $C_{21}H_{27}FN_2O_3S$: C, 62.05; H, 6.69; N, 6.89. Found: C, 62.31; H, 6.72; N, 6.90.

4.2.30. *N*-[3-(3,4-Dimethylphenyl)propyl]-(2*S*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (42)—Yield 95%, white solid, mp = 128–130 °C, ^{1}H NMR ($CDCl_3$) δ 7.50 (t, 1H, *J* = 8.3 Hz, H-5), 7.13 (dd, 1H, *J* = 1.95, 11.2 Hz, H-2), 7.0–7.07 (m, 2H, Ar-H), 6.83–6.92 (m, 2H, Ar-H), 6.57 (br s, 1H, $NHSO_2$), 3.41 (q, 1H, *J* = 7.1 Hz, CHMe), 3.2–3.3 (m, 2H, CH_2NH), 3.01 (s, 3H, SO_2CH_3), 2.51 (t, 2H, *J* = 7.6 Hz, CH_2Ar), 2.22 (s, 6H, 2 × CH_3), 1.7–1.8 (m, 2H, CH_2), 1.45 (d, 3H, *J* = 7.1 Hz, $CHCH_3$); IR (KBr) 3294, 2931, 1648, 1509, 1449, 1331, 1157 cm^{-1}; MS (FAB) *m/z* 407

(MH^+); [α] +4.34 (*c* 0.25, $CHCl_3$); Anal. Calcd for $C_{21}H_{27}FN_2O_3S$: C, 62.05; H, 6.69; N, 6.89. Found: C, 61.93; H, 6.71; N, 6.86.

4.2.31. *N*-[3-(3,4-Dimethylphenyl)-2-propenyl]-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (43)—Yield 78%, white solid, mp = 144–146 °C, ^{1}H NMR ($CDCl_3$) δ 7.52 (t, 1H, *J* = 8.3 Hz, H-5), 7.0–7.2 (m, 5H, Ar-H), 6.58 (br s, 1H, $NHSO_2$), 6.37 (d, 1H, *J* = 15.8 Hz, ArC*H*=CH), 6.06 (dt, 1H, *J* = 6.2, 15.8 Hz, ArCH=C*H*), 5.57 (br t, 1H, NHCO), 3.9–4.02 (m, 2H, CH_2NH), 3.53 (q, 1H, *J* = 7.14 Hz, CHMe), 3.01 (s, 3H, SO_2CH_3), 2.24 (s, 6H, 2 × CH_3), 1.52 (d, 3H, *J* = 7.14Hz, CH_3); IR (KBr) 3280, 1642, 1509, 1331, 1157 cm^{-1}; MS (FAB) *m/z* 405 (MH^+); Anal. Calcd for $C_{21}H_{25}FN_2O_3S$: C, 62.35; H, 6.23; N, 6.93. Found: C, 62.57; H, 6.21; N, 6.90.

4.2.32. *N*-[3-(4-Chloro-phenyl)-propyl]-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (44)—Yield 70%, white solid, mp = 141–143 °C, ^{1}H NMR ($CDCl_3$) δ 7.51 (t, 1H, *J* = 8.3 Hz, H-5), 7.02–7.25 (m, 6H, Ar-H), 6.52 (br s, 1H, $NHSO_2$), 5.38 (br t, 1H, NHCO), 3.44 (q, 1H, *J* = 7.14 Hz, CH_3CH), 3.24 (ddd, 2H, CH_2NH), 3.02 (s, 3H, SO_2CH_3), 2.55 (t, 2H, *J* = 7.5 Hz, $ArCH_2$), 1.76 (m, 2H, $ArCH_2CH_2$), 1.47 (d, 3H, *J* = 7.14 Hz, CH_3CH); IR (KBr) 3430, 2934, 1644, 1548, 1509, 1445, 1405, 1325, 1154, 1116 cm^{-1}; MS (FAB) *m/z* 413 (MH^+); Anal. Calcd for $C_{19}H_{22}ClFN_2O_3S$: C, 55.27; H, 5.37; N, 6.78. Found: C, 55.10; H, 5.39; N, 6.80.

4.2.33. *N*-[3-(4-Chloro-phenyl)-allyl]-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (45)—Yield 72%, white solid, mp = 151–153 °C, ^{1}H NMR ($CDCl_3$) δ 7.52 (t, 1H, *J* = 8.3 Hz, H-5), 7.08–7.3 (m, 6H, Ar), 6.60 (br s, 1H, $NHSO_2$), 6.37 (d, 1H, *J* = 15.8 Hz, ArC*H*=CH), 6.10 (dt, 1H, *J* = 6.2, 15.8 Hz, ArCH=CH), 5.61 (br t, 1H, NHCO), 3.9–4.1 (m, 2H, CH_2NH), 3.54 (q, 1H, *J* = 7.1 Hz, CHMe), 3.02 (s, 3H, SO_2CH_3), 1.52 (d, 3H, *J* = 7.1 Hz, CH_3); IR (KBr) 3430, 3318, 3216, 1644, 1543, 1508, 1407, 1326, 1156, 1092 cm^{-1}; MS (EI) *m/z* 410 (M^+); Anal. Calcd for $C_{19}H_{20}ClFN_2O_3S$: C, 55.54; H, 4.91; N, 6.82. Found: C, 55.77; H, 4.93; N, 6.80.

4.2.34. *N*-Benzyloxy-2-[3-fluoro-4-(methylsulfonylamino) phenyl]propionamide (46)—Yield 76%, white solid, mp = 182–183 °C, ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1H, ONH), 7.49 (t, 1H, *J* = 8.3 Hz, H-5), 7.25–7.35 (m, 5H, Ph), 7.12 (dd, 1H, *J* = 2, 11.2 Hz, H-2), 7.02 (dd, 1H, *J* = 2, 8.2 Hz, H-6), 6.52 (br s, 1H, $NHSO_2$), 4.87 (s, 2H, $PhCH_2O$), 3.35 (q, 1H, *J* = 7.1 Hz, C*H*CH_3), 3.02 (s, 3H, SO_2CH_3), 1.46 (d, 3H, *J* = 7.1 Hz, CHC*H*$_3$); IR (KBr) 3235, 1671, 1511, 1455, 1331, 1156 cm^{-1}; MS (FAB) *m/z* 367 (MH^+); Anal. Calcd for $C_{17}H_{19}FN_2O_4S$: C, 55.73; H, 5.23; N, 7.65. Found: C, 55.94; H, 5.21; N, 7.64.

4.2.35. *N*-Benzhydryl-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (47)—Yield 79%, white solid, mp = 160–161 °C, ^{1}H NMR ($CDCl_3$) δ 7.51 (t, 1H, *J* = 8.3 Hz, H-5), 7.0–7.4 (m, 10H, Ar), 6.20 (d, 1H, Ph_2CH), 6.04 (br t, 1H, NHCO), 3.58 (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*$_3$); IR (KBr) 3374, 3089, 1657, 1588, 1513, 1445, 1323, 1156 cm^{-1}; MS (FAB) *m/z* 427 (MH^+); Anal. Calcd for $C_{23}H_{23}FN_2O_3S$: C, 64.77; H, 5.44; N, 6.57. Found: C, 64.95; H, 5.42; N, 6.59.

4.2.36. *N*-(2,2-Diphenylethyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (48)—Yield 64%, white solid, mp = 129 °C, ^{1}H NMR ($CDCl_3$) δ 7.42 (t, 1H, J = 8.3 Hz, H-5), 7.1–7.3 (m, 10H, Ar), 6.95 (dd, 1H, H-6), 6.87 (d, 1H, H-2), 6.50 (br s, 1H, $NHSO_2$), 5.28 (br t, 1H, NHCO), 4.12 (t, 1H, Ph_2CH), 3.75–3.95 (m, 2H, CH_2NH), 3.37 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.01 (s, 3H, SO_2CH_3), 1.40 (d, 3H, J = 7.1 Hz, CHC*H*$_3$); IR (KBr) 3374, 3027, 1656, 1508, 1451, 1330, 1158, 1116 cm^{-1}; MS (FAB) *m/z* 441 (MH^+); Anal. Calcd for $C_{24}H_{25}FN_2O_3S$: C, 65.43; H, 5.72; N, 6.36. Found: C, 65.19; H, 5.74; N, 6.38.

4.2.37. *N*-(3,3-Diphenylpropyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (49)—Yield 76%, white solid, mp = 66–68 °C, ^{1}H NMR ($CDCl_3$) δ 7.51 (t, 1H, J = 8.3 Hz, H-5), 7.0–7.3 (m, 12H, Ar-H), 6.45 (br s, 1H, $NHSO_2$), 5.27 (br t, 1H, NHCO), 3.85 (t, 1H, J = 7.8 Hz, Ph_2CH), 3.34 (q, 1H, J = 7.1 Hz, CH_3CH), 3.21 (ddd, 2H, CH_2NH), 3.01 (s, 3H, SO_2CH_3), 2.24 (dd, 2H, CHC*H*$_2$), 1.43 (d, 3H, J = 7.1 Hz, C*H*$_3$CH); IR (KBr) 3290, 1649, 1510, 1450, 1331, 1156 cm^{-1}; MS (FAB) *m/z* 455 (MH^+); Anal. Calcd for $C_{25}H_{27}FN_2O_3S$: C, 66.06; H, 5.99; N, 6.16. Found: C, 66.29; H, 5.97; N, 6.13.

4.2.38. *N*-(3,3-Diphenyl-2-propenyl)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (50)—Yield 78%, white solid, mp = 155–157 °C, ^{1}H NMR ($CDCl_3$) δ 7.52 (t, 1H, J = 8.3 Hz, H-5), 7.05–7.4 (m, 12H, Ar), 6.50 (br s, 1H, $NHSO_2$), 6.00 (t, 1H, J = 7.0 Hz, >C=C*H*), 5.44 (br t, 1H, NHCO), 3.85–4.0 (m, 2H, CH_2NH), 3.46 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.01 (s, 3H, SO_2CH_3), 1.48 (d, 3H, J = 7.1 Hz, CHC*H*$_3$); IR (KBr) 3736, 1647, 1512, 1333, 1157 cm^{-1}; MS (EI) *m/z* 452 (M^+); Anal. Calcd for $C_{25}H_{25}FN_2O_3S$: C, 55.73; H, 5.23; N, 7.65. Found: C, 55.61; H, 5.22; N, 7.64.

4.2.39. *N*-(2,2-Diphenyl-cyclopropylmethyl)-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (51)—Yield 83%, white solid, mp = 166–168 °C, ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 1H, Ar-H), 7.24–7.06 (m, 12H, Ar-H), 6.52 (s, 1H, SO_2NH), 5.30 (s, 1H, NHCO), 3.49 (m, 4H, Ar_2CH, CH_2NH and COCH), 2.95 (s, 3H, SO_2CH_3), 1.95 (m, 1H), 1.50 (d, 3H, J = 4.95 Hz), 1.34 (m, 1H, cyclo-H), 1.16 (m, 1H, cyclo-H); IR (KBr) 3290, 2983, 1649, 1510, 1450, 1331, 1156, 1045, 974 cm^{-1}; MS (FAB) *m/z* 467 (MH^+); Anal. Calcd for $C_{26}H_{27}FN_2O_3S$: C, 66.93; H, 5.83; N, 6.00. Found: C, 66.68; H, 5.81; N, 6.03.

4.2.40. *N*-(2-Diphenylamino-ethyl)-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (52)—Yield 87%, white solid, mp = 156–158 °C, ^{1}H NMR ($CDCl_3$) δ 7.47 (t, 1H, J = 8.23 Hz, Ar), 7.25 (m, 4H, Ar), 7.07 (d, 1H, J = 11.16 Hz, Ar), 6.95 (m, 7H, Ar), 6.49 (s, 1H, Ar), 5.58 (br t, 1H, NH), 3.86 (q, 2H, CH_2NH), 3.46 (q, 2H, Ar_2NCH_2), 3.37 (q, 1H, $CHCH_3$), 2.99 (s, 3H, SO_2CH_3), 1.44 (d, 3H, J = 7.14Hz, $CHCH_3$); IR (KBr) 3296, 1651, 1589, 1498, 1332, 1157, 1116, 972, 909, 752, 697 cm^{-1}; MS (FAB) *m/z* 455 (MH^+); Anal. Calcd for $C_{24}H_{26}FN_3O_3S$: C, 63.28; H, 5.75; N, 9.22. Found: C, 63.57; H, 5.73; N, 9.20.

4.2.41. *N*-(3,3-Di-*p*-tolyl-propyl)-2-(3-fluoro-4-methansulfonylamino-phenyl)-propionamide (53)—Yield 90%, white solid, mp = 150–152 °C, ^{1}H NMR ($CDCl_3$) δ 7.51

(t, 1H, *J* = 8.40 Hz, Ar-H), 7.13–7.01 (m, 10H, Ar), 6.45 (br s, 1H, $NHSO_2$), 5.25 (br t, 1H, NHCO), 3.33 (q, 1H, *J* = 7.14 Hz, C*H*CH_3), 3.20 (m, 2H, CH_2NH), 3.01 (s, 3H, SO_2CH_3), 2.28 (s, 6H, $(Ar\text{-}CH_3)_2$), 2.18 (q, 2H, *J* = 7.50 Hz, Ar-CH_2), 1.42 (d, 3H, *J* = 7.14 Hz, CHC*H*$_3$); IR (KBr) 3292, 2928, 1649, 1511, 1448, 1332, 1158, 1118, 972 cm^{-1}; MS (EI) *m/z* 483 (M^+); Anal. Calcd for $C_{27}H_{31}FN_2O_3S$: C, 67.19; H, 6.47; N, 5.80. Found: C, 67.37; H, 6.45; N, 5.81.

4.2.42. *N*-[3,3-Di(4-methylphenyl)-2-propenyl]-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (54)—Yield 72%, white solid, mp = 163–165 °C, ^{1}H NMR ($CDCl_3$) *δ* 7.49 (t, 1H, *J* = 8.3 Hz, H-5), 6.95–7.2 (m, 10H, Ar-H), 5.93 (t, 1H, *J* = 7.0 Hz, >C=C*H*), 5.56 (br t, 1H, NHCO), 3.8–4.0 (m, 2H, CH_2NH), 3.47 (q, 1H, *J* = 7.1 Hz, C*H*CH_3), 3.00 (s, 3H, SO_2CH_3), 2.34 (d, 6H, 2 × CH_3), 1.47 (d, 3H, *J* = 7.1 Hz, CHC*H*$_3$); IR (KBr) 3279, 1648, 1511, 1451, 1332, 1158, 1116 cm^{-1}; MS (FAB) *m/z* 481 (MH^+); Anal. Calcd for $C_{27}H_{29}FN_2O_3S$: C, 67.48; H, 6.08; N, 5.83. Found: C, 67.19; H, 6.05; N, 5.80.

4.2.43. *N*-[3,3-Bis-(4-fluoro-phenyl)-propyl]-2-(3-fluoro-4-methansulfonylamino-phenyl)-propionamide (55)—Yield 93%, white solid, mp = 62–64 °C, ^{1}H NMR ($CDCl_3$) *δ* 7.52 (t, 1H, *J* = 8.43 Hz, Ar-H), 7.14–6.93 (m, 10H, Ar-H), 6.46 (br s, 1H, $NHSO_2$), 5.32 (s, 1H, NHCO), 3.82 (t, 1H, *J* = 7.71 Hz, Ar-CH), 3.40 (q, 1H, *J* = 7.14 Hz, C*H*CH_3), 3.18 (m, 2H, CH_2NH), 3.02 (s, 3H, SO_2CH_3), 2.17 (q, 2H, *J* = 7.50 Hz, CH–CH_2), 1.45 (d, 3H, *J* = 7.14 Hz, CHC*H*$_3$); IR (KBr) 3291, 1650, 1508, 1451, 1334, 1223, 1158, 970 cm^{-1}; MS (EI) *m/z* 491 (M^+); Anal. Calcd for $C_{25}H_{25}F_3N_2O_3S$: C, 61.21; H, 5.14; N, 5.71. Found: C, 61.48; H, 5.15; N, 5.70.

4.2.44. *N*-[3,3-Di(4-fluorophenyl)-2-propenyl]-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (56)—Yield 78%, white solid, mp = 57–60 °C, ^{1}H NMR ($CDCl_3$) *δ* 7.49 (t, 1H, *J* = 8.3 Hz, H-5), 6.9–7.2 (m, 10H, Ar), 6.72 (br s, 1H, $NHSO_2$), 5.92 (t, 1H, *J* = 7.0 Hz, >C=C*H*), 5.58 (br s, 1H, NHCO), 3.8–4.0 (m, 2H, CH_2NH), 3.48 (q, 1H, *J* = 7.1 Hz, C*H*CH_3), 3.02 (s, 3H, SO_2CH_3), 1.48 (d, 3H, *J* = 7.1 Hz, CHC*H*$_3$); IR (KBr) 3280, 1650, 1599, 1509, 1332, 1225, 1157 cm^{-1}; MS (FAB) *m/z* 489 (MH^+); Anal. Calcd for $C_{25}H_{23}F_3N_2O_3S$: C, 61.46; H, 4.75; N, 5.73. Found: C, 61.66; H, 4.73; N, 5.71.

4.2.45. *N*-[3,3-Bis-(4-chloro-phenyl)-allyl]-2-(3-fluoro-4-methanesulfonylamino-phenyl)-propionamide (57)—Yield 73%, white solid, mp = 72–74 °C, ^{1}H NMR ($CDCl_3$) *δ* 7.50 (t, 1H, *J* = 8.23 Hz, Ar), 7.34 (d, 2H, *J* = 8.61 Hz, Ar), 7.24 (d, 2H, *J* = 12.99 Hz, Ar), 7.15 (dd, 1H, *J* = 11.37 Hz, Ar), 7.10–7.02 (m, 5H, Ar), 6.60 (br s, 1H, NH), 5.97 (t, 1H, *J* = 6.87 Hz, $CCHCH_2$), 5.54 (br t, 1H, NH), 3.89 (m, 2H, CH_2NH), 3.47 (q, 1H, *J* = 7.14 Hz, $CHCH_3$), 3.02 (s, 3H, SO_2CH_3), 1.48 (d, 3H, *J* = 7.14 Hz, $CHCH_3$); IR (KBr) 3293, 1649, 1512, 1332, 1157, 1092, 973, 831, 757 cm^{-1}; MS (FAB) *m/z* 521 (MH^+); Anal. Calcd for $C_{25}H_{23}Cl_2FN_2O_3S$: C, 57.59; H, 4.45; N, 5.37. Found: C, 57.32; H, 4.43; N, 5.35.

4.2.46. 2-(3-Fluoro-4-methanesulfonylamino-phenyl)-N-[3-(4-fluoro-phenyl)-3-*p*-tolyl-propyl]-propionamide (58)—Yield 72%, white solid, mp = 63–65 °C, ^{1}H NMR

($CDCl_3$) δ 7.51 (t, 1H, Ar), 7.15–7.02 (m, 8H, Ar), 6.94 (t, 1H, Ar), 6.46 (br, 1H, NH), 5.28 (br t, 1H, NH), 3.78 (td, 1H, ArCHAr), 3.37 (q, 1H, J = 7.14 Hz, $CHCH_3$), 3.18 (m, 2H, CH_2NH), 3.01 (s, 3H, SO_2CH_3), 2.29 (s, 3H, $ArCH_3$), 2.17 (q, 2H, Ar_2CHCH_2), 1.44 (d, 3H, J = 7.14 Hz, $CHCH_3$); IR (KBr), 1649, 1509, 1454, 1332, 1222, 1157, 972, 819, 758 cm^{-1}; MS (FAB) m/z 487 (M^+); Anal. Calcd for $C_{26}H_{28}F_2N_2O_3S$: C, 64.18; H, 5.80; N, 5.76. Found: C, 64.39; H, 5.82; N, 5.75.

4.2.47. *N*-[2-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yliden)ethyl]-2-[3-fluoro-4-(methylsulfonylamino) phenyl]propionamide (59)—Yield 76%, white solid, mp = 67–69 °C, ^1H NMR ($CDCl_3$) δ 7.50 (t, 1H, J = 8.3 Hz, H-5), 7.05–7.25 (m, 10H, Ar), 6.49 (br s, 1H, $NHSO_2$), 5.80 (t, 1H, >C=C*H*), 5.40 (br t, 1H, NHCO), 4.13 (m, 1H, CH_2NH), 3.71 (m, 1H, CH_2NH), 3.43 (q, 1H, J = 7.1 Hz, C*H*CH_3), 3.2–3.4 (m, 4H, $PhCH_2CH_2Ph$), 3.01 (s, 3H, SO_2CH_3), 1.46 (d, 3H, J = 7.1 Hz, CHCH_3); IR (KBr) 3294, 2927, 1649, 1511, 1453, 1332, 1156 cm^{-1}; MS (FAB) m/z 479 (MH^+); Anal. Calcd for $C_{27}H_{27}FN_2O_3S$: C, 67.76; H, 5.69; N, 5.85. Found: C, 67.54; H, 5.70; N, 5.82.

4.2.48. *N*-[2-Dibenzo[*a,d*]cyclohepten-5-ylidene-ethyl]-2-(3-fluoro-4-methylsulfonylamino-phenyl)-propionamide (60)—Yield 91%, white solid, mp = 70–72 °C, ^1H NMR ($CDCl_3$) δ 7.48 (m, 1H, Ar-H), 7.33–7.26 (m, 8H, Ar-H), 7.16–7.00 (m, 3H, Ar-H), 6.85 (s, 2H, Ar-H and $NHSO_2$), 5.50 (m, 1H, >C=C*H*), 5.34 (br t, 1H, NHCO), 4.30 (m, 1H, CH_2NH), 3.55 (m, 1H, CH_2NH), 3.39 (q, 1H, J = 6.78 Hz, C*H*CH_3), 3.00 (s, 3H, SO_2CH_3), 1.44 (d, 3H, J = 7.14 Hz, CHCH_3); IR (KBr) 3450, 2951, 2938, 1650, 1511, 1448, 1332, 1160 cm^{-1}; MS (FAB) m/z 477 (MH^+); Anal. Calcd for $C_{27}H_{25}FN_2O_3S$: C, 68.05; H, 5.29; N, 5.88. Found: C, 68.31; H, 5.27; N, 5.86.

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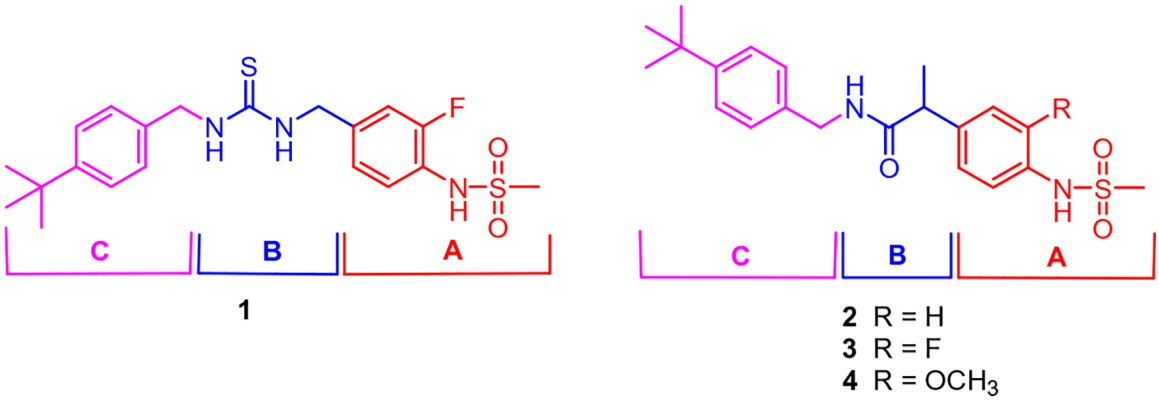
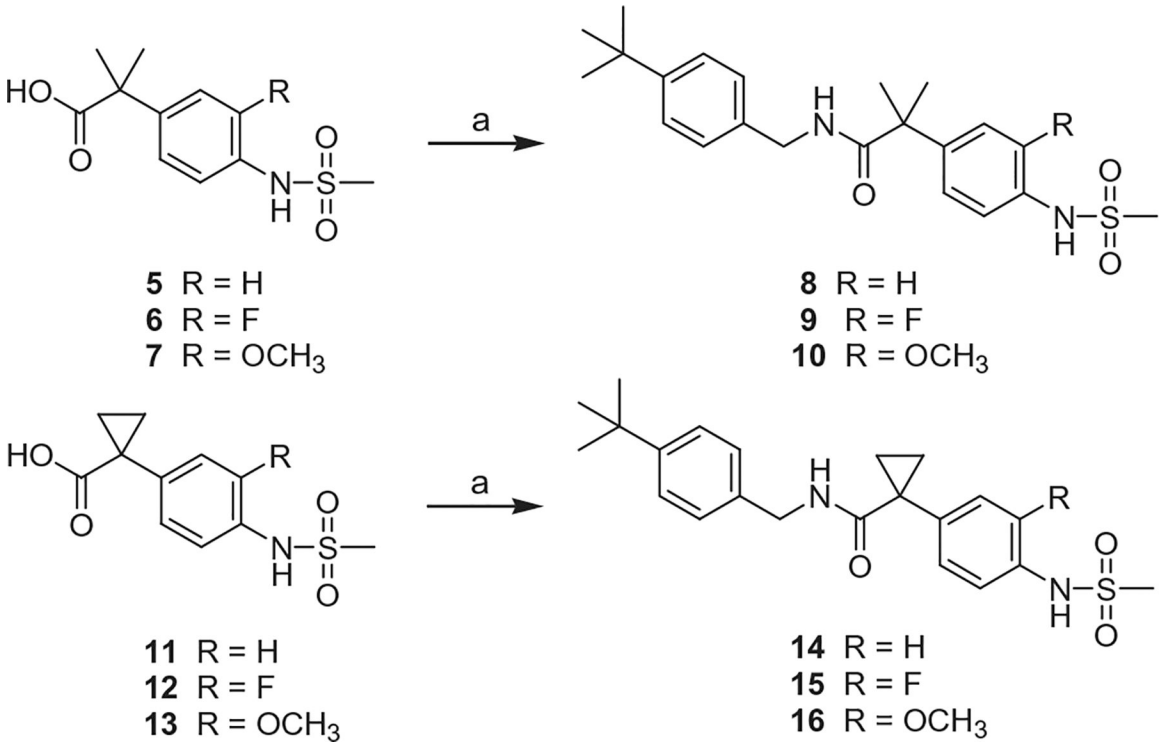
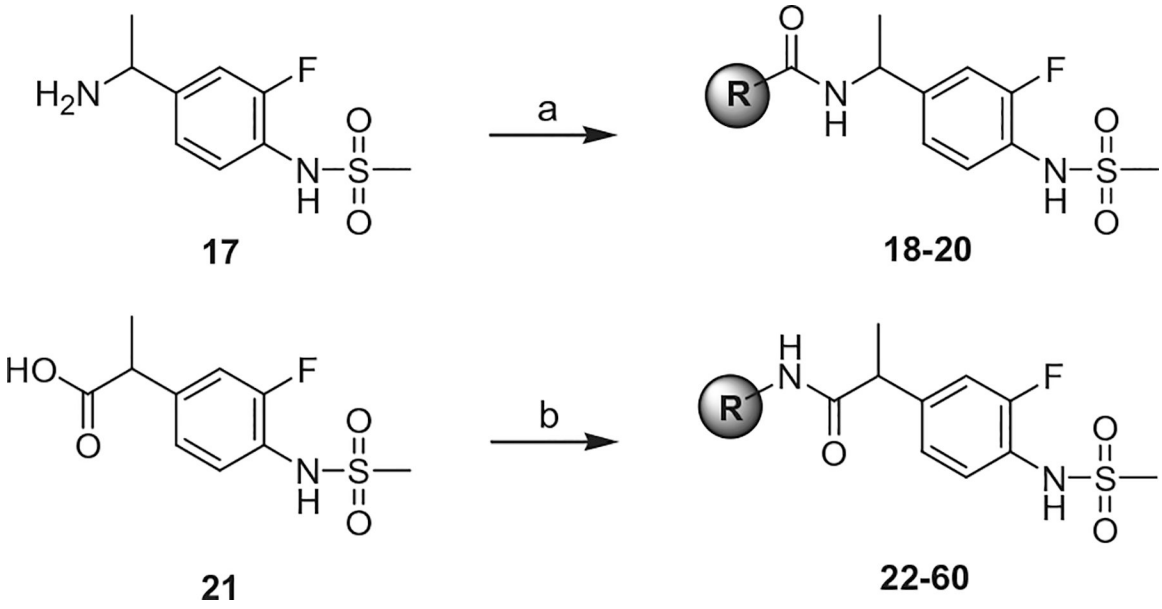


Figure 1.



Scheme 1.

Syntheses of dimethyl and cyclopropyl amide analogues. Reagents and conditions: (a) R-NH_2, EDC, CH_2Cl_2.

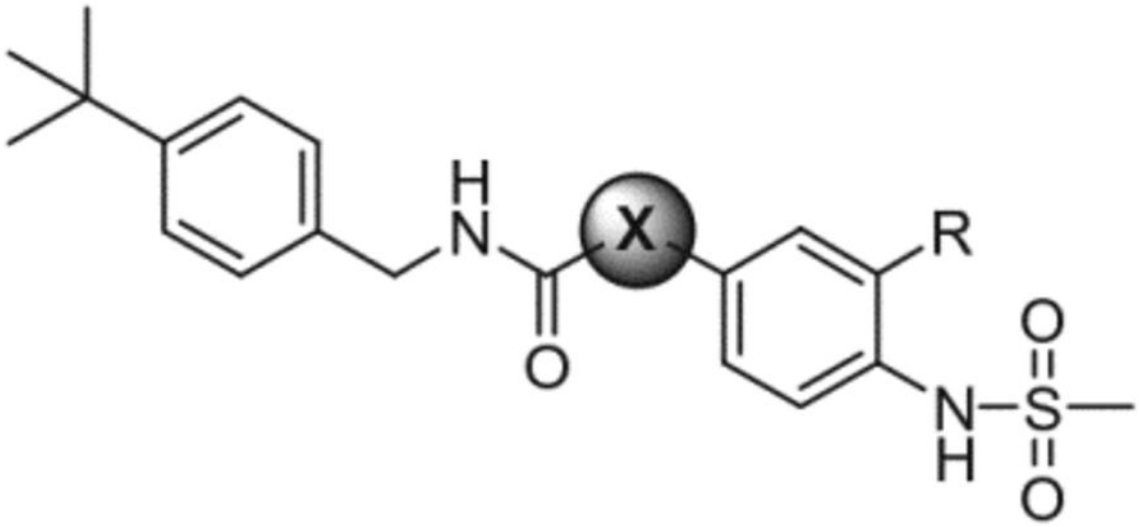


Scheme 2.

Syntheses of reverse amide and propanamide analogues. Reagents and conditions: (a) R-CO_2H, EDC, CH_2Cl_2; (b) R-NH_2, EDC, CH_2Cl_2.

Table 1

SAR-1 of B-region



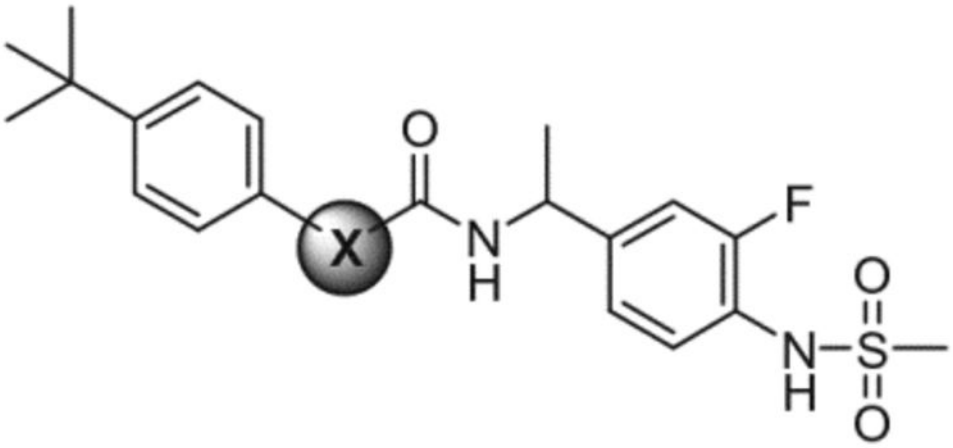
	X	R	K_i [a] (nM) binding affinity	EC_{50} [b] (nM) agonism	K_i [a] (nM) antagonism
2	>$CHCH_3$	H	106	NE	17.5
3	>$CHCH_3$	F	46.2	NE	7.6
4	>$CHCH_3$	OCH_3	540	NE	232
8	>$C(CH_3)_2$	H	430 (±120)	NE	2550 (±760)
9	>$C(CH_3)_2$	F	1070 (±330)	NE	467 (±86)
10	>$C(CH_3)_2$	OCH_3	414 (±55)	NE	707 (±81)
14	>$C(CH_2)_2$	H	610 (±130)	NE	1770 (±140)
15	>$C(CH_2)_2$	F	NE	NE	WE
16	>$C(CH_2)_2$	OCH_3	750 (±130)	NE	2250 (±610)

[a] Values represent mean ± SEM from 3 or more experiments.

[b] NE, no effect. WE, weak effect (quantitation of no effect/fractional agonism/antagonism is from 1 to 3 experiments).

Table 2

SAR-2 of B-region



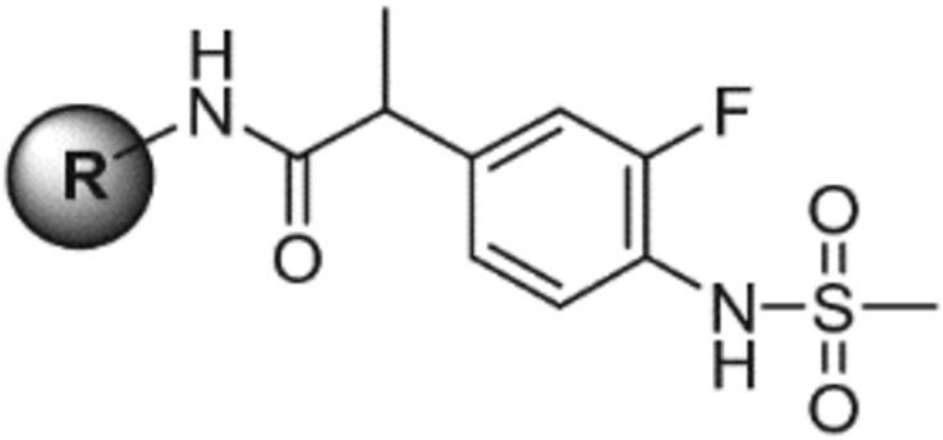
	X	K_i[a] (nM) binding affinity	EC_{50} (nM)[b] agonism	K_i[a] (nM) antagonism
3		46.2	NE	7.6
18	CH_2	2100 (±500)	NE	2220 (±400)
19	CH_2CH_2	380 (±100)	NE	104 (±24)
20	CH=CH(E)	105 (±14)	NE	23.9 (±4.6)

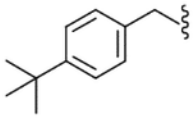
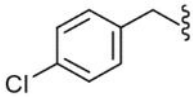
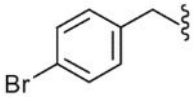
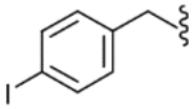
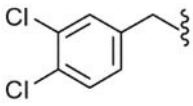
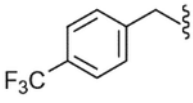
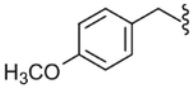
[a] Values represent mean ± SEM from 3 or more experiments.

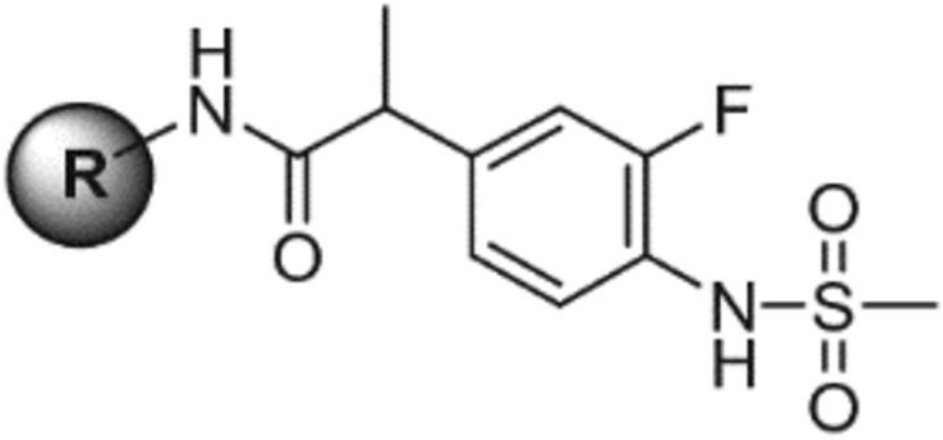
[b] NE, no effect. WE, weak effect (quantitation of no effect/fractional agonism/antagonism is from 1 to 3 experiments).

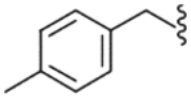
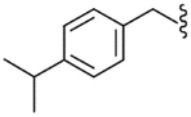
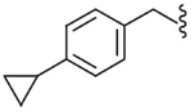
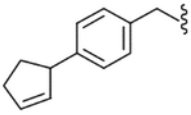
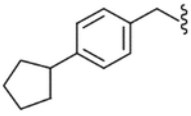
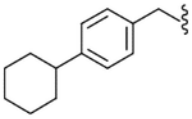
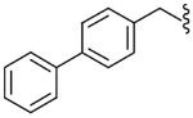
Table 3

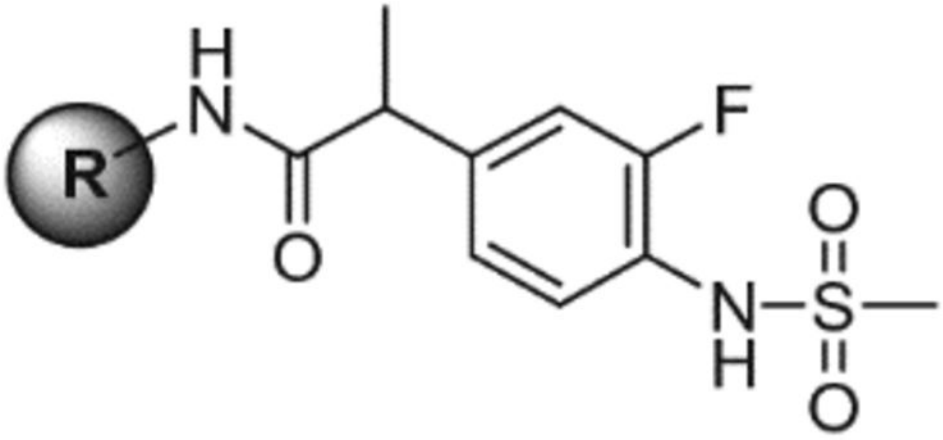
SAR-1 of C-region

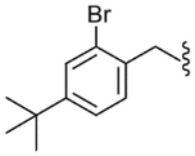
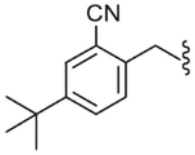
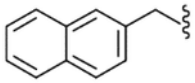
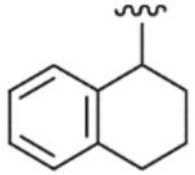
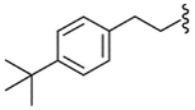
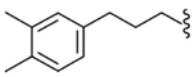
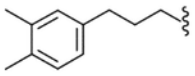


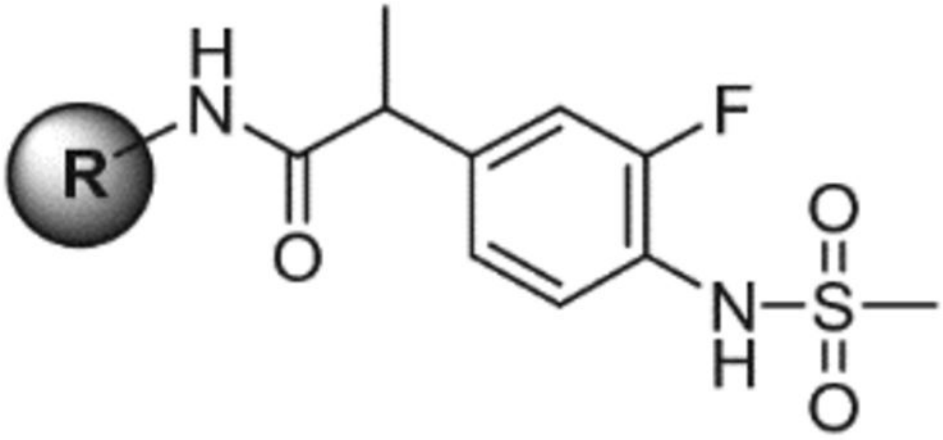
	R	K_i[a] (nM) binding affinity	EC_{50}[b] (nM) agonism	K_i[a] (nM) antagonism
3		46.2	NE	7.6
22		1060 (±220)	NE	367 (±23)
23		412 (±24)	NE	250 (±70)
24		502 (±84)	NE	107 (±38)
25		200 (±52)	NE	115 (±43)
26		660 (±170)	NE	274 (±90)
27		7800 (±1100)	NE	5350 (±810)

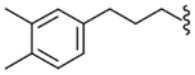
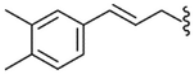
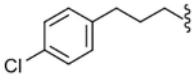
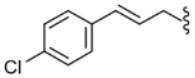
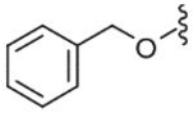


	R	K_i [a] (nM) binding affinity	EC_{50} [b] (nM) agonism	K_i [a] (nM) antagonism
28		3100 (±570)	NE	930 (±160)
29		127 (±23)	NE	144 (±28)
30		411 (±92)	NE	55.5 (±9.1)
31		162 (±31)	NE	15 (±1.1)
32		93 (±23)	NE	20.8 (±2.5)
33		138 (±49)	NE	43 (±17)
34		1750 (±480)	NE	261 (±69)



	R	K_i[a] (nM) binding affinity	EC_{50}[b] (nM) agonism	K_i[a] (nM) antagonism
35		47 (±11)	NE	12.7 (±3.4)
36		44.0 (±5.5)	NE	40 (±15)
37		960 (±110)	NE	240 (±95)
38		WE	NE	NE
39		554 (±64)	NE	43 (±11)
40		413 (±53)	NE	97 (±43)
41		950 (±140)	NE	204 (±28)



	R	K_i[a] (nM) binding affinity	EC_{50}[b] (nM) agonism	K_i[a] (nM) antagonism
42		257 (±47)	NE	33.7 (±6.4)
43		277 (±64)	NE	153 (±20)
44		470 (±140)	NE	135 (±40)
45		897 (±63)	NE	384 (±78)
46		9400 (±1400)	NE	(34%)[c]

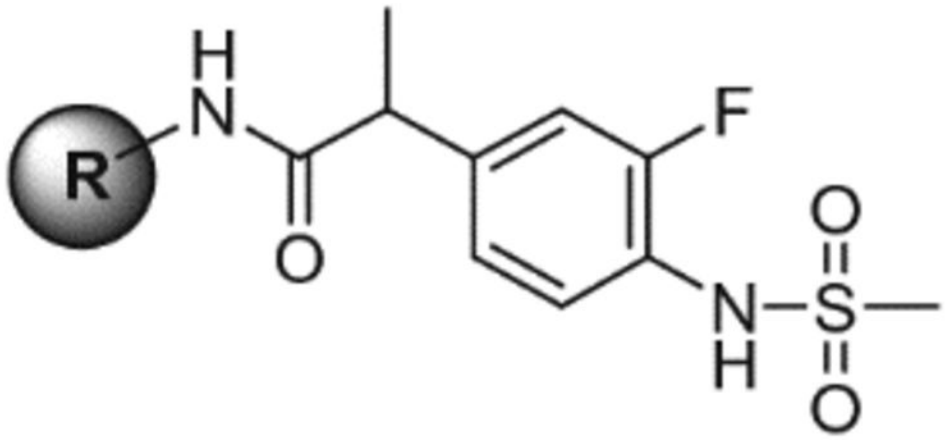
[a] Values represent mean ± SEM from 3 or more experiments.

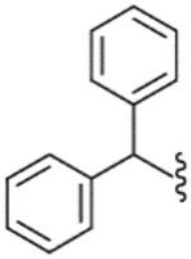
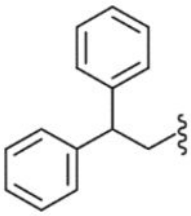
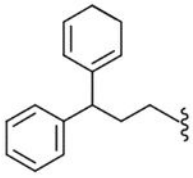
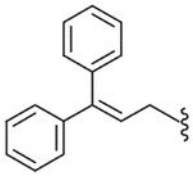
[b] NE, no effect. WE, weak effect (quantitation of no effect/fractional agonism/antagonism is from 1 to 3 experiments).

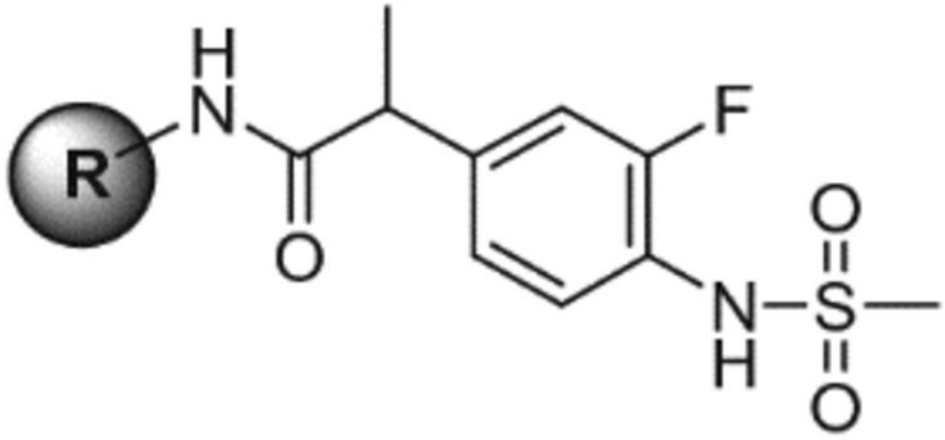
[c] Only fractional antagonism.

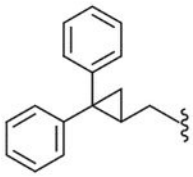
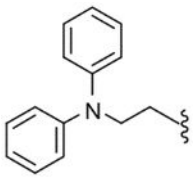
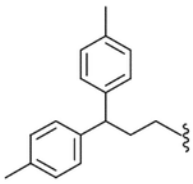
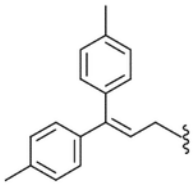
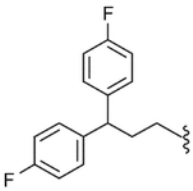
Table 4

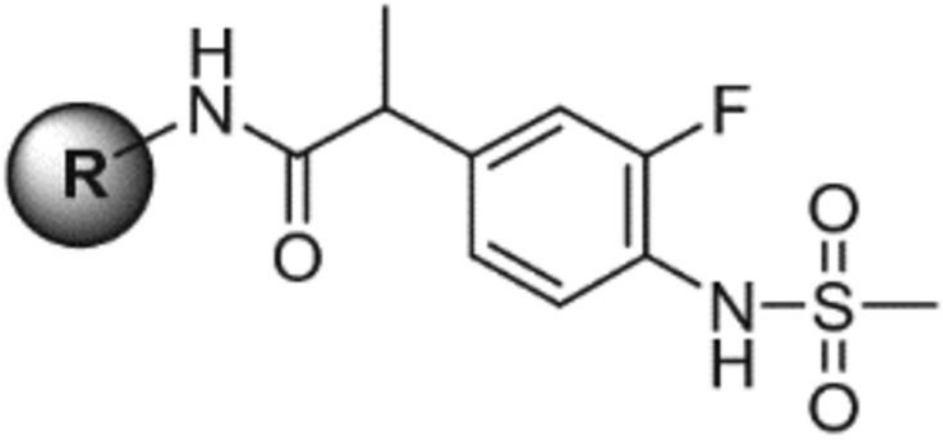
SAR-2 of C-region

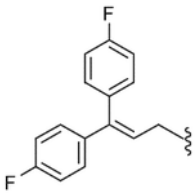
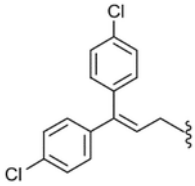
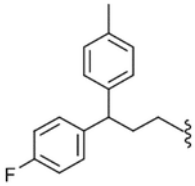
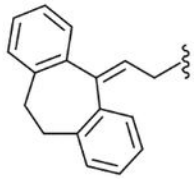


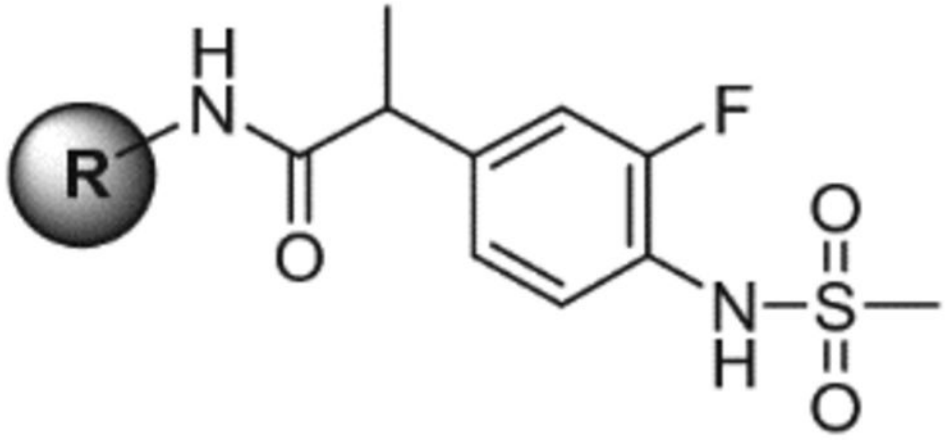
R	K_i[a] (nM) binding affinity[c]	EC_{50}[a] (nM) agonism[c]	K_i[a] (nM) antagonism[c]
47 	5900 (±1300)	NE	(58%)[b]
48 	1680 (±640)	NE	2490 (±880)
49 	130 (±21)	NE	36.6 (±7.2)
50 	21.5 (±5.1)	NE	14.2 (±4.0)

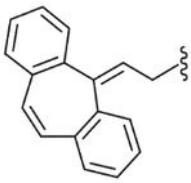


	R	K_i[a] (nM) binding affinity[c]	EC_{50}[a] (nM) agonism[c]	K_i[a] (nM) antagonism[c]
51		188 (±35)	NE	148 (±51)
52		115 (±25)	NE	47 (±24)
53		96 (±21)	NE	32.1 (±3.7)
54		30.9 (±5.5)	NE	8.0 (±1.9)
55		79 (±34)	NE	24.8 (±0.99)



	R	K_i[a] (nM) binding affinity[c]	EC_{50}[a] (nM) agonism[c]	K_i[a] (nM) antagonism[c]
56		43.3 (±8.1)	NE	29.2 (±5.4)
57		29.6 (±7.0)	NE	24.5 (±6.3)
58		121 (±48)	NE	31 (±11)
59		141 (±44)	NE	122 (±11)



R	K_i [a] (nM) binding affinity [c]	EC_{50} [a] (nM) agonism [c]	K_i [a] (nM) antagonism [c]
60 	117 (±31)	NE	163 (±7.6)

[a] Values represent mean ± SEM from 3 or more experiments.

[b] NE, no effect. WE, weak effect (quantitation of no effect/fractional agonism/antagonism is from 1 to 3 experiments).

[c] Only fractional antagonism.