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Original article

Conformationally constrained analogues of *N*′-(4-*tert*-butylbenzyl)-*N*-(4-methylsulfonylaminobenzyl)thiourea as TRPV1 antagonists

Ju-Ok Lim [a], Mi-Kyoung Jin [a], HyungChul Ryu [a], Dong Wook Kang [a], Jeewoo Lee [a,*], Larry V. Pearce [b], Richard Tran [b], Attila Toth [b], Peter M. Blumberg [b]

[a] *Laboratory of Medicinal Chemistry, Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Shinlim-Dong, Kwanak-Ku, Seoul 151-742, Republic of Korea*

[b] *Laboratory of Cancer Biology and Genetics, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD 20892, USA*

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Abstract

A series of bicyclic analogues having indan and tetrahydronaphthalene templates in the A-region were designed as conformationally constrained analogues of our previously reported potent TRPV1 antagonists (**1**, **3**). The activities for rat TRPV1 of the conformationally restricted analogues were moderately or markedly diminished, particularly in the case of the tetrahydronaphthalene analogues. The analysis indicated that steric constraints at the benzylic position in the bicyclic analogues may be an important factor for their unfavorable interaction with the receptor.

Keywords: TRPV1 antagonists; Analgesic; Conformationally constrained analogues

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 have attracted much attention as promising drug candidates for inhibiting the transmission of nociceptive signaling from the periphery to the CNS and for blocking other pathological states associated with this receptor. They have thus emerged as novel and promising analgesic and anti-inflammatory agents, particularly for chronic pain and inflammatory hyperalgesia [8]. The number of antagonists reported continues to increase and some of them have entered clinical trials [9,10].

Previously, we have demonstrated that a series of *N*-4-(methylsulfonylaminobenzyl)thiourea analogues were effective antagonists of the action of capsaicin on rat TRPV1 [11–14]. A prototype antagonist (**1**) showed high binding affinity and potent antagonism ($K_i = 63$ nM and $K_{i(\mathrm{ant})} = 54$ nM in rTRPV1/CHO) [11]. We further found that 3-substituents 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, $K_{i(\mathrm{ant})} = 9.2$ nM in rTRPV1/CHO) was a potent antagonist not only of capsaicin stimulation of rTRPV1 but also of stimulation by temperature and pH [11]. Conversely, the 3-methoxy derivative **3** showed a shift to partial agonism ($K_i = 51$ nM, 17% agonism and 84% antagonism in rTRPV1/CHO) while the binding affinity remained unaffected [12]. In order to optimize the *in vitro* activities of 4-methylsulfonamide TRPV1 antagonists, we have investigated extensively their structure–activity relationships as a function of the structural regions designated as the A, B and C-regions [15–17].

As part of our continuing effort to further optimize the receptor potency and antagonist efficacy of lead antagonists,

* Corresponding author. Tel.: +82 2 880 7846; fax: +82 2 888 0649.
E-mail address: jeewoo@snu.ac.kr (J. Lee).

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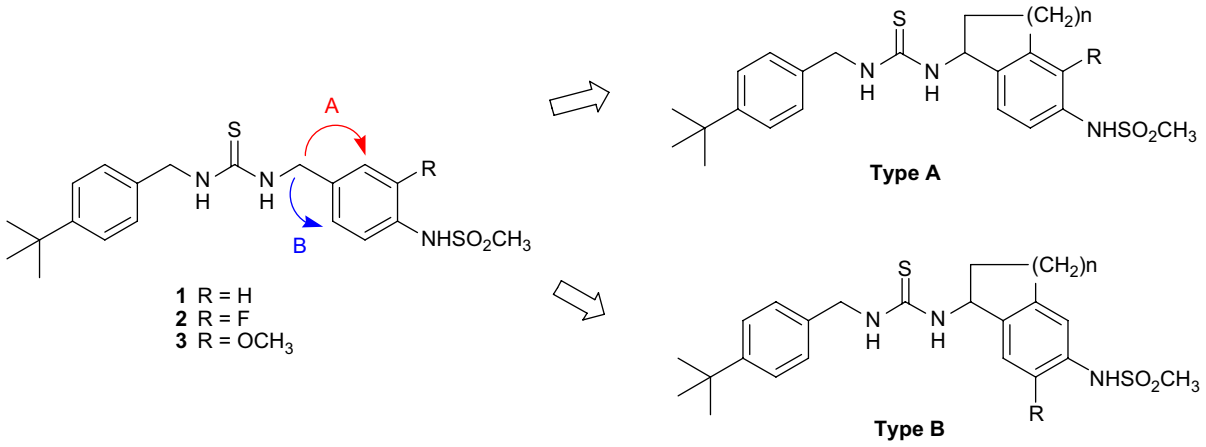


Fig. 1.

we have investigated conformationally constrained analogues of the lead antagonists with the goal of stabilizing a favorable "bioactive conformation". The target compounds were designed to impose conformational restriction between the benzylic position and the phenyl ring through incorporation of a carbon linker as shown in Fig. 1, providing indan and tetrahydronaphthalene templates. In the interest of synthetic accessibility, parent compounds **1** and **3** were chosen to evaluate the effect of the conformational constraint.

2. Chemistry

The synthetic strategy for preparation of the target compounds is shown in Fig. 2. The target thioureas were synthesized by the coupling of 4-*tert*-butylbenzyl isothiocyanate with the bicyclic amines of the A-region moieties, which were obtained from the corresponding ketones via oxime intermediates. The ketones were prepared either by benzylic oxidation of *N*-Boc substituted indan or by nitration of appropriately substituted 1-indanone/α-tetralone.

The syntheses of the target compounds having 5-(methylsulfonylamino)indanyl and 6-(methylsulfonylamino)-1,2,3,4-tetrahydro-1-naphthyl moieties in the A-region are outlined in Scheme 1. Benzylic oxidation of *N*-Boc substituted bicycles (**6**, **7**), prepared from commercially available 5-aminoindan (**4**) or tetrahydronaphthalene, by pyridinium chlorochromate provided 1-indanone (**8**) and 5-oxo-tetrahydronaphthalene (**9**) templates. After deprotection and mesylation, ketones of **12** and **13** were converted to the corresponding amines (**16**, **17**) via oximes, which were condensed with 4-*tert*-butylbenzyl isothiocyanate to afford the final thiourea compounds (**18**, **19**).

The syntheses of methoxy substituted analogues of **18** and **19** are shown in Schemes 2 and 3. Nitration [18] of commercially available 4-methoxy-1-indanone (**20**) and 5-methoxy-1-tetralone (**21**) provided the key intermediates, 4-methoxy-5-nitro-1-indanone (**22**) and 5-methoxy-6-nitro-1-tetralone (**23**), respectively. As by-products, *para*-nitration isomers, 7-nitro-1-indanone and 8-nitro-1-tetralone, were also isolated, respectively. The structures of isomers were assigned based on the comparison of chemical shifts and NOE enhancement of protons adjacent to the methoxy group. For example, the H7 and H8 protons of 5-methoxy-6-nitro-1-tetralone (**23**) shifted downfield compared to the H6 and H7 protons of 5-methoxy-8-nitro-1-tetralone (**23′**). Whereas only one NOE enhancement by

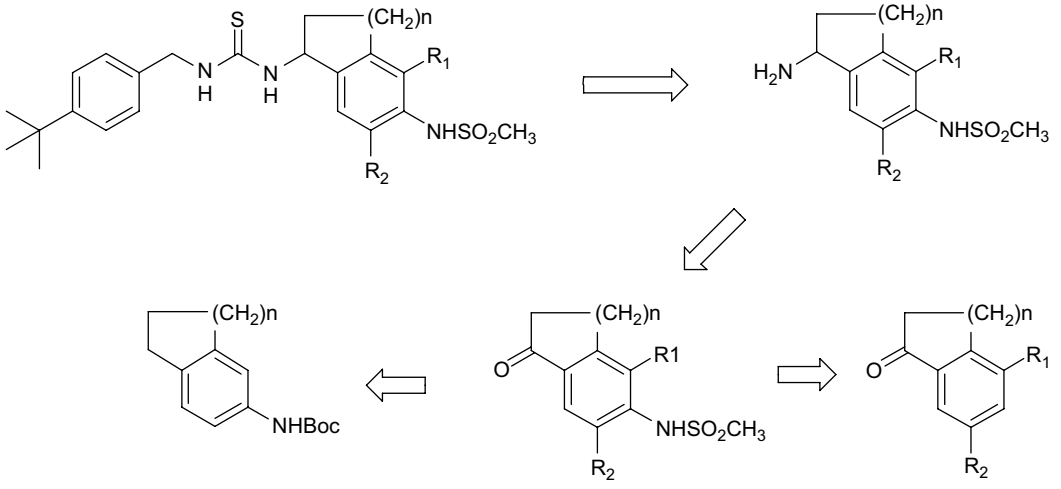
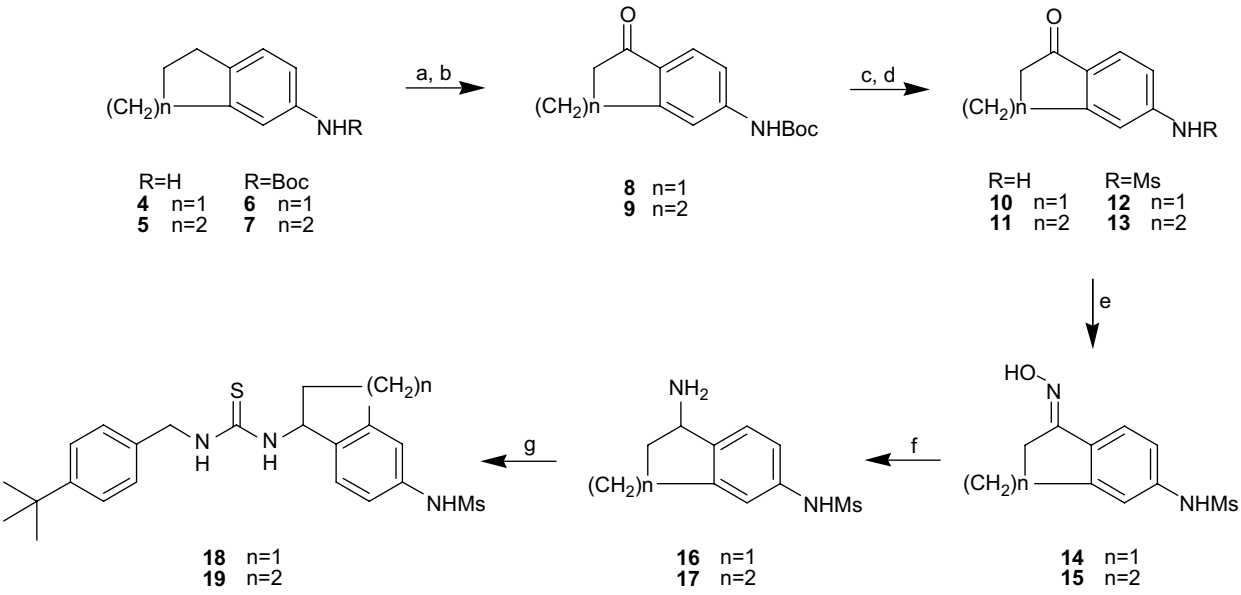


Fig. 2.



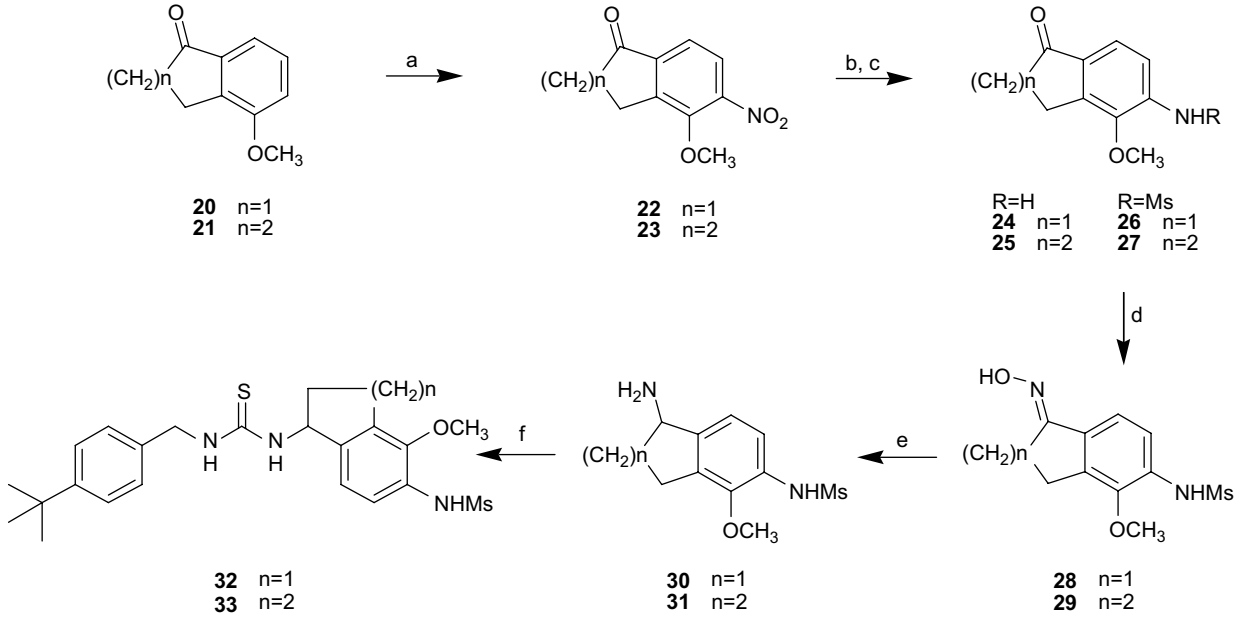
Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, NEt_3, CH_2Cl_2; (b) PCC, CH_2Cl_2; (c) TFA, CH_2Cl_2; (d) MsCl, pyridine; (e) NH_2OH–HCl, pyridine; (f) 10% Pd–C, H_2, concd. HCl, MeOH; (g) 4-*t*-$BuPhCH_2NCS$, DMF.

OCH_3 irradiation of **23** (6-nitro isomer) was observed, the two enhancements in **23′** (8-nitro isomer) were found (see Ref. [19]). Nitro groups of **22** and **23** were converted to the corresponding methylsulfonylamino groups (**26** and **27**) in two steps. The final 4-methoxy-1-indanyl (**32**) and 5-methoxy-1-naphthyl (**33**) compounds were prepared from **26** and **27** by the protocol described in Scheme 1.

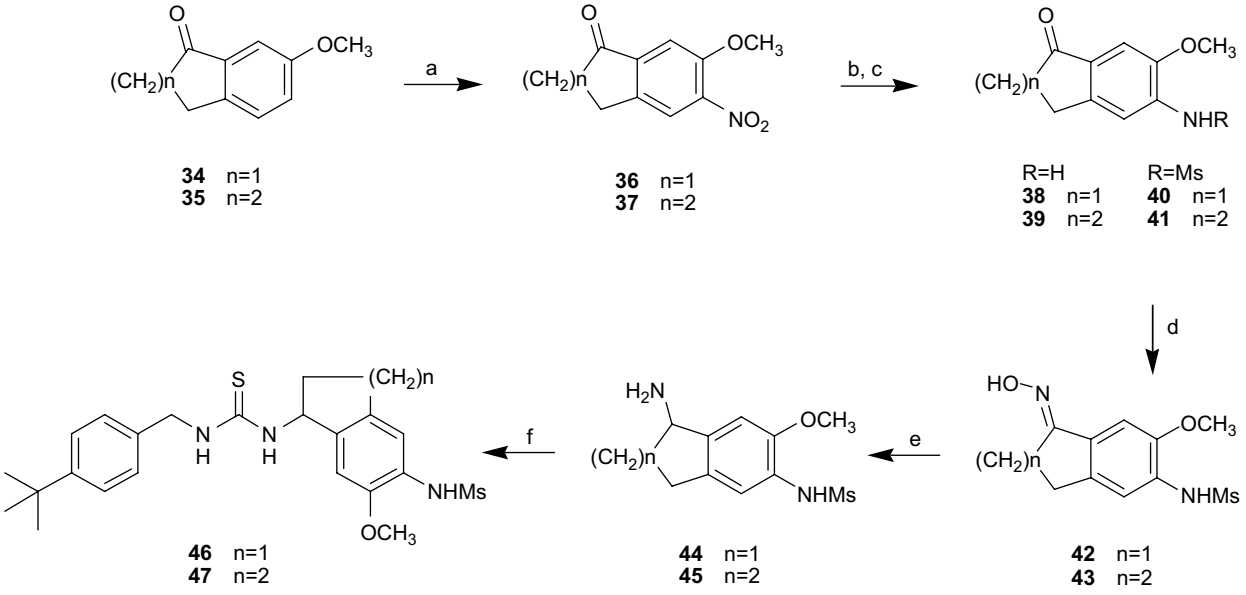
The syntheses of 6-methoxy-1-indanyl (**46**) and 7-methoxy-1-naphthyl (**47**) compounds as shown in Scheme 3 were carried out by a strategy similar to that described in Scheme 2, starting from 6-methoxy-1-indanone (**20**) and 7-methoxy-1-tetralone (**21**). The structures of the geometric isomers resulting from nitration of **34** and **35** were readily confirmed by the values of the *ortho* or *para* coupling constants.

3. Result and discussion

The binding affinities and potencies as agonists/antagonists of the synthesized TRPV1 ligands were assessed *in vitro* by a binding competition assay with [^3H]RTX and by a functional



Scheme 2. Reagents and conditions: (a) $Cu(NO_3)_2$, Ac_2O–ether (1:2); (b) 10% Pd–C, H_2, MeOH; (c) MsCl, pyridine; (d) NH_2OH–HCl, pyridine; (e) 10% Pd–C, H_2, concd. HCl, MeOH; (f) 4-*t*-$BuPhCH_2NCS$, DMF.

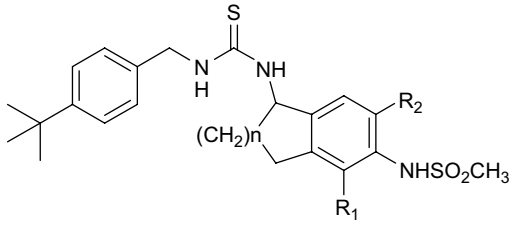


Scheme 3. Reagents and conditions: (a) $Cu(NO_3)_2$, Ac_2O–ether (1:2); (b) 10% Pd–C, H_2, MeOH; (c) MsCl, pyridine; (d) NH_2OH–HCl, pyridine; (e) 10% Pd–C, H_2, concd. HCl, MeOH; (f) 4-*t*-BuPhCH_2NCS, DMF.

$^{45}Ca^{2+}$ uptake assay using rat TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells, as previously described [13]. The results are summarized in Table 1, together with the potencies of the previously reported antagonists **1** and **3** [15].

The conformational restriction of the parent thiourea **1** by bridging between the benzylic position in the B-region and the phenyl in the A-region with a two (or three) carbon linker provided the two bicycles, indan (**18**) and tetrahydronaphthalene (**19**), respectively. These compounds revealed that the constraint led to the moderate loss of receptor activity compared to the parent antagonist. The binding affinities of **18** and **19** were reduced by 10-fold and 25-fold compared to **1**; their potencies as antagonists decreased by a similar extent, 14-fold and 50-fold, respectively. The reduction in activity for the tetrahydronaphthalene analogue (**19**) was greater than that for the indan analogue (**18**).

Table 1



	n	R_1	R_2	K_i (nM) binding affinity[c]	EC_{50} (nM) agonism[c]	K_i (nM) antagonism[c]
1				63 (±10)	NE	53.9 (±8.7)
18	1	H	H	660 (±190)	NE	740 (±320)
19	2	H	H	1590 (±270)	NE	2640 (±720)
3				50 (±17)	32.4 (±5.3)[a]	3.4 (±1.0)[b]
32	1	OCH_3	H	1820 (±260)	NE	1690 (±750)
33	2	OCH_3	H	1750 (±200)	NE	4700 (±2600)
46	1	H	OCH_3	3370 (±580)	NE	25000 (±6300)
47	2	H	OCH_3	6900 (±2200)	WE[a]	NE

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: **3**, 17%; **47**, 14%.

[b] Only fractional antagonism: **3**, 88%.

[c] Values represent mean ± SEM from three or more experiments.

Although conformational restriction might shift the conformations of the bicylic compounds away from the "bioactive conformation", the steric environment at the benzylic position appears to be dominant for favorable interaction with the receptor. We previously reported that incorporation of a methyl group, particularly with an (*R*)-configuration, at the benzylic position of the A-region in compound **1** enhanced specific binding to the receptor [17]. For example, the (*R*)-α-methyl analogue of compound **1** showed high potency with a $K_i = 41$ nM for receptor binding and $K_{i(ant)} = 4.5$ nM for antagonism of capsaicin stimulated calcium uptake. However, more bulky substituents such as ethyl, isopropyl, phenyl and benzyl groups resulted in modest to dramatic decreases in binding affinities and antagonistic potencies, with the antagonist potencies diminishing as the size of the substituents increased, Et > *i*-Pr > Bn > Ph. Our current findings, that the sterically more demanding tetrahydronaphthalene analogue (**19**) caused greater reduction in receptor activity compared to indan (**18**), are consistent with these observations.

To further investigate the conformationally constrained bicycles, we synthesized the conformationally constrained analogues of the parent compound **3** with a 3-methoxy group in the A-region. Depending upon the direction of cyclization and the length of the linker, there are four possible bicyclic analogues, as shown in Fig. 1.

The indan analogues representing the 4-isomer (**32**) and the 6-isomer (**46**) were prepared. As with the analogues described above, their activities were reduced compared to that of the

parent compound. The binding affinities of the 4-isomer (**32**) and the 6-isomer (**46**) decreased by 36-fold and 67-fold, respectively, and their potencies as antagonists were markedly reduced. The two tetrahydronaphthalene analogues, the 5-isomer (**33**) and the 7-isomer (**47**), similarly showed a reduction in receptor activities. The binding affinities of the 5-isomer (**33**) and the 7-isomer (**47**) decreased by 35-fold and 137-fold, respectively, and their potencies as antagonists were again markedly diminished, or, for compound **47**, undetectable over the range of concentrations that were tested. As observed with compounds **18** and **19**, the receptor activities of the tetrahydronaphthalenes were reduced more than those of the indans and this may be attributed to the more sterically demanding tetrahydronaphthalene ring. Interestingly, the 4- or 5-isomers were found to be more potent than their corresponding 6- or 7-isomers in the bicyclic analogues, and this positional effect of substitution is currently under investigation.

It should be noted that, at high (10–30 μM) ligand concentrations, interpretation of inhibitory responses on TRPV1 is somewhat less straightforward because of the possibility of superimposed specific and non-specific mechanisms of antagonism. However, for this series of ligands no change in the nature of the responses from antagonist to agonist was observed, as evidenced by the agonism assays. In any case, we believe that the ligand binding assays, because they circumvent issues of calcium processing, desensitization, and rates of ligand penetration into the cells, provide the most robust measure of the structure–activity relations for receptor–ligand recognition.

4. Conclusion

We have investigated conformationally constrained analogues of the potent TRPV1 antagonists (**1**, **3**), designed with the intention of stabilizing the bioactive conformation, and have analyzed their structure–activity relationships. The six bicyclic analogues, representing indan and tetrahydronaphthalene templates, were designed and synthesized employing regioselective nitration and reductive amination of benzylic ketones. Unfortunately, the synthesized bicyclic analogues showed moderate or weak receptor activities compared to parent compounds. The SAR analysis, together with our previous findings, suggests that the loss in activity may be attributed to steric restrictions at the benzylic position of the bicyclic analogues resulting in unfavorable interactions with the receptor.

5. Experimental

5.1. 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. 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.

5.1.1. 5,6,7,8-Tetrahydro-2-naphthylamine (*5*)

1,2,3,4-Tetrahydronaphthalene (3.965 g, 30 mmol) was added to a stirred suspension of copper(II) nitrate hydrate (5.62 g, 30 mmol) and acetic anhydride (10 mL) in diethyl ether (20 mL). The reaction mixture was stirred at room temperature until consumption of the starting material was completed, as monitored by TLC (ca. 3 h). The mixture was filtered through celite by washing with additional ether and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:10) as eluant to give a mixture of mono-nitrated products as a yellow oil (2.55 g, 48%). The compound (2.55 g, 57.6 mmol) in MeOH (50 mL) was treated with 10% palladium on carbon (0.3 g) and hydrogenated under a balloon of hydrogen for 1 h. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:5) as eluant to provide 2-naphthylamine (**5**) as a white solid (1.144 g, 54%) along with its isomer, 1-naphthylamine (**5′**) as a red oil (0.657 g, 31%).

*5,6,7,8-Tetrahydro-2-naphthylamine (**5**).* $R_f = 0.250$ (EtOAc:hexanes = 1:5), mp = 29–33 °C. ^{1}H NMR ($CDCl_3$) δ 6.85 (d, 1H, $J = 7.8$ Hz, H-4), 6.47 (dd, 1H, $J = 7.8$, 2.4 Hz, H-3), 6.41 (d, 1H, $J = 2.4$ Hz, H-1), 3.47 (br s, 2H, NH_2), 2.62–2.68 (m, 4H, H-5 and H-8), 1.70–80 (m, 4H, H-6 and H-7).

*5,6,7,8-Tetrahydro-1-naphthylamine (**5′**).* $R_f = 0.375$ (EtOAc:hexanes = 1:5). ^{1}H NMR ($CDCl_3$) δ 6.93 (t, 1H, $J = 7.6$ Hz, H-3), 6.50–6.54 (m, 2H, H-2 and H-4), 3.55 (br s, 2H, NH_2), 2.73 (t, 2H, $J = 6.1$ Hz, H-5), 2.45 (t, 2H, $J = 6.1$ Hz, H-8), 1.71–1.92 (m, 4H, H-6 and H-7).

5.1.2. tert-Butyl N-(indan-5-yl)carbamate (*6*)

A solution of 5-aminoindan (**4**) (3 g, 30 mmol) in CH_2Cl_2 (50 mL) was treated with triethylamine (8.36 mL, 60 mmol) and di-*tert*-butyl dicarbonate (7.857 g, 36 mmol), and stirred at room temperature for 3 h. The reaction mixture was diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:10) as eluant to provide **6** as a white solid (7.0 g, 100%): mp = 70–72 °C. ^{1}H NMR ($CDCl_3$) δ 7.33 (br s, 1H, H-4), 7.11 (d, 1H, $J = 8.0$ Hz, H-7), 6.99 (dd, 1H, $J = 1.7$, 8.0 Hz, H-6), 6.41 (br s, 1H, NHCO), 2.81–2.89 (m, 4H, H-1 and H-3), 2.00–2.10 (m, 2H, H-2), 1.51 (s, 9H, $C(CH_3)_3$).

5.1.3. tert-Butyl N-(5,6,7,8-tetrahydro-2-naphthyl) carbamate (*7*)

This compound was obtained from **5** by following the procedure described above to afford a white solid with a quantitative yield: mp = 85–87 °C. ^{1}H NMR ($CDCl_3$) δ 7.14 (br s, 1H, H-1), 6.96–7.00 (m, 2H, H-3 and H-4), 6.33 (br s, 1H, NH),

2.66–2.73 (m, 4H, H-5 and H-8), 1.72–1.78 (m, 4H, H-6 and H-7), 1.50 (s, 9H, $C(CH_3)_3$).

*5.1.4. tert-Butyl N-(1-indanone-5-yl)carbamate (**8**)*

To a suspension of pyridinium chlorochromate (8.622 g, 40 mmol) and 4 Å molecular sieve (10 g) in CH_2Cl_2 (200 mL) was added **6** (4.666 g, 20 mmol) portionwise. The reaction mixture was refluxed for 24 h, cooled and diluted with ether. After stirring for 1 h, the mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:3) as eluant to provide **8** as a white solid (3.46 g, 70%): mp = 175–176 °C. ^{1}H NMR ($CDCl_3$) δ 7.76 (br s, 1H, H-4), 7.67 (d, 1H, J = 8.3 Hz, H-7), 7.13 (dd, 1H, J = 1.7, 8.3 Hz, H-6), 6.81 (br s, 1H, NHCO), 3.09 (t, 2H, J = 5.6 Hz, H-3), 2.65–2.67 (m, 2H, H-2), 1.54 (s, 9H, $C(CH_3)_3$).

*5.1.5. tert-Butyl N-(5-oxo-5,6,7,8-tetrahydro-2-naphthyl) carbamate (**9**)*

This compound was obtained from **7** by following the procedure described above to afford a yellow solid in 65% yield: mp = 133–135 °C. ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1H, J = 8.6 Hz, H-4), 7.49 (br s, 1H, H-1), 7.10 (dd, 1H, J = 2.2 Hz, H-3), 6.76 (br s, 1H, NHCO), 2.93 (t, 2H, J = 6.1 Hz, H-8), 2.61 (t, 2H, J = 6.1 Hz, H-6), 2.10–2.14 (m, 2H, H-7), 1.53 (s, 9H, $C(CH_3)_3$); IR (KBr) 3311 (s), 1729 (m), 1662 (s), 1604 (s), 1585 (m), 1529 (m) cm^{-1}.

*5.1.6. 5-Amino-1-indanone (**10**)*

A cooled solution of **8** (3.46 g, 14 mmol) in CH_2Cl_2 (30 mL) at 0 °C was treated with trifluoroacetic acid (6 mL) and stirred at room temperature for 1 h. The mixture was removed *in vacuo*, neutralized with saturated $NaHCO_3$ solution, and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:1) as eluant to give **10** as a yellow solid (1.852 g, 90%): mp = 188–190 °C. ^{1}H NMR ($CDCl_3$) δ 7.58 (d, 1H, J = 9.0 Hz, H-7), 6.58–6.61 (m, 2H, H-4 and H-6), 4.21 (br s, 2H, NH_2), 3.00 (t, 2H, J = 5.8 Hz, H-3), 2.60–2.64 (m, 2H, H-2).

*5.1.7. 6-Amino-1-tetralone (**11**)*

This compound was obtained from **9** by following the procedure described above to afford a yellow solid in 92% yield: mp = 130–132 °C. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, 1H, J = 8.6 Hz, H-8), 6.54 (dd, 1H, J = 8.6, 2.2 Hz, H-7), 6.42 (d, 1H, J = 2.2 Hz, H-5), 4.10 (br s, 2H, NH_2), 2.83 (t, 2H, J = 6.1 Hz, H-4), 2.57 (t, 2H, J = 6.1 Hz, H-2), 2.06–2.10 (m, 2H, H-3).

*5.1.8. 5-(Methylsulfonylamino)-1-indanone (**12**)*

A cooled solution of **10** (0.59 g, 4 mmol) in pyridine (4 mL) at 0 °C was treated with methanesulfonyl chloride (0.62 mL, 8 mmol) and stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (2:1) as eluant to give **12** as a brown solid (0.8 g, 88%): mp = 222–223 °C. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 1H, J = 8.3 Hz, H-7), 7.36 (d, 1H, J = 1.7 Hz, H-4), 7.09 (dd, 1H, J = 1.7, 8.3 Hz, H-6), 6.87 (s, 1H, $NHSO_2$), 3.12–3.15 (m, 5H, H-3 and SO_2CH_3), 2.69–2.73 (m, 2H, H-2).

*5.1.9. 6-(Methylsulfonylamino)-1-tetralone (**13**)*

This compound was obtained from **11** by following the procedure described above to afford a white solid in 93% yield: mp = 170–172 °C. ^{1}H NMR ($CDCl_3$) δ 8.04 (d, 1H, J = 8.5 Hz, H-8), 7.09 (d, 1H, J = 2.2 Hz, H-5), 7.04 (dd, 1H, J = 8.5, 2.2 Hz, H-7), 6.69 (s, 1H, $NHSO_2$), 3.11 (s, 3H, SO_2CH_3), 2.96 (t, 2H, J = 6.1 Hz, H-4), 2.64 (t, 2H, J = 6.1 Hz, H-2), 2.12–2.16 (m, 2H, H-3).

*5.1.10. 5-(Methylsulfonylamino)-1-indanone oxime (**14**)*

A mixture of **12** (0.675 g, 3 mmol) and hydroxylamine hydrochloride (0.417 g, 6 mmol) in pyridine (3 mL) was heated at 70 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:1) as eluant to give **14** as a white solid (0.684 g, 95%): mp = 186–188 °C. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, 1H, J = 8.3 Hz, H-7), 7.23 (d, 1H, J = 1.7 Hz, H-4), 7.03 (dd, 1H, J = 1.7, 8.3 Hz, H-6), 6.42 (s, 1H, $NHSO_2$), 3.02–3.08 (m, 5H, H-3 and SO_2CH_3), 2.94–2.99 (m, 2H, H-2).

*5.1.11. 6-(Methylsulfonylamino)-1-tetralone oxime (**15**)*

This compound was obtained from **13** by following the procedure described above to afford a white solid in 93% yield: mp = 191–192 °C. ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 1H, J = 8.5 Hz, H-8), 7.02 (d, 1H, J = 2.2 Hz, H-5), 6.99 (dd, 1H, J = 8.5, 2.2 Hz, H-7), 6.33 (s, 1H, $NHSO_2$), 3.04 (s, 3H, SO_2CH_3), 2.79 (t, 2H, J = 6.1 Hz, H-4), 2.75 (t, 2H, J = 6.1 Hz, H-2), 1.82–1.89 (m, 2H, H-3).

*5.1.12. 5-(Methylsulfonylamino)-1-indanylamine (**16**)*

A suspension of **14** (0.48 g, 2 mmol) and 10% palladium on carbon (100 mg) in MeOH (20 mL) was treated with concentrated hydrochloric acid (10 drops) and hydrogenated under a balloon of hydrogen for 6 h. The reaction mixture was neutralized with solid $NaHCO_3$, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2:MeOH (5:1) as eluant to give **16** as a brown solid (0.443 g, 98%): mp = 146–148 °C. ^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H, J = 8.3 Hz, H-7), 7.10 (br s, 1H, H-4), 7.04 (dd, 1H, J = 1.7, 8.3 Hz, H-6), 4.36 (t, 1H, J = 7.1 Hz, H-1), 3.32 (br s, 2H, NH_2), 2.98 (s,

3H, SO_2CH_3), 2.90–2.94 (m, 1H, H-3a), 2.73–2.83 (m, 1H, H-3b), 2.45–2.56 (m, 1H, H-2a), 1.66–1.78 (m, 1H, H-2b).

5.1.13. 6-(Methylsulfonylamino)-1,2,3,4-tetrahydro-1-naphthylamine (**17**)

This compound was obtained from **13** by following the procedure described above to afford a white solid in 98% yield: mp = 197–199 °C. ^{1}H NMR (DMSO-d_6) δ 8.25 (br s, 3H, NH_2 and $NHSO_2$), 7.46 (d, 1H, J = 8.5 Hz, H-8), 7.05 (dd, 1H, J = 8.5, 2.2 Hz, H-7), 6.97 (d, 1H, J = 2.2 Hz, H-5), 4.28 (t, 1H, J = 5.6 Hz, H-1), 2.97 (s, 3H, SO_2CH_3), 2.65–2.75 (m, 2H, H-4), 1.62–2.10 (m, 4H, H-2 and H-3).

5.1.14. N-(4-tert-Butylbenzyl)-N′-[5-(methylsulfonylamino)-1-indanyl]thiourea (**18**)

A mixture of **16** (0.226 g, 1 mmol) and 4-*tert*-butylbenzyl isothiocyanate (0.205 g, 1 mmol) in DMF (4 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with EtOAc:hexanes (1:1) as eluant to give **18** as a white solid (0.363 g, 84%): mp = 170–172 °C. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2H, J = 8.3 Hz, *t*-BuPh), 7.25 (d, 2H, J = 8.3 Hz, *t*-BuPh), 7.11–7.15 (m, 2H, H-7 and H-4), 6.95 (dd, 1H, J = 1.7, 8.3 Hz, H-6), 6.48 (s, 1H, $NHSO_2$), 6.22 (br s, 1H, NH), 5.77 (br s, 2H, NH and H-1), 4.55 (br s, 2H, CH_2NHCS), 2.99 (s, 3H, SO_2CH_3), 2.75–2.94 (m, 2H, H-3), 2.62–2.66 (m, 1H, H-2a), 1.82–1.84 (m, 1H, H-2b), 1.32 (s, 9H, $C(CH_3)_3$); IR (KBr) 3433 (s), 2961 (w), 1628 (s), 1545 (s), 1489 (w), 1322 (m), 1148 (s) cm^{-1}; MS *m/z* 432 (MH^+). Anal. Calcd for $C_{22}H_{29}N_3O_2S_2$: C, 61.22; H, 6.77; N, 9.74; S, 14.86. Found: C, 61.43; H, 6.80; N, 9.70; S, 14.81.

5.1.15. N-(4-tert-Butylbenzyl)-N′-[6-(methylsulfonylamino)-1,2,3,4-tetrahydro-1-naphthyl]thiourea (**19**)

This compound was obtained from **17** by following the procedure described above to afford a white solid in 86% yield: mp = 130–131 °C. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2H, J = 8.3 Hz, *t*-BuPh), 7.21–7.25 (m, 3H, *t*-BuPh, H-8), 6.90–6.95 (m, 2H, H-5 and H-7), 6.38 (s, 1H, $NHSO_2$), 6.18 (br s, 1H, NH), 5.71 (br s, 1H, NH), 5.50 (br s, 1H, H-1), 4.51 (br s, 2H, CH_2NHCS), 3.00 (s, 3H, SO_2CH_3), 2.70–2.74 (m, 2H, H-4), 2.02–2.08 (m, 1H, H-2a), 1.71–1.92 (m, 3H, H-3 and H-2b), 1.31 (s, 9H, $C(CH_3)_3$); IR (KBr) 3430 (s), 2961 (w), 1616 (m), 1548 (s), 1505 (m), 1394 (s), 1311 (s), 1150 (m) cm^{-1}; MS *m/z* 446 (MH^+). Anal. Calcd for $C_{23}H_{31}N_3O_2S_2$: C, 61.99; H, 7.01; N, 9.43; S, 14.39. Found: C, 61.78; H, 7.03; N, 9.39; S, 14.34.

5.1.16. 4-Methoxy-5-nitro-1-indanone (**22**)

4-Methoxy-1-indanone (**20**) (1.62 g, 10 mmol) was added to a stirred suspension of copper(II) nitrate hydrate (1.88 g, 10 mmol) and acetic anhydride (10 mL) in diethyl ether (20 mL). The reaction mixture was stirred at room temperature until consumption of the starting material was completed, as monitored by TLC (ca. 3 h). The mixture was filtered through celite by washing with additional ether and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:2) as eluant to give the 5-nitro isomer (**22**) as a yellow solid (0.973 g, 47%) along with its 7-nitro isomer (**22′**) as a yellow solid (0.787 g, 38%).

*5-Nitro (**22**).* R_f = 0.29 (EtOAc:hexanes = 1:2), mp = 85–86 °C. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 1H, J = 8.3 Hz, H-6), 7.56 (d, 1H, J = 8.3 Hz, H-7), 4.05 (s, 3H, OCH_3), 3.27 (t, 2H, J = 6.1 Hz, H-3), 2.78–2.82 (m, 2H, H-2).

*7-Nitro (**22′**).* R_f = 0.23 (EtOAc:hexanes = 1:2), mp = 140–143 °C. ^{1}H NMR ($CDCl_3$) δ 7.82 (d, 1H, J = 8.5 Hz, H-6), 7.01 (d, 1H, J = 8.5 Hz, H-5), 4.00 (s, 3H, OCH_3), 3.04 (t, 2H, J = 6.1 Hz, H-3), 2.77–2.82 (m, 2H, H-2).

5.1.17. 5-Methoxy-6-nitro-1-tetralone (**23**)

This compound, along with its 8-nitro isomer (**23′**), was obtained from 5-methoxy-1-tetralone (**21**) by following the procedure described above.

*6-Nitro (**23**).* Yield 46%, R_f = 0.50 (EtOAc:hexanes = 1:2), yellow solid, mp = 75–76 °C. ^{1}H NMR ($CDCl_3$) δ 7.91 (d, 1H, J = 8.5 Hz, H-8), 7.67 (d, 1H, J = 8.5 Hz, H-7), 3.94 (s, 3H, OCH_3), 3.05 (t, 2H, J = 6.1 Hz, H-4), 2.71 (t, 2H, J = 6.1 Hz, H-2), 2.13–2.21 (m, 2H, H-3).

*8-Nitro (**23′**).* Yield 42%, R_f = 0.39 (EtOAc:hexanes = 1:2), yellow solid, mp = 104–106 °C. ^{1}H NMR ($CDCl_3$) δ 7.41 (d, 1H, J = 8.8 Hz, H-7), 6.96 (d, 1H, J = 8.8 Hz, H-6), 3.87 (s, 3H, OCH_3), 2.90 (t, 2H, J = 6.1 Hz, H-4), 2.71 (t, 2H, J = 6.1 Hz, H-2), 2.11–2.19 (m, 2H, H-3).

5.1.18. 5-Amino-4-methoxy-1-indanone (**24**)

A suspension of **22** (1.035 g, 5 mmol) and 10% palladium on carbon (150 mg) in MeOH (50 mL) was hydrogenated under a balloon of hydrogen for 1 h. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using EtOAc:hexanes (1:1) as eluant to give **24** as a yellow solid (0.78 g, 88%): mp = 147–148 °C. ^{1}H NMR ($CDCl_3$) δ 7.39 (d, 1H, J = 8.1 Hz, H-7), 6.71 (d, 1H, J = 8.1 Hz, H-6), 4.39 (br s, 2H, NH_2), 3.89 (s, 3H, OCH_3), 3.11 (t, 2H, J = 6.1 Hz, H-3), 2.62–2.66 (m, 2H, H-2).

5.1.19. 6-Amino-5-methoxy-1-tetralone (**25**)

This compound was obtained from **23** by following the procedure described above to afford a white solid in 93% yield: mp = 144 °C. ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 1H, J = 8.5 Hz, H-8), 6.64 (d, 1H, J = 8.5 Hz, H-7), 4.28 (br s, 2H, NH_2), 3.75 (s, 3H, OCH_3), 2.93 (t, 2H, J = 6.8 Hz, H-4), 2.56 (t, 2H, J = 6.8 Hz, H-2), 2.08 (m, 2H, H-3).

5.1.20. 4-Methoxy-5-(methylsulfonylamino)-1-indanone (**26**)

This compound was obtained from **24** by following the procedure described for the synthesis of **12** to afford a yellow solid in 95% yield: mp = 185–186 °C. ^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1H, J = 8.3 Hz, H-6), 7.54 (d, 1H, J = 8.3 Hz,

H-7), 7.31 (s, 1H, $NHSO_2$), 4.01 (s, 3H, OCH_3), 3.24 (t, 2H, $J = 6.1$ Hz, H-3), 3.10 (s, 3H, SO_2CH_3), 2.69–2.74 (m, 2H, H-2).

*5.1.21. 5-Methoxy-6-(methylsulfonylamino)-1-tetralone (**27**)*

This compound was obtained from **25** by following the procedure described for the synthesis of **12** to afford a white solid in 93% yield: mp = 178–179 °C. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, 1H, $J = 8.8$ Hz, H-7), 7.51 (d, 1H, $J = 8.8$ Hz, H-8), 7.25 (s, 1H, $NHSO_2$), 3.80 (s, 3H, OCH_3), 3.11 (s, 3H, SO_2CH_3), 2.97 (t, 2H, $J = 6.1$ Hz, H-4), 2.64 (t, 2H, $J = 6.1$ Hz, H-2), 2.08–2.16 (m, 2H, H-3).

*5.1.22. 4-Methoxy-5-(methylsulfonylamino)-1-indanone oxime (**28**)*

This compound was obtained from **26** by following the procedure described for the synthesis of **14** to afford a white solid in 90% yield: mp = 207–209 °C. ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1H, $J = 8.3$ Hz, H-6), 7.40 (d, 1H, $J = 8.3$ Hz, H-7), 7.28 (s, 1H, $NHSO_2$), 7.01 (s, 1H, OH), 3.94 (s, 3H, OCH_3), 3.18 (t, 2H, $J = 6.1$ Hz, H-3), 2.95–3.05 (m, 5H, SO_2CH_3 and H-2).

*5.1.23. 5-Methoxy-6-(methylsulfonylamino)-1-tetralone oxime (**29**)*

This compound was obtained from **27** by following the procedure described for the synthesis of **14** to afford a white solid in 99% yield: mp = 187–189 °C. ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1H, $J = 8.8$ Hz, H-7), 7.42 (d, 1H, $J = 8.8$ Hz, H-8), 7.37 (br s, 1H, OH), 6.99 (s, 1H, $NHSO_2$), 3.76 (s, 3H, OCH_3), 3.06 (s, 3H, SO_2CH_3), 2.76–2.80 (m, 4H, H-4 and H-2), 1.83–1.87 (m, 2H, H-3).

*5.1.24. 4-Methoxy-5-(methylsulfonylamino)-1-indanamine (**30**)*

This compound was obtained from **28** by following the procedure described for the synthesis of **16** to afford a white solid in 98% yield: mp = 217–218 °C. ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 1H, $J = 8.0$ Hz, H-6), 7.04 (d, 1H, $J = 8.0$ Hz, H-7), 4.33 (t, 1H, $J = 7.3$ Hz, H-1), 3.90 (s, 3H, OCH_3), 3.06–3.15 (m, 1H, H-3a), 2.98 (s, 3H, SO_2CH_3), 2.82–2.93 (m, 1H, H-3b), 2.46–2.57 (m, 1H, H-2a), 1.66–1.78 (m, 1H, H-2b).

*5.1.25. 5-Methoxy-6-(methylsulfonylamino)-1,2,3,4-tetrahydro-1-naphthylamine (**31**)*

This compound was obtained from **29** by following the procedure described for the synthesis of **16** to afford a white solid in 98% yield: mp = 129–132 °C. ^{1}H NMR ($CDCl_3$) δ 7.39 (d, 1H, $J = 8.5$ Hz, H-7), 7.26 (d, 1H, $J = 8.5$ Hz, H-8), 4.88 (br s, 2H, NH_2), 4.08–4.15 (m, 1H, H-1), 3.75 (s, 3H, OCH_3), 3.04 (s, 3H, SO_2CH_3), 2.81–2.88 (m, 2H, H-4), 1.92–2.04 (m, 2H, H-2), 1.79–1.84 (m, 2H, H-3).

*5.1.26. N-(4-tert-Butylbenzyl)-N′-[4-methoxy-5-(methylsulfonylamino)-1-indanyl] thiourea (**32**)*

This compound was obtained from **30** by following the procedure described for the synthesis of **18** to afford a white solid in 90% yield: mp = 92–96 °C. ^{1}H NMR ($CDCl_3$) δ 7.39 (d, 2H, $J = 8.3$ Hz, *t*-BuPh), 7.34 (d, 1H, $J = 8.3$ Hz, H-6), 7.25 (d, 2H, $J = 8.3$ Hz, *t*-BuPh), 6.82–6.85 (m, 1H, H-7 and $NHSO_2$), 6.17 (br s, 1H, NH), 5.72 (br s, 2H, NH and H-1), 4.55 (br s, 2H, CH_2NHCS), 3.88 (s, 3H, OCH_3), 2.85–3.15 (m, 5H, SO_2CH_3 and H-3), 2.68–2.73 (m, 1H, H-2a), 1.81–1.89 (m, 1H, H-2b), 1.32 (s, 9H, $C(CH_3)_3$); IR (KBr) 3433 (s), 2961 (w), 1635 (s), 1540 (s), 1483 (w), 1312 (m), 1155 (s) cm^{-1}; MS *m/z* 462 (MH^+). Anal. Calcd for $C_{23}H_{31}N_3O_3S_2$: C, 59.84; H, 6.77; N, 9.10; S, 13.89. Found: C, 60.00; H, 6.81; N, 9.05; S, 13.86.

*5.1.27. N-(4-tert-Butylbenzyl)-N′-[5-methoxy-6-(methylsulfonylamino)-1,2,3,4-tetrahydro-1-naphthyl]thiourea (**33**)*

This compound was obtained from **31** by following the procedure described for the synthesis of **18** to afford a white solid in 65% yield: mp = 169–172 °C. ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 2H, $J = 8.0$ Hz, *t*-BuPh), 7.34 (d, 1H, $J = 8.4$ Hz, H-7), 7.25 (d, 2H, $J = 8.0$ Hz, *t*-BuPh), 7.05 (d, 1H, $J = 8.4$ Hz, H-8), 6.86 (s, 1H, $NHSO_2$), 6.15 (br s, 1H, NH), 5.71 (br s, 1H, NH), 5.52 (br s, 1H, H-1), 4.53 (s, 2H, CH_2NHCS), 3.76 (s, 3H, OCH_3), 3.06 (s, 3H, SO_2CH_3), 2.70–2.74 (m, 2H, H-4), 2.07–2.11 (m, 1H, H-2a), 1.80–1.84 (m, 2H, H-3), 1.68–1.72 (m, 1H, H-2b), 1.34 (s, 9H, $C(CH_3)_3$); IR (KBr) 3434 (s), 2952 (w), 1635 (m), 1555 (s), 1487 (m), 1315 (s), 1152 (s) cm^{-1}; MS *m/z* 476 (MH^+). Anal. Calcd for $C_{24}H_{33}N_3O_3S_2$: C, 60.60; H, 6.99; N, 8.83; S, 13.48. Found: C, 60.82; H, 7.02; N, 8.79; S, 13.42.

*5.1.28. 6-Methoxy-5-nitro-1-indanone (**36**)*

This compound, along with its 7-nitro isomer (**36′**), was obtained from 6-methoxy-1-indanone (**34**) by following the procedure described for the synthesis of **22**.

*5-Nitro (**36**).* $R_f = 0.29$ (EtOAc:hexanes = 1:2), 22% yield, yellow solid, mp = 172–174 °C. ^{1}H NMR ($CDCl_3$) δ 7.81 (s, 1H, H-4), 7.40 (s, 1H, H-7), 3.98 (s, 3H, OCH_3), 3.16 (t, 2H, $J = 6.1$ Hz, H-3), 2.77–2.81 (m, 2H, H-2).

*7-Nitro (**36′**).* $R_f = 0.13$ (EtOAc:hexanes = 1:2), 64% yield, yellow solid, mp = 154–157 °C. ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 1H, $J = 8.5$ Hz, H-4), 7.33 (d, 1H, $J = 8.5$ Hz, H-5), 3.94 (s, 3H, OCH_3), 3.13 (t, 2H, $J = 6.1$ Hz, H-3), 2.76–2.80 (m, 2H, H-2).

*5.1.29. 7-Methoxy-6-nitro-1-tetralone (**37**)*

This compound, along with its 8-nitro isomer (**37′**), was obtained from 7-methoxy-1-tetralone (**35**) by following the procedure described for the synthesis of **22**.

*6-Nitro (**37**).* $R_f = 0.47$ (EtOAc:hexanes = 1:2), 20% yield, yellow solid, mp = 115–116 °C. ^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1H, H-5), 7.67 (s, 1H, H-8), 3.98 (s, 3H, OCH_3), 2.96 (t, 2H, $J = 6.1$ Hz, H-4), 2.71 (t, 2H, $J = 6.1$ Hz, H-2), 2.17–2.21 (m, 2H, H-3).

*8-Nitro (**37′**).* $R_f = 0.22$ (EtOAc:hexanes = 1:2), 76% yield, yellow solid, mp = 120–121 °C. ^{1}H NMR ($CDCl_3$) δ 7.35 (d, 1H, $J = 8.5$ Hz, H-5), 7.20 (d, 1H, $J = 8.5$ Hz, H-6), 3.89 (s, 3H, OCH_3), 2.95 (t, 2H, $J = 6.1$ Hz, H-4), 2.67 (t, 2H, $J = 6.1$ Hz, H-2), 2.09–2.17 (m, 2H, H-3).

*5.1.30. 5-Amino-6-methoxy-1-indanone (**38**)*

This compound was obtained from **36** by following the procedure described for the synthesis of **24** to afford a white solid in 86% yield: mp = 187–188 °C. ^{1}H NMR ($CDCl_3$) δ 7.10 (s, 1H, H-7), 6.65 (s, 1H, H-4), 4.44 (br s, 2H, NH_2), 3.88 (s, 3H, OCH_3), 2.96 (t, 2H, J = 6.1 Hz, H-3), 2.61–2.64 (m, 2H, H-2).

*5.1.31. 6-Amino-7-methoxy-1-tetralone (**39**)*

This compound was obtained from **37** by following the procedure described for the synthesis of **24** to afford a brown solid in 90% yield: mp = 152–155 °C. ^{1}H NMR ($CDCl_3$) δ 7.44 (s, 1H, H-8), 6.45 (s, 1H, H-5), 4.30 (br s, 2H, NH_2), 3.88 (s, 3H, OCH_3), 2.79 (t, 2H, J = 6.1 Hz, H-4), 2.56 (t, 2H, J = 6.1 Hz, H-2), 2.02–2.10 (m, 2H, H-3).

*5.1.32. 6-Methoxy-5-(methylsulfonylamino)-1-indanone (**40**)*

This compound was obtained from **38** by following the procedure described for the synthesis of **12** to afford a yellow solid in 93% yield: mp = 190–192 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (s, 1H, H-4), 7.25 (s, 1H, $NHSO_2$), 7.23 (s, 1H, H-7), 3.93 (s, 3H, OCH_3), 3.07–3.10 (m, 5H, H-3 and SO_2CH_3), 2.68–2.72 (m, 2H, H-2).

*5.1.33. 7-Methoxy-6-(methylsulfonylamino)-1-tetralone (**41**)*

This compound was obtained from **39** by following the procedure described for the synthesis of **12** to afford a white solid in 94% yield: mp = 165–167 °C. ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H, H-5), 7.40 (s, 1H, H-8), 7.14 (s, 1H, $NHSO_2$), 3.92 (s, 3H, OCH_3), 3.06 (s, 3H, SO_2CH_3), 2.91 (t, 2H, J = 6.1 Hz, H-4), 2.63 (t, 2H, J = 6.1 Hz, H-2), 2.04–2.16 (m, 2H, H-3).

*5.1.34. 6-Methoxy-5-(methylsulfonylamino)-1-indanone oxime (**42**)*

This compound was obtained from **40** by following the procedure described for the synthesis of **14** to afford a white solid in 90% yield: mp = 236–238 °C. ^{1}H NMR ($CDCl_3$) δ 7.49 (s, 1H, H-4), 7.15 (s, 1H, H-7), 7.06 (s, 1H, $NHSO_2$), 6.95 (s, 1H, OH), 3.90 (s, 3H, OCH_3), 2.95–3.05 (m, 7H, H-2, H-3 and SO_2CH_3).

*5.1.35. 7-Methoxy-6-(methylsulfonylamino)-1-tetralone oxime (**43**)*

This compound was obtained from **41** by following the procedure described for the synthesis of **14** to afford a white solid in 98% yield: mp = 186–188 °C. ^{1}H NMR ($CDCl_3$) δ 7.42 (s, 1H, H-5), 7.31 (s, 1H, H-8), 6.95 (s, 1H, $NHSO_2$), 3.86 (s, 3H, OCH_3), 3.00 (s, 3H, SO_2CH_3), 2.78 (t, 2H, J = 6.1 Hz, H-4), 2.71 (t, 2H, J = 6.1 Hz, H-2), 1.81–1.90 (m, 2H, H-3).

*5.1.36. 6-Methoxy-5-(methylsulfonylamino)-1-indanamine (**44**)*

This compound was obtained from **42** by following the procedure described for the synthesis of **16** to afford a white solid in 91% yield: mp = 217–220 °C. ^{1}H NMR ($CDCl_3$) δ 7.37 (s, 1H, H-4), 6.93 (s, 1H, H-7), 4.30–4.35 (m, 1H, H-1), 3.88 (s, 3H, OCH_3), 2.93 (s, 3H, SO_2CH_3), 2.70–2.95 (m, 2H, H-3), 2.48–2.56 (m, 1H, H-2a), 1.62–1.74 (m, 1H, H-2b).

*5.1.37. 7-Methoxy-6-(methylsulfonylamino)-1,2,3,4-tetahydro-1-naphthylamine (**45**)*

This compound was obtained from **43** by following the procedure described for the synthesis of **16** to afford a white solid in 93% yield: mp = 136–138 °C. ^{1}H NMR ($CDCl_3$) δ 7.21 (s, 1H, H-5), 7.02 (s, 1H, H-8), 3.92–3.94 (m, 1H, H-1), 3.87 (s, 3H, OCH_3), 2.94 (s, 3H, SO_2CH_3), 2.69–2.76 (m, 2H, H-4), 1.64–2.06 (m, 4H, H-2 and H-3).

*5.1.38. N-(4-tert-Butylbenzyl)-N′-[6-methoxy-5-(methylsulfonylamino)-1-indanyl]thiourea (**46**)*

This compound was obtained from **44** by following the procedure described for the synthesis of **18** to afford a white solid in 84% yield: mp = 101–104 °C. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2H, J = 8.3 Hz, *t*-BuPh), 7.37 (s, 1H, H-4), 7.25 (d, 1H, J = 8.3 Hz, *t*-BuPh), 6.91 (s, 1H, H-7), 6.75 (s, 1H, $NHSO_2$), 6.11 (br s, 1H, NH), 5.80 (br s, 2H, NH and H-1), 4.58 (br s, 2H, CH_2NHCS), 3.83 (s, 3H, OCH_3), 2.95 (s, 3H, SO_2CH_3), 2.70–2.95 (m, 2H, H-3), 2.60–2.63 (m, 1H, H-2a), 1.80–1.84 (m, 1H, H-2b), 1.30 (s, 9H, $C(CH_3)_3$); IR (KBr) 3430 (s), 2960 (w), 1617 (m), 1540 (s), 1494 (s), 1336 (s), 1147(s) cm^{-1}; MS *m/z* 462 (MH^+). Anal. Calcd for $C_{23}H_{31}N_3O_3S_2$: C, 59.84; H, 6.77; N, 9.10; S, 13.89. Found: C, 60.02; H, 6.80; N, 9.06; S, 13.85.

*5.1.39. N-(4-tert-Butylbenzyl)-N′-[7-methoxy-6-(methylsulfonylamino)-1,2,3,4-tetrahydro-1-naphthyl]thiourea (**47**)*

This compound was obtained from **45** by following the procedure described for the synthesis of **18** to afford a white solid in 82% yield: mp = 100–102 °C. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2H, J = 8.3 Hz, *t*-BuPh), 7.25 (d, 2H, J = 8.3 Hz, *t*-BuPh), 7.22 (s, 1H, H-5), 6.90 (s, 1H, H-8), 6.73 (s, 1H, $NHSO_2$), 6.18 (br s, 1H, NH), 5.79 (br s, 1H, NH), 5.53 (br s, 1H, H-1), 4.53 (s, 2H, CH_2NHCS), 3.82 (s, 3H, OCH_3), 2.96 (s, 3H, SO_2CH_3), 2.66–2.70 (m, 2H, H-4), 2.02–2.04 (m, 1H, H-2a), 1.74–1.92 (m, 3H, H-3 and H-2b), 1.32 (s, 9H, $C(CH_3)_3$); IR (KBr) 3433 (s), 2959 (w), 1635 (m), 1540 (s), 1457 (s), 1338 (m), 1153 (s) cm^{-1}; MS *m/z* 476 (MH^+). Anal. Calcd for $C_{24}H_{33}N_3O_3S_2$: C, 60.60; H, 6.99; N, 8.83; S, 13.48. Found: C, 60.84; H, 7.03; N, 8.80; S, 13.41.

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