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Ureas derived from camphor and fenchone reveal enantiomeric preference of human soluble epoxide hydrolase

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Abstract

The soluble epoxide hydrolase (sEH) is a potential target to treat cardiovascular, renal and neuronal diseases. A series of sEH inhibitors containing naturally occurring lipophilic groups (originating from camphor and fenchone) were developed. Inhibitory potency ranging from 0.7 nM to 6.47 μM was obtained. It was discovered that ureas derived from L-camphor were more active against sEH (2.3-fold average) than the corresponding analogues derived from D-camphor indicating enantiomeric preference of sEH. Ureas derived from fenchone possess lower activity against sEH (ca. 80-fold on average) than their camphor-derived analogs due to the specific structure of the lipophilic fragment and show less enantiomeric preference (1.75-fold on average). Moreover, fenchone-derived ureas show no consistency in enantiomeric preference. *Endo*/*exo*-form of compound **L-3a** derived from L-camphor is 4-fold more potent than the corresponding analogue prepared from D-camphor (IC_{50} = 0.7 nM vs. 2.8 nM) making it the most promising sEH inhibitor among the tested series.

Keywords

soluble epoxide hydrolase; inhibitor; epoxyeicosatrienoic acids; urea; camphor; fenchone

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Introduction

The human soluble epoxide hydrolase (sEH) is involved in the metabolism of epoxides derived from arachidonic acid and other natural unsaturated fatty acids via oxidation by CYPs.[1] Endogenous epoxides of arachidonic acid have multiple, largely beneficial physiological activities.[2] sEH converts these epoxides into the corresponding vicinal diols through the addition of a water molecule, leading to various pathological states such as pain and inflammation.[2] Thereby inhibition of sEH could be beneficial in treatment of numerous cardiovascular, neuronal, and renal diseases.[3,4]

Although thousands of various sEH inhibitors (sEHI) have been designed and tested over the last decades,[5–7] they are characterized by low water-solubility and high melting points, which makes them hard to formulate. Without proper formulation these properties diminish drug bioavailability and *in vivo* efficacy. Decent solubility appears critical to their success as a potential medicines for the treatment of neurological diseases.[8] Hundreds of sEHI featuring a common structure of R–NH–C(O)–NH–R' (where R is lipophilic fragment such as adamantantyl or aromatic and R' is alkyl, aryl or heterocyclic groups) have been synthesized and evaluated *in vitro* and in several *in vivo* models.[9–12] However, poor metabolic stability of the adamantane containing ureas limits their usefulness and application in many cases.

Recently, ureas containing natural occurring cyclic and bicyclic groups such as furan-2-yl, camphanyl and norcamphanyl were investigated as sEHI.[13] The replacement of adamantane or 4-trifluoromethoxyphenyl with bicyclic lipophilic groups led to increase of water solubility preserving the same level of inhibitory activity. We discovered that 1-(2-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea derived from L-camphor is 14-fold more potent than the corresponding analogue derived from D-camphor (IC_{50} = 3.7 nM vs. 50.6 nM).[13] Enantioselectivity of sEHI has previously been shown on the series of disubstituted ureas containing α-alkyl-α-phenylmethyl fragment.[14] Herein, we studied a wide series of disubstituted ureas and thioureas derived from L, D, and racemic camphor as well as ureas and thioureas derived from L and D-fenchone in an attempt to confirm and explain the enantiomeric preference of sEH.

Experiment

General methods

All of chemicals used in the current study were purchased from commercial vendors and employed as received without further purification, unless otherwise noted. All solvents were purified and dried using standard methods prior to use. Nuclear magnetic resonance (^{1}H, ^{13}C and ^{19}F) spectra were recorded on a Bruker Avance 600 (USA) spectrometer with chemical shifts reported as ppm at 600, 150 and 564 MHz, respectively in DMSO-d_6 or $CDCl_3$ with TMS as the internal standard. The mass spectra were obtained with an Agilent GC 7820/MSD 5975 instrument. Elemental analysis was performed using a Perkin Elmer 2400 Series II analyzer (USA). The melting points were measured on an OptiMelt MPA100 melting point apparatus (Stanford Research Systems, USA).

General Procedure for the synthesis of ureas 3a-d and thioureas 3e and 3f.

To 1.05 mmol of corresponding aromatic isocyanate or isothiocyanate in 5 mL of Et_2O were added 1.05 mmol of *L*-, *D*- or *rac*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine and 1.05 mmol of Et_3N at 0 °C. Reaction mass was stirred at room temperature overnight. After removing solvent and adding 1N HCl, the resulting white precipitates were collected by suction filtration.

L-1-(3-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (L-3a).

Prepared from *L*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-fluorophenyl isocyanate (140 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 202 mg (66%). Mp 230–231 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.75 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.91 (s, 3H, CH_3) 1.13–1.20 (m, 1H, CH_2), 1.27–1.34 (m, 1H, CH_2), 1.49–1.55 (m, 1H, CH_2), 1.60–1.65 (m, 2H, CH_2), 1.68–1.76 (m, 1H, CH_2), 2.21–2.27 (m, 1H, C<u>H</u>-C$(CH_3)_2$), 3.93–3.99 (m, 1H, C<u>H</u>NH), 6.29 (d, 1H, CHN<u>H</u>, J = 8.8 Hz), 6.68 (td, 1H, 4-H arom., J_{HH} = 8.4, 2.6 Hz), 6.96–6.98 (m, 1H, 6-H arom.), 7.20–7.26 (m, 1H, 5-H arom.), 7.43–7.48 (m, 1H, 2-H arom.), 8.52 (s, 1H, N<u>H</u>-Ph-F). ^{19}F NMR (DMSO-d_6), δ, ppm: −112.42 (1F). MS (EI) m/z: 290 (12.0%, $[M]^+$), 207 (12.0%, $[C_4H_6$-NH-C(O)-NH-Ph-F$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 153 (5.0%, [NH-C(O)-NH-Ph-F$]^+$), 137 (10.0%, $[C_{10}H_{17}]^+$), 110 (100.0%, [NH-Ph-F$]^+$), 95 (25.0%, [Ph-F$]^+$), 83 (8.0%, $[C_6H_{11}]^+$), 43 (12.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}FN_2O$) C 70.30, H 7.95, N 9.68. Calcd., %: C 70.32, H 7.98, N 9.65. M=290.38.

D-1-(3-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (D-3a).

Prepared from *D*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-fluorophenyl isocyanate (140 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 173 mg (57%). Mp 235–236 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.75 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.91 (s, 3H, CH_3) 1.13–1.20 (m, 1H, CH_2), 1.27–1.34 (m, 1H, CH_2), 1.49–1.55 (m, 1H, CH_2), 1.60–1.65 (m, 2H, CH_2), 1.68–1.76 (m, 1H, CH_2), 2.21–2.27 (m, 1H, C<u>H</u>-C$(CH_3)_2$), 3.93–3.99 (m, 1H, C<u>H</u>NH), 6.29 (d, 1H, CHN<u>H</u>, J = 8.8 Hz), 6.68 (td, 1H, 4-H arom., J_{HH} = 8.4, 2.6 Hz), 6.96–6.98 (m, 1H, 6-H arom.), 7.20–7.26 (m, 1H, 5-H arom.), 7.43–7.48 (m, 1H, 2-H arom.), 8.52 (s, 1H, N<u>H</u>-Ph-F). ^{19}F NMR (DMSO-d_6), δ, ppm: −112.42 (1F). MS (EI) m/z: 290 (12.0%, $[M]^+$), 207 (12.0%, $[C_4H_6$-NH-C(O)-NH-Ph-F$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 153 (5.0%, [NH-C(O)-NH-Ph-F$]^+$), 137 (10.0%, $[C_{10}H_{17}]^+$), 110 (100.0%, [NH-Ph-F$]^+$), 95 (25.0%, [Ph-F$]^+$), 83 (8.0%, $[C_6H_{11}]^+$), 43 (12.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}FN_2O$) C 70.29, H 7.96, N 9.69. Calcd., %: C 70.32, H 7.98, N 9.65. M=290.38.

rac-1-(3-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (rac-3a).

Prepared from *rac*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-fluorophenyl isocyanate (140 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 228 mg (74%). Mp 222–223 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.75 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.91 (s, 3H, CH_3) 1.13–1.20 (m, 1H, CH_2), 1.27–1.34 (m, 1H, CH_2), 1.49–1.55 (m, 1H, CH_2), 1.60–1.65 (m, 2H, CH_2), 1.68–1.76 (m, 1H, CH_2), 2.21–2.27 (m, 1H, C<u>H</u>-C$(CH_3)_2$), 3.93–3.99 (m, 1H, C<u>H</u>NH), 6.29 (d, 1H, CHN<u>H</u>, J = 8.8 Hz), 6.68 (td,

1H, 4-H arom., J_{HH} = 8.4, 2.6 Hz), 6.96–6.98 (m, 1H, 6-H arom.), 7.20–7.26 (m, 1H, 5-H arom.), 7.43–7.48 (m, 1H, 2-H arom.), 8.52 (s, 1H, NH-Ph-F). ^{19}F NMR (DMSO-d_6), δ, ppm: −112.42 (1F). MS (EI) m/z: 290 (12.0%, $[M]^+$), 207 (12.0%, $[C_4H_6$-NH-C(O)-NH-Ph-F$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 153 (5.0%, [NH-C(O)-NH-Ph-F$]^+$), 137 (10.0%, $[C_{10}H_{17}]^+$), 110 (100.0%, [NH-Ph-F$]^+$), 95 (25.0%, [Ph-F$]^+$), 83 (8.0%, $[C_6H_{11}]^+$), 43 (12.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}FN_2O$) C 70.29, H 7.96, N 9.69. Calcd., %: C 70.32, H 7.98, N 9.65. M=290.38.

L-1-(4-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (L-3b).

Prepared from *L*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 4-fluorophenyl isocyanate (140 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 249 mg (81%). Mp 211–212 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.75 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.91 (s, 3H, CH_3) 1.14–1.20 (m, 1H, CH_2), 1.27–1.33 (m, 1H, CH_2), 1.49–1.55 (m, 1H, CH_2), 1.61–1.65 (m, 2H, CH_2), 1.68–1.75 (m, 1H, CH_2), 2.21–2.27 (m, 1H, CH-C(CH_3)$_2$), 3.96 (dddd, 1H, CHNH, J_{HH} = 11.0, 8.8, 4.6, 2.2 Hz), 6.18 (d, 1H, CHNH, J = 8.7 Hz), 7.03–7.06 (m, 2H, 3,5-H arom., J_{HH} = 8.4, 2.6 Hz), 7.35–7.39 (m, 2H, 2,6-H arom.), 8.31 (s, 1H, NH-Ph-F). ^{13}C NMR (DMSO-d_6), δ, ppm: 12.14 (s, 1C, CH_3), 20.57 (s, 1C, CH_3), 20.71 (s, 1C, CH_3), 27.15 (s, 1C, 5-C bicyclohept.), 36.22 (s, 1C, 6-C bicyclohept.), 39.35 (s, 1C, 3-C bicyclohept.), 44.73 (s, 1C, 4-C bicyclohept.), 46.90 (s, 1C, 7-C bicyclohept.), 48.63 (s, 1C, 1-C bicyclohept.), 56.68 (s, 1C, 2-C bicyclohept.), 115.55 (d, 2C, 3,5-C Ph, J = 21.9 Hz), 119.32 (d, 2C, 2,6-C Ph, J = 7.6 Hz), 137.42 (d, 1C, 1-C Ph, J = 2.3 Hz), 155.30 (s, 1C, C=O), 157.22 (d, 1C, C-F, J = 237.0 Hz). ^{19}F NMR (DMSO-d_6), δ, ppm: −122.84 (1F). MS (EI) m/z: 290 (12.0%, $[M]^+$), 207 (12.0%, $[C_4H_6$-NH-C(O)-NH-Ph-F$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 153 (5.0%, [NH-C(O)-NH-Ph-F$]^+$), 137 (10.0%, $[C_{10}H_{17}]^+$), 110 (100.0%, [NH-Ph-F$]^+$), 95 (25.0%, [Ph-F$]^+$), 83 (8.0%, $[C_6H_{11}]^+$), 43 (12.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}FN_2O$) C 70.30, H 7.97, N 9.62. Calcd., %: C 70.32, H 7.98, N 9.65. M=290.38.

D-1-(4-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (D-3b).

Prepared from *D*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 4-fluorophenyl isocyanate (140 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 260 mg (85%). Mp 213–214 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.75 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.91 (s, 3H, CH_3) 1.14–1.20 (m, 1H, CH_2), 1.27–1.33 (m, 1H, CH_2), 1.49–1.55 (m, 1H, CH_2), 1.61–1.65 (m, 2H, CH_2), 1.68–1.75 (m, 1H, CH_2), 2.21–2.27 (m, 1H, CH-C(CH_3)$_2$), 3.96 (dddd, 1H, CHNH, J_{HH} = 11.0, 8.8, 4.6, 2.2 Hz), 6.18 (d, 1H, CHNH, J = 8.7 Hz), 7.03–7.06 (m, 2H, 3,5-H arom., J_{HH} = 8.4, 2.6 Hz), 7.35–7.39 (m, 2H, 2,6-H arom.), 8.31 (s, 1H, NH-Ph-F). ^{19}F NMR (DMSO-d_6), δ, ppm: −122.84 (1F). MS (EI) m/z: 290 (12.0%, $[M]^+$), 207 (12.0%, $[C_4H_6$-NH-C(O)-NH-Ph-F$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 153 (5.0%, [NH-C(O)-NH-Ph-F$]^+$), 137 (10.0%, $[C_{10}H_{17}]^+$), 110 (100.0%, [NH-Ph-F$]^+$), 95 (25.0%, [Ph-F$]^+$), 83 (8.0%, $[C_6H_{11}]^+$), 43 (12.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}FN_2O$) C 70.34, H 8.02, N 9.64. Calcd., %: C 70.32, H 7.98, N 9.65. M=290.38.

rac-1-(4-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (rac-3b).

Prepared from *rac*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 4-fluorophenyl isocyanate (140 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 235 mg (77%). Mp 200–201 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.75 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.91 (s, 3H, CH_3) 1.14–1.20 (m, 1H, CH_2), 1.27–1.33 (m, 1H, CH_2), 1.49–1.55 (m, 1H, CH_2), 1.61–1.65 (m, 2H, CH_2), 1.68–1.75 (m, 1H, CH_2), 2.21–2.27 (m, 1H, C<u>H</u>-C$(CH_3)_2$), 3.96 (dddd, 1H, C<u>H</u>NH, J_{HH} = 11.0, 8.8, 4.6, 2.2 Hz), 6.18 (d, 1H, CHN<u>H</u>, J = 8.7 Hz), 7.03–7.06 (m, 2H, 3,5-H arom., J_{HH} = 8.4, 2.6 Hz), 7.35–7.39 (m, 2H, 2,6-H arom.), 8.31 (s, 1H, N<u>H</u>-Ph-F). ^{19}F NMR (DMSO-d_6), δ, ppm: −122.84 (1F). MS (EI) m/z: 290 (12.0%, $[M]^+$), 207 (12.0%, $[C_4H_6$-NH-C(O)-NH-Ph-F$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 153 (5.0%, [NH-C(O)-NH-Ph-F$]^+$), 137 (10.0%, $[C_{10}H_{17}]^+$), 110 (100.0%, [NH-Ph-F$]^+$), 95 (25.0%, [Ph-F$]^+$), 83 (8.0%, $[C_6H_{11}]^+$), 43 (12.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}FN_2O$) C 70.34, H 8.02, N 9.64. Calcd., %: C 70.32, H 7.98, N 9.65. M=290.38.

L-1-(2-chlorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (L-3c).

Prepared from *L*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 2-chlorophenyl isocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 249 mg (77%). Mp 213–214 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.77 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.92 (s, 3H, CH_3) 1.15–1.21 (m, 1H, CH_2), 1.27–1.33 (m, 1H, CH_2), 1.51–1.56 (m, 1H, CH_2), 1.64 (t, 1H, CH_2, J = 4.4 Hz), 1.69 (t, 1H, CH_2, J = 4.4 Hz), 1.72–1.77 (m, 1H, CH_2) 2.25 (dddd, 1H, C<u>H</u>-C$(CH_3)_2$, J_{HH} = 13.1, 11.0, 4.7, 3.2 Hz), 3.99 (dddd, 1H, C<u>H</u>NH, J_{HH} = 11.0, 8.8, 4.6, 2.2 Hz), 6.93 (tt, 1H, 4-H Ph, J_{HH} = 7.6, 1.5 Hz), 7.06 (d, 1H, CHN<u>H</u>, J = 8.6 Hz), 7.22 (ddd, 2H, 5-H arom. J_{HH} = 8.7, 7.3, 1.6 Hz), 7.38 (dd, 1H, 3-H arom., J = 8.0, 1.5 Hz), 8.03 (s, 1H, N<u>H</u>-Ph-Cl), 8.19 (dd, 1H, 6-H arom., J = 8.4, 1.6 Hz). ^{13}C NMR (DMSO-d_6), δ, ppm: 12.10 (s, 1C, CH_3), 20.67 (s, 1C, CH_3), 20.74 (s, 1C, CH_3), 27.14 (s, 1C, 5-C bicyclohept.), 36.28 (s, 1C, 6-C bicyclohept.), 38.99 (s, 1C, 3-C bicyclohept.), 44.80 (s, 1C, 4-C bicyclohept.), 46.87 (s, 1C, 7-C bicyclohept.), 48.79 (s, 1C, 1-C bicyclohept.), 56.98 (s, 1C, 2-C bicyclohept.), 121.32 (s, 1C, 5-C Ph), 121.49 (s, 1C, 2-C Ph), 122.70 (s, 1C, 6-C Ph), 127.79 (s, 1C, 3-C Ph), 129.48 (s, 1C, 4-C Ph), 137.35 (s, 1C, 1-C Ph), 155.01 (s, 1C, C=O). MS (EI) m/z: 306 (5.0%, $[M]^+$), 279 (50.0%, $[C_8H_{14}$-NH-C(O)-NH-Ph-Cl$]^+$), 252 (20.0%, $[C_6H_{11}$-NH-C(O)-NH-Ph-Cl$]^+$), 209 (100.0%, $[C_3H_4$-NH-C(O)-NH-Ph-Cl$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 150 (7.0%, $[C_8H_{11}$-NH-CO$]^+$), 126 (25.0%, [NH-Ph-Cl$]^+$), 97 (15.0%, $[C_7H_{13}]^+$), 82 (3.0%, $[C_6H_{10}]^+$), 73 (16.0%, $[C_5H_{13}]^+$), 55 (5.0%, $[C_4H_7]^+$), 43 (15.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}ClN_2O$) C 66.56, H 7.59, N 9.10. Calcd., %: C 66.55, H 7.56, N 9.13. M=306.83.

D-1-(2-chlorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (D-3c).

Prepared from *D*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 2-chlorophenyl isocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 177 mg (55%). Mp 214–215 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.77 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.92 (s, 3H, CH_3) 1.15–1.21 (m, 1H, CH_2), 1.27–1.33 (m, 1H, CH_2), 1.51–1.56 (m, 1H, CH_2), 1.64 (t, 1H, CH_2, J = 4.4 Hz), 1.69 (t, 1H, CH_2, J = 4.4 Hz), 1.72–1.77 (m, 1H, CH_2) 2.25 (dddd, 1H, C<u>H</u>-C$(CH_3)_2$, J_{HH} = 13.1, 11.0, 4.7, 3.2 Hz), 3.99

(dddd, 1H, CHNH, J_{HH} = 11.0, 8.8, 4.6, 2.2 Hz), 6.93 (tt, 1H, 4-H Ph, J_{HH} = 7.6, 1.5 Hz), 7.06 (d, 1H, CHNH, J = 8.6 Hz), 7.22 (ddd, 2H, 5-H arom. J_{HH} = 8.7, 7.3, 1.6 Hz), 7.38 (dd, 1H, 3-H arom., J = 8.0, 1.5 Hz), 8.03 (s, 1H, NH-Ph-Cl), 8.19 (dd, 1H, 6-H arom., J = 8.4, 1.6 Hz). ^{13}C NMR (DMSO-d_6), δ, ppm: 12.12 (s, 1C, CH_3), 20.70 (s, 1C, CH_3), 20.76 (s, 1C, CH_3), 27.16 (s, 1C, 5-C bicyclohept.), 36.31 (s, 1C, 6-C bicyclohept.), 39.01 (s, 1C, 3-C bicyclohept.), 44.76 (s, 1C, 4-C bicyclohept.), 46.88 (s, 1C, 7-C bicyclohept.), 48.80 (s, 1C, 1-C bicyclohept.), 56.98 (s, 1C, 2-C bicyclohept.), 121.26 (s, 1C, 5-C Ph), 121.40 (s, 1C, 2-C Ph), 122.60 (s, 1C, 6-C Ph), 127.77 (s, 1C, 3-C Ph), 129.47 (s, 1C, 4-C Ph), 137.44 (s, 1C, 1-C Ph), 154.95 (s, 1C, C=O). MS (EI) m/z: 306 (5.0%, $[M]^+$), 279 (50.0%, $[C_8H_{14}$-NH-C(O)-NH-Ph-Cl$]^+$), 252 (20.0%, $[C_6H_{11}$-NH-C(O)-NH-Ph-Cl$]^+$), 209 (100.0%, $[C_3H_4$-NH-C(O)-NH-Ph-Cl$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 150 (7.0%, $[C_8H_{11}$-NH-CO$]^+$), 126 (25.0%, [NH-Ph-Cl$]^+$), 97 (15.0%, $[C_7H_{13}]^+$), 82 (3.0%, $[C_6H_{10}]^+$), 73 (16.0%, $[C_5H_{13}]^+$), 55 (5.0%, $[C_4H_7]^+$), 43 (15.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}ClN_2O$) C 66.52, H 7.60, N 9.12. Calcd., %: C 66.55, H 7.56, N 9.13. M=306.83.

rac-1-(2-chlorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (rac-3c).

Prepared from *rac*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 2-chlorophenyl isocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 234 mg (77%). Mp 209–210 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.77 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.92 (s, 3H, CH_3) 1.15–1.21 (m, 1H, CH_2), 1.27–1.33 (m, 1H, CH_2), 1.51–1.56 (m, 1H, CH_2), 1.64 (t, 1H, CH_2, J = 4.4 Hz), 1.69 (t, 1H, CH_2, J = 4.4 Hz), 1.72–1.77 (m, 1H, CH_2) 2.25 (dddd, 1H, CH-C$(CH_3)_2$, J_{HH} = 13.1, 11.0, 4.7, 3.2 Hz), 3.99 (dddd, 1H, CHNH, J_{HH} = 11.0, 8.8, 4.6, 2.2 Hz), 6.93 (tt, 1H, 4-H Ph, J_{HH} = 7.6, 1.5 Hz), 7.06 (d, 1H, CHNH, J = 8.6 Hz), 7.22 (ddd, 2H, 5-H arom. J_{HH} = 8.7, 7.3, 1.6 Hz), 7.38 (dd, 1H, 3-H arom., J = 8.0, 1.5 Hz), 8.03 (s, 1H, NH-Ph-Cl), 8.19 (dd, 1H, 6-H arom., J = 8.4, 1.6 Hz). MS (EI) m/z: 306 (5.0%, $[M]^+$), 279 (50.0%, $[C_8H_{14}$-NH-C(O)-NH-Ph-Cl$]^+$), 252 (20.0%, $[C_6H_{11}$-NH-C(O)-NH-Ph-Cl$]^+$), 209 (100.0%, $[C_3H_4$-NH-C(O)-NH-Ph-Cl$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 150 (7.0%, $[C_8H_{11}$-NH-CO$]^+$), 126 (25.0%, [NH-Ph-Cl$]^+$), 97 (15.0%, $[C_7H_{13}]^+$), 82 (3.0%, $[C_6H_{10}]^+$), 73 (16.0%, $[C_5H_{13}]^+$), 55 (5.0%, $[C_4H_7]^+$), 43 (15.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}ClN_2O$) C 66.52, H 7.60, N 9.12. Calcd., %: C 66.55, H 7.56, N 9.13. M=306.83.

L-1-(3-chlorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (L-3d).

Prepared from *L*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-chlorophenyl isocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 224 mg (69%). Mp 181–182 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.75 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.91 (s, 3H, CH_3) 1.15–1.20 (m, 1H, CH_2), 1.27–1.33 (m, 1H, CH_2), 1.51–1.55 (m, 1H, CH_2), 1.61–1.64 (m, 2H, CH_2), 1.71–1.76 (m, 1H, CH_2) 2.21–2.27 (m, 1H, CH-C(CH_3)), 3.96 (dddd, 1H, CHNH, J_{HH} = 11.0, 8.6, 4.6, 2.2 Hz), 6.33 (d, 1H, CHNH, J_{HH} = 8.7 Hz), 6.92 (dtd, 1H, 4-H arom., J_{HH} = 7.9, 2.0, 0.9 Hz), 7.03 (ddd, 1H, 6-H arom, J = 7.5, 2.1, 1.4 Hz), 7.12 (ddd, 1H, 5-H arom. J_{HH} = 8.2, 2.1, 1.0 Hz), 7.23 (dd, 1H, 2-H arom., J = 8.1, 1.5 Hz), 8.55 (s, 1H, NH-Ph-Cl). ^{13}C NMR (DMSO-d_6), δ, ppm: 12.13 (s, 1C, CH_3), 20.58 (s, 1C, CH_3), 20.71 (s, 1C, CH_3), 27.14 (s, 1C, 5-C bicyclohept.), 36.22 (s, 1C, 6-C bicyclohept.), 39.24 (s, 1C, 3-C bicyclohept.), 44.73 (s, 1C, 4-C bicyclohept.), 46.91 (s, 1C, 7-C bicyclohept.), 48.68 (s, 1C, 1-C bicyclohept.), 56.73

(s, 1C, 2-C bicyclohept.), 116.16 (s, 1C, 6-C Ph), 117.19 (s, 1C, 2-C Ph), 120.89 (s, 1C, 4-C Ph), 130.69 (s, 1C, 5-C Ph), 133.65 (s, 1C, 3-C Ph), 142.59 (s, 1C, 1-C Ph), 154.99 (s, 1C, C=O). MS (EI) m/z: 306 (5.0%, $[M]^+$), 279 (50.0%, $[C_8H_{14}$-NH-C(O)-NH-Ph-Cl$]^+$), 252 (20.0%, $[C_6H_{11}$-NH-C(O)-NH-Ph-Cl$]^+$), 209 (100.0%, $[C_3H_4$-NH-C(O)-NH-Ph-Cl$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 150 (7.0%, $[C_8H_{11}$-NH-CO$]^+$), 126 (25.0%, [NH-Ph-Cl$]^+$), 97 (15.0%, $[C_7H_{13}]^+$), 82 (3.0%, $[C_6H_{10}]^+$), 73 (16.0%, $[C_5H_{13}]^+$), 55 (5.0%, $[C_4H_7]^+$), 43 (15.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}ClN_2O$) C 66.51, H 7.56, N 9.09. Calcd., %: C 66.55, H 7.56, N 9.13. M=306.83.

D-1-(3-chlorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (D-3d).

Prepared from *D*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-chlorophenyl isocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 239 mg (74%). Mp 183–184 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.75 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.91 (s, 3H, CH_3) 1.15–1.20 (m, 1H, CH_2), 1.27–1.33 (m, 1H, CH_2), 1.51–1.55 (m, 1H, CH_2), 1.61–1.64 (m, 2H, CH_2), 1.71–1.76 (m, 1H, CH_2) 2.21–2.27 (m, 1H, C<u>H</u>-C(CH_3)), 3.96 (dddd, 1H, C<u>H</u>NH, J_{HH} = 11.0, 8.6, 4.6, 2.2 Hz), 6.33 (d, 1H, CHN<u>H</u>, J_{HH} = 8.7 Hz), 6.92 (dtd, 1H, 4-H arom., J_{HH} = 7.9, 2.0, 0.9 Hz), 7.03 (ddd, 1H, 6-H arom, J = 7.5, 2.1, 1.4 Hz), 7.12 (ddd, 1H, 5-H arom. J_{HH} = 8.2, 2.1, 1.0 Hz), 7.23 (dd, 1H, 2-H arom., J = 8.1, 1.5 Hz), 8.55 (s, 1H, N<u>H</u>-Ph-Cl). ^{13}C NMR (DMSO-d_6), δ, ppm: 12.06 (s, 1C, CH_3), 20.51 (s, 1C, CH_3), 20.64 (s, 1C, CH_3), 27.08 (s, 1C, 5-C bicyclohept.), 36.15 (s, 1C, 6-C bicyclohept.), 39.17 (s, 1C, 3-C bicyclohept.), 44.66 (s, 1C, 4-C bicyclohept.), 46.84 (s, 1C, 7-C bicyclohept.), 48.61 (s, 1C, 1-C bicyclohept.), 56.66 (s, 1C, 2-C bicyclohept.), 116.09 (s, 1C, 6-C Ph), 117.12 (s, 1C, 2-C Ph), 120.81 (s, 1C, 4-C Ph), 130.61 (s, 1C, 5-C Ph), 133.58 (s, 1C, 3-C Ph), 142.52 (s, 1C, 1-C Ph), 154.91 (s, 1C, C=O). MS (EI) m/z: 306 (5.0%, $[M]^+$), 279 (50.0%, $[C_8H_{14}$-NH-C(O)-NH-Ph-Cl$]^+$), 252 (20.0%, $[C_6H_{11}$-NH-C(O)-NH-Ph-Cl$]^+$), 209 (100.0%, $[C_3H_4$-NH-C(O)-NH-Ph-Cl$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 150 (7.0%, $[C_8H_{11}$-NH-CO$]^+$), 126 (25.0%, [NH-Ph-Cl$]^+$), 97 (15.0%, $[C_7H_{13}]^+$), 82 (3.0%, $[C_6H_{10}]^+$), 73 (16.0%, $[C_5H_{13}]^+$), 55 (5.0%, $[C_4H_7]^+$), 43 (15.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}ClN_2O$) C 66.59, H 7.59, N 9.15. Calcd., %: C 66.55, H 7.56, N 9.13. M=306.83.

rac-1-(3-chlorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (rac-3d).

Prepared from *rac*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-chlorophenyl isocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 254 mg (78%). Mp 185–186 °C. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.75 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.91 (s, 3H, CH_3) 1.15–1.20 (m, 1H, CH_2), 1.27–1.33 (m, 1H, CH_2), 1.51–1.55 (m, 1H, CH_2), 1.61–1.64 (m, 2H, CH_2), 1.71–1.76 (m, 1H, CH_2) 2.21–2.27 (m, 1H, C<u>H</u>-C(CH_3)), 3.96 (dddd, 1H, C<u>H</u>NH, J_{HH} = 11.0, 8.6, 4.6, 2.2 Hz), 6.33 (d, 1H, CHN<u>H</u>, J_{HH} = 8.7 Hz), 6.92 (dtd, 1H, 4-H arom., J_{HH} = 7.9, 2.0, 0.9 Hz), 7.03 (ddd, 1H, 6-H arom, J = 7.5, 2.1, 1.4 Hz), 7.12 (ddd, 1H, 5-H arom. J_{HH} = 8.2, 2.1, 1.0 Hz), 7.23 (dd, 1H, 2-H arom., J = 8.1, 1.5 Hz), 8.55 (s, 1H, N<u>H</u>-Ph-Cl). MS (EI) m/z: 306 (5.0%, $[M]^+$), 279 (50.0%, $[C_8H_{14}$-NH-C(O)-NH-Ph-Cl$]^+$), 252 (20.0%, $[C_6H_{11}$-NH-C(O)-NH-Ph-Cl$]^+$), 209 (100.0%, $[C_3H_4$-NH-C(O)-NH-Ph-Cl$]^+$), 180 (5.0%, $[C_{10}H_{17}$-NH-CO$]^+$), 150 (7.0%, $[C_8H_{11}$-NH-CO$]^+$), 126 (25.0%, [NH-Ph-Cl$]^+$), 97 (15.0%, $[C_7H_{13}]^+$), 82 (3.0%, $[C_6H_{10}]^+$),

73 (16.0%, $[C_5H_{13}]^+$), 55 (5.0%, $[C_4H_7]^+$), 43 (15.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}ClN_2O$) C 66.58, H 7.60, N 9.11. Calcd., %: C 66.55, H 7.56, N 9.13. M=306.83.

L-1-(3-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (L-3e).

Prepared from *L*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-fluorophenyl isothiocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 247 mg (76%). Mp 117–118 °C (decomp.). ^1H NMR (DMSO-d_6), δ, ppm: 0.82 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.93 (s, 3H, CH_3) 1.20–1.26 (m, 1H, CH_2), 1.34–1.40 (m, 1H, CH_2), 1.53–1.59 (m, 1H, CH_2), 1.65–1.70 (m, 2H, CH_2), 1.72–1.76 (m, 1H, CH_2) 2.26–2.33 (m, 1H, C<u>H</u>-C(CH_3)), 3..07–3.12 (m, 1H, C<u>H</u>NH), 6.86 (td, 1H, 4-H arom., J_{HH} = 8.4, 2.9 Hz), 7.19–7.26 (m, 1H, 6-H arom.), 7.31 (td,, 1H, 5-H arom. J_{HH} = 8.2, 6.8 Hz), 7.82 (d, 1H, 2-H arom., J = 12.1 Hz), 7.97 (d, 1H, N<u>H</u>-CH, J = 8.4 Hz), 9.76 (s, 1H, N<u>H</u>-Ph-F). ^{19}F NMR (DMSO-d_6), δ, ppm: −112.58 (1F). MS (EI) m/z: 274 (15.0%, $[C_{10}H_{17}$-NH-C-NH-Ph-F$]^+$), 164 (7.0%, $[C_{10}H_{17}$-NH-C$]^+$), 154 (15.0%, $[SC$-NH-Ph-F$]^+$), 137 (15.0%, $[C_{10}H_{17}]^+$), 110 (95.0%, $[NH$-Ph-F$]^+$), 95 (100.0%, $[Ph$-F$]^+$), 83 (5.0%, $[C_6H_{11}]^+$), 73 (3.0%, $[C_5H_{13}]^+$), 57 (5.0%, $[C_4H_9]^+$), 43 (15.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}FN_2S$) C 66.65, H 7.56, N 9.13, S 10.44. Calcd., %: C 66.63, H 7.57, N 9.14, S 10.46. M=306.44.

D-1-(3-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (D-3e).

Prepared from *D*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-fluorophenyl isothiocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 142 mg (44%). Mp 113–114 °C (decomp.). ^1H NMR (DMSO-d_6), δ, ppm: 0.82 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.93 (s, 3H, CH_3) 1.20–1.26 (m, 1H, CH_2), 1.34–1.40 (m, 1H, CH_2), 1.53–1.59 (m, 1H, CH_2), 1.65–1.70 (m, 2H, CH_2), 1.72–1.76 (m, 1H, CH_2) 2.26–2.33 (m, 1H, C<u>H</u>-C(CH_3)), 3..07–3.12 (m, 1H, C<u>H</u>NH), 6.86 (td, 1H, 4-H arom., J_{HH} = 8.4, 2.9 Hz), 7.19–7.26 (m, 1H, 6-H arom.), 7.31 (td,, 1H, 5-H arom. J_{HH} = 8.2, 6.8 Hz), 7.82 (d, 1H, 2-H arom., J = 12.1 Hz), 7.97 (d, 1H, N<u>H</u>-CH, J = 8.4 Hz), 9.76 (s, 1H, N<u>H</u>-Ph-F). ^{13}C NMR (DMSO-d_6), δ, ppm: 12.28 (s, 1C, CH_3), 20.60 (s, 1C, CH_3), 20.67 (s, 1C, CH_3), 27.14 (s, 1C, 5-C bicyclohept.), 36.36 (s, 1C, 6-C bicyclohept.), 38.92 (s, 1C, 3-C bicyclohept.), 44.73 (s, 1C, 4-C bicyclohept.), 47.23 (s, 1C, 7-C bicyclohept.), 49.32 (s, 1C, 1-C bicyclohept.), 60.77 (s, 1C, 2-C bicyclohept.), 109.01 (d, 1C, 4-C Ph, J = 26.0 Hz), 110.27 (d, 1C, 2-C Ph, J = 21.2 Hz), 117.96 (s, 6-C Ph), 130.33 (d, 1C, 5-C Ph, J = 9.7 Hz), 142.21 (d, 1C, 1-C Ph, J = 11.0 Hz), 162.20 (d, 1C, 3-C Ph, J = 241.1 Hz), 180.52 (s, 1C, C=S). ^{19}F NMR (DMSO-d_6), δ, ppm: −112.58 (1F). MS (EI) m/z: 274 (15.0%, $[C_{10}H_{17}$-NH-C-NH-Ph-F$]^+$), 164 (7.0%, $[C_{10}H_{17}$-NH-C$]^+$), 154 (15.0%, $[SC$-NH-Ph-F$]^+$), 137 (15.0%, $[C_{10}H_{17}]^+$), 110 (95.0%, $[NH$-Ph-F$]^+$), 95 (100.0%, $[Ph$-F$]^+$), 83 (5.0%, $[C_6H_{11}]^+$), 73 (3.0%, $[C_5H_{13}]^+$), 57 (5.0%, $[C_4H_9]^+$), 43 (15.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}FN_2S$) C 66.66, H 7.55, N 9.13, S 10.43. Calcd., %: C 66.63, H 7.57, N 9.14, S 10.46. M=306.44.

rac-1-(3-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (rac-3e).

Prepared from *rac*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-fluorophenyl isothiocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 142 mg (44%). Mp 116–117 °C (decomp.). ^1H NMR (DMSO-d_6), δ, ppm:

0.82 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.93 (s, 3H, CH_3) 1.20–1.26 (m, 1H, CH_2), 1.34–1.40 (m, 1H, CH_2), 1.53–1.59 (m, 1H, CH_2), 1.65–1.70 (m, 2H, CH_2), 1.72–1.76 (m, 1H, CH_2) 2.26–2.33 (m, 1H, C<u>H</u>-C(CH_3)), 3..07–3.12 (m, 1H, C<u>H</u>NH), 6.86 (td, 1H, 4-H arom., J_{HH} = 8.4, 2.9 Hz), 7.19–7.26 (m, 1H, 6-H arom.), 7.31 (td,, 1H, 5-H arom. J_{HH} = 8.2, 6.8 Hz), 7.82 (d, 1H, 2-H arom., J = 12.1 Hz), 7.97 (d, 1H, N<u>H</u>-CH, J = 8.4 Hz), 9.76 (s, 1H, N<u>H</u>-Ph-F). ^{19}F NMR (DMSO-d_6), δ, ppm: −112.58 (1F). MS (EI) m/z: 274 (15.0%, $[C_{10}H_{17}$-NH-C-NH-Ph-F$]^+$), 164 (7.0%, $[C_{10}H_{17}$-NH-C$]^+$), 154 (15.0%, [SC-NH-Ph-F$]^+$), 137 (15.0%, $[C_{10}H_{17}]^+$), 110 (95.0%, [NH-Ph-F$]^+$), 95 (100.0%, [Ph-F$]^+$), 83 (5.0%, $[C_6H_{11}]^+$), 73 (3.0%, $[C_5H_{13}]^+$), 57 (5.0%, $[C_4H_9]^+$), 43 (15.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}FN_2S$) C 66.66, H 7.55, N 9.19, S 10.43. Calcd., %: C 66.63, H 7.57, N 9.14, S 10.46. M=306.44.

L-1-(4-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (L-3f).

Prepared from *L*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 4-fluorophenyl isothiocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 237 mg (73%). Mp 100–101 °C (decomp.). ^{1}H NMR (DMSO-d_6), δ, ppm: 0.82 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.92 (s, 3H, CH_3) 1.20–1.25 (m, 1H, CH_2), 1.33–1.39 (m, 1H, CH_2), 1.51–1.58 (m, 1H, CH_2), 1.64–1.68 (m, 2H, CH_2), 1.70–1.76 (m, 1H, CH_2) 2.25–2.31 (m, 1H, C<u>H</u>-C(CH_3)), 3.07–3.12 (m, 1H, C<u>H</u>NH), 7.11–7.15 (m, 2H, 3,5-H arom.), 7.50–7.56 (m, 2H, 2,6-H arom.), 7.75 (d, 1H, N<u>H</u>-CH, J = 8.4 Hz), 9.47 (s, 1H, N<u>H</u>-Ph-F). ^{13}C NMR (DMSO-d_6), δ, ppm: 12.29 (s, 1C, CH_3), 20.61 (s, 1C, CH_3), 20.64 (s, 1C, CH_3), 27.14 (s, 1C, 5-C bicyclohept.), 36.31 (s, 1C, 6-C bicyclohept.), 39.01 (s, 1C, 3-C bicyclohept.), 44.72 (s, 1C, 4-C bicyclohept.), 47.20 (s, 1C, 7-C bicyclohept.), 49.28 (s, 1C, 1-C bicyclohept.), 60.88 (s, 1C, 2-C bicyclohept.), 115.39 (d, 2C, 3,5-C Ph, J = 22.4 Hz), 125.48 (d, 2C, 2,6-C Ph, J = 8.2 Hz), 136.46 (d, 1C, 1-C Ph, J = 2.7 Hz), 159.13 (d, 1C, 4-C Ph, J = 240.9 Hz), 181.20 (s, 1C, C=S). ^{19}F NMR (DMSO-d_6), δ, ppm: −119.11 (1F). MS (EI) m/z: 274 (15.0%, $[C_{10}H_{17}$-NH-C-NH-Ph-F$]^+$), 164 (7.0%, $[C_{10}H_{17}$-NH-C$]^+$), 154 (15.0%, [SC-NH-Ph-F$]^+$), 137 (15.0%, $[C_{10}H_{17}]^+$), 110 (95.0%, [NH-Ph-F$]^+$), 95 (100.0%, [Ph-F$]^+$), 83 (5.0%, $[C_6H_{11}]^+$), 73 (3.0%, $[C_5H_{13}]^+$), 57 (5.0%, $[C_4H_9]^+$), 43 (15.0%, $[C_3H_7]^+$). Anal., %: ($C_{17}H_{23}FN_2S$) C 66.62, H 7.58, N 9.14, S 10.47. Calcd., %: C 66.63, H 7.57, N 9.14, S 10.46. M=306.44.

D-1-(4-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (D-3f).

Prepared from *D*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 4-fluorophenyl isothiocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid Yield 239 mg (74%). Mp 98–99 °C (decomp.). ^{1}H NMR (DMSO-d_6), δ, ppm: 0.82 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.92 (s, 3H, CH_3) 1.20–1.25 (m, 1H, CH_2), 1.33–1.39 (m, 1H, CH_2), 1.51–1.58 (m, 1H, CH_2), 1.64–1.68 (m, 2H, CH_2), 1.70–1.76 (m, 1H, CH_2) 2.25–2.31 (m, 1H, C<u>H</u>-C(CH_3)), 3.07–3.12 (m, 1H, C<u>H</u>NH), 7.11–7.15 (m, 2H, 3,5-H arom.), 7.50–7.56 (m, 2H, 2,6-H arom.), 7.75 (d, 1H, N<u>H</u>-CH, J = 8.4 Hz), 9.47 (s, 1H, N<u>H</u>-Ph-F). ^{13}C NMR (DMSO-d_6), δ, ppm: 12.29 (s, 1C, CH_3), 20.61 (s, 1C, CH_3), 20.63 (s, 1C, CH_3), 27.14 (s, 1C, 5-C bicyclohept.), 36.31 (s, 1C, 6-C bicyclohept.), 39.00 (s, 1C, 3-C bicyclohept.), 44.72 (s, 1C, 4-C bicyclohept.), 47.20 (s, 1C, 7-C bicyclohept.), 49.28 (s, 1C, 1-C bicyclohept.), 60.88 (s, 1C, 2-C bicyclohept.), 115.39 (d, 2C, 3,5-C Ph, J = 22.4 Hz), 125.48 (d, 2C, 2,6-C Ph, J = 8.2 Hz), 136.44 (d, 1C, 1-C Ph, J = 2.7 Hz), 159.14 (d,

1C, 4-C Ph, J = 240.9 Hz), 181.20 (s, 1C, C=S). ^{19}F NMR (DMSO-d_6), δ, ppm: −119.11 (1F). MS (EI) m/z: 274 (15.0%, [$C_{10}H_{17}$-NH-C-NH-Ph-F]$^+$), 164 (7.0%, [$C_{10}H_{17}$-NH-C]$^+$), 154 (15.0%, [SC-NH-Ph-F]$^+$), 137 (15.0%, [$C_{10}H_{17}$]$^+$), 110 (95.0%, [NH-Ph-F]$^+$), 95 (100.0%, [Ph-F]$^+$), 83 (5.0%, [C_6H_{11}]$^+$), 73 (3.0%, [C_5H_{13}]$^+$), 57 (5.0%, [C_4H_9]$^+$), 43 (15.0%, [C_3H_7]$^+$). Anal., %: ($C_{17}H_{23}FN_2S$) C 66.61, H 7.59, N 9.11, S 10.47. Calcd., %: C 66.63, H 7.57, N 9.14, S 10.46. M=306.44.

rac-1-(4-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (rac-3f).

Prepared from *rac*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 4-fluorophenyl isothiocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 284 mg (88%). Mp 99–100 °C (decomp.). ^{1}H NMR (DMSO-d_6), δ, ppm: 0.82 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.92 (s, 3H, CH_3) 1.20–1.25 (m, 1H, CH_2), 1.33–1.39 (m, 1H, CH_2), 1.51–1.58 (m, 1H, CH_2), 1.64–1.68 (m, 2H, CH_2), 1.70–1.76 (m, 1H, CH_2) 2.25–2.31 (m, 1H, C<u>H</u>-C(CH_3)), 3.07–3.12 (m, 1H, C<u>H</u>NH), 7.11–7.15 (m, 2H, 3,5-H arom.), 7.50–7.56 (m, 2H, 2,6-H arom.), 7.75 (d, 1H, N<u>H</u>-CH, J = 8.4 Hz), 9.47 (s, 1H, N<u>H</u>-Ph-F). ^{19}F NMR (DMSO-d_6), δ, ppm: −119.11 (1F). MS (EI) m/z: 274 (15.0%, [$C_{10}H_{17}$-NH-C-NH-Ph-F]$^+$), 164 (7.0%, [$C_{10}H_{17}$-NH-C]$^+$), 154 (15.0%, [SC-NH-Ph-F]$^+$), 137 (15.0%, [$C_{10}H_{17}$]$^+$), 110 (95.0%, [NH-Ph-F]$^+$), 95 (100.0%, [Ph-F]$^+$), 83 (5.0%, [C_6H_{11}]$^+$), 73 (3.0%, [C_5H_{13}]$^+$), 57 (5.0%, [C_4H_9]$^+$), 43 (15.0%, [C_3H_7]$^+$). Anal., %: ($C_{17}H_{23}FN_2S$) C 66.61, H 7.59, N 9.11, S 10.47. Calcd., %: C 66.63, H 7.57, N 9.14, S 10.46. M=306.44.

1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (fenchylamine, 5).

To a solution of 10.2 g (0.061 mol) of 1-fenchone oxime in 100 ml of THF were added: a solution of 50 g (1.25 mol) KOH in 950 ml of water and 40 g of Raney nickel-aluminum alloy separated 7 equal servings with intensive stirring. The rate of addition of the alloy was controlled in such way that its next portion was introduced only after the release of H_2, caused by the addition of the previous portion, subsided. After the addition of entire alloy, the reaction mixture was boiled for 2 h under reflux with intensive stirring, cooled to room temperature, and filtered from the skeletal nickel precipitate on a Buchner funnel. The reaction flask and filter cake were washed with THF (2 × 50 ml), water (100 ml), and the catalyst cake was immediately dropped into water. The upper organic phase was separated from the filtrate and dried with KOH. The aqueous phase was taken up with MTBE (4 times 75 ml), the combined ether extracts were dried with KOH. The residue from the evaporation of both organic extracts was combined, and the product remaining in the still (containing> 99% of the main substance according to GC-MS analysis) was dissolved in anhydrous Et_2O and treated with a calculated amount of HCl solution in anhydrous Et_2O. The solvent was removed under normal pressure and then under reduced pressure, leaving in the residue the hydrochloride of the target product in the form of a mixture of diastereomers. Yield 10.57 g (91%). To analyze the structure of the obtained compound, it was converted from the hydrochloride to the free amine by generally known methods. MS (EI) m/z: 153 (80.0%, [M]$^+$), 136 (100.0%, [M - NH_3]$^+$). Anal., %: ($C_{10}H_{19}N$) C 78.40, H 12.48, N 9.13. Calcd., %: C 78.37, H 12.50, N 9.14. M=153.27.

General Procedure for the synthesis of ureas 6a-d and thioureas 6e and 6f.

To 1.05 mmol of corresponding aromatic isocyanate or isothiocyanate in 5 mL of Et_2O were added 1.05 mmol of *L*- or *D*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine and 1.05 mmol of Et_3N at 0 °C. Reaction mass was stirred at room temperature overnight. After removing solvent and adding 1N HCl, the resulting white precipitates were collected by suction filtration.

L-1-(3-fluorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)urea (L-6a).

Prepared from *L*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-fluorophenyl isocyanate (140 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 240 mg (79%). Mp 175–176 °C. ^1H NMR ($CDCl_3$), δ, ppm: 0.83 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.11 (s, 3H, CH_3) 1.18–1.23 (m, 2H, CH_2), 1.40–1.47 (m, 1H, CH_2 exo), 1.57–1.59 (m, 1H, CH_2 endo), 1.59–1.62 (m, 2H, CH_2), 1.74–1.77 (m, 1H, CH) 3.54 (d, 1H, C<u>H</u>NH, J_{HH} = 9.4 Hz), 5.28 (d, 1H, CHN<u>H</u>, J_{HH} = 9.5 Hz), 6.70–6.75 (m, 1H, 4-H arom.), 6.73 (br., s, 1H, N<u>H</u>-Ph) 7.00–7.04 (m, 1H, 6-H arom.), 7.17–7.21 (m, 2H arom.). MS (EI) m/z: 290 (12.2%, $[M]^+$), 247 (3.5%, $[M - 3CH_3]^+$), 153 (15.0%, $[C_{10}H_{17}\text{-}NH_2]^+$), 137 (19.5%, $[F\text{-}Ph\text{-}NCO]^+$), 111 (100.0%, $[F\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}FN_2O$) C 70.33, H 8.00, N 9.62. Calcd., %: C 70.32, H 7.98, N 9.65. M=290.38.

D-1-(3-fluorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)urea (D-6a).

Prepared from *D*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-fluorophenyl isocyanate (140 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 137 mg (45%). Mp 168–169 °C. ^1H NMR ($CDCl_3$), δ, ppm: 0.83 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.11 (s, 3H, CH_3) 1.18–1.23 (m, 2H, CH_2), 1.40–1.47 (m, 1H, CH_2 exo), 1.57–1.59 (m, 1H, CH_2 endo), 1.59–1.62 (m, 2H, CH_2), 1.74–1.77 (m, 1H, CH) 3.54 (d, 1H, C<u>H</u>NH, J_{HH} = 9.4 Hz), 5.28 (d, 1H, CHN<u>H</u>, J_{HH} = 9.5 Hz), 6.70–6.75 (m, 1H, 4-H arom.), 6.73 (br., s, 1H, N<u>H</u>-Ph) 7.00–7.04 (m, 1H, 6-H arom.), 7.17–7.21 (m, 2H arom.). MS (EI) m/z: 290 (13.1%, $[M]^+$), 247 (3.6%, $[M - 3CH_3]^+$), 153 (12.6%, $[C_{10}H_{17}\text{-}NH_2]^+$), 137 (19.0%, $[F\text{-}Ph\text{-}NCO]^+$), 111 (100.0%, $[F\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}FN_2O$) C 70.30, H 8.00, N 9.63. Calcd., %: C 70.32, H 7.98, N 9.65. M=290.38.

L-1-(4-fluorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)urea (L-6b).

Prepared from *L*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 4-fluorophenyl isocyanate (140 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 267 mg (88%). Mp 176–177 °C. ^1H NMR ($CDCl_3$), δ, ppm: 0.80 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.13 (s, 3H, CH_3) 1.18–1.23 (m, 2H, CH_2), 1.41–1.47 (m, 1H, CH_2 exo), 1.57–1.61 (m, 1H, CH_2 endo), 1.61–1.66 (m, 2H, CH_2), 1.74–1.78 (m, 1H, CH) 3.53 (d, 1H, C<u>H</u>NH, J_{HH} = 9.3 Hz), 4.89 (d, 1H, CHN<u>H</u>, J_{HH} = 9.4 Hz), 6.66 (s, 1H, N<u>H</u>-Ph), 6.99–7.04 (m, 2H, 3.5-H arom) 7.30 (d, 2H, 2,6-H arom J_{HH} = 4.9 Hz). MS (EI) m/z: 290 (12.0%, $[M]^+$), 247 (4.0%, $[M - 3CH_3]^+$), 153 (14.0%, $[C_{10}H_{17}\text{-}NH_2]^+$), 137 (19.0%, $[F\text{-}Ph\text{-}NCO]^+$), 111 (100.0%, $[F\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}FN_2O$) C 70.28, H 7.99, N 9.68. Calcd., %: C 70.32, H 7.98, N 9.65. M=290.38.

D-1-(4-fluorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)urea (D-6b).

Prepared from *D*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 4-fluorophenyl isocyanate (140 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 155 mg (51%). Mp 169–170 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 0.80 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.13 (s, 3H, CH_3) 1.18–1.23 (m, 2H, CH_2), 1.41–1.47 (m, 1H, CH_2 exo), 1.57–1.61 (m, 1H, CH_2 endo), 1.61–1.66 (m, 2H, CH_2), 1.74–1.78 (m, 1H, CH) 3.53 (d, 1H, CHNH, J_{HH} = 9.3 Hz), 4.89 (d, 1H, CHNH, J_{HH} = 9.4 Hz), 6.66 (s, 1H, NH-Ph), 6.99–7.04 (m, 2H, 3.5-H arom) 7.30 (d, 2H, 2,6-H arom J_{HH} = 4.9 Hz). MS (EI) m/z: 290 (12.0%, $[M]^+$), 247 (4.0%, $[M - 3CH_3]^+$), 153 (14.0%, $[C_{10}H_{17}\text{-}NH_2]^+$), 137 (19.0%, $[F\text{-}Ph\text{-}NCO]^+$), 111 (100.0%, $[F\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}FN_2O$) C 70.35, H 8.01, N 9.63. Calcd., %: C 70.32, H 7.98, N 9.65. M=290.38.

L-1-(2-chlorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)urea (L-6c).

Prepared from *L*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 2-chlorophenyl isocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 276 mg (86%). Mp 202–203 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 0.86 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.17 (s, 3H, CH_3) 1.23–1.27 (m, 2H, CH_2), 1.45–1.51 (m, 1H, CH_2 exo), 1.64–1.66 (m, 1H, CH_2 endo), 1.66–1.70 (m, 2H, CH_2), 1.77–1.80 (m, 1H, CH) 3.52 (br., s, 1H, CHNH), 4.81 (d, 1H, CHNH, J_{HH} = 9.3 Hz), 6.78 (s, 1H, NH-Ph), 6.98 (td, 1H, 4-H arom, J_{HH} = 7.7, 7.5 Hz) 7.24–7.27 (m, 1H, 5-H arom) 7.36 (dd, 1H, 3-H arom, J_{HH} = 8.0, 7.5 Hz) 8.11–8.15 (m, 1H, 6-H arom). MS (EI) m/z: 306 (12.0%, $[M]^+$), 154 (20.0%, $[Cl\text{-}Ph\text{-}NCO]^+$), 153 (15.0%, $[C_{10}H_{17}\text{-}NH_2]^+$), 127 (100.0%, $[Cl\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}ClN_2O$) C 66.52, H 7.58, N 9.16. Calcd., %: C 66.55, H 7.56, N 9.13. M=306.83.

D-1-(2-chlorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)urea (D-6c).

Prepared from *D*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 2-chlorophenyl isocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 160 mg (50%). Mp 177–178 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 0.86 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.17 (s, 3H, CH_3) 1.23–1.27 (m, 2H, CH_2), 1.45–1.51 (m, 1H, CH_2 exo), 1.64–1.66 (m, 1H, CH_2 endo), 1.66–1.70 (m, 2H, CH_2), 1.77–1.80 (m, 1H, CH) 3.52 (br., s, 1H, CHNH), 4.81 (d, 1H, CHNH, J_{HH} = 9.3 Hz), 6.78 (s, 1H, NH-Ph), 6.98 (td, 1H, 4-H arom, J_{HH} = 7.7, 7.5 Hz) 7.24–7.27 (m, 1H, 5-H arom) 7.36 (dd, 1H, 3-H arom, J_{HH} = 8.0, 7.5 Hz) 8.11–8.15 (m, 1H, 6-H arom). MS (EI) m/z: 306 (11.0%, $[M]^+$), 154 (18.0%, $[Cl\text{-}Ph\text{-}NCO]^+$), 153 (14.0%, $[C_{10}H_{17}\text{-}NH_2]^+$), 127 (100.0%, $[Cl\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}ClN_2O$) C 66.58, H 7.52, N 9.10. Calcd., %: C 66.55, H 7.56, N 9.13. M=306.83.

L-1-(3-chlorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)urea (L-6d).

Prepared from *L*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-chlorophenyl isocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 279 mg (87%). Mp 162–163 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 0.83 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.13 (s, 3H, CH_3) 1.19–1.24 (m, 2H, CH_2), 1.40–1.48 (m, 1H, CH_2 exo), 1.58–1.60 (m, 1H, CH_2 endo), 1.60–1.65 (m, 2H, CH_2), 1.74–1.78 (m, 1H, CH) 3.54 (br., s, 1H, CHNH), 5.51 (br., s, 1H, CHNH), 6.73 (br., s, 1H, NH-Ph), 6.97–7.01 (m, 1H, 4-H arom), 7.15–7.24 (m, 2H, 5,6-H arom), 7.39–7.44 (m, 1H, 2-H arom). MS (EI) m/z: 306

(13.0%, $[M]^+$), 154 (19.6%, $[Cl\text{-}Ph\text{-}NCO]^+$), 153 (14.0%, $[C_{10}H_{17}\text{-}NH_2]^+$), 127 (100.0%, $[Cl\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}ClN_2O$) C 66.56, H 7.60, N 9.12. Calcd., %: C 66.55, H 7.56, N 9.13. M=306.83.

D-1-(3-chlorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)urea (D-6d).

Prepared from *D*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-chlorophenyl isocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 175 mg (56%). Mp 150–151 °C. ^1H NMR ($CDCl_3$), δ, ppm: 0.83 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.13 (s, 3H, CH_3) 1.19–1.24 (m, 2H, CH_2), 1.40–1.48 (m, 1H, CH_2 exo), 1.58–1.60 (m, 1H, CH_2 endo), 1.60–1.65 (m, 2H, CH_2), 1.74–1.78 (m, 1H, CH) 3.54 (br., s, 1H, CHNH), 5.51 (br., s, 1H, CHNH), 6.73 (br., s, 1H, NH-Ph), 6.97–7.01 (m, 1H, 4-H arom), 7.15–7.24 (m, 2H, 5,6-H arom), 7.39–7.44 (m, 1H, 2-H arom). MS (EI) m/z: 306 (12.0%, $[M]^+$), 154 (19.0%, $[Cl\text{-}Ph\text{-}NCO]^+$), 153 (14.5%, $[C_{10}H_{17}\text{-}NH_2]^+$), 127 (100.0%, $[Cl\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}ClN_2O$) C 66.54, H 7.57, N 9.15. Calcd., %: C 66.55, H 7.56, N 9.13. M=306.83.

L-1-(3-fluorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (L-6e).

Prepared from *L*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-fluorophenyl isothiocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 279 mg (87%). Mp 160–161 °C. ^1H NMR ($CDCl_3$), δ, ppm: 0.78 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.15–1.21 (m, 2H, CH_2), 1.28 (s, 3H, CH_3), 1.42–1.49 (m, 1H, CH_2 exo), 1.56–1.59 (m, 1H, CH_2 endo), 159–1.64 (m, 2H, CH_2), 1.75–1.77 (m, 1H, CH) 4.29 (d, 1H, CHNH, J_{HH} = 9.2 Hz), 6.21 (d, 1H, CHNH, J_{HH} = 9.4 Hz), 6.98 (d, 1H, 2-H arom), 7.04 (td, 2H, 4,6-H arom J_{HH} = 8.4, 2.3 Hz) 7.45 (q, 1H, 5-H arom, J_{HH} = 7.8 Hz), 7.86 (s, 1H, NH-Ph, J_{HH} = 9.4 Hz). MS (EI) m/z: 306 (29.0%, $[M]^+$), 291 (6.0%, $[M - 3CH_3]^+$), 273 (11.0%, $[M - S]^+$), 153 (15.0%, $[C_{10}H_{17}\text{-}NH_2]^+$), 137 (18.0%, $[C_{10}H_{17}]^+$), 111 (100.0%, $[F\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}FN_2S$) C 66.66, H 7.55, N 9.12. Calcd., %: C 66.63, H 7.57, N 9.14. M=306.44.

D-1-(3-fluorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (D-6e).

Prepared from *D*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 3-fluorophenyl isothiocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 228 mg (71%). Mp 162–163 °C. ^1H NMR ($CDCl_3$), δ, ppm: 0.78 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.15–1.21 (m, 2H, CH_2), 1.28 (s, 3H, CH_3), 1.42–1.49 (m, 1H, CH_2 exo), 1.56–1.59 (m, 1H, CH_2 endo), 159–1.64 (m, 2H, CH_2), 1.75–1.77 (m, 1H, CH) 4.29 (d, 1H, CHNH, J_{HH} = 9.2 Hz), 6.21 (d, 1H, CHNH, J_{HH} = 9.4 Hz), 6.98 (d, 1H, 2-H arom), 7.04 (td, 2H, 4,6-H arom J_{HH} = 8.4, 2.3 Hz) 7.45 (q, 1H, 5-H arom, J_{HH} = 7.8 Hz), 7.86 (s, 1H, NH-Ph, J_{HH} = 9.4 Hz). MS (EI) m/z: 306 (37.0%, $[M]^+$), 291 (5.5%, $[M - 3CH_3]^+$), 273 (12.8%, $[M - S]^+$), 153 (19.0%, $[C_{10}H_{17}\text{-}NH_2]^+$), 137 (25.0%, $[C_{10}H_{17}]^+$), 111 (100.0%, $[F\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}FN_2S$) C 66.60, H 7.59, N 9.15. Calcd., %: C 66.63, H 7.57, N 9.14. M=306.44.

L-1-(4-fluorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (L-6f).

Prepared from *L*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 4-fluorophenyl isothiocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 260 mg (81%). Mp 131–132 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 0.73 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.12–1.16 (m, 2H, CH_2), 1.27 (s, 3H, CH_3), 1.40–1.46 (m, 1H, CH_2 exo), 1.52–1.56 (m, 1H, CH_2 endo), 170–1.73 (m, 2H, CH_2), 1.74–1.76 (m, 1H, CH) 4.27 (d, 1H, CHNH, J_{HH} = 9.4 Hz), 5.91 (br, s, 1H, CHNH), 7.18 (t, 2H, 3,5-H arom J_{HH} = 8.4 Hz) 7.26 (dt, 2H, 2,6-H arom, J_{HH} = 9.2, 4.8 Hz), 7.67 (s, 1H, NH-Ph). MS (EI) m/z: 306 (45.0%, $[M]^+$), 291 (5.0%, $[M - 3CH_3]^+$), 273 (12.0%, $[M - S]^+$), 153 (18.0%, $[C_{10}H_{17}\text{-}NH_2]^+$), 137 (24.0%, $[C_{10}H_{17}]^+$), 111 (100.0%, $[F\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}FN_2S$) C 66.60, H 7.58, N 9.16. Calcd., %: C 66.63, H 7.57, N 9.14. M=306.44.

D-1-(4-fluorophenyl)-3-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)thiourea (D-6f).

Prepared from *D*-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (160 mg, 1.05 mmol), 4-fluorophenyl isothiocyanate (160 mg, 1.05 mmol) and Et_3N (110 mg, 1.05 mmol). White solid. Yield 273 mg (85%). Mp 154–155 °C. ^{1}H NMR ($CDCl_3$), δ, ppm: 0.73 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.12–1.16 (m, 2H, CH_2), 1.27 (s, 3H, CH_3), 1.40–1.46 (m, 1H, CH_2 exo), 1.52–1.56 (m, 1H, CH_2 endo), 170–1.73 (m, 2H, CH_2), 1.74–1.76 (m, 1H, CH) 4.27 (d, 1H, CHNH, J_{HH} = 9.4 Hz), 5.91 (br, s, 1H, CHNH), 7.18 (t, 2H, 3,5-H arom J_{HH} = 8.4 Hz) 7.26 (dt, 2H, 2,6-H arom, J_{HH} = 9.2, 4.8 Hz), 7.67 (s, 1H, NH-Ph). MS (EI) m/z: 306 (44.0%, $[M]^+$), 291 (4.5%, $[M - 3CH_3]^+$), 273 (12.5%, $[M - S]^+$), 153 (16.0%, $[C_{10}H_{17}\text{-}NH_2]^+$), 137 (22.0%, $[C_{10}H_{17}]^+$), 111 (100.0%, $[F\text{-}Ph\text{-}NH_2]^+$). Anal., %: ($C_{17}H_{23}FN_2S$) C 66.61, H 7.60, N 9.15. Calcd., %: C 66.63, H 7.57, N 9.14. M=306.44.

Docking and structure preparation

The docking study was performed using Autodock Vina[15] with the exhaustiveness value equal to 500 for cases. Only automatically recognised rotatable torsions were allowed to rotate during docking study. The structure of the receptor was taken from Protein Data Bank (PDB code: 1ZD3) was prepared with MGL Tools.[16] Only C-terminal domain was retained for further work. The receptor was kept rigid during docking and the scoring function was not modified.

Ligand and protein parameters were assigned with GAFF[17] and Amber ff14SB force field, [18] respectively. Charges for the docked ligands were calculated with AM1-BCC method. [19] The resulting structures were solvated precisely utilizing 3D-RISM and Placevent[20] approaches. The resulting complex neutralization was performed by the addition of sodium ions and solvated (TIP3P water model) obtaining the octahedral boxes containing about 25,000 atoms.

Molecular dynamics simulations

All simulations were carried out in Amber18 package.[21] First, the energy minimization step included 1000 steps of steepest descent and 1000 steps of conjugate gradients minimization were performed. Second, the optimized structures were introduced to a heating phase with restrained Cartesian coordinates (force constant 2.0 kcal/(mol × Å2)) of protein Cα and all ligand atoms during the NVT simulation (50 ps) using Berendsen thermostat

with the default temperature coupling constant and integration step value set to 1 fs. Third, the NPT simulation (500 ps) with restraints applied identically to the heating phase was conducted for the obtained structures using Langevin thermostat (collision frequency γ set to 2.0 ps−1). The application of SHAKE algorithm allowed us to use an integration step of 2 fs. After the system density became stable, 3 trajectories each 25 ns length were recorded for each prepared system. Binding energy calculation was performed using MM-GBSA[22] approaches implemented in AmberTools18 with one trajectory approach based on the frames form the last 5 ns of simulations. MM-GBSA approach was applied using Generalized Born solvation model developed by Onufriev and Case.[23] RMSD and number of hydrogen bonds were computed using CPPTRAJ[24] program.

Determination of inhibitory potency (IC_{50})

The IC_{50} values reported herein were determined using a fluorescent based assay [25]. Enzyme (~1 nM human sEH) was incubated at 30 °C with inhibitors ([I]final = 0.4 – 100,000 nM) for 5 min in 100 mM sodium phosphate buffer (200 μL, pH 7.4) containing 0.1 mg/mL of BSA and 1% of DMSO. The substrate (cyano(2-methoxynaphthalen-6-yl)methyl *trans*-(3-phenyloxyran-2-yl)methylcarbonate, CMNPC) was then added ($[S]_{final}$ = 5 μM). Activity was assessed by measuring the appearance of the fluorescent 6-methoxynaphthaldehyde product (λ_{em} = 330 nm, λ_{ex} = 465 nm) at 30 °C during a 10 min incubation (Spectramax M2; Molecular Device, Inc., Sunnyvale, CA). The IC_{50} values that are the concentrations of inhibitors that reduce activity by 50% were calculated from at least five different concentrations, each in triplicate, with at least 2 on either side of 50% activity mark.

Single Crystal X-ray Diffraction

The X-ray diffraction (XRD) data for the single crystals of **3a** were collected on a Bruker D8 QUEST diffractometer with a PHOTON III area detector and an IμS DIAMOND microfocus X-ray tube using Mo *K*α (0.71073 Å) radiation. The data reduction package *APEX*3 v2019.11–0 was used for data processing. Analysis of the integrated data did not show any decay. Data were corrected for systematic errors and absorption: Numerical absorption correction based on integration over a multifaceted crystal model and empirical absorption correction based on spherical harmonics according to the point group symmetry using equivalent reflections. The structures were solved by the intrinsic phasing method using *SHELXT*-2018/2 [26] and refined by the full-matrix least-squares on F^2 using *SHELXL*-2018/3 [27]. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms at the heteroatoms were found from Fourier difference maps and refined isotropically or, if involved in disordering, inserted at the calculated positions and refined as riding atoms. The positions of the hydrogen atoms of the methyl group were found using a rotating group refinement with idealized tetrahedral angles. The other hydrogen atoms were inserted at the calculated positions and refined as riding atoms. The disorder was refined using a free variable and reasonable restraints on geometry and anisotropic displacement parameters.

Crystallographic data for L-3a.

$C_{17}H_{23}FN_2O$, colorless plate (0.393 × 0.214 × 0.046 mm^3), formula weight 290.37; orthorhombic, $P2_12_12_1$ (No. 19), a = 9.2249(7) Å, b = 11.7471(9) Å, c = 28.809(2) Å, V = 3121.9(4) $Å^3$, Z = 8, Z' = 2, T = 100(2) K, d_{calc} = 1.236 g cm^{-3}, μ(Mo $K\alpha$) = 0.085 mm^{-1}, F(000) = 1248; $T_{max/min}$ = 0.9839/0.9163; 43367 reflections were collected (1.872° ≤ θ ≤ 25.681°, index ranges: −11 ≤ h ≤ 11, −14 ≤ k ≤ 14, −32 ≤ l ≤ 35), 5934 of which were unique, R_{int} = 0.0591, R_σ = 0.0381; completeness to θ_{max} 100 %. The refinement of 494 parameters with 710 restraints converged to R_1 = 0.0572 and wR_2 = 0.1351 for 5296 reflections with $I > 2\sigma(I)$ and R_1 = 0.0642 and wR_2 = 0.1388 for all data with S = 1.095 and residual electron density, $\rho_{max/min}$ = 0.764 and −0.235 e $Å^{-3}$. Flack parameter x = −.6(4) determined using 1996 selected quotients by Parsons' method.

Crystallographic data for L/D-3a.

$C_{17}H_{23}FN_2O$, colorless needle (0.240 × 0.050 × 0.032 mm^3), formula weight 290.37; orthorhombic, *Pbca* (No. 61), a = 11.7481(12) Å, b = 9.2133(9) Å, c = 28.952(3) Å, V = 3133.7(5) $Å^3$, Z = 8, Z' = 1, T = 100(2) K, d_{calc} = 1.231 g cm^{-3}, μ(Mo $K\alpha$) = 0.085 mm^{-1}, F(000) = 1248; $T_{max/min}$ = 0.9960/0.9301; 54096 reflections were collected (2.233° ≤ θ ≤ 25.253°, index ranges: −14 ≤ h ≤ 14, −11 ≤ k ≤ 11, −34 ≤ l ≤ 34), 2831 of which were unique, R_{int} = 0.1178, R_σ = 0.0451; completeness to θ_{max} 100 %. The refinement of 385 parameters with 1259 restraints converged to R_1 = 0.0843 and wR_2 = 0.2256 for 2001 reflections with $I > 2\sigma(I)$ and R_1 = 0.1151 and wR_2 = 0.2527 for all data with S = 1.054 and residual electron density, $\rho_{max/min}$ = 1.225 and −0.452 e $Å^{-3}$.

Results and discussion

As a starting material we used L-, D-, and *rac*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (bornylamine, **1**) obtained according to a well-established method[28] from corresponding L-, D- and L/D-camphor. Reaction of **1** with aromatic isocyanates **2a-d** and isothiocyanates (**2e** and **2f**) was used to synthesize ureas **3a-d** and thioureas **3e** and **3f** (Scheme 1).

To expand the field of study, we synthesized L- and D-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (fenchylamine, **5**) from the corresponding enantiomerically pure oximes[29] of fenchone (**4**) under Schwenk–Papa reaction conditions (Scheme 2). According to GC-MS each enantiomer contains equal amounts of *exo*- and *endo*-isomers.

L- and D-fenchylamine were introduced into reaction with aromatic isocyanates **2a-d** and isothiocyanates **2e** and **2f** to produce 1,3-disubstituted ureas **6a-d** and thioureas **6e** and **6f** (Scheme 3). *Exo* and *endo* diastereomers were not separated.

To our knowledge, no systematic studies showing the effect of spatial structure of the lipophilic group on sEH inhibitory activity and water solubility has been performed before. Potency of the compounds was measured against the recombinant, affinity purified human sEH, and their solubility determined in phosphate buffer (Table 1).

A vast majority of ureas synthesized from bornylamine (**1**) showed high potency, inhibiting sEH in concentrations (IC_{50}) as low as 0.7 nM (Table 1). The only exceptions are compounds **3c** (L-**3c** 386.9 nM, D-**3c** 69.6 nM, L/D-**3c** 85.0 nM). Compound **3c** is also different in term of enantiomeric preference. While for compounds **3a**, **3b**, and **3d-f**, the L-form is more active (2.3-fold average), D-**3c** is 5.5-fold more active than L-**3c**. As expected, potencies of racemates lie between the IC_{50} values for L- and D-forms. Relatively low activity of thioureas **3e** (ca. 75-fold less active than **3a**) and **3f** (ca. 6.3-fold less active than **3b**) correlates with previous results on adamantane ureas and thioureas with the same lipophilic groups.[32]

Ureas **6a-d** and thioureas **6e** and **6f** derived from fenchylamine (**5**) possess lower activity against sEH (ca. 80-fold on the average) than their bornyl-derived analogs. Compounds **6a-f** also show less enantiomeric preference (ca. 1.75-fold on the average) and consistency. For compounds **3a**, **3c**, **3e**, and **3f**, L-forms are more active, while for **3b** and **3d**, D-forms show advantages. Thioureas **6e** and **6f** melt at range of 131–163 °C, while their bornyl-derived analogs (**3e** and **3f**) decompose at ca. 100 °C.

Solubility in sodium phosphate buffer for the most of synthesized ureas lays in a range of 40–60 μM, which is on the same level as the corresponding adamantane derivatives.[7] Besides being more active, camphor-derived ureas also have better solubility (10 μM in average) than fenchone-derived analogues. Further, thioureas were less soluble than ureas of the same structure (10–15 μM in average).

To understand the observed activity variation among the isomers of the bicyclic fragment, molecular dynamics (MD) simulations were conducted of different isomers and orientations of ligands in the binding site. It has been shown that the orientation of non-symmetric ureas in the sEH active site varies greatly with even minor structural changes in the ligand structure[31], thus MD simulations are important to discriminate between possible binding modes. Since all the compounds contain a mixture of *endo* and *exo* isomers both of them were docked and MD simulations have been performed. All studied inhibitors can have two possible orientations in the active site: (1) *p*-F-phenyl fragment forms **π-π** interaction with Trp336 and (2) bicyclic ring interacts with Trp336 (Figure 1). Based on the computed molecular mechanics generalized Born surface area (MM-GBSA) the orientation (2) is preferential for all the studied inhibitors except D-**3b**-*endo* (Table 2), but in that case the difference is quite small. In addition to this energetic preference, the average number of hydrogen bonds between simulated ligands and the protein is usually higher for the orientation (2).

All ligands and orientations have a consistently high population of a hydrogen bond with Tyr383, while the variability of hydrogen bond populations with Tyr466 and Asp335 is much higher. The main difference between simulations of different isomers of bicyclic fragment is a conformational change of the loop 494–504. In case of **6b** series this loop is shifted as it is shown in Figure 2 while it retains its X-ray conformation for **3b** isomers. This conformational change can explain the decrease in activity for all compounds having the same bicyclic fragment and is caused by its specific shape.

Slow crystallization of a solution of 1-(3-fluorophenyl)-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (**3a**) in ethanol gave crystals suitable for single-crystal X-ray diffraction (SC XRD) study. According to diffraction data, sample L-**3a** prepared from (1*S*,4*S*)-bornan-2-one crystallizes as a partial mixed crystal in the orthorhombic Sohncke space group $P2_12_12_1$ with two molecules A and B in the asymmetric cell (Figure 3a). The molecule A is characterized by (1*S*,2*R*,4*S*)-configuration; at the same time, the molecule B appeared to be substitutionally disordered onto two diastereomeric (1*S*,2*R*,4*S*)- and (1*S*,2*S*,4*S*)-components with a fraction of 0.706(4) for the former one. Sample L/D-**3a** forms a mixed crystal in the orthorhombic centrosymmetric space group *Pbca* with one symmetrically independent molecule (Figure 3b). Its camphor fragment is highly disordered at least into three components, with minor ones (ca. 14.4 % of each) are turned or mirrored with respect to the main (1*RS*,2*SR*,4*RS*)-component (with a fraction of 0.712(3)). Thus, both crystal structures studied can be referred to as a solid solution of stereoisomers.[33–35]

Deposition numbers 2151724 and 2151725 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Conclusion

In conclusion, ureas containing natural bicyclic lipophilic groups yielded a series of sEH inhibitors with high potency and revealed the enantiomeric preference of sEH for the L-enantiomers. This preference is in part explained by steric interaction with the side chain of Leu499, which is facing the catalytic cavity.

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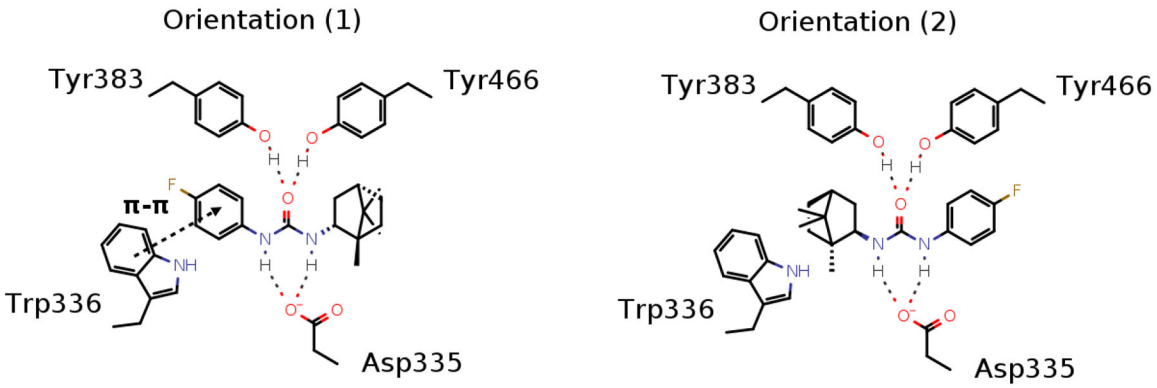


Figure 1.

Two possible orientations of the inhibitor in the binding site (L-**3b**-*endo*): (1) p-F-phenyl fragment interacts with Trp336 and (2) bicyclic fragment interacts with Trp336.

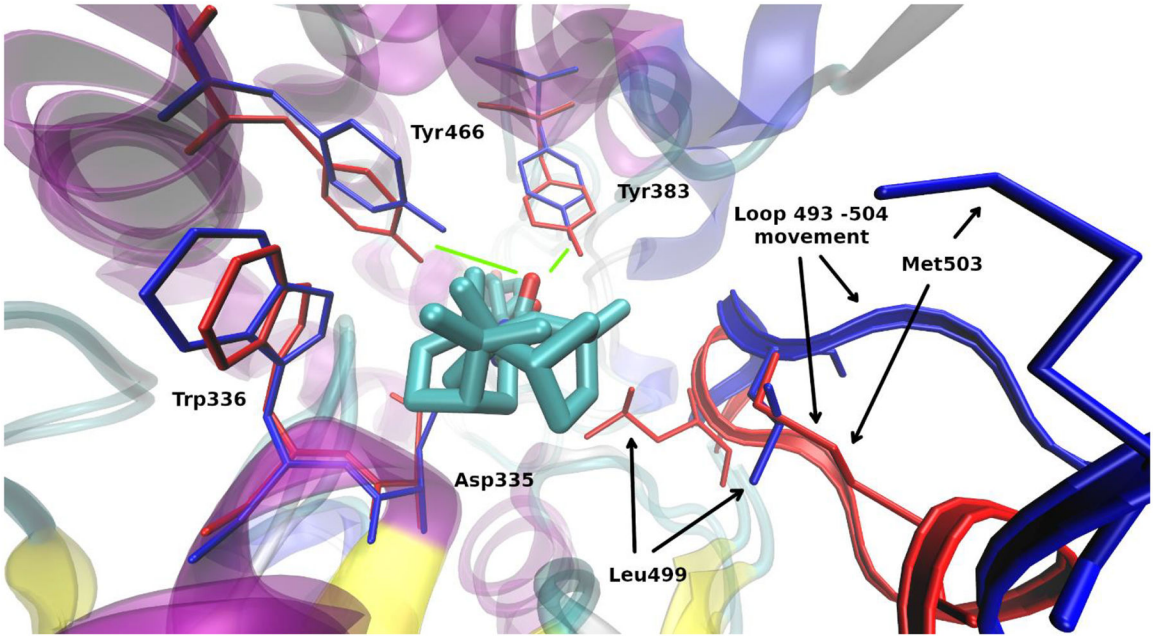


Figure 2.

Superposition of two MD frames after 25 ns of simulation of hSEH complexes with L-**3b**-*endo* (surrounding residues in red) and L-6b-*endo* (surrounding residues in blue). Hydrogen bonds are shown by green lines.

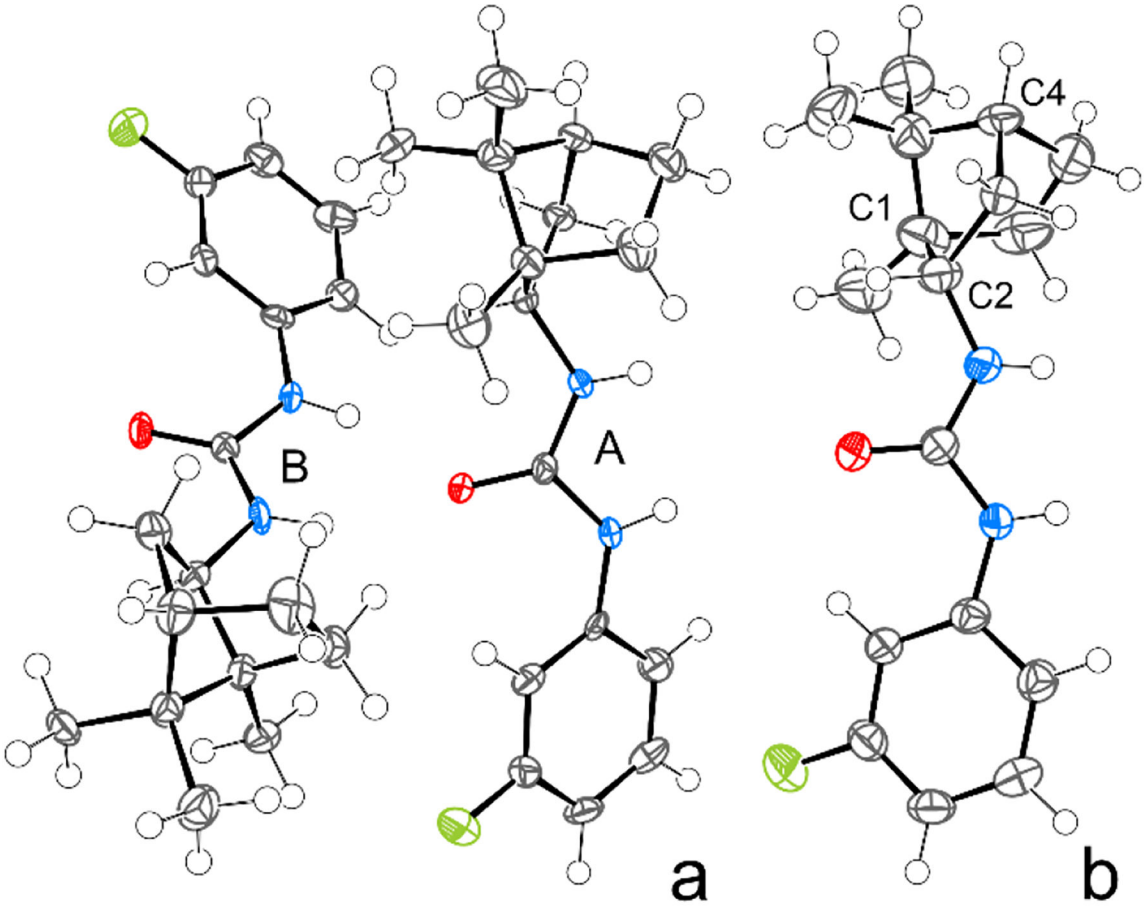
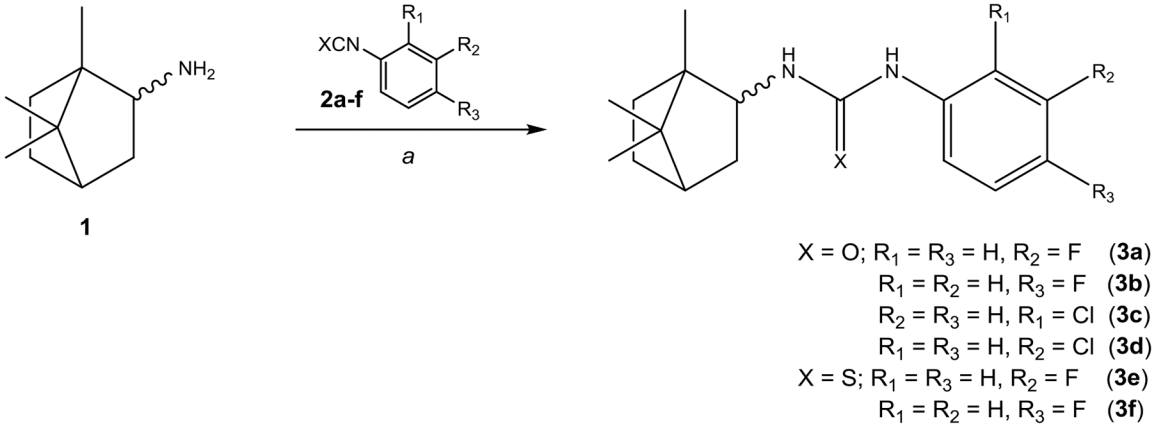


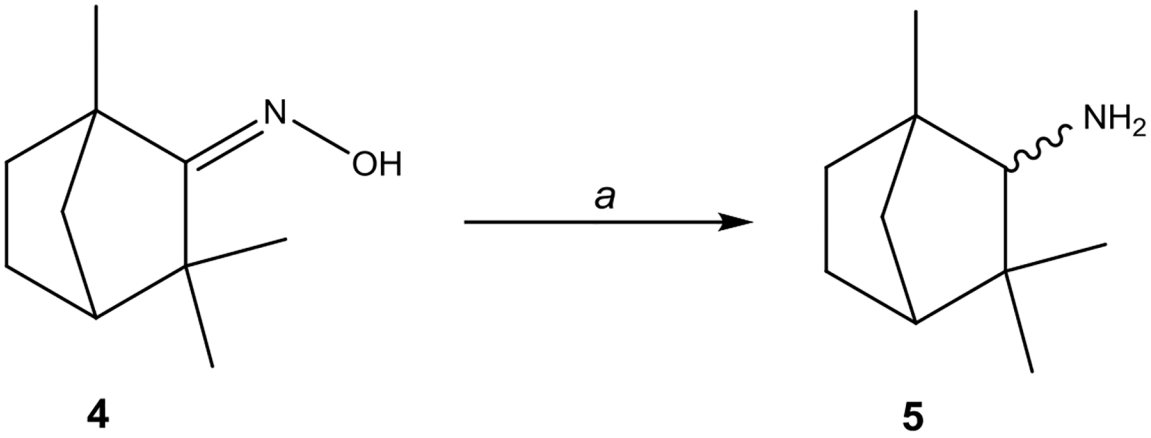
Figure 3.

ORTEP representation of asymmetric cell of crystals L-**3a** (a) and L/D-**3a** (b) at 60 % probability level for non-hydrogen atoms according to SC XRD. In the case of L-**3a**, two symmetrically independent molecules A and B are present. Minor disorder components of the camphor moiety are omitted for clarity.



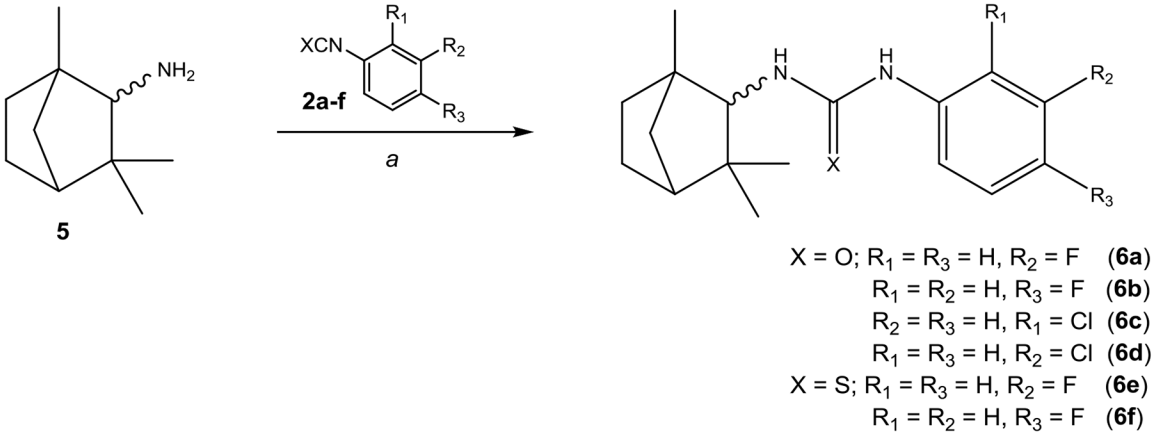
Scheme 1.

Reagents and conditions: *a.* Et_2O, Et_3N, rt, 3h.



4 **5**

Scheme 2.
Reagents and conditions: *a.* THF, KOH/H_2O, Ni-Al, reflux, 2h.

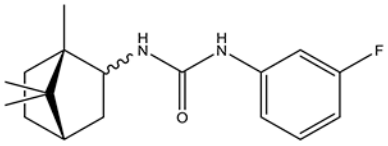
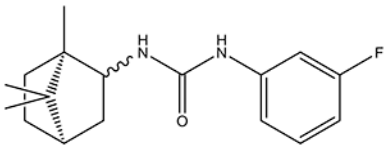
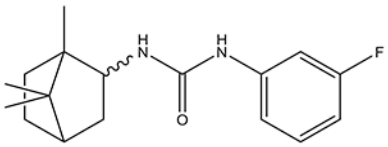
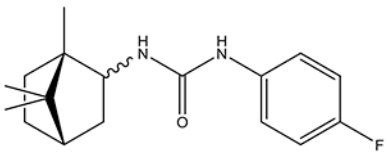
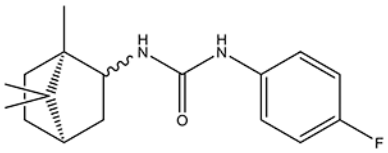
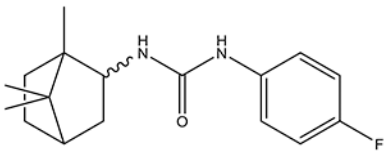
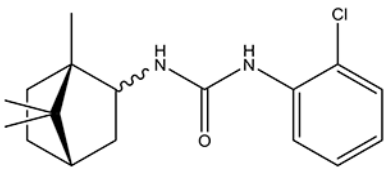


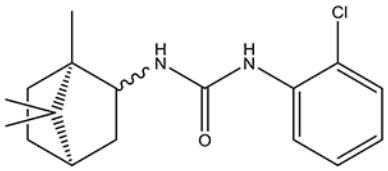
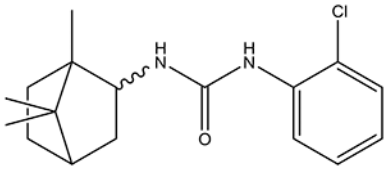
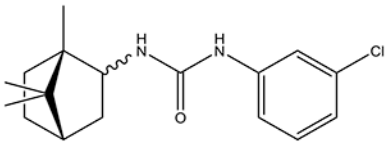
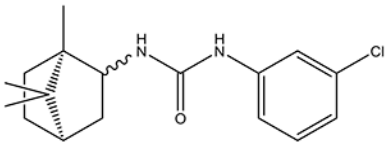
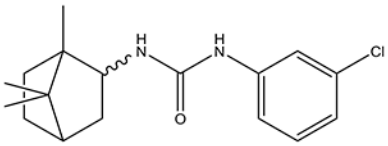
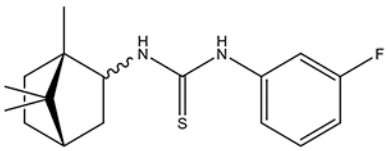
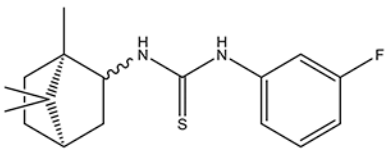
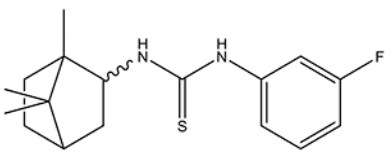
Scheme 3.

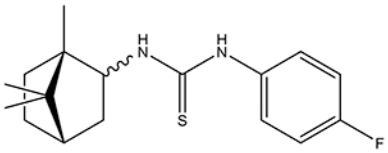
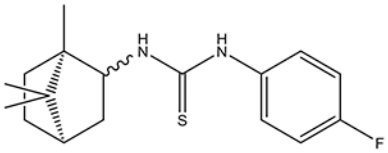
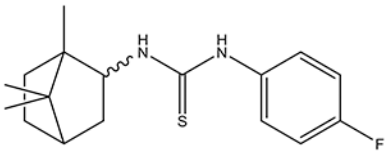
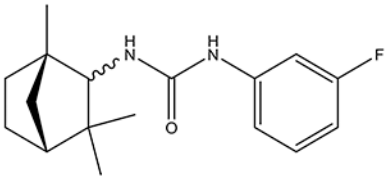
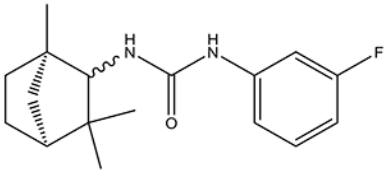
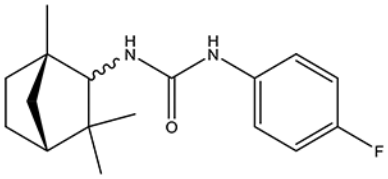
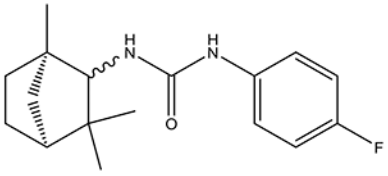
Reagents and conditions: *a*. Et_2O, Et_3N, rt, 3h.

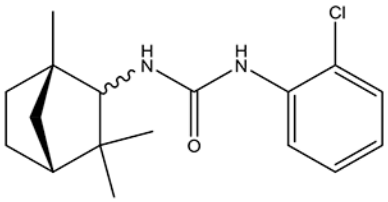
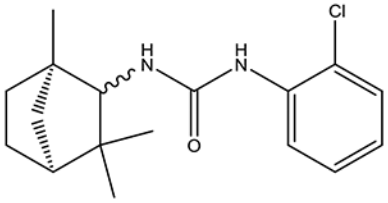
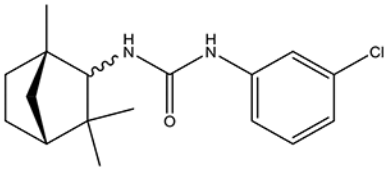
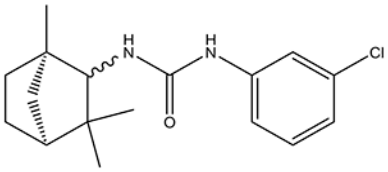
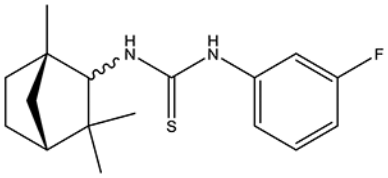
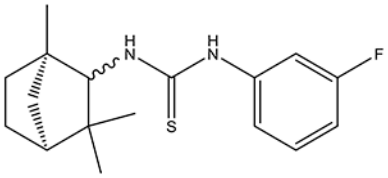
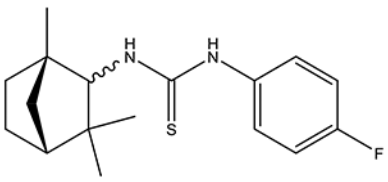
Table 1

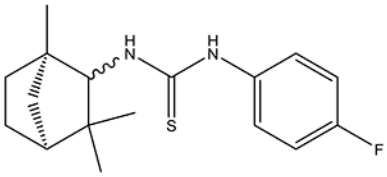
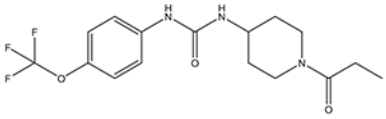
IC_{50} values and some physicochemical properties for ureas and thioureas **3a-f** and **6a-f**.

#	Structure	mp (°C)	logP[a]	Solubility (μM)[b]	Human sEH IC_{50} (nM)[c]
L-**3a**		230–231	4.25	50±10	0.7
D-**3a**		235–236	4.25	50±10	2.8
L/D-**3a**		222–223	4.25	50±10	1.5
L-**3b**		211–212	4.27	65±15	4.0
D-**3b**		213–214	4.27	65±15	8.2
L/D-**3b**		200–201	4.27	65±15	5.1
L-**3c**		213–214	4.74	30±10	386.9

#	Structure	mp (°C)	logP[a]	Solubility (μM)[b]	Human sEH IC_{50} (nM)[c]
D-**3c**		214–215	4.74	30±10	69.6
L/D-**3c**		209–210	4.74	30±10	85.0
L-**3d**		181–182	4.76	35±15	1.5
D-**3d**		183–184	4.76	35±15	1.7
L/D-**3d**		155–156	4.76	35±15	1.6
L-**3e**		117–118 dec	4.15	10±5	56.1
D-**3e**		113–114 dec	4.15	10±5	175.6
L/D-**3e**		116–117 dec	4.15	10±5	126.3

#	Structure	mp (°C)	logP[a]	Solubility (μM)[b]	Human sEH IC_{50} (nM)[c]
L-**3f**		100–101 dec	4.18	15±5	31.0
D-**3f**		98–99 dec	4.18	15±5	38.3
L/D-**3f**		99–100 dec	4.18	15±5	33.5
L-**6a**		175–176	4.25	45±10	221.1
D-**6a**		168–169	4.25	45±10	229.7
L-**6b**		176–177	4.27	65±15	412.1
D-**6b**		169–170	4.27	65±15	366.6

#	Structure	mp (°C)	logP[a]	Solubility (μM)[b]	Human sEH IC_{50} (nM)[c]
L-**6c**		202–203	4.74	40±10	1472
D-**6c**		177–178	4.74	40±10	4811
L-**6d**		162–163	4.76	40±10	166.1
D-**6d**		150–151	4.76	40±10	111.3
L-**6e**		160–161	4.15	10±5	2980
D-**6e**		162–163	4.15	10±5	6476
L-**6f**		131–132	4.18	15±5	4227

#	Structure	mp (°C)	logP[a]	Solubility (μM)[b]	Human sEH IC_{50} (nM)[c]
D-**6f**		154–155	4.18	15±5	6076
TPPU		198–200[d]	3.03	167[d]	3.7[d]

[a]Calculated using Molinspiration (http://www.molinspiration.com) © Molinspiration Cheminformatics.

[b]Solubilities were measured by turbidimetric assay in sodium phosphate buffer (pH 7.4, 0.1 M) containing 1% of DMSO according to reference [30].

[c]Determined via a kinetic fluorescent assay. Results are means of three separate experiments.[25]

[d]According to reference [31].

Table 2.

MD simulations results for different isomers and orientations in the binding site of L-6b, D-6b, L-3b, D-3b.

ID	*p*-F-phenyl stacking with Trp336	Average number of H-bonds between ligand and Asp335	Average number of H-bonds between ligand and Tyr383	Average number of H-bonds between ligand and Tyr466	Average number of H-bonds between ligand and protein	ΔH MM-GBSA, kcal/mol	sEH IC_{50}, nM
L-**6b**-*endo*	yes	1.17	0.94	0.60	2.71	−40.6	412.1
	no	1.57	0.93	0.40	2.90	−44.1	
L-**6b**-*exo*	yes	1.21	0.95	0.29	2.45	−38.8	
	no	1.60	0.96	0.14	2.70	−44.0	
D-**6b**-e*ndo*	yes	0.72	0.85	0.27	1.84	−36.6	366.6
	no	1.31	0.91	0.16	2.38	−39.8	
D-**6b**-*exo*	yes	1.52	0.90	0.57	2.99	−43.8	
	no	1.36	0.93	0.38	2.67	−44.1	
L-**3b**-*endo*	yes	1.26	0.95	0.60	2.81	−41.0	4.0
	no	1.29	0.70	0.34	2.33	−43.9	
L-**3b**-*exo*	yes	1.02	0.94	0.50	2.46	−39.8	
	no	1.47	0.90	0.44	2.81	−44.4	
D-**3b**-*endo*	yes	0.91	0.92	0.61	2.44	−42.9	8.2
	no	1.65	0.94	0.01	2.60	−42.1	
D-**3b**-*exo*	yes	1.03	0.97	0.08	2.08	−39.2	
	no	1.51	0.90	0.85	3.26	−47.1	