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# 1-(3-Chlorophenyl)-3-(6-((1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)amino)hexyl)thiourea

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**Abstract:** The compound 1-(3-chlorophenyl)-3-(6-((1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)amino)hexyl)thiourea was synthesized for the first time from 6-((1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)amino)hexan-1-amine and 3-chlorophenylisothiocyanate in DMF with a 60% yield. It was characterized by $^{1}H$, $^{13}C\{^{1}H\}$ NMR, FT-IR, MS, and elemental analysis.

**Keywords:** camphor; urea; thiourea; isothiocyanate; imine

## 1. Introduction

Previously, we have observed synthesis and inhibitory activity against human soluble epoxide hydrolase (sEH) of multiple series of adamantyl-containing 1,3-disubstituted ureas and thioureas, and the same findings have been reported by our colleagues [1–3]. sEH is involved in the metabolism of epoxy fatty acids to corresponding vicinal diols through a catalytic addition of water [4,5]. The resulting dihydroxyepoxyeicosatrienoic acids promote various pathological states, such as pain and inflammation [6]. Thus, inhibition of sEH could be beneficial in the treatment of cardiovascular, neuronal, and renal diseases [7,8]. 1,3-Disubstituted ureas containing lipophilic moieties such as adamantyl, bornyl, or 4-(trifluoromethoxy)phenyl (Figure 1) are among the most potent sEH inhibitors active in nanomolar concentrations [9–11].

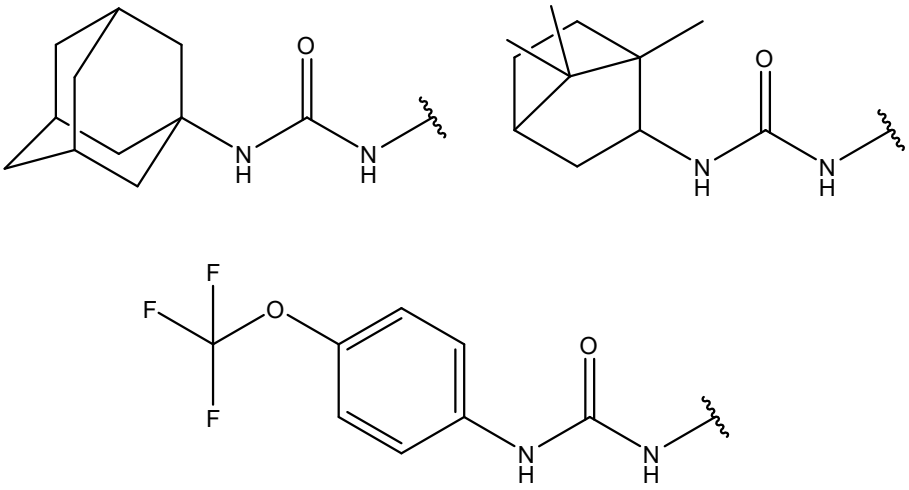

**Figure 1.** Most common fragments of soluble epoxide hydrolase inhibitors.

This makes the synthesis and evaluation of new adamantyl-containing 1,3-disubstituted thioureas as soluble epoxide hydrolase inhibitors relevant. The present study focuses on the preparation and identification of 1-(3-chlorophenyl)-3-(6-((1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)amino)hexyl)thiourea.

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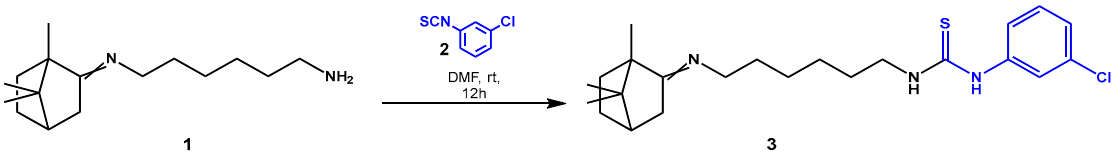
## 2. Results and Discussion

We chose to use imine derived from camphor as a fragment for our new class of soluble epoxide hydrolase inhibitors for a number of reasons. First of all, substitution of adamantane with natural monoterpene fragments [2] or their simultaneous introduction into the same molecule [12] can provide great benefits in the field of green chemistry. Secondly, compounds containing imines derived from camphor possess various biological activities, including strong antiviral activity [13]. Finally, the imine group, unlike the urea and thiourea groups, is slightly basic and is capable of forming salts with acids. These salts could be water-soluble, or could at least possess significantly higher water solubility compared to free imine.

Based on our previous experience, we proposed a method for the preparation and isolation of 1-(3-chlorophenyl)-3-(6-((1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)amino)hexyl) thiourea (**3**) (Scheme 1).




**Scheme 1.** Synthesis of compound **3** from 6-((1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)amino)hexan-1-amine (**1**) and 3-chlorophenylisothiocyanate (**2**).

Starting compound **1** has very poor solubility in hexane and diethyl ether, so we used DMF as a solvent for this reaction. We usually use anhydrous DMF for the reactions including isocyanates due to its water sensitivity. However, for isothiocyanates, this is not necessary. We also did not use $Et_3N$ in this reaction. Commonly, we use $Et_3N$ to increase the basicity of the medium and thus to speed up the reaction. However, to remove $Et_3N$ from the reaction mass, we rinse it with 1 N HCl and then with water. For this reaction, we could not use HCl due to the possibility of salt formation by the product. For the same reason, we did not use excess amine in this reaction. Excess amine is used to speed up the reaction and to make sure that no isocyanate or isothiocyanate remains. Excess amine is also removed by treating the reaction mass with 1 N HCl. Since we could not do this, we used the starting material in the equimolar ratio and increased the reaction time from 8 to 12 h.

After the reaction mass was stirred for 12 h, the formation of pale-yellow precipitate of crude compound **3** was observed. After the solvent was filtered off, the precipitate was washed with distilled water and dried in vacuo. Crystallization from ethanol produced pure compound **3** as a white solid.

## 3. Materials and Methods

$^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker DPX 300 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA) (at frequencies of 300 and 75 MHz) in DMSO-$d_6$ solution with TMS as the standard. The J values are given in Hz. The IR spectrum was recorded on a FT-801 FT-IR spectrometer (LLC Simex, Novosibirsk, Russia). The MS spectrum was recorded on an Agilent MS 5977b (Agilent Technologies, Inc., Santa Clara, CA, USA) using electron impact ionization (EI). The melting point was measured using a Büchi M-565 (Büchi Labortechnik AG, Flawil, Switzerland) and was calculated as the mean of 3 separate experiments. The elemental analysis was performed on a Perkin-Elmer Series II 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA). The TLC analysis was carried out on Merck silica gel chromatography plates with fluorescent indicator $F_{254}$ (1.05554); sorbent: Silica 60, with a layer thickness of 200 um; a pore size of 60 Å, and a particle size of 10-12 um; binder: organic polymer (Merck KGaA, Darmstadt, Germany). The solvents and reagents were purchased from commercial sources. The NMR signals of the bornylidene fragment were assigned according to data found in the literature [13].

Synthesis of 1-(3-chlorophenyl)-3-(6-((1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)amino) hexyl)thiourea (**3**) was performed according to the following procedure. Labelling of atoms in the compound **3** is given in Figure 2. For detailed spectral data see Supplementary Materials.

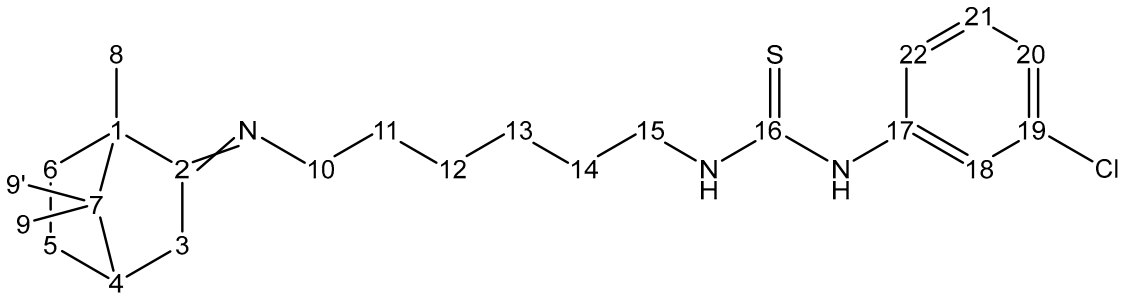



**Figure 2.** Carbon atoms labeling for compound **3**.

Into a flat-bottom flask equipped with a magnetic stirrer, we added 300 mg (1.20 mmol) of compound **1**, 5 mL of hexane and 200 mg (1.18 mmol) of compound **2**. The resulting mixture was left to stir for 12 h at rt. After that, pale-yellow precipitate of crude compound **3** was filtered off, washed with 30 mL of distilled water, and dried in vacuo. The resulting crude compound **3** was purified by crystallization from ethanol. Yield 298 mg, 0.70 mmol, 60% yield, white solid, m.p. = 112.7 °C. FT-IR (ATR, $cm^{-1}$): 549 (C-Cl), 738 (C=S), 1478 (C-N), 1545 (NH), 1673 (C=N), 2942 (CH). Mass spectrum, $m/z$ ($I_{rel}$.%): 421 (2% [M + 1]$^+$), 250 (20% [M-Cl-Ph-NCS]$^+$), 169 (100%, [Cl-Ph-NCS]$^+$). $^1$H NMR (DMSO-$d_6$), δ, ppm: 0.68 (s, 3H, **H-9**), 0.84 (s, 3H, **H-9**), 0.87 (s, 3H, **H-8**), 1.13–1.22 (m, 2H, (**H-5endo**, **H-6endo**)), 1.26–1.35 (m, 4H, **H-12**, **H-13**), 1.48–1.55 (m, 4H, **H-11**, **H-14**), 1.55–1.61 (m, 1H, **H-6exo**), 1.75–1.84 (m, 2H, (**H-3endo**, **H-5exo**)), 1.88 (t, 1H, *J* = 4.5 Hz, **H-4**), 2.27 (br.d, 1H, *J* = 17.2 Hz, **H-3exo**), 3.02–3.20 (m, 2H, **H-10**), 3.38–3.49 (m, 2H, **H-15**), 7.05–7.13 (m, 1H, **H-20**), 7.25–7.34 (m, 2H, **H-21**, **H-22**), 7.70 (s, 1H, **H-18**), 7.86 (br.s, 1H, N**H**-C-15), 9.48 (br.s, 1H, N**H**-C-17). $^{13}$C{$^1$H} NMR (DMSO-$d_6$), δ, ppm: 12.2 (**C-8**), 19.4 (**C-9**), 19.9 (**C-9**), 27.0 (**C-12**), 27.3 (**C-13**), 27.6 (**C-5**), 29.0 (**C-11**), 30.8 (**C-14**), 32.6 (**C-6**), 35.4 (**C-3**), 43.9 (**C-4**), 44.4 (**C-15**), 47.0 (**C-7**), 51.8 (**C-10**), 53.7 (**C-1**), 121,3 (**C-22**), 122.4 (**C-18**), 123.9 (**C-20**), 130.7 (**C-21**), 133.2 (**C-19**), 141.8 (**C-17**), 180.4 (**C-16**), 180.8 (**C-2**). Calcd. for $C_{23}H_{34}ClN_3S$: C 65.77; H 8.16; N 10.00; S 7.63. Found: C 65.80; H 8.15; N 10.05; S 7.60. M = 420.06.

## 4. Conclusions

In this work, we presented a method for the preparation of 1-(3-chlorophenyl)-3-(6-((1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)amino)hexyl)thiourea from 6-((1,7,7-trimethylbicyclo heptan-2-ylidene)amino)hexan-1-amine and 3-chlorophenylisothiocyanate in DMF with 60% yield. The compound, which was synthesized for the first time, was identified via $^1$H and $^{13}$C{$^1$H} NMR, MS, FT-IR, and elemental analyses.

**Supplementary Materials:** $^1$H NMR, $^{13}$C NMR and FT-IR spectra. Figure S1. $^1$H NMR spectrum of compound **3**. Figure S2. $^{13}$C NMR spectrum of compound **3**. Figure S3. FT-IR spectrum of compound **3**.

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