Studies on the Reactivity of Some *N*-Aryl- and *N*-Heteroaryl-*N'*-alkylthioureas Towards Electrophilic Reagents. Synthesis of new *N*-Pyridylthioureas and Thiazolines

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Here in we describe our findings about the behaviour of some *N*-aryl- and *N*-heteroaryl-*N'*-alkylthioureas towards electrophilic reagents. In acid medium, the treatment of thioureas bearing aryl groups with 4-chloropyridine in 2-propanol yielded *N*-aryl-*N*-(4-pyridyl)-*N'*-alkylthioureas and *N*-aryl-*N'*-alkylureas, whereas the heteroarylthioureas tested under similar reaction conditions afforded *N*-heteroaryl-*N'*-alkyl-*O*-(2-propyl)isoureas. The reaction of *N*-(5,6,7,8-tetrahydronaphth-1-yl)- and *N*-(2-benzimidazolyl)-*N'*-butylthiourea with propargyl bromide in acid medium led to the formation of 2-butylimino-3-arylthiazolines, in a regioselective way. However, when this reaction was carried out in basic conditions the regioselectivity failed and a mixture of isomeric thiazolines was obtained. The *Z*- or *E*-configuration of the imino group of the synthesized thiazolines was studied by molecular modelling and by selective nuclear Overhauser experiments in nuclear magnetic resonance.

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The urea and thiourea moieties represent essential substructures of a wide variety of bioactive compounds (*e.g.* acetylcholinesterase inhibitors [1], antioxidants [2], anti-HIV [3,4], anticonvulsant [5], and anti-hypercholesterolemia agents [6]) and they are also valuable starting products in heterocyclic synthesis [7], especially in thiazole chemistry [8]. Recently, we reported some applications of heteroarylthioureas as versatile intermediates in the synthesis of new heterocyclic systems of biological interest [9-13]. Combining the above results with our work on heterocyclic derivatives of 4-aminopyridine (**I**) with cholinergic and adrenergic properties [14,15], here we report new pyridyl thioureas and ureas (**II**), as well as new thiazolines (**III**) derived from the same starting thioureas (Figure 1).

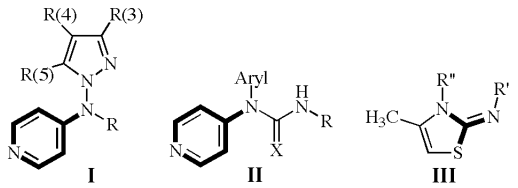
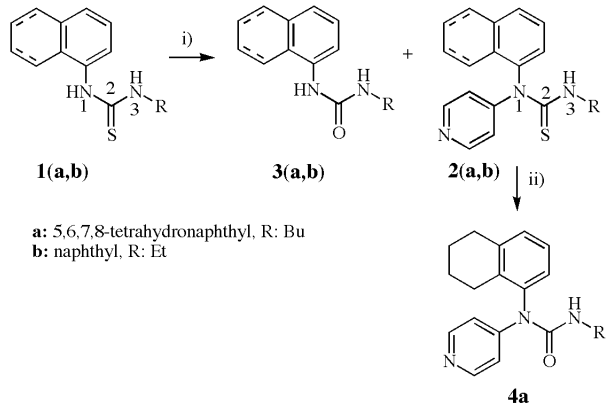


Figure 1

With the aim of obtaining *N*-(4-pyridyl)thioureas of general structure **II** (X = S, Figure 1) the starting thioureas **1(a-e)** were treated with 4-chloropyridine hydrochloride in 2-propanol at reflux. In the case of arylthioureas **1(a,b)** this reaction yielded two products: the target 1-(4-pyridyl)-thioureas **2(a,b)** and the ureas **3(a,b)** (Scheme 1). The formation of (4-pyridyl)thioureas was regioselective since only one isomer was obtained **2(a,b)**, that in both series was identified as the result of the substitution on the NH(1) of the thiourea moiety. Concerning the formation of ureas **3(a,b)**, it can be presumed that the reaction proceeded through the initial formation of a *S*-(4-pyridyl) intermediate, that was immediately hydrolyzed to afford the corresponding urea, in accordance to a precedent work [16]. The role of 4-chloropyridine in these transformations was probed, since when thioureas **1(a,b)** were refluxed with 2-propanol containing hydrogen chloride for 24 hours only starting materials were recovered. The fact that under these experimental conditions the ureas **3(a,b)** were isolated, represent an unexpected way to obtain these compounds, that is milder than other reported desulfurizations where more drastic conditions were used (*e.g.* 2-nitrobenzene sulfonyl chloride and potassium superoxide [17], acid or alkaline hydrogen peroxide [18,19]). Furthermore, the treatment of the pyridylthiourea **2a** with sulfuryl chloride provided the corresponding pyridylurea **4a**, in excellent yield.

Scheme 1



a: 5,6,7,8-tetrahydronaphthyl, R: Bu
b: naphthyl, R: Et

(i) 4-Chloropyridine•HCl (1 equivalent), 2-propanol, reflux, 7-10 hours. (ii) SO_2Cl_2, dichloromethane, reflux, 1 hour.

In derivatives **2(a,b)**, the pyridine position was established using ^1H and ^{13}C nmr spectroscopy. The decoupled carbon spectra showed a signal at ~182 ppm, assigned to C=S (Table 1), pointing out that the substitution did not occur at the sulphur atom. In the proton spectra, registered

in deuteriochloroform, a broad triplet at ~6 ppm was observed, attributable to the NH(3) based on its multiplicity due to the coupling with the first methylene of the alkyl chain, that appeared as a quartet when R = butyl (**2a**), and as a quintuplet when R = ethyl (**2b**). When some drops of deuterium oxide were added to the initial solution, the broad triplet disappeared and the multiplicity of the first methylene of the alkyl chain decreased. These data demonstrated that in **2(a,b)** the pyridine was attached to the N(1) of the thiourea moiety. Elemental analyses and the mass spectra are in accordance with the proposed structures.

The structures of the ureas **3(a,b)** and **4a** were confirmed on the basis of elemental analyses, mass spectra, ^{1}H, and ^{13}C nmr data. The mass spectra showed molecular peaks according to the above mentioned transformation of the thiourea into the urea function (molecular peaks at m/z 246 for **3a**, and at 323 for **4a**). The ^{13}C nmr spectra of these ureas showed a signal at δ = 155.1—157.2 ppm attributed to C=O (Table 1), that were about 30 ppm less deshielded than the C=S of the starting thioureas **1** and **2**. Moreover, in the urea derivatives the first methylene of the alkyl chain is observed at about 5 ppm (in ^{13}C nmr) and 0.4 ppm (in ^{1}H nmr) less deshielded than their counterparts in the thiourea series.

Table 1

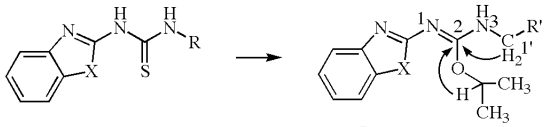
Selected ^{1}H and ^{13}C nmr data (δ, ppm) of **1(a,b)**, **2(a,b)**, **3(a,b)**, and **4a**

	^{1}H nmr			^{13}C nmr		
	NH(1)[a]	NH(3)[b]	CH_2(1')	C=S	C=O	CH_2(1')
1a	7.29	5.65	3.58 [c]	180.5	—	45.0
2a	—	5.86	3.56 [c]	182.0	—	45.5
3a	6.36	5.13	3.10 [c]	—	156.8	39.8
4a	—	4.42	3.14 [c]	—	155.1	40.4
1b	7.75	5.64	3.62 [d]	181.1	—	40.1
2b	—	6.08	3.60 [d]	182.7	—	40.5
3b	6.58	4.74	3.25 [d]	—	157.2	35.2

[a] Broad singlet, D_2O-exchangeable; [b] Broad triplet, D_2O-exchangeable; [c] Quartet, $J \approx 7$ Hz, becomes a triplet with D_2O; [d] Quint, $J \approx 7$ Hz, becomes a quartet with D_2O.

In contrast, the reaction of the heteroarylthioureas **1(c-e)** with 4-chloropyridine hydrochloride under the same experimental conditions previously used for the arylthioureas **1(a,b)** (reflux in 2-propanol) did not yield the target 1-(4-pyridyl)thioureas, even when two equivalents of the alkylating agent were used. In these cases, only one product was obtained, that was identified as the isourea **5(c-e)** (Scheme 2), as the result of a nucleophilic attack of a solvent molecule to the *S*-(4-pyridyl) intermediate. When heteroarylthioureas **1(c-e)** were refluxed with 2-propanol containing hydrogen chloride for 24 hours only starting materials were recovered, pointing out the existence of the proposed *S*-(4-pyridyl)isothiourea as the intermediate of these transformations.

Scheme 2



1(c-e)
c: X=NH, R=Bu
d: X=NH, R=Et
e: X=S, R=Et

5(c-e)
c: X=NH, R'=Pr
d: X=NH, R'=Me
e: X=S, R'=Me

4-Chloropyridine•HCl (2 equivalents), 2-propanol, reflux, 10 hours. Curved arrows show nmr spectra interactions in hmbc experiments.

The structures of these derivatives **5(c-e)** were established from mass, ^{1}H and ^{13}C NMR spectra, and mainly from the hmbc (heteronuclear multiple bond correlation) experiments (Table 2). In the hmbc experiment, it was observed that the C*H*$(Me)_2$ at δ = 5.3 ppm correlated only with one quaternary carbon at 158 ppm, attributable to C2 of the isourea moiety. If the substitution had occurred at any NH, the above mentioned proton might correlate in addition with another carbon atom: the C2 of the heterocycle or with the C1 of the *n*-alkyl chain.

It is worth mentioning that when the hereoarylthioureas **1(c-e)** were treated with 4-chloropyridine hydrochloride using aprotic solvents such as tetrahydrofuran the reaction did not take place, and only starting thiourea was recovered in every case.

Table 2

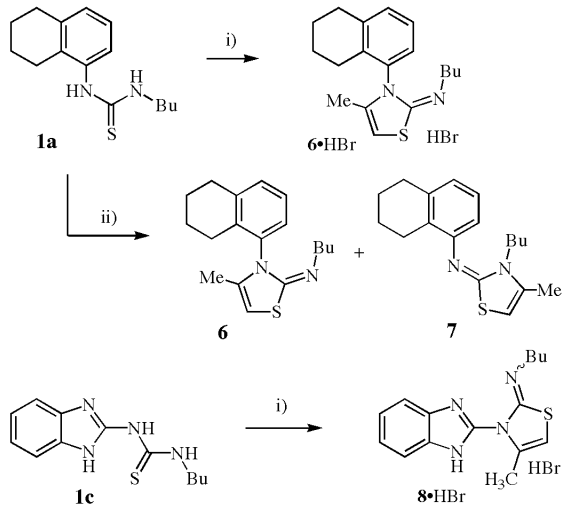
Selected Correlations Carbon-proton (δ, ppm) of **5(c-e)** by HMBC Experiments

		Connected Protons	
Compound	C(2)	C*H*Me_2	C*H*$_2$(1')
5c	158.6	5.27	3.33
5d	158.7	5.28	3.38
5e	157.4	5.59	3.60

With the aim of obtaining thiazolines of general structure **III** (See, Figure 1), the starting thioureas **1(a-c)** were treated with propargyl bromide in different reaction conditions. Condensation of **1a** and **1c** with propargyl bromide in boiling 2-propanol, in acid medium due to the hydrogen bromide released during the reaction, afforded only one product, the corresponding 3-aryl-2-butylimino-4-methyl-2,3-dihydrothiazole hydrobromide (**6**.HBr and **8**.HBr) (Scheme 3). However, when the treatment of the tetrahydronaphthylthiourea **1a** with propargyl bromide was carried out with an equivalent of sodium hydride, two isomeric thiazolines were obtained, **6** (as a free base) and the 2-arylimino-3-butyl derivative, **7**.

From these data some conclusions could be derived. In both acid or base conditions, the common intermediate might be a *S*-(2-propynyl)isothiourea that then could progress to two different thiazolines, depending on which nitrogen was implicated in the nucleophilic attack to the triple bond. In acid medium, only N(1) was involved in

Scheme 3



(i) Propargyl bromide, tetrahydrofuran, reflux, 4-7 hours.
(ii) Propargyl bromide, NaH, tetrahydrofuran, room temperature, 16 hours.

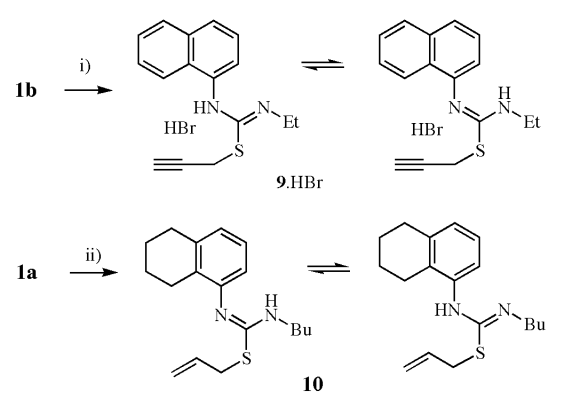
this second step and thus one thiazoline was isolated. In basic conditions, both nitrogen atoms were implicated and the two possible isomeric thiazolines were obtained.

It is worth mentioning that in the treatment of naphthylthiourea **1b** with propargyl bromide in acid conditions the main product was the *S*-(2-propynyl)isothiourea **9** (Scheme 4), that in this particular case did not progress to the corresponding thiazoline. This result could corroborate the structure of the proposed intermediate in acid conditions.

With the aim to verify if in basic medium the first step was also the *S*-alkylation, the starting thiourea **1a** was allowed to react with 3-bromopropene in the presence of sodium hydride, obtaining the expected *S*-(2-propen-1-yl)isothiourea **10** (Scheme 4).

Unfortunately, treatment of the benzothiazolylthiourea **1e** with propargyl bromide, both in acid or base medium, yielded intractable mixtures.

Scheme 4



(i) Propargyl bromide, tetrahydrofuran, reflux, 8 hours.
(ii) Allyl bromide, NaH, dimethylformamide, room temperature, 18 hours.

The structures of these products (**6-10**) were confirmed by elemental analyses, ^{1}H, ^{13}C NMR, hmbc (heteronuclear multiple quantum coherance), the one-bond heteronuclear correlation experiment, and hmbc experiments.

The ^{1}H nmr spectra of thiazolines **6-8** lacked the NH signals and showed two new singlets: the first at δ 5.4 -6.2 ppm integrated for one proton attributed to the H5 of the thiazoline ring, and the second at δ 1.7 - 2.1 ppm integrated for three protons assigned to the methyl group of the thiazoline. Their ^{13}C nmr spectra lacked the C=S signal and showed new carbons at ~160, ~135, ~95 and ~15 ppm, belonging to the methylthiazoline system. With the aim of unequivocally establishing their structures, we carried out heteronuclear two-dimensional nmr experiments. Thus, the unambiguous assignment of the protonated carbons was made from correlation observed on the hmqc diagrams, and the assignment of quaternary carbons from hmbc experiments. In every hmbc diagram, the new heterocyclic proton only correlated with the carbons belonging to the thiazoline: C2, C4 and the new methyl group. This fact demonstrated that the methyl group was located on the thiazoline C4 (and not on C5, because in this hypothetical case the new heterocyclic proton might correlate with an additional carbon from the aryl group in **6** and **8**, and from the butyl chain in **7**). The differentiation between the isomeric thiazolines was made from the heteronuclear correlations of the first methylene protons of the butyl chain in hmbc experiments (Table 3). In compounds **6** and **8** these protons only correlated with carbon 2 of the thiazoline, whereas in compound **7** these protons correlated with two carbons of the thiazoline ring: C2 and C4. The above mentioned correlations were only compatible with the proposed structures.

Table 3

Key Correlations Proton-carbon (δ, ppm) of **6-10** by HMBC Experiments

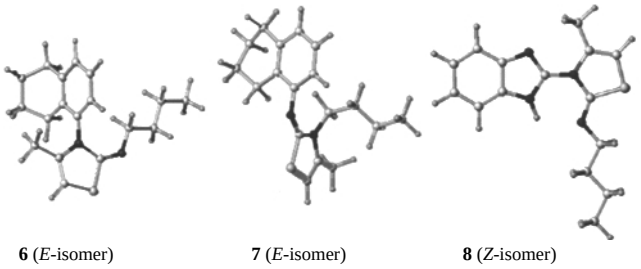
	^{1}H nmr	Connected Carbons
6	3.10 (NCH_2Pr)	158.4 (C2 thiazoline)
7	3.82 (NCH_2Pr)	158.5 (C2 thiazoline), 134.7 (C4 thiazoline)
8	3.14 (NCH_2Pr)	159.2 (C2 thiazoline)
9	3.34 ($SCH_2C{\equiv}CH$)	168.3 (C2 isothiourea), 102.0 (-$C{\equiv}$CH), 75.8 (-C$\equiv$$C$H)
10	3.43 ($SCH_2CH{=}CH_2$)	151.6 (C2 isothiourea), 134.7 (-$CH{=}CH_2$), 117.6 (-CH=CH_2)

In the case of isothioureas **9** and **10** their ^{1}H nmr spectra revealed a broad D_2O-exchangeable signal at 8.14 and 4.36 ppm respectively, attributable to a NH. Their hmbc experiments showed that the *S*-CH_2- protons correlated with the C2 of the isothiourea moiety, and not with C1 of the aryl group nor with C1 of the alkyl group, pointing out that the substitution had occurred at the sulphur atom (Table 3). It is worth mentioning that these isothioureas

showed some broad signals both in ^1H and ^{13}C nmr, probably due to a slow prototropy in the nmr time scale.

In order to ascertain the preferred *Z*- or *E*-configuration of the imino group of thiazolines **6**-**8** semiempirical AM1 molecular calculations [20] were carried out, using the SYBYL program [21] implemented on a Silicon Graphics station. As it can be observed in Figure 2, where the optimised structures have been depicted, in the case of thiazolines **6** and **7** the *E*-isomer is more stable than the corresponding *Z*-isomer. These results agree with the significant nOe (nuclear Overhauser effect) observed for thiazoline **6**, between the first methylene of the butyl chain and the H2 of the tetrahydronaphthalenic moiety, confirming that the isolated configuration is the *E*-isomer.

However, in thiazoline **8** the most stable configuration is the *Z*-isomer that, in addition, adopts a planar conformation, probably stabilised by an electrostatic interaction between the benzimidazolic NH and the nitrogen atom involved in the iminic bond.



6 (*E*-isomer) **7** (*E*-isomer) **8** (*Z*-isomer)

Figure 2. Optimised structures of thiazolines **6**-**8**, using AM1 method.

In conclusion, we found that in acid medium the treatment of *N*-aryl-*N'*-alkylthioureas with 4-chloropyridine in 2-propanol yielded *N*-aryl-*N*-(4-pyridyl)-*N'*-alkylthioureas and *N*-aryl-*N'*-alkylureas, whereas *N*-heteroaryl-*N'*-alkylthioureas tested under similar reaction conditions afforded *N*-heteroaryl-*N'*-alkyl-*O*-(2-propyl)isoureas. The reaction of *N*-(5,6,7,8-tetrahydronaphth-1-yl)- and *N*-(2-benzimidazolyl)-*N'*-butylthiourea with propargyl bromide in acid medium afforded 2-butylimino-3-arylthiazolines, in a regioselective way. However, when this reaction was carried out in basic conditions the regioselectivity failed and two isomeric thiazolines were obtained.

EXPERIMENTAL

Reagents and solvents were purchased from common commercial suppliers and were used without further purification. Chromatographic separations were performed on silica gel, using the following techniques: flash column chromatography (Kieselgel 60 Merck of 230-400 mesh) and preparative centrifugal circular thin layer chromatography (cctlc, on a circular plate coated with a 1 mm layer of Kieselgel 60 PF_{254} gipshaltig, Merck, using a Chromatotron®). Compounds were detected with uv light (254 nm), iodine chamber, or ninhydrin.

Melting points were determined with a Reichert-Jung Thermovar apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded in $CDCl_3$ solutions, using Varian Unity-500, Varian XL-300, and Gemini-200 spectrometers. Typical spectral parameters for ^1H nmr were: spectral width 10 ppm, pulse width 9 μs (57°), data size 32 K. The acquisition parameters in decoupled ^{13}C nmr spectra were: spectral width 16 kHz, acquisition time 0.99 s, pulse width 9 μs (57°), data size 32 K. Chemical shifts are reported in δ values (ppm) relative to internal Me_4Si (TMS) and *J* values are reported in Hertz. Other experiments such nOe (nuclear Overhauser enhancement), hmqc (heteronuclear multiple quantum coherance) and hmbc (heteronuclear multiple bond correlation) were obtained in standard conditions. Mass spectra (ms) were obtained by electronic impact (ei) at 70 eV in a Hewlett-Packard 5973 spectrometer (with direct insertion probe) or by atmospheric pressure chemical ionization (apci) in a Hewlett-Packard MSD 1100 spectrometer. Elemental analyses were carried out in a Perkin-Elmer 240C equipment in the Centro de Química Orgánica 'Manuel Lora-Tamayo' (CSIC) and the results are within ± 0.3% of the theoretical values.

General Procedure for the Reaction of Thioureas **1**(**a-e**) with 4-Chloropyridine.

A solution of the corresponding thiourea (1 equivalent) and 4-chloropyridine hydrochloride (1 equivalent) in 2-propanol was refluxed during 7 -12 hours. After cooling to room temperature, the mixture was poured into ice-water (50 mL) and made basic by slow addition of potassium carbonate. The resulting aqueous solution was extracted with dichloromethane (3 x 100 mL) and the organic layer was washed with water (100 mL), dried with Na_2SO_4 and evaporated to dryness *in vacuo* to give syrups, that were purified by column chromatography as indicated in each case.

N-(4-Pyridyl)-*N*-(5,6,7,8-tetrahydronaphth-1-yl)-*N'*-butylthiourea (**2a**) and *N*-(5,6,7,8-Tetrahydronaphth-1-yl)-*N'*-butylurea (**3a**).

Following the general method, the reflux of thiourea **1a** (1.31 g, 5.0 mmol) and 4-chloropyridine hydrochloride (0.75 g, 5.0 mmol) in 50 mL of 2-propanol for 7 hours, gave a mixture that was chromatographed on a silica gel column using as eluents hexane:ethyl acetate of increasing polarity (from 4:1 to 1:1). The first band (R_f = 0.4, hexane:ethyl acetate 3:1) aforded the urea **3a** (160 mg, 13%) as a white solid, mp 124-5 ºC; ^1H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 7.17 (1H, d, *J* = 7.7, H(4)-tetrahydronaphthyl), 6.98 (1H, t, *J* = 7.7, H(3)-tetrahydronaphthyl), 6.81 (1H, d, *J* = 7.7, H(2)-tetrahydronaphthyl), 6.36 (1H, br s, NH(1), D_2O-exchangeable), 5.13 (1H, br t, NH(3), D_2O-exchangeable), 3.10 (2H, q, *J* = 7.0, CH_2(1)-butyl, becomes as a triplet with D_2O), 2.67 (2H, br t, CH_2(5)-tetrahydronaphthyl), 2.50 (2H, br t, CH_2(8)-tetrahydronaphthyl), 1.67 (4H, br t, CH_2(6,7)-tetrahydronaphthyl), 1.32 (2H, quint, *J* = 7.0, CH_2(2)-butyl), 1.21 (2H, sext, *J* = 7.0, CH_2(3)-butyl), 0.81 (3H, t, *J* = 7.0, CH_3-butyl); ^{13}C nmr (50 MHz; $CDCl_3$; Me_4Si): δ 156.8 (C=O), 138.5, 136.0, 131.1, 126.3, 125.8, 122.1, 29.7, 24.7, 22.9 and 22.6 (tetrahydronaphthyl moiety), 39.8, 32.2, 20.0 and 13.7 (butyl chain); ms (ei): m/z 119 (42), 147 (100), 246 (22, M^+), 247 (5, M^++1).

Anal. Calcd. for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.98; H, 8.94; N, 11.16.

The second band (R_f = 0.2, hexane:ethyl acetate 3:1) yielded the pyridylthiourea **2a** (934 mg, 55%) as a white solid, mp 98-99 ºC; ir (KBr): NH 3190, C=S 1330; ^1H nmr (300 MHz; $CDCl_3$; Me_4Si): δ [8.38 (2H, dd, H(2,6)-pyridyl), 7.17 (2H, dd, H(3,5)-pyridyl), $J_{2,3}$ = $J_{5,6}$ = 4.8, $J_{2,6}$ = $J_{3,5}$ = 1.5], 7.15 (1H, d, *J* = 7.2, H(4)-

tetrahydronaphthyl), 7.11 (1H, t, *J* = 7.2, H(3)-tetrahydronaphthyl), 6.97 (1H, d, *J* = 7.2, H(2)-tetrahydronaphthyl), 5.86 (1H, br t, NH(3), D_2O-exchangeable), 3.56 (2H, q, *J* = 7.3, CH_2(1)-butyl, becomes as a triplet with D_2O), 2.75 (2H, br t, *J* = 3.2, CH_2(5)-tetrahydronaphthyl), [2.52 (1H, dt, CH_2(8)-tetrahydronaphthyl), 2.34 (1H, dt, CH_2(8)-tetrahydronaphthyl), J_{gem} = -17.3, J_{vic} = 3.2], 1.68 (4H, br quint, CH_2(6,7)-tetrahydronaphthyl), 1.43 (2H, quint, *J* = 7.3, CH_2(2)-butyl), 1.15 (2H, sext, *J* = 7.3, CH_2(3)-butyl), 0.82 (3H, t, *J* = 7.3, CH_3-butyl); ^{13}C nmr (50 MHz; $CDCl_3$; Me_4Si): δ 182.0 (C=S), 151.1, 150.0 and 120.8 (pyridyl group), 140.5, 139.9, 136.0, 130.3, 127.1, 126.4, 29.5, 25.0, 22.5 and 22.4 (tetrahydronaphthyl moiety), 45.5, 30.6, 20.0 and 13.7 (butyl chain); ms (ei): m/z 120 (36), 147 (28), 176 (100), 196 (22), 224 (36), 306 (47), 339 (66, M^+) and 340 (17, M^++1).

Anal. Calcd. for $C_{20}H_{25}N_3S$: C, 70.76; H, 7.42; N, 12.38; S, 9.44. Found: C, 70.83; H, 7.53; N, 12.37; S, 9.27.

N-(1-Naphthyl)-*N*-(4-pyridyl)-*N'*-ethylthiourea (**2b**) and *N*-(1-Naphthyl)-*N'*-ethylurea (**3b**).

Following the general method, the treatment of thiourea **1b** (1.15 g, 5.0 mmol) with 4-chloropyridine hydrochloride (0.75 g, 5.0 mmol) in 50 mL of 2-propanol, refluxing for 10 hours, gave a mixture of two products. These products were separated firstly by flash column chromatography (hexane:ethyl acetate, from 5:1 to 1:1) and then by preparative centrifugal circular thin layer chromatography (hexane:ethyl acetate, from 10:1 to 1:1).

From the fractions of R_f = 0.3 (hexane:ethyl acetate, 3:1) the urea **3b** was obtained (204 mg, 19% yield) as a pure solid, mp 198-199 °C (Reference [22] 199-200 °C); ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 8.07 (1H, m), 7.88 (1H, m), 7.77 (1H, d, *J* = 8.0, H(4)-naphthyl), 7.55 (2H, m), 7.53 (1H, d, *J* = 8.0, H(2)-naphthyl), 7.47 (1H, t, *J* = 8.0, H(3)-naphthyl), 6.58 (1H, br s, NH(1), D_2O-exchangeable), 4.74 (1H, br t, NH(3), D_2O-exchangeable), 3.25 (2H, quint, *J* = 7.2, CH_2-ethyl, becomes as a quartet with D_2O), 1.07 (3H, t, *J* = 7.2, CH_3-ethyl); ^{13}C nmr (50 MHz; $CDCl_3$; Me_4Si): δ 157.2 (C=O), 134.5, 131.8, 129.7, 128.5, 127.2, 126.7, 126.6, 125.6, 123.9 and 122.2 (naphthyl moiety), 35.2 and 15.4 (ethyl chain).

Anal. Calc. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.59; H, 6.45; N, 13.01.

Fractions of R_f = 0.1 (hexane:ethyl acetate, 3:1) were evaporated to dryness affording the pyridylthiourea **2b** (430 mg, 28%) as a white solid, mp 125-127 °C; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ [8.36 (2H, dd, H(2,6)-pyridyl), 7.25 (2H, dd, H(3,5)-pyridyl), $J_{2,3}$ = $J_{5,6}$ = 4.6, $J_{2,6}$ = $J_{3,5}$ = 1.5], 7.92 (2H, m, naphthyl), 7.90 (1H, d, *J* = 7.4, H(4)-naphthyl), 7.57 (2H, m, naphthyl), 7.50 (1H, t, *J* = 7.4, H(3)-naphthyl), 7.41 (1H, d, *J* = 7.4, H(2)-naphthyl), 6.08 (1H, br t, NH(3), D_2O-exchangeable), 3.60 (2H, q, *J* = 7.2, CH_2-ethyl, becomes as a quartet with D_2O), 0.99 (3H, t, *J* = 7.2, CH_3-ethyl); ^{13}C nmr (50 MHz; $CDCl_3$; Me_4Si): δ 182.7 (C=S), 152.4, 150.1 and 121.1 (pyridyl group), 137.9, 134.9, 130.3, 129.7, 128.7, 128.1, 127.5, 127.2, 126.0 and 122.5 (naphthyl moiety), 40.5 and 13.7 (ethyl chain).

Anal. Calcd. for $C_{18}H_{17}N_3S$: C, 70.33; H, 5.57; N, 13.67; S, 10.43. Found: C, 70.25; H, 5.69; N, 13.60; S, 10.26.

N-(2-Benzimidazolyl)-*N'*-butyl-*O*-(2-propyl)isourea (**5c**).

A solution of thiourea **1c** (100 mg, 0.4 mmol) and 4-chloropyridine hydrochloride (120 mg, 0.8 mmol) in 50 mL of isopropanol was refluxed for 9 hours. Following the general method, a syrup was obtained that was purified by flash column chromatography, using hexane:ethyl acetate (3:1) as eluent. From the fractions of R_f = 0.6 the isourea **5c** was isolated as a pure syrup (41 mg, 35%); ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 9.79 (1H, br t, NH(3), D_2O-exchangeable), 8.97 (1H, br s, H(1)-benzimidazolyl, D_2O-exchangeable), 7.45 (1H, br s, H(4)-benzimidazolyl), 7.23 (1H, br s, H(7)-benzimidazolyl), 7.08 (2H, s, H(5,6)-benzimidazolyl), 5.27 (1H, seven lines, *J* = 6.2, CH-isopropyl), 3.33 (2H, q, *J* = 7.0, CH_2(1)-butyl, becomes as a triplet with D_2O), 1.60 (2H, quint, *J* = 7.0, CH_2(2)-butyl), 1.42 (2H, sext, *J* = 7.0, CH_2(3)-butyl), 1.31 (6H, d, *J* = 6.2, 2 x CH_3-isopropyl), 0.96 (3H, t, *J* = 7.0, CH_3-butyl); ^{13}C nmr (50 MHz; $CDCl_3$; Me_4Si): δ 158.6 (C2-isourea), 156.9 (C2-benzimidazolyl), 120.7 (broad, C(5,6)-benzimidazolyl), 116.6 (broad, C(4,7)-benzimidazolyl), 108.8 (broad, C(8,9)-benzimidazolyl), 69.8 (CH-isopropyl), 40.7 (C1-butyl), 32.2 (C2-butyl), 22.1 (CH_3-isopropyl), 20.0 (C3-butyl), 13.8 (C4-butyl); ms (ei): m/z 105 (19), 133 (49), 159 (80), 160 (100), 274 (33, M^+), 275 (7, M^++1).

Anal. Calc. for $C_{15}H_{22}N_4O$: C, 65.67; H, 8.08; N, 20.42. Found: C, 65.59; H, 7.95; N, 20.30.

N-(2-Benzimidazolyl)-*N'*-ethyl-*O*-(2-propyl)isourea (**5d**).

A mixture of thiourea **1d** (100 mg, 0.45 mmol) and 4-chloropyridine hydrochloride (136 mg, 0.9 mmol) in isopropanol (50 mL) was refluxed for 8 hours. The reaction was processed as indicated in the general method, and the residue was purified by flash column chromatography. From the fractions of R_f = 0.5 (hexane:ethyl acetate, 3:1) the isourea **5d** was obtained (35 mg, 30%) as a white solid mp 83-84 °C; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 9.75 (1H, br t, NH(3), D_2O-exchangeable), 9.19 (1H, br s, H(1)-benzimidazolyl, D_2O-exchangeable), 7.32 (2H, br s, H(4,7)-benzimidazolyl), 7.07 (2H, s, H(5,6)-benzimidazolyl), 5.28 (1H, seven lines, *J* = 6.2, CH-isopropyl), 3.38 (2H, quint, *J* = 7.1, CH_2-ethyl, becomes as a quartet with D_2O), 1.32 (6H, d, *J* = 6.2, 2 x CH_3-isopropyl), 1.26 (3H, t, *J* = 7.1, CH_3-ethyl); ^{13}C nmr (50 MHz; $CDCl_3$; Me_4Si): δ 158.6 (C2-isourea), 156.9 (C2-benzimidazolyl), 120.8 (br, C(5,6)-benzimidazolyl), 116.6 (br, C(4,7)-benzimidazolyl), 109.0 (br, C(8,9)-benzimidazolyl), 69.9 (CH-isopropyl), 36.0 (C1-ethyl), 22.1 (CH_3-isopropyl) and 15.5 (C2-ethyl); ms (ei): m/z 105 (21), 133 (45), 159 (100), 160 (85), 246 (31, M^+), 247 (5, M^++1).

Anal. Calcd. for $C_{13}H_{18}N_4O$: C, 63.39; H, 7.37; N, 22.75. Found: C, 63.44; H, 7.29; N, 22.81.

N-(2-Benzothiazolyl)-*N'*-ethyl-*O*-(2-propyl)isourea (**5e**).

A solution of thiourea **1e** (75 mg, 0.32 mmol) and 4-chloropyridine hydrochloride (96 mg, 0.64 mmol) in 50 mL of isopropanol was refluxed for 8 hours. The reaction was worked-up as above and the residue was purified by flash column chromatography, using hexane:ethyl acetate (4:1) as eluent. From the fractions of R_f = 0.8 the isourea **5e** was isolated as a pure syrup (35 mg, 30%); ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 9.87 (1H, br t, NH(3), D_2O-exchangeable), 7.85 (2H, d, *J* = 7.2, H(4,7)-benzothiazolyl), 7.53 (1H, t, *J* = 7.2, H(5)-benzothiazolyl), 7.37 (1H, t, *J* = 7.2, H(6)-benzothiazolyl), 5.59 (1H, seven lines, *J* = 6.2, CH-isopropyl), 3.60 (2H, quint, *J* = 7.0, CH_2-ethyl, becomes as a quartet with D_2O), 1.55 (6H, d, *J* = 6.2, 2 x CH_3-isopropyl), 1.48 (3H, t, *J* = 7.0, CH_3-ethyl); ^{13}C nmr (50 MHz; $CDCl_3$; Me_4Si): δ 157.4 (C2-isourea), 151.5 (C2-benzothiazolyl), 131.9 and 129.8 (C8-, C9-benzothiazolyl), 125.3, 122.5, 120.8, 119.5 (C4-, C5-, C6-, C7-benzothiazolyl), 69.7 (CH-isopropyl), 36.1 (C1-ethyl), 22.0 (CH_3-isopropyl), 15.6 (C2-ethyl); ms (ei): m/z 150 (93), 176 (91), 177 (100), 221 (20), 263 (53, M^+), 264 (10, M^++1).

Anal. Calc. for $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.51; N, 15.96; S, 12.17. Found: C, 59.33; H, 6.32; N, 15.89; S, 12.07.

N-(4-Pyridyl)-*N*-(5,6,7,8-tetrahydronaphth-1-yl)-*N'*-butylurea (**4a**).

Sulphuryl chloride (130 mg, 77μL, 1.0 mmol) was added dropwise to a solution of the pyridylthiourea **2a** (339 mg, 1.0 mmol) in dichloromethane (25 mL). The mixture was refluxed for 1 hour and then poured into 25 mL of ice-water. The mixture was carefully neutralized with potassium carbonate and extracted with dichloromethane (3 x 50 mL). The organic layer was washed with water (50 mL), dried with Na_2SO_4 and evaporated to dryness *in vacuo* to give a syrup that was separated by column chromatography, using as eluents mixtures of hexane:ethyl acetate of increasing polarity (ranging from 3:1 to 1:1). The reaction product was completely purified by preparative centrifugal circular thin layer chromatography, using ethyl acetate:methanol (60:1) as eluent. The fractions of R_f = 0.2 (ethyl acetate:methanol, 60:1) were evaporated to dryness, rendering the title urea **4a** (265 mg, 82%) as a white solid mp 123-124 °C; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ [8.27 (2H, dd, H(2,6)-pyridyl), 7.09 (2H, dd, H(3,5)-pyridyl), $J_{2,3}$ = $J_{5,6}$ = 4.9, $J_{2,6}$ = $J_{3,5}$ = 1.6], 7.17 (1H, t, *J* = 6.7, H(3)-tetrahydronaphthyl), [7.18 (1H, dd, H(4)-tetrahydronaphthyl), 6.98 (1H, dd, H(2)-tetrahydronaphthyl), $J_{2,3}$ = $J_{3,4}$ = 6.7, $J_{2,4}$ = 2.2], 4.42 (1H, br t, NH(3), D_2O-exchangeable), 3.14 (2H, q, *J* = 7.1, CH_2(1)-butyl, becomes as a triplet with D_2O), 2.78 (2H, br t, CH_2(5)-tetrahydronaphthyl), [2.50 (1H, dt, CH_2(8)-tetrahydronaphthyl), 2.35 (1H, dt, CH_2(8)-tetrahydronaphthyl), J_{gem} = -16.9, J_{vic} = 5.8], 1.68 (4H, br quint, CH_2(6,7)-tetrahydronaphthyl), 1.31 (2H, quint, *J* = 7.1, CH_2(2)-butyl), 1.17 (2H, sext, *J* = 7.1, CH_2(3)-butyl), 0.81 (3H, t, *J* = 7.1, CH_3-butyl); ^{13}C nmr (50 MHz; $CDCl_3$; Me_4Si): δ 155.1 (C=O), 150.0, 149.5 and 115.1 (pyridyl group), 140.8, 137.7, 136.7, 130.6, 127.4, 127.1, 29.6, 24.5, 22.6 and 22.4 (tetrahydronaphthyl moiety), 40.4, 32.0, 19.9 and 13.7 (butyl chain); ms (ei): m/z 146 (38), 196 (50), 224 (100), 323 (32, M^+), 324 (8, M^++1).

Anal. Calcd. for $C_{20}H_{25}N_3O$: C, 74.71; H, 7.79; N, 12.99. Found: C, 74.65; H, 7.73; N, 12.86.

1-(2-*E*-Butylimino-4-methyl-2,3-dihydrothiazol-3-yl)-5,6,7,8-tetrahydronaphthalene (**6**).

A solution of thiourea **1a** (70 mg, 0.27 mmol) and propargyl bromide (48 μL, 0.54 mmol) in 50 mL of dry tetrahydrofuran was refluxed for 4 hours. After cooling to room temperature, the mixture was poured into 50 mL of ice-water and made basic by slow addition of potassium carbonate. The resulting aqueous solution was extracted with ethyl acetate (3 x 100 mL) and the organic layer was washed with water (100 mL), dried with Na_2SO_4 and evaporated to dryness *in vacuo* to give a syrup that was purified on a silica gel column using hexane:ethyl acetate (3:1) as eluent. The fractions of R_f = 0.6 were evaporated to dryness, rendering the thiazoline **6** (71 mg, 88%) as a pure syrup; ^{1}H nmr (500 MHz; $CDCl_3$; Me_4Si): δ 7.17 (1H, t, *J* = 7.6, H(3)-tetrahydronaphthyl), 7.11 (1H, d, *J* = 7.6, H(4)-tetrahydronaphthyl), 6.96 (1H, d, *J* = 7.6, H(2)-tetrahydronaphthyl), 5.61 (1H, s, H(5)-thiazoline), [3.19 (1H, dt, Ha(1)-butyl), 3.00 (1H, dt, Hb(1)-butyl), J_{gem} = -12.4, J_{vic} = 7.2], [2.83 (1H, dt, Ha(5)-tetrahydronaphthyl), 2.78 (1H, dt, Hb(5)-tetrahydronaphthyl), J_{gem} = -17.0, J_{vic} = 6.0], [2.62 (1H, dt, Ha(8)-tetrahydronaphthyl), 2.32 (1H, dt, Hb(8)-tetrahydronaphthyl), J_{gem} = -17.2, J_{vic} = 6.0], 1.78 (2H, m, CH_2(6)-tetrahydronaphthyl), 1.72 (2H, m, CH_2(7)-tetrahydronaphthyl), 1.68 (3H, s, CH_3-thiazoline), 1.52 (2H, quint, *J* = 7.2, CH_2(2)-butyl), 1.32 (2H, sextet, *J* = 7.2, CH_2(3)-butyl), 0.89 (3H, t, *J* = 7.2, CH_3-butyl); ^{13}C nmr (50 MHz; $CDCl_3$; Me_4Si): δ 158.4, 134.5 and 92.1 (thiazoline), 138.9, 136.7, 136.2, 129.7, 126.6, 126.1, 29.5, 24.5, 22.8 and 22.6 (tetrahydronaphthyl moiety), 55.2, 32.2, 20.6 and 14.0 (butyl chain), 15.1 (CH_3-thiazoline); ms (apci positive mode): m/z 301 (MH^+).

Anal. Calcd. for $C_{18}H_{24}N_2S$: C, 71.96; H, 8.05; N, 9.32; S, 10.67. Found: C, 71.95; H, 7.99; N, 9.36; S, 10.68.

1-(3-Butyl-4-methyl-2,3-dihydrothiazol-2-*E*-yliden)amino-5,6,7,8-tetrahydronaphthalene (**7**).

To a suspension of sodium hydride (0.19 mmol, oil free) in dry *N*,*N*-dimethylformamide (50 mL) under nitrogen, a solution of thiourea **1a** (50 mg, 0.19 mmol) and propargyl bromide (18 μL, 0.19 mmol) was added, and the mixture was stirred at room temperature over night (≈16 hours). Then, the mixture was poured into 50 mL of ice-water, carefully neutralised with dilute HCl, and extracted with dichloromethane (3 x 100 mL). The organic layer was dried with Na_2SO_4 and evaporated to dryness *in vacuo* to give a syrup that was purified on a silica gel column using using hexane:ethyl acetate of increasing polarity (from 6:1 to 1:1) as eluents. The fractions of R_f = 0.8 (hexane:ethyl acetate 3:1) were evaporated to dryness, rendering thiazoline **7** as a pure syrup (30 mg, 53%); ^{1}H nmr (500 MHz; $CDCl_3$; Me_4Si): δ 6.97 (1H, t, *J* = 7.5, H(3)-tetrahydronaphthyl), 6.72 (1H, d, *J* = 7.5, H(2)-tetrahydronaphthyl), 6.69 (1H, d, *J* = 7.5, H(4)-tetrahydronaphthyl), 5.37 (1H, q, *J* = 1.2, H(5)-thiazoline), 3.82 (2H, t, *J* = 7.3, CH_2(1)-butyl), 2.70 (2H, m, CH_2(5)-tetrahydronaphthyl), 2.54 (2H, m, CH_2(8)-tetrahydronaphthyl), 2.06 (3H, d, *J* = 1.2, CH_3-thiazoline), 1.69 (6H, m, CH_2(2)-butyl and CH_2(6,7)-tetrahydronaphthyl), 1.34 (2H, sextet, *J* = 7.3, CH_2(3)-butyl), 0.82 (3H, t, *J* = 7.3, CH_3-butyl); 13C nmr (50 MHz; $CDCl_3$; Me_4Si): δ 158.5, 134.7 and 92.0 (thiazoline), 150.3, 138.2, 130.0, 125.8, 123.8, 116.9, 29.9, 25.0, 23.3 and 23.0 (tetrahydronaphthyl moiety), 44.1, 30.4, 20.2 and 13.9 (butyl chain), 14.8 (CH_3-thiazoline); ms (ei): m/z 84 (100), 131 (48), 146 (27), 217 (30), 300 (10, M^+), 301 (1, M^++1).

Anal. Calcd. for $C_{18}H_{24}N_2S$: C, 71.96; H, 8.05; N, 9.32; S, 10.67. Found: C, 72.06; H, 7.96; N, 9.37; S, 10.59.

From the fractions of R_f = 0.6 (hexane : ethyl acetate 3:1) the previously mentioned thiazoline **6** was isolated as a pure syrup (19 mg, 33%).

2-(2-*Z*-Butylimino-4-methyl-2,3-dihydrothiazol-3-yl)-benzimidazole (**8**).

A solution of thiourea **1c** (100 mg, 0.4 mmol) and propargyl bromide (71 μL, 0.8 mmol) in 50 mL of dry tetrahydrofuran was refluxed for 7 hours. After cooling to room temperature, the mixture was poured into 50 mL of ice-water and made basic by slow addition of potassium carbonate. The resulting aqueous solution was extracted with dichloromethane (3 x 100 mL) and the organic layer was washed with water (100 mL), dried with Na_2SO_4 and evaporated to dryness *in vacuo* to give a syrup that was purified on a silica gel column using hexane : ethyl acetate (5:1) as eluent. The fractions of R_f = 0.5 were evaporated to dryness, rendering compound **8** (41 mg, 28%) as a white solid mp 90-91 °C; ^{1}H nmr (500 MHz; $CDCl_3$; Me_4Si) [7.45 (2H, dd, H(4,7)-benzimidazole), δ 7.13 (dd, 2H, H(5,6)-benzimidazole), $J_{4,5}$ = $J_{6,7}$ = 6.0, $J_{4,6}$ = $J_{5,7}$ = 3.2], 5.66 (1H, q, *J* = 1.1, H(5)-thiazoline), 3.14 (2H, t, *J* = 7.3, CH_2(1)-butyl), 2.67 (3H, d, *J* = 1.1, CH_3-thiazoline), 1.70 (2H, quint, *J* = 7.3, CH_2(2)-butyl), 1.42 (2H, sextet, *J* = 7.3, CH_2(3)-butyl) and 0.92 (3H, t, *J* = 7.3, CH_3-butyl); ^{13}C nmr (50 MHz; $CDCl_3$; Me_4Si) 159.2, 135.8 and 96.4 (thiazoline), 147.8,

135.9, 121.8 and 114.5 (benzimidazole moiety), 54.4, 32.7, 20.8 and 13.9 (butyl chain), 19.2 (CH_3-thiazoline); m/z (EI) 118 (62), 170 (100), 203 (79), 243 (43), 286 (53, M^+), 287 (10, M^++1).

Anal. Calc. for $C_{15}H_{18}N_4S$: C, 62.91; H, 6.34; N, 19.56; S, 11.19. Found: C, 62.85; H, 6.51; N, 19.60; S, 11.04.

N-(1-Naphthyl)-*N'*-ethyl-*S*-(2-propynyl)isothiourea Hydrobromide (**9**•HBr).

A solution of thiourea **1b** (100 mg, 0.43 mmol) and propargyl bromide (77 µL, 0.86 mmol) in 50 mL of dry tetrahydrofuran was refluxed for 8 hours. After cooling to room temperature a precipitate was observed, that was filtered off and washed with cold tetrahydrofuran, yielding isothiourea **9**.HBr (99 mg, 65%) as a white solid of mp 198-200 °C; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 8.14 (1H, br. s, D_2O-exchangeable, NH), 7.90 (2H, m, naphthyl), 7.55 (5H, m, naphthyl), 3.74 (2H, br. s, *N*-CH_2Me), 3.34 (2H, br. s, SCH_2CCH), 2.37 (1H, t, *J* = 2.6, SCH_2CCH), 1.47 (3H, t, *J* = 8.3, NCH_2CH_3); ^{13}C nmr (50 MHz; CD_3OD; Me_4Si): δ 168.3 (br., C2-isothiourea), 136.0, 130.0, 128.9, 128.3, 127.4, 126.7 and 123.0 (naphthyl moiety), 102.0 (SCH_2CCH), 75.8 (SCH_2CCH), 41.8 (NCH_2CH_3), 22.0 (SCH_2CCH), 14.3 (NCH_2CH_3).

Anal. Calcd. for $C_{16}H_{16}N_2S$•HBr: C, 55.02; H, 4.91; N, 8.02; S, 9.18. Found: C, 54.97; H, 5.01; N, 8.23; S, 8.99.

N-(5,6,7,8-Tetrahydronaphth-1-yl)-*N'*-butyl-*S*-(2-propen-1-yl)-isothiourea (**10**).

To a suspension of sodium hydride (0.29 mmol, oil free) in dry *N*,*N*-dimethylformamide (50 mL) under nitrogen, a solution of thiourea **1a** (75 mg, 0.29 mmol) and 3-bromopropene (allyl bromide) (27 µL, 0.29 mmol) was added, and the mixture was stirred at room temperature over night (≈18 hours). Then, the mixture was poured into 50 mL of ice-water, carefully neutralised with dilute HCl, and extracted with dichloromethane (3 x 100 mL). The organic layer was dried with Na_2SO_4 and evaporated to dryness *in vacuo* to give a syrup that was purified on cctlc using hexane:ethyl acetate of increasing polarity (from 25:1 to 2:1) as eluents. The fractions of R_f = 0.6 (hexane:ethyl acetate, 10:1) were evaporated to dryness yielding isothiourea **10** (20 mg, 23%) as a pure syrup; ^{1}H nmr (500 MHz; $CDCl_3$; Me_4Si): δ 6.93 (1H, t, *J* = 7.0, H(3)-tetrahydronaphthyl), 6.68 (1H, d, *J* = 7.0, H(4)-tetrahydronaphthyl), 6.51 (1H, d, *J* = 7.5, H(2)-tetrahydronaphthyl), [3.43 (2H, d, $CH^a_2CH^b$=CH^cH^d), 5.85 (1H, ddt, $CH^a_2CH^b$=CH^cH^d), 5.19 (1H, ddt, $CH^a_2CH^b$=CH^cH^d), 5.08 (1H, ddt, $CH^a_2CH^b$=CH^cH^d), $J_{a,b}$ = 6.8, $J_{a,c}$ = $J_{a,d}$ = 1.3, $J_{b,c}$ = 17.0, $J_{b,d}$ = 10.0, $J_{c,d}$ = 1.3], 4.36 (1H, br. s, NH), 3.22 (2H, br. t, CH_2(1)-butyl), 2.68 (2H, m, CH_2(5)-tetrahydronaphthyl), 2.44 (2H, m, CH_2(8)-tetrahydronaphthyl), 1.68 (4H, m, CH_2(6,7)-tetrahydrnaphthyl), 1.46 (2H, quint, *J* = 7.2, CH_2(2)-butyl), 1.27 (2H, sext, *J* = 7.2, CH_2(3)-butyl), 0.86 (2H, t, *J* = 7.2, CH_3-butyl); 13C nmr (50 MHz; CD_3OD; Me_4Si): δ 151.6 (br., C2-isothiourea), 147.8, 138.0, 129.4, 125.5, 123.6, 118.5, 29.9, 25.1, 23.3 and 23.1 (tetrahydronaphtyl moiety), 134.7 (CH_2CH=CH_2), 117.6 (CH_2CH=CH_2), 33.9 (CH_2CH=CH_2), 42.9, 31.9, 20.1 and 13.7 (butyl chain).

Anal. Calc. for $C_{18}H_{26}N_2S$: C, 71.48; H, 8.66; N, 9.26; S, 10.60. Found: C, 71.40; H, 8.67; N, 9.17; S, 10.61.

Molecular modelling studies.

SYBYL program [21], implemented on a Silicon Graphics working station, was used. Input geometries were taken from the standard ones within SYBYL program, that were optimised using the semiempirical AM1 method [20] in MOPAC V5.0 program package [23]. In all cases, full geometry optimisations with Fletcher-Powell algorithm were carried out.

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