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Reactivity and diastereoselectivity of Michael additions of amines to achiral α,β-unsaturated thioamides

Jacek G. Sośnicki,[a,*] Tadeusz S. Jagodziński[a] and Poul Erik Hansen[b]

[a]Institute of Fundamental Chemistry, Technical University of Szczecin, Al. Piastów 42, PL-71065 Szczecin, Poland
[b]Department of Life Sciences and Chemistry, Roskilde University, P.O. Box 260, DK-4000 Roskilde, Denmark

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Abstract—Heterocyclic, aliphatic amines add to acyclic and cyclic α,β-unsaturated thioamides yielding β-amino-functionalized derivatives. In the case of cyclic acceptors, the formation of both kinetic and thermodynamically controlled products is observed. Tailoring of *cis* or *trans* products is thus possible. A mechanism for the addition to cyclic acceptors is proposed and evidence presented to support it. Ease of addition is studied in relation to the structure of the acceptors. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The great utility of Michael addition reactions in organic synthesis is well documented.[1,2] During the last two decades α,β-unsaturated thioamides have been recognized as good Michael acceptors. They form C–C bonds in reactions with C-nucleophiles such as alkyllithiums, alkylmagnesiums,[3,4] lithium enolates[5] and nitromethane in the presence of base catalyst.[6] Reactions with heteronucleophiles have been only sparingly studied.[7] The diastereoselectivity of Michael addition reactions to α,β-disubstituted acceptors is an important feature. A series of papers concerning diastereoselectivity of addition of amines to electron deficient cyclic olefins, e.g. 1-nitrocyclopentenes,[8] 1-nitrocyclohexenes,[9] substituted 3′-enesulfones[10] or 3′-enenitriles[11] describe different diastereoselection, depending on the type of acceptor and amine.

Recently, we reported the diastereoselective Michael addition of nitrogen and sulphur nucleophiles to chiral 6-substituted α,β-unsaturated δ-thiolactams.[12] Owing to the synthetic value of thioamides as synthons,[13] we decided to investigate the addition of amines to 2-, 3-substituted acyclic and cyclic secondary and tertiary α,β-unsaturated thioamides other than thiolactams. As donors, we selected heterocyclic, aliphatic amines (piperidine, morpholine, pyrrolidine), diethylamine and as acceptors, various substituted secondary and tertiary thioamides, derivatives of acrylic- (**1a**), cinnamic- (**1b**,**c**,**j**), crotonic- (**1e**,**k**), methacrylic- (**1d**,**l**), 1-cyclohexene- (**1f**,**g**,**m**) and 1-cyclopentene- (**1h**,**i**,**n**) carboxylic acids. Applying achiral cyclic acceptors, **1f**–**n**, we examined the diastereoselectivity of the addition. The broad spectrum of applied acceptors has also allowed us to inspect the factors influencing the reactivity.

2. Results and discussion

2.1. Synthesis

Piperidine, morpholine and pyrrolidine led to stable products in reaction with tertiary acyclic thioamides **1j**–**l** (Scheme 1) while only six-membered amines (piperidine or morpholine) gave stable compounds with cyclic and acyclic secondary thioamides **1a**–**i** (Schemes 1 and 2). Addition of pyrrolidine to secondary thioamides resulted in unstable adducts (identified by TLC). The products were subsequently decomposed in a presumably retro-Michael reaction during purification. Diethylamine did not undergo addition to the thioamides studied. Except for **1a** and **d**, the reactions were conducted without solvent using neat thioamides **1b**,**c**,**e**–**n** and a 5–10-fold excess of amine in order to achieve complete conversion. In the case of **1a** and **d**, a smaller excess of piperidine was used and the reaction was conducted in etheral or alcoholic solution, respectively, using freshly prepared thioamide acceptors **1a** (crude) or **d** (carefully purified) due to their instability. The adducts were obtained in good to moderate yields and only regioselective 1,4-addition was observed. Yields and reaction conditions are given in Table 1.

The most interesting results were obtained using cyclic thioamides **1f**–**i**,**m**,**n** as starting materials. In this case, dependence on reactivity and diastereoselectivity of addition on the ring size, the character of thioamide moiety as well as the nucleophilicity and basicity of amine was observed (Scheme 2, Table 1). In general, the reactions were conducted at room temperature but for less reactive

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Keywords: Michael addition; α,β-unsaturated thioamides; *s-cis*/*s-trans* conformation; *Z*/*E* configuration; reactivity; FMO-theory; diastereoselectivity.

[*] Corresponding author; e-mail: sosnicki@carbon.tuniv.szczecin.pl

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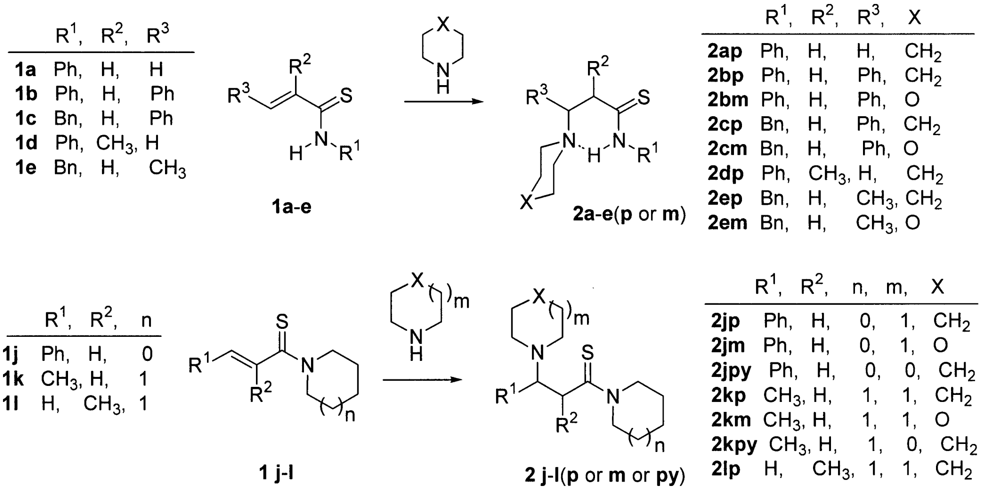
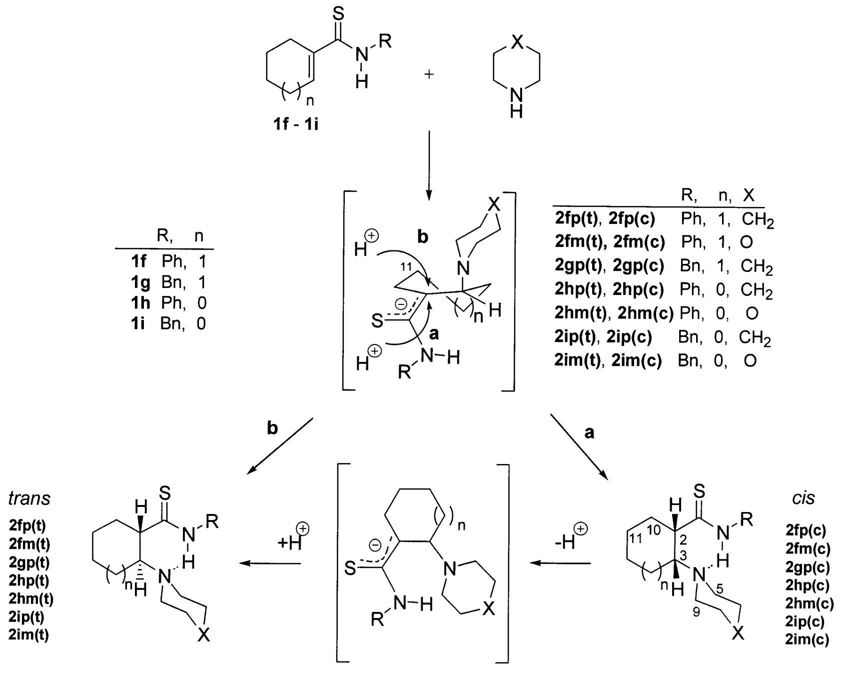


Scheme 1.

thioamides, a temperature of 80°C was applied. Both the tertiary thioamides **1m** and **n** were not reactive, producing only traces of the products after 40 days at room temperature as well as when kept at 80°C for 5 days. The reactions conducted at room temperature showed that among both pairs of secondary thioamides **1f**,**g** and **1h**,**i** *N*-Ph substituted derivatives, **1f**,**h** were more reactive than their N-Bn analogs **1g**,**i** (Table 1). Analogously, 1-cyclopentene derivatives **1h**,**i** were more reactive, respectively, to their 1-cyclohexene analogs **1f**,**g**. Moreover in this case, different stereoselectivity was observed. The course of the reaction using cyclic thioamides was followed by ^{1}H NMR spectroscopy. Thus in the reaction of *N*-phenyl 1-cyclohexenecarboxythioamide (**1f**) with piperidine for seven days only the *trans* isomer (Scheme 2, Table 1, entry 9) was formed in good yield, while its *N*-benzyl analog (**1g**), which reacted much more slowly (48 days), led to a 90:10 mixture of *cis*/*trans* isomers, respectively, in a total yield of 19% (Scheme 2 and Table 1, entry 12). Both reactions showed no variation in time in the diastereomer distribution in the crude mixture. It should be noted that the pure products **2gp(t)** and **2gp(c)** remained unchanged upon treatment with piperidine after 40 days.

In the case of 1-cyclopentenecarboxythioamides **1h** and **i**, the formation of *cis*/*trans* mixtures and further enrichment of the *trans* isomer was observed (Table 1). Only in the case of the reaction between **1i** and morpholine, the ratio of *trans* and *cis* isomers were slightly changed (Table 1, entry 17) while in all other cases (Table 1, entries 14–16), the isomerization reaction was fast enough to lead to single *trans* isomers after an appropriate time at room temperature. Treatment of a previously formed mixture lead to preferred formation of *trans* adducts as observed in the reactions



Scheme 2.

Table 1. Yield and the reaction conditions of addition of amines to α,β-unsaturated thioamides

Entry	Substrate	Amine[a]/solvent	Molar ratio of thioamide/amine	Temperature (°C)	Reaction time	Adducts[a] (diastereomeric ratio),[b] yield (%)
1	**1a**	p/diethyl ether	1:1.2	20	2 h	**2ap**, 64
2	**1b**	p/neat	1:8	20	24 h	**2bp**, 89
3	**1b**	m/neat	1:8	20	24 h	**2bm**, 83
4	**1c**	p/neat	1:8	20	24 h	**2cp**, 85
5	**1c**	m/neat	1:8	20	24 h	**2cm**, 87
6	**1d**	p/methanol	1:2	20	6 h	**2dp**, 74
7	**1e**	p/neat	1:8	20	20 h	**2ep**, 72
8	**1e**	m/neat	1:8	20	20 h	**2em**, 92
9	**1f**	p/neat	1:10	20		**2fp(t)/2fp(c)**
					1 day	(100:0)[c]
					7 days	(100:0) 77
10	**1f**	p/neat	1:20	80		**2fp(t)/2fp(c)**
					2 h	ca (50:50)[c]
					24 h	(100:0) 82
11	**1f**	m/neat	1:10	80		**2fm(t)/2fm(c)**
					14 h	(43:57)[c]
					82 h	(90:10)
					6 days	(>95:5) 82
12	**1g**	p/neat	1:10	20		**2gp(t)/2gp(c)**
					20 days	(10:90)[c]
					48 days	(10:90)[c] 19
13	**1g**	p/neat	1:10	80		**2gp(t)/2gp(c)**
					24 h	ca (30:70)[c]
					72 h	ca (75:25)[c]
					7 days	(100:0)[c] 39
14	**1h**	p/neat	1:5	20		**2hp(t)/2hp(c)**
					1.5 h	(55:45)
					20 h	(100:0) 90
15	**1h**	m/neat	1:5	20		**2hm(t)/2hm(c)**
					20 h	(59:41)
					64 h	(>99:1) 73
16	**1i**	p/neat	1:5	20		**2ip(t)/2ip(c)**
					3 days	(58:42)
					11 days	(>99:1) 69
17	**1i**	m/neat	1:5	20		**2im(t)/2im(c)**
					20 days	(31:69)
			Then 1:10	Then 80	3 days	(93:7) 84
18	**1j**	p/neat	1:10	20	5 days	**2jp** 72
19	**1j**	m/neat	1:10	20	5 days	**2jm** 46
20	**1j**	py/neat	1:10	20	5 days	**2jpy** 66
21	**1k**	p/neat	1:10	20	20 h	**2kp** 78
22	**1k**	m/neat	1:10	20	20 h	**2km** 72
23	**1k**	py/neat	1:10	20	20 h	**2kpy** 88
24	**1l**	p/neat	1:10	20	4 days	**2lp** 43

[a] p: piperidine; m: morpholine; py: pyrrolidine, (**t**): *trans*; (**c**): *cis*.

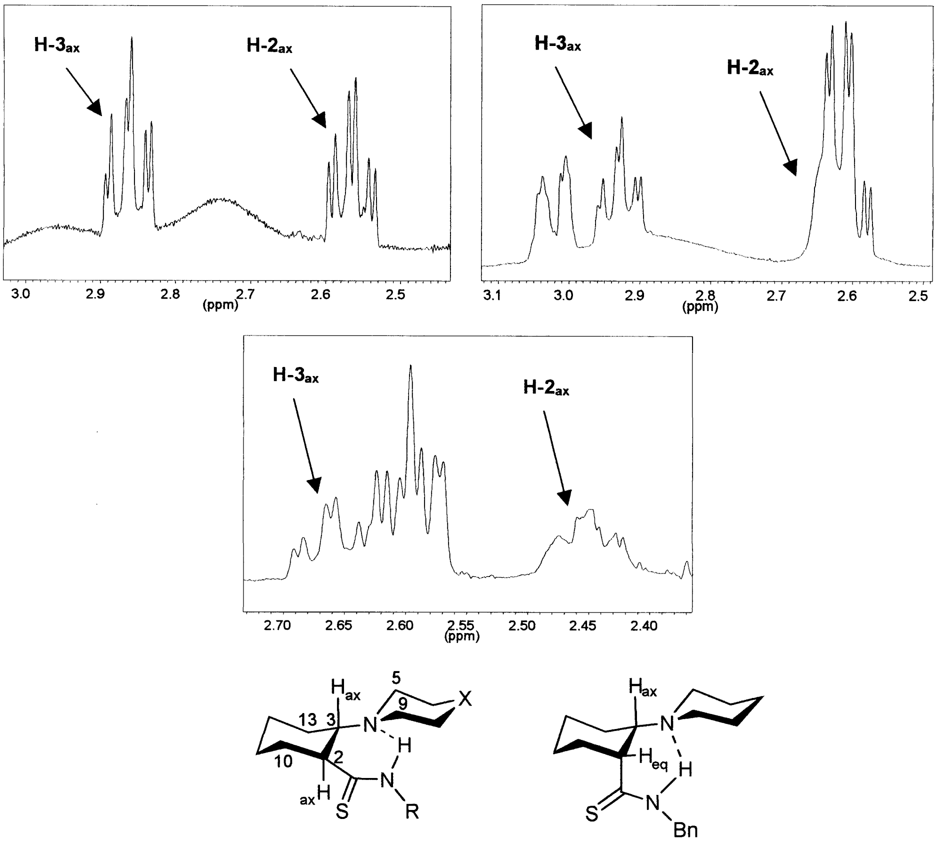
[b] The ratio of diastereoisomers was estimated by ^{1}H NMR spectra of crude reaction mixture after evaporation of amine.

[c] Substrate present.

between thioamides, derivatives of 1-cyclohexenecarboxylic acid and morpholine (**1f**, Table 1, entry 11) and piperidine (**1f**,**g**, Table 1, entries 10 and 13, respectively) conducted at 80°C. It should be emphasized that in the case of the reaction of **1g** with piperidine, the temperature conditions changed the ratio of the final products from 10% *trans*/90% *cis* (20°C) to 100% *trans* (80°C). For preparative reasons and because of considerable problems in separation of diastereoisomers, the reaction was prolonged at room temperature (Table 1, entries 14–17) or heated at 80°C (Table 1, entries 11, 13 and 17) in order to obtain the pure thermodynamically stable *trans*-isomer.

2.2. Structural assignment

The structures of all compounds were elucidated using 1D (^{1}H, ^{13}C, ^{13}C DEPT) and 2D (^{1}H, ^{1}H COSY, ^{13}C, ^{1}H COSY, ^{1}H, ^{1}H NOESY) NMR spectra. Adducts derived from secondary thioamides showed in $CDCl_3$ solution, six-membered quasi heterocyclic rings due to the strong N–H···N hydrogen bond formation (Schemes 1 and 2). *N*-benzyl and morpholinyl substituents caused formation of weaker hydrogen bonding relative to the *N*-phenyl and piperidinyl substituted analogs as judged from NH chemical shifts. The configuration of **2fp(t)**, **2fm(t)**, **2gp(t)**, **2gp(c)**, **2hp(t)**, **2hm(t)**, **2ip(t)** and **2im(t)** were based on coupling constants between H-2 and H-3 protons. Spectra of **2fp(t)** and **2fm(t)** were broad at room temperature and therefore were recorded at a lower temperature (240 K) and a Lorentzian to Gaussian resolution enhancement was applied (Fig. 1). In the case of **2fp(t)**, these operations allowed observation of two similar triplets of doublets (td,



2fp(t) (R= Ph), X=CH_2
2fm(t) (R= Ph), X=O
2gp(t) (R = Bn), X=CH_2

2gp(c)

Figure 1. The configuration, conformation of **2fp(t)**, **2fm(t)**, **2gp(t)**, **2gp(c)** and parts of the Gaussian to Lorentzian resolution enhanced spectra of compounds **2fp(t)** (240 K, upper-left), **2fm(t)** (240 K, upper-right) and **2gp(t)** (300 K, lower).

J_{1-2}=10.6 Hz, J_3=3.6 Hz; td, J_{1-2}=10.5 Hz, J_3=2.9 Hz) belonging to H-2; H-3, respectively (Fig. 1).

For **2fm(t)**, one triplet of doublets was seen, while the second one was overlapped. Two large and one small coupling constants indicate their *trans* relationship in antiperiplanary (diaxially) orientations and allowed assignment of the configuration as *trans* (Fig. 1). A *trans* configuration was also found for **2gp(t)** based on the spectra recorded at 300 K (Fig. 1). In the case of **2gp(c)**, signal multiplicities of the diagnostic protons H-2 (brs), H-3 (dt, J_{1-2}=3.8 Hz, J_3=11.4 Hz) established the configuration as *cis*. The lack of couplings at H-2 showed that this proton has to be equatorial and accordingly the thioamide group is axial. Two small and one large coupling constants at H-3 indicate its axial position and an equatorial orientation of the piperidine substituent (Fig. 1). For **2hp(t)**, **2hm(t)**, **2ip(t)**, **2im(t)**, the *trans* configuration was based on the presence of almost symmetrical multiplets (quartets) belonging to H-2 and H-3 in the ^{1}H spectra and on the non-existence of NOE effects between these protons in the ^{1}H, ^{1}H NOESY spectra.

2.3. Structure and reactivity of the thioamide acceptors

The experimental data showed that the success of the addition of heterocyclic amines to α,β-unsaturated thioamides depends both on the type of amine and on the type of acceptor. Among the reactions studied, the reactions using cyclic thioamide **1f–i** gave the most interesting results. In order to rationalize the experimental observations, the structures of all thioamide acceptors, except **1a**,**d** (not stable compounds) were examined using ^{1}H, ^{1}H NOESY spectra. The existence of *s-cis*/*s-trans* conformations (secondary and tertiary thioamides) and *Z*/*E* configuration (secondary thioamide) was taken into consideration. (Recently we demonstrated that ^{1}H, ^{1}H NOESY spectra are suitable for elucidation of *s-cis*/*s-trans* conformation in α,β-unsaturated compounds.[14]) Subsequently, for such estimated structures, optimization and calculation of frontier molecular orbital energies (LUMO/HOMO) were performed using the semi-empirical PM3 method.[15] The results of the NOESY structural analysis and the calculations are presented in Table 2. The results based on NOESY spectra showed that β-substituted derivatives (**1b**,**c**,**e**,**j**,**k**) are planar or almost planar and the *s-cis* conformation and the *Z* configuration (secondary thioamides) predominate in these cases. These results are in agreement with the calculated low value of the C=C–C=S dihedral angles. In the series of α-substituted and α,β-disubstituted compounds, the picture is more complicated. Judging by the magnitude of NOE effects (Table 2, integration), we could conclude that C=C–C=S dihedral angles are close to 90° (**1f–h**,**l–n**). These observations are also supported by PM3 calculations. Unexpectedly, in the case of **1i** contrary to the perpendicular orientation along

C=C–C=S bonds found by calculation, NOESY spectra indicated rather planar orientation.

As far as frontier molecular orbital (FMO) calculations are concerned, the energies for the LUMO (Table 2) are parallel to the reactivity (Table 1). This observation for the present Michael additions is in agreement with data found by ab initio calculations for other conjugated acceptors, e.g. alkenones.[1] For the thioamide acceptors, some structural dependence on LUMO level should be pointed out. The most striking is that the presence of a phenyl ring at nitrogen as well as at the β-position decreases the energy of the LUMO presumably because of the phenyl group conjugation. This effect is generally greater for *N*-phenyl derivatives than for β-phenyl substituted compounds and makes the *N*-phenyl thioamides more reactive. Moreover for non-aromatic tertiary, and *N*-benzyl secondary derivatives, the lower LUMO is seen for structures with planar C=C–C=S bonds, e.g. LUMO of planar **1e** is −0.93 eV while the LUMO of the non-planar **1g** is higher, −0.67 eV (Table 2). The same effect is observed for **1k** and **l**. Another factor, which could influence the reactivity, is the formation of NH···N hydrogen bonds between acceptor and donor (intermolecular system) and in the products (intramolecular system). This assumption could explain the higher reactivity of the *N*-phenyl derivative **1f** towards piperidine compared to its *N*-benzyl analog **1g** due to more acidic N-hydrogen in **1f** as well as the higher reactivity of piperidine with respect to morpholine, which the latter—as mentioned above—formed weaker NH···H bonds in the products. Compounds **1m** and **n** having the highest LUMO energies, the largest steric factors (molecules are not planar) and no possibility of NH(thioamide)···N(amine) bond formation are not very reactive.

2.4. Stereoselectivity of addition to cyclic acceptors—mechanism

The obtained results clearly indicated that the mechanism of addition of amines to the conjugated thioamides consists of a slow, rate determining addition of amine followed by rapid protonation of the intermediate carbanion from the same side (*syn*-addition, *trans*-product, Scheme 2, path **b**) or from the opposite side (*anti*-addition, *cis*-product, Scheme 2, path **a**). In the beginning of the reaction, the *anti*-addition process is preferred over the *syn* because of lower steric hindrance between incoming proton (H^+) and CH_2-11 fragment of cyclohexane ring (derivative of 1-cyclohexenecarboxylic acids) as well as the amine ring (derivative of 1-cyclohexene- and 1-cyclopentenecarboxylic acids). This is the picture seen for 1-*p*-tolylsulfonylcyclohexene[16] and is supported by the *trans*/*cis* mixture (10:90) of **2gp(t)/2gp(c)** (Table 1, entry 12) (non-isomerizating at room temperature) and the predominance of *cis* isomers in the beginning of the other reactions (Table 1, entries 11, 13 and 17). The kinetically controlled step is followed by basic isomerization (Scheme 2), which led to the thermodynamically more stable *trans*-products (Table 1). The calculations of heat of formations of *cis* and *trans* diastereoisomers (Table 3) support that *trans*-products are more stable than *cis*-isomers. The progress of the isomerization seems to be dependent on basicity of the amine used. The much more facile isomerization of the *N*-phenyl compared to *N*-benzyl derivatives support the mechanism, as the *N*-phenyl derivative has a much more acidic NH group.

3. Conclusions

The study has shown that addition of heterocyclic, aliphatic amines to α,β-unsaturated thioamides is a convenient method to obtain β-functionalized thioamides, which could be subsequently transformed to other type of compounds, e.g. by reduction to diamines or by hydrolysis to β-aminoacids. Furthermore, the low LUMO energy of acceptors, gained by planarity and/or aromatic substituents, and NH···N hydrogen bonding are factors influencing the reactivity of the addition. These factors and the possibility of basic isomerization towards thermodynamically favored products can be used to obtain selectively uncommon *trans*-1,2-disubstituted aminocarbocycles.

4. Experimental

Melting points were determined on a Boetius hot stage apparatus and are uncorrected. Infrared spectra were taken with a Specord M80 instrument. ^1H, ^{13}C NMR spectroscopic measurements were performed on a Bruker DPX 400 spectrometer equipped with an 5 mm ^1H/BB-inverse probehead, operating at 400.13 and 100.62 MHz with a digital resolution of 0.12 and 0.97 Hz per point for ^1H and ^{13}C, respectively. Low temperature spectra were recorded in $CDCl_3$. TMS was used as internal reference in all measurements. Two-dimensional spectra were acquired using standard Bruker software. Heteronuclear correlation (^{13}C, ^1H COSY) was optimized for a coupling 145 Hz. In ^1H, ^1H NOESY experiments, the mixing time between 0.9–1.1 s were applied. Enhanced resolution spectra were obtained by Lorentzian to Gaussian transformation (LB=−2.5, GB=0.64) using Bruker software for PC. Mass spectra (70 eV) were recorded with a HP 6890 (Hewlett–Packard) GCMS spectrometer equipped with a mass detector HP 5973. Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatography. Elemental analyses were performed on EuroEA 3000 series, EuroVector CHNS-O Elemental Analyser. All compounds gave satisfactory elemental analysis (C, H, N, S).

4.1. Synthesis of α,β-unsaturated thioamides (starting materials)

Thioamides **1b**,**c**,**e**–**g**,**i**–**n** were prepared from the corresponding amides according to a standard procedure using Lawesson reagent in refluxing benzene in a molar ratio of 0.55:1 (Lawesson reagent/amide).[17] The oxygen–sulphur exchange was completed after 1–4 h (established by TLC). Products were twice chromatographed on silica gel using *n*-hexane/ethyl acetate (8:2) as eluent.

The thioamides, **1b**: mp 138–139°C from ethyl acetate–*n*-hexane (lit.[18] 134°C), **1c**: mp 118–119°C from acetonitrile (lit.[19] 115–116°C), **1d**: mp 45–53°C from *n*-hexane, lit.[4] (This compound is not a stable semisolid even when kept in the refrigerator.) **1f**: mp 82–85°C from ethyl acetate–*n*-hexane (lit.[4] 85°C), **1k**: oil (lit.[7] 34°C) are known compounds.

Table 2. NOESY and PM3 analysis data

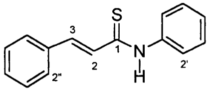
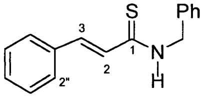
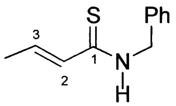
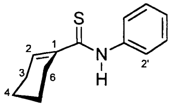
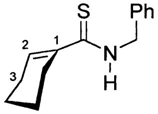
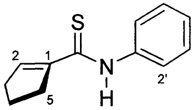
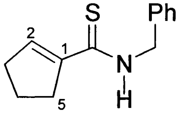
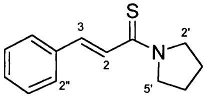
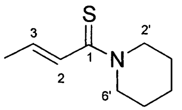
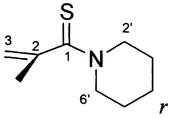
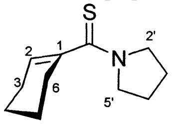
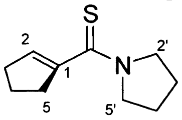
Acceptor	**1b**	**1c**	**1e**	**1f**
Conformation and configuration based on NOESY spectra	S=C-C=C planar (s-cis) S=C-N (Z) 	S=C-C=C planar (s-cis) S=C-N (Z) 	S=C-C=C planar (s-cis) S=C-N (Z) 	S=C-C=C perpendicular S=C-N (Z) 
Diagnostic NOEs diagonal signal—NOE effect[a]	NH—H-2′ (10.7), H-2 (20.2); H-2—H-2″ (24.1), NH (14.0); H-3—H-2″ (18.1)	NH—H-2 (8.5), CH_2 (6.5); H-2—NH (10.8), H-2″ (11.1); H-3—H-2″ (9.1)	NH—H-2 (4.4), CH_2 (3.1); H-2—NH (7.7), CH_3 (3.4); H-3—CH_3 (8.0)	NH—H-2′ (1.6), H-2 (2.6), CH_2-6 (3.5); H-2—NH (3.2), CH_2-3 (7.9)
PM3 calculation				
LUMO (eV)	−1.45	−1.29	−0.93	−1.05
HOMO (eV)	−8.53	−8.57	−8.54	−8.52
C=C–C=S dihedral angle (deg)	0.5	3.5	0.6	93.5
Acceptor	**1g**	**1h**	**1i**	**1j**
Conformation and configuration based on NOESY spectra	S=C-C=C almost perpendicular S=C-N (Z) 	S=C-C=C perpendicular S=C-N (Z) 	S=C-C=C planar (s-cis) S=C-N (Z) 	C=C-C=S planar (s-cis) 
Diagnostic NOEs diagonal signal—NOE answer[a]	NH—CH_2Ph (6.2), H-2 (1.7), CH_2-6 (7.8); H-2—NH (3.3), CH_2-3 (7.0)	NH—H-2′ (2.3), H-2 (2.0), CH_2-5 (7.2); H-2—NH (2.0), CH_2-3 (4.3)	NH—CH_2Ph (3.6), CH_2-5 (17.4); H-2—CH_2-3 (1.8)	H-2—CH-2″ (6.8), CH_2-5′ (11.1); H-3—CH-2″ (5.6)
PM3 calculation				
LUMO (eV)	−0.67	−1.12	−0.77	−1.08
HOMO (eV)	−8.54	−8.55	−8.53	−8.46
C=C–C=S dihedral angle (deg)	97.8	−115	−112	−35.5

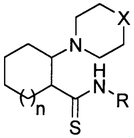
Table 2 (*continued*)

Acceptor	**1k**	**1l**	**1m**	**1n**
Conformation and configuration based on NOESY spectra	C=C-C=S planar (s-cis)  	C=C-C=S perpendicular  	C=C-C=S perpendicular  	C=C-C=S almost perpendicular 
Diagnostic NOEs diagonal signal—NOE effect[a]	H-2—CH_2-6′ (7.8); H-3—CH_3 (11.2); CH_2-6′—CH_2-2′ (−35.0)[b], H-2 (4.4)	CH_3—CH_2-2′ (4.5), CH_2-6′ (5.9), H-3$_{cis}$ (4.2); CH_2-5′— CH_3 (7.7), CH_2-1′ (−38.0)[b]	H-2—CH_2-2′ (2.6), CH_2-5′ (3.9), CH_2-3 (5.7); CH_2-2′—H-2 (0.8), CH_2-6 (1.9), CH_2-3 (2.4) CH_2-5′—H-2 (1.6), CH_2-6 (3.2), CH_2-3 (4.0)	H-2—CH_2-2′ (0.5), CH_2-5′ (3.4), CH_2-3 (2.8); CH_2-5′—CH_2-2′ (−1.7)[b], H-2 (0.9)
			PM3 calculation	
LUMO (eV)	−0.93	−0.69	−0.52	−0.53
HOMO (eV)	−8.43	−8.51	−8.44	−8.44
C=C–C=S dihedral angle (deg)	22.0	−93.6	93.5	−89.9

[a] Integrations of signals, calibrated relative to perturbed signals (value-100), are given in the parenthesis.

[b] Exchange process takes place.

Table 3. Heat of formation (kcal/mol) of *cis* and *trans* isomers of alicyclic compounds calculated by PM3 method

	**2fp** R=Ph, *n*=1, X=CH$_2$	**2fm** R=Ph, *n*=1, X=O	**2gp** R=Bn, *n*=1, X=CH$_2$	**2hp** R=Ph, *n*=0, X=CH$_2$	**2ip** R=Bn, *n*=0, X=CH$_2$	**2im** R=Bn, *n*=0, X=O
trans (**t**)	28.99[a]	2.88[a]	22.57[a]	33.86	28.07	1.89
cis (**c**)	32.64[b]	7.07[b]	26.22[b]	36.32	29.39	3.70
	29.96[c]	3.56[c]	23.22[c]			
$\Delta(H_{cis}-H_{trans})$	3.64	4.19	3.65	2.46	1.32	1.81
	0.97	0.68	0.65			

[a] Calculation performed for H_{ax}-2, H_{ax}-3 oriented chair conformation of cyclohexane.
[b] Calculation performed for H_{eq}-2, H_{ax}-3 oriented chair conformation of cyclohexane.
[c] Calculation performed for H_{ax}-2, H_{eq}-3 oriented chair conformation of cyclohexane.

4.1.1. (*E*) But-2-enethioic acid benzylamide (1e). Reflux 3 h, yield 64%. Pale yellow solid, mp 63–65°C from ethyl acetate/*n*-hexane [Found: C, 68.99; H, 6.82; N, 7.15; S, 17.01. $C_{11}H_{13}NS$ requires C, 69.07; H, 6.85; N, 7.32; S, 16.76%]; ν_{max}(KBr pellet) 3286, 3036, 1654, 1536, 1392, 1346, 1184, 956, 738, 696 cm^{-1}; δ_H (400.1 MHz, CDCl$_3$) 1.86 (3H, dd, *J*=6.9, 1.6 Hz, CH$_3$), 4.88 (2H, d, *J*=5.3 Hz, CH$_2$N), 6.23 (1H, dq, *J*=14.8, 1.6 Hz, H-2), 7.00 (1H, dq, *J*=14.8, 6.9 Hz, H-3), 7.26–7.38 (5H, m, C$_6$H$_5$), 7.41 (1H, brs, NH); δ_C (100.6 MHz, CDCl$_3$) 18.05 (q, CH$_3$), 49.87 (t, CH$_2$N), 128.07, 128.31, 128.89, 136.25 (C$_6$H$_5$), 132.06 (d, C-2), 140.96 (d, C-3), 196.18 (s, C=S); *m/z* (EI, 70 eV) 191 (82, M$^+$), 176 (74), 143 (50), 106 (38), 91 (100), 85 (19), 65 (22%).

4.1.2. Cyclohex-1-enecarbothioic acid benzylamide (1g). Reflux 4.5 h, yield 83%. Pale yellow plates, mp 78–80°C from ethyl acetate/*n*-hexane [Found: C, 72.82; H, 7.69; N, 6.05; S, 14.00. $C_{14}H_{17}NS$ requires C, 72.68; H, 7.41; N, 6.05; S, 13.86%]; ν_{max}(KBr pellet) 3260, 2932, 1630, 1524, 1324, 1184, 966, 736, 696 cm^{-1}; δ_H (400.1 MHz, CDCl$_3$) 1.56–1.62 (2H, m, CH$_2$-4), 1.65–1.72 (2H, m, CH$_2$-5), 2.12–2.20 (2H, m, CH$_2$-3), 2.41–2.48 (2H, m, CH$_2$-6), 4.89 (2H, d, *J*=5.2 Hz, CH$_2$N), 6.55–6.58 (1H, m, =CH), 7.27–7.40 (5H, m, C$_6$H$_5$), 7.45 (1H, brs, NH); δ_C (100.6 MHz, CDCl$_3$) 21.49 (t, CH$_2$-4), 22.35 (t, CH$_2$-5), 25.66 (t, CH$_2$-3), 26.93 (t, CH$_2$-6), 50.11 (t, CH$_2$N), 128.07, 128.28, 128.96, 136.44 (C$_6$H$_5$), 132.06 (d, =CH), 140.29 (s, C-1), 200.52 (s, C=S); *m/z* (EI, 70 eV) 231 (100, M$^+$), 202 (11), 198 (26), 189 (20), 188 (29), 175 (40), 156 (25), 126 (15), 106 (15), 91 (60), 79 (14), 77 (9%).

4.1.3. Cyclopent-1-enecarbothioic acid benzylamide (1i). Reflux 4 h, yield 63%. Pale yellow solid, mp 74–75°C from ethyl acetate/*n*-hexane [Found: C, 71.99; H, 6.84; N, 6.55; S, 15.01. $C_{13}H_{15}NS$ requires C, 71.84; H, 6.96; N, 6.44; S, 14.75%]; ν_{max}(KBr pellet) 3220, 1520, 1340, 696 cm^{-1}; δ_H (400.1 MHz, CDCl$_3$) 1.99 (2H, quintet, *J*=7.4 Hz, CH$_2$-4), 2.43–2.53 (2H, m, CH$_2$-3), 2.62–2.70 (2H, m, CH$_2$-5), 4.89 (2H, d, *J*=5.3 Hz, CH$_2$N), 6.65–6.68 (1H, m, =CH-2), 7.26–7.38 (5H, m, C$_6$H$_5$), 7.47 (1H, brs, NH); δ_C (100.6 MHz, CDCl$_3$) 23.43 (t, CH$_2$-4), 32.92 (t, CH$_2$-5), 33.46 (t, CH$_2$-3), 49.71 (t, NCH$_2$), 128.01, 128.18, 128.89, 136.40 (C$_6$H$_5$), 138.72 (d, CH-2), 144.71 (s, C-1), 194.26 (s, C=S); *m/z* (EI, 70 eV) 217 (100, M$^+$), 188 (39), 184 (27), 175 (66), 156 (18), 112 (15), 106 (17), 91 (59), 65 (21%).

4.1.4. (*E*) 3-Phenyl-1-pyrrolidin-1-yl-propenethione (1j). Reflux 3.5 h, yield 60%. Orange solid, mp 146–147°C from ethyl acetate/*n*-hexane [Found: C, 72.09; H, 7.03; N, 6.63; S, 14.71. $C_{13}H_{15}NS$ requires C, 71.84; H, 6.96; N, 6.44; S, 14.75%]; ν_{max}(KBr pellet) 2968, 1628, 1480, 1448, 972, 760, 696 cm^{-1}; δ_H (400.1 MHz, CDCl$_3$) 1.97–2.17 (4H, dm, CH$_2$-3′,CH$_2$-4′), 3.80 (2H, t, *J*=6.9 Hz, CH$_2$-5′), 3.99 (2H, t, *J*=6.9 Hz, CH$_2$-2′), 7.04 (1H, d, *J*=15.1 Hz, =CH-2), 7.30–7.39 (3H, m, C$_6$H$_5$), 7.53–7.56 (2H, m, C$_6$H$_5$), 8.01 (1H, d, *J*=15.1 Hz, =CH-3); δ_C (100.6 MHz, CDCl$_3$) 24.16, 26.27 (each t, CH$_2$-3′,CH$_2$-4′), 50.79, 54.10 (each t, CH$_2$-5′,CH$_2$-2′), 125.01 (d, CH-2), 128.01, 128.82, 129.67, 135.52 (C$_6$H$_5$), 144.15 (d, CH-3), 190.54 (s, C=S); *m/z* (EI, 70 eV) 217 (100, M$^+$), 184 (12), 156 (21), 147 (36), 130 (12), 115 (46), 103 (11), 70 (45%).

4.1.5. (*E*) 2-Methyl-1-piperidin-1-yl-propenethione (1l). (Reflux 4 h, yield 54%. Pale yellow oil [Found: C, 63.77; H, 9.01; N, 8.65; S, 19.02. $C_9H_{15}NS$ requires C, 63.85; H, 8.93; N, 8.27; S, 18.94%]; ν_{max}(liquid film) 2936, 2856, 1632, 1490, 1440, 1246, 1226, 1136, 1008, 896 cm^{-1}; δ_H (400.1 MHz, CDCl$_3$) 1.61–1.65 (2H, m, CH$_2$), 1.65–1.80 (4H, m, 2CH$_2$), 2.05 (3H, s, CH$_3$), 3.73 (2H, t, *J*=5.3 Hz, CH$_2$-6′), 4.22 (2H, brs, CH$_2$-2′), 4.87 (1H, s, =C*H*H), 4.92 (1H, t, *J*=1.4 Hz, =CH*H*); δ_C (100.6 MHz, CDCl$_3$) 22.48 (q, CH$_3$), 24.40, 25.36, 27.04 (each t, 3CH$_2$), 49.43, 52.25 (each t, CH$_2$NCH$_2$), 111.66 (t, =CH$_2$), 146.96 (s, C-2), 200.73 (s, C=S); *m/z* (EI, 70 eV) 169 (100, M$^+$), 154 (13), 136 (16), 135 (15), 127 (11), 94 (14), 86 (26), 85 (25), 84 (30%).

4.1.6. Cyclohex-1-enyl-pyrrolidin-1-yl-methanethione (1m). Reflux 3 h, yield 80%. White plates, mp 83–84°C from ethyl acetate/*n*-hexane [Found: C, 67.87; H, 9.01; N, 6.90; S, 16.10. $C_{11}H_{17}NS$ requires C, 67.64; H, 8.77; N, 7.17; S, 16.42%]; ν_{max}(KBr pellet) 2928, 1484, 1474, 1450, 1216 cm^{-1}; δ_H (400.1 MHz, CDCl$_3$) 1.58–1.67 (2H, m, CH$_2$-4), 1.67–1.76 (2H, m, CH$_2$-5), 1.95–2.05 (4H, m, CH$_2$-3′, CH$_2$-4′), 2.07–2.15 (2H, m, CH$_2$-3), 2.28–2.35 (2H, m, CH$_2$-6), 3.62 (2H, t, *J*=6.5 Hz, CH$_2$-5′ ′), 3.82 (2H, t, *J*=6.7 Hz, CH$_2$-2′), 5.66 (1H, septet, *J*=1.8 Hz, =CH); δ_C (100.6 MHz, CDCl$_3$) 21.57, 22.38, 24.49, 24.65, 26.26, 27.39 (each t, 6CH$_2$), 52.47, 52.56 (each t, CH$_2$-2′, CH$_2$-5′), 124.20 (d, CH-2), 141.96 (s, C-1), 199.65 (s, C=S); *m/z* (EI, 70 eV) 195 (100, M$^+$), 166 (26), 162 (32), 153 (16), 152 (33), 139 (27), 134 (34), 126 (21), 120 (18), 70 (18%).

4.1.7. Cyclopent-1-enyl-pyrrolidin-1-yl-methanethione (1n). Reflux 1.5 h, yield 82%. Yellow oil [Found: C, 66.00; H, 8.12; N, 7.75; S, 17.70. $C_{10}H_{15}NS$ requires C, 66.25; H, 8.34; N, 7.73; S, 17.69%]; ν_{max}(liquid film) 2952, 1468, 1446, 1328, 1260 cm^{-1}; δ_H (400.1 MHz, CDCl$_3$) 1.90–2.09 (6H, m, CH$_2$-4, CH$_2$-3′, CH$_2$-4′), 2.46–2.52 (2H, m, CH$_2$-3), 2.72–2.80 (2H, m, CH$_2$-5), 3.66 (2H, t, *J*=6.3 Hz, CH$_2$-5′), 3.86 (2H, t, *J*=6.7 Hz, CH$_2$-2′), 5.78–5.82 (1H, m, =CH); δ_C (100.6 MHz, CDCl$_3$) 23.03, 24.35, 26.30 (each t, CH$_2$-4, CH$_2$-3′, CH$_2$-4′), 33.58 (t, CH$_2$-3), 36.30 (t, CH$_2$-5), 52.84, 52.90 (each t, CH$_2$-5′, CH$_2$-2′), 129.68 (d, =CH), 145.60 (s, C-1), 194.34 (s, C=S); *m/z* (EI, 70 eV) 181 (100, M$^+$), 166 (11), 152 (35), 148 (26), 139 (35), 120 (66), 112 (23), 111 (17), 94 (12), 70 (25%).

Not previously published ^{1}H, ^{13}C NMR and MS spectroscopic data for **1d**,**f**,**k** were as follows:

4.1.8. 2-Methyl-*N*-phenyl-thioacrylamide (1d). δ_H (400.1 MHz, CDCl$_3$) 2.19 (3H, s, CH$_3$), 5.25 (1H, s, =C*H*H), 5.50 (1H, s, =CH*H*), 7.25 (1H, t, *J*=7.3 Hz, C$_6$H$_5$), 7.38 (2H, t, *J*=7.8 Hz, C$_6$H$_5$), 7.67 (2H, brs, C$_6$H$_5$), 8.94 (1H, brs, NH); δ_C (100.6 MHz, CDCl$_3$) 21.66 (q, CH$_3$), 115.3 br (t, =CH$_2$), 123.30, 126.81, 128.78, 138.34 (C$_6$H$_5$), 148.34 br (s, C-2), 199.38 (s, C=S); *m/z* (EI, 70 eV) 177 (79, M$^+$), 176 (100), 162 (6), 144 (31), 110 (22), 109 (10), 106 (12), 104 (10), 85 (54), 77 (31%).

4.1.9. Cyclohex-1-enecarbothioic acid phenylamide (1f). Reflux 2.5 h, yield 55%. δ_H (400.1 MHz, CDCl$_3$) 1.60–1.79

(4H, m, CH_2-4, CH_2-5), 2.21 (2H, brs, CH_2-3), 2.55 (2H, brs, CH_2-6), 6.54 (1H, brs, =CH), 7.24 (1H, t, J=7.5 Hz, C_6H_5), 7.37 (2H, t, J=8.0 Hz, C_6H_5), 7.63 (2H, brs, C_6H_5), 8.85 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 21.49 (t, CH_2-4), 22.43 (t, CH_2-5), 25.68 (t, CH_2-3), 27.25 (t, CH_2-6), 123.98, 126.74, 128.91, 142.06 (C_6H_5), 131.19 (d, =CH), 138.74 br (s, C-1), 200.16 br (s, C=S); m/z (EI, 70 eV) 217 (100, M^+), 216 (86), 188 (12), 184 (84), 156 (8), 125 (48), 92 (21), 77 (30%).

4.1.10. (*E*) 1-Piperidin-1-yl-but-2-ene-1-thione (1k). Reflux 2.5 h, 75%. δ_H (400.1 MHz, $CDCl_3$) 1.60–1.78 (6 H, m, CH_2-3′, CH_2-4′, CH_2-5′), 1.88 (3H, dd, J=6.8, 1.6 Hz, CH_3), 3.74–3.80 (2H, m, CH_2-6′), 4.27 (2H, brs, CH_2-2′), 6.47 (1H, dd, J=14.8, 1.6 Hz, =CH-2), 6.77 (1H, dq, J=14.8, 6.8 Hz, =CH-3); δ_C (100.6 MHz, $CDCl_3$) 14.48 (q, CH_3), 24.21, 25.44, 26.68 (each t, $3CH_2$), 51.41, 51.48 (each t, CH_2NCH_2), 130.11 (d, CH-2), 140.32 (d, CH-3), 194.89 (s, C=S); m/z (EI, 70 eV) 169 (99, M^+), 154 (100), 136 (8), 121 (32), 85 (32), 84 (54), 68 (20%).

4.1.11. Cyclopent-1-enecarbothioic acid phenylamide (1h). A solution of 1-bromocyclopentene (0.55 g, 3.7 mmol) in THF (6 cm^3) was cooled to −78 °C and 2.2 equiv. of *t*-BuLi (5.7 cm^3, 1.5 M in pentane) was added over 5 min. The yellowish suspension was stirred at −78°C for 10 min and PhNCS (1.2 equiv., 0.61 g, 4.5 mmol) was added dropwise over 5 min. The stirring was continued for further 5 min. at −78°C and then allowed to warm to −5°C during 1 h. The solution was quenched by addition of a saturated ammonium chloride solution (10 cm^3). The cooling bath was removed and the solution was allowed to warm to room temperature. Extracted with diethyl ether (80 cm^3), separated and the organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product purified by column chromatography on silica (*n*-hexane/ethyl acetate=9:1) and crystallized from the same solvents gave yellow crystalline product in 70%.

Mp 74–76°C from ethyl acetate/*n*-hexane [Found: C, 71.01; H, 6.82; N, 7.05; S, 15.57. $C_{12}H_{13}NS$ requires C, 70.89; H, 6.45; N, 6.89; S, 15.77%]; ν_{max}(KBr pellet) 3236, 1604, 1516, 1356, 696 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 2.03 (2H, quintet, J=7.5 Hz, CH_2-4), 2.46–2.56 (2H, m, CH_2-3), 2.79 (2H, brs, CH_2-5), 6.66 (1H, brs, =CH-2), 7.25 (1H, t, J=7.4 Hz, 4′-H), 7.39 (2H, t, J=7.7 Hz, H-3′, H-5′), 7.66 (2H, brd, J=6.51 Hz, H-2′, H-6′), 8.75 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 23.45 (t, CH_2-4), 33.55 (t, CH_2-5), 33.67 (t, CH_2-3), 124.03, 126.78, 128.98, 138.47 (C_6H_5), 137.60 (d, CH-2), 146.40 (s, C-1), 193.60 (brs, C=S); m/z (EI, 70 eV) 203 (82, M^+), 202 (100), 170 (39), 136 (10), 111 (77), 110 (22), 94 (11), 77 (32), 67 (27%).

4.2. Addition of amines to α,β-unsaturated thioamides: preparation of 2ap

To an ice-cooled (0°C) solution of phenyl isothiocyanate 1.3 g (9.6 mmol) in dry THF (25 cm^3), 10.5 mmol of vinyl magnesium chloride in hexane was added dropwise via syringe under stirring. Stirring was continued for 1 h at 0°C and 0.5 h at room temperature. The resulting product was hydrolyzed at 0°C with an excess of 20% solution of ammonium chloride in water and extracted twice with 25 cm^3 portions of diethyl ether. The combined organic layers were dried with anhydrous Na_2SO_4, filtered and 0.99 g (11.5 mmol) of piperidine was added in one portion. After 2 h, the diethyl ether was evaporated in vacuo and to oily residue 10 cm^3 of benzene was added. After 1 day, the precipitated urea (as a result of reaction of unconsumed phenyl isothiocyanate and piperidine) was filtered off and the solvent was removed from the mother-liquid in vacuo. The residue material chromatographed on silica gel with $CHCl_3/CH_3OH$ solution (changing the ratio of components from 99:1 to 96:4), yielded 1.54 g (64.5%) of dark yellow oil, which solidified on treatment with hexane. The solid was recrystallized from hexane.

4.2.1. *N*-Phenyl-3-piperidin-1-yl-thiopropionamide (2ap). Pale yellow needles, mp 63–65°C from *n*-hexane [Found: C, 68.01; H, 8.08; N, 11.35; S, 13.11. $C_{14}H_{20}N_2S$ requires C, 67.70; H, 8.12; N, 11.28; S, 12.91%]; ν_{max}(KBr pellet) 3100–2400 br, 2932, 1632, 1570, 1492, 1406, 1120, 1104, 910, 756 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.55 (2H, brs, CH_2-7), 1.68 (4H, quintet, J=5.7 Hz, CH_2-6, CH_2-8), 2.58 (4H, brs, CH_2-5, CH_2-9), 2.74–2.77 (2H, m, CH_2-3), 3.04–3.07 (2H, m, CH_2-2), 7.22 (1H, tt, J=7.4, 1.2 Hz, C_6H_5), 7.40 (2H, t, J=7.5 Hz, C_6H_5), 7.86 (2H, dd, J=8.7, 1.2 Hz, C_6H_5), 13.49 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 24.05 (t, CH_2-7), 26.09 (t, CH_2-6, CH_2-8), 42.06 (t, CH_2-2), 53.49 (t, CH_2-5, CH_2-9), 56.29 (t, CH_2-3), 122.36, 125.97, 128.76, 139.62 (C_6H_5), 201.89 (s, C-1); GCMS-decomposition (retro-Michael addition).

4.3. Preparation of 2bp, 2bm, 2cp, 2cm, 2dp, 2ep, 2em, 2fp(t), 2fm(t), 2gp(t), 2gp(c), 2hp(t), 2hm(t), 2ip(t), 2im(t), 2jp, 2jm, 2jpy, 2kp, 2km, 2kpy, 2lp: general procedure

To 2 mmol of α,β-unsaturated thioamide, an excess of appropriate amine was added (Table 1). If the crystalline thioamide were poorly soluble, the suspension was slightly warmed. In the case of **2dp**, 5 cm^3 MeOH was added. The reaction mixture was left standing at room temperature over the required period (see Table 1) and 20 cm^3 hexane (**2bp**, **2cp**, **2cm**, **2em**) or 5 cm^3 acetonitrile (**2bm**) was added. The mixture was kept at −20°C for 1–2 days. The crystalline product was filtered, dried and recrystallized. In all other cases, an amine was evaporated under low pressure (0.1 mmHg) at room temperature and the residue was treated with *n*-hexane. Crystalline product formed was filtered off, dried and recrystallized or chromatographed. Compounds **2jm**, **2dp**, **2ep**, **2km**, **2gp(t)/2gp(c) 2im(t)** were purified by column chromatography on silica gel using $CHCl_3$ or $CHCl_3$/MeOH=97:3 (**2kpy**) as eluent.

4.3.1. 3,*N*-Diphenyl-3-piperidin-1-yl-thiopropionamide (2bp). Pale yellow solid, mp 112–114°C from acetonitrile [Found: C, 73.95; H, 7.40; N, 8.60; S, 9.94. $C_{20}H_{24}N_2S$ requires C, 74.03; H, 7.46; N, 8.63; S, 9.88%]; ν_{max}(KBr pellet) 3100–2400 br, 2936, 2824, 1608, 1594, 1564, 1492, 1408, 1120, 740 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.39 (2H, brs, CH_2), 1.56–1.76 (1H, m, CHH), 2.35 (2H, brs, $C_5H_{10}N$), 2.71 (2H, brs, $C_5H_{10}N$), 3.16 (1H, dd, J=17.3, 2.3 Hz, 2-C*H*H), 3.67 (1H, dd, J=17.3, 12.1 Hz, 2-CH*H*), 4.13 (1H, dd, J=12.1, 2.3 Hz, 3-CH), 7.13 (2H, brdd, J=ca 6.2, ca 2.0 Hz, C_6H_5), 7.24 (1H, t, J=7.5 Hz, C_6H_5), 7.31–7.38 (3H, m, C_6H_5), 7.42 (2H, t, J=7.5 Hz, C_6H_5), 7.90 (2H, d, J=6.5 Hz, C_6H_5), 13.78 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 24.1 (CH_2), 26.4 (CH_2), 46.2 (C-2), 49.4 (CH_2NCH_2), 67.7 (C-3), 122.7, 126.0, 128.0, 128.1, 128.6, 128.8, 139.6 ($2C_6H_5$), 201.3 (C-1); GCMS-decomposition (retro-Michael addition).

4.3.2. 3-Morpholin-4-yl-3,*N*-diphenyl-thiopropionamide (2bm). Pale yellow solid, mp 134–136°C from acetonitrile [Found: C, 69.54; H, 6.72; N, 8.47; S, 9.44. $C_{19}H_{22}N_2OS$ requires C, 69.90; H, 6.79; N, 8.58; S, 9.82%]; ν_{max}(KBr pellet) 3100–2500 br, 2852, 1620, 1566, 1492, 1400, 1116 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 2.48 (2H, brs, CH_2N), 2.70–2.78 (2H, m, CH_2N), 3.22 (1H, dd, J=17.0, 2.6 Hz, $C\mathit{H}H$-2), 3.66 (1H, dd, J=17.0, 11.3 Hz, $CH\mathit{H}$-2), 3.78 (4H, m, CH_2OCH_2), 4.13 (1H, dd, J=11.3, 2.6 Hz, CH-3), 7.14 (2H, brd, J=ca 7.8 Hz, C_6H_5), 7.25 (1H, t, J=7.1 Hz, C_6H_5), 7.32–7.45 (5H, m, C_6H_5), 7.85 (2H, d, J=7.8 Hz, C_6H_5), 13.01 (1H, br. s, NH); δ_C (100.6 MHz, $CDCl_3$) 56.6 (t, C-2), 48.7 br (t, CH_2NCH_2), 67.1 (t, CH_2OCH_2), 67.7 (d, C-3), 122.7, 126.4, 128.4, 128.5 128.6, 129.0, 134.6, 139.3 ($2C_6H_5$), 200.9 (s, C-1); GCMS-decomposition (retro-Michael addition).

4.3.3. *N*-Benzyl-3-phenyl-3-piperidin-1-yl-thiopropionamide (2cp). White needles, mp 125–127°C from acetonitrile [Found: C, 75.19; H, 7.57; N, 8.57; S, 9.19. $C_{21}H_{26}N_2S$ requires C, 74.51; H, 7.74; N, 8.28; S, 9.47%]; ν_{max}(KBr pellet) 3150–2400 br, 2940, 1556, 1442, 768, 708, 700 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.09 (6H, brs, CH_2-6, CH_2-7, CH_2-8), 2.09 (2H, brs, $C\mathit{H}_2NCH_2$), 2.48 (2H, brs, $CH_2NC\mathit{H}_2$), 3.08 (1H, dd, J=17.4, 2.4 Hz, $C\mathit{H}H$-2), 3.52 (1H, dd, J=17.4, 12.1 Hz, $CH\mathit{H}$-2), 3.97 (1H, dd, J=12.1, 2.3 Hz, CH-3), 4.74–4.84 (2H, m, $C\mathit{H}_2Ph$), 7.06 (2H, brdd, J=7.8, 1.8 Hz, C_6H_5), 7.25–7.42 (8H, m, $2C_6H_5$), 12.14 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 23.89 (t, CH_2-7), 25.55 (t, CH_2NCH_2), 43.95 (t, CH_2-2), 49.19 br (t, CH_2NCH_2), 50.71 (t, $\mathit{C}H_2Ph$), 67.55 (d, CH-3), 127.87, 128.04, 128.48, 128.79, 128.87, 134.90, 136.59 ($2C_6H_5$), 202.04 (s, C-1); GCMS-decomposition (retro-Michael addition).

4.3.4. *N*-Benzyl-3-morpholin-4-yl-3-phenyl-thiopropionamide (2cm). White solid, mp 111–113°C from acetonitrile [Found: C, 70.28; H, 6.99; N, 8.05; S, 9.46. $C_{20}H_{24}N_2OS$ requires C, 70.55; H, 7.10; N, 8.23; S, 9.42%]; ν_{max}(KBr pellet) 3300–2500 br, 2964, 2936, 2852, 1552, 1440, 1116, 996, 708 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 2.21 (2H, brs, CH_2N), 2.51 (2H, brs, CH_2N), 3.11 (1H, dd, J=17.0, 2.8 Hz, $C\mathit{H}H$-2), 3.21 (2H, brs, CH_2O), 3.29 (2H, brs, CH_2O), 3.50 (1H, dd, J=17.0, 11.3 Hz, $CH\mathit{H}$-2), 3.97 (1H, dd, J=11.3, 2.8 Hz, CH-3), 4.75–4.77 (2H, m, $C\mathit{H}_2Ph$), 7.07 (2H, brd, J=6.1 Hz, C_6H_5), 7.25–7.41 (8H, m, $2C_6H_5$), 11.35 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 44.34 (t, CH_2-2), 48.43 br (t, CH_2NCH_2), 50.75 (t, $\mathit{C}H_2Ph$), 66.43 (t, CH_2OCH_2), 67.63 (d, CH-3), 128.21, 128.32, 128.46, 128.73, 129.03, 134.67, 136.44, ($2C_6H_5$), 201.63 (s, C-1); *m*/*z* (EI, 70 eV) 340 (11, M^+), 307 (5), 255 (9), 253 (12), 176 (100), 91 (35%).

4.3.5. 2-Methyl-*N*-phenyl-3-piperidin-1-yl-thiopropionamide (2dp). Pale yellow needles, mp 66–67°C from *n*-hexane/ethyl acetate [Found: C, 68.54; H, 8.45; N, 11.03; S, 12.13. $C_{15}H_{22}N_2S$ requires C, 68.65; H, 8.45; N, 10.68; S, 12.22%]; ν_{max}(KBr pellet) 3000–2300 br, 2932, 1594, 1570, 1496, 1364, 710 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.41 (3H, d, J=7.0 Hz, CH_3), 1.48–1.59 (2H, m, CH_2-7), 1.59–1.75 (4H, m, CH_2-6, CH_2-8), 2.45 (2H, brs, $C\mathit{H}_2NCH_2$), 2.54 (1H, dd, J=13.0, 3.2 Hz, $C\mathit{H}H$-3), 2.69 (1H, dd, J=13.0, 10.6 Hz, $CH\mathit{H}$-3), 2.72 (2H, brs, $CH_2NC\mathit{H}_2$), 2.82–2.91 (1H, m, CH-2), 7.21 (1H, t, J=7.5 Hz, C_6H_5), 7.39 (2H, t, J=7.7 Hz, C_6H_5), 7.78 (2H, d, J=7.7 Hz, C_6H_5), 13.45 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 19.19 (q, 2-CH_3), 23.97 (t, CH_2-7), 26.16 (t, $2CH_2$), 41.76 (d, CH-2), 54.09 br (t, CH_2NCH_2), 63.87 (t, CH_2-3), 122.89, 125.85, 128.74, 139.90 (C_6H_5), 206.87 (s, C-1); *m*/*z* (EI, 70 eV) 262 (5, M^+), 229 (22), 98 (100), 84 (9%).

4.3.6. *N*-Benzyl-3-piperidin-1-yl-thiobutyramide (2ep). Colourless oil [Found: C, 69.74; H, 8.45; N, 10.03; S, 11.13. $C_{16}H_{24}N_2S$ requires C, 69.52; H, 8.75; N, 10.13; S, 11.60%]; ν_{max}(liquid film) 3000–2400 br, 2964, 2932, 2852, 1406, 1262, 1112, 740, 700 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 0.92 (3H, d, J=6.6 Hz, CH_3), 1.00–1.27 (6H, m, $3CH_2$), 2.15–2.26 (2H, brs, CH_2N), 2.50–2.76 (2H, brs, CH_2N), 2.76–2.91 (2H, m, CH_2-2), 2.99–3.17 (1H, m, CH-3), 4.68–4.78 (2H, m, $C\mathit{H}_2Ph$), 7.24–7.42 (5H, m, C_6H_5), 12.26 (1H, brs, NH); δ_H (100.6 MHz, $CDCl_3$) 12.58 (q, CH_3), 24.17 (t, CH_2), 25.46 (t, $2CH_2$), 46.20 (t, CH_2-2), 48.04 br (t, $2CH_2N$), 50.50 (t, $\mathit{C}H_2Ph$), 58.66 (d, CH-3), 127.92, 128.71, 128.78, 136.60 (C_6H_5), 202.13 (s, C-1); *m*/*z* (EI, 70 eV) 276 (10, M^+), 243 (11), 191 (27), 176 (22), 143 (15), 112 (100), 91 (48%).

4.3.7. *N*-Benzyl-3-morpholin-4-yl-thiobutyramide (2em). White solid, mp 78–80°C from *n*-hexane/ethyl acetate [Found: C, 64.90; H, 8.02; N, 9.80; S, 11.41. $C_{15}H_{22}N_2OS$ requires C, 64.71; H, 7.96; N, 10.06; S, 11.52%]; ν_{max}(KBr pellet) 3000–2500 br, 1546, 1438, 1410, 1114, 896, 750, 704 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 0.99 (3H, d, J=6.6 Hz, CH_3), 2.28–2.34 (2H, m, CH_2N), 2.57–2.62 (2H, m, CH_2N), 2.85 (2H, d, J=11.1 Hz, CH_2-2), 3.03 (1H, sextet, J=6.6 Hz, CH-3), 3.21 (2H, brs, CH_2O), 3.28 (2H, brs, CH_2O), 4.68–4.77 (2H, m, $C\mathit{H}_2Ph$), 7.28–7.41 (5H, m, C_6H_5), 11.68 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 12.94 (q, CH_3), 46.05 (t, CH_2-2), 47.59 br (t, CH_2NCH_2), 50.62 (t, $\mathit{C}H_2Ph$), 58.42 (d, CH-3), 66.47 (t, CH_2OCH_2), 128.3, 128.7, 128.99, 136.57 (C_6H_5), 201.82 (s, C-1); *m*/*z* (EI, 70 eV) 278 (15, M^+), 245 (7), 191 (8), 176 (8), 143 (5), 114 (100), 91 (26%).

4.3.8. *trans* 2-Piperidin-1-yl-cyclohexanecarbothioic acid phenylamide [2fp(t)]. Yellow solid, mp 118–120°C from acetonitrile [Found: C, 71.41; H, 8.70; N, 9.37; S, 11.01. $C_{18}H_{26}N_2S$ requires C, 71.47; H, 8.66; N, 9.26; S, 10.60%]; ν_{max}(KBr pellet) 3252, 2928, 1598, 1496, 1368, 1192, 756, 688 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$, 220 K) 1.15–1.42 (5H, m, $C\mathit{H}H$-7, H-10_{ax}, $C\mathit{H}H$-11, $C\mathit{H}H$-12, H-13_{ax}), 1.43–1.67 (2H, m, $C\mathit{H}H$-6, $C\mathit{H}H$-8), 1.68–1.95 (5H, m, $CH\mathit{H}$-6, $CH\mathit{H}$-7, $CH\mathit{H}$-8, $CH\mathit{H}$-11, $CH\mathit{H}$-12), 2.03 (1H, brd, J=9.8 Hz, H-13_{eq}), 2.32 (1H, t, J=11.4 Hz, H-5_{ax}), 2.57 (1H, t, J=9.8 Hz, H-2_{ax}), 2.65–2.83 (2H, m, CH_2-9), 2.88 (1H, t, J=10.1 Hz, H-3_{ax}), 3.00 (1H, brd, J=10.0 Hz, H-5_{eq}), 3.12–3.25 (1H, m, H-10_{eq}), 7.31 (1H, t, J=6.8 Hz, C_6H_5), 7.48 (2H, t, J=8.0 Hz, C_6H_5), 7.60 (2H, d, J=7.6 Hz, C_6H_5), 15.65 (1H, s, NH); δ_C (100.6 MHz, $CDCl_3$ 220 K) 23.30

(t, CH_2-13), 24.01, 25.14, 26.31 (each t, CH_2-7, CH_2-11, CH_2-12), 25.66 br (t, CH_2-8), 26.39 br (t, CH_2-6), 34.47 (t, CH_2-10), 44.44 br (t, CH_2-5), 48.62 (d, CH-2), 51.27 br (t, CH_2-9), 67.16 (d, CH-3), 123.81, 126.30, 128.85, 139.28 (C_6H_5), 206.84 (s, C=S); δ_C (100.6 MHz, $CDCl_3$ 300 K) 23.70, 24.38, 25.57, 26.37, 26.62 (each t, $6CH_2$), 34.90 (t, CH_2-10), 48.34 br (t, CH_2-5,9), 50.29 (d, CH-2), 67.58 (t, CH-3), 123.75, 126.03, 128.73, 139.94 (C_6H_5), 206.95 (s, C=S); *m/z* (EI, 70 eV) 302 (35, M^+), 269 (100), 217 (28), 216 (24), 186 (31), 184 (52), 124 (73), 98 (36), 84 (77), 77 (42), 41 (24%).

4.3.9. *trans* 2-Morpholin-4-yl-cyclohexanecarbothioic acid phenylamide [2fm(t)]. Pale yellow needles, mp 135–140°C from *n*-hexane/ethyl acetate [Found: C, 67.32; H, 7.90; N, 9.02; S, 10.51. $C_{17}H_{24}N_2OS$ requires C, 67.07; H, 7.95; N, 9.20; S, 10.53%]; ν_{max}(KBr pellet) 3000–2300 br, 2936, 2852, 1450, 1414, 1114, 764, 692 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.23–1.35 (3H, m, C*H*H-11, C*H*H-12, C*H*H-13), 1.44 (1H, q, *J*=13.0 Hz, H-10_{ax}), 1.83–2.04 (3H, m, CH*H*-11 CH*H*-12 CH*H*-13), 2.54–2.65 (3H, m, CH-2, CH_2N), 2.81–2.91 (4H, m, CH-3, CH_2N, H-10_{eq}), 3.69–3.79 (4H, m, CH_2OCH_2), 7.24 (1H, t, *J*=7.4 Hz, C_6H_5), 7.40 (2H, t, *J*=7.6 Hz, C_6H_5), 7.66 (2H, d, *J*=7.6 Hz, C_6H_5), 12.75 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 23.82, 25.44, 26.38 (each t, CH_2-11, CH_2-12, CH_2-13), 34.47 (t, CH_2-10), 47.80 br (t, CH_2NCH_2), 52.52 br (d, CH-2), 67.00 (d, CH-3), 67.30 (t, CH_2OCH_2), 123.86, 126.46, 128.90, 139.41 (C_6H_5), 207.14 (s, C=S); *m/z* (EI, 70 eV) 304 (41, M^+), 271 (100), 218 (9), 186 (32), 184 (32), 178 (18), 152 (17), 126 (32), 100 (18), 77 (16%).

4.3.10. *cis* 2-Piperidin-1-yl-cyclohexanecarbothioic acid benzylamide [2gp(c)]. White solid, mp 91–92°C from *n*-hexane [Found: C, 72.29; H, 9.04; N, 8.75; S, 10.01. $C_{19}H_{28}N_2S$ requires C, 72.10; H, 8.92; N, 8.85; S, 10.13%]; ν_{max}(KBr pellet) 3000–2300 br, 2928, 1554, 1424, 1382, 1332, 764, 704 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 0.95–1.33 (14H, m, $6CH_2$, H-13_{ax}, H-12_{ax}), 1.39 (1H, tt, *J*=13.3, 3.9 Hz, H-10_{ax}), 1.48 (1H, dt *J*=13.3, 3.2 Hz, H-11_{eq}), 1.55 (1H, quintet of t, *J*=13.2, 3.4 Hz, H-11_{ax}), 1.79 (1H, brs, H-12_{eq}), 1.92 (1H, brs, H-13_{eq}), 2.40 (4H, brs, $2CH_2N$), 2.44 (1H, dt, *J*=11.4, 3.8 Hz, H-3_{ax}), 3.05 (1H, brs, H-2_{eq}), 3.12 (1H, dm, *J*=13.3 Hz, H-10_{eq}), 4.73–4.83 (2H, m, C*H*$_2$Ph), 7.27–7.35 (5H, m, C_6H_5), 12.95 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 21.40 (t, CH_2-11), 23.94 (t, CH_2-7), 25.24 (t, CH_2-13), 25.52 (t, $2CH_2$), 25.55 (t, CH_2-12), 30.87 (t, CH_2-10), 44.72 (d, CH-2), 50.32 br (t, CH_2NCH_2), 50.95 (t, *C*H_2Ph), 66.90 (d, CH-3), 127.75, 128.72, 136.80 (C_6H_5), 204.22 (s, C-1); *m/z* (EI, 70 eV) 316 (58, M^+), 283 (100), 231 (24), 225 (17), 192 (42), 150 (13), 151 (13), 124 (65), 111 (19), 98 (19), 91 (62), 84 (33%).

4.3.11. *trans* 2-Piperidin-1-yl-cyclohexanecarbothioic acid benzylamide [2gp(t)]. White solid, mp 97–100°C from hexane [Found: C, 72.02; H, 8.66; N, 9.03; S, 10.21. $C_{19}H_{28}N_2S$ requires C, 72.10; H, 8.92; N, 8.85; S, 10.13%]; ν_{max}(KBr pellet) 3204, 2932, 1538, 1452, 1262, 1102, 804, 698 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.00–1.31 (9H, m, CH_2-6, CH_2-7, CH_2-8, H-10_{ax}, H-12_{ax}, H-13_{ax}), 1.72–1.89 (3H, m, H-11_{eq}, H-12_{eq}, H-13_{eq}), 2.25 (2H, brs, CH_2N), 2.40–2.51 (1H, m, H-2_{ax}), 2.53–2.70 (3H, m, CH_2N, H-3_{ax}), 3.07 (1H, brd, *J*=ca 9.8 Hz, H-10_{eq}), 4.77 (2H, q, *J*=14.9 Hz, C*H*$_2$Ph), 7.27–7.38 (5H, m, C_6H_5), 12.84 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 23.62 (t, CH_2-11), 24.14 (t, CH_2-7), 25.33 (t, $2CH_2$), 25.53, 26.51 (each t, CH_2-12, CH_2-13), 34.35 (t, CH_2-10), 48.29 br (t, $2CH_2N$), 48.89 (d, CH-2), 50.96 (t, *C*H_2Ph), 67.60 (d, CH-3), 127.75, 128.73, 128.96, 136.82 (C_6H_5), 206.66 (s, C-1); *m/z* (EI, 70 eV) 316 (71, M^+), 283 (100), 225 (27), 192 (49), 166 (21), 151 (17), 150 (18), 124 (80), 111 (26), 98 (25), 96 (17), 91 (85), 84 (46%).

4.3.12. *trans* 2-Piperidin-1-yl-cyclopentanecarbothioic acid phenylamide [2hp(t)]. White needles, mp 127–128°C from acetonitrile [Found: C, 70.49; H, 8.54; N, 9.75; S, 11.21. $C_{17}H_{24}N_2S$ requires C, 70.79; H, 8.39; N, 9.71; S, 11.12%]; ν_{max}(KBr pellet) 3000–2400 br, 2940, 1596, 1564, 1498, 1396, 1374, 696 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.50–1.80 (10H, m, CH_2-6, CH_2-7, CH_2-8, CH_2-11, CH_2-12), 2.06–2.30 (2H, dm, CH_2-10), 2.57 (2H, brs, CH_2N), 2.77 (2H, brs, CH_2N), 2.92 (1H, quartet, *J*=10.4 Hz, CH_β-2), 3.12 (1H, quartet, *J*=10.4 Hz, CH_α-3), 7.20 (1H, t, *J*=7.4 Hz, C_6H_5), 7.39 (2H, t, *J*=8.3 Hz, C_6H_5), 7.84 (2H, dd, *J*=8.3, 0.8 Hz, C_6H_5), 13.02 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 20.79, 22.0 (each t, CH_2-11, CH_2-12), 24.50 (t, CH_2-7), 26.57 (t, $2CH_2$), 29.30 (t, CH_2-10), 49.37 (t, CH_2NCH_2), 50.86 (d, CH-2), 70.66 (d, CH-3), 122.56, 125, 73, 128.73, 139.84 (C_6H_5), 205.58 (s, C-1); *m/z* (EI, 70 eV) 288 (18, M^+), 255 (82), 201 (59), 202 (75), 124 (100), 111 (59), 34 (52%).

4.3.13. *trans* 2-Morpholin-4-yl-cyclopentanecarbothioic acid phenylamide [2hm(t)]. White solid, mp 138–141°C from acetonitrile [Found: C, 66.02; H, 7.65; N, 9.70; S, 10.85. $C_{16}H_{22}N_2OS$ requires C, 66.17; H, 7.64; N, 9.65; S, 11.04%]; ν_{max}(KBr pellet) 3000–2500 br, 2848, 2828, 1630, 1570, 1488, 1398, 1118, 760, 692 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.60–1.73 (2H, m, CH_2-11), 1.73–1.85 (2H, m, CH_2-12), 2.14–2.30 (2H, m, CH_2-10), 2.63–2.68 (2H, m, NCH_2), 2.79–2.84 (2H, m, CH_2N), 2.93 (1H, dd, *J*=10.1, 8.7 Hz, CH_β-2), 3.20 (1H, dd, *J*=10.1, 8.7 Hz, CH_α-3), 3.77–3.86 (4H, m, CH_2OCH_2), 7.22 (1H, t, *J*=7.4 Hz, C_6H_5), 7.40 (2H, t, *J*=7.7 Hz, C_6H_5), 7.81 (2H, d, *J*=7.7 Hz, C_6H_5), 12.39 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 21.24 (t, CH_2-11), 22.51 (t, CH_2-12), 29.74 (t, CH_2-10), 48.78 br (t, CH_2NCH_2), 51.19 (d, CH-2), 67.38 (t, CH2OCH2), 70.44 (d, CH-3), 122.60, 126.03, 128.88, 139.56 (C_6H_5), 205.41 (s, C=S); *m/z* (EI, 70 eV) 290 (12, M^+), 257 (49), 203 (13), 202 (13), 164 (14), 152 (8), 139 (7), 126 (100), 111 (10), 77 (13%).

4.3.14. *trans* 2-Piperidin-1-yl-cyclopentanecarbothioic acid benzylamide [2ip(t)]. White solid, mp 90–91°C from *n*-hexane [Found: C, 71.28; H, 8.70; N, 9.11; S, 10.41. $C_{18}H_{26}N_2S$ requires C, 71.47; H, 8.66; N, 9.26; S, 10.60%]; ν_{max}(KBr pellet) 3050–2500 br, 2932, 2856, 2816, 1546, 1408, 1158, 472 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.06–1.37 (6H, m, $3CH_2$), 1.52–1.71 (4H, m, CH_2-11, CH_2-12), 2.00–2.08 (1H, m, C*H*H-10), 2.09–2.39 (m, 3H, CH_2N, CH*H*-11), 2.49–2.52 (2H, brs, CH_2N), 2.78 (1H, quartet, *J*=9.3 Hz, CH_β-2), 2.97 (1H, quartet, *J*=9.3 Hz, CH_α-3), 4.69–4.79 (2H, m, C*H*$_2$Ph), 7.29–7.38 (5H, m, C_6H_5), 11.43 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 20.60, 21.78 (each t, CH_2-11, CH_2-12), 24.31, (t,

CH_2), 25.82 (t, 2CH_2), 29.24 (t, CH_2-10), 49.24 (d, CH-2), 49.50 br (t, CH_2NCH_2), 50.34 (t, *C*H_2Ph), 70.59 (d, CH-3), 127.84, 128.61, 128.75, 136.75 (C_6H_5), 206.30 (s, C=S); *m/z* (EI, 70 eV) 302 (33, M^+), 269 (53), 217 (50), 211 (25), 175 (34), 152 (13), 150 (11), 137 (16), 124 (100), 84 (39%).

4.3.15. *trans* 2-Morpholin-4-yl-cyclopentanecarbothioic acid benzylamide [2im(t)]. White solid, mp 95–97°C from *n*-hexane [Found: C, 67.05; H, 7.98; N, 8.92; S, 10.30. $C_{17}H_{24}N_2OS$ requires C, 67.07; H, 7.95; N, 9.20; S, 10.53%]; ν_{max}(KBr pellet) 3116, 3050–2600 br, 1550, 1414, 1334, 1114, 872, 706 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.58–1.75 (4H, m, CH_2-11, CH_2-12), 2.01–2.20 (1H, m, C*H*H-10), 2.21–2.26 (1H, m, CH*H*-10), 2.31–2.50 (2H, m, CH_2N), 2.50–2.66 (2H, m, CH_2N), 2.79 (1H, quartet, *J*=9.1 Hz, CH_β-2), 3.05 (1H, quartet, *J*=9.1 Hz, CH_α-3), 3.19–3.41 (4H, m, CH_2OCH_2), 4.69–4.79 (2H, m, CH_2Ph), 7.27–7.40 (5H, m, C_6H_5), 10.74 (1H, brs, NH); δ_C (100.6 MHz, $CDCl_3$) 21.07 (t, CH_2-11), 22.49 (t, CH_2-12), 29.73 (t, CH_2-10), 48.64 br (t, CH_2NCH_2), 49.78 (d, CH-2), 50.43 (t, *C*H_2Ph), 66.77 (t, CH_2OCH_2), 70.47 (d, CH-3), 128.17, 128.62, 128.96, 136.71 (C_6H_5), 206.24 (s, C=S); *m/z* (EI, 70 eV) 304 (48, M^+), 271 (42), 213 (21), 178 (27), 164 (12), 154 (19), 152 (12), 139 (17), 127 (30), 126 (100), 91 (59%).

4.3.16. 3-Phenyl-3-piperidin-1-yl-1-pyrrolidin-1-yl-propane-1-thione (2jp). Yellow solid, mp 113–115°C from *n*-hexane/ethyl acetate [Found: C, 71.08; H, 8.44; N, 9.18; S, 10.60. $C_{18}H_{26}N_2S$ requires C, 71.47; H, 8.66; N, 9.26; S, 10.60%]; ν_{max}(KBr pellet) 2932, 1476, 1448, 1266, 1204, 776, 712 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.35–1.47 (2H, m, CH_2), 1.50–1.62 (4H, m, 2CH_2), 1.62–1.78 (2H, m, CH_2), 1.78–1.92 (2H, m, CH_2), 2.38–2.57 (4H, m, 2CH_2), 2.96–3.16 (2H, m, CH_2-4′), 3.42 (1H, dd, *J*=12.7, 5.6 Hz, C*H*H-2), 3.45–3.52 (1H, m, CH*H*-2), 3.53–3.63 (1H, m, C*H*H-1′), 3.77–3.82 (1H, m, CH*H*-1′), 4.21 (1H, dd, *J*=8.1, 5.6 Hz, CH-3), 7.20–7.30 (3H, m, C_6H_5), 7.36 (2H, brd, *J*=7.0 Hz, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 24.16 (t, CH_2-2′), 24.45 (t, CH_2-7), 26.15 (t, CH_2-3′), 26.22 (t, 2CH_2), 47.71 (t, CH_2-4′), 50.83 (t, CH_2-2), 52.21 (t, CH_2NCH_2), 53.77 (t, CH_2-1′), 71.25 (d, CH-3), 127.25, 127.91, 128.47, 140.28 (C_6H_5); GCMS-decomposition (retro-Michael addition).

4.3.17. 3-Morpholin-4-yl-3-phenyl-1-pyrrolidin-1-yl-propane-1-thione (2jm). Yellow oil [Found: C, 67.34; H, 7.94; N, 8.95; S, 10.51. $C_{17}H_{24}N_2OS$ requires C, 67.07; H, 7.95; N, 9.20; S, 10.53%]; ν_{max}(KBr pellet) 2952, 2848, 2800, 1500, 1448, 1120, 880, 708 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.54–1.74 (2H, m, C*H*H-3′, C*H*H-2′), 1.74–1.86 (2H, m, CH*H*-3′, CH*H*-2′), 2.52 (4H, brt, *J*=4.1 Hz, CH_2NCH_2), 2.82–2.89 (1H, m, C*H*H-4′), 2.97 (1H, dd, *J*=12.5, 9.1 Hz, C*H*H-2), 3.31–3.42 (2H, m, CH*H*-2, CH*H*-4′), 3.47–3.58 (1H, m, C*H*H-1′), 3.62–3.80 (5H, m, CH*H*-1′, CH_2OCH_2), 4.12 (1H, dd, *J*=9.1, 4.1 Hz, CH-3), 7.23–7.37 (3H, m, C_6H_5), 7.39 (2H, d, *J*=8.2 Hz, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 24.09 (t, 2CH_2-2′), 26.09 (t, CH_2-3′), 47.74 (t, CH_2-2), 50.80 (t, CH_2-4′), 51.64 (t, CH_2NCH_2), 53.73 (t, CH_2-1′), 67.16 (t, CH_2OCH_2), 71.08 (d, C-3), 127.57, 128.10, 128.38, 140.00 (C_6H_5), 197.13 (s, C-1); *m/z* (EI, 70 eV) 304 (11, M^+), 271 (14), 219 (20), 217 (30), 176 (100), 174 (24), 147 (14), 128 (24), 115 (17), 91 (11), 70 (14%).

4.3.18. 3-Phenyl-1,3-dipyrrolidin-1-yl-propane-1-thione (2jpy). White solid, mp 67–69°C from *n*-hexane [Found: C, 71.06; H, 8.54; N, 9.90; S, 10.99. $C_{17}H_{24}N_2S$ requires C, 70.79; H, 8.39; N, 9.71; S, 11.12%]; ν_{max}(KBr pellet) 2948, 2780, 1492, 1448, 1256, 1132, 706 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.40–1.52 (1H, m, C*H*H-3′), 1.56–1.70 (1H, m, C*H*H-2′), 1.70–183 (6H, m, 2CH_2, CH*H*-2′, CH*H*-3′), 2.53–2.66 (5H, m, CH_2NCH_2, C*H*H-4′), 3.09 (1H, dd, *J*=12.0, 10.0 Hz, C*H*H-2), 3.24–3.30 (1H, m, CH*H*-4′), 3.37 (1H, dd, *J*=12.0, 4.2 Hz, CH*H*-2), 3.45–3.52 (1H, m, C*H*H-1′), 3.69–3.76 (1H, m, CH*H*-1′), 3.98 (1H, dd, *J*=10.0, 4.2 Hz, CH-3), 7.20–7.29 (3H, m, C_6H_5), 7.44 (2H, brd, *J*=6.6 Hz, C_6H_5); δ_C (100.6 MHz, $CDCl_3$) 23.56 (t, 2CH_2), 24.10 (t, CH_2-3′), 26.08 (t, CH_2-4′), 50.74 (t, CH_2-5′), 51.28 (t, CH_2-2), 52.99 (t, CH_2NCH_2), 53.60 (t, CH_2-2′), 71.81 (d, CH-3), 127.39, 127.91, 127.99, 142.07 (C_6H_5), 196.90 (s, C-1); GCMS-decomposition (retro-Michael addition).

4.3.19. 1,3-Dipiperidin-1-yl-butane-1-thione (2kp). White solid, mp 68–70°C from *n*-hexane [Found: C, 66.07; H, 10.57; N, 11.05; S, 12.31. $C_{14}H_{26}N_2S$ requires C, 66.09; H, 10.30; N, 11.01; S, 12.60%]; ν_{max}(KBr pellet) 2932, 2852, 2800, 1502, 1264 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.13 (3H, d, *J*=6.7 Hz, CH_3), 1.39–1.45 (2H, m, CH_2), 1.52–1.58 (2H, m, CH_2), 1.58–1.75 (6H, m, 3CH_2), 2.45–2.55 (4H, m, 2CH_2N), 2.85–2.94 (1H, m, C*H*H-2), 3.08–3.19 (2H, m, CH*H*-2, CH-3), 3.69–3.83 (2H, m, NCH_2), 4.23–4.35 (2H, m, NCH_2); δ_C (100.6 MHz, $CDCl_3$) 15.08 (q, CH_3), 24.13, 24.79, 25.41 (each t, 3CH_2), 26.43 (t, 2CH_2), 27.01 (t, CH_2), 46.68 (t, CH_2-2), 49.74 (t, CH_2NCH2), 51.29, 51.73 (each t, CH_2-2′, CH_2-6′), 60.38 (d, CH-3), 201.16 (s, C-1); GCMS-decomposition (retro-Michael addition).

4.3.20. 3-Morpholin-4-yl-1-piperidin-1-yl-butane-1-thione (2km). Yellow oil [Found: C, 61.09; H, 9.18; N, 10.75; S, 12.31. $C_{13}H_{24}N_2OS$ requires C, 60.89; H, 9.43; N, 10.93; S, 12.51%]; ν_{max}(liquid film) 2936, 1492, 1442, 1260, 1116 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.14 (3H, d, *J*=6.6 Hz, CH_3), 1.65–1.77 (6H, m, 3CH_2), 2.56–2.60 (4H, m, 2CH_2N), 2.88 (1H, dd, *J*=13.0, 8.5 Hz, C*H*H-2), 3.12 (1H, dd, *J*=13.0, 4.9 Hz, CH*H*-2), 3.14–3.25 (1H, m, CH-3), 3.65–3.78 (6H, m, CH_2OCH_2, CH_2N), 4.25–4.31 (2H, m, CH_2N); δ_C (100.6 MHz, $CDCl_3$) 14.80 (q, CH_3), 24.10, 25.40, 26.99 (each t, 3CH_2), 46.41 (t, CH_2-2), 49.03 (t, CH_2NCH_2), 51.30, 51.76 (each t, CH_2NCH_2), 60.03 (d, CH-3), 67.29 (t, CH_2OCH_2), 200.44 (s, C=S); *m/z* (EI, 70 eV) 256 (11, M^+), 223 (9), 169 (9), 154 (11), 114 (100), 84 (11%).

4.3.21. 1-Piperidin-1-yl-3-pyrrolidin-1-yl-butane-1-thione (2kpy). Brown oil [Found: C, 65.06; H, 9.94; N, 11.85; S, 13.22. $C_{13}H_{24}N_2S$ requires C, 64.95; H, 10.06; N, 11.65; S, 13.34%]; ν_{max}(liquid film) 2936, 2856, 1488, 1442, 1264, 1148, 1010 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.19 (3H, d, *J*=6.0 Hz, CH_3), 1.52–1.83 (10H, m, 5CH_2), 2.69 (4H, brs, 2CH_2N), 2.98 (1H, dd, *J*=13.6, 10.8 Hz, C*H*H-2), 3.11–3.21 (2H, m, CH-3, CH*H*-2), 3.75–3.86 (2H, m, CH_2N), 4.26–4.36 (2H, m, CH_2N); δ_C (100.6 MHz, $CDCl_3$) 17.64 (q, CH_3), 23.44 (t, 2CH_2N), 24.12, 25.45, 26.90 (t, 3CH_2), 47.58 (t, CH_2-2), 50.68 (t, 2CH_2N), 51.40, 51.72 (t, CH_2NCH_2), 58.96 (d, CH-3), 199.90 (s, C═S); *m*/*z* (EI, 70 eV) 240 (5, M^+), 207 (5), 169 (20), 154 (23), 98 (100), 97 (28), 84 (19), 69 (15), 56 (10), 41 (15%).

4.3.22. 2-Methyl-1,3-dipiperidin-1-yl-propane-1-thione (2lp). White solid, mp 55–56°C from *n*-hexane [Found: C, 66.08; H, 10.31; N, 10.72; S, 12.28. $C_{14}H_{26}N_2S$ requires C, 66.09; H, 10.30; N, 11.01; S, 12.60%]; ν_{max}(KBr pellet) 2936, 2852, 1485, 1468, 1284, 1258, 1238 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$) 1.23 (3H, d, *J*=6.5 Hz, CH_3), 1.30–1.44 (2H, m, CH_2-7), 1.46–1.60 (4H, m, $2CH_2$), 1.62–1.82 (6H, m, CH_2-3′, CH_2-4′, CH_2-5′), 2.30–2.41 (4H, m, CH_2NCH_2), 2.44 (1H, dd, *J*=12.7, 6.5 Hz, C*H*H-3), 2.77 (1H, dd, *J*=12.7, 6.5 Hz, CH*H*-3), 3.26 (1H, sextet, *J*=6.5 Hz, CH-2), 3.72–3.88 (2H, m, CH_2-6′), 4.20–4.27 (1H, m, C*H*H-2′), 4.32–4.48 (1H, m, CH*H*-2′); δ_C (100.6 MHz, $CDCl_3$) 20.32 (q, CH_3), 24.37, 24.52, 25.45 (each t, $3CH_2$), 26.18 (t, 2-CH_2), 27.26 (t, CH_2), 40.25 (d, CH-2), 50.59, 51.87 (each t, $2NCH_2$), 55.43 (t, CH_2NCH_2), 66.34 (t, CH_2-3), 207.68 (s, C═S); *m*/*z* (EI, 70 eV) 254 (10, M^+), 221 (5), 170 (4), 98 (100%).

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