DOI: 10.1002/ejoc.200800859

Thiols in Ugi- and Passerini–Smiles-Type Couplings

Anaëlle Barthelon,[a] Laurent El Kaïm,*[a] Marie Gizolme,[b] and Laurence Grimaud*[b]

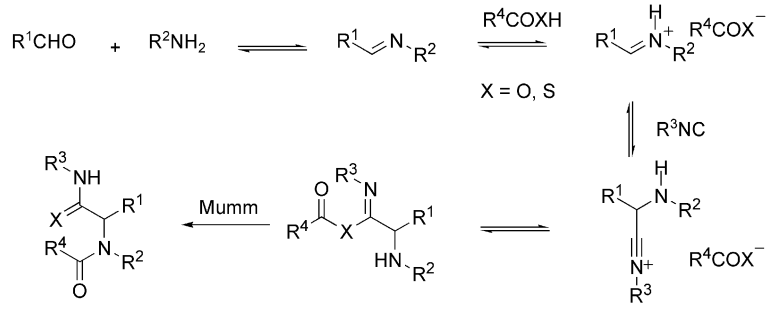
Keywords: Ugi reaction / Smiles reaction / Isocyanides / Rearrangement / Thiols / Multicomponent reactions

The use of the Smiles rearrangement in Ugi-type couplings with aromatic mercaptans allows for the straightforward, multicomponent formation of α-arylamino thiocarboxamides. The scope of this new four-component coupling is further broadened with the use of heterocyclic mercapto derivatives that afford thioamides of high biological interest in one step. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2008)

Introduction

Stimulated by the development of high-throughput screening in the pharmaceutical industry, the use of isocyanide-based multicomponent reactions (IMCR)[1] has increased dramatically over the last few years due to the growing demand for new scaffolds. The interest in IMCRs is mainly due to the efficiency of the Ugi reaction.[2] First described in 1959, this reaction affords peptide derivatives by a four-component coupling involving an isocyanide, an amine, a carbonyl compound and a carboxylic acid. Although it was discovered more than thirty years ago, this reaction has become increasingly popular since the beginning of the 1990s thanks to the publication of numerous post-condensation transformations that provide heterocycles.[1c,j] In addition to these post-condensation reactions, the most significant development of this reaction lies in the modification of the partners involved in the coupling. For instance, imines have been successfully replaced by oximes[3] or hydrazones.[4] These modifications may slightly alter the classical mechanism of the Ugi reaction, which involves a series of equilibria displaced by an irreversible Mumm-type rearrangement (Scheme 1, X = O).[1c,j] In order to be successful, the replacement of the acidic derivative requires new rearrangements of the imidoyl intermediate resulting from the nitrilium trapping. The most significant alterations were proposed by Ugi shortly after his first publication on this coupling. In the case of hydrazoic,[5] isocyanic[6] or isothiocyanic acid,[7] the last step involves a cyclization into tetrazole or hydantoin derivatives. Coupling with sulfur derivatives such as $H_2S_2O_3$ were reported early on by Ugi.[8] More recently, Dömling and coworkers described the use of thiocarboxylic acids to form thioamides by a Mumm-type conversion of the thioimidate intermediate (Scheme 1, X = S).[9]

We have recently been able to increase the synthetic scope of these Ugi couplings by introducing Smiles rearrangements of the nitrilium manifold.[10] If electron-poor phenols

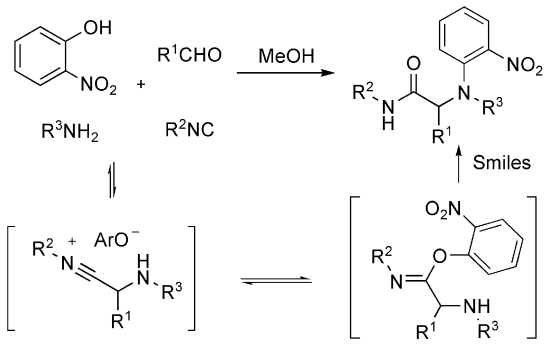


Scheme 1. Mechanism of the Ugi and thio-Ugi reaction.

are introduced as acidic partners, an *N*-arylation occurs with overall transfer of the aryl moiety onto the nitrogen of the starting amine (Scheme 2). The success of this new coupling is combined with an irreversible Smiles rearrangement of the imidate resulting from the trapping of the nitrilium by the phenolate (Scheme 2). The greater thermo-

[a] E.N.S.T.A.,
32, Bd. Victor, 75015 Paris, France
Fax: +33-1-45525537
E-mail: laurent.elkaim@ensta.fr
[b] E.N.S.T.A.,
32, Bd. Victor, 75015 Paris, France
Fax: +33-1-45526565
E-mail: laurence.grimaud@ensta.fr

dynamic stability of the final amide in comparison to that of the phenolate intermediate vouches for the irreversibility of the process.

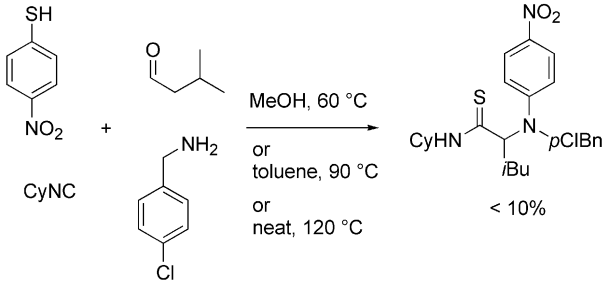


Scheme 2. Ugi–Smiles coupling of *o*-nitrophenol.

Considering the successful substitution of carboxylic acids by thiocarboxylic acids in the Ugi coupling, we assumed that similar modifications with phenols could give rise to a new pathway to *N*-aryl-substituted thioamides. In that coupling, the higher nucleophilicity of the thiolate compared to that of the phenolate should favour the first steps. However, a less efficient Smiles rearrangement could be expected, since the conversion of the thioimidate to the thiocarbonyl derivative would bring less stabilization to the system. Following our first communications on the Ugi–Smiles reactions of thiophenols,[11] we now wish to give a full report on the subject.

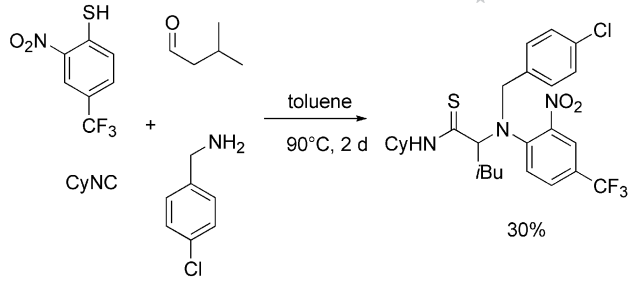
Results and Discussion

When 4-nitrobenzenethiol was stirred with a stoichiometric amount of cyclohexyl isocyanide, isovaleraldehyde and *p*-chlorobenzylamine in MeOH at 60 °C, or in toluene at 90 °C, or even neat at 120 °C, only a trace of the desired adduct could be isolated (Scheme 3). No improvement was observed upon preforming the imine or adding Lewis acids such as magnesium perchlorate.[12]



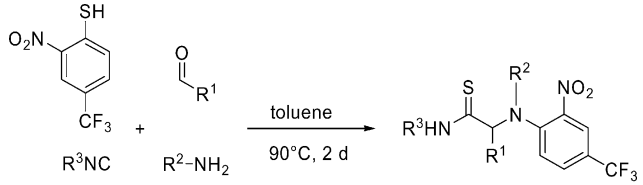
Scheme 3. Ugi–Smiles coupling with *p*-nitrothiophenol.

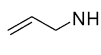
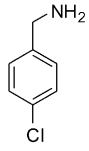
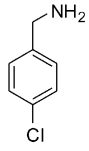
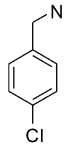
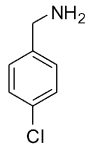
The best results were obtained with the more activated 2-nitro-4-(trifluoromethyl)benzenethiol in toluene at 90 °C. After 2 d, the expected thioamide was isolated in 30% yield (Scheme 4). Varying the other three partners gave very disappointing results, as yields were very low (Table 1).



Scheme 4. Ugi–Smiles coupling of *o*-nitrothiophenol.

Table 1. Ugi–Smiles couplings using 2-nitro-4-(trifluoromethyl)-thiophenol (Cy = cyclohexyl).

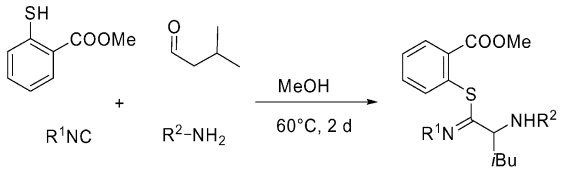


Entry	R^1CHO	R^2NH_2	R^3NC	Isolated yields (%)
1			CyNC	26
2			*t*BuNC	< 10
3				< 10
4			CyNC	< 10

Surprisingly, the less-activated methyl mercaptosalicylate reacted in MeOH at 60 °C to form a four-component adduct. The examination of the ^{13}C NMR spectra clearly showed the formation of the thioimidates instead of the desired thioamides. The latter were obtained in good yields whatever carbonyl compound, amine and isocyanide substrates were used (Table 2).

The isolation of this non-rearranged product seemed to contradict the mechanism we proposed for the phenol derivatives. Indeed, we had postulated that the final Smiles rearrangement insured the efficiency of the four-component

Table 2. Mercaptosalicylate as acidic inputs.



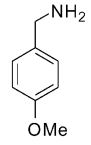
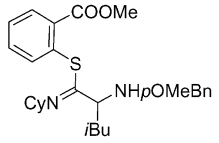
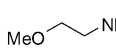
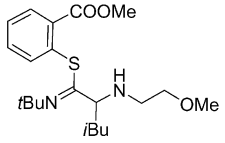
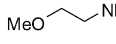
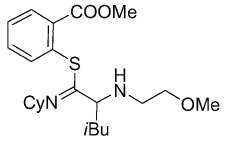
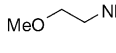
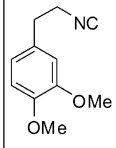
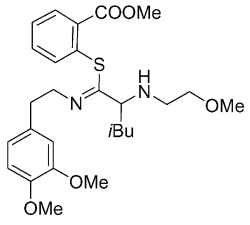
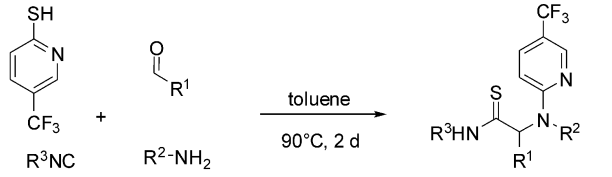
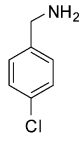
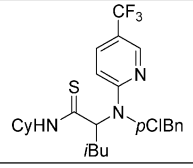
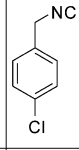
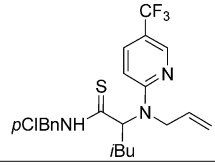
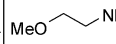
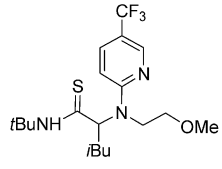
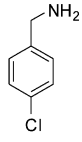
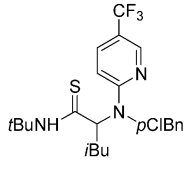
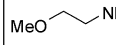
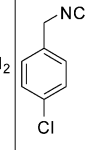
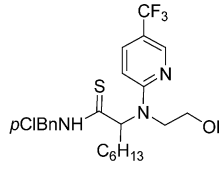
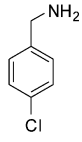
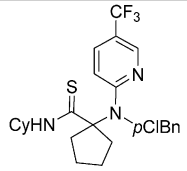
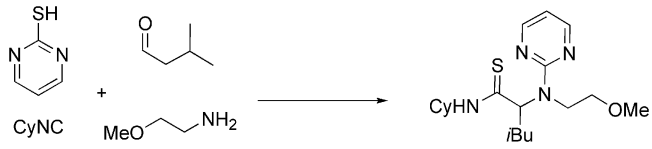
Entry	R^2NH_2	R^3NC	Product	Yield (%)
1		CyNC		82
2		*t*BuNC		84
3		CyNC		65
4				45

Table 3. Mercaptopyridine in Ugi–Smiles couplings.



Entry	R^1CHO	R^2NH_2	R^3NC	Product	Yield (%)
1			CyNC		60
2					46
3			*t*BuNC		66
4			*t*BuNC		52
5					26
6			CyNC		42



Conditions	Isolated yields
MeOH, 60°C	8-15%
Toluene, 90°C	19-24%
DMF, 90°C	12%
CF_3CH_2OH, reflux	9%
neat, 90°C	77%

Scheme 5. Ugi–Smiles coupling of 2-mercaptopyrimidine; Cy = cyclohexyl.

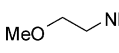
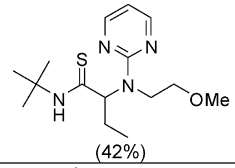
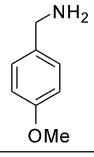
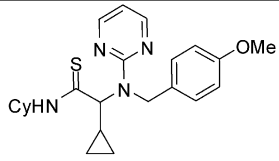
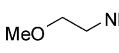
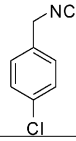
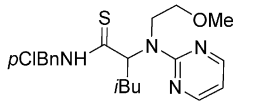
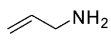
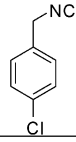
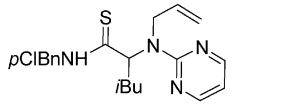
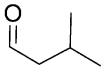
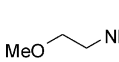
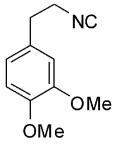
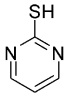
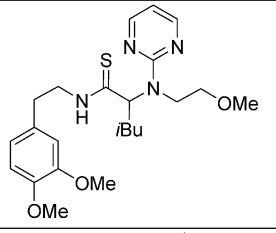
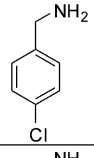
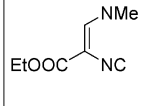
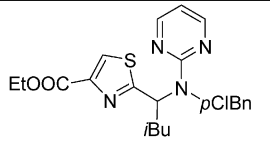
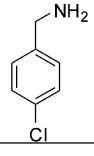
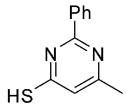
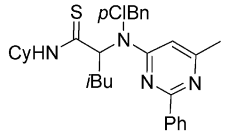
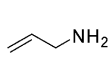
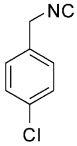
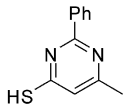
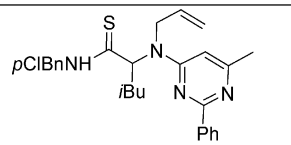
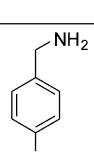
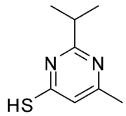
coupling by displacing all the equilibria. The driving force of the whole process is probably the creation of the particularly energetic C=O bond. In the thiocoupling, the higher nucleophilicity of the thiolate compared to that of the phenolate is probably sufficient to allow the formation of thioimidates in good yields. They turned out to be very stable and failed to rearrange in 1,2-dichloroethane at 120 °C, in 1:1 EtOH/H_2O at reflux or under basic conditions (LiOH, DMF, 80 °C). Acidic hydrolysis [$Hg(OAc)_2$ in 1:1 EtOH/H_2O at reflux or TFA in CH_2Cl_2 at 40 °C] did not affect these compounds either. The peculiar stability of such derivatives could be explained by a possible intramolecular hydrogen bond between the NH of the amine and one oxygen of the ester group. This assumption is based upon the dramatic *ortho* substituent effect observed with nitrophenol.[10,13]

To further explore the scope of this mercapto coupling, we envisioned the use of heterocyclic systems known to easily undergo the Smiles rearrangement. As observed with the hydroxy derivatives, mercaptopyridine did not react when treated with a stoichiometric amount of an aldehyde, an amine and an isocyanide in MeOH at 45 °C, or in toluene at 90 °C or neat at 90 °C. However, when activated with an electron-withdrawing substituent such as the trifluoro-

methyl group, mercaptopyridine provided the expected four-component coupling. The best yields were obtained in toluene at 90 °C. Under these conditions, the desired thioamides were obtained in moderate to good yields with aliphatic aldehydes (Table 3, Entries 1–5) as well as with ketones (Table 3, Entry 6), which required a longer reaction time, as is usually observed. Unfortunately, no aromatic or α,β-unsaturated aldehydes reacted under these experimental conditions.

As previously reported in the Ugi–Smiles coupling,[13] hydroxypyrimidines do not require further activation to provide the desired adducts. However, mercaptopyrimidine

Table 4. Mercaptopyrimidine in Ugi–Smiles couplings.

Entry	R^1CHO	R^2NH_2	R^3NC	Mercaptan	Product (isolated yield)
1			*t*BuNC		 (42%)
2			CyNC		 (71%)
3					 (33%)
4					 (52%)
5					 (75%)
6					 (35%)
7			CyNC		 (33%)
8					 (57%)
9			CyNC		(69%)

analogues do not form any adduct unless the experimental conditions are modified. Indeed, in MeOH (1–3 M) at 60 °C or in toluene (1–3 M) at 90 °C with or without additives (such as magnesium perchlorate or lithium chloride), the reaction was sluggish, and small amounts of the corresponding thioamides were isolated (less than 25%). The use of DMF or TFA as the solvent did not improve these results either. However, when 2-mercaptopyrimidine was stirred neat at 90 °C with a stoichiometric amount of methoxyethylamine, isovaleraldehyde and cyclohexyl isocyanide, the desired thioamide was isolated in 77% yield (Scheme 5).

The reaction works with a wide range of partners and various 2-aminopyrimidines have been prepared efficiently from aliphatic aldehydes (Table 4, Entries 1–5). Most interestingly, when using ethyl β-(dimethylamino)-α-isocyanoacrylate,[9,14] the pyrimidothiazole was isolated in 35% yield in one step (Table 4, Entry 6). As previously observed, aromatic aldehydes, α,β-unsaturated aldehydes and ketones did not react under these conditions. Tosylmethyl isocyanide failed to react as well.

4-Mercaptopyrimidines, easily prepared from the corresponding 4-hydroxypyrimidines by treatment with P_2S_5,[15] provide the desired 4-aminopyrimidines in moderate to good yields as well (Table 4, Entries 7–9).

Mercaptopyrazines and quinoxalines were then submitted to the coupling conditions. Unfortunately, these substrates turned out to be less efficient than the corresponding hydroxy derivatives, and the corresponding thioamides were isolated in rather low yields (Table 5).[16]

Table 5. Mercaptopyrazines and related in Ugi–Smiles couplings.

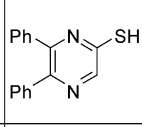
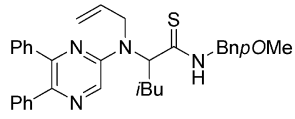
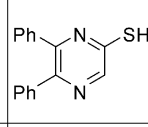
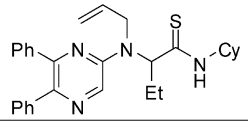
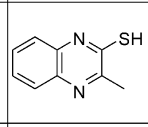
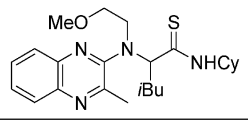
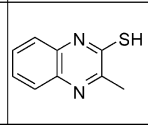
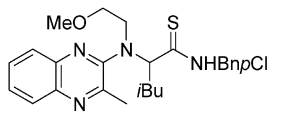
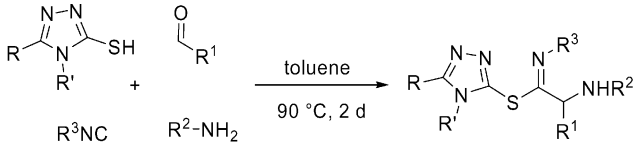
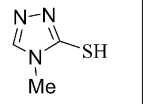
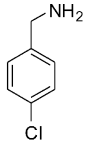
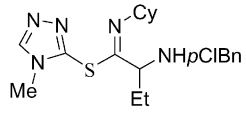
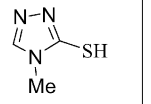
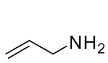
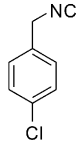
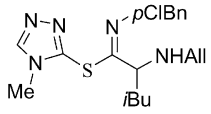
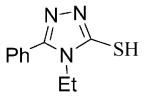
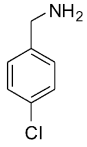
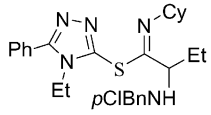
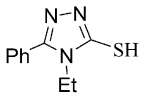
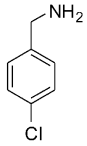
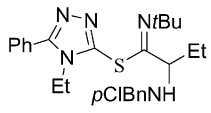
Entry	Mercapto derivative	Time	Product	Yield (%)
1		12 h		76
2		12 h		36
3		12 h		31
4		12 h		9

Table 6. Mercaptotriazoles in Ugi–Smiles couplings.



Entry	Triazole	R^1CHO	R^2NH_2	R^3NC	Product	Yield (%)
1				CyNC		47
2						32
3				CyNC		41
4				*t*BuNC		9

We next investigated heterocyclic five-membered rings. We were not able to perform a coupling with 2-mercaptoimidazoles or thiazoles or with 5-mercaptopyrazoles or isoxazoles, whatever the reaction conditions tested (MeOH, toluene or neat at different temperatures, Figure 1). These results are consistent with the electron-rich nature of these heterocyclic cores.

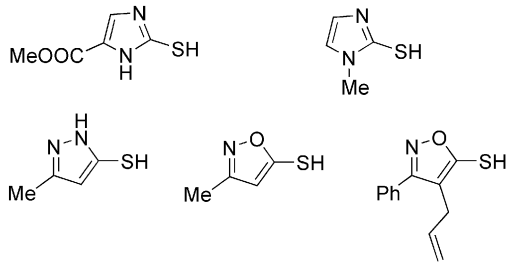
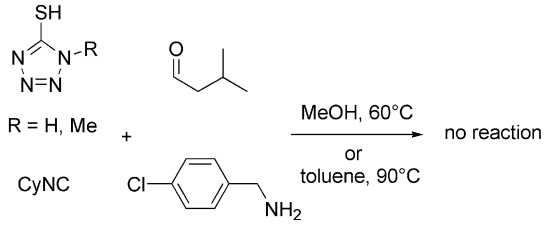


Figure 1. Unefficient acidic partners in Ugi–Smiles couplings.

Similarly, 3-mercapto-4*H*-1,2,4-triazole failed the coupling, but 3-mercapto-4-alkyl-1,2,4-triazoles reacted in toluene at 90 °C with cyclohexyl isocyanide, propionaldehyde and *p*-chlorobenzylamine to form the corresponding thioimidate in 47% yield (Table 6, Entry 1). As for the thiosalicylate, the reasons why the Smiles rearrangement did not occur are still unclear at the moment. Several thioimidates bearing a triazole core have been prepared in modest yields (Table 6).

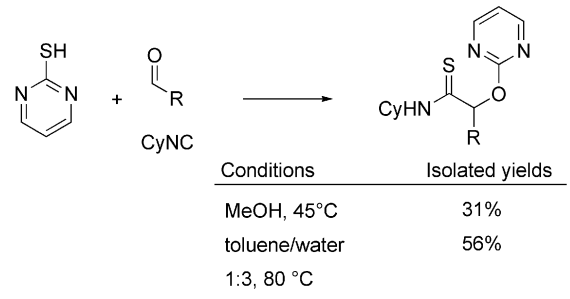
Among those heterocyclic five-membered rings, the most promising were the ones classically involved in the Julia–Kocienski olefination such as tetrazoles or benzo-fused heterocycles. Unfortunately, mercaptotetrazoles did not undergo coupling (Scheme 6).



Scheme 6. Failed couplings with mercaptotetrazoles (Cy = cyclohexyl).

Nonetheless, when mixing 2-mercaptobenzoxazole with an amine, an aldehyde and an isocyanide, the reaction proceeded smoothly in toluene at 50 °C within 2 d.[17] The scope of the reaction was examined with various substrates. The desired thioamides were isolated in good yields with aliphatic aldehydes (Table 7, Entries 1–6) as well as with ketones (Table 7, Entry 8). The reaction was less efficient with aromatic aldehydes (Table 7, Entry 7). The use of 2-mercaptobenzothiazole required a slight increase in temperature to obtain similar results. Various aldehydes, amines and isocyanides were tested successfully in this coupling (Table 7, Entries 9–18). When the reaction was performed with ethyl β-(dimethylamino)-α-isocyanoacrylate, the bisthiazole was isolated in 32% yield in one step (Table 7, Entry 16).

In connection with this new thio coupling, we next examined the feasibility of a thio Passerini–Smiles reaction. Given that the three-component coupling generally requires stronger acidic conditions than Ugi couplings (as the carbonyl is less reactive than the corresponding iminium), we wondered whether mercaptans would perform such a coupling. We subsequently tested a wide range of thio derivatives, with a stoichiometric amount of aldehyde and isocyanide, varying the experimental conditions (solvents and temperatures). 4-Nitrothiophenol failed to react with propionaldehyde and cyclohexyl isocyanide in MeOH at 45 °C, in toluene at 80 °C, in 1:3 toluene/water at 80 °C or in the presence of a Lewis acid such as diethylaluminium chloride in dichloromethane. With mercaptopyridines, propionaldehyde and cyclohexyl isocyanide, the yields did not exceed 15% either in toluene at 80 °C or in MeOH at 45 °C. Mercaptobenzo-fused compounds failed to react under both conditions as well. Finally, 2-mercaptopyrimidine gave the desired adduct in 31% yield in MeOH at 45 °C within 3 d (Scheme 7). This coupling could be improved slightly if performed in 1:3 toluene/water at 80 °C for 2 d (56%), but Lewis acids [$ZnCl_2$, $TiCl_4$, $SiCl_4$, $Mg(ClO_4)_2$ in toluene, or Et_2AlCl in CH_2Cl_2] seemed to have no effect. However, the efficiency of the reaction was restricted by the narrow range of reactive aldehydes (*i*BuCHO, PrCHO). Disappointed by these preliminary results, we did not study the thio-Passerini–Smiles coupling further.



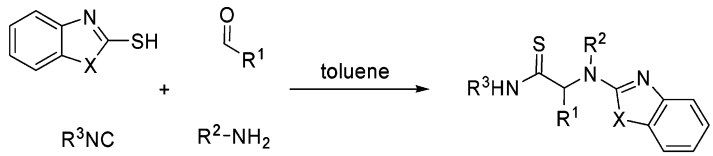
Conditions	Isolated yields
MeOH, 45°C	31%
toluene/water 1:3, 80 °C	56%

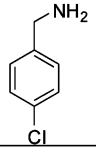
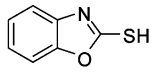
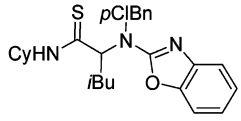
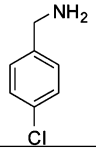
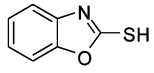
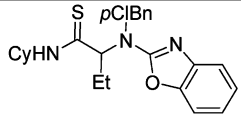
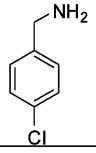
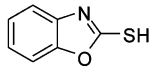
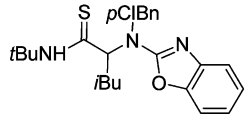
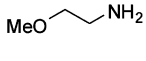
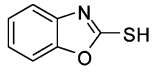
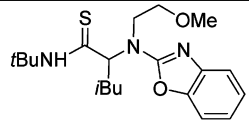
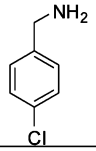
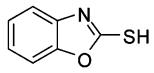
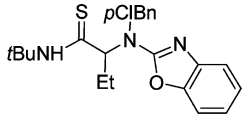
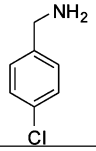
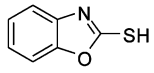
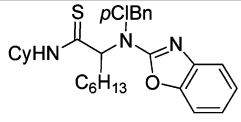
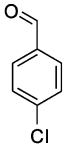
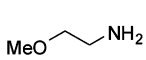
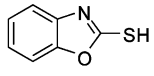
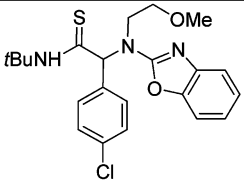
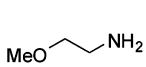
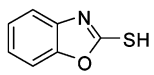
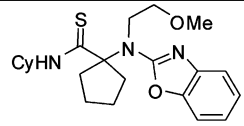
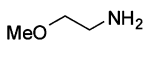
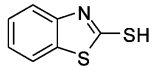
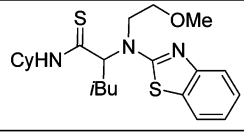
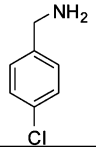
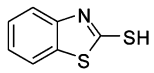
Scheme 7. Passerini–Smiles coupling with mercaptans (Cy = cyclohexyl).

Conclusions

The use of thiols in Ugi reactions combined the advantages of the classical Ugi reaction with the selective synthesis of thioamides, which would otherwise be difficult to obtain. The application of the Ugi–Smiles approach to thiols allowed for the formation of α-arylamino-thiocarboxamides, but a different reactivity pattern was observed when compared with hydroxy derivatives. The reactions with thiophenol derivatives were poorly efficient. In the case of salicylic acid derivatives, the Smiles rearrangement was not ob-

Table 7. Mercaptobenzooxazoles and -benzothiazoles in Ugi–Smiles couplings.



Entry	R^1CHO	R^2NH_2	R^3NC	Mercaptan	Product (isolated yield)
1			CyNC		 (61%)
2			CyNC		 (59%)
3			*t*BuNC		 (61%)
4			*t*BuNC		 (66%)
5			*t*BuNC		 (61%)
6			CyNC		 (44%)
7			*t*BuNC		 (22%)
8			CyNC		 (45%)
9			CyNC		 (59%)
10			CyNC		(77%)

served, and thioimidates were the only isolated adducts. The behaviour of heteroaromatic thiols was much more satisfying, and good yields were obtained for nitrogen-containing, six-membered-ring systems. More interestingly, five-membered ring-fused systems such as benzoxazoles gave adducts when they were thiol-substituted, whereas the corresponding hydroxy analogue failed to give any coupling. Thus, hydroxy and thiol derivatives seemed complementary in the Ugi–Smiles system. We are further exploring the reactivity of more complex heterocyclic thiols.

Experimental Section

General: ^{1}H NMR spectra were recorded with a Bruker Avance 400 spectrometer, with $CDCl_3$ as the solvent. ^{13}C NMR spectra were recorded with a Bruker Avance 400 (100.6 MHz) spectrometer. Two-dimensional NMR spectroscopy [H-H COSY spectra, H-C COSY spectra (HSQC) and long-range H-C COSY spectra (HMBC)], were carried out to determine the correlation between H and C. The chemical shifts for all NMR spectra are expressed in parts per million (ppm) downfield from the TMS reference. Coupling constants (*J*) are quoted in Hz and are recorded to the nearest 0.1 Hz. The IR spectra were obtained with a Bruker IFS 66 or a Perkin–Elmer FT 1600 spectrometer. Low-resolution mass spectral analysis (EI and CI) were recorded with a Hewlett–Packard HP5989 mass spectrometer by either direct injection or GC/MS coupling with a Hewlett–Packard HP5890 chromatograph. High-resolution (HR) mass spectra were performed with a JEOL JMS-Gcmate II, GC/MS system spectrometer. TLC was carried out with precoated plates of silica gel 60F254. All the reactions were performed under a nitrogen atmosphere with reagent-grade solvents and starting materials without further purification. These reactions were not moisture-sensitive.

General Procedure for the Ugi–Smiles Coupling: To a solution of the carbonyl compound (1 M, 1 mmol) in the indicated solvent was added successively 1.0 equiv. of amine, 1.0 equiv. of isocyanide and 1.0 equiv. of the acidic partner under an inert atmosphere. The resulting mixture was stirred at the indicated temperature for the indicated time. The mixture was then concentrated in vacuo, and the crude product was purified by flash chromatography on silica gel.

2-{(4-Chlorobenzyl)[2-nitro-4-(trifluoromethyl)phenyl]amino}-*N*-cyclohexyl-4-methylpentanethioamide: See Scheme 4; yield (90 °C in toluene for 2 d) 30% (163 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.35 (br. s, 1 H), 7.81 (d, J = 2.0 Hz, 1 H), 7.52 (dd, J = 8.6, 2.0 Hz, 1 H), 7.15–7.10 (m, 3 H), 6.94 (d, J = 8.4 Hz, 2 H), 4.29–4.20 (m, 2 H), 4.06 (d, J = 15.5 Hz, 1 H), 3.98 (dd, J = 8.5, 5.0 Hz, 1 H), 2.00–1.90 (m, 2 H), 1.81–1.76 (m, 1 H), 1.68–1.62 (m, 1 H), 1.59–1.48 (m, 3 H), 1.34–1.24 (m, 2 H), 1.18–1.01 (m, 4 H), 0.69 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.1, 145.9, 145.4, 134.4, 134.1, 129.8 (q, $J_{C,F}$ = 3.4 Hz), 129.6, 129.4, 128.7 (q, $J_{C,F}$ = 6.7 Hz), 126.7, 125.5 (q, $J_{C,F}$ = 204.5 Hz), 123.4 (q, $J_{C,F}$ = 3.7 Hz), 72.6, 54.1, 53.2, 41.7, 31.6, 31.4, 25.9, 25.8, 24.9, 23.4, 22.4 ppm. MS (DI, CI NH_3): m/z = 542. IR (thin film): $\tilde{\nu}$ = 2359, 1539, 1322, 1157, 1087 cm^{-1}. HRMS: calcd. for $C_{26}H_{31}ClF_3N_3O_2S$: 541.1778, found: 541.1778.

2-{Allyl[2-nitro-4-(trifluoromethyl)phenyl]amino}-*N*-cyclohexyl-4-methylpentanethioamide: See Table 1, Entry 1; yield (90 °C in toluene for 2 d): 26% (118 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.60 (br. s, 1 H), 8.00 (s, 1 H), 7.73 (dd, J = 8.7, 1.9 Hz, 1 H), 7.38 (d, J = 8.7 Hz, 1 H), 5.72–5.62 (m, 1 H), 5.19 (d, J = 11.2 Hz, 1 H), 5.15 (d, J = 17.9 Hz, 1 H), 4.40–4.31 (m, 1 H), 4.17 (t, J = 6.5 Hz, 1 H), 3.89 (dd, J = 16.2, 5.7 Hz, 1 H), 3.55 (dd, J = 16.2, 5.7 Hz, 1 H), 2.22–2.15 (m, 1 H), 2.02–1.96 (m, 2 H), 1.77–1.72 (m, 2 H), 1.67–1.63 (m, 1 H), 1.58–1.51 (m, 1 H), 1.46–1.35 (m, 2 H), 1.30–1.17 (m, 4 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.79 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.1, 145.8, 144.7, 132.1, 129.8 (q, $J_{C,F}$ = 3.5 Hz), 125.7 (q, $J_{C,F}$ = 34.6 Hz), 125.5, 123.5 (q, $J_{C,F}$ = 3.8 Hz), 123.3 (q, $J_{C,F}$ = 271.9 Hz), 120.1, 72.3, 54.3, 52.3, 42.1, 31.8, 31.2, 26.0, 25.8, 24.9, 22.9 ppm. MS (DI, CI NH_3): m/z = 458. IR (thin film): $\tilde{\nu}$ = 2360, 1323, 1159, 1127, 1090 cm^{-1}. HRMS: calcd. for $C_{22}H_{30}F_3N_3O_2S$ 457.2011; found 457.2010.

Methyl 2-[1-(Cyclohexylimino)-2-(4-methoxybenzylamino)-4-methylpentylthio]benzoate: See Table 2, Entry 1; yield (60 °C in MeOH for 2 d): 82% (395 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.83–7.81 (m, 1 H), 7.40–7.37 (m, 1 H), 7.34–7.31 (m, 2 H), 7.23 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 3.90 (s, 3 H), 3.85–3.80 (m, 1 H), 3.79 (s, 3 H), 3.40 (d, J = 12.5 Hz, 2 H), 3.12 (dd, J = 10.1, 3.1 Hz, 1 H), 2.23 (br. s, 1 H), 1.91–1.78 (m, 3 H), 1.74–1.59 (m, 2 H), 1.51–1.35 (m, 5 H), 1.30–1.19 (m, 3 H), 0.81 (d, J = 6.6 Hz, 3 H), 0.39 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 167.4, 161.5, 158.9, 136.4, 134.9, 133.6, 132.8, 132.0, 131.1, 129.7, 128.4, 114.0, 61.9, 60.5, 55.6, 52.7, 51.3, 45.1, 34.0, 33.4, 26.2, 25.1, 24.9, 24.2, 21.3 ppm. MS (DI, CI NH_3): m/z = 483. IR (thin film): $\tilde{\nu}$ = 1709, 1512, 1434, 1247, 1174, 1106 cm^{-1}. HRMS: calcd. for $C_{28}H_{38}N_2O_3S$ 482.2603; found 482.2612.

Methyl 2-[1-(*tert*-Butylimino)-2-(2-methoxyethylamino)-4-methylpentylthio]benzoate: See Table 2, Entry 2; yield (60 °C in MeOH for 2 d): 84% (331 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.81 (d, J = 7.5 Hz, 1 H), 7.49 (d, J = 7.5 Hz, 1 H), 7.43 (td, J = 7.5, 1.0 Hz, 1 H), 7.37 (t, J = 7.5 Hz, 1 H), 3.89 (s, 3 H), 3.38–3.31 (m, 2 H), 3.30 (s, 3 H), 2.94 (d, J = 8.6 Hz, 1 H), 2.82–2.75 (m, 1 H), 2.34–2.28 (m, 1 H), 2.20 (br. s, 1 H), 1.73–1.65 (m, 1 H), 1.42 (s, 9 H), 1.36–1.24 (m, 1 H), 1.15–1.08 (m, 1 H), 0.75 (d, J = 6.4 Hz, 3 H), 0.38 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 167.5, 158.4, 136.8, 135.4, 133.1, 132.0, 131.0, 128.6, 73.1, 61.7, 58.9, 56.6, 52.7, 47.0, 45.4, 29.9, 25.1, 24.1, 21.2 ppm. MS (DI, CI NH_3): m/z = 395. IR (thin film): $\tilde{\nu}$ = 1709, 1653, 1459, 1252, 1105 cm^{-1}. HRMS: calcd. for $C_{21}H_{34}N_2O_3S$ 394.2290; found 394.2278.

Methyl 2-[1-(Cyclohexylimino)-2-(2-methoxyethylamino)-4-methylpentylthio]benzoate: See Table 2, Entry 3; yield (60 °C in MeOH for 2 d): 65% (273 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.86 (d, J = 7.5 Hz, 1 H), 7.48 (d, J = 7.5 Hz, 1 H), 7.44 (t, J = 7.5 Hz, 1 H), 7.37 (t, J = 7.5 Hz, 1 H), 3.91 (s, 3 H), 3.78–3.72 (m, 1 H), 3.42–3.33 (m, 2 H), 3.31 (s, 3 H), 3.08 (dd, J = 9.5, 3.3 Hz, 1 H), 2.86–2.80 (m, 1 H), 2.44–2.38 (m, 1 H), 2.08 (br. s, 1 H), 1.81–1.73 (m, 3 H), 1.69–1.61 (m, 2 H), 1.44–1.36 (m, 3 H), 1.35–1.29 (m, 2 H), 1.28–1.19 (m, 3 H), 0.79 (d, J = 6.3 Hz, 3 H), 0.49 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 167.3, 158.5, 136.0, 135.2, 133.5, 132.1, 131.2, 128.2, 73.0, 62.1, 61.6, 58.9, 52.7, 46.9, 44.8, 33.8, 33.3, 26.1, 25.1, 24.9, 24.8, 24.0, 21.5 ppm. MS (DI, CI NH_3): m/z = 421. IR (thin film): $\tilde{\nu}$ = 1709, 1653, 1436, 1291, 1106 cm^{-1}. HRMS: calcd. for $C_{23}H_{36}N_2O_3S$ 420.2447; found 420.2443.

Methyl 2-[1-(3,4-Dimethoxyphenethylimino)-2-(2-methoxyethylamino)-4-methylpentylthio]benzoate: See Table 2, Entry 4; yield (60 °C in MeOH for 2 d): 45% (226 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.88 (dd, J = 7.9, 1.8 Hz, 1 H), 7.39 (t, J = 7.9 Hz, 2 H), 7.30–7.28 (m, 1 H), 6.80 (s, 3 H), 3.90–3.84 (m, 10 H), 3.79–3.71 (m, 1 H), 3.38–3.33 (m, 2 H), 3.32 (s, 3 H), 3.14 (dd, J = 9.4, 3.8 Hz, 1 H), 2.96 (t, J = 7.2 Hz, 2 H), 2.76–2.71 (m, 1 H), 2.41–2.35 (m, 1 H), 1.91 (br. s, 1 H), 1.75–1.67 (m, 1 H), 1.41–1.36 (m, 1 H), 1.30–1.23 (m, 1 H), 0.80 (d, J = 6.6 Hz, 3 H), 0.52 (d, J =

6.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 167.4, 158.2, 149.3, 140.8, 135.4, 134.5, 133.5, 132.2, 131.9, 131.4, 128.2, 121.3, 112.6, 111.5, 72.9, 62.3, 59.0, 56.3, 56.2, 55.7, 52.7, 47.1, 44.6, 36.8, 25.1, 23.9, 21.5 ppm. MS (DI, CI NH_3): *m*/*z* = 503. IR (thin film): $\tilde{\nu}$ = 1709, 1622, 1436, 1237, 1141 cm^{-1}. HRMS: calcd. for $C_{27}H_{38}N_2O_5S$ 502.2501; found 502.2504.

2-{(4-Chlorobenzyl)[5-(trifluoromethyl)pyridin-2-yl]amino}-*N*-cyclohexyl-4-methylpentanethioamide: See Table 3, Entry 1; yield (90 °C in toluene for 16 h): 60% (298 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.22 (br. s, 1 H), 8.42 (d, *J* = 2.3 Hz, 1 H), 7.55 (dd, *J* = 9.0, 2.3 Hz, 1 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 6.35 (d, *J* = 9.0 Hz, 1 H), 5.62 (br. s, 1 H), 5.02 (d, *J* = 17.8 Hz, 1 H), 4.60 (d, *J* = 17.8 Hz, 1 H), 4.38–4.29 (m, 1 H), 2.26–2.18 (m, 1 H), 2.09–2.03 (m, 1 H), 1.88–1.82 (m, 1 H), 1.77–1.68 (m, 2 H), 1.63–1.54 (m, 2 H), 1.48–1.26 (m, 4 H), 1.22–1.17 (m, 2 H), 0.90 (d, *J* = 6.8 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 200.7, 160.3, 144.9 (q, $J_{C,F}$ = 4.3 Hz), 136.5, 135.3 (q, $J_{C,F}$ = 3.0 Hz), 133.2, 129.3, 128.1, 124.7 (q, $J_{C,F}$ = 270.3 Hz), 116.6 (q, $J_{C,F}$ = 33.1 Hz), 108.7, 61.0, 53.6, 49.1, 40.5, 31.6, 31.2, 25.8, 25.5, 24.6, 23.3, 23.0 ppm. MS (DI, CI NH_3): *m*/*z* = 498. IR (thin film): $\tilde{\nu}$ = 2363, 1612, 1502, 1320, 1159, 1115, 1093 cm^{-1}. HRMS: calcd. for $C_{25}H_{31}ClF_3N_3S$: 497.1879, found: 497.1892.

2-{Allyl[5-(trifluoromethyl)pyridin-2-yl]amino}-*N*-(4-chlorobenzyl)-4-methylpentanethioamide: See Table 3, Entry 2; yield (90 °C in toluene for 16 h): 46% (209 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.59 (br. s, 1 H), 8.21 (d, *J* = 2.3 Hz, 1 H), 7.66 (dd, *J* = 9.0, 2.3 Hz, 1 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.08 (d, *J* = 8.3 Hz, 2 H), 6.61 (d, *J* = 9.0 Hz, 1 H), 5.82–5.73 (m, 1 H), 5.69–5.63 (m, 1 H), 5.21 (d, *J* = 10.2 Hz, 1 H), 5.18 (d, *J* = 17.1 Hz, 1 H), 4.80 (dd, *J* = 15.2, 4.9 Hz, 1 H), 4.71 (dd, *J* = 15.2, 4.9 Hz, 1 H), 4.44 (d, *J* = 18.1 Hz, 1 H), 3.92 (d, *J* = 18.1 Hz, 1 H), 2.24–2.16 (m, 1 H), 1.91–1.83 (m, 1 H), 1.65–1.57 (m, 1 H), 0.94 (d, *J* = 6.7 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 203.5, 160.4, 144.8 (q, $J_{C,F}$ = 4.3 Hz), 135.2, 134.1, 129.6, 129.3, 124.7 (q, $J_{C,F}$ = 270.3 Hz), 117.5, 116.2 (q, $J_{C,F}$ = 33.2 Hz), 108.6, 60.6, 49.1, 48.5, 40.4, 25.4, 23.2, 23.0 ppm. MS (DI, CI NH_3): *m*/*z* = 456. HRMS: calcd. for $C_{22}H_{25}ClF_3N_3S$ 455.1410; found 455.1423.

***N*-*tert*-Butyl-2-{(2-methoxyethyl)[5-(trifluoromethyl)pyridin-2-yl]amino}-4-methylpentanethioamide:** See Table 3, Entry 3; yield (90 °C in toluene for 16 h): 66% (267 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.52 (br. s, 1 H), 8.36 (d, *J* = 2.4 Hz, 1 H), 7.67 (dd, *J* = 9.0, 2.4 Hz, 1 H), 6.85 (d, *J* = 9.0 Hz, 1 H), 5.10–5.02 (m, 1 H), 3.86–3.79 (m, 1 H), 3.76–3.70 (m, 1 H), 3.67–3.62 (m, 1 H), 3.60–3.54 (m, 1 H), 3.35 (s, 3 H), 2.14–2.07 (m, 1 H), 2.00–1.93 (m, 1 H), 1.55–1.50 (m, 1 H), 1.47 (s, 9 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 202.1, 160.4, 144.7 (q, $J_{C,F}$ = 4.4 Hz), 135.1 (q, $J_{C,F}$ = 3.1 Hz), 124.8 (q, $J_{C,F}$ = 270.2 Hz), 116.5 (q, $J_{C,F}$ = 33.1 Hz), 108.7, 71.1, 65.7, 59.3, 55.6, 46.2, 40.5, 27.7, 25.5, 23.6, 22.5 ppm. MS (DI, CI NH_3): *m*/*z* = 406. IR (thin film): $\tilde{\nu}$ = 1612, 1326, 1113, 1078 cm^{-1}. HRMS: calcd. for $C_{19}H_{30}F_3N_3OS$ 405.2062; found 405.2051.

***N*-*tert*-Butyl-2-{(4-chlorobenzyl)[5-(trifluoromethyl)pyridin-2-yl]amino}-4-methylpentanethioamide:** See Table 3, Entry 4; yield (90 °C in toluene for 16 h): 52% (245 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.41 (br. s, 1 H), 8.40 (d, *J* = 2.4 Hz, 1 H), 7.55 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.12 (d, *J* = 8.3 Hz, 2 H), 6.35 (d, *J* = 9.0 Hz, 1 H), 5.54 (br. s, 1 H), 4.93 (d, *J* = 17.7 Hz, 1 H), 4.66 (d, *J* = 17.7 Hz, 1 H), 2.20–2.13 (m, 1 H), 1.81–1.73 (m, 1 H), 1.60–1.54 (m, 1 H), 1.52 (s, 9 H), 0.90 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 200.9, 160.2, 144.8 (q, $J_{C,F}$ = 4.4 Hz), 136.4, 135.3 (q, $J_{C,F}$ = 4.4 Hz), 133.2, 129.2, 128.2, 124.7 (q, $J_{C,F}$ = 270.7 Hz), 116.6 (q, $J_{C,F}$ = 33.2 Hz), 108.7, 63.1, 55.7, 49.1, 40.4, 27.9, 25.5, 23.3, 23.1 ppm. MS (DI, CI NH_3): *m*/*z* = 472. IR (thin film): $\tilde{\nu}$ = 2359, 1612, 1502, 1320, 1293, 1160, 1115 cm^{-1}. HRMS: calcd. for $C_{23}H_{29}ClF_3N_3S$ 471.1723; found 471.1735.

***N*-(4-Chlorobenzyl)-2-{(2-methoxyethyl)[5-(trifluoromethyl)pyridin-2-yl]amino}octanethioamide:** See Table 3, Entry 5; yield (90 °C in toluene for 16 h): 26% (130 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.23 (br. s, 1 H), 8.36 (d, *J* = 2.4 Hz, 1 H), 7.68 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.26 (d, *J* = 8.3 Hz, 2 H), 7.09 (d, *J* = 8.3 Hz, 2 H), 6.83 (d, *J* = 9.0 Hz, 1 H), 4.84–4.71 (m, 3 H), 3.98–3.91 (m, 1 H), 3.78–3.72 (m, 2 H), 3.61–3.56 (m, 1 H), 3.02 (s, 3 H), 2.51–2.43 (m, 1 H), 2.10–2.00 (m, 1 H), 1.37–1.24 (m, 8 H), 0.87 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 204.7, 160.1, 145.3 (q, $J_{C,F}$ = 4.3 Hz), 135.3, 135.0 (q, $J_{C,F}$ = 3.1 Hz), 134.0, 129.6, 129.3, 124.8 (q, $J_{C,F}$ = 270.7 Hz), 116.5 (q, $J_{C,F}$ = 32.2 Hz), 108.7, 71.0, 70.7, 58.9, 49.5, 32.4, 32.0, 29.4, 27.5, 22.9, 14.5 ppm. MS (DI, CI NH_3): *m*/*z* = 502. IR (thin film): $\tilde{\nu}$ = 1612, 1503, 1320, 1116 cm^{-1}. HRMS: calcd. for $C_{24}H_{31}ClF_3N_3OS$ 501.1828; found 501.1828.

1-{(4-Chlorobenzyl)[5-(trifluoromethyl)pyridin-2-yl]amino}-*N*-cyclohexylcyclopentanecarbothioamide: See Table 3, Entry 6; yield (90 °C in toluene for 16 h): 42% (208 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.99 (br. s, 1 H), 8.41 (d, *J* = 2.5 Hz, 1 H), 7.59 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 6.56 (d, *J* = 9.0 Hz, 1 H), 4.98 (br. s, 2 H), 4.36–4.27 (m, 1 H), 3.09–2.97 (m, 2 H), 2.13–2.05 (m, 2 H), 1.99–0.92 (m, 2 H), 1.90–1.85 (m, 2 H), 1.84–1.79 (m, 2 H), 1.75–1.70 (m, 2 H), 1.66–1.58 (m, 3 H), 1.43–1.32 (m, 2 H), 1.25–1.17 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 204.3, 160.5, 144.5 (q, $J_{C,F}$ = 4.3 Hz), 138.7, 134.6 (q, $J_{C,F}$ = 3.1 Hz), 133.5, 129.5, 128.4, 124.7 (q, $J_{C,F}$ = 270.7 Hz), 117.3 (q, $J_{C,F}$ = 33.0 Hz), 110.2, 79.3, 54.5, 51.8, 39.8, 31.3, 25.8, 24.7, 24.5 ppm. MS (DI, CI NH_3): *m*/*z* = 496. IR (thin film): $\tilde{\nu}$ = 1611, 1503, 1491, 1325, 1294, 1148, 1114 cm^{-1}. HRMS: calcd. for $C_{25}H_{29}ClF_3N_3S$ 495.1723; found 495.1728.

***N*-Cyclohexyl-2-[(2-methoxyethyl)pyrimidin-2-yl-amino]-4-methylpentanethioamide:** See Scheme 5; yield (90 °C neat for 12 h): 77% (280 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.36 (br. s, 1 H), 8.35 (d, *J* = 4.8 Hz, 2 H), 6.61 (t, *J* = 4.8 Hz, 1 H), 5.21 (br. s, 1 H), 4.41–4.31 (m, 1 H), 3.92–3.85 (m, 1 H), 3.78–3.75 (m, 2 H), 3.61–3.57 (m, 1 H), 3.36 (s, 3 H), 2.32–2.25 (m, 1 H), 2.04–1.90 (m, 3 H), 1.68–1.56 (m, 2 H), 1.52–1.48 (m, 1 H), 1.42–1.35 (m, 2 H), 1.28–1.08 (m, 4 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 202.4, 162.5, 157.8, 111.4, 70.6, 59.1, 53.9, 40.7, 31.5, 31.2, 26.0, 25.5, 27.7, 24.8, 23.6, 22.4 ppm. MS (DI, CI NH_3): *m*/*z* = 365. IR (thin film): $\tilde{\nu}$ = 2929, 2854, 1585, 1507, 1477, 1359, 1116 cm^{-1}. HRMS: calcd. for $C_{19}H_{32}N_4OS$ 364.2297; found 364.2304.

***N*-*tert*-Butyl-2-[(2-methoxyethyl)pyrimidin-2-yl-amino]thiobutyramide:** See Table 4, Entry 1; yield (80 °C neat for 12 h): 42% (130 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.52 (br. s, 1 H), 8.33 (d, *J* = 4.8 Hz, 2 H), 6.59 (t, *J* = 4.8 Hz, 1 H), 4.80 (br. s, 1 H), 3.86 (t, *J* = 6.0 Hz, 2 H), 3.69–3.63 (m, 1 H), 3.62–3.56 (m, 1 H), 3.34 (s, 3 H), 2.45–2.34 (m, 1 H), 2.14–2.03 (m, 1 H), 1.46 (s, 9 H), 0.87 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 202.1, 162.2, 157.7, 111.3, 70.6, 59.1, 55.3, 46.2, 25.8, 24.5, 11.6 ppm. MS (DI, CI NH_3): *m*/*z* = 311. IR (thin film): $\tilde{\nu}$ = 2964, 2360, 2341, 1585, 1476, 1116 cm^{-1}. HRMS: calcd. for $C_{15}H_{26}N_4OS$ 310.1827; found 310.1823.

***N*-Cyclohexyl-2-cyclopropyl-2-[(4-methoxybenzyl)pyrimidin-2-yl-amino]thioacetamide:** See Table 4, Entry 2; yield (80 °C neat for 12 h): 71% (291 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.30 (br. s, 1 H), 8.35 (d, *J* = 4.8 Hz, 2 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 6.84 (d,

J = 8.8 Hz, 2 H), 6.61 (t, *J* = 4.8 Hz, 1 H), 5.22 (d, *J* = 16.0 Hz, 1 H), 4.90 (d, *J* = 16.0 Hz, 1 H), 4.38–4.29 (m, 1 H), 4.18 (br. s, 1 H), 3.81 (s, 3 H), 2.01–1.95 (m, 1 H), 1.92–1.86 (m, 1 H), 1.82–1.74 (m, 1 H), 1.67–1.55 (m, 2 H), 1.47–1.35 (m, 2 H), 1.28–1.14 (m, 4 H), 0.74–0.66 (m, 1 H), 0.45–0.39 (m, 1 H), 0.27–0.20 (m, 1 H), 0.14–0.04 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 200.8, 162.4, 158.9, 157.9, 132.0, 129.3, 114.0, 111.2, 73.0, 55.7, 53.6, 49.6, 31.5, 31.2, 25.9, 24.6, 13.3, 6.8, 5.7 ppm. MS (DI, CI NH_3): *m*/*z* = 410. IR (thin film): $\tilde{\nu}$ = 2927, 2852, 2360, 2341, 1583, 1478, 1174 cm^{-1}.

***N*-(4-Chlorobenzyl)-2-[(2-methoxyethyl)(pyrimidin-2-yl)amino]-4-methylpentanethioamide:** See Table 4, Entry 3; yield (80 °C neat for 12 h): 33% (134 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.98 (br. s, 1 H), 8.33 (d, *J* = 4.8 Hz, 2 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 7.12 (d, *J* = 8.3 Hz, 2 H), 6.63 (t, *J* = 4.8 Hz, 1 H), 5.35 (br. s, 1 H), 4.85 (dd, *J* = 15.3, 5.2 Hz, 1 H), 4.78 (dd, *J* = 15.3, 5.2 Hz, 2 H), 3.93–3.53 (m, 4 H), 3.10 (s, 3 H), 2.43–2.35 (m, 1 H), 2.08–1.99 (m, 1 H), 1.57–1.47 (m, 1 H), 0.95 (d, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 205.4, 161.8, 157.9, 135.6, 133.7, 129.5, 129.1, 111.7, 70.5, 58.9, 49.3, 41.1, 25.6, 23.7, 22.2 ppm. MS (DI, CI NH_3): *m*/*z* = 407. IR (thin film): $\tilde{\nu}$ = 1584, 1498, 1386, 1186, 1089 cm^{-1}. HRMS: calcd. for $C_{20}H_{17}ClN_4OS$ 406.1594; found 406.1589.

2-[Allyl(pyrimidin-2-yl)amino]-*N*-(4-chlorobenzyl)-4-methylpentanethioamide: See Table 4, Entry 4; yield (80 °C neat for 12 h): 52% (202 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.64 (br. s, 1 H), 8.28 (d, *J* = 4.7 Hz, 2 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 7.12 (d, *J* = 8.2 Hz, 2 H), 6.58 (t, *J* = 4.7 Hz, 1 H), 6.01–5.91 (m, 1 H), 5.40 (br. s, 1 H), 5.20 (d, *J* = 17.2 Hz, 2 H), 5.12 (d, *J* = 10.2 Hz, 2 H), 4.80 (dd, *J* = 15.3, 5.0 Hz, 1 H), 4.71 (dd, *J* = 15.3, 5.0 Hz, 1 H), 4.39 (dd, *J* = 16.1, 6.0 Hz, 1 H), 4.21 (dd, *J* = 16.1, 6.0 Hz, 1 H), 2.19–2.13 (m, 1 H), 2.04–1.96 (m, 1 H), 1.62–1.54 (m, 1 H), 0.93 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 204.4, 162.2, 158.0, 135.4, 135.2, 133.9, 129.6, 129.3, 116.9, 111.2, 49.3, 48.2, 40.5, 25.3, 23.1, 22.9 ppm. MS (DI, CI NH_3): *m*/*z* = 389. IR (thin film): $\tilde{\nu}$ = 2366, 2350, 1583, 1490, 1385, 1089 cm^{-1}. HRMS: calcd. for $C_{20}H_{25}ClN_4S$ 388.1488; found 388.1504.

2-[(2-Methoxyethyl)pyrimidin-2-yl-amino]-4-methylpentanethioic Acid [2-(3,4-dimethoxyphenyl)ethyl]amide: See Table 4, Entry 5; yield (80 °C neat for 12 h): 75% (335 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.53 (br. s, 1 H), 8.22 (d, *J* = 4.8 Hz, 2 H), 6.66–6.63 (m, 2 H), 6.60–6.55 (m, 2 H), 5.32 (br. s, 1 H), 3.97–3.88 (m, 4 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.77–3.71 (m, 1 H), 3.53–3.47 (m, 1 H), 3.28 (s, 3 H), 2.86 (t, *J* = 6.8 Hz, 2 H), 2.31–2.24 (m, 1 H), 2.00–1.92 (m, 1 H), 1.51–1.43 (m, 1 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 204.6, 162.4, 157.7, 149.3, 147.9, 131.5, 121.0, 112.0, 111.5, 111.3, 70.5, 59.1, 56.3, 56.2, 47.0, 40.9, 33.6, 25.5, 23.6, 22.3 ppm. MS (DI, CI NH_3): *m*/*z* = 447. IR (thin film): $\tilde{\nu}$ = 2927, 2360, 2342, 1515, 1114 cm^{-1}. HRMS: calcd. for $C_{23}H_{34}N_4O_3S$ 446.2352; found 446.2358.

Ethyl 2-{1-[(4-Chlorobenzyl)(pyrimidin-2-yl)amino]-3-methylbutyl}thiazole-4-carboxylate: See Table 4, Entry 6; yield (80 °C in toluene for 16 h): 35% (155 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.40 (d, *J* = 4.7 Hz, 2 H), 8.02 (s, 1 H), 7.15 (br. s, 4 H), 6.64 (t, *J* = 4.7 Hz, 1 H), 6.42 (br. s, 1 H), 4.90 (d, *J* = 16.2 Hz, 1 H), 4.68 (d, *J* = 16.2 Hz, 1 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 2.23–2.15 (m, 1 H), 2.12–2.05 (m, 1 H), 1.52–1.46 (m, 1 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 0.76 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 172.2, 162.4, 161.7, 158.3, 146.8, 138.3, 132.6, 129.2, 128.5, 128.3, 111.6, 61.7, 55.8, 47.5, 40.4, 25.3, 23.2, 22.5, 14.8 ppm. MS (DI, CI NH_3): *m*/*z* = 445. IR (thin film): $\tilde{\nu}$ = 2955, 1582, 1550, 1469, 1203 cm^{-1}. HRMS: calcd. for $C_{22}H_{25}ClN_4O_2S$ 444.1387; found 444.1383.

2-[(4-Chlorobenzyl)(6-methyl-2-phenylpyrimidin-4-yl)amino]-*N*-cyclohexyl-4-methylpentanethioamide: See Table 4, Entry 7; yield (80 °C neat for 12 h): 33% (172 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.30 (br. s, 1 H), 8.40–8.31 (m, 2 H), 7.54–7.51 (m, 3 H), 7.31 (d, *J* = 8.3 Hz, 2 H), 7.16 (d, *J* = 8.3 Hz, 2 H), 6.06 (s, 1 H), 5.88 (br. s, 1 H), 4.99 (d, *J* = 17.9 Hz, 1 H), 4.59 (d, *J* = 17.9 Hz, 1 H), 4.30–4.21 (m, 1 H), 2.39 (s, 3 H), 2.28–2.19 (m, 2 H), 1.93–1.87 (m, 2 H), 1.76–1.69 (m, 2 H), 1.65–1.58 (m, 1 H), 1.52–1.42 (m, 2 H), 1.29–1.20 (m, 4 H), 0.92 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 200.9, 167.2, 163.2, 138.5, 136.4, 131.0, 129.3, 129.0, 128.2, 102.3, 53.0, 40.3, 31.5, 31.1, 25.7, 25.5, 25.1, 24.5, 23.1 ppm. MS (DI, CI NH_3): *m*/*z* = 521. IR (thin film): $\tilde{\nu}$ = 1590, 1529, 1442, 1173, 1092 cm^{-1}. HRMS: calcd. for $C_{30}H_{37}ClN_4S$ 520.2427; found 520.2422.

2-[Allyl(6-methyl-2-phenylpyrimidin-4-yl)amino]-*N*-(4-chlorobenzyl)-4-methylpentanethioamide: See Table 4, Entry 8; yield (80 °C neat for 16 h): 57% (273 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.59 (br. s, 1 H), 8.12 (d, *J* = 7.4 Hz, 2 H), 7.46 (tt, *J* = 7.4, 1.2 Hz, 1 H), 7.36 (t, *J* = 7.4 Hz, 2 H), 6.96 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 6.27 (s, 1 H), 5.96 (br. s, 1 H), 5.87–5.77 (m, 1 H), 5.26 (d, *J* = 17.2 Hz, 1 H), 5.22 (d, *J* = 10.4 Hz, 1 H), 4.61 (td, *J* = 15.0, 4.9 Hz, 2 H), 4.39 (d, *J* = 14.1 Hz, 1 H), 3.92 (br. s, 1 H), 2.47 (s, 3 H), 2.26–2.17 (m, 1 H), 2.05–1.91 (m, 1 H), 1.71–1.61 (m, 1 H), 0.98 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 203.3, 166.9, 163.1, 138.2, 134.5, 133.9, 130.8, 129.7, 129.1, 128.9, 127.9, 117.6, 102.2, 49.6, 47.7, 40.1, 25.4, 25.1, 23.1 ppm. MS (DI, CI NH_3): *m*/*z* = 479. IR (thin film): $\tilde{\nu}$ = 1590, 1528, 1472, 1378 cm^{-1}. HRMS: calcd. for $C_{27}H_{31}ClN_4S$ 478.1958; found 478.1946.

2-[(4-Chlorobenzyl)(2-isopropyl-6-methylpyrimidin-4-yl)amino]-*N*-cyclohexyl-4-methylpentanethioamide: See Table 4, Entry 9; yield (80 °C neat for 16 h): 69% (336 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.95 (br. s, 1 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.09 (d, *J* = 8.3 Hz, 2 H), 5.93 (s, 1 H), 5.84 (br. s, 1 H), 4.86 (d, *J* = 17.6 Hz, 1 H), 4.55 (d, *J* = 17.6 Hz, 1 H), 4.38–4.29 (m, 1 H), 3.07 (sept, *J* = 6.9 Hz, 1 H), 2.27 (s, 3 H), 2.12–2.03 (m, 2 H), 1.96–1.90 (m, 1 H), 1.84–1.72 (m, 2 H), 1.69–1.62 (m, 1 H), 1.54–1.47 (m, 1 H), 1.39–1.34 (m, 8 H), 1.26–1.13 (m, 2 H), 1.06–0.95 (m, 2 H), 0.86 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 201.6, 173.9, 166.5, 163.2, 136.4, 133.1, 129.1, 128.2, 101.5, 54.2, 47.7, 40.3, 38.0, 32.1, 31.8, 25.8, 25.4, 25.2, 25.1, 24.9, 23.1, 22.9, 22.3 ppm. MS (DI, CI NH_3): *m*/*z* = 487. IR (thin film): $\tilde{\nu}$ = 2361, 1469, 1582, 1431, 1092 cm^{-1}. HRMS: calcd. for $C_{27}H_{39}ClN_4S$ 486.2584; found 486.2579.

2-[Allyl(5,6-diphenylpyrazin-2-yl)amino]-*N*-(4-methoxybenzyl)-4-methylpentanethioamide: See Table 5, Entry 1; yield (110 °C in toluene for 12 h): 76% (408 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.36 (br. s, 1 H), 8.13 (s, 1 H), 7.35–7.17 (m, 10 H), 6.86 (d, *J* = 8.6 Hz, 1 H), 6.62 (d, *J* = 8.6 Hz, 1 H), 5.92–5.82 (m, 1 H), 5.61 (s br, 1 H), 5.32–5.26 (m, 2 H), 4.64 (dd, *J* = 15.2, 5.3 Hz, 1 H), 4.56–4.46 (m, 2 H), 4.11 (dd, *J* = 17.9, 2.5 Hz, 1 H), 3.75 (s, 3 H), 2.22–2.14 (m, 1 H), 2.05–1.98 (m, 1 H), 1.69–1.63 (m, 1 H), 1.00–0.96 (m, 6 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 203.0, 152.1, 152.1, 143.5, 141.6, 139.1, 139.0, 134.3, 129.8, 129.7, 129.6, 128.8, 128.6, 128.5, 117.9, 114.3, 66.3, 55.6, 49.8, 48.5, 40.3, 25.3, 23.3, 23.1 ppm.

2-[Allyl(5,6-diphenylpyrazin-2-yl)amino]-*N*-cyclohexylbutanethioamide: See Table 5, Entry 2; yield (110 °C in toluene for 3 d): 36% (169 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40 (br. s, 1 H), 8.13 (s, 1 H), 7.40–7.26 (m, 10 H), 5.96–5.87 (m, 1 H), 5.33–5.27 (m, 2

H), 5.08 (br. s, 1 H), 4.52 (dd, *J* = 18.2, 4.8 Hz, 1 H), 4.20–4.07 (m, 2 H), 2.47–2.37 (m, 1 H), 2.15–2.04 (m, 1 H) 1.78–1.60 (m, 2 H), 1.43–1.27 (m, 3 H), 1.20–1.10 (m, 2 H) 1.00 (dd, *J* = 7.6, 7.0 Hz, 3 H), 0.86–0.77 (m, 1 H), 0.70–0.60 (m, 1 H), 0.52–0.43 (m, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 200.5, 152.1, 148.1, 141.4, 139.8, 138.9, 134.3, 130.5, 129.9, 129.8, 129.0, 128.8, 128.5, 127.9, 117.7, 67.3, 53.6, 49.0, 31.3, 30.8, 25.4, 24.8, 24.4, 11.7 ppm. HRMS: calcd. for $C_{29}H_{34}N_4S$ 470.2504; found 470.2509.

***N*-Cyclohexyl-2-[(2-methoxyethyl)(3-methylquinoxalin-2-yl)amino]-4-methylpentanethioamide:** See Table 5, Entry 3; yield (110 °C in toluene for 12 h): 31% (89 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.8 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.66–7.5 (m, 2 H), 5.56–5.49 (m, 2 H), 4.08 (d, *J* = 13.1 Hz, 1 H), 3.67–3.65 (m, 1 H), 3.58–3.53 (m, 1 H), 3.35–3.27 (m, 1 H), 3.25 (s, 3 H), 2.65 (s, 3 H), 2.36–2.28 (m, 1 H), 2.16 (d, *J* = 11.6 Hz, 2 H), 2.02–1.96 (m, 1 H), 1.84–1.72 (m, 3 H), 1.50–1.24 (m, 6 H), 0.80 (d, *J* = 6.6 Hz, 3 H), 0.53 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 201.2, 154.3, 150.6, 139.2, 139.0, 129.6, 128.4, 127.5, 127.0, 70.5, 70.2, 59.1, 55.0, 46.4, 42.3, 31.8, 31.7, 26.1, 25.4, 25.2, 24.0, 23.6, 20.7 ppm. HRMS: calcd. for $C_{24}H_{36}N_4OS$ – $C_9H_6N_2$ 286.2079; found 286.2069.

2-[Allyl(3-methylquinoxalin-2-yl)amino]-*N*-(4-chlorobenzyl)-4-methylpentanethioamide: See Table 5, Entry 4; yield (110 °C in toluene for 12 h): 9% (41 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.88 (m, 2 H), 7.70–7.59 (m, 1 H), 7.58–7.53 (m, 1 H), 7.19–7.45 (m, 1 H), 7.32 (s, 2 H), 6.77 (d, *J* = 8.1 Hz, 1 H), 5.89–5.79 (m, 1 H), 5.37 (d, *J* = 16.9 Hz, 1 H), 5.27 (d, *J* = 10.3 Hz, 1 H), 4.91–4.84 (m, 2 H), 4.73 (dd, *J* = 14.9, 4.3 Hz, 1 H), 4.05–3.94 (m, 2 H), 2.72 (s, 3 H), 2.14–2.08 (m, 1 H), 1.86–1.79 (m, 2 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 0.76 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 205.6, 158.0, 153.2, 151.6, 142.1, 139.2, 143.3, 133.3, 130.6, 129.8, 129.6, 129.0, 128.4, 128.3, 128.0, 126.0, 120.7, 70.1, 53.9, 50.7, 40.4, 27.1, 24.1, 23.8, 21.6 ppm. HRMS: calcd. for $C_{25}H_{29}ClN_4S$ 452.1801; found 452.1789.

4-Methyl-4*H*-1,2,4-triazol-3-yl-2-(4-chlorobenzylamino)-*N*-cyclohexylbutanimidothioate: See Table 6, Entry 1; yield (90 °C in toluene for 2 d): 47%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.87 (s, 1 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 4.00 (d, *J* = 13.1 Hz, 1 H), 3.78 (d, *J* = 13.1 Hz, 1 H), 3.67 (dd, *J* = 6.9, 4.7 Hz, 1 H), 3.61 (s, 3 H), 3.24–3.17 (m, 1 H), 1.81–1.71 (m, 6 H), 1.58–1.41 (m, 4 H), 1.30–1.20 (m, 2 H), 0.90 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 167.4, 149.3, 141.2, 139.7, 132.7, 130.3, 128.7, 62.8, 60.0, 51.3, 33.8, 33.6, 33.0, 26.3, 26.0, 24.5, 10.0 ppm. MS (DI, CI NH_3): *m*/*z* = 406. HRMS: calcd. for $C_{20}H_{28}ClN_5S$ 405.1754; found 405.1734.

4-Methyl-4*H*-1,2,4-triazol-3-yl-2-(allylamino)-*N*-(4-chlorobenzyl)-4-methylpentanimidothioate: See Table 6, Entry 2; yield (90 °C in toluene for 2 d): 32% (125 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.92 (s, 1 H), 7.29 (s, 4 H), 5.95–5.85 (m, 1 H), 5.19 (d, *J* = 17.2 Hz, 1 H), 5.07 (d, *J* = 10.1 Hz, 1 H), 4.66 (d, *J* = 16.6 Hz, 1 H), 4.45 (d, *J* = 16.6 Hz, 1 H), 3.84 (q, *J* = 4.7 Hz, 1 H), 3.63 (s, 3 H), 3.30–3.16 (m, 2 H), 1.96–1.87 (m, 1 H), 1.72–1.60 (m, 1 H), 1.46–1.39 (m, 1 H), 0.90 (t, *J* = 6.6 Hz, 3 H), 0.84 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 167.4, 153.5, 137.9, 137.3, 132.9, 128.9, 116.6, 60.8, 54.8, 50.6, 41.0, 33.1, 25.3, 23.7, 22.4 ppm. MS (DI, CI NH_3): *m*/*z* = 392.

4-Ethyl-5-phenyl-4*H*-1,2,4-triazol-3-yl 2-(4-chlorobenzylamino)-*N*-cyclohexylbutanimidothioate: See Table 6, Entry 3; yield (90 °C in toluene for 2 d): 41% (203 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.61–7.56 (m, 5 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.04 (d, *J* = 13.1 Hz, 1 H), 3.82 (d, *J* = 13.1 Hz, 1 H), 3.77 (dd, *J* = 6.9, 4.8 Hz, 1 H), 3.41–3.24 (m, 1 H), 1.90–1.77 (m, 6 H), 1.63–1.49 (m, 4 H), 1.37 (t, *J* = 7.1 Hz, 3 H), 1.31–1.26 (m, 2 H), 0.99 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 167.6, 151.9, 146.9, 140.0, 132.6, 131.7, 130.4, 129.7, 128.9, 128.7, 126.0, 62.9, 60.2, 51.3, 41.0, 33.8, 33.6, 26.5, 24.7, 24.6, 14.2, 10.2 ppm. MS (DI, CI NH_3): *m*/*z* = 496. HRMS: calcd. for $C_{27}H_{34}ClN_5S$ 495.2223; found 495.2239.

2-[Benzo[*d*]oxazol-2-yl(4-chlorobenzyl)amino]-*N*-cyclohexyl-4-methylpentanethioamide: See Table 7, Entry 1; yield (50 °C in toluene for 2 d): 61% (286 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.00 (br. s, 1 H), 7.40 (d, *J* = 7.8 Hz, 1 H), 7.36–7.28 (m, 5 H), 7.25 (td, *J* = 7.8, 1.0 Hz, 1 H), 7.12 (td, *J* = 7.8, 1.0 Hz, 1 H), 4.95 (d, *J* = 16.2 Hz, 1 H), 4.81 (t, *J* = 6.8 Hz, 1 H), 4.75 (d, *J* = 16.2 Hz, 1 H), 4.36–4.28 (m, 1 H), 2.12–1.87 (m, 4 H), 1.70–1.54 (m, 2 H), 1.48–1.39 (m, 3 H), 1.38–1.27 (m, 4 H), 0.81 (d, *J* = 5.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.3, 163.0, 148.9, 142.3, 136.5, 133.9, 129.7, 129.1, 124.8, 121.8, 116.5, 109.7, 77.7, 54.0, 51.5, 39.9, 31.2, 30.9, 25.9, 25.3, 24.3, 23.0, 22.7 ppm. MS (DI, CI NH_3): *m*/*z* = 470. IR (thin film): $\tilde{\nu}$ = 2359, 1458, 1625, 1569, 1245, 1091 cm^{-1}. HRMS: calcd. for $C_{26}H_{32}ClN_3OS$ 469.1955; found 469.1945.

2-[Benzoxazol-2-yl(4-chlorobenzyl)amino]-*N*-cyclohexylthiobutyramide: See Table 7, Entry 2; yield (50 °C in toluene for 2 d): 59% (221 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.95 (br. s, 1 H), 7.39–7.37 (m, 1 H), 7.35–7.30 (m, 5 H), 7.24 (td, *J* = 7.8, 1.3 Hz, 1 H), 7.11 (td, *J* = 7.8, 1.3 Hz, 1 H), 4.98 (d, *J* = 16.2 Hz, 1 H), 4.75 (d, *J* = 16.2 Hz, 1 H), 4.62 (t, *J* = 7.6 Hz, 1 H), 4.37–4.28 (m, 1 H), 2.35–2.24 (m, 1 H), 2.12–2.03 (m, 1 H), 1.97–1.86 (m, 2 H), 1.68–1.53 (m, 2 H), 1.47–1.25 (m, 6 H), 0.81 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 198.9, 162.9, 148.9, 142.3, 136.5, 133.9, 129.7, 129.1, 124.8, 121.8, 116.5, 109.7, 71.8, 54.0, 51.5, 31.2, 30.9, 25.9, 24.3, 24.2, 11.3 ppm. MS (DI, CI NH_3): *m*/*z* = 442. IR (thin film): $\tilde{\nu}$ = 2360, 2341, 1627, 1572, 1360, 1240, 1091 cm^{-1}. HRMS: calcd. for $C_{24}H_{28}ClN_3OS$ 441.1642; found 441.1662.

2-[Benzo[*d*]oxazol-2-yl(4-chlorobenzyl)amino]-*N*-*tert*-butyl-4-methylpentanethioamide: See Table 7, Entry 3; yield (50 °C in toluene for 2 d): 61% (270 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.10 (br. s, 1 H), 7.39–7.30 (m, 6 H), 7.24 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.12 (td, *J* = 7.7, 1.2 Hz, 1 H), 4.92 (d, *J* = 16.0 Hz, 1 H), 4.80–4.67 (m, 2 H), 2.08–2.01 (m, 2 H), 1.50 (s, 9 H), 1.48–1.41 (m, 1 H), 0.81 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.6, 162.9, 148.9, 142.0, 136.4, 133.8, 129.8, 129.1, 124.8, 121.8, 116.6, 109.7, 70.6, 56.0, 51.7, 39.8, 27.6, 25.3, 23.1, 22.6 ppm. MS (DI, CI NH_3): *m*/*z* = 444. IR (thin film): $\tilde{\nu}$ = 2357, 1625, 1569, 1458, 1245, 1091 cm^{-1}. HRMS: calcd. for $C_{24}H_{30}ClN_3OS$ 443.1798; found 443.1778.

2-[Benzo[*d*]oxazol-2-yl(2-methoxyethyl)amino]-*N*-*tert*-butyl-4-methylpentanethioamide: See Table 7, Entry 4; yield (50 °C in toluene for 2 d): 66% (249 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.26 (br. s, 1 H), 7.37–7.32 (m, 2 H), 7.22 (td, *J* = 7.9, 1.0 Hz, 1 H), 7.10 (td, *J* = 7.9, 1.0 Hz, 1 H), 4.66 (dd, *J* = 8.9, 6.6 Hz, 1 H), 3.94–3.85 (m, 1 H), 3.79–3.71 (m, 2 H), 3.68–3.63 (m, 1 H), 3.36 (s, 3 H), 2.26–2.18 (m, 1 H), 2.16–2.09 (m, 1 H), 1.63–1.55 (m, 1 H), 1.52 (s, 9 H), 0.96 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 200.7, 163.0, 148.9, 142.3, 124.6, 121.6, 116.4, 109.6, 71.5, 70.8, 59.2, 55.9, 48.7, 39.9, 27.4, 25.4, 23.5, 22.7 ppm. MS (DI, CI NH_3): *m*/*z* = 378. IR (thin film): $\tilde{\nu}$ = 2360, 1626, 1570, 1459, 1362, 1246, 1116 cm^{-1}. HRMS: calcd. for $C_{20}H_{31}N_3O_2S$ 377.2137; found 377.2145.

2-[Benzoxazol-2-yl(4-chlorobenzyl)amino]-*N*-*tert*-butylthiobutyramide: See Table 7, Entry 5; yield (50 °C in toluene for 2 d): 61% (253 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.0 (br. s, 1 H), 7.38–7.28 (m, 6 H), 7.24 (td, *J* = 7.8, 1.3 Hz, 1 H), 7.12 (td, *J* = 7.8,

1.3 Hz, 1 H), 4.96 (d, J = 16.2 Hz, 1 H), 4.76 (d, J = 16.2 Hz, 1 H), 4.53 (t, J = 7.6 Hz, 1 H), 2.36–2.24 (m, 1 H), 2.12–2.02 (m, 1 H), 1.52 (s, 9 H), 0.82 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.2, 162.8, 148.9, 142.3, 136.5, 133.9, 129.7, 129.1, 124.8, 121.8, 116.5, 109.7, 74.1, 56.0, 51.7, 27.5, 24.2, 11.3 ppm. MS (DI, CI NH_3): m/z = 416. IR (thin film): $\tilde{\nu}$ = 2965, 2930, 2349, 1625, 1563, 1458, 1362, 1245, 1210, 1014 cm^{-1}. HRMS: calcd. for $C_{22}H_{26}ClN_3OS$ 415.1485; found 415.1471.

2-[Benzo[*d*]oxazol-2-yl(4-chlorobenzyl)amino]-*N*-cyclohexyloctanethioamide: See Table 7, Entry 6; yield (50 °C in toluene for 2 d): 44% (279 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.99 (br. s, 1 H), 7.39 (t, J = 7.6 Hz, 1 H), 7.34–7.31 (m, 5 H), 7.24 (td, J = 7.6, 1.2 Hz, 1 H), 7.11 (td, J = 7.6, 1.2 Hz, 1 H), 4.97 (d, J = 16.2 Hz, 1 H), 4.74 (d, J = 16.2 Hz, 1 H), 4.69 (t, J = 7.6 Hz, 1 H), 4.36–4.28 (m, 1 H), 2.26–2.17 (m, 1 H), 2.11–2.01 (m, 1 H), 1.96–1.87 (m, 2 H), 1.66–1.55 (m, 2 H), 1.45–1.28 (m, 6 H), 1.23–1.11 (m, 8 H), 0.84 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.1, 162.9, 148.9, 142.3, 136.5, 133.9, 129.7, 129.1, 124.8, 121.8, 116.6, 109.7, 70.3, 54.0, 51.5, 31.9, 31.2, 30.9, 29.2, 26.6, 25.9, 24.4, 24.3, 22.9, 14.4 ppm. MS (DI, CI NH_3): m/z = 498. IR (thin film): $\tilde{\nu}$ = 1925, 1626, 1570, 1459, 1244, 1092 cm^{-1}. HRMS: calcd. for $C_{28}H_{36}ClN_3OS$ 497.2268; found 497.2263.

2-[Benzoxazol-2-yl(2-methoxy-ethyl)amino]-*N*-*tert*-butyl-2-(4-chlorophenyl)thioacetamide: See Table 7, Entry 7; yield (50 °C in toluene for 2 d): 22% (95 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.94 (br. s, 1 H), 7.38–7.28 (m, 6 H), 7.20 (td, J = 7.8, 1.3 Hz, 1 H), 7.11 (td, J = 7.8, 1.3 Hz, 1 H), 6.02 (s, 1 H), 3.97 (ddd, J = 10.0, 7.6, 4.3 Hz, 1 H), 3.75 (dt, J = 15.0, 4.3 Hz, 1 H), 3.61 (ddd, J = 15.0, 7.6, 4.3 Hz, 1 H), 3.47 (dt, J = 10.0, 4.3 Hz, 1 H), 3.35 (s, 3 H), 1.59 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 198.0, 161.9, 149.3, 142.2, 135.0, 134.6, 130.4, 129.3, 124.7, 121.9, 117.1, 109.8, 77.2, 70.4, 59.2, 56.4, 49.4, 27.8 ppm. MS (DI, CI NH_3): m/z = 432. IR (thin film): $\tilde{\nu}$ = 2360, 2341, 1625, 1570, 1458, 1243, 1090 cm^{-1}. HRMS: calcd. for $C_{22}H_{26}ClN_3O_2S$ 431.1434; found 431.1405.

1-[Benzo[*d*]oxazol-2-yl(2-methoxyethyl)amino]-*N*-cyclohexylcyclopentanecarbothioamide: See Table 7, Entry 8; yield (50 °C in toluene for 2 d): 45% (181 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.95 (m, 2 H), 6.82 (td, J = 7.4, 2.2 Hz, 1 H), 6.73 (dd, J = 7.4, 1.0 Hz, 1 H), 5.06–4.89 (m, 1 H), 3.32 (t, J = 6.2 Hz, 2 H), 3.08 (s, 3 H), 3.00 (t, J = 6.2 Hz, 2 H), 2.74–2.54 (m, 2 H), 2.33–2.27 (m, 2 H), 2.07–1.99 (m, 2 H), 1.88–1.80 (m, 4 H), 1.76–1.71 (m, 2 H), 1.68–1.62 (m, 2 H), 1.43–1.30 (m, 2 H), 1.28–1.15 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 209.9, 148.8, 147.7, 133.3, 123.7, 121.3, 119.8, 114.5, 82.7, 69.5, 59.1, 57.8, 43.2, 41.3, 27.6, 26.6, 25.6 ppm. MS (DI, CI NH_3): m/z = 402. IR (thin film): $\tilde{\nu}$ = 1653, 1489, 1414, 1391, 1358, 1295, 1231, 1172, 1148, 1116 cm^{-1}. HRMS: calcd. for $C_{22}H_{31}N_3O_2S$ 401.2137; found 401.2129.

2-[Benzo[*d*]thiazol-2-yl(2-methoxyethyl)amino]-*N*-cyclohexyl-4-methylpentanethioamide: See Table 7, Entry 9; yield (90 °C in toluene for 16 h): 59% (247 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.28 (br. s, 1 H), 7.64 (d, J = 7.8 Hz, 1 H), 7.56 (d, J = 7.8 Hz, 1 H), 7.35 (t, J = 7.8 Hz, 1 H), 7.15 (t, J = 7.8 Hz, 1 H), 4.90 (br. s, 1 H), 4.39–4.31 (m, 1 H), 3.91–3.85 (m, 1 H), 3.83–3.78 (m, 1 H), 3.74–3.69 (m, 1 H), 3.68–3.63 (m, 1 H), 3.38 (s, 3 H), 2.24–2.18 (m, 2 H), 1.99–1.94 (m, 2 H), 1.67–1.56 (m, 3 H), 1.44–1.34 (m, 2 H), 1.29–1.18 (m, 4 H), 0.96 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 200.6, 169.8, 151.7, 131.1, 126.5, 122.3, 121.2, 119.3, 70.5 (C_4, C_{10}), 59.3, 54.3, 51.3, 40.4, 31.3, 31.1, 25.9, 25.5, 24.6, 23.5, 22.5 ppm. MS (DI, CI NH_3): m/z = 416. IR (thin film): $\tilde{\nu}$ = 2928, 1534, 1444, 1115 cm^{-1}. HRMS: calcd. for $C_{26}H_{32}ClN_3S_2$ 419.2065; found 419.2055.

2-[Benzo[*d*]thiazol-2-yl(4-chlorobenzyl)amino]-*N*-cyclohexyl-4-methylpentanethioamide: See Table 7, Entry 10; yield (90 °C in toluene for 16 h): 77% (371 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.08 (br. s, 1 H), 7.59 (d, J = 7.4 Hz, 2 H), 7.37 (d, J = 7.4 Hz, 1 H), 7.31 (br. s, 4 H), 7.15 (t, J = 7.4 Hz, 1 H), 5.20 (br. s, 1 H), 4.93 (d, J = 17.2 Hz, 1 H), 4.62 (d, J = 17.2 Hz, 1 H), 4.37–4.30 (m, 1 H), 2.25–2.17 (m, 1 H), 2.03–1.97 (m, 2 H), 1.90–1.85 (m, 1 H), 1.71–1.65 (m, 1 H), 1.60–1.53 (m, 3 H), 1.46–1.22 (m, 5 H), 0.89 (d, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.2, 169.9, 151.3, 135.5, 133.9, 131.0, 129.1, 126.7, 122.5, 121.3, 119.3, 68.3, 54.7, 53.9, 40.0, 31.3, 31.0, 25.9, 25.5, 24.4, 23.1 ppm. MS (DI, CI NH_3): m/z = 486. IR (thin film): $\tilde{\nu}$ = 2359, 1513, 1490, 1093 cm^{-1}. HRMS: calcd. for $C_{26}H_{32}ClN_3S_2$ 485.1726; found 485.1728.

2-[Benzo[*d*]thiazol-2-yl(4-chlorobenzyl)amino]-*N*-cyclohexyloctanethioamide: See Table 7, Entry 11; yield (90 °C in toluene for 16 h): 60% (308 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.03 (br. s, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H), 7.37 (dt, J = 7.6, 1.0 Hz, 1 H), 7.31 (br. s, 4 H), 7.15 (t, J = 7.6 Hz, 1 H), 5.06 (br. s, 1 H), 4.95 (d, J = 17.3 Hz, 1 H), 4.60 (d, J = 17.3 Hz, 1 H), 4.37–4.28 (m, 1 H), 2.35–2.27 (m, 1 H), 2.08–1.97 (m, 2 H), 1.90–1.85 (m, 1 H), 1.70–1.65 (m, 2 H), 1.58–1.53 (m, 2 H), 1.45–1.20 (m, 12 H), 0.85 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.1, 169.8, 151.4, 135.5, 133.9, 131.0, 129.3, 129.1, 126.7, 122.5, 121.3, 119.2, 54.7, 53.9, 31.9, 31.4, 31.0, 29.4, 26.8, 25.9, 24.4, 24.3, 22.9, 14.5 ppm. MS (DI, CI NH_3): m/z = 514. IR (thin film): $\tilde{\nu}$ = 1515, 1490, 1442, 1093 cm^{-1}. HRMS: calcd. for $C_{28}H_{36}ClN_3S_2$ 513.2039; found 513.2042.

2-[Benzo[*d*]thiazol-2-yl(4-chlorobenzyl)amino]-*N*-*tert*-butyl-4-methylpentanethioamide: See Table 7, Entry 12; yield (90 °C in toluene for 16 h): 45% (207 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.24 (br. s, 1 H), 7.58 (d, J = 7.5 Hz, 2 H), 7.36 (td, J = 7.5, 1.0 Hz, 1 H), 7.31 (s, 4 H), 7.15 (td, J = 7.5, 1.0 Hz, 1 H), 5.15–5.06 (m, 1 H), 4.87 (d, J = 17.2 Hz, 1 H), 4.65 (d, J = 17.2 Hz, 1 H), 2.22–2.12 (m, 1 H), 2.06–1.97 (m, 1 H), 1.61–1.65 (m, 1 H), 1.52 (s, 9 H), 0.90 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.9, 169.7, 151.2, 135.5, 133.9, 131.1, 129.2, 126.7, 122.5, 121.3, 119.2, 70.2, 55.8, 54.9, 39.9, 27.7, 25.5, 23.2, 23.0 ppm. MS (DI, CI NH_3): m/z = 460. HRMS: calcd. for $C_{24}H_{30}ClN_3S_2$ 459.1570; found 459.1556.

2-[Benzo[*d*]thiazol-2-yl(4-chlorobenzyl)amino]-*N*-*tert*-butyloctanethioamide: See Table 7, Entry 13; yield (90 °C in toluene for 16 h): 43% (210 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.20 (br. s, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.36 (td, J = 8.0, 1.0 Hz, 1 H), 7.31 (s, 4 H), 7.15 (td, J = 8.0, 1.0 Hz, 1 H), 5.00–4.95 (m, 1 H), 4.90 (d, J = 17.2 Hz, 1 H), 4.63 (d, J = 17.2 Hz, 1 H), 2.33–2.24 (m, 1 H), 2.11–2.03 (m, 1 H), 1.52 (s, 9 H), 1.28–1.20 (m, 8 H), 0.86 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.2, 169.6, 151.3, 144.2, 135.5, 133.9, 129.2, 126.7, 122.5, 121.3, 119.1, 72.1, 55.8, 55.3, 32.0, 27.7, 31.0, 29.4, 26.8, 22.9, 14.5 ppm. MS (DI, CI NH_3): m/z = 488. IR (thin film): $\tilde{\nu}$ = 1590, 1437, 1362, 1213, 1093, 1014 cm^{-1}. HRMS: calcd. for $C_{26}H_{34}ClN_3S_2$ 487.1883; found 487.1886.

2-[Allyl(benzo[*d*]thiazol-2-yl)amino]-*N*-(4-chlorobenzyl)-4-methylpentanethioamide: See Table 7, Entry 14; yield (90 °C in toluene for 16 h): 46% (205 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.50 (br. s, 1 H), 7.63 (d, J = 7.9 Hz, 1 H), 7.35–7.27 (m, 2 H), 7.20 (d, J = 8.4 Hz, 2 H), 7.17–7.10 (m, 3 H), 5.92–5.82 (m, 1 H), 5.37 (d, J = 17.2 Hz, 1 H), 5.28 (d, J = 10.2 Hz, 2 H), 4.81 (dd, J = 15.4, 4.7 Hz, 1 H), 4.67 (dd, J = 15.4, 4.7 Hz, 1 H), 3.99 (dd, J = 17.2, 4.9 Hz, 1 H), 3.34 (dd, J = 17.2, 4.9 Hz, 1 H), 2.23–2.16 (m, 1 H), 2.13–2.05 (m, 1 H), 1.70–1.61 (m, 1 H), 0.97 (d, J = 6.6 Hz, 6 H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 201.9, 169.8, 151.1, 135.0, 133.9, 132.9, 130.9, 129.8, 129.3, 126.5, 122.4, 121.2, 119.2, 77.7, 53.5, 49.8, 39.9, 25.4, 23.1 ppm. MS (DI, CI NH_3): *m*/*z* = 444. IR (thin film): $\tilde{\nu}$ = 2350, 1512, 1491, 1444, 1309, 1216, 1092, 1015 cm^{-1}. HRMS: calcd. for $C_{23}H_{26}ClN_3S_2$ 443.1257; found 443.1263.

Ethyl 2-(2-(Benzo[*d*]thiazol-2-yl(4-chlorobenzyl)amino)-4-methylpentylthiocarbonylamino)ethanoate: See Table 7, Entry 15; yield (90 °C in toluene for 16 h): 65% (318 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.52 (br. s, 1 H), 7.72 (d, *J* = 7.4 Hz, 1 H), 7.58 (d, *J* = 7.4 Hz, 1 H), 7.38 (t, *J* = 7.4 Hz, 1 H), 7.31 (br. s, 4 H), 7.15 (t, *J* = 7.4 Hz, 1 H), 5.38 (br. s, 1 H), 4.92 (d, *J* = 17.3 Hz, 1 H), 4.58 (d, *J* = 17.3 Hz, 1 H), 4.36 (d, *J* = 4.7 Hz, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 2.26–2.19 (m, 1 H), 2.01–1.93 (m, 1 H), 1.62–1.54 (m, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 202.2, 169.8, 168.7, 151.1, 135.5, 133.9, 131.1, 129.3, 129.1, 126.7, 122.5, 121.2, 120.0, 66.3, 62.1, 54.0, 48.0, 40.2, 25.4, 23.1, 22.9, 14.5 ppm. MS (DI, CI NH_3): *m*/*z* = 490. IR (thin film): $\tilde{\nu}$ = 1550, 1340, 1200, 1091 cm^{-1}. HRMS: calcd. for $C_{24}H_{28}ClN_3O_2S_2$ 489.1311; found 489.1315.

Ethyl 2-(1-(Benzo[*d*]thiazol-2-yl(4-chlorobenzyl)amino)-3-methylbutyl)thiazole-4-carboxylate: See Table 7, Entry 16; yield (90 °C in toluene for 16 h): 32% (160 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07 (s, 1 H), 7.66 (d, *J* = 7.8 Hz, 1 H), 7.60 (dd, *J* = 7.8, 1.1 Hz, 1 H), 7.36 (td, *J* = 7.8, 1.1 Hz, 1 H), 7.22 (s, 4 H), 7.13 (td, *J* = 7.8, 1.1 Hz, 1 H), 6.00 (t, *J* = 8.1 Hz, 1 H), 4.71 (d, *J* = 8.5 Hz, 2 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 2.26–2.20 (m, 2 H), 1.66–1.57 (m, 1 H), 1.42 (t, *J* = 7.1 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 0.88 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 169.9, 168.8, 161.6, 152.6, 147.0, 135.9, 133.5, 131.4, 129.1, 128.9, 128.6, 126.5, 122.2, 121.2, 120.0, 61.8, 60.3, 51.7, 40.5, 25.4, 23.2, 22.7, 14.8 ppm. MS (DI, CI NH_3): *m*/*z* = 500. HRMS: calcd. for $C_{25}H_{26}ClN_3O_2S_2$ 499.1155; found 499.1166.

2-[Allyl(6-ethoxybenzo[*d*]thiazol-2-yl)amino]-*N*-(4-chlorobenzyl)-4-methylpentanethioamide: See Table 7, Entry 17; yield (90 °C in toluene for 16 h): 66% (322 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.44 (br. s, 1 H), 7.21–7.10 (m, 6 H), 6.91 (dd, *J* = 8.8, 2.5 Hz, 2 H), 5.89–5.82 (m, 1 H), 5.35 (d, *J* = 17.1 Hz, 1 H), 5.27 (d, *J* = 10.2 Hz, 1 H), 5.20 (br. s, 1 H), 4.81 (dd, *J* = 15.4, 4.7 Hz, 1 H), 4.65 (dd, *J* = 15.4, 4.7 Hz, 1 H), 4.31 (dd, *J* = 17.2, 5.4 Hz, 1 H), 4.06 (q, *J* = 7.0 Hz, 2 H), 3.96 (dd, *J* = 17.2, 5.4 Hz, 1 H), 2.21–2.13 (m, 1 H), 2.12–2.03 (m, 1 H), 1.71–1.61 (m, 1 H), 1.46 (t, *J* = 7.0 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 202.0, 168.2, 155.1, 145.2, 135.1, 133.9, 133.2, 131.9, 129.8, 129.3, 119.7, 119.0, 114.8, 106.2, 66.7, 64.9, 53.6, 49.8, 39.9, 25.4, 23.2, 23.1, 15.4 ppm. MS (DI, CI NH_3): *m*/*z* = 488. IR (thin film): $\tilde{\nu}$ = 2356, 1520, 1463, 1224 cm^{-1}. HRMS: calcd. for $C_{25}H_{30}ClN_3OS_2$ 487.1519; found 487.1498.

2-[(4-Chlorobenzyl)(6-ethoxybenzo[*d*]thiazol-2-yl)amino]-*N*-cyclohexyl-4-methylpentanethioamide: See Table 7, Entry 18; yield (90 °C in toluene for 16 h): 32% (169 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.97 (br. s, 1 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 7.30 (s, 4 H), 7.10 (d, *J* = 2.5 Hz, 1 H), 6.95 (dd, *J* = 8.8, 2.5 Hz, 1 H), 5.13 (br. s, 1 H), 4.89 (d, *J* = 17.2 Hz, 1 H), 4.57 (d, *J* = 17.2 Hz, 1 H), 5.28–4.38 (m, 1 H), 4.04 (d, *J* = 7.0 Hz, 2 H), 2.21–2.14 (m, 1 H), 2.01–1.95 (m, 2 H), 1.88–1.83 (m, 1 H), 1.69–1.64 (m, 1 H), 1.59–1.53 (m, 2 H), 1.44 (t, *J* = 7.0 Hz, 3 H), 1.39–1.21 (m, 6 H), 0.88 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 199.4, 168.2, 155.2, 145.3, 135.8, 133.8, 132.0, 129.1, 119.7, 115.2, 106.1, 68.5, 64.6, 54.8, 53.8, 40.0, 31.3, 30.9, 25.9, 25.5, 24.3, 23.1, 23.0, 15.3 ppm. MS (DI, CI NH_3): *m*/*z* = 530. IR (thin film): $\tilde{\nu}$ = 2361, 1521, 1463, 1224 cm^{-1}. HRMS: calcd. for $C_{28}H_{36}ClN_3OS_2$ 529.1988; found 529.1984.

***N*-Cyclohexyl-2-(pyrimidin-2-yloxy)butanethioamide:** See Scheme 7; yield 58% (162 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.55 (d, *J* = 4.8 Hz, 2 H), 7.99 (br. s, 1 H), 7.02 (t, *J* = 4.8 Hz, 1 H), 5.89 (dd, *J* = 6.5, 3.9 Hz, 1 H), 4.45–4.36 (m, 1 H), 2.28–2.21 (m, 1 H), 2.19–2.12 (m, 1 H), 2.10–2.03 (m, 1 H), 1.89–1.82 (m, 1 H), 1.76–1.70 (m, 1 H), 1.66–1.59 (m, 1 H), 1.46–1.06 (m, 6 H), 1.00 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 198.9, 164.2, 160.0, 116.0, 84.3, 53.7, 31.8, 31.6, 28.4, 25.8, 25.0, 24.9, 9.0 ppm. MS (DI, CI NH_3): *m*/*z* = 280. IR (thin film): $\tilde{\nu}$ = 2939, 1580, 1530, 1300, 1042 cm^{-1}. HRMS: calcd. for $C_{14}H_{21}N_3OS$ 279.1405; found 279.1405.

Acknowledgments

Financial support was provided by the Ecole Nationale des Techniques Avancées. M. G. and A. B. thank the Ministère de l'Enseignement Supérieur et de la Recherche for a fellowship, and A. B. thanks the Ecole Normale de Cachan for an additional fellowship.

[1] For recent reviews, see: a) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123–131; b) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321–3329; c) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; d) A. Dömling, *Curr. Opin. Chem. Bio.* **2002**, *6*, 306–313; e) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144; f) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899–907; g) I. Ugi, B. Werner, A. Dömling, *Molecules* **2003**, *8*, 53–66; h) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–80; i) R. Riva, L. Banfi, *Org. React.* **2005**, *65*, 1–140; j) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89.

[2] a) I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 386; b) I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267–268. For recent applications of Ugi reactions, see: c) M. C. Pirrung, K. D. Sarma, *J. Am. Chem. Soc.* **2004**, *126*, 444–445; d) F. Bonnaterre, M. Bois-Choussy, J. Zhu, *Org. Lett.* **2006**, *8*, 4351–4354; e) A. Ilyin, V. Kysil, M. Krasavin, I. Kurashvili, A. V. Ivachtchenko, *J. Org. Chem.* **2006**, *71*, 9544–9547; f) Q. Lin, J. C. O'Neill, H. E. Blackwell, *Org. Lett.* **2005**, *7*, 4455–4458; g) M. Sanudo, S. Marcaccini, S. Basurto, T. Torroba, *J. Org. Chem.* **2006**, *71*, 4578–4584; h) Z. Ma, Z. Xiang, T. Luo, K. Lu, Z. Xu, J. Chen, Z. Yang, *J. Comb. Chem.* **2006**, *8*, 696–704.

[3] G. Zinner, D. Moderhack, W. Kliegel, *Chem. Ber.* **1969**, *102*, 2536; D. Moderhack, *Justus Liebigs Ann. Chem.* **1973**, 359; G. Zinner, D. Moderhack, O. Hantelmann, W. Bock, *Chem. Ber.* **1974**, *107*, 2947; A. Basso, L. Banfi, G. Guanti, R. Riva, *Tetrahedron Lett.* **2005**, *46*, 8003–8006.

[4] I. Ugi, F. Bodesheim, *Justus Liebigs Ann. Chem.* **1963**, *666*, 61; T. Torroba, G. Zinner, W. Bock, *Arch. Pharm.* **1973**, *306*, 94–96; S. Zinner, W. Bock, *Arch. Pharm., Ber. Dtsch. Pharm. Ges.* **1971**, *304*, 933–935; S. Marcaccini, R. Pepino, C. Polo, M. Cruz Pozo, *Synthesis* **2001**, *1*, 85–88; C. F. Marcos, S. Marcaccini, R. Pepino, C. Polo, T. Torroba, *Synthesis* **2003**, *5*, 691–694; M. Sanudo, S. Marcaccini, S. Basurto, *J. Org. Chem.* **2006**, *71*, 4578–4584.

[5] I. Ugi, *Angew. Chem.* **1960**, *72*, 639; I. Ugi, C. Steinbruckner, *Chem. Ber.* **1961**, *94*, 734–742.

[6] I. Ugi, K. Offermann, *Chem. Ber.* **1964**, *97*, 2276–2281.

[7] I. Ugi, F. K. Rosendahl, *Justus Liebigs Ann. Chem.* **1963**, *670*, 80–82; I. Ugi, F. K. Rosendahl, F. Bodensheim, *Justus Liebigs Ann. Chem.* **1963**, *666*, 54–57.

[8] I. Ugi, C. Steinbruckner, *Angew. Chem.* **1960**, *72*, 267.

[9] S. Heck, A. Doemling, *Synlett* **2000**, 424–426.

[10] L. El Kaim, L. Grimaud, J. Oble, *Angew. Chem. Int. Ed.* **2005**, *44*, 7961–7964; L. El Kaim, M. Gizolme, L. Grimaud, J. Oble, *J. Org. Chem.* **2007**, *72*, 4169–4180.
[11] L. El Kaim, M. Gizolme, L. Grimaud, J. Oble, *Org. Lett.* **2006**, *8*, 4019–4021; L. El Kaim, M. Gizolme, L. Grimaud, J. Oble, *Synlett* **2007**, 465–469.
[12] We have already observed improvements in Ugi–Smiles couplings between nitrophenols, isocyanides, amines and aromatic aldehyde by adding Lewis acids such as magnesium perchlorate. For previous examples, see ref.[9]
[13] L. El Kaim, M. Gizolme, L. Grimaud, J. Oble, *J. Org. Chem.* **2007**, *72*, 5835–5838.
[14] J. Kolb, B. Beck, A. Dömling, *Tetrahedron Lett.* **2002**, *43*, 6897–6901; U. Schöllkopf, H. Porsch, H. H. Lau, *Liebigs Ann. Chem.* **1979**, 95.
[15] H. C. Koppel, R. H. Springer, R. K. Robins, C. C. Cheng, *J. Org. Chem.* **1961**, *26*, 792–803.
[16] A. Barthelon, A. Dos Santos, L. El Kaïm, L. Grimaud, *Tetrahedron Lett.* **2008**, *49*, 3208–3211.
[17] L. El Kaim, M. Gizolme, L. Grimaud, J. Oble, *Synlett* **2007**, 465–469.

Received: September 5, 2008
Published Online: October 31, 2008

