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Rapid Synthesis of Highly Functionalised α-Amino Amides and Medium Ring Lactones using Multicomponent Reactions of Amino Alcohols and Isocyanides

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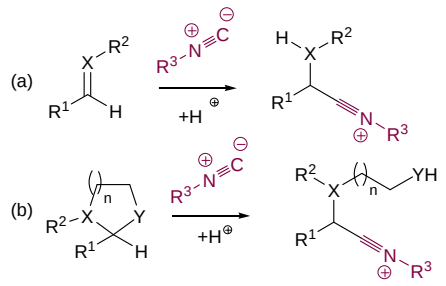
Four-component reactions between amino alcohols, aldehydes, isocyanides and thiols proceed rapidly under microwave or conventional heating at 60 °C in methanol. The reaction is successful with a wide range of components and gives access to potentially drug-like products containing amine, amide and thioether functionality in moderate to excellent yield. The reaction conditions are also applicable to the synthesis of a range of 8-10 membered medium-ring lactones via three-component reactions of aminoalcohols, isocyanides and acid-aldehydes. Incorporation of L-prolinol as the aminoalcohol component in each case gives access to multicomponent products with moderate to high diastereoselectivity.

Introduction

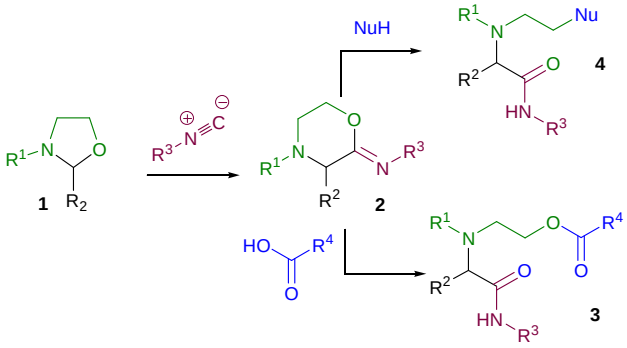
Multicomponent reactions (MCRs) – reactions in which three or more reagents are combined to give a single product – enable the efficient synthesis of complex molecular structures in a single step.[1] Reactions of this type which provide access to drug-like structures containing appropriate H-bond donors and acceptors are particularly valuable, as libraries of potentially bioactive compounds can be quickly synthesized. Isocyanides are widely used components in such reactions, as they typically lead to the formation of an amide or aromatic heterocycle in the resulting product. The Ugi reaction,[2] the 4-component reaction (4-CR) between an amine, aldehyde, isocyanide and carboxylic acid, is of particular note, as it can provide access to large numbers of diverse amino acid amides from readily available starting materials. Acetals can potentially act as an alternative to the carbonyl component in an Ugi-type MCR, leading to more complex product skeletons and a greater scope for structural diversity (Scheme 1).[3-6]



Scheme 1 Replacement of a carbonyl derivative (a) with an acetal (b) to give a novel Ugi-like isocyanide MCR.

In the case of an Ugi (or related) reaction, addition of the isocyanide to the C=X bond leads to a molecule containing nucleophilic (XH) and electrophilic (nitrilium cation) sites in a 1,3 relationship (a), which then go on to react with the other components to generate the MCR product. By replacement of the C=X multiple bond with an acetal (b), a spacer is inserted between the nucleophilic (YH) and electrophilic (nitrilium cation) sites in the resulting adduct, providing an opportunity for greater diversity in the resulting MCR product.

We have recently reported that 1,3-oxazolidines **1** (simple *N*,*O*-acetals derived from ethanolamines) readily undergo 3-CRs with isocyanides and carboxylic acids to give *N*-acyloxyethylamino acid amides **3**, via the cyclic imino ester intermediate **2** (Scheme 2).[4,5]



Scheme 2 3-CRs of 1,3-oxazolidines.

We also demonstrated that the carboxylic acid component could be replaced by thiophenol, thiobenzoic acid or 4-phenyltetrazole, providing access to different 3-CR products **4** via nucleophilic

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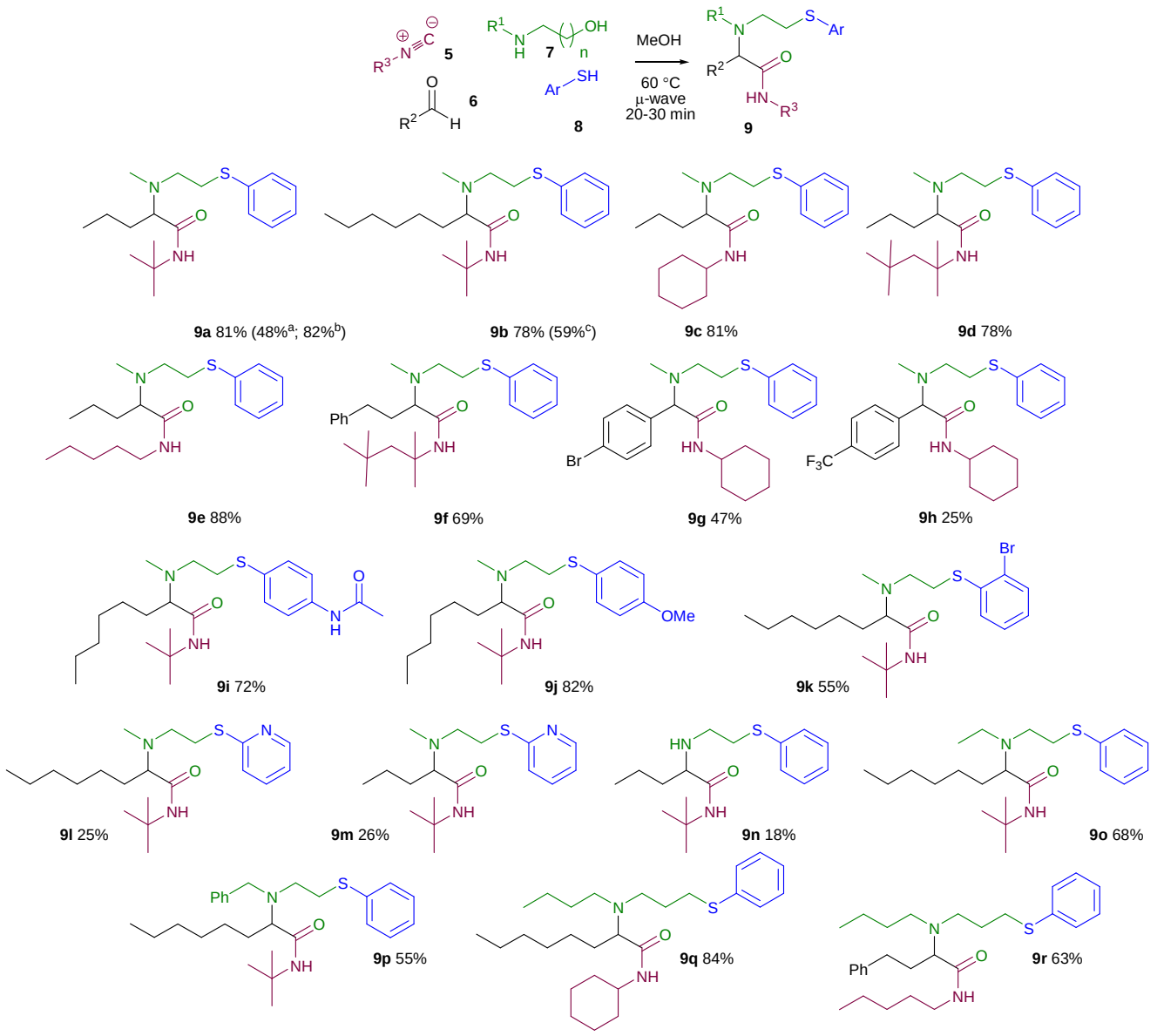


Scheme 3 [a]TsOH, MeCN, reflux, 24 h (NMR yield). [b]Yield of 4-CR under conventional heating (60 °C, MeOH, 20 min). [c]Yield obtained under 3-CR conditions from the corresponding 1,3-oxazolidine (TsOH, MeCN, reflux, 24 h).[5]

ring-opening of intermediate **2**.[7] The yields for these latter 3-CRs with sulfur nucleophiles were low, and therefore only limited examples were explored. Given the fact that a large number of functionalised thiols are commercially available, we recognized that this reaction could be potentially valuable. We therefore sought to develop improved conditions for the reaction with a view to developing a more robust method applicable to 4-CRs, which could then be applied to a wide range of aldehydes, isocyanides, amino alcohols and thiols.

Results and Discussion

4-CR of aminoalcohols, aldehydes, isocyanides and thiols

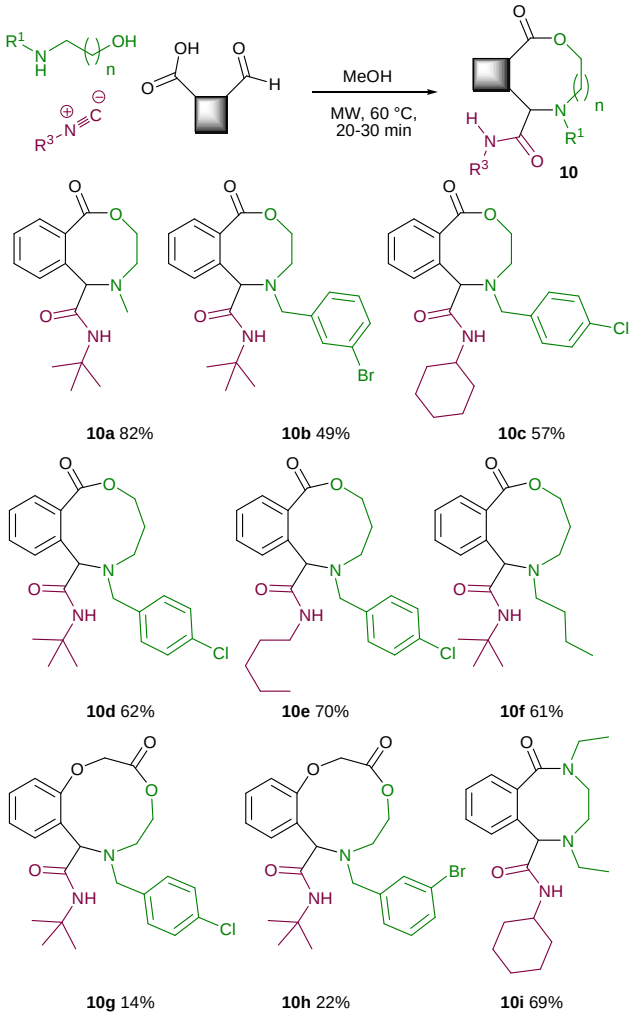
As a representative reaction, we chose to optimise the 4-CR leading to amide **9a** (Scheme 3). Our previous 3-CRs of pre-formed oxazolidines were carried out in MeCN in the presence of catalytic quantities of TsOH, but these conditions gave only a moderate yield of the product from a 4-CR. We subsequently found that MeOH was a superior solvent for this reaction, and

that the acid catalyst was unnecessary. Although the reaction did proceed at room temperature, it was somewhat sluggish. However, heating the reaction at 60 °C for 20 minutes under microwave irradiation led to the formation of 4-CR product **9a** in 81% isolated yield.

These optimized reaction conditions were then applied to a wide range of isocyanides, aldehydes, thiols and aminoalcohols (Scheme 3). The yields of this new 4-CR were superior to those we employed previously in the corresponding 3-CR (**9b**)[5] and could be applied to a range of aldehydes, including both aliphatic systems (e.g. **9a**, **9b**, **9f**) and functionalised aryl aldehydes (e.g. **9g**, **9h**). Several different isocyanides could be employed, enabling the nitrogen substituent on the amide to be varied (e.g. **9a**, **9c**, **9d**). A variety of commercially available aromatic thiols, including those bearing bromide (**9k**), methoxy (**9j**) and acetamide substituents (**9i**) gave multicomponent products in good yield. 2-Pyridyl thiol could also be employed providing access to MCR products containing heteroaromatic rings, albeit in lower yield (**9l** and **9m**). In terms of the aminoalcohol component, a variety of *N*-substituted ethanolamines could be used (e.g. **9a**, **9o**, **9p**). The scaffold of the MCR products could also be extended by incorporating an *N*-substituted 1,3-propanolamine as one of the components (e.g. **9q**, **9r**), with good yields of the homologous MCR products being obtained. Unsubstituted ethanolamine could also be used, although this gave the corresponding secondary amine product **9n** in low yield. Although the reactions were typically carried out under microwave heating, an equally high yield was obtained for one example under thermal conditions (**9a**).

3-CR of acid-aldehydes, aminoalcohols and isocyanides to give medium ring lactones

In our previous report,[5] we also carried out a brief examination of the 3-CR of an acid aldehyde,[8] amino alcohol and isocyanide to give medium-ring lactone products (Scheme 4). Under our original conditions (TsOH, ^{i}PrOH), prolonged reaction times were required and only moderate yields of the MCR products were obtained. Pleasingly under our new microwave conditions this reaction was also successful, giving rapid access to a wide range of medium-ring lactone products in moderate to excellent yield. Structural variation of the amino alcohol and/or the acid-aldehyde components enabled a variety of eight- (**10a-10c**), nine- (**10d-10f**) and ten-membered (**10g-10h**) lactones to be accessed. A *bis*-secondary amine component[6] could also be used to synthesise an eight-membered lactam (**10i**). The synthesis of medium rings is often difficult due to the unfavourable thermodynamics of the ring closing process.[9] These reactions are therefore potentially valuable as they offer an efficient one-step route to densely functionalised medium ring systems from readily available starting materials.



Scheme 4 3-CRs of acid aldehydes, amino alcohols and isocyanides to give medium ring lactones.

We also examined the use of L-prolinol as a chiral aminoalcohol component in both of these MCRs (Fig. 1).[10] Interestingly, the 4-CR products **11a-11c** were obtained as single diastereoisomers in good yield.[11] In contrast, the 3-CR of L-prolinol with an acid-aldehyde and an isocyanide led to the diastereomeric eight-membered lactones **12** in a 1.5:1 ratio. Pleasingly, these lactones could be easily separated by chromatography and the relative stereochemistry of each isomer was then assigned using nOe experiments.[12]

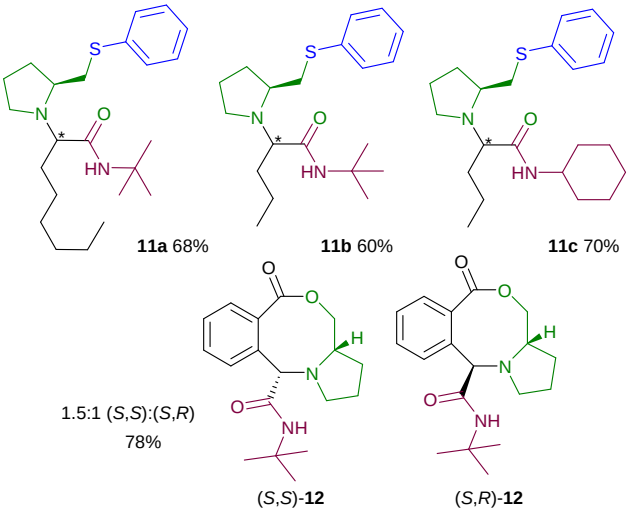


Fig. 1 4-CR and 3-CR products obtained using L-prolinol.

Conclusions

In conclusion, we have developed a generally high yielding and rapid procedure for the 4-CR of aminoalcohols, aldehydes, thiols and isocyanides to give arylthioalkylamino acid amides. The reaction conditions can also be applied to the synthesis of medium ring 3-CR products by reaction of an amino alcohol and isocyanide with a bifunctional acid-aldehyde. In addition, we have shown that diastereoselective MCRs can be achieved is some cases using L-prolinol as a chiral aminoalcohol component. Further work is underway on the development of other novel MCRs which will be reported in due course.

Experimental Section

All solvents and chemicals were used as obtained from commercial suppliers. Column chromatography was carried out using BDH (40-63 μm) silica gel and analytical thin layer chromatography was carried out using Merck Kieselgel aluminium-backed plates coated with silica gel. Components were visualised using combinations of ultra-violet lights, phosphomolybdic acid and potassium permanganate. Melting points were determined using a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 343 polarimeter (sodium D-line, 529 nm) and α_D values are given in 10^{-1} degcm^{2}g^{-1}, concentration (*c*) in g per 100 mL. Infrared (IR) spectra were recorded on a Perkin-Elmer spectrum 100 FT-IR spectrometer as thin films. ^{1}H and ^{13}C NMR spectra were recorded respectively at 400 MHz and 100 MHz on a Bruker Avance 400 spectrometer or at 600 MHz and 150 MHz on a Bruker Avance 600 spectrometer in the stated solvent. Mass spectra were obtained using either a VG70-SE or MAT 900XP spectrometer at the Department of Chemistry, University College London.

General procedure for 4-CRs of Amino Alcohols, Aldehydes, Isocyanides and Thiols

Aldehyde (1.0 mmol), isocyanide (1.0 mmol) and thiophenol (1.0 mmol) were added to a solution of amino alcohol (1.0 mmol) in methanol (1 ml). The mixture was stirred under microwave irradiation[13] at 60 °C for 20 min. The solvent was evaporated and the crude product was purified by flash chromatography (Petroleum ether/EtOAc 15:1 to 1:1) to afford the *amide*.

N-*tert*-Butyl-2-(methyl(2-(phenylthio)ethyl)amino)pentanamide (9a)

Colourless oil. 81% yield. ν_{max}/cm^{-1} 3336 (NH), 2960, 2871 (CH), 1668 (CO), 1584, 1509, 1453 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 0.90 (3 H, t, *J* 7.3, CH_2CH_3), 1.29-1.35 (1 H, m, alkyl), 1.34 (9 H, s, *t*Bu), 1.41-1.47 (1 H, m, alkyl), 1.49-1.54 (1 H, m, alkyl), 1.69-1.75 (1 H, m, alkyl), 2.25 (3 H, s, NCH_3), 2.76 (1 H, dt, *J* 13.4, 6.8, NC*H*H), 2.78 (1 H, dt, *J* 13.4, 6.5, NCH*H*), 2.87 (1 H, dd, *J* 7.0, 5.3, NC*H*), 3.04 (1 H, dt, *J* 12.8, 6.5, SC*H*H), 3.07 (1 H, dt, *J* 12.8, 6.8, SCH*H*), 7.18 (1 H, t, *J* 7.7, Ar), 7.20 (1 H, s, N*H*), 7.28 (2 H, app. t, *J* 7.7, Ar), 7.33 (2 H, dd, *J* 7.7, 1.2, Ar); δ_C (150 MHz; $CDCl_3$; Me_4Si) 14.4, 21.0, 28.9, 29.4, 32.9, 37.5, 50.6, 53.8, 68.6, 126.2, 129.1, 129.3, 136.5, 172.6; LRMS (CI) 323, 275, 222, 189; HRMS calcd for $C_{18}H_{31}N_2OS$ [MH]$^+$ 323.2157, found 323.2153.

N-(*tert*-Butyl)-2-(methyl(2-(phenylthio)ethyl)amino)octanamide (9b)[5]

Colourless oil. 78% yield. ν_{max}/cm^{-1} 3335 (NH), 2957, 2927; 2856 (CH), 1661 (CO), 1585, 1509, 1453 (Ar); δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.87 (3 H, t, *J* 6.7, CH_2CH_3), 1.23-1.32 (7 H, m, alkyl), 1.35 (9 H, s, *t*Bu), 1.37-1.47 (1 H, m, alkyl), 1.49-1.60 (1 H, m, alkyl), 1.69-1.81 (1 H, m, alkyl), 2.26 (3 H, s, NCH_3), 2.76 (1 H, dt, *J* 13.4, 7.0, NC*H*H), 2.80 (1 H, dt, *J* 13.4, 6.5, NCH*H*), 2.87 (1 H, dd, *J* 7.0, 5.8, NC*H*), 3.04 (1 H, dt, *J* 13.0, 6.5, SC*H*H), 3.08 (1 H, dt, *J* 13.0, 7.0, SCH*H*), 7.15-7.22 (2H, m, Ar, N*H*), 7.28 (2H, br t, *J* 8.0, Ar), 7.34 (2H, br d, *J* 8.0, Ar); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.1, 22.6, 27.2, 27.5, 28.8, 29.6, 31.7, 32.8, 37.4, 50.4, 53.8, 68.7, 126.1, 129.0, 129.2, 136.4, 172.4; LRMS (ES) 363, 279, 227; HRMS calcd for $C_{21}H_{35}N_2OS$ [M-H]$^-$ 363.2470, found 363.2470.

N-Cyclohexyl-2-(methyl(2-(phenylthio)ethyl)amino)pentanamide (9c)

Colourless oil. 81% yield. ν_{max}/cm^{-1} 3314 (NH), 2929, 2853 (CH), 1641 (CO), 1584, 1509, 1450 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 0.89 (3 H, t, *J* 7.2, CH_2CH_3), 1.11-1.20 (3 H, m, cy), 1.28-1.38 (3 H, m, cy), 1.39-1.46 (1 H, m, alkyl), 1.50-1.60 (2 H, m, alkyl), 1.64-1.77 (3 H, m, alkyl), 1.81-1.87 (2 H, m, cy), 2.25 (3 H, s, NCH_3), 2.76 (1 H, dt, *J* 13.1, 6.8, NC*H*H), 2.78 (1 H, dt, *J* 13.1, 6.5, NCH*H*), 2.95 (1 H, t, *J* 6.4, NC*H*CO), 3.03 (1 H, dt, *J* 13.1, 6.5, SC*H*H), 3.06 (1 H, dt, *J* 13.1, 6.8, SCH*H*), 3.68-3.76 (1 H, m, NHC*H*), 7.18 (1 H, tt, *J* 7.7, 1.4, Ar), 7.21 (1 H, br d, *J* 7.8, N*H*), 7.27 (2 H, app. t, *J* 7.7, Ar), 7.32 (2 H, dd, *J* 7.7, 1.4, Ar); δ_C (150 MHz; $CDCl_3$; Me_4Si) 14.4, 20.8, 24.9, 25.7, 29.7, 32.9, 33.3, 37.6, 47.8, 53.9, 68.0, 126.3, 129.1, 129.4, 136.4, 172.3; LRMS (CI) 349, 239, 222, 137; HRMS calcd for $C_{20}H_{33}N_2OS$ [MH]$^+$ 349.2314, found 349.2326.

2-(Methyl(2-(phenylthio)ethyl)amino)-*N*-(2,4,4-trimethylpentan-2-yl)pentanamide (9d)

Colourless oil. 78% yield. ν_{max}/cm^{-1} 3334 (NH), 2955, 2871 (CH), 1671 (CO), 1585, 1507, 1480 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 0.90 (3 H, t, *J* 7.2, CH_2CH_3), 1.00 (9 H, s, *t*Bu), 1.28-1.37 (1 H, m, alkyl), 1.40 (6 H, s, 2 × CH_3), 1.42-1.52 (2 H, m, alkyl), 1.59 (1 H, d, *J* 14.9, C*H*H*t*Bu), 1.72-1.80 (1 H, m, alkyl), 1.83 (1

H, d, *J* 14.9, CH*H*tBu), 2.24 (3 H, s, NCH_3), 2.78 (1 H, dt, *J* 13.2, 6.9, NC*H*H), 2.81 (1 H, dt, *J* 13.2, 6.4, NCH*H*), 2.87 (1 H, t, *J* 6.4, NC*H*), 3.03 (1 H, dt, *J* 12.8, 6.4, SC*H*H), 3.06 (1 H, dt, *J* 12.8, 6.9, SCH*H*), 7.17 (1 H, t, *J* 7.5, Ar), 7.27 (2 H, app. t, *J* 7.5, Ar), 7.31 (2 H, d, *J* 7.5, Ar), 7.33 (1 H, br s, N*H*); δ_C (150 MHz; $CDCl_3$; Me_4Si) 14.4, 21.4, 28.7, 28.9, 29.2, 31.7, 32.9, 37.6, 52.5, 54.0, 54.5, 68.5, 126.2, 129.1, 129.2, 136.5, 172.2; LRMS (CI) 379, 269, 222, 137; HRMS calcd for $C_{22}H_{39}N_2OS$ $[MH]^+$ 379.2783, found 379.2777.

2-(Methyl(2-(phenylthio)ethyl)amino)-*N*-pentylpentanamide (9e)

Colourless oil. 88% yield. ν_{max}/cm^{-1} 3334 (NH), 2960, 2932, 2873 (CH), 1655 (CO), 1518, 1481, 1439 (Ar); δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.86 (3 H, t, *J* 6.9, CH_3), 0.88 (3 H, t, *J* 7.3, CH_3), 1.22-1.37 (5 H, m, alkyl), 1.37-1.58 (4 H, m, alkyl), 1.69-1.80 (1 H, m, alkyl), 2.24 (3 H, s, NCH_3), 2.76 (2 H, app. t, *J* 6.5, CH_2NMe), 2.96 (1 H, t, *J* 6.4, NC*H*), 3.02 (1 H, dt, *J* 13.1, 6.5, SC*H*H), 3.05 (1 H, dt, *J* 13.1, 6.5, SCH*H*), 3.10-3.26 (2 H, m, CH_2NH), 7.14 (1 H, t, *J* 7.5, Ar), 7.25 (2 H, app. t, *J* 7.5, Ar), 7.30 (2 H, d, *J* 7.5, Ar), 7.32 (1 H, br s, N*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.0, 14.2, 20.7, 22.3, 29.2, 29.3, 29.5, 32.7, 37.6, 39.0, 53.8, 67.9, 126.0, 128.9, 129.0, 136.3, 173.0; LRMS (CI) 337, 222, 137; HRMS calcd for $C_{19}H_{33}N_2OS$ $[MH]^+$ 337.2314, found 337.2314.

2-(Methyl(2-(phenylthio)ethyl)amino)-4-phenyl-*N*-(2,4,4-trimethylpentan-2-yl)butanamide (9f)

Colourless oil. 69% yield. ν_{max}/cm^{-1} 3338 (NH), 2950 (CH), 1672 (CO), 1584, 1507, 1454 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 1.02 (9 H, s, *t*Bu), 1.42 (3 H, s, NCCH_3), 1.44 (3 H, s, NCCH_3), 1.60 (1 H, d, *J* 14.9, C*H*H*t*Bu), 1.72-1.80 (1 H, m, C*H*HCH), 1.90 (1 H, d, *J* 14.9, CH*H*tBu), 2.10-2.18 (1 H, m, CH*H*CH), 2.25 (3 H, s, NCH_3), 2.64 (1 H, ddd, *J* 13.5, 9.8, 6.9, C*H*HPh), 2.71 (1 H, dt, *J* 12.9, 6.5, NC*H*H), 2.77 (1 H, dt, *J* 12.9, 6.5, NCH*H*), 2.85-3.00 (4 H, m, CH*H*Ph, NC*H*, SCH_2), 7.15-7.21 (4 H, m, Ar), 7.24-7.31 (6 H, m, Ar), 7.31 (1 H, br s, N*H*); δ_C (150 MHz; $CDCl_3$; Me_4Si) 27.6, 28.8, 29.3, 31.7, 31.8, 32.7, 34.2, 37.6, 52.4, 54.7, 66.9, 126.0, 126.2, 128.5, 128.7, 129.1, 129.2, 136.4, 142.1, 171.9; LRMS (CI) 441, 331, 284; HRMS calcd for $C_{23}H_{32}N_2OS$ $[MH]^+$ 441.2940, found 441.2936.

2-(4-Bromophenyl)-*N*-cyclohexyl-2-(methyl(2-(phenylthio)ethyl)amino)acetamide (9g)

White solid. 47% yield. M.p. 114-115°C (hexanes); ν_{max}/cm^{-1} 3296 (NH), 2928, 2851 (CH), 1645 (CO), 1584, 1521, 1480 (Ar); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.14-1.29 (3 H, m, cy), 1.30-1.44 (2 H, m, cy), 1.58-1.67 (1 H, m, cy), 1.67-1.78 (2 H, m, cy), 1.80-1.95 (2 H, m, cy), 2.20 (3 H, s, NCH_3), 2.66 (2 H, app. t, *J* 6.7, NCH_2), 3.06 (1 H, dt, *J* 13.2, 6.7, SC*H*H), 3.09 (1 H, dt, *J* 13.2, 6.7, SCH*H*), 3.70-3.82 (1 H, m, NHC*H*), 3.96 (1 H, s, NC*H*Ar), 7.15 (2 H, d, *J* 8.3, Ar), 7.19-7.27 (2 H, m, Ar), 7.28-7.32 (4 H, m, Ar, N*H*), 7.44 (2 H, d, *J* 8.3, Ar); δ_C (100 MHz; $CDCl_3$; Me_4Si) 24.8, 25.5, 31.9, 33.0, 39.4, 47.8, 53.9, 74.4, 122.1, 126.2, 129.0, 129.2, 130.7, 131.5, 134.9, 136.1, 169.7; LRMS (CI) 463, 461, 352, 336; HRMS calcd for $C_{23}H_{30}N_2OSBr$ $[MH]^+$ 461.1262, found 461.1271.

***N*-Cyclohexyl-2-(methyl(2-(phenylthio)ethyl)amino)-2-(4-(trifluoromethyl)phenyl)acetamide (9h)**

White solid. 25% yield. M.p. 97-98°C (hexanes); ν_{max}/cm^{-1} 3302 (NH), 2933, 2853 (CH), 1649 (CO), 1583, 1543, 1481 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 1.13-1.28 (3 H, m, cy), 1.28-1.40 (2 H, m, cy), 1.56-1.64 (1 H, m, cy), 1.66-1.75 (2 H, m, cy), 1.78-1.92 (2 H, m, cy), 2.18 (3 H, s, NCH_3), 2.64 (2 H, app. t, *J* 6.7, NCH_2), 3.06 (1 H, dt, *J* 13.3, 6.7, SC*H*H), 3.09 (1 H, dt, *J* 13.3, 6.7, SCH*H*), 3.70-3.78 (1 H, m, NHC*H*), 4.05 (1 H, s, NC*H*Ar), 7.18 (1 H, tt, *J* 7.7, 1.5, Ar), 7.24-7.30 (4 H, m, Ar), 7.31 (1 H, br s, N*H*), 7.37 (2 H, d, *J* 7.7, Ar), 7.44 (2 H, d, *J* 7.7, Ar); δ_C (150 MHz; $CDCl_3$; Me_4Si) 24.9, 25.6, 32.0, 33.1, 39.4, 48.0, 54.0, 74.6, 124.2 (q, *J* 272), 125.4 (q, *J* 3.6), 126.4, 129.2, 129.3, 129.6, 130.2 (q, *J* 32.4), 136.1, 139.9, 169.6; LRMS (ES) 449, 339, 324, 189; HRMS calcd for $C_{24}H_{28}N_2OSF_3$ $[M-H]^-$ 449.1874, found 449.1874.

2-((2-((4-Acetamidophenyl)thio)ethyl)(methyl)amino)-*N*-(*tert*-butyl)octanamide (9i)

Colourless oil. 72% yield. ν_{max}/cm^{-1} 3307 (NH), 2958, 2928, 2857 (CH), 1651 (CO), 1593, 1521, 1493, 1454 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 0.84 (3 H, t, *J* 6.6, CH_2CH_3), 1.17-1.28 (7 H, m, alkyl), 1.33 (9 H, s, *t*Bu), 1.29-1.40 (1 H, m, alkyl), 1.48-1.56 (1 H, m, alkyl), 1.67-1.75 (1 H, m, alkyl), 2.15 (3 H, s, CH_3CO), 2.22 (3 H, s, NCH_3), 2.72 (2 H, app. t, *J* 6.6, NCH_2), 2.83 (1 H, t, *J* 6.2, NC*H*), 2.97 (1 H, dt, *J* 12.9, 6.6, SC*H*H), 3.00 (1 H, dt, *J* 12.9, 6.6, SCH*H*), 7.24 (1 H, br s, N*H*tBu), 7.29 (2 H, d, *J* 8.3, Ar), 7.46 (2 H, d, *J* 8.3, Ar), 7.93 (1 H, br s, N*H*Ac); δ_C (150 MHz; $CDCl_3$; Me_4Si) 14.2, 22.7, 24.6, 27.4, 27.6, 28.9, 29.7, 31.8, 33.8, 37.4, 50.6, 54.0, 68.9, 120.6, 130.9, 131.1, 137.0, 168.8, 172.8; LRMS (CI) 422, 366, 321, 255; HRMS calcd for $C_{23}H_{40}N_3O_2S$ $[MH]^+$ 422.2841, found 422.2833.

***N*-(*tert*-Butyl)-2-((2-((4-methoxyphenyl)thio)ethyl)(methyl)amino)octanamide (9j)**

Colourless oil. 82% yield. ν_{max}/cm^{-1} 3331 (NH), 2957, 2926, 2855 (CH), 1671 (CO), 1593, 1493, 1453 (Ar); δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.87 (3 H, t, *J* 6.7, CH_2CH_3), 1.24-1.32 (7 H, m, alkyl), 1.35 (9 H, s, *t*Bu), 1.33-1.45 (1 H, m, alkyl), 1.48-1.58 (1 H, m, alkyl), 1.68-1.80 (1 H, m, alkyl), 2.24 (3 H, s, NCH_3), 2.72 (2 H, app. t, *J* 6.7, CH_2N), 2.86 (1 H, dd, *J* 7.0, 5.8, NC*H*), 2.93 (1 H, dt, *J* 13.0, 6.7, SC*H*H), 2.96 (1 H, dt, *J* 13.0, 6.7, SCH*H*), 3.80 (3 H, s, OCH_3), 6.85 (2 H, d, *J* 8.8, Ar), 7.24 (1 H, br s, N*H*), 7.35 (2 H, d, *J* 8.8, Ar); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.1, 22.6, 27.2, 27.5, 28.8, 29.6, 31.7, 34.9, 37.4, 50.4, 54.0, 55.3, 68.6, 114.7, 126.2, 133.3, 159.1, 172.5; LRMS (CI) 395, 229, 173, 105; HRMS calcd for $C_{22}H_{39}N_2O_2S$ $[MH]^+$ 395.2732, found 395.2727.

2-((2-((2-Bromophenyl)thio)ethyl)(methyl)amino)-*N*-(*tert*-butyl)octanamide (9k)

Colourless oil. 55% yield. ν_{max}/cm^{-1} 3342 (NH), 2956, 2926, 2856 (CH), 1665 (CO), 1576, 1509, 1449 (Ar); δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.89 (3 H, t, *J* 6.8, CH_2CH_3), 1.24-1.35 (7 H, m, alkyl), 1.37 (9 H, s, *t*Bu), 1.40-1.50 (1 H, m, alkyl), 1.51-1.63 (1 H, m, alkyl), 1.71-1.84 (1 H, m, alkyl), 2.30 (3 H, s, NCH_3), 2.85 (1 H, dt, *J* 13.0, 6.7, NC*H*H), 2.89 (1 H, dt, *J* 13.0, 6.3, NCH*H*), 2.92 (1 H, dd, *J* 7.2, 5.4, NC*H*), 3.07 (1 H, dt, *J* 12.4, 6.3, SC*H*H), 3.12 (1 H, dt, *J* 12.4, 6.7, SCH*H*), 7.05 (1 H, ddd, *J* 8.0, 6.4, 2.5, Ar), 7.12 (1 H, br s, N*H*), 7.26-7.30 (2 H, m, Ar), 7.56 (1 H, dd, *J* 8.0, 1.1, Ar); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.1, 22.6, 27.1, 27.6, 28.8, 29.6, 31.7, 31.9, 37.4, 50.5, 53.1, 68.7, 123.6, 126.6, 127.8,

128.0, 133.1, 138.1, 172.3; LRMS (CI) 445, 443, 344, 255; HRMS calcd for $C_{21}H_{36}N_2OSBr$ $[MH]^+$ 443.1732, found 443.1715.

_N_-(_tert_-Butyl)-2-(methyl(2-(pyridin-2-ylthio)ethyl)amino)octanamide (9l)

Colourless oil. 25% yield. ν_{max}/cm^{-1} 3330 (NH), 2956, 2926, 2856 (CH), 1671 (CO), 1578, 1509, 1453, 1414 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 0.85 (3 H, t, _J_ 6.8, CH_2CH_3), 1.21-1.29 (7 H, m, alkyl), 1.31 (9 H, s, _t_Bu), 1.36-1.46 (1 H, m, alkyl), 1.53-1.61 (1 H, m, alkyl), 1.69-1.77 (1 H, m, alkyl), 2.28 (3 H, s, NCH_3), 2.79 (1 H, dt, _J_ 13.3, 6.5, NC_H_H), 2.83 (1 H, dt, _J_ 13.3, 6.8, NCH_H_), 2.89 (1 H, br t, _J_ 5.4, NC_H_), 3.32 (1 H, dt, _J_ 13.4, 6.5, SC_H_H), 3.35 (1 H, dt, _J_ 13.4, 6.8, SCH_H_), 6.97 (1 H, dd, _J_ 6.8, 5.0, Ar), 7.15 (1 H, d, _J_ 8.0, Ar), 7.18 (1 H, br s, N_H_), 7.46 (1 H, app. td, _J_ 8.0, 1.6, Ar), 8.40 (1 H, br d, _J_ 5.0, Ar); δ_C (150 MHz; $CDCl_3$; Me_4Si) 14.2, 22.8, 27.4, 27.6, 28.6, 28.8, 29.7, 31.8, 37.7, 50.5, 54.1, 68.9, 119.5, 122.4, 136.0, 149.6, 158.8, 172.7; LRMS (CI) 366, 229, 173; HRMS calcd for $C_{20}H_{36}N_3OS$ $[MH]^+$ 366.2579, found 366.2564.

_N_-(_tert_-Butyl)-2-(methyl(2-(pyridin-2-ylthio)ethyl)amino)pentanamide (9m)

Colourless oil. 26% yield. ν_{max}/cm^{-1} 3331 (NH), 2954, 2854 (CH), 1670 (CO), 1578, 1508, 1453, 1415 (Ar); δ_H (600 MHz, $CDCl_3$) 0.91 (3 H, t, _J_ 7.3, CH_2CH_3), 1.31-1.36 (10 H, m, CH_3CH_H, _t_Bu), 1.44-1.47 (1 H, m, CH_3CH_H), 1.52-1.57 (1 H, m, NCHCH_H_), 1.69-1.73 (1 H, m, NCHCH_H_), 2.29 (3 H, s, NCH_3), 2.78-2.84 (2 H, m, SCH_2), 2.90 (1 H, dd, _J_ 7.2, 5.5, NC_H_), 3.34 (2 H, m, NCH_2), 6.97 (1 H, ddd, _J_ 7.6, 4.8, 0.9, Ar), 7.16 (1 H, br d, _J_ 7.8, Ar), 7.18 (1 H, br s, N_H_), 7.46 (1 H, ddd, _J_ 7.8, 7.6, 1.8, Ar), 8.40 (1 H, br d, _J_ 4.8, Ar); δ_C (150 MHz, $CDCl_3$) 14.5, 20.9, 28.6, 28.9, 29.5, 37.8, 50.5, 54.0, 68.6, 119.5, 122.4, 136.0, 149.6, 158.8, 172.7; LRMS (CI) 324, 223, 221, 213, 84; HRMS calcd for $C_{17}H_{30}N_3OS$ $[MH]^+$ 324.2110, found 324.2111.

_N_-(_tert_-Butyl)-2-((2-(phenylthio)ethyl)amino)pentanamide (9n)

Colourless oil. 18% yield. ν_{max}/cm^{-1} 3314 (NH), 2960, 2931, 2872 (CH), 1652 (CO), 1584, 1517, 1453 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 0.90 (3 H, t, _J_ 7.4, CH_2CH_3), 1.27-1.42 (2 H, m, alkyl), 1.31 (9 H, s, _t_Bu), 1.44-1.52 (1 H, m, alkyl), 1.61-1.68 (1 H, m, alkyl), 1.77 (1 H, br s, N_H_tBu), 2.73 (1 H, ddd, _J_ 12.4, 7.0, 5.6, NC_H_H), 2.81 (1 H, ddd, _J_ 12.4, 6.6, 5.4, NCH_H_), 2.88 (1 H, dd, _J_ 7.8, 4.8, NC_H_), 2.99 (1 H, ddd, _J_ 13.1, 6.6, 5.6, SC_H_H), 3.05 (1 H, ddd, _J_ 13.1, 7.0, 5.4, SCH_H_), 7.14 (1 H, br s, CHN_H_), 7.19 (1 H, t, _J_ 7.7, Ar), 7.27 (2 H, app. t, _J_ 7.7, Ar), 7.33 (2 H, d, _J_ 7.7, Ar); δ_C (150 MHz; $CDCl_3$; Me_4Si) 14.1, 19.2, 28.8, 34.6, 36.0, 47.2, 50.4, 63.3, 126.5, 129.1, 129.7, 135.7, 173.5; LRMS (CI) 309, 208, 130; HRMS calcd for $C_{17}H_{29}N_2OS$ $[MH]^+$ 309.2001, found 309.2007.

_N_-(_tert_-Butyl)-2-(ethyl(2-(phenylthio)ethyl)amino)octanamide (9o)

White solid. 68% yield. M.p. 52-53°C (ether); ν_{max}/cm^{-1} 3334 (NH), 2961, 2926, 2854 (CH), 1674 (CO), 1585, 1508, 1453 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 0.85 (3 H, t, _J_ 6.9, $CH_2CH_2CH_3$), 0.99 (3 H, t, _J_ 7.1, NCH_2CH_3), 1.21-1.30 (7 H, m, alkyl), 1.32 (9 H, s, _t_Bu), 1.41-1.50 (2 H, m, alkyl), 1.74-1.83 (1 H, m, alkyl), 2.49 (1 H, dq, _J_ 13.2, 7.1, NC_H_HCH$_3$), 2.54 (1 H, dq, _J_ 13.2, 7.1, NCH_H_CH$_3$), 2.78 (1 H, dt, _J_ 13.5, 7.0, NC_H_H), 2.81 (1 H, dt, _J_ 13.5, 6.8, NCH_H_), 2.97-3.05 (3 H, m, NC_H_, SCH_2), 7.16 (1 H, tt, _J_ 6.9, 1.4, Ar), 7.24-7.28 (2 H, m, Ar), 7.29-7.32 (2 H, m, Ar), 7.36 (1 H, br s, N_H_); δ_C (150 MHz; $CDCl_3$; Me_4Si) 13.6, 14.2, 22.8, 26.6, 28.5, 28.9, 29.7, 31.8, 33.2, 44.4, 49.6, 50.5, 65.3, 126.2, 129.1, 129.2, 136.4, 173.3; LRMS (CI) 379, 243, 159, 143; HRMS calcd for $C_{22}H_{39}N_2OS$ $[MH]^+$ 379.2783, found 379.2779.

2-(Benzyl(2-(phenylthio)ethyl)amino)-_N_-(_tert_-butyl)octanamide (9p)

Colourless oil. 55% yield. ν_{max}/cm^{-1} 3338 (NH), 2957, 2926, 2856 (CH), 1671 (CO), 1584, 1508, 1453 (Ar); δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.92 (3 H, t, _J_ 6.8, CH_2CH_3), 1.26-1.36 (7 H, m, alkyl), 1.37 (9 H, s, _t_Bu), 1.47-1.64 (2 H, m, alkyl), 1.82-1.94 (1 H, m, alkyl), 2.83-3.11 (5 H, m, NCH_2, SCH_2, NC_H_), 3.63 (1 H, d, _J_ 13.8, ArC_H_H), 3.80 (1 H, d, _J_ 13.8, ArCH_H_), 6.85 (1 H, br s, N_H_), 7.14-7.19 (1 H, m, Ar), 7.22-7.37 (9 H, m, Ar); δ_C (150 MHz; $CDCl_3$; Me_4Si) 14.3, 22.8, 25.9, 28.6, 28.9, 29.8, 31.9, 32.7, 49.3, 50.7, 55.3, 64.4, 126.1, 127.5, 128.6, 128.9, 129.0, 129.1, 136.4, 139.1, 172.7; LRMS (CI) 441, 363, 171; HRMS calcd for $C_{27}H_{41}N_2OS$ $[MH]^+$ 441.2940, found 441.2940.

2-(Butyl(3-(phenylthio)propyl)amino)-_N_-cyclohexyloctanamide (9q)

Colourless oil. 84% yield. ν_{max}/cm^{-1} 3376 (NH), 2926, 2854 (CH), 1623 (CO), 1583, 1449, 1439 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 0.78 (3 H, t, _J_ 7.3, CH_3), 0.87 (3 H, t, _J_ 7.1, CH_3), 0.87-1.66 (21 H, m, alkyl), 1.71-1.81 (4 H, m, alkyl), 1.81-1.89 (1 H, m, alkyl), 2.30 (1 H, ddd, _J_ 12.9, 11.0, 5.2, NC_H_HPr), 2.47 (1 H, ddd, _J_ 12.9, 11.0, 5.2, NCH_H_Pr), 2.49-2.54 (1 H, m, NC_H_HCH$_2$CH$_2$S), 2.95 (1 H, ddd, _J_ 12.9, 9.1, 3.5, NCH_H_CH$_2$CH$_2$S), 3.39 (1 H, dd, _J_ 9.5, 4.3, NC_H_CO), 3.64-3.73 (2 H, m, SCH_2), 3.79-3.86 (1 H, m, NHC_H_), 5.00 (1 H, br s, N_H_), 7.28-7.36 (3 H, m, Ar), 7.41-7.47 (2 H, m, Ar); δ_C (150 MHz; $CDCl_3$; Me_4Si) 14.1, 14.2, 20.8, 22.7, 24.5, 25.9, 26.4, 26.5, 28.4, 29.5, 30.2, 31.8, 33.2, 49.9, 50.9, 61.7, 61.9, 64.5, 128.5, 129.3, 132.0, 134.9, 156.7; LRMS (ES) 447, 393, 282; HRMS calcd for $C_{27}H_{47}N_2OS$ $[MH]^+$ 447.3409, found 447.3405.

2-(Butyl(3-(phenylthio)propyl)amino)-_N_-pentyl-4-phenylbutanamide (9r)

Colourless oil. 63% yield. ν_{max}/cm^{-1} 3365 (NH), 2955, 2928, 2858 (CH), 1622 (CO), 1583, 1496, 1455 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 0.78 (3 H, t, _J_ 7.5, CH_3), 0.80-0.91 (2 H, m, alkyl), 0.95 (3 H, t, _J_ 7.1, CH_3), 1.03-1.16 (2 H, m, alkyl), 1.37-1.49 (5 H, m, alkyl), 1.55-1.63 (1 H, m, alkyl), 1.72-1.81 (3 H, m, alkyl, NCHC_H_H), 2.17-2.25 (1 H, m, NCHCH_H_), 2.30 (1 H, ddd, _J_ 12.8, 10.8, 5.3, NC_H_HPr), 2.41 (1 H, ddd, _J_ 13.8, 10.1, 6.9, NHC_H_H), 2.46 (1 H, ddd, _J_ 12.8, 10.8, 5.3, NCH_H_Pr), 2.61 (1 H, ddd, _J_ 13.8, 10.1, 4.9, NHCH_H_), 2.52 (1 H, ddd, _J_ 12.8, 5.4, 4.2, NCH_H_CH$_2$CH$_2$S), 2.95 (1 H, ddd, _J_ 12.8, 9.0, 4.9, NC_H_HCH$_2$CH$_2$S), 3.53 (1 H, dd, _J_ 9.3, 4.4, NC_H_CO), 3.57 (1 H, app. quin, _J_ 7.0, C_H_HAr), 3.65 (1 H, app. quin, _J_ 7.0, CH_H_Ar), 3.64-3.69 (1 H, m, SC_H_H), 3.70-3.75 (1 H, m, SCH_H_), 4.64 (1 H, br s, N_H_), 7.15 (2 H, d, _J_ 7.0, Ar), 7.19 (1 H, t, _J_ 7.5, Ar), 7.26-7.33 (5 H, m, Ar), 7.37-7.40 (2 H, m, Ar); δ_C (150 MHz; $CDCl_3$; Me_4Si) 14.1, 14.3, 20.7, 22.6, 28.0, 28.7, 30.0, 30.0, 30.4, 32.9,

49.6, 50.9, 53.6, 61.5, 64.1, 126.0, 128.5, 128.6, 128.7, 129.4, 131.5, 134.9, 142.2, 159.6; LRMS (CI) 455, 248, 195; HRMS calcd for $C_{28}H_{43}N_2OS$ $[MH]^+$ 455.3096, found 455.3103.

General Procedure for 3-Component Reactions of Amino Alcohols, Isocyanides and Acid-Aldehydes

A solution of acid-aldehyde (1.00 mmol), amino alcohol (1.00 mmol) and isocyanide (1.00 mmol) in methanol (1 ml) was stirred under microwave irradiation[13] at 60 °C for 20 min. The solvent was removed *in vacuo* and the residue purified by column chromatography (Petroleum ether/EtOAc 9:1) to afford the *amide*.

***N*-*tert*-Butyl-4-methyl-8-oxo-2,3,5-trihydrobenzo[*f*][1,4]oxazocine-5-carboxamide (10a)**

White solid. 82% yield. M.p. 123-125 ˚C (hexanes); ν_{max}/cm^{-1} 3332 (NH), 2968 (CH), 1704 (CO ester), 1665 (CO amide), 1602, 1515, 1454 (Ar); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.29 (9 H, s, *t*Bu), 2.43 (3 H, s, NCH_3), 2.95-3.00 (1 H, m, NC*H*H), 3.05-3.09 (1 H, m, NCH*H*), 3.83-3.87 (1 H, m, OC*H*H), 4.07-4.11 (1 H, m, OCH*H*), 4.21 (1 H, s, NC*H*), 6.79 (1 H, br s, N*H*), 7.14 (1 H, d, *J* 7.0, Ar), 7.33-7.36 (3 H, m, Ar); δ_C (150 MHz; $CDCl_3$; Me_4Si) 28.5, 42.2, 51.2, 55.7, 64.8, 71.5, 128.3, 128.5, 128.6, 130.2, 130.8, 134.8, 168.7, 173.3; LRMS (CI) 291, 206, 190; HRMS calcd for $C_{16}H_{23}N_2O_3$ $[MH]^+$ 291.1709, found 291.1713.

4-(3-Bromobenzyl)-*N*-(*tert*-butyl)-8-oxo-2,3,5-trihydrobenzo[*f*][1,4]oxazocine-5-carboxamide (10b)

Pale yellow solid. 49% yield. M.p. 135-136 °C (hexanes); ν_{max}/cm^{-1} 3344 (NH), 2966 (CH), 1706, 1674 (CO), 1538 (Ar); δ_H (600 MHz, $CDCl_3$, Me_4Si) 1.30 (9 H, s, *t*Bu), 2.80 (1 H, ddd, *J* 14.2, 6.9 and 4.4, OCH_2CH*H*), 3.15 (1 H, ddd, *J* 14.2, 6.0 and 4.5, OCH_2CH*H*), 3.64 (1 H, br d, *J* 14.4, ArCH*H*), 3.72 (1 H, d, *J* 14.4, ArCH*H*), 3.84 (1 H, ddd, *J* 12.7, 6.0 and 4.5, OCH*H*), 4.07 (1 H, ddd, *J* 12.7, 6.9 and 4.4, OCH*H*), 4.40 (1 H, s, COCH), 6.57 (1 H, br s, NH), 7.20-7.21 (1 H, m, Ar), 7.22 (1 H, t, *J* 7.7, Ar), 7.27 (1 H, ddd, *J* 7.7, 1.6 and 1.3, Ar), 7.35-7.36 (3 H, m, Ar), 7.39 (1 H, ddd, *J* 7.8, 2.0 and 1.2, Ar), 7.44 (1 H, t, *J* 1.9, Ar); δ_C (150 MHz, $CDCl_3$) 28.7, 51.1, 51.7, 58.2, 65.0, 71.1 (br), 122.9, 127.0, 128.2, 128.67, 128.74, 130.4, 130.7, 130.8, 130.9, 131.5, 135.5, 140.1, 168.9, 173.8 (br); LRMS (CI) 447, 445, 348, 346, 259, 84; HRMS calcd for $C_{22}H_{26}O_3N_2Br$ $[MH]^+$ 445.1127, found 445.1116.

4-(4-Chlorobenzyl)-*N*-cyclohexyl-8-oxo-2,3,5-trihydrobenzo[*f*][1,4]oxazocine-5-carboxamide (10c)

Pale yellow solid. 57% yield. M.p. 117-119 °C (hexanes); ν_{max}/cm^{-1} 3307 (NH), 2929 (CH), 1703, 1665 (CO), 1540 (Ar); δ_H (600 MHz, $CDCl_3$, Me_4Si) 1.06-1.18 (3 H, m, Cy), 1.26-1.35 (2 H, m, Cy), 1.55-1.57 (1 H, br m, Cy), 1.63-1.66 (2 H, m, Cy), 1.73 (1 H, m, Cy), 1.83 (1 H, m, Cy), 2.75 (1 H, ddd, *J* 13.9, 10.3 and 5.6, OCH_2CH*H*), 3.13 (1 H, ddd, *J* 13.9, 7.2 and 5.6, OCH_2CH*H*), 3.68-3.81 (3 H, m, ArCH_2 and NHC*H*), 3.85 (1 H, ddd, *J* 12.4, 7.2 and 5.6 OCH*H*), 4.08 (1 H, ddd, *J* 12.4, 10.3 and 5.6, OCH*H*), 4.45 (1 H, s, COCH), 6.28 (1 H, br d, *J* 7.2, NH), 7.28-7.30 (3 H, m, Ar), 7.35 (2 H, d, *J* 8.5, Ar), 7.40-7.43 (3 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 24.7, 25.5, 32.8, 48.5, 51.6, 58.6, 65.1, 71.5, 128.0, 128.8, 128.9, 129.2, 129.9, 130.4, 130.6, 133.6, 135.5, 135.9, 168.8, 174.1; LRMS (EI) 428, 426, 302, 300, 215; HRMS calcd for $C_{24}H_{27}O_3N_2Cl$ $[M]^+$ 426.1705, found 426.1703.

***N*-(*tert*-Butyl)-5-(4-chlorobenzyl)-9-oxo-2,3,4,6-tetrahydrobenzo[*g*][1,5]oxazonine-6-carboxamide (10d)**

Pale yellow foam. 62% yield. ν_{max}/cm^{-1} 3335 (NH), 2970 (CH), 1723, 1660 (CO), 1565 (Ar); δ_H (600 MHz, $CDCl_3$, Me_4Si) 1.42 (9 H, s, *t*Bu), 1.47-1.54 (1 H, m, OCH_2CH*H*) 1.74-1.84 (1 H, m, OCH_2CH*H*), 2.85 (1 H, ddd, *J* 14.2, 6.2 and 3.3, OCH_2CH_2CH*H*), 3.00 (1 H, ddd, *J* 14.2, 9.1 and 3.4, OCH_2CH_2CH*H*), 3.66 (1 H, d, *J* 13.8, ArCH*H*), 3.85 (1 H, d, *J* 13.8, ArCH*H*), 4.26 (1 H, ddd, *J* 14.8, 6.1 and 3.4, OCH*H*), 4.47 (1 H, ddd, *J* 14.8, 8.4 and 2.4, OCH*H*), 4.79 (1 H, s, COCH), 6.05 (1 H, br s, NH), 7.23 (2 H, d, *J* 8.4, Ar), 7.27 (2 H, d, *J* 8.4, Ar), 7.32-7.42 (3 H, m, Ar), 7.55 (1 H, dt, *J* 6.6 and 1.7, Ar); δ_C (150 MHz, $CDCl_3$) 25.6, 28.8, 50.9, 51.8, 55.8, 68.1, 69.4 (br), 127.8, 128.3, 128.4, 128.6, 130.2, 131.1, 133.0, 133.1, 136.8, 139.2, 169.0, 171.6; LRMS (CI) 417, 415, 316, 314, 273, 125; HRMS calcd for $C_{23}H_{28}O_3N_2Cl$ $[MH]^+$ 415.1789, found 415.1792.

5-(4-Chlorobenzyl)-9-oxo-*N*-pentyl-2,3,4,6-tetrahydrobenzo[*g*][1,5]oxazonine-6-carboxamide (10e)

Colorless oil. 70% yield. ν_{max}/cm^{-1} 3325 (NH), 2858 (CH), 1710, 1651 (CO), 1491 (Ar); δ_H (600 MHz, $CDCl_3$, Me_4Si) 0.92 (3 H, t, *J* 7.1, CH_3), 1.29-1.39 (4 H, pentyl), 1.48-1.55 (3 H, m, pentyl, OCH_2CH*H*), 1.72-1.78 (1 H, m, OCH_2CH*H*), 2.83 (1 H, ddd, *J* 14.1, 6.5, 3.3, NCH*H*CH_2), 2.99 (1 H, ddd, *J* 14.1, 8.6, 3.5, NCH*H*CH_2), 3.26-3.38 (2 H, m, NHCH_2), 3.64 (1 H, d, *J* 13.8, ArCH*H*), 3.85 (1 H, d, *J* 13.8, ArCH*H*), 4.26 (1 H, ddd, *J* 11.2, 6.4, 3.3, OCH*H*), 4.48 (1 H, ddd, *J* 11.2, 8.4, 2.9, OCH*H*), 4.91 (1 H, s, NC*H*CO), 6.26 (1 H, br s, N*H*), 7.21 (2 H, d, *J* 8.5, Ar), 7.26 (2 H, d, *J* 8.5, Ar), 7.35-7.40 (3 H, m, Ar), 7.54-7.56 (1 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 13.8, 22.2, 25.6, 29.0, 29.1, 39.5, 51.1, 56.0, 68.0, 69.3 (br), 127.9, 128.3, 128.50 (br), 128.51 (br), 128.6, 130.3, 131.1, 133.1, 136.8, 139.1, 169.4, 171.7; LRMS (ES) 429, 427, 378, 302, 230; HRMS calcd for $C_{24}H_{28}N_2O_3Cl$ $[M-H]^-$ 427.1788, found 427.1778.

***N*-(*tert*-Butyl)-5-butyl-9-oxo-2,3,4,6-tetrahydrobenzo[*g*][1,5]oxazonine-6-carboxamide (10f)**

White solid. 61% yield. M.p. 152-154˚C (hexanes); ν_{max}/cm^{-1} 3297 (NH), 2963, 2867 (CH), 1724 (CO ester), 1650 (CO amide), 1548, 1453 (Ar); δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.86 (3 H, t, *J* 7.3, CH_2CH_3), 1.17-1.28 (2 H, m, alkyl), 1.38-1.49 (2 H, m, alkyl), 1.40 (9 H, s, *t*Bu), 1.74-1.91 (2 H, m, OCH_2CH_2), 2.52-2.67 (2 H, m, NCH_2Pr), 2.80-2.92 (1 H, m, NC*H*H), 3.03-3.14 (1 H, m, NCH*H*), 4.21-4.30 (1 H, m, OC*H*H), 4.49-4.60 (1 H, m, OC*H*H), 4.70 (1 H, s, NC*H*CO), 6.31 (1 H, br s, N*H*), 7.31-7.43 (3 H, m, Ar), 7.47 (1 H, br d, *J* 7.1, Ar); δ_C (100 MHz; $CDCl_3$; Me_4Si) 13.7, 20.5, 25.3, 26.0, 28.7, 50.8, 51.2, 51.5, 67.7, 70.4, 127.6, 127.9, 128.5, 130.0, 133.3, 139.5, 169.3, 171.3; HRMS calcd for $C_{20}H_{30}N_2O_3$ $[MNa]^+$ 369.2154, found 369.2146.

***N*-(*tert*-Butyl)-7-(2-chlorobenzyl)-3-oxo-2,3,5,6,7,8-hexahydrobenzo[*i*][1,4,7]dioxazecine-8-carboxamide (10g)**

White solid. 14% yield. M.p. 138-140 °C (hexanes); ν_{max}/cm^{-1} 3378 (NH), 2965 (CH), 1741, 1673 (CO), 1489 (Ar); δ_H (600 MHz, $CDCl_3$, Me_4Si) 1.32 (9 H, s, *t*Bu), 2.54-2.60 (1 H, m, OCH_2CH*H*), 2.75 (1 H, ddd, *J* 15.0, 11.6 and 3.1, OCH_2CH*H*), 3.85 (1 H, d, *J* 13.9, NCH*H*Ar), 3.98 (1 H, d, *J* 13.9, NCH*H*Ar),

4.16 (1 H, ddd, *J* 11.6, 3.6 and 2.0, CO_2CHH), 4.30-4.33 (1 H, m, CO_2CHH), 4.54 (1 H, d, *J* 13.4, ArOCH*H*), 4.73 (1 H, d, *J* 13.4, ArOCH*H*), 5.08 (1 H, s, ArC*H*), 6.56 (1 H, s, NH), 7.11 (1 H, ddd, *J* 7.9, 7.3 and 1.1, Ar), 7.17 (1 H, dd, *J* 8.3 and 1.1, Ar), 7.31 (1 H, ddd, *J* 8.3, 7.3 and 1.7, Ar), 7.34 (2 H, d, *J* 8.5, Ar), 7.37 (2 H, d, *J* 8.5, Ar), 7.42 (1 H, d, *J* 7.9, Ar); δ_C (150 MHz, $CDCl_3$) 28.8, 45.7, 51.1, 53.9, 60.8, 65.5, 72.9, 121.4, 124.8, 128.9, 129.0, 129.8, 129.9, 130.7, 133.3, 136.6, 157.0, 168.5, 171.3; LRMS (ES) 433, 431, 330, 224, 208; HRMS calcd for $C_{23}H_{28}O_4N_2Cl$ $[MH]^+$ 431.1738, found 431.1730.

7-(3-Bromobenzyl)-*N*-(*tert*-butyl)-3-oxo-2,3,5,6,7,8-hexahydrobenzo[*i*][1,4,7]dioxazecine-8-carboxamide (10h)

White solid. 22% yield. M.p. 135-136 °C (hexanes); ν_{max}/cm^{-1} 3373 (NH), 2965 (CH), 1742, 1675 (CO), 1506, 1453 (Ar); δ_H (600 MHz, $CDCl_3$, Me_4Si) 1.33 (9 H, s, *t*Bu), 2.56-2.59 (1 H, m, OCH_2CHH), 2.78 (1 H, ddd, *J* 15.4, 11.8 and 3.2, OCH_2CHH), 3.84 (1 H, d, *J* 14.0, NCH*H*Ar), 3.98 (1 H, d, *J* 14.0, NCH*H*Ar), 4.17 (1 H, ddd, *J* 11.8, 4.0 and 1.9, CO_2CHH), 4.32-4.37 (1 H, m, CO_2CHH), 4.55 (1 H, d, *J* 13.4, ArOCH*H*), 4.73 (1 H, d, *J* 13.4, ArOCH*H*), 5.06 (1 H, s, ArC*H*), 6.58 (1 H, s, NH), 7.12 (1 H, ddd, *J* 8.3, 7.5 and 0.9, Ar), 7.17 (1 H, dd, *J* 8.2 and 0.9, Ar), 7.23-7.26 (1 H, m, Ar), 7.31 (1 H, ddd, *J* 8.2, 7.5 and 1.7, Ar), 7.37 (1 H, d, *J* 7.7, Ar), 7.41 (2 H, m, Ar), 7.59 (1 H, s, Ar); δ_C (150 MHz, $CDCl_3$) 28.8, 45.9, 51.3, 54.1 60.8, 65.5, 73.1, 121.4, 123.0, 124.8, 127.2, 128.9, 130.0, 130.4, 130.6, 130.8, 131.5, 140.5, 157.1, 168.5, 171.3; LRMS (EI) 476, 474, 377, 375, 218, 162; HRMS calcd for $C_{23}H_{27}O_4N_2Br$ $[M]^+$ 474.1149, found 474.1149.

***N*-Cyclohexyl-1,4-diethyl-8-oxo-2,3,5-trihydrobenzo[*f*][1,4]diazocine-5-carboxamide (10i)**

Colourless oil. 69% yield. ν_{max}/cm^{-1} 3326 (NH), 2859 (CH), 1645 (CO), 1490 (Ar); δ_H (600 MHz, $CDCl_3$, Me_4Si) 0.91-0.95 (1 H, m, Cy), 0.96 (6 H, app. t, *J* 7.1, CH_3), 1.03-1.32 (4 H, m, Cy), 1.57-1.72 (4 H, m, Cy), 1.93-1.95 (1 H, m, Cy), 2.47-2.60 (4 H, m, NCH_2CH_3), 2.70 (1 H, app. dt, *J* 13.5, 6.3, CONCH*H*CH_2), 2.81 (1 H, app. dt, *J* 13.5, 6.2, CONCH*H*CH_2), 3.29 (1 H, app. dt, *J* 14.1, 6.3, CHNCH*H*CH_2), 3.70 (1 H, tdt, *J* 11.2, 7.9, 3.9, NHC*H*), 3.94 (1 H, app. dt, *J* 14.1, 6.4, CHNCH*H*CH_2), 5.26 (1 H, s, NC*H*CO), 6.56 (1 H, d, *J* 7.9, N*H*), 7.43 (1 H, dd, *J* 7.6, 7.4, Ar), 7.54 (1 H, ddd, *J* 7.6, 7.5, 1.1, Ar), 7.68-7.71 (2 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 11.7, 25.0, 25.1, 25.5, 32.6, 33.1, 41.2, 47.6, 48.9, 50.6, 65.9, 123.0, 123.6, 128.9, 131.0, 132.3, 141.8, 167.3, 170.3; LRMS (CI) 358, 263, 247, 231; HRMS calcd for $C_{21}H_{32}N_3O_2$ $[MH]^+$ 358.2495, found 358.2488.

***N*-(*tert*-Butyl)-2-((*S*)-2-((phenylthio)methyl)pyrrolidin-1-yl)octanamide (11a)**

Colourless oil. 68% yield. α_D^{25} −44.0 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3336 (NH), 2957, 2926, 2858 (CH), 1656 (CO), 1584, 1514, 1453 (Ar); δ_H (600 MHz; $CDCl_3$; Me_4Si) 0.86 (3 H, t, *J* 7.1, CH_2CH_3), 1.19-1.31 (8 H, m, alkyl), 1.29 (9 H, s, *t*Bu), 1.50-1.57 (1 H, m, alkyl), 1.58-1.65 (1 H, m, alkyl), 1.67-1.81 (3 H, m, NCH_2CHHCH_2), 1.89-1.99 (1 H, m, NCH_2CHH), 2.74 (1 H, dt, *J* 9.0, 7.5, NC*H*H), 2.82 (1 H, dd, *J* 12.5, 8.2, SC*H*H), 2.95 (1 H, dd, *J* 8.4, 6.1, NC*H*CO), 2.96-3.00 (1 H, m, $NCHCH_2$), 3.04 (1 H, dd, *J* 12.5, 3.6, SCH*H*), 3.14 (1 H, ddd, *J* 11.8, 8.2, 3.6, SCH_2CH), 6.25 (1 H, br s, N*H*), 7.15 (1 H, t, *J* 7.6, Ar), 7.26 (2 H, app. t, *J* 7.6, Ar), 7.32 (2 H, d, *J* 7.6, Ar); δ_C (150 MHz; $CDCl_3$; Me_4Si) 14.2, 22.7, 23.4, 26.7, 28.9, 29.5, 31.1, 31.5, 31.8, 39.9, 50.7, 52.1, 58.4, 67.2, 126.0, 129.0, 129.2, 136.8, 172.8; LRMS (CI) 391, 290, 267, 137; HRMS calcd for $C_{23}H_{39}N_2OS$ $[MH]^+$ 391.2783, found 391.2790.

***N*-(*tert*-Butyl)-2-((*S*)-2-((phenylthio)methyl)pyrrolidin-1-yl)pentanamide (11b)**

Colourless oil. 70% yield. α_D^{25} −51.3 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3334 (NH), 2934 (CH), 1663 (CO), 1514 (Ar); δ_H (600 MHz, $CDCl_3$, Me_4Si) 0.87 (3H, t, *J* 7.4, CH_2CH_3), 1.28-1.36 (11H, m, *t*Bu, CH_3CH_2), 1.50-1.55 (1H, m, NCHCH*H*), 1.58-1.63 (1H, m, NHCHCH*H*), 1.70-1.80 (3H, m, NCH_2CH_2, NCH_2CH_2CHH), 1.93-1.97 (1H, m, NCH_2CH_2CHH), 2.74 (1H, app. q, *J* 8.2, NCH*H*), 2.82 (1H, dd, *J* 12.6, 8.3, SCH*H*), 2.96-3.00 (2H, m, NC*H*CO, NCH*H*), 3.04 (1H, dd, *J* 12.6, 3.7, SCH*H*), 3.13-3.17 (1H, m, $NCHCH_2$), 6.26 (1H, br s, N*H*), 7.16 (1H, t, *J* 7.6, Ar), 7.26 (2H, dd, *J* 7.8, 7.6, Ar), 7.33 (2H, d, *J* 7.8, Ar); δ_C (150 MHz, $CDCl_3$) 14.3, 20.0, 23.5, 28.9, 31.1, 33.7, 39.9, 50.8, 52.1, 58.4, 67.0, 126.1, 129.0, 129.2, 136.8, 172.8; LRMS (ES) 349, 248, 239, 180; HRMS calcd for $C_{20}H_{33}N_2OS$ $[MH]^+$ 349.2314, found 349.2319.

***N*-(Cyclohexyl)-2-((*S*)-2-((phenylthio)methyl)pyrrolidin-1-yl)pentanamide (11c)**

Colourless oil. 60% yield. α_D^{25} −30.7 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3306 (NH), 2931 (CH), 1643 (CO), 1520, 1439 (Ar); δ_H (600 MHz, $CDCl_3$, Me_4Si) 0.85 (3H, t, *J* 7.4, CH_2CH_3), 1.01-1.14 (3H, m, Cy), 1.29-1.34 (4H, m, CH_3CH_2, Cy), 1.51-1.79 (10H, m, $NCHCH_2$, NCH_2CH_2, SCH_2CHCHH, Cy), 1.89-1.96 (1H, m, SCH_2CHCHH), 2.74 (1H, app. q, *J* 8.1, NCH*H*), 2.81 (1H, dd, *J* 12.7, 8.3, SCH*H*), 2.95-2.99 (1H, m, NCH*H*), 3.02-3.07 (2H, m, SCH*H*, NC*H*CO), 3.10-3.14 (1H, m, SCH_2CH), 3.67-3.74 (1H, m, NHC*H*), 6.24 (1H, br d, *J* 7.2, N*H*), 7.15 (1H, tt, *J* 7.7, 1.3, Ar), 7.25 (2H, dd, *J* 8.3, 7.7, Ar), 7.32 (2H, dd, *J* 8.3, 1.3, Ar); δ_C (150 MHz, $CDCl_3$) 14.3, 19.9, 22.4, 25.0, 25.6, 31.0, 33.1, 33.4, 39.8, 47.6, 51.9, 58.5, 66.2, 126.1, 129.1, 129.3, 136.8, 172.3; LRMS (ES) 375, 248, 208, 180; HRMS calcd for $C_{22}H_{35}N_2OS$ $[MH]^+$ 375.2470, found 375.2465.

(3*S*,8*S*)-*N*-(*tert*-Butyl)-8-oxo-2,5-dihydrobenzo[*f*]pyrrolo[3,4-*c*][1,4]oxazocine-5-carboxamide and (3*S*,8*R*)-*N*-(*tert*-Butyl)-8-oxo-2,5-dihydrobenzo[*f*]pyrrolo[3,4-*c*][1,4]oxazocine-5-carboxamide (12)

White solid. 78% yield (*S*,*S*:*S*,*R* 1.5:1). *S*,*S*-isomer: M.p. 133-135 °C (hexanes); α_D^{25} −96.1 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3305 (NH), 2968 (CH), 1737, 1662 (CO), 1539, 1455 (Ar); δ_H (600 MHz, $CDCl_3$, Me_4Si) 1.17 (9H, s, *t*Bu), 1.72-1.76 (1H, m, NCH_2CHH), 1.81-1.93 (2H, m, NCH_2CHH, NCHCH*H* pyrrolo), 2.04 (1H, dddd, *J* 16.5, 12.5, 8.0, 4.3, NCHCH*H* pyrrolo), 2.68 (1H, ddd, *J* 15.9, 8.7, 7.2, NCH*H*), 2.78 (1H, ddd, *J* 15.9, 7.8, 4.3, $NCHCH_2$), 3.20 (1H, app. ddd, *J* 9.5, 7.5, 5.3, NCH*H*), 3.72 (1H, dd, *J* 12.3, 4.4, OCH*H*), 3.95 (1H, app. d, *J* 12.3, OCH*H*), 4.13 (1H, s, NC*H*CO), 6.13 (1H, br s, N*H*), 7.26-7.27 (1H, m, Ar), 7.34-7.40 (3H, m, Ar); δ_C (150 MHz, $CDCl_3$) 22.4, 28.3, 31.4, 51.2, 52.9, 62.6, 68.8, 75.4, 127.1, 127.8, 128.8, 130.0, 130.2, 136.4, 169.6, 174.8; *S*,*R*-isomer: M.p. 144-145 °C (hexanes); α_D^{25} +73.4 (*c* 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3305, 2968, 1737, 1662, 1539, 1455; δ_H (600 MHz, $CDCl_3$, Me_4Si) 1.42 (9H, s, *t*Bu), 1.67-1.71 (1H, m,

NCH_2CHH), 1.78-1.82 (2H, m, NCH_2CHH, NCHCH*H* pyrrolo), 1.96-1.99 (1H, m, NCHCH*H* pyrrolo), 3.04-3.06 (2H, m, NCH_2), 3.60 (1H, app. ddd, *J* 9.0, 5.9, 3.6, $NCHCH_2$), 3.75 (1H, dd, *J* 12.1, 3.6, OCH*H*), 3.85 (1H, app. d, *J* 12.1, OCH*H*), 4.23 (1H, s, NC*H*CO), 6.48 (1H, d, *J* 7.3, Ar), 7.12 (1H, ddd, *J* 7.8, 7.6, 1.1, Ar), 7.19 (1H, dd, *J* 7.6, 1.0, Ar), 7.23 (1H, br s, N*H*), 7.26 (1H, dd, *J* 7.8, 7.3, Ar); δ_C (150 MHz, $CDCl_3$) 23.7, 29.0, 30.7, 52.0, 54.4, 55.8, 65.3, 69.3, 126.8, 127.0, 127.8, 130.2, 131.4, 137.3, 168.3, 174.7; LRMS (ES) 316, 217, 84; HRMS calcd for $C_{18}H_{24}N_2O_3$ $[MH]^+$ 317.1865, found 317.1874.

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Notes and references

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13 Microwave reactions were performed using a CEM Explorer microwave with an external IR temperature sensor (150 W power).

