Synthesis of spiro-fused polycyclic β-lactam derivatives

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Abstract

Several spiro-fused polycyclic β-lactam derivatives were synthesized in moderate to good yields by Staudinger reaction of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines and dibenzo[*b*,*f*][1,4]oxazepines with cyclohexanecarboxylic chloride in the presence of triethylamine in anhydrous benzene. 1,5-Benzothiazepines gave rise to *trans*-diaryl-substituted fused spiro[1,2-*d*]benzo[*b*][1,4]thiazepine-2,1'-cyclohexane]-1(2a*H*)-ones. In most cases, the corresponding amides were obtained resulting from the hydrolysis of zwitterionic intermediates generated from cyclic imines and cyclohexanecarboxylic chloride; the mechanism of their formation is proposed.

Keywords: 1,5-Benzothiazepine, cycloaddition, cyclohexanecarboxylic chloride, dibenzo[*b*,*f*][1,4]oxazepine, β-lactam, Staudinger reaction

Introduction

β-Lactam-fused five- and six-membered heterocycles are important antibiotics.[1–6] For instance, the antibiotics penicillin, penam and penem have fused thiazolidine- β-lactam structures, and the antibiotics cephalosporin and cephem are fused dihydrothiazine- β-lactams.[1–6] The synthesis of bicyclic β-lactams has been a desirable goal since the discovery of penicillin and cephalosporin. Numerous heterocycle-fused β-lactam derivatives have been synthesized and assayed for biological activities.[1,4,5] Recently, spiro- β-lactams became particularly interesting compounds because their antiviral[7] and antibacterial properties[8] as well as their inhibition of cholesterol absorption[9] make them potentially useful candidates for drug development. They can also be used as β-turn mimetics in peptide chemistry[10–12] and, particularly 4-spiro-β-lactams, are synthetic precursors for cyclic α,α-disubstituted β-amino acids and peptide derivatives.[13,14] Thus, the synthesis of spiro- β-lactam derivatives has recently received much attention. Several synthetic methods for spiro- β-lactams have been developed.[7–11,13–9] Among these, the cyclic ketene-participating Staudinger reaction is one of important strategies.[10,20,21]

In recent years, our group investigated the synthesis and stereochemistry of β-lactam

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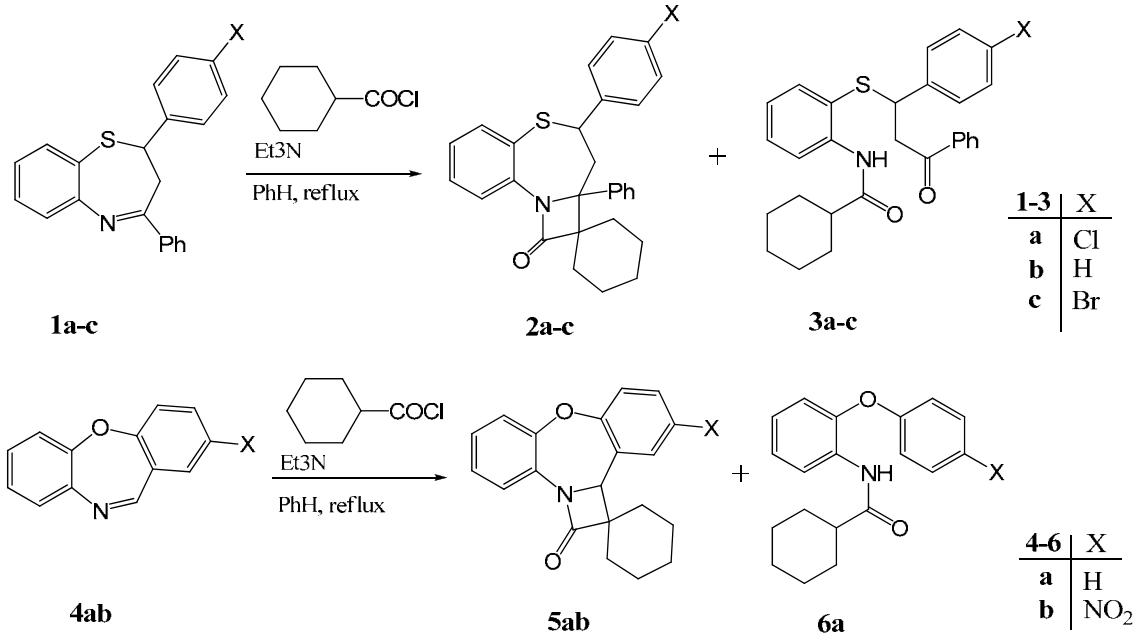
derivatives of benzothiazepines, benzodiazepines, and dibenzo[*b*,*f*]oxazepines because of their potential biological and pharmaceutical importance.[22–29] Up to now, a few examples of spiro-fused β-lactam derivatives of 1,4-benzodiazepines have been prepared via the Staudinger reaction.[30] In continuation of our efforts to prepare structurally diverse β-lactam derivatives of benzoheteroazepines, we set out to synthesize some novel spiro-fused polycyclic β-lactam derivatives for bioassay of antibacterial activity in response to the growing resistance of bacteria against penicillin and cephalosporin-like compounds and the request for medicines with a more specific antibacterial activity or other biological activities. Herein, we report the synthesis of fused seven-membered heterocycle-β-lactam derivatives from 2,3-dihydro-1,5-benzothiazepines and dibenzo[*b*,*f*]oxazepines with pentamethyleneketene. Cyclic ketenes with electron-rich substituents generated from prolines,[10,11] tetrahydrofuran-2-carboxylic acid,[30,31] 1,3-thiazolidine-2-carboxylic acids,[32,33] 1,3-thiazolidine-4-carboxylic acids,[20,21] and 1,3-oxazolidine-4-carboxylic acids,[20,21] have been widely used in the synthesis of spiro-β-lactam derivatives. In this report a disubstituted cyclic ketene with weak electron-donating substituents is employed in the Staudinger reaction with heterocyclic imines.

Results and Discussion

The reaction of 2-(4-chlorophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine (**1a**) with cyclohexanecarboxylic chloride in the presence of triethylamine was first carried out using commercially available benzene as solvent affording colorless crystals upon recrystallization from ethanol. The spectroscopic analysis indicated that the product was amide **3a**, not the β-lactam derivative **2a** (Entry 1, Table 1). The ^{1}H NMR shows a broad singlet at δ 8.85, and the IR displays two carbonyl absorptions at 1683 and 1700 cm^{-1}. Only a trace of β-lactam **2a** (<5%) was obtained from the mother liquid after chromatography on silica gel. Using sodium-dried benzene as solvent, the reaction also afforded amide **3a** as the major product together with a 16% yield of β-lactam **2a** and some recovered 1,5-benzothiazepine **1a** (Entry 2, Table 1). β-Lactam **2a** and amide **3a** were separated and purified by chromatography. A longer reaction time of 8 h increased the yield of β-lactam **2a** to 27% (Entry 3, Table 1), but with a more extended reaction time no further improvement of the yield was achieved. In the same way, spiro-fused β-lactams **2b,c** and amides **3b,c** together with recovered starting materials were obtained from 1,5-benzothiazepines **1b,c** (Entries 4 and 5, Table 1). In our previous investigation,[23,24,27] the reaction of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines **1** with monosubstituted ketenes, generated from substituted acetyl chlorides in the presence of triethylamine gave β-lactam derivatives in good to excellent yields. The lower yields of β-lactams **2** in the current cases are possibly due to steric hindrance of the disubstituted ketene, pentamethyleneketene,

We also conducted the reaction of the 2-unsubstituted dibenzo[*b*,*f*][1,4]oxazepine (**4a**) with pentamethyleneketene affording spiro-β-lactam derivative **5a** in satisfactory yield (56%) companied by amide **6a** (Entry 6, Table 1). According to our previous results and suggested model,[28,29] imines with electron-deficient substituents favor the formation of β-lactam derivatives with an increased ring closure rate. The reaction of cyclohexanecarboxylic chloride and 4-nitrodibenzo[*b*,*f*][1,4]oxazepine (**4b**) afforded the β-lactam derivative, 11-nitrospiro[azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepine-1,1'-cyclohexane]-2(12b*H*)-one (**5b**) in good

yield (81%) without concomitant formation of an amide derivative (Entry 7, Table 1). The results indicate that the weak electron-donating disubstituted ketene shows poor reactivity in the Staudinger reaction and shows good reactivity only with an imine **4b** possessing an electron-deficient C-substituent (Scheme 1, Table 1).



Scheme 1. Reaction of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines **1** and dibenzo[*b*,*f*][1,4] oxazepines with cyclohexanecarboxylic chloride in the presence of triethylamine.

Table 1. Reaction of 2,3-dihydro-1,5-benzothiazepines **1** and dibenzo[*b*,*f*][1,4]oxazepines **4** with cyclohexanecarboxylic chloride in the presence of triethylamine[a]

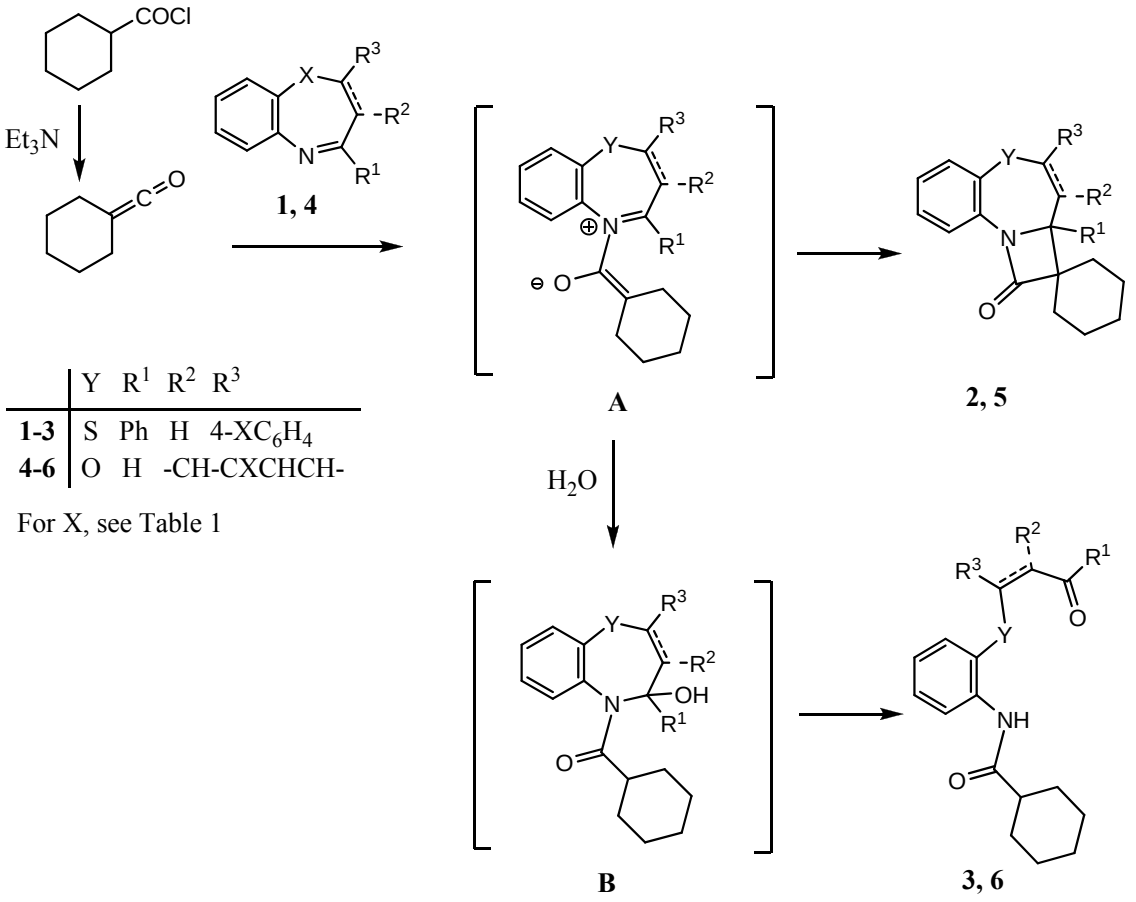
Entry	Imine **1**	X	Reaction time [h][c]	Yield of Lactams **2** or **5** [%][d]	Yield of Amides **3** or **6** [%][d]	Recovery of Imines **1** [%]
1[b]	**1**a	Cl	2+2	<5	25	–[e]
2	**1**a	Cl	2+2	16	32	–[e]
3	**1**a	Cl	2+6	27	18	24
4	**1**b	H	2+6	54	38	5
5	**1**c	Br	2+6	34	16	39
6	**4**a	H	2+6	56	20	–[e]
7	**4**b	NO_2	2+6	81	0	–[e]

[a] Conducted with imines **1** or **4** (1 mmol), Et_3N (2.2 mmol), cyclohexanecarboxylic chloride (1.5 mmol) in anhydrous benzene (10 mL). [b] The reaction was conducted in commercially available benzene. [c] Reaction time: 2 h for the addition of cyclohexanecarboxylic chloride to the reaction solution and 2 or 6 h for extended stirring under reflux. [d] Isolated yield. [e] Not investigated.

For the reaction of dibenzo[*b*,*f*][1,4]oxazepines **4** with cyclohexanecarboxylic chloride, a pair

of enantiomeric β-lactam products **5** was obtained. The reaction of racemic mixtures of 1,5-benzothiazepines **1** with cyclohexanecarboxylic chloride provided only one diastereomer of enantiomeric β-lactams **2** as revealed by ^{1}H and ^{13}C NMR spectral analysis. This indicates that the cycloaddition reaction is stereospecific like in the reactions of 1,5-benzoheteroazepines with substituted acetyl chlorides, as has been discussed previously.[22–25]

The mechanism of the formation of amides **3** and **6** is considered to be similar to that of the reported reaction of oxazolidines with phenoxyacetyl chloride in the presence of triethylamine.[34] Imines **1** and **4** react with pentamethyleneketene to form zwitterionic intermediates **A**, which undergo a conrotatory ring closure to form β-lactam derivatives **2** and **5**, respectively. The zwitterionic intermediates **A** was not completely converted into β-lactams and reacted with water during workup to generate hemiaminal intermediates **B**, which, in turn, underwent ring opening forming the respective amides **3** and **6** (Scheme 2). Formation of β-lactams and amides is competitive in the Staudinger reaction with the weak electron-donating disubstituted ketene. Only imine **4b** with a C-electron-deficient substituent did not produce an amide.



	Y	R^1	R^2	R^3
1-3	S	Ph	H	4-XC_6H_4
4-6	O	H	-CH-CXCHCH-	

For X, see Table 1

Scheme 2. Proposed reaction progress of benzoheteroazepines with cyclohexanecarboxylic chloride in the presence of triethylamine.

In summary, the reactions of cyclic imines, 2,4-disubstituted 2,3-dihydro-1,5-

benzothiazepines **1** and dibenzo[*b*,*f*][1,4]oxazepines **4** with cyclohexanecarboxylic chloride in the presence of triethylamine were investigated and the respective spiro-fused polycyclic β-lactam derivatives **2** and **5** were obtained in satisfactory to good yields. In most cases, the β-lactam derivatives were accompanied by the corresponding amides **3** and **6**, hydrolysis products of zwitterionic intermediates generated from imines and pentamethyleneketene. 1,5-Benzothiazepines **1** produced stereo-specifically *trans*-diaryl-substituted fused spiro[1,2-*d*]benzo[*b*][1,4]thiazepine-2,1'-cyclohexane]-1(2a*H*)-ones. The results also suggest that the ketene with a weak electron-donating substituent shows poor reactivity in this Staudinger reaction.

Experimental Section

Melting points were obtained on a Yanaco-M500 melting point apparatus. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer with TMS as an internal standard in the $CDCl_3$ solution. The IR spectra were taken on a Bruker Vector 22 FT-IR spectrophotometer in KBr. Mass spectra were obtained on a Bruker ESQUIRE~LC^{TM} ESI ion trap mass spectrometer. HRMS was carried out on an Agilent LC/MSD TOF mass spectrometer. TLC separations were performed on silica gel GF-254 plates with petroleum ether (60–90 °C)/ethyl acetate (10:1); the plates were visualized with UV light.

2,4-Diaryl-2,3-dihydro-1,5-benzo–thiazepines **1** and dibenzo[b,*f*][1,4]oxazepines **4** were prepared according to literature methods.[35–37] Cyclohexanecarboxylic chloride was prepared from cyclohexanecarboxylic acid and sulfonyl chloride. Triethylamine was refluxed with sodium hydroxide and distilled prior to use. Benzene was refluxed with sodium and distilled prior to use.

Reaction of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines and dibenzo[b,*f*][1,4] oxazepines, respectively, with cyclohexanecarboxylic chloride in the presence of triethylamine. General Procedures

To a stirred solution of 1,5-benzothiazepine **1** or dibenzo[*b*,*f*][1,4]oxazepine **4**) (1 mmol) and dried triethylamine (222 mg, 2.2 mmol) in anhydrous benzene (10 mL) was added dropwise cyclohexanecarboxylic chloride (220 mg, 1.5 mmol) in anhydrous benzene (5 mL) over a period of 2 h. The mixture was heated under reflux for 2 or 6 h (see Table 1). The crystalline precipitate of triethylamine hydrochloride was filtered off, the benzene solution was washed with water, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on a silica gel column with petroleum ether (60–90 °C)/ethyl acetate (20:1) to afford colorless crystals of β-lactams **2** or **5**, and amides **3** or **6**.

***rel*-(2a*R*,4*S*)-4-(4-Chlorophenyl)-2a-phenyl-3,4-dihydrospiro[azeto[1,2-*d*]benzo[*b*][1,4] thiazepine-2,1'-cyclohexane]-1(2a*H*)-one (2a).** Colorless crystals (124 mg, 27%); mp 218–219 °C; R_f 0.37 (petroleum ether/AcOEt 10:1, silica gel). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85–0.98

(m, 1H in CH_2), 1.10–1.27 (m, 1H in CH_2), 1.32–1.48 (m, 2H, CH_2), 1.60–1.80 (m, 4H, $2CH_2$), 1.84–1.98 (m, 1H in CH_2), 2.36–2.47 (m, 1H in CH_2), 3.11–3.23 (m, 2H, CH_2), 3.84 (dd, *J* = 3.3, 8.4 Hz, 1H, CH), 7.03-7.11 (m, 2H, ArH), 7.17–7.40 (m, 10H, ArH), 7.98–8.01 (m, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.2, 23.8, 25.5, 29.8, 31.6, 45.4, 46.2, 62.4, 71.9, 125.9, 126.4, 126.8, 127.5, 128.2, 128.57, 128.62, 128.7, 129.1, 132.0, 133.6, 138.8, 139.4, 140.0, 172.0. IR (KBr): $\tilde{\nu}$ 1737 (C=O), 1581 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{28}H_{27}ClNOS$ $[M+H]^+$ 460.1496; found: 460.1483.

***rel*-(2a*R*,4*S*)-2a,4-Diphenyl-3,4-dihydrospiro[azeto[1,2-*d*]benzo[*b*][1,4]thiazepine-2,1'-cyclohexane]-1(2a*H*)-one (2b).** Colorless crystals (230 mg, 54%); mp 213–215 °C; R_f 0.22 (petroleum ether/AcOEt 20:1, silica gel). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90–0.99 (m, 1H in CH_2), 1.12–1.18 (m, 1H in CH_2), 1.33–1.47 (m, 2H, CH_2), 1.60–1.75 (m, 4H, $2CH_2$), 1.85–1.93 (m, 1H in CH_2), 2.38–2.47 (m, 1H in CH_2), 3.15–3.27 (m, 2H, CH_2), 3.87 (dd, *J* = 3.3, 8.4 Hz, 1H, CH), 7.03–7.14 (m, 2H, ArH), 7.19–7.38 (m, 11H, ArH), 7.98–8.01 (m, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.2, 23.8, 25.4, 29.8, 31.5, 46.1, 46.2, 62.3, 72.0, 125.8, 126.3, 126.8, 126.9, 127.3, 127.8, 128.0, 128.2, 128.4, 128.5, 128.9, 129.1, 132.0, 138.8, 139.4, 141.5, 172.0. IR (KBr): $\tilde{\nu}$ 1744 (C=O), 1600 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{28}H_{28}NOS$ $[M+H]^+$ 426.1886; found: 426.1900.

***rel*-(2a*R*,4*S*)-4-(4-Bromophenyl)-2a-phenyl-3,4-dihydrospiro[azeto[1,2-*d*]benzo[*b*][1,4] thiazepine-2,1'-cyclohexane]-1(2a*H*)-one (2c).** Colorless crystals (171 mg, 34%); mp 187–188 °C; R_f 0.35 (petroleum ether/AcOEt 10:1, silica gel). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88–0.98 (m, 1H in CH_2), 1.15–1.22 (m, 1H in CH_2), 1.35–1.43 (m, 2H, CH_2), 1.59–1.80 (m, 4H, $2CH_2$), 1.81–1.99 (m, 1H in CH_2), 2.39–2.43 (m, 1H in CH_2), 3.11–3.22 (m, 2H, CH_2), 3.82 (dd, *J* = 3.3, 8.4 Hz, 1H, CH), 7.02–7.48 (m, 12H, ArH), 7.99 (d, *J* = 8.1 Hz, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.2, 23.9, 25.5, 29.9, 31.6, 45.5, 46.2, 62.4, 72.0, 121.7, 126.0, 126.4, 126.8, 127.5, 128.2, 128.3, 128.61, 128.65, 128.7, 132.05, 132.10, 138.9, 139.4, 140.5, 172.0. IR (KBr): $\tilde{\nu}$ 1740 (C=O), 1581 cm^{-1}. ESI-MS: *m/z* 528 $[M+Na]^+$. HRMS (ESI): *m/z* calcd. for $C_{28}H_{27}BrNOS$ $[M+H]^+$ 504.0991; found: 504.0986.

(±)-*N*-[2-[1-(4-Chlorophenyl)-3-oxo-3-phenylpropylthio]phenyl]cyclohexanecarboxamide (3a). Colorless crystals (86 mg, 18%); mp 151–153 °C; R_f 0.23 (petroleum ether/AcOEt 10:1, silica gel). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.62 (m, 5H, 1H in CH_2 and $2CH_2$), 1.69–2.90 (m, 5H, 1H in CH_2 and $2CH_2$), 2.45–2.54 (m, 1H, CH), 3.46 (dd, *J* = 4.8, 18.2 Hz, 1H in CH_2), 3.74 (dd, *J* = 9.2, 18.2 Hz, 1H in CH_2), 4.51 (dd, *J* = 4.8, 9.2 Hz, 1H, CH), 6.86 (dt, *J* = 0.6, 7.2 Hz, 1H, ArH), 7.07 (d, *J* = 8.4 Hz, 3H, ArH), 7.22 (d, *J* = 8.4 Hz, 2H, ArH), 7.33 (dt, *J* = 1.2, 8.1 Hz, 1H, ArH), 7.50 (t, *J* = 7.8 Hz, 2H, ArH), 7.62 (t, *J* = 7.2 Hz, 1H, ArH), 7.98 (d, *J* = 7.2 Hz, 2H, ArH), 8.53 (d, *J* = 8.1 Hz, 1H, ArH), 8.85 (s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.76, 25.79, 25.9, 29.5, 29.7, 43.4, 46.5, 48.0, 119.6, 120.0, 123.2, 128.0, 128.6, 128.8, 131.0, 133.3, 133.7, 136.3, 137.3, 140.0, 141.1, 175.0, 196.3. IR (KBr): $\tilde{\nu}$ 3333, 1700 (C=O), 1683 (C=O), 1578 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{28}H_{29}ClNO_2S$ $[M+H]^+$ 478.1602; found: 478.1578.

(±)-*N*-[2-(3-Oxo-1,3-diphenylpropylthio)phenyl]cyclohexanecarboxamide (3b). Colorless

crystals (168 mg, 38%); mp 121–122 °C; R_f 0.22 (petroleum ether/AcOEt 20:1, silica gel). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.62 (m, 5H, 1H in CH_2 and $2CH_2$), 1.59–2.07 (m, 5H, 1H in CH_2 and $2CH_2$), 2.39–2.52 (m, 1H, CH), 3.49 (dd, *J* = 5.0, 18.0 Hz, 1H in CH_2), 3.78 (dd, *J* = 9.5, 18.0 Hz, 1H in CH_2), 4.55 (dd, *J* = 5.0, 9.5 Hz, 1H, CH), 6.85 (dt, *J* = 1.2, 7.5 Hz, 1H, ArH), 7.09–7.15 (m, 3H, ArH), 7.34 (m, 4H, ArH), 7.46–7.52 (m, 2H, ArH), 7.58–7.64 (m, 1H, ArH), 7.96–7.99 (m, 2H, ArH), 8.50 (dd, *J* = 1.2, 8.4 Hz, 1H, ArH), 8.80 (s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.7, 25.8, 29.5, 29.6, 43.5, 46.4, 48.8, 119.8, 120.0, 123.0, 127.4, 127.6, 128.0, 128.5, 128.7, 130.7, 133.5, 136.4, 137.3, 141.1, 141.4, 174.9, 196.5. IR (KBr): $\tilde{\nu}$ 3320, 1681 (C=O), 1574 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{28}H_{30}NO_2S$ $[M+H]^+$ 444.1991; found: 444.1974.

(±)-*N*-[2-[1-(4-Bromophenyl)-3-oxo-3-phenylpropylthio]phenyl]cyclohexanecarboxamide (3c). Colorless crystals (83 mg, 16%); mp 146–148 °C; R_f 0.21 (petroleum ether/AcOEt 10:1, silica gel). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.62 (m, 5H, 1H in CH_2 and $2CH_2$), 1.65–2.10 (m, 5H, 1H in CH_2 and $2CH_2$), 2.45–2.58 (m, 1H, CH), 3.46 (dd, *J* = 4.8, 17.9 Hz, 1H in CH_2), 3.74 (dd, *J* = 9.2, 17.9 Hz, 1H in CH_2), 4.50 (dd, *J* = 4.8, 9.2 Hz, 1H, CH), 6.87 (dt, *J* = 1.2, 7.2 Hz, 1H, ArH), 7.01 (d, *J* = 8.4 Hz, 2H, ArH), 7.08 (dd, *J* = 1.5, 7.8 Hz, 1H, ArH), 7.31–7.39 (m, 3H, ArH), 7.48–7.55 (m, 2H, ArH), 7.62 (t, *J* = 7.2 Hz, 1H, ArH), 7.96–7.99 (m, 2H, ArH), 8.53 (d, *J* = 8.4 Hz, 1H, ArH), 8.84 (s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.8, 25.9, 29.5, 29.7, 43.4, 46.5, 48.0, 120.0, 121.4, 123.2, 128.0, 128.8, 129.1,131.0, 131.6, 133.8, 136.3, 137.3, 140.6, 141.1, 175.0, 196.3. IR (KBr): $\tilde{\nu}$ 3332, 1700 (C=O), 1683 (C=O), 1578 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{28}H_{29}BrNO_2S$ $[M+H]^+$ 522.1069; found: 522.1061.

(±)-Spiro(azeto[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepine-1,1'-cyclohexane)-2(12b*H*)-one (5a). Colorless crystals (171 mg, 56%); mp 135–137 °C; R_f 0.53 (petroleum ether/AcOEt 5:1, silica gel). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22–1.38 (m, 1H in CH_2), 1.45–1.54 (m, 2H, CH_2), 1.63–2.02 (m, 6H, $3CH_2$), 2.20–2.35 (m, 1H in CH_2), 4.76 (s, 1H, CH), 7.08–7.30 (m, 7H, ArH), 7.55–7.58 (m, 1H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 23.5, 25.4, 30.0, 33.2, 62.0, 64.7, 121.3, 122.3, 124.2, 125.0, 125.8, 126.4, 127.7, 128.6, 129.1, 129.2, 152.3, 155.2, 171.6. IR (KBr): $\tilde{\nu}$ 1747 (C=O), 1597 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{20}H_{20}NO_2$ $[M+H]^+$ 306.1489; found: 306.1499.

(±)-Spiro(11-nitroazeto[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepine-1,1'-cyclohexane)-2(12b*H*)-one (5b). Yellowish crystals (284 mg, 81%); mp 206–208 °C; R_f 0.50 (petroleum ether/AcOEt 10:1, silica gel). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23–2.10 (m, 9H, 1H in CH_2 and $4CH_2$), 2.30–2.39 (m, 1H in CH_2), 4.78 (s, 1H, CH), 7.19–7.26 (m, 3H, ArH), 7.39 (d, *J* = 9.0 Hz, 1H, ArH), 7.60–7.63 (m, 1H, ArH), 8.04–8.05 (m, 1H, ArH), 8.13–8.17 (m, 1H, ArH). ^{13}C NMR (75.5MHz, $CDCl_3$): δ 22.8, 23.5, 25.3, 30.4, 33.2, 62.8, 64.1, 121.3, 123.4, 124.2, 124.5, 125.7, 127.1, 128.0, 128.3, 143.5, 150.6, 159.3, 170.2. IR (KBr): $\tilde{\nu}$ 1743 (C=O), 1604 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{20}H_{19}N_2O_4$ $[M+H]^+$ 351.1339; found: 351.1331.

***N*-[2-(2-Formylphenoxy)phenyl]cyclohexanecarboxamide (6a).** Colorless crystals (65 mg, 20%); mp 132–134 °C; R_f 0.41 (petroleum ether/AcOEt 10:1, silica gel). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98–1.40 (m, 3H, 1H in CH_2 and CH_2), 1.41–1.58 (m, 2H, CH_2), 1.62–1.96 (m, 5H, 1H in CH_2 & $2CH_2$), 2.19–2.35 (m, 1H, CH), 6.89–6.93 (m, 2H, ArH), 7.05 (dt, *J* = 1.5, 7.5 Hz, 1H, ArH), 7.16–7.28 (m, 2H, ArH), 7.54 (dt, *J* = 1.5, 8.4 Hz, 1H, ArH), 7.85 (s, 1H, NH), 7.94

(dd, J = 1.6, 7.8 Hz, 1H, ArH), 8.45 (d, J = 8.1 Hz, 1H, ArH), 10.48 (s, 1H, CHO). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 25.47, 25.55, 29.5, 46.3, 118.2, 118.5, 121.8, 124.0, 124.1, 125.1, 126.7, 129.5, 130.2, 136.0, 145.0, 158.7, 174.5, 189.0. IR (KBr): $\tilde{\nu}$ 3216, 1686 (C=O), 1652 (C=O), 1599 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{20}H_{22}NO_3$ $[M+H]^+$ 324.1594; found: 324.1589.

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