Novel Syntheses of 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones and 2*H*-1,4-Benzothiazin-3(4*H*)-ones

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Nucleophilic additions of α-mercaptoalkanoate esters and *β*-mercaptoalkanoate acids to benzoquinone diimines, followed by cyclization with trifluoroacetic acid or 1,3-dicyclohexylcarbodiimide (DCC), provide novel, high-yielding syntheses of 2*H*-1,4-benzothiazin-3(4*H*)-ones (**3a**−**f**) and 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (**5a**−**c**), respectively.

Introduction

Over the past 20 years, syntheses of benzothiazepinones and benzothiazinones have been of great interest, due to the broad spectrum of biological activities of these types of compounds.

1,5-Benzothiazepin-4-ones participate as calcium antagonists by interacting with the L-type voltage gated Ca^{2+} channel.[1a,b] Their uses for the treatment of cardiovascular disorders as vasodilators,[2] as hypertension and isochemic cardiopathy agents,[3] as spasmolytic,[4] and angiotensive converting enzyme inhibitors[5] and as squalene synthetase inhibitors[6] have been well documented. Various benzothiazinones have been patented as therapeutic agents having calcium-antagonistic properties[7a,b] and several other biological activities.[8]

The importance and utility of benzothiazepinones and benzothiazinones have led to the development of numerous synthetic routes.[9] For benzothiazepinones, the major approaches are cyclization and ring expansion. Depending on the retrosynthetic disconnection of the basic skeleton, these approaches can be subdivided into different categories; three of the most important are shown as A, B, and C[10] (Scheme 1). In the approach A, nucleophilic attack of substituted 2-aminothiophenols or 2-nitrothiophenols on aliphatic electrophiles, such as *β*-halopropionic acids,[11] α,*β*-unsaturated carboxylic acids,[12] *β*-propionolactones,[13] malonic acids, or arylglycidic esters,[14a,b] afforded the desired products. In the approach B, 2-fluoronitroarenes were treated with a *β*-mercapto acid, followed by nitro group reduction and cyclization.[15] A solid-phase synthesis using approach B has been reported.[10] In the approach C, ring expansion via Beckmann or Schmidt rearrangements of thiochromanone or thioflavone precursors produced the desired 6,7-fused ring systems[16a,b] (Scheme 1).

In the case of benzothiazinones, similar nucleophilic reactions of 2-aminothiophenols have been employed. Benzothiazinones can be prepared (i) by condensation of 2-aminobenzenethiol with *β*-benzoylacrylic acids, maleamic acids,[17] maleanilic/fumaranilic acids or esters,[12] acetylenic nitriles or esters,[18] (ii) by treatment of *N*-unsubstituted and *N*,*N*′-dialkyldithiodianilines with *β*-ketoesters,[19] and (iii) by reaction of 2-aminobenzenethiol with α-haloacetic acids or esters.[20a,b] Ring enlargement of 2-chlo-

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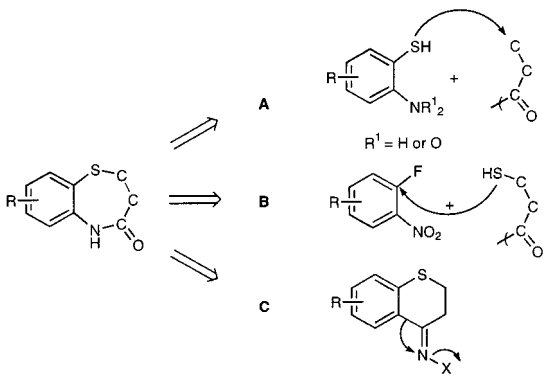
Scheme 1



romethylbenzothiazole[21] and ring contraction of benzothiazepinones[22] have also been reported to produce benzothiazinones (Scheme 2).

During an investigation on the synthesis of 2-alkylthio-1,4-benzoquinone diimines,[23] we determined that the nucleophilic addition of methyl 3-mercaptopropanoate ester to *N*-{4-[(1,3-dimethylbutyl)imino]-2,5-cyclohexadien-1-ylidene}aniline (**1a**) proceeded regioselectively by addition at the C-3 position of the benzoquinoid ring forming methyl 3-(5-anilino-2-[(1,3-dimethylbutyl)amino]-phenylsulfanyl)propanoate (**4a**). The structure of adduct **4a** was established[23] on the basis of NOE and 2D NMR experiments. In the present work, we have investigated the syntheses of benzothiazepinones and benzothiazinones via additions of α- or *β*-mercaptoalkanoate esters and acids to benzoquinone diimines followed by cyclization.

Results and Discussion

Some generalized NMR discussion for compounds (**2**, **3**, **4**, and **6**) is provided in the beginning of the Supporting Information section.

2*H*-1,4-Benzothiazin-3(4*H*)-ones (3a−f). N^1-(Alkyl)-2-(alkylsulfanyl)-N^4-phenyl-1,4-benzenediamines **2a**−**f** were prepared in 87−97% yields by treatment of *N*-4-[(alkyl)imino]-2,5-cyclohexadien-1-ylideneanilines (**1a**−**c**) with the corresponding α-mercaptoalkanoate esters. The ^{1}H NMR spectra of **2a**−**f** displayed a consistent chemical shift pattern containing a doublet (overlapped by a triplet from the anilino group signals) at 7.12−7.21 ppm, a doublet at 6.70−6.72 ppm and a doublet of doublets at 6.47−6.50 ppm for the principal phenyl ring core with a sulfur atom at the *meta* position to the phenylamino group. These three signals could be assigned to the protons attached to the C-3, C-6 and C-4 positions, respectively (see Scheme 3).

2*H*-1,4-Benzothiazin-3(4*H*)-ones **3a**−**f** were prepared in 89−97% yields by intramolecular cycloadditions of compounds **2a**−**f** on treatment with trifluoroacetic acid under reflux overnight (Table 1). The structures **3a**−**f** were supported by CHN analytical data, high-resolution mass spectra, and ^{1}H and ^{13}C NMR spectra. In ^{13}C NMR spectra, the signal of the newly formed quaternary lactam carbonyl in compounds **3a**−**f** is shifted upfield (about 6 ppm) to around 164.0−167.0 ppm.

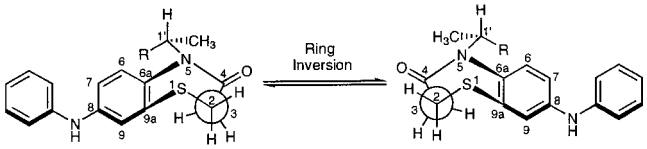


Figure 1. Ring inversion of compound **5**.

2,3-Dihydro-1,5-benzothiazepin-4(*5H*)-ones (5a−c). Alkyl 3-{[5-anilino-2-(alkyl-amino)phenyl]sulfanyl}-propanoates **4a**−**f** were prepared in 86−92% yields by treatment of *N*-4-[(alkyl)imino]-2,5-cyclohexadien-1-yl-ideneanilines (**1a**−**c**) with the corresponding *β*-mercapto-alkanoate esters (Scheme 4, Table 2). The assignment of protons at the C-3, C-6 and C-4 positions in the NMR spectra of compounds **4a**−**f** was comparable with that of compounds **2a**−**f**.

Subsequently, cyclization of compounds**4a**−**f** by heating with trifluoroacetic acid at 70 °C was attempted. Compounds **4a**−**f** failed to provide the desired cyclized **5a**−**f** under these reaction conditions. Refluxing compounds **4d**−**f** in chlorobenzene for 2 days led only to recovery of the starting materials. When Decalin was used as a solvent, decomposition of the starting materials occurred after heating at 190 °C for 3 days. We then approached the synthesis of benzothiazepinones by treating benzoquinone diimines **1a**−**c** with 3-mercaptopropionic acid. It was envisioned that once the addition products, 3-{[5-anilino-2-(alkylamino)phenyl]sulfanyl}-propanoic acids **6a**−**c** were made, cyclization could be achieved upon addition of 1,3-dicyclohexylcarbodiimide (DCC) (Scheme 4, Table 2). Intermediate compounds **6a**−**c** were isolated (but characterized only by ^{1}H NMR) and further used in the final cyclization step to obtain **5a**−**c**.

Treatment of the intermediates **6a**−**c** with DCC, and subsequent purification by flash column chromatography gave the compounds **5a**−**c** in 81−97% yields. Compounds **5a,b** were obtained as mixtures of conformers:[24] their ^{1}H NMR showed sets of two multiplets in a 1:1 ratio at 4.78−4.84 and at 4.68−4.75 ppm for **5a** and at 4.68−4.75 and 4.50−4.57 ppm for **5b**. These signals were assigned to the CH proton adjacent to the alkylamido group (1′−H, Figure 1). After cyclization with DCC, the sets of two triplets assigned to the CH_2 groups in **6a,b** became a set of two broad multiplets at 3.20−3.28 (2-H) and 2.41−2.52 ppm (3-H) in the ^{1}H NMR spectra of **5a,b** (Table 3, Figure 1). This broadening of these signals can be attributed to slow conformational changes of the CH_2 groups in the benzothiazepinone ring. The ^{13}C NMR spectra also displayed two peaks per carbon in both the aromatic and the alkyl region and the signal of the new lactam carbonyl group was found at 172.1 ppm for both **5a** and **5b**.

To justify our conclusions that the seven-membered rings display two different conformations at room temperature, a sealed tube variable high-temperature ^{1}H NMR experiment was performed. At 75 °C, coalescence began to take effect, showing two broad singlets with chemical shifts at 4.69 and 4.76 ppm for **5a** and at 4.50 and 4.70 ppm for **5b**. By 90 °C, a narrower peak was observed at 4.73 ppm for **5a** and a doublet with a

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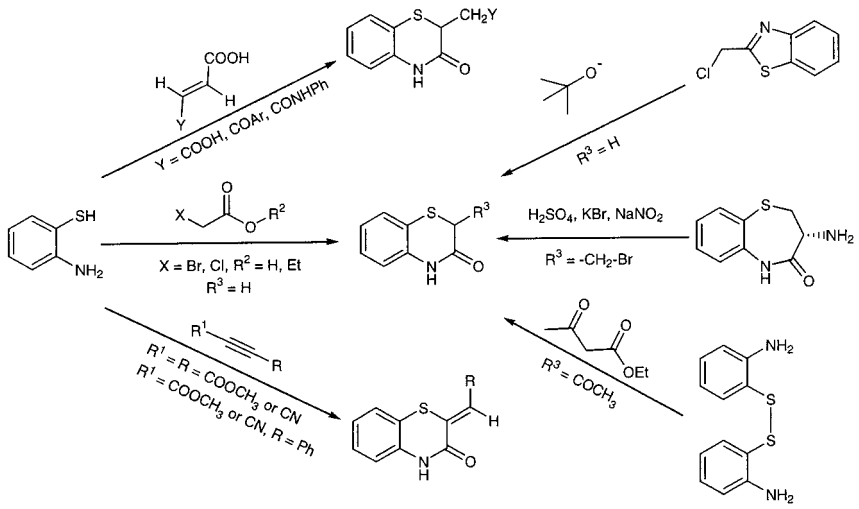
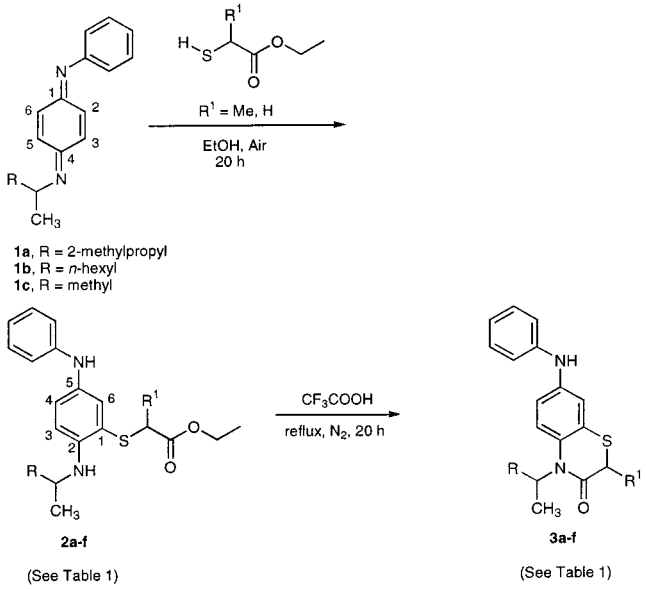
Scheme 2



Scheme 3



chemical shift at 4.59 ppm was observed for **5b**. After 100 °C, coalescence is at full, and a sharp singlet was observed at 4.71 and 4.62 ppm for compounds **5a** and **5b** accordingly. Significantly, the signals assigned to the methyl groups in the *N*-alkyl chain also showed some changes with temperature, being a complex set of doublets at room temperature but becoming a set of broad singlets at 100 °C. Using the Eyring equation,[24] the coalescence temperature indicates an energy barrier of ca. 17 kcal. Slow rotation around the 5−1′ bond is involved in compounds **5a,b** (Figure 1).

This conformational phenomenon can be compared with those of benzothiazepinones,[25] and other seven-membered ring analogues.[26a,b] Spectroscopic investigations using ^{1}H and ^{13}C NMR selective decoupling and two-dimensional NMR techniques demonstrate ring inversion for benzothiazepinones: the dominant conformer was determined by analysis of the coupling constants.[25] Systematic variable temperature ^{1}H NMR study of methyl- and phenyl-substituted 1,5-benzodiazepines and 1,5-benzothiazepines disclosed several cases of conformational changes at room temperature.[26b] Variable temperature ^{1}H NMR spectra of 1-substituted 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-ones gave ring inversion barriers from the observed coalescence temperatures: boat to boat conformational inversion via rapid ring inversion with no significant rotation about the CO−N bond was proposed.[26a]

In summary, we have developed a new method to produce benzothiazepinones and benzothiazinones. This clean and efficient two-step synthesis for these target compounds provides a novel synthetic route for their preparation. Employing an *N*-phenyl group at the C-1 position as an electron accepting group to accommodate for the addition of an α- or *β*-mercaptoalkanoate ester or acid nucleophile at the C-3 position of the benzoquinone diimine enables control of the regioselectivity of the nucleophilic attack resulting in only one regioisomer.

Experimental Section

General Methods. Absolute ethanol was used as a solvent for the addition of thiol esters and acids to benzoquinone diimines. Trifluoroacetic acid and starting material **1a** are commercially available, whereas **1b,c** were obtained upon oxidation of the corresponding commercially available benzenediamines with Ag_2O.[23] All cyclization reactions were carried out under nitrogen atmosphere. Column chromatography was conducted with silica gel 230−400 mesh. NMR was run at 300 MHz (^{1}H) or 75 MHz (^{13}C).

General Procedure for the Preparation of *N*-4-[(Alkyl)-imino]-2,5-cyclohexadien-1-ylideneanilines 1b−c. The corresponding 1,4-benzenediamine (10.0 mmol) was dissolved in toluene (25 mL) and treated with Ag_2O (4.63 g, 20.0 mmol) and $MgSO_4$ (3.37 g, 28.0 mmol) for 20 h. The orange slurry was filtered (Celite), the solvent was evaporated and the residue was purified by flash silica gel column chromatography [Hex/EtOAc (9:1) and (1:1)] to give the corresponding *N*-4-[(alkyl)imino]-2,5-cyclohexadien-1-ylideneaniline as a mixture of stereoisomers.

***N*-[4-(Phenylimino)-2,5-cyclohexadien-1-ylidene]-2-octanamine (1b).** Yield 99%: (as a 6:4 ratio mixture of stereoisomers), orange oil. ^{1}H NMR δ (major isomer): 7.37 (d, J = 7.6 Hz, 2H), 7.15 (t, J = 7.0 Hz, 1H), 6.99−6.92 (m, 2H), 6.88−6.80 (m, 2H), 6.77−6.71 (m, 2H), 3.96−3.83 (m, 1H), 1.66−1.61 (m, 2H), 1.27−1.19 (m, 11H), 0.87−0.85 (m, 3H). ^{13}C NMR δ (major isomer): 158.7, 157.2, 150.1, 139.1, 136.8, 128.9,

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Scheme 4

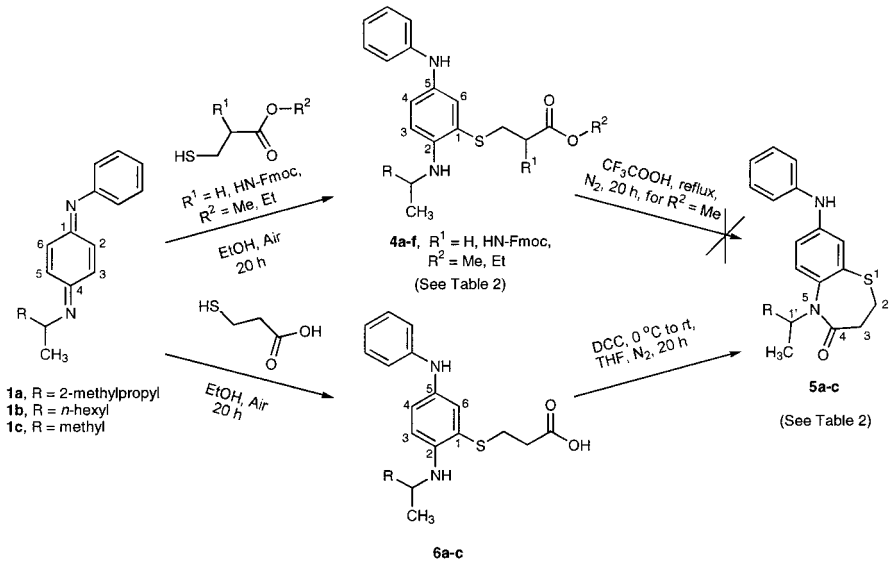

Table 1. Preparation of N^1-(Alkyl)-2-(alkylsulfanyl)-N^4-phenyl-1,4-benzenediamines (2a−f) and 2*H*-1,4-Benzothiazin-3(4*H*)-ones (3a−f)

entry	R	R^1	yield (%)	entry	R	R^1	yield (%)
2a	2-methylpropyl	Me	90	**3a**	2-methylpropyl	Me	91
2b	2-methylpropyl	H	87	**3b**	2-methylpropyl	H	97
2c	*n*-hexyl	Me	97	**3c**	*n*-hexyl	Me	93
2d	*n*-hexyl	H	95	**3d**	*n*-hexyl	H	90
2e	Me	Me	89	**3e**	Me	Me	93
2f	Me	H	94	**3f**	Me	H	89

Table 2. Preparation of Alkyl 3-{[5-anilino-2-(alkylamino)phenyl]sulfanyl}propanoates (4a−f), 3-{[5-anilino-2-(alkylamino)phenyl]sulfanyl}propanoic Acid 6a−c and 2,3-Dihydro-1,5-Benzothiazepin-4(5*H*)-ones (5a−c)

entry	R	R^1	R^2	yield (%)	entry	R	R^1	yield (%)
4a[a]	2-methylpropyl	H	Me	90	**5a**	2-methylpropyl	H	85
4b	*n*-hexyl	H	Me	89	**5b**	*n*- hexyl	H	97
4c	methyl	H	Me	86	**5c**	Me	H	81
4d	2-methylpropyl	HN−Fmoc	Et	88	**6a**	2-methylpropyl	H	71
4e	*n*-hexyl	HN−Fmoc	Et	90	**6b**	*n*-hexyl	H	63
4f	Methyl	HN−Fmoc	Et	92	**6c**	Me	H	70

[a] The preparation of compound **4a** has been described in a previous paper.[23]

Table 3. Variable Temperature 300 MHz ^{1}H NMR Spectroscopy of 2,3-Dihydro-1,5-Benzothiazepin-4(5*H*)-ones 5a and 5b

	temp (°C)	1′-H (ppm)	2-H (ppm)	3-H (ppm)
	25	4.78−4.84 (m) 4.68−4.75 (m)	3.20−3.28 (m)	2.41−2.51 (m)
	50	4.78−4.85 (m) 4.68−4.75 (m)	3.22−3.28 (m)	2.40−2.50 (m)
5a	75	4.76 (br s) 4.69 (br s)	3.50 (br s)	2.47 (br s)
	90	4.73 (d)	3.25 (br s)	2.46 (br s)
	100	4.71 (br s)	3.25 (br s)	2.46 (br s)
	25	4.72−4.79 (m) 4.53−4.59 (m)	3.24−3.27 (m)	2.41−2.52 (m)
	50	4.68−4.75 (m) 4.50−4.57 (m)	3.26−3.29 (m)	2.44−2.50 (m)
5b	75	4.70 (br s) 4.50 (br s)	3.26 (br s)	2.48 (br s)
	90	4.59 (d)	3.26 (br s)	2. 47 (br s)
	100	4.62 (br s)	3.25 (br s)	2.47 (br s)

124.7, 120.4, 56.3, 38.4, 31.7, 29.2, 26.6, 22.6, 22.3, 14.0. ^{13}C NMR δ (minor isomer): 158.7, 157.0, 150.1, 137.9, 134.3, 124.7, 122.3, 121.8, 56.4, 38.4, 31.7, 29.2, 26.6, 22.4, 22.3, 14.0. Anal. Calcd for $C_{20}H_{26}N_2$: N, 9.51. Found: N, 9.59.

General Procedure for the Preparation of N^1-(Alkyl)-2-(alkylsulfanyl)-N^4-phenyl-1,4-benzenediamines 2a−f and 4a−f. The corresponding benzoquinone diimine (3.0 mmol) was dissolved in ethanol (25 mL) and treated with a mercaptoester derivative (3.0 mmol) under a constant gentle stream of air. The dark reaction mixture was stirred for 20 h. The solvent was evaporated and the dark brown slurry was purified by silica gel column chromatography [Hex/EtOAc (9:1), (7:3), and (1:1)] to give the corresponding 2-alkylthio-1,4-benzenediamines.

Ethyl 2-(5-anilino-2-[(1-methylheptyl)amino]phenylsulfanyl)acetate (2d). Yield: 95%, orange oil. ^{1}H NMR δ 7.21−7.12 (m, 3H), 6.90 (d, J = 7.8 Hz, 2H), 6.81 (t, J = 7.2 Hz, 1H), 6.76 (d, J = 2.7 Hz, 1H), 6.49 (dd, J = 7.8, 2.7 Hz, 1H), 6.19 (s, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.47 (s, 2H), 3.40−3.35 (m, 1H), 3.27 (br s, 1H), 1.53−1.46 (m, 1H), 1.37−1.20 (m, 9H), 1.16 (t, J = 6.6 Hz, 6H), 0.88 (t, J = 6.6 Hz, 3H). ^{13}C NMR δ 170.0, 145.0, 143.4, 133.5, 129.1, 126.2, 123.9, 121.9, 119.4, 118.0, 115.8, 114.6, 113.9, 61.3, 48.9, 37.1, 31.7, 29.3, 26.0, 22.5, 20.6, 14.0. Anal. Calcd for $C_{24}H_{34}N_2O_2S$: N, 6.76. Found: N, 6.78.

Methyl 2-{[5-anilino-2-(isopropylamino)phenyl]sulfanyl}acetate (2f). Yield: 94%, yellow microcrystals. Mp: 47−50 °C. ^{1}H NMR δ 7.21−7.13 (m, 3H), 6.91 (d, J = 7.8 Hz, 2H), 6.80 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 2.6 Hz, 1H), 6.50 (dd, J = 7.8, 2.6 Hz, 1H), 6.20 (s, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.57−3.53 (m, 1H), 3.47 (s, 2H), 3.18 (br s, 1H), 1.19 (d, J = 6.2 Hz, 6H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR δ 170.0, 144.9, 143.1, 133.7, 129.1, 126.1, 121.8, 119.4, 118.2, 115.9,

114.9, 61.4, 44.6, 37.2, 22.9, 13.9. Anal. Calcd for $C_{19}H_{24}N_2O_2S$: C, 66.25; H, 7.02; N, 8.13. Found: C, 66.18; H, 7.31; N, 8.11.

Methyl 3-({5-anilino-2-[(1-methylheptyl)amino]phenyl}sulfanyl)propanoate (4b). Yield: 89% orange oil. ^{1}H NMR δ 7.21−7.13 (m, 3H), 6.91 (d, J = 7.8 Hz, 2H), 6.80 (t, J = 7.2 Hz, 1H), 6.70 (d, J = 2.7 Hz, 1H), 6.48 (dd, J = 7.8, 2.7 Hz, 1H), 6.06 (s, 1H), 3.61 (s, 3H), 3.41−3.35 (m, 1H), 3.28 (br s, 1H), 2.94 (t, J = 7.2 Hz, 2H), 2.55 (t, J = 6.9 Hz, 2H), 1.55−1.49 (m, 1H), 1.44−1.20 (m, 9H), 1.16 (d, J = 6.3 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR δ 172.1, 145.0, 143.2, 133.6, 129.1, 125.8, 121.5, 119.5, 118.2, 115.9, 114.2, 51.7, 48.9, 37.1, 33.9, 31.7, 29.4, 29.3, 26.0, 22.5, 20.7, 14.0. Anal. Calcd for $C_{24}H_{34}N_2O_2S$: C, 69.53; H, 8.27;N, 6.76. Found: C, 69.81; H, 8.40; N, 7.08.

Ethyl (2*R*)-3-{[5-anilino-2-(isopropylamino)phenyl]sulfanyl}-2-{[(9*H*-fluoren-9-yl-methoxy)carbonyl]amino}propanoate (4f). Yield: 92%, beige microcrystals. Mp: 58−61 °C. ^{1}H NMR δ 7.75 (d, J = 7.3 Hz, 2H), 7.56 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.28 (t, J = 7.3 Hz, 2H), 7.20 (t, J = 7.9 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 7.9 Hz, 2H), 6.83 (t, J = 7.3 Hz, 1H), 6.78 (s, 1H), 6.47 (dd, J = 8.8, 2.0 Hz, 1H), 6.06 (s, 1H), 5.71 (d, J = 7.3 Hz, 1H), 4.58−4.56 (m, 1H), 4.36−4.25 (m, 2H), 4.20−4.10 (m, 2H), 4.07−3.98 (m, 1H), 3.55−3.49 (m, 1H), 3.35−3.17 (m, 2H), 1.20−0.88 (m, 9H). ^{13}C NMR δ 170.4, 155.5, 144.8, 143.8, 143.0, 141.2, 134.3, 129.2, 127.6, 127.0, 125.1, 125.0, 121.5, 119.9, 119.8, 119.1, 116.5, 115.0, 67.2, 61.8, 54.1, 47.1, 44.7, 37.4, 23.0, 14.0. Anal. Calcd for $C_{35}H_{37}N_3O_4S$: C, 70.56; H, 6.26; N, 7.05. Found: C, 70.63; H, 6.70; N, 6.90.

General Procedure for the Preparation of 3-{[5-Anilino-2-(alkylamino)phenyl]-sulfanyl}propanoic acids 6a−c. The corresponding benzoquinone diimine (3.0 mmol) was dissolved in ethanol (25 mL) and treated with 3-mercaptopropionic acid (0.33 mL, 3.0 mmol) under a constant gentle stream of air. The dark reaction mixture was allowed to stir for 20 h. The solvent was evaporated and the dark brown slurry was purified by silica gel column chromatography [Hex/EtOAc (9:1), (7:3), and (1:1)] to give the corresponding 3-{[5-anilino-2-(alkylamino)phenyl]sulfanyl}propanoic acid.

3-{(5-Anilino-2-[(1,3-dimethylbutyl)amino]-phenylsulfanyl)}propanoic acid (6a). Yield: 71% brown oil, used without further purification. ^{1}H NMR δ 7.42−6.29 (m, 10H), 3.48 (br s, 1H), 2.88 (t, J = 7.0 Hz, 2H), 2.52 (t, J = 7.0 Hz, 2H), 1.86−1.65 (m, 1H), 1.62−1.46 (m, 1H), 1.34−1.19 (m, 2H), 1.15 (d, J = 6.1 Hz, 3H), 0.96−0.80 (m, 6H).

General Procedure for the Preparation of Benzothiazinones 3a−f. The corresponding 2-alkylthio-1,4-benzenediamine **2** (3.4 mmol) was dissolved in trifluoroacetic acid (15 mL) and the dark reaction mixture was allowed to stir at 70 °C (reflux) for 20 h under nitrogen. Trifluoroacetic acid was evaporated and CH_2Cl_2 (50 mL) was added to the dark slurry. The organic layer was washed with saturated sodium bicarbonate and water, dried ($MgSO_4$), and filtered (Celite). The solvent was evaporated and the dark slurry was purified by silica gel column chromatography [Hex/EtOAc (9:1), (7:3), and (1:1)] to give the desired benzothiazinones.

7-Anilino-4-(1-methylheptyl)-2*H*-1,4-benzothiazin-3(4*H*)-one (3d). Yield: 90%, yellow oil. ^{1}H NMR δ 7.43 (t, J = 7.3 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 6.53 (s, 1H), 6.30 (d, J = 8.8 Hz, 1H), 6.21 (d, J = 8.8 Hz, 1H), 3.51−3.46 (m, 3H), 3.35−3.33 (m, 1H), 1.49−1.47 (m, 1H), 1.42−1.27 (m, 9H), 1.12 (d, J = 6.1 Hz, 3H), 0.87 (t, J = 6.1 Hz, 3H). ^{13}C NMR δ 164.3, 143.8, 139.6, 131.5, 129.3, 128.4, 127.6, 124.3, 121.3, 111.6, 111.0, 48.4, 36.9, 32.3, 31.6, 29.1, 25.9, 22.4, 20.5, 14.0. Anal. Calcd for $C_{22}H_{28}N_2OS$: C, 71.70; H, 7.66; N, 7.60. Found: C, 71.92; H, 7.61; N, 7.61.

7-Anilino-4-isopropyl-2*H*-1,4-benzothiazin-3(4*H*)-one (3f). Yield: 89%, white microcrystals. Mp: 87−89 °C. ^{1}H NMR δ 7.35 (t, J = 7.3 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 7.3 Hz, 2H), 6.46 (d, J = 2.4 Hz, 1H), 6.22 (d, J = 8.8 Hz, 1H), 6.13 (dd, J = 8.8, 2.4 Hz, 1H), 3.47−3.37 (m, 4H), 1.07 (d, J = 6.1 Hz, 6H). ^{13}C NMR δ 164.3, 143.6, 139.5, 131.6, 129.4, 128.4, 127.6, 121.3, 111.8, 111.2, 44.1, 32.3, 22.7. Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39. Found: C, 68.42; H, 6.46; N, 9.35.

General Procedure for the Preparation of Benzothiazepinones 5a−c. The corresponding 2-alkylthio-1,4-benzenediamine (3.4 mmol) was dissolved in THF (15 mL) in an ice bath and treated with DCC (3.4 mmol). The reaction mixture was allowed to stir at 0 °C for 1 h and at room temperature for 20 h under nitrogen. THF was evaporated and water (50 mL) was added to the yellowish slurry and the reaction mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), and filtered (Celite). The solvent was evaporated and the dark slurry was purified by silica gel column chromatography [Hex/EtOAc (9:1), (7:3), and (1:1)] to give the desired benzothiazepinones.

8-Anilino-5-(1,3-dimethylbutyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (5a). Yield: 85% (as a 1.3:1 ratio mixture of conformers), yellow microcrystals. Mp: 68−71 °C. ^{1}H NMR δ (major conformer): 7.31 (pseudo t, J = 7.6 Hz, 3H), 7.26−7.05 (m, 3H), 7.00 (t, J = 7.6 Hz, 2H), 6.06 (s, 1H), 4.88−4.81 (m, 1H), 3.29−3.19 (m, 2H), 2.56−2.41 (m, 2H), 1.78−1.66 (m, 1H), 1.56−1.44 (m, 1H), 1.40 (d, J = 6.4 Hz, 3H), 1.35−1.13 (m, 1H), 1.11−0.95 (m, 3H), 0.88 (d, J = 6.4 Hz, 3H). ^{1}H NMR δ (minor conformer): 7.31 (pseudo t, J = 7.6 Hz, 3H), 7.26−7.05 (m, 3H), 7.00 (t, J = 7.6 Hz, 2H), 6.06 (s, 1H), 4.79−4.72 (m, 1H), 3.29−3.19 (m, 2H), 2.56−2.41 (m, 2H), 1.78−1.66 (m, 1H), 1.56−1.44 (m, 1H), 1.40 (d, J = 6.4 Hz, 3H), 1.35−1.13 (m, 1H), 1.11−0.95 (m, 3H), 0.77 (d, J = 6.4 Hz, 3H). ^{13}C NMR δ (major conformer): 172.1, 142.8, 141.8, 136.5, 130.7, 129.4, 126.6, 122.9, 122.0, 118.9, 117.0, 51.4, 45.9, 43.1, 34.6, 25.2, 23.0, 21.1, 18.4. ^{13}C NMR δ (minor conformer): 171.8, 142.8, 141.8, 136.5, 130.6, 129.4, 126.5, 122.9, 122.0, 118.8, 117.0, 51.4, 45.9, 43.1, 33.9, 24.9, 22.4, 21.1, 18.4. Anal. Calcd for $C_{21}H_{26}N_2OS$: N, 7.90. Found: N, 8.01. HRMS (FAB) calcd for $C_{21}H_{26}N_2OS$ (M): 354.1766, found: 354.1768.

8-Anilino-5-isopropyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (5c). Yield: 81%, yellow microcrystals. Mp: 163−166 °C. ^{1}H NMR δ 7.37−7.30 (m, 2H), 7.23−7.15 (m, 3H), 6.84 (t, J = 2.7 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.46 (dd, J = 8.8, 2.7 Hz, 1H), 3.66−3.48 (m, 2H), 3.40 (br s, 2H), 2.71 (br s, 2H), 1.22 (d, J = 6.3 Hz, 6H). ^{13}C NMR δ 171.9, 146.3, 142.3, 136.0, 128.9, 128.8, 127.5, 127.1, 126.3, 118.2, 114.2, 44.2, 34.4, 34.1, 22.9. Anal. Calcd for $C_{18}H_{20}N_2OS$: N, 8.97. Found: N, 8.75. HRMS (FAB) calcd for $C_{18}H_{20}N_2OS$ (M): 312.1299, found: 312.1296.

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Supporting Information Available: Experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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