Solid-Phase Synthesis of 3,5-Disubstituted 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones

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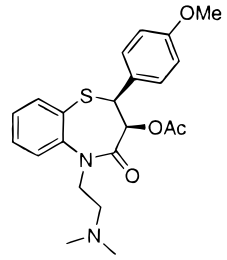
A solid-phase route affording novel 3,5-disubstituted 1,5-benzothiazepin-4(5*H*)-ones in optically pure form has been enabled. S_NAr reaction of polymer-bound 4-fluoro-3-nitrobenzoic acid, **12**, with L-Fmoc-cysteine, L-**13**, under basic conditions, followed by tin(II) chloride mediated nitro group reduction, furnished the primary aniline **15**. Reductive alkylation of **15** to the corresponding secondary anilines **17** was shown to be feasible for a wide range of aldehydes, using an optimized solvent system composed of $CH(OMe)_3$, DMF, MeOH, and HOAc, with $NaCNBH_3$ as the reducing agent. In cases of enolizable aldehydes, benzotriazole was found to be a beneficial additive for the suppression of side-products due to imine−enamine tautomerization. Subsequent cyclization of the secondary anilines **17** using DIC in apolar solvents furnished the corresponding N(5)-alkylated 1,5-benzothiazepin-4-ones **19**. Following Fmoc removal from **19**, the primary amino group was finally reacted with carboxylic acids, isocyanates, sulfonyl chlorides, or aldehydes to afford the respective amides **32**, ureas **33**, sulfonamides **34**, or secondary amines **35**. Performing the synthesis with the D-form of Fmoc-cysteine, D-**13**, resulted in the corresponding antipodal products, with no detectable scrambling at C(3). The solid-phase assembly of 1,5-benzothiazepin-4-ones was also shown to be compatible with chemical encoding based on dialkylamine tags, enabling the construction of large combinatorial libraries of the title compounds.

Introduction

Over the past two decades, substituted 1,5-benzothiazepin-4-ones have elicited considerable pharmacological interest, primarily as a result of their role as calcium antagonists interacting with the L-type voltage-gated Ca^{2+} channel.[1] Along with the dihydropyridines (e.g., nifedipine) and the phenylalkylamines (e.g., verapamil), the 1,5-benzothiazepinones (e.g., diltiazem, **1**) are nowadays among the most widely used drugs in the treatment of cardiovascular disorders.[2] Moreover, further potential therapeutic applications can be inferred from literature data on different representative benzothiazepinones, most notably the 3-amino-substituted analogues **2**.[3]

Spurred by the success of **1** in clinical studies, a wealth of synthetic procedures affording 1,5-benzothiazepin-4-ones have been developed.[4] These can formally be subdivided into three classes, **A**, **B**, and **C**, based on the retrosynthetic disconnection of the basic skeleton **3**. In strategy **A** (by far the most frequently employed), **3** was derived from nucleophilic attack of substituted 2-aminothiophenols, **4**, or 2-nitrothiophenols, **5**, on aliphatic electrophiles, **6**, such as β-halo-propionic acids,[5] α,β-unsaturated carboxylic acids,[6] β-propiolactones,[7] malonic acids,[8] or phenylglycidic esters.[9] In the converse scenario **B**, a β-mercapto acid (typically a cysteine derivative), **8**, was allowed to react with substituted 2-fluoronitroarenes, **7**, followed by nitro group reduction and cyclization.[3] Finally, in **C**, the 6,7-fused ring system **3** was shown to also be accessible from 6,6-fused systems, **9**, such as



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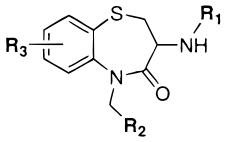

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§ Abbreviations: Fmoc = 9-fluorenylmethoxycarbonyl; HATU = 2-(1*H*-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; DIEA = *N*,*N*-diisopropylethylamine; DIC = 1,3-diisopropylcarbodiimide; HOBt = 1-hydroxybenzotriazole; DMAP = 4-(dimethylamino)pyridine; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DECP = diethyl cyanophosphonate; NMM = 4-methylmorpholine; Alloc = allyloxycarbonyl; NMP = 1-methyl-2-pyrrolidinone.

(1) (a) Rampe, D.; Triggle, D. J. *Prog. Drug Res.* **1993**, *40*, 191. (b) Chaffman, M.; Brogden, R. N. *Drugs* **1985**, *29*, 387.

(2) (a) Pitt, B. *Clin. Ther.* **1997**, *19* (Suppl. A), 3. (b) Ferrari, R. *Eur. Heart J.* **1997**, *18* (Suppl. A), A56.

(3) See for example: (a) Slade, J.; Stanton, J. L.; Ben-David, D.; Mazzenga, G. C. *J. Med. Chem.* **1985**, *28*, 1517. (b) Wyvratt, M.; Devita, R.; Bochis, R.; Schoen, W. U.S. Patent 5,672,596, 1997. (c) Nagel, A. A. PCT Int. Appl. WO 9401421, 1994.

(4) For a recent review, see: Lévai, A. *Trends Heterocycl. Chem.* **1995**, *4*, 51. See also: Wünsch, K.-H.; Ehlers, A. *Z. Chem.* **1970**, *10*, 361.

(5) (a) Floyd, D. M.; Moquin, R. V.; Atwal, S. K.; Ahmed, S. Z.; Spergel, S. H.; Gougoutas, J. Z.; Malley, M. F. *J. Org. Chem.* **1990**, *55*, 5572. (b) Lévai, A.; Puzicha, G. *Synth. Commun.* **1985**, *15*, 623. (c) Mayer, F.; Horst, C. *Ber. Dtsch. Chem. Ges.* **1923**, *56*, 1415.

(6) See for example: (a) Ambrogi, V.; Giampietri, A.; Grandolini, G.; Perioli, L.; Ricci, M.; Tuttobello, L. *Arch. Pharm.* **1992**, *325*, 569. (b) Lévai, A.; Duddeck, H. *Pharmazie* **1983**, *38*, 827. (c) Krapcho, J.; Spitzmiller, E. R.; Turk, C. F. *J. Med. Chem.* **1963**, *6*, 544. (d) Mills, W. H.; Whitworth, J. B. *J. Chem. Soc.* **1927**, 2738.

(7) Ambrogi, V.; Grandolini, G. *Synthesis* **1987**, 724.

(8) Ried, W.; Sell, G. *Chem. Ber.* **1980**, *113*, 2314.

(9) See for example: (a) Schwartz, A.; Madan, P. B.; Mohacsi, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851. (b) Hashiyama, T.; Inoue, H.; Takeda, M.; Murata, S.; Nagao, T. *Chem. Pharm. Bull.* **1985**, *33*, 2348. (c) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. *Chem. Pharm. Bull.* **1971**, *19*, 595.

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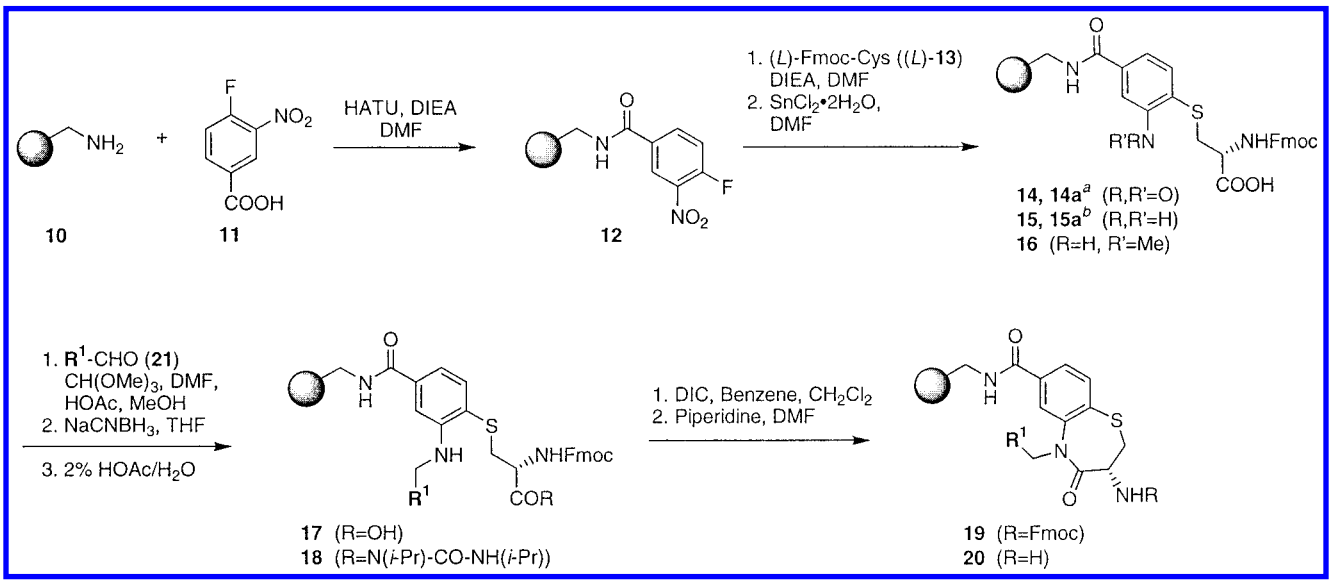
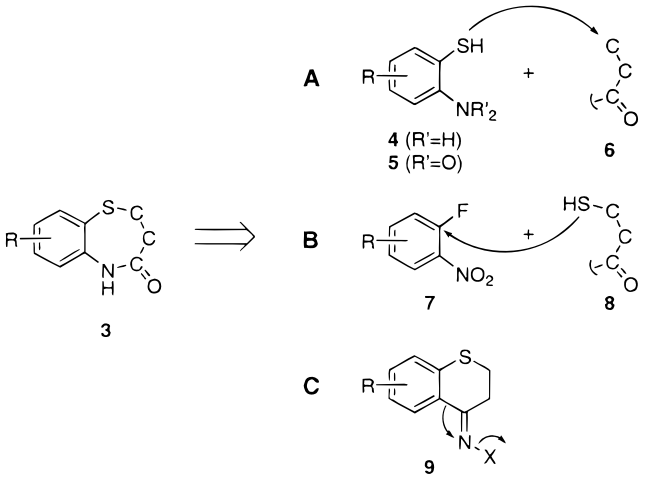
Scheme 1



[a] Product derived from TFA cleavage of **14**. [b] Product derived from TFA cleavage of **15**.

1-thioflavanones or thiochromanones, by ring enlargement via Beckmann or Schmidt-type rearrangements.[10] As a notable common feature of all these approaches, functionalization of N(5) was invariably effected *after* formation of the seven-membered ring had been completed, using alkyl halides under basic conditions.



To date, no solid-phase synthesis of substituted 1,5-benzothiazepin-4-ones has been reported. Based on our previous experience with solid-phase syntheses of 1,5-benzodiazepin-2-ones from polymer-bound 4-fluoro-3-nitrobenzoic acid, **12**,[11] and inspired by the solution-phase strategy **B** above, a related approach leading to 1,5-benzothiazepin-4-ones was envisaged (see Scheme 1). Thus, the benzothiazepine skeleton was to be assembled from **12** and a suitably protected form of cysteine. However, in contrast to the previously reported solution protocols, we planned to introduce the substituents at N(5) by reductive alkylation with aldehydes *prior* to cyclization, with a view to gaining access to novel functionalities at this critical position. The present report details the results of these studies, which culminated in high-yielding syntheses of novel, optically pure 1,5-benzothiazepin-4-ones on solid support, as well as in the construction of large combinatorial libraries of such compounds. We also disclose a new method for performing reductive alkylations with enolizable aliphatic aldehydes that was developed during the course of this work.

Results and Discussion

Following Fmoc deprotection, ArgoGel-Rink resin, **10**,[12] was allowed to react with 4-fluoro-3-nitrobenzoic acid, **11**, in the presence of HATU and DIEA in DMF (Scheme 1). The resulting intermediate **12**, which has previously been shown to undergo facile S_NAr-type reactions with sulfur[13] and/or nitrogen-nucleophiles,[14] was then exposed to a solution of L-Fmoc-cysteine, **13**,[15] and DIEA in DMF. With as little as 1.5 equiv of **13** relative to the theoretical loading of the resin, HPLC analysis[16] showed complete conversion of **12** to **14** after a reaction time of 24 h at ambient temperature. The presence of an Fmoc group in the majority of the synthetic intermediates provided a convenient means of determining the amount of desired compound present on the resin. In conjunction with HPLC data on the purity of the crude compounds after TFA cleavage, this was used as an estimate of the yields

(10) See for example: (a) Kaye, P. T.; Mphahlele, M. J. *Synth. Commun.* **1995**, *25*, 1495. (b) Lévai, A. *Acta Chim. Acad. Sci. Hung.* **1981**, *107*, 361.

(11) Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *Tetrahedron Lett.* **1998**, *39*, 8397. A synopsis of all results obtained was presented at the 2nd Canadian Conference of Combinatorial Chemistry, Montreal, Canada, Oct. 6 and 7, 1997. Described were solid-phase syntheses of 1,5-benzothiazepin-4-ones, 1,6-benzothiazocin-5-ones, 1,5-benzodiazepin-2-ones, 4-alkoxy-1,4-thiazin-3-ones, quinoxalin-2-ones, and of a thieno-thiazepine.

(12) Loading: 0.33 mmol/g.

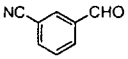
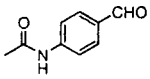
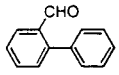
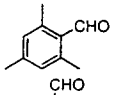
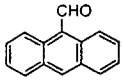
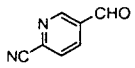
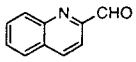
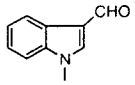
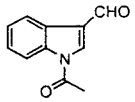
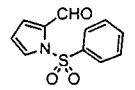
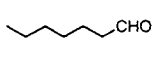
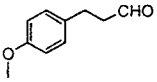
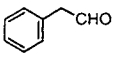
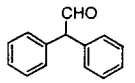
(13) Yan, B.; Kumaravel, G. *Tetrahedron* **1996**, *52*, 843.

(14) See for example: (a) ref 11. (b) Wei, G. P.; Phillips, G. B. *Tetrahedron Lett.* **1998**, *39*, 179. (c) Lee, J.; Murray, W. V.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 3874.

(15) **13** was obtained from the corresponding commercially available *N*-Fmoc-*S*-trityl-protected form by treatment with TFA in CH_2Cl_2 (see Experimental Section).

(16) At every stage of the synthetic sequence, an aliquot of resin was subjected to TFA cleavage conditions (90% TFA/CH_2Cl_2) to liberate the products for the purpose of analysis. After thorough evaporation of the solvent and gravimetric estimation of the crude yields, the residues were routinely analyzed by HPLC (UV detection at 220/280 nm) and ESI−MS.

Table 1. Yields of Secondary Anilines 22, Obtained after TFA Cleavage of Resin 17 Derived from Reductive Alkylation of 15, and of *N*(5)-Substituted 1,5-Benzothiazepin-4-ones 23, Obtained from Cyclization of 17 Followed by TFA Cleavage, as a Function of the Aldehyde Structure (R^1-CHO)

Aldehyde (R^1-CHO)			Yields [b] (from cleavage of **17**)			Yields [b] (from cleavage of **19**)		
Entry	Structure	Cd[a]	Entry	x [b]	y [b]	Entry	x [b]	y [b]
21a		A	**22a**	93	63	**23a**	90	63
21b		A	**22b**	93	67	**23b**	84	63
21c		A	**22c**	63 [c]	46 [c]	**23c**	83	61
21d		A	**22d**	71 [c]	-	**23d**	85	-
21e		A	**22e**	51 [c]	35 [c]	**23e**	84	65
21f		A	**22f**	< 5	-	**23f**	< 5	-
21g		A	**22g**	97	70	**23g**	93	72
21h		A	**22h**	89	56	**23h**	81	65
21i		A	**22i**	91	-	**23i**	86	-
21j		A	**22j**	43	-	**23j**	31	-
21k		A	**22k**	< 5	-	**23k**	< 5	-
21l		A	**22l**	45 [c]	-	**23l**	76	-
21m		A	**22m**	68 [c]	47 [c]	**23m**	96	69
21n		A	**22n**	90	-	**23n**	87	-
21o		A	**22o**	93	62	**23o**	90	60
21p		A	**22p**	90	-	**23p**	92	-
21q		A	**22q**	< 5	-	**23q**	< 5	-
21r		A	**22r**	54 [c]	33 [c]	**23r**	80	70
21s		A	**22s**	< 5	-	**23s**	< 5	-
21t		A	**22t**	68	-	**23t**	74	-
21u		B	**22u**	98	-	**23u**	94	-
21v		B	**22v**	100	73	**23v**	96	62
21w		B	**22w**	96	-	**23w**	94	-
21x		B	**22x**	98	72	**23x**	98	55
21y		B	**22y**	57	-	**23y**	51	-
21z		B	**22z**	< 5	-	**23z**	< 5	-

[a] Conditions: **A** = 10 equiv aldehyde (0.2 M), $CH(OMe)_3$/DMF/MeOH 9:1:2 (1% HOAc), 50 °C, 18 h; then added 50 equiv $NaCNBH_3$ (1 M), THF, 50 °C, 6 h; **B** = 10 equiv aldehyde + 10 equiv benzotriazole (0.2 M), $CH(OMe)_3$/DMF/MeOH 9:1:2 (1% HOAc), rt, 18 h; then added 50 equiv $NaCNBH_3$ (1 M), THF, rt, 6 h; reagent equivalents are given relative to theoretical resin loading (see ref 12). [b] Determination of yields (all in percent): **x** = yields, as determined from Fmoc number readings in conjunction with analytical HPLC (UV detection at λ = 220 nm); **y** = yields of isolated, HPLC-purified compounds, derived from cleavage of 100−200 mg of resin; calculations relative to resin loading based on Fmoc numbers. [c] For certain electron-rich aldehydes, TFA treatment was found to cause partial dealkylation of the secondary anilines **17** (affording **15**) but not of the corresponding cyclic products **19**.

associated with a given reaction step (Table 1, footnote b). Reduction of the nitro group of **14** with $SnCl_2 \cdot 2H_2O$ in DMF smoothly afforded the primary aniline **15**.[17]

In accordance with literature data,[18] the subsequent reductive alkylation of **15** proved to be problematic, as a result of the poor nucleophilicity of the aniline nitrogen as compared with aliphatic amino groups. Thus, using a high molar excess of aldehyde in a mixture of trimethylorthoformate, MeOH, and acetic acid (HOAc) at room temperature[19] afforded low yields of the corresponding secondary anilines **17** for aromatic aldehydes bearing either electron-donating or *ortho* substituents, as well as for all aliphatic aldehydes. By adding small amounts

(17) Pinori, M.; Di Gregorio, G.; Mascagni, P. In *Innovation and Perspectives in Solid-Phase Synthesis*; Epton, R., Ed.; Mayflower Worldwide: Kingswinford, 1994; pp 635−638.

(18) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(19) (a) Szardenings, A. K.; Burkoth, T. S.; Look, G. C.; Campbell, D. A. *J. Org. Chem.* **1996**, *61*, 6720. (b) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937.

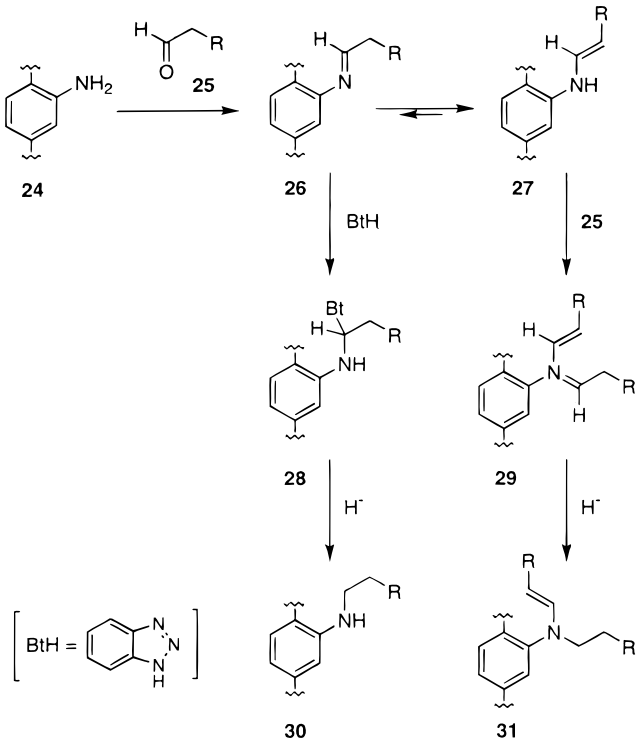
(10% v/v) of DMF to the above solvent system and raising the temperature to 50 °C, the majority of reactions involving aromatic aldehydes could be driven to completion (Table 1).

The only significant side-product occasionally present in minor amounts (5−10%) was identified as the *N*-methyl-aniline **16**, arising from incorporation of the methine carbon of the orthoformate.[20] As a notable exception, highly electron-rich aldehydes such as *N*-alkylamino-benzaldehydes (e.g., **21f**) and, by analogy, *N*-methylated indole- and pyrrole-carboxaldehydes (**21q** and **21s**) did not give satisfactory results, presumably because of failure in imine formation.[21] The related *N*-acetylated and/or *N*-sulfonylated aldehydes **21g**, **21r**, and **21t**, however, readily afforded the desired products in high purities. A drop in yields ascribable to steric factors was observed only in cases with substituents in *both* ortho positions (**21j**, **21k**). Ortho monosubstitution, such as in **21h** or **21i**, however, did not adversely affect the outcome of the reaction, regardless of the size of the substituents. Under the above conditions, both at 50 °C and at room temperature, aliphatic aldehydes such as **21u**−**z** invariably afforded complex mixtures of products, among which only few could tentatively be identified (on the basis of their molecular weights) as dialkylated and dehydro-dialkylated compounds, **31**. The latter products were rationalized as being derived from tautomerization of the initially formed imine **26** to the thermodynamically more stable enamine **27**, followed by reaction with a second aldehyde molecule **25** and subsequent reduction (see Scheme 2).

We explored addition of benzotriazole (BtH) to the reaction mixture to suppress formation of enamine-derived side-products, because of the known ability of BtH to form stable adducts with imines.[22] Thus, by blocking the tautomerization of **26** to **27** through in situ formation of the benzotriazolyl derivative **28**, it was hoped that subsequent hydride displacement of the Bt moiety would cleanly afford the desired monoalkylated products **30**. Indeed, the analytical HPLC traces revealed a remarkable improvement in terms of product purity, especially for reactions carried out at room temperature, with the desired secondary anilines **30** being essentially the only detectable products. In further studies, the benzotriazole-mediated suppression of enamine-derived side-product formation was shown to be of broad scope, failing only in those cases in which the driving force for tautomerization was particularly strong (such as for aldehydes **21y** and **21z**).

The reductive alkylation of the primary aniline **15** could be expected to render N(5) more basic but less nucleophilic because of increased steric crowding and hence less amenable to cyclization to form the seven-membered ring. Indeed, most of the coupling reagents that had successfully been used to effect cyclization of

Scheme 2



the primary aniline **15** failed when applied to the secondary anilines **17**, among them HATU/DIEA, DIC/HOBt, DIC/DMAP, and EDC, as well as some noncarbodiimide-type reagents such as DECP and Mukaiyama's reagent. A breakthrough was the finding that DIC solutions in DMF, devoid of any additives such as HOBt or DMAP, were able to furnish the desired N(5)-alkylated benzothiazepinones **19** as major products, along with varying amounts (20−50%) of the corresponding *N*-acylureas, **18**. Common byproducts in carbodiimide-mediated peptide coupling reactions,[23] *N*-acylureas arise via rearrangement of the initially formed *O*-acylisourea intermediates in competition with amide bond formation. In further studies, formation of **18** could almost completely be suppressed in favor of the desired cyclization reaction by replacing DMF with solvents of lower polarity, such as CH_2Cl_2 or benzene.[24] Gratifyingly, the newly established cyclization conditions proved to be of wide generality, allowing essentially all secondary anilines **17** to be smoothly converted into the corresponding N(5)-substituted 1,5-benzothiazepinones **19** (Table 1). It was found to be imperative, however, that the resin batches **17** originating from reductive alkylation be subjected to a wash with aqueous acetic acid (2% v/v) prior to cyclization. Omitting the washing step completely inhibited cyclization of the secondary anilines **17**. It appeared that under the reductive alkylation conditions the carboxyl function in **17** had been converted into its sodium salt, which was unreactive toward carbodiimide-type reagents.

(20) (a) Crotchet, R. A.; Blanton, C. D. *Synthesis* **1974**, 55. (b) Perrault, W. R.; Shephard, K. P.; Lapean, L. A.; Krook, M. A.; Dobrowolski, P. J.; Lyster, M. A.; McMillan, M. W.; Knoechel, D. J.; Evenson, G. N.; Watt, W.; Pearlman, B. A. *Org. Process Res. Dev.* **1997**, *1*, 106. For mechanistically related reactions of $CH(OMe)_3$ see: (c) Zupet, R.; Tisler, M.; Golic, L. *J. Heterocycl. Chem.* **1991**, *28*, 1731. (d) Wentrup, C.; Briehl, H.; Lorencak, P.; Vogelbacher, U. J.; Winter, H.-W.; Maquestiau, A.; Flammang, R. *J. Am. Chem. Soc.* **1988**, *110*, 1337.

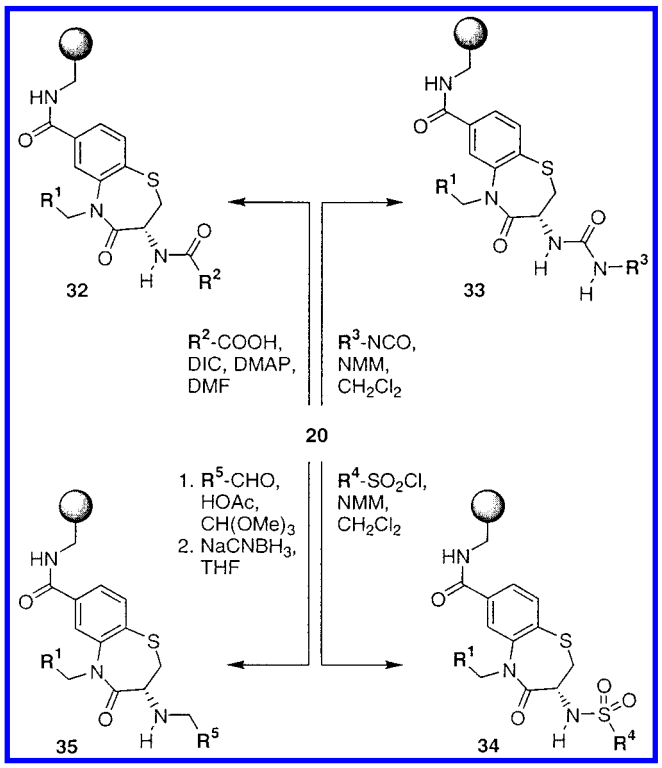
(21) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(22) (a) Katritzky, A. R.; Lan, X.; Fan, W.-Q. *Synthesis* **1994**, 445. (b) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683.

(23) Kiso, Y.; Yajima, H. Amide-Formation, Deprotection, and Disulfide Formation in Peptide Synthesis. In *Peptides: Synthesis, Structures, and Applications;* Gutte, B., Ed.; Academic Press: San Diego, New York, Boston, London, Sydney, Tokyo, Toronto, 1995; pp 40−93.

(24) The importance of solvent choice with regard to limiting the extent of *N*-acylureas formation has long been appreciated: Sheehan, J. C.; Goodman, M.; Hess, G. P. *J. Am. Chem. Soc.* **1956**, *78*, 1367.

Scheme 3



The remaining steps completing the synthetic sequence involved further functionalization of the exocyclic amino group of the 1,5-benzothiazepinone template. This included Fmoc removal from **19** and treatment of the resulting primary amines **20** with carboxylic acids, isocyanates, sulfonyl chlorides, and/or aldehydes to generate the corresponding amides **32**, ureas **33**, sulfonamides **34**, and/or secondary amines **35**, respectively (see Scheme 3).

These four transformations reliably afforded the desired 3,5-disubstituted 1,5-benzothiazepin-4-ones in high purities and yields, showing full compatibility with all types of functional groups examined, whether already present as $\mathbf{R^1}$ or newly introduced as $\mathbf{R^{2-5}}$. In one model study (Table 2, top), large resin batches of selected benzothiazepinones **20** with five different $\mathbf{R^1}$ groups spanning a broad range of functionalities were each split into four aliquots to be reacted with 3-methoxypropionic acid and DIC in DMF, 2-chloroethyl isocyanate and NMM in CH_2Cl_2, 3,5-dimethylisoxazole-4-sulfonyl chloride and NMM in CH_2Cl_2, and 3-(methylthio)propionaldehyde in $CH(OMe)_3$ (0.3% v/v HOAc), followed by $NaCNBH_3$ in THF. The products **36**−**39** were purified by RP-HPLC and fully characterized.[25] A parallel study based on **21c** as the $\mathbf{R^1}$ aldehyde component was designed to compare analytical data, in particular the optical rotations, of the respective benzothiazepines (*R*)-**36c**−**40c** and (*S*)-**36c**−**40c**,[26] derived from L-Fmoc-cysteine, L-**13**, and D-Fmoc-cysteine, D-**13**, respectively (Table 2, bottom).

The $[\alpha]_D$ values obtained corroborate the results of earlier solution-phase studies showing that 1,5-benzothiazepin-4-ones can be assembled from cysteine derivatives and fluoronitroarenes without racemization at the α-carbon atom.[3] Given, however, that these solution protocols differ substantially from the present solid-phase approach in terms of the sequence of steps and the reaction conditions used, it was desirable to accumulate additional data on the optical purity of the compounds originating from synthesis on solid support. To that end, pairs of selected benzothiazepines, (*R*)-**20** and (*S*)-**20**, derived from L- and D-Fmoc-cysteine, respectively, were reacted with optically pure entities such as L-amino acids to afford, after cleavage from the resin, pairs of diastereomers, e.g., (*R*,*S*)-**41w** and (*S*,*S*)-**41w** (Figure 1).

Subsequent analysis by RP-HPLC showed no detectable amounts of (*R*,*S*)-**41w** present in sample (*S*,*S*)-**41w** and vice versa. Analogous experiments carried out for different $\mathbf{R^1}$ groups, as well as for 1,5-benzothiazepinones of the general structures **33**−**35**, furnished no evidence of racemization in any of the samples examined.

We have previously described how the use of chemical encoding strategies greatly facilitates the identification of bioactive compounds from large combinatorial libraries.[27] To explore the compatibility of our dialkylamine encoding method with the 1,5-benzothiazepinone chemistry, synthesis on an orthogonally differentiated resin **42** was carried out according to Scheme 4.

Thus, differentiated TentaGel resin **42**[28] was submitted to the conditions outlined in Scheme 1, using *n* different aldehydes $\mathbf{R^1}$-CHO in the reductive alkylation step, to afford *n* batches of resin bearing Fmoc-protected N(5)-substituted 1,5-benzothiazepin-4-ones, **43**. Removal of the Alloc group was followed by coupling of the first set of tags, $\mathbf{T^1}$, encoding the $\mathbf{R^1}$ position. Subsequently, all batches were pooled and split anew into *m* aliquots, which were provided with the second set of tags, $\mathbf{T^2}$, defining the $\mathbf{R^2}$ position. Functionalization at the $\mathbf{R^2}$ position proceeded according to the protocols summarized in Scheme 3 and afforded the final two-position-encoded resin batches carrying 3,5-disubstituted 1,5-benzothiazepin-4-ones, **44**. In model studies, it was shown that the extra steps devoted to the introduction of the chemical codes did not adversely affect the purity of the ligands, further validating the robustness of this chemical encoding strategy.[27]

In summary, an efficient, high-yielding solid-phase route to 3,5-disubstitued 1,5-benzothiazepin-4(5*H*)-ones has been developed, which lends itself to both the synthesis of discrete, optically pure compounds and the generation of large (>10K member) encoded libraries. In the two key steps of the synthetic sequence (and in contrast to previous solution-phase approaches) alkylation of N(5) was effected prior to cyclization, using aldehydes under reductive alkylation conditions. Benzotriazole was found to be a beneficial additive in reductive alkylation reactions with enolizable aliphatic aldehydes. In subsequent experiments, the underlying synthetic strategy of assembling benzo-fused heterocycles via S_NAr chemistry from resin-bound 4-fluoro-3-nitrobenzoic acid, **12**, has been extended to the synthesis of related

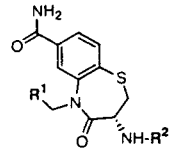
(25) See Experimental Section.

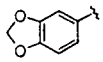
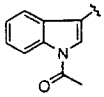
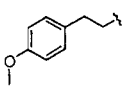
(26) Terminology based on the absolute configuration at C(3). Compound **38c** was not synthesized.

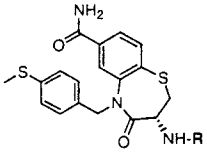
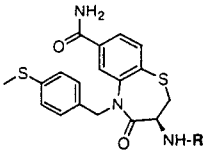
(27) (a) Ni, Z.-J.; Maclean, D.; Holmes, C. P.; Murphy, M. M.; Ruhland, B.; Jacobs, J. W.; Gordon, E. M.; Gallop, M. A. *J. Med. Chem.* **1996**, *39*, 1601. (b) Maclean, D.; Schullek, J. R.; Murphy, M. M.; Ni, Z.-J.; Gordon, E. M.; Gallop, M. A. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2805.

(28) TentaGel HL-NH_2 (loading: 0.41 mmol/g) was differentiated using a 9:1 molar ratio of Fmoc-Cl and Alloc-Cl and, following Fmoc deprotection, coupled with the Rink-type, acid-labile linker *p*-[(*R*,*S*)-[1-(9*H*-fluoren-9-yl)-methoxyformamido]-2,4-dimethoxybenzyl]-phenoxyacetic acid (Bernatowicz, M. S.; Daniels, S. B.; Köster, H. *Tetrahedron Lett.* **1989**, *30*, 4645). Fmoc removal from the latter furnished the starting resin **42**.

Table 2. (Top) Yields of Representative 3,5-Disubstituted 1,5-Benzothiazepin-4-ones, 36−39 (Bottom) Yields of Representative Enantiomeric 3,5-Disubstituted 1,5-Benzothiazepin-ones, (*R*)-36−40 and (*S*)-36−40,[26] Derived from L- and D-Fmoc-cysteine, Respectively



R^1	(from)	Fmoc [a] Entry	Yield[b] (Purity)[c]	Entry	Yield[b] (Purity)[c]	Entry	Yield[b] (Purity)[c]	Entry	Yield[b] (Purity)[c]	Entry	Yield[b] (Purity)[c]
	**21e**	**23e**	65 (84)	**36e**	67 (89)	**37e**	70 (85)	**38e**	67 (90)	**39e**	51 (80)
	**21m**	**23m**	69 (96)	**36m**	58 (88)	**37m**	57 (83)	**38m**	64 (90)	**39m**	42 (83)
	**21r**	**23r**	70 (80)	**36r**	53 (92)	**37r**	58 (87)	**38r**	50 (90)	**39r**	37 (81)
	**21v**	**23v**	62 (96)	**36v**	73 (90)	**37v**	83 (98)	**38v**	80 (98)	**39v**	49 (85)
	**21x**	**23x**	55 (98)	**36x**	54 (93)	**37x**	56 (90)	**38x**	56 (93)	**39x**	46 (82)

Core structure	R	Fmoc [a] Entry Y.[b] (P.)[c]	$[\alpha]_D$	Entry Y.[b] (P.)[c]	$[\alpha]_D$	Entry Y.[b] (P.)[c]	$[\alpha]_D$	Entry Y.[b] (P.)[c]	$[\alpha]_D$	Entry Y.[b] (P.)[c]	$[\alpha]_D$
		(*R*)-**23c** 61 (83)	-79.0	(*R*)-**36c** 72 (90)	-106.5	(*R*)-**37c** 61 (85)	-86.0	(*R*)-**40c** 59 (80)	-72.2	(*R*)-**39c** 51 (80)	-52.8
		(*S*)-**23c** 69 (80)	+77.4	(*S*)- **36c** 64 (91)	+111.5	(*S*)-**37c** 61 (89)	+81.1	(*S*)-**40c** 65 (85)	+62.2	(*S*)-**39c** 41 (83)	+48.2

[a] See Table 1. [b] Yields of isolated, RP-HPLC-purified products derived from cleavage of 300 mg of resin; in percent relative to resin loading based on Fmoc numbers. [c] Purity of the crude product derived from TFA cleavage; in percent as determined by analytical HPLC (UV detection at $\lambda = 220$ nm).

structures such as 1,5-benzodiazepin-2-ones,[11] 2,2-dimethyl-1,5-benzothiazepin-4-ones, 1,6-benzothiazocin-5-ones, and 4-alkoxy-1,4-thiazin-3-ones. The results of these studies will be reported in detail soon.

Experimental Section

General. Reagents were purchased in the highest quality available from Aldrich, Lancaster, Maybridge, Novabiochem, and Advanced ChemTech and were used as received unless otherwise stated. ArgoGel-Rink resin was purchased from Argonaut Technologies (loading: 0.33 mmol/g), and TentaGel HL-NH_2 was purchased from Rapp Polymere (loading: 0.41 mmol/g). Resins were washed twice each with DMF and CH_2Cl_2 prior to use. All reactions carried out at room temperature were conducted in either glass standard peptide vessels (Chemglass) or polypropylene Extract-CleanTM filter tubes (Alltech Associates) placed on a vortex shaker. For reactions performed at elevated temperature, screw-cap borosilicate glass vials (Wheaton) were used, which had previously been silanated by brief (10 min) exposure to a 10% solution of TMS-Cl in hexane, rinsed several times with CH_2Cl_2, and oven-dried. Charged with the resin and reagents, the vials were then placed in a heat block situated on a shaker. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Varian Mercury at 300 and 75 MHz, respectively. Chemical shifts were internally referenced to the residual proton resonance of DMSO-d_5 (δ 2.50) and to the signal corresponding to the ^{13}C methyl resonance in DMSO-d_6 (δ 39.51). ESI mass spectra were recorded on a Hewlett-Packard Series 1100MSD instrument. High-resolution mass spectra were run by the UC Berkeley Mass Spectrometry Facility on a double focusing high-resolution Micromass ZAB2 EQ @ 8000 v accelerator potential using FAB ionization. Optical rotations were determined using a

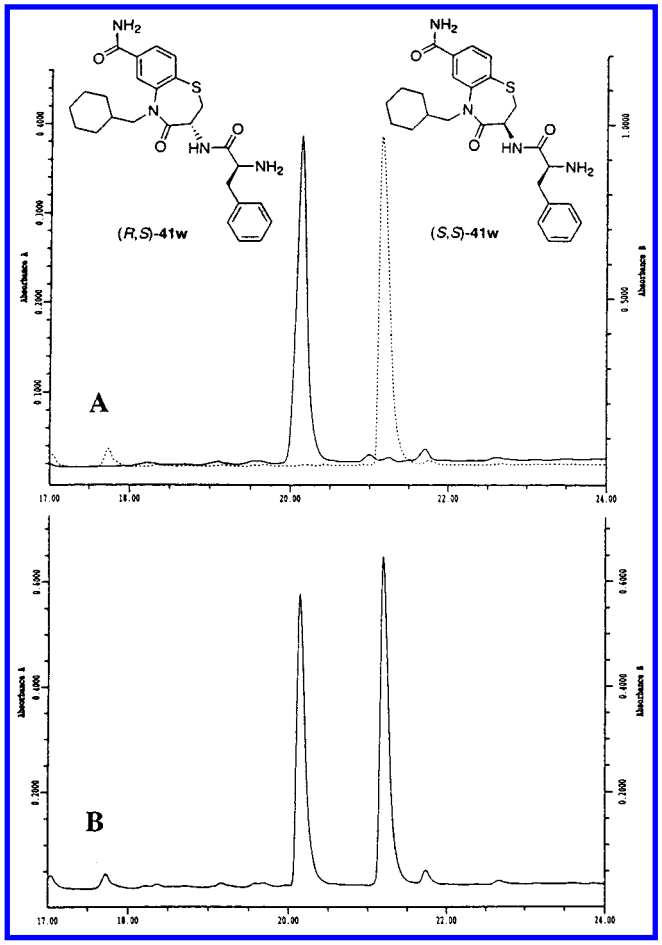
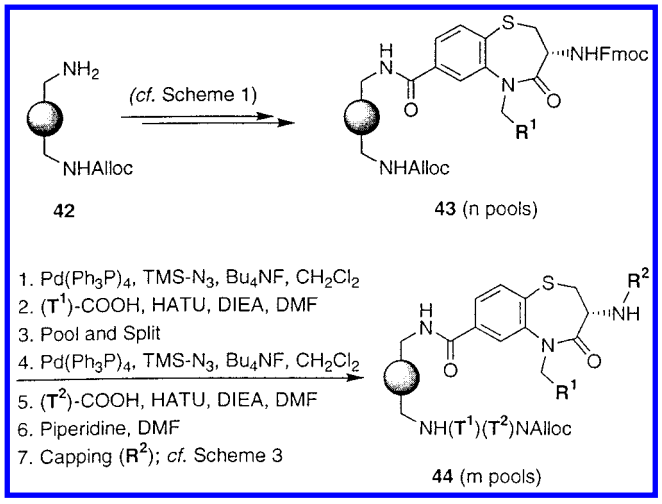


Figure 1. RP-HPLC analysis of (*R*,*S*)-**41w** (assembled from L-Fmoc-cysteine and L-Boc-Phe) vs (*S*,*S*)-**41w** (from D-Fmoc-cysteine and L-Boc-Phe), with UV detection at $\lambda = 220$ nm. **A**: Chromatogram of (*R*,*S*)-**41w** (solid line) superimposed with that of (*S*,*S*)-**41w** (dotted line); **B**: Chromatogram obtained by co-injection of (*R*,*S*)-**41w** and (*S*,*S*)-**41w**.

Scheme 4



Japan Spectroscopic Digital Polarimeter, model DIP-370. Analytical HPLC relied on the use of a Beckman System Gold module 126, equipped with a diode array module 168 detector (detection at $\lambda = 220/280$ nm), and a Vydac RP column 218TP (4.6 mm × 250 mm), used at a flow-rate of 1 mL/min. Preparative HPLC was carried out using a Beckman System Gold module 126, equipped with a Waters PrepPak column charged with DeltaPak cartridges (40 mm × 100 mm, C18, 15 μm, 100 Å), monitoring at $\lambda = 220$ nm. Mixtures of acetonitrile and H_2O, containing 0.1% (v/v) TFA, were used as the solvent system, with a gradient starting at 15% acetonitrile and increasing to 95% within 30 min.

General Procedure for Determination of Fmoc Numbers. A measured quantity *n* of resin (0.002 g < *n* < 0.010 g) was placed in a 4 mL Alltech tube and allowed to react with 500 μL of a solution of 30% (v/v) piperidine in NMP for 30 min. The solution was collected, and an aliquot (20 μL) was removed, diluted by a factor of 50 with 30% piperidine in NMP, and analyzed in a Hewlett-Packard 8452A Diode Array spectrophotometer ($d = 1$ cm), measuring the absorbance *D* at $\lambda = 302$ nm. Given the molar extinction coefficient of the piperidine/dibenzofulvene adduct of 8100 L mol^{-1} cm^{-1}, the loading *L* in mmol of compound per g of resin was then calculated as $L = (25 \times D)/(8100 \times n)$.

General Method for Isolation and Purification of the Products. From the dry resin, an aliquot of 300 mg was removed and submitted to TFA cleavage by adding 6 mL of a 90% (v/v) solution of TFA in CH_2Cl_2 at room temperature. After 30 min, the supernatant was collected, the resin was washed with another 6 mL of CH_2Cl_2, and the combined filtrates were concentrated on a SpeedVac. The dried residue was subsequently redissolved in 3−4 mL of DMSO for purification by preparative RP-HPLC (vide supra). The product fractions were lyophilized to afford the desired compound as a white to off-white powder, in purities exceeding 99% based on HPLC analysis with UV detection at $\lambda = 220$ nm. Yields were calculated on the basis of the loading of the resin as determined from its Fmoc number value.

Coupling of 11 to Resin (12). To 25 g of ArgoGel-Rink resin (8.25 mmol) in a 250 mL peptide vessel was added 100 mL of a 20% (v/v) solution of piperidine in DMF at room temperature. The suspension was allowed to mix at room temperature for 20 min. The supernatant was drained off and replaced by another 100 mL of fresh reagent. After another 20 min mixing time, the solution was drained off, and the resin was washed with DMF (6×), CH_2Cl_2 (2×), MeOH (2×), and CH_2Cl_2 (4×) and then dried in vacuo. To the dry resin was added a solution of **11** (5.55 g, 30 mmol), HATU (11.40 g, 30 mmol), and DIEA (10.2 mL, 60 mmol) in anhydrous DMF (150 mL) at room temperature, and the mixture allowed to react at room temperature for 12 h. The supernatant was drained off, and the resin was washed with DMF (5×), CH_2Cl_2 (3×), MeOH (3×), and CH_2Cl_2 (3×) and dried in vacuo.

L-*N*-(Fluorenylmethyloxycarbonyl)-cysteine and D-*N*-(Fluorenylmethyloxycarbonyl)-cysteine (L-13 and D-13). To a solution of L-Fmoc-Cys(Trt)-OH (10.0 g, 17 mmol) in 50 mL of CH_2Cl_2 were added triethylsilane (13.6 mL, 85 mmol) and TFA (6.5 mL, 85 mmol) at room temperature. After 60 min, the mixture was concentrated in vacuo to afford a yellowish oil. The latter was redissolved in CH_2Cl_2 and again concentrated several times, until a white precipitate formed, at which point the suspension was diluted with an equal volume of hexane. After removal of the solvents, the dry white solid was placed in a Büchner funnel and washed twice with 80 mL of toluene to remove most of the triphenylmethane. The remaining white solid (4.9 g, 84%, purity >92% by HPLC), L-**13**, was dried in vacuo and used without further purification for the ensuing fluorine displacement. $[\alpha]^{23}_D = -24.8$ (*c* 2.3, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73 (m, broad, 1H), 3.0 (m, 1H), 3.1 (m, 1H), 4.15 (m, 1H), 4.2−4.3 (m, 3H), 7.6 (m, 4H), 7.9 (m, 3H), 8.1 (m, 2H), 13.1 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.5, 46.6, 56.6, 65.7, 120.1, 125.3, 127.1, 127.6, 140.7, 143.8, 156.0, 171.9. The same protocol was used for D-Fmoc-Cys(Trt)-OH, providing D-**13**. $[\alpha]^{23}_D = +26.3$ (*c* 2.0, DMF); all other analytical data identical to those of L-**13**.

(*R*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-(2-nitro-4-carbamoylphenyl)-cysteine ((*R*)-14a). To 2.0 g of resin **12** (approximately 0.6 mmol) placed in a 25 mL peptide vessel was added a solution of L-**13** (340 mg, 1.0 mmol) and DIEA (350 μL, 2.0 mmol) in 15 mL of anhydrous DMF at room temperature. After a 24 h mixing period at ambient temperature, the supernatant was drained off, and the resin (*R*)-**14** was washed with DMF (5×), CH_2Cl_2 (1×), MeOH (2×), and CH_2Cl_2 (5×) and dried in vacuo. The product was isolated

according to the standard method (vide supra) to yield 29 mg (76%) of (*R*)-**14a** as a yellow powder. $[\alpha]^{23}_D = +11.1$ (*c* 0.97, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.34 (dd, 1H, J = 13.8, 10.2 Hz), 3.62 (dd, 1H, J = 13.5, 4.2 Hz), 4.2−4.3 (m, 4H), 7.31 (t, 2H, J = 7.2 Hz), 7.41 (t, 2H, J = 7.5 Hz), 7.68 (s, broad, 1H), 7.69 (d, 2H, J = 8.1 Hz), 7.78 (d, 1H, J = 9.0 Hz), 7.89 (d, 2H, J = 7.2 Hz), 7.97 (d, 1H, J = 8.7 Hz), 8.19 (dd, 1H, J = 8.7, 1.5 Hz), 8.29 (s, broad, 1H), 8.68 (d, 1H, J = 1.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 33.0, 46.5, 52.3, 65.8, 120.0, 124.9, 125.0, 125.1, 126.9, 127.0, 127.5, 130.9, 132.3, 139.1, 140.5, 143.5, 145.3, 155.7, 165.0, 171.3; HR−FABMS *m/z* calcd for MH^+ ($C_{25}H_{22}N_3O_7S^+$) 508.1178, obsd 508.1168.

(*S*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-(2-nitro-4-carbamoylphenyl)-cysteine ((*S*)-14a). The same synthetic protocol was followed as for (*S*)-**14a**, using D-**13** (340 mg, 1.0 mmol) instead of L-**13**. The product was isolated according to the standard method (vide supra): 30 mg (79%) of (*S*)-**14a** as a yellow powder. $[\alpha]^{23}_D = -8.6$ (*c* 1.01, DMF); all other analytical data identical to those of (*R*)-**14a**.

(*R*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-(2-amino-4-carbamoylphenyl)-cysteine ((*R*)-15a). To 2.0 g of resin (*R*)-**14** (approximately 0.5 mmol) placed in a 25 mL peptide vessel was added a solution of $SnCl_2 \cdot 2H_2O$ (6.77 g, 30 mmol) in 15 mL DMF at room temperature. After 24 h, the solution was drained off, and the resin (*R*)-**15** was washed with DMF (5×), CH_2Cl_2 (1×), MeOH (2×), and CH_2Cl_2 (4×) and dried in vacuo. The product was isolated according to the standard method (vide supra): 30 mg (84%) of (*R*)-**15a** as an off-white powder. $[\alpha]^{23}_D = -57.8$ (*c* 0.83, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.98 (dd, 1H, J = 13.5, 9.9 Hz), 3.18 (dd, 1H, J = 13.5, 3.9 Hz), 4.0 (m, 1H), 4.2−4.35 (m, 3H), 7.05 (dd, 1H, J = 8.1, 2.1 Hz), 7.2−7.45 (m, 7H), 7.73 (d, 2H, J = 7.5 Hz), 7.8−7.9 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.7, 46.6, 53.3, 65.7, 114.3, 115.8, 120.0, 125.1, 126.9, 127.5, 133.9, 135.2, 140.5, 143.6, 147.5, 155.7, 167.7, 171.9; HR−FABMS *m/z* calcd for MH^+ ($C_{25}H_{24}N_3O_5S^+$) 478.1437, obsd 478.1430.

(*S*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-(2-amino-4-carbamoylphenyl)-cysteine ((*S*)-15a). The same synthetic protocol was followed as for (*R*)-**15a**, starting from 2.0 g of resin (*S*)-**14**. The product was isolated according to the standard method (vide supra): 27 mg (76%) of (*S*)-**15a** as an off-white powder. $[\alpha]^{23}_D = +62.7$ (*c* 1.17, DMF); all other analytical data identical to those of (*R*)-**15a**.

General Procedure for the Reductive Alkylation of the Primary Aniline (15) with Nonenolizable Aldehydes. To 200 mg portions (approximately 50 μmol) of resin **15** in 8 mL screw-cap glass vials were added 3.0 mL of a 0.2M solution of the respective aldehydes in dry $CH(OMe)_3$/DMF 9:1 and 600 μL of a 6% (v/v) solution of HOAc in MeOH at room temperature. The vials were then placed in a heat block heated to 45−50 °C, and the reactions were allowed to proceed under gentle agitation from a shaker for 18 h. After this time, 3.0 mL of a 1 M solution of $NaCNBH_3$ in THF was added, and agitation at 45−50 °C was continued for another 6 h. The resulting resin batches **17** were then transferred to 8 mL polypropylene filter tubes and washed with MeOH (3×), H_2O (2×), 2% HOAc (aqueous) (4×), H_2O (2×), MeOH (2×), CH_2Cl_2 (1×), DMF (3×), and CH_2Cl_2 (4×). The secondary anilines **22** were isolated from **17** according to the standard method described above.

(*R*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-(2-{[(4-methylthiophenyl)methyl]amino}-4-carbamoylphenyl)-cysteine ((*R*)-22c). The product was synthesized from resin (*R*)-**15** and aldehyde **21c** by means of the general synthetic procedure and isolated according to the standard method (vide supra): 18 mg (46%) of (*R*)-**22c** as an off-white powder. $[\alpha]^{23}_D = -53.3$ (*c* 0.15, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.41 (s, 3H), 2.99 (dd, 1H, J = 13.5, 10.2 Hz), 3.25 (dd, 1H, J = 13.8, 4.2 Hz), 3.99 (m, 1H), 4.2−4.35 (m, 3H), 4.41 (s, 2H), 6.2 (s, broad, 1H), 7.0 (m, 2H), 7.15−7.45 (m, 10H), 7.74 (d, 2H, J = 7.5 Hz), 7.8−7.9 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.8, 34.8, 45.5, 46.6, 53.3, 65.7, 109.2, 114.9, 118.8, 120.0, 125.1, 125.9, 126.9, 127.3, 127.5, 134.6, 135.4, 135.9, 136.2, 140.5, 143.6, 147.8, 155.8, 167.6, 171.9; HR−FABMS *m/z* calcd for MH^+ ($C_{33}H_{32}N_3O_5S_2^+$) 614.1783, obsd 614.1778.

(*S*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-(2-{[(4-methylthiophenyl)methyl]amino}-4-carbamoylphenyl)-cysteine ((*S*)-22c). The product was synthesized from resin (*S*)-**15** and aldehyde **21c** by means of the general synthetic procedure and isolated according to the standard method (vide supra): 21 mg (51%) of (*S*)-**22c** as an off-white powder. $[\alpha]^{23}_D = +59.3$ (*c* 1.35, DMF); all other analytical data identical to those of (*R*)-**22c**.

(*R*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-(2-{[(3,4-methylenedioxyphenyl)methyl]amino}-4-carbamoylphenyl)-cysteine ((*R*)-22e). The product was synthesized from resin (*R*)-**15** and aldehyde **21e** by means of the general synthetic procedure and isolated according to the standard method (vide supra): 16 mg (35%) of (*R*)-**22e** as an off-white powder. $[\alpha]^{23}_D = -52.9$ (*c* 0.51, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.99 (dd, 1H, J = 13.5, 10.2 Hz), 3.22 (dd, 1H, J = 13.5, 3.9 Hz), 4.0 (m, 1H), 4.2−4.3 (m, 3H), 4.34 (s, 2H), 5.935 (s, 1H), 5.941 (s, 1H), 6.2 (s, broad, 1H), 6.80 (s, 2H), 6.89 (s, 1H), 7.02 (m, 2H), 7.25 (s, broad, 1H), 7.3−7.45 (m, 5H), 7.74 (d, 2H, J = 6.9 Hz), 7.84 (s, broad, 1H), 7.86 (d, 1H, J = 8.4 Hz), 7.90 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.9, 45.8, 46.6, 53.3, 65.6, 100.6, 107.3, 107.9, 109.2, 114.9, 119.0, 119.7, 120.0, 125.1, 126.9, 127.5, 133.3, 134.4, 135.3, 140.5, 143.6, 145.8, 147.1, 147.8, 155.8, 167.6, 171.8; ESI−MS *m/z* calcd for MH^+ ($C_{33}H_{30}N_3O_7S^+$) 612.18, obsd 612.25.

(*R*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-(2-{[(thien-3-yl)methyl]amino}-4-carbamoylphenyl)-cysteine ((*R*)-22m). The product was synthesized from resin (*R*)-**15** and aldehyde **21m** by means of the general synthetic procedure and isolated according to the standard method (vide supra): 20 mg (47%) of (*R*)-**22m** as an off-white powder. $[\alpha]^{23}_D = -48.0$ (*c* 1.00, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.99 (dd, 1H, J = 13.5, 10.2 Hz), 3.21 (dd, 1H, J = 13.5, 4.5 Hz), 3.99 (m, 1H), 4.2−4.35 (m, 3H), 4.43 (s, 2H), 7.0−7.1 (m, 3H), 7.25−7.45 (m, 8H), 7.74 (d, 2H, J = 7.2 Hz), 7.85 (s, broad, 1H), 7.86 (d, 1H, J = 8.4 Hz), 7.90 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 35.0, 42.1, 46.6, 53.3, 65.7, 109.2, 115.0, 119.1, 120.0, 121.1, 125.1, 126.2, 126.9, 127.0, 127.5, 134.5, 135.3, 140.5, 140.6, 143.6, 147.9, 155.8, 167.7, 171.9; ESI−MS *m/z* calcd for MH^+ ($C_{30}H_{28}N_3O_5S_2^+$) 574.15, obsd 574.15.

(*R*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-(2-{[(*N*-acetylindole-3-yl)methyl]amino}-4-carbamoylphenyl)-cysteine ((*R*)-22r). The product was synthesized from resin (*R*)-**15** and aldehyde **21r** by means of the general synthetic procedure and isolated according to the standard method (vide supra): 16 mg (33%) of (*R*)-**22r** as an off-white powder. $[\alpha]^{23}_D = -40.5$ (*c* 0.57, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.57 (s, 3H), 2.98 (dd, 1H, J = 13.5, 9.9 Hz), 3.18 (dd, 1H, J = 13.5, 4.5 Hz), 3.99 (m, 1H), 4.2−4.3 (m, 3H), 4.57 (s, 2H), 6.1 (s, broad, 1H), 7.38 (dd, 1H, J = 8.1, 1.8 Hz), 7.2−7.45 (m, 9H), 7.71 (d, 2H, J = 7.5 Hz), 7.75−7.9 (m, 6H), 8.29 (d, 1H, J = 7.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.8, 35.1, 38.5, 46.6, 53.3, 65.6, 109.3, 115.2, 115.8, 119.0, 119.3, 119.4, 120.0, 123.1, 124.5, 124.7, 125.1, 126.9, 127.5, 129.2, 134.5, 135.2, 135.3, 140.5, 143.5, 147.9, 155.7, 167.6, 168.9, 171.8; HR−FABMS *m/z* calcd for MH^+ ($C_{36}H_{33}N_4O_6S^+$) 649.2120, obsd 649.2128.

General Procedure for the Reductive Alkylation of the Primary Aniline (15) with Enolizable Aldehydes. To 200 mg portions (approximately 50 μmol) of resin **15** in 8 mL screw-cap glass vials were added 3.0 mL of a 0.2 M solution of the respective aldehydes and benzotriazole (24 mg per ml) in dry $CH(OMe)_3$/DMF 9:1 and 600 μL of a 6% (v/v) solution of HOAc in MeOH at room temperature. The reactions were allowed to proceed at room temperature under gentle agitation from a shaker for 18 h. After this time, 3.0 mL of a 1 M solution of $NaCNBH_3$ in THF was added, and agitation at ambient temperature continued for another 6 h. The resulting resin batches **17** were then transferred to 8 mL polypropylene filter tubes and washed with MeOH (3×), H_2O (2×), 2% HOAc (aqueous) (4×), H_2O (2×), MeOH (2×), CH_2Cl_2 (1×), DMF (3×), and CH_2Cl_2 (4×). The secondary anilines **22** were isolated from **17** according to the standard method described above.

(*R*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-[2-(isopentyl)-amino]-4-carbamoylphenyl)-cysteine ((*R*)-22v). The product was synthesized from resin (*R*)-**15** and aldehyde **21v** by

means of the general synthetic procedure and isolated according to the standard method (vide supra): 30 mg (73%) of (*R*)-**22v** as an off-white powder. $[\alpha]^{23}_D = -60.1$ (*c* 1.34, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.88 (d, 6H, *J* = 6.6 Hz), 1.45 (m, 2H), 1.64 (non, 1H, *J* = 6.6 Hz), 2.97 (dd, 1H, *J* = 13.5, 10.2 Hz), 3.15 (m, 3H), 3.97 (m, 1H), 4.3 (m, 3H), 7.06 (dd, 1H, *J* = 7.5, 1.8 Hz), 7.09 (d, 1H, *J* = 1.8 Hz), 7.3 (s, broad, 1H), 7.33 (t, 2H, *J* = 7.2 Hz), 7.35 (d, 1H, *J* = 7.5 Hz), 7.42 (t, 2H, *J* = 7.2 Hz), 7.74 (d, 2H, *J* = 7.5 Hz), 7.84 (d, 1H, *J* = 8.1 Hz), 7.90 (d, 2H, *J* = 7.5 Hz), 7.9 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.47, 22.50, 25.5, 35.4, 37.4, 41.1, 46.6, 53.4, 65.7, 108.8, 114.9, 119.0, 120.0, 125.1, 126.9, 127.5, 134.5, 135.5, 140.5, 143.5, 143.6, 148.2, 155.8, 167.7, 171.8; HR−FABMS *m*/*z* calcd for MH^+ ($C_{30}H_{34}N_3O_5S^+$) 548.2219, obsd 548.2213.

(*R*)-*N*-(Fluorenylmethyloxycarbonyl)-*S*-(2-{[3-(4-methoxyphenyl)propyl]-amino}-4-carbamoylphenyl)-cysteine ((*R*)-22x). The product was synthesized from resin (*R*)-**15** and aldehyde **21x** by means of the general synthetic procedure and isolated according to the standard method (vide supra): 33 mg (72%) of (*R*)-**22x** as an off-white powder. $[\alpha]^{23}_D = -44.6$ (*c* 1.42, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.83 (quin, 2H, *J* = 7.5 Hz), 2.58 (t, 2H, *J* = 7.5 Hz), 2.98 (dd, 1H, *J* = 13.5, 10.2 Hz), 3.15 (m, 3H), 3.68 (s, 3H), 3.98 (m, 1H), 4.2−4.3 (m, 3H), 6.0 (s, broad, 1H), 6.78 (d, 2H, *J* = 8.4 Hz), 7.07 (m, 4H), 7.3−7.45 (m, 6H), 7.72 (d, 2H, *J* = 7.2 Hz), 7.85 (d, 1H, *J* = 8.7 Hz), 7.9 (s, broad, 1H), 7.90 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 30.4, 31.7, 35.5, 42.4, 46.6, 53.4, 54.9, 65.7, 108.7, 113.5, 114.9, 119.0, 120.0, 125.1, 126.9, 127.5, 129.0, 133.3, 134.6, 135.6, 140.5, 143.5, 143.6, 148.2, 155.8, 157.2, 167.8, 171.9; ESI−MS *m*/*z* calcd for MH^+ ($C_{35}H_{36}N_3O_6S^+$) 626.23, obsd 626.20.

General Procedure for the Cyclization of the Secondary Anilines (17). To 300 mg resin portions of the general structure **17** (approximately 75 μmol) in 15 mL polypropylene filter tubes was added 6 mL of a 1% (v/v) solution of DIC in CH_2Cl_2/benzene (1:1 v/v) at room temperature, and the mixtures were gently agitated for 6 h at ambient temperature. After this time, the supernatants were removed, and the resulting resin batches of general structure **19** were washed with CH_2Cl_2 (3×), DMF (3×), and CH_2Cl_2 (3×) and finally dried in vacuo. The 1,5-benzothiazepin-4-ones **23** were isolated from **19** according to the standard method described above.

(*R*)-7-Carbamoyl-3-[*N*-(fluorenylmethyloxycarbonyl)-amino]-*N*(5)-[(4-methylthiophenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-23c). The product was derived from the corresponding secondary aniline according to the general synthetic procedure and isolated following the standard method (vide supra): 22 mg (61%) of (*R*)-**23c** as a snow-white powder. $[\alpha]^{23}_D = -79.0$ (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.39 (s, 3H), 3.16 (t, 1H, *J* = 11.8 Hz), 3.52 (dd, 1H, *J* = 11.3, 6.9 Hz), 4.1−4.3 (m, 4H), 4.83 (d, 1H, *J* = 15.4 Hz), 5.39 (d, 1H, *J* = 15.4 Hz), 7.09 (d, 2H, *J* = 8.5 Hz), 7.20 (d, 2H, *J* = 8.2 Hz), 7.32 (t, 2H, *J* = 7.4 Hz), 7.41 (t, 2H, *J* = 7.4 Hz), 7.58 (s, broad, 1H), 7.7 (m, 4H), 7.88 (d, 2H, *J* = 7.4 Hz), 8.01 (m, 2H), 8.15 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.5, 37.2, 46.5, 50.5, 51.4, 65.8, 120.0, 123.2, 125.0, 125.4, 125.9, 126.9, 127.5, 128.2, 130.1, 133.1, 135.3, 136.2, 136.6, 140.5, 143.46, 143.54, 144.4, 155.2, 166.1, 170.8; HR−FABMS *m*/*z* calcd for MH^+ ($C_{33}H_{30}N_3O_4S_2^+$) 596.1678, obsd 596.1675.

(*S*)-7-Carbamoyl-3-[*N*-(fluorenylmethyloxycarbonyl)-amino]-*N*(5)-[(4-methylthiophenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*S*)-23c). The product was derived from the corresponding secondary aniline according to the general synthetic procedure and isolated following the standard method (vide supra): 27 mg (69%) of (*S*)-**23c** as a snow-white powder. $[\alpha]^{23}_D = +77.4$ (*c* 1.87, $CHCl_3$); all other analytical data identical to those of (*R*)-**23c**.

(*R*)-7-Carbamoyl-3-[*N*-(fluorenylmethyloxycarbonyl)-amino]-*N*(5)-[(3,4-methylenedioxyphenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-23e). The product was derived from the corresponding secondary aniline according to the general synthetic procedure and isolated following the standard method (vide supra): 29 mg (65%) of (*R*)-**23e** as a snow-white powder. $[\alpha]^{23}_D = -68.9$ (*c* 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.17 (t, 1H, *J* = 11.5 Hz), 3.51 (dd, 1H, *J* = 11.4, 7.2 Hz), 4.15−4.3 (m, 4H), 4.77 (d, 1H, *J* = 15.1 Hz), 5.35 (d, 1H, *J* = 15.4 Hz), 5.92 (s, 2H), 6.65 (dd, 1H, *J* = 7.8, 0.9 Hz), 6.74 (d, 1H, *J* = 7.8 Hz), 6.82 (d, 1H, *J* = 0.9 Hz), 7.32 (t, 2H, *J* = 7.5 Hz), 7.41 (t, 2H, *J* = 7.2 Hz), 7.58 (s, broad, 1H), 7.65−7.75 (m, 4H), 7.88 (d, 2H, *J* = 7.5 Hz), 8.00 (s, 1H), 8.01 (d, 1H, *J* = 8.1 Hz), 8.15 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 37.2, 46.5, 50.5, 51.4, 65.8, 100.7, 107.7, 108.1, 120.0, 121.0, 123.2, 125.0, 125.9, 126.9, 127.5, 130.2, 130.3, 135.3, 136.2, 140.5, 143.47, 143.54, 144.3, 146.1, 146.8, 155.3, 166.2, 170.8; ESI−MS *m*/*z* calcd for MH^+ ($C_{33}H_{28}N_3O_6S^+$) 594.17, obsd 594.25.

(*R*)-7-Carbamoyl-3-[*N*-(fluorenylmethyloxycarbonyl)-amino]-*N*(5)-[(thien-3-yl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-23m). The product was derived from the corresponding secondary aniline according to the general synthetic procedure and isolated following the standard method (vide supra): 23 mg (69%) of (*R*)-**23m** as a snow-white powder. $[\alpha]^{23}_D = -86.1$ (*c* 1.45, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.15 (1H, t, *J* = 11.7 Hz), 3.51 (dd, 1H, *J* = 11.7, 6.9 Hz), 4.1−4.3 (m, 4H), 4.91 (d, 1H, *J* = 15.3 Hz), 5.32 (d, 1H, *J* = 15.6 Hz), 6.96 (dd, 1H, *J* = 4.9, 0.8 Hz), 7.2−7.4 (m, 6H), 7.58 (s, broad, 1H), 7.5 (m, 4H), 7.88 (d, 2H, *J* = 7.4 Hz), 7.99 (d, 1H, *J* = 1.4 Hz), 8.02 (s, broad, 1H), 8.14 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 37.1, 46.5, 46.8, 51.4, 65.8, 120.0, 122.5, 123.2, 125.0, 125.9, 126.0, 126.9, 127.3, 127.5, 130.1, 135.2, 136.2, 137.4, 140.5, 143.47, 143.54, 144.4, 155.3, 166.2, 170.5; ESI−MS *m*/*z* calcd for MH^+ ($C_{30}H_{26}N_3O_4S_2^+$) 556.14, obsd 556.15.

(*R*)-7-Carbamoyl-3-[*N*-(fluorenylmethyloxycarbonyl)-amino]-*N*(5)-[(*N*-acetylindole-3-yl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-23r). The product was derived from the corresponding secondary aniline according to the general synthetic procedure and isolated following the standard method (vide supra): 33 mg (70%) of (*R*)-**23r** as a snow-white powder. $[\alpha]^{23}_D = -52.5$ (*c* 1.65, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.47 (s, 3H), 3.18 (t, 1H, *J* = 11.5 Hz), 3.54 (dd, 1H, *J* = 11.3, 4.4 Hz), 4.1−4.3 (m, 4H), 5.19 (d, 1H, *J* = 16.2 Hz), 5.28 (d, 1H, *J* = 16.2 Hz), 7.2−7.4 (m, 6H), 7.54 (d, 1H, *J* = 7.7 Hz), 7.57 (s, broad, 1H), 7.7 (m, 5H), 7.9 (m, 2H), 8.01 (d, 1H, *J* = 1.7 Hz), 8.10 (d, 1H, *J* = 8.0 Hz), 8.16 (s, broad, 1H), 8.27 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.6, 36.9, 43.7, 46.6, 51.8, 65.8, 115.7, 117.3, 119.4, 119.93, 119.99, 123.0, 124.8, 124.9, 125.0, 125.9, 126.9, 127.4, 127.5, 128.7, 129.8, 135.0, 135.3, 136.4, 140.48, 140.54, 143.4, 143.5, 144.8, 155.5, 166.3, 168.8, 170.8; HR−FABMS *m*/*z* calcd for MH^+ ($C_{36}H_{31}N_4O_5S^+$) 630.2015, obsd 630.2005.

(*R*)-7-Carbamoyl-3-[*N*-(fluorenylmethyloxycarbonyl)-amino]-*N*(5)-isopentyl-1,5-benzothiazepin-4(5*H*)-one ((*R*)-23v). The product was derived from the corresponding secondary aniline according to the general synthetic procedure and isolated following the standard method (vide supra): 25 mg (62%) of (*R*)-**23v** as a snow-white powder. $[\alpha]^{23}_D = -134.9$ (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 (d, 3H, *J* = 6.6 Hz), 0.83 (d, 3H, *J* = 6.6 Hz), 1.19 (m, 1H), 1.35 (m, 1H), 1.54 (m, 1H), 3.10 (t, 1H, *J* = 11.5 Hz), 3.5 (m, 2H), 4.08 (m, 1H), 4.15−4.35 (m, 4H), 7.32 (t, 2H, *J* = 7.4 Hz), 7.41 (t, 2H, *J* = 7.1 Hz), 7.60 (s, broad, 1H), 7.68 (dd, 2H, *J* = 6.9, 5.5 Hz), 7.73 (d, 1H, *J* = 8.0 Hz), 7.79 (dd, 1H, *J* = 8.1, 1.4 Hz), 7.88 (d, 2H, *J* = 7.1 Hz), 7.90 (d, 1H, *J* = 6.9 Hz), 7.99 (d, 1H, *J* = 1.5 Hz), 8.18 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.2, 22.4, 25.3, 36.2, 37.0, 46.5, 46.6, 51.1, 65.7, 119.9, 123.5, 125.0, 126.0, 126.9, 127.5, 130.7, 135.1, 136.3, 140.5, 143.5, 144.7, 155.2, 166.1, 169.9; HR−FABMS *m*/*z* calcd for MH^+ ($C_{30}H_{32}N_3O_4S^+$) 530.2114, obsd 530.2115.

(*R*)-7-Carbamoyl-3-[*N*-(fluorenylmethyloxycarbonyl)-amino]-*N*(5)-[3-(4-methoxyphenyl)propyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-23x). The product was derived from the corresponding secondary aniline according to the general synthetic procedure and isolated following the standard method (vide supra): 25 mg (55%) of (*R*)-**23x** as a snow-white powder. $[\alpha]^{23}_D = -113.0$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.66 (m, 2H), 2.47 (m, 2H), 3.13 (t, 1H, *J* = 12.0 Hz), 3.5 (m, 2H), 3.68 (s, 3H), 4.1 (m, 1H), 4.15−4.3 (m, 4H), 6.77 (d, 2H, *J* = 8.4 Hz), 6.97 (d, 2H, *J* = 8.7 Hz), 7.31 (t, 2H, *J* = 7.2 Hz), 7.41 (t, 2H, *J* = 7.5 Hz), 7.60 (s, broad, 1H), 7.68 (t, 2H,

J = 6.6 Hz), 7.75 (d, 1H, J = 8.1 Hz), 7.80 (dd, 1H, J = 8.1, 1.5 Hz), 7.88 (d, 2H, J = 7.5 Hz), 7.92 (d, 1H, J = 8.1 Hz), 7.96 (d, 1H, J = 1.5 Hz), 8.16 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.6, 31.6, 37.0, 46.5, 47.9, 51.2, 54.8, 65.7, 113.5, 120.0, 123.7, 125.0, 126.1, 126.9, 127.5, 128.9, 130.6, 133.1, 135.1, 136.3, 140.5, 143.5, 144.7, 155.2, 157.1, 166.2, 170.0; ESI−MS m/z calcd for MH^+ ($C_{35}H_{34}N_3O_5S^+$) 608.22, obsd 608.20.

General Procedure for the Synthesis of the 3-(Acylamino)-1,5-benzothiazepin-4-ones (32). To 300 mg resin portions of the general structure **19** (approximately 75 μmol) in 15 mL polypropylene filter tubes was added 6 mL of a 20% (v/v) solution of piperidine in DMF at room temperature, and the mixtures were gently agitated for 20 min. After removal of the supernatants, the resulting resin batches of general structure **20** were washed with DMF (6×), CH_2Cl_2 (4×), and DMF (3×) and subsequently resuspended in a solution containing 3-methoxypropionic acid (76 μL, 0.8 mmol), DIC (128 μL, 0.8 mmol), and a spatula tip of DMAP in 4 mL of anhydrous DMF. After a reaction time of 2 h at ambient temperature, the supernatants were removed, and the resulting resin batches of general structure **32** were washed with DMF (5×), CH_2Cl_2 (1×), MeOH (2×), and CH_2Cl_2 (4×) and finally dried in vacuo. The 3-(acylamino)-1,5-benzothiazepinones **36** were isolated from **32** according to the standard method described above.

(*R*)-7-Carbamoyl-3-[*N*-(3-methoxypropionyl)amino]-*N*-(5)-[(4-methylthiophenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-36c). The product was isolated according to the standard method (vide supra): 20 mg (72%) of (*R*)-**36c** as a snow-white powder. $[\alpha]^{23}_D = -106.5$ (c 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (t, 2H, J = 6.3 Hz), 2.40 (s, 3H), 3.09 (t, 1H, J = 11.7 Hz), 3.17 (s, 3H), 3.45 (m, 1H), 3.46 (t, 2H, J = 6.3 Hz), 4.45 (m, 1H), 4.81 (d, 1H, J = 15.6 Hz), 5.42 (d, 1H, J = 15.9 Hz), 7.10 (d, 2H, J = 8.4 Hz), 7.20 (d, 2H, J = 8.4 Hz), 7.58 (s, broad, 1H), 7.65 (d, 1H, J = 8.1 Hz), 7.71 (dd, 1H, J = 8.1, 1.8 Hz), 8.01 (d, 1H, J = 1.8 Hz), 8.15 (s, broad, 1H), 8.50 (d, 1H, J = 8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.5, 35.4, 37.5, 48.9, 50.3, 57.8, 67.9, 123.3, 125.4, 125.9, 128.3, 130.2, 133.1, 135.2, 136.2, 136.7, 144.3, 166.1, 169.4, 170.3; HR−FABMS m/z calcd for MH^+ ($C_{22}H_{26}N_3O_4S_2^+$) 460.1365, obsd 460.1366.

(*S*)-7-Carbamoyl-3-[*N*-(3-methoxypropionyl)amino]-*N*-(5)-[(4-methylthiophenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*S*)-36c). The product was isolated according to the standard method (vide supra): 18 mg (64%) of (*S*)-**36c** as a snow-white powder. $[\alpha]^{23}_D = +111.5$ (c 0.82, $CHCl_3$); all other analytical data identical to those of (*R*)-**36c**.

(*R*)-7-Carbamoyl-3-[*N*-(3-methoxypropionyl)amino]-*N*-(5)-[(3,4-methylenedioxyphenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-36e). The product was isolated according to the standard method (vide supra): 23 mg (67%) of (*R*)-**36e** as a snow-white powder. $[\alpha]^{23}_D = -91.9$ (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (t, 2H, J = 6.3 Hz), 3.09 (t, 1H, J = 12.0 Hz), 3.16 (s, 3H), 3.45 (m, 3H), 4.45 (m, 1H), 4.76 (d, 1H, J = 15.3 Hz), 5.36 (d, 1H, J = 15.0 Hz), 5.93 (dd, 2H, J = 3.0, 1.2 Hz), 6.69 (dd, 1H, J = 7.8, 1.8 Hz), 6.74 (d, 1H, J = 7.8 Hz), 6.82 (d, 1H, J = 1.2 Hz), 7.58 (s, broad, 1H), 7.65 (d, 1H, J = 8.1 Hz), 7.71 (dd, 1H, J = 8.1, 1.8 Hz), 8.00 (d, 1H, J = 1.8 Hz), 8.15 (s, broad, 1H), 8.50 (d, 1H, J = 8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 35.4, 37.5, 49.0, 50.4, 57.8, 67.9, 100.7, 107.7, 108.1, 121.1, 123.3, 125.9, 130.28, 130.30, 135.2, 136.2, 144.2, 146.1, 146.8, 166.2, 169.5, 170.4; HR−FABMS m/z calcd for MH^+ ($C_{22}H_{24}N_3O_6S^+$) 458.1386, obsd 458.1397.

(*R*)-7-Carbamoyl-3-[*N*-(3-methoxypropionyl)amino]-*N*-(5)-[(thien-3-yl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-36m). The product was isolated according to the standard method (vide supra): 15 mg (58%) of (*R*)-**36m** as a snow-white powder. $[\alpha]^{23}_D = -126.7$ (c 0.36, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (t, 2H, J = 6.3 Hz), 3.08 (t, 1H, J = 11.4 Hz), 3.16 (s, 3H), 3.45 (m, 3H), 4.45 (m, 1H), 4.91 (d, 1H, J = 15.6 Hz), 5.31 (d, 1H, J = 15.9 Hz), 6.96 (dd, 1H, J = 5.1, 1.2 Hz), 7.26 (dd, 1H, J = 3.0, 1.2 Hz), 7.39 (dd, 1H, J = 4.8, 3.0 Hz), 7.57 (s, broad, 1H), 7.66 (d, 1H, J = 8.1 Hz), 7.72 (dd, 1H, J = 8.1, 1.8 Hz), 7.99 (d, 1H, J = 1.8 Hz), 8.14 (s, broad, 1H), 8.50 (d, 1H, J = 7.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 35.4, 37.4, 46.6, 49.0, 57.8, 67.9, 122.5, 123.3, 125.9, 126.0, 127.4, 130.2, 135.2, 136.2, 137.4, 144.4, 166.2, 169.4, 170.1; HR−FABMS m/z calcd for MH^+ ($C_{19}H_{22}N_3O_4S_2^+$) 420.1052, obsd 420.1057.

(*R*)-7-Carbamoyl-3-[*N*-(3-methoxypropionyl)amino]-*N*-(5)-[(*N*-acetylindole-3-yl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-36r). The product was isolated according to the standard method (vide supra): 20 mg (53%) of (*R*)-**36r** as a snow-white powder. $[\alpha]^{23}_D = -80.1$ (c 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.36 (t, 2H, J = 6.6 Hz), 2.55 (s, 3H), 3.10 (t, 1H, J = 11.4 Hz), 3.17 (s, 3H), 3.47 (t, 2H, J = 6.3 Hz), 3.49 (m, 1H), 4.46 (m, 1H), 5.13 (d, 1H, J = 16.5 Hz), 5.32 (d, 1H, J = 16.5 Hz), 7.21 (td, 1H, J = 7.8, 1.2 Hz), 7.31 (td, 1H, J = 7.4, 1.2 Hz), 7.64 (d, 1H, J = 7.5 Hz), 7.58 (s, broad, 1H), 7.65 (d, 1H, J = 8.1 Hz), 7.72 (dd, 1H, J = 8.1, 1.8 Hz), 7.72 (s, 1H), 8.03 (d, 1H, J = 1.8 Hz), 8.16 (s, broad, 1H), 8.25 (d, 1H, J = 8.1 Hz), 8.58 (d, 1H, J = 7.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.7, 35.4, 37.1, 43.4, 49.5, 57.8, 67.8, 115.6, 117.2, 119.4, 123.0, 123.2, 124.7, 125.2, 125.9, 128.8, 130.0, 135.0, 135.2, 136.3, 144.7, 166.3, 168.9, 169.7, 170.3; HR−FABMS m/z calcd for M^+ ($C_{25}H_{26}N_4O_5S^+$) 494.1624, obsd 494.1623.

(*R*)-7-Carbamoyl-3-[*N*-(3-methoxypropionyl)amino]-*N*-(5)-isopentyl-1,5-benzothiazepin-4(5*H*)-one ((*R*)-36v). The product was isolated according to the standard method (vide supra): 22 mg (73%) of (*R*)-**36v** as a snow-white powder. $[\alpha]^{23}_D$ = N/A; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 (d, 3H, J = 6.6 Hz), 0.83 (d, 3H, J = 6.6 Hz), 1.19 (m, 1H), 1.35 (m, 1H), 1.54 (non, 1H, J = 6.6 Hz), 2.32 (t, 2H, J = 6.3 Hz), 3.01 (t, 1H, J = 11.7 Hz), 3.16 (s, 3H), 3.45 (m, 4H), 4.3 (m, 2H), 7.59 (s, broad, 1H), 7.73 (d, 1H, J = 8.1 Hz), 7.78 (dd, 1H, J = 8.1, 1.5 Hz), 7.98 (d, 1H, J = 1.5 Hz), 8.17 (s, broad, 1H), 8.39 (d, 1H, J = 8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.2, 22.4, 25.3, 35.4, 36.2, 37.3, 46.5, 48.6, 57.8, 67.9, 123.6, 126.1, 130.7, 135.1, 136.3, 144.6, 166.1, 169.3, 169.5; HR−FABMS m/z calcd for MH^+ ($C_{19}H_{28}N_3O_4S^+$) 394.1801, obsd 394.1789.

(*R*)-7-Carbamoyl-3-[*N*-(3-methoxypropionyl)amino]-*N*-(5)-[3-(4-methoxyphenyl)propyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-36x). The product was isolated according to the standard method (vide supra): 19 mg (54%) of (*R*)-**36x** as a snow-white powder. $[\alpha]^{23}_D = -151.9$ (c 0.49, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.66 (m, 2H), 2.33 (t, 2H, J = 6.3 Hz), 2.5 (m, 2H), 3.04 (t, 1H, J = 12.0 Hz), 3.17 (s, 3H), 3.4−3.55 (m, 4H), 3.68 (s, 3H), 4.29 (m, 1H), 4.38 (m, 1H), 6.77 (d, 2H, J = 8.4 Hz), 6.97 (d, 2H, J = 8.4 Hz), 7.59 (s, broad, 1H), 7.75 (d, 1H, J = 8.1 Hz), 7.80 (dd, 1H, J = 8.1, 1.8 Hz), 7.95 (d, 1H, J = 1.5 Hz), 8.15 (s, broad, 1H), 8.41 (d, 1H, J = 8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.6, 31.6, 35.4, 37.3, 47.7, 48.7, 54.9, 57.7, 67.9, 113.5, 123.8, 126.1, 128.9, 130.7, 133.0, 135.1, 136.3, 144.6, 157.1, 166.2, 169.4, 169.6; HR−FABMS m/z calcd for MH^+ ($C_{24}H_{30}N_3O_5S^+$) 472.1906, obsd 472.1908.

General Procedure for the Synthesis of the 3-Ureido-1,5-benzothiazepin-4-ones (33). To 300 mg resin portions of the general structure **19** (approximately 75 μmol) in 15 mL polypropylene filter tubes was added 6 mL of a 20% (v/v) solution of piperidine in DMF at room temperature, and the mixtures were gently agitated for 20 min. After removal of the supernatants, the resulting resin batches of general structure **20** were washed with DMF (6×), CH_2Cl_2 (1×), and DMF (2×), CH_2Cl_2 (3×) and subsequently resuspended in a solution of 2-chloroethyl isocyanate (104 μL, 1.2 mmol) and NMM (132 μL, 1.2 mmol) in 4 mL of anhydrous CH_2Cl_2. After a reaction time of 2 h at ambient temperature, the supernatants were removed, and the resulting resin batches of general structure **33** were washed with CH_2Cl_2 (3×), DMF (3×), CH_2Cl_2 (1×), MeOH (2×), and CH_2Cl_2 (4×) and finally dried in vacuo. The 3-ureido-1,5-benzothiazepinones **37** were isolated from **33** according to the standard method described above.

(*R*)-7-Carbamoyl-3-{*N*-[(2-chloroethylamino)carbonyl]-amino}-*N*(5)-[(4-methylthiophenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-37c). The product was isolated according to the standard method (vide supra): 17 mg (61%) of (*R*)-**37c** as a snow-white powder. $[\alpha]^{23}_D = -86.0$ (c 0.61, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (s, 3H), 3.02 (t,

1H, J = 11.7 Hz), 3.25 (m, 2H), 3.5 (m, 3H), 4.36 (m, 1H), 4.82 (d, 1H, J = 15.3 Hz), 5.43 (d, 1H, J = 15.3 Hz), 6.55 (t, broad, 1H, J = 6 Hz), 6.71 (d, broad, 1H, J = 8 Hz), 7.10 (d, 2H, J = 8.7 Hz), 7.21 (d, 2H, J = 8.4 Hz), 7.57 (s, broad, 1H), 7.65 (d, 1H, J = 8.1 Hz), 7.70 (dd, 1H, J = 8.1, 1.5 Hz), 8.00 (d, 1H, J = 1.5 Hz), 8.14 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.5, 38.5, 41.3, 44.4, 49.8, 50.3, 123.3, 125.4, 125.9, 128.3, 130.4, 133.1, 135.1, 136.1, 136.6, 144.3, 156.2, 166.2, 171.2; HR−FABMS m/z calcd for MH$^+$ ($C_{21}H_{24}ClN_4O_3S_2^+$) 479.0978, obsd 479.0974.

(*S*)-7-Carbamoyl-3-{*N*-[(2-chloroethylamino)carbonyl]-amino}-*N*(5)-[(4-methylthiophenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*S*)-37c). The product was isolated according to the standard method (vide supra): 19 mg (61%) of (*S*)-**37c** as a snow-white powder. $[\alpha]^{23}_D$ = +81.1 (*c* 0.32, MeOH); all other analytical data identical to those of (*R*)-**37c**.

(*R*)-7-Carbamoyl-3-{*N*-[(2-chloroethylamino)carbonyl]-amino}-*N*(5)-[(3,4-methylenedioxyphenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-37e). The product was isolated according to the standard method (vide supra): 25 mg (70%) of (*R*)-**37e** as a snow-white powder. $[\alpha]^{23}_D$ = −72.9 (*c* 0.53, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.03 (t, 1H, J = 11.7 Hz), 3.25 (m, 2H), 3.5 (m, 3H), 4.33 (m, 1H), 4.76 (d, 1H, J = 15.0 Hz), 5.38 (d, 1H, J = 15.6 Hz), 5.93 (dd, 2H, J = 2.4, 1.2 Hz), 6.55 (t, broad, 1H, J = 6 Hz), 6.71 (d, broad, 1H, J = 8 Hz), 6.70 (dd, 1H, J = 7.8, 1.8 Hz), 6.74 (d, 1H, J = 7.8 Hz), 6.83 (d, 1H, J = 1.2 Hz), 7.57 (s, broad, 1H), 7.66 (d, 1H, J = 8.1 Hz), 7.70 (dd, 1H, J = 8.1, 1.5 Hz), 7.99 (d, 1H, J = 1.5 Hz), 8.13 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 38.5, 41.3, 44.4, 49.8, 50.4, 100.7, 107.7, 108.1, 121.0, 123.4, 125.9, 130.3, 130.4, 135.1, 136.1, 144.2, 146.1, 146.8, 156.3, 166.3, 171.2; HR−FABMS m/z calcd for MH$^+$ ($C_{21}H_{22}ClN_4O_5S^+$) 477.0999, obsd 477.1001.

(*R*)-7-Carbamoyl-3-{*N*-[(2-chloroethylamino)carbonyl]-amino}-*N*(5)-[(thien-3-yl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-37m). The product was isolated according to the standard method (vide supra): 15 mg (57%) of (*R*)-**37m** as a snow-white powder. $[\alpha]^{23}_D$ = −108.0 (*c* 0.40, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.01 (t, 1H, J = 11.7 Hz), 3.25 (m, 2H), 3.5 (m, 3H), 4.33 (m, 1H), 4.91 (d, 1H, J = 15.3 Hz), 5.34 (d, 1H, J = 15.3 Hz), 6.55 (t, broad, 1H, J = 5 Hz), 6.71 (d, broad, 1H, J = 8 Hz), 6.97 (dd, 1H, J = 5.1, 1.2 Hz), 7.28 (d, 1H, J = 1.2 Hz), 7.39 (dd, 1H, J = 5.1, 3.0 Hz), 7.56 (s, broad, 1H), 7.67 (d, 1H, J = 8.1 Hz), 7.71 (dd, 1H, J = 8.1, 1.5 Hz), 7.99 (d, 1H, J = 1.5 Hz), 8.13 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 38.3, 41.3, 44.4, 46.6, 49.8, 122.6, 123.4, 125.9, 126.0, 127.4, 130.4, 135.1, 136.1, 137.4, 144.4, 156.2, 166.3, 170.9; HR−FABMS m/z calcd for MH$^+$ ($C_{18}H_{20}ClN_4O_3S_2^+$) 439.0665, obsd 439.0668.

(*R*)-7-Carbamoyl-3-{*N*-[(2-chloroethylamino)carbonyl]-amino}-*N*(5)-[(*N*-acetylindole-3-yl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-37r). The product was isolated according to the standard method (vide supra): 22 mg (58%) of (*R*)-**37r** as a snow-white powder. $[\alpha]^{23}_D$ = −54.2 (*c* 0.71, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.55 (s, 3H), 3.04 (t, 1H, J = 11.7 Hz), 3.27 (m, 2H), 3.5 (m, 3H), 4.36 (m, 1H), 5.13 (d, 1H, J = 16.2 Hz), 5.35 (d, 1H, J = 16.2 Hz), 6.54 (t, broad, 1H, J = 6 Hz), 6.78 (d, broad, 1H, J = 8 Hz), 7.22 (td, 1H, J = 7.8, 1.2 Hz), 7.30 (td, 1H, J = 7.5, 1.4 Hz), 7.55 (d, 1H, J = 7.2 Hz), 7.57 (s, broad, 1H), 7.65 (d, 1H, J = 8.1 Hz), 7.70 (dd, 1H, J = 8.1, 1.5 Hz), 7.75 (s, 1H), 8.02 (d, 1H, J = 1.5 Hz), 8.14 (s, broad, 1H), 8.25 (d, 1H, J = 8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.7, 38.0, 41.4, 43.2, 44.3, 50.2, 115.6, 117.2, 119.4, 123.0, 123.3, 124.7, 125.2, 125.9, 128.8, 130.2, 135.0, 135.1, 136.2, 144.6, 156.5, 166.4, 168.8, 171.2; HR−FABMS m/z calcd for M$^+$ ($C_{24}H_{24}ClN_5O_4S^+$) 513.1238, obsd 513.1249.

(*R*)-7-Carbamoyl-3-{*N*-[(2-chloroethylamino)carbonyl]-amino}-*N*(5)-isopentyl-1,5-benzothiazepin-4(5*H*)-one ((*R*)-37v). The product was isolated according to the standard method (vide supra): 26 mg (83%) of (*R*)-**37v** as a snow-white powder. $[\alpha]^{23}_D$ = −154.6 (*c* 0.93, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 (d, 3H, J = 6.6 Hz), 0.83 (d, 3H, J = 6.6 Hz), 1.20 (m, 1H), 1.36 (m, 1H), 1.54 (non, 1H, J = 6.6 Hz), 2.93 (t, 1H, J = 11.7 Hz), 3.24 (m, 2H), 3.43 (dd, 1H, J = 10.8, 6.6 Hz), 3.5 (m, 3H), 4.3 (m, 2H), 6.55 (t, broad, 1H, J = 6 Hz), 6.61 (d, broad, 1H, J = 8 Hz), 7.58 (s, broad, 1H), 7.73 (d, 1H, J = 8.1 Hz), 7.78 (dd, 1H, J = 8.1, 1.5 Hz), 7.97 (d, 1H, J = 1.5 Hz), 8.16 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.2, 22.4, 25.3, 36.2, 38.3, 41.3, 44.4, 46.4, 49.4, 123.7, 126.1, 130.9, 135.0, 136.2, 144.6, 156.2, 166.2, 170.3; HR−FABMS m/z calcd for MH$^+$ ($C_{18}H_{26}ClN_4O_3S^+$) 413.1414, obsd 413.1415.

(*R*)-7-Carbamoyl-3-{*N*-[(2-chloroethylamino)carbonyl]-amino}-*N*(5)-[3-(4-methoxyphenyl)propyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-37x). The product was isolated according to the standard method (vide supra): 21 mg (56%) of (*R*)-**37x** as a snow-white powder. $[\alpha]^{23}_D$ = −112.4 (*c* 0.11, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.66 (m, 2H), 2.50 (m, 2H), 2.97 (t, 1H, J = 11.4 Hz), 3.24 (m, 2H), 3.5 (m, 4H), 3.68 (s, 3H), 4.28 (m, 2H), 6.54 (t, broad, 1H, J = 6 Hz), 6.63 (d, broad, 1H, J = 8 Hz), 6.77 (d, 2H, J = 8.7 Hz), 6.97 (d, 2H, J = 8.4 Hz), 7.59 (s, broad, 1H), 7.75 (d, 1H, J = 8.1 Hz), 7.79 (dd, 1H, J = 8.1, 1.5 Hz), 7.93 (d, 1H, J = 1.5 Hz), 8.14 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.7, 31.6, 38.2, 41.3, 44.4, 47.7, 49.5, 54.9, 113.5, 123.8, 126.1, 128.9, 130.8, 133.0, 135.0, 136.3, 144.6, 156.2, 157.2, 166.2, 170.4; HR−FABMS m/z calcd for MH$^+$ ($C_{23}H_{28}ClN_4O_4S^+$) 491.1520, obsd 491.1508.

General Procedure for the Synthesis of the 3-(Sulfonylamino)-1,5-benzothiazepin-4-ones (34). To 300 mg resin portions of the general structure **19** (approximately 75 μmol) in 15 mL polypropylene filter tubes was added 6 mL of a 20% (v/v) solution of piperidine in DMF at room temperature, and the mixtures were gently agitated for 20 min. After removal of the supernatants, the resulting resin batches of general structure **20** were washed with DMF (6×), CH_2Cl_2 (1×), DMF (2×), and CH_2Cl_2 (3×) and subsequently resuspended in a solution of 3,5-dimethylisoxazole-4-sulfonyl chloride (235 mg, 1.2 mmol) and NMM (132 μL, 1.2 mmol) in 4 mL of anhydrous CH_2Cl_2. In the case of the 1,5-benzothiazepinones derived from aldehyde **21c**, a solution of 1-propanesulfonyl chloride (136 μL, 1.2 mmol) and NMM (132 μL, 1.2 mmol) in 4 mL of anhydrous CH_2Cl_2 was used. After a reaction time of 2 h at ambient temperature, the supernatants were removed, and the resulting resin batches of general structure **34** were washed with CH_2Cl_2 (3×), DMF (3×), CH_2Cl_2 (1×), MeOH (2×), and CH_2Cl_2 (4×) and finally dried in vacuo. The 3-(sulfonylamino)-1,5-benzothiazepinones **38** and **40** were isolated from **34** according to the standard method described above.

(*R*)-7-Carbamoyl-3-[*N*-(propanesulfonyl)amino]-*N*(5)-[(4-methylthiophenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-40c). The product was isolated according to the standard method (vide supra): 17 mg (59%) of (*R*)-**40c** as a snow-white powder. $[\alpha]^{23}_D$ = −72.2 (*c* 0.49, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89 (t, 3H, J = 7.5 Hz), 1.6 (m, 2H), 2.40 (s, 3H), 2.85 (m, 2H), 3.10 (t, 1H, J = 11.7 Hz), 3.57 (dd, 1H, J = 11.1, 6.9 Hz), 3.98 (m, 1H), 4.87 (d, 1H, J = 15.3 Hz), 5.32 (d, 1H, J = 15.6 Hz), 7.11 (d, 2H, J = 8.4 Hz), 7.20 (d, 2H, J = 8.1 Hz), 7.59 (s, broad, 1H), 7.67 (d, 1H, J = 8.4 Hz), 7.73 (dd, 1H, J = 8.4, 1.8 Hz), 7.91 (d, 1H, J = 9.0 Hz), 8.01 (d, 1H, J = 1.8 Hz), 8.16 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.6, 14.6, 16.8, 51.0, 53.1, 54.5, 123.3, 125.4, 126.0, 128.2, 130.0, 133.2, 135.4, 136.3, 136.7, 144.3, 166.1, 170.5; HR−FABMS m/z calcd for MH$^+$ ($C_{21}H_{26}N_3O_4S_3^+$) 480.1085, obsd 480.1081.

(*S*)-7-Carbamoyl-3-[*N*-(propanesulfonyl)amino]-*N*(5)-[(4-methylthiophenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*S*)-40c). The product was isolated according to the standard method (vide supra): 21 mg (65%) of (*S*)-**40c** as a snow-white powder. $[\alpha]^{23}_D$ = +62.2 (*c* 1.11, MeOH); all other analytical data identical to those of (*R*)-**40c**.

(*R*)-7-Carbamoyl-3-[*N*-(3,5-dimethylisoxazole-4-sulfonyl)amino]-*N*(5)-[(3,4-methylenedioxyphenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-38e). The product was isolated according to the standard method (vide supra): 26 mg (67%) of (*R*)-**38e** as a snow-white powder. $[\alpha]^{23}_D$ = −38.9 (*c* 1.13, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 2.41 (s, 3H), 3.14 (t, 1H, J = 11.7 Hz), 3.55 (dd, 1H, J = 11.4, 6.9 Hz), 3.76 (m, 1H), 4.57 (d, 1H, J = 15.0 Hz), 5.08 (d, 1H, J = 15.3 Hz), 5.91 (d, 2H, J = 1.2 Hz), 6.58 (dd, 1H, J = 7.8, 1.7 Hz), 6.69 (m, 2H), 7.64 (s, broad, 1H), 7.67 (d, 1H, J = 7.8

Hz), 7.75 (dd, 1H, J = 7.8, 1.8 Hz), 8.01 (d, 1H, J = 1.8 Hz), 8.19 (s, broad, 1H), 8.92 (d, 1H, J = 9.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.5, 12.1, 38.4, 49.8, 52.7, 100.7, 107.7, 108.2, 115.6, 121.2, 122.9, 126.3, 129.7, 130.0, 135.8, 136.2, 143.4, 146.2, 146.8, 157.4, 165.8, 169.2, 172.0; HR−FABMS *m/z* calcd for M^+ ($C_{23}H_{22}N_4O_7S_2^+$) 530.0930, obsd 530.0931.

(*R*)-7-Carbamoyl-3-[*N*-(3,5-dimethylisoxazole-4-sulfonyl)amino]-*N*(5)-[(thien-3-yl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-38m). The product was isolated according to the standard method (vide supra): 19 mg (64%) of (*R*)-**38m** as a snow-white powder. $[\alpha]^{23}_D$ = −58.6 (*c* 0.50, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 2.40 (s, 3H), 3.12 (t, 1H, J = 11.7 Hz), 3.54 (dd, 1H, J = 11.1, 6.6 Hz), 3.9 (m, 1H), 4.73 (d, 1H, J = 15.3 Hz), 5.05 (d, 1H, J = 15.0 Hz), 6.82 (dd, 1H, J = 5.1, 1.5 Hz), 7.16 (d, 1H, J = 1.8 Hz), 7.35 (dd, 1H, J = 5.1, 3 Hz), 7.63 (s, broad, 1H), 7.68 (d, 1H, J = 7.8 Hz), 7.76 (dd, 1H, J = 8.1, 1.8 Hz), 8.00 (d, 1H, J = 1.8 Hz), 8.18 (s, broad, 1H), 8.92 (d, 1H, J = 9.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.5, 12.1, 38.2, 46.0, 52.7, 115.6, 122.9, 123.0, 126.0, 126.3, 127.3, 129.9, 135.7, 136.3, 136.6, 143.6, 157.4, 165.8, 168.9, 172.0; HR−FABMS *m/z* calcd for MH^+ ($C_{20}H_{21}N_4O_5S_3^+$) 493.0674, obsd 493.0663.

(*R*)-7-Carbamoyl-3-[*N*-(3,5-dimethylisoxazole-4-sulfonyl)amino]-*N*(5)-[(*N*-acetylindole-3-yl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-38r). The product was isolated according to the standard method (vide supra): 21 mg (50%) of (*R*)-**38r** as a snow-white powder. $[\alpha]^{23}_D$ = −11.6 (*c* 0.89, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 3.11 (t, 1H, J = 11.7 Hz), 3.52 (dd, 1H, J = 11.1, 6.9 Hz), 3.8 (m, 1H), 4.82 (d, 1H, J = 15.3 Hz), 5.27 (d, 1H, J = 15.6 Hz), 7.16 (td, 1H, J = 7.5, 1.2 Hz), 7.26 (td, 1H, J = 7.4, 1.2 Hz), 7.41 (d, 1H, J = 7.5 Hz), 7.62 (d, 1H, J = 8.1 Hz), 7.64 (s, 1H), 7.65 (s, broad, 1H), 7.74 (dd, 1H, J = 8.1, 1.8 Hz), 8.11 (d, 1H, J = 1.8 Hz), 8.18 (d, 1H, J = 8.1 Hz), 8.20 (s, broad, 1H), 8.94 (d, 1H, J = 9.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.5, 12.1, 23.7, 38.1, 41.9, 53.0, 115.5, 115.7, 116.2, 122.9, 123.3, 124.7, 125.9, 126.4, 128.8, 130.1, 134.7, 135.8, 136.2, 143.4, 157.3, 165.9, 168.7, 169.1, 172.0; HR−FABMS *m/z* calcd for M^+ ($C_{26}H_{25}N_5O_6S_2^+$) 567.1246, obsd 567.1255.

(*R*)-7-Carbamoyl-3-[*N*-(3,5-dimethylisoxazole-4-sulfonyl)amino]-*N*(5)-isopentyl-1,5-benzothiazepin-4(5*H*)-one ((*R*)-38v). The product was isolated according to the standard method (vide supra): 28 mg (80%) of (*R*)-**38v** as a snow-white powder. $[\alpha]^{23}_D$ = −110.4 (*c* 1.01, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73 (d, 3H, J = 6.3 Hz), 0.79 (d, 3H, J = 6.6 Hz), 1.07 (m, 1H), 1.27 (m, 1H), 1.45 (m, 1H), 2.28 (s, 3H), 2.37 (s, 3H), 3.07 (t, 1H, J = 11.7 Hz), 3.5 (m, 2H), 3.68 (m, 1H), 3.83 (m, 1H), 7.63 (s, broad, 1H), 7.75 (d, 1H, J = 8.1 Hz), 7.81 (dd, 1H, J = 8.1, 1.8 Hz), 7.89 (d, 1H, J = 1.5 Hz), 8.21 (s, broad, 1H), 8.80 (d, 1H, J = 9.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.5, 12.0, 22.1, 22.3, 25.2, 36.0, 38.1, 46.6, 52.6, 115.6, 122.9, 126.3, 130.1, 135.7, 136.4, 144.4, 157.3, 165.8, 168.4, 171.9; HR−FABMS *m/z* calcd for MH^+ ($C_{20}H_{27}N_4O_5S_2^+$) 467.1423, obsd 467.1421.

(*R*)-7-Carbamoyl-3-[*N*-(3,5-dimethylisoxazole-4-sulfonyl)amino]-*N*(5)-[3-(4-methoxyphenyl)propyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-38x). The product was isolated according to the standard method (vide supra): 23 mg (56%) of (*R*)-**38x** as a snow-white powder. $[\alpha]^{23}_D$ = −75.9 (*c* 1.00, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (m, 2H), 2.28 (s, 3H), 2.37 (s, 3H), 2.39 (m, 2H), 3.09 (t, 1H, J = 11.7 Hz), 3.44 (quin, 1H, J = 6.9 Hz), 3.53 (dd, 1H, J = 11.1, 6.9 Hz), 3.69 (s, 3H), 3.69 (m, 1H), 3.86 (m, 1H), 6.76 (d, 2H, J = 8.7 Hz), 6.94 (d, 2H, J = 8.4 Hz), 7.64 (s, broad, 1H), 7.77 (d, 1H, J = 8.1 Hz), 7.84 (dd, 1H, J = 8.1, 1.8 Hz), 7.90 (d, 1H, J = 1.5 Hz), 8.20 (s, broad, 1H), 8.82 (d, 1H, J = 9.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.5, 12.0, 29.3, 31.4, 38.1, 47.9, 52.6, 54.9, 113.5, 115.6, 123.2, 126.4, 128.8, 130.1, 132.9, 135.7, 136.5, 144.3, 157.2, 157.3, 165.8, 168.5, 171.9; HR−FABMS *m/z* calcd for M^+ ($C_{25}H_{28}N_4O_6S_2^+$) 544.1450, obsd 544.1449.

General Procedure for the Synthesis of the 3-(Alkylamino)-1,5-benzothiazepin-4-ones (35). To 300 mg resin portions of the general structure **19** (approximately 75 μmol) in 15 mL polypropylene filter tubes was added 6 mL of a 20% (v/v) solution of piperidine in DMF at room temperature, and the mixtures were gently agitated for 20 min. After removal of the supernatants, the resulting resin batches of general structure **20** were washed with DMF (6×), CH_2Cl_2 (2×), DMF (2×), and THF (3×) and subsequently resuspended in a solution of 3-(methylthio)propionaldehyde (40 μL, 0.4 mmol) and benzotriazole (48 mg, 0.4 mmol) in 4 mL of $CH(OMe)_3$/0.3% HOAc. After a reaction time of 6 h at ambient temperature, 4 mL of a 0.5 M solution of $NaCNBH_3$ in THF was added, and the reactions were allowed to continue for another 2 h at room temperature. The supernatants were removed, and the resulting resin batches of general structure **35** were washed with MeOH (5×), CH_2Cl_2 (1×), DMF (3×), and CH_2Cl_2 (4×) and finally dried in vacuo. The 3-(alkylamino)-1,5-benzothiazepinones **39** were isolated from **35** according to the standard method described above.

(*R*)-7-Carbamoyl-3-{*N*-[(3-(methylthio)propyl]amino}-*N*(5)-[(4-methylthiophenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-39c). The product was isolated according to the standard method (vide supra): 14 mg (51%) of (*R*)-**39c** as a snow-white powder. $[\alpha]^{23}_D$ = −52.8 (*c* 0.61, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.82 (quin, 2H, J = 7.2 Hz), 2.01 (s, 3H), 2.40 (s, 3H), 2.5 (m, 2H), 2.9 (m, 2H), 3.24 (t, 1H, J = 11.7 Hz), 3.82 (dd, 1H, J = 11.1, 6.9 Hz), 4.19 (m, 1H), 4.88 (d, 1H, J = 15.6 Hz), 5.46 (d, 1H, J = 15.3 Hz), 7.11 (d, 2H, J = 8.7 Hz), 7.20 (d, 2H, J = 8.7 Hz), 7.62 (s, broad, 1H), 7.69 (d, 1H, J = 7.8 Hz), 7.77 (dd, 1H, J = 8.1, 1.8 Hz), 8.08 (d, 1H, J = 1.8 Hz), 8.20 (s, broad, 1H), 9.2−9.6 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 14.5, 25.0, 29.8, 35.0, 44.5, 50.9, 56.4, 124.2, 125.4, 126.5, 128.5, 129.5, 132.3, 135.3, 136.5, 137.1, 143.1, 166.0, 167.0; HR−FABMS *m/z* calcd for MH^+ ($C_{22}H_{28}N_3O_2S_3^+$) 462.1344, obsd 462.1353.

(*S*)-7-Carbamoyl-3-{*N*-[(3-(methylthio)propyl]amino}-*N*(5)-[(4-methylthiophenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*S*)-39c). The product was isolated according to the standard method (vide supra): 11 mg (41%) of (*S*)-**39c** as a snow-white powder. $[\alpha]^{23}_D$ = +48.3 (*c* 0.56, MeOH); all other analytical data identical to those of (*R*)-**39c**.

(*R*)-7-Carbamoyl-3-{*N*-[(3-(methylthio)propyl]amino}-*N*(5)-[(3,4-methylenedioxyphenyl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-39e). The product was isolated according to the standard method (vide supra): 18 mg (51%) of (*R*)-**39e** as a snow-white powder. $[\alpha]^{23}_D$ = −34.5 (*c* 0.53, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.82 (quin, 2H, J = 7.2 Hz), 2.01 (s, 3H), 2.5 (m, 2H), 2.9 (m, 2H), 3.25 (t, 1H, J = 11.4 Hz), 3.81 (dd, 1H, J = 11.4, 6.6 Hz), 4.20 (dd, 1H, J = 12.0, 7.5 Hz), 4.82 (d, 1H, J = 15.0 Hz), 5.43 (d, 1H, J = 15.0 Hz), 5.95 (dd, 2H, J = 2.4, 0.9 Hz), 6.70 (dd, 1H, J = 7.8, 1.5 Hz), 6.76 (d, 1H, J = 8.1 Hz), 6.82 (d, 1H, J = 1.5 Hz), 7.63 (s, broad, 1H), 7.70 (d, 1H, J = 8.1 Hz), 7.78 (dd, 1H, J = 8.1, 1.8 Hz), 8.08 (d, 1H, J = 1.5 Hz), 8.20 (s, broad, 1H), 9.2−9.5 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 25.0, 29.8, 35.0, 44.6, 51.0, 56.4. 100.8, 107.8, 108.3, 121.4, 124.2, 126.5, 129.5, 135.3, 136.5, 142.9, 146.3, 146.9, 166.0, 167.1; HR−FABMS *m/z* calcd for MH^+ ($C_{22}H_{26}N_3O_4S_2^+$) 460.1365, obsd 460.1366.

(*R*)-7-Carbamoyl-3-{*N*-[(3-(methylthio)propyl]amino}-*N*(5)-[(thien-3-yl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-39m). The product was isolated according to the standard method (vide supra): 11 mg (42%) of (*R*)-**39m** as a snow-white powder. $[\alpha]^{23}_D$ = −71.4 (*c* 0.51, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.82 (quin, 2H, J = 7.2 Hz), 2.01 (s, 3H), 2.5 (m, 2H), 2.9 (m, 2H), 3.24 (t, 1H, J = 11.7 Hz), 3.81 (dd, 1H, J = 11.1, 6.9 Hz), 4.19 (dd, 1H, J = 11.4, 6.9 Hz), 4.97 (d, 1H, J = 15.3 Hz), 5.39 (d, 1H, J = 15.3 Hz), 6.97 (dd, 1H, J = 4.8, 0.9 Hz), 7.31 (d, 1H, J = 1.8 Hz), 7.43 (dd, 1H, J = 5.1, 2.7 Hz), 7.62 (s, broad, 1H), 7.71 (d, 1H, J = 8.1 Hz), 7.79 (dd, 1H, J = 8.1, 1.8 Hz), 8.06 (d, 1H, J = 1.5 Hz), 8.19 (s, broad, 1H), 9.2−9.6 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 25.0, 29.8, 34.9, 44.6, 47.0, 56.4, 123.2, 124.2, 126.2, 126.5, 127.4, 129.5, 135.3, 136.5, 143.1, 166.0, 166.8; HR−FABMS *m/z* calcd for MH^+ ($C_{19}H_{24}N_3O_2S_3^+$) 422.1031, obsd 422.1039.

(*R*)-7-Carbamoyl-3-{*N*-[(3-(methylthio)propyl]amino}-*N*(5)-[(*N*-acetylindole-3-yl)methyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-39r). The product was isolated according to

the standard method (vide supra): 14 mg (37%) of (*R*)-**39r** as a snow-white powder. $[\alpha]^{23}_D = -13.6$ (*c* 0.45, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.83 (quin, 2H, J = 7.2 Hz), 2.02 (s, 3H), 2.5 (m, 2H), 2.52 (s, 3H), 2.95 (m, 2H), 3.22 (t, 1H, J = 11.4 Hz), 3.78 (dd, 1H, J = 11.1, 6.9 Hz), 4.23 (m, 1H), 5.11 (d, 1H, J = 15.3 Hz), 5.53 (d, 1H, J = 15.6 Hz), 7.20 (td, 1H, J = 7.2, 1.2 Hz), 7.31 (td, 1H, J = 7.2, 1.2 Hz), 7.50 (d, 1H, J = 7.2 Hz), 7.65 (s, broad, 1H), 7.68 (d, 1H, J = 8.1 Hz), 7.73 (s, 1H), 7.79 (dd, 1H, J = 8.1, 1.8 Hz), 8.15 (d, 1H, J = 1.5 Hz), 8.20 (s, broad, 1H), 8.24 (d, 1H, J = 8.4 Hz), 9.2−9.6 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 23.8, 25.0, 29.8, 34.9, 43.1, 44.6, 56.5, 115.6, 116.3, 119.3, 123.0, 124.5, 124.8, 125.9, 126.6, 128.8, 129.6, 134.9, 135.3, 136.5, 143.0, 166.1, 166.9, 168.8; HR−FABMS *m*/*z* calcd for MH^+ ($C_{25}H_{29}N_4O_3S_2^+$) 497.1681, obsd 497.1672.

(*R*)-7-Carbamoyl-3-{*N*-[(3-(methylthio)propyl]amino}-*N*(5)-isopentyl-1,5-benzothiazepin-4(5*H*)-one ((*R*)-39v). The product was isolated according to the standard method (vide supra): 15 mg (49%) of (*R*)-**39v** as a snow-white powder. $[\alpha]^{23}_D = -91.6$ (*c* 0.39, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.79 (d, 3H, J = 6.6 Hz), 0.86 (d, 3H, J = 6.6 Hz), 1.25 (m, 1H), 1.38 (m, 1H), 1.58 (non, 1H, J = 6.6 Hz), 1.79 (quin, 2H, J = 7.2 Hz), 2.00 (s, 3H), 2.5 (m, 2H), 2.9 (m, 2H), 3.20 (t, 1H, J = 11.4 Hz), 3.6 (m, 1H), 3.76 (dd, 1H, J = 11.4, 6.9 Hz), 4.11 (m, 1H), 4.37 (m, 1H), 7.64 (s, broad, 1H), 7.79 (d, 1H, J = 8.1 Hz), 7.85 (dd, 1H, J = 8.1, 1.5 Hz), 8.02 (d, 1H, J = 1.8 Hz), 8.20 (s, broad, 1H), 9.1−9.3 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 22.1, 22.4, 25.0, 25.3, 29.8, 34.7, 36.0, 44.5, 47.0, 56.2, 124.2, 126.6, 129.8, 135.3, 136.6, 143.3, 166.0, 166.3; HR−FABMS *m*/*z* calcd for MH^+ ($C_{19}H_{30}N_3O_2S_2^+$) 396.1779, obsd 396.1780.

(*R*)-7-Carbamoyl-3-{*N*-[(3-(methylthio)propyl]amino}-*N*(5)-[3-(4-methoxyphenyl)propyl]-1,5-benzothiazepin-4(5*H*)-one ((*R*)-39x). The product was isolated according to the standard method (vide supra): 17 mg (46%) of (*R*)-**39x** as a off-white powder. $[\alpha]^{23}_D = -75.2$ (*c* 0.11, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.70 (quin, 2H, J = 7.5 Hz), 1.79 (quin, 2H, J = 7.2 Hz), 2.00 (s, 3H), 2.5 (m, 4H), 2.9 (m, 2H), 3.22 (t, 1H, J = 11.7 Hz), 3.6 (m, 1H), 3.69 (s, 3H), 3.78 (dd, 1H, J = 11.1, 6.9 Hz), 4.12 (m, 1H), 4.33 (m, 1H), 6.87 (d, 2H, J = 9.0 Hz), 6.98 (d, 2H, J = 8.7 Hz), 7.64 (s, broad, 1H), 7.80 (d, 1H, J = 8.1 Hz), 7.86 (dd, 1H, J = 8.4, 1.5 Hz), 7.99 (d, 1H, J = 1.5 Hz), 8.19 (s, broad, 1H), 9.1−9.3 (s, broad, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 25.0, 29.4, 29.8, 31.5, 34.7, 44.6, 48.2, 54.9, 56.3, 113.6, 124.4, 126.6, 128.9, 129.8, 132.8, 135.3, 136.6, 143.4, 157.2, 166.0, 166.5; HR−FABMS *m*/*z* calcd for MH^+ ($C_{24}H_{32}N_3O_3S_2^+$) 474.1885, obsd 474.1888.

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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