JOC Article

Efficient Syntheses of Benzothiazepines as Antagonists for the Mitochondrial Sodium−Calcium Exchanger: Potential Therapeutics for Type II Diabetes

Yazhong Pei,*,† Michael J. Lilly,‡ David J. Owen,‡ Lawrence J. D'Souza,† Xiao-Qing Tang,† Jinghua Yu,† Ramina Nazarbaghi,† Andrew Hunter,‡ Christen M. Anderson,† Susan Glasco,† Nicholas J. Ede,‡ Ian W. James,‡ Uday Maitra,§ S. Chandrasekaran,§ Walter H. Moos,† and Soumitra S. Ghosh†

MitoKor, Inc., 11494 Sorrento Valley Road, San Diego, California 92121, Mimotopes, Pty. Ltd., 11 Duerdin Street, Clayton, Victoria 3168, Australia, and Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

peiy@mitokor.com

Received July 3, 2002

Type II diabetes mellitus is a chronic metabolic disorder that can lead to serious cardiovascular, renal, neurologic, and retinal complications. While several drugs are currently prescribed to treat type II diabetes, their efficacy is limited by mechanism-related side effects (weight gain, hypoglycemia, gastrointestinal distress), inadequate efficacy for use as monotherapy, and the development of tolerance to the agents. Consequently, combination therapies are frequently employed to effectively regulate blood glucose levels. We have focused on the mitochondrial sodium−calcium exchanger (mNCE) as a novel target for diabetes drug discovery. We have proposed that inhibition of the mNCE can be used to regulate calcium flux across the mitochondrial membrane, thereby enhancing mitochondrial oxidative metabolism, which in turn enhances glucose-stimulated insulin secretion (GSIS) in the pancreatic β-cell. In this paper, we report the facile synthesis of benzothiazepines and derivatives by *S*-alkylation using 2-aminobenzhydrols. The syntheses of other bicyclic analogues based on benzothiazepine, benzothiazecine, benzodiazecine, and benzodiazepine templates are also described. These compounds have been evaluated for their inhibition of mNCE activity, and the results from the structure−activity relationship (SAR) studies are discussed.

Introduction

Type II diabetes mellitus accounts for about 90% of diagnosed diabetes cases[1] and is characterized by impaired insulin secretion, insulin resistance, and excessive hepatic gluconeogenesis. This metabolic disorder affects protein and lipid metabolism and leads to serious complications that include peripheral nerve damage, kidney damage, impaired blood circulation, and retinal diseases. The incidence of such complications can be reduced by aggressively treating diabetic individuals to maintain blood glucose within the normal range.[2] Existing treatments for type II diabetes include insulin and modified insulins, insulin secretagogues (sulfonylureas and metiglinides), insulin sensitizers (thiazolidinediones and biguanides), and blockers of glucose uptake (acarbose and pramlintide).[3−5] Although agents in each class have proved useful, multidrug therapies are often required to effectively control hyperglycemia. Commonly used sulfonylureas may lose their efficacy after prolonged drug treatment as a result of overstimulation of pancreatic β-cells, which leads to β-cell fatigue.[3,5] More critically, the available insulin secretagogues also stimulate insulin secretion under fasting conditions, thereby increasing the risk of hypoglycemia. Clearly, new therapeutic agents that are orally effective and safe for chronic administration are needed for treating diabetes.

Mitochondrial oxidative metabolism plays a central role in glucose-stimulated insulin secretion (GSIS) in the β-cell.[6−8] Elevation of blood glucose triggers uptake of glucose by the pancreatic β-cell. Oxidative metabolism of glucose transiently increases cellular ATP, causing influx of calcium into the β-cell and subsequent uptake of calcium by the mitochondria. The transient rise of mitochondrial Ca^{2+} concentration after a nutrient load acts as a "feed-forward" mechanism to control GSIS,[6] because calcium-sensitive dehydrogenases of the tricar-

† MitoKor, Inc.
‡ Mimotopes, Pty. Ltd.
§ Indian Institute of Science.

(1) Kenny, S. J.; Aubert, R. E.; Geiss, L. S. Prevalence and incidence of non-insulin-dependent diabetes. In *Diabetes In America*. 2nd ed.; National Diabetes Data Group; National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases: Washington, DC, 1995; NIH Publication no. 95-1468.
(2) U.K. Prospective Diabetes Study Group. *Lancet* **1998**, *352*(9131), 837.
(3) DeFronzo, R. A. *Ann. Intern. Med.* **1999**, *131*, 281.
(4) Nuss, J. M.; Wagman, A. S. *Annu. Rep. Med. Chem.* **2000**, *35*, 211.
(5) Krentz, A. J.; Ferner, R. E.; Bailey, C. J. *Drug Safety* **1994**, *11*(4), 223.
(6) Wollheim, C. B. *Diabetologia* **2000**, *43*, 265.
(7) Prentki, M. *Eur. J. Endocrinol.* **1996**, *134*, 272.
(8) Gerbitz, K. D.; Gempel, K.; Brdiczka, D. *Diabetes* **1996**, *45*, 113.

10.1021/jo020446t CCC: $25.00
Published on Web 11/20/2002

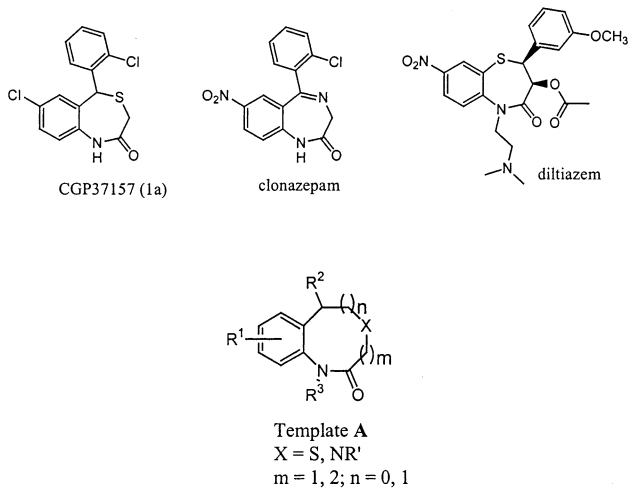


FIGURE 1.

boxylic acid (TCA) cycle are activated, further enhancing oxidative flux. Under normal conditions, mitochondria take up Ca^{2+} through the mitochondrial calcium uniporter in response to the glucose-induced rise in cytoplasmic calcium, and they release calcium through the mitochondrial sodium−calcium exchanger (mNCE).[9−11] We have demonstrated that agents that inhibit the mNCE increase the magnitude and duration of the glucose-induced transient rise in mitochondrial Ca^{2+} concentration, and as a result, they enhance GSIS.[12] We propose that an important advantage of these agents over the existing drugs will be their glucose-dependent efficacy. While such compounds are expected to correct hyperglycemia, they should not lower fasting/basal blood glucose levels, thus avoiding the liability of hypoglycemia.

Compounds from different structural classes, such as CGP37157 (1,4-benzothiazepin-2-one), diltiazem (1,5-benzothiazepin-2-one), clonazepam (1,4-benzodiazepin-2-one), and prenylamine and fendiline (both phenylalkylamines), have been reported to inhibit mNCE activity[13] (Figure 1). CGP37157 is the most potent inhibitor for mNCE, with a reported IC_{50} of 0.4 μM. However, its poor solubility and short half-life ($t_{1/2}$ = 0.9 h, in vivo)[14] preclude its use for extensive preclinical studies. Pharmacological studies around mNCE have been hampered by the limited number of analogues from each class tested thus far and particularly by the lack of structure activity relationship (SAR) information for mNCE around the benzothiazepine template. In this report, we describe efficient syntheses of a series of benzothiazepinones and derivatives based on the template **A**. To broaden the SAR analysis of mNCE inhibition and to identify new mNCE inhibitors with improved pharmacological profiles, we have varied the substitutions on the benzothiazepinone template and made changes in the cyclic skeleton. In addition, we report a microwave-assisted one-pot conversion of 2-aminobenzhydrol and methyl thioglycolate to benzothiazepinones that is suitable for multigram synthesis. The compounds have been evaluated for their ability to functionally inhibit mNCE activity, and the results from our initial SAR studies are presented.

Results and Discussion

The synthesis of benzothiazepinones, described previously by Hirai et al., requires five steps starting from 2-aminobenzophenones.[15] The key steps, which involve the conversion of 2-aminobenzhydrol to the corresponding 2-aminobenzhydryl thio-alcohol via benzothiazine-2-thione intermediates, proved highly variable in our hands. Kuch et al. reported a two-step synthesis of benzothiazepinones in excellent overall yield.[16] This approach was characterized by the *S*-alkylation of thioglycolic acid with 2-aminobenzhydrol in the presence of HCl, followed by cyclization to furnish the benzothiazepinones. However, the *S*-alkylation step was sluggish and takes 2−3 days to complete.

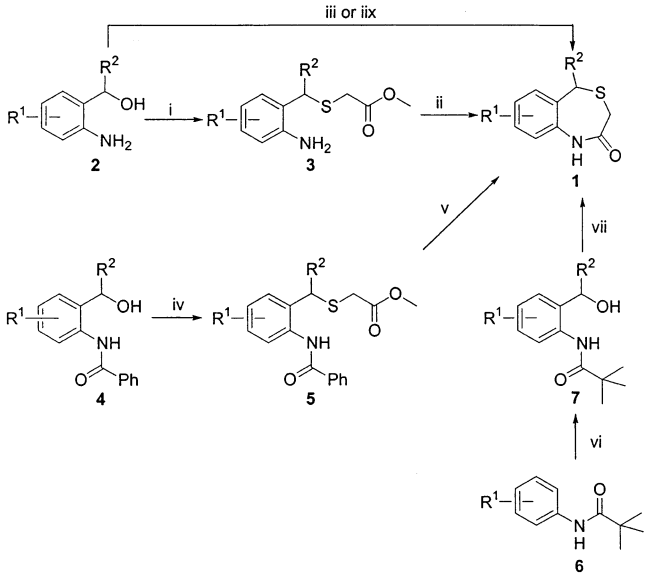
We have established an efficient *S*-alkylation method using various benzhydrol derivatives in the presence of TFA. On the basis of this method, alternative syntheses for benzothiazepinones and their derivatives have been developed, as illustrated in Scheme 1. These routes employ fewer reaction steps and allow the straightforward incorporation of various substituents onto the benzothiazepinone template. In method A, *S*-alkylation of methyl thioglycolate with 2-aminobenzhydrols[17] **2** in neat TFA gave thioethers **3** in good yield in a few hours. In some cases, the corresponding *N*-trifluoroacetyl derivatives of **3** were also obtained as a less polar component in the crude product. The amides could be readily converted to **3** upon treatment with aqueous NaOH without affecting the overall yield of the benzothiazepinones. The formation of the *N*-trifluoroacetyl byproduct was minimized when the *S*-alkylation reaction was carried out with 1 equiv of TFA in CH_2Cl_2. Ester **3** was hydrolyzed under basic conditions to furnish the corresponding acid, which was cyclized using EDC to afford the desired benzothiazepinones **1**.

A one-step synthesis of benzothiazepinone **1** was also achieved when **2** and methyl thioglycolate were heated at 80−85 °C in neat TFA (method B). Under these conditions, TFA also facilitated the intramolecular aminolysis of the methyl ester **3** in situ to generate **1**. The reaction temperature appeared to be crucial for this one-step process. When the reaction was carried out below 60 °C, no intramolecular cyclization was observed, and thioether **3** was obtained as the sole product.

This TFA-facilitated *S*-alkylation reaction also worked well with *N*-acylated benzhydrol (method C). 2-(*N*-Ben-

(9) Rizzuto, R.; Bernardi, P.; Pozzan, T. *J. Physiol.* **2000**, *529*, 37.
(10) Bernardi, P. *Physiol. Rev.* **1999**, *79*(4), 1127.
(11) Gunter, T. E.; Gunter, K. K.; Sheu, S.-S.; Gavin, C. E. *Am. J. Physiol.* **1994**, *267*(2 Pt1), C313.
(12) Lee, B.; Vargas, L.; Glasco, S.; Kushnareva, Y.; Zapf-Colby, A.; Anderson, C. M. Inhibitors of the mitochondrial sodium−calcium exchanger enhance glucose-stimulated insulin secretion. Keystone Symposia Diabetes Mellitus: Molecular mechanisms, genetics and new therapies; Abstract 401; 2002.
(13) For review, see: Cox, D. A.; Matlib, M. A. *Trends Pharmacol. Sci.* **1993**, *14*, 408 and references therein.
(14) MitoKor, unpublished data.
(15) Hirai, K.; Matsutani, S.; Ishiba, T.; Makino, I. U.S. Patent 4,297,280, 1981.
(16) Kuch, H.; Seidl, G.; Schmitt, K. *Arch. Pharm.* **1967**, *300 Bd. 4*, 299.
(17) 2-Aminobenzhydrol and derivatives were prepared from corresponding benzophenones by reduction using $NaBH_4$[15] or a modified procedure using $LiAlH_4$.[18] The 2-aminobenzophenones used were synthesized using established methods.[19]

SCHEME 1[a]



[a] Reagents and conditions. Method A: (i) methyl thioglycolate, TFA (neat) or TFA/CH_2Cl_2, room temperature; (ii) (a) 1.0 N aqueous NaOH, THF/CH_3OH, room temperature, (b) EDC, DIEA, DMAP, THF, room temperature. Method B: (iii) methyl thioglycolate, TFA (neat), 80−85 °C. Method C: (iv) methyl thioglycolate, TFA, room temperature; (v) (a) 1.0 N aqueous NaOH, THF/CH_3OH, reflux; (b) EDC, DIEA, DMAP, THF, room temperature. Method D: (vi) *n*-butyllithium, THF, −78 to 0 °C, 2 h; aldehydes, 0 °C to room temperature, 1 h; (vii) methyl thioglycolate, TFA (neat), 80−85 °C, 24 h. Method E: (iix) methyl thioglycolate, TFA, basic alumina, microwave radiation; saturated aqueous Na_2CO_3, microwave radiation at reduced power.

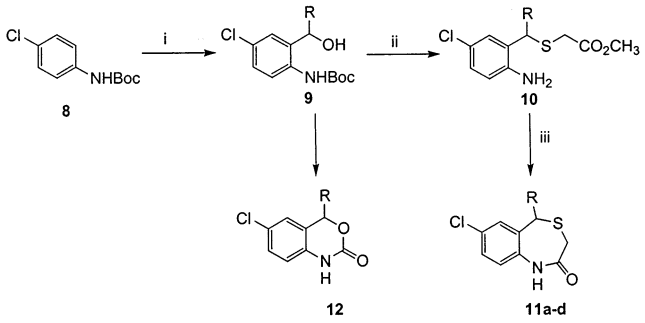
zoylamino)benzhydrol[20] **4** underwent *S*-alkylation with methyl thioglycolate in neat TFA to afford the corresponding thioether **5** in 61% yield. Hydrolysis using aqueous NaOH in THF/CH_3OH under reflux simultaneously hydrolyzed the *N*-benzamide and methyl ester groups of **5** to give the corresponding acid, which then underwent EDC-facilitated lactam formation to furnish **1**. Selective hydrolysis of the methyl ester was observed when the hydrolysis was carried out at ambient temperature. The route depicted for method C was not pursued further because it was anticipated that the harsh hydrolysis conditions necessary for the removal of the benzamide functionality would not be compatible with other base-sensitive functionalities.

Method D outlines a more general synthetic route to benzothiazepinones. Following a literature procedure,[21] selective *ortho*-lithiation of pivaloylanilide **6** using *n*-butyllithium, followed by condensation with aromatic aldehydes, afforded **7** in good yield. Treatment of **7** in neat TFA at 80 °C with methyl thioglycolate effected three reactions in one pot, namely, *S*-alkylation, pivalamide hydrolysis, and cyclization, to yield **1** in good overall yield. This process is advantageous since benzothiazepinones with various aromatic substitutions can be synthesized from widely available anilines and aldehydes in two steps.

We also discovered that benzothiazepinones could be prepared by microwave-assisted one-pot conversion of 2-aminobenzhydrols and methyl thioglycolate (method E). Conventional microwave irradiation of a slurry of benzhydrol **2**, methyl thioglycolate, TFA, and basic alumina provided a mixture of the thioether **3** (major component), the corresponding trifluoroacetamide of **3**, and benzothiazepinone **1**. The presence of basic alumina minimizes the charring that can result from uneven heating. Complete conversion to **1** was obtained by neutralizing the mixture with saturated aqueous Na_2CO_3, followed by microwave radiation at reduced power. The ratio of **2**, TFA, and basic alumina should be carefully controlled at the beginning of this one-pot procedure (see Experimental Section for detail), as excess TFA required more Na_2CO_3 for neutralization in the following step. Partial hydrolysis of **3** during the Na_2CO_3 treatment step was also observed to give the corresponding acid as a minor contaminant in the crude product. This hydrolysis was minimized by adding the Na_2CO_3 solution in small portions and exposure to microwave radiation after each addition. The acid could be removed by basic aqueous washes to furnish analytically pure benzothiazepinones in good overall yield. This procedure was successfully adapted for several large-scale (>10 g) syntheses of **1**, because it did not require silica gel chromatography purification.

To examine further the effect of alterations at the C-5 position, several analogues with 5-alkyl replacements were synthesized. To simplify the SAR comparisons, the 7-chloro substituent was retained in these analogues. As shown in Scheme 2, *ortho*-lithiation of *N*-Boc-4-chloroaniline (**8**) using *tert*-butyllithium, followed by addition of alkyl aldehydes at −78 °C, gave **9**. This reaction had to be kept at −78 °C and quenched within 2−3 h. Prolonged reaction time and/or warming resulted in the formation of benzoxazin-2-one **12** as a significant side product. Benzyl alcohol **9** was reacted with methyl thioglycolate

SCHEME 2[a]



[a] Reagents and conditions: (i) *t*-BuLi, RCHO, THF, −78 °C; (ii) methyl thioglycolate, 50% TFA in CH_2Cl_2, room temperature; (iii) (a) 1.0 N aqueous NaOH, methanol, (b) EDC, DIEA, DMAP, THF, room temperature.

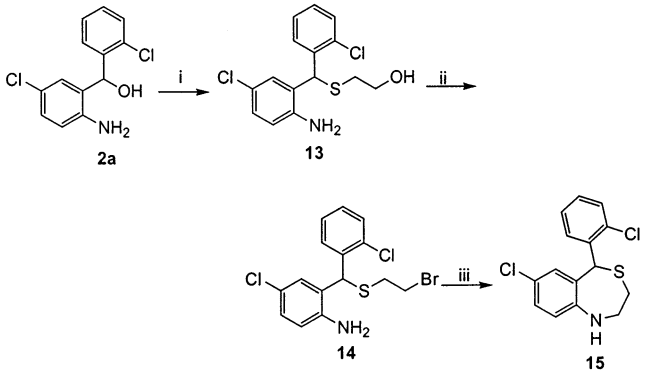
(18) To a solution of 2-aminobenzophenone (1.0 mmol) in THF (5 mL) at 0 °C was added lithium aluminum hydride (0.5 mL of 1.0 M solution in diethyl ether). The progress of the reaction was monitored using TLC. Normally, the reaction was complete within 1 h. Saturated aqueous sodium bicarbonate (20 mL) was carefully added and the resulting solution was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield the corresponding benzhydrol, which was used in the *S*-alkylation reaction without further purification.

(19) (a) Walsh, D. A. *Synthesis* **1980**, 677 and references therein. (b) Frye, S. V.; Johnson, M. C.; Valvano, N. L. *J. Org. Chem.* **1991**, *56*, 3750.

(20) Okabe, M.; Sun, R. C. *Tetrahedron*, **1995**, *51*(7), 1861.

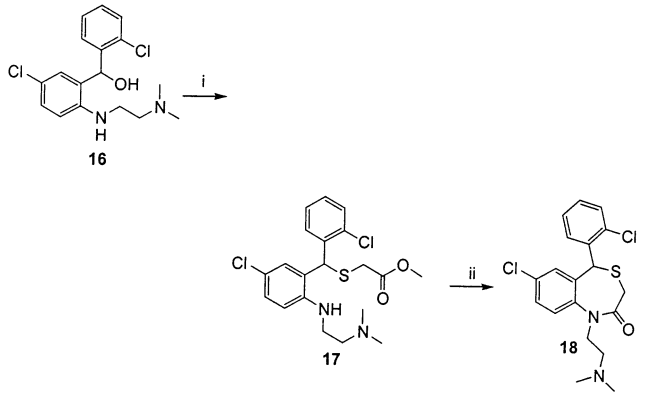
(21) (a) Turner, J. A. *J. Org. Chem.* **1990**, *55*, 4744. (b) Úbeda, J. I.; Villacampa, M.; Avandaño, C. *Synthesis* **1998**, 1176.

SCHEME 3[a]



[a] Reagents and conditions: (i) mercaptoethanol, TFA, room temperature; (ii) PPh_3, CBr_4, CH_2Cl_2, room temperature; (iii) K_2CO_3, DMF.

SCHEME 4[a]



[a] Reagents and conditions: (i) methyl thioglycolate, TFA, room temperature; (ii) LHMDS, THF, −78 °C.

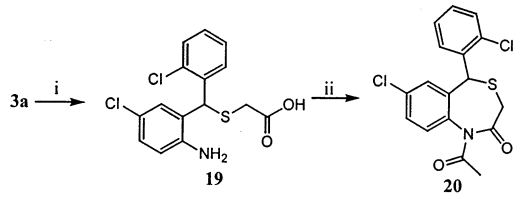
in neat TFA to yield the thioether **10**. In this reaction, *S*-alkylation occurred in concert with the *N*-Boc deprotection. Hydrolysis of ester **10** using aqueous NaOH, followed by EDC-mediated cyclization, furnished 5-alkylbenzothiazepinone **11**.

To explore the contribution of the carbonyl at the 2-position of **1a** toward mNCE inhibition, benzothiazepine **15** with the aromatic substitution pattern conserved was synthesized from **2a** (Scheme 3). *S*-Alkylation of mercaptoethanol with **2a** in TFA gave **13**. Thioether alcohol **13** was converted to the corresponding bromide **14** using CBr_4/Ph_3P in CH_2Cl_2. Cyclization of **14** in the presence of K_2CO_3 in DMF furnished **15**.

The *N*-alkyl and *N*-acyl benzothiazepinones **18** and **20**, respectively, were synthesized to ascertain the influence of *N*-substitution on mNCE activity (Schemes 4 and 5). *S*-Alkylation of methyl thioglycolate with benzhydrol **16** in neat TFA gave thioether **17**. Intramolecular aminolysis of **17** in the presence of LHMDS furnished benzothiazepinone **18**. The corresponding *N*-acetyl derivative **20** was obtained from acid **19** by treatment with an excess of acetyl chloride.

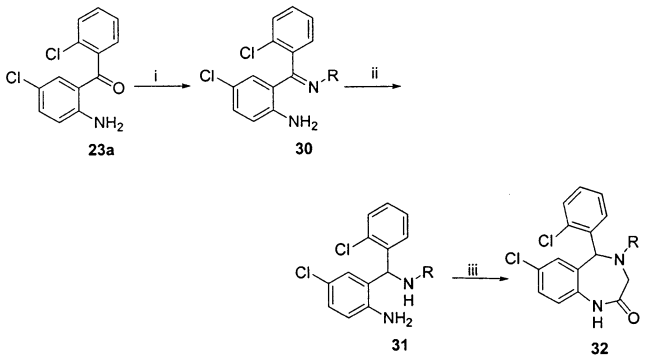
Benzodiazepinone derivatives were also prepared to examine the effect of replacing the sulfur at the 4-position with nitrogen. These tertiary amine derivatives could potentially have improved solubility and stability compared to the thioethers. It also allowed the introduction

SCHEME 5[a]



[a] Reagents and conditions: (i) 1.0 N aqueous NaOH, THF/CH_3OH, room temperature; (ii) AcCl, DIEA, DMAP, THF, room temperature, 3 h.

SCHEME 6[a]



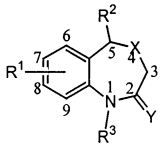
[a] Reagents and conditions: (i) amine (neat), 140 °C; (ii) $NaBH_3(CN)$, methanol/acetic acid, 0 °C to room temperature; (iii) bromoacetyl bromide, 0 °C to room temperature, 18 h; DIEA, 50 °C, 5 h.

of various functionalities at the 4-position for further SAR exploration. As illustrated in Scheme 6, 2-aminobenzophenone **23a** was condensed with various amines to give **30**. Imine **30** was reduced using $NaBH_3(CN)$ to give **31**. Reaction of **31** with bromoacetyl bromide in the presence of DIEA gave **32**.

Structure Activity Relationship Studies. Using the strategies illustrated above, a diverse set of benzothiazepinones and their derivatives were synthesized. These compounds were evaluated for their ability to inhibit mNCE function, wherein the exchanger-mediated Na^+/Ca^{2+} translocation in mitochondria in permeabilized cells was monitored by using a Ca^{2+}-sensing fluorescence-based assay (see Experimental Section). The results are summarized in Table 1.

CGP37157 (**1a**) exhibited an IC_{50} of 1.4 μM in our assay system, which was comparable to the reported literature value of 0.4 μM.[13] Substitutions on the 5-phenyl ring appeared to be crucial for mNCE activity. The unsubstituted phenyl derivative **1b** displayed a 10-fold reduction in activity compared to that of analogue **1a** containing 2-chlorophenyl. Monomethyl substitutions anywhere on the phenyl ring all resulted in decreased activity (**1a** vs **1c**−**e**), with 4-methyl substitution being the least tolerated (**1e**). In a similar vein, dimethyl substitution resulted in decreased mNCE inhibitory activity (**1a** vs **1f**−**j**). Replacement of the 5-(2-chlorophenyl) functionality with aromatic heterocycles also decreased mNCE activity dramatically (**1a** vs **1k**−**n**). Substitutions at C7 in the fused phenyl ring also played a critical role in mNCE activity, with the chloro group being the most preferred (**1a** vs **1p**, **1b** vs **1o**, **1c** vs **1q**). Whereas the 5-alkyl analogues were significantly weaker in their inhibition

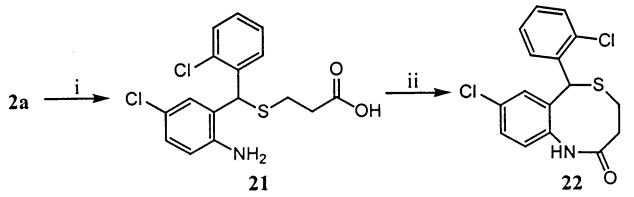
TABLE 1. mNCE Activity of Benzothiazepines and Their Derivatives



compd	R^1	R^2	R^3	X	Y	mNCE (IC_{50}, μM)
1a	7-Cl	2-Cl-C_6H_4-	H	S	O	1.4
1b	7-Cl	C_6H_5-	H	S	O	12.6
1c	7-Cl	2-Me-C_6H_4-	H	S	O	6.3
1d	7-Cl	3- Me-C_6H_4-	H	S	O	12.6
1e	7-Cl	4- Me-C_6H_4-	H	S	O	39.8
1f	7-Cl	2,3-diMe-C_6H_3-	H	S	O	10.0
1g	7-Cl	2,5-diMe-C_6H_3-	H	S	O	25.1
1h	7-Cl	2,6-diMe-C_6H_3-	H	S	O	25.1
1i	7-Cl	3,4-diMe-C_6H_3-	H	S	O	20.0
1j	7-Cl	3,5-diMe-C_6H_3-	H	S	O	15.9
1k	7-Cl	2-benzothiazolyl	H	S	O	20.0
1l	7-Cl	2-thiophenyl	H	S	O	25.1
1m	7-Cl	2-thiazolyl	H	S	O	200
1n	7-Cl	4-pyridyl	H	S	O	31.6
1o	7-NO_2	C_6H_5-	H	S	O	20.0
1p	H	2-Cl-C_6H_4-	H	S	O	15.9
1q	H	2-Me-C_6H_4-	H	S	O	25.1
11a	7-Cl	3-BnO-Pr-	H	S	O	3.2
11b	7-Cl	cyclohexyl	H	S	O	15.9
11c	7-Cl	isopropyl	H	S	O	50.1
11d	7-Cl	isobutyl	H	S	O	25.1
15	7-Cl	2-Cl-C_6H_4-	H	S	H, H	6.3
18	7-Cl	2-Cl-C_6H_4-	$Me_2NCH_2CH_2$	S	O	39.8
20	7-Cl	2-Cl-C_6H_4-	acetyl	S	O	20.0
32a	7-Cl	2-Cl-C_6H_4-	H	$EtOCH_2CH_2CH_2N$	O	3.2
32b	7-Cl	2-Cl-C_6H_4-	H	$HO\text{-}CH_2CH_2N$	O	7.9
32c	7-Cl	2-Cl-C_6H_4-	H	$2\text{-}(Pr)_2NCH_2CH_2N$	O	6.3
32d	7-Cl	2-Cl-C_6H_4-	H	$(MeOCH_2CH_2)_2NCH_2CH_2N$	O	2.0
32e	7-Cl	2-Cl-C_6H_4-	H	$3,4\text{-}(MeO)_2PhCH_2CH_2N$	O	5.0

(**1a** vs **11b**−**d**), the exception was the derivative with the more flexible 5-(3′-benzyloxypropyl) substituent, which exhibited good mNCE inhibition (**11a** vs **1a**). Benzothiazepine **15** showed slightly decreased mNCE activity (IC_{50} = 6.3 μM) compared to that of **1a** (IC_{50} = 1.4 μM). This indicated that the 2-carbonyl moiety may not play a crucial role for mNCE inhibitory activity, particularly when this observation is compared to the results obtained with 1-substituted analogues **18** and **20**. Both **18** and **20** caused a significant decrease in mNCE inhibition (IC_{50} = 39.8 and 20.0 μM, respectively), suggesting that the amide NH may be involved as a hydrogen bond donor. The benzodiazepinones **32a**−**e** exhibited good mNCE inhibitory activities that were comparable to that of **1a**. When compared to benzothiazepines, this compound series is expected to display improved properties in terms of solubility and stability because of the replacement of the sulfur atom at the 4-position with a substituted amino group. The lack of tolerance of substitution around the benzothiazepine template has been noted above. Unlike the benzothiazepine template, the benzodiazepinone system provides an additional attachment point at the 4-position for various substituents, which allows the exploration of new diversity elements. Initial results of compounds **32a**−**e** clearly indicate that substitutions at this position are accommodated without having adverse affects on inhibitory potency. Also, it should be noted that replacement of the sulfur atom with a nitrogen atom reduces the size of the seven-membered ring.

SCHEME 7[a]



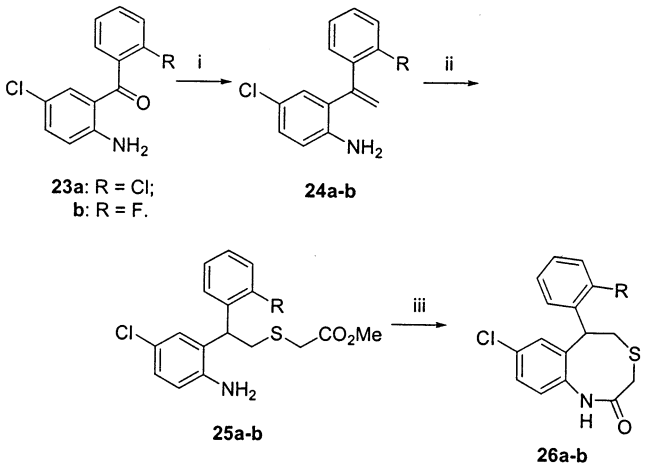
[a] Reagents and conditions: (i) 3-mercaptopropionic acid, TFA (neat), room temperature; (ii) EDC, DIEA, DMAP, THF, room temperature.

[6,8]Bicyclic Analogues. To examine the effects of modifications of the benzothiazepinone skeleton, compounds based on several [6,8]bicyclic templates were prepared. Benzhydrol **2a** was allowed to react with 3-mercaptopropionic acid in TFA to give **21**. Cyclization of **21** using EDC yielded **22** (Scheme 7).

1,4-Benzothiazocinones **26** were synthesized from benzophenone **23** (Scheme 8). Benzophenone **23** was converted to **24** using $(Ph_3PCH_3)^+Br^-$ and t-$C_5H_{11}OK$. Styrene **24** was allowed to react with methyl thioglycolate in the presence of 1,1′-azobis(cyclohexanecarbonitrile) to give thioether **25**. Cyclization of **25** using LHMDS yielded **26**.

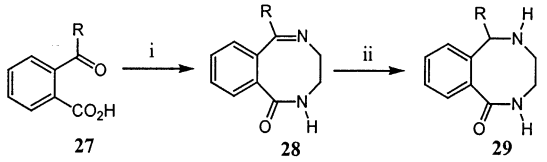
Non-sulfur-containing [6,8]bicyclic analogues **28** were obtained from the coupling reaction of 2-carboxyl benzophenone **27** with ethylenediamine (Scheme 9). The double bond in 2,5-benzodiazocin-1-one **28** was saturated

SCHEME 8[a]



[a] Reagents and conditions: (i) Ph_3PMeBr, *t*-$C_5H_{11}OK$, THF; (ii) $HSCH_2CO_2Me$, 1,1′-azobis(cyclohexanecarbonitrile), 1,4-dioxane; (iii) LHMDS, THF.

SCHEME 9[a]



[a] Reagents and conditions: (i) ethylenediamine, CDI, DMF, room temperature; (ii) 10% Pd/C, formic acid.

TABLE 2. nNCE Activity of 2,5-Benzodiazocin-1-ones

compd	R	mNCE (IC_{50}, μM)
28a	phenyl	159
28b	4-methylphenyl	100
29a	phenyl	63.1
29b	4-methylphenyl	79.4

using palladium on activated carbon in formic acid to give **29**. Attempted transformation of **28** to **29** using other conditions, including Pd/C under hydrogen atmosphere, $NaBH_3(CN)$ in DMF/acetic acid, and $LiAlH_4$, failed to provide satisfactory yields.

The 1,5-benzothiazocinone **22** exhibited an IC_{50} of 12.6 μM for mNCE, whereas the 1,4-benzothiazocinone **26a** (R = Cl) and **26b** (R = F) showed IC_{50} values of 6.3 and 15.9 μM, respectively. As shown in Table 2, compounds based on the 2,5-benzodiazocin-1-one template failed to inhibit mNCE significantly. It should be noted that the geometry of the amide moiety in **28** and **29** has been reversed compared to that in **22**. The inhibitory activities of these compounds underscore the desirable characteristics of the benzothiazepine system and the 2-chloro substituent in the pendant phenyl ring as discussed in earlier sections.

Conclusion

In this report, we have provided the efficient syntheses of several benzothiazepinones and derivatives via several alternative pathways involving a key *S*-alkylation reaction using 2-aminobenzhydrols. A diverse set of benzothiazepinones and derivatives were prepared and evaluated for their ability to inhibit the mNCE. We have established broad SAR around these benzothiazepinones and derivatives and defined core molecular elements for activity. The SAR studies were expanded to include other bicyclic analogues based on benzothiazecine, benzodiazecine, and benzodiazepine templates. This SAR information provides a necessary foundation for further optimization. Initial data suggest that additional analogues based on the benzodiazepine templates are worthy of further investigation.

Experimental Section

General Procedures. All commercially available reagents were used without further purification, unless otherwise noted. Anhydrous THF was distilled from Na/benzophenone. The melting points are uncorrected. Unless otherwise noted, TLC analysis was performed using glass plate or plastic sheet precoated with silica gel 60 F_{254}. Analytical HPLC was carried out on a C18 (5 μm, 100 Å) 50 mm × 4.6 mm column using a linear gradient of 0−100% solvent B over 11 min at 1.5 mL/min (solvent A: 0.1% H_3PO_4 in H_2O; solvent B: 0.1% H_3PO_4 in 90% aqueous CH_3CN.) Wavelength detection was carried out at 214 and 254 nm. ESMS was carried out using an electrospray inlet. LC-MS analyses were performed using two different systems (A and B). System A: A mass spectrometer using electron spray ionization technique was employed. HPLC was performed on a 5 μm C18 column (50 mm × 4.6 mm) using a linear gradient of 0−100% solvent B over 11 min (solvent A: 0.01% TFA in H_2O; solvent B: 0.01% TFA in 90% aqueous CH_3CN) at a flow rate of 1.5 mL/min. System B: A HPLC system coupled with a mass spectrometer using electrospray ionization technique. HPLC was performed on a 5 μm betasil C8 column (100 mm × 2 mm) using a linear gradient of 5−95% solvent B over 5 min followed by 95% solvent B for 3 min and 5% solvent B for two min (solvent A: 0.05% TFA in H_2O; solvent B: 0.05%TFA in CH_3CN) at a flow rate of 0.30 mL/min. IR was carried out with samples presented on disposable microporous polyethylene disks.

Cell Culture Methods. INS-1 cells were grown as described by Asfari et al.[22] in RMPI 1640 medium supplemented with 10% fetal calf serum, 50 μM 2-mercaptoethanol, 10 mM HEPES, 1 mM pyruvate, 100 IU/mL penicillin, and 100 μg/mL streptomycin, in a humidified 5% CO_2 atmosphere at 37 °C.

Measurement of Mitochondrial Sodium−Calcium Exchange Activity. INS-1 pancreatic β-cells were harvested by trypsinization and resuspended at 10 × 10^6 cells/mL in 250 mM sucrose, 10 mM HEPES, 2.5 mM K_2HPO_4, and 5 mM succinic acid, pH 7.4. Digitonin (final concentration 0.007% v/v), Calcium Green 5 N (0.05 μM; membrane impermeant form), rotenone (1 μM), cyclosporin A (1 μM), and calcium chloride (60 μM) were added, followed by 1 μM ruthenium red. The cells were transferred to 96 well plates (10^6 cells/well), and test agents were added. Fluorescence was monitored continuously before, during, and after the addition of 20 mM NaCl. Activity was reported as the slope of the fluorescent signal following NaCl addition.

[(2-Amino-5-chlorophenyl)-(2-chlorophenyl)-methylsulfanyl]-acetic Acid Methyl Ester (3a). To a stirred solution of 2-amino-2′,5-dichlorobenzhydrol (**2a**) (268 mg, 1.0 mmol) in TFA (2 mL) at room temperature was added methyl thioglycolate (0.357 mL, 4.0 mmol). After 96 h of stirring, the TFA was evaporated, and the residue was partitioned between CH_2Cl_2 and 10% aqueous NaOH. The aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and

(22) Asfari M.; Janjic D.; Meda P.; Li, G.; Halban, P. A.; Wollheim, C. B. *Endocrinology* **1992**, *130*, 167.

filtered. The filtrate was concentrated under vacuum to give the crude product, which was purified on a silica gel column using petroleum ether and ethyl acetate as eluents to give **3a** as a pale yellow solid (167 mg, 47%). R_f [petroleum ether/ethyl acetate (5:1)] = 0.40; HPLC (214 nm) t_R = 9.20 (98.2%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (d, J = 16.0 Hz, 1H), 3.22 (d, J = 16.0 Hz, 1H), 3.73 (s, 3H), 4.52 (brs, 2H), 5.80 (s, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.4 Hz, 1H), 7.05 (dd, J = 2.4, 8.8 Hz, 1H), 7.27−7.31 (m, 1H), 7.37−7.42 (m, 2H), 7.91−7.93 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6, 46.1, 52.6, 118.1, 123.8, 125.2, 127.2, 128.1, 128.5, 129.2, 130.1, 130.3, 134.7, 135.4, 142.6, 170.9 ppm; ESMS m/z 250.3 [M − $C_3H_4O_2S$]$^+$, 356.2 [M + H]$^+$; LC-MS t_R (system A) 9.27 (356.0 [M + H]$^+$) min.

Using similar procedures, additional examples **3b**−**g**, **3i**, and **3o,p** were also synthesized. Their experimental details are described in Supporting Information.

7-Chloro-5-(2-chlorophenyl)-1,2,3,5-tetrahydro-4,1-benzothiazepin-2-one (1a). Step (a). To a stirred solution of **3a** (1.128 g 3.2 mmol) in 120 mL of THF/methanol (1/1) at room temperature was added 60 mL of 1.0 M aqueous NaOH. After 1 h of stirring, the solvents were evaporated, and the residue was partitioned between brine and CH_2Cl_2. The aqueous phase was titrated to pH 7.0 with 10% aqueous HCl and extracted with CH_2Cl_2 twice. The combined organic layers were dried over anhydrous sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated under vacuum to give the crude carboxylic acid, which was used in the following step without further purification.

Step (b). To a stirred solution of the crude carboxylic acid (3.2 mmol) in THF (300 mL, high dilution to minimize intermolecular coupling) at room temperature was added DIEA (0.84 mL, 4.8 mmol), EDC (0.842 mL, 4.8 mmol), and DMAP (39 mg, 0.32 mmol). After 20 h of stirring, the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (300 mL); washed successively with 10% aqueous citric acid (150 mL), saturated aqueous sodium bicarbonate (150 mL), and brine (150 mL); dried over sodium sulfate; filtered; and concentrated under vacuum. The crude product was purified by flash chromatography on a silica gel column using a mixture of petroleum ether and ethyl acetate as eluent to give **1a** a white solid (0.462 g, 45%). R_f [petroleum ether/ethyl acetate (2:1)] = 0.30; HPLC (214 nm) t_R = 8.42 (92.6%) min; ^{1}H NMR (400 MHz, $CDCl_3$) 3.04 (dd, J = 1.6, 12.0 Hz, 1H), 3.33 (d, J = 12.0 Hz, 1H), 6.15 (s, 1H), 6.73 (d, J = 1.6 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.26−7.44 (m, 5H), 7.82−7.84 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 31.3, 43.5, 125.1, 127.1, 128.0, 128.7, 129.6, 130.3, 130.8, 133.2, 134.0, 134.1, 134.9, 135.4, 169.9 ppm; ESMS m/z 324.2 [M + H]$^+$; LC-MS t_R (system A) 8.64 (323.8 [M + H]$^+$, 647.1 [2M + H]$^+$) min; HRMS [M + Na]$^+_{calcd}$ = 345.9836, [M + Na]$^+_{obsd}$ = 345.9832; IR 3201, 1681, 1483, 1355, 1114, 755 cm^{-1}.

Using similar procedures, additional examples **1b**−**g**, **1i**, and **1o,p** were also synthesized. Their experimental details are described in Supporting Information.

General Procedure for Method B. 2-Aminobenzhydrol **2** (1.0 mmol) was mixed with methyl thioglycolate (6 equiv) and TFA (2 mL). The mixture was stirred at 85 °C for 18 h. The black solution was diluted with CH_2Cl_2 (80 mL) and washed with 1.0 M aqueous NaOH (20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on a silica gel column using a mixture of petroleum ether and ethyl acetate as eluent to give **1**. In some cases, the corresponding thioether **3** was also isolated as a minor component from the crude products. Using this general procedure the following compounds were synthesized:

7-Chloro-5-(3,5-dimethylphenyl)-1,2,3,5-tetrahydro-4,1-benzothiazepin-2-one (1j). Compound **1j** was obtained from **2j** using Method B as an off-white solid (86.7 mg, 28% yield): R_f [petroleum ether/ethyl acetate (2:1)] = 0.31; HPLC (214 nm) t_R = 9.06 (92.7%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.97 (d, J = 12.2 Hz, 1H), 3.33 (d, J = 12.2 Hz, 1H), 5.61 (s, 1H), 6.95 (d, J = 2.2 Hz, 1H), 7.00 (s, 1H), 7.04−7.07 (m, 2H), 7.24 (dd, J = 2.2, 8.4 Hz, 1H), 8.52 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 31.5, 47.2, 125.1, 127.1, 128.5, 128.7, 130.2, 133.0, 134.8, 135.8, 136.7, 138.5, 170.5 ppm; ESMS m/z 318.3 [M + H]$^+$, 635.0 [2M + H]$^+$; LC-MS t_R (system A) = 9.47 (318.0 [M + H]$^+$, 635.1 [2M + H]$^+$, 954.1 [3M + H]$^+$) min; HRMS [M + Na]$^+_{calcd}$ = 340.0539, [M + Na]$^+_{obsd}$ = 340.0529; IR 3202, 1681, 1482, 1357, 1115, 816 cm^{-1}.

7-Chloro-5-(2-benzothiazolyl)-1,2,3,5-tetrahydro-4,1-benzothiazepin-2-one (1k). Compound **1k** was obtained from **2k** using Method B as an off-white solid (19.6 mg, 17.7% yield): R_f [petroleum ether/ethyl acetate (2:1)] = 0.33; HPLC (214 nm) t_R = 7.57 (85.0%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (d, J = 12.4 Hz, 1H), 3.20 (d, J = 12.4 Hz, 1H), 5.65 (s, 1H), 7.02 (d, J = 9.0 Hz, 1H), 7.34−7.40 (m, 3H), 7.41 (dd, J = 1.1, 7.3 Hz, 1H), 7.77 (brs, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 47.0, 121.7, 123.3, 125.4, 126.2, 126.3, 129.7, 133.4, 134.7, 135.8, 153.8, 169.1, 171.1 ppm; ESMS m/z 379.3 [M + H]$^+$; LC-MS t_R (system A) = 7.89 (347.2 [M + H]$^+$, 693.2 [2M + H]$^+$) min; HRMS [M + Na]$^+_{calcd}$ = 368.9899, [M + Na]$^+_{obsd}$ = 368.9899; IR 1682, 1489, 1473, 1462 1116, 759 cm^{-1}.

7-Chloro-5-(2-thiophenyl)-1,2,3,5-tetrahydro-4,1-benzothiazepin-2-one (1l). Compound **1l** was obtained from **2l** using Method B as an off-white solid (33.4 mg, 23.7% yield): R_f [petroleum ether/ethyl acetate (2:1)] = 0.21; HPLC (214 nm) t_R = 7.82 (97.9%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (d, J = 12.3 Hz, 1H), 3.31 (d, J = 12.3 Hz, 1H), 5.83 (s, 1H), 7.04−7.06 (m, 2H), 7.11 (d, J = 2.2 Hz, 1H), 7.17 (d, J = 3.5 Hz, 1H), 7.28 (dd, J = 2.2, 8.3 Hz, 1H), 7.32 (d, J = 5.1 Hz, 1H), 8.52 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 42.5, 125.4, 126.1, 127.3, 127.7, 128.5, 128.9, 133.2, 134.6, 136.3, 139.8, 170.3 ppm; ESMS m/z 296.2 [M + H]$^+$; LC-MS t_R (system A) = 8.13 (295.9 [M + H]$^+$, 591.2 [2M + H]$^+$, 887.9 [3M + H]$^+$) min; HRMS [M + Na]$^+_{calcd}$ = 317.9790, [M + Na]$^+_{obsd}$ = 317.9779; IR 3199, 1680, 1482, 1358, 1111, 710 cm^{-1}.

7-Chloro-5-(2-thiazolyl)-1,2,3,5-tetrahydro-4,1-benzothiazepin-2-one (1m). Compound **1m** was obtained from **2m** using Method B as a mustard brown solid (66 mg, 21.5% yield): R_f [petroleum ether/ethyl acetate (1:1)] = 0.15; HPLC (214 nm) t_R = 6.10 (92.8%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (d, J = 12.4 Hz, 1H), 3.21 (d, J = 12.4 Hz, 1H), 5.64 (s, 1H), 7.01 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 2.3 Hz, 1H), 7.32 (dd, J = 2.3, 8.4 Hz, 1H), 7.38 (d, J = 3.2 Hz, 1H), 7.70 (d, J = 3.2 Hz, 1H), 8.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 45.9, 120.8, 126.0, 129.4, 129.5, 133.1, 134.7, 134.9, 143.7, 169.4, 169.8 ppm; ESMS m/z 297.2 [M + H]$^+$; LC-MS t_R (system A) = 6.22 (297.0 [M + H]$^+$) min; HRMS [M + Na]$^+_{calcd}$ = 318.9742, [M + Na]$^+_{obsd}$ = 318.9739; IR 3195, 1681, 1490, 1351, 1115, 811 cm^{-1}.

Synthesis of [(2-Benzamidophenyl)−(2-methylphenyl)-methylsulfanyl]-acetic Acid Methyl Ester (5). To a stirred solution of **4** (287 mg, 0.904 mmol) in TFA (5.0 mL) under a nitrogen atmosphere at room temperature was added methyl thioglycolate (0.323 mL, 4 equiv). After 18 h of stirring, the TFA was evaporated, and the residue was partitioned between CH_2Cl_2 and aqueous NaOH (1 M). The aqueous phase was back extracted with CH_2Cl_2, and the combined organics were dried with brine and sodium sulfate, filtered, and evaporated to give the crude product (317 mg) as a yellow solid. The crude material was purified by flash chromatography on silica (15 g) by eluting with petroleum ether/ethyl acetate (5:1 then 2:1) to give the thioether **5** as a yellow oil (225 mg, 61%): R_f [petroleum ether/ethyl acetate (2:1)] = 0.65; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (brs, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.88−7.96 (m, 2H), 7.70 (dd, J = 0.8, 7.6 Hz, 1H), 7.40−759 (m, 3H), 7.01−7.36 (m, 6H), 5.83 (s, 1H), 3.41 (s, 3H), 3.13 (s, 2H), 2.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 170.79, 165.98,

137.35, 136.22, 135.46, 134.76, 133.50, 131.77, 131.11, 130.12, 129.08, 128.55, 128.49, 128.44, 127.89, 127.53, 126.46, 125.26, 124.61, 52.25, 46.41, 33.27, 19.12 ppm; ESMS *m/z* 406.1 $[M + 1]^+$.

5-(2-Methylphenyl)-1,2,3,5-tetrahydro-4,1-benzothiazepin-2-one (1q). Step (a). To a stirred solution of **6** in THF (3 mL) and methanol (3 mL) was added 1.0 N NaOH (3 mL). The mixture was refluxed for 18 h. The solvents were evaporated, and the residue was partitioned between brine and CH_2Cl_2. The aqueous phase was titrated to pH 7.0 with 10% HCl and then was back extracted twice with CH_2Cl_2. The combined organic layers were extracted with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to give the crude carboxylic acid/amine (117 mg, 83% crude yield) as a white solid. R_f [petroleum ether/ethyl acetate (2:1)] = 0.

Step (b). To a stirred solution of the crude carboxylic acid (117 mg, ~0.407 mmol) in THF (40.7 mL, to give an overall concentration of ~10 mM) under a nitrogen atmosphere at room temperature were added DIEA (0.213 mL, 1.22 mmol), EDC (117 mg, 0.61 1 mmol), and DMAP (5 mg, 0.041 mmol). After 18 h of stirring, the THF was evaporated, and the residue was dissolved in CH_2Cl_2, partitioned against 10% citric acid and saturated aqueous $NaHCO_3$, and finally washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated. The crude material (116 g) was adsorbed onto silica (1 g) and purified by flash chromatography on silica (5 g) with petroleum ether/ethyl acetate (2:1) to give **5** as an off-white solid (20 mg, 20% yield for two steps): R_f [petroleum ether/ethyl acetate (2:1)] = 0.30; HPLC (214 nm) t_R = 7.89 (88.8%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (brs, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.23−7.37 (m, 3H), 7.08−7.23 (m, 3H), 7.78 (dd, J = 0.8, 7.6 Hz 1H), 5.97 (s, 1H), 3.37 (d, J = 12.0 Hz, 1H), 3.02 (dd, J = 2.0, 12.0 Hz, 1H), 2.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.43, 136.47, 136.43, 135.18, 134.02, 130.91, 129.27, 128.42, 128.19, 127.98, 127.69, 126.15, 123.50, 43.63, 31.49, 19.35 ppm; ESMS *m/z* 270.0 $[M + 1]^+$, 539.1 $[2M + 1]^+$; LC-MS t_R (system A) = 8.06 (270.3 $[M + H]^+$, 339.4 $[2M + H]^+$, 808.1 $[3M + 1]^+$) min.

Synthesis of 7a,b. To a solution of **6** (2.4 mmol) in THF (10 mL) under an atmosphere of nitrogen at −78 °C was added *n*-butyllithium (2.5 mL, 2.4 M solution in diethyl ether) over 5 min. The reaction was allowed to warm to 0 °C and kept at this temperature for 2 h. A solution of aldehyde (4.8 mmol) in THF (2 mL) was added. The mixture was allowed to warm to room temperature over 1 h. The reaction was quenched with 1.0 N aqueous HCl (10 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified on a silica gel column using petroleum spirit/ethyl acetate as eluents.

***N*-{4-Chloro-2-[(2,6-dimethyl-phenyl)-hydroxy-methyl]-phenyl}-2,2-dimethyl-propionamide (7a)** was obtained as white crystals (585 mg, 76%): R_f [petroleum ether/ethyl acetate (1:1)] = 0.31; HPLC (214 nm) t_R = 8.20 (98.1%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 5.74 (s, 1H), 7.07 (d, J = 2.4 Hz, 1H), 7.24−7.30 (m, 4H), 8.10 (d, J = 8.8 Hz, 1H), 8.34 (d, J = 5.7 Hz, 2H), 9.08 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 39.5, 73.9, 121.4, 124.4, 128.8, 129.0, 132.5, 135.9, 149.0, 151.2, 177.1 ppm; ESMS *m/z* 319.3 $[M + H]^+$, 637.3 $[2M + H]^+$; LC/MS t_R (system A) = 5.22 (319.1 $[M + H]^+$, 637.1 $[2M + H]^+$) min.

***N*-{4-Chloro-2-[(4-pyridyl)-hydroxy-methyl]-phenyl}-2,2-dimethyl-propionamide (7b)** was obtained as a viscous oil (285 mg, 44% yield): R_f [petroleum ether/ethyl acetate (1:1)] = 0.41; HPLC (214 nm) t_R = 9.42 (84.4%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 2.18 (s, 6H), 6.23 (s, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.99−7.01 (m, 2H), 7.11 (s, 1H), 7.13 (dd, J = 2.4, 8.8 Hz, 1H), 8.04 (d, J = 8.8 Hz, 2H), 9.67 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 27.5, 39.8, 71.0, 123.4, 127.0, 128.0, 128.2, 128.4, 128.5, 129.6, 130.9, 136.1, 136.6, 137.1, 177.4 ppm; ESMS *m/z* 328.4 $[M - OH]^+$, 346.5 $[M + H]^+$; LC-MS t_R (system A) = 9.74 (328.1 $[M - OH]^+$, 346.3 $[M + H]^+$, 691.4 $[2M + H]^+$) min.

Synthesis of 1h and 1n. A solution of benzhydrol **7** (1.8 mmol) in methyl thioglycolate (0.5 mL) and TFA (2 mL) was stirred at 80 °C for 24 h. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with brine (20 mL), 1.0 N aqueous NaOH (20 mL), and brine (20 mL). The combined aqueous layers were back extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on a silica gel column using a mixture of petroleum ether and ethyl acetate as eluent to yield **1**.

7-Chloro-5-(2,6-dimethylphenyl)-1,2,3,5-tetrahydro-4,1-benzothiazepin-2-one (1h) was obtained as a white amorphous solid (11.3 mg, 24.6%): R_f [petroleum ether/ethyl acetate (1:1)] = 0.55; HPLC (214 nm) t_R = 8.72 (97.8%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 6H), 2.97 (dd, J = 1.9, 12.6 Hz, 1H), 3.58 (d, J = 12.6 Hz, 1H), 6.28 (s, 1H), 6.96 (d, J = 2.3 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.10−7.12 (m, 2H), 7.17 (d, J = 7.5 Hz, 1H), 7.27 (dd, J = 2.3, 8.4 Hz, 2H), 8.11 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 31.5, 41.7, 125.2, 128.3, 128.7, 129.9, 132.2, 132.6, 132.8, 135.5, 170.6 ppm; LC-MS t_R (system A) = 9.04 (317.9 $[M + H]^+$, 358.8 $[M + CH_3CN]^+$, 635.2 $[2M + H]^+$) min; HRMS $[M + Na]^+_{calcd}$ = 340.0539, $[M + Na]^+_{obsd}$ = 340.0541; IR 3201, 1681, 1482, 1116, 772 cm^{-1}.

7-Chloro-5-(4-pyridinyl)-1,2,3,5-tetrahydro-4,1-benzothiazepin-2-one (1n) was obtained as a white amorphous solid (40.5 mg, 42%): R_f [petroleum ether/ethyl acetate (1:1)] = 0.10; HPLC (214 nm) t_R = 4.85 (93.3%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (d, J = 12.3 Hz, 1H), 3.19 (d, J = 12.3 Hz, 1H), 5.43 (s, 1H), 7.01 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.33 (dd, J = 2.4, 8.4 Hz, 1H), 7.40 (d, J = 5.0 Hz, 2H), 8.63 (d, J = 5.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 47.4, 123.8, 126.2, 129.4, 129.5, 133.5, 135.0, 135.8, 146.8, 150.4, 169.4 ppm; ESMS *m/z* 291.4 $[M + H]^+$; LC-MS t_R (system A) = 4.86 (290.9 $[M + H]^+$, 581.0 $[2M + H]^+$, 872.9 $[3M + H]^+$) min; HRMS $[M + Na]^+_{calcd}$ = 313.0178, $[M + Na]^+_{obsd}$ = 313.0188; IR 3053, 1688, 1484, 1416, 1352 848 cm^{-1}.

Microwave-Assisted One-Pot Synthesis of 1a (Method E). To a mixture of **2a** (1.0 g, 3.75 mmol), $HSCH_2COOMe$ (1.40 mL, 15.0 mmol), and TFA (4.0 mL, 52.0 mmol) in a 50-mL beaker was added basic alumina (13.0 g). The heterogeneous mixture was mixed well and subjected to microwave irradiation in a domestic oven for 7 min at full power (800 W). TLC of the reaction mixture showed a small amount of the desired product **1a**, a less polar spot, and a major amount of compound **3a**. To the above reaction mixture was added saturated aqueous Na_2CO_3 (5 mL). The mixture was stirred well with a glass rod and microwaved for 5 min at 20% power. This procedure (addition of saturated aqueous Na_2CO_3 followed by microwave irradiation at 20% power) was repeated four times. TLC indicated complete disappearance of **3a** and the formation of **1a** (major) and a small amount of the hydrolysis product of **3a**. The mixture was extracted with 10% MeOH/$CHCl_3$. The combined organic extracts were concentrated under vacuum, redissolved in CH_2Cl_2, washed with saturated aqueous Na_2CO_3 and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give pure **1a** (0.61 g, 51%) whose analytical data were identical with the sample obtained using method A above.

Syntheses of 9a. To a solution of **8** (3 g, 1.32 mmol) at −78 °C in dry THF (10 mL) was added *t*-BuLi (22 mL, 1.6 M in THF, 3.3 mmol) slowly over a period of 30 min. The mixture was stirred at 0 °C for 2 h and cooled to −78 °C. A solution of 4-benzyloxy-1-butanal (2.6 g, 1.45 mmol) in THF (5 mL) was added slowly. The reaction mixture was stirred for an additional 2 h, quenched with saturated aqueous NH_4Cl (30 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water, saturated aqueous $NaHCO_3$, and brine and dried over anhydrous sodium sulfate. The solvents were filtered and evaporated, and the crude material

was purified over flash silica gel column chromatography using a mixture of ethyl acetate and hexane as eluent to give **9a** as an oil (2 g, 37%). The undesired product **12a** was isolated in 30% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (m, 2H), 1.48 (s, 9H), 1.97 (m, 2H), 3.53 (m, 2H), 4.52 (s, 2H), 4.70 (s, 1H), 7.08 (d, 1H, J = 2.3 Hz), 7.20 (m, 1H), 7.34 (m, 6H) ppm; LC-MS t_R (system B) = 8.58 (288 [M + H − (Boc + H_2O)]$^+$) min.

Synthesis of 10a. To a solution of **9a** (0.6 g, 1.48 mmol) in dry CH_2Cl_2 (3 mL) were added methyl thioglycolate (0.78 g, 7.4 mmol) and TFA (3.4 g, 29 mmol). The mixture was stirred at room temperature for 18 h. The solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (30 mL); washed with saturated aqueous $NaHCO_3$ solution, water, and brine; and dried over anhydrous sodium sulfate. The crude material was purified using silica gel chromatography (40−60% ethyl acetate in hexane) to give **10a** as an oil (0.35 g, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (m, 2H), 2.05 (s, 2H), 3.01 (d, J = 12.25 Hz, 1H), 3.13 (d, J = 12.25 Hz, 1H), 3.48 (m, 2H), 3.66 (s, 3H), 4.11 (m, 1H), 4.47 (s, 2H), 6.57 (d, J = 9.0 Hz, 1H), 7.00 (m, 1H), 7.12 (s, 1H), 7.34 (m, 6H) ppm; LC-MS t_R (system B) = 8.39 (289 [M + H − (SCH_2COOMe)]$^+$) min.

Synthesis of 7-Chloro-5-[(3-benzoxyl)propyl]-1,2,3,5-tetrahydro-4,1-benzothiazepin-2-one (11a). Step (a). To a solution of compound **10a** (0.3 g, 0.76 mmol) in MeOH (2 mL) at 0 °C was added a solution of NaOH (0.62 g, 1.5 mmol) in water (0.5 mL). The mixture was stirred for an additional 2 h at 0 °C. The solvent was removed under vacuum. The residue was dissolved in ethyl acetate (30 mL) and carefully acidified using 1 N HCl. The organic layer was separated, washed with water and brine, dried over sodium sulfate, filtered, and concentrated to give the acid (0.29 g, 0.76 mmol), which was used in the next step without further purification.

Step (b). A solution of the acid from above (0.29 g, 0.76 mmol) in DMF (10 mL) was added via a syringe pump to a solution of EDC (0.22 g, 1.14 mmol), HOBt (0.31 g, 2.3 mmol), and DMAP (0.018 g, 0.15 mmol) in dry DMF (5 mL) over a period of 24 h. The mixture was stirred for an additional 24 h. The DMF was removed under high vacuum. The residue was dissolved in CH_2Cl_2 (30 mL), thoroughly washed with water and brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified using silica gel column chromatography (40−60% ethyl acetate in hexane) to give **11a** as a white solid (0.15 g, 56% overall yield for two steps); the starting acid (26%) was also recovered. Data for **11a**: mp 122−123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (m, 1H), 1.81 (m, 1H), 2.02 (m, 1H), 2.17 (m, 1H), 2.93 (d, 1H, J = 12.28 Hz), 3.11 (d, 1H, J = 12.28 Hz), 3.53 (m, 2H), 4.30 (t, 1H, J = 7.46 Hz), 4.50 (s, 2H), 7.01 (d, 1H, J = 8.30 Hz), 7.25 (m, 2H), 7.33 (m, 5H), 7.60 (s, 1H); LC-MS t_R (system B) = 7.53 (362 [M + H]$^+$) min.

Compounds **11b**−**c** were synthesized following the same route as illustrated above from **8** to **11a**.

Compound **11b** was obtained as a white solid (0.08 g, 35% overall yield for four steps): mp 170−171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.74 (m, 1H), 0.98 (m, 1H), 1.20 (m, 2H), 1.32 (m, 2H), 1.61 (m, 2H), 1.81 (m, 1H), 2.11 (m, 1H), 2.34 (m, 1H), 2.87 (d, 1H, J = 12.28 Hz), 3.10 (d, 1H, J = 12.28 Hz), 3.73 (d, 1H, J = 10.94 Hz), 6.99 (d, 1H, J = 8.01 Hz), 7.27 (m, 2H, J = 2.10 Hz), 7.44 (s, 1H); LC-MS t_R (system B) = 7.49 (296 [M + H]$^+$) min.

Compound **11c** was obtained as a white solid (0.15 g, 30% overall yield for four steps): mp 113−114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.785 (d, 3H, J = 6.87 Hz), 1.25 (d, 3H, J = 6.84 Hz), 2.45 (m, 1H), 2.89 (d, 1H, J = 12.3 Hz), 3.08 (d, 1H, J = 12.3 Hz), 3.67 (d, 1H, J = 10.6 Hz), 7.02 (d, 1H, J = 7.9 Hz), 7.25 (m, 1H), 7.26 (m, 1H), 8.00 (s, 1H) ppm; LC-MS t_R (system B) = 6.74 (256 [M + H]$^+$) min.

Compound **11d** was obtained as a white solid (0.10 g, 43% overall yield for four steps): mp 106−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, 3H, J = 10.34 Hz), 0.96 (d, 3H, J = 10.34 Hz), 1.76 (m, 1H), 1.85 (t, 2H, J = 7.23 Hz), 2.91 (d, 1H, J = 12.25 Hz), 3.12 (d, 1H, J = 12.25 Hz), 7.02 (d, 1H, J = 8.30 Hz), 7.27 (m, 1H), 7.30 (m, 1H), 7.80 (s, 1H) ppm; LC-MS t_R (system B) = 7.20 (270 [M + H]$^+$) min.

Synthesis of 13. To a solution of **2a** (1 g, 3.7 mmol) and mercaptoethanol (1.448 g, 19 mmol) in dry CH_2Cl_2 (7 mL) was added TFA (7.4 mL, 65 mmol). The mixture was stirred at room temperature for 18 h. The solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (30 mL); washed with saturated aqueous $NaHCO_3$, water, and brine; dried over sodium sulfate; filtered; and concentrated under vacuum. The crude material was purified using silica gel column chromatography (40−60% ethyl acetate in hexane) to give **13** as a white solid (0.65 g, 54%): mp 104−105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.657 (t, J = 6.00 Hz, 2H), 3.79 (m, 2H), 5.66 (s, 1H), 6.63 (d, J = 8.30 Hz, 1H), 7.05 (m, 1H), 7.13 (d, J = 2.1 Hz, 1H), 7.265 (m, 1H), 7.33 (m, 1H), 7.42 (d, J = 7.0 Hz, 1H), 7.65 (d, 8.73 Hz, 1H) ppm; LC-MS t_R (system B) = 7.12 (250 [M + H − SCH_2CH_2OH]$^+$) min.

Synthesis of 14. To a solution of **13** (0.25 g, 0.76 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C were added triphenylphosphine (0.81 g, 3.1 mmol), imidazole (0.26 g, 3.8 mmol), and carbon tetrabromide (0.3 g, 0.9 mmol). After 2 h, the mixture was diluted with CH_2Cl_2 (30 mL) and quenched with water (20 mL). The organic layer was separated, washed with water and brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified using silica gel column chromatography (40−60% ethyl acetate in hexane) to give **14** as pale yellow semisolid (0.25 g, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (t, J = 7.5 Hz, 2H), 3.50 (t, J = 7.5 Hz, 2H), 3.95 (s 2H), 5.65 (s, 1H), 6.65 (d, J = 8.5 Hz, 1H), 7.05 (m, 1H), 7.13 (d, J = 2.1 Hz, 1H), 7.265 (m, 1H), 7.33 (m, 1H), 7.42 (d, J = 7.0 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H) ppm; LC-MS t_R (system B) = 8.66 (250 [M + H − (SCH_2CH_2Br)]$^+$) min.

Synthesis of 7-Chloro-5-(2-chlorophenyl)-1,2,3,5-tetrahydro-4,1-benzothiazepine (15). To a solution of **14** (0.1 g, 0.26 mmol) in dry DMF (2 mL) was added powdered K_2CO_3 (0.07 g, 0.51 mmol), and the solution was heated at 80 °C for 5 h. The reaction was quenched with water (20 mL), and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were thoroughly washed with water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified using silica gel column chromatography (40−60% ethyl acetate in hexane) to give **15** as a semisolid (0.069 g, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.84 (m, 1H), 3.05 (m, 1H), 3.18 (m, 1H), 3.68 (m, 1H), 3.79 (s, 1H), 5.73 (s, 1H), 6.54 (d, 1H, J = 2.00 Hz), 6.85 (d, 1H, J = 8.30 Hz), 7.02 (m, 1H), 7.28 (m, 1H), 7.38 (m, 2H), 7.58 (m, 1H) ppm; LC-MS t_R (system B) = 8.10 (310 [M + H]$^+$) min.

Synthesis of 17. Using a similar procedure as for **10a**, compound **17** was synthesized from **16** as a pale yellow oil (0.05 g, 50%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.97 (s, 6H), 3.14 (d, J = 17.5 Hz, 1H), 3.24 (d, J = 17.5 Hz, 1H), 3.50 (m, 2H), 3.72 (m, 2H), 3.76 (s, 3H), 5.67 (s, 1H), 6.63 (d, J = 8,73 Hz, 1H), 6.54 (d, J = 2.70 Hz, 1H), 7.13 (m, 1H), 7.30 (m, 1H), 7.375 (m, 1H), 7.44 (m, 1H), 8.07 (m, 1H) ppm; LC-MS t_R (system B) = 6.64 (321 [M + H − (SCH_2COOMe)]$^+$) min.

Synthesis of 18. To a solution of **17** (0.05 g, 0.12 mmol) in dry THF (2 mL) at −78 °C was added LHMDS (1 M THF, 0.175 mL, 0.18 mmol) slowly, and the mixture was stirred for 5 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic portions were washed with water, saturated aqueous $NaHCO_3$, and brine; dried over anhydrous Na_2SO_4; filtered; and concentrated under vacuum. The crude product was purified using flash silica gel column chromatography (5−10% MeOH/ CH_2Cl_2) to give **18** as a pale yellow oil (0.030 g, 66%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 6H), 2.53 (m, 1H), 2.74 (m, 1H), 3.02 (d, 1H, J = 12.3 Hz), 3.20 (d, 1H, J = 12.3 Hz), 3.65 (m, 1H), 4.28 (m, 1H),

5.94 (s, 1H), 6.53 (s, 1H), 7.40 (m, 3H), 7.45 (m, 2H), 7.79 (d, 1H, J = 7.8 Hz) ppm; LC-MS t_R (system B) = 6.16 (395 [M + H]$^+$) min.

Synthesis of 19. To a stirred solution of **3a** (684 mg, 1.92 mmol) in THF/methanol (1/1, 40 mL) at room temperature was added 1.0 M aqueous NaOH (20 mL). After 1 h of stirring, the solvents were evaporated, and the residue was partitioned between brine and CH_2Cl_2. The aqueous phase was titrated to exactly pH 7.0 with 10% aqueous HCl and extracted with CH_2Cl_2 twice. The combined organic layers were dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the filtrate was concentrated under vacuum to give analytically pure **19** as a white solid (657 mg, 100% yield): R_f [CH_2Cl_2/methanol (9:1)] = 0.25; HPLC (214 nm) t_R = 8.27 (94.2%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (d, J = 16.0 Hz, 1H), 3.22 (d, J = 16.0 Hz, 1H), 6.02 (s, 1H), 7.07 (d, J = 2.4 Hz, 1H), 7.31−7.37 (m, 2H), 7.40−7.47 (m, 2H), 7.80−7.89 (m, 2H), 9.02 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.8, 45.0, 126.1, 127.6, 129.0, 129.8, 129.9, 130.5, 131.7, 132.6, 132.7, 133.9, 134.6, 175.0 ppm; ESMS m/z 250.2 [(M − $HSCH_2CO_2H$ + H)]$^+$, 342.1 [(M + H)]$^+$. LC-MS t_R (system A) = 8.66 (346.0 [(M − $HSCH_2CO_2H$ + CF_3CO + H)]$^+$, 438.1 [(M + CF_3CO + H)]$^+$, 874.8 [(2(M + CF_3CO) + H)]$^+$ min.

1-Acetyl-7-chloro-5-(2-chlorophenyl)-1,2,3,5-tetrahydro-4,1-benzodiazepin-2-one (20). To a stirred solution of carboxylic acid **19** (100 mg, 0.292 mmol) in THF (5.0 mL) under a nitrogen atmosphere at room temperature were added diisopropylethylamine (0.508 mL, 2.92 mmol), acetyl chloride (104 μL, 1.46 mmol), and DMAP (3.6 mg, 0.029 mmol). After 3 h of stirring, the reaction mixture was partitioned between CH_2Cl_2 and brine. The aqueous phase was back extracted twice with CH_2Cl_2 and the combined organic phase was dried with sodium sulfate, then filtered and concentrated under vacuum. The crude material was purified by flash chromatography first on silica (15 g) by eluting with dichloromethane:methanol (10:1) and then again on silica (10 g) with dichloromethane (100%) to give **20** as a bright yellow solid (45 mg, 40%): R_f [silica, CH_2Cl_2 (100%) = 0.50; HPLC (214 nm) t_R = 9.16 (96.7%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 3H), 3.14 (s, 2H), 5.93 (s, 1H), 6.69 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 8.4, 2.4 Hz, 1H), 7.39 (dd, J = 7.6, 1.6 Hz, 1H), 7.42−7.49 (m, 2H), 7.76 (dd, J = 7.6, 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 34.9, 43.0, 126.5, 127.2, 128.7, 129.5, 129.9, 130.4, 132.8, 134.4, 135.0, 35.5, 168.7, 172.0 ppm; ESMS m/z 366.0 [M+H]$^+$, 383.9 [M + H_2O + H]$^+$; LC-MS t_R (system A) = 9.36 (365.9 [M + H]$^+$, 748.1 [2M + NH_4]$^+$) min.

Synthesis of 21. To a stirred solution of **2a** (500 mg, 1.86 mmol) in TFA (10 mL) under a nitrogen atmosphere at room temperature was added 3-mercaptopropionic acid (989 mg, 9.32 mmol). After 96 h of stirring, the reaction mixture was partitioned between CH_2Cl_2 and brine (80 mL) containing aqueous NaOH (10 M × 20 mL). The aqueous phase was titrated to exactly pH 7.0 using concentrated HCl and then extracted three times with CH_2Cl_2. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to give the crude thioether (873 mg) as a brown oil. The crude material was purified by flash chromatography on silica (20 g) by eluting with 40−60 petroleum ether/ethyl acetate (2:1 then 1:1) to give **21** as a yellow gum (311 mg, 47%): R_f [40−60 petroleum ether/ethyl acetate (1:1)] = 0.42; HPLC (214 nm) t_R = 8.28 (86.7%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64−2.76 (m, 4H), 5.66 (s, 1H), 6.63 (d, J = 8.4 Hz, 1H), 6.83 (s, 3H), 7.03−7.08 (m, 2H), 7.25 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.30−7.36 (m, 1H), 7.38−7.40 (m, 1H), 7.74 (dd, J = 8.0, 1.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) d 27.1, 34.0, 45.7, 118.1, 123.8, 125.8, 127.3, 128.30, 128.34, 128.9, 129.8, 130.4, 133.9, 136.2, 142.7, 177.4 ppm; ESMS m/z 250.0 [M − $HS(CH_2)_2CO_2H$ + H]$^+$, 356.1 [M + H]$^+$; LC-MS t_R (system A) = 8.43 (250.0 [M − $HS(CH_2)_2CO_2H$ + H]$^+$, 355.9 [M + H]$^+$, 710.9 [2M + H]$^+$) min.

Synthesis of 22. To a stirred solution of **21** (105 mg, 0.294 mmol) in THF (29.4 mL) at room temperature under nitrogen were added diisopropylethylamine (0.257 mL, 1.47 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (150 mg, 0.589 mmol). After 48 h of stirring, the reaction mixture was filtered, and the THF was evaporated. The residue was partitioned between brine and CH_2Cl_2, and the aqueous layer was back extracted twice with CH_2Cl_2. The combined organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated. The crude material was purified by flash chromatography on silica (15 g) by eluting with 40−60 petroleum ether/ethyl acetate (1:1) to give lactam **22** as a white solid (97.0 mg, 98%): R_f [40−60 petroleum ether/ethyl acetate (1:1)] = 0.25; HPLC (214 nm) t_R = 8.16 (96.3%) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38−2.47 (m, 1H), 2.71−2.80 (m, 1H), 2.87−2.95 (m, 1H), 3.20 (dd, J = 14.4, 10.4 Hz, 1H), 5.33 (s, 1H), 6.96 (d, J = 2.4 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.16 (dd, J = 8.4, 2.4 Hz, 1H), 7.20−7.29 (m, 2H), 7.35−7.41 (m, 1H), 7.65−7.71 (m, 1H), 8.68 (brs, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 35.6, 43.5, 127.0, 127.4, 127.7, 128.3, 128.9, 129.0, 129.6, 132.0, 133.0, 134.4, 138.2, 143.3, 174.6 ppm; ESMS m/z 379.2 [M + CH_3CN + H]$^+$; LC-MS t_R (system A) = 8.39 (337.8 [M + H]$^+$, 379.0 [M + CH_3CN + H]$^+$, 675.0 [2M + H]$^+$) min; HRMS [M + Na]$^+_{calcd}$ = 359.9993, [M + Na]$^+_{obsd}$ = 359.9985; IR 3058, 1665, 1487, 1472, 1111, 747 cm^{-1}.

General Procedure for the Preparation of 24a,b. To a solution of Ph_3PMeBr (1.5 equiv) in dry THF was added t-$C_5H_{11}OK$ (1.5 equiv) in portions under argon. After the mixture was stirred at room temperature for 0.5 h, a solution of the corresponding benzophenone derivative **23** in THF was added dropwise. The reaction mixture was then stirred at room temperature under argon overnight. The reaction mixture was quenched with H_2O and extracted twice with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, filtered,and concentrated, and the residue was purified by column chromatography on silica gel.

For 24a: following the general procedure, **23a** (2.66 g, 10.0 mmol), t-$C_5H_{11}OK$ (1.74 g, 15.0 mmol), and Ph_3PMeBr (5.36 g, 15.0 mmol) were employed to give **24a** as slightly orange oil (1.95 g, 73%) after chromatography (EtOAc/hexane 10:90): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (b, 2H), 5.61 (s, 1H), 5.87 (s, 1H), 6.57 (d, J = 8.4 Hz, 1H), 7.06 (m, 2H), 7.17−7.23 (m, 3H), 7.26−7.31 (m, 1H) ppm; LC-MS t_R (system B) = 7.78 (264.0 [M + H]$^+$) min.

For 24b: following the general procedure, **23b** (7.50 g, 30.0 mmol), t-$C_5H_{11}OK$ (5.22 g, 45.0 mmol), and Ph_3PMeBr (16.08 g, 45.0 mmol) were employed to give **24b** (5.93 g, 80%) as colorless oil after chromatography (EtOAc/hexane 10:90): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (b, 2H), 5.61 (s, 1H), 5.86 (s, 1H), 6.62 (d, J = 8.3 Hz, 1H), 7.04−7.10 (m, 3H), 7.16−7.19 (m, 1H), 7.25−7.35 (m, 2H) ppm; LC-MS t_R (system B) = 7.53 (248 [M + H]$^+$) min.

General Procedure for the Preparation of 25a,b. To a solution of the corresponding styrene derivative **24** and $HSCH_2CO_2Me$ (3.0 equiv) in 1,4-dioxane was added 1,1′-azobis-(cyclohexanecarbonitrile) (0.1 equiv). The reaction mixture was then warmed to 80 °C under argon and stirred at that temperature overnight. Additional 1,1′-azobis(cyclohexanecarbonitrile) (0.05−0.1 equiv) was added to the reaction mixture, which was stirred at 80 °C until TLC analysis indicated disappearance of **24**. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, filtered, and concentrated, and the residue was purified by column chromatography on silica gel.

For 25a: following the general procedure, **24a** (2.66 g, 10.08 mmol), $HSCH_2CO_2Me$ (3.21 g, 30.23 mmol), and 1,1′-azobis-(cyclohexanecarbonitrile) (369 mg, 1.51 mmol) were employed to give **25a** (3.15 g, 84%) as colorless oil after chromatography (EtOAc/hexane 15:85):^{1}H NMR (500 MHz, $CDCl_3$) δ 3.10−3.30 (m, 2H), 3.18 and 3.23 (AB q, J = 14.8 Hz, 2H), 3.74 (s, 3H), 4.68 (t, J = 7.7 Hz, 1H), 6.60 (d, J = 8.9 Hz, 1H), 7.02 (t, J =

2.0 Hz, 1H), 7.03 (s, 1H), 7.16−7.26 (m, 3H), 7.40 (d, J = 8.5 Hz, 1H) ppm; LC-MS t_R (system B) = 7.37 (370.1 $[M + H]^+$) min.

For 25b: following the general procedure, **24b** (1.74 g, 7.03 mmol), $HSCH_2CO_2Me$ (2.25 g, 21.2 mmol), and 1,1′-azobis-(cyclohexanecarbonitrile) (258 mg, 1.06 mmol) were employed to give **25b** (2.05 g, 82%) as a colorless oil after chromatography (EtOAc/hexane 20:80): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.18 and 3.23 (AB q, J = 15.2 Hz, 2H), 3.22−3.34 (m, 2H), 3.74 (s, 3H), 3.77 (b, 2H), 4.54 (t, J = 7.8 Hz, 1H), 6.59 (d, J = 8.7 Hz, 1H), 7.00−7.26 (m, 6H) ppm; LC-MS t_R (system B) = 7.15 (354 $[M + H]^+$) min.

General Procedure for the Preparation of 26a,b. To a solution of the corresponding ester **25** in dry THF was added dropwise a solution of LiHMDS (1.0 M, 2 equiv) in THF at −78 °C under argon. The reaction mixture was then stirred at −78 °C to room temperature overnight. The reaction mixture was quenched with aqueous NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, filtered, and concentrated, and the residue was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$ 2:98).

Data for 26a: white solid (125 mg, 90%); mp 238−239 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.00 (d, J = 13.8 Hz, 1H), 3.05 (d, J = 13.8 Hz, 1H), 3.23 (dd, J = 13.5 Hz, 9.5 Hz, 1H), 3.33 (d, J = 13.5 Hz, 1H), 4.91 (d, J = 9.4 Hz, 1H), 6.91 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.40 (t, J = 7.4 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.87 (s, 1H) ppm; LC-MS t_R (system B) = 6.85 (337.9 $[M + H]^+$) min.

Data for 26b: white solid (210 mg, 82%); mp 181−182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.01 (s, 2H), 3.20−3.33 (m, 2H), 4.82 (d, J = 9.3 Hz, 1H), 6.99 (t, J = 9.2 Hz, 1H), 7.04 (d, J = 1.9 Hz, 1H), 7.15−7.29 (m, 4H), 7.40 (t, J = 7.1 Hz, 1H), 7.98 (s, 1H) ppm; LC-MS t_R (system B) = 6.75 (322 $[M + H]^+$) min.

General Procedure for the Preparation of 28a,b. To a solution of **27** (10 mmol) in dry DMF (3.3 mL) were added 1,1-carbonyldiimidazole (1.6 g, 10 mmol) and ethylenediamine (6.7 mL, 100 mmol) at room temperature. The mixture was then stirred at room temperature for 18 h. The mixture was diluted with ethyl acetate (100 mL), washed with saturated aqueous $NaHCO_3$ (100 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give analytically pure **28**.

Compound **28a** was prepared from **27a** as a white solid (2.48 g, 99%): ^{1}H NMR (500 MHz, MeOH-d_4), 2.77 (s, 2H), 2.99 (s, 2H), 7.36 (m, 5H), 7.52 (m, 3H), 7.56 (d, J = 7.4 Hz, 2H) ppm; LC-MS t_R (system B) = 4.63 (251 $[M + H]^+$) min.

Compound **28b** was prepared from **27b** as a yellowish oil (2.56 g, 96%): ^{1}H NMR (500 MHz, MeOH-d_4), 2.31 (s, 3H), 2.79 (s, 2H), 2.99 (s, 2H), 7.05 (s, 1H), 7.18 (m, 1H), 7.24(m, 2H), 7.52 (m, 2H), 7.57 (s, 1H), 7.77 (d, J = 7.3 Hz, 1H), 7.97 (S, 1H) ppm; LC-MS t_R (system B) = 5.57 (265 $[M + H]^+$) min.

General Procedure for the Preparation of 29a,b. To a solution of corresponding **28** (0.025 g, 0.1 mole) in formic acid (1 mL) was added palladium, 10 wt % on activated carbon (0.015 g). The mixture was stirred at room temperature under a hydrogen atmosphere for 18 h. The catalyst was removed by filtration through a bed of Celite. The filtrate was concentrated under vacuum to give analytically pure **29**.

Compound **29a** was prepared from **28a** as a white solid (18.9 mg, 75%): ^{1}H NMR (500 MHz, MeOH-d_4), 1.99 (s, 1H), 3.06 (m, 3H), 3.35 (m, 2H), 5.75 (S, 1H), 7.37 (m, 4H), 7.41 (m, 3H), 7.57 (m, 1H), 7.88 (d, J = 7.2 Hz, 2H) ppm; LC-MS t_R (system B) = 4.95 (253 $[M + H]^+$) min.

Compound **29b** was prepared from **28b** as a white solid (19.2 mg, 72%): ^{1}H NMR (500 MHz, MeOH-d_4) 1.99 (s, 1H), 3.31 (s, 3H), 3.05 (m, 2H), 3.37 (m, 2H), 5.70 (s, 1H), 7.10 (m, 2H), 7.24 (m, 2H), 7.58 (m, 3H), 7.86(m, 2H) ppm; LC-MS t_R (system B) = 5.48 (267 $[M + H]^+$) min.

Synthesis of 30a. In a sealed reaction tube were stirred 2-amino-2′,5-dichlorobenzophenone (0.5 g, 1.88 mmol) and 3-ethoxypropylamine (3 mL, 25 mmol) at 140 °C for 18 h. The mixture was cooled to room temperature and diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The crude product was purified using silica gel column chromatography (hexane/ethyl acetate 6:1 then 4:1) to give **30a** as a light yellow oil (0.59 g, 88.5%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.48 (m, 1H), 7.41−7.35 (m, 2H), 7.09−7.03 (m, 2H), 6.80 (brs, 1H), 6.65−6.63 (m, 2H), 3.52−3.49 (m, 2H), 3.46−3.42 (m, 2H), 3.32−3.28 (m, 1H), 3.26−3.22 (m, 1H), 1.97−1.94 (m, 2H), 1.16 (t, J = 6.9 Hz, 3H) ppm. LC-MS t_R (system B) = 7.88 (351 $[M + H]^+$) min.

Synthesis of 31a. To a stirred solution of **30a** (0.57 g 1.6 mmol) in 10 mL of MeOH/AcOH (100/1) at 0 °C was added $NaBH_3(CN)$ (0.5 g, 8.12 mmol). The mixture was stirred for 18 h and allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated to pure **31a** as a light yellow oil (0.57 g, 100%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, J = 6.6 Hz, 2H), 7.29−7.23 (m, 2H), 7.03 (dd, J = 8.3, 2.5 Hz, 1H), 6.95 (d, J = 2.5 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 5.24 (s, 1H), 3.51−3.44 (m, 4H), 2.77−2.71 (m, 2H), 1.83−1.81 (m, 2H), 1.16 (t, J = 7.0 Hz, 3H) ppm; LC-MS t_R (system B) = 5.83 (353 $[M + H]^+$) min.

Synthesis of 32a. To the stirred solution of **31a** (0.067 g, 0.189 mmol) in 1.5 mL of CH_2Cl_2 at 0 °C was added bromoacetyl bromide (0.020 mL, 0.228 mmol), and the mixture was stirred at 0 °C for 1 h and then at room temperature for 18 h. DIEA (0.5 mL, 2.87 mmol) was added, and the mixture was stirred at 50 °C for 5 h. The mixture was cooled to room temperature and diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated to dryness, and the crude product was purified using silica gel chromatography (hexane/ethyl acetate 4:1 then 2:1) to give **32a** as a white solid (0.052 g, 70%): mp 54.5−56 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.54 (d, J = 6.7 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.34−7.21 (m, 3H), 6.93 (d, J = 8.5, 1H), 6.63 (d, J = 2.0 Hz, 1H), 5.23 (s, 1H), 3.50−3.39 (m, 6H), 2.75−2.69 (m, 2H), 1.86−1.82 (m, 2H), 1.13 (t, J = 7.0 Hz, 3H) ppm; LC-MS t_R (system B) = 7.60 (393 $[M + H]^+$) min. Using similar procedures as illustrated above from **30a** to **32a**, the following compounds were synthesized:

Data for 32b: light yellow oil (0.6 g, 59%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29(s, 1H), 7.46−7.44 (m, 1H), 7.31−7.24 (m, 4H), 6.97 (d, J = 8.5 Hz, 1H), 6.82 (d, J = 2.2, 1H), 5.40 (s, 1H), 3.77−3.65 (m, 2H), 3.5 (s, 2H), 2.96−2.86 (m, 2H), 2.46 (t, J = 6.1 Hz, 3H) ppm; LC-MS t_R (system B) = 6.20 (351 $[M + H]^+$) min.

Data for 32c: light yellow oil (0.034 g, 65%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.66 (d, J = 6.8 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.34 (t, J = 6.8 Hz, 1H), 7.29 (t, J = 6.8 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.60 (s, 1H), 5.24 (s, 1H), 3.47 (s, 2H), 2.85−2.73 (m, 1H), 2.65−2.53 (m, 3H), 2.30 (t, J = 7.5 Hz, 4H), 1.41−1.35 (m, 4H), 0.81 (t, J = 7.3 Hz, 6H) ppm; LC-MS t_R (system B) = 5.97 (434 $[M + H]^+$) min.

Data for 32d: light yellow oil (0.033 g, 49%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.61 (d, J = 6.7 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.34 (t, J = 6.8 Hz, 1H), 7.29 (t, J = 6.8 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 5.25 (s, 1H), 3.50−3.43 (m, 2H), 3.39 (t, J = 5.9 Hz, 4H), 3.29 (s, 6H), 2.86−2.75 (m, 4H), 2.74−2.65 (m, 4H) ppm; LC-MS t_R (system B) = 5.75 (466 $[M + H]^+$) min.

Data for 32e: white solid (0.018 g, 32%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.37−7.33 (m, 2H), 7.28−7.19 (m, 3H), 6.92 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.57 (s, 1H), 6.62 (s, 1H), 5.22 (s, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.51 (s, 2H), 2.98−2.95 (m, 1H), 2.75−2.83

(m, 1H), 2.84−2.75 (m, 2H) ppm; LC-MS t_R (system B) = 7.63 (471 $[M + H]^+$) min.

Acknowledgment. We dedicate this paper to the memory of Professor Henry Rapoport, whose teaching and guidance were a source of great inspiration. We also thank Piyali Datta Chaudhuri and V. Pramela Devi at the Indian Institute of Science who helped in the large-scale syntheses of benzothiazepinones and intermediates.

Supporting Information Available: Experimental details for compounds **1b**−**g**, **1i**, **1o,p**, **3b**−**g**, **3i**, and **3o,p** and copies of ^{1}H NMR, ^{13}C NMR, and LC-MS spectra of all new compounds reported in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020446T