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Development of Selective CBP/P300 Benzoxazepine Bromodomain Inhibitors

Tobias A. Popp,[†] Cynthia Tallant,[‡,§] Catherine Rogers,[‡,§] Oleg Fedorov,[‡,§] Paul E. Brennan,[‡,§] Susanne Müller,[‡,§] Stefan Knapp,[*,‡,∥] and Franz Bracher[*,†]

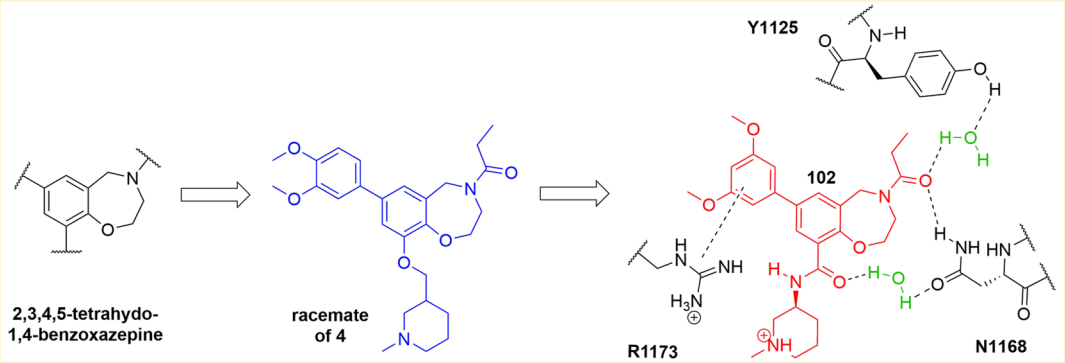
[†]Department für Pharmazie—Zentrum für Pharmaforschung, Ludwig-Maximilians-Universität München, Butenandtstrasse 5-13, D-81377 München, Germany

[‡]Nuffield Department of Clinical Medicine, University of Oxford, Structural Genomics Consortium, Old Road Campus Research Building, Roosevelt Drive, Oxford OX3 7DQ, U.K.

[§]Nuffield Department of Clinical Medicine, University of Oxford, Target Discovery Institute (TDI), Roosevelt Drive, Oxford OX3 7BN, U.K.

[∥]Institute for Pharmaceutical Chemistry and Buchmann Institute for Life Sciences, Johann Wolfgang Goethe-University, Max-von-Laue-Strasse 9, D-60438 Frankfurt am Main, Germany

Supporting Information



ABSTRACT: CBP (CREB (cAMP responsive element binding protein) binding protein (CREBBP)) and P300 (adenovirus E1A-associated 300 kDa protein) are two closely related histone acetyltransferases (HATs) that play a key role in the regulation of gene transcription. Both proteins contain a bromodomain flanking the HAT catalytic domain that is important for the targeting of CBP/P300 to chromatin and which offeres an opportunity for the development of protein−protein interaction inhibitors. Here we present the development of CBP/P300 bromodomain inhibitors with 2,3,4,5-tetrahydro-1,4-benzoxazepine backbone, an *N*-acetyl-lysine mimetic scaffold that led to the recent development of the chemical probe I-CBP112. We present comprehensive SAR of this inhibitor class as well as demonstration of cellular on target activity of the most potent and selective inhibitor TPOP146, which showed 134 nM affinity for CBP with excellent selectivity over other bromodomains.

INTRODUCTION

CBP/P300 are two evolutionary conserved and closely related histone acetyl transferases (HATs) that function as transcriptional regulators by acetylating histone tails and other nuclear proteins and by acting as scaffolds for the assembly of multiprotein complexes through protein interaction domains.[1] CBP/P300 activity is regulated on several levels: autoacetylation of a HAT domain adjacent loop inhibits CBP/P300 activity by competing with the binding of substrates, the RING domain that regulates CBP/P300 turnover, and the PHD bromodomain that is required for substrate recruitment.[2] Studies in mice demonstrated that *Cbp* and *p300* are essential genes required for development. Homozygous deletion of *Cbp* or *p300* results in embryonic lethality early in development due to impaired hematopoiesis, neurulation, cell proliferation, and heart development,[3] while heterozygous $Cbp^{\pm}$ mice showed defects in stem cell renewal. In adult mice, conditional deletion of *Cbp* in the hematopoetic system resulted in cell differentiation defects and impaired self-renewal of hematopoietic stem cells (HSC).[4] Deregulation of CBP/P300 has been reported in cancer and chromosomal rearrangement of the CBP/P300 locus results in oncogenic fusions with either MOZ acetyltransferase or the mixed linage leukemia (MLL) gene product and CBP/MLL fusions have been detected in acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) after treatment with topoisomerase inhibitors.[5]

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Because of the central function of CBP/P300 in disease development and its critical role in many cellular processes, a number of inhibitors have been developed that target domains in CBP/P300. These inhibitors and chemical probes constitute a rich resource that facilitates functional studies on CBP/P300 protein interaction and catalytic domains. The catalytic function has been targeted by the pyrazolone C646, a competitive HAT inhibitor.[6] However, C646 is reactive and has multiple off-target activities and its thiol reactivity limits its applications as a chemical probe in cellular systems.[7]

The KIX domain, an interaction domain mediating cAMP response element binding protein (CREB) interaction, has been targeted by several different scaffolds.[8] The bromodomain has been targeted by the inhibitor "ischemin", an acetyl-lysine competitive inhibitor with low μM activity. In addition, a number of nonspecific fragments have been reported to target the CBP bromodomain.[9] Bromodomains are acetyl-lysine dependent protein interaction domains with predicted good druggability,[10] which has been first demonstrated by the identification of highly potent and selective inhibitors developed for the BET (bromodomain and extraterminal domain) family of transcriptional regulators.[11] Despite their conserved fold, the large sequence and structural diversity of bromodomains offers multiple opportunities for target or family specific targeting using small molecules,[12] a property that has been explored for the development of a large diversity of inhibitors and chemical probes.[13]

The first potent inhibitors for the CBP/P300 bromodomains were based on 5- and 6-isoxazolylbenzimidazoles, acetyl-lysine mimetic moieties that were initially developed for targeting BET bromodomains[14] and that have been been later optimized for CBP/P300 inhibition, such as compound **1** (CBP30)[15] (Figure 1), as well as on a dihydroquinoxalinone based scaffold,

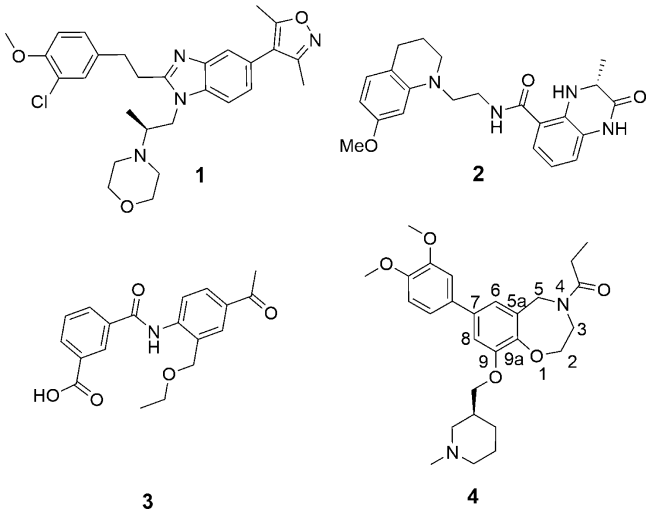

Figure 1. Structures of potent CBP/P300 inhibitors.

compound **2**.[15] The most selective inhibitor of the isoxazolylbenzimidazole series, **1**, has a K_D of 21 nM for the CBP bromodomain but maintains still considerable BET bromodomain activity.[16] **1** has strong anti-inflammatory activity, reducing immune cell production of IL-17A and other proinflammatory cytokines.[16] At a later stage, benzoic acid derivatives, such as **3**, were also proposed as CBP inhibitors.[17] Inhibitors carrying a 1,4-benzoxazepine core led to the development of **4** (I-CBP112), a selective CBP/P300 dual inhibitor with good cellular activity.[18] Here we present the optimization of the oxazepine series that led to the racemic variant of **4** as well as the synthesis and a comprehensive SAR analysis of 2,3,4,5-tetrahydro-1,4-benzoxazepines as selective CBP/P300 bromodomain inhibitors.

RESULTS AND DISCUSSION

First CBP/P300 bromodomain inhibitors of this series were identified by screening a commercial library of compounds from Chembridge for CBP inhibition. This library was extended to 48 compounds bearing a 2,3,4,5-tetrahydro-1,4-benzoxazepine scaffold. Structures were screened by differential scanning fluorimetry (DSF) against CBP and BRD4(1) as an example for a BET family bromodomain and an indicator for inhibitor's selectivity. Screened structures and their T_m shifts with CBP and BRD4(1) are shown in Chart 1 (compounds **5**–**52**). Substances in this chart are sorted two dimensionally in columns and rows, the first row showing chlorophenyl moieties at C-7 of the bicyclic scaffold and the second row electron richer (methoxy/alkyl/thiomethyl)phenyl moieties at the same position. Row 3 depicts heteroaromatic moieties at C-7, and row 4 contains further and more advanced molecules with several modifications. Substances with a cyclopropanecarbonyl residue at N-4 are displayed in the first column, then propionic acid amides and acetamides in the next column, and in the last column amides of bulkier carboxylic acids (row 1 and row 2 only). The best structure was **52**, of which the (*S*)-enantiomer is already established as the chemical probe **4**.

The active compounds of this commercial library did bind to both CBP and BRD4(1), and an increase or decrease of potency through exchange of structure elements mostly affected potency toward both bromodomains in equal measure. Among the *N*-acyl moieties in the commercial compounds, cyclopropanecarbonyl and propanoyl groups appeared to be superior to both smaller (acetyl in **14**, **26**, **27**) and larger (e.g., compounds **15**, **19**, **28**, **36**) ones. It is noteworthy that activity on CBP was found with compounds bearing a phenyl group at C-7 with chloro and/or methoxy substituents (e.g., **9**, **21**). At the same time, replacement of the methoxy group at C-9 with a bulky, basic amine moiety resulted in enhanced binding (**8**), whereas introduction of neutral alkyl ether moieties of similar size at C-9 showed no clear tendency (**6**, **11**). Introduction of a thienylmethoxy residue at C-9 was detrimental (**7**, **12**). Potency was greatly reduced for compounds bearing basic, nitrogen containing heterocycles at C-7 (**37**–**39**) and slightly reduced for thiophene derivatives (**40** vs **8**). The introduction of benzothiazole (**41**, **42**) had no effect compared to chlorophenyl analogues (**8**, **11**) but confirmed the impression that the combination of an electron-rich aromatic moiety at C-7 and a bulky, basic amine moiety at C-9 might lead to potent inhibitors. This hypothesis was strongly supported by very strong CBP inhibition of the synthesized compounds **47**, **51**, and especially **52**. The (*S*)-enantiomer of **52** has meanwhile been established as potent and to a good extent selective chemical probe **4**. Nevertheless, improvement of selectivity was still a challenge because even the very potent CBP inhibitors mentioned above still showed residual effects on BRD4(1). This prompted us to start a synthesis campaign in which all edges of the 1,4-benzoxazepine scaffold were reinvestigated systematically in order the gain further insight into the influence of any single modification on potency and selectivity of these inhibitors.

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Chart 1. (This Page: Compounds 5−36) T_m Shifts in °C, n = 3; (Next Page: Compounds 37−52) The (*S*)-Enantiomer of 52 Is Inhibitor 4, T_m shifts in °C, n = 3

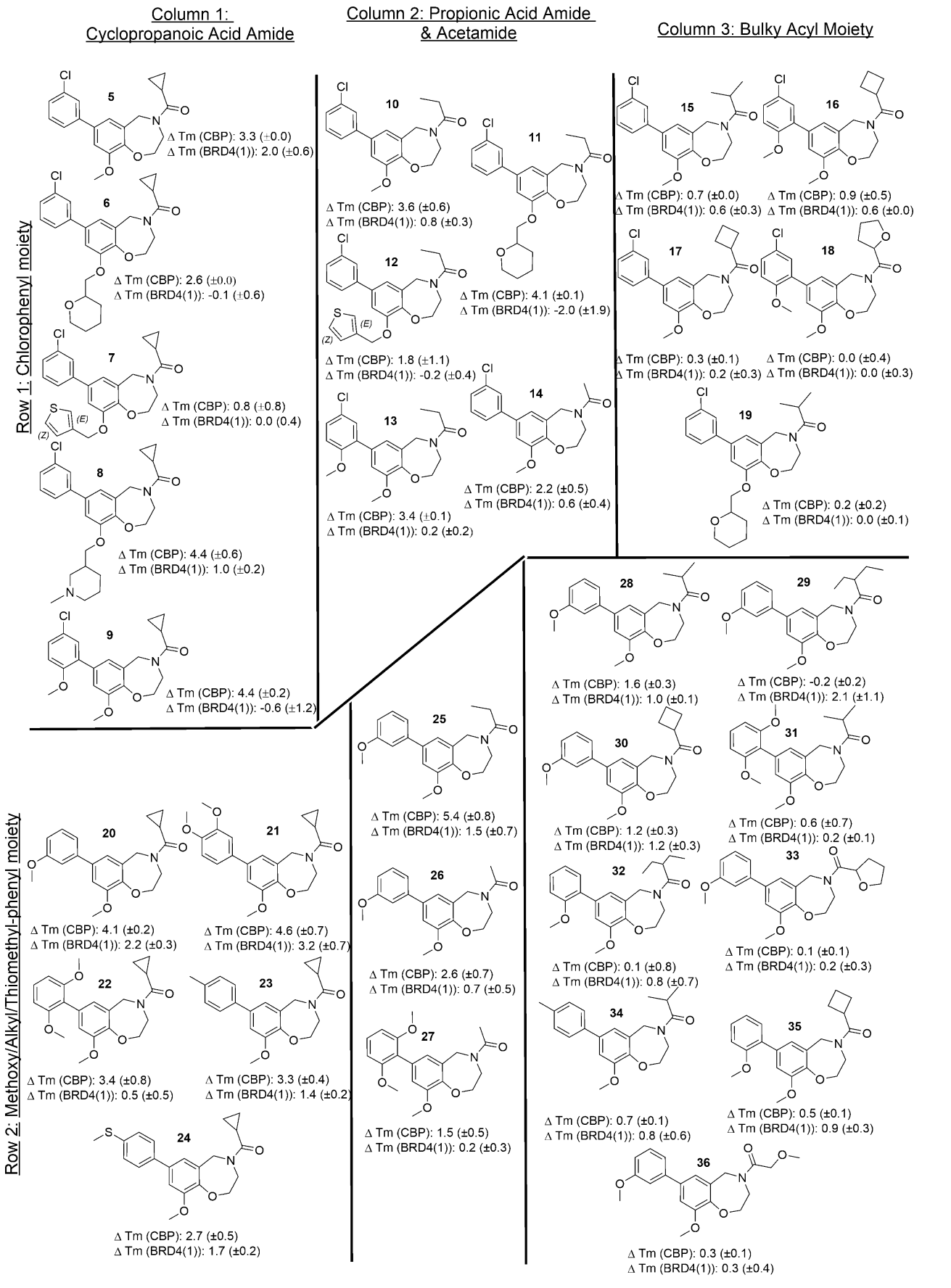

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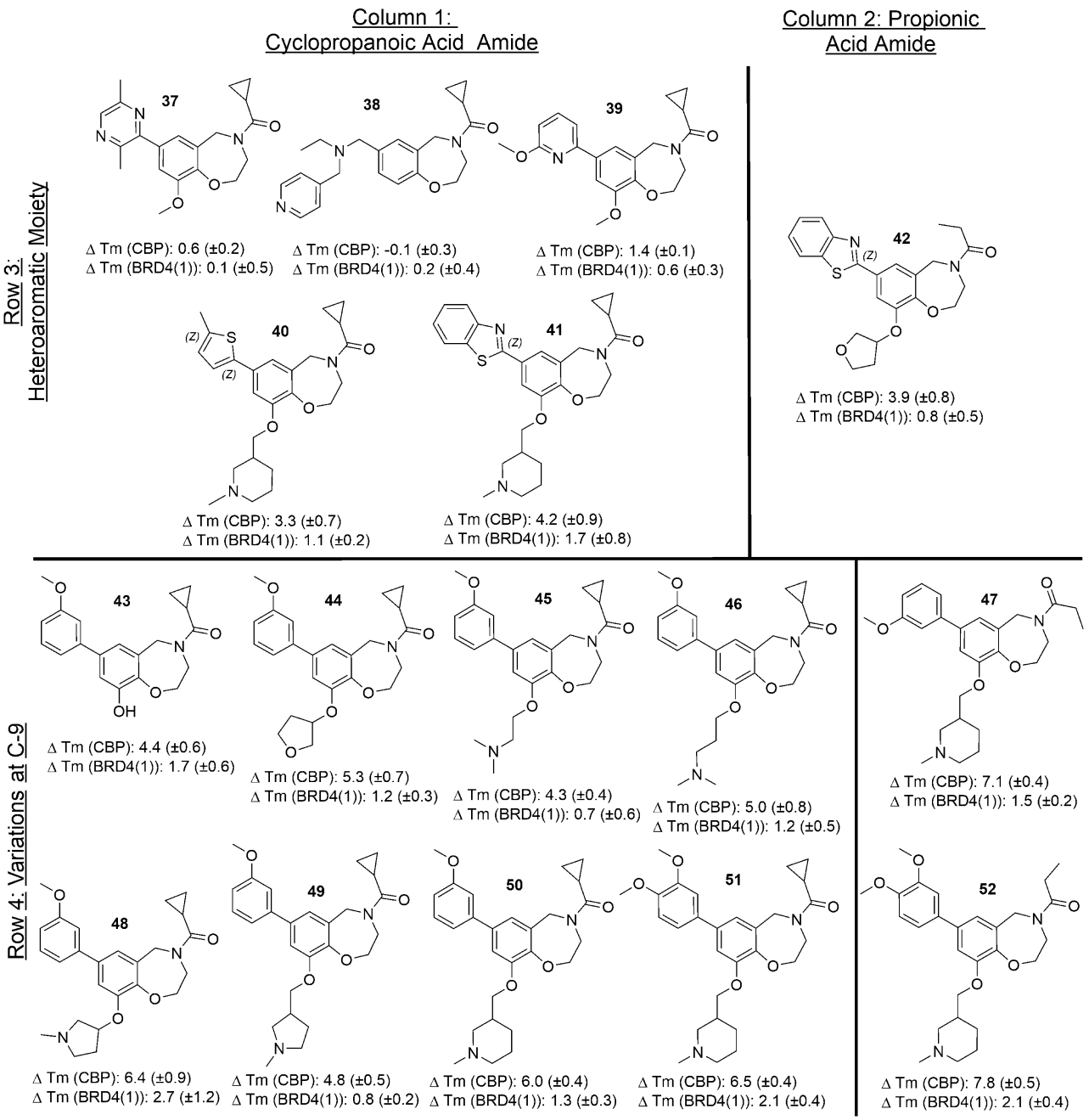
Chart 1. continued



For investigation of variations at C-7, we used a readily available 2,3,4,5-tetrahydro-1,4-benzoxazepine scaffold **53** bearing a methoxy residue at C-9, and screening results are displayed in Table 1. Most of the heteroaromatic variations at C-7 (**54**−**57**) yielded only compounds with poor activity. Only isoxazole **58** showed a significant temperature shift (4.9 °C), while in contrast to active benzothiazoles **41** and **42**, benzothiophene **59** interacted only weakly. Upon replacement of the phenyl moiety at C-7 by an acetyl moiety (**60**), potency was completely lost. While potency decreased according to our expectations for some compounds bearing electron-deficient phenyl moieties at C-7 (**61**, **62**), the nitrophenyl compound **63** showed modest activity (less than 4 °C). Surprisingly, the electron-rich aminophenyl derivatives (**64**, **65**) showed similar temperature shifts, and modifications of the amino group (sulfonamide **66**, urea **67**) led to increased potency. Regarding the compounds with electron-rich phenyl moiety, **68** with a 3,5-dimethoxyphenyl group showed the highest T_m shift in this series, while related compounds **69**, **70**, **71**, **72**, and **73** still showed acceptable ΔT_m on CBP.

Because the initial evaluation of purchased benzoxazepines had already revealed that only small *N*-acyl residues on N-4 are tolerated, we performed further modifications of the hitherto most promising acyl groups without increasing the size of this moiety too much (Table 2). These investigations were performed on the basis of **77** (bearing a 3-chloro-4-methoxyphenyl residue at C-7). We mainly aimed at the introduction of small polar groups, enabling further polar contacts, either to or mediated through the conserved water molecules in the binding pocket. However, the compact and polar urea derivatives **78** and **79** and the glycolic amide **80** showed no ΔT_m. The thiourea **81** and the thioamide **82**

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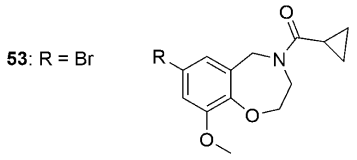
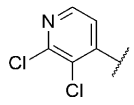
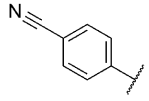
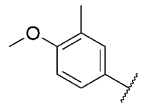
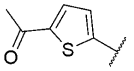
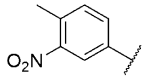
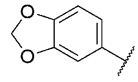
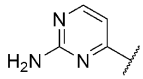
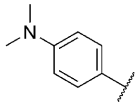
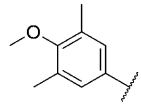
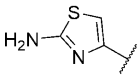
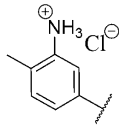
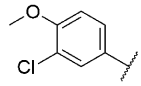
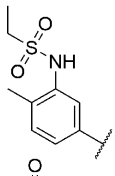
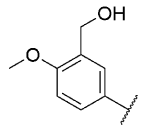
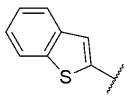
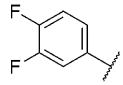
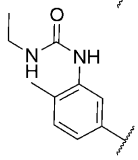
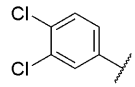
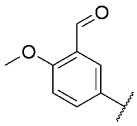
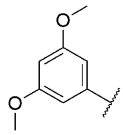
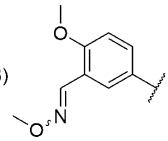
Table 1. DSF Results for Compounds with Different Moieties at C-7 (n = 3)[a]



R	Nr	Δ T_m (°C): CBP	Δ T_m (°C): BRD4(1)	R	Nr	Δ T_m (°C): CBP	Δ T_m (°C): BRD4(1)	R	Nr	Δ T_m (°C): CBP	Δ T_m (°C): BRD4(1)
	54	1.7 (±0.3)	1.1 (±0.1)		62	2.3 (±0.3)	1.9 (±0.3)		69	4.8 (±0.4)	3.0 (±0.5)
	55	2.3 (±0.2)	2.7 (±0.4)		63	3.4 (±0.6)	1.5 (±0.3)		70	3.9 (±0.4)	1.6 (±1.2)
	56	0.3 (±0.2)	0.6 (±0.2)		64	3.3 (±0.2)	2.1 (±0.8)		71	4.5 (±0.6)	2.6 (±0.7)
	57	2.1 (±0.1)	1.0 (±0.2)		65	3.1 (±0.6)	2.5 (±0.7)		72	4.4 (±0.4)	3.3 (±0.3)
	58	4.9 (±1.2)	4.1 (±0.7)		66	4.6 (±0.9)	3.6 (±0.5)		73	4.4 (±0.9)	2.3 (±0.3)
	59	1.5 (±0.9)	1.8 (±0.2)						74	3.5 (±0.9)	2.6 (±0.5)
	60	0.3 (±0.6)	0.1 (±0.3)		67	4.3 (±1.6)	1.5 (±0.9)		75	2.7 (±0.9)	2.2 (±1.3)
	61	1.5 (±2.6)	1.2 (±1.6)		68	6.7 (±0.9)	4.5 (±0.8)		76	6.0 (±0.7)	2.5 (±0.6)

[a] T_m shifts for lead structure **52**: CBP 7.8 ± 0.5 °C, BRD4(1) 2.1 ± 0.4 °C.

showed reduced activity, too. Attempts to obtain more subtle interactions via introduction of fluorine atoms in the acyl residue failed as well (**83**–**85**). Finally, the propionyl residue was most favorable (**86**), and only the cyclopropanoyl (**72**) and the methyl carbamate (**87**) were nearly as active. These data suggest that water molecules in the CBP/P300 binding pocket cannot be substituted by polar groups without losing some or all binding activity of the inhibitor.

To investigate whether a 2,3,4,5-tetrahydro-1,4-benzothiazepine can act as a bioisoster of the 2,3,4,5-tetrahydro-1,4-benzoxazepine here, three benzothiazepine analogues (**88**–**90**) bearing promising moieties at both C-7 and N-4 were synthesized, but these compounds were found to be significantly less active than their benzoxazepine congeners (compare **68** and **72**) (Table 3). Consequently, further investigation of this scaffold was not attractive. Likewise, a newly developed approach to 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines did not give a potent benzodiazepine analogue.[19]

The insights into the SAR based on purchased and synthesized compounds were used to design a final CBP inhibitor with the following key features: 2,3,4,5-tetrahydro-1,4-benzoxazepine scaffold, propionyl residue on N-4, dimethoxyphenyl moiety at C-7, then combined with a polar substituent bearing an amino group at C-9. This final modification was inspired by the very potent but not absolutely selective CBP inhibitors **47**, **51**, and **52** (racemate of **4**). Starting from a newly developed 2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxylate building block **91** (Scheme 5) and various diamines, a number of *N*-aminoalkylamides were prepared and screened. Even the intermediates **92**–**95** without amine function showed promising activity toward CBP combined with very high selectivity (Table 4). While the *N*-piperidinoethyl amides **96** and **97** showed almost no activity toward BRD4(1) and good activity

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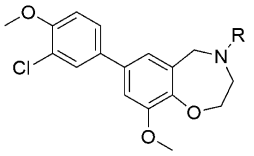
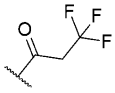
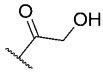
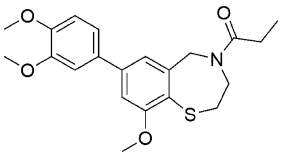
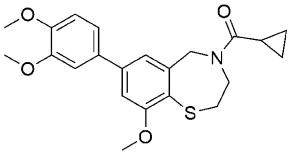
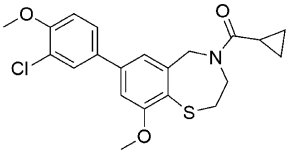
Table 2. DSF Results for Compounds with Different *N*-Acyl Residues (n = 3)[a]



R	No.	Δ T_m (°C): CBP	Δ T_m (°C): BRD4(1)	R	No.	Δ T_m (°C): CBP	Δ T_m (°C): BRD4(1)
	72	4.4 (±0.4)	3.3 (±0.3)		83	0.2 (±0.8)	-0.1 (±0.8)
	78	0.2 (±0.2)	1.5 (±0.1)		84	-0.1 (±0.1)	0.5 (±0.1)
	79	0.7 (±0.1)	3.6 (±0.6)		85	0.5 (±1.4)	0.8 (±0.3)
	80	0.0 (±0.1)	1.4 (±0.3)		86	6.0 (±0.1)	2.5 (±0.1)
	81	3.4 (±0.2)	2.6 (±0.5)		87	4.3 (±1.8)	3.9 (±0.4)
	82	0.7 (±0.6)	0.3 (±0.5)				

[a] T_m shifts for lead structure **52**: CBP 7.8 ± 0.5 °C, BRD4(1) 2.1 ± 0.4 °C.

Table 3. DSF Results for Benzothiazepine Compounds (n = 3)[a]

No.	Structure	Δ T_m (°C)
88		CBP: 4.2 (±0.3) BRD4(1):3.1 (±0.9)
89		CBP: 3.0 (±0.1) BRD4(1): 3.3 (±0.8)
90		CBP: 2.0 (±0.4) BRD4(1): 1.4 (±0.2)

[a] T_m shifts for lead structure **52**: CBP 7.8 ± 0.5 °C, BRD4(1) 2.1 ± 0.4 °C.

toward CBP, open chain compounds **98** and **99** were slightly less potent but very selective, too. The compounds with 3,5-dimethoxy phenyl substitution at C-7 (**92**, **94**, **96**) proved more promising than those with 3,4-dimethoxy substitution (**93**, **95**, **97**). Finally, the 3-aminopiperidine-derived amides **100**−**103** showed very good potency toward CBP and very little potency toward BRD4(1). Surprisingly, almost identical activities and selectivities were obtained for the pairs of enantiomers and for piperidine and *N*-methylpiperidine analogues.

To assess the selectivity of **100** and **102** (named TPOP146) over other bromodomains, these inhibitors were tested with 44 further bromodomains by DSF (Figure 2), and outstanding selectivity was accomplished. It appears that the very low T_m shifts with BRD4(1) result from the newly introduced amide group at C-9. Noteworthy and strong activity was only confirmed for P300, which was not surprising due to the very high sequence conservation of these two bromodomains: Out of the 114 amino acids of the CBP bromodomain, P300 only differs by two amino acids in its α_C helix (tyrosine for phenylalanine and serine for alanine), and one remote amino acid in each of the α_B- (isoleucine for valine) and α_{AZ} helices (serine for asparagine). Conserved is the BC loop and the ZA loop, lining the Kac binding site and influencing binding specifity.[20]

We selected therefore **102** for further analysis. The K_d of **102** was determined in solution by isothermal titration calorimetry (ITC). A constant of 134 ± 10 nM was determined for CBP (**4**: 151 ± 6 nM) and 5.02 μM for BRD4(1), thus revealing more than 30-fold selectivity (Figure 3).

A crystal structure of **102** with the CBP bromodomain confirmed the anticipated acetyl-lysine mimetic binding mode and thus competitive inhibition mode. The structure was

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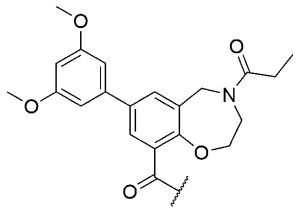
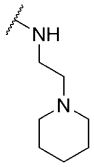
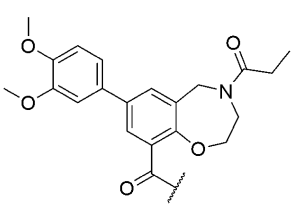
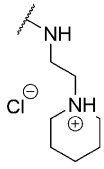
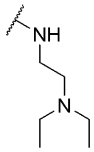
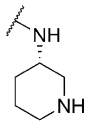
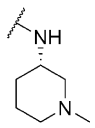
Table 4. DSF Results for Compounds with Different Moieties at C-9 (n = 3)[a]

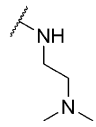
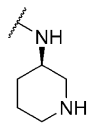
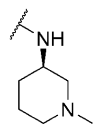


R	No.	Δ T_m (°C): CBP	Δ T_m (°C): BRD4(1)
	92	5.4 (±0.2)	0.5 (±0.3)
	94	4.9 (±0.6)	0.1 (±0.1)
	96	6.5 (±0.5)	0.7 (±0.5)



R	No.	Δ T_m (°C): CBP	Δ T_m (°C): BRD4(1)
	93	4.7 (±0.8)	1.8 (±0.6)
	95	4.1 (±1.1)	0.1 (±0.2)
	97	4.9 (±0.3)	0.6 (±0.6)

R	No.	Δ T_m (°C): CBP	Δ T_m (°C): BRD4(1)
	98	5.7 (±0.4)	0.4 (±0.3)
	100	7.2 (±0.4)	0.8 (±0.6)
	102	7.1 (±0.4)	0.5 (±0.3)

R	No.	Δ T_m (°C): CBP	Δ T_m (°C): BRD4(1)
	99	4.4 (±0.5)	0.2 (±0.2)
	101	6.8 (±0.4)	0.6 (±0.3)
	103	7.7 (±0.4)	1.2 (±0.2)

[a] T_m shifts for lead structure **52**: CBP 7.8 ± 0.5 °C, BRD4(1) 2.1 ± 0.4 °C.

refined at atomic resolution (1.05 Å) with good data collection and refinement statistics (Supporting Information, pp S-4, S-5). The ligand was well-defined except for the distal ring atoms of the 1-methylpiperidine ring that was oriented toward the solvent (Figure 4A). The last amino acid of this bromodomain's α_B helix (N1168) and the first amino acid of the α_C helix (R1173) greatly contribute to binding, while ZA loop's Y1125 lines the binding site and binds via conserved water molecules inside the pocket (Figure 4B,C). The electron-rich phenyl moiety at C-7 interacts with R1173 by a π−cation interaction and an induced binding mode (Figure 4D) as also described for dihydroquinoxalinone based CBP inhibitors.[21] The newly introduced carbonyl group at C-9 interacts through a water-mediated hydrogen bond with N1168 (Figure 4E), and the acyl group at N-4 acts as a Kac mimic moiety forming a hydrogen bond to N1168 (Figure 4E) and a water-mediated hydrogen bond to Y1125 (Figure 4F), as also conceivable in co-crystal structures with **4**.[18]

We next investigated whether **102** was able to inhibit recruitment of CBP to chromatin in cells and studied the effect of this inhibitor using a fluorescent recovery after photo bleaching (FRAP) assay. Full-length CBP contains a large number of protein and DNA interaction domains and is not significantly displaced by bromodomain inhibitors.[18] We used therefore a construct harboring three CBP bromodomains fused in frame by a linker region and a nuclear localization signal fused to GFP (3xCBP^{BRD}/GFP) and increased affinity of this fusion protein by inhibiting HDAC activity using the pan-HDAC inhibitor SAHA, which resulted in a sufficient FRAP signal and residence time. Exposure to 1 μM **102** resulted in a significant decrease of recovery half-life that was comparable to the construct that contained the bromodomain inactivating mutation N1168F, demonstrating that **102** targets the CBP bromodomain in the nucleus and is capable of competing with acetyl-lysine mediated interactions of the CBP bromodomain in cellular environments (Figure 5).

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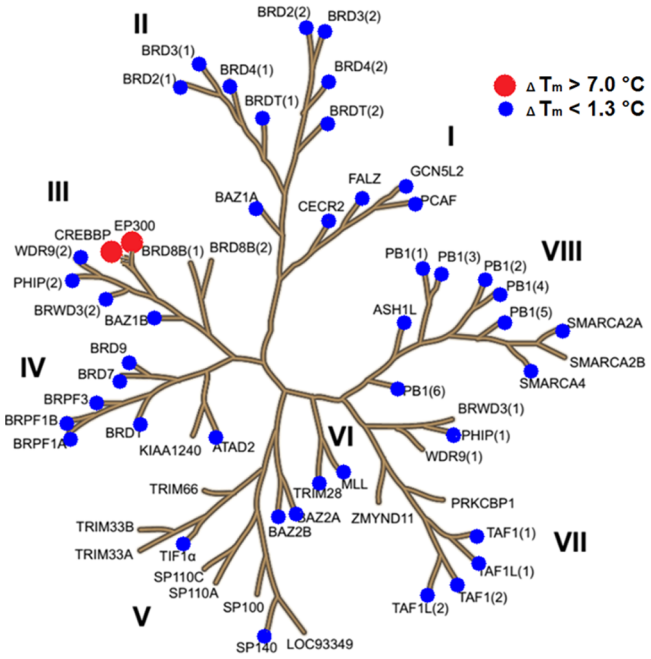

Figure 2. Selectivity profile of **102**. Screened targets are indicated by a colored dot. Temperature shifts are highlighted by red spheres according to the magnitude of the T_m shift as shown in the figure capture.

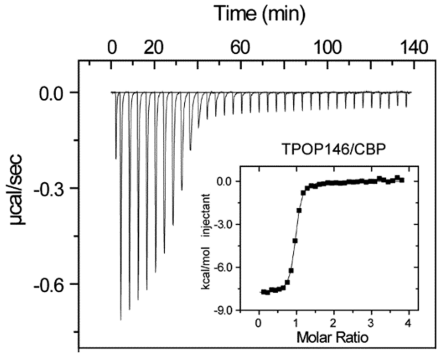

Figure 3. K_d determination of **102** with CBP by isothermal titration calorimetry.

The in vitro results of compound **102** were particularly promising because DSF results showed an excellent selectivity of this compound for bromodomains of CBP and P300 sparing BET bromodomains. Simultaneously to this report on the SAR, the closely related 1,4-benzoxazepine **4** (*S*-isomer of **52**) demonstrated interesting activity in leukemia models, suppressing clonogenic growth of primary blasts and cell differentiation. An interesting aspect of this study was that **4** showed synergism with BET inhibition, suggesting that design of dual BET/CBP(P300) inhibitors may represent a new strategy for leukemia treatment.[18] Because of the close structural similarity, we did not repeat these experiments with **102**. However, the presented SAR of this compound series will provide interesting insights for the further improvements of this scaffold for future in vivo application of CBP/P300 bromodomain inhibitors.

CHEMISTRY

The 7-bromobenzoxazepine scaffold **53** served as a backbone for the synthesis and assessment of compounds with different aromatic moieties at C-7. Intermediate **53** was prepared following an established approach to the 2,3,4,5-tetrahydro-1,4-benzoxazepine backbone[22] but starting with 5-bromo-2-hydroxy-3-methoxybenzaldehyde (Scheme 1). Thus, reductive amination with 2-aminoethanol and $NaBH_4$ in THF/MeOH gave intermediate **104** in 93% yield. After Boc-protection of the amino group, ring closure to the benzoxazepine **106** was performed in 91% yield using the Mitsunobu reagents DIAD and triphenylphosphine. Acidic *N*-deprotection gave an almost quantitative yield of the amine **107**, which was reacted with cyclopropanecarbonyl chloride to give the amide **53** with 71% yield.

Suzuki cross-coupling of aryl bromide **53** with $Pd(dppf)Cl_2$ catalyst and various boronic acids and boronic acid pinacol esters gave biaryls **54**−**55**, **57**−**59**, **61**−**64**, **68**−**72**, and **74**−**75** (Scheme 2, for details on the aryl residues, see Table 1).

Furthermore, aromatic aldehyde **61** was converted quantitatively with *O*-methylhydroxylamine into the *O*-methyloxime **76** and reduced to the benzyl alcohol **73** with $NaBH_4$ with 97% yield. The nitrophenyl compound **63** was reduced to the corresponding aniline **65** using Raney nickel and hydrazine in 38% yield. This aniline was further functionalized with mediocre yields into the sulfonamide **66** with ethanesulfonyl chloride and the urea derivative **67** using ethyl isocyanate. Finally, Stille cross-coupling of **53** with $Pd(PPh_3)_2Cl_2$ catalyst and tributyl(1-ethoxyvinyl)tin followed by acidic workup[23] gave the methyl ketone **60** in 67% yield, which was further converted into the aminopyrimidine **56** in 57% using Bredereck's reagent and guanidinium carbonate.[24] The same Stille coupling, but with neutral aqueous workup, gave an enolether, which was further converted to the aminothiazole **57** by treatment with NBS and subsequent cyclization with thiourea[25] (20% yield over three steps).

The evaluation of the best moiety at the nitrogen at position 4 was performed with a benzoxazepine scaffold bearing a 3-chloro-4-methoxyphenyl substituent at C-7, since at that time this substitution pattern looked most promising. Intermediate **107** (Scheme 1) was subjected to a Suzuki cross-coupling reaction with 3-chloro-4-methoxyphenylboronic acid to give biaryl **77** in 48% yield (Scheme 3). Treatment of the secondary amine **77** with acyl chlorides or carboxylic acid anhydrides gave the urea **78**, amides **83** and **86**, and carbamate **87** (for details on the acyl residues, see Table 2). EDC as coupling reagent and appropriate carboxylic acids were used to obtain amides **84** and **85**. (Thio)ureas **79** and **81** were accessible through iso(thio)-cyanates, and glycolic acid amide **80** was obtained in acceptable yield through reaction with neat ethyl glycolate. Finally, Lawesson's reagent was used to convert carboxamide **86** into the corresponding thioamide **82**.

To investigate the relevance of the heterocyclic backbone, benzothiazepine analogues were prepared (Scheme 4). 2-Amino-5-bromo-3-methoxybenzoic acid[26] was converted into the thiol **108** with 62% yield in a multistep reaction comprising diazotation, reaction with potassium ethyl xanthate, and alkaline hydrolysis.[27] Acid-catalyzed esterification[27b] gave methyl ester **109**, which underwent conversion into the benzothiazepinone **110** in a two-step reaction (thioetherification with 2-chloroethylamine,[28] followed by base-mediated lactamization[29]) with 63% yield. Reduction of the lactam function with BH_3−THF gave the crude amine, which was directly acylated to give the amides **111** and **112** in moderate yields. Finally, a standard Suzuki protocol gave good yields for the 7-aryl derivatives **88**, **89**, and **90**.

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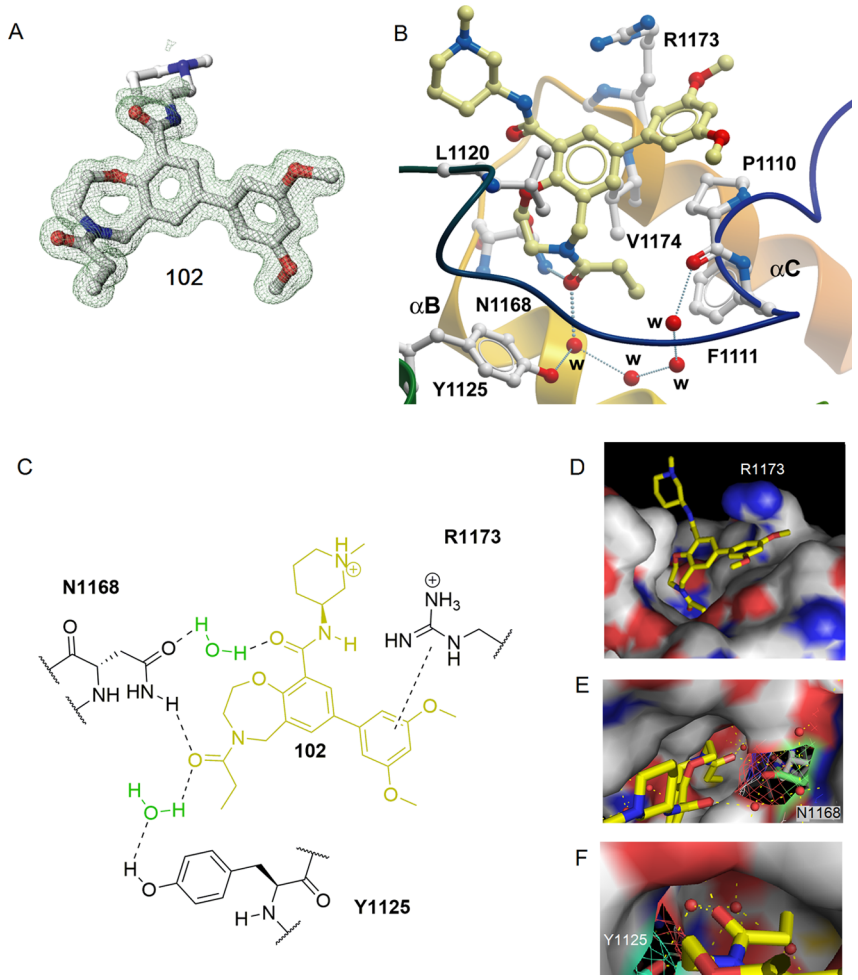

Figure 4. Co-crystallization of CBP with **102**. (A) 2FoFc OMIT map contoured at 2σ around the ligand. (B) Orientation of **102** with CBP and details of the interactions with CBP's *N*-acetyllysine binding site. The inhibitor and most relevant side chains are shown in ball and stick representation. Water molecules are indicated by red spheres, and hydrogen bonds within the Kac binding pocket are shown as dotted lines. (C) Overview on all interactions of **102** with CBP. (D) π−Cation interaction between R1173 of CBP (surface representation) and the electron-rich 3,5-dimethoxyphenyl moiety of **102** (golden stick representation). (E) Water mediated hydrogen bond from the newly introduced amide group at C-9 to Y1168. (F) Conserved water molecules in the pocket binding to inhibitor and Y1125.

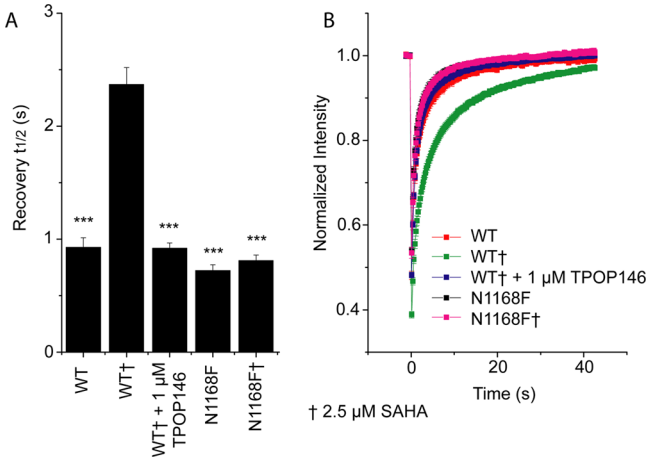

Figure 5. FRAP experiment demonstrating displacement of the CBP bromodomain by **102** from chromatin. SAHA treated cells are indicated by †. Representative raw data traces are shown in the right panel. The bromodomain inactivating mutant (N1168F) served as a positive control.

Having checked further scaffolds and having optimized the *N*-acyl residue (*N*-propanoyl best) and the 7-aryl substituent (dimethoxyphenyl best), we performed final modifications at C-9. Inspired by the most potent Chembridge substances bearing a piperidinylmethoxy residue at this position, we prepared the benzoxazepine scaffold **91**, bearing an ester group at C-9 as an attractive intermediate for the introduction of aminoalkyl side chains. Starting point for the synthesis of **91** was 5-bromosalicylic acid, which underwent Duff formylation and subsequent esterification in good yields.[30] Then, following the protocol described above for benzoxazepine scaffold **53**, the obtained methyl 5-bromo-3-formyl-2-hydroxybenzoate was converted in four steps via intermediate **91** into benzoxazepine **115** (Scheme 5). Suzuki cross-coupling reactions and subsequent alkaline ester hydrolyses gave the two isomeric 7-(dimethoxyphenyl)-9-carboxy derivatives **94** and **95** in high yields. EDC-mediated amidation of these carboxylic acids with three different diamines gave the amides **96**−**99** in moderate yields.

Chiral compounds **100** and **101** were synthesized accordingly from carboxylic acid **94** using both (*S*)- and (*R*)-configured 3-amino-1-Boc-piperidine as building blocks and

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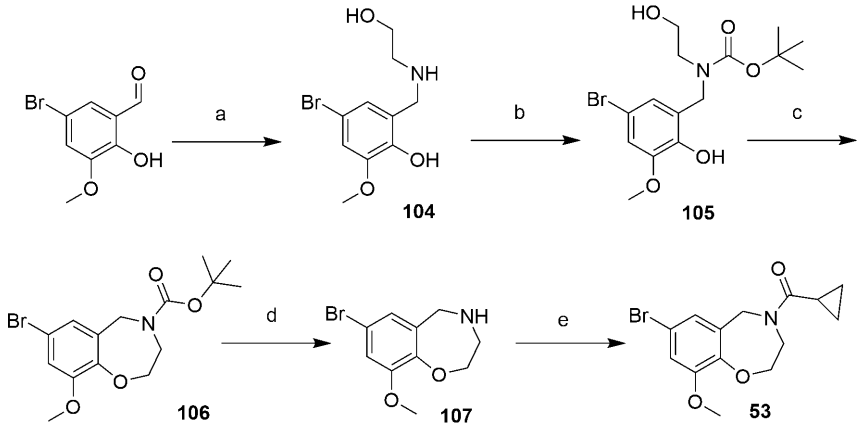
Scheme 1. Preparation of 1,4-Benzoxazepine Scaffold 53[a]



[a]Reagents and conditions: (a) 2-aminoethanol, $NaBH_4$, THF, MeOH, RT, 93%; (b) di-*tert*-butyl dicarbonate, $NaHCO_3$ solution, EtOAc, RT, 69%; (c) PPh_3, DIAD, CH_2Cl_2, RT, 91%; (d) HCl, 1,4-dioxane, MeOH, reflux, 94%; (e) cyclopropanecarbonyl chloride, DIPEA, CH_2Cl_2, 0 °C to RT, 71%.

subsequent, acidic Boc-deprotection. Finally these secondary amines were *N*-methylated using formaldehyde and $NaCNBH_3$, yielding *N*-methylpiperidines **102** and **103** (Scheme 6).

CONCLUSION

For the first time we herein present the systematic optimization and the SAR of benzoxazepine-type compounds for the inhibition of the closely related CBP/P300 bromodomains. This study yielded **52** for CBP/P300 inhibition, which is the racemate to the similarly potent, enantiomerically pure, and meanwhile commercially available inhibitor **4**. This selective and potent compound has initially been developed as chemical probe, but due to the involvement of the CBP/P300 bromodomains in several diseases (cancer, inflammatory diseases, Rubinstein−Taybi syndrome) and promising results in in vitro and in vivo experiments,[18] 1,4-benzoxazepine-type CBP/P300 inhibitors prove to be valuable candidates for further preclinical studies. The preparation and characterization of several series of novel 1,4-benzoxazepine compounds with new substitution patterns and moieties is described in the next section, allowing a comprehensive discussion of the SAR of the 1,4-benzoxazepines. The best, newly synthesized compound **102** exceeds **4** with regard to selectivity, and was well characterized in biological experiments (K_d, FRAP, cocrystallization). Its binding mode and orientation with CBP is exemplarily shown and discussed in detail. The preparation of novel 2,3,4,5-tetrahydro-1,4-benzothiazepines is also shown, giving a total of 62 newly prepared and characterized compounds. Because the 1,4-benzoxazepine element is reported in various substances with anti-inflammatory,[31] antithrombotic,[32] antitumor,[22,33] and antiamyloid-β plaque activity,[34,35] this manuscript contains not only relevant information for bromodomain researchers but also for scientists longing for similar compounds for various applications.

EXPERIMENTAL SECTION

Protein Expression. cDNA encoding human bromodomains were cloned, expressed, and purified as previously described:[11a] To obtain CBP for screenings and co-crystallization, the Genbank ID gi|4758056 and expression cell line BL21(DE3)-R3 were used to express the sequence MHHHHHHSSGVDLGTENLYFQSMRKKIFKPEELRQALMPTLEALYRQDPESLPFRQPVDPQLLGIPDYFDIVKNPMDLSTIKRKLDTGQYQEPWQYVDDVWLMFNNAWLYNRKTSRVYKFCSKLAEVFEQEIDPVMQSLG (140 amino acids).

Likewise for BRD4(1) the Genbank ID was gi|19718731 and expression cell line BL21(DE3)-R3-pRARE2 was used to express the sequence MHHHHHHSSGVDLGTENLYFQSMNPPPPETSNPNKPKRQTNQLQYLLRVVLKTLWKHQFAWPFQQPVDAVKLNLPDYYKIIKTPMDMGTIKKRLENNYYWNAQECIQDFNTMFTNCYIYNKPGDDIVLMAEALEKLFLQKINELPTEE (148 amino acids).

Isothermal Titration Calorimetry (ITC). Experiments were carried out on a VP-ITC microcalorimeter (MicroCal). All experiments were performed at 15 °C in 20 mM HEPES, pH 7.5, 150 mM NaCl. The titrations were conducted using an initial injection of 2 μL followed by 34 identical injections of 8 μL. The dilution heats were measured on separate experiments and were subtracted from the titration data. Thermodynamic parameters were calculated using $\Delta G = \Delta H - T\Delta S = -RT \ln K_B$, where ΔG, ΔH, and ΔS are the changes in free energy, enthalpy, and entropy of binding, respectively. In all cases, a single binding site model was employed.

Thermal Shift Assay. Thermal melting experiments were carried out using an Mx3005p real-time PCR machine (Stratagene). Proteins were buffered in 10 mM HEPES, pH 7.5, 500 mM NaCl and assayed in a 96-well plate at a final concentration of 2 μM in 20 μL volume. Compounds were added at a final concentration of 10 μM. SYPRO Orange (Molecular Probes) was added as a fluorescence probe at a dilution of 1:1000. Excitation and emission filters for the SYPRO Orange dye were set to 465 and 590 nm, respectively. The temperature was raised with a step of 3 °C per minute from 25 to 96 °C, and fluorescence readings were taken at each interval. Data was analyzed as previously described.[11a]

Protein Crystallization. Aliquots of the purified proteins were set up for crystallization using a mosquito crystallization robot (TTP Labtech). Coarse screens were typically setup onto Greiner 3-well plates using three different drop ratios of precipitant to protein per condition (200 + 100 nL, 150 + 150 nL, and 100 + 200 nL). All crystallizations were carried out using the sitting drop vapor diffusion method at 4 °C. CBP crystals with compound 102 (3 mM final concentration) were grown by mixing 100 nL of the protein (12.75 mg/mL) with 200 nL of reservoir solution containing 25% PEG 3350, 0.2 M $MgCl_2$, 0.1 M Bis Tris, pH 7.5.

Data Collection and Structure Solution. Crystals were cryoprotected using the well solution supplemented with additional ethylene glycol and were flash frozen in liquid nitrogen. Data were collected at diamond beamline I04 at a wavelength of 1.0121 Å. Indexing and integration was carried out using MOSFLM,[36] and scaling was performed with SCALA.[37] Initial phases were calculated by molecular replacement with PHASER[38] using an ensemble of known

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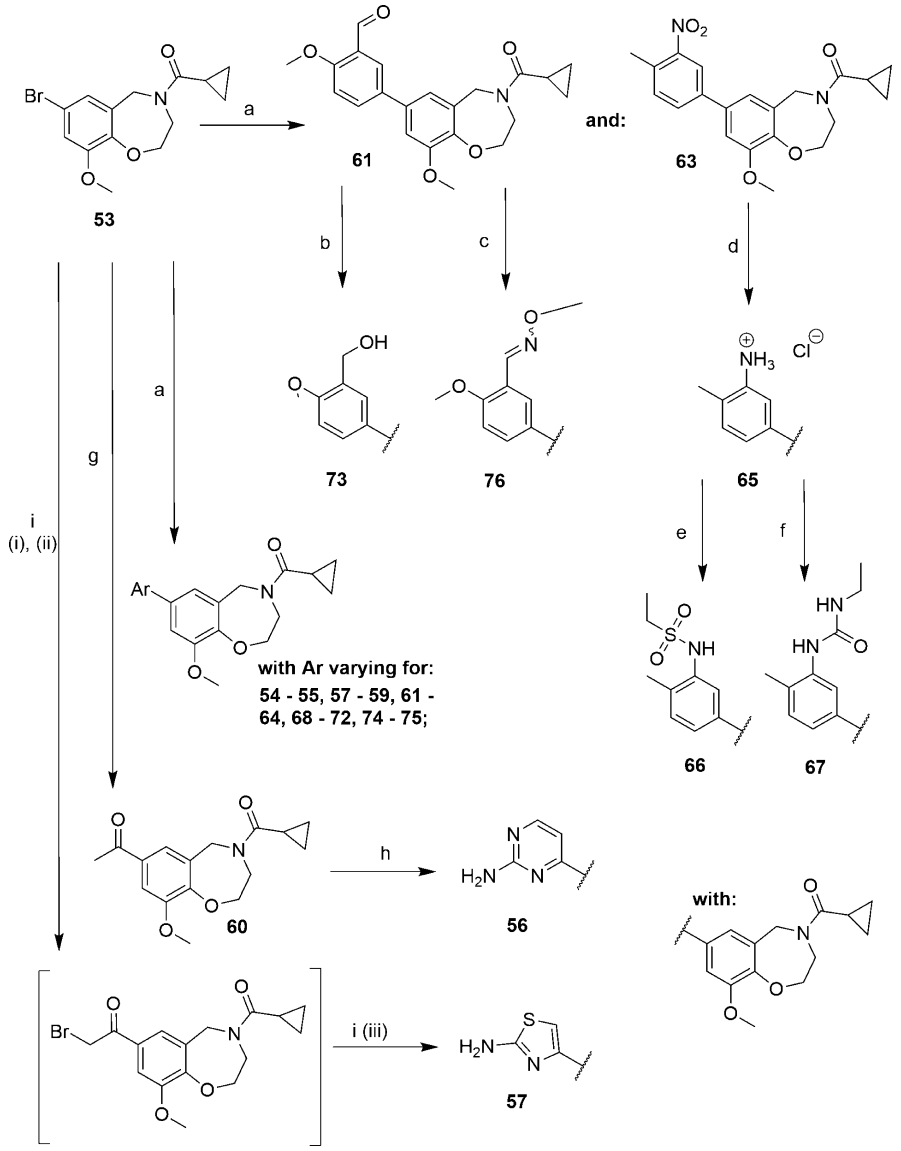
Scheme 2. Preparation of Benzoxazepine Inhibitors with Different Moieties at C-7[a]



[a]Reagents and conditions: (a) various boronic acids/pinacol esters (see Experimental Section), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, DIPEA, H_2O/1,4-dioxane, 95 °C, 31−94%; (b) $NaBH_4$, CH_2Cl_2, MeOH, RT, 97%; (c) *O*-methylhydroxylamine, K_2CO_3, EtOH, RT, 99%; (d) Raney nickel, N_2H_4, MeOH, EtOH, reflux, 38%; (e) ethanesulfonyl chloride, DMAP, pyridine, 0 °C to RT, 60%; (f) ethyl isocyanate, DIPEA, CH_2Cl_2, RT, 47%; (g) (i) $Pd(PPh_3)_2Cl_2$, tributyl(1-ethoxyvinyl)tin, 1,4-dioxane, 140 °C, (ii) HCl, H_2O RT, 67%; (h) Bredereck's reagent, DMF, 160 °C, then guanidinium carbonate, K_2CO_3, DMF, 160 °C, 57%; (i) (i) $Pd(PPh_3)_2Cl_2$, tributyl(1-ethoxyvinyl)tin, 1,4-dioxane, 140 °C, (ii) NBS, THF, 0 °C to RT, (iii) thiourea, DMF, RT, 20%.

bromodomain models (PDB IDs 3DWY, 2OSS, 2OUO, 2GRC, 2OO1, 3DAI, 3D7C). Initial models were built by ARP/wARP,[39] and building was completed manually with COOT.[40] Refinement was carried out in REFMAC5.[41] Thermal motions were analyzed using TLSMD,[42] and hydrogen atoms were included in late refinement cycles. Data collection and refinement statistics are compiled in the Supporting Information, Table S5. The models and structure factors have been deposited with PDB accession code 5J0D.

Fluorescence Recovery After Photo Bleaching (FRAP). FRAP studies were performed essentially as described.[43] In brief, U2OS cells were transfected (Fugene HD; Roche) with mammalian over-expression constructs a triplicated CBP bromodomain harboring a nuclear localization sequence.[18] The imaging system consisted of a Zeiss LSM 710 laser-scanning and control system (Zeiss) coupled to an inverted Zeiss Axio Observer.Z1 microscope equipped with a high-numerical-aperture (N.A. 1.3) 40× oil immersion objective (Zeiss). Samples were placed in an incubator chamber in order to maintain temperature and humidity. FRAP and GFP fluorescence imaging were both carried out with an argon-ion laser (488 nm) and with a PMT detector set to detect fluorescence between 500 and 550 nm. Once an initial scan had been taken, a region of interest corresponding to approximately 50% of the entire GFP positive nucleus was empirically selected for bleaching. A time lapse series was then taken to record GFP recovery using 1% of the power used for bleaching. The image data sets and fluorescence recovery data were exported from ZEN 2009, the microscope control software, into Origin to determine the average half-time for full recovery for 10−20 cells per treatment point. Data were analyzed using one-way ANOVA with Dunnetts's multiple comparisons test.

Compound Characterization. Melting points were determined with a Büchi melting point B-540 and are uncorrected. ^1H and ^{13}C NMR spectra were recorded either with Avance III HD 400 MHz Bruker BioSpin or Avance III HD 500 MHz Bruker BioSpin spectrometers. Chemical shifts (δ) are given in ppm relative to TMS

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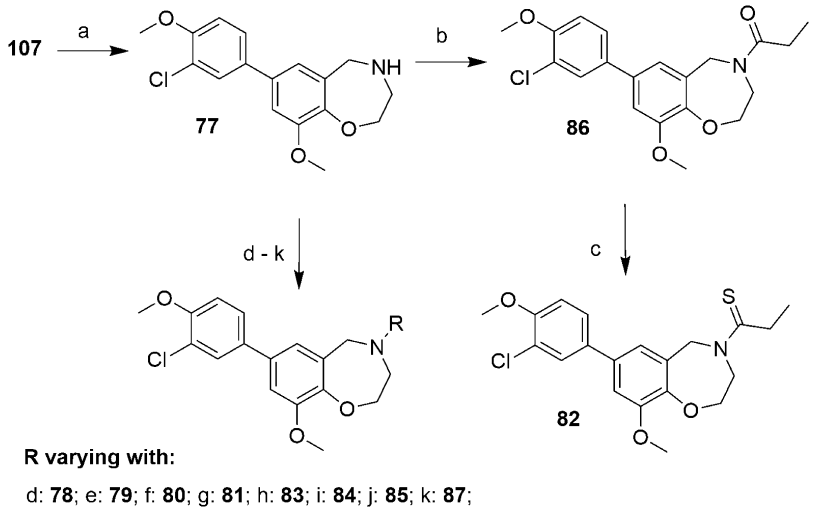
Scheme 3. Functionalizations at N-4[a]



[a]Reagents and conditions: (a) 3-chloro-4-methoxyphenylboronic acid, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, DIPEA, H_2O/1,4-dioxane, 95 °C, 48%; (b) propionyl chloride, DIPEA, CH_2Cl_2, 0 °C to RT, 40%; (c) Lawesson's reagent, THF, RT, 96%; (d) dimethylcarbamoyl chloride, DIPEA, CH_2Cl_2, 0 °C to RT, 74%; (e) (trimethylsilyl)isocyanate, CH_2Cl_2, then HCl in 1,4-dioxane, RT, 87%; (f) ethyl glycolate, 60 °C, 51%; (g) NaH, THF, then methyl isothiocyanate, RT, 69%; (h) trifluoroacetic anhydride, DIPEA, DMAP, CH_2Cl_2, 0 °C to RT, 92%; (i) 3,3,3-trifluoropropionic acid, DMAP, EDC·HCl, CH_2Cl_2, 0 °C to RT, 94%; (j) 2-fluoropropionic acid, DMAP, EDC·HCl, 0 °C to RT, 81%; (k) methyl chloroformate, DIPEA, CH_2Cl_2, 0 °C to RT, 94%.

or residual undeuterated solvent, and coupling constants (J) are given in hertz (Hz). Splitting patterns are abbreviated as follows: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublet; m = multiplet, br s = broad singlet. Some NMR spectra were recorded at elevated temperature to suppress the appearance of rotameric double peaks. Those occurred in the NMR spectra of almost all tested substances and arise from the amide bond of the nitrogen of the seven-membered ring. EI-Mass spectra were recorded at an ionization energy of 70 eV either with a JMS GCmate II Jeol or a JEOL JMS-700 MStation. ESI-Mass spectra were recorded on a Thermo Finnigan LTQ FT at 4 kV. Purification by flash column chromatography (FCC) was performed using Silica Gel 60 from Merck KGaA. HPLC purity analysis was individually performed on an Agilent 1100 series apparatus with a G1311A QuatPump, a G1329A ALS autosampler, and a G1316A ColComp column oven and Agilent ChemStation rev. B04.02 as software. A G1315A DAD detector was set to 210 nm for detection. Injection volume was 5 or 10 μL of a dilution of 100 μg/mL (sample in mobile phase). Column temperature was 50 °C, flow either 0.3 mL/min or 0.8 mL/min or 1.0 mL/min. Different solvent mixtures were used as mobile phase, from 50% to 25% water and from 50% to 75% acetonitrile, respectively. The water used for preparation of the mobile phase contained 1% THF. The following columns were used: Kinetex 2.6 u PFP, 100 A, (100 mm × 2.10 mm), Agilent Poroshell 120, PFP 2.7 μm, (3.0 mm × 100 mm), Varian Pursuit UPS 2.4 diphenyl (50 mm × 2.0 mm), and Agilent Poroshell 120, EC-C18 2.7 μm, (3.0 mm × 100 mm). All tested substances showed a purity >95.0%. For microwave experiments, a CEM Discover was used with power set to 300 W. Optical rotations were determined with a PerkinElmer 241 polarimeter. Potent compounds were particularly examined for assay interferences (PAINS), but the potent structures offered little chemical reactivity. Moreover, assays based on different principles were used to assess their potency. Finally, selectivity was shown among similar targets (BRD4(1)). All this makes assay interferences unlikely.

Standard Synthetic Protocols. Standard protocol 1 (*N*-acylation of benzoxazepines and benzothiazepines): Typically, 0.50 mmol of educt was dissolved in 1.0 mL of CH_2Cl_2 and 1.5 mmol of DIPEA was added at 0 °C. Then 1.3 mmol acyl chloride was added, and the mixture warmed to RT and stirred for 1.5 h. Then 2 M NaOH was added and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by FCC with EtOAc and hexanes.

Standard protocol 2 (Suzuki cross-coupling of 7-bromobenzoxazepines and 7-bromobenzothiazepines with boronic acids and boronic acid pinacol esters): Typically, to 0.30 mmol bromoarene, 0.36 mmol boronic acid or boronic acid pinacol ester and 0.03 mmol [1.1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) were added. A mixture of 0.50 mL of water, 2.0 mL of 1,4-dioxane, and 1.2 mmol of DIPEA was added, and the mixture was heated under nitrogen atmosphere with vigorous stirring to 95 °C for 3.5 h. To this solution was added either water or 0.5 M NaOH for compounds with basic moieties or 0.5 M HCl for compounds with acidic moieties. The mixture was extracted with CH_2Cl_2 three times, and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo and purified by FCC with EtOAc and hexanes.

Standard protocol 3 (conversion of the carboxylic acids **94** and **95** to carboxamides): Typically, 0.29 mmol of carboxylic acid and 0.35 mmol of EDC−HCl were dissolved in 3.0 mL of CH_2Cl_2 and cooled to 0 °C. Then 0.29 mmol of DIPEA, 0.35 mmol of the required primary amine, and 2 mg of DMAP were added. The solution was stirred at RT overnight. Then 1 M NaOH was added and the mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by FCC.

*1-(7-Bromo-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)-1-(cyclopropyl)methanone (**53**).* Standard protocol 1 with 7.9 g (31 mmol) of **107** and 3.6 mL (40 mmol) of cyclopropanecarbonyl chloride. FCC with EtOAc and hexanes (1:2, Rf 0.1) gave 7.4 g (22 mmol, 71%) of **53** as a white solid; mp 85−86 °C. ^{1}H NMR (RT, mixture of rotamers, 500 MHz, DMSO-d_6) δ = 7.29 (d, J = 2.1 Hz, 0.6H), 7.12 (d, J = 2.1 Hz, 0.6H), 7.08 (d, J = 2.1 Hz, 0.4H), 6.97 (d, J = 2.1 Hz, 0.4H), 4.77 (s, 1.2H), 4.51 (s, 0.8H), 4.10−4.06 (m, 1.6H), 3.99−3.94 (m, 1.2H), 3.87−3.81 (m, 1.2H), 3.76 (s, 3H), 2.14−2.08 (m, 0.6H), 1.96−1.89 (m, 0.4H), 0.71−0.63 (m, 4H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, DMSO-d_6) δ = 173.1, 172.6, 153.1, 152.9, 148.3, 148.2, 134.9, 134.7, 124.9, 124.0, 116.1, 115.7, 115.5, 115.2, 73.2, 72.5, 57.0, 51.3, 49.8, 49.0, 48.2, 11.6, 8.4, 8.0. MS (EI+): m/z calcd for ($C_{14}H_{16}{}^{79}BrNO_3$) 325.0314, found 325.0316.

*1-Cyclopropyl-1-[7-(2,3-dichloropyridin-4-yl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methanone (**54**).* Standard protocol 2 with 0.098 g (0.30 mmol) of **53** and 0.069 g (0.36 mmol) of 2,3-dichloropyridine-4-boronic acid. FCC with EtOAc and hexanes (3:1,

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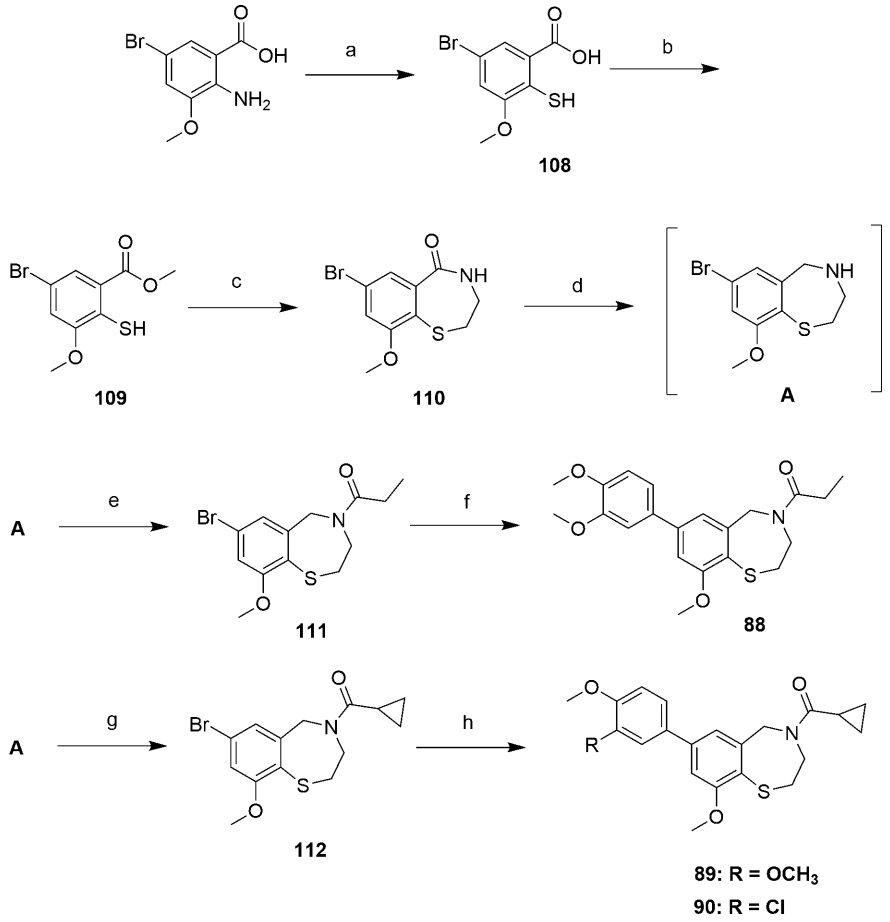
Scheme 4. Synthetic Route to 2,3,4,5-Tetrahydro-1,4-benzothiazepines[a]



[a]Reagents and conditions: (a) (i) $NaNO_2$, HCl, H_2O, 0 °C, (ii) KOAc, potassium ethyl xanthate, H_2O, 90 °C, (iii) NaOH, $NaHSO_3$, 85 °C, 62%; (b) MeOH, H_2SO_4, reflux, 72%; (c) (i) 2-chloroethylamine, NaOMe, DMF, 0 °C to RT, (ii) *t*BuOK, THF, 0−45 °C, 63%; (d) BH_3-THF, −30 °C to reflux; (e) propionyl chloride, DIPEA, CH_2Cl_2, 0 °C to RT, 49%; (f) 3,4-dimethoxyphenylboronic acid, Pd(dppf)Cl_2·CH_2Cl_2, DIPEA, H_2O/1,4-dioxane, 95 °C, 59%; (g) cyclopropanecarbonyl chloride, DIPEA, CH_2Cl_2, 0 °C to RT, 45%; (h) 3,4-dimethoxyphenylboronic acid or 3-chloro-4-methoxyphenylboronic acid, Pd(dppf)Cl_2·CH_2Cl_2, DIPEA, H_2O/1,4-dioxane, 95 °C, 85% and 70%.

Rf 0.2) gave 0.091 g (0.23 mmol, 77%) of **54** as an orange solid; mp 186−187 °C. ^{1}H NMR (RT, mixture of rotamers, 400 MHz, CD_2Cl_2) δ = 8.34−8.23 (m, 1H), 7.29−7.20 (m, 1H), 7.04−6.89 (m, 2H), 4.77 (s, 1.2H), 4.67 (s, 0.8H), 4.28−4.21 (m, 0.8H), 4.14−4.08 (m, 2H), 4.03−3.97 (m, 1.2H), 3.88−3.82 (m, 3H), 1.91−1.81 (m, 0.6H), 1.78−1.65 (m, 0.4H), 0.89−0.82 (m, 2H), 0.78−0.69 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, CD_2Cl_2) δ = 172.6, 172.1, 152.0, 151.2, 150.4, 150.4, 149.2, 149.1, 146.8, 146.7, 132.7, 132.4, 132.0, 131.6, 128.6, 128.5, 124.9, 124.7, 122.6, 121.1, 113.0, 112.5, 72.6, 56.4, 51.1, 50.9, 48.8, 48.2, 11.4, 11.3, 7.4, 7.2. MS (EI+): *m*/*z* calcd for ($C_{19}H_{18}{}^{35}Cl_2N_2O_3$) 392.0694, found 392.0699.

*1-{5-[4-(Cyclopropanecarbonyl)-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]thiophen-2-yl}ethan-1-one (**55**).* Standard protocol 2 with 0.098 g (0.30 mmol) oof **53** and 0.061 g (0.36 mmol) of 5-acetyl-2-thienylboronic acid. FCC with EtOAc and hexanes (2:1, Rf 0.2) gave 0.079 g (0.21 mmol, 71%) of **55** as an orange solid; mp 85−87 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.58 (d, *J* = 3.9 Hz, 1H), 7.20 (d, *J* = 3.9 Hz, 1H), 7.15−7.03 (m, 2H), 4.70 (s, 2H), 4.21−4.09 (m, 2H), 4.04−3.92 (m, 2H), 3.88 (s, 3H), 2.49 (s, 3H), 1.81−1.64 (m, 1H), 0.98−0.84 (m, 2H), 0.79−0.64 (m, 2H). ^{13}C NMR (110 °C, 101 MHz, $C_2D_2Cl_4$) δ = 189.7, 172.4, 152.4, 151.9, 149.8, 143.3, 133.0, 132.7, 129.1, 123.9, 119.8, 111.8, 72.5, 57.1, 49.8, 49.6, 26.4, 11.8, 7.3. MS (EI+): *m*/*z* calcd for ($C_{20}H_{21}NO_4S$) 371.1191, found 371.1192.

*1-[7-(2-Aminopyrimidin-4-yl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]-1-(cyclopropyl)methanone (**56**).* A solution of 0.20 g (0.69 mmol) of **60** in 5 mL of anhydrous DMF was heated to 160 °C under N_2. Then 0.52 mL (2.5 mmol) of Bredereck's reagent was added and heating continued for 1 h. Then 0.66 g (3.7 mmol) of guanidinium carbonate and 0.34 g (2.5 mmol) of K_2CO_3 were added and the mixture was heated for further 4 h. After cooling, saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with CH_2Cl_2 with 5% MeOH (Rf 0.1) gave 0.13 g (0.39 mmol, 57%) of **56** as a yellow solid; mp 136−137 °C. ^{1}H NMR (RT, mixture of rotamers, 500 MHz, CD_2Cl_2) δ = 8.34−8.26 (m, 1H), 7.63−7.47 (m, 2H), 7.06−6.98 (m, 1H), 5.25−5.13 (m, 2H), 4.79 (s, 1.1H), 4.68 (s, 0.9H), 4.24−4.18 (m, 0.9H), 4.13−4.06 (m, 2H), 4.01−3.95 (m, 1.1H), 3.92−3.88 (m, 3H), 1.92−1.83 (m, 0.6H), 1.74−1.68 (m, 0.4H), 0.89−0.81 (m, 2H), 0.77−0.69 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, CD_2Cl_2) δ = 173.0, 172.5, 164.62, 164.57, 163.8, 159.2, 159.1, 152.6, 152.1, 151.1, 150.9, 132.9, 132.7, 121.3, 119.8, 111.1, 110.6, 107.6, 107.5, 73.1, 72.8, 56.64, 56.58, 51.5, 51.3, 49.0, 48.8, 11.8, 11.6, 7.7, 7.6. MS (EI+): *m*/*z* calcd for ($C_{18}H_{20}N_4O_3$) 340.1535, found 340.1538.

*1-[7-(2-Aminothiazol-4-yl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]-1-(cyclopropyl)methanone (**57**).* To a solution of 1.0 g (3.1 mmol) of **53** and 0.11 g (0.16 mmol) of Pd(PPh_3)$_2Cl_2$ in 12 mL of anhydrous 1,4-dioxane under N_2 were added 1.4 mL (4.0 mmol) of tributyl(1-ethoxyvinyl)tin. The mixture was heated to 140 °C under microwave irradiation with 300 W for 40 min. After cooling, 50 mL of water was added and the mixture extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and

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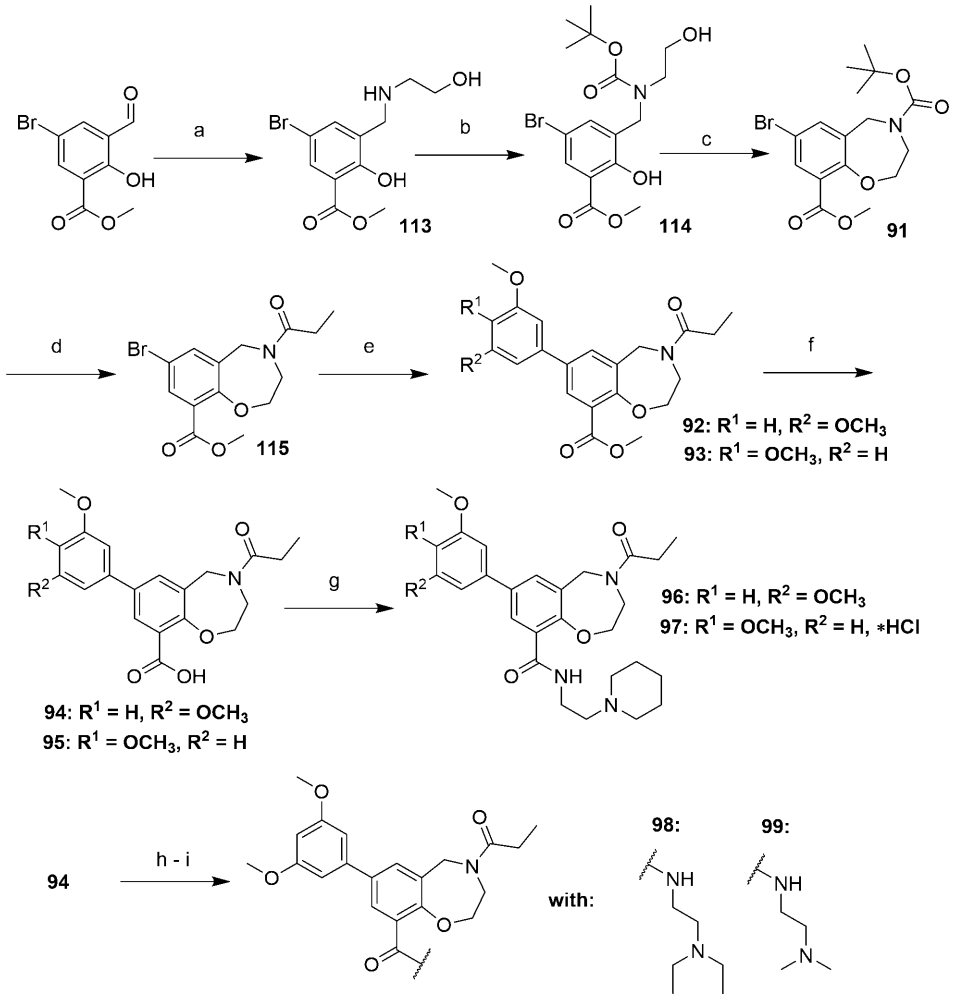
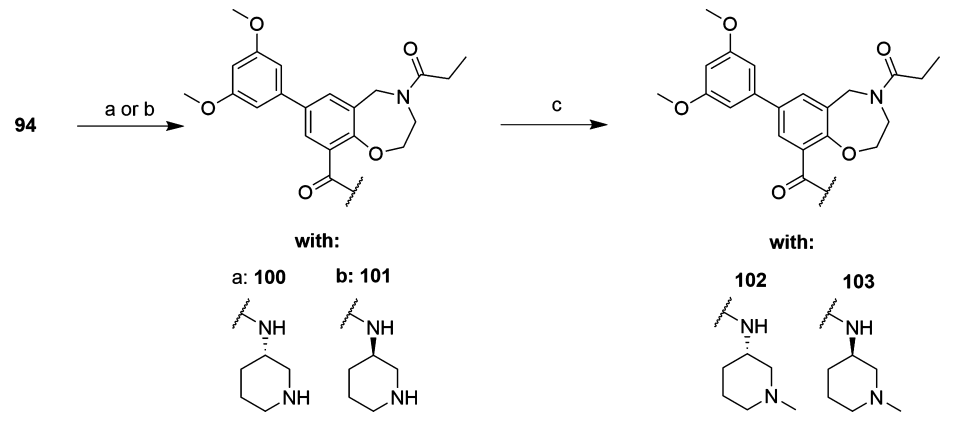
Scheme 5. Introduction of the Carbonyl Function at C-9[a]



[a]Reagents and conditions: (a) 2-aminoethanol, $NaBH_4$, MeOH, THF, RT, 93%; (b) di-*tert*-butyl dicarbonate, EtOAc, $NaHCO_3$ solution, RT, 56%; (c) PPh_3, DIAD, THF, 0 °C to RT, 85%; (d) (i) HCl, 1,4-dioxane, RT, (ii) propionyl chloride, DIPEA, CH_2Cl_2, 0 °C to RT, 74%; (e) 3,5-/3,4-dimethoxyphenylboronic acid, Pd(dppf)Cl_2·CH_2Cl_2, DIPEA, H_2O, 1,4-dioxane, 95 °C, 72%/80%; (f) NaOH, MeOH, THF, 70 °C, 93%/87%; (g) (i) 1-(2-aminoethyl)piperidine, EDC, DMAP, DIPEA, CH_2Cl_2, 0 °C to RT, 31%, (ii, **97** only) HCl, 1,4-dioxane, RT, 43%; (h) *N*,*N*-dimethylethylenediamine, EDC, DMAP, DIPEA, CH_2Cl_2, 0 °C to RT, 69%; (i) *N*,*N*-diethylethylenediamine, EDC, DMAP, DIPEA, CH_2Cl_2, 0 °C to RT, 46%.

Scheme 6. Preparation of 100−103[a]



[a]Reagents and conditions: (a) (i) (*S*)-3-amino-1-Boc-piperidine, EDC, DMAP, DIPEA, CH_2Cl_2, 0 °C to RT, (ii) HCl, 1,4-dioxane, RT, 31%; (b) (i) (*R*)-3-amino-1-Boc-piperidine, EDC, DMAP, DIPEA, CH_2Cl_2, 0 °C to RT; (ii) HCl, 1,4-dioxane, RT, 55%; (c) formaldehyde solution, $NaCNBH_3$, AcOH, MeCN, RT, 35% and 36%.

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concentrated in vacuo. FCC with EtOAc and hexanes (2:1, Rf 0.3) gave 1.0 g of the crude enol ether. This intermediate was dissolved in a mixture of 10 mL of THF and 10 mL of water and treated at 0 °C with 0.56 g (2.9 mmol) of *N*-bromosuccinimide. After 1 h at RT, the mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to obtain 0.47 g of the crude α-bromoketone. Then 0.2 g (43%, 0.54 mmol) of this residue and 0.20 g (2.6 mmol) of thiourea were dissolved in 5 mL of anhydrous DMF and stirred overnight. After the addition of water, the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with CH_2Cl_2 with 3% MeOH (Rf 0.2) gave 0.090 g (0.26 mmol, 20%) of **57** as a yellow solid; mp 103−104 °C. ^{1}H NMR (100 °C, 400 MHz, DMSO-d_6) δ = 7.41−7.30 (m, 2H), 6.84 (s, 1H), 6.65 (s, 2H), 4.71 (s, 2H), 4.13−4.04 (m, 2H), 4.04−3.91 (m, 2H), 3.82 (s, 3H), 2.06−1.88 (m, 1H), 0.75−0.63 (m, 4H). ^{13}C NMR (100 °C, 101 MHz, DMSO-d_6) δ = 171.2, 167.5, 150.7, 149.2, 147.2, 131.3, 129.8, 118.5, 110.3, 100.5, 71.2, 55.9, 48.6, 48.4, 10.5, 6.2. MS (ESI+): *m*/*z* calcd for $[(C_{17}H_{20}N_3O_3S)^+]$ 346.1225, found 346.1219.

*1-Cyclopropyl-1-[7-(3,5-dimethylisoxazol-4-yl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methanone (**58**).* Standard protocol 2 with 0.098 g (0.30 mmol) of **53** and 0.080 g (0.36 mmol) of 3,5-dimethylisoxazole-4-boronic acid pinacol ester. FCC with EtOAc and hexanes (3:1, Rf 0.2) gave 0.089 g (0.26 mmol, 87%) of **58** as a white solid; mp 175−176 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 6.74−6.66 (m, 2H), 4.69 (s, 2H), 4.20−4.10 (m, 2H), 4.05−3.95 (m, 2H), 3.84 (s, 3H), 2.35 (s, 3H), 2.21 (s, 3H), 1.80−1.64 (m, 1H), 0.96−0.87 (m, 2H), 0.76−0.66 (m, 2H). ^{13}C NMR (110 °C, 101 MHz, $C_2D_2Cl_4$) δ = 172.4, 165.0, 158.4, 152.2, 148.4, 132.7, 126.0, 122.4, 116.3, 114.7, 72.4, 57.1, 50.1, 49.6, 11.7, 11.4, 10.6, 7.3. MS (EI+): *m*/*z* calcd for $(C_{19}H_{22}N_2O_4)$ 342.1580, found 342.1572.

*1-[7-(Benzo[b]thiophen-2-yl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]-1-(cyclopropyl)methanone (**59**).* Standard protocol 2 with 0.12 g (0.36 mmol) of **53** and 0.080 g (0.43 mmol) of benzo[*b*]thien-2-ylboronic acid. FCC with EtOAc and hexanes (2:1, Rf 0.2) gave 0.13 g (0.34 mmol, 94%) of **59** as a white solid; mp 83−84 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ = 7.95−7.87 (m, 1H), 7.87−7.79 (m, 1H), 7.79−7.70 (m, 1H), 7.43−7.25 (m, 4H), 4.79 (s, 2H), 4.20−4.08 (m, 2H), 4.06−3.92 (m, 2H), 3.89 (s, 3H), 2.12−1.95 (m, 1H), 0.78−0.66 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6, 100 °C) δ = 171.4, 151.2, 148.3, 142.5, 140.0, 138.2, 131.9, 128.2, 124.1, 123.8, 122.9, 121.6, 119.2, 119.1, 110.6, 71.2, 56.1, 48.4, 48.4, 10.5, 6.3. MS (EI+): *m*/*z* calcd for $(C_{22}H_{21}NO_3S)$ 379.1242, found 379.1240.

*1-[4-(Cyclopropanecarbonyl)-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]ethan-1-one (**60**).* To a solution of 0.49 g (1.5 mmol) of **53** and 0.053 g (0.075 mmol) of $Pd(PPh_3)_2Cl_2$ in 6.0 mL of anhydrous 1,4-dioxane under N_2 were added 0.66 mL of (2.0 mmol) tributyl(1-ethoxyvinyl)tin. The mixture was heated to 140 °C under microwave irradiation with 300 W for 40 min. After cooling, 30 mL of 10% aqueous HCl was added and the mixture extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (4:1, Rf 0.5) gave 0.29 g (1.0 mmol, 67%) of **60** as a white solid; mp 76−77 °C. ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 80 °C): δ = 7.47−7.38 (m, 2H), 4.73 (s, 2H), 4.30−4.16 (m, 2H), 4.08−3.95 (m, 2H), 3.87 (s, 3H), 2.53 (s, 3H), 1.81−1.63 (m, 1H), 0.93−0.87 (m, 2H), 0.79−0.70 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, $C_2D_2Cl_4$): δ = 196.9, 196.7, 172.8, 172.4, 152.4, 152.1, 151.5, 151.1, 132.2, 132.1, 130.8, 130.2, 123.5, 121.3, 111.4, 110.2, 72.1, 71.7, 56.3, 56.2, 50.4, 50.4, 48.1, 47.6, 26.5, 26.4, 11.5, 11.4, 7.7, 7.6. MS (ESI+): *m*/*z* calcd for $[(C_{16}H_{20}NO_4)^+]$ 290.1392, found 290.1386.

*5-[4-(Cyclopropanecarbonyl)-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-methoxybenzaldehyde (**61**).* Standard protocol 2 with 1.5 g (4.6 mmol) of **53** and with 0.96 g (5.4 mmol) of 3-formyl-4-methoxyphenylboronic acid. FCC with EtOAc and hexanes (3:1, Rf 0.2) gave 1.4 g of **61** as a yellow solid (3.7 mmol, 80%); mp 152−153 °C. ^{1}H NMR (100 °C, 400 MHz, DMSO-d_6) δ = 10.42 (s, 1H), 7.97−7.88 (m, 2H), 7.32−7.26 (m, 1H), 7.20 (s, 1H), 7.16 (d, *J* = 2.2 Hz, 1H), 4.78 (s, 2H), 4.14−4.06 (m, 2H), 4.01−3.94 (m, 5H), 3.87 (s, 3H), 2.11−1.95 (m, 1H), 0.75−0.66 (m, 4H). ^{13}C NMR (100 °C, 101 MHz, DMSO-d_6) δ = 188.5, 171.4, 160.4, 151.2, 147.4, 133.6, 133.5, 132.1, 131.9, 125.2, 124.4, 119.0, 113.1, 111.0, 71.2, 56.1, 55.9, 48.5, 48.4, 10.4, 6.3. MS (ESI+): *m*/*z* calcd for $[(C_{22}H_{24}NO_5)^+]$ 382.1654, found 382.1647.

*4-[4-(Cyclopropanecarbonyl)-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]benzonitrile (**62**).* Standard protocol 2 with 0.098 g (0.30 mmol) of **53** and 0.053 g (0.36 mmol) of 4-cyanophenylboronic acid. FCC with EtOAc and hexanes (2:1, Rf 0.2) gave 0.091 g (0.26 mmol, 87%) of **62** as an orange solid; mp 157−158 °C. ^{1}H NMR (RT, mixture of rotamers, 400 MHz, CD_2Cl_2) δ = 7.80−7.62 (m, 4H), 7.20−7.02 (m, 2H), 4.78 (s, 1.1H), 4.68 (s, 0.9H), 4.26−4.17 (m, 0.9H), 4.17−4.04 (m, 2H), 4.04−3.96 (m, 1.1H), 3.92−3.86 (m, 3H), 1.95−1.83 (m, 0.6H), 1.75−1.65 (m, 0.4H), 0.89−0.80 (m, 2H), 0.80−0.67 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, CD_2Cl_2) δ = 172.9, 172.4, 152.8, 152.3, 149.5, 149.3, 145.4, 145.3, 135.2, 134.8, 133.4, 133.3, 133.0, 132.9, 128.0, 127.9, 121.3, 119.8, 119.3, 119.2, 111.6, 111.3, 111.1, 110.9, 73.2, 73.0, 56.7, 51.5, 51.3, 49.1, 48.8, 11.8, 11.6, 7.7, 7.5. MS (EI+): *m*/*z* calcd for $(C_{21}H_{20}N_2O_3)$ 348.1474, found 348.1473.

*1-Cyclopropyl-1-[9-methoxy-7-(4-methyl-3-nitrophenyl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methanone (**63**).* Standard protocol 2 with 0.80 g (2.5 mmol) of **53** and 0.51 g (2.8 mmol) of 4-methyl-3-nitrophenylboronic acid. FCC with CH_2Cl_2 with 1% MeOH Rf 0.3) gave 0.56 g (1.5 mmol, 60%) of **63** as a yellow solid; mp 141−142 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 8.04 (d, *J* = 2.0 Hz, 1H), 7.63 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.06−7.00 (m, 2H), 4.73 (s, 2H), 4.22−4.13 (m, 2H), 4.04−3.97 (m, 2H), 3.89 (s, 3H), 2.58 (s, 3H), 1.80−1.68 (m, 1H), 0.95−0.87 (m, 2H), 0.78−0.68 (m, 2H). ^{13}C NMR (110 °C, 101 MHz, $C_2D_2Cl_4$) δ = 172.2, 152.2, 149.9, 149.1, 139.7, 133.9, 132.8, 132.5, 131.6, 130.7, 122.3, 120.0, 112.2, 72.2, 56.9, 49.7, 49.4, 19.1, 11.6, 7.0. MS (ESI+): *m*/*z* calcd for $[(C_{21}H_{23}N_2O_5)^+]$ 383.1607, found 383.1600.

*1-Cyclopropyl-1-{7-[4-(dimethylamino)phenyl]-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl}methanone (**64**).* Standard protocol 2 with 0.30 g (0.92 mmol) of **53** and 0.23 g (1.4 mmol) of 4-(dimethylamino)phenylboronic acid. FCC with EtOAc and hexanes (1:2, Rf 0.1) gave 0.17 g (0.46 mmol, 50%) of **64** as a white solid; mp 79−80 °C. ^{1}H NMR (RT, mixture of rotamers, 400 MHz, $C_2D_2Cl_4$) δ = 7.52−7.39 (m, 2H), 7.09−6.93 (m, 2H), 6.78 (d, *J* = 8.2 Hz, 2H), 4.73 (s, 1.3H), 4.67 (s, 0.7H), 4.28−3.93 (m, 4H), 3.88 (s, 3H), 3.03−2.93 (m, 6H), 1.91−1.80 (m, 0.7H), 1.69−1.62 (m, 0.3H), 0.96−0.87 (m, 2H), 0.81−0.69 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $C_2D_2Cl_4$) δ = 172.6, 172.0, 151.6, 151.1, 149.6, 146.6, 146.5, 136.8, 136.4, 131.9, 131.7, 128.1, 127.5, 127.4, 119.4, 118.1, 112.5, 110.2, 109.5, 72.4, 56.1, 51.0, 50.9, 48.6, 48.4, 40.4, 11.6, 11.4, 7.6, 7.4. MS (ESI+): *m*/*z* calcd for $[(C_{22}H_{27}N_2O_3)^+]$ 367.2021, found 367.2017.

*5-[4-(Cyclopropanecarbonyl)-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-methylbenzenaminium chloride (**65**).* To a suspension of 6 g of Raney nickel in 60 mL of water was added 9.2 g of NaOH. Upon complete activation after 15 min, this suspension was washed three times with water and then three times with EtOH. Separately, 0.45 g (1.2 mmol) of **63** were dissolved in a mixture of 15 mL of MeOH and 25 mL of EtOH and then 2.2 mL of (44 mmol) hydrazine monohydrate were added. The activated Raney nickel suspension was then added to this solution, and the mixture was refluxed for 40 min. The suspension was filtrated and the filtrate concentrated in vacuo to give 0.18 g (0.46 mmol, 38%) of **65** as a purple solid; mp 221 °C (decomposition). ^{1}H NMR (100 °C, 400 MHz, DMSO-d_6) δ = 7.19−7.05 (m, 4H), 7.05−6.94 (m, 1H), 5.62 (s, 3H), 4.75 (s, 2H), 4.19−4.02 (m, 2H), 4.02−3.92 (m, 2H), 3.85 (s, 3H), 2.19 (s, 3H), 2.10−1.92 (m, 1H), 0.78−0.66 (m, 4H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, DMSO-d_6) δ = 172.7, 172.0, 152.0, 151.8, 148.2, 139.1, 138.9, 134.7, 134.1, 133.2, 132.8, 132.5, 132.2, 132.1, 130.9, 130.7, 126.1, 125.9, 121.6, 121.4, 120.1, 119.4, 110.9, 110.4, 72.7, 72.1, 56.3, 50.9, 50.1, 48.7, 48.3, 17.3, 11.2, 11.1, 7.9, 7.6. MS (EI+): *m*/*z* calcd for $(C_{21}H_{24}N_2O_3)$ 352.1787, found 352.1787.

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*N-{5-[4-(Cyclopropanecarbonyl)-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-methylphenyl}ethanesulfonamide (**66**).* To a solution of 0.058 g (0.15 mmol) of **65** and 5 mg (0.04 mmol) of DMAP in 2.0 mL of pyridine were added 0.015 mL of (0.16 mmol) ethanesulfonyl chloride at 0 °C. The mixture was warmed to RT and stirred overnight. Then 1 M HCl was added and the mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (2:1, Rf 0.3) gave 0.040 g (0.090 mmol, 60%) of **66** as a white solid; mp 155−156 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.59 (d, J = 1.9 Hz, 1H), 7.28 (dd, J = 7.9, 1.9 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.04−6.99 (m, 2H), 6.00 (br s, 1H), 4.72 (s, 2H), 4.19−4.09 (m, 2H), 4.03−3.95 (m, 2H), 3.88 (s, 3H), 3.14 (q, J = 7.4 Hz, 2H), 2.32 (s, 3H), 1.83−1.69 (m, 1H), 1.37 (t, J = 7.4 Hz, 3H), 0.94−0.86 (m, 2H), 0.78−0.68 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, $C_2D_2Cl_4$) δ = 172.7, 172.1, 151.7, 151.2, 147.8, 147.6, 139.7, 135.7, 135.3, 135.1, 135.0, 132.1, 131.7, 131.5, 128.5, 124.3, 124.2, 120.4, 120.2, 119.0, 111.0, 110.4, 72.4, 72.2, 56.2, 51.6, 50.8, 48.5, 48.2, 46.7, 46.6, 17.6, 11.6, 11.4, 8.2, 7.7, 7.5. MS (EI+): m/z calcd for ($C_{23}H_{28}N_2O_5S$) 444.1719, found 444.1727.

*1-{5-[4-(Cyclopropanecarbonyl)-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-methylphenyl}-3-ethylurea (**67**).* To a solution of 0.058 g (0.15 mmol) of **65** in 1.0 mL of CH_2Cl_2 were added 0.30 mL of (1.7 mmol) DIPEA and 0.080 mL of (1.3 mmol) ethyl isocyanate, and the mixture was stirred for 72 h. Then 0.1 M HCl was added and the mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (2:1, Rf 0.3) gave 0.030 g (0.071 mmol, 47%) of **67** as a white solid; mp 190−191 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.63 (d, J = 1.9 Hz, 1H), 7.31−7.16 (m, 2H), 7.09−6.98 (m, 2H), 5.99 (br s, 1H), 4.71 (s, 2H), 4.59 (br s, 1H), 4.17−4.08 (m, 2H), 4.03−3.95 (m, 2H), 3.87 (s, 3H), 3.24 (q, J = 7.2 Hz, 2H), 2.25 (s, 3H), 1.81−1.69 (m, 1H), 1.12 (t, J = 7.2 Hz, 3H), 0.94−0.86 (m, 2H), 0.79−0.68 (m, 2H). ^{13}C NMR (110 °C, 101 MHz, $C_2D_2Cl_4$) δ = 172.4, 156.0, 152.1, 148.5, 139.6, 137.1, 136.2, 132.3, 131.2, 130.8, 123.8, 123.4, 120.2, 112.6, 72.4, 57.1, 50.2, 49.7, 35.5, 17.3, 15.4, 11.8, 7.3. MS (EI+): m/z calcd for ($C_{24}H_{29}N_3O_4$) 423.2158, found 423.2157.

*1-Cyclopropyl-1-[7-(3,5-dimethoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methanone (**68**).* Standard protocol 2 with 0.12 g (0.37 mmol) of **53** and 0.078 g (0.43 mmol) of 3,5-dimethoxyphenylboronic acid. FCC with EtOAc and hexanes (2:1, Rf 0.4) gave 0.090 g (0.23 mmol, 62%) of **68** as a white solid; mp 50−51 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.10−6.96 (m, 2H), 6.66 (d, J = 2.2 Hz, 2H), 6.44 (t, J = 2.2 Hz, 1H), 4.72 (s, 2H), 4.20−4.09 (m, 2H), 4.04−3.95 (m, 2H), 3.87 (s, 3H), 3.81 (s, 6H), 1.85−1.70 (m, 1H), 0.99−0.85 (m, 2H), 0.79−0.66 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $C_2D_2Cl_4$) δ = 172.6, 172.1, 160.8, 160.8, 151.6, 151.1, 147.8, 147.7, 142.6, 142.3, 136.5, 136.0, 131.9, 131.5, 120.4, 119.1, 111.0, 110.4, 105.5, 105.1, 99.1, 98.6, 72.3, 72.2, 56.2, 55.4, 50.9, 48.5, 48.2, 11.6, 11.4, 7.6, 7.5. MS (EI+): m/z calcd for ($C_{22}H_{25}NO_5$) 383.1733, found 383.1759.

*1-Cyclopropyl-1-[9-methoxy-7-(4-methoxy-3-methylphenyl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methanone (**69**).* Standard protocol 2 with 0.50 g (1.5 mmol) of **53** and 0.28 g (1.7 mmol) of 4-methoxy-3-methylphenylboronic acid. FCC with EtOAc and hexanes (3:2, Rf 0.3) gave 0.38 g (1.0 mmol, 68%) of **69** as a pale-brown solid; mp 109−110 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.32−7.27 (m, 2H), 7.02−6.96 (m, 2H), 6.87−6.82 (m, 1H), 4.71 (s, 2H), 4.15−4.10 (m, 2H), 4.00−3.95 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.26 (s, 3H), 1.81−1.69 (m, 1H), 0.94−0.87 (m, 2H), 0.75−0.68 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $C_2D_2Cl_4$) δ = 172.6, 172.0, 157.22, 157.17, 151.6, 151.1, 147.0, 146.9, 136.6, 136.2, 132.4, 132.1, 131.9, 131.7, 129.2, 129.1, 126.9, 126.8, 125.2, 125.1, 120.0, 118.6, 110.7, 110.1, 110.0, 72.4, 72.3, 56.2, 55.4, 50.9, 48.6, 48.4, 16.4, 16.3, 11.6, 11.4, 7.6, 7.4. MS (EI+): m/z calcd for ($C_{22}H_{25}NO_4$) 367.1784, found 367.1784.

*1-[7-(Benzo[d][1,3]dioxol-5-yl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]-1-(cyclopropyl)methanone (**70**).* Standard protocol 2 with 0.20 g (0.61 mmol) of **53** and 0.11 g (0.67 mmol) of 3,4-(methylenedioxy)phenylboronic acid. FCC with EtOAc and hexanes (3:2, Rf 0.4) gave 0.21 g (0.58 mmol, 94%) of **70** as a pale-brown solid; mp 127−128 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.01−6.94 (m, 4H), 6.82 (dd, J = 7.7, 0.8 Hz, 1H), 5.94 (s, 2H), 4.71 (s, 2H), 4.15−4.10 (m, 2H), 4.01−3.96 (m, 2H), 3.86 (s, 3H), 1.81−1.70 (m, 1H), 0.95−0.87 (m, 2H), 0.76−0.69 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $C_2D_2Cl_4$) δ = 172.6, 172.0, 151.6, 151.1, 147.9, 147.3, 147.2, 146.9, 146.8, 136.4, 136.0, 134.7, 134.5, 132.0, 131.7, 120.4, 120.1, 118.7, 110.8, 110.1, 108.5, 108.5, 107.4, 107.4, 101.2, 101.1, 72.4, 56.2, 50.9, 48.6, 48.3, 11.6, 11.4, 7.6, 7.5. MS (EI+): m/z calcd for ($C_{21}H_{21}NO_5$) 367.1420, found 367.1433.

*1-Cyclopropyl-1-(9-methoxy-7-(4-methoxy-3,5-dimethylphenyl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)methanone (**71**).* Standard protocol 2 with 0.20 g (0.61 mmol) of **53** and 0.12 g (0.68 mmol) of 3,5-dimethyl-4-methoxyphenylboronic acid. FCC with EtOAc and hexanes (3:2, Rf 0.4) gave 0.071 g (0.19 mmol, 31%) of **71** as a pale-brown solid; mp 146−147 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.16−7.12 (m, 2H), 7.02−6.97 (m, 2H), 4.71 (s, 2H), 4.16−4.10 (m, 2H), 4.01−3.96 (m, 2H), 3.87 (s, 3H), 3.73 (s, 3H), 2.31 (s, 6H), 1.81−1.70 (m, 1H), 0.94−0.88 (m, 2H), 0.75−0.68 (m, 2H). ^{13}C NMR (110 °C, 101 MHz, $C_2D_2Cl_4$) δ = 172.6, 156.9, 152.0, 148.1, 136.8, 135.9, 132.2, 131.0, 127.4, 120.2, 112.6, 72.5, 59.7, 57.1, 50.2, 49.6, 16.2, 11.9, 7.2. MS (EI+): m/z calcd for ($C_{23}H_{27}NO_4$) 381.1940, found 381.1940.

*1-(7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)-1-(cyclopropyl)methanone (**72**).* Standard protocol 2 with 0.20 g (0.61 mmol) of **53** and 0.13 g (0.67 mmol) of 3-chloro-4-methoxyphenylboronic acid. FCC with EtOAc and hexanes (3:2, Rf 0.3) gave 0.16 g (0.42 mmol, 69%) of **72** as a pale-brown solid; mp 130−131 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.52 (d, J = 2.3 Hz, 1H), 7.36 (dd, J = 8.5, 2.3 Hz, 1H), 7.00−6.93 (m, 3H), 4.71 (s, 2H), 4.16−4.11 (m, 2H), 4.01−3.96 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 1.79−1.69 (m, 1H), 0.94−0.88 (m, 2H), 0.76−0.68 (m, 2H). ^{13}C NMR (110 °C, 101 MHz, $C_2D_2Cl_4$) δ = 172.3, 154.9, 152.2, 148.5, 135.3, 134.5, 132.5, 128.8, 126.2, 123.6, 120.0, 113.4, 112.4, 72.5, 57.1, 56.7, 50.1, 49.6, 11.8, 7.3. MS (ESI+): m/z calcd for [($C_{21}H_{23}{}^{35}ClNO_4$)$^+$] 388.1316, found 388.1317.

*1-Cyclopropyl-1-{7-[3-(hydroxymethyl)-4-methoxyphenyl]-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl}methanone (**73**).* To a suspension of 0.078 g (2.0 mmol) of sodium borohydride in a mixture of 7.5 mL of CH_2Cl_2 and 2.5 mL of MeOH were added 0.43 g (1.1 mmol) of **61**, and the mixture was stirred for 2 h. Then 20 mL of 2 M HCl was added, and after 15 min of stirring, the mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give 0.42 g (1.9 mmol, 97%) of **73** as a white solid; mp 74−75 °C. ^{1}H NMR (RT, mixture of rotamers, 500 MHz, $CDCl_3$): δ = 7.52−7.39 (m, 2H), 7.14−6.87 (m, 3H), 4.82−4.66 (m, 4H), 4.29−4.21 (m, 0.7H), 4.19−4.00 (m, 3.3H), 3.95−3.86 (m, 6H), 2.35 (s, 1H), 1.92−1.85 (m, 0.7H), 1.73−1.67 (m, 0.3H), 1.01−0.90 (m, 2H), 0.82−0.69 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $CDCl_3$): δ = 172.8, 172.1, 157.0, 156.9, 152.0, 151.3, 147.5, 147.1, 136.7, 136.4, 133.2, 132.4, 132.0, 129.5, 129.3, 127.43, 127.39, 127.3, 120.5, 118.9, 110.8, 110.5, 110.5, 110.1, 72.81, 72.75, 62.1, 62.0, 56.3, 56.2, 55.5, 51.2, 51.2, 48.9, 48.6, 11.6, 11.5, 7.7, 7.5. MS (ESI+): m/z calcd for [($C_{22}H_{26}NO_5$)$^+$] 384.1811, found 384.1806.

*1-Cyclopropyl-1-[7-(3,4-difluorophenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methanone (**74**).* Standard protocol 2 with 0.12 g (0.37 mmol) of **53** and 0.068 g (0.43 mmol) of 3,4-difluorophenylboronic acid. FCC with EtOAc and hexanes (2:1, Rf 0.4) gave 0.090 g (0.25 mmol, 68%) of **74** as a white solid; mp 136−137 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.34−7.26 (m, 1H), 7.26−7.09 (m, 2H), 7.04−6.91 (m, 2H), 4.72 (s, 2H), 4.22−4.10 (m, 2H), 4.04−3.94 (m, 2H), 3.88 (s, 3H), 1.83−1.66 (m, 1H), 0.95−0.86 (m, 2H), 0.79−0.66 (m, 2H). ^{13}C NMR (110 °C, 101 MHz, $C_2D_2Cl_4$) δ = 172.4, 152.3, 150.6 (dd, $^1J_{CF}$ = 248.6 Hz, $^2J_{CF}$ = 12.8 Hz), 150.0 (dd, $^1J_{CF}$ = 248.9 Hz, $^2J_{CF}$ = 12.6 Hz), 149.0, 137.9, 134.8, 132.6, 122.9 (dd, $^3J_{CF}$ = 5.5, $^4J_{CF}$ = 3.4 Hz), 120.2, 117.5 (d, $^2J_{CF}$ = 17.4 Hz), 115.9 (d, $^2J_{CF}$ = 17.8 Hz), 112.5, 72.5, 57.1, 50.0, 49.6, 11.8, 7.3. MS (EI+): m/z calcd for ($C_{20}H_{19}F_2NO_3$) 359.1333, found 359.1335.

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*1-Cyclopropyl-1-[7-(3,4-dichlorophenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]methanone (**75**).* Standard protocol 2 with 0.098 g (0.30 mmol) of **53** and 0.068 g (0.36 mmol) of 3,4-dichlorophenylboronic acid. FCC with EtOAc and hexanes (2:1, Rf 0.4) gave 0.095 g (0.24 mmol, 81%) of **75** as a pale-brown solid; mp 115−116 °C. ^{1}H NMR (RT, mixture of rotamers, 500 MHz, CD_2Cl_2) δ = 7.75−7.60 (m, 1H), 7.59−7.46 (m, 1H), 7.46−7.36 (m, 1H), 7.17−6.96 (m, 2H), 4.77 (s, 1.2H), 4.66 (s, 0.8H), 4.23−4.16 (m, 0.8H), 4.12−4.05 (m, 2H), 4.01−3.95 (m, 1.2H), 3.93−3.84 (m, 3H), 1.94−1.82 (m, 0.6H), 1.74−1.68 (m, 0.4H), 0.89−0.82 (m, 2H), 0.79−0.67 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, CD_2Cl_2) δ = 172.9, 172.4, 152.7, 152.2, 149.1, 149.0, 141.2, 141.1, 134.6, 134.3, 133.4, 133.3, 133.0, 131.6, 131.4, 131.1, 131.0, 129.1, 129.0, 126.8, 120.9, 119.5, 111.3, 110.7, 73.2, 72.9, 56.7, 51.6, 51.3, 49.1, 48.8, 11.8, 11.6, 7.7, 7.5. MS (EI+): m/z calcd for ($C_{20}H_{19}NO_3{}^{35}Cl_2$) 391.0742, found 391.0749.

*5-[4-(Cyclopropanecarbonyl)-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-methoxybenzaldehyde O-methyl Oxime (**76**).* To a suspension of 0.15 g (0.39 mmol) of **61** in 6 mL of EtOH were added 0.13 g (1.5 mmol) of *O*-methylhydroxylamine hydrochloride and 0.21 g (1.5 mmol) of K_2CO_3. After 12 h, the mixture was concentrated in vacuo, treated with EtOAc and saturated NaCl solution, and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with CH_2Cl_2 with 2% MeOH (Rf 0.3) gave 0.16 g (0.39 mmol, 99%) of **76** as a white solid; mp 78−79 °C. ^{1}H NMR (RT, mixture of rotamers, 500 MHz, CD_2Cl_2): δ = 8.45 (s, 1H), 7.95 (d, J = 2.4 Hz, 1H), 7.60−7.50 (m, 1H), 7.13−6.95 (m, 3H), 4.77 (s, 1.3H), 4.67 (s, 0.7H), 4.23−4.13 (m, 0.7H), 4.10−4.04 (m, 2H), 4.00−3.95 (m, 4.3H), 3.90−3.86 (m, 6H), 1.96−1.88 (m, 0.7H), 1.73−1.67 (m, 0.3H), 0.91−0.80 (m, 2H), 0.80−0.67 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, CD_2Cl_2): δ = 172.9, 172.3, 157.5, 152.5, 152.0, 148.2, 148.0, 144.74, 144.65, 136.6, 136.1, 133.7, 133.5, 133.2, 133.1, 129.9, 124.9, 124.7, 121.4, 120.6, 119.3, 111.9, 111.3, 110.7, 73.2, 73.0, 62.2, 56.7, 56.2, 51.6, 51.4, 49.2, 49.0, 11.8, 11.6, 7.7, 7.5. MS (ESI+): m/z calcd for [($C_{23}H_{27}N_2O_5$)$^+$] 411.1920, found 411.1912.

*7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepine (**77**).* Standard protocol 2 with 1.5 g (5.8 mmol) of **107** and 1.3 g (7.0 mmol) of 3-chloro-4-methoxyphenylboronic acid. FCC with EtOAc with 5% triethylamine (Rf 0.1) gave 0.90 g (2.8 mmol, 48%) of **77** as a white solid; mp 117−118 °C. ^{1}H NMR (RT, 500 MHz, $CDCl_3$) δ = 7.56 (d, J = 2.3 Hz, 1H), 7.40 (dd, J = 8.5, 2.3 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 6.89 (d, J = 2.1 Hz, 1H), 4.14−4.10 (m, 2H), 4.02 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.29−3.24 (m, 2H). ^{13}C NMR (RT, 101 MHz, $CDCl_3$) δ = 154.3, 151.8, 148.5, 136.7, 135.0, 134.4, 128.7, 126.1, 122.7, 119.5, 112.2, 109.8, 75.5, 56.33, 56.27, 53.2, 52.3. MS (EI+): m/z calcd for ($C_{17}H_{18}{}^{35}ClNO_3$) 319.0975, found 319.0972.

*7-(3-Chloro-4-methoxyphenyl)-9-methoxy-N,N-dimethyl-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide (**78**).* Standard protocol 1 with 0.10 g (0.31 mmol) of **77** and 0.24 mL (2.6 mmol) of *N,N*-dimethylcarbamoyl chloride. FCC with EtOAc and hexanes (5:1, Rf 0.1) gave 0.090 g (0.23 mmol, 74%) of **78** as a white solid; mp 85−86 °C. ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.58 (d, J = 2.3 Hz, 1H), 7.44 (dd, J = 8.5, 2.3 Hz, 1H), 7.05−6.94 (m, 3H), 4.38 (s, 2H), 4.17−4.14 (m, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.67−3.62 (m, 2H), 2.80 (s, 6H). ^{13}C NMR (RT, 126 MHz, CD_2Cl_2) δ = 164.9, 154.7, 152.0, 148.7, 135.0, 134.5, 133.2, 128.9, 126.6, 122.8, 120.2, 112.7, 110.4, 73.0, 56.60, 56.57, 52.8, 52.7, 39.1. MS (EI+): m/z calcd for ($C_{20}H_{23}{}^{35}ClN_2O_4$) 390.1346, found 390.1348.

*7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide (**79**).* To a solution of 0.10 g (0.31 mmol) of **77** in 2 mL of CH_2Cl_2 was added 0.42 mL of (3.1 mmol) (trimethylsilyl)isocyanate and the mixture was stirred for 2.5 h. The solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and 7 mL of a solution of 4 M HCl in 1,4-dioxane was added, and the mixture stirred for 1 h. After adjustment to pH 9 with 1 M NaOH, the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and 3% MeOH (Rf 0.2) gave 0.098 g (0.27 mmol, 87%) of **79** as a white solid; mp 153−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (d, J = 2.3 Hz, 1H), 7.30 (dd, J = 8.5, 2.3 Hz, 1H), 6.92−6.87 (m, 3H), 4.72 (s, 2H), 4.41 (s, 2H), 4.10−4.05 (m, 2H), 3.87−3.81 (m, 6H), 3.81−3.76 (m, 2H). ^{13}C NMR (RT, 101 MHz, $CDCl_3$) δ = 157.0, 153.4, 151.0, 146.5, 134.4, 132.9, 131.1, 127.6, 125.1, 121.7, 118.1, 111.2, 109.6, 71.5, 55.3, 49.4, 49.0. MS (EI+): m/z calcd for ($C_{18}H_{19}{}^{35}ClN_2O_4$) 362.1033, found 362.1029.

*1-[7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]-2-hydroxyethan-1-one (**80**).* A solution of 0.10 g (0.31 mmol) of **77** in 0.95 mL (10 mmol) of ethyl glycolate was heated to 60 °C. After 24 and 48 h, EtOH was removed in vacuo. After 84 h, purification by FCC with EtOAc and hexanes (5:1, Rf 0.2) gave 0.060 g (0.16 mmol, 51%) of **80** as a white solid; mp 160−161 °C. ^{1}H NMR (RT, mixture of rotamers, 500 MHz, $CDCl_3$) δ = 7.57 (d, J = 2.3 Hz, 0.4H), 7.54 (d, J = 2.3 Hz, 0.6H), 7.42 (dd, J = 8.5, 2.3 Hz, 0.4H), 7.38 (dd, J = 8.5, 2.3 Hz, 0.6H), 7.12 (d, J = 2.2 Hz, 0.4H), 7.02−6.96 (m, 2H), 6.87 (d, J = 2.2 Hz, 0.6H), 4.76 (s, 0.8H), 4.42 (s, 1.2H), 4.35−4.31 (m, 1.2H), 4.21−4.06 (m, 4H), 3.98−3.89 (m, 6H), 3.72−3.65 (m, 0.8H), 3.52 (t, J = 4.4 Hz, 0.4H), 3.48 (t, J = 4.4 Hz, 0.6H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, $CDCl_3$) δ = 171.2, 170.6, 154.6, 154.5, 152.2, 151.6, 147.6, 147.4, 136.0, 135.8, 133.9, 133.7, 131.4, 131.1, 128.72, 128.71, 126.24, 126.21, 122.9, 122.8, 120.1, 119.0, 112.3, 112.2, 111.1, 110.4, 72.5, 72.1, 60.0, 56.31, 56.28, 56.2, 49.4, 49.3, 49.2, 48.7. MS (EI+): m/z calcd for ($C_{19}H_{20}{}^{35}ClNO$) 377.1030, found 377.1021.

*7-(3-Chloro-4-methoxyphenyl)-9-methoxy-N-methyl-2,3-dihydro-1,4-benzoxazepine-4(5H)-carbothioamide (**81**).* To a solution of 0.15 g (0.47 mmol) of **77** in 3 mL of anhydrous THF was added 0.028 g (0.71 mmol) of a 60% suspension of NaH. After 15 min, a solution of 0.068 g (0.94 mmol) of methyl isothiocyanate in 1.0 mL of anhydrous THF was added and the mixture was stirred for 3 h at RT. Saturated $NaHCO_3$ solution was added and the mixture extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (3:2, Rf 0.3) gave 0.13 g (0.32 mmol, 69%) of **81** as a white solid; mp 200−201 °C. ^{1}H NMR (RT, mixture of rotamers, 500 MHz, $CDCl_3$) δ = 7.54 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 8.5, 2.3 Hz, 1H), 7.07−6.81 (m, 3H), 5.80−5.63 (m, 1H), 4.85−4.66 (m, 2H), 4.51−4.42 (m, 2H), 4.28−4.15 (m, 2H), 4.01−3.79 (m, 6H), 3.15−3.05 (m, 3H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, $CDCl_3$) δ = 182.9, 154.5, 152.2, 147.2, 135.6, 133.8, 130.3, 130.1, 128.7, 126.2, 124.0, 122.8, 120.4, 119.0, 112.6, 112.3, 111.0, 72.0, 71.9, 56.3, 56.1, 54.7, 54.4, 52.0, 51.8, 33.2, 33.1. MS (EI+): m/z calcd for ($C_{19}H_{21}{}^{35}ClN_2O_3S$) 392.0961, found 392.0953.

*1-[7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propane-1-thione (**82**).* A solution of 0.052 g (0.13 mmol) of **86** and 0.073 g (0.18 mmol) of Lawesson's reagent in 1.0 mL of anhydrous THF was stirred at RT for 72 h. Water was added and the mixture extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (3:1, Rf 0.7) gave 0.051 g (0.13 mmol, 96%) of **82** as a white solid; mp 82−83 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.61−6.82 (m, 5H), 5.30 (s, 0.9H), 4.85 (s, 1.1H), 4.68 (s, 1.1H), 4.32−4.03 (m, 2.9H), 3.94−3.83 (m, 6H), 2.98−2.64 (m, 2H), 1.35−1.21 (m, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $C_2D_2Cl_4$) δ = 206.4, 205.1, 154.3, 154.2, 151.9, 151.3, 147.24, 147.19, 135.4, 134.8, 133.6, 133.5, 129.4, 129.0, 128.5, 126.2, 122.5, 122.4, 121.6, 119.2, 112.3, 112.2, 111.1, 110.4, 71.5, 70.8, 56.4, 56.4, 56.3, 56.2, 54.9, 54.4, 54.1, 37.0, 35.9, 13.9, 13.5. MS (EI+): m/z calcd for ($C_{20}H_{22}{}^{35}ClNO_3S$) 391.1009, found 391.0988.

*1-[7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]-2,2,2-trifluoroethan-1-one (**83**).* To a solution of 0.040 g (0.13 mmol) of **77** and 5 mg (0.04 mmol) of DMAP in 1.0 mL of CH_2Cl_2 was added 0.070 mL of (0.50 mmol) trifluoroacetic anhydride at 0 °C. The mixture was stirred and warmed to RT. Then 0.70 mL of (41 mmol) DIPEA was added and the mixture stirred for a further 12 h. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:2, Rf 0.2) gave 0.050 g (0.12

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mmol, 92%) of **83** as a white solid; mp 143−144 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.52 (d, J = 2.3 Hz, 1H), 7.36 (dd, J = 8.6, 2.3 Hz, 1H), 7.09−6.90 (m, 3H), 4.69 (s, 2H), 4.18−4.12 (m, 2H), 4.05−3.93 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $C_2D_2Cl_4$) δ = 156.2, 156.2, 155.9, 155.8, 155.52, 155.45, 155.2, 154.3, 151.6, 147.4, 135.6, 135.5, 133.5, 133.4, 130.6, 129.9, 128.5, 126.2, 122.5, 120.1, 119.2, 117.6, 117.5, 114.8, 114.6, 112.31, 112.25, 111.1, 110.8, 72.6, 71.7, 56.3, 56.2, 51.3, 50.6, 50.0, 49.9. MS (EI+): m/z calcd for ($C_{19}H_{17}{}^{35}ClF_3NO_4$) 415.0798, found 415.0792.

*1-[7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]-3,3,3-trifluoropropan-1-one (**84**).* To a solution of 0.066 g (0.21 mmol) of **77** and 5 mg (0.04 mmol) of DMAP in 2.0 mL of CH_2Cl_2 was added 0.035 mL of (0.40 mmol) 3,3,3-trifluoropropionic acid at 0 °C. After 5 min, 0.058 g (0.30 mmol) of EDC·HCl was added, and the mixture warmed to RT and stirred for further 12 h. Saturated $NaHCO_3$ solution was added and the mixture extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated. FCC with EtOAc and hexanes (1:1, Rf 0.4) gave 0.082 g (0.19 mmol, 94%) of **84** as a white solid; mp 105−106 °C. ^{1}H NMR (RT, mixture of rotamers, 400 MHz, $CDCl_3$) δ = 7.56 (d, J = 2.3 Hz, 0.4H), 7.54 (d, J = 2.3 Hz, 0.6H), 7.46−7.34 (m, 1H), 7.11 (d, J = 2.1 Hz, 0.4H), 7.07−6.92 (m, 2H), 6.88 (d, J = 2.1 Hz, 0.6H), 4.72 (s, 0.8H), 4.57 (s, 1.2H), 4.24−4.13 (m, 2H), 4.11−4.01 (m, 1.2H), 4.00−3.84 (m, 6.8H), 3.31 (q, J = 9.9 Hz, 1.2H), 3.23 (q, J = 9.9 Hz, 0.8H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $CDCl_3$) δ = 162.7 (q, $^3J_{CF}$ = 2.9 Hz), 161.9 (q, $^3J_{CF}$ = 2.9 Hz), 154.7, 154.4, 152.3, 151.4, 147.6, 147.4, 136.1, 135.7, 133.9, 133.7, 131.2, 131.0, 128.8, 128.7, 126.2, 125.3, 122.9, 122.7, 122.6, 120.5, 118.3, 112.3, 112.2, 111.3, 110.4, 72.3, 72.2, 56.32, 56.31, 56.27, 56.23, 51.8, 51.6, 48.8, 48.3, 38.4 (q, $^2J_{CF}$ = 29.4 Hz), 38.1 (q, $^2J_{CF}$ = 29.4 Hz). MS (EI+): m/z calcd for ($C_{20}H_{19}{}^{35}ClF_3NO_4$) 429.0954, found 429.0950.

*1-[7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]-2-fluoropropan-1-one (**85**).* To a solution of 0.050 g (0.16 mmol) of **77** and 5 mg (0.04 mmol) of DMAP in 1.0 mL of CH_2Cl_2 was added 0.019 mL (0.23 mmol) of 2-fluoropropionic acid at 0 °C. After 5 min, 0.061 g (0.32 mmol) of EDC·HCl was added and the mixture warmed to RT and stirred for a further 12 h. Saturated $NaHCO_3$ solution was added and the mixture extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:1, Rf 0.3) gave 0.50 g (0.13 mmol, 81%) of **85** as a colorless oil. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.53 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 8.5, 2.4 Hz, 1H), 7.05−6.91 (m, 3H), 5.23 (dq, $^2J_{HF}$ = 48.5 Hz, $^3J_{HH}$ 6.7 Hz, 1H), 4.75−4.59 (m, 2H), 4.25−4.06 (m, 2H), 4.03−3.76 (m, 8H), 1.52 (dd, J = 24.6, 6.6 Hz, 3H). ^{13}C NMR (110 °C, 101 MHz, $C_2D_2Cl_4$) δ = 168.1 (d, $^2J_{CF}$ = 18.8 Hz), 155.0, 152.1, 148.5, 135.5, 134.4, 131.8, 128.8, 126.2, 123.6, 120.3, 113.4, 112.5, 87.2 (d, $^1J_{CF}$ = 178.2 Hz), 72.5, 57.1, 56.7, 49.9, 17.8 (d, $^2J_{CF}$ = 22.9 Hz). MS (EI+): m/z calcd for ($C_{20}H_{21}{}^{35}ClFNO_4$) 393.1143, found 393.1139.

*1-[7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propan-1-one (**86**).* Standard protocol 1 with 0.16 g (0.50 mmol) of **77** and 0.16 mL (0.65 mmol) of propionyl chloride. FCC with EtOAc and hexanes (3:1, Rf 0.4) gave 0.075 g (0.20 mmol, 40%) of **86** as a white solid; mp 66−67 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.52 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = 8.5, 2.3 Hz, 1H), 7.06−6.86 (m, 3H), 4.59 (s, 2H), 4.15−4.06 (m, 2H), 3.94−3.84 (m, 8H), 2.47−2.24 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $C_2D_2Cl_4$) δ = 172.9, 172.3, 154.3, 154.1, 151.9, 151.3, 147.6, 147.5, 135.1, 134.7, 133.7, 133.6, 132.1, 131.8, 128.5, 128.4, 126.2, 126.1, 122.5, 122.4, 120.0, 118.8, 112.3, 112.2, 110.7, 110.0, 72.4, 72.3, 56.29, 56.24, 56.22, 50.8, 48.3, 47.9, 26.7, 26.4, 9.19, 9.15. MS (EI+): m/z calcd for ($C_{20}H_{22}{}^{35}ClNO_4$) 375.1237, found 375.1235.

*Methyl 7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (**87**).* Standard protocol 1 with 0.10 g (0.31 mmol) of **77** and 0.20 mL (2.6 mmol) of methyl chloroformate. FCC with EtOAc and hexanes (1:1, Rf 0.3) gave 0.11 g (0.29 mmol, 94%) of **87** as a white solid; mp 67−68 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.62−7.58 (m, 1H), 7.50−7.41 (m, 1H), 7.09−6.97 (m, 3H), 4.56−4.48 (m, 2H), 4.08−4.02 (m, 2H), 3.92 (s, 3H), 3.89−3.82 (m, 5H), 3.68−3.59 (m, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $C_2D_2Cl_4$) δ = 156.4, 156.1, 154.8, 152.4, 152.3, 148.4, 135.4, 135.3, 134.4, 134.3, 133.9, 133.7, 128.9, 126.6, 122.9, 120.2, 119.8, 112.7, 110.8, 110.6, 73.2, 56.6, 53.0, 52.9, 50.7, 50.6, 50.5, 50.3. MS (EI+): m/z calcd for ($C_{19}H_{20}{}^{35}ClNO_5$) 377.1030, found 377.1026.

*1-[7-(3,4-Dimethoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl]propan-1-one (**88**).* Standard protocol 2 with 0.20 g (0.61 mmol) of **111** and 0.22 g (1.2 mmol) of 3,4-dimethoxyphenylboronic acid. FCC with EtOAc and hexanes (1:4, Rf 0.3) gave 0.14 g (0.36 mmol, 59%) of **88** as a white solid; mp 82−83 °C. ^{1}H NMR (RT, mixture of rotamers, 500 MHz, CD_2Cl_2) δ = 7.37 (d, J = 1.9 Hz, 0.5H), 7.20−7.06 (m, 2.5H), 7.02−6.92 (m, 2H), 4.82−4.64 (m, 2H), 4.08−3.89 (m, 8H), 3.89−3.86 (m, 3H), 2.93−2.76 (m, 2H), 2.44 (q, J = 7.4 Hz, 0.8H), 2.27 (q, J = 7.4 Hz, 1.2H), 1.2 (t, J = 7.4 Hz, 3H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, CD_2Cl_2) δ = 173.6, 172.6, 159.4, 159.2, 149.9, 149.8, 149.7, 149.6, 144.6, 143.4, 141.4, 141.2, 133.6, 133.5, 123.8, 123.2, 122.7, 121.2, 119.4 119.79, 112.2, 112.1, 111.1, 111.0, 109.4, 108.8, 56.74, 56.67, 56.38, 56.30, 56.26, 52.33, 52.25, 49.7, 35.3, 34.0, 27.11, 27.06, 9.42, 9.40. MS (ESI+): m/z calcd for [($C_{21}H_{26}NO_4S$)$^+$] 388.1583, found 388.1575.

*1-Cyclopropyl-1-[7-(3,4-dimethoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl]methanone (**89**).* Standard protocol 2 with 0.18 g (0.53 mmol) of **112** and 0.25 g (1.4 mmol) of 3,4-dimethoxyphenylboronic acid. FCC with EtOAc and hexanes (1:1, Rf 0.1) gave 0.18 g (0.45 mmol, 85%) of **89** as a white solid; mp 92−93 °C. ^{1}H NMR (RT, mixture of rotamers, 400 MHz, CD_2Cl_2) δ = 7.36−6.89 (m, 5H), 4.91 (s, 1H), 4.75 (s, 1H), 4.21−3.97 (m, 2H), 3.97−3.82 (m, 9H), 2.96−2.80 (m, 2H), 2.00−1.88 (m, 0.5H), 1.70−1.64 (m, 0.5H), 0.90−0.81 (m, 2H), 0.79−0.65 (m, 2H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, CD_2Cl_2) δ = 173.4, 172.2, 159.3, 159.2, 149.80, 149.77, 149.7, 149.6, 144.7, 143.7, 141.4, 141.2, 133.62, 133.56, 123.8, 123.1, 122.6, 120.9, 119.81, 119.77, 112.08, 112.05, 111.01, 110.97, 109.3, 108.8, 56.71, 56.66, 56.4, 56.3, 56.2, 52.7, 52.6, 49.9, 35.4, 33.9, 12.1, 11.6, 8.0, 7.4. MS (ESI+): m/z calcd for [($C_{22}H_{26}NO_4S$)$^+$] 400.1583, found 400.1577.

*1-[7-(3-Chloro-4-methoxyphenyl)-9-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl]-1-(cyclopropyl)methanone (**90**).* Standard protocol 2 with 0.18 g (0.53 mmol) of **112** and 0.26 g (1.4 mmol) of 3-chloro-4-methoxyphenylboronic acid. FCC with EtOAc and hexanes (1:1, Rf 0.2) gave 0.15 g (0.37 mmol, 70%) of **90** as a white solid; mp 95−96 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 7.55 (d, J = 2.4 Hz, 1H), 7.40 (dd, J = 8.5, 2.4 Hz, 1H), 7.22−7.09 (m, 1H), 7.05−6.87 (m, 2H), 4.81 (s, 2H), 4.12−3.99 (m, 2H), 3.98−3.84 (m, 6H), 2.97−2.81 (m, 2H), 1.81−1.64 (m, 1H), 0.95−0.84 (m, 2H), 0.77−0.63 (m, 2H). ^{13}C NMR (110 °C, 101 MHz, $C_2D_2Cl_4$) δ = 172.4, 159.2, 155.2, 143.4, 139.4, 134.2, 128.9, 126.3, 124.7, 123.7, 121.7, 113.4, 109.8, 56.9, 56.7, 52.9, 50.6, 34.3, 12.0, 7.3. MS (EI+): m/z calcd for ($C_{21}H_{22}{}^{35}ClNO_3S$) 403.1009, found 403.0998.

*4-(tert-Butyl) 9-Methyl 7-Bromo-2,3-dihydro-1,4-benzoxazepine-4,9(5H)-dicarboxylate (**91**).* To a solution of 2.0 g (7.6 mmol) of triphenylphosphine in 50 mL of anhydrous THF was added 1.5 mL (7.6 mmol) of DIAD at 0 °C under N_2. After 20 min, a solution of 2.0 g (5.0 mmol) of **110** in 80 mL of anhydrous THF was added and the mixture was stirred overnight. After concentration in vacuo, FCC with EtOAc and hexanes (1:4, Rf 0.3) gave 1.7 g (4.3 mmol, 85%) of **114** as a white solid; mp 89−90 °C. ^{1}H NMR (70 °C, 400 MHz, DMSO-d_6) δ = 7.65 (d, J = 2.6 Hz, 1H), 7.60 (d, J = 2.6 Hz, 1H), 4.44 (s, 2H), 4.09−4.03 (m, 2H), 3.82 (s, 3H), 3.78−3.71 (m, 2H), 1.35 (s, 9H). ^{13}C NMR (70 °C, 101 MHz, DMSO-d_6) δ = 164.5, 156.5, 153.8, 135.5, 134.9, 130.6, 126.6, 113.8, 79.2, 71.9, 51.9, 48.8, 48.4, 27.6. MS (EI+): m/z calcd for ($C_{16}H_{20}{}^{79}BrNO_5$) 385.0525, found 385.0503.

*Methyl 7-(3,5-Dimethoxyphenyl)-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxylate (**92**).* Standard protocol 2 with 1.0 g (2.9 mmol) of **115** and 1.1 g (6.0 mmol) of 3,5-dimethoxyphenylboronic acid. FCC with EtOAc and hexanes (2:1, Rf 0.3) gave 0.84 g (2.1 mmol, 72%) of **92** as a colorless oil. ^{1}H NMR (100 °C, 400 MHz, DMSO-d_6) δ = 7.84−7.66 (m, 2H), 6.76 (d, J = 2.2 Hz, 2H),

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6.53 (t, J = 2.2 Hz, 1H), 4.71 (s, 2H), 4.20−4.13 (m, 2H), 3.95−3.86 (m, 2H), 3.86−3.79 (m, 9H), 2.38 (q, J = 7.3 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, DMSO-d_6) δ = 172.4, 172.0, 166.32, 166.30, 160.9, 156.9, 156.7, 140.7, 140.6, 134.8, 134.7, 133.3, 132.7, 131.7, 130.8, 126.9, 126.7, 125.5, 125.2, 104.9, 104.6, 99.6, 99.4, 72.5, 71.7, 55.3, 52.21, 52.19, 50.0, 49.3, 47.3, 25.8, 25.7, 9.3, 9.2. MS (EI+): m/z calcd for ($C_{22}H_{25}NO_6$) 399.1682, found 399.1662.

*Methyl 7-(3,4-Dimethoxyphenyl)-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxylate (**93**).* Standard protocol 2 with 0.30 g (0.88 mmol) of **115** and 0.32 g (1.8 mmol) of 3,4-dimethoxyphenylboronic acid. FCC with EtOAc and hexanes (3:1, Rf 0.3) gave 0.28 g (0.70 mmol, 80%) of **93** as a white solid; mp 107−108 °C. ^{1}H NMR (RT, mixture of rotamers, 400 MHz, $CDCl_3$) δ = 7.83 (d, J = 2.5 Hz, 0.5H), 7.81 (d, J = 2.5 Hz, 0.5H), 7.72 (d, J = 2.5 Hz, 0.5H), 7.49 (d, J = 2.5 Hz, 0.5H), 7.19−7.00 (m, 2H), 7.00−6.86 (m, 1H), 4.71 (s, 1H), 4.61 (s, 1H), 4.23−4.14 (m, 2H), 4.09−4.03 (m, 1H), 3.98−3.87 (m, 10H), 2.46 (q, J = 7.4 Hz, 1H), 2.32 (q, J = 7.4 Hz, 1H), 1.18−1.08 (m, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $CDCl_3$) δ = 172.9, 172.4, 166.72, 166.70, 157.5, 157.4, 149.3, 149.2, 149.0, 148.8, 136.64, 136.57, 133.6, 133.2, 132.28, 132.25, 132.2, 130.5, 128.5, 127.9, 125.8, 124.7, 119.5, 119.4, 111.6, 111.4, 110.3, 110.2, 73.12, 73.06, 56.1, 56.0, 52.4, 52.3, 51.1, 50.9, 48.33, 48.31, 26.8, 26.5, 9.2. MS (EI+): m/z calcd for ($C_{22}H_{25}NO_6$) 399.1682, found 399.1682.

*7-(3,5-Dimethoxyphenyl)-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxylic Acid (**94**).* A solution of 0.30 g (0.75 mmol) of **92** in a mixture of 5 mL of MeOH, 5 mL of THF, and 10 mL of 1 M NaOH was heated to 70 °C for 45 min. Then the mixture was acidified with 2 M HCl and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc with 2% AcOH (Rf 0.5) gave 0.27 g (0.70 mmol, 93%) of **94** as a colorless oil. ^{1}H NMR (90 °C, 400 MHz, DMSO-d_6) δ = 7.80−7.68 (m, 2H), 6.76 (d, J = 2.2 Hz, 2H), 6.52 (t, J = 2.2 Hz, 1H), 4.70 (s, 2H), 4.24−4.12 (m, 2H), 3.96−3.87 (m, 2H), 3.83 (s, 6H), 2.44−2.32 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, DMSO-d_6) δ = 172.9, 172.4, 168.0, 161.4, 157.2, 157.0, 141.4, 141.2, 135.2, 135.1, 133.7, 133.1, 131.6, 130.7, 127.5, 127.2, 127.1, 127.0, 105.3, 105.0, 100.1, 99.9, 72.9, 72.2, 55.8, 50.5, 49.8, 47.9, 26.2, 9.7, 9.6. MS (EI+): m/z calcd for ($C_{21}H_{23}NO_6$) 385.1525, found 385.1519.

*7-(3,4-Dimethoxyphenyl)-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxylic Acid (**95**).* A solution of 0.30 g (0.75 mmol) of **93** in a mixture of 5 mL of MeOH, 5 mL of THF, and 10 mL of 1 M NaOH was heated to 70 °C for 45 min. Then the mixture was acidified with 2 M HCl and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc with 2% AcOH (Rf 0.5) gave 0.25 g (0.65 mmol, 87%) of **95** as a white solid; mp 97−98 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 8.16 (d, J = 2.5 Hz, 1H), 7.72−7.55 (m, 1H), 7.18−7.04 (m, 2H), 6.93 (d, J = 8.3 Hz, 1H), 4.68 (s, 2H), 4.39−4.25 (m, 2H), 4.02−3.93 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 2.36 (q, J = 7.4 Hz, 2H), 1.12 (t, J = 7.4 Hz, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $C_2D_2Cl_4$) δ = 173.0, 172.7, 165.2, 165.1, 156.8, 149.4, 149.2, 137.9, 137.7, 134.1, 132.7, 132.0, 131.6, 131.4, 131.3, 130.5, 129.8, 121.8, 121.0, 119.7, 111.9, 111.8, 110.5, 110.3, 74.6, 56.3, 56.1, 50.7, 50.0, 47.9, 47.4, 26.8, 26.6, 9.32, 9.28. MS (EI+): m/z calcd for ($C_{21}H_{23}NO_6$) 385.1525, found 385.1518.

*7-(3,5-Dimethoxyphenyl)-N-[2-(piperidin-1-yl)ethyl]-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxamide (**96**).* Standard protocol 3 with 0.11 g (0.29 mmol) of **94** and 0.050 mL (0.35 mmol) of 1-(2-aminoethyl)piperidine. FCC with CH_2Cl_2 with 0.6% MeOH and 3% triethylamine (Rf 0.3) gave 0.055 g (0.11 mmol, 31%) of **96** as a white solid; mp 88−89 °C. ^{1}H NMR (RT, mixture of rotamers, 400 MHz, $CDCl_3$) δ = 8.57−8.26 (m, 2H), 7.71 (d, J = 2.5 Hz, 0.3H), 7.49 (d, J = 2.5 Hz, 0.7H), 6.77−6.67 (m, 2H), 6.53−6.39 (m, 1H), 4.73 (s, 0.7H), 4.63 (s, 1.3H), 4.30−4.22 (m, 2H), 4.15−4.06 (m, 1.3H), 3.96−3.91 (m, 0.7H), 3.87−3.82 (m, 6H), 3.63−3.55 (m, 2H), 2.61−2.29 (m, 8H), 1.63−1.46 (m, 6H), 1.16−1.10 (m, 3H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, $CDCl_3$) δ = 173.0, 172.3, 164.8, 164.4, 161.2, 161.0, 157.1, 156.9, 141.7, 141.6, 137.1, 136.9, 132.2, 131.7, 130.6, 130.0, 129.2, 126.0, 125.4, 105.3, 105.1, 100.0, 99.5, 73.3, 73.2, 57.3, 57.2, 55.5, 54.3, 51.0, 50.4, 48.1, 47.7, 36.62, 36.56, 26.8, 26.5, 26.1, 24.4, 9.21, 9.18. MS (EI+): m/z calcd for ($C_{28}H_{37}N_3O_5$) 495.2733, found 495.2734.

*1-{2-[7-(3,4-Dimethoxyphenyl)-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxamido]ethyl}piperidin-1-ium Chloride (**97**).* Standard protocol 3 with 0.090 g (0.23 mmol) of **95** and 0.033 mL (0.27 mmol) of 1-(2-aminoethyl)piperidine. FCC with CH_2Cl_2 with 10% MeOH (Rf 0.46) gave a colorless oil. **92** was then precipitated from a solution in 1,4-dioxane as hydrochloride by addition of 4 N solution of HCl in 1,4-dioxane. The precipitate was washed with diethyl ether to obtain 0.043 g (0.10 mmol, 43%) of **97** as a white solid; mp 98−99 °C. ^{1}H NMR (110 °C, 400 MHz, $C_2D_2Cl_4$) δ = 12.45 (br s, 1H), 8.56 (br s, 1H), 8.30−8.00 (m, 1H), 7.69−7.39 (m, 1H), 7.19−7.01 (m, 2H), 6.91 (d, J = 8.7 Hz, 1H), 4.67 (s, 2H), 4.58−4.31 (m, 2H), 4.16−3.80 (m, 10H), 3.66−3.32 (m, 2H), 3.29−3.11 (m, 2H), 2.98−2.48 (m, 2H), 2.45−2.04 (m, 4H), 1.90−1.44 (m, 4H), 1.10 (t, J = 7.0 Hz, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $C_2D_2Cl_4$) δ = 172.9, 172.6, 165.8, 165.7, 156.5, 149.04, 148.95, 148.8, 148.6, 136.4, 136.1, 132.2, 131.9, 131.8, 131.4, 131.3, 130.8, 129.0, 128.4, 124.9, 123.9, 119.3, 111.54, 111.50, 110.3, 110.1, 73.2, 73.0, 57.5, 57.3, 56.1, 55.9, 54.9, 54.9, 50.6, 50.0, 47.6, 47.5, 35.6, 35.5, 26.7, 26.4, 22.5, 21.7, 9.2, 9.1. MS (ESI+): m/z calcd for [($C_{28}H_{38}N_3O_5$)$^+$] 496.2811, found 496.2804.

*N-[2-(Diethylamino)ethyl]-7-(3,5-dimethoxyphenyl)-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxamide (**98**).* Standard protocol 3 with 0.050 g (0.13 mmol) of **94** and 0.028 mL (0.20 mmol) of *N*,*N*-diethylethylenediamine. FCC with CH_2Cl_2 with 0.6% MeOH and 3% triethylamine (Rf 0.3) gave 0.029 g (0.060 mmol, 46%) of **98** as a colorless oil. ^{1}H NMR (RT, mixture of rotamers, 400 MHz, $CDCl_3$) δ = 8.50 (s, 0.6H), 8.40 (s, 0.4H), 8.37 (d, J = 2.5 Hz, 0.6H), 8.29 (d, J = 2.5 Hz, 0.4H), 7.70 (d, J = 2.5 Hz, 0.4H), 7.49 (d, J = 2.5 Hz, 0.6H), 6.76−6.70 (m, 2H), 6.50−6.43 (m, 1H), 4.73 (s, 0.6H), 4.62 (s, 1.4H), 4.29−4.19 (m, 2H), 4.11−4.05 (m, 1.4H), 3.95−3.89 (m, 0.6H), 3.88−3.81 (m, 6H), 3.61−3.52 (m, 2H), 2.76−2.57 (m, 6H), 2.47 (q, J = 7.4 Hz, 1.4H), 2.33 (q, J = 7.4 Hz, 0.6H), 1.17−1.03 (m, 9H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $CDCl_3$) δ = 173.0, 172.3, 164.9, 164.5, 161.2, 161.1, 157.1, 156.9, 141.7, 141.6, 137.0, 136.9, 132.2, 132.1, 131.7, 130.6, 130.0, 129.2, 126.1, 125.4, 105.3, 105.1, 100.0, 99.6, 73.3, 73.1, 55.5, 51.5, 51.4, 51.0, 50.4, 48.1, 47.7, 46.8, 46.6, 37.5, 37.4, 26.8, 26.5, 11.7, 9.2. MS (EI+): m/z calcd for ($C_{27}H_{37}N_3O_5$) 483.2733, found 483.2720.

*7-(3,5-Dimethoxyphenyl)-N-[2-(dimethylamino)ethyl]-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxamide (**99**).* Standard protocol 3 with 0.11 g (0.29 mmol) of **94** and 0.039 mL (0.35 mmol) of *N*,*N*-dimethylethylenediamine. FCC with CH_2Cl_2 with 1% MeOH and 1% triethylamine (Rf 0.3) gave 0.09 g (0.20 mmol, 69%) of **99** as a colorless oil. ^{1}H NMR (RT, mixture of rotamers, 400 MHz, $CDCl_3$) δ = 8.53−8.46 (m, 0.7H), 8.40−8.34 (m, 1H), 8.28 (d, J = 2.5 Hz, 0.3H), 7.71 (d, J = 2.5 Hz, 0.3H), 7.49 (d, J = 2.5 Hz, 0.7H), 6.77−6.69 (m, 2H), 6.50−6.43 (m, 1H), 4.72 (s, 0.6H), 4.62 (s, 1.4H), 4.23−4.17 (m, 2H), 4.12−4.06 (m, 1.4H), 3.96−3.91 (m, 0.6H), 3.87−3.83 (m, 6H), 3.61−3.52 (m, 2H), 2.55−2.50 (m, 2H), 2.46 (q, J = 7.4 Hz, 1.4H), 2.34−2.27 (m, 6.6H), 1.16−1.10 (m, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $CDCl_3$) δ = 173.0, 172.2, 164.8, 164.5, 161.2, 161.0, 157.0, 156.8, 141.7, 141.6, 137.2, 137.0, 132.4, 132.2, 131.9, 130.6, 129.9, 129.2, 126.2, 125.5, 105.3, 105.2, 100.0, 99.6, 73.3, 73.2, 57.8, 57.7, 55.5, 51.1, 50.5, 48.2, 47.8, 45.23, 45.19, 37.3, 26.8, 26.5, 9.2. MS (EI+): m/z calcd for ($C_{25}H_{33}N_3O_5$) 455.2420, found 455.2426.

*(S)-7-(3,5-Dimethoxyphenyl)-N-(piperidin-3-yl)-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxamide (**100**).* Standard protocol 3 with 0.75 g (2.0 mmol) of **94** and 0.50 g (2.5 mmol) of (*S*)-(+)-3-amino-1-Boc-piperidine. FCC with EtOAc and hexanes (5:1, Rf 0.2) gave a white solid, which was dissolved in 3 mL of 1,4-dioxane. Then 3 mL of a 4 N solution of HCl in 1,4-dioxane was added and the mixture stirred overnight. Then 1 M NaOH was added and the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$. After concentration in vacuo,

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purification by FCC with CH_2Cl_2 with 5% MeOH and 2% triethylamine (Rf 0.2) gave 0.29 g (0.62 mmol, 31%) of **100** as a white solid; mp 91−92 °C; $[\alpha]^{20}_D$ −4.5 (*c* 0.16, MeOH). ^{1}H NMR (RT, mixture of rotamers, 500 MHz, $C_2D_2Cl_4$) δ = 8.40 (br s, 1H), 8.34−8.21 (m, 1H), 7.69 (d, *J* = 2.6 Hz, 0.4H), 7.51 (d, *J* = 2.6 Hz, 0.6H), 6.76−6.70 (m, 2H), 6.50−6.43 (m, 1H), 4.77−4.56 (m, 2H), 4.31−3.87 (m, 5H), 3.87−3.82 (m, 6H), 3.21−3.05 (m, 1H), 2.92−2.69 (m, 3H), 2.46−2.39 (m, 1.2H), 2.32−2.26 (m, 0.8H), 1.91−1.55 (m, 4H), 1.13−1.05 (m, 3H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, $C_2D_2Cl_4$) δ = 172.8, 172.2, 163.7, 163.5, 160.9, 156.8, 156.7, 141.2, 136.5, 132.2, 131.9, 131.8, 130.5, 129.5, 128.8, 125.9, 125.3, 105.2, 104.9, 99.8, 99.4, 73.1, 55.5, 50.9, 50.7, 50.1, 47.9, 47.5, 46.1, 46.0, 45.5, 29.8, 26.6, 26.4, 23.2, 23.1, 9.1. MS (EI+): *m*/*z* calcd for ($C_{26}H_{33}N_3O_5$) 467.2420, found 467.2419.

*(R)-7-(3,5-Dimethoxyphenyl)-N-(piperidin-3-yl)-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxamide (**101**).* Standard protocol 3 with 0.75 g (2.0 mmol) of **94** and 0.50 g (2.5 mmol) of (*R*)-(−)-3-amino-1-Boc-piperidine. FCC with EtOAc and hexanes (5:1, Rf 0.2) gave a white solid, which was dissolved in 3 mL of 1,4-dioxane. Then 3 mL of a 4 N solution of HCl in 1,4-dioxane was added and the mixture stirred overnight. Then 1 M NaOH was added, and the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$. It was concentrated in vacuo, and purification by FCC with CH_2Cl_2 with 5% MeOH and 2% triethylamine (Rf 0.2) gave 0.50 g (1.1 mmol, 55%) of **101** as a white solid; mp 91−92 °C; $[\alpha]^{20}_D$ + 4.4 (*c* 0.16, MeOH). ^{1}H NMR (RT, mixture of rotamers, 500 MHz, $C_2D_2Cl_4$) δ = 8.44 (br s, 0.6H), 8.35 (br s, 0.4H), 8.32 (d, *J* = 2.5 Hz, 0.6H), 8.27 (d, *J* = 2.5 Hz, 0.4H), 7.69 (d, J = 2.5 Hz, 0.4H), 7.51 (d, J = 2.5 Hz, 0.6H), 6.75 (d, *J* = 2.3 Hz, 0.8H), 6.73 (d, *J* = 2.3 Hz, 1.2H), 6.48 (t, *J* = 2.3 Hz, 0.6H), 6.46 (t, *J* = 2.3 Hz, 0.4H), 4.79−4.57 (m, 2H), 4.30−3.89 (m, 5H), 3.87−3.82 (m, 6H), 3.10−3.03 (m, 1H), 2.83−2.67 (m, 3H), 2.47−2.38 (m, 1.2H), 2.35−2.24 (m, 0.8H), 1.91−1.55 (m, 4H), 1.12−1.07 (m, 3H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, $C_2D_2Cl_4$) δ = 172.8, 172.2, 163.7, 163.4, 160.88, 160.85, 156.8, 156.7, 141.2, 136.5, 132.3, 131.9, 131.8, 130.5, 129.5, 128.8, 125.9, 125.3, 105.2, 104.9, 99.8, 99.4, 73.1, 55.5, 50.7, 50.1, 47.9, 47.5, 46.1, 45.7, 45.5, 29.8, 26.6, 26.4, 23.2, 9.2, 9.1. MS (EI+): *m*/*z* calcd for ($C_{26}H_{33}N_3O_5$) 467.2420, found 467.2420.

*(S)-7-(3,5-Dimethoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxamide (**102**).* To a solution of 0.16 g (0.34 mmol) of **100** in 1 mL of acetonitrile, 0.14 mL (1.7 mmol) of a 35% solution of formaldehyde in water, and 34 mg (0.54 mmol) of $NaCNBH_3$ were added. The mixture was stirred for 1 h, then 2 M NaOH was added and the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$. FCC with CH_2Cl_2 with 5% MeOH (Rf 0.2) gave 0.060 g (0.12 mmol, 35%) of **102** as a white solid; mp 75−76 °C; $[\alpha]^{20}_D$ −1.7 (*c* 0.41, MeOH). ^{1}H NMR (RT, mixture of rotamers, 500 MHz, $CDCl_3$) δ = 8.56 (br s, 0.7H), 8.43 (br s, 0.3H), 8.36 (d, *J* = 2.5 Hz, 0.7H), 8.28 (d, *J* = 2.5 Hz, 0.3H), 7.71 (d, *J* = 2.5 Hz, 0.3H), 7.49 (d, *J* = 2.5 Hz, 0.7H), 6.74 (d, *J* = 2.3 Hz, 0.6H), 6.72 (d, *J* = 2.3 Hz, 1.4H), 6.48 (t, *J* = 2.2 Hz, 0.7H), 6.45 (t, *J* = 2.2 Hz, 0.3H), 4.72 (s, 0.6H), 4.62 (s, 1.4H), 4.34−4.28 (m, 1H), 4.24−4.19 (m, 2H), 4.14−4.08 (m, 1.4H), 3.97−3.91 (m, 0.6H), 3.87−3.83 (m, 6H), 2.65−2.30 (m, 5H), 2.29−2.26 (m, 3H), 2.23−2.13 (m, 1H), 1.78−1.71 (m, 2H), 1.67−1.58 (m, 2H), 1.15−1.11 (m, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $CDCl_3$) δ = 173.0, 172.2, 163.8, 163.4, 161.2, 161.0, 157.0, 156.8, 141.7, 141.6, 137.2, 137.1, 132.5, 132.1, 132.0, 130.5, 129.9, 129.2, 126.4, 125.8, 105.3, 105.2, 100.0, 99.6, 73.3, 60.5, 60.4, 56.0, 55.5, 51.1, 50.5, 48.3, 47.9, 46.7, 45.44, 45.36, 28.5, 28.4, 26.8, 26.5, 22.1, 22.0, 9.20, 9.18. MS (EI+): *m*/*z* calcd for ($C_{27}H_{35}N_3O_5$) 481.2577, found 481.2591.

*(R)-7-(3,5-Dimethoxyphenyl)-N-(1-methylpiperidin-3-yl)-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxamide (**103**).* To a solution of 0.27 g (0.58 mmol) of **101** in 1.7 mL of acetonitrile, 0.23 mL (2.9 mmol) of a 35% solution of formaldehyde in water, and 58 mg (0.92 mmol) of $NaCNBH_3$ was added. The mixture was stirred for 1 h, then 2 M NaOH was added and the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$. FCC with CH_2Cl_2 with 5% MeOH (Rf 0.2) gave 0.10 g (0.21 mmol, 36%) of **103** as a white solid; mp 75−76 °C; $[\alpha]^{20}_D$ + 1.6 (*c* 0.40, MeOH). ^{1}H NMR (RT, mixture of rotamers, 400 MHz, $CDCl_3$) δ = 8.56 (br s, 0.7H), 8.43 (br s, 0.3H), 8.35 (d, *J* = 2.5 Hz, 0.7H), 8.27 (d, *J* = 2.5 Hz, 0.3H), 7.71 (d, *J* = 2.5 Hz, 0.3H), 7.49 (d, *J* = 2.5 Hz, 0.7H), 6.74 (d, *J* = 2.3 Hz, 0.6H), 6.71 (d, *J* = 2.3 Hz, 1.4H), 6.48 (t, *J* = 2.2 Hz, 0.7H), 6.45 (t, *J* = 2.3 Hz, 0.3H), 4.72 (s, 0.6H), 4.62 (s, 1.4H), 4.34−4.28 (m, 1H), 4.25−4.18 (m, 2H), 4.13−4.08 (m, 1.4H), 3.98−3.90 (m, 0.6H), 3.86−3.82 (m, 6H), 2.62−2.30 (m, 5H), 2.28 (s, 3H), 2.23−2.13 (m, 1H), 1.78−1.70 (m, 2H), 1.67−1.57 (m, 2H), 1.16−1.09 (m, 3H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, $CDCl_3$) δ = 173.1, 172.2, 163.8, 163.4, 161.2, 161.1, 157.0, 156.8, 141.6, 141.6, 137.2, 137.1, 132.5, 132.1, 132.0, 130.5, 129.9, 129.2, 126.4, 125.8, 105.3, 105.2, 100.0, 99.6, 73.3, 60.4, 56.0, 55.5, 51.1, 50.5, 48.3, 47.9, 46.7, 45.5, 45.4, 28.4, 26.8, 26.5, 22.1, 9.2. MS (ESI+): *m*/*z* calcd for [($C_{27}H_{36}N_3O_5$)$^+$] 482.2649, found 482.2650.

*4-Bromo-2-{[(2-hydroxyethyl)amino]methyl}-6-methoxyphenol (**104**).* To a solution of 9.9 g (43 mmol) of 5-bromo-3-methoxysalicylaldehyde in 200 mL of THF and 20 mL of MeOH, 3.3 g (54 mmol) of 2-aminoethanol were added, and the mixture was stirred for 25 min. Over 1.5 h, three equal portions of 1.5 g (40 mmol) of $NaBH_4$ were added and the mixture stirred overnight. The solvent was evaporated under reduced pressure and the residue dissolved in EtOAc. Upon addition of 200 mL of water, the product partially precipitated as white solid and was collected by filtration. The EtOAc/water mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC of precipitate and concentrate of organic phases with EtOAc and MeOH (4:1, Rf 0.3) gave 11 g (40 mmol, 93%) of **104** as a white solid; mp 153−154 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.96 (d, *J* = 2.2 Hz, 1H), 6.88 (d, *J* = 2.2 Hz, 1H), 3.80 (s, 2H), 3.75 (s, 3H), 3.46 (t, *J* = 5.7 Hz, 2H), 2.54 (t, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 148.3, 145.9, 126.3, 122.7, 113.5, 108.8, 59.7, 55.8, 50.2, 49.5. MS (EI+): *m*/*z* calcd for ($C_{10}H_{14}{}^{79}BrNO_3$) 275.0157, found 275.0157.

*tert-Butyl (5-Bromo-2-hydroxy-3-methoxybenzyl)(2-hydroxyethyl)carbamate (**105**).* To a suspension of 11 g (40 mmol) of **104** in 100 mL of EtOAc and 58 mL of saturated $NaHCO_3$ solution, 12 g (53 mmol) of di-*tert*-butyl dicarbonate were added, and the mixture was stirred overnight. The suspension turned into a clear two-phase system, and the organic layer was separated. The aqueous phase was extracted three times with EtOAc, and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (3:2, Rf 0.5) gave 11 g (28 mmol, 69%) of **105** as a white solid; mp 95−96 °C. ^{1}H NMR (70 °C, 400 MHz, DMSO-d_6) δ = 8.75 (s, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 4.53−4.32 (m, 3H), 3.81 (s, 3H), 3.53−3.43 (m, 2H), 3.32−3.19 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (70 °C, 101 MHz, DMSO-d_6) δ = 154.9, 148.3, 143.3, 127.1, 122.3, 113.5, 109.4, 78.6, 58.9, 56.1, 49.0, 45.2, 27.7. MS (EI+): *m*/*z* calcd for ($C_{15}H_{22}{}^{79}BrNO_5$) 375.0681, found 375.0685.

*tert-Butyl 7-Bromo-9-methoxy-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (**106**).* To a solution of 9.7 g (26 mmol) of **105** and 11 g (42 mmol) of triphenylphosphine in 260 mL of CH_2Cl_2, 8.7 mL of (40 mmol) DIAD were added, and the mixture was stirred overnight. Water was added, and the mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:4, Rf 0.3) gave 8.6 g (24 mmol, 91%) of **106** as a white solid; mp 96−97 °C. ^{1}H NMR (70 °C, 400 MHz, DMSO-d_6) δ = 7.09 (d, *J* = 2.3 Hz, 1H), 6.98 (d, *J* = 2.3 Hz, 1H), 4.38 (s, 2H), 4.05−3.93 (m, 2H), 3.78 (s, 3H), 3.74−3.67 (m, 2H), 1.35 (s, 9H). ^{13}C NMR (70 °C, 101 MHz, DMSO-d_6) δ = 154.6, 152.8, 148.2, 134.9, 124.4, 116.0, 114.7, 79.8, 72.3, 56.9, 49.9, 49.3, 28.5. MS (EI+): *m*/*z* calcd for ($C_{15}H_{20}{}^{79}BrNO_4$) 357.0576, found 357.0575.

*7-Bromo-9-methoxy-2,3,4,5-tetrahydro-1,4-benzoxazepine (**107**).* To a suspension of 10 g (28 mmol) of **106** in 120 mL of MeOH was added a mixture of 80 mL of 36% HCl and 120 mL of 1,4-dioxane. The mixture was refluxed for 2 h and then concentrated in vacuo. Saturated Na_2CO_3 solution was carefully added, and the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were

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dried over $MgSO_4$ and concentrated in vacuo to give 6.7 g (26 mmol, 94%) of **107** as a white solid; mp 119−120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.05 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 3.93−3.83 (m, 2H), 3.81−3.70 (m, 5H), 3.06−2.94 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 153.1, 149.0, 140.0, 124.1, 115.1, 115.1, 75.8, 56.9, 52.9, 52.8. MS (EI+): m/z calcd for ($C_{10}H_{12}{}^{79}BrNO_2$) 257.0051, found 257.0052.

*5-Bromo-2-mercapto-3-methoxybenzoic Acid (**108**).* A suspension of 9.6 g (30 mmol) of 4-bromo-2-carboxy-6-methoxybenzenaminium bromide,[25] 2.4 g (60 mmol) NaOH, and 2.1 g (30 mmol) of $NaNO_2$ in 60 mL of water was added over 0.5 h to a mixture of 20 mL of conc HCl with ice, and the temperature was kept at 0 °C by the addition of ice. After 0.5 h at 0 °C, potassium acetate was used to adjust to neutral pH. The resulting yellow solution was added to a stirred solution of 23 g (140 mmol) of potassium ethyl xanthate in 40 mL of water at 90 °C. After 0.5 h at 90 °C, the solution was cooled to 0 °C. Concentrated HCl was added until acidic pH. The resulting precipitate was collected by filtration and dissolved in 100 mL of 10% NaOH. The solution was heated to 85 °C for 2 h. Then 3.1 g (30 mmol) of $NaHSO_3$ were added and 85 °C was maintained for 0.25 h. The solution was filtered, cooled to 0 °C, and acidified with conc HCl. The precipitate was separated by filtration and dissolved in a mixture of EtOAc and THF (1:1). This organic layer was washed with saturated NaCl solution twice, dried over $MgSO_4$, and concentrated in vacuo. Purification by FCC with CH_2Cl_2 with 4% EtOH and 5% AcOH (Rf 0.2) gave 4.9 g (19 mmol, 62%) of **108** as a white solid; mp 208−209 °C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.90 (d, J = 2.0 Hz), 7.20 (d, J = 2.0 Hz), 5.28 (br s, 1H), 3.96 (s, 3 H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ = 169.2, 155.3, 129.0, 127.1, 127.0, 118.0, 117.3, 57.4 MS (EI+): m/z calcd for ($C_8H_5O_2{}^{79}BrS$) 243.9193, found 243.9195.

*Methyl 5-Bromo-2-mercapto-3-methoxybenzoate (**109**).* A solution of 3.0 g (12 mmol) of **108** in 25 mL of anhydrous MeOH and 1.0 mL of 96% sulfuric acid was refluxed under N_2 for 12 h and then concentrated in vacuo. Ice was added, and the mixture was extracted with EtOAc three times. After drying over $MgSO_4$ and concentration in vacuo, FCC with hexanes and EtOAc (9:1, Rf 0.4) gave 2.3 g (8.6 mmol, 72%) of **109** as a yellow solid; mp 60−61 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.69−7.65 (m, 1H), 7.45−7.42 (m, 1H), 5.42−5.39 (m, 1H), 3.95 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 165.2, 154.8, 127.7, 126.3, 125.1, 117.3, 116.7, 57.3, 52.6. MS (EI+): m/z calcd for ($C_9H_9O_3{}^{79}BrS$) 275.9456, found 275.9452.

*7-Bromo-9-methoxy-3,4-dihydro-1,4-benzothiazepin-5(2H)-one (**110**).* To a solution of 2.3 g (8.3 mmol) of **109** and 1.0 g (9.0 mmol) of 2-chloroethylamine hydrochloride in 17 mL of anhydrous DMF at 0 °C under N_2, 1.0 g (19 mmol) of NaOMe was added and the mixture stirred for 12 h. Water was added, the pH adjusted with 2 M NaOH to 12, and the mixture extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in 60 mL of anhydrous THF and cooled to 0 °C. Then 7.2 g (64 mmol) of *t*-BuOK was added and the mixture stirred at 45 °C for 1 h. Saturated ammonium chloride solution was added and the mixture extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with CH_2Cl_2 with 4% MeOH (Rf 0.3) gave 1.5 g (5.2 mmol, 63%) of **110** as a yellow solid; mp 185−186 °C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.33 (d, J = 2.0 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.02 (br s, 1H), 3.87 (s, 3H), 3.32−3.26 (m, 2H), 3.10−3.05 (m, 2H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ = 170.9, 160.3, 144.1, 124.4, 123.7, 117.1, 116.9, 57.0, 40.2, 37.4. MS (ESI+): m/z calcd for [($C_{10}H_{11}{}^{79}BrNO_2S$)$^+$] 287.9694, found 287.9688.

*1-(7-Bromo-9-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)propan-1-one (**111**) and 1-(7-Bromo-9-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)-1-(cyclopropyl)methanone (**112**).* A solution of 1.3 g (4.5 mmol) of **110** in 16 mL of anhydrous THF and cooled to −30 °C under N_2. Then 45 mL of 1 M BH_3-THF solution (45 mmol) was added and the mixture refluxed for 40 h. A mixture of 15 mL of MeOH, 15 mL of conc HCl, and 30 mL of water was added at RT, and the mixture was refluxed for 1 h. pH was adjusted to 12 with K_2CO_3, and the mixure was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. A short FCC with CH_2Cl_2 with 5% MeOH and 2% triethylamine gave the secondary amine as crude intermediate. The standard protocol for the *N*-acylation was applied to equal portions of this intermediate with propionyl chloride to obtain **111** or with cyclopropanecarbonyl chloride to obtain **112**.

*1-(7-Bromo-9-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)propan-1-one (**111**).* FCC with EtOAc and hexanes (1:3, Rf 0.2) gave 0.36 g (1.1 mmol, 49%) of **111** as a white solid; mp 118−119 °C. ^{1}H NMR (100 °C, 400 MHz, DMSO-d_6) δ = 7.20 (d, J = 2.1 Hz, 1H), 7.08 (d, J = 2.1 Hz, 1H), 4.62 (s, 2H), 3.93−3.86 (m, 2H), 3.82 (s, 3H), 2.98−2.91 (m, 2H), 2.30 (q, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, DMSO-d_6) δ = 172.8, 171.9, 158.5, 158.2, 144.3, 142.6, 125.8, 124.6, 124.0, 123.7, 119.9, 119.6, 113.4, 113.0, 56.4, 50.9, 50.6, 50.3, 47.9, 33.6, 31.7, 25.8, 25.6, 9.2, 9.1. MS (ESI+): m/z calcd for [($C_{13}H_{17}{}^{79}BrNO_2S$)$^+$] 330.0163, found 330.0158.

*1-(7-Bromo-9-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)-yl)-1-(cyclopropyl)methanone (**112**).* FCC with EtOAc and hexanes (1:3, Rf 0.2) gave 0.34 g (1.0 mmol, 45%) of **112** as a white solid; mp 87−88 °C. ^{1}H NMR (100 °C, 400 MHz, DMSO-d_6) δ = 7.34−7.19 (m, 1H), 7.08 (d, J = 2.0 Hz, 1H), 4.73 (s, 2H), 4.11−3.93 (m, 2H), 3.83 (s, 3H), 2.96−2.90 (m, 2H), 1.95−1.85 (m, 1H), 0.73−0.66 (m, 4H). ^{13}C NMR (RT, mixture of rotamers, 101 MHz, DMSO-d_6) δ = 173.1, 172.0, 158.9, 158.8, 144.7, 144.0, 126.2, 125.1, 124.4, 124.0, 120.35, 120.33, 113.9, 113.5, 56.94, 56.91, 51.6, 51.4, 51.1, 49.0, 34.3, 32.4, 11.7, 11.1, 8.0, 7.5. MS (ESI+): m/z calcd for [($C_{14}H_{17}{}^{79}BrNO_2S$)$^+$] 342.0163, found 342.0157.

*Methyl 5-Bromo-2-hydroxy-3-{[(2-hydroxyethyl)amino]methyl}-benzoate (**113**).* To a solution of 1.7 g (6.5 mmol) of methyl 5-bromo-3-formyl-2-hydroxybenzoate[29] in a mixture of 4 mL of MeOH and 36 mL of anhydrous THF, 0.48 mL of (8.1 mmol) 2-aminoethanol was added. The solution was stirred for 0.5 h, and then 0.22 g (5.8 mmol) of $NaBH_4$ was added in portions over 15 min. After 1 h of stirring, the solution was concentrated and water and EtOAc were added. The product partially precipitated as white solid, the remaining product was extracted from the water phase at alkaline pH with EtOAc. After drying over $MgSO_4$ and evaporation of the solvent, 1.8 g (6.0 mmol, 93%) of **113** were obtained; mp 150−151 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.69 (d, J = 2.7 Hz, 1H), 7.57 (d, J = 2.7 Hz, 1H), 3.86−3.80 (m, 5H), 3.49 (t, J = 5.7 Hz, 2H), 2.61 (t, J = 5.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 167.3, 159.1, 135.7, 130.6, 129.8, 116.1, 108.3, 59.7, 52.4, 50.4, 48.3. MS (EI+): m/z calcd for ($C_{11}H_{14}{}^{79}BrNO_4$) 303.0106, found 303.0095.

*Methyl 5-Bromo-3-{[(tert-butoxycarbonyl)(2-hydroxyethyl)-amino]methyl}-2-hydroxybenzoate (**114**).* To a dispersion of 2.8 g (9.2 mmol) of **113** in a mixture of 100 mL of EtOAc and 60 mL of saturated $NaHCO_3$ solution, 2.8 g (13 mmol) of di-*tert*-butyl dicarbonate was added and the mixture was stirred for 12 h. The organic layer was separated and the aqueous phase extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:2, Rf 0.5) gave 2.1 g (5.2 mmol, 56%) of **114** as a colorless oil. ^{1}H NMR (70 °C, 400 MHz, DMSO-d_6) δ = 7.81 (d, J = 2.6 Hz, 1H), 7.45 (d, J = 2.6 Hz, 1H), 4.44 (s, 2H), 3.94 (s, 3H), 3.51 (t, J = 6.1 Hz, 2H), 3.31 (t, J = 6.1 Hz, 2H), 3.10 (br s, 1H), 1.38 (s, 9H). ^{13}C NMR (70 °C, 101 MHz, DMSO-d_6) δ = 168.2, 156.8, 154.7, 135.7, 129.9, 129.7, 114.0, 109.6, 78.7, 59.0, 52.5, 49.5, 45.3, 27.7. MS (EI+): m/z calcd for ($C_{16}H_{22}{}^{79}BrNO_6$) 403.0630, found 403.0637.

*Methyl 7-Bromo-4-propionyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-9-carboxylate (**115**).* To a solution of 0.89 g (2.3 mmol) of **91** in 5 mL of 1,4-dioxane, 10 mL of a 4 M solution of HCl in 1,4-dioxane was added. After 5 h, the supernatant was removed and the white precipitate washed with diethyl ether. The solid was dissolved in 10 mL of CH_2Cl_2 and cooled to 0 °C. Then 1.6 mL of (9.2 mmol) of DIPEA and 0.40 mL (4.6 mmol) of propionyl chloride were added. The mixture was warmed to RT and stirred for 12 h. $NaHCO_3$ solution was added and the mixture extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. FCC with EtOAc and hexanes (1:1, Rf 0.3)

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gave 0.58 g (1.7 mmol, 74%) of **91** as a white solid; mp 112−113 °C. ^{1}H NMR (100 °C, 400 MHz, DMSO-d_6) δ = 7.80−7.57 (m, 2H), 4.62 (s, 2H), 4.17−4.11 (m, 2H), 3.90−3.86 (m, 2H), 3.83 (s, 3H), 2.34 (q, J = 7.4 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (RT, mixture of rotamers, 126 MHz, CD_2Cl_2) δ = 172.4, 172.1, 164.9, 156.8, 156.6, 135.7, 135.6, 134.9, 134.7, 131.2, 130.9, 126.8, 126.6, 114.3, 114.2, 72.7, 71.8, 52.42, 52.40, 49.9, 48.5, 47.1, 46.8, 25.70, 25.68, 9.2, 9.1. MS (EI+): m/z calcd for ($C_{14}H_{16}{}^{79}BrNO_4$) 341.0263, found 341.0260.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.6b00774.

NMR spectra, PX table, DSF data, and ITC determinations (PDF)

Molecular formula strings (CSV)

Accession Codes

102 with CBP: 5J0D. The authors will release the atomic coordinates and experimental data upon article publication.

■ AUTHOR INFORMATION

Corresponding Authors

*For F.B.: phone, +49 89 218077301; fax, +49-89-218077803; E-mail, franz.bracher@cup.uni-muenchen.de.

*For S.K.: phone, +44 1865 612933; E-mail, Stefan.Knapp@sgc.ox.ac.uk.

Author Contributions

Tobias Popp, compound preparation and characterization, writing of paper; Cynthia Tallant, protein production and structure determination; Catherine Rogers, FRAP; Oleg Fedorov, compound screening, supervision; Paul Brennan, supervision of research; Susanne Müller, supervision of research; FRAP, editing of paper and provision of figures; Stefan Knapp, supervision of research, writing/editing of paper; Franz Bracher, supervision of research, writing/editing of paper.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

BET, bromodomain and extraterminal domain; CBP/CREBBP, cAMP responsive element binding protein binding protein; DIAD, diisopropyl azodicarboxylate; DIPEA, *N*,*N*-diisopropyl ethylamine; DSF, differential scanning fluorimetry; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; FRAP, fluorescence recovery after photobleaching; HAT, histone acetyl transferase; ITC, isothermal titration calorimetry; Kac, *N*-acetylated lysine; MOZ, monocytic leukemia zinc-finger; P300, adenovirus E1A-associated 300 kDa protein; T_m, melting point

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