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Exploring the Neuroleptic Substituent in Octoclothepin: Potential Ligands for Positron Emission Tomography with Subnanomolar Affinity for α_1-Adrenoceptors

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A series of 1-(10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-4-methylpiperazine analogues substituted in the 8-position of the 10,11-dihydrodibenzo[*b*,*f*]thiepine scaffold with aryl, heteroaryl, amine, and amide substituents are described. The compounds were designed using the previously reported Liljefors−Bøgesø pharmacophore model for dopamine D_2 and α_1-adrenoceptor antagonists, with the aim of obtaining selective α_1-adrenoceptor antagonists suitable for development as radioligands for imaging of central α_1-adrenoceptors by positron emission tomography. Sixteen aryl and heteroaryl substituted octoclothepin analogues were prepared by a convergent synthesis via coupling of 1-methyl-4-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine with aryl and heteroaryl halides under palladium catalysis. The most selective compound obtained, (*S*)-*N*-((11-(4-methylpiperazin-1-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)methyl)isobutyramide (*S*)-**35**, showed a similar subnanomolar affinity compared to α_{1a}, α_{1b}, and α_{1d}-adrenoceptors and a selectivity ratio of 20, 440, and 20 with respect to D_2, 5-HT_{2C}, and H_1 receptors, respectively.

Introduction

The α_1-adrenoceptors belong to the superfamily of G-protein-coupled receptors and are subdivided into three subtypes α_{1A}, α_{1B}, and α_{1D}. The receptors mediate the response of the endogenous transmitters adrenaline and noradrenaline and are widespread in both the peripheral nervous system and the central nervous system (CNS[a]). In the peripheral nervous system the effects of adrenaline and noradrenaline have been associated with "fight and flight" and result in effects like vasoconstriction, increase in heart rate, and increase in blood sugar levels, all of which may be considered to prepare the organism to survive a threat.[1] The role of α_1-adrenoceptors in the central nervous system is much more complex; noradrenergic nerves innervate almost all areas of the brain, suggesting that noradrenaline and adrenergic receptors may play an important role in central processing[2] and a detailed understanding of the role of α_1-adrenoceptors in relation to CNS-related diseases[3] has only started to emerge.

Interestingly, a common feature of atypical antipsychotic drugs such as clozapine and sertindole (**1**, Table 1) is in vitro nanomolar affinity for α_1-adrenoceptors in addition to high affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors.[4] In man, the receptor occupancy of these drugs at D_2 and 5-HT_{2A} receptors at therapeutic doses is relatively well understood, as positron emission tomography (PET) ligands exist for these receptors.[5] At D_2 receptors, for example, the typical antipsychotics like haloperidol may provide optimal antipsychotic response with little extrapyramidal side effects (EPS) at D_2 receptor occupancies of 60−80%, while EPS will appear at D_2 receptor occupancies above 80%. The various atypical antipsychotic drugs differ with respect to their D_2 receptor occupancy, but in general all atypical antipsychotics display a higher occupancy of the 5-HT_{2A} than D_2 receptors. Thus, the means for measuring D_2 and 5-HT_{2A} receptor occupancies in preclinical models and in man exist and can significantly aid the translation of preclinical data to the clinic and backward.[6] In contrast, the role of the α_1-adrenceptor component in these drugs is still relatively unclear but could most likely be better understood if imaging ligands were available. Several drug augmentation studies have indicated the importance of α_1-adrenoceptor blockade both in relation to antipsychotic efficacy[7] and in relation to the propensity to induce EPS.[8] An important role of the α_1-component in distinguishing typical from atypical antipsychotics is also indicated by the different effects of haloperidol and clozapine in up-regulation of α_1-adrenoceptors in the CNS in rats following chronic treatment; both drugs result in up-regulation of α_1-adrenoceptors in the thalamus, whereas clozapine selectively up-regulates α_1-adrenoceptors in the frontal cortex.[9] Recently Cohen et al. have reviewed the role of α_1-adrenoceptors in relation to antipsychotic drugs and also shown that expression of α_1-adrenoceptors is a common feature for rat neurons responding to antipsychotic drug treatment.[10]

Thorough in vivo investigation of the role of α_1-adrenoceptors in relation to CNS-related disorders has been hampered by the lack of selective and subtype selective tool

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[a]Abbreviations: PET, positron emission tomography; CNS, central nervous system; EPS, extrapyramidal side effects; S-Phos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; PCy_3, tricyclohexylphosphane; SFC, super critical fluid chromatography; dppf, 1,1′-bis(diphenylphosphino)ferrocene; ELSD, evaporative light scattering detection.

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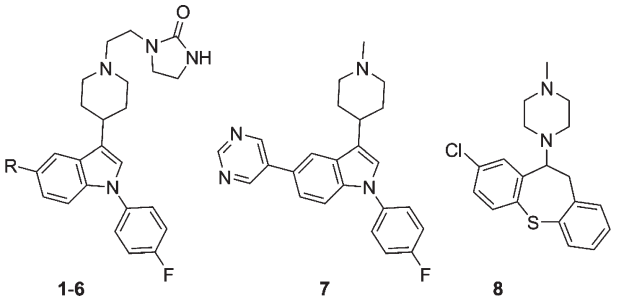
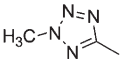
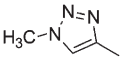
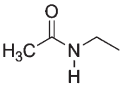
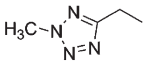
Table 1. Receptor Binding Affinities for Reference Compounds[f]



		K_i (nM)					
No.	**R =**	α_{1a}	α_{1b}	α_{1d}	D_2	**5-HT$_{2A}$**	**5-HT$_{2C}$**
1	Cl	0.37[a]	0.33[a]	0.66[a]	0.45[a]	0.20[a]	0.51[a]
2		0.23[a]	1.1[a]	2.0[a]	140[a]	60[a]	500[a]
3		3.0[b]	6.0[b]	8.6[b]	310[a]	110[a]	1500[a]
4		0.18[c]	1.1[c]	0.69[c]	37[c]	22[c]	64[c]
5		0.68[b]	2.0[b]	2.9[b]	3.1[c]	11[c]	64[c]
6		0.66[b]	0.56[b]	0.77[b]	2.7[c]	NT	NT
7		0.52[d]	1.9[d]	2.5[d]	260[d]	NT	NT
(*R/S*)-8		0.66	0.56	0.77	0.67	0.57[e]	0.19

[a] Reference 11. [b] Reference 27. [c] Reference 12. [d] Reference 15. [e] IC_{50}, ref 17. [f] NT = not tested.

compounds efficiently penetrating the blood−brain barrier. We have previously reported a series of α_1-adrenoceptor antagonists derived from the atypical antipsychotic sertindole (**1**).[11] Replacement of the "neuroleptic" chlorine atom in **1** with heteroaromatic substituents led to a series of compounds (**2** and **3**, Table 1) with significantly reduced affinity for D_2 and 5-HT$_{2A/C}$ receptors, while affinity for α_1-adrenoceptors was significantly less affected (compound **3**) or even intact (compound **2**). Similarly, an aminomethyl substituent in the indole 5-position (**4**) also gave rise to high selectivity.[12] In contrast, replacement of chlorine with more flexible substituents led to unselective compounds, as exemplified by the acetylaminomethyl derivative **5**, and the tetrazolylmethyl derivative **6** (Table 1).[12] On the basis of molecular modeling studies, it was concluded that substituents coplanar with the indole ring favored α_1/D_2 selectivity whereas substituents introducing bulk above or below the plane of the indole ring did not. Carbon-11 labeled analogues of **2** and **3** were investigated as potential PET ligands in cynomolgus monkeys but failed because of lack of brain uptake.[13] Subsequent investigation of the SAR around the piperidinyl substituent has recently led to the identification of the pyrimidyl analogue **7** as a new potential PET ligand (Table 1).[14] [^{11}C]**7** efficiently penetrates into the brain of cynomolgus monkeys, and high uptake of radioactivity is observed in regions known to have high concentrations of α_1-adrenoceptors.[15] However, the binding could not be displaced by prazosin, indicating that the observed in vivo binding was either not α_1-adrenoceptor specific or the dose of prazosin was to low. As part of our continuous effort to develop a PET tracer for imaging of α_1-adrenoceptors in the CNS in man, we turned our attention to the 10,11-dihydrodibenzo[*b*,*f*]thiepine scaffold present in the antipsychotic octoclothepin (**8**, Table 1). Like **1**, **8** exerts in vitro nanomolar affinity for dopamine D_2, serotonin 5-HT$_{2A}$, and adrenergic α_1 adrenoceptors. The uncluttered Liljefors−Bøgesø pharmacophore model for dopamine D_2 receptor antagonists based on superimposition (*S*)-**8** and (1*R*,2*S*)-tefludazine[16,17] provides a solid framework for this investigation; numerous dopamine D_2 receptor antagonists, including indoles, have over the years been included in the model, and it has been shown to be valid also for dopamine D_4,[18] serotonin 5-HT$_{2A}$,[19] and α_1-adrenoceptor antagonists.[11] A study of the enantiomers of **8** has shown that the highest binding affinity for dopamine D_2,[17] D_4,[18] and α_1-receptors[11] resides in the (*S*)-enantiomer. However, the eudismic ratio is consistently low (< 5) and has been shown to correlate with the conformational energy penalty paid by (*R*)-**8** to assume a conformation almost identical to the proposed bioactive conformation of (*S*)-**8**. Superposition of (*S*)-**8** and **1** in their proposed bioactive conformations,[20] as shown in Figure 1, suggests that the neuroleptic chloro substituent of

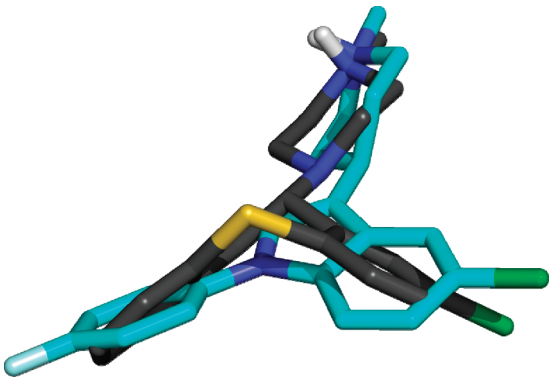


Figure 1. Superimposition of (*S*)-**8** (gray) and **1** (cyan) in their proposed bioactive conformations. The imidazolidinone ethyl side chain of **1** is replaced with a methyl group for clarity. Nonpolar hydrogens have been removed for clarity: carbon, gray/cyan; nitrogen, blue; sulfur, yellow; chlorine, green; fluorine, pale cyan; hydrogen, white.

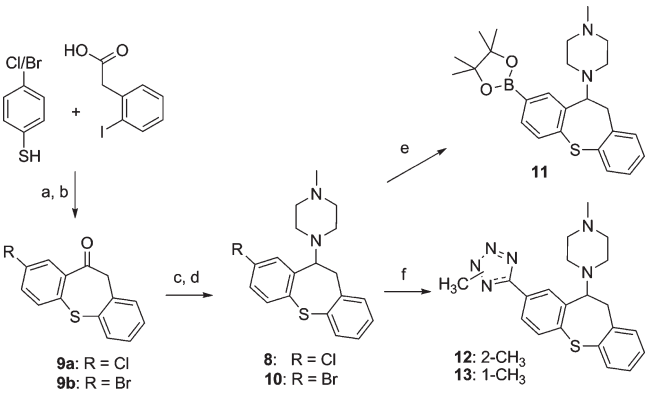
1 and (*S*)-**8** points in the same direction. Since selective α_1-adrenoceptor antagonists could be obtained by replacing the chlorine of **1** with heteroaromatic substituents, it was hypothesized that a similar change in activity could be obtained within this series of compounds upon replacement of the chlorine in **8** with more bulky groups. However, the aromatic rings bearing the neuroleptic substituents are not completely coplanar, as shown in Figure 1. This detail suggests that the structure−activity relationships for the two series of compounds may not turn out to be entirely parallel. With the aim of identifying new tools for imaging of central α_1-adrenoceptors in vivo, we here report the results of a thorough investigation of the effects of introducing bulky substituents in the 8-position of the 10,11-dihydrodibenzo[*b*,*f*]thiepine scaffold.

Chemistry

In order to access the appropriately substituted octoclothepin analogues, it was investigated if **8** could be used directly as a substrate in various palladium (Pd) catalyzed cross-coupling reactions. In particular, the use of **8** as the precursor for the corresponding pinacol boronic ester **11** via coupling with bis(pinacolato)diboron was pursued, as **11** would be suitably poised to be coupled with aryl and heteroaryl halides.[21] Coupling of aryl chloride **8** proved to be difficult, presumably because of the electron-rich nature of the aromatic ring. Therefore, the bromo analogue of octoclothepin **10**, which in theory should enter more readily into Pd-catalyzed reaction, was prepared and tested in parallel (see Scheme 1). Racemic **8** was prepared from *p*-chlorothiophenol and (2-iodophenyl)acetic acid via **9a** in four steps in 67% overall yield.[22] The corresponding bromo analogue **10** was accessed, using a similar approach from *p*-bromothiophenol, in 63% yield over four steps.[23]

Coupling of **8** with bis(pinacolato)diboron to give the pinacol boronic ester **11** required very electron rich alkylphosphines and extended reaction times (Pd_2dba_3/PCy_3, 80 °C, 44 h, 66% isolated yield), whereas **10** reacted much more readily with less sensitive catalysts, within shorter reaction times, and in higher yield ($PdCl_2$(dppf), 100 °C, 18 h, 77% isolated yield). Aryl bromide **10** could also be coupled directly with arylboronic acids using $Pd(PPh_3)_4$ as catalyst (see Table 1, compounds **21** and **23**), but because of the ready availability of a wide selection of aryl and heteroaryl halides, **11** was chosen as the key intermediate for the synthesis of the desired compounds. After a series of different conditions were screened, it was found that a combination of Pd_2dba_3 and S-Phos with K_3PO_4 in THF or dioxane promotes the coupling of **11** with heteroaryl bromides and iodides, giving the desired products (**14**−**20**, **22**) in 48−86% isolated yield. Aryl iodides were the most efficiently coupled using Pd_2dba_3/PCy_3 as catalyst, giving **24**−**29** in 75−88% yield. Fourteen different substituted octoclothepin derivatives were prepared from **11**, in addition to those prepared directly from **8**, giving a total of 16 aryl and heteroaryl substituted octoclothepin derivatives (**14**−**29**) (see Table 2).

Scheme 1[a]



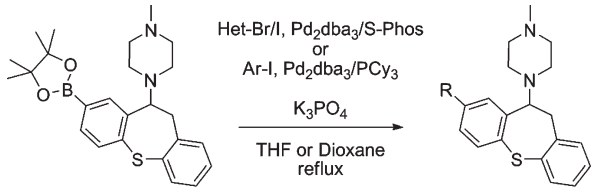
[a] Reagents and conditions: (a) Cu, KOH, H_2O, reflux 24 h. R = Cl: 95%. R = Br: 100%. (b) Polyphosphoric acid, 140 °C, 2 h. R = Cl: 73%. R = Br: 73%. (c) 1-Methylpiperazine, $TiCl_4$, toluene, reflux 24 h. R = Cl: 99%. R = Br: 94%. (d) $NaBH_4$, CH_3CO_2H, room temp, 24 h. R = Cl: 80%. R = Br: 92%. (e) From **8**: bis(pinacolato)diboron, Pd_2dba_3/PCy_3, 80 °C, 44 h, 66%. From **10**: bis(pinacolato)diboron, $PdCl_2$(dppf), 100 °C, 18 h, 77%. (f) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 165 °C, 120 s, microwave, then NaN_3, 165 °C, 30 min, then K_2CO_3, MeI, 200 °C, 40 min. **12**: 26%, **13**: 11%.

The tetrazole derivatives **12** and **13** were prepared in a one-pot procedure from **10**, as shown in Scheme 1, via Pd-catalyzed cyanation with $Zn(CN)_2$ followed by tetrazole formation using NaN_3 and finally methylation with MeI.[24] The isomeric tetrazoles **12** and **13** were separated using silica gel chromatography and isolated in 26% and 11% yield, respectively.

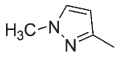
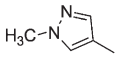
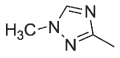
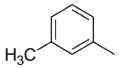
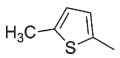
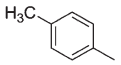
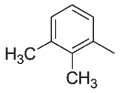
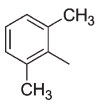
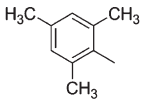
Cyanation of **10** gave the cyano derivative **30** that subsequently was reduced to the aminomethyl derivative **31** using $LiAlH_4$, as shown in Scheme 2. The amides **34**−**36** were obtained via reaction of **31** with the corresponding acid chlorides. The enantiomers of **34** and **35** were separated using chiral supercritical fluid chromatography (SFC), and crystals suitable for X-ray analysis were obtained of both enantiomers of **35**, unveiling the absolute configuration. Unfortunately, we were not able to get crystals of **34** of sufficient quality, and the absolute configuration of the two enantiomeres of **34** is thus tentatively assigned based on order of elution on the chiral SFC column and the pharmalogical data discussed below.

The extended tetrazoles **32** and **33** were accessed as shown in Scheme 2. Coupling of *tert*-butyl cyanoacetate with **10** gave the indicated intermediate in 87% yield.[25] Subsequent tetrazole formation using sodium azide with concomitant decarboxylation gave the crude tetrazole in quantative yield. Methylation of the tetrazole gave a mixture of **32** and **33** which could be separated by silica gel chromatography, albeit in very low yield presumably due to competing quarternization of the piperazine ring. The relative positions of the methyl groups in **32** and **33** were distinguished by their different chemical shifts in the ^{1}H NMR spectra.[26]

Table 2. Synthesis of Aryl- and Heteroaryl Octoclothepin Derivatives



11 **14-20, 22, 24-29**

No.	R=	Yield (%)	No.	R=	Yield (%)
14		67	**22**		86
15		48	**23**[a]		78
16		78	**24**		75
17		66	**25**		76
18		82	**26**		76
19		47	**27**		85
20		78	**28**		88
21[a]		73	**29**		88

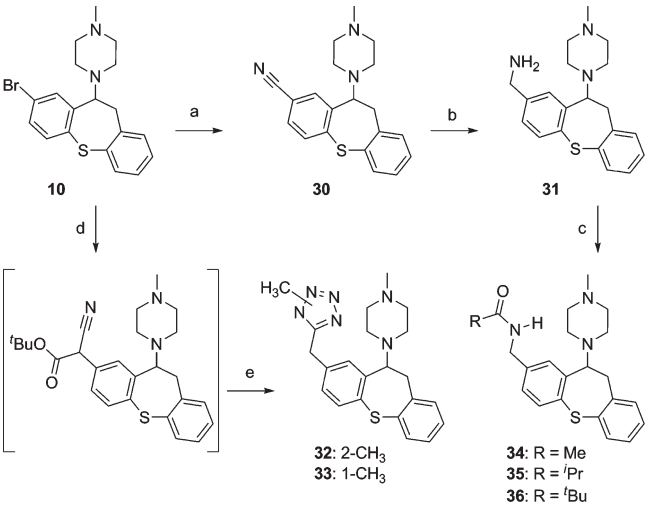
[a] Prepared directly from **10** via coupling with either phenylboronic acid or 4-pyridylboronic acid. See Experimental Section for details.

Results and Discussion

The prepared compounds were characterized in receptor binding assays at cloned bovine α_{1a}, hamster α_{1b}, and rat α_{1d} adrenoceptors by displacement of [^{3}H]prazosin and at cloned human dopamine D_2 receptors using [^{3}H]spiperone as radioligand. The data are compiled in Table 3. The compounds displaying the highest α_1/D_2 selectivity ratio were further tested at serotonin 5-HT_{2C} receptors and histamine H_1 receptors by displacement of [^{3}H]mesulergine and [^{3}H]pyrilamine (Table 4). For compounds **32** and **33** binding at α_1-adrenoceptors in rat cerebral cortex membranes was determined using [^{3}H]prazosin, and to ensure comparability with data on the remaining compounds, analogue **12** was assayed under the same conditions.

In general, compounds with aromatic or heteroaromatic substituents directly attached to the 8-position of the 10,11-dihydrodibenzo[*b*,*f*]thiepine scaffold (**12**−**23**) show increased binding affinity at α_{1a} receptors compared to the reference compound **8**. For most compounds the increase is 2- to 3-fold, whereas compounds **17** and **12** show 7- and 10-fold increased affinity, respectively. A similar trend (2- to 3-fold increase) is observed for α_{1b} receptors, whereas affinities at α_{1d} and D_2 receptors are unchanged or slightly decreased (2- to 8-fold) compared to **8**.

Scheme 2[a]



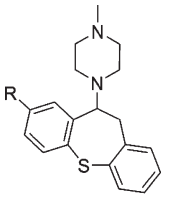
[a] Reagents and conditions: (a) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 140 °C, 20 min, 95%; (b) $LiAlH_4$, THF, room temp, 100%; (c) RCOCl, NEt_3, THF. **34**: 88%. **35**: 82%. **36**: 98%. (d) *tert*-Butyl cyanoacetate, Pd((P-*tert*-butyl)$_3$)$_2$, Na_3PO_4, toluene, 100 °C, 87%; (e) (i) NaN_3, DMF, 165 °C, 1 h, 100%; (ii) K_2CO_3, MeI, DMF, 200 °C, 40 min. **32**: 4%. **33**: 1%.

In contrast, the affinities of the compounds with the most bulky substituents (**24**−**29**) show decreased affinity compared to **8**. This is most pronounced at α_{1d} receptors, where the affinities are reduced by a factor of 7−41 compared to **8**. These results are in good agreement with results from a previous 3D-QSAR study, indicating more sterical hindrance in α_{1d}-adrenoceptors compared to α_{1a} and α_{1b} in the area corresponding to the neuroleptic substituent of **1**[27] and thus presumably also **8**.

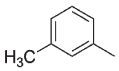
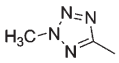
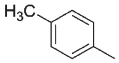
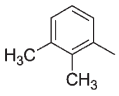
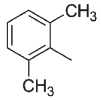
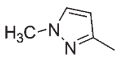
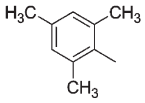
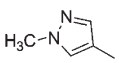
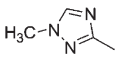
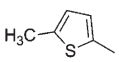
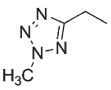
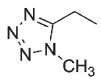
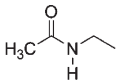
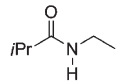
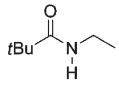
The compounds substituted with heteroaromatic substituents (**12**−**22**) tend to have higher affinities compared to those substituted with phenyl or methyl-substituted phenyl rings (**23**−**29**). In the indole series,[11] a hydrogen bond acceptor in the heteroaromatic substituent was proposed to be responsible for the high affinity of the compounds.[27] Furthermore, indoles substituted with five-membered heterocyclic substituents bearing a methyl group in the 2-position relative to the point of attachment to the indole ring (as in **13**) were less α_1/D_2 selective compared to those bearing the methyl substituent in the 3-position[11] (as in **12**), a fact that supported the need of coplanarity[12] of the two rings to obtain selectivity. The same trends are not observed in the octoclothepin series; comparing the compound bearing a phenyl substituent (**23**) to the pyridines **19**−**21**, where the pyridine nitrogen is systematically shuffled in all possible positions of the ring, does not indicate a direct hydrogen bond to the receptor and nor does the position of the methyl group in the five-membered heterocycles seem to influence α_1/D_2 selectivity as apparent by comparing the affinities of pyrazole **14** to those of pyrazoles **15** and **16**. Similarly, introducing mono-, di-, and trimethyl substituted phenyl groups in the octoclothepin 8-position to challenge the steric capabilities of the receptors did not lead to α_1/D_2 selective ligands.

Interestingly, the substituents that gave rise to the least selective compounds in the indole series (e.g., **5** and **6**) turned

Table 3. Receptor Binding Affinities for New Octoclothepin Analogues[d]



12-36

		K_i (nM)[a]						K_i (nM)[a]			
No.	**R =**	α_{1a}	α_{1b}	α_{1d}	D_2	**No.**	**R =**	α_{1a}	α_{1b}	α_{1d}	D_2
8	Cl	0.66	0.56	0.77	0.67	**25**		0.95	0.95	9.4	3.4
12		0.17	0.35	1.0	2.3	**26**		1.1	0.82	5.9	6.3
		0.15[b]			0.44[c]						
13		0.067	0.36	2.8	NT	**27**		1.5	1.2	16	2.0
14		0.41	0.32	0.97	0.86	**28**		1.0	6.9	25	4.6
15		0.26	0.25	1.9	1.6	**29**		2.0	1.8	13	4.9
16		0.24	0.20	1.4	2.3						
17		0.086	1.2	0.32	5.9	**30**		0.096	0.088	0.084	1.4
18		0.52	0.72	3.6	2.9	**31**		0.082	0.039	0.15	35
19		0.24	1.6	0.61	1.9	**32**		0.10[b]	NT	NT	0.35[c]
20		0.19	0.26	1.0	0.62	**33**		0.15[b]	NT	NT	1.9[c]
21		1.5	1.9	0.66	1.1	**34**		0.088	0.081	0.14	7.1
22		0.20	0.17	0.24	0.73	**35**		0.12	0.31	0.17	12
23		0.50	0.40	6.6	1.8	**36**		1.3	0.52	0.37	6.1
24		0.87	4.9	32	1.6						

[a] All compounds were tested as racemates. [b] [^{3}H]Prazosin, rat cerebral cortex membranes. [c] [^{3}H]Spiperone, HEK293 cells. [d] NT: not tested.

out to give rise to the most selective compounds in the octoclothepin series with the aminomethyl derivative **31** representing the link between the two series. Compound **31** has a receptor binding profile very similar to that of the corresponding compound in the indole series (**4**) with high affinity at α_1-adrenoceptors and significantly reduced affinity at dopamine D_2 receptors. Superimposing **31** and **4** as shown in Figure 2 suggests that the amino group may end up in the same position in space despite the lack of coplanarity of the aromatic rings bearing the substituent and may thus account for the similar receptor binding profile of the two compounds. Intrigued by these results, more flexible analogues (**32**−**34**) that would

Table 4. Receptor Binding Profile for Individual Enantiomers of **34** and **35**

	K_i (nM)					
compd	α_{1a}	α_{1b}	α_{1d}	D_2	5-HT_{2C}	H_1
1	0.37[a]	0.33[a]	0.66[a]	0.45[b]	0.51[b]	NT
(*R*/*S*)-**8**	0.66	0.56	0.77	0.67	0.19	3.9
(*R*)-**8**	0.70	0.42	0.23	7.3	NT	12
(*S*)-**8**	0.28	0.099	0.076	1.1	2.9	15
(*R*/*S*)-**34**	0.088	0.081	0.14	7.1	NT	NT
(*R*)-**34**[c]	0.42	0.90	1.5	27	3.1	3.6
(*S*)-**34**[c]	0.34	0.42	0.98	3.3	26	2.5
(*R*/*S*)-**35**	0.12	0.31	0.17	12	NT	NT
(*R*)-**35**	0.43	0.27	0.64	31	8.0	4.5
(*S*)-**35**	0.16	0.20	0.21	4.5	93	5.0

[a] Reference 11. [b] Reference 4. [c] Absolute configuration tentatively assigned (see Chemistry).

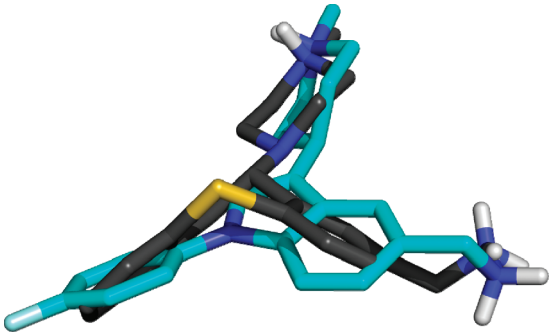


Figure 2. Superimposition of and (*S*)-**31** (gray) and **4** (cyan). Nonpolar hydrogens have been removed for clarity: carbon, gray/cyan; nitrogen, blue; sulfur, yellow; chlorine, green; fluorine, pale cyan; hydrogen, white.

allow for a head to head comparison with compounds in the indole series were prepared. The methyltetrazolylmethyl derivatives **32** and **33** have subnanomolar affinity for α_1-adrenoceptors, and **33** shows a 12-fold α_1/D_2 selectivity ratio. The acetylaminomethyl derivative **34** displays significant (5- to 7-fold) increased affinity for α_1-adrenoceptors and a 10-fold reduced affinity for dopamine D_2 receptors when compared to (*R*/*S*)-**8**, which results in an α_1/D_2 selectivity ratio of 50. The selectivity ratio for the corresponding compounds in the indole series (**5** and **6**) is close to unity.

Increasing the steric bulk by replacement of the acetyl moiety of **34** with an isobutyryl moiety (**35**) resulted in a compound with a similar level of subnanomolar affinity for α_1 adrenoceptors and an α_1/D_2 selectivity ratio of 38. Introduction of the more bulky pivalyl derivative **36** resulted in reduced affinity for α_{1a} adrenoceptors by a factor of 10 compared to **35**, indicating the limitations to the amount of bulk allowed in the binding cavity.

Heteroaromatic substituents directly attached to the indole nucleus resulted in α_1/D_2 selective compounds,[11] whereas the same substituents directly attached to the octoclothepin 8-position did not. A similar discrepancy is observed for the more flexible analogues **5** and **6** which in the indole series are nonselective but have increased selectivity in the octoclothepin series (**33**−**35**). This apparently "antiparallel" behavior may be explained by the lack of coplanarity of the two aromatic rings bearing the substituents as illustrated in Figure 2; superimposition of the selective compounds **2** and (*S*)-**35** (Figure 3A) shows that the steric bulk of the isobutyryl moiety of (*S*)-**35** may be positioned in the same area as the bulk of the heteroaromatic substituent of **2**, whereas superimposition of the nonselective compounds **6** and (*S*)-**12** (Figure 3B) shows

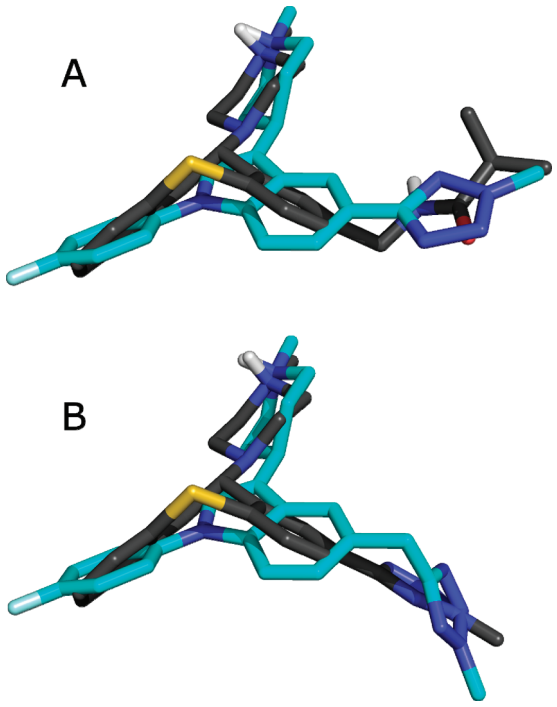


Figure 3. Superimposition of (A) α_1/D_2 selective compounds (*S*)-**35** (gray) and **2** (cyan) and of (B) α_1/D_2 unselective compounds (*S*)-**12** (gray) and **6** (cyan). Nonpolar hydrogens have been removed for clarity: carbon, gray/cyan; nitrogen, blue; sulfur, yellow; chlorine, green; fluorine, pale cyan; hydrogen, white.

that the steric bulk of the two substituents may also be superimposed, thus explaining the "antiparallel" behavior of the two series.

As evident from the results described above, three compounds (**31**, **34**, and **35**) show slightly increased affinity for α_1 adrenoceptors and decreased affinity for D_2 receptors compared to **8**. The most selective of these compounds, the aminomethyl derivative **31**, was disregarded because it has previously been found to be without significant CNS activity.[28] The compound is likely diprotonated under physiological conditions, and diamines in general are likely to bind to polyanions and phospholipids[29] which would result in high degrees of nonspecific binding. For compounds **34** and **35**, having α_1/D_2 selectivity ratios of 50−87 and 38−100, respectively, additional pharmacological data to illustrate selectivity with regard to serotonin 5-HT_{2A} and histamine H_1 receptors are shown in Table 4 for the individual enantiomers of the compounds. The affinity for serotonin 5-HT_{2C} receptors was significantly decreased compared to **8**, and both enantiomers of **34** and **35** bind with nanomolar affinity to histamine H_1 receptors and do not display any stereoselectivity at this receptor. As expected, on the basis of the results previously reported for the enantiomers of **8**,[17] the eutomer of **35** with regard to affinity for adrenergic α_1 and dopamine D_2 receptors is the (*S*)-enantiomer. The eudismic ratio at α_{1a}, α_{1d}, and D_2 receptors correlates well with the conformational energy penalty paid by (*R*)-**8** to adopt a conformation very similar to that of (*S*)-**8**.[17] These results strongly indicate that the compounds bind in a mode similar to that of **8** and therefore that the substituents investigated in the present study adds information about the area in the receptor complementary to the area of the neuroleptic substituents in antipsychotic drugs. The absolute stereochemistry of (*R*)- and (*S*)-**34** was not experimentally determined but tentatively assigned based on comparison of the eudismic ratios of the two enantiomers to those of **8** and **35**.

Table 5. Permeability and Lipophilicity for **34** and **35** Compared to Previously Investigated PET Ligands

	Caco-2		
compd	P_{app}, 10^{-6} cm s^{-1}	ratio	log *D*
raclopride	66[c]	0.50[c]	2.35[a]
2	12[b]	2.8[b]	3.06[b]
7	13[c]	0.7[c]	1.90[c]
34	33	1.7	2.65
35	57	0.60	3.10

[a] Referenc 36. [b] Referrence 13. [c] Reference 14.

Interestingly, the eutomer of **34** and **35** at 5-HT_{2C} receptors was the (*R*)-enantiomer, a detail that could indicate a different binding mode in the 5-HT_{2C} receptor binding site compared to α_{1a}, D_2, D_4, and 5-HT_{2A} receptors where the eutomer consistently is the (*S*)-enantiomer as discussed above.

The most selective compounds investigated in the present study are (*S*)-**35** and the opposite enantiomer (*R*)-**35**. Both compounds display similar subnanomolar affinity for α_1-adrenoceptors, and the selectivity ratios with regard to D_2, 5-HT_{2C}, and H_1 receptors are 20, 440, 20 and 45, 10, 7 for the (*S*)- and (*R*)-enantiomer, respectively.

Apart from high affinity and selectivity, permeability and lipophilicity also play an important role for a PET ligand. As shown in Table 5, compound **35** displays high permeability across a monolayer of CACO-2 cells and has a profile comparable to that of raclopride. A drawback of compound **35** in relation to the use as PET ligand is the relatively high log $D_{7.4}$ value of 3.10 (Table 4) which is considerably higher than for raclopride but within the range of lipophilicities of other well established CNS PET tracers.[30] Previous studies have shown that ratios of specific to nonspecific binding of radioligands in brain depend on both binding potential (B_{max}/K_D) and lipophilicity,[31] suggesting that high lipophilicity to some extent may be tolerated if B_{max}/K_D is also high. Considering this, (*S*)-**35** could turn out to be superior to the PET ligand [^{11}C]**2**. With α_1/D_2 and α_1/H_1 selectivity ratios around 20, specific binding to dopamine D_2 receptors and histamine H_1 receptors is a concern. However, for both receptor types, selective ligands are available that could potentially be used to displace specific binding to these receptors and therefore to increase the potential of (*S*)-**35** as a CNS α_1 selective PET ligand.

Conclusions

On the basis of the Liljefors−Bøgesø pharmacophore model for dopamine D_2, D_4, serotonin 5-HT_{2A}, and adrenergic α_1-adrenoceptor antagonists and a series of selective α_1-adrenoceptor antagonists derived from the antipsychotic sertindole (**1**), a series of octoclothepin derivatives were designed and prepared by palladium catalyzed cross-couplings directly from **8** or from the corresponding bromo- (**10**) or pinacolatoboronic ester (**11**) derivatives. Interestingly, the heteroaromatic substituents, observed to lower affinity for dopamine D_2 receptors when compared to α_1-adrenoceptor in the sertindole series, did not affect this ratio in the octoclothepin series. In contrast, the "out of plane" substituents like the acetylaminomethyl substituent which did not affect dopamine D_2 receptor affinity in the sertindole series gave rise to diminished D_2 receptor affinity in the octoclothepin series when compared to α_1-adrenoceptor and thus to compounds that are relatively selective for α_1. This apparently "antiparallel" behavior may be explained by the lack of coplanarity of the aromatic rings of the indole and the 10,11-dihydrodibenzo[*b*,*f*]thiepine scaffold when superimposed on each other which may place bulk from "out of plane" substituents in the same area in space as occupied by heteroaromatic substituents directly attached to the indole ring. The most selective compound obtained in the present study, (*S*)-**35**, binds with similar subnanomolar affinity to α_{1a}-, α_{1b}-, and α_{1d}-adrenoceptors and is selective with regard to D_2, 5-HT_{2C}, and H_1 receptors by factors of 21, 442, and 23, respectively. Compound **35** has a log $D_{7.4}$ value of 3.1 and permeability properties in CACO-2 cells comparable to those of the well-established PET-ligand raclopride. Despite the relatively low selectivity ratios and high lipophilicity that may give rise to a low signal-to-noise ratio in vivo, the ease of labeling and the high rates and nonpolarized transport across a monolayer of CACO-2 cells suggest that (*S*)-**35** could be suitable for evaluation as a PET ligand for in vivo imaging of α_1-adrenoceptors in both the peripheral nervous system and the CNS.

Experimental Section

General. Dry THF was distilled under N_2 from sodium/benzophenone immediately before use. Thin layer chromatography was performed on Merck 60 F_{254} 0.25 μm silica gel plates. Solvent A consisted of 75% EtOAc and 25% heptane. Solvent B consisted of 90% EtOAc and 10% MeOH, and solvent C consisted of 20% MeOH and 80% EtOAC. The spots were visualized with UV 254 nm, iodine, and the phenols with $FeCl_3$. Microwave-assisted reactions were performed with Emrys Optimizer from Personal Chemistry. Melting points were measured on a Büchi 535 apparatus. ^{1}H NMR and ^{13}C NMR were recorded at 500.13 and 125.67 MHz on a Bruker Advance DRX 500 instrument. Chemical shifts for ^{1}H NMR are reported in ppm with TMS as internal reference. Chemical shifts for ^{13}C NMR are reported in ppm relative to chemical shifts of the deuterated solvents. Coupling constants (*J* values) are in hertz. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, dd = double doublet, m = multiplet, br = broad. LC−MS data were obtained on a PE Sciex API150EX instrument equipped with an ion spray source and Shimadzu LC-8A/SLC-10A LC system: column, 30 mm × 4.6 mm Waters Symmmetry C18 column with 3.5 μm particle size; solvent system, A = water/TFA (100:0.05) and B = water/acetonitrile/TFA (5:95:0.03) (TFA = trifluoroacetic acid); method, linear gradient elution with 90% A to 100% B in 2.4 min and then 10% B in 0.4 min, with a flow rate of 3.3 mL/min. Total time including equilibration was 2.8 min. Injection volume was 10 μL from a Gilson 215 autosampler. The purity of compounds submitted for biological testing were in all cases ≥95% as determined using evaporative light scattering detection[32] (ELSD) and ≥95% using UV detection (254 nm) unless specifically indicated below. Preparative LC−MS were performed on a PE Sciex API150EX instrument equipped with an ion spray source and Shimadzu LC-8A/SLC-10A LC system: column, 50 mm × 10 mm Waters Symmetry C18 column with 5 μm particle size; solvent system, A = water/TFA (100:0.05) and B = water/acetonitrile/TFA (5:95:0.03); method, linear gradient elution with 90% A to 100% B in 7 min and then 10% B in 1 min, with a flow rate of 5.7 mL/min. Injection volume was 0−300 μL from a Gilson 233XL autosampler. HRMS spectra were obtained on a Bruker Daltonic MicroTOF with internal calibration using ESI in positive mode. Chiral compounds **34** and **35** were resolved by chiral super critical fluid chromatography (SFC) on a Berger SFC multigram II instrument equipped with a Chiralpak AD 21.2 mm × 250 mm column. The solvent system is specified below. The method consisted of a constant gradient with a flow rate of 50 mL/min. The fraction collection was performed by UV 230 nm detection.

8-Chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (9a). 4-Chlorothiophenol (20.45 g, 141.4 mmol) was added to a solution of KOH (26.0 g, 472 mmol) in water (270 mL). The solution was heated to 50 °C, and copper powder (2.61 g, 41.8 mmol) was added,

followed by 2-iodophenylacetic acid (35.3 g, 135 mmol). The mixture was refluxed for 24 h under stirring, cooled, and filtrated. The filtrate was acidified with 2 M HCl (20 mL), and EtOAc (250 mL) was added. The phases were separated, and the aqueous phase was extracted with EtOAc (5 × 250 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to give 35.6 g (95%) of 2-(2-((4-chlorophenyl)thio)phenyl)acetic acid as a light yellow solid. LC−MS: ELSD, 92.1%; UV, 93.2%; M^+, 278.0. This material (17.00 g, 60.98 mmol) was added in small portions to polyphosphoric acid (68 g) at 135−140 °C under rapid stirring. After 2 h the mixture was cooled and ice−water (330 mL) was added and the mixture was extracted with EtOAc (4 × 250 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to give 13.0 g of **9a** as dark brown solid. The crude product was filtered through silica gel (heptane/EtOAc) and recrystallized from EtOH/water to yield 11.6 g (73%) of **9a** as light yellow crystals: mp 124−125 °C (lit. 125 °C[23]). LC−MS: ELSD, 98.6%; UV, 94.6%; MH^+, 261.0; R_f = 0.53 (solvent A). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.15 (d, 2.4), 7.65 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 6.6 Hz, 1H), 7.40 (m, 2H), 7.20 (dt, J = 1.4 Hz, J = 8.0 Hz, 1H), 4.35 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 190.7, 139.0, 137.7, 137.6, 134.4, 133.7, 132.8, 132.7, 131.8, 131.5, 130.6, 130.0, 127.8, 51.2. Anal. Calcd for $C_{14}H_9ClO_2S$: C, 64.49; H, 3.48. Found: C, 64.30; H, 3.56.

8-Bromodibenzo[*b*,*f*]thiepin-10(11*H*)-one (9b). 4-Bromothiophenol (74.3 g, 0.393 mol) was added to a solution of KOH (72.1 g, 1.31 mol) in water (750 mL). The solution was heated to 50 °C, and copper powder (7.25 g, 0.116 mol) was added, followed by 2-iodophenylacetic acid (98.0 g, 0.374 mol). The mixture was refluxed for 24 h under stirring, cooled, and filtrated. The filtrate was acidified with 2 M HCl (200 mL), and EtOAc (600 mL) was added. The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 500 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to give 120.5 g (100%) of 2-(2-((4-bromophenyl)thio)phenyl)acetic acid as a light yellow solid. LC−MS: ELSD, 98.3%; UV, 79.2%; MH^+, 324.0. This material (120 g, 0.373 mol) was added in small portions to polyphosphoric acid (417 g) at 140−145 °C under rapid stirring. After 1.5 h the mixture was cooled and ice−water (1.5 L) was added and the mixture was extracted with EtOAc (3 × 750 mL). The combined organic phases were washed with 2 M NaOH (750 mL), brine, dried ($MgSO_4$), and concentrated to give 105.6 g of **9b** as a dark brown solid. The crude product was recrystallized from EtOH/water to yield 83.2 g (73%) of **9b** as light yellow crystals: mp 112−113 °C (lit. 113 °C[23]). LC−MS: ELSD, 98.8%; UV, 94.3%; MH^+, 305.9; R_f = 0.58 (solvent A). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.13 (d, 2.4), 7.63 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.52 (dd, J = 8.5 Hz, J = 2.4 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.38 (dt, J = 0.94 Hz, J = 7.5 Hz, 1H), 7.21 (dt, J = 1.4 Hz, J = 7.5 Hz, 1H), 4.36 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 190.7, 139.0, 137.7, 137.6, 134.4, 133.7, 132.8, 132.7, 131.8, 131.5, 130.6, 130.0, 127.8, 51.2. Anal. Calcd for $C_{14}H_9BrO_2S$: C, 55.09; H, 2.97. Found: C, 55.11; H, 2.79.

(*R*/*S*)-Octoclothepin (8). A stirred solution of **9a** (3.47 g, 13.3 mmol) and 1-methylpiperazine (6.53 g, 65.2 mmol) in toluene (133 mL) was slowly treated with $TiCl_4$ (1.89 g, 10.0 mmol) under an argon atmosphere. The mixture was heated to reflux and stirred for 24 h. After the mixture was cooled, ice−water (300 mL) was added and TiO_2 was filtered off and washed with THF (3 × 100 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 250 mL). The combined organic phases were washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated to give 1-(8-chlorodibenzo-[*b*,*f*]thiepin-10-yl)-4-methylpiperazine 4.50 g (99%) as a dark red solid. LC−MS: ELSD, 99.6%; UV, 86.6%; MH^+, 343.2. To a cold (0 °C) solution of this material (4.50 g, 13.31 mmol) in CH_3CO_2H (97.2 mL), $NaBH_4$ (7.35 g, 194 mmol) was added in small portions. The resulting mixture was stirred at room temperature for 23 h. EtOAc (250 mL) was added, and the mixture was quenched with saturated $NaHCO_3$ (100 mL) and 9 M NaOH (100 mL) to pH 6−7. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 250 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (20% MeOH in EtOAc) to yield 3.65 g (80%) of **8** as a white solid: mp 99−100 °C (lit. 99−101 °C[23]). LC−MS: ELSD, 99.2%; UV, 99.0%, M^+, 345.1; R_f = 0.30 (solvent C). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (d, J = 2.4 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.23−7.30 (m, 2H), 7.11 (dt, J = 1.4 Hz, J = 7.1 Hz, 1H), 7.05 (dd, J = 2.4 Hz, J = 8.5 Hz, 1H), 3.96 (dd, J = 3.3 Hz, J = 11.7 Hz, 1H), 3.88 (t, J = 12.3 Hz, 1H), 3.17 (dd, J = 3.3 Hz, J = 12.3 Hz, 1H), 2.50−2.90 (m, 8H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 142.5, 142.3, 136.6, 134.1, 133.5, 133.2, 132.5, 131.7, 130.0, 129.4, 127.4, 126.9, 65.9, 55.6, 47.9, 45.8, 32.9. Anal. Calcd for $C_{19}H_{21}ClN_2S$: C, 66.17; H, 6.14; N, 8.12. Found: C, 65.71; H, 6.18; N, 8.06.

1-(8-Bromo-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-4-methylpiperazine (10). A stirred solution of **9b** (68.9 g, 0.226 mol) and 1-methylpiperazine (100 g, 0.111 mol) in toluene (1.13 L) was slowly treated with $TiCl_4$ (32.12 g, 0.169 mol) under an argon atmosphere. The mixture was heated to reflux and stirred for 24 h. After the mixture was cooled to 0 °C, ice−water (1.0 L) was added and TiO_2 was filtered off and washed with THF (300 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 500 mL). The combined organic phases were washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated to give 1-(8-bromodibenzo[*b*,*f*]thiepin-10-yl)-4-methylpiperazine, 82.0 g (94%), as a dark red solid. LC−MS: ELSD, 98.6%; UV, 89.5%; MH^+, 388.1. To a cold (0 °C) solution of this material (82.0 g, 0.212 mmol) in CH_3CO_2H (1.54 L), $NaBH_4$ (117 g, 3.09 mol) was added in small portions over 30 min. The resulting mixture was stirred at room temperature for 24 h. EtOAc (500 mL) was added. The mixture was quenched with saturated $NaHCO_3$ (500 mL), and 9 M NaOH (1.00 L) was added to obtain pH 6−7. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 500 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was filtered through silica gel (300 g) (20% MeOH in EtOAc) and recrystallized from EtOH/water to yield 76.2 g (92%) of **10** as white crystals: mp 116−117 °C (lit. 118−119 °C[23]). LC−MS: ELSD, 99.2%; UV, 95.7%; M^+, 389.2; R_f = 0.16 (solvent B). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.82 (d, J = 1.9 Hz, 1H), 7.49 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.22−7.30 (m, 3H), 7.18 (dd, J = 8.0 Hz, J = 1.9 Hz, 1H), 7.10 (dt, J = 7.5 Hz, J = 1.9 Hz, 1H), 3.94 (dd, J = 11.8 Hz, J = 3.3 Hz, 1H), 3.87 (t, J = 12.7 Hz, 1H), 3.16 (dd, J = 12.7 Hz, J = 3.3 Hz, 1H), 2.36−2.80 (m, 8H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 142.8, 142.8, 136.5, 135.5, 134.7, 133.3, 131.7, 130.1, 129.9, 129.3, 126.8, 121.5, 65.8, 55.9, 48.5, 46.4, 33.0. Anal. Calcd for $C_{19}H_{21}BrN_2S$: C, 58.61; H, 5.44; N, 7.26. Found: C, 58.77; H, 5.45; N, 7.09.

1-Methyl-4-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10,11-dihydrodibenzo [*b*,*f*]thiepin-10-yl)piperazine (11). 10 (3.89 g, 10.0 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ [1:1] (0.366 g, 0.50 mmol, 5 mol %), bis(pinacolato)diboron (3.18 g, 12.5 mmol), and KOAc (3.93 g, 40.0 mmol) were dissolved in anhydrous DMF (60 mL). The flask was flushed with Ar, and the solution was heated at 100 °C for 14 h. Then $^1/_2$ saturated $NaHCO_3$ (150 mL) and EtOAc (150 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 250 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (5% Et_3N in EtOAc) to yield 3.36 g (77%) as white crystals: mp 271−272 °C. LC−MS: ELSD, 99.3%; UV, 92.4%; M^+, 437.2; R_f = 0.18 (solvent C). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (s, 1H), 7.48 (d, J = 6.4 Hz,

1H), 7.41 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 6.4 Hz, 1H), 7.20 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.05 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 4.02 (dd, J = 11.3 Hz, J = 4.2 Hz, 1H), 3.86 (dd, J = 13.2 Hz, J = 11.3 Hz, 1H), 3.19 (dd, J = 13.6 Hz, J = 4.2 Hz, 1H), 2.29−2.75 (m, 8H), 2.26 (s, 3H), 1.31 (s, 12H). ^{13}C NMR ($CDCl_3$) δ: 142.4, 139.6, 139.3, 139.1, 137.3, 133.1, 130.2, 128.8, 126.6, 84.2, 66.3, 56.1, 49.1, 46.5, 34.9, 25.3, 25.2. Anal. Calcd for $C_{25}H_{33}BN_2O_2S$: C, 68.80; H, 7.62; N, 6.42. Found: C, 68.63; H, 7.60; N, 6.13.

1-Methyl-4-(8-(2-methyl-2*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (12) and 1-Methyl-4-(8-(1-methyl-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (13). A 25 mL vial was charged with **10** (389 mg, 1.00 mmol), $Zn(CN)_2$ (117 mg, 1.00 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.100 mmol) dissolved in DMF (10 mL) and flushed with argon. The vial was capped and heated for 120 s at 165 °C (100 W) in a microwave reactor. The vial was allowed to reach room temperature before it was charged with NaN_3 (780 mg, 12.0 mmol) and NH_4Cl (642 mg, 12.0 mmol) and flushed with argon. The vial was recapped and heated for 30 min at 165 °C (100 W) in a microwave reactor. The reaction tube was allowed to reach room temperature before it was charged with K_2CO_3 (1.65 g, 14.0 mmol) and MeI (705 mg, 5.00 mmol). The vial was recapped and heated for 40 min at 200 °C (150 W, max 11 bar) in a microwave reactor. The vial was allowed to reach room temperature before saturated $NaHCO_3$ (100 mL) and EtOAc (100 mL) were added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified directly by column chromatography on silica gel (20% MeOH in EtOAc). Yield: 240 mg (26%) of **12**·2HCl as white crystals. **12**: mp 259−260 °C. LC−MS: ELSD, 98.7%; UV, 93.7%; MH^+, 393.4; R_f = 0.13 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 8.26 (d, J = 1.4 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.51 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.35 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.21 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 4.43 (s, 3H), 3.89 (t, J = 11.8 Hz, 1H), 2.90−3.55 (m, 8H), 2.73 (s, 3H). HRMS $C_{21}H_{24}N_6S$ [M + H^+] calcd 393.1856, found 393.1859.

The fractions containing **13** were purified by HPLC. Yield: 53 mg (11%) of **13**·TFA salt as pale yellow oil. **13**: LC−MS, ELSD, 98.0%; UV, 97.6%, MH^+, 393.4; R_f = 0.15 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 9.82−9.96 (b, 1H), 8.04 (d, J = 1.4 Hz, 1H), 7.65−7.70 (m, 2H), 7.57 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.52 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.37 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.22 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 4.30−4.74 (b, 2H), 4.27 (dd, J = 11.3 Hz, J = 4.2 Hz, 1H), 4.17 (s, 3H), 3.80 (dd, J = 13.2 Hz, J = 11.3 Hz, 1H), 3.44 (d, J = 11.8 Hz, 1H), 3.34 (d, J = 11.3 Hz, 1H), 3.24 (dd, J = 13.2 Hz, J = 4.2 Hz, 1H), 3.15 (d, J = 11.8 Hz, 1H), 3.02−3.12 (m, 1H), 2.62−2.87 (m, 7H). ^{13}C NMR (DMSO) δ: 153.8, 141.7, 140.2, 138.4, 135.5, 133.2, 132.2, 131.3, 130.7, 129.6, 127.5, 127.2, 123.0, 64.5, 53.6, 46.9, 42.5, 35.6, 32.9. HRMS $C_{21}H_{24}N_6S$ [M + H^+] calcd 393.1856, found 393.1860.

General Procedures A, B, and C for the Coupling of 11 with Heteroaryl Bromides and Iodides. Procedure A. A 5 mL vial was charged with **11** (100 mg, 0.229 mmol), $Pd_2(dba)_3$ (5.2 mg, 0.0057 mmol, 5 mol %), S-Phos (9.4 mg, 0.023 mmol), heteroaryl halide (0.344 mmol), and K_3PO_4 (195 mg, 0.917 mmol). The vial was sealed with a pressure sure cap and evacuated and refilled with argon three times. THF/H_2O (10:1) (2 mL) was added, and the resulting mixture was stirred for 15 min at room temperature, then for 13 h at 85 °C, concentrated, and purified directly by column chromatography on silica gel (20% MeOH in EtOAc).

Procedure B. A 5 mL vial was charged with **11** (100 mg, 0.229 mmol), $Pd_2(dba)_3$ (5.2 mg, 0.0057 mmol, 5 mol %), S-Phos (9.4 mg, 0.023 mmol), heteroaryl halide (0.344 mmol), and K_3PO_4 (145 mg, 0.687 mmol). The vial was sealed with a pressure sure cap and evacuated and refilled with argon three times. THF (3 mL) was added, and the resulting mixture was stirred for 15 min at room temperature, then for 20 h at 85 °C, concentrated, and purified directly by column chromatography on silica gel (20% MeOH in EtOAc).

Procedure C. 11 (200 mg, 0.458 mmol), heteroaryl halide (0.687 mmol), Pd_2dba_3 (4.2 mg, 0.005 mmol), and PCy_3 (3.1 mg, 0.011 mmol) were added to a 5 mL vial. The vial was sealed with a pressure sure cap and evacuated and refilled with argon three times. Dioxane (1.22 mL) and aqueous K_3PO_4 (1.27 M, 0.61 mL, 0.78 mmol) were added by syringe. The mixture was then stirred at room temperature for 30 min and then at 100 °C for 14 h with vigorous stirring. The mixture was concentrated and purified directly by column chromatography on silica gel (up to 20% MeOH in EtOAc).

1-Methyl-4-(8-(1-methyl-1*H*-pyrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (14). General procedure A and 5-iodo-1-methyl-1*H*-pyrazole were used. Yield: 59.5 mg (67%) of **14** as a white solid. The product was dissolved in MeOH (1.0 mL), and 2 M HCl in Et_2O (1.5 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 71.6 mg (67%) of **14**·2HCl as white crystals, mp 246−247 °C. LC−MS: ELSD, 99.0%; UV, 98.9%, MH^+, 391.3; R_f = 0.07 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 7.77−7.87 (b, 1H), 7.66−7.69 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.43−7.48 (m, 2H), 7.36 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.22 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 6.53 (s, 1H), 3.95 (t, J = 11.8 Hz, 1H), 3.93 (s, 3H), 3.00−3.70 (m, 8H), 2.77 (s, 3H). HRMS $C_{23}H_{26}N_4S$ [M + H^+] calcd 391.1951, found 391.1937.

1-Methyl-4-(8-(1-methyl-1*H*-pyrazol-3-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (15). General procedure A and 5-iodo-1-methylpyrazole were used. Yield: 85 mg (48%) of **15** as a white solid. The product was dissolved in MeOH (2.0 mL), and 2 M HCl in Et_2O (3.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 99.3 mg (47%) of **15**·2HCl as white crystals: mp 259−260 °C. LC−MS: ELSD, 99.2%; UV, 97.7%, MH^+, 391.5; R_f = 0.05 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 8.06−8.16 (b, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.55 (dd, J = 8.0 Hz, J = 0.9 Hz, 1H), 7.50 (d, J = 7.1 Hz, 1H), 7.33 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.21 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 6.80 (s, 1H), 4.80−5.70 (b, 8H), 3.94 (t, J = 11.8 Hz, 1H), 3.92 (s, 3H), 2.77 (s, 3H). HRMS $C_{23}H_{26}N_4S$ [M + H^+] calcd 391.1951, found 391.1967.

1-Methyl-4-(8-(1-methyl-1*H*-pyrazol-4-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (16). General procedure B and 4-bromo-1-methylpyrazole were used. Yield: 69 mg (78%) of **16** as a white solid. The product was dissolved in MeOH (1.0 mL), and 2 M HCl in Et_2O (1.5 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 76 mg (72%) of **16**·2HCl as white crystals: mp 218−219 °C. LC−MS: ELSD, 98.7; UV, 97.1%; MH^+, 388.3; R_f = 0.05 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 8.18 (s, 1H), 7.87−7.98 (b, 2H), 7.47−7.56 (m, 3H), 7.43 (d, J = 7.5 Hz, 1H), 7.33 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.20 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 3.81−3.93 (b, 4H), 2.97−3.68 (m, 8H), 2.77 (s, 3H). HRMS $C_{23}H_{26}N_4S$ [M + H^+] calcd 391.1951, found 391.1947.

1-Methyl-4-(8-(1-methyl-1*H*-1,2,4-triazol-3-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (17). General procedure C and 3-bromo-1-methyl-1,2,4-triazole were used. Yield: 117.4 (66%) of **17** as white crystals. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (4.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 135 mg (64%) of **17**·2HCl as white crystals: mp 240−241 °C. LC−MS: ELSD, 99.8%; UV, 99.6%; MH^+, 392.4; R_f = 0.02 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 11.38−11.62 (b, 1H), 8.65 (s, 1H), 8.17 (d, J = 1.4 Hz, 1H), 7.87 (dd, J = 8.0 Hz, J = 1.9 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.55 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.58

(d, J = 6.6 Hz, 1H), 7.34 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.21 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 3.97 (t, J = 12.7 Hz, 1H), 3.92 (s, 3H), 3.12−3.76 (m, 8H), 2.75 (s, 3H). HRMS $C_{22}H_{25}N_5S$ [M + H^+] calcd 392.1903, found 392.1910.

1-Methyl-4-(8-(5-methylthiophen-2-yl)-10,11-dihydrodibenzo-[*b*,*f*]thiepin-10-yl)piperazine (18). General procedure C and 2-iodo-5-methylthiophene were used. Yield: 152 mg (82%) of **18** as white crystals. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (4.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 177 mg (80%) of **18**·HCl as white crystals: mp 180−181 °C. LC−MS: ELSD, 99.5%; UV, 99.3%; MH^+, 407.4; R_f = 0.02 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 10.93−11.28 (b, 1H), 7.86 (s, 1H), 7.50 (m, 3H), 7.41 (d, J = 7.0 Hz, 1H), 7.37 (m, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 4.51−4.76 (br, 37H), 2.92−3.99 (m, 10H), 2.75 (s, 3H), 2.46 (s, 3H). HRMS $C_{24}H_{26}N_2S_2$ [M + H^+] calcd 407.1610, found 407.1601.

1-Methyl-4-(8-(pyridin-2-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (19). General procedure B and 2-iodopyridine were used. Yield: 83 mg (47%) of **19** as a white solid. The product was dissolved in MeOH (1.0 mL), and 2 M HCl in Et_2O (1.5 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 101 mg (48%) of **19**·2HCl as white crystals: mp 246−247 °C. LC−MS: ELSD, 98.7; UV, 97.1%; MH^+, 391.4; R_f = 0.07 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 8.78 (d, J = 5.2 Hz, 1H), 8.37−8.41 (b, 1H), 8.25−8.31 (m, 2H), 7.99 (d, J = 8.0 Hz, 1H), 7.68−7.75 (m, 2H), 7.58 (dd, J = 8.0 Hz, J = 0.9 Hz, 1H), 7.54 (dd, J = 8.0 Hz, J = 0.9 Hz, 1H), 7.37 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.23 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 3.91 (t, J = 11.8 Hz, 1H), 2.93−3.60 (m, 8H), 2.75 (s, 3H). HRMS $C_{24}H_{25}N_3S$ [M + H^+] calcd 388.1842, found 388.1845.

1-Methyl-4-(8-(pyridin-3-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (20). General procedure A and 3-iodopyridine were used. Yield: 69 mg (78%) of **20** as a white solid. The product was dissolved in MeOH (1.0 mL), and 2 M HCl in Et_2O (1.5 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 71.7 mg (68%) of **20**·2HCl as white crystals, mp 234−236 °C. LC−MS: ELSD, 99.5%; UV, 98.6%; MH^+, 388.2; R_f = 0.05 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 9.31 (s, 1H), 8.87 (d, J = 5.2 Hz, 2H), 8.10−8.20 (b, 1H), 8.07 (dd, J = 8.0 Hz, J = 5.6 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.36 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.22 (dt, J=7.5 Hz, J = 0.9 Hz, 1H), 3.96 (t, J = 11.8 Hz, 1H), 2.86−3.77 (m, 8H), 2.77 (s, 3H). HRMS $C_{24}H_{25}N_3S$ [M + H^+] calcd 388.1842, found 388.1839.

5-(11-(4-Methylpiperazin-1-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)pyrimidine (22). General procedure B and 5-bromopyrimidine were used. Yield: 153 mg (86%) of **22** as a white solid. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (6.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 205 mg (97%) of **22**·2HCl as white crystals, mp 246−247 °C. LC−MS: ELSD, 97.7; UV, 99.8%; MH^+, 389.3; R_f = 0.07 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 9.23−9.27 (b, 2H), 9.20 (s, 1H), 8.11−8.23 (b, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.36 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.22 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 3.97 (t, J = 11.8 Hz, 1H), 2.99−3.88 (m, 8H), 2.77 (s, 3H). HRMS $C_{23}H_{24}N_4S$ [M + H^+] calcd 389.1794, found 389.1806.

Synthesis of 21 and 23 via Coupling of 8 with R-B(OH)$_2$. A 5 mL vial was charged with **10** (389 mg, 1.00 mmol), $Pd(PPh_3)_4$ (58 mg, 0.50 mmol, 5 mol %), and arylboronic acid (1.50 mmol). The vial was sealed with a pressure sure cap and evacuated and refilled with argon three times. Then 2 M aqueous Na_2CO_3 (2.0 mL) and toluene (3.0 mL) were added and the resulting mixture was stirred for 15 min at room temperature, then for 18 h at 100 °C, concentrated, and purified directly by column chromatography on silica gel (20% MeOH in EtOAc).

1-Methyl-4-(8-(pyridin-4-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (21). Arylboronic acid: 4-pyridinylboronic acid (184 mg, 1.50 mmol). Yield: 282 mg (73%) of **21** as a pale yellow solid. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 276 mg (60%) of **21**·2HCl as white crystals: mp 220−221 °C. LC−MS: ELSD, 99.18%; UV, 94.9%; MH^+, 388.3; R_f = 0.03 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 8.99 (d, J = 6.6 Hz, 2H), 8.50 (d, J = 5.7 Hz, 2H), 8.31−8.40 (b, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 3.91 (t, J = 11.8 Hz, 1H), 2.88−3.68 (m, 8H), 2.77 (s, 3H). HRMS $C_{24}H_{25}N_3S$ [M + H^+] calcd 388.1842, found 388.1848.

1-Methyl-4-(8-phenyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-piperazine (23). Arylboronic acid: phenylboronic acid (183 mg, 1.50 mmol). Yield: 302 mg (78%) of **23** as a white solid. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 363 mg (79%) of **23**·2HCl as white crystals: mp 223−225 °C. LC−MS: ELSD, 98.8%; UV, 94.4%; MH^+, 387.4; R_f = 0.28 (solvent C). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80−7.90 (b, 1H), 7.62 (d, J = 7.0 Hz, 2H), 7.53 (d, J = 7.5 Hz, 1H), 7.47 (t, J = 6.6 Hz, 1H), 7.42 (d, J = 5.5 Hz, 1H), 7.36 (t, J = 7.0 Hz, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.25 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.11 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 3.83 (t, J = 11.8 Hz, 1H), 2.76−3.65 (m, 8H), 2.66 (s, 3H). HRMS $C_{25}H_{27}N_2S$ [M + H^+] calcd 287.1889, found 387.1887.

General Procedure for the Coupling of 11 with Aryl Iodides. 11 (300 mg, 0.687 mmol), aryl iodide (1.03 mmol), Pd_2dba_3 (6.3 mg, 0.007 mmol), and PCy_3 (4.6 mg, 0.016 mmol) were added to a 5 mL thick walled vial. The vial was sealed with a pressure sure cap and evacuated and refilled with argon three times. Dioxane (1.8 mL) and aqueous K_3PO_4 (1.27 M, 0.92 mL, 1.17 mmol) were added by syringe. The mixture was stirred at room temperature for 30 min and then at 100 °C for 13 h with vigorous stirring. The mixture was concentrated and purified directly by column chromatography on silica gel (up to 20% MeOH in EtOAc).

1-Methyl-4-(8-*o*-tolyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-piperazine (24). Aryl iodide: 1-iodo-2-methylbenzene. Yield: 206 mg (75%) of **24** as white crystals. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 220 mg (68%) of **24**·2HCl as white crystals: mp 264−266 °C. LC−MS: ELSD, 99.1%; UV, 98.6%; MH^+, 401.3; R_f = 0.55 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 7.52−7.60 (m, 3H), 7.47−7.51 (d, J = 6.6 Hz, 1H), 7.35 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.16 (m, 6H), 4.36−4.97 (m, 5,7H), 3.87 (t, J = 12.3 Hz, 1H), 2.79−3.50 (m, 8H), 2.73 (s, 3H), 2.21 (s, 3H). HRMS $C_{26}H_{28}N_2S$ [M + H^+] calcd 401.2046, found 401.2050.

1-Methyl-4-(8-*m*-tolyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-piperazine (25). Aryl iodide: 1-iodo-3-methylbenzene. Yield: 208 mg (76%) of **25** as white crystals. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 222 mg (68%) of **25**·2HCl as white crystals: mp 231−233 °C. LC−MS: ELSD, 99.6%; UV, 98.9%; MH^+, 401.3; R_f = 0.55 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 7.90−8.00 (b, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.48−7.58 (m, 5H), 7.30−7.38 (m, 2H), 7.18 (d, J = 8.0 Hz, 1H), 7.21 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 4.62−5.66 (m, 2H), 3.94 (t, J = 11.8 Hz, 1H), 2.91−3.77 (m, 8H), 2.75 (s, 3H), 2.35 (s, 3H). HRMS $C_{26}H_{28}N_2S$ [M + H^+] calcd 401.2046, found 401.2050.

1-Methyl-4-(8-*p*-tolyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-piperazine (26). Aryl iodide: 1-iodo-4-methylbenzene. Yield: 210 mg (76%) of **26** as white crystals. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 225 mg (69%) of **26**·2HCl as white crystals: mp 252−253 °C. LC−MS: ELSD, 99.6%; UV, 98.8%; MH^+, 401.3; R_f = 0.55 (solvent C).

^{1}H NMR (500 MHz, DMSO) δ: 7.84−7.94 (b, 1H), 7.53−7.63 (m, 4H), 7.47−7.53 (m, 2H), 7.34 (dt, J = 7.53 Hz, J = 0.9 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.20 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 4.01−4.40 (m, 6H), 3.90 (t, J = 12.2 Hz, 1H), 2.85−3.60 (m, 8H), 2.74 (s, 3H), 2.33 (s, 3H). HRMS $C_{26}H_{28}N_2S$ [M + H$^+$] calcd 401.2046, found 401.2064.

1-(8-(2,3-Dimethylphenyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-4-methylpiperazine (27). Aryl iodide: 1-iodo-2,3-dimethylbenzene. Yield: 242 mg (85%) of **27** as white crystals. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 288 mg (85%) of **27**·2HCl as white crystals, mp 251−252 °C. LC−MS: ELSD, 99.5%; UV, 98.5%; MH$^+$, 415.3.; R_f = 0.55 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 7.48−7.60 (m, 4H), 7.35 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.21 (dt, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.13−7.19 (m, 2H), 7.11 (t, J = 7.5 Hz, 1H), 7.02−7.08 (m, 1H), 4.36−5.07 (m, 5H), 3.88 (t, J = 12.2 Hz, 1H), 2.83−3.56 (m, 8H), 2.73 (s, 3H), 2.28 (s, 3H), 2.08 (s, 3H). HRMS $C_{27}H_{30}N_2S$ [M + H$^+$] calcd 415.2203, found 415.2201.

1-(8-(2,5-Dimethylphenyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-4-methylpiperazine (28). Aryl iodide: 1-iodo-2,6-dimethylbenzene. Yield: 252 mg (88%) of **69** as white crystals. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 281 mg (84%) of **28**·2HCl as white crystals, mp 264−265 °C. LC−MS: ELSD, 99.5%; UV, 99.3%; MH$^+$, 415.4; R_f = 0.55 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 7.57 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.49−7.56 (m, 2H), 7.43 (b, 1H), 7.36 (dt, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.22 (dt, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.06−7.17 (m, 3H), 6.96−7.03 (m, 1H), 4.87−5.42 (m, 4H), 3.86 (t, J = 12.2 Hz, 1H), 2.74−3.47 (m, 8H), 2.72 (s, 3H), 1.99 (s, 3H), 1.88 (s, 3H). HRMS $C_{27}H_{30}N_2S$ [M + H$^+$] calcd 415.2203, found 415.2202.

1-(8-Mesityl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-4-methylpiperazine (29). Aryl iodide: 1-iodo-2,4,6-trimethylbenzene. Yield: 259 mg (88%) of **70** as white crystals. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 301 mg (87%) of **29**·2HCl as white crystals, mp 265−266 °C. LC−MS: ELSD, 99.2%; UV, 99.2%; MH$^+$, 429.3; R_f = 0.55 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 7.48−7.60 (m, 3H), 7.45 (b, 1H), 7.37 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.22 (dt, J = 7.5 Hz, J = 1.4 Hz, 1H), 6.95−7.02 (m, 1H), 6.92 (s, 1H), 6.89 (s, 1H), 5.33−5.85 (m, 2H), 3.86 (t, J = 12.2 Hz, 1H), 2.78−3.55 (m, 8H), 2.72 (s, 3H), 2.20 (s, 3H), 1.97 (s, 3H), 1.83 (s, 3H). HRMS $C_{28}H_{32}N_2S$ [M + H$^+$] calcd 429.2359, found 429.2365.

11-(4-Methylpiperazin-1-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepine-2-carbonitrile (30). 10 (7.00 g, 18.0 mmol), $Zn(CN)_2$ (2.10 g, 18.0 mmol), and $Pd(PPh_3)_4$ (2.08 g, 1.80 mmol) dissolved in DMF (180 mL) was flushed with Ar. The mixture was stirred in a preheated oil bath at 140 °C for 20 min. After the mixture was cooled, $^1/_2$ saturated $NaHCO_3$ (250 mL) and EtOAc (250 mL) were added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 250 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to give 8.32 g of light red crystals. The crude product was purified by flash chromatography (10% MeOH in EtOAc) to yield 5.72 g (95%) of **30** as a white solid: mp 172−173 °C (lit. mp 171−173 °C[28]). LC−MS: ELSD, 99.5%; UV, 95.3%; MH$^+$, 336.4; R_f = 0.15 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 8.10 (d, J = 1.4 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.26−7.33 (m, 3H), 7.11−7.16 (m, 1H), 3.90 (dd, J = 11.8 Hz, J = 2.8 Hz, 1H), 3.85 (dd, J = 12.7 Hz, J = 11.8 Hz, 1H), 3.17 (dd, J = 12.7 Hz, J = 2.8 Hz, 1H), 2.34−2.83 (m, 8H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 143.0, 142.2, 141.8, 136.6, 135.2, 131.9, 131.6, 129.8, 129.7, 127.0, 119.3, 110.7, 76.9, 65.6, 55.9, 55.0, 46.4, 32.4. Anal. Calcd for $C_{20}H_{21}N_3S$: C, 71.60; H, 6.31; N, 12.53. Found: C, 71.51; H, 6.26; N, 12.44.

(11-(4-Methylpiperazin-1-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)methanamine (31). 30 (1.50 g, 4.47 mmol) dissolved in dry THF (26.8 mL) was cooled to 0 °C. Then 1 M $LiAlH_4$ (17.9 mL,17.9 mmol, 4 equiv) in THF was slowly added over 3−4 min. The mixture was allowed to reach room temperature and was stirred for a further 1.5 h. The mixture was cooled on an ice bath and quenched with wet Na_2SO_4 and Et_2O (10 mL). The mixture was filtered through Na_2SO_4 and washed with Et_2O (200 mL). The filtrate was evaporated to dryness yielding 1.63 g of **31** (quantitative) as light yellow oil. A sample of 200 mg was dissolved in MeOH (5 mL), and 2 M HCl in Et_2O (4.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 241 mg (98%) of **31**·3HCl as white crystals, mp 207−208 °C. LC−MS: ELSD, 99.1%; UV, 94.4%; MH$^+$, 340.1; R_f = 0.02 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 8.57−8.78 (b, 3H), 7.88 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.55 (dd, J = 8.0 Hz, J = 0.9 Hz, 1H), 7.51 (d, J = 7.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.35 (dt, J = 7.5 Hz, J = 1.42 Hz, 1H), 7.20 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 4.02−5.00 (m, 4H), 3.84−4.02 (m, 3H), 3.00−3.70 (m, 9H), 2.77 (s, 3H). HRMS $C_{20}H_{25}N_3S$ [M + H$^+$] calcd 340.1842, found 340.1843.

***N*-((11-(4-Methylpiperazin-1-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)methyl)acetamide (34). 31** (300 mg, 0.884 mmol) and triethylamine (0.20 mL, 1.43 mmol) were dissolved in dry THF (6.8 mL) and cooled to 0 °C. Acetyl chloride (90 mg, 1.15 mmol) dissolved in dry THF (2.0 mL) was added over 2 min to the solution. After the mixture was stirred for 30 min at room temperature, $^1/_2$ saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL) were added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (10% MeOH in EtOAc) to yield 298 mg (88%) of **34** as a colorless oil. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 353 mg (88%) of **34**·2HCl as white crystals: mp 185−186 °C. LC−MS: ELSD, 99.0%; UV, 95.2%; MH$^+$, 382.3; R_f = 0.04 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 11.54−11.79 (b, 1H), 8.37 (t, J = 5.8 Hz, 1H), 7.48−7.63 (m, 4H), 7.34 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 4.27−5.27 (m, 6H), 4.22 (dd, J = 15.5 Hz, J = 5.6 Hz, 1H), 4.18 (dd, J = 15.5 Hz, J = 5.6 Hz, 1H), 3.95 (t, J = 12.3 Hz, 1H), 3.25−3.85 (m, 9H), 2.79 (s, 3H), 1.87 (s, 3H). HRMS $C_{22}H_{27}N_3OS$ [M + H$^+$] calcd 382.1948, found 382.1935.

The enantiomers of **34** (200 mg, 0.49 mmol) were separated using SFC (solvent system, CO_2/EtOH/Et_2NH 80/20/0.1) to afford approximately 100 mg of (*R*)-**34** and approximately 100 mg of (*S*)-**34**. (*R*)-**34** was dissolved in a minimum amount of MeOH, and HCl in Et_2O was added slowly. The precipitated salt was filtered off and dried. Yield: 59 mg of (*R*)-**34**·2HCl as a white solid. LC/MS: ELSD, 100%; UV, 100%; MH$^+$, 382.1.%; >98.0% ee. Mp 169−171 °C. (*S*)-**34** was dissolved in a minimum amount of MeOH, and HCl in Et_2O was added slowly. The precipitated salt was filtered off and dried. Yield: 54 mg of (*S*)-**34**·2HCl as a white solid. LC/MS: ELSD, 100%; UV, 100%; MH$^+$, 382.1; >99.6% ee. Mp 169−171 °C. The absolute stereochemistry of (*R*)-**34** and (*S*)-**34** is tentatively assigned based on the order of elution on the SFC column and the pharmacological data, both compared to those of (*R*)-**35** and (*S*)-**35**.

***N*-((11-(4-Methylpiperazin-1-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)methyl)isobutyramide (35). 31** (300 mg, 0.884 mmol) and triethylamine (0.20 mL, 1.43 mmol) were dissolved in dry THF (6.8 mL) and cooled to 0 °C. Isobutyryl chloride (122 mg, 1.15 mmol) dissolved in dry THF (2.0 mL) was added over 2 min. After the mixture was stirred for 30 min at room temperature, $^1/_2$ saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL) were added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude

product was purified by flash chromatography (10% MeOH in EtOAc) to yield 297 mg (82%) of **35** as white crystals. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 369 mg (87%) of **35**·2HCl as white crystals, mp 209−210 °C. LC−MS: ELSD, 99.5%; UV, 99.2%; MH^+, 410.3; R_f = 0.06 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 11.71−12.12 (b, 1H), 8.26 (t, J = 8.3 Hz, 1H), 7.61 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.55 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.51 (d, J = 7.1 Hz, 1H), 7.34 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.2 (m, 2H), 5.70−6.60 (b, 2H), 5.10−5.30 (b, 1H), 4.25 (dd, J = 15.5 Hz, J = 5.6 Hz, 1H), 4.18 (dd, J = 15.5 Hz, J = 5.6 Hz, 1H), 3.98 (t, J = 12.3 Hz, 1H), 3.30−3.95 (m, 9H), 2.79 (s, 3H), 2.48 (heptet, J = 7.1 Hz, 1H), 1.02 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 7.1 Hz, 3H). HRMS $C_{24}H_{31}N_3OS$ [M + H^+] calcd 410.2261, found 410.2257.

The enantiomers of **35** (200 mg, 0.49 mmol) were separated by SFC (solvent system, CO_2/EtOH/Et_2NH 70/30/0.5) to afford 86 mg of (*R*)-**35** and 79 mg of (*S*)-**35**. (*R*)-**35** (86 mg, 0.21 mmol) was dissolved in a minimum amount of MeOH, and HCl in Et_2O was added. The precipitated salt was filtered off and dried. Yield: 88 mg (87%) of (*R*)-**35**·2HCl as a white solid. LC/MS (method 350): t_R = 0.88; ELSD, 100%; UV, 95.0%; MH^+, 410.5; >97.6% ee. Mp 216−217 °C. (*S*)-**35** (79 mg, 0.19 mmol) was dissolved in a minimum amount of MeOH, and HCl in Et_2O was added. The precipitated salt was filtered off and dried. Yield: 87 mg (93%) of (*S*)-**35**·2HCl as a white solid. LC/MS (method 350): t_R = 0.89; ELSD, 100%; UV, 96.0%; MH^+, 410.5; >96.0% ee. Mp 213-215 °C. The absolute configuration was determined by X-ray crystallography after recrystallization from MeOH.

***N*-((11-(4-Methylpiperazin-1-yl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)methyl)pivalamide (36). 31** (300 mg, 0.884 mmol) and triethylamine (0.20 mL, 1.43 mmol) were dissolved in dry THF (6.8 mL) and cooled to 0 °C. Pivaloyl chloride (139 mg, 1.15 mmol) dissolved in dry THF (2.0 mL) was added over 2 min to the solution. After the mixture was stirred for 30 min at room temperature, $^1/_2$ saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL) were added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (10% MeOH in EtOAc) to yield 332 mg (98%) of **36** as colorless oil. The product was dissolved in MeOH (5.0 mL), and 2 M HCl in Et_2O (7.0 mL) was added slowly. The generated HCl salt was filtered and dried in vacuum. Yield: 393 mg (90%) of **36**·2HCl as white crystals: mp 210−211 °C. LC−MS: ELSD, 99.6%; UV, 98.8%; MH^+, 424.3; R_f = 0.10 (solvent C). ^{1}H NMR (500 MHz, DMSO) δ: 11.70−11.96 (b, 1H), 8.01 (t, J = 5.7 Hz, 1H), 7.52−7.59 (m, 3H), 7.50 (d, J = 6.6 Hz, 1H), 7.34 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.20 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 4.67−6.13 (m, 5H), 4.26 (dd, J = 15.5 Hz, J = 5.6 Hz, 1H), 4.20 (dd, J = 15.5 Hz, J = 5.6 Hz, 1H), 3.97 (t, J = 12.3 Hz, 1H), 3.11−3.91 (m, 10H), 2.78 (s, 3H), 2.51 (s, 9H). HRMS $C_{25}H_{33}N_3OS$ [M + H^+] calcd 424.2417, found 424.2409.

1-Methyl-4-[8-(2-methyl-2*H*-tetrazol-5-ylmethyl)-10,11-dihydro-dibenzo[*b*,*f*]thiepin-10-yl]piperazine (32) and 1-Methyl-4-[8-(1-methyl-1*H*-tetrazol-5-ylmethyl)-10,11-dihydrodibenzo-[*b*,*f*]thiepin-10-yl]piperazine (33). Bis(tri-*tert*-butylphosphine)-palladium(0) (0.4 g, 0.8 mmol), Na_3PO_4 (8.0 g, 50 mmol), and *tert*-butyl cyanoacetate (6.6 mL, 45 mmol) were added to a solution of **10** (6.0 g, 15 mmol) in toluene (150 mL). The mixture was stirred at 100 °C for 4 h, cooled to room temperature, and filtered. Water (100 mL) was added, and the phases were separated. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (eluent: EtOAc in heptane 0−100%, MeOH in EtOAc 0−10%) to yield 6.0 g (87%) of crude cyano-[11-(4-methyl-piperazin-1-yl)-10,11-dihydrodibenzo[*b*,*f*]-thiepin-2-yl]acetic acid *tert*-butyl ester. LC/MS (method 350): t_R = 0.74; ELSD, 100.0%; UV, 38.3%; MH^+, 450.2). To a vial containing this intermediate (500 mg, 1.1 mmol) dissolved in DMF (11.2 mL), NaN_3 (870 mg, 13.3 mmol) and NH_4Cl (715 mg, 13.3 mmol) were added. The vial was flushed with argon and the reaction mixture heated at 165 °C for 60 min in a microwave reactor. Then 2 M HCl (40 mL) and EtOAc (10 mL) were added. The phases were separated, and another 100 mL of EtOAc was added. The water phase was made basic by slowly adding 12 M NaOH. The phases were separated and the organic phase dried over Na_2SO_4 and concentrated to yield 390 mg (100%) of 1-methyl-4-[8-(1*H*-tetrazol-5-ylmethyl)-10,11-dihydrodibenzo-[*b*,*f*]thiepin-10-yl]piperazine. LC/MS: ELSD, 96.2%; UV, 62.1%; MH^+, 393.1. To a vial containing this intermediate (390 mg, 1.0 mmol) dissolved in DMF, K_2CO_3 (690 mg, 5.0 mmol) and MeI (310 μL, 5.0 mmol) were added. The vial was flushed with argon, and the mixture was heated at 200 °C for 40 min. The mixture was poured into water (30 mL), and EtOAc (50 mL) was added. The phases were separated and the organic phase washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified using silica gel chromatography (eluent, EtOAc in heptane 0−100%, MeOH in EtOAc 0−10%) and HPLC to yield 15 mg (3.7%) of **32**. LC/MS: ELSD, 100%; UV, 100%; MH^+, 407.7. ^{1}H NMR (500 MHz, DMSO) δ: 2.53−2.66 (m, 2H), 2.72 (d, J = 12.1, 1H), 3.78 (s, 3H), 2.84 (d, J = 8.69, 1H), 3.04 (q, J = 9.23 Hz, 1H), 3.16 (t, J = 15.5 Hz, 2H), 3.34 (d, J = 11.5 Hz, 1H), 3.42 (d, J = 11.5 Hz, 2H), 3.73 (t, J = 12.1 Hz, 1H), 4.10−4.20 (m, 3H), 4.28 (s, 3H), 7.08 (d, J = 8.11 Hz, 1H), 7.16 (t, J = 7.45 Hz, 1H), 7.31 (t, J = 7.16 Hz, 1H), 7.38 (d, J = 7.64, 1H), 7.44 (d, J = 7.16, 3H), 7.46−7.52 (m, 2H). HRMS $C_{22}H_{27}N_6S_1$ [M + H^+] calcd 407.2012, found 407.2017. The column was eluted further to give 5 mg (1.2%) of **33**. LC/MS: ELSD, 100%; UV, 94%; MH^+, 407.6. ^{1}H NMR (500 MHz, DMSO) δ: 2.47−2.60 (m, 1H), 2.60−2.73 (m, 2H), 3.78 (s, 4H), 2.97 (q, J = 10.2 Hz, 1H), 3.12 (d, J = 12.1 Hz, 1H), 3.18 (d, J = 12.5 Hz, 1H), 3.25−3.58 (m, 2H), 3.72 (t, J = 12.1 Hz, 1H), 3.96 (s, 3.00), 4.14 (d, J = 9.33 Hz, 1H), 4.27 (s, 2H), 7.07 (d, J = 7.90 Hz, 1H), 7.17 (t, J = 7.18 Hz, 1H), 7.31 (t, J = 7.18 Hz, 1H), 7.40 (d, J = 7.90, 1H), 7.44 (s, 3H), 7.50 (d, J = 7.90, 1H). HRMS $C_{22}H_{27}N_6S_1$ [M + H^+] calcd 407.2012, found 407.2023.

In Vitro Binding Assays. CHO cell lines expressing the rat α_{1d} and human D_2 and BHK cells expressing bovine α_{1a} adrenoceptors were generated in-house at H. Lundbeck using standard stable transfection techniques. The rat-1 cell line expressing the hamster α_{1B} adrenoceptor was obtained from the University of Utah, Salt Lake City, UT. The CHO cell lines expressing the human 5-HT_{2C} (VSV) and human H_1 receptors was purchased from Euroscreen (Brussels, Belgium) and grown according to the company's instructions.

The cells were grown to 90% confluence, detached, and homogenized in ice-cold 50 mM Tris, pH 7.4, using an Ultra-Turrax, and the homogenates were either kept on ice or stored at −80 °C until used.

In all α_1 assays 50 mM Tris, pH 7.7, was used as assay buffer and [^{3}H]prazosin was used as radioligand at 0.3 nM (α_{1a} and α_{1d}) or 0.5 nM (α_{1b}), and nonspecific binding was defined as the binding in the presence of WB-4101 (1 μM). Then 50 mM Tris, pH 7.7, was used as assay buffer in the h5-HT_{2C} assay, 0.5 nM [^{3}H]mesulergine was used as radioligand, and nonspecific binding was defined as the binding in the presence 1 μM mianserine.

For the D_2 assay 50 mM Tris, pH 7.4, was used as assay buffer and [^{3}H]spiperone (0.1 nM) was used as radioligand. Nonspecific binding was defined as the binding in the presence haloperidol (10 μM).

The human H_1 assay was performed as a SPA-based competition-binding assay in a 50 mM Tris, pH 7.4, assay buffer containing 120 mM NaCl, 5 mM KCl, 4 mM $MgCl_2$, 1.5 mM $CaCl_2$, and 1 mM EDTA. 1.0 nM [^{3}H]pyrilamine was used as radioligand and nonspecific binding defined as the binding in the presence of 10 μM clozapine.

In all the α_1 assays, samples were incubated at 25 °C for 20 min. The D_2 and 5-HT_{2C} assay were incubated for 30 min at 37 °C, and the H_1 assay was incubated for 60 min at room temperature.

In the α_1, D_2, and 5-HT_{2C} assays bound and free radioactivity was separated by vacuum filtration on GF/B filters, scintillation fluid (Optiphase Supermix, PerkinElmer) was added, and the samples were counted in a scintillation counter (Wallac Trilux).

External testing of indicated compounds was done at Cerep according to the assays catalog reference 802-1a (unselective α_1) and catalog reference 803-2h (human D_{2s}).

Data shown in the tables are the mean from a minimum of two full concentration−response curves using 10 concentrations of drugs (covering 3 decades). The results are given as K_i values (nM) derived from computer fitted IC_{50} values converted to K_i values using the Cheng−Prusoff equation[33] ($(K_i = IC_{50}/(1 + (L/K_D)))$). Standard errors for p$K_i$ values were within 0.3 for all reported compounds.

The assessment of permeability in CACO-2 cells was conducted using Transwell (Corning Costar) kit as previously described.[13]

The log $D_{7.4}$ values were determined using Autotitrator GLpKa from Sirius Instruments.[34] The pK_a values were determined by titration at ~25 °C and an ion strength of 0.16 M using methanol as cosolvent. Different methanol concentrations were used. A difference curve was created from each of these titrations by blank subtraction, and from these difference curves, methanol concentration dependent pK_a values were calculated. The real aqueous pK_a values were determined by extrapolation to zero-methanol content. Three titrations with methanol concentrations in the range 27−50% were included. The log $D_{7.4}$ values were determined by titration. Three repeated titrations on the same sample in solution were performed, from low to high pH. The first titration was performed with a small amount of *n*-octanol present in the solution. The second and third were performed with increasing amounts. A difference curve was created from each of these titrations by blank subtraction, and from these difference curves, the apparent pK_a values were calculated. From the change in the apparent pK_a values with the *n*-octanol/water ratio combined with the real pK_a values, the log *P* values (neutral and ionized) were calculated. The log $D_{7.4}$ value is calculated from the pK_a value and the log *P* value.

Molecular Modeling. Compounds **1** and (*S*)-**8** were superimposed in their previously proposed bioactive conformations[20] (Figure 1). In all subsequent calculations these conformations were kept by imposing dihedral constraints of 100 (kJ/mol)/Å^2 on rotatable bonds but allowing the substituents in the indole 5- and 10,11-dihydrodibenzo[*b*,*f*]thiepine 8-positions to move freely. Conformations were sampled using Monte Carlo molecular mechanics in MacroModel, version 9.7,[35] with the MMFFs force field in aqueous solvent and otherwise standard settings. For indoles, the global energy minimum with respect to the substituent in the 5-position was selected. For octoclothepin analogues, the structures giving rise to the best overlay of the 5/8-substituents using the same superposition scheme as for **1** and (*S*)-**8** were selected. In all cases these were low energy conformations with the following energy penalties: (*S*)-**31**, +0.71 kcal/mol; (*S*)-**35**, +1.77 kcal/mol; (*S*)-**12**, +0.14 kcal/mol. Overlays are shown in Figures 1−3.

Crystal Data. (*S*)-**35.** $C_{24}H_{35}Cl_2N_3O_2S$, M = 500.52 g mol^{-1}, *P*212121, a = 6.2789(6) Å; b = 14.0206(19) Å, c = 29.065(5)°, α = 90°, β = 90°, γ = 90°, volume of 2558.7(6) Å^3, temp of 295 K, Z = 4, Dx = 1.299 g cm^{-3}, F(000) = 1064.0, μ = 0.361 mm^{-1}, R = 0.0517(2921), wR2 = 0.1040(4781). The data are deposited at CCDC under the following deposition number: CCDC 778837.

(*R*)-**35.** $C_{24}H_{35}Cl_2N_3O_2S$, M = 500.52 g mol^{-1}, *P*212121, a = 6.2752(6) Å, b = 14.0077(17) Å, c = 29.032(3) Å, α = 90°, β = 90°, γ = 90°, volume of 2552.0(5) Å^3, temp of 295 K, Z = 4, Dx = 1.303 g cm^{-3}, F(000) = 1066.01, μ = 0.362 cm^{-1}, R = 0.0440 (4362), wR2 = 0.1101 (6126). The data are deposited at CCDC under the following deposition number: CCDC 778836.

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Supporting Information Available: Ellipsoid plots of the refined structures of (*R*)-**35** and (*S*)-**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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