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Analogues of the Potential Antipsychotic Agent 1192U90: Amide Modifications

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Abstract—Analogues of 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)benzamide hydrochloride (1192U90) were prepared and evaluated in receptor binding assays for the dopamine D_2, serotonin 5-HT_{1a}, and serotonin 5-HT_2 receptors. Eight compounds have been synthesized in which the amide group of 1192U90 has been replaced with a variety of functional groups (i.e. ester, ketone, thioamide, butyramide, butyranilide, sulfonamide, alkoxyamide and hydrazide). These compounds exhibited moderate to potent affinities (0.55–200 nM) for all three receptors. Several analogues exhibited improved selectivity for the 5-HT_2 receptor with D_2/5-HT_2 binding ratios greater than 1192U90.

Introduction

Schizophrenia is a mental illness which affects millions of people worldwide. Since the 1950's, drugs such as haloperidol and chlorpromazine have been used to treat this devastating disease. While these drugs effectively treat the positive symptoms of schizophrenia (i.e. delusions, hallucinations) they are ineffective against the negative symptoms (i.e. social withdrawal, apathy).[1–4] Furthermore, these drugs may produce extrapyramidal side effects (EPS) such as acute dystonia, Parkinsonism, and tardive dyskinesia. In the 1970's a major breakthrough in the treatment of this disease was achieved with the discovery of clozapine which is effective against both the positive and negative symptoms of the disease. Clozapine also lacks the extrapyramidal side-effects associated with the typical antipsychotic drugs.[5–7] Unfortunately, clozapine causes agranulocytosis, a potentially fatal blood dyscrasia, in up to 1% of patients.[8] Hence, research efforts have been focused on the discovery of drugs that exhibit clozapine's atypical antipsychotic profile and lack the potential for agranulocytosis.

One approach to the discovery of new atypical antipsychotic agents has focused on compounds which are mixed dopamine D_2 and serotonin 5-HT_2 antagonists. Meltzer has postulated that mixed D_2/5-HT_2 antagonists that potently bind to the 5-HT_2 receptor and exhibit moderate affinity for the D_2 receptor (i.e. D_2/5-HT_2 ratio >1) are more likely to have good antipsychotic activity with a lower propensity to produce extrapyramidal side effects.[9] New atypical antipsychotic agents which combine dopamine D_2 and serotonin 5-HT_2 antagonism include risperidone,[10] sertindole,[11] iloperidone,[12] and the clozapine derivative olanzapine.[13] In fact, risperidone is now the most widely prescribed antipsychotic drug in the United States.[14]

Affinity for the 5-HT_{1a} receptor may reduce the EPS liability of a potential antipsychotic agent and alleviate the negative symptom of social withdrawal. The 5-HT_{1a} agonist buspirone has been shown to reverse the haloperidol-induced catalepsy in animal models[15] and reduce stress-induced psychosocial deficits in chronic schizophrenic patients.[16] Lowe and co-workers have

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described a series of potential atypical antipsychotic agents which are mixed 5-HT_{1a} agonists and D_2/5-HT_2 antagonists.[17] Similarly, Hrib and co-workers prepared a series thiazolidinones which potently bind to the 5-HT_{1a} receptor as well as the D_2, D_4, and 5-HT_2 receptors.[18] These compounds exhibited activity in an animal model for the negative symptom of social withdrawal and are believed to be 5-HT_{1a} agonists.

We have recently disclosed the discovery of a series of substituted benzamides with dopamine D_2, serotonin 5-HT_2, and serotonin 5-HT_{1a} binding activities.[19] Structure–activity relationship investigations in this series identified the 2-aminobenzamide, 1192U90 (**1**), as the lead compound (Figure 1). This compound is a mixed D_2/5-HT_2 antagonist and a serotonin 5-HT_{1a} agonist which exhibits in vivo activity in animal models predictive of antipsychotic activity.[20]

In order to better understand the structure–activity relationship in this series of benzamides, we have prepared analogues of 1192U90 in which the amide group has been replaced with a variety of functional groups. We herein describe the synthesis and receptor binding activity of these compounds.

Chemistry

Replacement of the amide group of 1192U90 with other functional groups (i.e. ester, ketone, thioamide, butyramide, butyranilide, sulfonamide, *N*-alkoxybenzamide and hydrazide) required a variety of synthetic approaches which are illustrated in Schemes 1–7.

Ester **5** was synthesized in three steps from 4-iodo-1-(*tert*-butyldimethylsilyloxy)butane[21] (**2**) as shown in Scheme 1. Reaction of **2** with 3-(1-piperazinyl)-1,2-benzisothiazole[22] gave the desired *tert*-butyldimethylsilyl ether (**3**). Treatment of **3** with HCl in THF afforded the intermediate alcohol (**4**) which was condensed with anthranilic acid in the presence of HOBt and DCC to give the desired ester (**5**).

The synthesis of ketone **10** is illustrated in Scheme 2. Initially, we attempted to prepare haloketone **9** directly from BOC-protected aniline (**7**) via formation of the dilithium anion with *tert*-butyllithium followed by

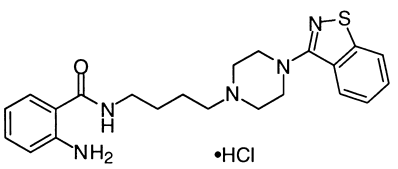
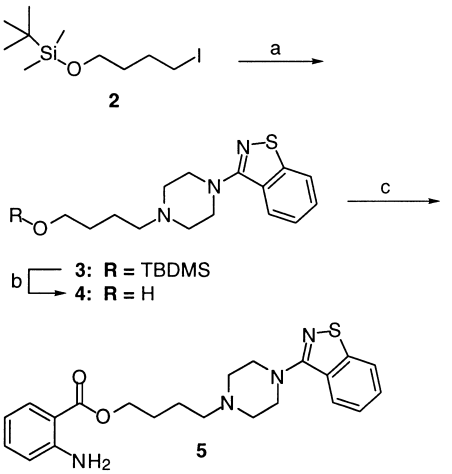


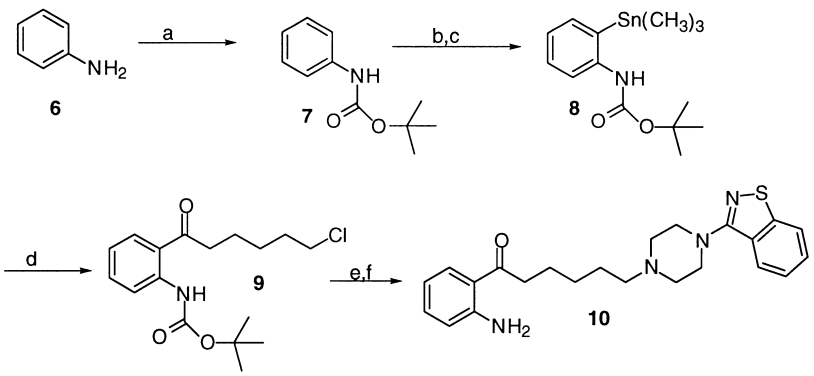
Figure 1. 1192U90(**1**).



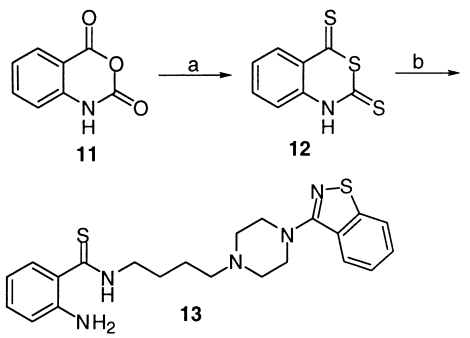
Scheme 1. (a) 3-(1-Piperazinyl)-1,2-benzisothiazole, Et_3N, CH_3CN, reflux; (b) 1.0 N HCl, THF, rt; (c) anthranilic acid, 1-hydroxybenzotriazole hydrate, 1,3-dicyclohexylcarbodiimide, DMF, rt.

quenching with 6-chlorohexanoyl chloride. However, attempts via this route yielded either largely unreacted starting material or numerous unidentified products. Stille and co-workers described the synthesis of an aryl ketone in which phenyltrimethyltin is coupled to a bromoalkanoyl bromide using a palladium catalyst.[23] They reported that no reaction occurred at the primary bromide site. Since **9** contained an alkyl chloride, this approach appeared to be ideally suited for the preparation of this intermediate. Treatment of aniline with di-*tert*-butyldicarbonate in THF gave the BOC-protected aniline (**7**). The dilithium anion of **7** was prepared according to a procedure described by Muchowski and Venuti using *tert*-butyllithium as a base.[24] Treatment of the dilithium anion of **7** with trimethyltin chloride gave the organotin intermediate (**8**) that was reacted with 6-chlorohexanoyl chloride in the presence of a palladium catalyst to give the desired intermediate chloride (**9**). Displacement of the chloride with 3-(1-piperazinyl)-1,2-benzisothiazole followed by removal of the BOC protecting group with trifluoroacetic acid gave the desired ketone analogue (**10**).

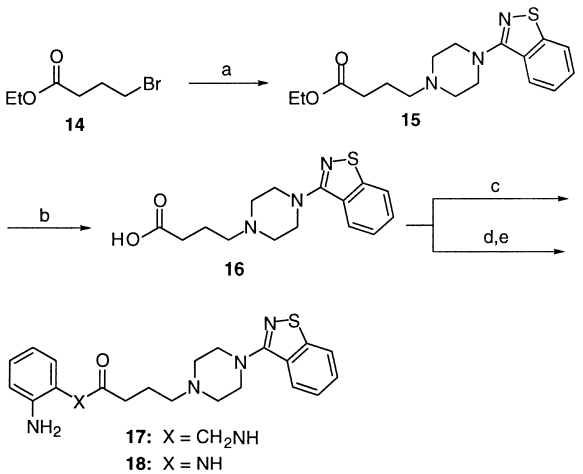
Treatment of 1192U90 with either Lawesson's reagent or phosphorus pentasulfide failed to give thioamide **13**. Therefore, an alternative synthetic approach was needed for the preparation of this compound. Wagner and Roth prepared a series of 2-aminothiobenzamides by reacting a variety of amines with thiazine dithione **12** which was obtained by treatment of isatoic anhydride with P_4S_{10}.[25] Thus, reaction of isatoic anhydride with phosphorus pentasulfide in refluxing xylenes gave intermediate **12** which was reacted with 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole[26] in THF to give the desired thioamide (**13**) (Scheme 3).



Scheme 2. (a) di-*tert*-Butyl dicarbonate, THF, reflux; (b) *tert*-butyllithium, THF, −78 °C to −20 °C; (c) trimethyltin chloride, THF, −70 °C to −78 °C; (d) 6-chlorohexanoyl chloride, bis(acetonitrile)Pd II chloride, toluene, reflux; (e) 3-(1-piperazinyl)-1,2-benzisothiazole, Et_3N, CH_3CN, reflux; (f) trifluoroacetic acid, CH_2Cl_2, anisole, rt.



Scheme 3. (a) Phosphorus pentasulfide, xylenes, reflux; (b) 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, THF, rt.

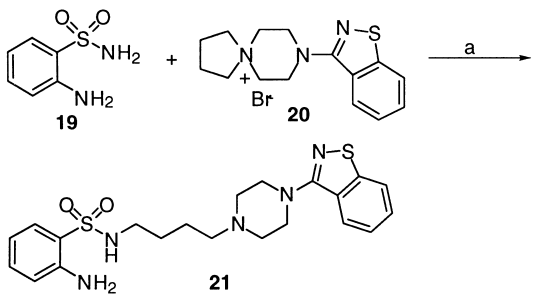


Scheme 4. (a) 3-(1-Piperazinyl)-1,2-benzisothiazole, Et_3N, CH_3CN, rt to reflux; (b) NaOH, EtOH, reflux, 1.5 h; (c) 2-aminobenzylamine, 1-hydroxybenzotriazole hydrate, 1,3-dicyclohexylcarbodiimide, DMF, rt; (d) isobutylchloroformate, Et_3N, THF, −15 °C; (e) 1,2-phenylenediamine, −15 °C to rt.

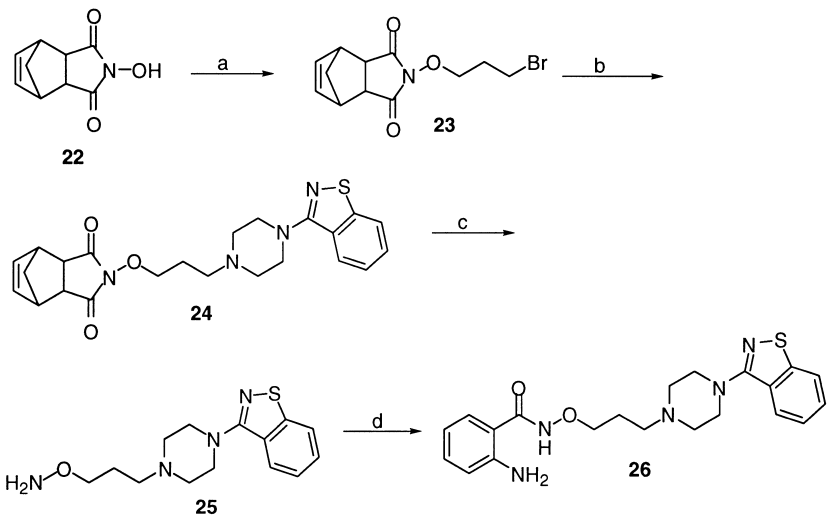
The butyramide and butyranilide analogues (**17** and **18**, respectively) were prepared according to the routes illustrated in Scheme 4. Alkylation of 3-(1-piperazinyl)-1,2-benzisothiazole with ethyl-4-bromobutyrate (**14**) gave ester **15**, which was subsequently hydrolyzed with aqueous NaOH to give carboxylic acid **16**. Condensation of **16** with 2-aminobenzylamine in the presence of DCC and HOBt in DMF gave analogue **17**. The butyranilide (**18**) was prepared from the carboxylic acid via the formation of the mixed anhydride using isobutylchloroformate followed by treatment with 1,2-phenylenediamine.

Sulfonamide **21** was conveniently prepared in one step (Scheme 5) via treatment of 2-aminobenzene sulfonamide (**19**) with NaH followed by alkylation of the sulfonamide salt with 8-(1,2-benzisothiazol-3-yl)-8-aza-5-azoniaspiro[4.5]decane bromide[22] (**20**).

For alkoxyamide **26** and hydrazide **29** the methylene group alpha to the amide nitrogen of 1192U90 was replaced with a heteroatom. Alkoxyamide **26** was prepared in four steps from *endo-N*-hydroxy-5-norbornene-2,3-dicarboximide (**22**) as illustrated in Scheme 6. Alkylation of **22** with 1,3-dibromopropane in the presence of



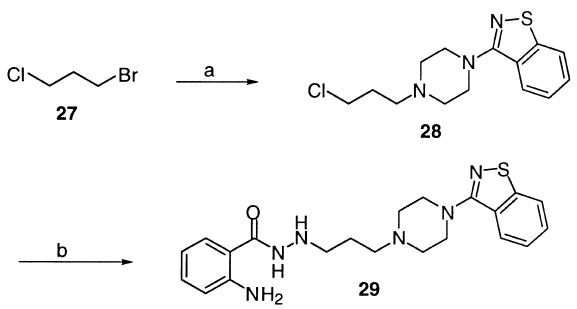
Scheme 5. (a) NaH, DMF, 0 °C to reflux.



Scheme 6. (a) 1,3-Dibromopropane, diisopropylethylamine, CH_3CN, 70 °C; (b) 3-(1-piperazinyl)-1,2-benzisothiazole, diisopropylethylamine, CH_3CN, reflux; (c) hydrazine hydrate, EtOH, reflux; (d) isatoic anhydride, THF, rt.

Hunig's base gave **23** which was treated with 3-(1-piperazinyl)-1,2-benzisothiazole to give the alkoxyimide intermediate (**24**). Deprotection with hydrazine hydrate gave hydroxylamine **25** which was converted to the desired alkoxyamide (**26**) upon treatment with isatoic anhydride in THF. In an earlier attempt to prepare this analogue, *N*-hydroxyphthalimide was used in lieu of **22**. However, reaction of the corresponding bromide with 3-(1-piperazinyl)-1,2-benzisothiazole failed to yield the desired alkoxyphthalimide intermediate. This result is in agreement with the findings of Amlaiky and co-workers who reported that nucleophilic attack on phthalimide ethers of this type readily occurs at the imide carbonyl group.[27]

Hydrazide **29** was prepared in two steps as illustrated in Scheme 7. Alkylation of 3-(1-piperazinyl)-1,2-benzisothiazole with 1-bromo-3-chloropropane gave chloride **28** in good yield. Treatment of this intermediate with 2-aminobenzhydrazide in refluxing ethanol gave the desired hydrazide analogue (**29**).



Scheme 7. (a) 3-(1-Piperazinyl)-1,2-benzisothiazole, Et_3N, CH_2Cl_2, rt; (b) 2-aminobenzhydrazide, EtOH, reflux.

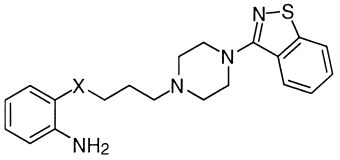
Discussion

The structure–activity investigations reported previously for this series of compounds have focused on substitutions on the benzamide ring as well as replacement of the benzamide ring with heterocyclic carboxamides.[19,28] In those studies, modification to the amide functional group was limited to methylation of the benzamide nitrogen. To further develop the SAR in this series of benzamides we focused on the amide functional group of 1192U90. In this study, we replaced the carbonyl group with a sulfone or thiocarbonyl, substituted the amide nitrogen with a methylene group or an oxygen, introduced heteroatoms alpha to the amide nitrogen, and changed the position of the carbonyl relative to the nitrogen. These compounds were evaluated in receptor binding assays for the dopamine D_2, serotonin 5-HT_2, and serotonin 5-HT_{1a} receptors according to methods described previously.[26] The receptor binding data as well as the D_2/5-HT_2 ratios for these compounds are shown in Table 1. The receptor binding data for 1192U90 is included for comparison.

In general, the compounds described herein exhibited moderate to potent affinities at all three receptors and maintained favorable D_2/5-HT_2 binding ratios (i.e. D_2/5-$HT_2 > 1$).

Replacement of the amide group of 1192U90 with either a thioamide (**13**) or sulfonamide (**21**) resulted in small

Table 1. In vitro receptor binding affinities of 1192U90 analogues



Compound[a]	X	Receptor binding[b,c] IC_{50} (nM)			
		D_2	5-HT_{1a}	5-HT_2	D_2/5-HT_2[d]
5	$C(O)OCH_2$	10	14	3	3.3
10	$C(O)CH_2CH_2$	2.6	4	0.55	4.7
13	$C(S)NHCH_2$	21	1	1.8	11.7
17[e]	$CH_2NHC(O)$	56	40	1.6	35
18	NHC(O)	200	120	9.2	21.7
21	$S(O)_2NHCH_2$	66	170	3.9	16.9
26	C(O)NHO	15	13	1.1	13.6
29	C(O)NHNH	15	12	4	3.8
1 (1192U90)	$C(O)NHCH_2$	32	3.8	3.3	9.7

[a]Hydrochloride salts unless noted otherwise.
[b]D_2 [^{3}H]raclopride binding; 5-HT_{1a}, [^{3}H]-8-OH-DPAT binding; 5-HT_2, [^{3}H]ketanserin binding.
[c]For experimental protocol, see ref. 26.
[d]Ratio of dopamine D_2 IC_{50} to serotonin 5-HT_2 IC_{50} receptor binding.
[e]Fumarate salt.

changes in D_2 and 5-HT_2 receptor binding affinities as well as the D_2/5-HT_2 ratios. While the D_2 and 5-HT_2 receptors tolerated these structural modifications quite well, the 5-HT_{1a} receptor exhibited a 40-fold decrease in affinity for the sulfonamide analogue.

If the amide -NH of 1192U90 participates in significant hydrogen bonding interactions at these receptors, we would expect substitution of the amide nitrogen with a methylene group to reduce binding affinity. However, ketone **10** potently binds to all three receptors, and in fact, has slightly greater affinities for the D_2 and 5-HT_2 receptors than does 1192U90. This suggests that hydrogen bonding interactions of the amide hydrogen do not contribute significantly to binding at these receptors. This is consistent with earlier observations in which the *N*-methyl analogue of 1192U90 maintained its potent binding affinity for all three receptors.[19] Similarly, ester **5** maintains good binding affinity at these receptors. However, both the ketone and ester exhibited less favorable D_2/5-HT_2 binding ratios due to an increase in D_2 binding relative to 5-HT_2.

The presence of a heteroatom alpha to the amide nitrogen (i.e. hydrazide **29** and alkoxyamide **26**) resulted in small changes to the receptor binding affinities. The small increase in D_2 binding exhibited by hydrazide **29** resulted in a less favorable D_2/5-HT_2 ratio.

In butyramide (**17**) and butyranilide (**18**) the position of the carbonyl group has been changed relative to the amide nitrogen. In both cases however, the four-carbon chain between the amide nitrogen and the piperazine benzisothiazole group has been maintained. In a previous study the four-carbon spacer was found to provide optimal receptor binding activity in an analogous series of phthalimides and isoindolinones.[29] In general, this structural modification led to a decrease in receptor affinity. Most notable was the 30-fold decrease in binding affinity of butyranilide (**18**) for the 5-HT_{1a} receptor. The loss of binding affinity was more significant for the butyranilide analogue and may be due in part to the decreased chain length between the aromatic ring and the piperazine benzisothiazole moiety. Butyramide **17** had the greatest selectivity in this series of compounds with a D_2/5-HT_2 ratio three times greater than 1192U90.

Conclusion

Replacement of the amide group of 1192U90 with alternative functional groups was generally well tolerated by the dopamine D_2, serotonin 5-HT_{1a}, and serotonin 5-HT_2 receptors. Several of these analogues showed selectivity for the serotonin 5-HT_2 receptor as evidenced by their favorable D_2/5-HT_2 binding ratios

(i.e. $D_2/5\text{-}HT_2 > 1$) and therefore may exhibit an atypical antipsychotic profile.

Experimental

Pharmacology

In vitro binding affinity to the dopamine D_2 receptor was determined by displacement of [^{3}H]raclopride from the D_2 receptor.[26] Binding to the serotonin 5-HT_{1a} and 5-HT_2 receptors was determined by the ability of the compounds to displace [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)-tetralin and [^{3}H]ketanserin, respectively.[26]

Chemistry

General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. 3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole was prepared as previously reported.[26] Anhydrous solvents such as dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane, and toluene were obtained from Aldrich Chemical Co. in Sure/Seal bottles. All reactions involving air- or moisture-sensitive compounds were performed under a N_2 atmosphere. Flash chromatography and flush chromatography were performed using EM Science silica gel 60 (230–400-mesh ASTM). The term flush chromatography refers to column chromatography when suction is applied to the bottom of the column to increase the flow rate of the eluant. Preparative radial chromatography was performed using a Harrison Research Chromatotron. Thin-layer chromatography (TLC) was performed with Analtech silica gel GF TLC plates (250 μm). ^{1}H NMR spectra were determined with superconducting FT NMR spectrometers operating at 200, 300, and 500 MHz. ^{13}C NMR were measured at 50.29, 75.43, or 125.706 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet), number of protons, and coupling constants in Hz. Elemental analyses were performed by either Atlantic Microlab, Inc., Norcross, GA, or Galbraith Laboratories, Inc., Knoxville, TN. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected.

3-(4-(4-((*tert*-Butyldimethylsilyl)oxy)butyl)-1-piperazinyl)-1,2-benzisothiazole (3). To a 250 mL round-bottomed flask were added 4-iodo-1-(*tert*-butyldimethylsilyloxy) butane[21] (**2**) (3.65 g, 11.61 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (2.57 g, 11.72 mmol, 1.01 equiv), triethylamine (2.0 mL, 1.45 g, 14.35 mmol, 1.24 equiv.) and acetonitrile (50 mL). The flask was equipped with a magnetic stirring bar, reflux condenser and nitrogen inlet. The stirred yellow suspension was heated at reflux under nitrogen. The reaction mixture became a gold-yellow solution upon heating. After 3 h, the oil bath was removed and the reaction mixture was allowed to stand at room temperature. The reaction mixture was concentrated in vacuo and the residue was partitioned between EtOAc and saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give the crude product as a thin-orange oil. The crude material was purified by flush chromatography with EtOAc:Hex (1:1) to give 2.87 g (61%) of the title compound as a pale-yellow oil. A portion of this material was dried in an abderholden apparatus under high vacuum. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 0.02 (s, 6), 0.85 (s, 9), 1.48 (m, 4), 2.34 (m, 2), 2.55 (m, 4), 3.42 (m, 4), 3.59 (m, 2), 7.41 (t, 1, $J = 7.6$), 7.53 (t, 1, $J = 7.6$), 8.02 (d, 1, $J = 8.4$), 8.03 (d, 1, $J = 7.9$); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ −4.91, 18.30, 22.94, 26.19, 30.57, 50.04, 52.85, 57.95, 62.74, 121.38, 124.47, 124.70, 127.68, 128.16, 152.29, 163.86. Anal. calcd for $C_{21}H_{35}N_3OSiS$: C, 62.18; H, 8.70; N, 10.36. Found: C, 62.14; H, 8.75; N, 10.31.

3-(4-(4-Hydroxybutyl)-1-piperazinyl)-1,2-benzisothiazole (4). To a 250 mL round-bottomed flask were added 3-(4-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-1-piperazinyl)-1,2-benzisothiazole (**3**) (2.37 g, 5.84 mmol), 1.0 N aqueous HCl (30 mL) and THF (30 mL). The flask was equipped with a magnetic stirring bar and the pale yellow solution was stirred at room temperature. After 42 h, the pH of the reaction mixture was adjusted to between 7–8 via the addition of saturated $NaHCO_3$. Ethyl acetate was added and the heterogeneous mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give 2.39 g of a yellow oil. The crude product was used without further purification. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 1.47 (m, 4), 2.33 (t, 2, $J = 6.7$), 2.55 (t, 4, $J = 4.6$), 3.41 (m, 6), 4.50 (br s, 1), 7.41 (ddd, 1, $J = 1.1$, 7.0, 8.1), 7.53 (ddd, 1, $J = 1.2$, 7.0, 8.1), 8.02 (d, 1, $J = 8.1$), 8.03 (d, 1, $J = 8.1$); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 23.32, 30.91, 50.03, 52.87, 58.17, 61.03, 121.37, 124.45, 124.69, 127.68, 128.14, 152.30, 163.87.

4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl-2-aminobenzoate hydrochloride (5). To a 500 mL round-bottomed flask were added 3-(4-(4-hydroxybutyl)-1-piperazinyl)-1,2-benzisothiazole (**4**) (1.82 g, 6.25 mmol), anthranilic acid (1.27 g, 9.26 mmol, 1.48 equiv.), 1-hydroxybenzotriazole hydrate (1.27 g, 9.40 mmol, 1.50 equiv.) and anhydrous DMF (30 mL). The flask was

equipped with a magnetic stirring bar, addition funnel and nitrogen inlet. The pale-yellow solution was cooled in an ice-water bath and a solution of 1,3-dicyclohexylcarbodiimide (2.06 g, 9.98 mmol, 1.60 equiv) in anhydrous DMF (20 mL) was added dropwise. The ice-water bath was removed and the reaction mixture was stirred at room temperature. After 20 h, the reaction mixture was concentrated in vacuo. Ethyl acetate was added to the residue and the suspension was filtered. The filtrate was washed with saturated $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give the crude product as a mixture of fine solids and an orange oil. Ethyl acetate was added to the free base and the suspension was filtered. The filtrate was concentrated to give an orange oil. The crude product was purified by flash chromatography with CH_2Cl_2 followed by CH_2Cl_2:MeOH (95:5) to give 2.31 g of the free base as a yellow–beige solid. The free base was dissolved in CH_2Cl_2 and 1 N ethereal HCl (5.62 mL, 1.0 equiv) was added. The resulting hydrochloride salt was recrystallized from EtOH and H_2O to give 0.985 g (35%) of the title compound as a beige solid. Melting point 201–203 °C. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 1.75 (m, 2), 1.90 (m, 2), 3.24 (m, 4), 3.53 (m, 4), 4.04 (d, 2, J = 13.7), 4.23 (t, 2, J = 6.2), 6.51 (ddd, 1, J = 1.2, 7.0, 8.1), 6.65 (br s, 2), 6.76 (dd, 1, J = 1.3, 8.4), 7.23 (ddd, 1, J = 1.7, 7.0, 8.5), 7.45 (ddd, 1, J = 1.2, 7.0, 8.1), 7.57 (ddd, 1, J = 1.1, 7.0, 8.1), 7.73 (dd, 1, J = 1.6, 8.1), 8.10 (tm, 2, J = 8.8), 11.23 (br s, 1); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 20.42, 25.94, 46.72, 50.83, 55.48, 63.46, 109.06, 115.07, 116.86, 121.54, 124.35, 124.96, 127.31, 128.46, 131.00, 134.38, 151.76, 152.45, 162.56, 167.69. Anal. calcd for $C_{22}H_{26}N_4O_2S$·HCl: C, 59.11; H, 6.09; N, 12.53. Found: C, 59.17; H, 6.11; N, 12.47.

Phenyl-carbamic acid *tert*-butyl ester (7). To a 250 mL, round-bottomed flask were added aniline (1.43 g, 15.35 mmol), di-*tert*-butyl dicarbonate (3.68 g, 16.86 mmol, 1.1 equiv.) and THF (30 mL). The flask was equipped with a magnetic stirring bar, reflux condenser, and nitrogen inlet and the solution was heated at reflux. After 4 h, the oil bath was removed and the reaction mixture was allowed to cool to room temperature. The solvent was removed in vacuo to give the crude product as an orange liquid, which crystallized to a beige solid. The solid was partitioned between 1.0 N aqueous HCl and EtOAc. The layers were separated and the organic phase was washed with 1.0 N aqueous HCl followed by saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a beige solid. The carbamate was recrystallized from hexanes and ethyl acetate to give 1.72 g (58%) of the title compound as fine white needles. Melting point 134–137 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.47 (s, 9), 6.93 (t, 1, J = 7.4), 7.22 (t, 2, J = 8.0), 7.43 (d, 2, J = 8.0) 9.28 (s, 1); ^{13}C NMR (DMSO-d_6; 125 MHz) δ 28.06, 78.84, 118.05, 121.88, 128.47, 139.46, 152.70. Anal. calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.40; H, 7.77; N, 7.28.

(2-Trimethylstannyl-phenyl)-carbamic acid *tert*-butyl ester (8). To a 2 L, three-necked, round-bottomed flask was added phenyl-carbamic acid *tert*-butyl ester (**7**) (15.0 g, 77.6 mmol) and anhydrous THF (300 mL). The flask was equipped with a magnetic stirring bar, thermometer, addition funnel and nitrogen inlet. The clear colorless solution was cooled to −78 °C with a dry ice/acetone bath. The addition funnel was charged with a solution of *tert*-butyllithium (1.7 M in pentane) (110.0 mL, 187 mmol, 2.41 equiv.) and the base was added dropwise to the stirred cold carbamate solution while maintaining the temperature between −70 and −78 °C. The cloudy yellow solution was stirred at −78 °C for 30 min and between −20 and −30 °C for 2 h. The addition funnel was charged with a solution of trimethyltin chloride (1 M in THF) (98.0 mL, 98.0 mmol, 1.26 equiv.) and the gold-yellow reaction mixture was cooled to −78 °C with a dry ice/acetone bath. The trimethyltin chloride solution was added dropwise to the cold reaction mixture. The temperature was maintained between −70 and −78 °C during the addition of the trimethyltin chloride. To the yellow solution was slowly added 276 g of a 15% aqueous NH_4Cl solution. The dry ice/acetone bath was removed shortly after the addition of NH_4Cl had begun. Diethyl ether was added to the quenched reaction and the two-phase mixture was allowed to stir for 15 min. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give the crude product as a yellow liquid. The unreacted BOC-protected aniline precipitated from the yellow liquid upon standing. Hexanes was added to the suspension and the mixture was filtered. The filtrate was concentrated to give the crude product as a yellow liquid which was partially purified by flash chromatography with Hex:EtOAc (93:7) as eluant to give 6.65 g (24%) of the desired product as a clear colorless oil. This material was used in the Stille coupling reaction without further purification. A small portion (0.14 g) of this material was purified further by flash chromatography with Hex:EtOAc (98:2) as eluant to give 0.07 g of the analytically pure product as a white solid. Melting point 61–63.5 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 0.24 (t, 9, J = 28.0 (Sn–H coupling)), 1.44 (s, 9), 7.04 (d, 1, J = 8.0), 7.11 (t, 1, J = 7.0), 7.24 (dt, 1, J = 1.5, 7.6), 7.38 (dd, 1, J = 1.4, 7.2), 8.89 (br s, 1); ^{13}C NMR (DMSO-d_6; 125 MHz) δ −7.09, 28.71, 79.21, 125.26, 125.48, 129.14, 136.83, 144.35, 155.19. Anal. calcd for $C_{14}H_{23}NO_2Sn$: C, 47.23; H, 6.51; N, 3.93. Found: C, 47.44; H, 6.44; N, 3.99.

***tert*-Butyl-*N*-(2-(6-chlorovaleryl)phenyl)carbamate (9).** To a 300 mL, round-bottomed flask were added 6-chlorohexanoyl chloride (3.6 g, 18.7 mmol), bis(acetonitrile)Pd II chloride (54 mg) and toluene (25 mL). A solution of (2-trimethylstannyl-phenyl)-carbamic acid *tert*-butyl ester (**8**) (6.53 g, 18.3 mmol) in toluene (50 mL) was added to the acid chloride solution. The flask was equipped with a reflux condenser and a nitrogen inlet and the pale-yellow solution was heated at reflux. After 1 h, the oil bath was removed and the reaction mixture was allowed to cool to room temperature. The reaction mixture was filtered and the filtrate was concentrated to give the crude product as a gold–yellow liquid. The crude product was partitioned beween Et_2O and H_2O. The layers were separated and the organic layer was washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give the crude product as an orange liquid. The crude product was partially purified by flash chromatography with Hex:EtOAc (16:1) as eluant to give 4.39 g of the title compound as a pale-yellow liquid. A solid precipitated from the yellow liquid upon standing. Hexanes was added and the suspension was filtered to give analytically pure product (0.538 g) as clear colorless plates. The filtrate was concentrated to give 3.82 g of slightly impure product as a pale-yellow liquid which was used without further purification. Melting point 53.5–55 °C. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 1.42 (m, 2), 1.46 (s, 9), 1.61 (quin, 2, J = 7.4), 1.74 (quin, 2, J = 7.1), 3.06 (t, 2, J = 7.2), 3.63 (t, 2, J = 6.7), 7.11 (ddd, 1, J = 1.2, 7.2, 8.3), 7.56 (ddd, 1, J = 1.6, 7.4, 8.7), 8.02 (dd, 1, J = 1.6, 8.1), 8.19 (dd, 1, J = 1.2, 8.5), 10.78 (s, 1); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 23.48, 26.20, 28.25, 32.26, 39.46, 45.64, 80.44, 119.04, 122.01, 122.55, 131.62, 134.63, 140.56, 152.58, 204.95. MS (CI/CH_4, 50 mA/s): M + Na^+ (348), base (216). Anal. calcd for $C_{17}H_{24}ClNO_3$: C, 62.67; H, 7.42; N, 4.30. Found: C, 62.75; H, 7.43; N, 4.30.

1-(2-Aminophenyl)-6-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-1-hexanone hydrochloride (10). To a 250 mL, round-bottomed flask were added *tert*-butyl-*N*-(2-(6-chlorovaleryl)phenyl)carbamate (**9**) (2.92 g, 8.96 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (1.94 g, 8.85 mmol, 1.0 equiv.), triethylamine (2.0 mL, 1.45 g, 14.35 mmol, 1.6 equiv.), and CH_3CN (50 mL). The flask was equipped with a magnetic stirring bar, reflux condenser and nitrogen inlet and the reaction mixture was heated at reflux. After 42 h the reaction mixture was concentrated to give a beige solid. Dichloromethane (30 mL), anisole (7.0 mL), and trifluoroacetic acid (30 mL) were added to the solid and the orange solution was stirred under a nitrogen atmosphere at room temperature for 1 h. The reaction mixture was concentrated and the resulting orange liquid was partitioned between saturated K_2CO_3 and EtOAc. The layers were separated and the organic layer was washed with saturated K_2CO_3. The aqueous layers were combined and extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give the crude product as an orange liquid, which contained white solids. The crude amine was purified by flash chromatography with CH_2Cl_2:MeOH (98:2) followed by CH_2Cl_2:MeOH (96:4) as eluant to give 1.07 g of the free base. The free base (1.07 g) was dissolved in CH_2Cl_2 and 1.0 N ethereal HCl (2.6 mL, 1.0 equiv) was added. The hydrochloride salt was recrystallized from EtOH and H_2O to give 0.758 g (19%) of the title compound as a beige solid. Melting point 237–239 °C. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 1.36 (m, 2), 1.64 (quin, 2, J = 7.4), 1.74 (m, 2), 2.95 (t, 2, J = 7.1), 3.17 (m, 2), 3.34 (m, 4), 3.59 (d, 2, J = 11.3), 4.07 (d, 2, J = 12.9), 6.53 (ddd, 1, J = 1.2, 7.0, 8.1), 6.74 (dd, 1, J = 1.3, 8.4), 7.20 (s, 2), 7.22 (ddd, 1, J = 1.6, 6.8, 8.4), 7.46 (ddd, 1, J = 1.2, 7.0, 8.4), 7.58 (ddd, 1, J = 1.2, 7.0, 8.1), 7.76 (dd, 1, J = 8.1, 1.6), 8.11 (t, 2, J = 8.4), 10.24 (br s, 1); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 23.25, 24.19, 26.12, 38.39, 46.74, 50.78, 55.68, 114.68, 116.83, 117.30, 121.55, 124.35, 124.97, 127.31, 128.47, 131.61, 134.32, 151.40, 152.45, 162.57, 202.21. MS (CI/CH_4, 50 mA/s): M + 1, base (409). Anal. calcd for $C_{23}H_{28}N_4OS$·HCl: C, 62.08; H, 6.57; N, 12.59. Found: C, 62.16; H, 6.59; N, 12.57.

1*H*-Benzo[*d*][1,3]thiazine-2,4-dithione (12). To a 100 mL round-bottomed flask were added isatoic anhydride (0.56 g, 3.43 mmol), phosphorus pentasulfide (2.98 g, 6.70 mmol, 1.95 equiv.) and xylenes (25 mL). The flask was equipped with a magnetic stirring bar, reflux condenser and nitrogen inlet and the suspension was heated at reflux under nitrogen. After 16 h, the oil bath was removed and the reaction mixture was allowed to cool to room temperature. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The filtered maroon solids were washed with THF and the filtrate was combined with the crude product. The THF was removed in vacuo to give the crude product as a maroon solid. The crude product was purified by flash chromatography with Hex:EtOAc (3:1) as eluant to give 0.27 g (37%) of the title compound as a dark maroon solid. Melting point 232.5–235.5 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 7.34 (tm, 1, J = 7.7), 7.48 (d, 1, J = 8.2), 7.81 (tm, 1, J = 7.7), 8.23 (dd, 1, J = 1.4, 8.4), 13.89 (br s, 1); ^{13}C NMR (DMSO-d_6; 125 MHz) δ 120.15, 126.23, 126.70, 127.32, 137.75, 137.89, 187.20, 214.05. Anal. calcd for $C_8H_5NS_3$: C, 45.47; H, 2.38; N, 6.63. Found: C, 45.60; H, 2.42; N, 6.53.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)thiobenzamide hydrochloride (13). 1*H*-Benzo[*d*][1,3]thiazine-2,4-dithione (**12**) (2.9 g, 13.7 mmol) was dissolved in anhydrous THF (40 mL) in a 1 L round-bottomed flask. The flask was equipped with a magnetic stirring bar, rubber septum, and nitrogen inlet. To the

red–orange solution was slowly added a solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (4.2 g, 14.4 mmol, 1.05 equiv) in anhydrous THF (35 mL) via syringe. The reaction mixture was stirred under nitrogen at room temperature for 15 min. Thin-layer chromatography (CH_2Cl_2:MeOH, 95:5) indicated that the reaction was incomplete. Another 0.25 equiv. of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol) in anhydrous THF (10 mL) was slowly added to the orange suspension via syringe. After stirring at room temperature for 15 min, the reaction mixture was filtered and the filtrate was concentrated to give 7.6 g of the crude product as a viscous red–orange residue. The crude product was combined with 0.62 g of crude product obtained in an earlier reaction and the combined material was partially purified by flash chromatography with CH_2Cl_2:MeOH (97:3) as eluant to give 1.0 g of an orange oil. ^{1}H NMR and thin-layer chromatography (CH_2Cl_2:MeOH, 95:5) indicated that impurities remained in the product. A second attempt to purify the free base by flash chromatography with CH_2Cl_2:MeOH (97:3) as eluant failed to remove the impurities as indicated by ^{1}H NMR. The desired free base was finally purified by radial chromatography using CH_2Cl_2 followed by CH_2Cl_2:MeOH (99:1) and finally CH_2Cl_2:MeOH (97:3) as eluant to give 0.718 g of the desired material as a yellow oil. The amine was dissolved in EtOAc and 1.69 mL of 1.0 N ethereal HCl (1.0 equiv.) was added. The hydrochloride salt was filtered, washed with EtOAc and Et_2O, and recrystallized from EtOH to give 0.23 g of the title compound as a yellow solid. Melting point 198–201 °C. ^{1}H NMR (DMSO-d_6; 200 MHz) δ 1.78 (m, 4), 3.05–3.80 (m, 10), 4.10 (br d, 2, J = 12.7), 5.74 (br s, 2), 6.59 (t, 1, J = 7.5), 6.74 (d, 1, J = 8.0), 7.08 (m, 2), 7.50 (t, 1, J = 7.7), 7.63 (t, 1, J = 7.6), 8.15 (t, 2, J = 7.2), 10.30 (m, 1), 10.83 (m, 1); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 21.74, 25.35, 45.37, 47.32, 51.43, 56.10, 118.56, 118.78, 122.18, 124.98, 125.59, 127.93, 128.49, 129.11, 129.37, 130.98, 143.37, 153.08, 163.20, 197.17. MS (CI/CH_4, 50 mA/s) M + 1, base (426). Anal. calcd for $C_{22}H_{27}N_5S_2$·HCl: C, 57.19; H, 6.11; N, 15.16. Found: C, 56.95; H, 6.17; N, 14.98.

4-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-butyric acid ethyl ester (15). To a 250 mL, round-bottomed flask were added 3-(1-piperazinyl)-1,2-benzisothiazole (1.54 g, 7.02 mmol), triethylamine (1.50 mL, 1.09 g, 10.8 mmol, 1.53 equiv) and CH_3CN (30 mL). The flask was equipped with a magnetic stirring bar, addition funnel and nitrogen inlet and a solution of ethyl-4-bromobutyrate (1.44 g, 7.4 mmol, 1.05 equiv) in CH_3CN (10 mL) was slowly added dropwise to the stirred reaction mixture at room temperature. The addition funnel was replaced with a reflux condenser and the reaction mixture was heated at reflux under N_2. After 6 h, the oil bath was removed and the gold–yellow solution was allowed to cool to room temperature. Ethyl acetate was added to the reaction mixture and the solution was washed with saturated aqueous K_2CO_3. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give the crude product as an orange liquid. The crude product was purified by flash chromatography with Hex:EtOAc (1:1) as eluant to give 1.65 g (70%) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.27 (t, 3, J = 7.2), 1.88 (quin, 2, J = 7.3), 2.38 (t, 2, J = 7.3), 2.47 (t, 2, J = 7.1), 2.68 (m, 4), 3.56 (m, 4), 4.15 (q, 2, J = 7.2), 7.35 (t, 1, J = 7.5), 7.46 (t, 1, J = 7.5), 7.81 (d, 1, J = 8.1), 7.91 (d, 1, J = 8.2); ^{13}C NMR ($CDCl_3$; 125 MHz) δ 14.21, 22.09, 32.21, 50.04, 52.91, 57.68, 60.22, 120.48, 123.77, 123.86, 127.42, 128.01, 152.71, 163.88, 173.48. Anal. calcd for $C_{17}H_{23}N_3O_2S$: C, 61.23; H, 6.95; N, 12.60. Found: C, 61.25; H, 6.97; N, 12.60.

4-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-butyric acid (16). To a 300 mL, round-bottomed flask was added 4-(4-benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-butyric acid ethyl ester (**15**) (3.34 g, 10.0 mmol), 0.1 N aqueous NaOH (40 mL) and EtOH (1.5 mL). The flask was equipped with a magnetic stir bar and reflux condenser and the reaction mixture was heated at reflux for 1.5 h. The reaction mixture was cooled in an ice-water bath and the pH was adjusted to ~6–7 via the addition of 1.0 N aqueous HCl. The reaction mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated to give 0.88 g of the product as an oil which solidified to a white solid (^{1}H NMR data shown below). White solids were filtered from the aqueous phase and dried to give 1.82 g of a second crop of the carboxylic acid. The aqueous filtrate was partially concentrated in vacuo and the white solids were filtered, washed with water, and dried to give a third crop of the desired material (0.40 g) for a total yield of 3.1 g (100%). This material was used without further purification. ^{1}H NMR (DMSO-d_6; 200 MHz) δ 1.72 (m, 2), 2.29 (t, 2, J = 7.2), 2.40 (t, 2, J = 7.0), 2.61 (br t, 4, J = 4.6), 3.45 (br t, 4, J = 4.5), 7.45 (tm, 1, J = 7.4), 7.54 (tm, 1, J = 8.01), 8.07 (d, 2, J = 8.2).

***N*-(2-Aminobenzyl)-4-(4-(1,2-benzothiazol-3-yl)-1-piperazinyl) butyramide fumarate (17).** To a 1-L, round-bottomed flask were added 4-(4-benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-butyric acid (**16**) (1.38 g, 4.52 mmol), 2-aminobenzylamine (0.65 g, 5.32 mmol, 1.18 equiv.), 1-hydroxybenzotriazole hydrate (0.61 g, 4.51 mmol, 1.0 equiv), and DMF (25 mL). The flask was equipped with a magnetic stirring bar and an addition funnel. A solution of 1,3-dicyclohexylcarbodiimide (1.2 g, 5.82 mmol, 1.29 equiv.) in DMF (15 mL) was added dropwise to the stirred reaction mixture. Additional portions of 1-hydroxybenzotriazole hydrate (0.12 g, 0.89 mmol, 0.2 equiv.) and DMF (10 mL) were added to the reaction mixture which was allowed to stir at room

temperature for 3 days. Ethyl acetate was added to the reaction mixture and the organics were washed with saturated aqueous K_2CO_3. The layers were separated and the aqueous phase was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give the crude product as a pale orange oil. The crude material was purified by flash chromatography with CH_2Cl_2:MeOH (95:5) as eluant to give 1.56 g of the free base as an orange oil. The free base (0.48 g, 1.2 mmol) was dissolved in EtOH and CH_2Cl_2 and fumaric acid (0.14 g, 1.2 mmol, 1.0 equiv.) was added. The solution was filtered and the filtrate was concentrated to give a pale-yellow oil. Ethyl acetate was added to the oil and crystallization was initiated via scraping the wall of the flask with a spatula. The suspension was heated and the product was filtered as an off-white solid. The solid was dried to give 0.349 g (63%) of the desired product. Melting point 135–136 °C. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 1.73 (quin, 2, J = 7.0), 2.19 (t, 2, J = 7.3), 2.36 (t, 2, J = 7.1), 2.58 (m, 4), 3.44 (m, 4), 4.12 (br d, 2, J = 6.1), 6.49 (dt, 1, J = 1.0, 7.3), 6.61 (m, 2), 6.96 (m, 2), 7.44 (ddd, 1, J = 1.1, 7.0, 8.1), 7.56 (ddd, 1, J = 1.2, 7.0, 8.1), 8.05 (d, 1, J = 8.2), 8.06 (d, 1, J = 8.2), 8.23 (br t, 1, J = 6.0); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 23.23, 34.04, 40.13, 50.43, 53.27, 58.03, 115.45, 116.58, 122.02, 123.14, 125.09, 125.34, 128.28, 128.80, 130.13, 135.29, 147.20, 152.93, 164.43, 167.48, 173.24. Anal. calcd for $C_{22}H_{27}N_5OS{\cdot}0.5\ C_4H_4O_4$: C, 61.65; H, 6.25; N, 14.98. Found: C, 61.58; H, 6.30; N, 14.89.

2′-Amino-4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyranilide hydrochloride (18). To a flame-dried 100 mL, three-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum, thermometer, and nitrogen inlet was added 4-(4-benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-butyric acid (**16**) (2.70 g, 8.84 mmol), Et_3N (2.59 mL, 1.88 g, 18.6 mmol, 2.1 equiv.) and THF (35 mL). The suspension was cooled to −15 °C with an isopropyl alcohol/CO_2 bath and isobutylchloroformate (1.15 mL, 1.21 g, 8.84 mmol, 1.0 equiv.) was added while maintaining the temperature at −15 °C. After 10 min, a solution of *o*-phenylenediamine (1.05 g, 9.72 mmol, 1.1 equiv.) in THF (20 mL) was added to the cold reaction mixture. The isopropyl alcohol/CO_2 bath was removed and the reaction mixture was allowed to stir at room temperature for 1 h. The solvent was removed in vacuo and the crude product was partitioned between EtOAc and saturated aqueous K_2CO_3. The organic phase was dried over $MgSO_4$, filtered, and the filtrate was concentrated to give an oil. The free base was partially purified by flash chromatography with EtOAc:0.1% Et_3N, EtOAc:0.2% Et_3N, EtOAc:0.4% Et_3N and finally MeOH as eluant. The impure material obtained from this column was combined with 0.1 g of partially purified free base (flash chromatography Hex:-EtOAc (2:1):0.1% Et_3N, Hex:EtOAc (1:1):0.1% Et_3N, EtOAc:0.1% Et_3N and EtOAc:0.2% Et_3N as eluant) obtained in an earlier reaction to give a total of 0.9 g of impure amine. Approximately 0.4 g of this material was applied to a chromatotron and eluted with CH_2Cl_2:MeOH (97:3) to give 0.14 g of the desired compound. The pure free base was dissolved in EtOAc and 0.35 mL of 1 N ethereal HCl (1.0 equiv.) was added. The resulting white solid was filtered and dried in a vacuum oven to give 0.116 g of the desired hydrochloride salt. The impure fractions from the chromatotron run were combined with the remaining partially purified amine and the material was purified by flash chromatography with $CHCl_3$:MeOH (9:1) as eluant. The free base (0.21 g) was dissolved in EtOAc and CH_2Cl_2 and 0.53 mL of 1 N ethereal HCl (1.0 equiv.) was added. The second crop of the desired hydrochloride salt was filtered as a white solid and dried in a vacuum oven to give another 0.19 g. The two crops of the hydrochloride salt were combined and dried further in a vacuum oven to give a final yield of 0.24 g (5.4%). Melting point 177–181 °C. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 2.10 (m, 2), 3.25 (m, 2), 3.25–3.90 (m, 8), 4.05 (m, 2), 4.70–5.90 (br s, 2), 6.54 (t, 1, J = 7.1), 6.73 (d, 1, J = 8.0), 6.90 (t, 1, J = 7.0), 7.21 (d, 1, J = 7.9), 7.47 (t, 1, J = 7.5), 7.60 (t, 1, J = 7.5), 8.12 (t, 2, J = 9.0), 9.38 (s, 1); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 19.47, 32.54, 46.55, 50.65, 55.28, 115.87, 116.14, 121.24, 123.33, 124.05, 124.67, 125.43, 125.82, 127.01, 128.17, 141.80, 152.15, 162.28, 169.99. Anal. calcd for $C_{21}H_{25}N_5OS\cdot HCl$: C, 58.39; H, 6.07; N, 16.21. Found: C, 58.12; H, 6.04; N, 16.12.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)benzenesulfonamide hydrochloride (21). To a 100 mL, flame-dried, three-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, glass stopper and nitrogen inlet was added sodium hydride (80% dispersion in oil) (0.139 g, 4.62 mmol). The sodium hydride was washed three times with hexanes. The waste hexanes were removed with the aid of a 2 mL pasteur pipet. Anhydrous DMF (10 mL) was added to the sodium hydride and the grey suspension was cooled under nitrogen in an ice-water bath. A solution of 2-aminobenzene sulfonamide (**19**) (0.73 g, 4.20 mmol) in anhydrous DMF (5.0 mL) was slowly added to the cold NaH suspension via syringe. After several minutes, a solution of 8-(1,2-benzisothiazol-3-yl)-8-aza-5-azoniaspiro[4.5]decane bromide[22] (**20**) (1.5 g, 4.2 mmol) in anhydrous DMF (12 mL) was added to the sulfonamide salt and the reaction mixture was allowed to stir at 0 °C under N_2. After 0.5 h, the ice-water bath was replaced with an oil bath and the reaction mixture was heated at reflux under N_2. After 18 h, the oil bath was removed and the reaction mixture was allowed to cool to room temperature. The reaction mixture was

concentrated and the residue was partitioned between H_2O and EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give an orange oil. The crude free base was purified by flash chromatography with EtOAc:Hex (1:1): 0.1% Et_3N followed by EtOAc:Hex (2:1): 0.1% Et_3N as eluant to give 0.645 g of the free base as an oil. The free base was dissolved in EtOAc and 1.45 mL of 1 N ethereal HCl (1.0 equiv.) was added. The hydrochloride salt was recrystallized from EtOH and H_2O to give 0.412 g (20%) of the title compound as an off-white solid. Melting point 214–216 °C. ^{1}H NMR (DMSO-d_6; 200 MHz) δ 1.46 (m, 2), 1.75 (m, 2), 2.80 (m, 2), 3.00–3.65 (m, 8), 4.09 (br d, 2, J = 13.1), 5.97 (br s, 2), 6.65 (ddd, 1, J = 1.2, 7.1, 8.1), 6.86 (dd, 1, J = 1.2, 8.2), 7.30 (ddd, 1, J = 1.6, 7.1, 8.5), 7.60 (m, 4), 8.14 (d, 1, J = 7.9), 8.17 (d, 1, J = 7.4), 10.95 (br s, 1); ^{13}C NMR (DMSO-d_6; 50.29 MHz) δ 20.46, 26.33, 41.66, 46.56, 50.63, 55.20, 115.45, 117.22, 120.19, 121.53, 124.34, 124.97, 127.31 128.47, 129.38, 133.78, 145.56, 152.49, 162.59. Anal. calcd for $C_{21}H_{27}N_5S_2O_2$·HCl: C, 52.32; H, 5.85; N, 14.53. Found: C, 52.42; H, 5.87; N, 14.51.

4-(3-Bromo-propoxy)-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (23). *endo-N*-Hydroxy-5-norborene-2,3-dicarboxamide (**22**) (9.8 g, 54.7 mmol) and CH_3CN (200 mL) were combined in a 1 L round-bottomed flask. To the stirred suspension was added dropwise 1,3-dibromopropane (17.0 mL, 167.5 mmol, 3.06 equiv.) followed by the dropwise addition of *N*,*N*-diisopropylethylamine (19.5 mL, 111.9 mmol, 2.04 equiv). The flask was equipped with a reflux condenser and a nitrogen inlet and the reaction mixture was heated at 70 °C under nitrogen for 5.5 h and allowed to stir at room temperature overnight. The reaction mixture was concentrated and EtOAc was added to the crude product. The suspension was filtered and the solids were washed with EtOAc. The combined filtrates were concentrated to give a yellow–orange oil. The crude bromide was purified by flash chromatography with Hex:EtOAc (4:1) followed by Hex:EtOAc (3:1) as eluant to give 13.85 g (84%) of the desired product as a white solid. Melting point 58.5–60.5 °C. ^{1}H NMR ($CDCl_3$; 500 MHz) δ 1.50 (d, 1, J = 9.1), 1.76 (dt, 1, J = 9.0, 1.7), 2.16 (quin, 2, J = 6.2), 3.18 (dd, 2, J = 1.4, 2.8), 3.42 (s, 2), 3.58 (t, 2, J = 6.4), 4.09 (t, 2, J = 5.9), 6.16 (t, 2, J = 1.8); ^{13}C NMR ($CDCl_3$; 125 MHz) δ 29.16, 31.37, 42.57, 44.72, 51.37, 75.02, 134.54, 172.01. Anal. calcd for $C_{12}H_{14}NO_3Br$: C, 48.02; H, 4.70; N, 4.67. Found: C, 48.15; H, 4.67; N, 4.69.

2-(3-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)propoxy-2,3,3A,4,7,7A-hexahydro-4,7-methano-1*H*-isoindoline-1,3-dione hydrochloride (24). To a 500 mL, round-bottomed flask was added 4-(3-bromo-propoxy)-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (**23**) (2.77 g, 9.23 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (2.02 g, 9.21 mmol, 1.0 equiv.), *N*,*N*-diisopropylethylamine (2.0 mL, 1.48 g, 11.5 mmol, 1.25 equiv.), and CH_3CN (100 mL). The flask was equipped with a magnetic stirring bar, reflux condenser, and nitrogen inlet and the reaction mixture was heated at reflux under a N_2 atmosphere. After 4 h, the oil bath was removed and the reaction mixture was allowed to stand at room temperature overnight. Ethyl acetate and saturated aqueous $NaHCO_3$ were added to the flask and the mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc. The organic layers were combined and concentrated in vacuo to give an orange oil. The crude product was purified by flash chromatography with CH_2Cl_2:MeOH (98:2) as eluant to give 3.27 g of the free base. The free base was dissolved in EtOAc and 7.43 mL of 1 N ethereal HCl (1.0 equiv.) was added. The solvent was removed in vacuo and the salt was recrystallized from EtOH to give 2.2 g (51%) of the title compound as a white solid. Melting point 196–200 °C. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 1.49 (d, 1, J = 8.7), 1.57 (d, 1, J = 8.7), 2.07 (m, 2), 3.29 (m, 8), 3.52 (m, 4), 4.01 (m, 4), 6.14 (s, 2), 7.46 (t, 1, J = 7.5), 7.58 (t, 1, J = 7.7), 8.11 (t, 2, J = 8.3), 11.33 (br s, 1); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 22.64, 42.55, 44.43, 46.74, 51.00, 51.30, 53.14, 74.19, 121.55, 124.37, 124.97, 127.32, 128.47, 134.89, 152.45, 162.56, 172.62. Anal. calcd for $C_{23}H_{26}N_4O_3S$·HCl: C, 58.16; H, 5.73; N, 11.79. Found: C, 58.19; H, 5.75; N, 11.75.

***O*-[3-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-propyl]-hydroxylamine (25).** To a 100 mL, round-bottomed flask were added the free base of 2-(3-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)propoxy-2,3,3A,4,7,7A-hexahydro-4,7-methano-1*H*-isoindoline-1,3-dione (**24**) (2.49 g, 5.68 mmol), hydrazine hydrate (55% aq solution, 0.38 g, 6.45 mmol, 1.14 equiv.), and EtOH (95%, 10 mL). The flask was equipped with a magnetic stirring bar, reflux condenser and nitrogen inlet and the yellow solution was heated at reflux. After 0.75 h, the oil bath was removed and the reaction mixture was concentrated in vacuo. The crude product was partitioned between EtOAc and 1 N aqueous HCl. The layers were separated and the pH of the aqueous solution was adjusted to ~12 with 1 N aqueous NaOH. The basic aqueous phase was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 1.28 g (77%) of the desired product as a yellow oil. The product was used without further purification. ^{1}H NMR (DMSO-d_6; 300 MHz) δ 1.68 (quin, 2, J = 7.0), 2.37 (t, 2, J = 7.4), 2.56 (br t, 4, J = 4.7), 3.42 (br t, 4, J = 4.7), 3.55 (t, 2, J = 6.5), 5.89 (s, 2), 7.41 (t, 1, J = 7.6), 7.54 (t, 1, J = 7.5), 8.03 (d, 1, J = 7.9), 8.04 (d, 1, J = 8.4); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 25.85, 50.04, 52.91, 55.24, 73.52, 121.39, 124.47, 124.71, 127.67, 128.17, 152.29, 163.87.

2-Amino-*N*-(3-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) propoxy)benzamide hydrochloride (26). To a 300 mL, round-bottomed flask were added *O*-[3-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-hydroxylamine (**25**) (1.27 g, 4.34 mmol), isatoic anhydride (0.75 g, 4.57 mmol, 1.05 equiv) and THF (28 mL). The orange solution was stirred at room temperature under a nitrogen atmosphere for 18 h. The reaction mixture was concentrated and the crude product was purified by flash chromatography with EtOAc:MeOH (95:5) as eluant to give 1.54 g of the free base as a viscous yellow oil. The amine was dissolved in CH_2Cl_2 and 3.74 mL (1.0 equiv.) of 1 N ethereal HCl was added. The solvent was removed in vacuo and the salt was dissolved in MeOH (~4 mL). The methanol solution was filtered and the filtrate was slowly added to rapidly stirred EtOAc (75 mL). The solid was filtered, washed with Et_2O, and dried to give 0.79 g (40%) of the title compound as an off-white solid. Melting point 106–112 °C (softens and shrinks). ^{1}H NMR (DMSO-d_6; 300 MHz) δ 2.13 (m, 2), 3.44 (m, 6), 3.66 (br d, 2, J = 10.8), 3.99 (br t, 2, J = 5.2), 4.09 (br d, 2, J = 13.1), 6.49 (ddd, 1, J = 1.4, 7.1, 8.1), 6.71 (dd, 1, J = 1.2, 8.3), 7.16 (ddd, 1, J = 1.4, 7.1, 8.4), 7.38 (dd, 1, J = 1.6, 7.9), 7.46 (ddd, 1, J = 1.1, 6.8, 8.1), 7.58 (ddd, 1, J = 1.1, 6.8, 7.9), 8.09 (d, 1, J = 8.1), 8.13 (d, 1, J = 8.1), 10.98 (br s, 1); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 22.58, 46.86, 51.13, 54.20, 73.76, 111.79, 115.03, 116.79, 121.56, 124.35, 124.99, 127.31, 128.18, 128.49, 132.75, 149.98, 152.47, 162.54, 167.97. Anal. calcd for $C_{21}H_{25}N_5O_2$·HCl: C, 56.30; H, 5.85; N, 15.63. Found: C, 56.07; H, 5.90; N, 15.45.

3-[4-(3-Chloropropyl)-piperazin-1-yl]-benzo[*d*]isothiazole (28). To a 250 mL, round-bottomed flask were added 3-(1-piperazinyl)-1,2-benzisothiazole (3.0 g, 13.7 mmol), 1-bromo-3-chloropropane (4.31 g, 27.4 mmol, 2.0 equiv.), triethylamine (2.86 mL, 2.1 g, 25.2 mmol, 1.8 equiv.) and CH_3CN (50 mL). The reaction mixture was stirred under a N_2 atmosphere at room temperature for 21 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and the filtrate was concentrated to give an orange liquid. The crude product was purified by flash chromatography with CH_2Cl_2 followed by CH_2Cl_2:MeOH (99:1) as eluant to give 3.44 g (85%) of the title compound as a yellow oil, which solidified to a pale-yellow solid. Melting point 52–53.5 °C. ^{1}H NMR ($CDCl_3$; 500 MHz) δ 2.00 (quin, 2, J = 6.8), 2.58 (t, 2, J = 7.1), 2.68 (t, 4, J = 4.9), 3.56 (t, 4, J = 4.9), 3.64 (t, 2, J = 6.5), 7.35 (t, 1, J = 7.6), 7.46 (t, 1, J = 7.5), 7.80 (d, 1, J = 8.2), 7.90 (d, 1, J = 8.2); ^{13}C NMR ($CDCl_3$; 125 MHz) δ 29.82, 43.13, 50.02, 53.02, 55.42, 120.51, 123.82, 123.84, 127.47, 127.98, 152.70, 163.85. Anal. calcd for $C_{14}H_{18}N_3SCl$: C, 56.84; H, 6.13; N, 14.20. Found: C, 56.87; H, 6.10; N, 14.16.

2-Amino-*N*′-(3-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) propyl)benzhydrazide hydrochloride hydrate (29). 2-Aminobenzhydrazide (0.79 g, 5.23 mmol), 3-[4-(3-chloropropyl)-piperazin-1-yl]-benzo[*d*]isothiazole (**28**) (1.55 g, 5.24 mmol, 1.0 equiv.) and absolute EtOH (25 mL) were combined in a 100 mL, round-bottomed flask and stirred at reflux under a N_2 atmosphere. After 24 h, the oil bath was removed and the reaction mixture was allowed to stand at room temperature for 2 days. The solvent was removed in vacuo and the crude product was partially purified by flash chromatography with CH_2Cl_2:MeOH:Et_3N, 96:3:1 as eluant. A second flash chromatographic separation with CH_2Cl_2:MeOH (98:2):0.1% Et_3N followed by CH_2Cl_2:MeOH (97:3):0.3% Et_3N as eluant gave 1.41 g of the free base. This material was combined with 0.51 g of the free base obtained in an earlier reaction (purified by flash chromatography with CH_2Cl_2:MeOH:Et_3N (96:3:1) as eluant). The combined crops of the free base were dissolved in CH_2Cl_2 and the solution was washed with saturated aqueous $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered, and the filtrate was concentrated to give 1.67 g (58% yield based on the two reactions) of the desired free base as a yellow amorphous solid. The amine was dissolved in CH_2Cl_2 and 4.0 mL of 1 N ethereal HCl (1.0 equiv.) was added to the solution. The solvent was removed in vacuo and the salt was crystallized from MeOH:EtOAc:Et_2O to give 0.944 g (29%) of the title compound as an off-white solid. Melting point 83–93 °C (softens and shrinks). ^{1}H NMR (DMSO-d_6; 300 MHz) δ 1.93 (m, 2), 2.91 (t, 2, J = 6.0), 3.31 (t, 2, J = 7.2), 3.45 (br s, 4), 3.80 (br s, 4), 6.49 (ddd, 1, J = 1.2, 7.1, 8.1), 6.71 (dd, 1, J = 1.2, 8.3), 7.13 (ddd, 1, J = 1.6, 7.0, 8.4), 7.45 (ddd, 1, J = 1.1, 7.1, 8.1), 7.51 (dd, 1, J = 1.6, 7.9), 7.57 (ddd, 1, J = 1.1, 7.1, 8.1), 8.00 (br s, 2), 8.08 (d, 1, J = 8.1), 8.13 (d, 1, J = 7.9); ^{13}C NMR (DMSO-d_6; 75.43 MHz) δ 21.73, 46.86, 49.23, 51.03, 55.14, 113.16, 115.03, 116.72, 121.52, 124.36, 124.96, 127.33, 128.34, 128.46, 132.38, 149.94, 152.46, 162.58, 168.87. MS (CI/CH_4, 50 mA/s) M + 1, base (411). Anal. calcd for $C_{21}H_{26}N_6OS$·HCl·0.75 H_2O: C, 54.77; H, 6.24; N, 18.25; Cl, 7.70. Found: C, 54.87; H, 6.20; N, 18.05; Cl, 7.73.

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