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Scalable Synthesis of a Cis-Substituted Cyclobutyl-Benzothiazole Pyridazinone: Process Development of an Efficient Copper Catalyzed C−N Cross-Coupling Reaction

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ABSTRACT: A scalable process for the preparation of 2-(2-(*cis*-3-(piperidin-1-yl)cyclobutyl)benzothiazol-6-yl)pyridazin-3(2H)-one in multi-kilogram amounts and in high purity has been developed. The key features of this synthesis are the copper-catalyzed C−N cross-coupling reaction and the development of a highly diastereoselective reductive amination using $NaBH(OPiv)_3$ as a reducing agent. Controls were implemented to minimize both base- and acid-catalyzed isomerization of the 1,3-*cis*-substituted cyclobutane ring.

INTRODUCTION

A number of histamine-3 (H_3) antagonists have in recent years entered and completed clinical trials for the treatment of central nervous system (CNS) disorders such as attention deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), and the cognitive deficits of schizophrenia (CDS).[1−4] Compound **1** (Figure 1) exhibits potent and selective binding to human and

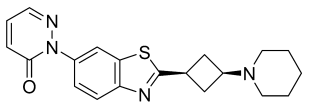

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Figure 1. Structure of API **1**.

rat H_3 receptors, where it acts as a competitive antagonist. In order to further evaluate its effectiveness and profile in extended studies, a large quantity of the drug substance was required. The process research and development efforts resulted in a reliable and scalable synthesis to provide multi-kilogram quantities of **1** in high purity.

The key structural features of **1** are the 1,3-*cis*-substitution of the benzothiazole and piperidine substituents on the cyclobutane ring as well as the pyridazinone heterocycle.[5,6] The initial synthesis (Scheme 1) begins by hydrolysis of the commercially available 6-bromo-2-benzothiazolinone (**2**), followed by construction of the benzothiazole heterocycle via condensation of the aryl aminothiol **3** and cyclobutene substituted acid chloride **4** promoted by Et_3N and pyridinium *p*-toluenesulfonate. Oxidative cleavage of the cyclobutene **5** to the ketone **6** followed by reduction and copper-catalyzed C−N cross-coupling with pyridazinone **7** affords alcohol **8**. Oxidation of **8** to ketone **9** followed by reductive amination with sodium cyanoborohydride, $NaBH_3CN$, afforded a mixture of the *cis*- and *trans*-isomers, **1** and *trans*-**1**. These isomers could be separated by SiO_2 chromatography, affording a 35% yield of **1**. The initial synthesis provided **1** in seven steps with an overall yield of 12%.[5,6]

On analysis of this synthesis, several scale-up concerns and areas of improvement were identified to develop a synthesis of multi-kilogram quantities of **1**. First, it would be desirable to avoid the use of the toxic OsO_4 during the synthesis of **6**. Second, removal of the reduction and oxidation steps, which were used as a protecting group strategy to minimize impurity formation in the cross-coupling reaction, would afford a significant increase in efficiency. Finally, we identified a stereoselective reductive amination as being the pivotal step to set the desired *cis*-stereochemistry, improve the yield, and avoid a tedious chromatography.[7,8] This stereoselective reductive amination could occur either early in the reaction sequence as a way to avoid the reduction and subsequent oxidation of the cyclobutanone (*via* intermediate **10**) or as the last step (*via* intermediate **9**) (Scheme 2). This led to identification of the key intermediate **6**, which would serve as precursor to both routes.

DISCUSSION AND RESULTS

To quickly determine the feasibility of the proposed routes and identify which one showed more promise, the key experiments were performed first. Compound **10** was prepared in a 97:3 dr after purification and was subjected to the CuCl catalyzed cross-coupling with **7** to afford **1** in 99% conversion. Surprisingly, **1** was obtained in a 79:21 dr as both **10** and **1** were observed to isomerize over the course of the reaction. A series of control studies shows that the isomerization of **1** is catalyzed by CuCl under the reaction conditions. Modification of the reaction conditions by varying the catalyst loading and lowering reaction temperature helped attenuate the isomerization to less than 5% but resulted in longer reaction times or lower conversions. The propensity of the isomerization to occur under a variety of reaction conditions led us to abandon this route and focus on improving the route via intermediate **9**.

As in the initial route, the synthesis of **6** began with the hydrolysis of **2** to the aminothiol **3** in aqueous NaOH. After

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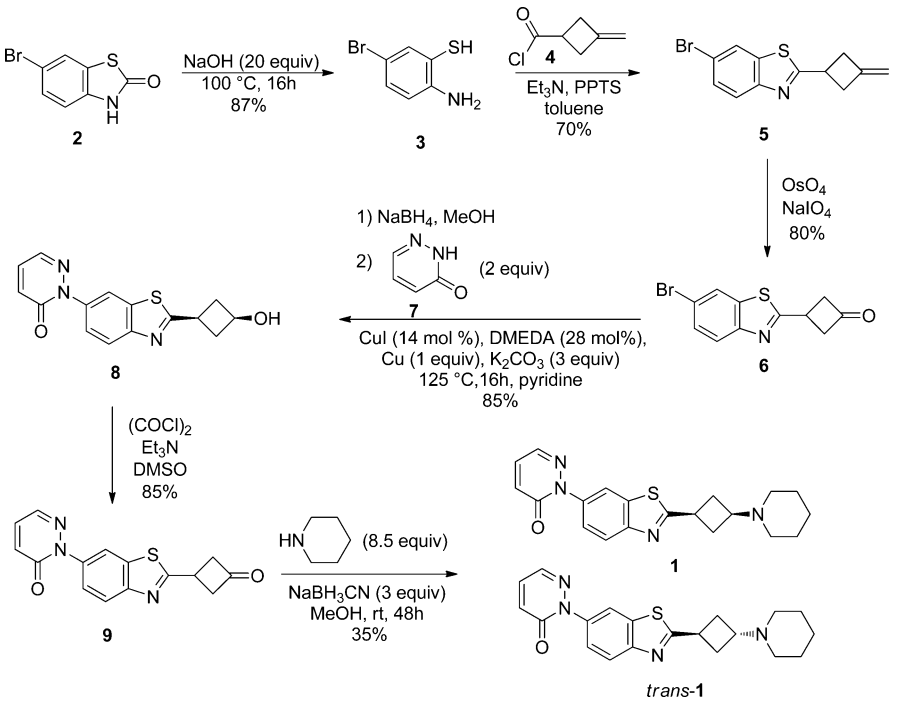
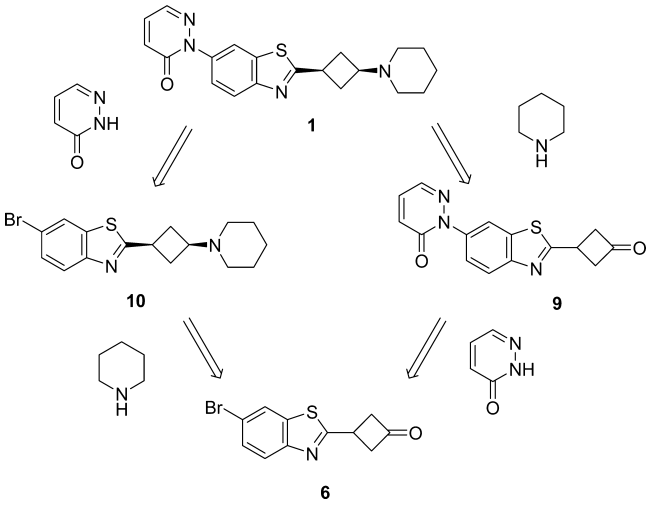
Scheme 1. Initial Route



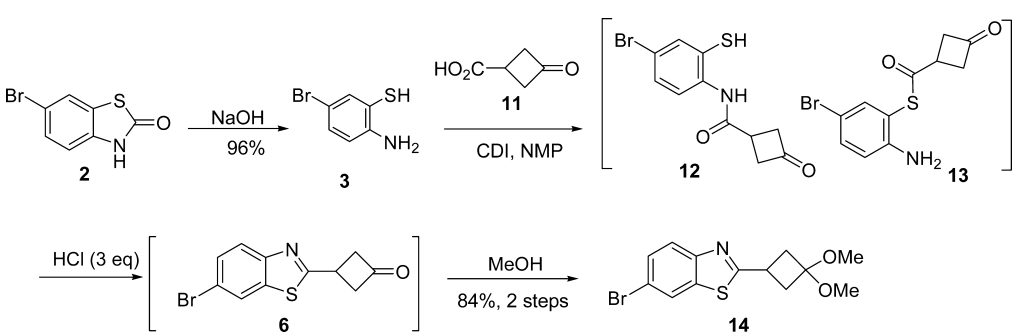
Scheme 2. Retrosynthesis



acidification, the product precipitated from the reaction mixture and was isolated by filtration to afford a 96% yield of **3**. This substrate was air sensitive and required sparging of solvents and reaction vessels prior to hydrolysis and during isolation. The isolated product **3** was also susceptible to oxidation to the disulfide; however, drying and keeping the solid under a N_2 atmosphere minimized the amount of oxidation which occurred.[9]

To avoid the OsO_4 oxidative cleavage, condensation of **3** with the commercially available cyclobutanone carboxylic acid **11** was studied (Scheme 3). This condensation proceeded by activating the carboxylic acid with *N,N′*-carbonyldiimidazole (CDI)[10] followed by slow addition of the activated carboxylic acid intermediate to **3** ,which resulted in reaction at either the amine or the thiol functionality to afford a mixture of intermediates **12** and **13**. Slow addition of 1.05 equiv of the activated carboxylic acid intermediate minimized the formation of the *bis*-acylated impurity, which did not undergo further conversion to **6**. Addition of HCl to the reaction mixture promoted the condensation of **12** and **13** to the benzothiazole to form the key intermediate **6** (**12** converted at rt; however, **13** required mild heating to 45 °C for the condensation to occur). It was found that the cyclobutanone could be efficiently protected as the dimethyl ketal **14** by addition of MeOH to the

Scheme 3. Synthesis of 6 and 14



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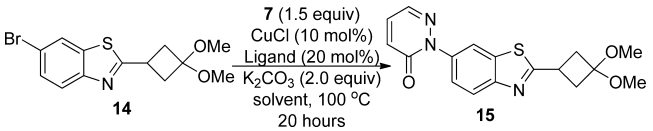
acidic reaction mixture after the condensation to form intermediate **6** was complete. This telescoped process resulted in the isolation of **14** as a crystalline solid in an 84% overall yield from **3**.

Intermediates **6** and **14** were both evaluated in the C−N cross-coupling reaction with **7**. Direct cross-coupling of intermediate **6** with **7** resulted in the formation of a number of impurities, which had been addressed in the initial route by using the reduction/oxidation sequence. Conversely, the intermediate **14** was found to undergo smooth C−N cross-coupling reaction with **7** so the reaction conditions for the copper-catalyzed cross-coupling were then further optimized. The commonly used 1,10-phenanthroline ligand[11] resulted in low conversion to product **15** (Table 1, entry 1) whereas

Table 1. Ligand and Solvent Optimization



entry	ligand	solvent	conversion, %
1	1,10-phenanthroline	NMP	47%
2	8-hydroxyquinoline	NMP	100%[a]
3	DMEDA	NMP	24%
4	DMEDA	pyridine	100%[b]
5	DMEDA	toluene	15%
6	DMEDA	dioxane	5%
7	DMEDA	5:1 toluene/pyridine	75%

[a]Peak area purity of 85% [b]Peak area purity of 96%.

employment of 8-hydroxyquinoline[12] in NMP (entry 2) or *N*,*N*′-dimethylethylene diamine (DMEDA)[13] in pyridine (entry 4) resulted in complete conversion of the starting material. On closer evaluation of the 8-hydroxyquinoline reaction, up to 15% of an impurity arising from a cross-coupling reaction between **14** and ligand was observed, which was difficult to remove by crystallization from the desired product. This low purity led to the choice of DMEDA as the preferred ligand. A 2:1 loading of ligand/catalyst was found to result in the fastest reaction, and a solvent survey found pyridine to be the most effective solvent for this conversion (entries 3−7).

To complete the optimization of the C−N cross-coupling step, a number of bases were screened. K_2CO_3 was found to give the highest conversion while minimizing the amount of ligand cross-coupled impurity **16** (Figure 2). The use of other

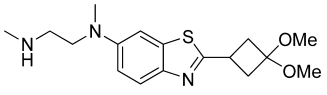
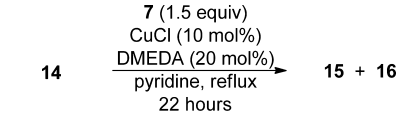


Figure 2. Impurity **16**.

bases was inferior, such as K_2HPO_4, which resulted in poor conversion to product (Table 2, entry 1) or K_3PO_4 or KOTMS, which resulted in significant formation of **16** (entries 3, 4).

Effective removal of the residual copper from the reaction mixture was achieved by a 5% NH_4OH wash. It was found that only minimal product was lost to the first 5% NH_4OH wash; additional washes resulted in significant loss of product due to the pyridine solvent. It was found that a solvent switch from pyridine to toluene followed by additional washes minimized the loss of product as well as providing a convenient isolation of

Table 2. Base Optimization



entry	base	conversion, %	**16**, %
1	K_2HPO_4	10%	ND
2	K_2CO_3	100%	1%
3	K_3PO_4	98%	6%
4	KOTMS	92%	8%

the product through a toluene/heptane recrystallization. This procedure provided crystalline **15** in an 84% yield with >98% purity and <20 ppm of residual copper.

The ketal protecting group could be efficiently removed by treating **15** with aqueous HCl in CH_3CN to provide the desired ketone **9** in 92% yield and >98% purity.

To set the key *cis*-stereochemistry on the cyclobutane ring, a variety of reductive amination procedures were investigated.[7] Using $NaBH_3CN$, the same reductant as for the initial route, gave a poor *cis*/*trans* ratio as well as significant alcohol side-product, **8** (Table 3, entry 1). Switching reducing agent to $NaBH(OAc)_3$ greatly improved the reaction profile by lowering the amount of impurity **8** and improving the diastereoselectivity (entry 2). To further increase the diastereoselectivity, more hindered reducing agents were prepared by reaction of $NaBH_4$ with a variety of carboxylic acids.[14] While increasing the substituent size from Me to Et to *i*-Pr had little improvement in selectivity, the *t*-Bu substituent in the prepared $NaBH(OPiv)_3$ resulted in a significant increase in *cis* to *trans* selectivity as well as a decrease in the amount of alcohol side-product formed. Further modification of solvent and temperature to toluene at 10 °C resulted in a 55:1 diastereoselectivity.

The $NaBH(OPiv)_3$ reagent is conveniently prepared by addition of pivalic acid to $NaBH_4$ in THF in a 3.0:1.0 molar ratio, and it can be used directly in solution or isolated as a white solid after concentration of the THF and precipitation with heptane. In the course of determining the robustness of this reagent for the reductive amination, the equivalents of pivalic acid to $NaBH_4$ were varied from 2.7 to 3.3 equiv. To our surprise, no reaction occurred when 2.7 equiv was employed, and a significant rate increase was observed with 3.3 equiv of pivalic acid, reducing the reaction time from 16 h to as little as 2 h with no impact to yield or diastereoselectivity. Increasing the pivalic acid to 4.0 equiv resulted in no further increase in reaction rate. The excess pivilac acid may be catalyzing the formation of the iminium intermediate. The initial preparation of the $NaBH(OPiv)_3$ using a 3.0:1.0 ratio may have had sufficient acid catalyst present for the reaction to proceed, albeit at a slower rate, whereas with preparation of the reagent using a 2.7:1.0 ratio, no acid catalyst was present, resulting in no conversion. To ensure the reaction proceeded on scale, a 3.3:1.0 ratio of pivalic acid/$NaBH_4$ was used and **1** was isolated in 99% yield in a 98:2 *cis*/*trans* ratio.

To further improve the *cis*/*trans* ratio and for pharmaceutical formulation purposes, preparation of a salt was explored. Both succinate and hydrochloride salts were shown to have acceptable physical properties, and upon crystallization, the ratio of *cis*/*trans* could be improved to >99.5:<0.5. However, high levels of *trans*-**1** were observed in the mother liquor of the succinate salt recrystallization process, and a mass balance calculation corresponded to rejection of 2.8% of *trans* isomer,

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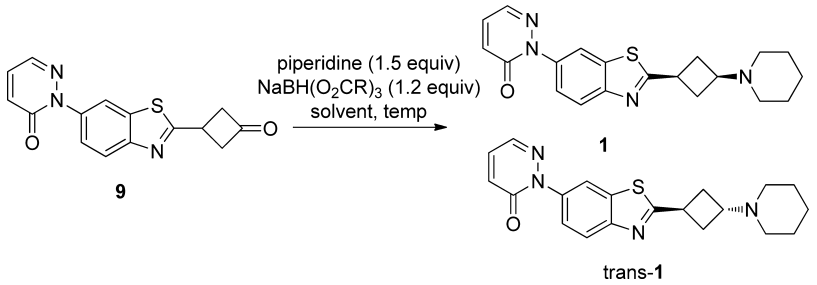
Table 3. Optimization of Reductive Amination

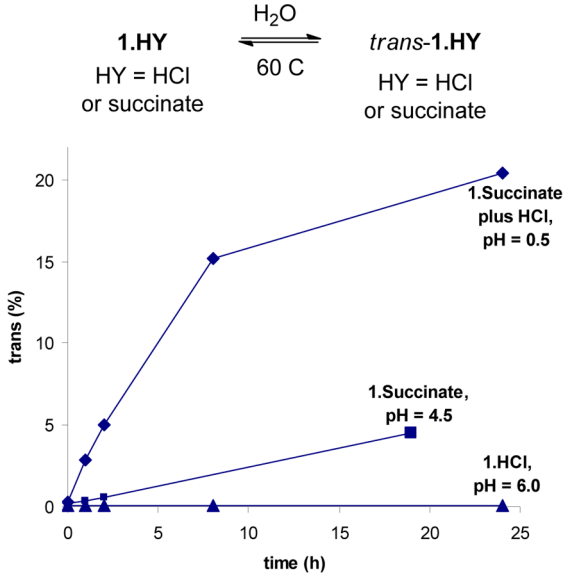


entry	R	time, h	solvent	temp, °C	*cis*/*trans*	**8**, %
1	$NaBH_3CN$	8	MeOH	22	7:1	40
2	Me	0.5	THF	22	17:1	3.5
3	Et	0.5	THF	22	13:1	5.6
4	*i*-Pr	0.5	THF	22	17:1	0.3
5	*t*-Bu	0.5	THF	22	30:1	<0.1
6	*t*-Bu	3	THF	0	36:1	<0.1
7	*t*-Bu	2	CH_3CN	22	12:1	<0.1
8	*t*-Bu	2	CH_2Cl_2	22	31:1	<0.1
9	*t*-Bu	18	IPA	22	25:1	<0.1
10	*t*-Bu	2	toluene	22	41:1	<0.1
11	*t*-Bu	24	toluene	0	55:1	0.8
12	*t*-Bu	16	toluene	10	55:1	0.3

and not the 1.8% as anticipated. To understand the origin of this high level of *trans*-isomer, a series of control studies were performed. Both the succinate and HCl salts of **1** were dissolved in water and stirred at 60 °C. Heating of the succinate salt resulted in an increase of *trans*-**1** to 4.5% overnight, whereas heating of the HCl salt resulted in no significant increase of *trans*-**1**. Due to the slightly lower solution pH of the succinate salt solution (pH = 4.5) compared to the HCl salt solution (pH = 6.0), owing to a free carboxylic acid in the succinate, an acid-catalyzed isomerization was hypothesized. This was confirmed by heating **1·Succinate** in 0.5 M HCl, which resulted in formation of 20.4% of *trans*-**1** overnight (Chart 1).

To determine the site of isomerization, a deuterium exchange reaction was performed by heating **1** in DCl and D_2O (Scheme 4). After 2 h, an 85:15 mixture of the *cis*/*trans* isomers had formed. The *cis*-isomer had 15% deuterium incorporation whereas the *trans*-isomer contained 100% deuterium, indicating that an equilibrium was not yet established. ^1H NMR analysis of *trans*-**1** showed that all of the proton adjacent to the benzothiazole ring had been exchanged for deuterium. These results clearly indicated that the isomerization occurred at the carbon adjacent to the benzothiazole ring.

Chart 1. pH Dependence on Isomerization



The free base of **1** was not isolated after the reductive amination workup but was carried directly into the salt formation. To minimize the amount of isomerization on salt formation, 0.95 equiv of HCl was used in the crystallization to ensure the acid-catalyzed isomerization did not occur. Recrystallization from toluene/MeOH afforded an 86% yield of **1·HCl** with 99.6:0.4 dr (Scheme 5). A total of 4.3 kg of **1** was prepared using this process.

CONCLUSION

We have developed an efficient and scalable six-step process for the synthesis of **1** in high purity with an improved overall yield of 53% versus 12% in the initial process. The improved process successfully overcomes the drawbacks associated with the initial route involving an undesirable OsO_4 oxidative cleavage reaction, an inefficient cyclobutaneketone reduction−oxidation sequence and the nonstereoselective reductive amination reaction. The scalable process features a highly diastereoselective reductive amination reaction of the cyclobutaneketone to set the key *cis* stereochemistry and an optimized copper-catalyzed C−N cross-coupling reaction. Mechanistic understanding of the potential isomerization of the product **1** catalyzed by both acid and base led to development of conditions to produce **1** in a 99.6:0.4 dr. This improved column chromatograph-free process involved several simple workup and purification procedures and several new crystalline intermediates which allow purification by crystallization, and it was successfully demonstrated on scale to produce 4.3 kg of high purity product **1**.

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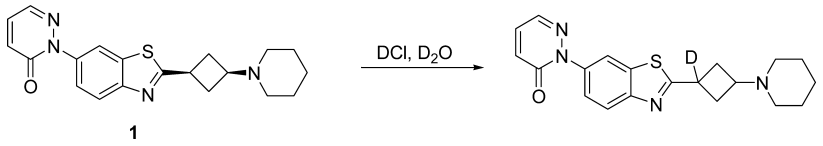
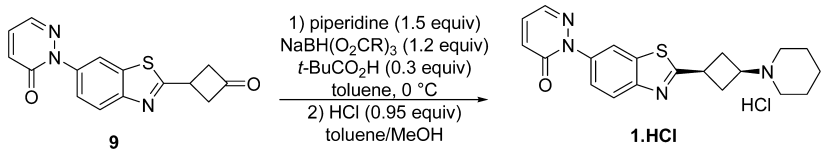
Scheme 4. Deuterium Incorporation



Scheme 5. Synthesis of 1·HCl



EXPERIMENTAL SECTION

HPLC analyses were conducted on an Agilent 1100 series HPLC using the following methods. HPLC Method 1: Zorbax RX-C8, Isocratic 70% (0.1% H_3PO_4/acetonitrile)/(0.1% H_3PO_4/water), col temp 35 °C, 1.5 mL/min, 10 min, 254 nm, t_R: **3**, 2.58 min; **17**, 3.78 min; **6**, 2.87 min; **14**, 3.66 min. HPLC Method 2: Gemini C18, 4.6 × 150 3 μm column, 70% to 10% 0.15% NH_4OH, 30% to 90% ACN over 10 min, hold 5 min, 3 min equilibration, 1.0 mL/min, col temp 35 °C, 254 nm, t_R: **15**, 5.59 min; **9**, 3.35 min; **1**, 13.0 min; *trans*-**1**, 11.9 min. ^{1}H and ^{13}C NMR spectra were collected on a Varian Mercury 400 NMR (400 MHz for ^{1}H and 100 MHz for ^{13}C).

2-Amino-5-bromobenzenethiol (3). A mixture of 6-bromobenzothiazolinone (**2**; 100 g, 0.435 mol, 1.0 equiv) and nitrogen-sparged water (500 mL) was heated to 90 °C while maintaining a continuous nitrogen sparge. To the slurry was added nitrogen sparged 26% sodium hydroxide solution (674 g, 4.35 mol, 10.0 equiv). The resulting solution was stirred at reflux for 16 h and monitored by HPLC until starting material had been consumed (<3 A% **2** by HPLC). After the solution was cooled to 0 °C, the pH was adjusted to 3 with concentrated HCl (350 mL) at <35 °C [Note: As the hydrochloric acid was added, off-gassing occurred, and solids formed as the pH approached 7]. The product was collected by filtration, washed with water (500 mL), and dried under vacuum/nitrogen to afford 85 g (96%) of **3** as a light yellow solid. The crude **3** was used directly in the next step. HPLC and ^{1}H NMR were collected for **3**, and additional analytical data were collected after complete conversion to 2,2′-disulfanediylbis(4-bromoaniline) (**17**). 91.7 A% purity (HPLC Method 1). ^{1}H NMR (400 MHz, D_6-DMSO) δ 7.12 (bs, 2H), 6.61 (bs, 1H), 5.38 (bs, 3H).

2,2′-Disulfanediylbis(4-bromoaniline) (17). A mixture of 6-bromobenzothiazolinone (**2**; 5 g, 21.74 mmol, 1.0 equiv), water (10 mL), and 50% NaOH (34.8 g, 434.78 mmol, 20 equiv) was heated to reflux for 16 h. The reaction was monitored by HPLC until starting material had been consumed (<3 A% **2** by HPLC). After cooling the solution to 0 °C, the pH was adjusted to pH 7 with concentrated HCl (35 mL) at <35 °C. [Note: As the hydrochloric acid was added, off-gassing occurred, and solids formed as the pH approached 7]. Methanol (30 mL) was added, and the suspension was stirred at 0 °C. $NaClO_2$ (80%, 1.83 g, 16.30 mmol, 0.75 equiv) in water (4 mL) was slowly added. After 30 min, the product was collected by filtration, washed with water (20 mL), and dried under vacuum/nitrogen to afford 4.45 g of 2,2′-disulfanediylbis-(4-bromoaniline) (**17**). Purification by silica chromatography (5% EtOAc/95% heptane to 100% EtOAc) provided analytically pure **17**. mp: 122−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.21 (m, 4H), 6.63−6.57 (m, 2H), 4.30 (bs, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.15, 138.18, 134.15, 119.60, 116.37, 108.73. IR (KBr): 3415 (w), 3295 (w), 3185 (w, br), 1624 (w, br), 1471.2 (s), 1387 (w), 1294 (w), 1244 (w), 1152 (w), 1107 (w), 1075 (w), 884 (w), 845 (w), 819 (s), 722 (w), 644 (w), 615 (m), 551(m). MS (ESI+): 406.8 (100) [M^+ + H]. 97.3 A% purity (HPLC Method 1). Anal. Calcd for $C_{12}H_{10}Br_2N_2S_2$: C, 35.49; H, 2.48; N, 6.90. Found: C, 35.32; H, 2.17; N, 6.81.

3-(6-Bromobenzothiazol-2-yl)cyclobutanone (6). To a solution of 1,1′-carbonyldiimidazole (CDI, 65.1 g, 0.402 mol, 1.05 equiv) in nitrogen-sparged NMP (100 mL) was slowly added a nitrogen sparged solution of 3-oxocyclobutane carboxylic acid (**11**; 48 g, 0.421 mol, 1.1 equiv) in NMP (100 mL) over 15 min to control the gas evolution at <25 °C. The activated carboxylic acid solution was mixed for 30 min at 25 °C. A solution of 2-amino-5-bromobenzenethiol (**3**; 78 g, 0.383 mol, 1.0 equiv) in nitrogen-sparged NMP (200 mL) was cooled to 0 °C while maintaining a nitrogen sparge. To this solution was added the activated acid solution over 20 min at <10 °C. The mixture was agitated at 10 °C for 30 min until the reaction was complete (<1 A% **3** by HPLC). The mixture was cooled to 0 °C, and 4 M HCl in 1,4-dioxane (301 g, 1.148 mol, 3.0 equiv) was slowly added over 1 h at <10 °C. The mixture was agitated at 10 °C for 30 min until **12** had been converted to **6** (<1 A% **12** by HPLC). The mixture was then agitated at 50 °C for 16 h until **13** had been converted to **6** (<1 A% **13** by HPLC). The solution was cooled to 22 °C and was used directly in the next step. This afforded 900 g of a 10.75% (w/w) solution of **6** in NMP (96.75 g of 6, 89.5% yield). A small amount of **6** was isolated by precipitation with water (1 L) and purified by silica chromatography (Biotage 40 + S, 5% ethyl acetate/heptane to 100% ethyl acetate) to provide analytically pure **6**. mp: 93−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (dd, J = 1.9, 0.5, 1H), 7.83 (dd, J = 8.6, 0.5, 1H), 7.58 (dd, J = 8.6, 1.9, 1H), 4.09−3.97 (m, 1H), 3.74−3.55 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.92, 172.41, 151.52, 136.48, 129.52, 123.92, 123.74, 118.52, 54.68, 27.96. IR (KBr): 1783 (s), 1587 (w), 1541 (w), 1513 (w), 1440 (w), 1395 (w), 1371 (w), 1302 (w), 1269 (w), 1164 (w), 1117 (m), 1102 (m), 1086 (m), 1037 (w), 945 (w), 863 (w), 817 (s), 745 (w), 712 (w), 668 (w), 563 (w). MS (ESI+): m/z 283.7 (100) [M^+ + H]. 99.1 A% purity (HPLC Method 1). Anal. Calcd for $C_{11}H_8BrNOS$: C, 46.82; H, 2.86; N, 4.96. Found: C, 46.71; H, 2.63; N, 4.99.

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6-Bromo-2-(3,3-dimethoxycyclobutyl)benzothiazole (14). In a 3-L 3-necked round-bottomed glass flask equipped with a mechanical stirrer was charged 900 g of a 10.75 wt % solution of **6** in NMP (96.75 g of **6**, 0.295 mol, 1.0 equiv) followed by MeOH (1.56 L) at 22 °C. The solution was stirred for 16 h until the reaction was complete (<2% area **6** by HPLC). The resulting slurry was cooled to 15 °C, and 50% NaOH (46 g, 0.575 mol, 1.9 equiv) and water (80 mL) were added. The pH was adjusted to 7 with the addition of 50% NaOH (50 g, 0.625 mol, 2.1 equiv). To this mixture was added water (1.1 L), and the resulting solids were collected by filtration, washed with water (500 mL), and dried in a vacuum oven at 50 °C to afford 112 g of crude **14** (83.8% w/w by HPLC analysis) as a light grey solid.

To half of the crude **14** (56 g) was added EtOAc (1.07 L), and the mixture was stirred for 16 h at 22 °C. After filtration of an insoluble material, the filtrate was concentrated to dryness, diluted with methanol (800 mL), and heated to reflux to afford a light yellow solution. Water (100 mL) was added while maintaining the temperature above 60 °C. The solution was slowly cooled to −5 °C over 4 h and held at −5 °C for 1 h. The resulting solid was collected by vacuum filtration and dried in a vacuum oven at 50 °C to afford 46.9 g (93% yield, 95.5% w/w by HPLC analysis) of **14** as an off-white solid. To obtain an analytically pure sample, a small amount of **14** was purified by silica chromatography (5% ethyl acetate/heptane to 100% ethyl acetate). mp: 116−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 1.9, 1H), 7.80 (d, J = 8.6, 1H), 7.53 (dd, J = 8.7, 2.0, 1H), 3.75−3.63 (m, 1H), 3.23 (s, 3H), 3.19 (s, 3H), 2.84−2.74 (m, 2H), 2.60−2.51 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.91, 151.70, 136.50, 129.14, 123.81, 123.53, 118.02, 99.63, 49.02, 48.70, 39.42, 29.70. IR (KBr): 2953 (w), 2830 (w), 1587 (w), 1510 (w), 1438 (w), 1408 (w), 1393 (w), 1301 (w), 1270 (s), 1226 (w), 1198 (w), 1149 (s), 1125 (w), 1095 (m), 1078 (w), 1037 (m), 1018 (w), 932 (w), 850 (m), 821 (w), 809 (m), 747 (w), 709 (w), 566.8 (w). MS (ESI+): m/z 327.8 (100) [M^+ + H]. 100 A% purity (HPLC Method 1). Anal. Calcd for $C_{13}H_{14}BrNO_2S$: C, 47.57; H, 4.30; N, 4.27. Found: C, 47.43; H, 3.98; N, 4.30.

2-(2-(3,3-Dimethoxycyclobutyl)benzothiazol-6-yl)-pyridazin-3(2H)-one (15). A flask containing **14** (13.2 g, 40.2 mmol, 1.0 equiv), **7** (5.79 g, 60.2 mmol, 1.5 equiv), K_2CO_3 (11.1 g, 80.4 mmol, 2.0 equiv), and CuCl (0.597 g, 6.03 mmol, 0.15 equiv) was sequentially evacuated and backfilled with N_2 three times. A nitrogen sparged solution of pyridine (80 mL) and *N*,*N*′-dimethylethylenediamine (1.30 mL, 12.1 mmol, 0.30 equiv) was added. The dark yellow mixture was heated to reflux under N_2. After 16.5 h, the reaction was shown to be complete by HPLC analysis. After cooling the reaction to 40 °C, 5% NH_4OH (80 g) was added, and the resulting solution was stirred for 30 min. Toluene (172 g) was added, the upper organic layer was isolated, and pyridine was removed by continuous distillation while adding toluene (320 mL) as needed to maintain a 200-mL distillation volume. This toluene solution was washed with 5% NH_4OH (80 g), concentrated to approximately 66 mL, and then heated to 68 °C. Heptane (110 g) was added via addition funnel over 20 min, which resulted in crystallization of the product. The slurry was cooled to 30 °C over 1 h and then placed in an ice bath, where it was stirred for 45 min. The product was collected by vacuum filtration, washed with heptanes (58 mL), and dried in a vacuum oven to afford 11.55 g (84%) of **15** as a light yellow solid. mp: 117−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 0.4, 2.1, 1H), 8.03 (dd, J = 0.4, 8.7, 1H), 7.90 (dd, J = 1.7, 3.8, 1H), 7.68 (dd, J = 2.1, 8.7, 1H), 7.25 (dd, J = 3.8, 9.5, 1H), 7.06 (dd, J = 1.7, 9.5, 1H), 3.80−3.66 (m, 1H), 3.24 (s, 3H), 3.20 (s, 3H), 2.87−2.75 (m, 2H), 2.64−2.53 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.07, 159.64, 152.31, 137.77, 136.44, 134.88, 131.01, 130.84, 123.36, 122.36, 118.46, 99.64, 49.01, 48.69, 39.46, 29.84. IR (KBr): 3026 (w), 2949 (w), 2928 (w), 1658 (s), 1585 (m), 1519 (m), 1457 (m), 1272 (m), 1228 (w), 1150 (s), 1047 (m), 860 (m), 828 (s). MS (DCI): 344 (M + H, 100), 312 (M − 31). 97.8 A% purity (HPLC Method 2). Anal. Calcd for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24. Found: C, 59.44; H, 4.80; N, 12.25.

2-(2-(3-Oxocyclobutyl)benzothiazol-6-yl)pyridazin-3(2H)-one (9). To a mixture of **15** (4.7 kg, 13.7 mol, 1.0 equiv), CH_3CN (27.8 kg), and H_2O (2.5 kg, 140 mol, 10 equiv) was added concentrated HCl (410 g, 4.2 mol, 0.30 equiv). The reaction mixture was heated to 35 °C and held at 35 °C for 1.5 h. The reaction mixture was then heated to 70 °C, and H_2O (64.8 kg) was added over 40 min. The product slurry was cooled to −7 °C over 3.5 h and held at −7 °C for 15.75 h. The product was collected by filtration, washed with H_2O (30 kg), and dried in a vacuum oven to afford 3.75 kg (92%) of **9** as an off-white solid. mp: >200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 2.1, 1H), 8.07 (d, J = 8.8, 1H), 7.93 (dd, J = 1.7, 3.8, 1H), 7.74 (dd, J = 2.1, 8.8, 1H), 7.28 (dd, J = 3.7, 9.5, 1H), 7.08 (dd, J = 1.7, 9.5, 1H), 4.08 (tt, J = 6.9, 8.9, 1H), 3.92−3.41 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.99, 173.53, 159.56, 152.02, 138.09, 136.52, 134.84, 130.98, 130.89, 123.66, 122.49, 118.49, 54.65, 28.01. IR (KBr): 1781 (s), 1671 (s), 1656 (s), 1591 (m), 1519 (w), 1461 (m), 1415 (w), 1373 (w), 1315 (w), 1305 (w), 130 (m), 862 (m), 822 (s). MS (DCI): 298 (M + H, 100). 98.8 A% purity (HPLC Method 2). Anal. Calcd for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.73; N, 14.13. Found: C, 60.42; H, 3.52; N, 14.22.

Preparation of $NaBH(OPiv)_3$ in Toluene. A mixture of $NaBH_4$ (0.915 kg, 24.2 mol, 1.0 equiv) and THF (35 kg) was cooled to 0 °C, and a solution of pivalic acid (7.46 kg, 73.0 mol, 3.02 equiv) in THF (21 kg) was added over 2 h. The reaction was warmed to 25 °C and stirred under N_2 for 6 h. The THF solvent was then exchanged to toluene by continuous distillation at 38 L, adding 130 kg of toluene as needed to maintain the 38 L distillation volume. The clear, colorless toluene solution was transferred to a tared drum, and the reactor was rinsed with toluene (10 kg). This afforded 53.4 kg of a clear, colorless, nominally 15.3% (w/w) solution of $NaBH(OPiv)_3$ in toluene.

2-(2-(*cis*-3-(Piperidin-1-yl)cyclobutyl)benzothiazol-6-yl)pyridazin-3(2H)-one (1). A mixture of **9** (3.75 kg, 12.6 mol, 1.0 equiv), pivalic acid (0.365 kg, 3.6 mol, 0.3 equiv), toluene (53 kg), and piperidine (1.6 kg, 18.6 mol, 1.5 equiv) was cooled under N_2 to 5 °C. The toluene solution of $NaBH(OPiv)_3$ (15.3% w/w, 33.4 kg, 15.1 mol, 1.2 equiv) was added over 20 min. The reaction mixture was stirred at 5 °C for 16 h, at which time HPLC analysis showed complete consumption of **9**. The product was extracted with 0.5 M sodium succinate solution buffered at pH 5.0 (60 kg, 2 × 28 kg). To the combined aqueous layers was added toluene (60 kg), and the pH was adjusted to 9.7 using 50% NaOH (3.8 kg). The resulting two-layer mixture was filtered through an in-line filter, and the lower aqueous layer was removed and extracted with toluene (38 kg). The combined organic layers were washed with water (39 kg), distilled to approximately 100 L, and transferred to a tared drum. This gave 72.5 kg of a light

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yellow solution, whose concentration was determined to be 6.3% w/w of **1** (4.57 kg, 99% yield) by quantitative HPLC analysis versus an external standard. This solution was used directly in the HCl salt formation.

2-(2-(*cis*-3-(Piperidin-1-yl)cyclobutyl)benzothiazol-6-yl)pyridazin-3(2H)-one Hydrochloride (1·HCl). The 6.3% w/w solution of **1** in toluene (72.5 kg, 12.5 mol) was concentrated to approximately 55 L, methanol (10.6 kg) was added, and the solution was heated to 55 °C. A solution of 13.3% w/w anhydrous HCl in EtOH (3.22 kg, 11.7 mol, 0.94 equiv) was added. The reaction solution was cooled to 45 °C over 1 h and held at this temperature for 2 h, and toluene (53 kg) was added over 1 h. The resulting mixture was cooled to 5 °C over 4 h and held at 5 °C for 14 h. The solid was collected by filtration and was washed with toluene (20 kg). The wet cake was dried in a vacuum oven and afforded 4.3 kg (86%) of **1·HCl** as an off-white crystalline solid. mp: >200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.76 (s, 1H), 8.13 (d, J = 2.1, 1H), 7.98 (d, J = 8.8, 1H), 7.90 (dd, J = 1.7, 3.8, 1H), 7.69 (dd, J = 2.1, 8.7, 1H), 7.25 (dd, J = 3.8, 9.5, 1H), 7.05 (dd, J = 1.7, 9.5, 1H), 3.80−3.62 (m, 1H), 3.57−3.36 (m, 3H), 3.35−3.17 (m, 2H), 2.92−2.75 (m, 2H), 2.59−2.44 (m, 2H), 2.40−2.24 (m, 2H), 1.99−1.76 (m, 3H), 1.50−1.30 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.99, 173.53, 159.56, 152.02, 138.09, 136.52, 134.84, 130.98, 130.89, 123.66, 122.49, 118.49, 54.65, 28.01. MS (DCI): 367 (M + H, 100). IR (KBr): 3064 (w), 3030 (w), 2977 (w), 2440 (w), 1660 (s), 1588 (m), 1517 (w), 1456 (m), 1330 (w), 1303 (w), 1142 (w), 846 (m), 826 (s), 714 (w). 99.3 A% purity, 0.5 A% ***trans*-1** (HPLC Method 2). Anal. Calcd for $C_{20}H_{23}ClN_4OS$: C, 59.62; H, 5.75; N, 13.90. Found: C, 59.50; H, 5.75; N, 13.83.

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Notes

The authors declare no competing financial interest.

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