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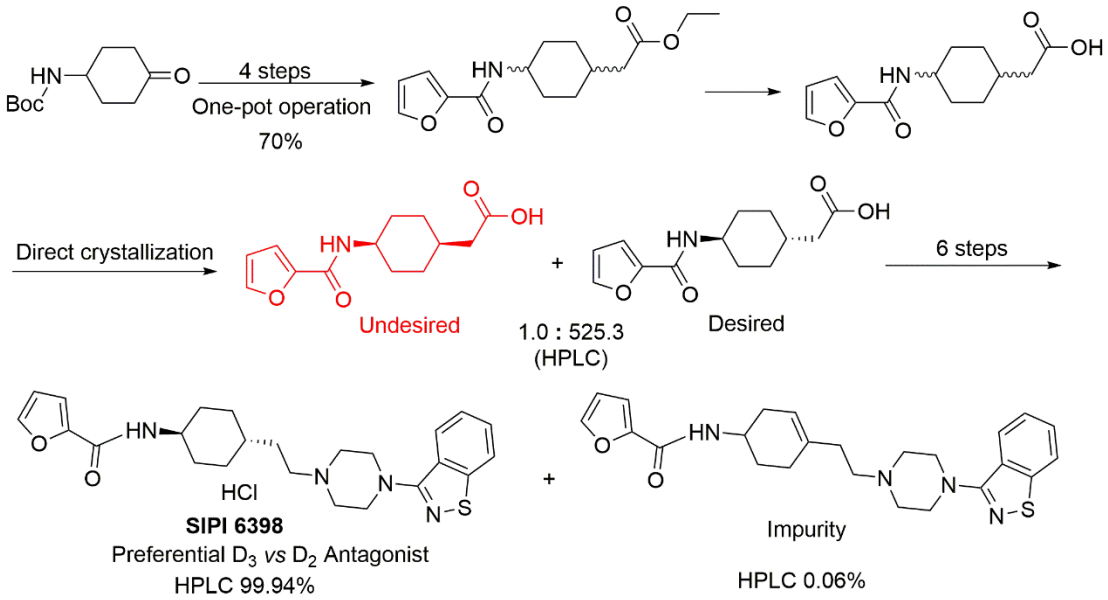
Process Development of an Efficient Kilogram-scale Preparation of a Preferential Dopamine D_3 versus D_2 Receptor Antagonist SIPI 6398 as a New Antipsychotic Candidate

Ai-Nan Zhou,[†,‡,1] Xiao-Wen Chen,[‡,1] Yang-Li Qi,[†‡] Geng-Li Duan,[*,†] Jian-Qi Li[*,‡]

[†]School of Pharmacy, Fudan University, 220 Handan Rd, Shanghai 200433, PR China

[‡]Novel Technology Center of Pharmaceutical Chemistry, Shanghai Institute of Pharmaceutical Industry, China State Institute of Pharmaceutical Industry, 285 Gebaini Rd, Shanghai 201203, PR China

TOC Graphic:


HN
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4 steps
One-pot operation
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Direct crystallization
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OH
1.0 : 525.3
(HPLC)
Desired
6 steps
HN
O
O
HCl
N
N
N
S
SIPI 6398
Preferential D3 vs D2 Antagonist
HPLC 99.94%
+
HN
O
O
N
N
N
S
Impurity
HPLC 0.06%

ABSTRACT: Herein we describe the development of a kilogram-scale preparation of a preferential dopamine D_3 versus D_2 receptor antagonist SIPI 6398 (**1**) as a new alternative treatment for schizophrenia. Modification and optimization of the route includes one-pot synthesis of a *trans/cis* mixture of cyclohexyl ethyl acetate **19**, direct crystallization of cyclohexyl acetic acid **21** in *trans* configuration, avoidance of hazardous reagents to obtain mesylate **24**, and a salinization and recrystallization protocol to efficiently remove the olefinic impurity **31** from **12** (free base of **1**). Ultimately these improvements led to the successful and facile preparation of 2.7 kilogram of SIPI 6398 in nine steps with HPLC purity of > 99.9%.

Keywords: schizophrenia, D_3/D_2 receptor preferential antagonist, practical preparation, crystallization

INTRODUCTION

Schizophrenia is among the most severe and debilitating of the brain disorders and affects nearly 1% of the world's population.[1,2] The symptoms of schizophrenia fall into three main categories: a) positive b) negative and c) cognitive. Most clinically available antipsychotic agents effectively alleviate positive and negative symptoms, but are ineffective at managing cognitive impairment. Therefore, antipsychotic agents with cognitive improvement efficacy represent an urgent clinical need for schizophrenic patients.

Preferential D_3 versus D_2 receptor antagonists enhance frontocortical cholinergic transmission and improve social cognition, which may be beneficial in alleviating cognitive impairment in schizophrenia.[3] Our research team has been devoted to the discovery of potential atypical antipsychotics with D_3 versus D_2 receptor subtype selectivity. Recently we discovered a series of novel and potent N-(*trans*-4-(2-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)ethyl)cyclohexyl)amides exhibiting this binding profile.[4,5] Among these compounds, SIPI 6398 (**1**; Figure 1) was identified as our preferential D_3 versus D_2 receptor (22-fold) antagonist candidate showing cognitive improvement in animal models.[4] To support its preclinical

development and investigational new drug (IND) application, it is necessary to develop an efficient, practical and kilogram-scale process for the preparation of SIPI 6398.

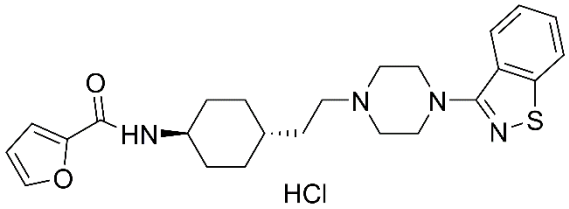
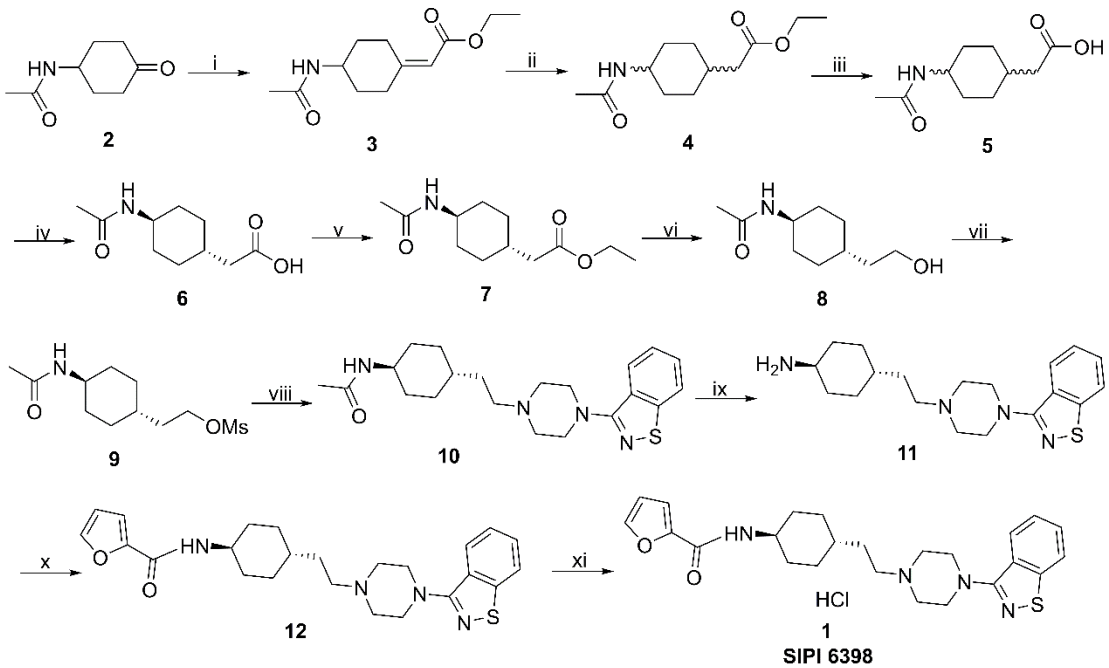


Figure 1. Structure of SIPI 6398 (**1**).

The initial synthetic route for SIPI 6398 (Scheme 1) possesses some major drawbacks upon scale-up, specifically (i) low yield in the preparation of 4-((2-hydroxyethyl)cyclohexyl)acetamide **8**; (ii) use of hazardous reagents such as methylsulfonyl chloride; and (iii) the difficult hydrolysis of N-acetyl for the synthesis of cyclohexan-1-amine **11**. Therefore, a second generation synthesis of SIPI 6398 should be envisaged.

Scheme 1. Initial synthetic route of SIPI 6398[a]



[a]Reagents and conditions: (i) Triethyl phosphonoacetate, *t*BuOK, THF, 0~5 °C, 82-88%; (ii) H_2, 10%Pd/C, EA, rt, 89-92%; (iii) LiOH.H_2O, THF, H_2O, 40 °C, 80-85%; (iv) DMF, recrystallization, 50-55%; (v) EtOH, conc. H_2SO_4, reflux,

83-87%; (vi) $NaBH_4$, MeOH, THF, reflux, 50-60%; (vii) Et_3N, MsCl, CH_2Cl_2, 0~5 °C, 81-86%; (viii) 3-(piperazin-1-yl)benzo[*d*]isothiazole, Na_2CO_3, KI, CH_3CN, reflux, 54-61%; (ix) 5%HCl, reflux, 80-85%; (x) 2-furoyl chloride, Et_3N, CH_2Cl_2, 0~5 °C, 89-92%; (xi) EtOH, 10%HCl, reflux, 80-84%.

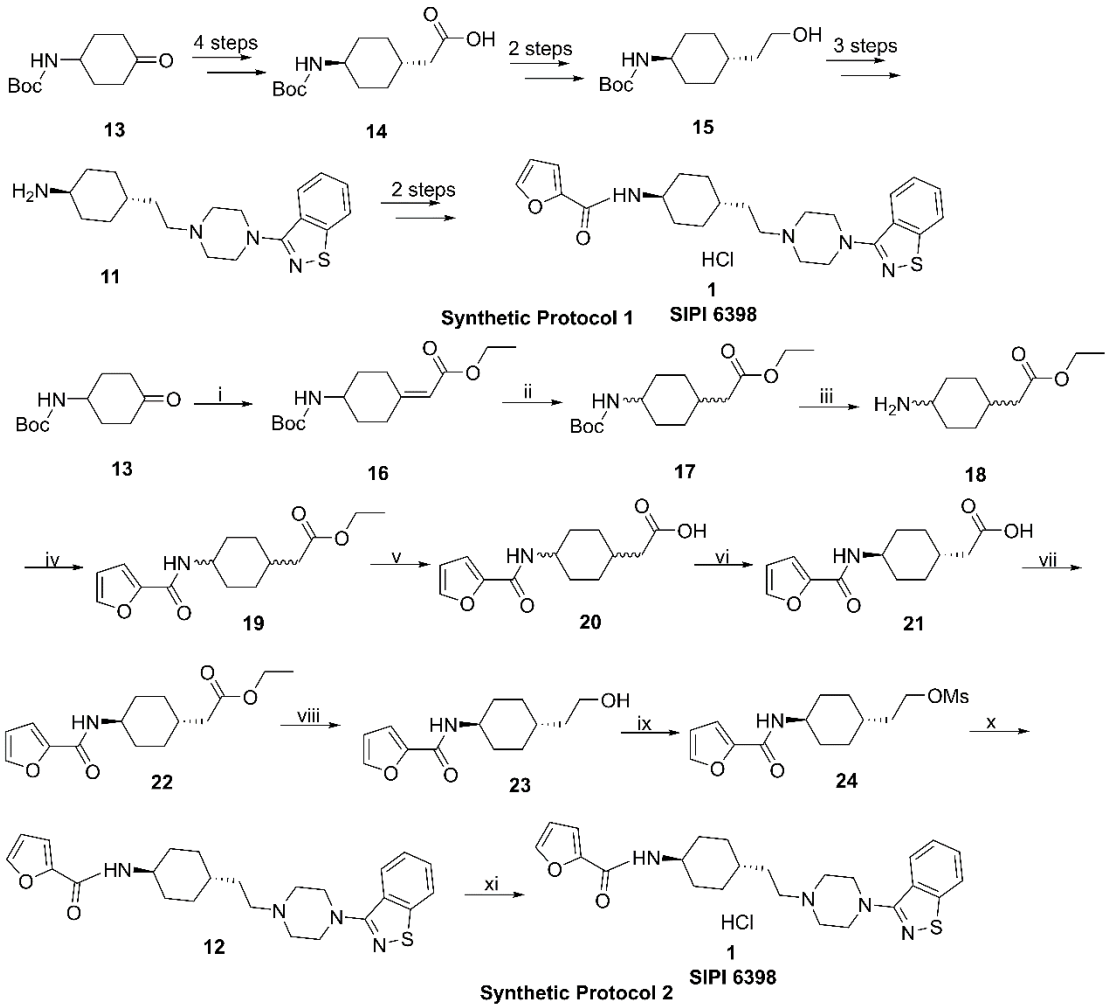
Second-Generation Synthesis. Using N-(4-oxocyclohexyl)acetamide (**2**, Scheme 1) as the starting material resulted in water soluble product **8** bearing both acetamido and hydroxy substituents. Intermediate **8** was achieved through a tedious operation (three to four extractions) in acetone with low yield (50-60%) after concentration of the reaction mixture. Another shortcoming of using **2** as the starting material was that the N-acetyl was difficult to remove in the hydrolysis step to prepare **11**.[6] Therefore, our first focus was to identify a starting material containing a more hydrophilic and readily removable protective group that was commercially available on a large scale. Boc-4-aminocyclohexan-1-one **13** was selected as shown in Scheme 2.

First, two synthetic protocols were envisioned to prepare **1** (Scheme 2). In protocol 1, **1** was synthesized via steps similar to the initial synthetic route. Although the primary alcohol **15** could be obtained via facile extraction as well as easy deprotection of the Boc group to afford **11**, the key intermediate **14** was inefficiently obtained,[6] which aborted this protocol. Our tentative experiments showed that the early introduction of the furoyl group produced positive results, and protocol 2 (Scheme 2) was worthy of further scale-up study.

One-pot Synthesis of a Trans/cis Mixture of Cyclohexyl Ethyl Acetate 19. The same reaction solvent (THF) used in the Wittig-Horner reaction (step 1) and hydrogenation (step 2) enabled one-pot synthesis of 2-(4-((tert-butoxycarbonyl)amino)cyclohexyl)acetate **17** as a trans/cis mixture (trans/cis isomer ratio, 1.51:1.0, GC method A) accompanied by higher isolated yield (enhanced from 81% to 90%) compared to the stepwise process. N-Boc deprotection with TFA in CH_2Cl_2 (step 3) to obtain **18** (trans/cis isomer ratio, 1.6:1.0, GC method B) followed by acylation with 2-furoyl chloride in CH_2Cl_2 afforded **19** (step 4, trans/cis isomer ratio, 1.67:1.0, HPLC method A). Similarly, one-pot operation of

steps 3 and 4 was implemented using CH_2Cl_2 as the reaction solvent with improved isolated yield (enhanced from 70% to 85%). By virtue of CH_2Cl_2 used during the posttreatment of hydrogenation for the preparation of **17**, the two one-pot steps were incorporated into a one-step operation to synthesize **19** in the same solvent. Thus, the synthetic route was shortened to three steps. The improved and facile operation facilitated high overall yield (70%, four steps) and work up of **19** at a scale of over 11 kg.

Scheme 2. Second-generation synthesis of SIPI 6398[a]



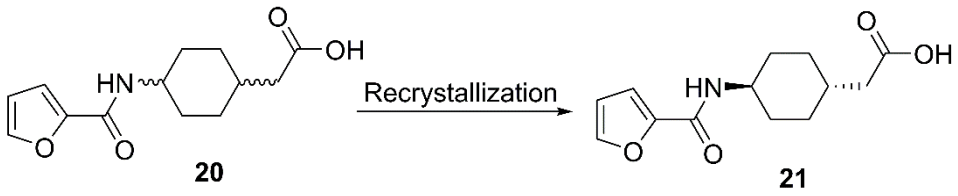
[a]Reagents and conditions: (i) Triethyl phosphonoacetate, *t*BuOK, THF, 0~5 °C; (ii) H_2, 5%Pd/C-53%water, THF, rt; (iii) TFA, CH_2Cl_2, rt; (iv) 2-furoyl chloride, Et_3N, CH_2Cl_2, 0~5 °C; (v) $LiOH.H_2O$, THF, H_2O, 40 °C; (vi) CH_3CN, recrystallization; (vii) EtOH, EDC.HCl, DMAP, rt; (viii) $NaBH_4$, MeOH, THF, reflux; (ix) Et_3N, MsCl, CH_2Cl_2, 0~5 °C; (x) 3-(piperazin-1-yl)benzo[*d*]isothiazole, Na_2CO_3, KI, CH_3CN,

reflux; (xi) EtOH, 10%HCl, reflux.

Direct Recrystallization Method to Prepare 2-(trans-4-(Furan-2-carboxamido)cyclohexyl)acetic Acid 21. In the initial synthetic route, the key intermediate **6** was obtained in *trans* configuration using direct recrystallization. We envisioned a similar protocol to achieve acid **21** in *trans* configuration. The *trans/cis* mixture of acid **20** was synthesized after hydrolysis of **19** using lithium hydroxide monohydrate in THF/H_2O. Then, a direct recrystallization was used to efficiently obtain **21** by solvent screening (Table 1). The purity was monitored by HPLC.

The results from Table 1 showed that the initial *trans/cis* isomer ratio (entry 1) was 3.6:1.0. Several solvents were screened, and ethanol (74.2:1.0) and dichloromethane (43.7:1.0) were ineffective. 2-Butanone (184.1:1.0), tetrahydrofuran (242.9:1.0) and isopropanol (237.1:1.0) exhibited moderate effects. Acetone (665.7:1.0), ethyl acetate (499.0:1.0), isopropyl acetate (402.8:1.0) and acetonitrile (525.3:1.0) gave the best results. Finally, acetonitrile was chosen as the optimal solvent considering both high yield (58%) and relatively low solvent usage (21 volumes). The direct recrystallization method using acetonitrile as the solvent was applied to produce **21** at multiple kilogram-scale.

Table 1. Screening of recrystallization solvents to prepare 21



20 **21**

entry	**20** (g)	solvent /**20**	trans/cis ratio[b]	yield[c] (%)
1		/[a]	3.6:1.0	
2	5	EtOH (5)	74.2:1.0	34
3	4	Acetone (22)	665.7:1.0	52
4	5	2-Butanone (36)	184.1:1.0	48
5	3	THF (8)	242.9:1.0	33

6	6	Isopropanol (8)	237.1:1.0	40
7	5	Ethyl acetate (42)	499.0:1.0	64
8	10	Isopropyl acetate (56)	402.8:1.0	62
9	6	CH_3CN (21)	525.3:1.0	58
10	8	CH_2Cl_2 (60)	43.7:1.0	82[d]

[a] Before recrystallization. [b] The trans/cis isomer ratio was determined by HPLC. [c] Isolated yield. [d] Insoluble in CH_2Cl_2.

Condition Optimization for the Synthesis of Mesylate 24. With **21** in hand, mesylate **24** was achieved by three further steps: esterification under EDC.HCl/DMAP conditions (**22**, 95% isolated yield), reduction by $NaBH_4$-MeOH (**23**, 90% isolated yield), and methylation by methanesulfonyl chloride (90% isolated yield). The hazardous and expensive transportation of methanesulfonyl chloride limits its use at large scale. We further investigated 4-methylbenzensulfonate and halogenated (Cl, Br and I) derivatives (compounds **25**-**28**) as substitute for methanesulfonyl chloride. Our tentative explorations showed that all four derivatives were obtained in low isolated yield (Scheme 3) by chromatography attributed to massive unconverted **23** (TLC analysis). Methanesulfonic anhydride was chosen as the alternative acylating agent due to the characteristics of good reactivity, low volatilization, and convenient transportation and storage. After investigation of bases (Na_2CO_3, NaOH, ammonium hydroxide, diisopropylethylamine and triethylamine), equivalent DMAP and anhydride, solvent (acetonitrile, ethyl acetate, CH_2Cl_2 and DMF), and triethylamine/DMAP/methanesulfonic anhydride (equivalent, 2.5:0.2:1.5)/DMF conditions displayed the highest isolated yield (88%) (Table 2, entry 8). The optimizations facilitated the work-up of **24** through simple operation without chromatography under mild conditions.

Scheme 3. Synthesis of derivatives of 24

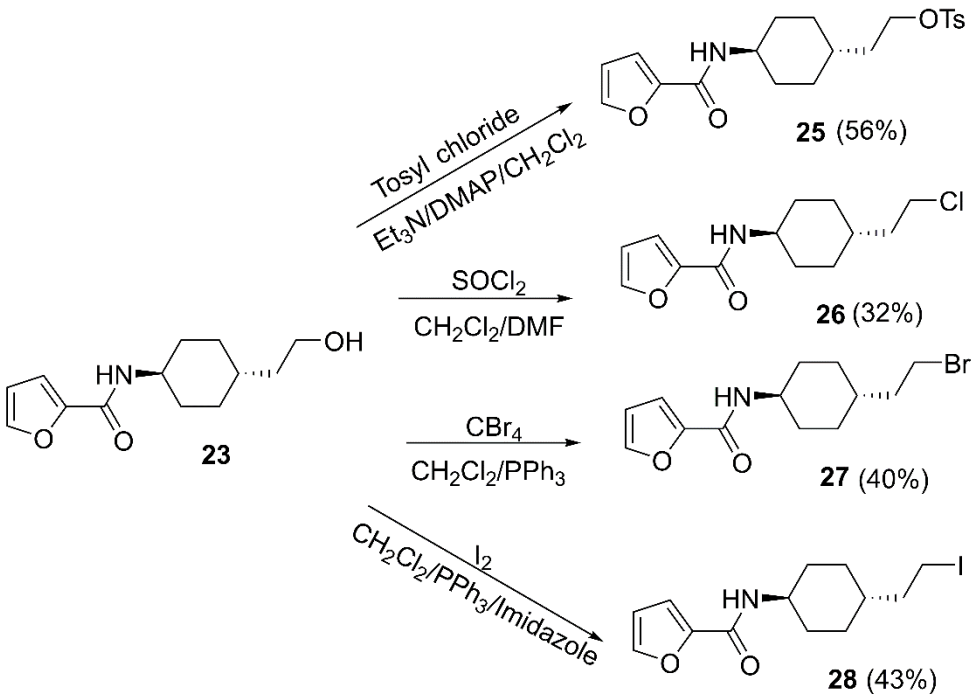
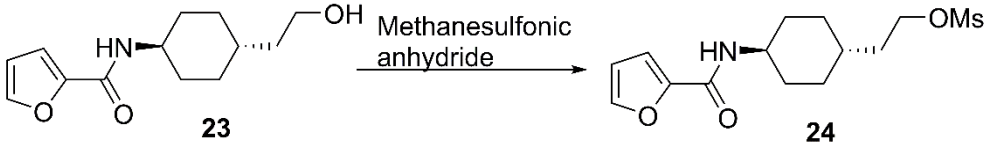


Table 2. Sulfonylation conditions for preparing 24

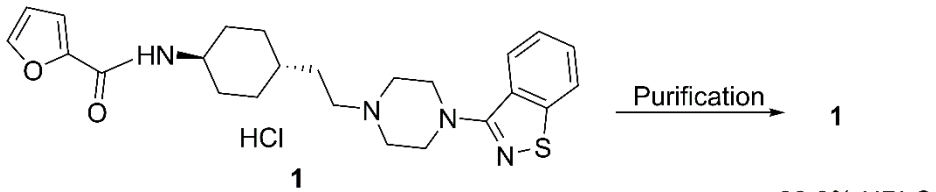


entry	solvent	DMAP (equivalent)	base (equivalent)	anhydride (equivalent)	temp (°C)	yield (%)[b]
1	CH_3CN[a]	0.5	Na_2CO_3 (2.0)	1.7	0-5	28
2	CH_2Cl_2[a]	0.5	NaOH (2.0)	1.5	0-5	51
3	Ethyl acetate[a]	0.3	NaOH (2.0)	1.5	0-10	39
4	CH_2Cl_2[a]	0.5	Et_3N (3.0)	1.6	0-5	62
5	DMF	0.5	Et_3N (2.0)	1.5	0-5	87
6	DMF	0.3	DIPEA (2.5)	1.5	0-10	83
7	DMF	0.5	NH_4OH (3.0)	2.0	0-15	81
8	DMF	0.2	Et_3N (2.5)	1.5	0-5	88
9	DMF	0.2	Et_3N (2.5)	1.4	0-5	83
10	DMF	0.1	Et_3N (2.5)	1.5	0-5	79

[a] Insoluble in 30 volumes of solvent. [b] Isolated yield.

Removal of the Olefinic Impurity 31. The synthesis of the free base of SIPI 6398 (**12**) was then completed by the S_N2 coupling of **24** and 3-(piperazin-1-yl)benzo[*d*] isothiazole under mild basic conditions. The HPLC purity of crude product **12** was 98.5%, and the content of the main impurity was 1.5% (HPLC) (Table 3, entry 1). The results from LC/MS analysis showed that the molecular weight of the main impurity was 436, two units less than that of **1**, indicating the existence of an olefinic moiety (**29** or **31**, Scheme 4). We proposed the possible process of forming the impurity: unconverted **16** during the hydrogenation step took part in the following steps to form the exocyclic olefin compound **29**; or the Wittig-Horner reaction byproduct **30** (Scheme 5) joined in similar steps to form the endo olefin compound **31** (Scheme 4). **16** was not detected in **17** by HPLC analysis, discrediting the existence of **29**. **31**[7] was obtained by a preparative separation method from crude product **12**. We then focused on the removal of **31**.

Table 3. Purification of 1

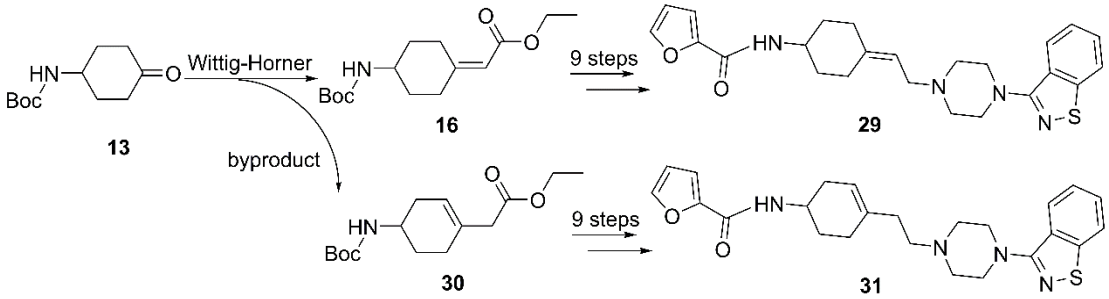


entry	substrate	recrystallization solvent	**12** or **1** (area %)[d]	**31** (area %)[d]	yield[e] (%)
1	**12**	/	98.50	1.50	/
2	**1**	EtOH/H_2O	99.08	0.92	85
3	**1**	MeOH/H_2O[a]	99.31	0.69	81
4	**1**	MeOH/H_2O[b]	99.39	0.61	62
5	**1**	MeOH/H_2O[c]	99.45	0.55	46
6	**1**	CH_3CN/H_2O	99.17	0.83	86
7	**1**	AcOH	98.89	1.01	58

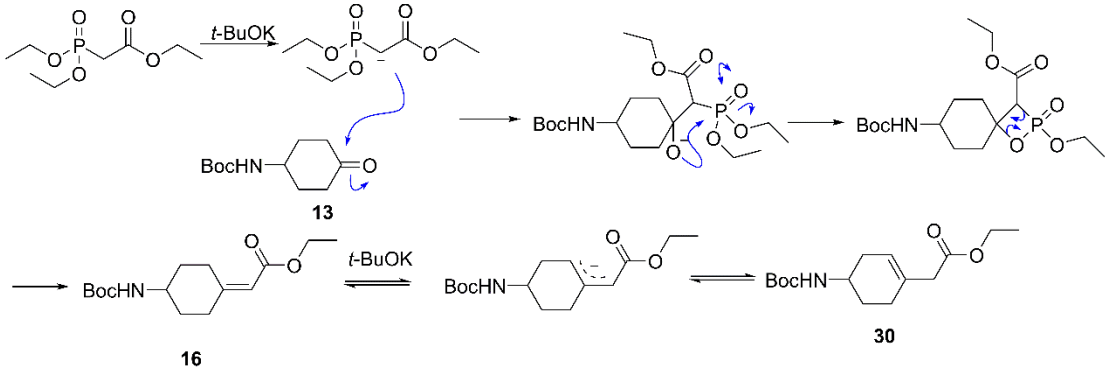
8	**1**	DMF/H_2O	99.20	0.80	65

[a] Once. [b] Twice. [c] Three times. [d] Determined by HPLC analysis. [e] Isolated yield.

Scheme 4. Formation of the impurity



Scheme 5. Proposed mechanism for the formation of byproduct 30



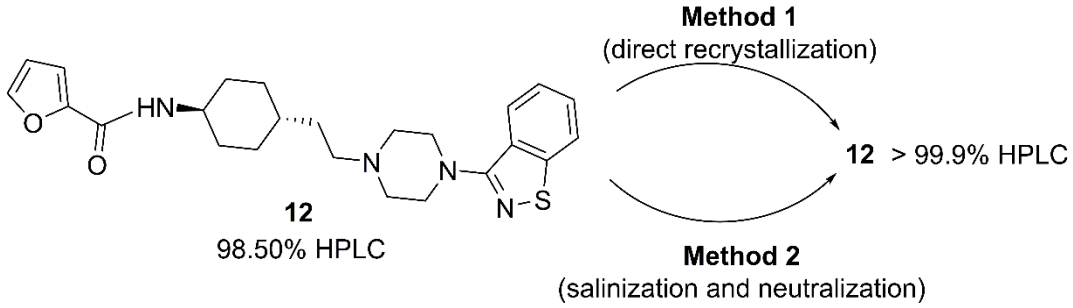
Serious regulations and quality control are necessary to be considered an API (Active Pharmaceutical Ingredient). To obtain the API in high quality, the aim was to decrease the content of **31** to less than 0.1%. Our tentative experiments showed that the following salt formation step to prepare **1** under EtOH/10% HCl aqueous solution condition and further recrystallization from EtOH and water was inefficient at improving the purity (entry 2, HPLC 99.08%). Investigation of alternative recrystallization solvents (acetonitrile, methanol, DMF, etc.) and the number of recrystallizations failed to remove **31** (entries 3-8). Thus, we envisioned two possible methods to conduct scrupulous impurity control of **12**.

Method 1–Recrystallization of 12. The direct recrystallization method was applied to remove **31** from **12**. Unexpectedly the purity was barely improved after

screening of several solvents (Table 4, entries 1-4). The inefficient recrystallization method was attributed to the similar polarities of **12** and **31** observed from HPLC result.

Method 2–Salt Formation Screening of 12 and recrystallization. Considering the potential solubility difference between **12** and **31** after acidifying with acids, several acids (oxalic acid, methanesulfonic acid, fumaric acid, etc.) were screened. The results from Table 4 (entries 7-11) showed that methanesulfonic acid (**31**, 0.55% HPLC), fumaric acid (**31**, 0.53% HPLC), succinic acid (**31**, 0.73% HPLC), acetic acid (**31**, 0.81% HPLC) and lactic acid (**31**, 0.66% HPLC) were ineffective. Both oxalic acid (entry 5, **31**, 0.08% HPLC) and maleic acid (entry 6, **31**, 0.29% HPLC) were efficient. Oxalic acid was chosen as the optimal acid because of its purity (99.92% HPLC) and yield (80% isolated yield).

Table 4. Salt formation screening of 12



entry	acid	recrystallization solvent	12 (area %)[a]	31 (area %)[a]	Yield[b] (%)
1	/	CH_3CN/MeOH	98.59	1.41	72
2	/	Acetone/MeOH	98.72	1.28	75
3	/	Ethyl acetate /MeOH	98.68	1.32	80
4	/	Ethyl acetate /CH_2Cl_2	98.69	1.31	88
5	Oxalic acid	MeOH/H_2O	99.92	0.08	80
6	Maleic acid	MeOH/H_2O	99.71	0.29	72
7	Methanesulfonic acid	MeOH/H_2O	99.45	0.55	81
8	Fumaric acid	MeOH/H_2O	99.47	0.53	75

9	Succinic acid	MeOH/H_2O	99.27	0.73	77
10	Acetic acid	MeOH/H_2O	99.19	0.81	83
11	Lactic acid	MeOH/H_2O	99.34	0.66	80

[a] Determined by HPLC analysis. [b] Isolated yield (three steps: salinization, recrystallization and neutralization).

The successful optimization was applied for the scale up of **12** with high HPLC purity (> 99.9%) at > 4-kg scale.

Ultimately, treatment of **12** with 10%HCl aqueous solution in EtOH furnished the crude product of **1** which was further slurried in EtOH to successfully prepare **1** as a white solid at 2.7-kilogram scale in 15% overall yield with high purity (> 99.9%, HPLC). The trans configuration of SIPI 6398 (**1**) was assigned via an X-ray crystallographic study (Figure 2).[8]

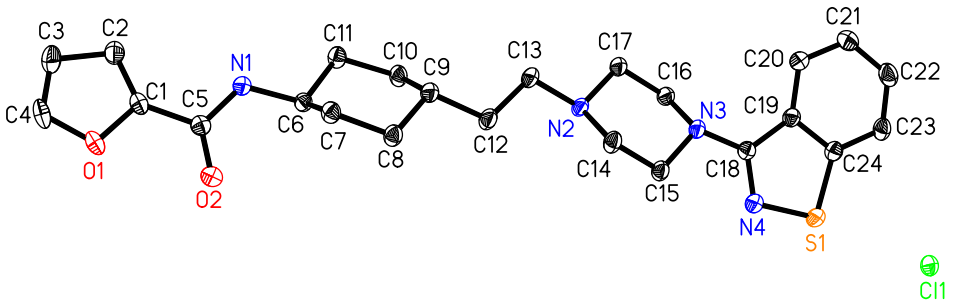


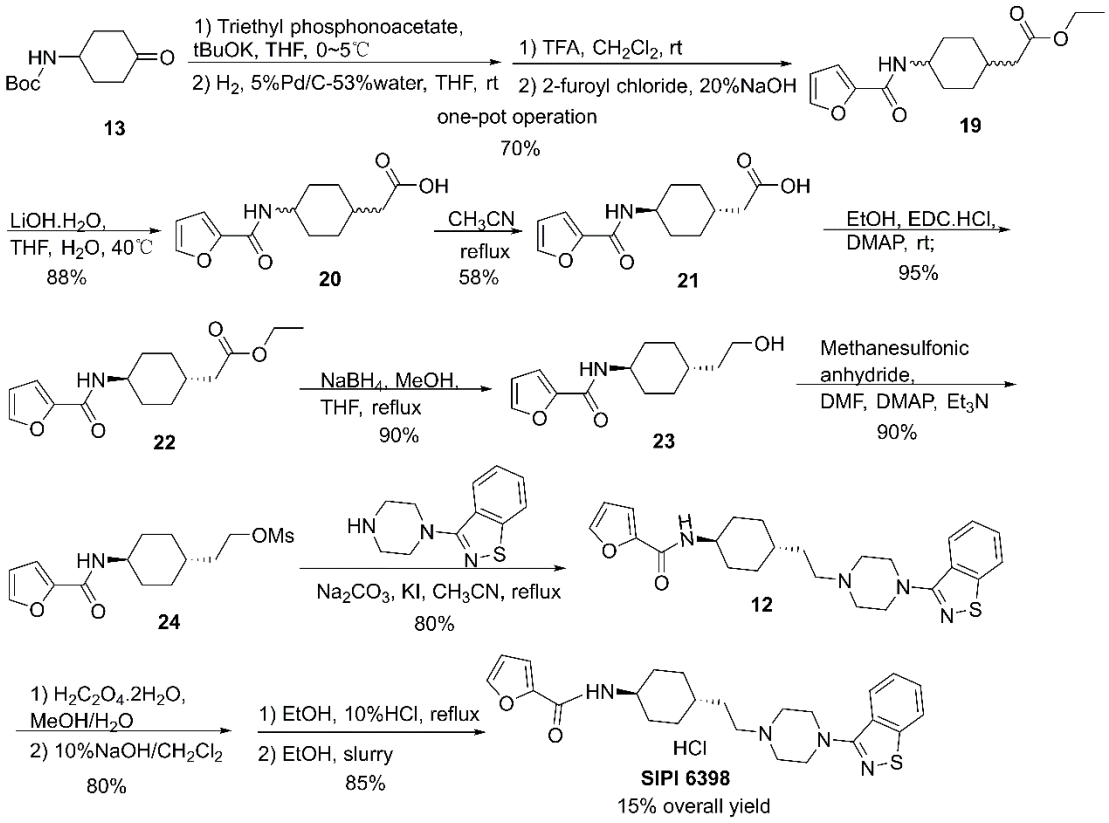
Figure 2. ORTEP diagram of **1** with 30% thermal ellipsoid plot for non hydrogen atoms with atom labeling

CONCLUSION

In summary, a practical and kilogram-scale preparation of preferential D3 versus D2 receptor antagonist SIPI 6398 (**1**) has been developed (Scheme 6). The new process addressed the main issues encountered in the original synthesis by changing the starting material and optimizing the conditions. In particular, **21**, the key intermediate in constructing the trans configuration of **1**, was facilely prepared using a direct crystallization method. Furthermore, a salinization and recrystallization

protocol to efficiently remove the olefinic impurity **31** guaranteed the quality of the API. Finally, these improvements led to the successful and easy preparation of 2.7 kilograms of SIPI 6398 in nine steps with high HPLC purity (99.94%).

Scheme 6. Final process route for the synthesis of SIPI 6398



EXPERIMENTAL SECTION

All solvents and reagents were used without further purification, unless otherwise stated. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AVANCE II 400 (400 MHz) with TMS as an internal standard in $CDCl_3$ or DMSO solution. Chemical shifts are given in δ values (ppm) and coupling constants (*J* values) are given in Hz. ESI mass spectra was acquired on a Waters ZQ2000 spectrometer. HRMS was performed on a Q-Tof micro spectrometer. Gas chromatography (GC) and high-performance liquid chromatography (HPLC) data were obtained using the following methods: GC method A: GC-FID DB-5 (30 m, 0.25 μm × 320 μm); split ratio: 20:1; temperature

programming: temp 70 °C for 3 min, temp 250 °C for 10 min; carrier gas: N_2; flow rate = 1.0 mL/min; temp 250 °C. GC method B: GC-FID DB624 (30 m, 1.4 μm × 250 μm); split ratio: 20:1; temperature programming: temp 50 °C for 3 min, temp 250 °C for 10 min; carrier gas: N_2; flow rate = 1.0 mL/min; temp 250 °C. HPLC method A: Phenomenex Luna PFP (2) (5 μm, 4.6 mm × 250 mm); mobile phase A (CH_3CN) and B (10 mM K_2HPO_4 (pH = 3.0)), from 20:80 A/B to 80:20 A/B over 45 min; detection at 254 nm; flow rate = 1.0 mL/min; temp 30 °C. HPLC method B: Waters Sunfire C18 column, C18 (5 μm, 250 mm ×4.6 mm); mobile phase A (MeOH) and B (20 mM K_2HPO_4 (pH = 5.5)), from 70:30 A/B to 10:90 A/B over 80 min; detection at 230 nm; flow rate = 1.0 mL/min; temp 30 °C.

Ethyl 2-(*trans/cis*-4-(furan-2-carboxamido)cyclohexyl)acetate (19). To a stirred solution of potassium tert-butanolate (8.8 kg, 78.8 mol) in THF (53 L) was added dropwise triethyl phosphonoacetate (13.9 kg, 61.9 mol) in THF (35 L) at 0-5 °C, and the solution was then stirred at room temperature for 1 h. A suspension of *tert*-butyl (4-oxocyclohexyl) carbamate (**13**) (12.0 kg, 56.3 mol) in THF (60 L) was added dropwise to the solution at 0-5 °C. The resulting solution was stirred for another 5 h at room temperature and subsequently quenched with water (30 L). The resultant mixture was extracted with THF (2 × 10 L) after separation. 5%Pd/C-53%water (702 g) was added to the organic layer and hydrogenation was conducted with ambient temperature and pressure conditions. The resulting solution was stirred for 20 h and filtered. The filtrate was evaporated in vacuo to give a colorless semisolid. The residue was dissolved in dichloromethane (60 L) followed by washing with water (10 L) and brine (10 L). To the organic layer at room temperature was added TFA (19.3 kg, 168.9 mol) followed by stirring for 12 h. The resulting mixture was evaporated in vacuo to remove most of the TFA. CH_2Cl_2 (50 L) and 20% aqueous sodium hydroxide (14 kg) were added to the residual at 0-10 °C, stirred for 0.5 h and separated. After separation, another portion of 20% aqueous sodium hydroxide (12 kg) was added to the organic layer at room temperature, followed by a dropwise addition of 2-furoyl chloride (7.3 kg, 56.3 mol) in CH_2Cl_2 (8 L) at 0-5 °C

and stirring at room temperature for 4 h. The resulting mixture was separated, and the organic layer was washed with water (20 L), brine (20 L), dried over anhydrous sodium sulfate and evaporated in vacuo to give **19** (11.0 kg, 70%) as a white semisolid. MS *m/z* 280.2 $[M + H]^+$.

2-(*trans*-4-(Furan-2-carboxamido)cyclohexyl)acetic acid (21). A mixture of **19** (10.0 kg, 35.8 mol), lithium hydroxide monohydrate (3.5 kg, 82.3 mol), water (25 L) and THF (100 L) was stirred at 40 °C for 19 h. The resulting solution was evaporated in vacuo to remove most of the THF and acidified by hydrochloric acid (6.0 mol/L, 41 L) at 0-5 °C followed by stirring at room temperature for 5 h. The resulting mixture was filtered and washed with water (5 L) to yield a white solid, which was further recrystallized from CH_3CN (110 L) to yield **21** (4.6 kg, 51%) as a white solid with the trans/cis isomer ratio of 517.4:1.0 (HPLC method A, t_R = 13.8 min). Mp 185-187 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 12.09 (br, 1H), 8.11-8.10 (m, 1H), 7.80 (d, J = 0.8 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.60 (dd, J = 2.0, 0.8 Hz, 1H), 3.69-3.66 (m, 1H), 2.11 (d, J = 4.4 Hz, 2H), 1.79-1.73 (m, 4H), 1.61-1.59 (m, 1H), 1.38-1.32 (m, 2H), 1.08-1.01 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.21, 157.35, 148.58, 145.14, 113.53, 112.18, 47.99, 41.54, 34.05, 32.35, 31.58; MS *m/z* 252.1 $[M + H]^+$.

Ethyl 2-(*trans*-4-(furan-2-carboxamido)cyclohexyl)acetate (22). To a mixture of **21** (4.5 kg, 17.9 mol) and ethanol (5.2 kg) in CH_2Cl_2 (14 L), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.1 kg, 21.5 mol) and 4-dimethylaminopyridine (1.7 kg, 14.3 mol) in CH_2Cl_2 (18 L) were added at room temperature. The resulting mixture was stirred at room temperature for 3 h and water (5 L) was added. The resulting solution was separated and washed with water (5 L), hydrochloric acid (2.0 mol/L, 11 L), brine (5 L); dried over anhydrous sodium sulfate; and evaporated in vacuo to yield **22** (4.7 kg, 95%) as a white solid in 97.2% purity (HPLC method A, t_R = 31.7 min). Mp 104-106 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.10 (d, J = 1.6 Hz, 1H), 7.80 (s, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.60 (dd, J = 2.0, 1.6 Hz, 1H), 4.06 (q, J = 4.8 Hz, 2H), 3.68-3.67 (m, 1H), 2.19 (d, J = 4.8 Hz, 2H), 1.79-1.77 (m, 2H), 1.70-1.72 (m, 2H), 1.68-1.61 (m, 1H), 1.37-1.34 (m, 2H), 1.18 (t, J

= 4.8 Hz, 3H), 1.09-1.05 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.56, 157.35, 148.57, 145.14, 113.54, 112.18, 60.12, 47.92, 41.23, 34.20, 32.29, 31.56, 14.63; MS *m/z* 280.2 $[M + H]^+$.

N-(*trans*-4-(2-Hydroxyethyl)cyclohexyl)furan-2-carboxamide (23). A mixture of **22** (4.5 kg, 16.1 mol), sodium borohydride (3.0 kg, 80.5 mol) and THF (36 L) was stirred under reflux for 0.5 h, and then methanol (9 L) was added dropwise to this mixture for 2 h at room temperature under the condition of a nitrogenous atmosphere. The resulting solution was stirred under reflux for 12 h and quenched with hydrochloric acid (6.0 mol/L, 27 L) at 0-35 ℃. The resulting mixture was stirred for 1 h and alkalized with 50% sodium hydroxide solution (11 L). The resultant mixture was extracted with dichloromethane (2 × 24 L). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated in vacuo to yield **23** (3.4 kg, 90%) as a white solid in 97.7% purity (HPLC method A, t_R = 16.2 min). Mp 135-137 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.09 (d, *J* = 1.2 Hz, 1H), 7.79 (s, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.60 (dd, *J* = 2.0, 1.2 Hz, 1H), 4.33 (t, *J* = 3.2, 1H), 3.68-3.66 (m, 1H), 3.43 (dd, *J* = 7.2, 4.0 Hz, 2H), 1.79-1.74 (m, 4H), 1.34-1.30 (m, 5H), 0.98-0.96 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.33, 148.61, 145.11, 113.49, 112.17, 58.99, 48.36, 33.51, 32.61, 32.16; MS *m/z* 238.1 $[M + H]^+$.

2-(*trans*-4-(Furan-2-carboxamido)cyclohexyl)ethyl methanesulfonate (24). To a solution of **23** (3.3 kg, 13.9 mol) and triethylamine (3.5 kg, 34.7 mol) in DMF (13.2 L), methanesulfonic anhydride (3.6 kg, 20.8 mol) in DMF (7 L) was added dropwise at 0~5 °C, and the resulting mixture was stirred for 3 h at ambient temperature. The resultant mixture was supplemented with water (80 L) and extracted with dichloromethane (2 × 8 L). The combined organic extracts were washed with water (2 × 5 L) and brine (10 L) and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give crude **24**, which was further slurried in petroleum ether/ethyl acetate (1:1, 32 L) under reflux to afford **24** (3.9 kg, 12.2 mol) as a colorless solid in 98.2% purity (HPLC method A, t_R = 40.9 min). Mp 140-142 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.10 (d, *J* = 5.6 Hz, 1H), 7.80 (d, *J* = 1.2

Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.60 (dd, *J* = 2.4, 1.2 Hz, 1H), 4.24 (t, *J* = 4.4, 2H), 3.70-3.66 (m, 1H), 3.17 (s, 3H), 1.80-1.76 (m, 4H), 1.60-1.57 (m, 2H), 1.37-1.32 (m, 3H), 1.06-1.00 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.35, 148.58, 145.14, 113.54, 112.19, 69.15, 48.15, 37.00, 35.82, 33.32, 32.38, 31.62; MS *m/z* 316.1 [M + H]$^+$.

N-(*trans*-4-(2-(4-(Benzo[*d*]isothiazol-3-yl)piperazin-1-l)ethyl)cyclohexyl)furan-2-carboxamide (12). A mixture of **24** (3.6 kg, 11.4 mol), 3-(piperazin-1-yl)benzo[*d*]isothiazole (2.4 kg, 10.9 mol), sodium carbonate (2.9 kg, 27.3 mol), potassium iodide (9.0 g, 54.5 mmol), and CH_3CN (72 L) was stirred under reflux for 24 h. The resulting solution was cooled to ambient temperature and filtered and then washed with CH_3CN (2 × 3 L). The filter cake was slurried in CH_2Cl_2 (15 L) and water (20 L) and then separated. The organic layer was washed with water (5 L) and brine (5 L) and concentrated under reduced pressure to yield crude product **12** (3.8 kg, 80%) as a colorless solid. To a stirred solution of oxalate dihydrate (1.2 kg, 9.5 mol) in MeOH (77 L) and water (11 L) was added crude **12** (3.8 kg, 8.7 mol). The mixture was stirred under reflux for 1 h after clarification, cooled to room temperature and filtered. The obtained solid was recrystallized from MeOH/water (8:1) and alkalized with 10% sodium hydroxide solution in CH_2Cl_2. The organic layer was washed with water (5 L) and brine (5 L) and then concentrated under reduced pressure to afford **12** (3.1 kg, 80%) as a white solid with 99.92% purity (HPLC method B, t_R = 61.7 min). Mp 188-190 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.15-8.11 (m, 3H), 7.81 (s, 1H), 7.60 (t, *J* = 4.8 Hz, 1H), 7.48 (t, *J* = 4.8 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 6.60 (t, *J* = 0.8 Hz, 1H), 4.08-4.06 (m, 2H), 3.60-3.58 (m, 1H), 3.50-3.48 (m, 2H), 3.27-3.25 (m, 2H), 3.21-3.18 (m, 4H), 1.82-1.77 (m, 4H), 1.68-1.65 (m, 2H), 1.38-1.36 (m, 3H), 1.07-1.05 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.70, 157.39, 152.62, 148.58, 145.17, 128.62, 127.45, 125.12, 124.50, 121.69, 113.55, 112.19, 54.38, 50.97, 48.14, 46.89, 34.81, 32.30, 31.72, 30.32; MS *m/z* 439.2 [M + H]$^+$; HRMS (ESI) m/z calcd for $C_{24}H_{31}N_4O_2S$ [M + H]$^+$ 439.2168, found 439.2271.

N-(*trans*-4-(2-(4-(Benzo[*d*]isothiazol-3-yl)piperazin-1-l)ethyl)cyclohexyl)furan-2-carboxamide hydrochloride (SIPI 6398). A mixture of **12** (3.0 kg, 6.8 mol),

EtOH (30 L) and 10% aqueous hydrochloric acid solution (7.5 mol) was stirred under reflux for 1 h. The resulting mixture was cooled to room temperature and filtered to yield a white solid, which was slurried in ethanol (24 L) at 60 °C and filtered to afford 2.7 kg of SIPI 6398 with 99.94% purity (HPLC method B, t_R = 61.7 min) as a white solid (85% yield). Mp > 270 °C; Anal.Calcd for $C_{24}H_{30}N_4O_2S.HCl$: C, 60.68; H, 6.58; N, 11.79. Found: C, 60.60; H, 6.61; N, 11.74.

AUTHOR INFORMATION

Corresponding Author

Jianqi Li.

*Telephone: +86 21 20572000. E-mail: lijianqb@126.com.

Gengli Duan.

*Telephone: +86-21-54237208. E-mail: glduan@shmu.edu.cn.

[1] Authors Ai-Nan Zhou and Xiao-Wen Chen contributed equally.

Notes

The authors declare no competing financial interest.

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(7) The impurity **31** was isolated by preparative separation method (Instrument: Shimadzu LC-20AP*3 Prep HPLC (PrepL-GB); Column: Ximate C18, 5 μm, 150 × 25 mm I.D.; Mobile phase: A for H_2O (0.05% ammonia hydroxide) and B for MeOH; Gradient: B 65% in 13 min linearly; Flow rate: 35 mL/min; Column temperature: R.T.; Wavelength: 220 nm; Sample preparation: Compound dissolved in MeOH with 10 mg/mL concentration; Injection: 500 μL per injection.) and confirmed by ^{1}H NMR, MS and HRMS. Mp 152-154 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.89-7.82 (m, 2H), 7.49 (t, J = 5.2 Hz, 1H), 7.43-7.39 (m, 1H), 7.36 (d, J = 5.2 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 6.49 (dd, J = 2.0 Hz, 0.8 Hz, 1H), 6.37 (d, J = 5.2 Hz, 1H), 5.47-5.46 (m, 1H), 4.28-4.26 (m, 1H), 3.77 (brs, 4H), 3.77 (brs, 4H), 2.78-2.74 (m, 2H), 2.48-2.38 (m, 3H), 2.18-2.15 (m, 2H), 1.97-1.94 (m, 2H), 1.76-1.74 (m, 1H); MS *m/z* 437.2 $[M + H]^+$; HRMS (ESI) m/z calcd for $C_{24}H_{29}N_4O_2S$ $[M + H]^+$ 437.2011, found 437.2018.

(8) Crystallographic data for SIPI 6398 have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1907982). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK,

(fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).