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Development and Kilogram-Scale Synthesis of a D_2/5-HT_{2A} Receptor Dual Antagonist (±)-SIPI 6360

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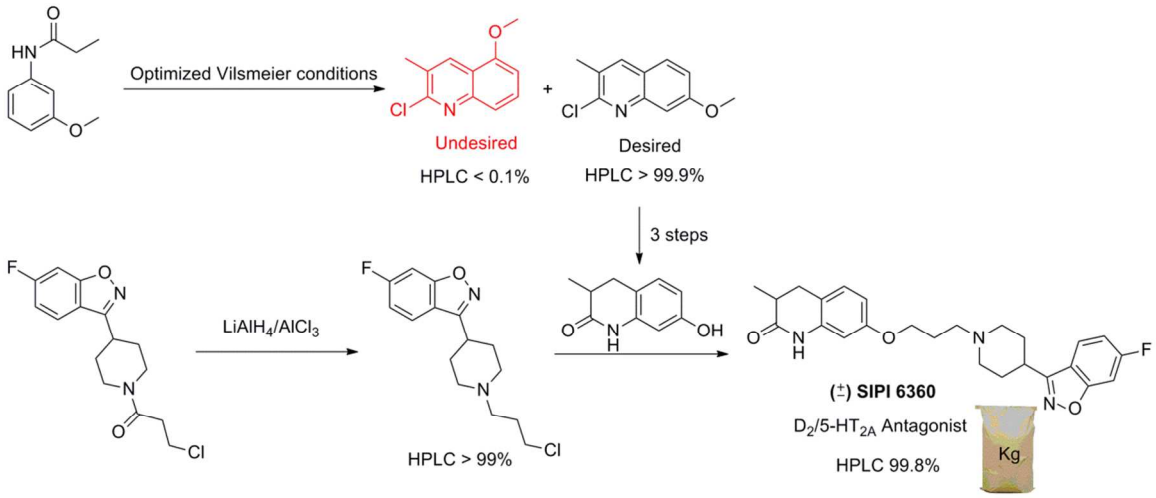
TOC Graphic:


Optimized Vilsmeier conditions
Undesired
HPLC < 0.1%
Desired
HPLC > 99.9%
3 steps
LiAlH4/AlCl3
HPLC > 99%
(±) SIPI 6360
D2/5-HT2A Antagonist
HPLC 99.8%
Kg

ABSTRACT: The kilogram-scale synthesis of a D_2/5-HT_{2A} receptor dual antagonist (±)-SIPI 6360 was developed as an alternative treatment for schizophrenia. Specifically, three conditions were modified and optimized, including the Vilsmeier conditions, to prepare quinoline **3**. In addition, the palladium-catalyzed hydrogenation was modified to synthesize dihydroquinolin-2(1*H*)-one **5**, and the reduction of *β*-chloroamide was altered to form 3-chloropropanamine **8**. Ultimately these improvements led to the preparation of 1.5 kilogram of (±)-SIPI 6360 batch in eight steps with an overall yield of 34% and purity of 99.8%.

Keywords: schizophrenia, D_2/5-HT_{2A} receptor antagonist, Vilsmeier condition, palladium-catalyzed hydrogenation

INTRODUCTION

Schizophrenia is one of the most serious mental illnesses, causing suicides and a broad societal burden.[1,2] As potent dopamine D_2 receptor antagonists, the "typical" antipsychotic agents (e.g., Haloperidol) are effective in the treatment of positive symptoms of schizophrenia, but largely ineffective in the management of negative symptoms and cognitive impairment. Typical antipsychotics can also induce severe side effects, such as extrapyramidal symptoms (EPS).[3] These extrapyramidal symptoms include acute dyskinesia and dystonic reactions, tardive dyskinesia, Parkinsonism, akinesia, akathisia, and neuroleptic malignant syndrome. Characterized by a multiple target effect, the "atypical" antipsychotic agents, such as the D_2/5-HT_{2A} receptor dual antagonist Risperidone, offer therapeutic advantages over typical antipsychotics accompanied by a lower incidence of EPS .[4]

Our research team has been devoted to the discovery of potential atypical antipsychotics for several years,[5] and we have discovered a series of novel and potent aralkyl substituted piperidine or piperazine D_2/5-HT_{2A} receptor dual antagonist candidates, such as (±)-SIPI 6360 (Scheme 1).[6] To support preclinical development and safety studies, it was necessary to produce a scalable and practical synthesis of (±)-SIPI 6360 suitable for kilogram-scale preparation..

According to the initial synthetic route for (±)-SIPI 6360, its increase in scale appears to be a great challenge due to the following specific disadvantages: (a) the low yield in preparation of quinoline **3**; (b) the chromatographic step and low yield in preparation of both 3,4-dihydro-2(1*H*)-quinolinone **5** and 3-chloropropanamine **8**; (c) the 1% overall yield. Herein, we report a kilogram-scale chromatography-free synthesis of (±)-SIPI 6360 in which critical conditions were modified and optimized to yield an overall high yield of excellent purity.

Scheme 1. Initial Synthesis of (±)-SIPI 6360

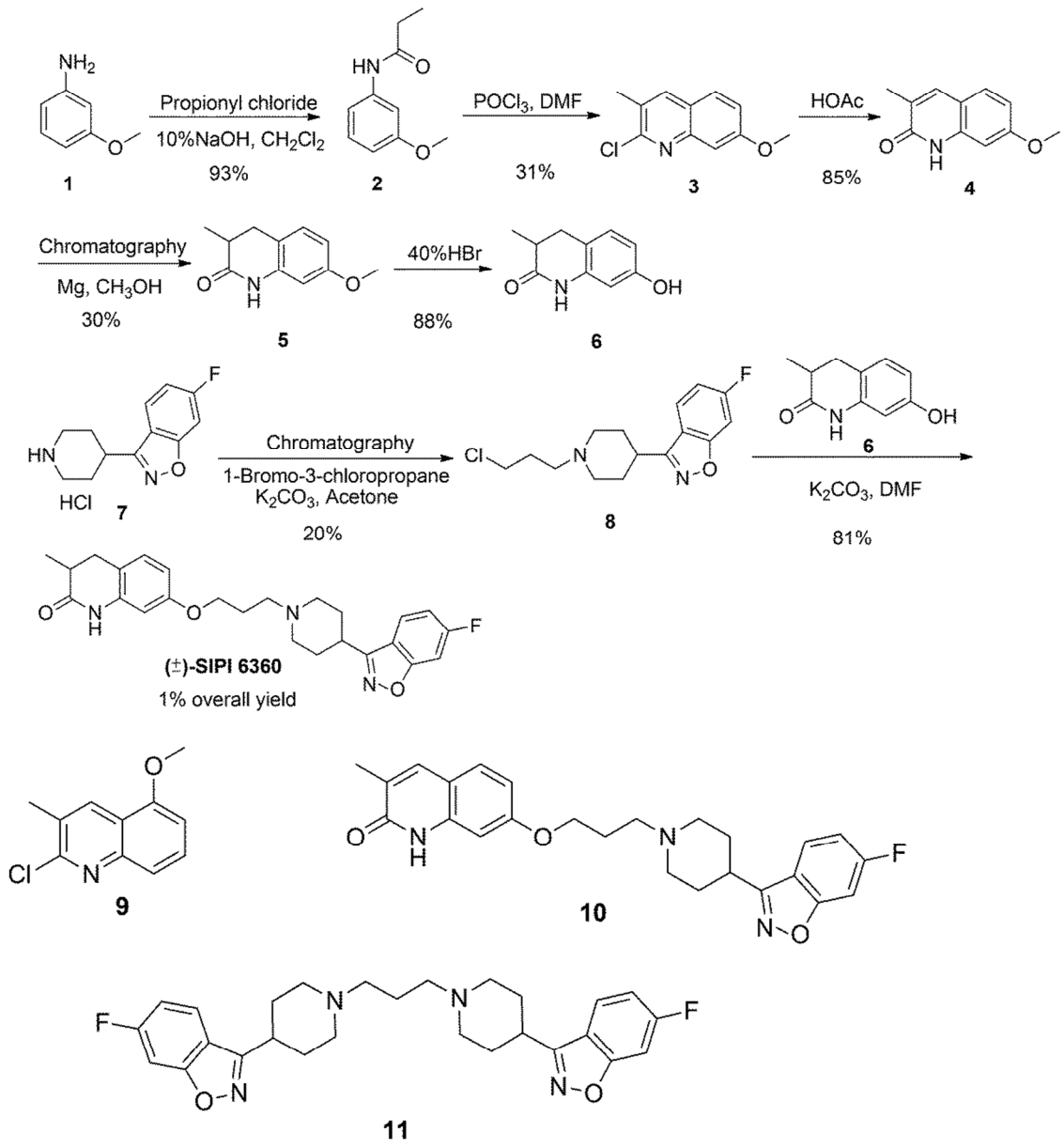


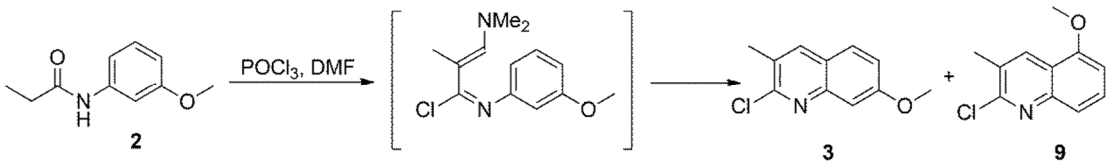
Figure 1. Chemical structures of byproducts **9**, **10** and **11**.

RESULTS AND DISCUSSION

Our efforts were made to optimize the existing process to improve the yield of quinoline **3**. This yield of **3** was obtained under Vilsmeier conditions[7] accompanied by formation of a regioisomer **9**[8] (Figure 1), which was removed via recrystallization, and resulting in a massive loss of **3** (31% isolated yield, Table 1, entry 1). Previously, Vázquez and colleagues found that regioselectivity is governed by temperature and the

addition of the $POCl_3$ reagent for their aldehyde products under Vilsmeier conditions.[9] Our tentative experiments showed that a lower temperature favored the formation of the desired regioisomer **3** (entry 2). Further investigation into the amount of reagent revealed that the formation of the undesired regioisomer **9** was reduced with the decreasing usage of DMF (entry 3). Thus, an optimal feed ratio of DMF was further studied to facilitate the regioselectivity. As shown in Table 1, a 1.5 equivalent of DMF was deemed the optimal amount with < 0.1% content of **9**, which was removed by slurry in petroleum ether with a good yield (86%) of **3** (entry 4). Moreover, decreasing the $POCl_3$ reagent amount from 7 to 5.5 equivalent barely influenced the regioselectivity (entry 5). The reaction mixture was semi-solidified and difficult to stir after decreasing the $POCl_3$ reagent amount to 5.0 equivalent. Thus, 5.5 equivalent of $POCl_3$ was regarded as the optimal amount for the reaction. This improvement facilitated the isolation of regioisomer **9** and work up of **3** in good yield (84%) and high purity (> 99.9%, HPLC).

Table 1. The optimization of Vilsmeier conditions for 3



entry	DMF Moles	$POCl_3$ Moles	temp (°C)	**3** (area %)[a]	**9** (area %)[a]	yield (%)[b]
1	5.5	7	95	90.9[c] 98.6[d]	7.4[c] 1.2[d]	31
2	5.5	7	80	95.3[c] 98.9[d]	3.1[c] 0.7[d]	48
3	4	7	80	97.0[c] 99.1[d]	1.4[c] 0.5[d]	55
4	3	7	80	98.1[c] 99.6[d]	0.3[c] 0.1[d]	71

5	1.5	7	80	98.6[c] > 99.9[e]	0.04[c] 0[e]	86
6	1.5	5.5	80	98.5[c] > 99.9[e]	0.06[c] 0[e]	84

[a] Determined by HPLC analysis. [b]Isolated yield. [c]Crude product. [d]Recrystallization. [e]Slurry.

The quinoline **3** was subsequently hydrolyzed in the presence of acetic acid to give the quinolone **4** at kilogram-scale.

Further synthetic modifications were carried out for the yield improvement of **5**. The low yield (30% isolated yield) was attributed to the insufficient conversion of **4** and the chromatography work up. Furthermore, the unconverted **4** took part in the following steps forming a byproduct **10**[10], which was detrimental to purity control of the API (active pharmaceutical ingredient). To address this issue, palladium-catalyzed hydrogenation[11] was employed instead of a magnesium system. As shown in Table 2, ethanol was found to be the optimal solvent to drive the reaction process after the screening of several other solvents (entry 1-3). Temperature was another influencing factor and an almost 80% conversion of **4** was detected at reflux (entry 5). When the pressure was increased to 2.5 MPa, **4** was completely consumed in 24 hours (entry 6-7). In order to reduce cost, the catalytic performance of 5% Pd-C was investigated under the same amount of Pd-C compared with 10% Pd-C. 5% Pd-C showed poor catalytic performance–(entry 8). Eventually, the conditions of 10% Pd-C/EtOH at 2.5 MPa and 90°C were applied for the scaling of **5**. These synthetic modifications resulted in a kilogram-scale (> 2 kg) batch of **5** in excellent yield (92%) without chromatography. These kilogram quantities of **5** were subsequently converted to **6** by demethylation in 40% aqueous hydrobromic acid.

Table 2. Hydrogenation of 4 under different conditions

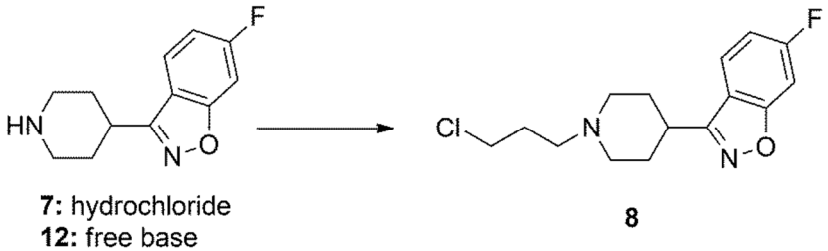
4 **5**

entry	catalyst	solvent	temp (°C)	pressure (MPa)	time (h)	**4** (area %)[a]	**5** (area %)[a]
1	10% Pd/C	AcOH	70	0.1	72	80.1	19.9
2	10% Pd/C	THF	70	0.1	72	96.3	3.7
3	10% Pd/C	EtOH	70	0.1	72	71.6	28.4
4	10% Pd/C	EtOH	80	0.1	72	48.5	51.5
5	10% Pd/C	EtOH	90	0.1	72	23.7	76.3
6	10% Pd/C	EtOH	90	1.5	24	14.2	85.8
7	10% Pd/C	EtOH	90	2.5	24	0	100
8	5% Pd/C	EtOH	90	2.5	24	47.9	52.1

[a]Determined by HPLC analysis.

Finally we utilized a more practical approach for the work up of **8**. Initially, the coupling of 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole hydrochloride (**7**) and 1-bromo-3-chloropropane resulted in low yield (20% isolated yield) when compared to a literature yield[12] due to the formation of a bilateral substituent byproduct (**11**)[13] (Figure 1), which could only be removed by chromatography. Investigation of alternative bases ($NaHCO_3$, diisopropylethylamine and triethylamine), solvents (acetonitrile, ethanol, DMF, etc.) and a reagent (**12**, free base of **7**) failed to improve the yield and inhibited the formation of **11** (Table 3). In an attempt to develop a more practical process to synthesize **8**, we envisioned three possible methods to prepare **8** by avoiding or decreasing the formation of **11** (Scheme 2).

Table 3. Condensation conditions for preparing 8



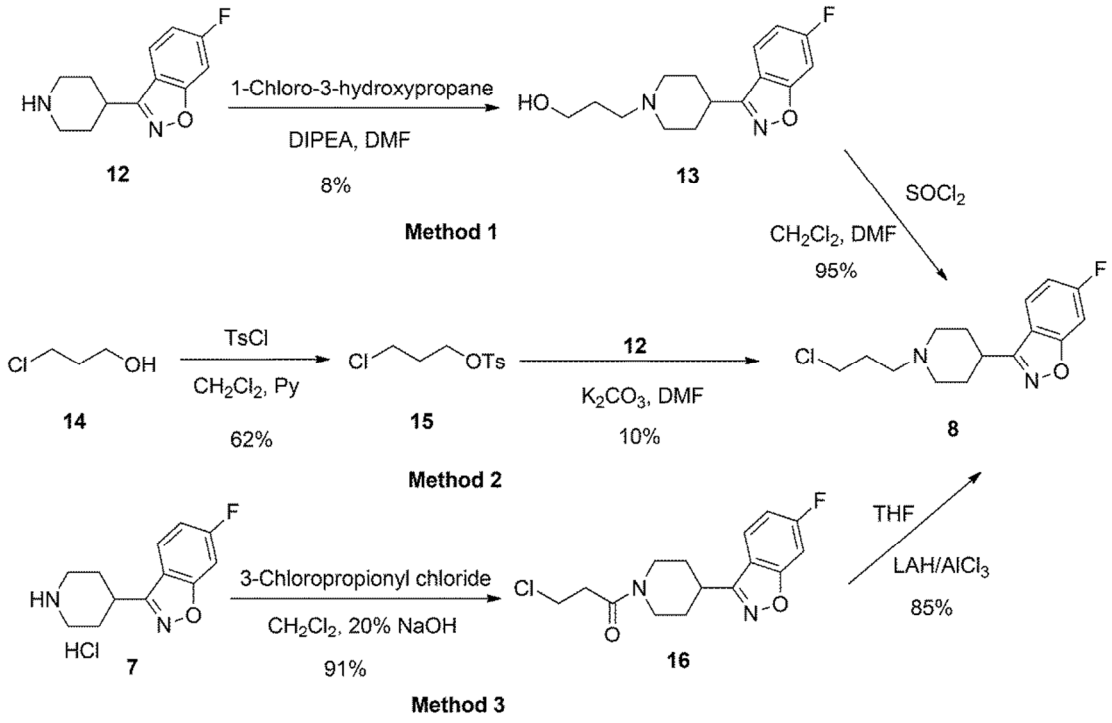
7: hydrochloride
12: free base

8

entry	reagent	solvent	base	temp (°C)	yield (%)[a]
1	**12**	Acetone	K_2CO_3	70	28
2	**7**	Acetone	$NaHCO_3$	70	25
3	**7**	CH_3CN	K_2CO_3	60	12
4	**7**	EtOH	K_2CO_3	90	10
5	**7**	DMF	K_2CO_3	60	14
6	**7**	DMF	DIPEA	60	27
7	**7**	NMP	DIPEA	60	36
8	**7**	NMP	Et_3N	60	29
9	**7**	DMSO	DIPEA	60	31

[a]Isolated yield.

Scheme 2. New process for the synthesis of 8



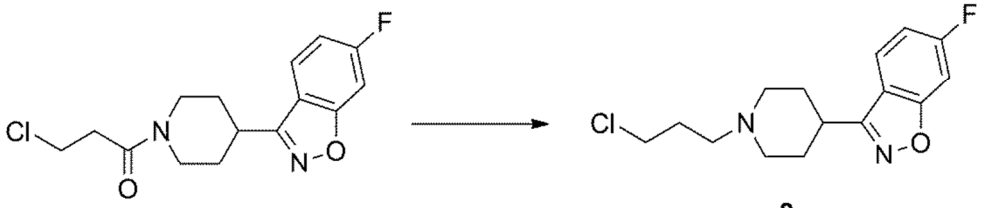
In method 1, the coupling of **12** and 3-chloropropan-1-ol resulted in low yield (5~10%) due to substantial unreacted **12** after investigation into the reaction conditions, such as solvent, base and temperature, which inhibited this approach.

The major drawback of method 2 was the low yield (10%) of the coupling between active ester **15** and **12**. Considerable unconverted **12** was detected by HPLC analysis despite the consumption of **15**. This large amount was attributed to the self-elimination of **15** in an alkaline condition. Based on these results, it is unsuitable to produce **8** on a large scale via method 1 or method 2.

In method 3, compound **16** was obtained in high yield (91%) via acylation. The subsequent reduction of the amide group was implemented in the presence of BH_3 at reflux, resulting **8** in only 14% isolated yield (Table 4, entry 1) due to multiple byproducts and chromatographic purification. Lowering the temperature was found to favor the yield (38%, entry 2) until above the 0°C point. In addition, different reductants were screened and we found that Vitride (entry 4) and sodium borohydride systems (entry 5-6)[14-17] were ineffective, whereas lithium aluminum hydride was effective (71% isolated yield, entry 7), in situations where an allylic product **17**[18] (10.5%, HPLC) (Figure 2) and a de-chlorination product **18**[19] (2.4%, HPLC, Figure 2) were detected. Early studies indicated that acidic hydrides retard reduction of the halogen whereas more basic reagents, such as lithium aluminum hydride, facilitate the reduction.[20] Those results illustrated that **18** had formed in the presence of lithium aluminum hydride.

It is known that **17** can be formed through a self-elimination process under alkaline conditions, and so the lithium aluminum hydride-aluminum chloride reagent as acidic hydride was therefore employed to prepare **8**. Under this acidic condition only small quantities **17** and **18** (2.6% and 0.5%, respectively) were observed in crude **8** by HPLC analysis, and these were easily removed by recrystallization (petroleum ether/ethyl acetate, 1:1) with 85% isolated yield and 99.3% HPLC purity of **8**. Similar conditions were successfully applied for the scale up of **8**, resulting in a chromatography-free production of **8** in good yield (77%) via two steps from **7** at >1-kg scale.

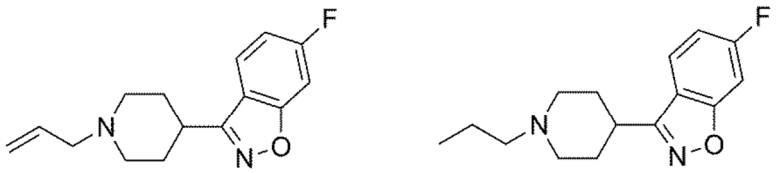
Table 4. Screening of reductants



16 8

entry	reductant	temp (°C)	time (h)	yield (%)[a]
1	BH_3	70	5	14
2	BH_3	25	16	38
3	BH_3	0	8	0
4	Vitride	25	24	0
5	$NaBH_4/I_2$[b]	25	72	0
6	$NaBH_4/(Me)_3SiCl$[c]	25	72	0
7	$NaBH_4/(Me)_3SiCl$[d]	70	24	0
8	$NaBH_4/AlCl_3$[e]	70	24	0
9	$LiAlH_4$	0~10	3	71
10	$LiAlH_4/AlCl_3$	0~10	3	85

[a]Isolated yield. [b]See ref 14. [c]See ref 15. [d]See ref 16. [e]See ref 17.



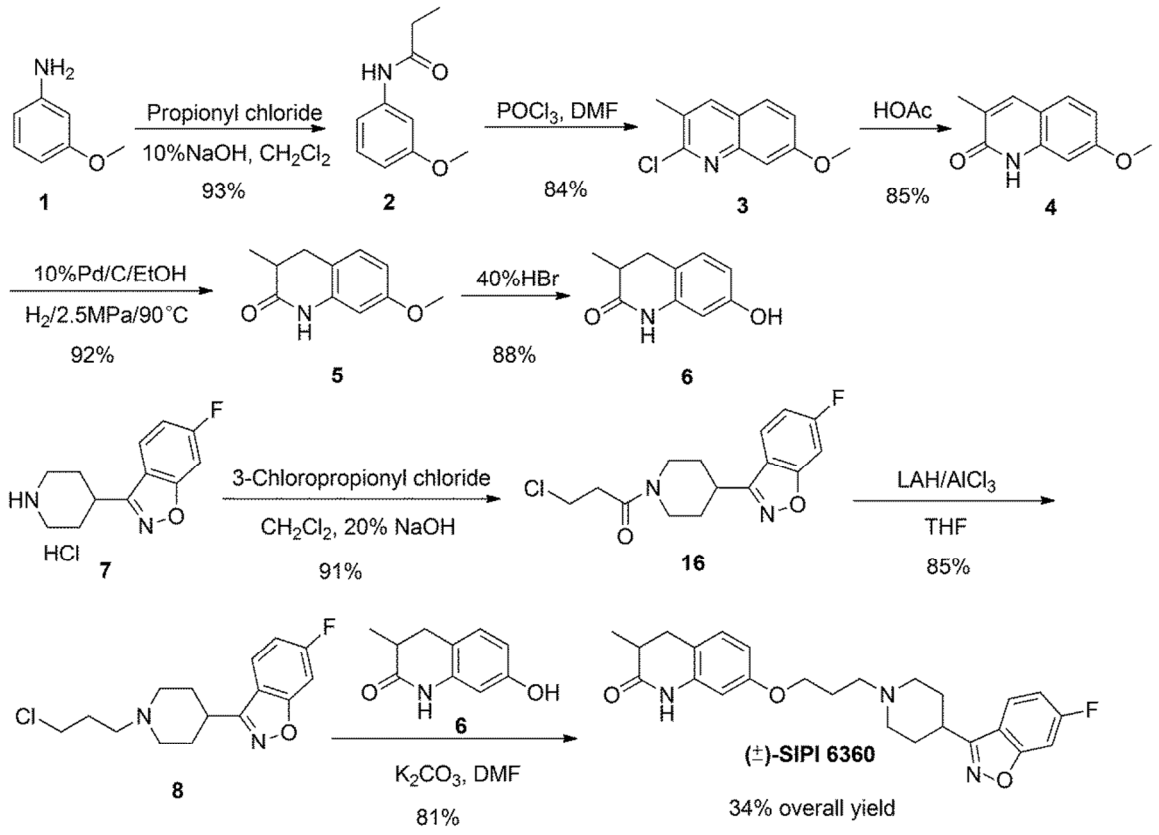
17 18

Figure 2. Chemical structures of byproducts **17** and **18**.

The synthesis of (±)-SIPI 6360 was then completed by the S_N2 coupling of **6** and **8** under mild basic conditions followed by slurry of the crude API from ethanol to give the product at kilogram-scale in 34% overall yield and high purity (99.8%, HPLC).

Through these improvements, the final process route (Scheme 3) was established for the kilogram-scale preparation of (±)-SIPI 6360.

Scheme 3. Final process route for the synthesis of (±)-SIPI 6360



CONCLUSION

In summary, we have developed a manageable and kilogram-scale eight-step process for the preparation of (±)-SIPI 6360 and improved the overall yield from 1% to 34%. We achieved this by controlling the formation of undesired regioisomer **9** to obtain **3**, careful screening of reduction conditions in the preparation of **5**, and rational route design and careful reductant screening in the preparation of **8**. Finally, we have successfully optimized protocols for the preparation of **3**, **5** and **8** which resulted in chromatography-free production of 1.5 kilogram of (±)-SIPI 6360 in 99.8% purity.

EXPERIMENTAL SECTION

Reaction progress and compound purity was determined by high performance liquid chromatography (HPLC). HPLC method A: Welch Ultimate® XB-C18 column, C18 (5 μm, 250 mm × 4.6 mm); mobile phase A (0.05% trifluoroacetic acid in water) and B (CH_3CN), from 75:25 A/B to 5:95 A/B over 25 min; detection at 237 nm; flow rate = 1.0 mL/min; temp 42 °C. HPLC method B: Welch Ultimate® XB-C18 column, C18 (5 μm, 250 mm ×4.6 mm); mobile phase A (CH_3CN) and B (20 mM NaH_2PO_4 (pH = 5.5)), 20:80 v/v; detection at 254 nm; flow rate = 1.0 mL/min; temp 30 °C.

N-(3-methoxyphenyl)propionamide (2). To a stirred solution of 3-methoxyaniline (**1**) (3.0 kg, 24.4 mol) and 10% aqueous sodium hydroxide (13.4 L) in dichloromethane (12 L) was added propionyl chloride (2.5 kg, 26.8 mol) in dichloromethane (2.5 L) at 0-5 °C and stirred at room temperature for 3 h. The organic layer was washed with water (5 L), brine (5 L), dried over anhydrous sodium sulfate, and evaporated *in vacuo* to give compound **2** (4.1 kg, 93%) as a white solid with 99.7% purity (HPLC method A, t_R = 9.6 min). Mp 74-75 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.67 (br, 1H), 7.33 (s, 1H), 7.20-7.16 (m, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.64 (dd, J = 8.0, 0.8 Hz, 1H), 3.77 (s, 3H), 2.38 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.44, 160.11, 139.44, 129.61, 111.96, 110.03, 105.53, 55.26, 30.73, 9.68; MS *m/z* 180.4 $[M + H]^+$.

2-Chloro-7-methoxy-3-methylquinoline (3). To a stirred solution of N,N-dimethylformamide (2.5 L) was added phosphorus oxychloride (18.8 kg, 122.6 mol) at 0°C. The resulting mixture was stirred at room temperature for 20 min, followed by addition of **2** (4.0 kg, 22.3 mol) in batches at 0°C over 1 h. The mixture was stirred at room temperature for 20 min and heated at 80 °C for 9 h. The reaction mixture was cooled to room temperature, poured into ice-water and stirred for 2 h. The precipitate was collected by filtration, washed with water, and dried to give crude **3**, which was further purified by slurry in petroleum ether and dried to give compound **3** (3.7 kg, 84%) as a white solid with > 99.9% purity (HPLC method A, t_R = 16.8 min). Mp 90-91 °C; ^{1}H

NMR (400 Hz, $CDCl_3$) δ 7.87 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.16 (dd, J = 8.8, 2.4 Hz, 1H), 3.92 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.75, 152.17, 148.11, 137.62, 127.75, 127.50, 122.72, 119.96, 106.44, 55.52, 19.81; MS *m/z* 208.0 $[M + H]^+$; HRMS (ESI) m/z calcd for $C_{11}H_{11}ClNO$ $[M + H]^+$ 208.0524, found 208.0523.

7-Methoxy-3-methylquinolin-2(1*H*)-one (4). A mixture of **3** (3.5 kg, 16.9 mol) and acetic acid (17.5 L) was stirred at 125 °C for 15 h. The resulting mixture was cooled to 60-70 °C and evaporated *in vacuo* to give a light yellow solid, which was slurried in water (3 L) at room temperature to give compound **4** (2.7 kg, 85%) as a white solid with 98.9% purity (HPLC method A, t_R = 9.0 min). Mp 174-176 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 12.08 (br, 1H), 7.58 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.78 (dd, J = 8.8, 2.4 Hz, 1H), 3.90 (s, 3H), 2.26 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.07, 160.80, 139.21, 137.43, 128.11, 126.53, 114.58, 111.85, 98.16, 55.55, 16.57; MS *m/z* 190.1 $[M + H]^+$.

7-Methoxy-3-methyl-3,4-dihydroquinolin-2(1*H*)-one (5). To a stirred solution of **4** (2.5 kg, 13.2 mol) and ethanol (12.5 L) was added 10% Pd-C (125 g, dry catalyst, **4**: 10% Pd-C = 20: 1 (w/w)) in ethanol (500 mL) at room temperature. The resulting solution was hydrogenated of H_2 (2.5 Mpa) at 90 °C for 24 h. After cooling to room temperature, the reaction mixture was filtered through a Celite pad and washed with EtOH (1 L × 2). Concentration *in vacuo* provided compound **5** (2.3 kg, 92%) as a whitish solid with 99.3% purity (HPLC method A, t_R = 10.5 min). Mp 113-115 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.70 (br, 1H), 7.27 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.52 (dd, J = 8.4, 2.4 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 3.78 (s, 3H), 2.92-2.89 (m, 1H), 2.67-2.61 (m, 2H), 1.29-1.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.84, 159.16, 138.14, 128.73, 115.74, 107.96, 101.38, 55.41, 35.22, 32.66, 15.33; MS *m/z* 192.2 $[M + H]^+$.

7-Hydroxy-3-methyl-3,4-dihydroquinolin-2(1*H*)-one (6). A mixture of **5** (2.0 kg, 10.5 mol) and 40% HBr (20 L) was stirred at 135 °C for 16 h. The resulting mixture was

cooled to room temperature and filtered to obtain a whitish solid, which was dissolved in methanol (1 L), stirred for 0.5 h, and filtered. The filtrate was evaporated *in vacuo* to give a whitish solid, which was slurried in 95% ethanol (3 L) at room temperature to give compound **6** (1.6 kg, 88%) as a white solid with 99.9% purity (HPLC method A, t_R = 6.3 min). Mp 233-235 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 9.91 (br, 1H), 9.24 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.33-6.29 (m, 2H), 2.81-2.74 (m, 1H), 2.50-2.36 (m, 2H), 1.23-1.06 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.91, 156.43, 138.86, 128.32, 113.60, 109.06, 102.00, 34.52, 32.08, 15.47; MS *m/z* 178.1 $[M + H]^+$; HRMS (ESI) m/z calcd for $C_{10}H_{12}NO_2$ $[M + H]^+$ 178.0863, found 178.0863.

3-Chloro-1-(4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)propan-1-one (16). To a stirred solution of 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole hydrochloride (1.5 kg, 5.9 mol) and 20% aqueous sodium hydroxide (2.4 L) in dichloromethane (7.5 L) was added 3-chloropropanoyl chloride (0.9 kg, 7.1 mol) in dichloromethane (1 L) at 0-5 °C and stirred at room temperature for 5 h. The organic layer was washed with water (2 L), brine (2 L), dried over anhydrous sodium sulfate, evaporated *in vacuo*, and slurried in 95% ethanol (1.5 L) at room temperature to give compound **16** (1.6 kg, 91%) as a light yellow solid with 99.7% purity (HPLC method A, t_R = 15.0 min). Mp 88-90 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.64-7.62 (m, 1H), 7.27-7.26 (m, 1H), 7.13-7.07 (m, 1H), 4.67-4.65 (m, 1H), 4.03-4.01 (m, 1H), 3.87 (t, J = 4.8 Hz, 2H), 3.38-3.29 (m, 2H), 2.98-2.83 (m, 3H), 2.18-2.14 (m, 2H), 2.06-2.00 (m, 1H), 1.95-1.89 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.04, 164.98, 163.55-163.34 (m), 161.37, 124.26 (d, J = 7.0 Hz), 117.59, 113.04 (d, J = 17.0 Hz), 97.84 (d, J = 18.0 Hz), 45.12, 41.24, 35.69, 33.66, 30.72; MS *m/z* 311.1 $[M + H]^+$.

3-(1-(3-Chloropropyl)piperidin-4-yl)-6-fluorobenzo[*d*]isoxazole (8). To a stirred solution of THF (12 L) was added lithium aluminum hydride (0.40 kg, 11.1 mol) at 0-10 °C and stirred for 1 h. The resulting mixture was added aluminum chloride (0.70 kg, 5.1 mol) in batches and stirred for 3 h at 0-10 °C, followed by addition of **16** (1.5 kg, 4.8

mol) at 0-5 °C. The solution was kept at 0-5 °C and stirred for 2 h. Water (2 L) was added dropwise to the solution at 0-5 °C and stirred for 2 h. The resulting mixture was stirred for another 1 h at room temperature, followed by addition of magnesium sulfate (400 g), stirring for 1 h, and filtration. The filter cake was slurried in THF (2 L) at room temperature and filtrated. The combined filtrate was evaporated *in vacuo* followed by recrystallization in petroleum ether/ethyl acetate (1:1) to give compound **8** (1.3 kg, 85%) as a white solid with 99.3% purity (HPLC method A, t_R = 7.8 min). Mp 71-72 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.62 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.19-7.16 (m, 1H), 6.99-6.97 (m, 1H), 3.56 (t, *J* = 4.4 Hz, 2H), 3.03-2.96 (m, 3H), 2.48 (t, *J* = 4.8 Hz, 2H), 2.20-2.10 (m, 2H), 2.08-1.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.91, 162.87 (d, *J* = 9.0 Hz), 160.06, 121.54 (d, *J* = 8.0 Hz), 116.29, 111.30 (d, *J* = 17.0 Hz), 96.43 (d, *J* = 18.0 Hz), 54.65, 52.60, 42.27, 33.57, 29.56, 29.04; MS *m/z* 296.6 $[M + H]^+$; HRMS (ESI) m/z calcd for $C_{15}H_{19}ClFN_2O$ $[M + H]^+$ 297.1170, found 297.1171.

7-(3-(4-(6-Fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)propoxy)-3-methyl-3,4-dihydroquinolin-2(1*H*)-one ((±)-SIPI 6360). A mixture of **6** (0.80 kg, 4.2 mol), **8** (1.2 kg, 4.0 mol), potassium carbonate (1.7 kg, 12.1 mol), and N,N-dimethylformamide (12 L) was stirred at 60°C for 12 h. The resulting mixture was cooled to room temperature and evaporated *in vacuo* to remove most of the solvent. The resulting residue was poured into water (16 L), stirred for 1 h, and filtrated. The filter cake was slurried in ethanol (2 L) at 60 °C and filtrated to afford 1.5 kg of (±)-SIPI 6360 in 99.8% purity (HPLC method B, t_R = 12.6 min) as a white solid (81% yield). Mp 154-155 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.41 (br, 1H), 7.70 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.27-7.23 (m, 1H), 7.08-7.03 (m, 2H), 6.53 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.11-3.08 (m, 3H), 2.94-2.92 (m, 1H), 2.67-2.56 (m, 4H), 2.18-2.00 (m, 8H), 1.28 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.61, 164.10 (d, *J* = 249.0 Hz), 163.86 (d, *J* = 14.0 Hz), 161.11, 158.59, 138.06, 128.74, 122.59 (d, *J* = 11.0 Hz), 117.30, 115.71, 112.31 (d, *J* = 25.0 Hz), 108.45, 101.96, 97.44 (d, *J* = 27.0 Hz), 66.43, 55.38, 53.62, 35.25, 34.61, 32.68,

30.55, 26.88, 15.34; MS *m/z* 437.6 $[M + H]^+$; HRMS (ESI) m/z calcd for $C_{25}H_{29}FN_3O_3$ $[M + H]^+$ 438.2193, found 438.2210.

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Notes

The authors declare no competing financial interest.

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(8) The byproduct **9** was isolated by preparative separation method (Instrument: Shimadzu LC-20AP Prep HPLC (PrepL-GB); Column: Luna C18, 10μm, 250 × 50 mm I.D.; Mobile phase: A for H_2O and B for Acetonitrile; Gradient: B 50-80% in 30 min linearly; Flow rate: 80 mL/min; Column temperature: R.T.; Wavelength: 254 nm; Sample preparation: Compound dissolved in ~30 mL Acetonitrile; Injection: 8 mL per injection.) and confirmed by ^{1}H NMR, MS and HRMS. Mp 105-107 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.39 (s, 1H), 7.59-7.56 (m, 2H), 6.47 (dd, J = 5.2, 2.8 Hz, 1H), 4.00 (s, 3H), 2.54 (s, 3H); MS *m/z* 208.0 $[M + H]^+$; HRMS (ESI) m/z calcd for $C_{11}H_{11}ClNO$ $[M + H]^+$ 208.0524, found 208.0523.

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(13) The byproduct **11** was isolated by column chromatography (CH_2Cl_2/MeOH, 100:1-50:1) and confirmed by ^{1}H NMR and MS. Mp 127-129 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.72-7.69 (m, 2H), 7.26-7.23 (m, 2H), 7.08-7.03 (m, 2H), 3.11-3.08 (m, 6H), 2.48-2.33 (m, 4H), 2.20-2.08 (m, 12H), 1.83-1.75 (m, 2H); MS *m/z* 481.2 $[M + H]^+$.

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(18) The byproduct **17** was isolated by column chromatography (CH_2Cl_2/MeOH, 100:1-20:1) and confirmed by ^{1}H NMR and MS. Mp 78-79 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.11 (dd, *J* = 6.0, 4.4 Hz, 1H), 7.25-7.23 (m, 1H), 7.10-7.03 (m, 1H), 5.95-5.88 (m, 1H),

5.24-5.17 (m, 2H), 3.09-3.06 (m, 5H), 2.17-2.07 (m, 6H); MS *m/z* 261.3 $[M + H]^+$.

(19) The byproduct **18** was isolated by column chromatography (CH_2Cl_2/MeOH, 100:1-20:1) and confirmed by ^1H NMR and MS. Mp 58-59 °C; ^1H NMR (400 Hz, $CDCl_3$) δ 7.14 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.25-7.23 (m, 1H), 7.07-7.02 (m, 1H), 3.10-3.05 (m, 3H), 2.38-2.34 (m, 2H), 2.16-2.05 (m, 6H), 1.61-1.51 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H); MS *m/z* 262.8 $[M + H]^+$.

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