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Industry Oriented Route Evaluation and Process Optimization for the Preparation of Brexpiprazole

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ABSTRACT

Efforts toward route evaluation and process optimization for the preparation of brexpiprazole (**1**) are described. Starting from the commercially available dihydroquinolinone **11**, a three-step synthetic route composed of *O*-alkylation, oxidation and *N*-alkylation was selected for industry oriented process development aiming to reduce side reactions and achieve better impurity profiles. The reaction conditions of the three steps were investigated and the control strategy for the process-related impurities was established. The optimized process was validated at kilogram scale and now is viable for commercialization, with the results of not less than 99.90% purity of **1** (by HPLC) and not more than 0.05% of the persistent impurities **15** and **16**.

Keywords: brexpiprazole; route evaluation; process optimization; impurity control strategy

INTRODUCTION

Brexpiprazole (**1**), discovered by Otsuka Pharmaceutical Co., Ltd. and approved by FDA in 2015, is an antipsychotic drug for the treatment of schizophrenia and also used as adjunctive therapy for the treatment of major depressive disorder (MDD)[1-2]. Brexpiprazole is considered to be a possible successor of Otsuka's top-selling antipsychotic drug aripiprazole.[3]

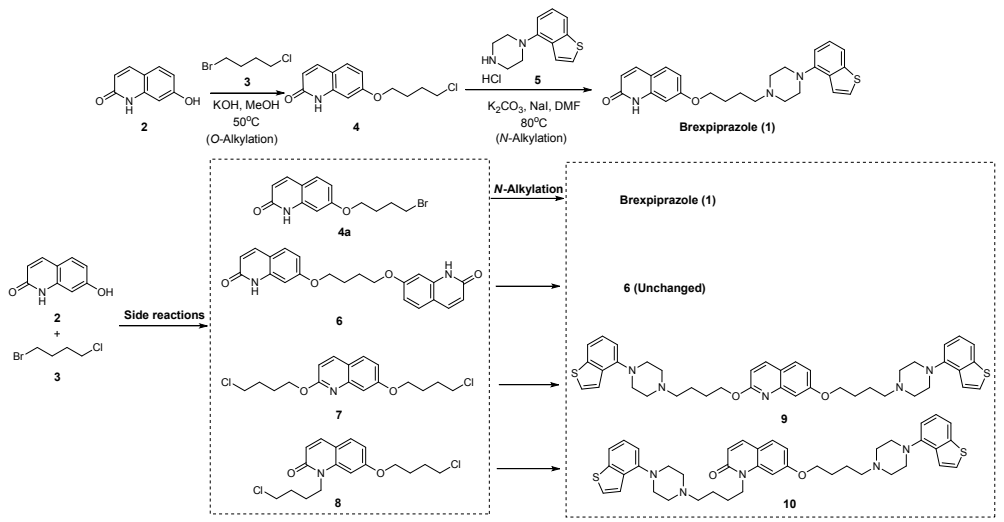
Many synthetic strategies have been reported for the preparation of **1**,[1-2, 4-10] however, as commented recently by Micro Labs,[11] most of the reported synthetic routes were feasible from an academic perspective, but of limited practical value. We herein report our results from the R&D campaign of route evaluation and the process optimization in pursuit of a commercially viable process.

RESULTS AND DISCUSSION

As shown in scheme 1, the original route accomplished by Yamashita and coworkers was suggested to be feasible for commercialization.[1, 11] Quinolinone **2** was *O*-alkylated with 1-bromo-4-chlorobutane **3** to afford chlorobutoxy-quinolinone **4**[12] and followed by *N*-alkylation with arylpiperazine **5**[13] to give **1**.

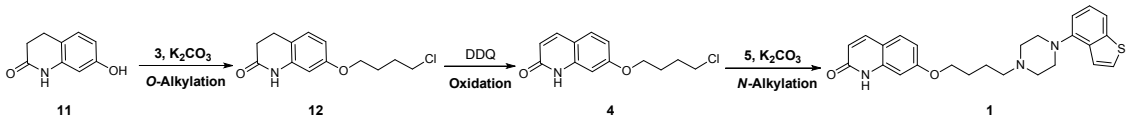
In the first *O*-alkylation step, the bromo-substituted impurity **4a** was considered to be the equivalents of **4** for it was also transformed to **1** in the following step, but formation of significant amounts of the dimeric impurity **6** was unavoidable.[14] Moreover, two major side-products **7** and **8** generated from quinolinone **2** under basic conditions,[15] which have also been reported recently by Micro Labs,[11] were a significant concern during the manufacturing process. These two side-products were unavoidable in the intermediate **4** despite extensive optimization, and formed the downstream impurities **9** and **10** in the subsequent *N*-alkylation reaction. [11]

Scheme 1. Original Route to Brexpiprazole: *O*-Alkylation and *N*-Alkylation



Our lab investigated an alternate route (Scheme 2) in which *O*-alkylation of dihydroquinolinone **11** produced chlorobutoxy-dihydroquinolinone **12**,[16] which was then oxidated to chlorobutoxy-quinolinone **4.** This route has greater commercial potential due to improved control of the impurities described above.

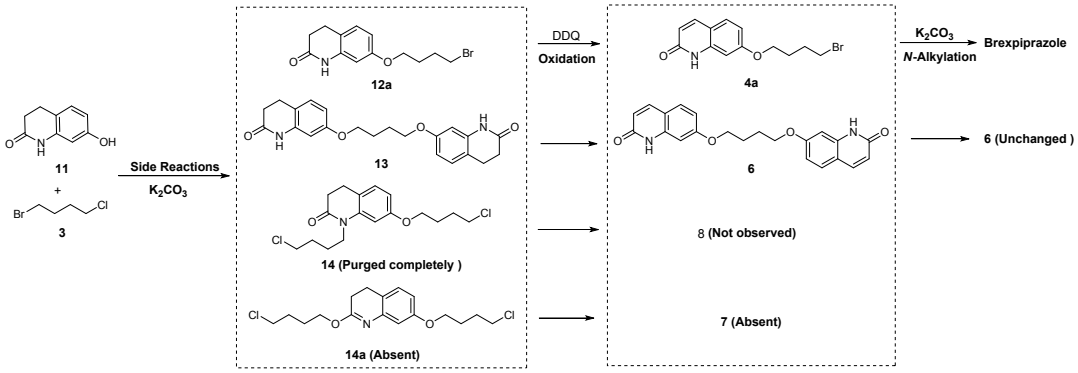
Scheme 2. Revised Route to Brexpiprazole: *O*-Alkylation, Oxidation and *N*-Alkylation



For the first *O*-alkylation step (Scheme 3), the bromo-analogue **12a** was unavoidable, but formation of the dimeric impurity **13** was minimal. Moreover, because of the relatively high p*K*a value of dihydroquinolinone **11** as well as the weak nucleophilicity of the 2-oxygen atom under basic conditions, only the *N,O*-dialkylated impurity **14** was observed, and the *O,O*-dialkylated impurity **14a** was not found in the reaction mixture. Due to the weaker nucleophilicity of the nitrogen atom compared with that of quinolinone **2**, the level of impurity **14** (below 0.5% in the reaction mixture) was lower than that of the corresponding impurity **8** (more than 1.0%) in the original route. Impurity **14** was proved to be an oil that was readily purged during the isolation and purification of **12**.

The following oxidation step with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produced the key intermediate **4**,[17] accompanied with its bromo-analogue **4a** and the unchanged impurity **6**.[18] The unavoidable impurities **9** and **10** in the original route were not formed at all in the final *N*-alkylation step owing to the absence of the dehydrogenated impurities **7** and **8** in the revised route.

Scheme 3. Major Side Reactions in Revised Route



A comparison of the impurity profile between the revised route and the original route is shown in Table 1. The revised route produced the improved purity profiles at both intermediate **4** and brexpiprazole, with dimer **6** being the sole observed impurity in the final product.

Table 1. Improved Impurity Profile of Revised Route in Comparison with that of Original Route

Stage	Intermediate **12**	Intermediate **4**	Brexpiprazole (*N*-Alkylation)
Revised route	12a, 13, 14 (*O*-Alkylation)	4a, 6 (Oxidation)	6
Original route	-	4a, 6, 7, 8 (*O*-Alkylation)	6, 9, 10

Based on our initial evaluation, the revised route starting from dihydroquinolinone **11** appeared to have improved the efficiency. Further optimization of the process was then conducted in order to control side reactions and optimize charges of starting materials.

O-Alkylation Optimization (step 1)

In the initial stage of the lab work, up to 10.5% and 13.8% of **12a** was found in the reaction of **11** with 1-bromo-4-chlorobutane **3** using K_2CO_3/DMF and KOH/DMF, respectively (Table 2, entries 1–2). Using *i*-PrOH or EtOH/H_2O instead of DMF at relatively higher temperatures, a higher level of impurity **13** (Table 2, entries 3–4) was observed. The impurity had poor solubility in commonly used solvents, and was difficult to separate from intermediate **12**. DMF gave a relatively small amount of **13**, so it was chosen for further condition optimizations.

With respect to the reaction temperature, as shown in entries 5–6, lower levels of **13** and **12a** were observed at 10–20 °C but longer reaction times were required. With decreased molar ratio of K_2CO_3 (Table 2, entry 7), **11** was not consumed completely and there was no significant decrease in the level of **12a**.

1,4-Dichlorobutane was also investigated as the alkylating agent. As expected, bromo impurity **12a** was not observed and low levels of *N*-alkylated impurity **14** were formed. However, side product **13** was produced at unacceptably high levels (up to 6%) regardless of conversion.

As shown in entries 9–10, the level of impurity **13** was correlated with the equivalents of 1-bromo-4-chlorobutane. Increasing the amount of 1-bromo-4-chlorobutane produced lower levels

of **13**. For instance, 3.0 equiv of the halogenated reagent led to a level of 0.72%, but further increase of the charge was not explored in consideration of the cost.

Table 2. Trials for the *O*-Alkylation Step

Entry	Base[a]	Solvent (5V)	**3** (equiv)	Temp (°C)	HPLC purity in reaction mixture (%)[b,c]				
					12	**11**	**12a**	Imp **13**	Imp **14**
1	K_2CO_3	DMF	2.5	30–40	85.16	0.43	10.52	0.89	0.35
2	KOH	DMF	2.5	20–30	83.26	0.40	13.80	0.87	0.45
3	K_2CO_3	*i*-PrOH	2.5	82–84	91.79[d]	0.15	2.80	2.51	0.63
4	K_2CO_3	EtOH/H_2O(1:1)	2.5	50–60	89.82[d]	0.10	5.79	1.41	0.17
5	K_2CO_3	DMF	2.5	20–30	93.10	0.13	3.98	0.82	0.33
6	K_2CO_3	DMF	2.5	10–20[e]	95.25	0.08	2.91	0.75	0.25
7	K_2CO_3[f]	DMF	2.5	20–30	87.13	8.01	3.12	0.89	0.12
8	K_2CO_3	DMF	2.5[g]	40–45	51.38	41.05	-	5.93	0.11
9	K_2CO_3	DMF[h]	2.0	20–30	93.44	0.32	4.13	1.10	0.18
10	K_2CO_3	DMF[h]	3.0	20–30	94.33	0.15	3.69	0.72	0.25

[a] The molar ratio of base was 1.5 times unless otherwise mentioned; [b] HPLC analysis after checking the reaction endpoint by TLC (about 24 hours unless otherwise noted); [c] Calculated from the HPLC area; [d] performed for 15 hours; [e] The reaction was finished after more than 40 hours; [f] The molar ratio was 1.2 times; [g] 1,4-dichlorobutane was used; [h] 4V DMF was used.

Utilizing the optimized conditions (1.5 times moles ratio of K_2CO_3, 3.0 equiv of 1-bromo-4-chlorobutane and 4V DMF, 20–30°C), three batches were performed and the above side reactions were well controlled. After a general work-up procedure and slurry with *t*-butyl methyl ether, the *O*-alkylated intermediate **12** was obtained with consistent quality and more than 90% yield at 720 g scale (Table 3). Additionally, the levels of impurity **13** were acceptable and impurity **14** was not detected.

Table 3. The Impurity Profile of Three Batches for the *O*-Alkylation Step

Batch No.[a]		**12** (%)[b]	**12a** (%)	**13** (%)	**14** (%)
1st	Reaction mixture	93.02	3.90	0.62	0.22
	Purified intermediate	95.57	3.65	0.58	N.D.[c]
2nd	Reaction mixture	92.56	3.89	0.70	0.28
	Purified intermediate	95.60	3.56	0.67	N.D.
3rd	Reaction mixture	93.21	3.59	0.63	0.25
	Purified intermediate	95.69	3.42	0.61	N.D.

[a] Performed at 720 g scale of **11** per batch; [b] Calculated from the HPLC area; [c] Not detected.

Oxidation Optimization (step 2)

The oxidation was initially performed with DDQ in 1,4-dioxane (Table 4, entry 1). Considering the potential carcinogenicity of 1,4-dioxane,[19] alternative solvents such as acetonitrile, 2-MeTHF, and CPME[20] were investigated, but **12** was not consumed completely, even at higher temperature or over prolonged reaction time (Table 4, entries 2–4). The reaction in THF gave lower levels of residual **12** as entry 5, but when DDQ was reduced to 1.1 equiv, 7% of intermediate **12** was not consumed in reaction mixture after 4 hours (Table 4, entry 6) and no further decrease was observed even if prolonging the reaction time. The harmful and environmentally unfriendly byproduct 4,5-dichloro-3,6-dihydroxyphthalonitrile (DDHQ)[21] could be recovered and oxidized to DDQ with concentrated nitric acid as in Walker's method.[22]

Table 4. Solvent Screening for the Oxidation Step[a]

Entry	DDQ (equiv)	Solvent	Temp (°C)	Reaction time	HPLC purity in reaction mixture (%)[b]	
					4 + **4a**[c]	Residual **12**
1	1.2	1,4-dioxane	50–60	3h	98.84	0.05
2	1.2	Acetonitrile	20–30	4h	96.43	1.71
3	1.2	2-MeTHF	20–30	4h	53.43	42.63
			30–40	6h[d]	86.86	11.55
4	1.2	CPME	20–30	4h	96.07	2.52
			20–30	6h[d]	96.42	2.44
5	1.2	THF	20–30	4h	98.93	0.16
6	1.1	THF	20–30	4h	90.96	7.07

[a] Unless otherwise indicated, DDQ was added in portions into the solution of **4** in 5-fold volume of solvent. The reaction was stirred for 4 hours and monitored by TLC prior to HPLC analysis; [b] Calculated from the HPLC area; [c] **4a** was calculated together with **4**; [d] The reaction was performed for additional 6 hours after stirring for 4 hours at 20–30 °C.

In the oxidation step performed in THF, no further impurity apart from bromo-analogue **4a** and impurity **6** was observed. After slurrying in hot ethyl acetate, off-white intermediate **4** was obtained with the result of at least 95.9% purity and 3.1~3.5% of **4a**, as shown in Table 5.

Table 5. The Impurity Profile of Three Batches for the Oxidation Step

Batch No.[a]		**4** (%)[b,c]	**4a** (%)	**6** (%)
1st	Reaction mixture	95.39	3.46	0.56
	Purified intermediate	95.95	3.46	0.34
2nd	Reaction mixture	93.91	3.30	0.58
	Purified intermediate	96.04	3.34	0.39
3rd	Reaction mixture	95.30	3.17	0.60
	Purified intermediate	96.34	3.18	0.38

[a] Performed at 1 kg scale **12** per batch; [b] Calculated from the HPLC area; [c] DDHQ and residual DDQ in the reaction mixture were not calculated from the HPLC area.

N-Alkylation Optimization (step 3)

For the *N*-alkylation step, besides the carry-over impurity **6** mentioned above, two additional process-related impurities (**15** and **16**) were observed in accordance with the results of the original route (Figure 1).[11, 18] These impurities were consistently observed and the next goal of our optimization efforts was to establish a robust control strategy for their levels in brexpiprazole.

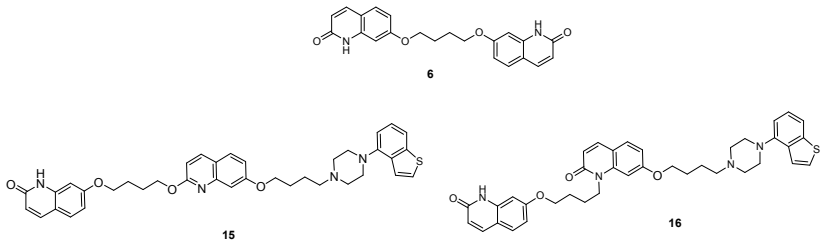


Figure 1. Process-related Impurities of the *N*-Alkylation Step

Firstly, the reaction was conducted using 2.1 times molar ratio of K_2CO_3 in heated DMF to give the two impurities at a very high level (Table 6, entry 1). When the molar ratio of base was reduced to 1.2 times, lower levels of the impurities were obtained but the reaction ran slowly (Table 6, entries 2–3). Though the reaction was accelerated in the presence of catalytic potassium iodide,[4] 15.4% of intermediate **4** was left after 15 hours.

When EtOH/H_2O (1:1) was utilized,[2] impurities **15** and **16** were obtained at the levels of 0.56% and 0.25%, respectively (Table 6, entry 4). Then, a significant decrease of the two impurities was observed by modifying the ratio of ethanol and water to 1:2.5, as shown in entry 5.

It was also discovered that the two impurities were further reduced by increasing the equivalents of arylpiperazine **5** (Table 6, entries 6–7). However, when the loading was up to 1.2 equiv, the impurity profile was not significantly altered, compared with that of the use of 1.1 equivalents. Finally, the conditions were defined as 1.1 equiv of arylpiperazine **5** and 1.2 times molar ratio of K_2CO_3 in EtOH/H_2O (1:2.5).

Table 6. Trials for the *N*-Alkylation Step[a]

Entry	**5** (equiv)	K_2CO_3 (times molar ratio)	Solvent[b]	HPLC purity in reaction mixture (%)[c]		
				Brexpiprazole (1)	**Imp 15**	**Imp 16**
1	1.03	2.1	DMF	66.67	9.75	3.32
2	1.03	1.2	DMF	55.77[d]	0.47	0.16
3	1.03[e]	1.2	DMF	69.03[f]	0.19	0.15
4	1.03	1.2	EtOH/H_2O (1:1)	84.62	0.56	0.25
5	1.05	1.2	EtOH/H_2O (1:2.5)	88.59	0.27	0.21
6	1.1	1.2	EtOH/H_2O (1:2.5)	88.61	0.15	0.08

7	1.2	1.2	EtOH/H_2O (1:2.5)	85.29		0.15	0.07

[a] The reactions were performed at 80–85 °C for 15 hours and monitored by TLC prior to HPLC analysis; [b] The volume was 10-fold of **4**; [c] Calculated from the HPLC area; [d] TLC indicated that high level of **4** was not consumed after 15 hours. After additional 15 hours, 22.12% of **4** was still left in reaction mixture by HPLC; [e] 0.1 equiv of KI was used as catalyst; [f] 15.45% of **4** was left.

Following work-up, the crude product was purified by means of an acid-base treatment (salt-formation with hydrochloric acid, re-crystallization, and basification with sodium hydroxide).[2, 23] According to the optimized conditions and purification method, three batches of final API were obtained at kilogram scale, and the impurities **15** and **16** were controlled to below 0.05% along with the absence of impurity **6**, as shown in Table 7.

Table 7. The Impurity Profile of Three Batches for the *N*-Alkylation Step

Batch No.[a]		Brexpiprazole (%)[b]	**6** (%)	**15** (%)	**16** (%)
1st	Reaction mixture	88.62	0.22	0.16	0.08
	Final API	99.90	N.D.[c]	0.03	0.01
2nd	Reaction mixture	87.88	0.21	0.16	0.08
	Final API	99.95	N.D.	0.03	N.D.[d]
3rd	Reaction mixture	88.32	0.28	0.16	0.09
	Final API	99.90	N.D.	0.04	0.01

[a] Performed at 800 g scale of **4** per batch; [b] Calculated from the HPLC area; [c] Not detected (Limit of Detection = 0.004%); [d] Not detected (Limit of Detection = 0.003%).

CONCLUSION

In summary, an industry oriented route consisting of *O*-alkylation, oxidation, and *N*-alkylation to brexpiprazole was established by exploring the reaction conditions of each step in conjunction with detailed analysis of the in-process impurity profiles. The major side reactions of three steps were investigated, and as a result the process-related impurities were avoided or well-controlled. After the process was optimized and finalized, three validation batches were performed to obtain high quality of brexpiprazole with not more than 0.10% of total impurities and not more than 0.05% of impurities (**15** and **16)** at kilogram scale. From a commercial perspective, the present work has provided viable solutions for the preparation of brexpiprazole.

EXPERIMETNAL SECTION

General Information. All commercially available materials and solvents were used directly without further purification unless otherwise noted. TLC analyses were performed on silica gel 60 F_{254} plates. The process mass intensity (PMI) was defined as the total mass of materials used to

produce a specified mass of product (PMI=Σ mass of materials/ mass of product). Materials included reactants, reagents, solvents used for reaction, workup and purification.[24] The ESI mass spectra were determined on a THERMO LTQ. ^{1}H NMR and ^{13}C NMR data were recorded with a Bruker spectrometer using TMS as internal standard and reported relative to residual solvent signals and are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

***O*-Alkylation (Step 1): Preparation of chlorobutoxy-dihydroquinolinone 12 from 11.** K_2CO_3 (913 g, 6.60 mol) and dihydroquinolinone **11** (720 g, 4.41 mol) were mixed in DMF (2880 mL). 1-bromo-4-chlorobutane **3** (2270 g, 13.24 mol) was charged and the mixture was intensively stirred with a mechanical agitator at 20–30 °C for 24 hours. The reaction was monitored the endpoint by TLC prior to HPLC analysis until the starting material **11** was below 0.5% by HPLC (24–30 hours). The reaction mixture was added into water (10 L) with stirring. The crude product was collected by filtration and slurried in *t*-butyl methyl ether (1440 mL) below 30 °C for 1–2 hours. The isolated material was dried to give 1044 g of purified **12** (4.11mol, 93.2% yield) with PMI data 17. HPLC analysis showed that the purity of **12** was 95.6% with 3.6% of **12a**.

ESI-MS: *m/z* = 254.11 [M+H]. ^{1}H NMR (500 MHz, DMSO-d6) δ (ppm): 10.00 (s, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.48 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.43 (d, *J* = 2.4 Hz, 1H), 3.92 (t, *J* = 6.0 Hz, 2H), 3.70 (t, *J* = 6.0 Hz, 2H), 2.78 (t, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.91–1.74 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 170.39, 157.85, 139.30, 128.49, 115.69, 107.57, 101.82, 66.78, 45.28, 30.84, 28.99, 26.26, 24.09.

Oxidation (step 2): Preparation of chlorobutoxy-quinolinone 4 from 12. To the solution of intermediate **12** (1010 g, 3.98 mol) in THF (5050 mL) was added DDQ (1085 g, 4.78 mol) in portions. During the addition, the temperature was allowed to go up to 35 °C. The reaction was stirred for 4 hours and monitored the endpoint by TLC prior to HPLC analysis. The reaction was stirred until residual **12** was below 0.5% by HPLC (4–6 hours). The reaction mixture was concentrated and the residue was dispersed into water (5.05L), then the solution of sodium bicarbonate (685 g, 8.15 mol) in water (5.05 L) was added carefully. The mixture was stirred at 20–30 °C for 2 hours. After filtration, the wet material was purified with hot ethyl acetate (3.03 L). The dry 810 g of **4** (3.22 mol, 80.9% yield) was obtained as a light yellow solid with PMI data 25. HPLC analysis showed that the purity of **4** was 96.0% with 3.3% of **4a**.

ESI-MS: *m/z* = 250.20 [M-H]. ^{1}H NMR (500 MHz, DMSO-d6) δ (ppm): 11.61 (s, 1H), 7.81 (d, *J* = 9.4 Hz, 1H), 7.56 (d, *J* = 9.3 Hz, 1H), 6.80 (m, 2H), 6.31 (d, *J* = 9.4 Hz, 1H), 4.05 (t, *J* = 5.8 Hz, 2H), 3.72 (t, *J* = 5.8 Hz, 2H), 1.95–1.78 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 162.34, 160.40, 140.73, 140.10, 129.35, 118.64, 113.43, 110.85, 98.72, 67.08, 45.25, 28.92, 26.16.

***N*-Alkylation (step 3): Preparation of Brexpiprazole (1).**

*Preparation of crude **1**:* The intermediate **4** (800 g, 3.18 mol) was charged into the suspension of K_2CO_3 (526.3 g, 3.81 mol) and arylpiperazine **5** (890.7 g, 3.50 mol) in the solution of ethanol and water (1:2.5 by volume, 8.0 L). Under nitrogen atmosphere, the mixture was heated to reflux for 15 hours and monitored by TLC prior to HPLC analysis. When the un-reacted **4** was below 2.0% by HPLC (15–20 hours), the heterogeneous reaction mixture was cooled to 20–30 °C. The crude product was filtered and dried to give 1374g (3.17 mol, ~100% yield) as a light yellow solid.

Salt-formation and purification: The crude product (1354g, 3.12 mol) was added into the solution of ethanol (27.08 L) and glacial acetic acid (1625 mL). When a solution was given after heating, concentrated hydrochloric acid (35%, ~342 mL, 3.28 mol) was added drop-wise successively. The mixture was cooled to below 20 °C and filtered to give brexpiprazole hydrochloride, which was dried to obtain 1435g (3.05 mol, 97.7% yield) as an off-white solid.

The hydrochloride salt (1435g, 3.05 mol) was added into the solution of ethanol (12.9 L) and water (8.6 L). After the mixture was heated to obtain a solution, activated carbon (114 g) was added and stirred for 1–2 hours at refluxing temperature. The mixture was filtered over 70 °C and the filtrate was cooled to below 20 °C. Then filtered and dried to give 1176 g of purified brexpiprazole hydrochloride (2.50 mol, 81.9% yield).

*Basification to **1**:* The purified salt (1156 g, 2.46 mol) was dissolved in the solution of ethanol (10.4 L) and purified water (6.9 L) at refluxing temperature. The solution of NaOH (108 g, 2.70 mol) in purified water (346 mL) was added drop-wise and kept refluxing for 30–60 minutes. Then the mixture was cooled to 30–40 °C, filtered and washed with purified water. The wet product was dried to obtain the purified API (987g, 2.28 mol) with 92.7% yield and 99.95% HPLC purity.

The PMI of this *N*-alkylation step was 73. For the entire process, the PMI of the three steps from starting material **11** was 103, 45% of which was recyclable solvent (ethyl acetate, t-butyl methyl ether and ethanol) and 40% of water.

ESI-MS: *m/z* = 434.22 [M+H]. ^{1}H NMR (500 MHz, DMSO-d6) δ (ppm): 11.61 (s, 1H), 7.80 (d, *J* = 9.4 Hz, 1H), 7.69 (d, *J* = 5.5 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 9.4 Hz, 1H), 7.40 (d, *J* = 5.5 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.30 (d, *J* = 9.4 Hz, 1H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.06 (brs, 4H), 2.61 (brs, 4H), 2.43 (t, *J* = 7.1 Hz, 2H), 1.86 – 1.75 (m, 2H), 1.69–1.57 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 162.35, 160.55, 148.36, 140.76, 140.49, 140.12, 133.47, 129.34, 125.92, 125.19, 121.99, 118.57, 116.73, 113.36, 112.11, 110.96, 98.68, 67.71, 57.47, 53.08, 51.83, 26.66, 22.81.

ASSOCIATED CONTENT

Supporting Information

Experimental and/or spectroscopic data for the compounds (**12**, **4** and **1**) and the impurities (**4a**, **6, 7, 8, 12a, 13, 14, 15 and 16**) (PDF)

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXXX.

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Notes

The authors declare no competing financial interest.

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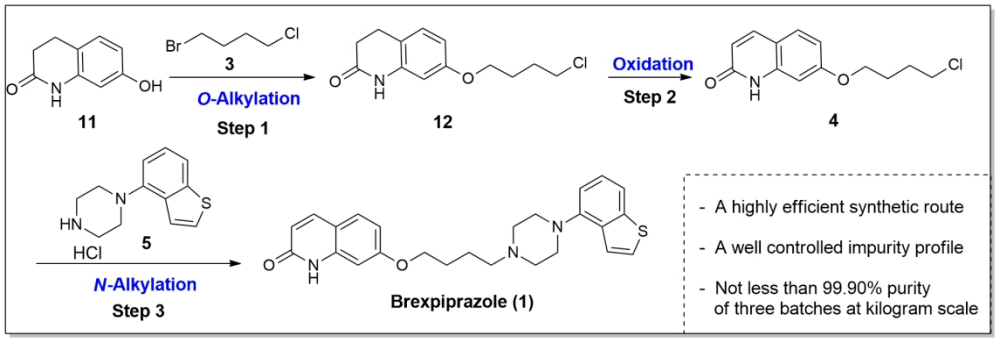

Table of Contents Graphic

169x58mm (300 x 300 DPI)