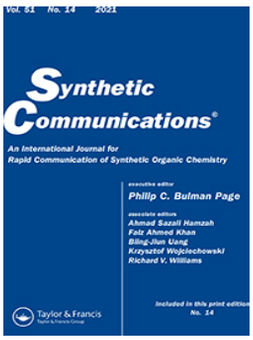

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Identification, synthesis and strategy for minimization of potential impurities in the synthesis of suvorexant

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ABSTRACT

Eight process-related impurities in the synthesis of suvorexant were identified, while six of them were described for the first time. In order to get the references for the process optimization and quality control of API, the eight compounds were synthesized. According to the possible formation pathways, a modified synthesis and the strategy for impurity control in the corresponding reactions were established.

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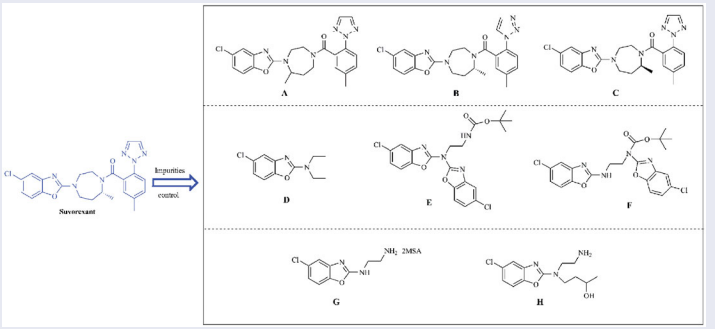
KEYWORDS
Impurities; suvorexant; synthesis

GRAPHICAL ABSTRACT



Introduction

Suvorexant (**1**, Scheme 1), a dual orexin receptor (OX1R and OX2R) antagonist, was approved in 2014 by FDA for the clinical treatment of insomnia characterized by difficulty achieving and/or maintaining sleep.[1] At present, the main method to produce suvorexant was chemical synthesis.

The presence of impurities (also called the related substances) in an active pharmaceutical ingredient (API) can influence significantly the safety and efficacy of the drug

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*Contributed equally to this work.

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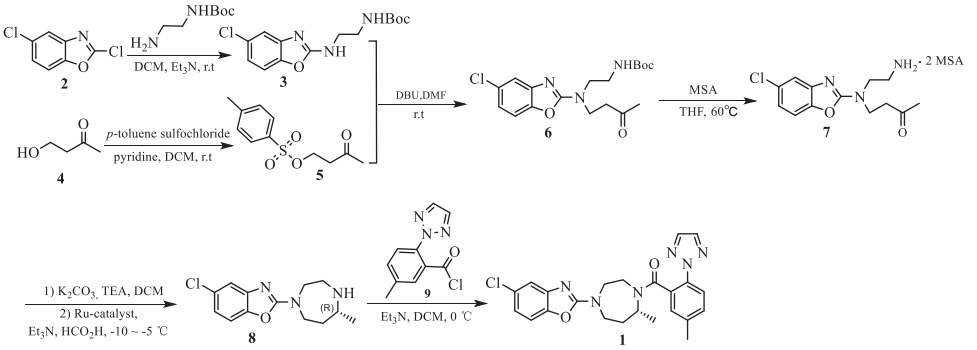


Scheme 1. Synthesis of suvorexant 1.

substance. So, the research on the impurity profile which is the basis of specification setting for API is of great significance. Meanwhile, identification of the impurities or the by-products can help the organic chemists to understand the reactions better in order to optimize the process. Although there are many publications on the synthesis of suvorexant,[2–9] to the best of our knowledge, no systematic study of the impurity profile of suvorexant has been reported.

In this context, the identification and synthesis of eight observed or potential impurities of suvorexant were presented. Among them, compound **B**, **D**, **E**, **F**, **G** and **H** were reported for the first time and two (**A** and **C**) appeared in the literatures.[7,10] At the same time, according to the possible formation pathways of impurities, an improved synthesis and the strategy for minimization of the impurities were established.

Results and discussion

Various synthetic methods were available in literatures[2–8] for the preparation of **1**. The route in Scheme 1 was regarded as the process synthesis. It involves the following steps: the nucleophilic substitution of 2,5-dichlorobenzoxazole (**2**) with Boc-protected ethylenediamine to give (2-((5-chloro-1,3-benzoxazol-2-yl)amino)ethyl)carbamic *tert*-butyl ester (**3**), alkylation of **3** with 4-tosyloxy-2-butanone (**5**), deprotection of (2-((5-chlorobenzoxazol-2-yl)-(3-oxo-butyl)-amino)ethyl)carbamic *tert*-butyl ester (**6**) with methanesulfonic acid (MSA), asymmetric reductive amination of 4-((2-amino-ethyl)-(5-chlorobenzoxazol-2-yl)amino)butan-2-one-bis-MSA Salt (**7**), and acylation of (*R*)-5-chloro-2-(5-methyl-[1,4]diazepan-1-yl)-benzoxazole (**8**) with 5-methyl-2-[1,2,3]triazol-2-yl-benzoyl chloride (**9**) to afford suvorexant (**1**).

The crude product was obtained by the above route and two trace impurities were detected by HPLC (Figure 1) and HPLC-MS showed that they both had the same molecular weight as compound **1**. It was reported that compound **8** could undergo an intramolecular ring flip to form **8a** and then coupled with **9** to give impurity **A**[7,8] (Scheme 2). Another impurity (called as impurity **B**) might be referred to the preparation of 5-methyl-2-[1,2,3]triazol-2-yl-benzoic acid (**10**) where the regio-isomer 5-methyl-2-[1,2,3]triazol-1-yl-benzoic acid (**11**) might be the by-product. If trace of **11** in compound **10** underwent the same reactions, impurity **B** was formed (Scheme 3). In order to confirm the above inference, compound **A** and **B** were synthesized respectively (Scheme 4).

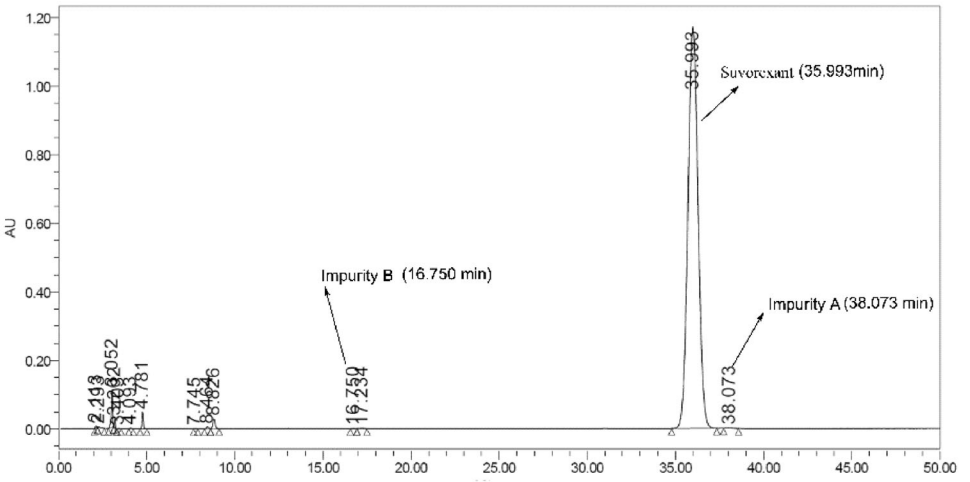
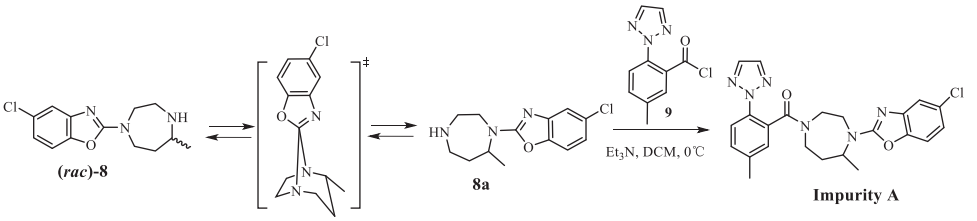
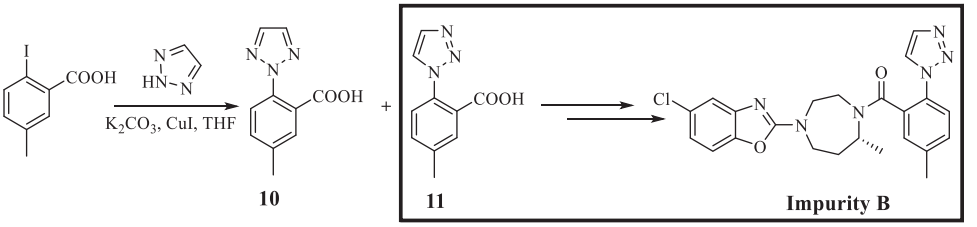


Figure 1. HPLC chromatogram of crude 1.



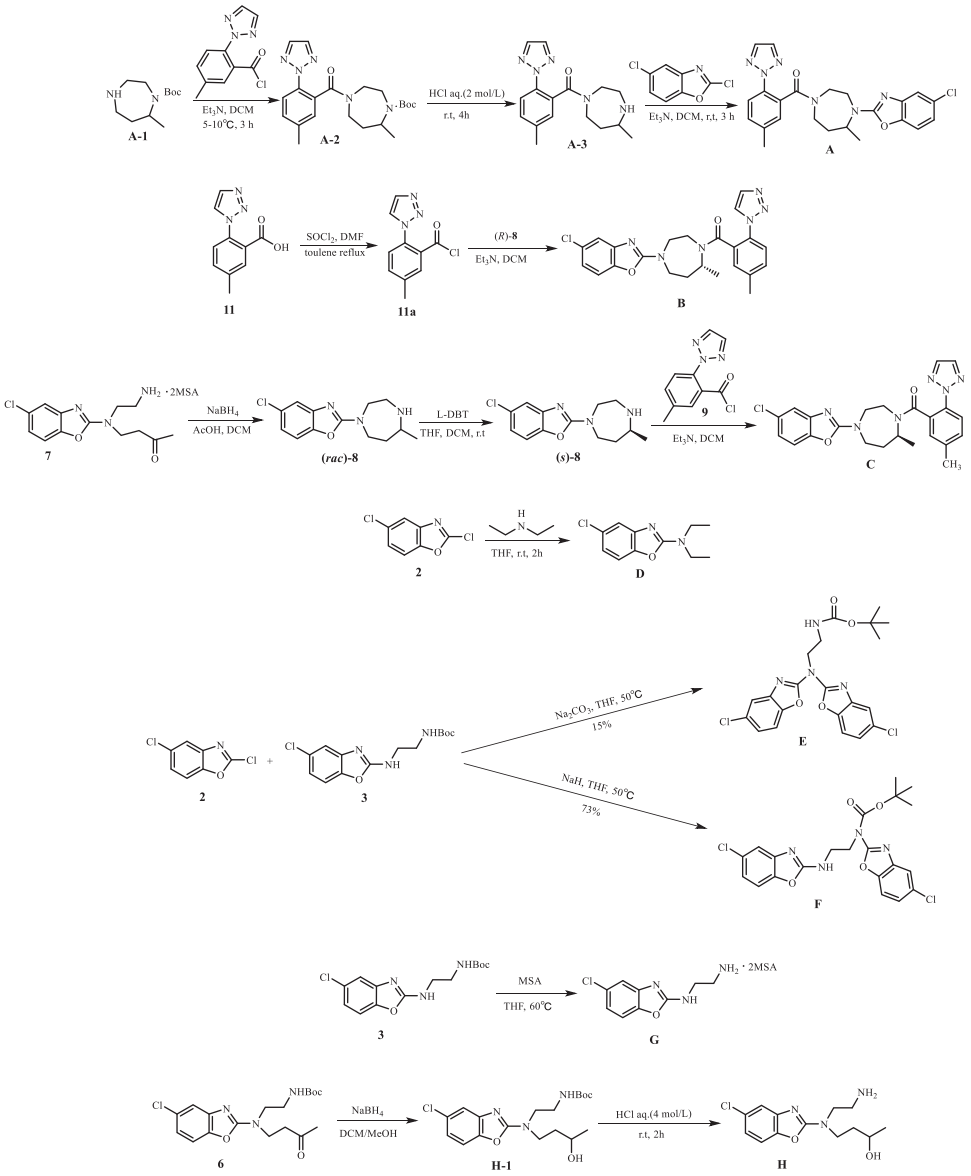
Scheme 2. Proposed pathway to impurity A.



Scheme 3. Proposed pathway to impurity B.

1-*tert*-butoxycarbonyl-7-methyl-1,4-diazabicycloheptane (**A-1**) reacted with compound **9** to give 1-*tert*-butoxycarbonyl-4-(5-methyl-2-[1,2,3]triazol-2-yl-benzoyl)-7-methyl-1,4-diazabicycloheptane (**A-2**), after deprotection of **A-2**, 4-(5-methyl-2-[1,2,3]triazol-2-yl-benzoyl) −7-methyl-1,4-diazabicycloheptane (**A-3**) reacted with **2** to give compound **A** (Scheme 4).Then, with the identified synthetic compounds **A** and **B** as the references, the HPLC proved that the impurity at RT (retention time) of 38.073 min was compound **A** and that at RT of 16.750 min was compound **B** (Figure 1, RT of compound 1: 35.993 min).

There is a chiral carbon atom in **1** and the *R*-isomer is used as the API. According to the International Council for Harmonization of Technical Requirements for



Scheme 4. Synthesis of A–H.

Pharmaceuticals (ICH), control of the content of the corresponding enantiomer (*S*-isomer, called impurity **C**) was necessary in order to secure the safety and efficacy of the drug. Impurity **C** may come from the asymmetric reductive amination. In order to get (*S*)-**8** and compound **C**, (*rac*)-**8** was subjected to resolution with dibenzoyl-*L*-tartaric acid (*L*-DBT) to give the desired (*S*)-**8**, further reaction with **9** afforded compound **C** (Scheme 4). Subsequently, a chiral HPLC method was established to separate suvorexant and impurity **C** or (*R*)-**8** and (*S*)-**8**, as showed in Figures 2 and 3.

It is important to control the quality of compound **8** because it could result in the formation of both impurity **A** and **C**. The salt formation of the crude **8** with dibenzoyl-

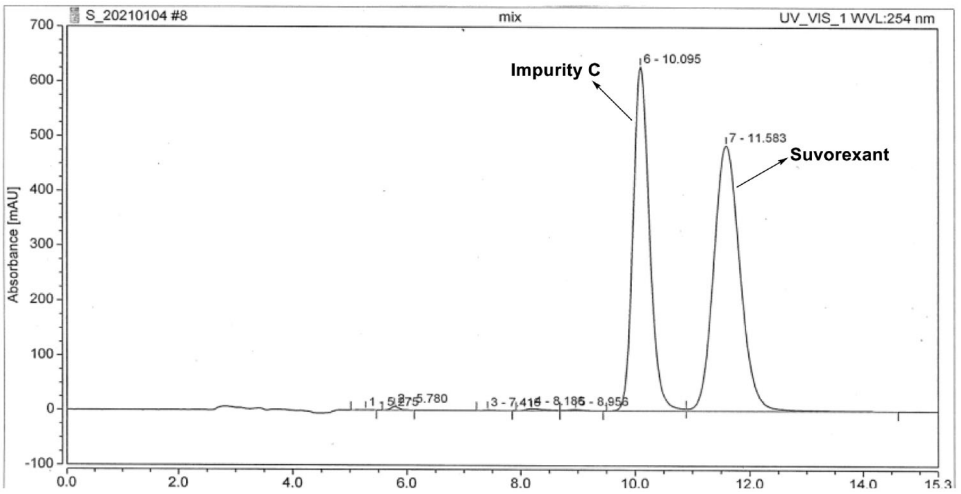


Figure 2. Chiral HPLC chromatogram of suvorexant and impurity C.

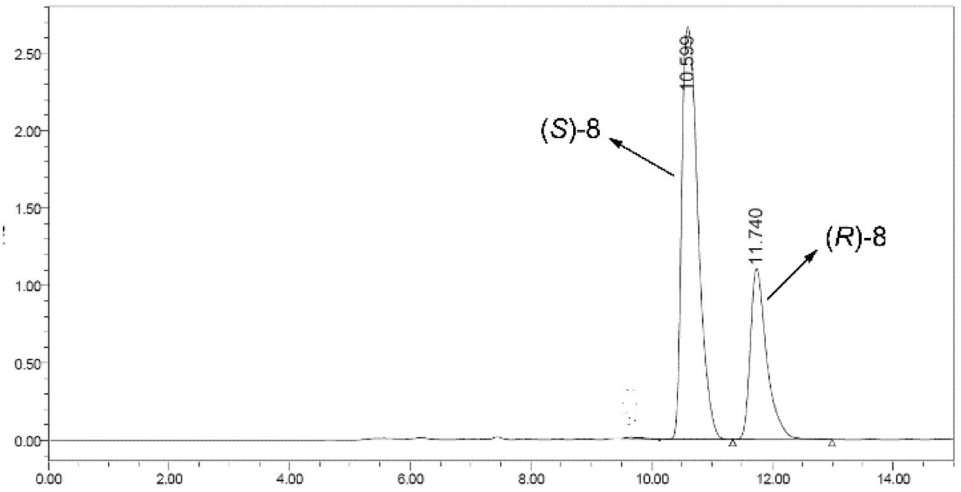
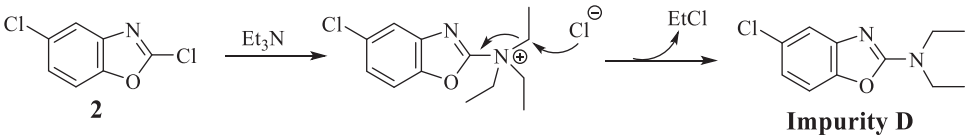


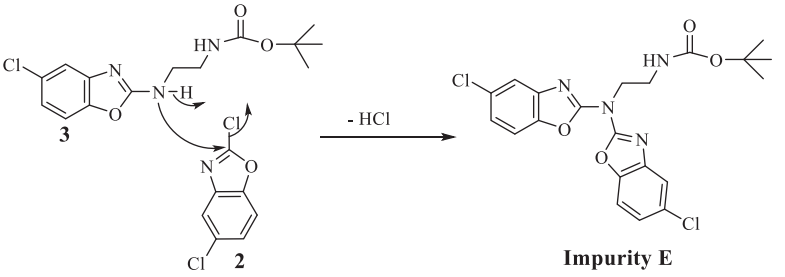
Figure 3. Chiral HPLC chromatogram of (*R*)-**8** and (*S*)-**8**.

D-tartaric acid (*D*-DBT) in isopropyl acetate (IPA) followed by washing with IPA + MeOH was an effective way to purify compound **8**. The asymmetric reductive amination gave compound **8** with a chiral purity of 96.94%, after these operations, the chiral purity was improved to 99.47% and the achiral purity reached 100%. Meanwhile, in order to monitor the competitive reduction of the ketone in the synthesis of compound **8**, the potential impurity **H** was also synthesized from compound **6** via reduction and deprotection (Scheme 4). The analysis of compound **8** also showed that it was contaminated with about 0.02% of impurity **H,** which could be eliminated by above salt formation.

As far as impurity **B** was concerned, the tests showed that if the content of compound **11** in product **10** was controlled under a reasonable level (less than 0.5%),



Scheme 5. Proposed pathway to impurity D.



Scheme 6. Proposed pathway to impurity E.

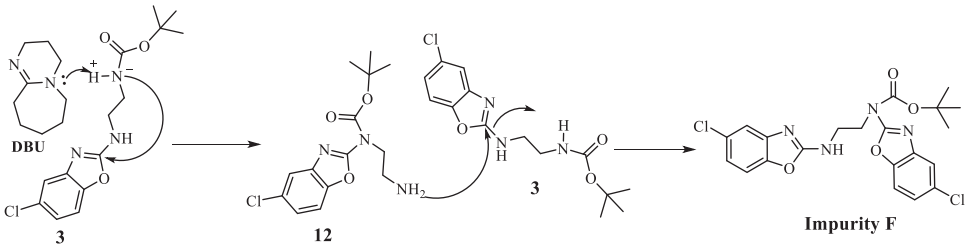
impurity **B** in API could be minimized (below 0.1%) or eliminated. In the end, suvorexant was obtained with an achiral purity of 100% and a chiral purity of 99.93%.

In the beginning, compound **3** was prepared by substitution between **2** and Boc-protected ethylenediamine in dichloromethane with triethylamine as a base, according to the literature.[7] Although the reaction went quite well, two impurities were separated from crude **3**, and the structures were identified as compound **D** and compound **E** by MS and ^{1}H NMR (Scheme 4). The diethylamino fragment in **D** should come from the reaction of **2** with triethylamine via S_NAr mechanism, as reported in the similar literature[11] (Scheme 5). For the preparation, compound **D** was obtained from the reaction of compound **2** with diethylamine (Scheme 4). It seems that compound **E** was caused by the overreaction of product **3** with **2** (Scheme 6). In practice, compound **E** was synthesized from compound **3** and **2** in THF with Na_2CO_3 as a base (Scheme 4).

In order to eliminate impurity **D,** the reaction of **2** with Boc-protected ethylenediamine was carried out in heterogeneous system (toluene/H_2O) with NaOH as base. Although impurity **E** was detected in the reaction mixture, it could be removed by workup (filtration) and compound **3** was obtained with a yield of 95% and a purity of 99.98%.

When compound **6** was prepared by alkylation of **3** with **5**, an impurity (called impurity **F**) with the same molecular weight as compound **E** was separated. Compared with compound **E**, besides the different behave in HPLC, impurity **F** showed two sets of benzoxazole ^{1}H NMR signals, so its structure was identified. The formation pathway was proposed in Scheme 7. For preparation, compound **F** was obtained also by the condensation of **2** and **3**, but the reaction went under much more rigorous condition than the preparation of compound **E**, shown in Scheme 4.

It seems that both **E** and **F** are related to the preparation of compounds **3** and **6**, so the crude of both **3** and **6** was reexamined by HPLC with **E** and **F** as the references.



Scheme 7. Proposed pathway to impurity F.

About 0.07% of **E** was determined with no detection of **F** in the crude of **3**, meanwhile, in the crude of **6**, the content of **F** was 0.10%, but no track of **E** was found.

During the synthesis of compound **7**, another trace impurity was observed, which was identified as compound **G** by MS and ^{1}H NMR. Obviously, it was caused by trace residue of **3** in compound **6** (Scheme 4).

Both impurity **F** and **G** can be completely removed by recrystallization of compound **6** with iPrOH: heptane (8:2).

Conclusion

In summary, eight impurities in the synthetic process of suvorexant have been identified and these compounds were synthesized as the references for both the process modification and the quality control on API. Among them, six compounds have not been found in the literature before. The possible formation pathways were discussed and the strategy for minimization or elimination of impurities has also been demonstrated in the synthetic process of suvorexant.

Experimental section

General methods

Solvents and reagents from commercial were used as received unless otherwise indicated. NMR spectra were measured on a Bruker Avance III 400 or 600 MHz spectrometer with TMS as an internal standard. Mass spectra were recorded with a Q-TOF mass spectrometer using electrospray positive ionization (ESI^+). The HRMS data were obtained using Q-TOF micro mass spectrometry. Melting points were determined on a Büchi melting point M-565 apparatus. Optical rotation was recorded on a Rudolph Autopol IV polarimeter. The angle of rotation was recorded at 20 °C on 1% solutions in MeOH. Column chromatography was carried out on silica gel (HF254) purchased from Qingdao Ocean Chemical Company of China. HPLC Method in Figure 1: Agilent Extend C18 column (4.6 mm × 250 mm, 5 µm) with mobile phase A: tetrabutylammonium bisulfate aqueous solution; mobile phase B: acetonitrile; Column temperature: 40 °C; flow rate: 1.0 mL/min. Gradient (A: B = 58:42, v/v). HPLC Method in Figure 2: Chiralpak IA column (4.6 mm × 250 mm, 5 µm) with mobile phase A: hexane (75); mobile phase B: isopropanol (25); Column temperature: 40 °C; flow rate: 1.0 mL/min. Gradient (A: B = 75:25, v/v). HPLC Method in Figure 3: Chiralpak AD-H column (4.6 mm × 250 mm, 5 µm) with mobile phase A: hexane; mobile phase B: 0.1%

diethylamine ethanol solution; Column temperature: 35 °C; flow rate: 0.6 mL/min. Gradient (A:B = 60:40, v/v).

(4-(5-Chlorobenzoxazol-2-yl)-5-methyl- [1,4] diazepan-1-yl)-(5-methyl-2-[1,2,3] triazol-2-yl-phenyl)methanone (compound A)

Compound 9 (3.25 g, 14.67 mmol) was dissolved in DCM (25 mL) and cooled to 0–10 °C. Then the solution of A-1[8] (2.86 g, 13.36 mmol) in 20 ml DCM and Et_3N (1.53 g, 15.14 mmol) were added drop-wise and the resulting mixture stirred for 3 h. The reaction mixture was poured into water (50 mL). The organic phase was separated and the aqueous layer was extracted with DCM (2 × 25 mL). The organic extracts were combined and washed with water (3 × 100 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain the crude product, which was purified by column chromatography (1:5 EtOAc/petroleum) to yield A-2 (3.20 g, 60%). Compound A-2 (2.00 g) were stirred in HCl (2 M in MeOH) (50 mL) for 4 h at room temperature. The reaction mixture was poured into DCM (100 mL) and the pH of the solution was adjusted to 9 with NaOH aq. (2 mol/L). The organic phase was separated and the aqueous layer was extracted with DCM (2 × 50 mL). The organic extracts were combined and washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford A-3 (1.2 g, 81%). Compound A-3 (0.80 g, 2.66 mmol), compound 2 (0.50 g, 2.66 mol), and Et_3N (0.30 g, 2.97 mmol) were dissolved in DMF (10 mL) and stirred for 4 h at room temperature. The reaction mixture was poured into water (50 mL). The mixture was then extracted with DCM (3 × 50 mL) and the combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to yield the crude product which was purified by column chromatography (70:1 DCM/MeOH) to give a white solid. Yield: 80% (0.96 g); **HPLC**: 99.79%. Mp:172–174 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.91–7.61 (m, 3H), 7.33–7.24 (m, 2H), 7.19–7.06 (m, 2H), 6.99–6.92 (m, 1H), 4.81–4.02 (m, 2H), 4.23–3.81(m, 1H), 3.70–3.46 (m, 1H), 3.44–3.11 (m, 2H), 3.07–2.82 (m, 1H), 2.43–2.31 (m, 3H), 2.03–1.61 (m, 2H), 1.36–1.16 (m, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 169.28, 169.08, 169.05, 168.77, 162.89, 162.79, 162.65, 147.44, 147.41, 147.34, 144.72, 144.61, 138.66, 138.52, 135.75, 135.62, 135.58, 134.23, 133.84, 130.70, 130.63, 130.56, 129.39, 129.34, 129.31, 128.92, 128.89, 128.70, 128.45, 128.30, 128.09, 122.60, 122.44, 122.15, 122.03, 120.30, 120.21, 116.21, 109.31, 109.17, 64.33, 52.78, 52.72, 52.64, 49.97, 49.38, 46.56, 46.36, 45.11, 44.06, 43.98,43.62, 43.40, 41.88, 41.16, 35.81, 35.02, 34.43, 34.36, 25.40, 21.07, 21.02, 20.94, 19.35, 19.02, 18.86. **HRMS** (ESI): *m/z* calcd. for $C_{23}H_{23}ClN_6O_2$ $[M+H]^+$: 451.1644, found 451.1643.

((R)-4-(5-chlorobenzoxazol-2-yl)-7-methyl-[1,4]diazepan-1-yl)-(5-methyl-2-[1,2,3] triazol-1-yl-phenyl)methanone (compound B)

Compound 11a (1.63 g, 7.38 mmol) was dissolved in DCM (25 mL) and cooled to 0–10 °C. Then the solution of (*R*)-8 (2.15 g, 8.12 mmol) in 20 ml DCM and Et_3N (0.89 g, 8.81 mmol) were added drop-wise and the resulting mixture stirred for 1 h. The reaction mixture was poured into water (50 mL). The organic phase was separated and the aqueous layer was extracted with DCM (2 × 25 mL). The organic extracts were combined

and washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain the crude product which was purified by column chromatography (2:1 EtOAc/petroleum) to afford a white solid. Yield:69% (2.3 g); **HPLC**: 99.20%. Mp: 86–89 °C. $[\alpha]^{20}_D = -14.94$ (*c* 1.00, MeOH); **^{1}H NMR** (600 MHz, $CDCl_3$) *δ*: 8.04–7.90 (m, 1H), 7.80–7.71 (m, 1H), 7.59–7.44 (m, 1H), 7.40–7.37 (m, 1H), 7.31–7.17 (m, 2H), 7.15–7.05 (m, 1H), 6.98–6.93 (m, 1H), 4.44–4.19 (m, 1H), 4.05–3.93 (m, 1H), 3.85–3.73 (m, 1H), 3.56–3.38 (m, 1H), 3.20–3.07 (m, 1H), 3.03–2.66 (m, 1H), 2.47–2.40 (m, 3H), 2.27–1.99 (m, 2H), 1.74 − 1.49 (m, 1H), 1.18–0.62 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) *δ* 168.07, 167.89, 167.75, 162.30, 162.23, 162.16, 147.04, 147.00, 144.18, 144.01, 140.19, 139.87, 139.79, 133.61, 133.51, 133.68, 132.07, 131.71, 130.65, 130.53, 130.41, 128.95, 128.82, 127.40, 127.17, 126.90, 125.27, 125.03, 124.92, 124.88, 124.77, 124.56, 120.05, 119.86, 115.88, 115.74, 108.91, 108.82, 108.77, 72.35, 52.13, 51.53, 48.98, 48.40, 47.80, 47.28, 46.42, 45.78, 44.70,43.81, 43.65, 40.91, 39.31, 35.68, 34.67, 33.14, 32.78, 30.76, 26.51, 24.89, 20.77, 19.71, 17.82, 17.30, 16.85. **HRMS** (ESI): *m/z* calcd. for $C_{23}H_{23}ClN_6O_2$ $[M+H]^+$: 451.1644, found 451.1646.

((S)-4-(5-chlorobenzoxazol-2-yl)-7-methyl-[1,4]diazepan-1-yl)-(5-methyl-2-[1,2,3] triazol-2-yl-phenyl)methanone (compound C)

$NaBH_4$ (2.40 g, 63.35 mmol) was added into acetic acid (25.30 g, 422.38 mmol) and stirred for 10 min at room temperature. DCM (200 mL) and sodium acetate (3.46 g, 42.23 mmol) were then added and stirred at 0–10 °C for 10 min. Compound **7** (20.00 g, 42.23 mmol) was then added and the resulting mixture stirred for 1.5 h. HCl aq. (2 mol/L) (50 mL) was then added to quench the reaction and the pH of the solution was adjusted to 9 with NaOH aq. (5 mol/L). The organic phase was separated and the aqueous layer was extracted with DCM (2 × 100 mL). The organic extracts were combined and washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain (*rac)*-8 (10.5 g, 93.66%). Dibenzoyl-*L*-tartaric acid (33.7 g, 94.13 mmol) was dissolved in THF (40 mL) and the solution cooled to 10 °C. Compound (*rac*)-8 (10 g, 37.66 mmol) (dissolved in DCM (10 mL)/THF (60 mL)) was added drop-wise to the solution and left to stirred for 5 h at 20 °C. The slurry was filtered and the solid washed with THF (3 × 10 mL) to give a white solid 10.50 g. The *L*-DBT salt 8 (10 g, 16.03 mmol), iPAc (80 mL) and MeOH (30 mL) were added to a 250 ml round bottomed flask. The slurry stirred for 20 h at room temperature and filtered to give a white solid 6.70 g. The *L*-DBT salt 8 (5.20 g) was treat with NaOH aq. (4 mol/L) in DCM to give (s)-8, 2.20 g. Compound 9 (1.83 g, 8.28 mmol) was dissolved in DCM (25 mL) and cooled to 0–10 °C. Then the solution of (*s*)-8 (2.00 g, 7.53 mmol) in DCM (20 mL) and Et_3N (0.91 g, 9.01 mmol) were added drop-wise and the resulting mixture stirred for 1 h. The reaction mixture was poured into water (50 mL). The organic phase was separated and the aqueous layer was extracted with DCM (2 × 25 mL). The organic extracts were combined and washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain the crude product which was purified by recrystallization from acetonitrile/water (1:1) to give a white solid. Yield: 82% (2.78 g). **HPLC**: 98.25%, chiral HPLC: 98.69%. Mp:132–134 °C; $[\alpha]^{20}_D = +11.21$ (*c* 1.00, MeOH); ^{1}H-NMR and ^{13}C-NMR and melting point data were in accordance with published patents.[5,6,10] **^{1}H NMR** (600 MHz, $CDCl_3$)

δ: 7.96–7.89 (m, 1H), 7.82–7.69 (m, 2H), 7.36–7.27 (m, 2H), 7.22–7.05 (m, 2H), 7.01–6.98 (m, 1H), 7.15–7.05 (m, 1H), 6.98–6.93 (m, 1H), 5.05–4.57 (m, 1H), 4.25–4.03 (m, 2H), 3.93–3.83 (m, 1H), 3.77–3.39 (m, 2H), 3.24–3.07 (m, 1H), 2.44–2.34 (m, 3H), 2.14–1.85 (m, 1H), 1.82–1.54 (m, 1H), 1.32–1.16 (3H, m), 1.00–1.18 (3H, m); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 169.91, 169.43, 169.40, 169.27, 163.04, 162.90, 162.75, 162.68, 147.49, 147.47, 147.42, 144.73, 144.62, 144.60, 144.54, 138.59, 138.56, 138.44, 138.19, 135.67, 135.60, 135.55, 135.46, 134.03, 133.92, 133.60, 133.56, 130.59, 129.41, 129.37, 128.92, 128.80, 128.69, 128.48, 128.40, 128.27, 122.54, 122.20, 122.11, 120.44, 120.38, 120.31, 116.33, 116.21, 109.32, 109.22, 109.12, 52.21, 51.51, 48.88, 48.36, 48.10, 47.62, 47.28, 47.05, 45.57,45.13, 44.90, 44.39, 44.05, 43.83, 41.02, 39.92, 36.26, 35.48, 34.23, 33.90, 21.02, 21.00, 20.96, 20.94, 19.90, 17.91, 17.81, 16.69. **HRMS** (ESI): *m/z* calcd. for $C_{23}H_{23}ClN_6O_2$ $[M+H]^+$: 451.1644, found 451.1646.

2-Diethylamino-5-chlorobenzoxazol (compound D). Compound **2** (5.00 g, 26.6 mmol) was dissolved in THF (25 mL) and the solution cooled to 0–10 °C. Diethylamine (5.83 g, 79.86 mmol) was then added drop-wise and the resulting mixture stirred for 1 h at room temperature. The reaction mixture was poured into water (50 mL). The mixture was then extracted with ethyl acetate (3 × 50 mL) and the organic extracts were combined and washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give the crude. The crude product was recrystallized from isopropanol (19 ml) to give a yellow solid. Yield: 39% (2.32 g); **HPLC**: 99.16%. Mp:42–45 °C.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.22 (d, $J = 3$ Hz, 1H,), 7.05 (d, $J = 12.6$ Hz, 1H), 6.86 (dd, $J = 12.6$ Hz, 3.6 Hz, 1H), 3.46–3.52 (m, 4H), 1.20 (t, $J = 10.8$ Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.94, 146.43, 144.05, 128.03, 118.64, 114.81, 107.91, 42.01, 12.40. **HRMS** (ESI): *m/z* calcd. for $C_{11}H_{13}ClN_2O$ $[M+H]^+$: 225.0789, found 225.0793.

(2-(Bis(5-chlorobenzoxazol-2-yl)amino)ethyl)carbamic acid tert-butyl ester (compound E)

Compound **3** (2.00 g, 6.42 mmol) and compound 2 (2.00 g, 10.63 mmol) were dissolved in THF (30 mL). Saturated Na_2CO_3 aq. (16 mL) was then added and the solution was allowed to warm to 50 °C for 36 h. The reaction was cooled to room temperature. The mixture was then extracted with ethyl acetate (3 × 50 mL) and the organic extracts were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give the crude which was purified by column chromatography (10:1 DCM/MeOH) give a white solid. Yield:15% (0.48 g); HPLC: 98.45%. Mp: 167–170 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.58 (d, $J = 2.4$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.24 (dd, $J = 8.4$ Hz, 2.4 Hz, 2H), 5.10 (br, 1H), 4.53–4.55 (t, $J = 5.4$ Hz, 2H), 3.67–3.68 (m, 2H) 1.30 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.41, 155.94, 147.63, 142.12, 130.31, 123.76, 118.73, 110.84, 79.52, 50.20, 39.14, 28.23. **HRMS** (ESI): *m/z* calcd. for $C_{21}H_{20}Cl_2N_4O_4$ $[M+Na]^+$: 485.0754, found 485.0755.

(5-Chlorobenzo[d]oxazol-2-yl)(2-((5-chlorobenzoxazol-2-yl)amino)ethyl)carbamic acid tert-butyl ester (compound F)

Compound 3 (5.00 g, 16.05 mmol) was dissolved in THF (50 mL) and the solution cooled to 5 °C. Then NaH (60%) (0.71 g, 17.65 mmol) was then added and the resulting mixture stirred for 0.5 h at 50 °C. After cooling to 10 °C, compound 2 (3.30 g, 17.65 mmol) was added into the mixture and stirred for 2 h at 50 °C. The resulting mixture was poured into ice water (500 mL) and filtered to give the crude product. The crude F was washed in 80 mL isopropanol to give a white solid. Yield: 73% (5.40 g); **HPLC**: 97.81%. Mp: 263–266 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56 (d, $J = 2.4$ Hz, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.30 (d, $J = 1.8$ Hz, 1H), 7.23 (dd, $J = 8.4$ Hz, 1.8 Hz, 1H), 7.12 (d, $J = 8.4$ Hz, 1.8 Hz, 1H), 7.0 (dd, $J = 8.4$ Hz, 1.8 Hz, 1H), 6.38 (br, 1H), 4.29 (t, $J = 5.4$ Hz, 2H), 3.85 (m, 2H), 1.53 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.63, 159.37, 151.15, 147.86, 147.20, 144.32, 141.29, 130.12, 129.25, 124.13, 120.81, 118.80, 116.55, 110.86, 109.26, 84.54, 47.88, 42.50, 27.98. **HRMS** (ESI): *m/z* calcd. for $C_{21}H_{20}Cl_2N_4O_4$ $[M+H]^+$: 463.0934, found 463.0936.

2-((5-Chloro-1,3-benzoxazol-2-yl)amino)ethylamine bis-MSA salt (compound G). Compound 3 (3.00 g, 9.63 mol) was dissolved in THF (30 mL) and the solution cooled to 5 °C. Methane sulfonic acid (2.77 g, 28.85 mmol) was then added drop-wise and the resulting mixture stirred for 3 h at 60 °C. The reaction was cooled to room temperature and filtered. The solid was washed with THF (3 × 10 mL) to give white solid. Yield: 96% (3.72 g); **HPLC**: 99.78%. mp: 210 − 212 °C. **^{1}H NMR** (600 MHz, D_2O) δ 7.36 (d, $J = 9$ Hz, 1H), 7.32 (d, $J = 2.4$ Hz, 1H), 7.22 (dd, $J = 9$ Hz, 2.4 Hz, 1H), 3.80 (t, $J = 6$ Hz, 2H), 3.29 (t, $J = 6$ Hz, 2H), 2.69 (s, 6H); **^{13}C NMR** (150 MHz, D_2O) δ 159.95, 144.48, 132.72, 130.77, 124.03, 113.33, 111.67, 40.06, 38.42, 38.18. **HRMS** (ESI): *m/z* calcd. for $C_9H_{10}ClN_3O$ $[M+H]^+$: 212.0585, found 212.0582.

4-((2-Amino-ethyl)-(5-chlorobenzoxazol-2-yl)amino)butan-2-ol (compound H). Compound 6 (20 g, 52.42 mmol) was dissolved in solvent (300 mL DCM + 300 mL MeOH) and the solution cooled to −10 °C. $NaBH_4$ (2.97 g, 78.63 mmol) was then added and the resulting mixture stirred for 1 h. Saturated NH_4Cl aq. (100 mL) was then added to quench the reaction, which was then concentrated in vacuo to remove organic solvent. The mixture was then extracted with DCM (3 × 100 mL) and the organic extracts were combined and washed with water (2 × 200 mL), dried over anhydrous $NaSO_4$, filtered and evaporated under reduced pressure to give the crude intermediate as a white solid, which was used in the next step without any further purification H-1 (18.50 g, 92.5%). Reaction mixture of compound H-1 (5.00 g) and HCl aq. (4 mol/L) (50 mL) was stirred for 48 h at room temperature. The pH of the reaction solution was adjusted to 9 with NaOH aq. (4 mol/L). The mixture was then extracted with DCM (3 × 100 mL) and the organic extracts were combined and washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give compound H as an oil. Yield: 64% (2.3 g); **HPLC**: 99.17%. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.28 (d, $J = 2$ Hz, 1H), 7.14 (d, $J = 8$ Hz, 1H), 6.97 (dd, $J = 8$ Hz, 2 Hz, 1H,), 4.02–3.95 (m, 2H), 3.80–3.72 (m, 1H), 3.66–3.59 (m, 1H), 3.52–3.44 (m, 1H), 3.02 (t, $J = 6.4$ Hz 2H), 1.93–1.84 (m, 1H), 1.65–1.56 (m, 1H), 1.22(d, $J = 8$ Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.96, 147.31,

143.99, 129.45, 120.34, 116.15, 109.26, 63.38, 51.52, 46.57, 40.37, 37.71, 23.08. **HRMS** (ESI): *m/z* calcd. for $C_{13}H_{18}ClN_3O_2$ $[M+H]^+$: 284.1160, found 284.1165.

The materials of ^1H NMR, ^{13}C NMR, HRMS and HPLC Spectra of **A, B, C, D, E, F, G, H and 1** can be found via the "Supplementary Material" section of this article's webpage.

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