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SYNTHESIS OF ANTI-INSOMNIA DRUG SUVOREXANT

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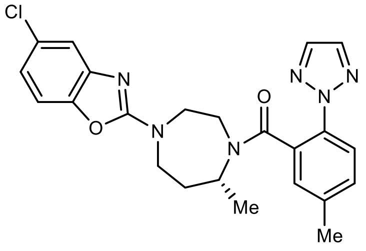
Abstract – Suvorexant is the first dual orexin receptor antagonist for treating insomnia. Although numerous methods have been developed to construct suvorexant, a generally efficient, mild, facile synthesis platform for the conversion of simple starting material to this highly enantioselective scaffold via successive C–N bond forming steps remains in high demand. Here we report an efficient synthetic route without using chiral HPLC separation, resolution, enzyme catalysis or transition metal catalysis, and the total yield is up to 37%.

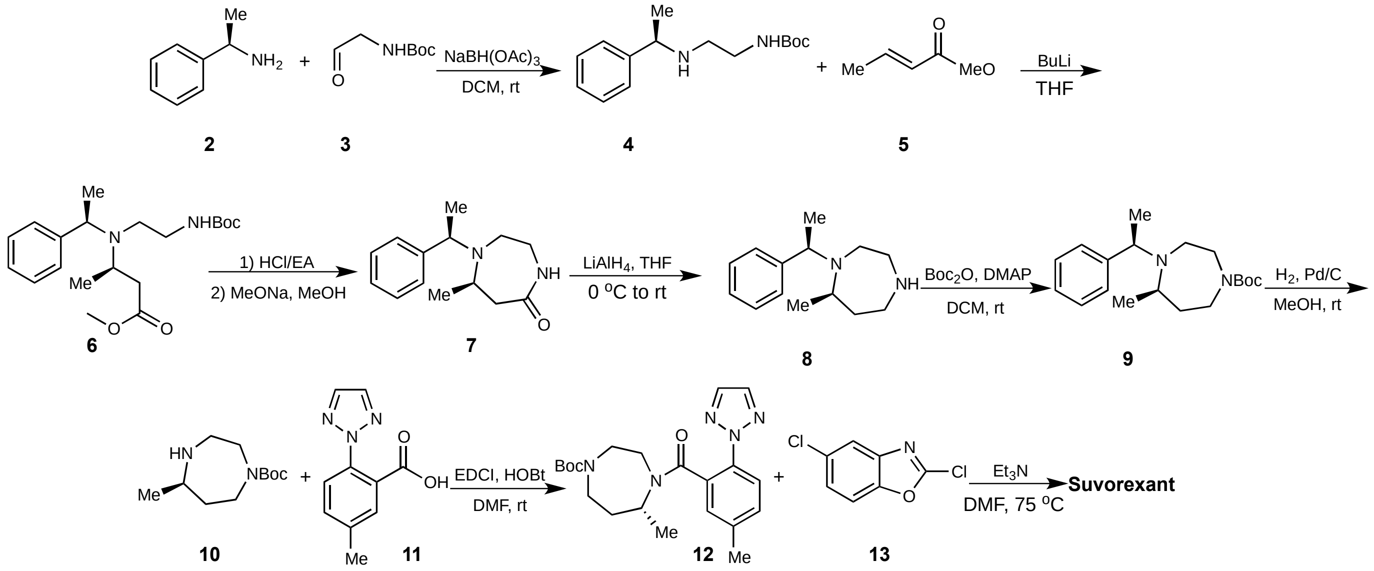
The anti-insomnia drug suvorexant (Belsomra) developed by Merck & Co. is the only dual orexin receptor antagonist approved by the FDA to market.[1] Suvorexant has the advantage that no side effects such as residual effects the next day, rebound insomnia, and withdrawal effects, and launched in the United States in 2014 for the treatment of adult insomnia (**Figure 1**).[2]



Suvorexant

Figure 1. Structural formula of suvorexant

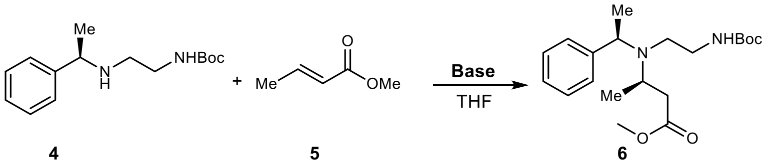
Over the last decade, there have been some reports on the construction of suvorexant in the literature.[3] Notably, Coleman and co-workers[4] reported the synthesis of suvorexant via a chiral stationary phase HPLC resolution carried out on racemic suvorexant lead compound to provide the desired (*R*)-enantiomer 1-benzyl 4-*tert*-butyl 5-methyl-1,4-diazepane-1,4-dicarboxylate as the key intermediates. Almost at the same time, Wallace and co-workers[5] realized the first large-scale synthesis of suvorexant by the classical resolution protocol. Wright[6] reported a ruthenium catalyzed intramolecular asymmetric reductive amination route to synthesis the dual orexin inhibitor suvorexant. Later, Fleitz[7] group reported enantioselective synthesis of suvorexant, where key features of the synthesis include copper-catalyzed amination, chemoselective conjugate addition, and a tandem enantioselective transamination, etc. Here, we demonstrate an efficient method to synthesis of anti-insomnia drug suvorexant, starting from simple chiral starting material, going through reductive amination, Michael addition, enantioselective seven-membered ring annulation, Clemmensen reduction, deprotection, amidation and addition-elimination reaction (**Scheme 1**).



Scheme 1. Synthetic route of suvorexant

The synthesis of compound **4** from compound **2** and compound **3** by reductive amination according to existing literature[8] is outlined in Scheme 1. Treatment of **4** with base was conducted in THF to give nitrogen anions through hydrogen abstraction, then the Michael receptor compound **5** adds to the nitrogen of **4** to generate compound **6**. In order to obtain **6** with excellent yield and diastereoselectivity, screened a series of bases, including inorganic bases and organic bases (**Table 1**). As shown in Table 1, a series of base efficiently underwent the desired Michael addition, affording the product **6** in good yields and high to excellent diastereoselectivity. Compared with inorganic base (**Entries 1 and 2**), organolithium is more efficient (**Entries 3-5**), Pleasingly, BuLi, one of relatively mild organolithium turned out to be a viable base, yielding product **6** with good yield and diastereoselectivity (95% yield, 25:1 dr).

Table 1. Screening of base



Entry	Temperature	Base	Yield	DR
1	0 °C	$NaHCO_3$	42%	3:1
2	0 °C	Cs_2CO_3	51%	3:1
3	-78 °C	LDA	83%	15:1
4	-78 °C	LiHMDS	62%	20:1
5	-78 °C	BuLi	95%	25:1

Later, treatment of **6** gave seven-membered cyclization product **7** under acidic conditions. The product **7** underwent Clemson reduction to get compound **8**, where the carbonyl group in compound **7** was reduced to methylene, followed by using protecting group (Boc) to gain the target product **9**. Compound **10** was obtained by catalytic hydrogenolysis to remove the benzyl protecting group of **9**. We applied **10** and **11** to the expedient synthesis of the lead compound **12** for the anti-insomnia drug suvorexant by amidation. Finally, treatment of **12** with **13** was conducted in DCM to give target product suvorexant.

In conclusion, we developed an efficient synthetic route to construction the anti-insomnia drug suvorexant. This protocol allows for the conversion of simple starting material to this highly enantioselective scaffold via successive C–N bond forming steps without using chiral HPLC separation, resolution and enzyme catalysis, etc. We expect that the operational simplicity and generality of this route and readily availability of the starting materials will allow it to enjoy extensive application in the area of organic chemistry target product suvorexant.

EXPERIMENTAL

Chromatographic purification of products was accomplished by flash chromatography using silica gel. Thin-layer chromatography (TLC) was performed on Silicycle 250 mm silica gel F-254 plates.^{1}H and ^{13}C NMR spectra were recorded on Bruker 500 (500 MHz) and are internally referenced to residual solvent signals ($CDCl_3$, 7.26 and 77.0 ppm). Optical rotations were measured on an automatic polarimeter with $[\alpha]_D^{25}$ values reported in degress; concentration (c) is in 1 g/100 mL. High resolution mass spectra were obtained at Shanghai Institute of Organic Chemistry mass spectrometry facilities. All of the organic solvents used in this study were dried over appropriate drying agents prior to use. All reagents used in this study were commercially available.

Typical procedure for the preparation of suvorexant *tert*-Butyl (*R*)-(2-((1-phenylethyl)amino)ethyl)carbamate (4): Compound **3** (7.0 g, 44 mmol) and (*R*)-1-phenylethylamine (8.0 g, 66 mmol) were dissolved in DCM (500 mL), and to the stirred solution was added sodium triacetoxyborohydride (28.0 g, 132 mmol), and the reaction was stirred at room temperature overnight. The mixture was diluted with DCM (300 mL) and then washed with water (2×200 mL) and saturated brine (200 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo, which was then separated and purified to obtain compound **4** as a white solid (10.6 g, yield 91%), Mp 81.9-83.2 °C. $[\alpha]_D^{18}$ +28.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 4H), 7.26-7.18 (m, 1H), 4.95 (s, 1H), 3.75 (q, *J* = 6.6 Hz, 1H), 3.22-3.07 (m, 2H), 2.65-2.58 (m, 1H), 2.56-2.48 (m, 1H), 1.44 (s, 9H), 1.34 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.09, 145.49, 128.45, 126.94, 126.49, 79.09, 57.96, 46.98, 40.57, 28.41, 24.36. HRMS (ESI) *m/e* calcd for $C_{15}H_{24}N_2O_2^+$ $(M+H)^+$, 265.19105, found 265.19101.

Methyl (*R*)-3-((2-((*tert*-butoxycarbonyl)amino)ethyl)((*R*)-1-phenylethyl)amino)butanoate (6): Under N_2 protection, compound **4** (5.8 g, 22 mmol) was dissolved in THF (80 mL) and then cooled to 0 °C. A solution of *n*-butyllithium in hexane (30.0 mL, 44 mmol) was slowly added to the system, the resulting solution was stirred for 30 min, and then cooled to -78 °C, Then a solution of compound **5** (2.0 g, 20 mmol) dissolved in anhydrous THF (20 mL) was added dropwise. The mixture was stirred at -78 °C for 1.5 h. Saturated aqueous NH_4Cl (20 mL) was added dropwise to quenching the reaction, and the resulting solution was slowly warmed to room temperature. The system was extracted with EtOAc (2×30 mL). The obtained organic phases were combined, dried with anhydrous $MgSO_4$, and then distilled under reduced pressure. Then it was purified to obtain compound **6** as a colorless liquid (6.9 g, yield 95%). $[\alpha]_D^{18}$ +25.5 (*c* 1.0, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H), 7.23-7.16 (m, 1H), 5.25-5.13 (m, 1H), 3.85 (q, *J* = 6.6 Hz, 1H), 3.67 (s, 3H), 3.20-3.01 (m, 2H), 2.68-2.54 (m, 2H), 2.47-2.31 (m, 1H), 2.21-2.07 (m, 1H), 1.42 (s, 9H), 1.33 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 1H), 0.70 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.94, 156.19, 144.50, 128.19, 127.55, 126.98, 78.69, 58.18, 51.48, 50.76, 50.32, 44.37, 40.93, 28.45, 19.67, 17.42, 16.12. HRMS (ESI) *m/e* calcd for $C_{20}H_{32}N_2O_4^+(M+H)^+$, 365.24348, found 365.24343.

(*R*)-7-Methyl-1-((*R*)-1-phenylethyl)-1,4-diazepan-5-one (7): A solution of compound **6** (3.6 g, 10 mmol) dissolved in DCM (20 mL) was added saturated HCl/ EtOAc (20 mL), and the reaction was stirred for 4 h. The solvent was removed by rotary evaporation, and the residue was basified with saturated aqueous $NaHCO_3$ and extracted with DCM. The concentrated organic phase was dried over anhydrous $MgSO_4$. Under N_2 protection, the resulting compound was dissolved in anhydrous MeOH (40 mL), MeONa (0.65 g, 12 mmol) was added, and stirred at room temperature, quenched with saturated aqueous NH_4Cl (15 mL), and then the reaction system was poured into a solution containing 5% Na_2CO_3 in a separatory funnel of the aqueous solution, and it was thoroughly shaken and extracted with DCM (2×20 mL). The organic phases were combined, dried with $MgSO_4$, and concentrated in vacuo to obtain compound **7** as a white solid (2.1 g, 90% yield in two steps). Mp 161.8-168.4 °C. $[\alpha]_D^{18}$ +15 (*c* 1.0, $CHCl_3$) ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.27 (m, 4H), 7.27-7.18 (m, 1H), 6.78 (s, 1H), 3.79 (q, *J* = 6.5 Hz, 1H), 3.55-3.42 (m, 1H), 3.19-3.10 (m, 1H), 3.09-3.00 (m, 1H), 2.95-2.83 (m, 2H), 2.81-2.72 (m, 1H), 2.27 (dd, *J* = 14.1, 6.3 Hz, 1H), 1.32 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.87, 145.72, 128.48, 126.94, 126.88, 60.45, 48.30, 44.74, 44.02, 42.90, 22.01, 10.72. HRMS (ESI) *m/e* calcd for $C_{14}H_{20}N_2O^+(M+H)^+$, 233.16484, found 233.16489.

(*R*)-7-Methyl-1-((R)-1-phenylethyl)-1,4-diazepane (8): Compound **7** was dissolved in THF (60 mL), and the temperature of the system was reduced to about 0 °C. $LiAlH_4$ (1.4 g, 36.0 mmol) was added in portions to treat the substrate (1.4 g, 6.0 mmol). Then, the reaction was slowly warmed to room temperature. After the reaction was completed, the reaction was cooled to -10 °C, and the reaction was quenched with water (1.5 mL), 15% NaOH (1.5 mL), and then water (4.5 mL) was added to quench. An appropriate amount of $MgSO_4$ was added, the mixture was stirred for 1 h, and then filtered. The filtrate was concentrated to obtain compound **8** as a yellow oil (1.1 g, yield 84%). $[\alpha]_D^{18}$ +13.1 (*c* 1.0, $CHCl_3$) ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H), 7.24-7.18 (m, 1H), 3.93 (q, *J* = 6.5 Hz, 1H), 3.03-2.60 (m, 7H), 1.98-1.88 (m, 1H), 1.57-1.44 (m, 1H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 6.3 Hz, 1H), 0.96 (d, *J* = 6.3 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 145.85, 128.61, 127.07, 127.01, 60.58, 48.43, 44.87, 44.15, 43.03, 34.08, 22.14, 10.85. HRMS (ESI) *m/e* calcd for $C_{14}H_{20}N_2^+(M+H)^+$, 219.18557, found 219.18563.

***tert*-Butyl (*R*)-5-methyl-4-((*R*)-1-phenylethyl)-1,4-diazepane-1-carboxylate (9):** To the flask, compound **8** (4.4 g, 20 mmol) dissolve with DCM (60 mL) and 4-dimethylaminopyridine (244 mg, 2 mmol, 10 mol%) were added. Then di-*tert*-butyl dicarbonate (5.1 mL, 22 mmol) was dissolved in DCM (10 mL) and slowly added under ice bath conditions. The mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The solution was washed with water and brine, then dried over anhydrous $MgSO_4$ and concentrated to give compound **9** as a yellow oil (6.0 g, yield 95%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.25 (m, 4H), 7.23-7.16 (m, 1H), 3.88-3.78 (m, 1H), 3.64-3.28 (m, 4H), 3.21-3.07 (m, 1H), 2.87-2.64 (m, 2H), 2.06-1.79 (m, 1H), 1.47 (s, 10H), 1.31 (dd, *J* = 9.1, 6.6 Hz, 3H), 1.07-0.92 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ155.40, 146.26, 146.05, 128.22, 127.34, 127.09, 126.62, 67.29, 59.56, 51.66, 46.70, 46.17, 44.24, 42.47, 41.67, 34.57, 34.11, 28.44, 27.76, 22.16, 14.66, 14.16. HRMS (ESI) *m/e* calcd for $C_{19}H_{30}N_2O_2^+(M+H)^+$, 319.23800, found 319.23806.

***tert*-Butyl (*R*)-5-methyl-1,4-diazepane-1-carboxylate (10):** Compound **9** (4.8 g, 15.0 mmol) was dissolved in MeOH (60 mL). After adding a portion of 10% Pd/C (0.5 g), the reaction was placed at room temperature, stirred for 4 h with the participation of H_2, the reaction was filtered through a pad of celite, and the filtrate was concentrated to obtain compound **10** as a yellow oil (2.8 g, yield 87%). $[\alpha]_D^{18}$ +16.2

(*c* 1.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70-3.17 (m, 4H), 3.12-2.99 (m, 1H), 2.86-2.62 (m, 2H), 2.02-1.77 (m, 2H), 1.44 (s, 9H), 1.11 (dd, *J* = 6.5, 3.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.83, 54.63, 49.75, 49.12, 48.39, 48.17, 44.99, 44.04, 37.98, 28.47, 27.74, 23.37. HRMS (ESI) *m/e* calcd for $C_{11}H_{22}N_2O_2^+(M+H)^+$, 215.17540, found 215.17534.

***tert*-Butyl (*R*)-5-methyl-4-(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoyl)-1,4-diazepane-1-carboxylate (12):** Dissolve compound **10** (1.1 g, 5 mmol) and compound **11** (1.0 g, 5 mmol) in DMF (50 mL), then EDCI (1.2 g, 6 mmol), HOBt (0.8 g, 6 mmol) and triethylamine (2.9 mL, 25 mmol) were added to the stirred solution and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (25 mL), the organic phase was separated after stirring well with saturated aqueous 5% $NaHCO_3$ (25 mL), and the aqueous mixture was extracted with EtOAc (25 mL). The organic phase and extract were combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was separated and purified on a silica gel chromatography column to obtain compound **12** as a colorless liquid (1.7 g, yield 85%). $[\alpha]_D^{18}$ -34.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94-7.64 (m, 3H), 7.34-7.00 (m, 2H), 4.93-2.81 (m, 7H), 2.36 (s, 3H), 2.22-1.59 (m, 1H), 1.43 (s, 9H), 1.26-1.02 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ169.22, 169.01, 155.13, 138.41, 138.35, 138.05, 135.58, 135.56, 135.46, 135.38, 133.87, 133.51, 130.35, 129.24, 128.50, 128.37, 128.33, 128.18, 122.36, 122.13, 122.06, 52.26, 51.53, 48.44, 46.61, 45.74, 44.97, 43.62, 28.45, 28.41, 28.38, 20.96, 20.90, 16.90. HRMS(ESI) *m/e* calcd for $C_{21}H_{29}N_5O_3^+(M+H)^+$, 400.23432, found 400.23421.

(*R*)-(4-(5-Chlorobenzo[*d*]oxazol-2-yl)-7-methyl-1,4-diazepan-1-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)-phenyl)methanone (Suvorexant): At room temperature, compound **12** (2.0 g, 5 mmol) was dissolved in DCM (50 mL), a saturated solution of HCl/EtOAc (15 mL) was added to the stirred solution, and the resulting mixed solution was stirred until the raw materials were completely consumed. The solvent was removed by rotary evaporation, and the residue was basified with saturated aqueous $NaHCO_3$ and extracted with DCM (2×20 mL). The concentrated organic phase was dried over anhydrous $MgSO_4$. The amine obtained above was dissolved in DMF (60 mL) at room temperature, compound **13** and triethylamine (1.5 g, 15 mmol) were added to the stirred solution, and the resulting mixture was stirred at 75 °C for 2 h. The reaction mixture was diluted with DCM (2×50 mL) and filtered through a pad of celite, and the filtrate was concentrated in vacuo. The residue was separated and purified to obtain compound **1** (1.8 g, yield 80%). $[\alpha]_D^{25}$ -12.1 (*c* 1.0, MeOH) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.62 (m, 3H), 7.35-6.88 (m, 5H), 5.05-3.31 (m, 6H), 3.23-3.02 (m, 1H), 2.45-2.24 (m, 3H), 2.14-1.39 (m, 2H), 1.31-1.07 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.90, 169.39, 163.01, 162.72, 147.46, 144.71, 144.60, 144.52, 138.56, 138.54, 138.17, 135.65, 135.59, 135.54, 133.99, 133.53, 130.58, 130.57, 129.34, 129.31, 128.87, 128.64, 128.44, 128.37, 128.24, 128.05, 122.54, 122.51, 122.16, 122.07, 120.39, 120.33, 120.26, 120.23, 116.25, 116.19, 116.13, 109.32, 109.21, 109.13, 77.30, 52.18, 51.49, 48.81, 48.34, 48.08, 47.57, 47.23, 47.00, 45.53, 45.08, 44.86, 44.33, 44.01, 43.78, 40.97, 39.86, 36.22, 35.42, 34.16, 33.85, 21.00, 20.98, 20.94, 19.86, 17.88, 17.76, 16.65. HRMS (ESI) *m/e* calcd for $C_{23}H_{23}ClN_6O_2^+(M+H)^+$, 451.16438, found 451.16417.

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