Chinese Chemical Letters 26 (2015) 103–107

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Facile synthesis of suvorexant, an orexin receptor antagonist, *via* a chiral diazepane intermediate

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ARTICLE INFO

Article history:
Received 8 July 2014
Received in revised form 6 August 2014
Accepted 5 September 2014
Available online 28 September 2014

Keywords:
Synthesis
Suvorexant
Chiral diazepane

ABSTRACT

A facile synthesis of suvorexant, an orexin receptor antagonist, is described. The key intermediate **6** was prepared from *R*-3-aminobutyric acid through protection, condensation, deprotection, cyclization, and hydrogenation steps. The title product was obtained with a total yield of 31% (>99% *ee*) after eight linear steps using commercially available raw materials.

1. Introduction

Insomnia is characterized by difficulties in initiating, maintaining, or obtaining good quality sleep and is a prevalent public health problem affecting large segments of the population on a situational, recurrent, or chronic basis. The estimated annual costs associated with insomnia number into the billions of dollars [1–4]. Over the past several years, the orexin system has gained major popularity as a novel mechanism for the control of sleep disorders due to its highly conserved nature and its ability to regulate arousal and wakefulness [5]. Orexin A (OX-A) and orexin B (OX-B) (the hypocretins), neuropeptides produced by neurons in the hypothalamus, are derived from the same precursor protein [6,7]. The relationship between reduced orexin levels and narcolepsy has been demonstrated in rodents, dogs, and humans [8]. These studies suggest the potential of an orexin receptor antagonist in the treatment of sleep disorders. Suvorexant (Fig. 1), a dual orexin receptor antagonist developed by Merck & Co. [9] completed phase III clinical trials for the treatment of primary insomnia.

In recent years, several protocols have been developed for the synthesis of suvorexant (Scheme 1). The original synthetic route was developed by Cox and coworkers in 2010 [9]. Central to this approach was the synthesis of the core diazepane R-**11**, which was afforded by a preparative chiral high-performance liquid chromatography (HPLC) separation of orthogonally protected racemic **11**. Removal of the Boc protecting group, coupling with acid **5**, and hydrogenolysis of the Cbz group yielded compound **9**. Finally, treatment of **9** with 2,5-dichloro-1,3-benzoxazole **8** in the presence of potassium carbonate completed the synthesis of **1**.

The large-scale synthesis of suvorexant was reported in 2011 [10]. The key intermediate, *R*-isomer **12** could be achieved *via* the classical resolution, while the racemic **12** was prepared through the reductive amination of **13**, and **1** was accomplished followed by condensation with **5**. However, in addition to the desired product racemic **12** it was found that impurities **15** and **16** were generated [10] (Scheme 1).

Strotman *et al.* [11] offered the first asymmetric reductive amination of a dialkyl ketone with an alkyl amino. The desired diazepane ring *R*-**12** was produced in 97% yield and high enantiopurity (94.5% *ee*) by mediation with a novel Ru-based transfer hydrogenation catalyst.

More recently, Mangion *et al.* [12] reported yet another strategy for the synthesis of suvorexant. The transamination of compound **14** was conducted with a biological enzyme (*i.e.*, CDX-017), resulting in good conversion yields and high enantiopurity (>99% *ee*).

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http://dx.doi.org/10.1016/j.cclet.2014.09.020

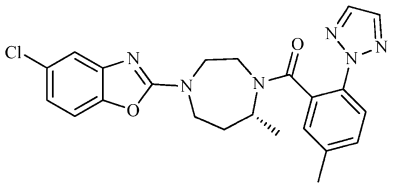


Fig. 1. Structure of suvorexant.

As a part of our continuing interest in developing practical and efficient processes for the synthesis of active pharmaceutical ingredients (APIs) and related intermediates, the current study describes recent efforts to develop a practical route to synthesizing suvorexant.

2. Experimental

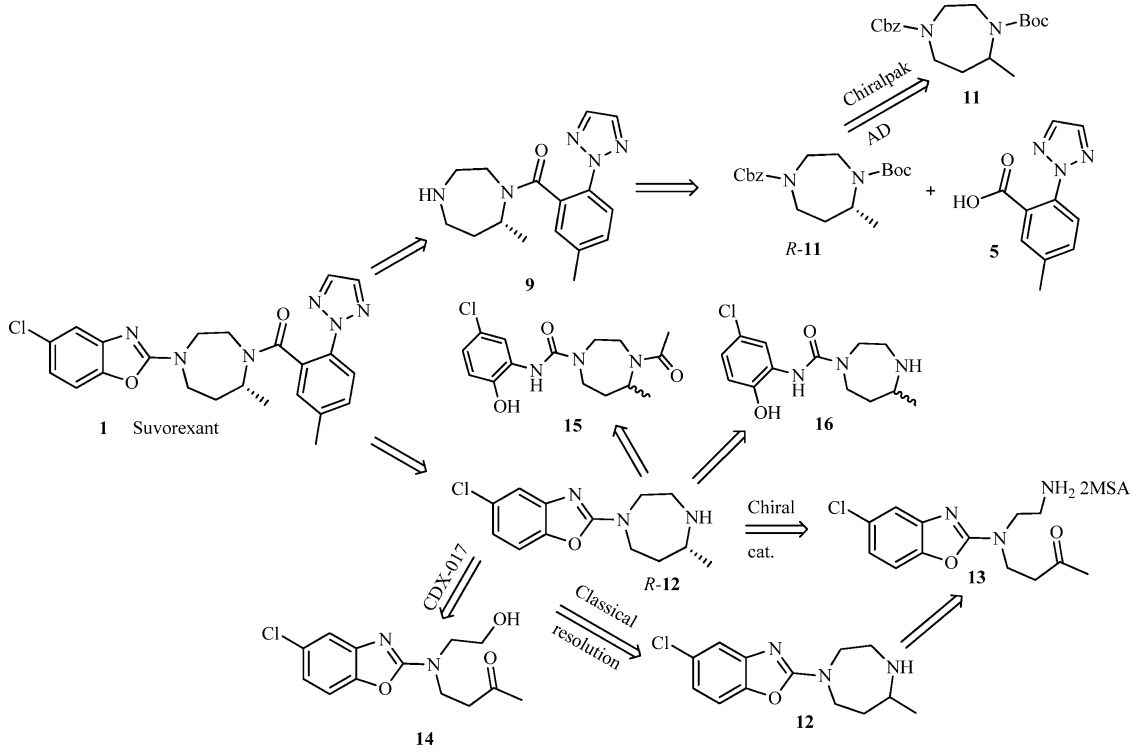
R-3-aminobutyric acid and compound **8** were purchased from commercial suppliers. Melting points were determined in open capillary tubes and are uncorrected. The reactions were monitored by thin-layer chromatography to detect the completion of the reaction. NMR spectra were recorded on a Bruker Ascend™ 600 spectrometer. Mass spectra were provided on Agilent 1100 LC-MS.

*2.1. Synthesis of (R)-methyl 2-(N-benzyl-3-((tert-butoxycarbonyl) amino)butanamido)acetate (**3**)*

To a solution of methyl 2-(benzylamino)acetate (compound **10**, 50.14 g, 0.28 mol), (*R*)-3-((*tert*-butoxycarbonyl)amino)butanoic acid (50.75 g, 0.25 mol), 1-hydroxy-1*H*-benzotriazole (41.88 g, 0.31 mol), and dry triethylamine (37.95 g, 0.38 mol) in 320 mL of DMF was added EDC hydrochloride (57.51 g, 0.30 mol), and the reaction was stirred for 5 h at room temperature. The reaction was partitioned between EtOAc and 10% aqueous citric acid, the layers were separated and the organic was washed with 5% aqueous Na_2CO_3, then with brine, dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was recrystallized from a mixture solvent (PE:EtOAc = 2:1) to provide compound **3** as a white solid, 83.01 g in 91% yield. Mp: 107 °C, $[\alpha]_D^{25}$ 22.0 (*c* 0.52, MeOH). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.38–7.23 (m, 5H), 6.73–6.72 (d, 1H, *J* = 6 Hz), 4.75–4.43 (m, 2H), 4.31–3.95 (m, 2H), 3.89–3.87 (t, 1H, *J* = 12 Hz), 3.64–3.62 (d, 3H, *J* = 12 Hz), 2.64–2.50 (m, 1H), 2.37–2.23 (m, 1H), 1.38–1.37 (d, 9H, *J* = 6 Hz), 1.08–1.06 (m, 3H); MS (ESI) *m*/*z*: 365.20 $[M+H]^+$. HR-MS(ESI): *m*/*z* [M+H] calcd. for $C_{19}H_{28}N_2O_5$: 365.2071; found: 365.2066.

*2.2. Synthesis of (R)-4-benzyl-7-methyl-1,4-diazepane-2,5-dione (**4**)*

A solution of compound **3** (15.93 g, 43.74 mmol) in 10 mL EtOAc was added 150 mL 45% HCl/EtOAc and the reaction was stirred for 4 h. The solvents were removed by rotary evaporation, and the residue was basified with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts were concentrated. The residue was dissolved in 150 mL of dehydrated MeOH, treated with CH_3ONa (2.84 g, 52.49 mmol), and stirred at room temperature overnight (N_2 protected, slightly exothermic). The reaction was cooled to room temperature and quenched with aqueous NH_4Cl. Most of the solvent was removed and the reaction was then dumped into a separatory funnel containing 5% aqueous Na_2CO_3 and extracted with CH_2Cl_2 three times. The organic layers were combined, dried over $MgSO_4$, and concentrated to provide compound **4** as a white solid 9.50 g in 94% yield. Analytical HPLC analysis carried out on Chiralpak AD column (4.6 mm × 250 mm) with 60% EtOH in hexanes (containing 0.1% diethylamine as a modifier), flow rate of 1 mL/min, indicated that intermediate (*R*)-**4** was of >99% *ee*. Mp: 122–123 °C. $[\alpha]_D^{25}$ 33.5 (*c* 0.56, MeOH). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.77–7.76



Scheme 1. Reported synthetic route of suvorexant.