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Synthesis and evaluation of carbon-linked analogs of dual orexin receptor antagonist filorexant

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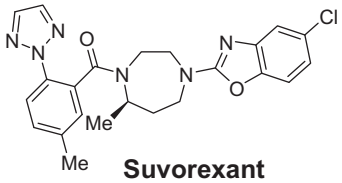
ABSTRACT

Analogs of the dual orexin receptor antagonist filorexant were prepared. Replacement of the ether linkage proved highly sensitive toward modification with an acetylene linkage providing compounds with the best in vitro and in vivo potency profiles.

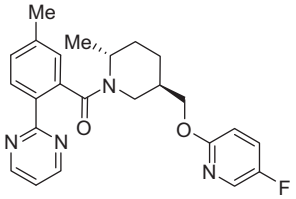
The orexin neuropeptides and their receptors have a demonstrated role in regulating sleep/wake state and recent research has generated significant interest in targeting the orexin receptors for related disorders. The characterization of a novel neuropeptide secreted from the hypothalamus, naming the peptide hypocretin[1] and orexin,[2] was achieved via genetic and biochemical approaches, with the orexin naming most frequently utilized.[3] Orexin neuropeptides (OX-A and OX-B) are derived from orexinergic neurons localized in the lateral hypothalamus, and signal through two G-protein coupled receptors (GPCR's), Orexin Receptor 1 (OX_1R) and Orexin Receptor 2 (OX_2R).[3]

These receptors are disseminated in key brain regions responsible for governing wake, vigilance and reward seeking behaviors. Orexin signaling is most active during the normal wake period and falls silent during the sleep period.[4–6] Several companies have identified dual orexin receptor antagonists (DORAs) targeting both OX_1R and OX_2R, or selective orexin receptor antagonists (SORAs), and many have advanced through late stage clinical development.[7–10] Numerous reviews are available in this context.[11–14]

Two DORAs, suvorexant and filorexant, have been discovered and advanced into clinical development at Merck (Fig. 1). Filorexant was most recently described as a potent DORA that is efficacious in promoting sleep in rats and dogs, and has been reported to be in Phase II trials. Limited SAR data has been reported for filorexant, mostly to the carboxamide and fluoro-pyridine regions of the molecule.[15] In this Letter, we describe SAR analysis of the role of the ether linkage between the piperidine central ring



Suvorexant



Filorexant

Figure 1.

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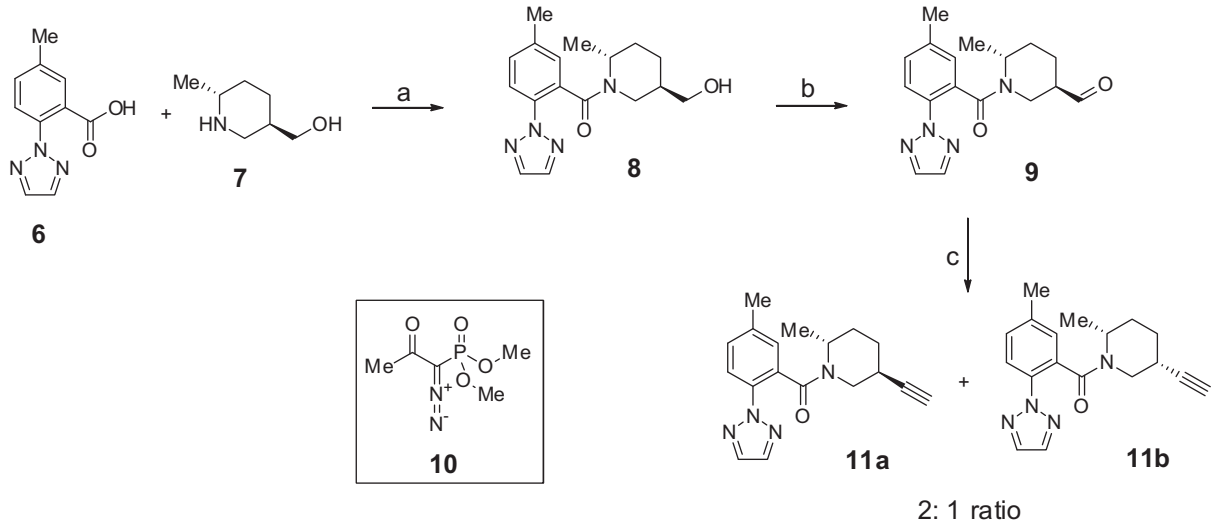
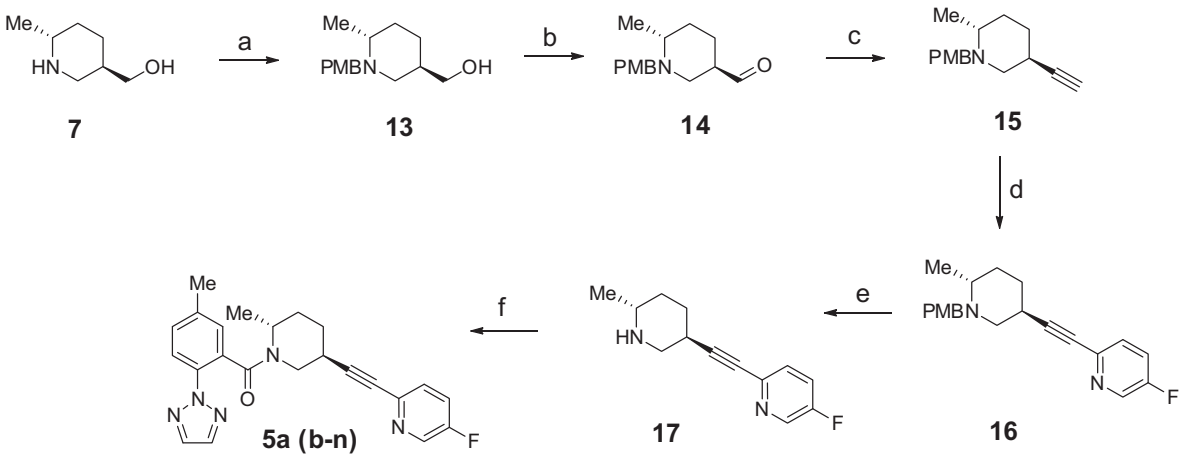
and the fluoropyridine, with an emphasis of all carbon linkages (ethyl) with varied degrees of flexibility (sp3, sp2, and sp hybridization).

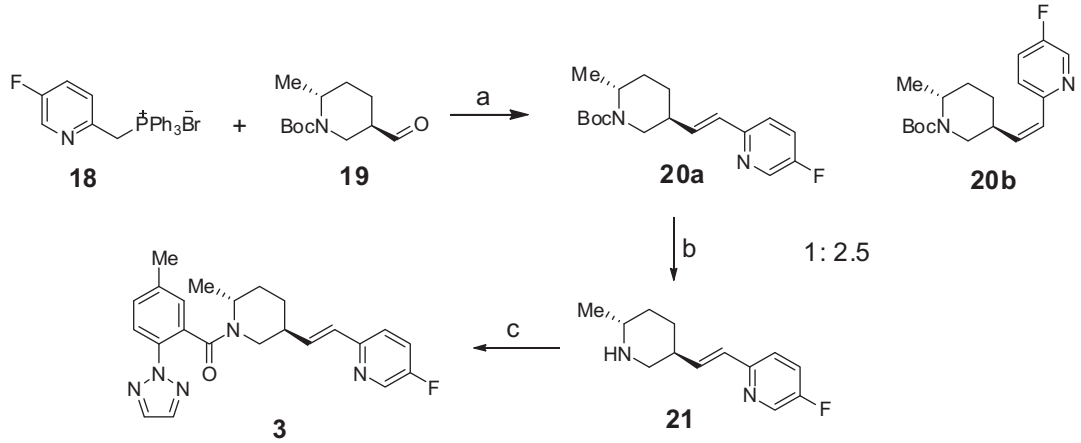
The synthetic route used to access carbon-linked target molecules is shown in Schemes 1–3. Coupling of triazole carboxylic acid **6** and piperidinol **7** was mediated by EDC followed by



Scheme 1. (a) EDC, HOBt, Hunig's base, DMF. (b) Diacetoxyiodobenzene, TEMPO, CH_2Cl_2. (c) Potassium carbonate, 10, MeOH.



Scheme 2. (a) *p*-Anisaldehyde, $NaBH_3CN$, MeOH. (b) Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2. (c) Potassium carbonate, 10. (d) 2-Bromo-5-fluoropyridine, $Pd(PPh_3P)_4$, CuI, Et_3N. (e) (1) 1-Chloroethyl chloroformate, Et_3N, CH_2Cl_2; (2) MeOH, reflux. (f) EDC, HOAt, Hunig's base, DMF.



Scheme 3. (a) NaH, THF, 0 °C-rt. (b) HCl, dioxane. (C) 6, EDC, HOAt, Hunig's base.