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Discovery of dual orexin receptor antagonists with rat sleep efficacy enabled by expansion of the acetonitrile-assisted/diphosgene-mediated 2,4-dichloropyrimidine synthesis

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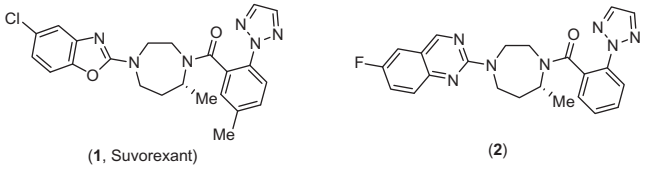
ABSTRACT

Recent clinical studies have demonstrated that dual orexin receptor antagonists (OX_1R and OX_2R antagonists or DORAs) represent a novel treatment option for insomnia patients. Previously we have disclosed several compounds in the diazepane amide DORA series with excellent potency and both preclinical and clinical sleep efficacy. Additional SAR studies in this series were enabled by the expansion of the acetonitrile-assisted, diphosgene-mediated 2,4-dichloropyrimidine synthesis to novel substrates providing an array of Western heterocycles. These heterocycles were utilized to synthesize analogs in short order with high levels of potency on orexin 1 and orexin 2 receptors as well as in vivo sleep efficacy in the rat.

The discovery of novel orexin receptor antagonists has evolved rapidly in the past decade from the generation of novel peptide analogs[1] to small molecule clinical candidates[2] to the NDA filing of suvorexant (**1**, Fig. 1) in 2012 for the treatment of patients suffering from insomnia.[3] Suvorexant (**1**) and DORA **2** antagonize the action of wake-promoting orexin peptides (orexin A and B) at orexin 1 (OX_1R) and orexin 2 (OX_2R) receptors, hence, they are categorized as dual orexin receptor antagonists (DORAs). Several reviews have been published detailing the pharmacology and therapeutic utility associated with orexin antagonism and are beyond the scope of this manuscript.[4] Herein we report the expansion of the acetonitrile-assisted, diphosgene-mediated 2,4-dichloropyrimidine synthesis as it applies to the discovery of orexin antagonists.

As shown in Figure 1, Suvorexant and DORA **2** are both potent antagonists of OX_1R and OX_2R with nanomolar to subnanomolar binding potency and high levels of functional antagonism as determined in the FLIPR (fluorometric imaging plate reader) assay.[5] DORA **2** possessed similar in vivo efficacy in rat sleep studies compared to suvorexant, however, bioactivation concerns were confirmed through glutathione (GSH) trapping studies in microsomal incubations.[2c] Through additional diazepane core and heterocycle modifications and GSH trapping experiments, the 6-fluoroquinazoline moiety was determined to be the substructure responsible for the observed bioactivation. These findings encouraged us to examine the SAR of potential 6-fluoroquinazoline replacements. In order to effectively examine this new SAR, we sought an efficient synthesis of appropriately functionalized bicyclic pyrimidines.



OX_1R K_i (IC_{50}) = 0.6 nM (50 nM)
OX_2R K_i (IC_{50}) = 0.4 nM (56 nM)

OX_1R K_i (IC_{50}) = 1.8 nM (27 nM)
OX_2R K_i (IC_{50}) = 0.2 nM (27 nM)

Figure 1. Potent, optimized diazepane-containing dual orexin receptor antagonists (DORAs) suvorexant (**1**) and **2** that have demonstrated excellent sleep efficacy.

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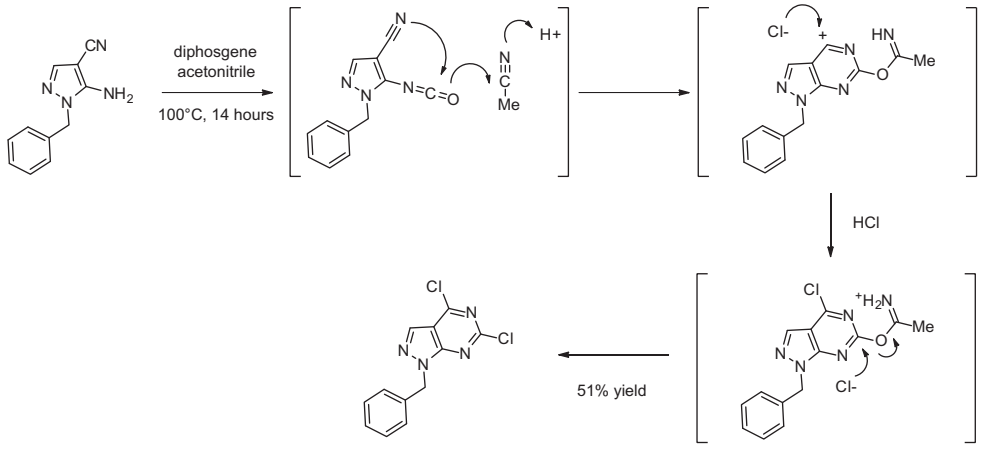


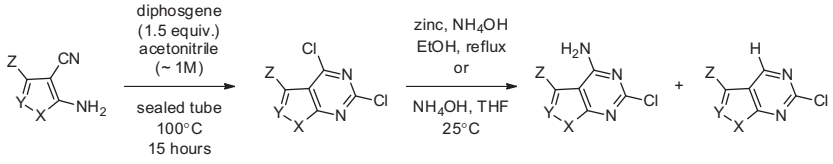
Scheme 1. Mechanism proposed by Chi et al. for their acetonitrile-assisted fused 2,4-dichloropyrimidine synthesis.

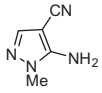
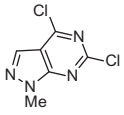
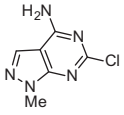
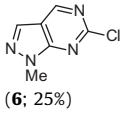
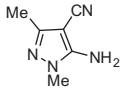
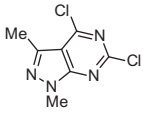
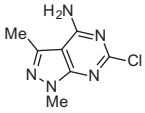
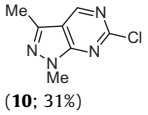
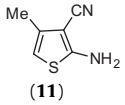
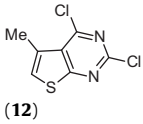
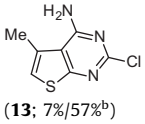
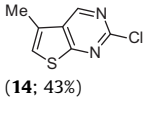
Chi and co-workers published a synthesis of 2,4-dichloroquinolines and 2,4-dichloroquinazolines in a single step from 2-ethynylanilines or anthranilonitriles, respectively, using diphosgene in acetonitrile.[6] A single example of a five-membered ring substrate, 5-amino-1-benzyl-1*H*-pyrazole-4-carbonitrile, demonstrated that this methodology would also provide fused pyrimidine heterocycles that could serve as interesting quinazoline replacements for the diazepane series shown in Figure 1. The mechanism proposed by Chi and co-workers for this transformation is depicted in Scheme 1, and it involves isocyanate formation, ring closure assisted by acetonitrile, and two subsequent chloride ion attacks to afford the final products in modest yield. Our group sought to further evaluate the scope of this reaction and to test its application toward the synthesis of DORAs with diminished bioactivation potential compared to DORA **2**.[7]

A series of commercially available five-membered heterocyclic 2-aminocarbonitriles were subjected to the conditions described in Scheme 1 and the results are shown in Table 1. Truncated pyrazole substrates **3** and **7** provided fused dichloropyrimidines **4** and **8** in slightly reduced yields (39% and 24%, respectively) compared to the pyrazole substrate exemplified in Scheme 1. Substituted thiophene scaffolds were also competent substrates under the reaction conditions with precursors **11** and **15** affording products **12** and **16** in 52% and 65% yields, respectively. Substrate **18**, 2-aminothiophene-3-carbonitrile, provided the desired product with less overall yield (19%). Finally, substituted furans **21** and **25** performed well giving rise to products **22** and **26** in acceptable to good yields.

Standard nucleophilic substitution reactions (S_NAr) of 2,4-dichloropyrimidines using secondary amines such as our diazepane substrates provide 4-substituted products with high regioselectivity.[8] In order to afford the 2-substituted analogs similar to DORA **2**, bicyclic 2,4-dichloropyrimidine substrates were subjected to a variant of known conditions for selective dechlorination of the 4-position. Treatment with excess elemental zinc and ammonium hydroxide in refluxing ethanol afforded a mixture of desired dechlorinated-, aminated-, and ethoxy substituted products.[9] In

Table 1
Acetonitrile-assisted synthesis of 2,4-dichloropyrimidines and subsequent amination/dechlorination



Substrate	Product	Yield (%)	Amine substitution (yield)[a]	Dechlorination (yield)[a]
 (**3**)	 (**4**)	39	 (**5**)	 (**6**; 25%)
 (**7**)	 (**8**)	24	 (**9**; 51%)	 (**10**; 31%)
 (**11**)	 (**12**)	52	 (**13**; 7%/57%[b])	 (**14**; 43%)