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Disubstituted piperidines as potent Orexin (hypocretin) receptor antagonists

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Abstract

A series of orexin receptor antagonists was synthesized based on a substituted piperidine scaffold. Through traditional medicinal chemistry structure activity relationships (SAR), installation of various groups at the 3–6-positions of the piperidine led to modest enhancement in receptor selectivity. Compounds were profiled *in vivo* for plasma and brain levels in order to identify candidates suitable for efficacy in a model of drug addiction.

Orexins/hypocretins (Orexin-A and B, or hypocretin-1 and 2), simultaneously discovered by two groups in 1998, are a pair of hypothalamic neuropeptides with substantial amino acid identities.^{1, 2} Though produced by a small population of neurons in the posterior and lateral hypothalamus (LH), orexins exert multiple functions particularly in areas related to energy homeostasis, sleep, arousal and brain reward when binding to their respective G-protein coupled receptors OX₁ and OX₂ (Hcr₁ and Hcr₂ receptors, respectively). Due to the pharmacological potential from the modulation of these receptors, a significant effort has been poured into this area of research mostly in the area of insomnia.^{3–9} The most advanced candidate Almorexant (a dual OX₁–OX₂ antagonist) from Actelion/GlaxoSmithKline(GSK) for the treatment of sleep disorders was dropped in late stage clinical development for safety concerns. Merck is also advancing a dual OX₁–OX₂ antagonist (Suvorexant) for sleep and is currently in PhIII.¹⁰ Both of these drug candidates are dual OX₁–OX₂ antagonists with roughly equal potency on each receptor.

A growing body of evidence indicates that OX₁ receptors may play an important role in the behavioral adaptations associated with chronic drug exposure that may contribute to the development of addiction. Recently, compelling evidence has shown that activation of OX₁ in the brain plays a critical role in reward-seeking, drug relapse and addiction.¹¹ Chemical activation of LH orexin neurons reinstates extinguished morphine seeking behavior in rats, an effect blocked by the selective OX₁ receptor antagonist SB-334867.¹¹ Blockade of OX₁ transmission also decreases nicotine, and alcohol self-administration and attenuates cue-induced reinstatement of extinguished nicotine, alcohol and cocaine seeking, and attenuates stress-induced reinstatement of extinguished cocaine and alcohol seeking.^{11–15} Injection of SB-334867 directly into the ventral tegmental area (VTA), a key brain area in drug addiction, attenuated the rewarding effects of morphine, as measured in a conditioned place

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preference (CPP) procedure and also mediated cue-induced cocaine seeking behavior.¹⁶ These data suggest that orexin receptors, particularly those in the VTA, regulate the rewarding effects of drugs of abuse and support an important role for orexin transmission in drug-seeking and drug-taking behaviors. Thus, blockade of OX₁ receptors with OX₁ selective antagonists may provide a new mechanism and a promising therapeutic treatment for a variety of addiction related disorders.

The first OX₁ selective antagonist reported in the literature was SB-334867 (Figure 1, **1**).^{17, 18} It has a reported OX₁ IC₅₀ = 40nM (Ca²⁺) and is >100-fold selective for OX₁ vs OX₂. It was developed by GSK by modification of lead compounds from high throughput screening and is widely used *in vitro* and *in vivo* for OX₁ target validation. However, the undesirable pharmacokinetic profile (t_{1/2}=0.4 h, 10% oral bioavailability) and potential for off-target activity at 5HT_{2B} and 5HT_{2C} hampered its progress beyond discovery phase.¹⁸ Recently, another group further optimized this scaffold to dial out OX₂ completely, though no data is given with regards to off-target activity or pharmacokinetics.¹⁹ Evaluation of both the primary and patent literature revealed that several orexin receptor antagonists have been developed based on a pyrrolidine or piperidine core with differentially substituted appendages at the N-1 and C-2 positions (Figure 1, **2**).⁶ When our research investigation began, there were scant reports of disubstituted piperidine antagonists (**3**). It wasn't clear if this was because ring substitution wasn't tolerated, or the chemistry simply hadn't yet advanced to this stage. We wondered if ring substitution could alter the chair topography of the piperidine ring, and subsequently affect selectivity for OX₁ vs OX₂. Recently, a patent application from Rottapharm S.P.A. published validating just such a strategy.²⁰ Herein we report the results of our investigation into substituted piperidines as orexin receptor antagonists.

To get a baseline and establish controls for comparison, we initially synthesized a variety of differentially substituted piperidines wherein we modified the N-1 acyl group and the substitution at C-2. These molecules have been reported mostly in the patent literature and contain little *in vitro* functional data.^{21–24} Compounds were synthesized as described in the applications and screened in a functional cell-based assay using CHO cells stably expressing OX₁ (or OX₂ as a counterscreen) which is based on OX_A-stimulated intracellular calcium mobilization using a combination of calcium-sensitive dyes and a fluorescent imaging plate reader (FLIPR) (Table 1).²⁵

These 2-substituted piperidines bearing a variety of heterocycles are potent dual OX₁–OX₂ receptor antagonists (Table 1). The most popular amides from the patent literature were chosen for N-1 substitution. The 2-biphenyl aryl amide and both phenyl-substituted thiazole isomers provided potent compounds (**4–9**). The 8-quinoline and 4-benzofuran amides, as well as the trifluoromethylpyridine anilines were chosen as C-2 substitutions. Compound **7** is the racemic version of SB649868, GSK's initial dual OX₁–OX₂ antagonist that advanced as far as PhII clinical trials before being pulled for preclinical toxicology findings.²⁶

To probe the effects of additional substitution, we introduced substituents at positions 3–6 of the piperidine ring using the chemistry highlighted in Schemes 1–3.

We commenced the first round of SAR by introduction of substitution at the 3-position of the piperidine ring. This required access to 3-substituted 2-cyanopyridines, which were fairly easy to secure (**10**). Stepwise reduction and protection of the primary amine at C-2 followed by saturation of the pyridine ring using Nishimura's catalyst afforded the 2,3-disubstituted piperidines (**12**). Compounds were almost exclusively 2,3-cis-oriented.^{27–29} Standard manipulations afforded final products (Table 2). Synthesis of the 2,3-trans analogs was achieved from a common intermediate through a step-wise reduction of the pyridine

ring after activation, followed by hydrogenation of the N-benzyl tetrahydropiperidine (**16**) to the deprotected piperidine (**17**). We were pleased to find that 3-substitution was indeed tolerated as most compounds exhibited good *in vitro* potency (Table 2).

A pair of bis-amide analogs showed almost 100-fold selectivity for OX₁ vs OX₂ (**19** and **23**) in the calcium flux assay, however, this trend was difficult to track as many analogs showed a more modest 10–20-fold selectivity. In the bis-amides, the bulkier CF₃ group provided no advantage over a standard methyl group (**25** vs **20**), nor did it appear that cis or trans methyl substitution made a difference (**27** vs **26**) in this bisamide series. Interestingly, a 3-methyl substituted mono amide with an aminobenzoxazole in the side chain afforded a compound with an enhanced selectivity for OX₁ vs OX₂ (**28**). More analogs of this type are currently being synthesized to see if OX₂ activity can be completely abolished from this series.

2,4-Disubstituted piperidine analogs were synthesized following standard literature chemistry as described in Scheme 2. Only a few analogs were made, as initial results weren't promising with regards to selectivity (Table 3). It's not clear how a simple fluorine substitution for hydrogen (**30** vs **4**) could result in an almost 50-fold drop in activity, but these results encouraged us to move on and to look at the C-5 and C-6 positions. In fact, all 2,4-disubstituted derivatives synthesized were less potent than their corresponding 2-substituted analogs.

2,5-Disubstituted compounds could be made following chemistry as outlined in Scheme 1, but we also developed an alternate synthetic route, as we desired to expand the range of groups at this position on the ring. To that end, we synthesized 5-ketopipicolinic acid (**33**) as a starting material as described in the literature.³⁰ Chemistry as outlined in Scheme 3 led to 2,5-disubstituted analogs (Table 4). Compounds resulting from reductive amination of the 5-ketopiperidine (**40**) gave mostly trans-2,5-disubstituted analogs resulting from axial delivery of hydride in the reduction step.³¹

Compounds in this series also tolerated substitution of the piperidine ring, and exhibited good *in vitro* activity (Table 4). There didn't appear to be much benefit, however, with regards to selectivity towards OX₁ vs OX₂. Some compounds showed a modest 5–10-fold selectivity for OX₁ (**43,44,46**), whereas others showed no selectivity at all.

Finally, the effect of installing a group at C-6 was examined (Table 5). Compounds were again synthesized following the general protocol as described in Scheme 1. Following saturation of the pyridine ring, a single diastereomer was produced as indicated by ¹H-NMR analysis (also single peak by reverse-phase analytical HPLC). It is presumed to be cis based on literature precedent.^{27, 32} No effort was made to synthesize the 2,6-trans isomer. A 6-methyl group was tolerated and imparted a modest 10-fold selectivity for OX₁ vs OX₂ (**48–51**). Synthesis of bulkier 6-substituted analogs is still on-going to see if more selectivity can be derived.

While chemical SAR has been on-going, in parallel, we have been routinely profiling compounds through drug metabolism in order to identify a compound suitable for *in vivo* use. We have been profiling compounds in microsomal stability, as well as looking for plasma and brain exposure in mice following IP dosing. Data is compiled in Table 6.

The microsomal stability of most compounds examined in all three species (mouse, rat, human) was poor. Compounds were metabolized quite quickly. Even the racemate of GSK's PhII compound (**7**) was rapidly metabolized in microsomes. When compounds were dosed to mice (10mg/kg, IP), there was little drug in plasma at t=1h, and even less in the brain.³³ Hence, the dose was increased to 50 mg/kg in an effort to increase plasma and brain levels

that would support a compound's use *in vivo*. Data from these higher dosing experiments is shown in Table 6. For several analogs, plasma and brain levels at t=1h were quite high. In these cases, it is possible the metabolic mechanisms leading to low drug levels are being overwhelmed. However, this still does not explain the disconnect between microsomal stability and the fact that the enantiomer of **7** advanced into man. Nonetheless, these plasma and brain levels are likely sufficient to provide receptor coverage within the parameters of the *in vivo* study. Given the enhanced OX₁ selectivity of **23** and **28**, as well as their favorable drug plasma and brain levels at t=1h, these compounds may be useful *in vivo* candidates. Results of their *in vivo* efficacy in a model of drug addiction will be reported elsewhere. Table 6. *In vitro* and *in vivo* parameters of selected orexin antagonists.

In summary, we have described a series of orexin receptor antagonists based on substituted piperidines. SAR focusing on the 3-position revealed that it is possible to synthesize compounds with enhanced selectivity for the OX₁ receptor relative to OX₂. Substitution at other piperidine positions afforded potent compounds, with reduced or no selectivity for OX₁ vs OX₂. Further exploration of substitutions at the piperidine 3-position are still ongoing. Evaluation of compounds such as **23** and **28** in an animal model of drug addiction will be reported in due course.

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1OX₁ pK_b 7.4 **2**

n=0,1

3

Fig. 1.
Orexin Antagonist Scaffolds

Scheme 1.

Synthesis of 2,3- and 2,6-disubstituted piperidine orexin receptor antagonists.

Reagents and conditions: (a) $ZnCN_2$, $Pd(PPh_3)_4$; (b) $SOCl_2$, NH_4OH ; Tf_2O , DCM; (c) H_2 , Pd/C , $HOAc$; (d) $(BOC)_2O$, Et_3N , DCM; (e) H_2 , $HOAc$, Nishimura's catalyst; (f) Ar^1CO_2H , HATU, DIEA, DCM; (g) TFA, DCM; (h) Ar^2CO_2H , HATU, DIEA, DCM; (i) Ar^2Br , xantphos, CS_2CO_3 , DMAC; (j) 1. $BnBr$, CH_3CN ; 2. $NaBH_4$, CH_3OH ; (k) $Pd(OH)_2$, H_2 , CH_3OH .

Scheme 2.

Synthesis of 2,4-disubstituted piperidine orexin receptor antagonists.

Reagents and conditions: (a) OHCCO_2H , CH_3CN , 4A sieves; (b) H_2 , Pd/C, MeOH; (c) $\text{Ar}^1\text{CO}_2\text{H}$, HATU, DIEA, DCM; (d) For $\text{R} = \text{OMe}$, MeI, NaH, DMF; (e) LiBH_4 , THF; (f) Phthalimide, DIAD, Ph_3P , THF; (g) N_2H_4 , MeOH; (h) $\text{Ar}^2\text{CO}_2\text{H}$, HATU, DIEA, DMAC; (i) DAST, DCM; (j) Dess-Martin periodinane, DCM; (k) Deoxo-Fluor, DCM.

Scheme 3.

Synthesis of 2,5-disubstituted piperidines.

Reagents and conditions: (a) SOCl_2 , EtOH; (b) $\text{Ar}^1\text{CO}_2\text{H}$, HATU, DIEA, DMAC; (c) TFA, DCM; (d) Deoxo-Fluor, DCM; (e) LiBH_4 , THF; (f) Phthalimide, DIAD, Ph_3P , THF; (g) N_2H_4 , CH_3OH ; (h) $\text{Ar}^2\text{CO}_2\text{H}$, HATU, DIEA, DMAC; (i) Ar^2Br , $\text{Pd}(\text{OAc})_2$, xantphos, Cs_2CO_3 ; (j) NaBH_4 , CH_3OH ; (k) RNH_2 , $\text{NaBH}(\text{OAc})_3$, DCM.

Table 1

2-Substituted piperidine (R=H) orexin receptor antagonists based on **2**.

#	Ar ¹	Ar ²	X	OX ₁ IC ₅₀ nM ^a	OX ₂ IC ₅₀ nM ^a
4			CO	3	2
5			CO	5	23
6			CO	4	4
7			CO	<1	<1
8			CO	6	8
9			-	13	8

^aValues are means of at least three experiments.

Table 2

2,3-Disubstituted piperidine orexin receptor antagonists.

#	Ar ¹	Ar ²	X	R	OX ₁ IC ₅₀ nM ^a	OX ₂ IC ₅₀ nM ^a
19			CO	Me (cis)	8	658
20			CO	Me (cis)	0.8	8.7
21			CO	Me (cis)	15	221
22			CO	CF ₃ (cis)	9	40
23			CO	Me (cis)	145	>10000
24			CO	Me (cis)	7	50
25			CO	CF ₃ (cis)	10	40
26			CO	Me (cis)	2	58

#	Ar ¹	Ar ²	X	R	OX ₁ IC ₅₀ nM ^a	OX ₂ IC ₅₀ nM ^a
27			CO	Me (trans)	2	82
28			-	Me (cis)	6	447

^aValues are means of at least three experiments.

Table 3

2,4-Disubstituted piperidine orexin receptor antagonists.

#	Ar ¹	Ar ²	R	OX ₁ IC ₅₀ nM ^a	OX ₂ IC ₅₀ nM ^a
29			4-OH (cis)	40	62
30			4-F (trans)	146	541
31			4,4-diF	>2000 ^b	NT

#	Ar ¹	Ar ²	R	OX ₁ IC ₅₀ nM ^a	OX ₂ IC ₅₀ nM ^a
32			4-OMe (cis)	390	NT

^aValues are means of at least three experiments;

^bNT = not tested.

Table 4

2,5-Disubstituted piperidine orexin receptor antagonists.

#	Ar ¹	Ar ²	X	R	OX ₁ IC ₅₀ nM ^a	OX ₂ IC ₅₀ nM ^a
42			CO	F, F	2	2
43			CO	NH(CH ₂) ₂ OH	27	137
44			CO	OH	2	13
45			CO	F	1	<1
46			CO	NH ₂	121	2000
47			-	F	7	7

^aValues are means of at least three experiments.

Table 5

2,6-Diubstituted piperidine orexin receptor antagonists.

#	Ar ¹	Ar ²	X	OX ₁ IC ₅₀ nM ^a	OX ₂ IC ₅₀ nM ^a
48			CO	0.8	8
49			CO	12	151
50			-	14	96
51			-	6	125

^aValues are means of at least three experiments.

Table 6*In vitro* and *in vivo* parameters of selected orexin antagonists.

<i><u>a</u></i> Microsome stability		<i><u>b</u></i> Mouse <i>in vivo</i>		
#	t _{1/2} (min)	c _[plasma] [_{brain}] (μM)		d _{b.p.} (%)
5	1/ ^c NT/NT	1.5	0.06	4
7	1/1/1	33.7	18.7	55
9	NT/2/3	8.6	17.9	208
21	1/1/1	12.5	3	24
22	1/3/3	12.8	7.8	61
23	NT/NT/NT	20.8	10.1	49
28	1/1/1	1.6	0.9	56
45	1/7/1	4.6	0.5	11
46	7/15/52	27.6	1.4	5
49	4/6/5	0.3	0.1	33
50	1/3/2	12.4	14.3	115
51	1/1/1	3	1	33

^a in mouse/rat/human liver microsomes;^b doses 50mg/kg IP;^c drug levels at 1h timepoint;^d brain penetration;^e NT = not tested.