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Identification of MK-8133: An orexin-2 selective receptor antagonist with favorable development properties

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ABSTRACT

Antagonism of orexin receptors has shown clinical efficacy as a novel paradigm for the treatment of insomnia and related disorders. Herein, molecules related to the dual orexin receptor antagonist filorexant were transformed into compounds that were selective for the OX_2R subtype. Judicious selection of the substituents on the pyridine ring and benzamide groups led to **6b**; which was highly potent, OX_2R selective, and exhibited excellent development properties.

Introduction

Orexin neuropeptides and their receptors have a critical role in maintaining wakefulness thus generating significant interest in targeting the orexin receptors for sleep and wake disorders. These excitatory neuropeptides, named hypocretin[1] and orexin (most commonly used),[2] have been characterized via genetic and biochemical approaches.[3] Orexinergic neurons localized in the lateral hypothalamus generate orexin neuropeptides (OX-A and OX-B), and signal via two G-protein-coupled receptors (GPCR's), Orexin Receptor 1 (OX_1R) and Orexin Receptor 2 (OX_2R).[3]

Orexin receptors are dispersed in areas of the brain that direct wake, vigilance and reward seeking behaviors. During the normal wake period, orexin signaling is most active and falls nearly silent during the sleep period.[4–6] Numerous companies have described dual OX_1R and OX_2R orexin receptor antagonists (DORAs), or selective orexin receptor antagonists (SORAs), and a few have advanced through late stage clinical development.[7–10] Numerous reviews are available in this context.[11–16]

Recently, Merck received FDA approval of the first DORA suvorexant (Belsomra®) for the treatment of insomnia (Fig. 1). Another DORA, filorexant, was discovered and advanced into clinical development by the same discovery team.[17] In addition to DORAs, novel tri-aryl OX_2R Selective Orexin Receptor Antagonists (SORAs) have been described by Merck.[18–20]

Some limited SAR data has been reported for filorexant at the carboxamide, *O*-methylene linkage, and fluoro-pyridine regions of the molecule, but all within the framework of DORAs.[17,21] More recently, we have shown that elimination of the methylene linking unit and replacement of the pyridine with quinoline heterocycles has led to OX_2R SORAs within the filorexant chemotype (Fig. 2).[22] For example, compound **1**, lacking the methylene linkage and possessing a quinoline heterocycle, was found to be a very potent and highly OX_2R SORA (FLIPR IC_{50}'s: OX_1R>10,000 nM; OX_2R = 47 nM). The related isoquinoline **2** was found to be a DORA (FLIPR IC_{50}'s: OX_1R = 25 nM; OX_2R = 36 nM). Genetic studies suggested that the OX_2R rodent knockout has a stronger sleep phenotype relative to OX_1R and there is an active discussion in the field whether an OX_2R SORA would have a potential advantage over a DORA.[23] Herein, we describe the surprising SAR switch of the DORA **2** into a 2-substituted pyridine OX_2R SORA, and

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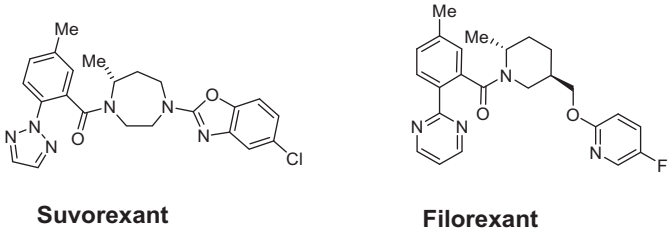


Figure 1. MRL clinical DORAs.

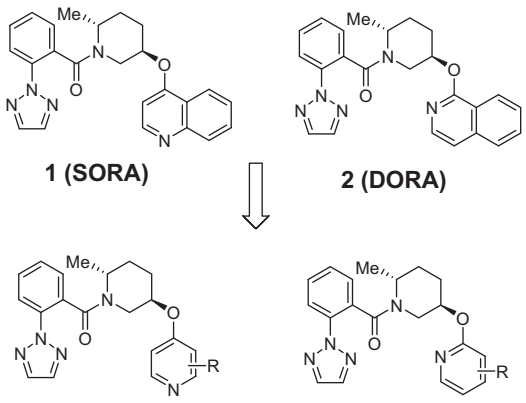


Figure 2. Evolution to piperidine SORAs.

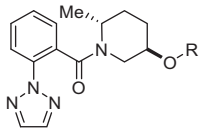
subsequent optimal carboxamide selection leading to the identification of SORA clinical candidate MK-8133.

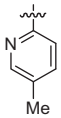
Compounds prepared herein were evaluated for OX_2R and OX_1R binding affinity (K_i) through in vitro radioligand competition binding assays using membranes from CHO-K1 cells overexpressing the human orexin receptors.[21] Moreover, cell-based functional FLIPR (fluorometric imaging plate reader) assays in which Ca^{2+} fluxes were measured as functional determinants of orexin receptor antagonist activities, were also conducted as the readout of choice for determining receptor subtype selectivity between human OX_2R and OX_1R.[24]

In order to get a sense of the potential for the 2-substituted pyridines to exhibit orexin antagonist activity and potential OX_2R selectivity, a simple methyl scan of the four positions on the pyridine ring was conducted (Table 1). Compounds **3** and **4** with substitution at the 5- and 6-positions, maintained reasonable binding (K_i's = 7.6–182 nM) and functional activity in a FLIPR assay (IC_{50} = 9–745 nM), with a modest preference for OX_2R over OX_1R (16- to 23-fold). This served as the first indication that SORAs could be generated from DORA lead **2**. Moreover, the 4-methyl pyridine **5b** showed high affinity at OX_2R (K_i = 2.6 nM) and was also 49-fold selective for OX_2R over OX_1R with excellent potency (OX_2R IC_{50} = 16 nM). Lastly, the 3-methyl pyridine **6** showed very weak affinity for both receptor subtypes. Although the selectivity of **5b** was below a preferred target of >100× for OX_2R over OX_1R, it was promising that a quinolone ring system was not required to generate a SORA and an encouraging sign that selectivity could be discovered from isoquinoline **2** with a relatively modest change.

Having observed an OX_2R preference with substitution at the 4-position, replacements for the methyl group in **5b** were examined to measure effects on potency and selectivity (Table 2). Appropriate substitutions on the pyridine proved critical as the simple pyridine (**5a**) lost almost a thousand-fold in binding affinity. Larger alkyl groups such as ethyl (**5c**), trifluoromethyl (**5d**), and alkynyl (**5e**) increased affinity and functional antagonism, but had attenuated selectivity. Nitrile **5f** exhibited very similar functional potency to the isoelectronic alkyne **5e**, but with exceptional preference (~300-fold) for OX_2R. To follow this up, additional electron-withdrawing groups were examined. Ester **5g** showed somewhat reduced affinity relative to the nitrile, but 82-fold subtype selectivity was notable. The di-methyl amide also exhibited high preference for OX_2R (>100-fold), but was considerably weaker (OX_2R IC_{50} = 95 nM) than the nitrile or ester. Halogens (**5i**–**l**) provided potent antagonists with high affinity, especially for the larger nuclei, but selectivity remained in the 37–68-fold range; similar to that seen for methyl. Additional heteroatom containing groups such as methoxy (**5m**) and thiomethyl (**5n**) provided potent, high affinity antagonists, but selectivity was still quite modest.

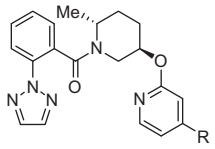
Table 1
Pyridine SAR[a]



Compd	R	OX2R BIND (K_i, nM)	OX1R BIND (K_i, nM)	OX2R FLIPR (IC_{50}, nM)	OX1R FLIPR (IC_{50}, nM)	FLIPR ratio (OX1R/2R)
3		7.6	12	33	745	23×
4		2.6	37	9	142	16×
5b		2.6	166	16	788	49×
6		621	4756	ND	ND	ND

[a] Values represent the average of $n \geqslant 2$ experiments.

Table 2
4-Pyridyl SAR[a]



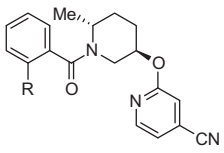
Compd	R	OX2R BIND (K_i, nM)	OX1R BIND (K_i, nM)	OX2R FLIPR (IC_{50}, nM)	OX1R FLIPR (IC_{50}, nM)	FLIPR ratio (OX1R/2R)
5a	H	2400	14,000	nd	nd	—
5b	Me	2.6	170	16	790	49×
5c	Et	0.6	57	11	310	28×
5d	CF_3	0.2	64	18	370	21×
5e	C≡CH	0.6	49	10	240	23×
5f	C≡N	1.6	830	13	3800	293×
5g	CO_2Me	3.9	310	22	1800	82×
5h	$CON(Me)_2$	6.5	470	95	>10,000	>105×
5i	F	3.9	430	34	2300	68×
5j	Cl	1.4	120	11	550	51×
5k	Br	1.8	130	10	380	37×
5l	I	0.4	59	7.2	410	57×
5m	OMe	1.3	140	13	620	49×
5n	SMe	0.2	39	6.7	110	16×
5o	SO_2Me	0.9	350	16	510	33×
5p	$N(Me)_2$	4.5	1400	130	1500	12×
5q	Ph	3.8	360	45	2400	54×

[a] Values represent the average of $n \geqslant 2$ experiments.

Methylsulfone (**5o**) gave a very similar profile, but the dimethylamine lost substantial activity in the FLIPR assay. Lastly, a lipophilic group in the form of a phenyl ring (**5q**) provided a similar preference for OX_2R relative to methyl **5b**, but ~4-fold reduced potency. Overall, the nitrile group was optimal providing for very high selectivity while maintaining good binding affinity and FLIPR potency.

To further build upon the cyanopyridine finding, a series of *ortho*-substituted benzamides were evaluated as replacements for the triazole benzamide in **5f**. In addition to functional potency, human microsomal stability and physicochemical parameters such as solubility and lipophilicity were assessed to guide further prioritization of compounds (Table 3). The parent triazole **5f** possessed a desirable low human intrinsic clearance (<16 mL/min/kg) and exhibited reasonable solubility (148 μM) at pH 7. Replacement of the triazole with a methyl oxadiazole heterocycle (**6a**) led to a slight drop in OX_2R potency, although other desirable properties such as selectivity, microsomal stability and good solubility were maintained. A 2-pyrimidine group (**6b**), which has been utilized in the identification of DORAs such as filorexant, gave a very similar in vitro profile to the oxadiazole in terms of potency and low intrinsic clearance, but with an additional increase in solubility. As the oxadiazole heterocycle is often employed as an ester isostere, a number of esters were also

Table 3
Amide scan[a]



Compd	R	OX2R FLIPR (IC_{50}, nM)	OX1R FLIPR (IC_{50}, nM)	FLIPR ratio	Microsomal Cl (human)	Sol (pH 7)	HPLC log*D*
5f		13	3800	293×	16	148	3.0
6a		25	8400	361×	23	162	3.0
6b		28	4900	174×	17	183	2.9
6c	CO_2Me	21	~10,000	>490×	< 16	151	2.9
6d	CO_2Et	21	7100	349×	37	121	3.2
6e	CO_2iPr	38	3300	87×	nd	115	3.6
6e	$OCHF_2$	37	>10,000	>314×	43	Insol.	Insol.
6f	CH_2CF_3	32	>10,000	>312×	132	95	3.6

[a] Values represent the average of $n \geqslant 2$ experiments.

examined. Methyl (**6c**) and ethyl (**6d**) esters were quite similar with respect to FLIPR potency and selectivity, although the ethyl had higher intrinsic clearance. The larger isopropyl ester **6e** led to a decrease in functional antagonism and erosion of OX_2R preference relative to methyl and ethyl. While the methyl ester did show low microsomal clearance, it was anticipated that plasma stability would be an issue, and **6c** did prove to be unstable in both rat and human plasma. Lastly, difluoromethyl ether **6e** and trifluoroethyl **6f** showed good FLIPR potency and high selectivity, but were the most lipophilic (HPLC log$D$ = 3.6) amongst the compounds in Table 3. This increase in lipophilicity led to higher intrinsic clearance and significantly lower solubility for **6e** and **6f**.

Given the promising in vitro profiles noted in Table 3, compounds **5f**, **6a**, and **6b** were taken on for further characterization. Pharmacokinetic parameters of these three compounds were determined in rat and dog after intravenous and oral administration. Amongst the group, triazole **5f** exhibited the lowest oral bioavailability (<20%) in both species, and was moderate clearance in rat and high clearance in dog. Oxadiazole **6a** and pyrimidine **6b** demonstrated low to moderate plasma clearance and high oral bioavailability in dog (>50%). In rat, pyrimidine **6b** exhibited moderate clearance and an oral bioavailability of 80%. Oxadiazole **6a** also demonstrated moderate clearance in rat, but had an oral bioavailability of only 26% (Table 4).

Pyrimidine **6b** emerged as a leading compound and was selected for additional in vitro and in vivo characterization. This compound was predicted to have low human clearance and good bioavailability. The level of plasma protein binding for **6b** varied significantly across species. At a concentration of 1 μM, the unbound fraction in human, rat, dog, and monkey plasma was 2.8%, 7.6%, 16.6%, and 23.9%, respectively. In terms of achieving adequate drug levels in the CNS, **6b** exhibited high passive permeability in LLC-PK1 cells (33×10^6 cm/s) and was a weak substrate for rat P-gp efflux (ER = 2.3) and a non-substrate for human P-gp efflux (ER = 0.7).[25] In rats, the CSF to plasma concentration ratio (0.1) was similar to the unbound fraction in plasma, indicating that P-gp has apparently little effect on the brain distribution of **6b** in this species. Furthermore, this compound was not a CYP (cytochrome P450) inhibitor or inducer, showing minimal potential for drug–drug interactions. Compound **6b** had no appreciable off-target affinities when measured against a panel of 115 biological targets (Ricerca) at a concentration of 10 μM. Lastly, pyrimidine **6b**, which showed excellent pharmaceutical properties as a crystalline form suitable for development, was identified with solubility at pH 7.4 of 0.25 mg/mL; exceptional for compounds of this class.

Compound **6b** was further characterized in vivo for its ability to attenuate arousal The resulting sleep architecture was measured in ambulatory mice, rats and dogs implanted with radio-telemetry transmitters measuring electrocorticogram (ECoG) and electromyogram (EMG) activity as previously described.[26] When dosed to mice at 30 mg/kg (P.O. in 20% Vit. E TPGS), **6b** significantly attenuated active wake while increasing slow wave sleep (SWS) with no associated effect on rapid eye movement (REM) sleep (Fig. 3). No significant effects of the compound at this high dose were observed in mice harboring with a targeted disruption of the *Hcrtr2* gene encoding OX_2R, demonstrating that these effects were selectively mediated through its target receptor. In rats, dose dependent decreases in active wake were seen in the 2 h following treatment with 1 and 3 mg/kg of the compound, and were associated with significant increases in both SWS and REM sleep. In beagles, substantially lower doses, 0.01 and 0.05 mg/kg, were efficacious in promoting sleep, likely attributable to increased free fraction and central exposure in these animals. In this case, dose dependent reductions in active wake relative to the vehicle condition were accompanied by increases in non-REM NREM I and NREM II sleep, the latter characterized by a greater preponderance of delta sleep. There was a trend toward increased REM sleep that did reach significance following treatment with either dose in dogs.[27]

The synthetic route used to access target molecules detailed in this manuscript is shown in Scheme 1. Hydrogenation of **7** provides a 4:1 mixture of *trans*:*cis* piperidines. This is a modified route from what has been described previously[17,28] in that the minor *cis* product was used in our previous disclosure to access targets via a Mitsunobu inversion. In this work, after SFC separation of **9** to obtain the desired *trans* (2*R*, 5*S*) enantiomer **10**, a protecting group

Table 4
Rat and dog PK data

#	Rat F (%)[a]	Rat $t_{1/2}$ (h) [a]	Rat Cl [a]	Rat V_{dss}	Dog F (%)[a]	Dog $t_{1/2}$ (h) [a]	Dog Cl [a]	Dog V_{dss}
5f	17	1.7	18	1.7	13	1.1	27	1.5
6a	26	1.3	30	1.3	54	1.5	4.6	0.54
6b	80	4.3	37	1.3	53	0.8	15	0.97

[a] *F*% oral bioavailability, half-life is represented in hours, Cl in mL/min/kg. Wistar Han rats (n = 2). Oral dose = 10 mg/kg in PEG400:Tween80/water 40:10:50, IV dose = 2 mg/kg in DMSO/PEG400/water 20:60:20.

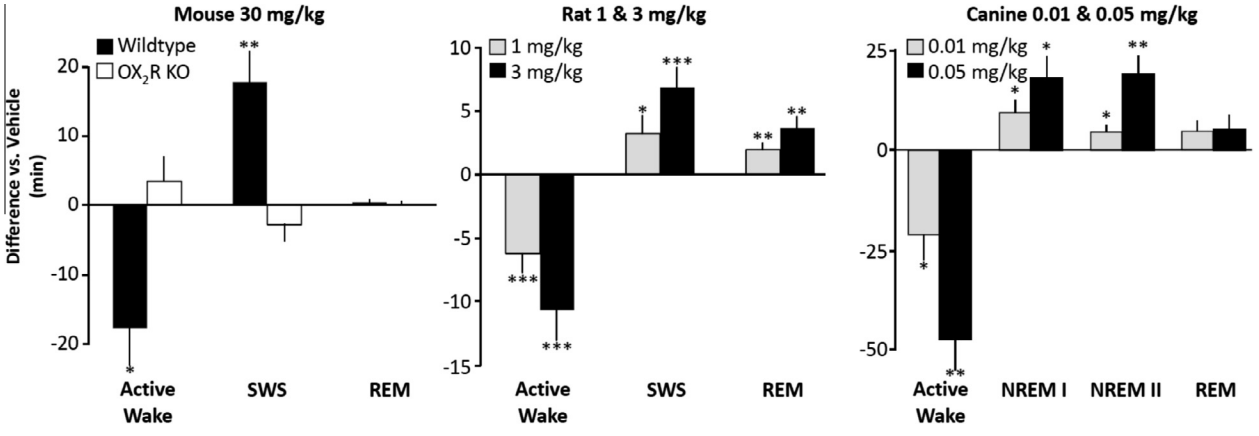
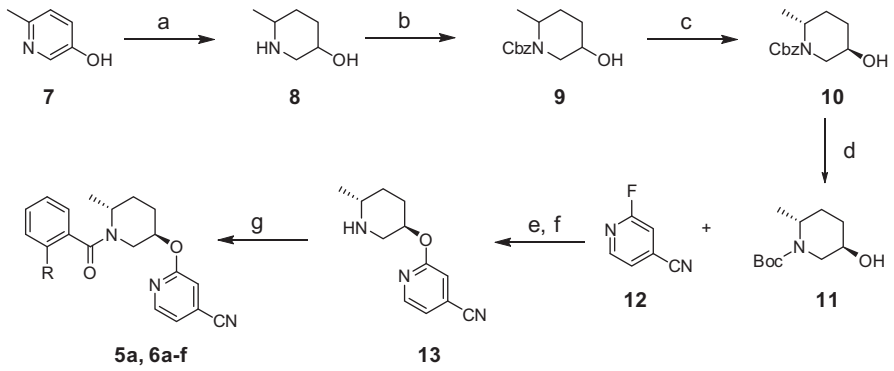


Figure 3. Effects of compound **6b** on mean time in active wake, SWS, and REM sleep in mice and rats, and in active wake, NREM I, NREM II, and REM sleep 1 h following administration. Vehicle (20% Vitamin E TPGS, po) and compound **6b** (30 mg/kg mouse; 1 & 3 mg/kg rat; 0.01 & 0.05 mg/kg canine) was administered in a balanced cross-over design such that each subject received both vehicle and drug treatments (5 days of consecutive treatments for mouse and dogs; 3 days for rat). Mean within-subject change relative to vehicle is shown (N = 7 [mouse WT], N = 6 [OX_2R KO]; N = 16 [rat], N = 6 [canine]); $^*p$<0.05, $^{**}p$<0.01, $^{***}p$<0.001, paired within subject t test versus vehicle.



Scheme 1. Reagents and conditions: (a) H_2, PtO_2, MeOH, HCl, 55 °C; (b) CbzCl, TEA, CH_2Cl_2; (c) chiral SFC; (d) Boc_2O, H_2, Pd/C (10%), EtOAc; (e) NaH, DMSO, rt; (f) HCl, dioxane, 0 °C; (g) T_3P, DIEA, DMF.

switch was executed to afford **11**. Subsequent substitution reactions were carried out as exemplified with 2-fluoro-5-cyanopyridine **12**, followed by removal of the Boc protecting group to afford **13**. Lastly, coupling of amine **13** with the appropriate carboxylic acid using the reagent T3P provided target compounds for evaluation.

In summary, we have described the alteration of the isoquinoline ring in piperidine ether DORA **2** into a 2-pyridyl OX_2R selective series of orexin antagonists. It was found that after excision of the phenyl group of the isoquinoline ring, the position where a substituent was placed on the 2-pyridyl ring played a key role in modulating DORA versus SORA selectivity. The critical discovery was that a cyano group at the 4-position of the pyridine ring resulted not only in potent functional antagonism, but provided the highest OX_2R selectivity amongst all the groups examined. Further SAR modification of the aryl carboxamide led to highly potent SORA pyrimidine **6b** with excellent development properties, now identified as MK-8133. MK-8133 proved to highly efficacious in rodent polysomnography sleep studies as well as non-rodent species and those studies will be the subject of future reports.

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