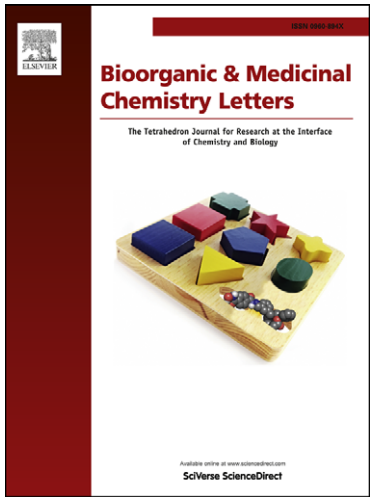

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Discovery, synthesis, selectivity modulation and DMPK characterization of 5-azaspiro[2.4]heptanes as potent orexin receptor antagonists.

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ABSTRACT

Starting from a orexin 1 receptor selective antagonist 4,4-disubstituted piperidine series a novel potent 5-azaspiro[2.4]heptane dual orexin 1 and orexin 2 receptor antagonist class has been discovered. SAR and Pharmacokinetic optimization of this series is herein disclosed. Lead compound **15** exhibits potent activity against orexin 1 and orexin 2 receptors along with low cytochrome P450 inhibition potential, good brain penetration and oral bioavailability in rats.

Orexins, also known as hypocretins, are hypothalamic neuropeptides secreted by a discrete number of neurons in the lateral and posterior hypothalamus. The orexin system is highly conserved across species and it is based on two hypothalamic peptides, orexin A (OXA) and orexin B (OXB), arising from a common 130 amino acids precursor protein named prepro-orexin peptide. Discovered in 1998 by independent research groups[1], the orexin peptides were found to bind at two previously identified orphan G-protein coupled receptors, which following this discovery were classified as orexin 1 (OX_1) and orexin 2 (OX_2) receptors. These receptors are widely distributed, though differentially, in the brain and periphery. In the central nervous system (CNS) OX_1 receptors are found mainly in the locus coeruleus, frontal cortex, ventral tegmental area and lateral hypothalamus while OX_2 receptors are mainly located into tuberomammillary nucleus[2,3,4]. Outside the central nervous system (CNS) orexin receptors are distributed in the gut, in adipose brown tissue and in pancreatic islets[5]. As shown in many studies, OXA binds with similar affinity to OX_1 and OX_2, whereas OXB displays higher affinity vs. OX_2. Neuronal OX_1 and OX_2 display a common signal transduction mechanism based on the activation of Gq proteins followed by the modulation of several ion channel activities to enhance synaptic transmission. Considerable evidences have been accumulated in literature regarding the utility of antagonizing the orexin receptors. Selective blockade of central OX_1 receptors has been reported to modulate addiction and craving to rewarding drugs such as alcohol, cocaine and morphine[6]. The modulation of binge eating episodes, induced by highly palatable food, has been recently observed in rats by using a centrally acting OX_1 antagonist[7]. Selective OX_1 receptor antagonists (SORA) also have been shown to be potentially useful in managing other disorders like

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diabetes[8] or post-menopausal syndrome[9]. However no SORA reached the clinical stage so far to validate the aforementioned hypothesis, most probably because of the poor drug likeness of the tools identified so far (among which the widely used SB-334867 and GSK1059865[10], **Figure 1**). OXA has a central pro-arousal effect in several species[11] and for this reason dual OX_1 and OX_2 receptor antagonists (DORA) have been intensively studied to identify novel hypnotic agents. Almorexant[12,13], Suvorexant[14] and SB-649868[15] DORAs (**Figure 1**) achieved clinical proof of concept, being able to enhance sleep duration and reduce latency to fall asleep in patients. Remarkably, these clinical endpoints achievement were obtained without the side effects profile typical of benzodiazepines and Z-drugs (the current clinical gold standards in insomnia) such as motor impairments, next day hangover, potentiation of alcohol effects and memory impairment. Recently, the use of DORA has been associated to the potential treatment of Alzheimer disease, by modulating the level of amyloid αβ42 filaments into the brain[16]. This discovery is paving the way to the use of the DORA class in the poorly treated neurodegenerative CNS disorders, where the unmet clinical need is extremely high.

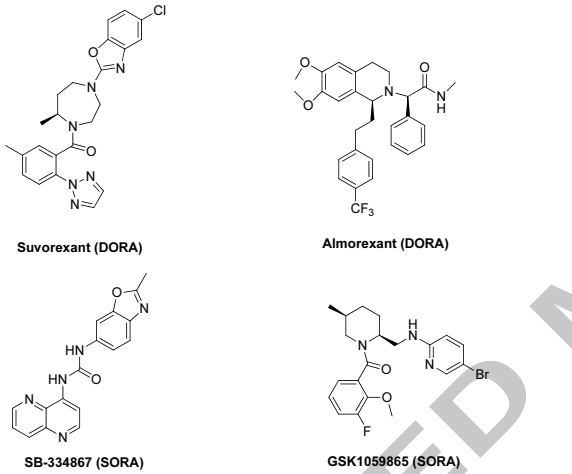


Figure 1. Representative examples of SORA and DORA antagonists.

We have been recently engaged[17] in the orexin antagonists arena and we have identified a novel 6-azaspiro[2.5]octan-6-yl SORA drug-like series. We then decided to expand the exploration of this series by contracting the core six membered piperidine ring into a five membered pyrrolidine ring while keeping the distinctive cyclopropane spiro-ring system at the same relative position with respect to the nitrogen carrying the amide bond (**Figure 2**). We in fact believed that the distinctive cyclopropane spiro-ring system was an important feature for modulating the selectivity among the orexin receptors. We also decided to keep the same absolute configuration of the chiral center (2-S) in the novel series. No obvious clues were reported in literature regarding the impact of this transformation into the SAR against the OX_1 and OX_2 receptors.

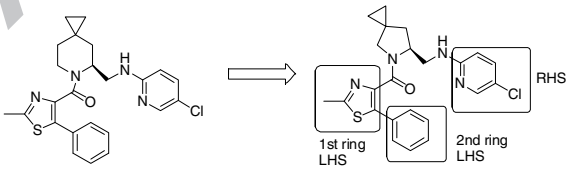
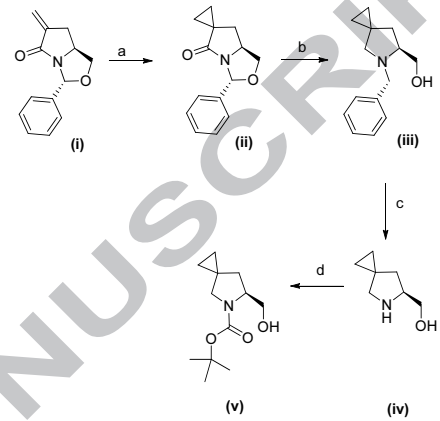


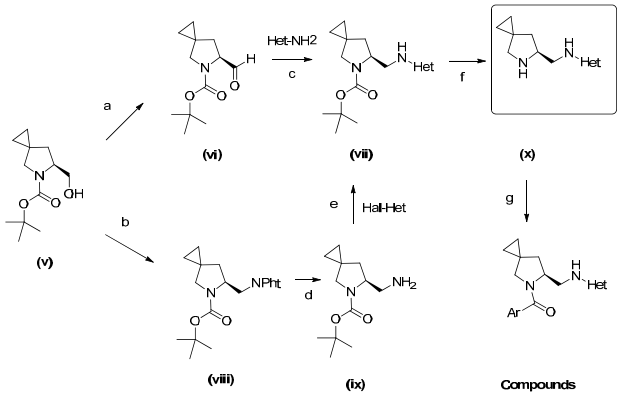
Figure 2. Planned exploration of our SORA series.

The new 6-azaspiro[2.5]octane scaffold core could be synthesized (**Scheme 1**) starting from the known[18] (3R,7aS)-6-Methylene-3-phenyl-tetrahydro-pyrrolo[1,2-c]oxazol-5-one **(i)** which was converted to the cyclopropane intermediate **(ii)** by Corey's reagent in 41% yield; reduction of this lactam by $LiAlH_4$ in THF at reflux gave the amino-alcohol derivative **(iii)** in 74% yield. Pyrrolidine **(iv)** was then prepared by hydrogenation of **(iii)** over Pd/C. Protection of the cyclic amine moiety with boc anhydride gave the key alcohol intermediate **(v)** in 82% yield. Intermediate **(v)** was then used in two alternative synthetic pathways (**Scheme 2**) leading to advanced intermediates **(x)**, which were the immediate precursors of the compounds to screen against orexin receptors. In particular, the oxidation of alcohol **(v)** was accomplished by using TEMPO/BAIB procedure[19] in 82% yield followed by a reductive amination with the desired amino heterocycle and $Na(OAc)_3BH$, usually in DCE at room temperature to get intermediates **(vii)**.



Scheme 1. Synthesis of (S)-tert-butyl 6-(hydroxymethyl)-5-azaspiro[2.4]heptane-5-carboxylate, key intermediate **(v).** Reagents and conditions: a) DMF, NaH, trimethylsulphoxonium iodide, r.t., 41% yield. b) THF, $LiAlH_4$, reflux, 74% yield c) H_2, Pd/c (10%), EtOAc/AcOH, r.t., quant. d) H_2O, NaOH, $(Boc)_2O$, 82% yield.

Alternatively, when reductive aminations on aldehyde **(vi)** were problematic, due to the poor nucleophylicity of the amino heterocycles employed, alcohol **(v)** was transformed into its phtalimido derivative **(viii)** by Mitsunobu reaction in 97% yield; hydrazinolysis of **(viii)** gave amino derivative **(ix)** in 88% yield. Intermediate **(ix)** was then reacted with the desired halogen heterocycles by using a SnAr reaction to get the heteroaryl intermediates **(vii).** These were transformed in the advanced intermediates **(x) by** removing the Boc group with TFA in DCM) (**Scheme 2**).

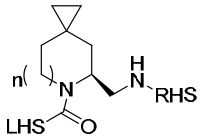


Scheme 2. Synthesis of compounds **2**, **4**, **6** and **7-32.** Reagents and conditions: a) DCM, BAIB, TEMPO, 81% yield. b) Ph_3P, Phtalimide, THF, DEAD, r.t., 97% yield. c) d) EtOH, $NH_2NH_2(H_2O)$, r.t., 88% yield. e) DMF,

K_2CO_3, Hal-Het, MW 100°C. f) DCM, TFA, r.t.. g) N-methyl morpholine, 2-chloro-4,6-dimethoxy-1,3,5-triazine, 1,4-dioxane, r.t. to 60°C.

Final compounds were obtained by reacting intermediates (**x)** with the desired carboxylic acids or acyl chlorides by using standard coupling procedures (**Scheme 2**). Compounds were then screened in a functional cell-based assay (CHO or HEK-293 cells stably expressing human recombinant OX_1 or OX_2 receptors, respectively) based on OXA or OXB stimulated intracellular calcium mobilization using a combination of calcium-sensitive dyes and a fluorescent imaging plate reader (FLIPR)[20].

With chemistry set-up, the first round of exploration was aimed at comparing the effect of spiro-pyrrolidine instead of spiro-piperidine ring by leaving intact the other two points of variations, namely the left hand side (LHS) amides and the right hand side (RHS) heterocycles. RHSs and LHSs were initially chosen among those used in the exploration of the spiro-piperidine scaffold[17]. First data showed this modification had some influence on OX_1 activity with respect to the former series: compounds **2** and **4** were found slightly more active against OX_1 receptor with respect to compounds **1** and **3**, whereas compounds **6** reported a 1 log unit drop of potency with respect to its corresponding spiro-piperidine **5**. For compounds **1-6** a wide selectivity against the OX_2 receptor was achieved (**Table 1**).



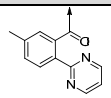
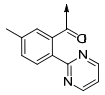
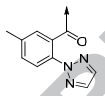
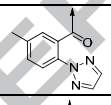
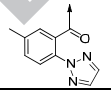
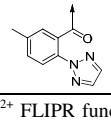
Compound	n	LHS	RHS	OX_1[a]	OX_2[a]
1	1			7.6	<5.0
2	0			8.2	<5.0
3	1			7.5	<5.0
4	0			8.1	<5.0
5	1			8.2	<5.0
6	0			7.1	<5.0

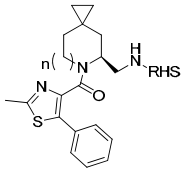
Table 1. (a) pK_b values in Ca^{2+} FLIPR functional assays are means from at least two independent experiments.

Spiro-pyrrolidine **2** emerged from this first iteration as an interesting OX_1 selective hit and for this reason it was further progressed in rat DMPK studies and cytochrome P450s inhibition (CyP450) characterization (**Table 2**). In rats compound **2** showed low *in vivo* plasmatic clearance (Clp) and good oral bioavailability; its ability to cross the blood brain barrier was investigated by sampling the concentration of the compound in brain homogenate one hour after its *iv* administration and by comparing it against its plasma level at the same time point. Although this procedure gives a static picture of the brain penetration capability for drugs it is often used in preliminary screens to understand the CNS potential of new drugs.

Cmpd	Clp[a]	F%[b]	Vdss[c]	B/P[d]	CyP450s[e]
2	11.0	40	6.21	0.03	All<53%
6	33.1	NT	0.48	0.2	All<34%

Table 2. (a) rat Clp given in ml/min/Kg, 1mg/kg iv dose (b) rat oral bioavailability, 1mg/Kg po dose (c) Vdss given in L/Kg (d) rat brain to plasma ratio obtained after 1mg/kg iv dose administration (e) CyP450s Gentest™ microplated – based fluorimetric assay with recombinant human P450 enzymes against CYP450 3A4, 2D6, 1A2, 2C19 and 2C9 isoforms (CYP3A4 two substrates were used, DBF = Dibenzyl fluorescein and BFC = 7-benzyloxy-4-trifluoromethyl coumarin): data reported as % inhibition @ 1μM compound's concentration. NT= not tested.

Compound **2** showed a very low B/P ratio (in the range of blood content of brain tissue) suggesting the preclusion of the brain compartment for this product. Also compound **6** was submitted to rat DMPK (*iv* and B/P studies only) showing moderate *in vivo* plasmatic clearance and significant brain penetration, thus showing that in this series it is possible to achieve good metabolic stability, oral bioavailability and both a peripheral or a central distribution pattern (**Table 2**). Based on these encouraging results we decided to enlarge the exploration of the spiro-pyrrolidine series initially by expanding the RHSs used so far; in this round we also decided to introduce the known thiazol-phenyl group as LHS because its usage in the preparation of orexin antagonists was widely described. In addition to that, it proved very easy to prepare (**Table 3**).



Compound	n	RHS	OX_1[a]	OX_2[a]
7	1		7.9	<5.0
8	0		8.3	7.1
9	1		7.7	<5.0
10	0		8.4	7.7
11	0		7.3	7.6
12	0		7.5	8.6
13	0		6.8	6.8
14	0		6.1	7.0

Table 3. (a) pK_b values in Ca^{2+} FLIPR functional assays are means from at least two independent experiments.

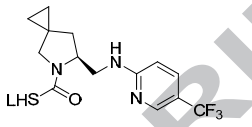
To our surprise spiro-pyrrolidine compounds **8** and **10-14** (**Table 3**) emerged from this new array showing a dual OX_1/OX_2 antagonist activity. Clearly, OX_2 activity was found to be peculiar to the spiro-pyrrolidine series because spiro-piperidine compounds **7** and **9** were showing a selective OX_1 activity pattern even when decorated with the thiazolo phenyl LHS (**Table 3**). However, the spiro-pyrrolidine moiety was not sufficient *per se* to gain OX_2 activity which, we discovered, was indeed linked to the nature of both the amide LHS and the pyridine RHS. For the LHS, shifting from a phenyl-pyrimidine to a thiazolo-phenyl system was key to get OX_2 activity on the new series (compared to e.g. compounds **8** *vs.* **2, Table 3** and **2** respectively). The 5-CF_3-pyridine moiety RHS was also discovered to be important to increase OX_2 activity on the new series (compared to e.g. compounds **10** *vs.* **8, Table 3**). Very interestingly a couple of examples prepared in the pyrimidine RHS sub-series (compounds **12** and **14**) showed an OX_2 preferred antagonist pattern. In particular the 4,6-dimethyl substitution pattern (compound **12**) brought a 40-fold increase in the OX_2 potency when compared with its 6-methyl derivative (compound **14**). This result suggested that the 4-position of the pyrimidine RHS could be further explored in order to enhance OX_2 activity in this sub-series.

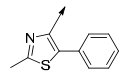
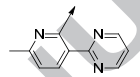
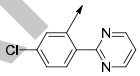
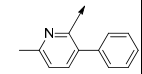
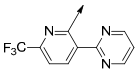
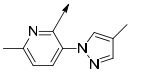
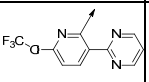
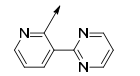
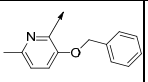
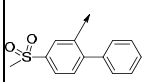
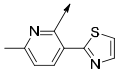
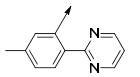
In view of their potent OX_1/OX_2 antagonism profile, compounds **10** and **12** were submitted to DMPK characterization: *in vivo* rat PK, CyP450s inhibition and CYP 3A4 Time Dependent Inhibition[21] (TDI) (**Table 4**).

Cmpd	Clp[a]	F%[b]	Vdss[c]	B/P[d]	CyP450s[e] 3A4 IC_{50}[f]	3A4 TDI[g]
10	55.2	20	3.0	0.6	All<20% >100μM	Yes
12	41.4	NT	0.7	0.1	All<16% 7.9μM	Yes

Table 4. (a) rat plasmatic clearance given in ml/min/Kg, 1mg/kg iv dose (b) rat oral bioavailability, 1mg/Kg po dose (c) Vdss: Volume of distribution at steady state, given in L/Kg (d) CyP450s Gentest™ microplated – based fluorimetric assay with recombinant human P450 enzymes against CYP450 3A4, 2D6, 1A2, 2C19 and 2C9 isoforms (CYP3A4 two substrates were used, DBF = Dibenzyl fluorescein and BFC = 7-benzyloxy-4-trifluoromethyl coumarin): data reported as % inhibition @ 1μM compound's concentration. NT= not tested. (f) 3A4 BFC (g) Time Dependent Inhibition of CYP3A4 enzyme with BFC as substrate was examined by comparing IC_{50} value from experiment with pre-incubation (30 min) to the IC_{50} value from experiment without pre-incubation; a substantial decrease in IC_{50} after pre-incubation (IC_{50} fold shift >1.5) is characteristic of compound showing TDI.

Both compounds showed a higher plasmatic clearance with respect to the lead compound **2** (**Table 2**), although the moderate-high metabolism in this case did not compromise the oral absorption of compound **10.** The measured brain-plasma ratio of compound **10** was much higher with respect to compounds **12** and especially **2** (respectively in **Table 4 & Table 2**) thus showing how the brain penetration of this series was deeply influenced from chemical variations on both the RHS and LHS points of variation. Further, compound **10**, although having a very low CyP450s inhibition profile, still carried on some concerns because it showed to be a time dependent inhibitor (TDI) of the 3A4 enzyme. Following these results, we decided to focus the exploration of the newly identified spiro-pyrrolodine series in order to achieve DORA endowed with improved physico-chemical features and possibly with no TDI liability. For this reason we decided to modulate the polarity of the LHS to achieve less lipophilic compounds while removing the thiazole ring, a known structural alert for mechanism-based inactivation of Cytochrome P450 Enzymes[21](**Table 5**). From this iterations we discovered that polarity was well tolerated in both the LHS aromatic rings (see ad e.g. in **Table 5** cmpds **15** *vs.* **19**), that the methyl in position 2 of the first LHS pyridine ring is important for OX activity (**Table 5,** cmpds **15** *vs.* **21)** and that the second LHS pyrimidine ring could be well replaced with a benzyloxy moiety (**Table 5,** cmpds **15** *vs.* **22).** We also observed that the introduction of polarity in the position 2 of first LHS pyridine was generally not tolerated (see ad e.g. in **Table 5** cmpds **15** *vs.* **20 & 23).** Interestingly the introduction of a CN group into the first LHS ring was well tolerated (**Table 5,** entry **26**).



Cmpd	LHS	OX_1[a]	OX_2[a]	ClogP[b]	Cyp450s[c]
10		8.4	7.7	5.29	All<20%
15		8.4	7.5	3.09	All<28%
16		8.1	7.2	4.43	All<22%
17		8.6	8.0	5.25	All<20%
18		6.7	5.0	3.70	All<39%
19		8.9	8.3	3.96	All<85%
20		7.0	6.9	5.01	All<58%
21		7.7	5.0	2.59	All<47%
22		8.6	8.6	5.50	All<71%
23		6.7	7.1	4.63	All<41%
24		8.6	8.0	3.87	All<89%
25		8.7	6.6	4.19	NT

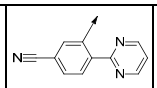
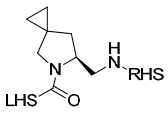
26		8.0	8.1	3.25	All<32%

Table 5. (a) pK_b values in Ca^{2+} FLIPR functional assays are means from at least two independent experiments. (b) ClogP was measured by using ChemBioDrawUltra 12.0.2 (c) CyP450s Gentest™ microplated–based fluorimetric assay with recombinant human P450 enzymes: data reported as % inhibition @ 3μM compound's concentration against CYP450 3A4, 2D6, 1A2, 2C19 and 2C9 isoforms (CYP3A4 two substrates were used, DBF = Dibenzyl fluorescein and BFC = 7-benzyloxy-4-trifluoromethyl coumarin). NT= not tested.

Importantly, from this exploration emerged that, by keeping a CF_3-pyridine as the RHS, OX_2 activity could be maintained through a broader range of different LHS amides than it was previously noted in the initial exploration, where all active compounds were OX_1 selective (even when the amide LHS was a phenyl-pyrimidine moiety, which at the beginning of the exploration was giving exclusively OX_1 selective compounds, compare ad e.g. entry **2**, **4** and **6** *vs.* **16** and **25, Table 2** and **5,** respectively). We thus decided to further explore the RHS pyridine pattern of substitution, particularly considering the excellent gain in activity against OX_2 receptor observed with this strategy. For this reason a small library of 4-substituted pyridine compounds was prepared (**Table 6**).



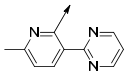
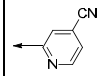
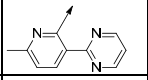
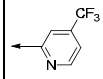
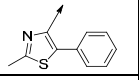
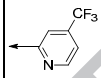
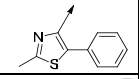
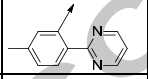
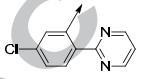
Cmpd	LHS	RHS	OX_1[a]	OX_2[a]	Cyp450s[b] / ClogP[c]
27			NI	NI	All<17% / 1.72
28			6.0	8.1	All<39% / 3.09
29			8.2	8.5	All<55% / 5.29
30			7.8	8.6	All<69% / 5.79
31			7.3	7.8	All<72% / 4.19
32			8.1	7.1	All<57% / 4.43

Table 6. (a) pK_b values in Ca^{2+} FLIPR functional assays are means from at least two independent experiments. (b) CyP450s Gentest™ microplated – based fluorimetric assay with recombinant human P450 enzymes against CYP450 3A4, 2D6, 1A2, 2C19 and 2C9 isoforms (CYP3A4 two substrates were used, DBF = Dibenzyl fluorescein and BFC = 7-benzyloxy-4-trifluoromethyl coumarin): data reported as % inhibition @ 1μM compound's concentration. (c) ClogP was measured by using ChemBioDrawUltra 12.0.2

From this exploration emerged that very good OX_2 activity was achievable by using 4-CF_3-pyridine RHSs (e.g. compounds **29** and **30, Table 6**). OX_1 activity was however generally lower with respect to corresponding 3-CF_3-pyridine derivatives (compared to e.g. compounds **15** *vs.* **28**, **Table 5** and **6** respectively) except when thiazole-phenyl was used as amide LHS (entry **29, table 6)** . Further, the increase in polarity was not well tolerated (entry **27**, **Table 6**). Interestingly, compound **28** was identified as an OX_2 selective antagonist (>100 fold separation between OX_2 and OX_1 activities) which is a remarkable achievement considering that the starting point of this exploration was an OX_1 selective series.

Eventually, compounds **15**[22] and **17**[23] (**Table 5**), in light of their good *in vitro* features, were further characterized into DMPK assays (*in vivo* rat PK and CYP 3A4 TDI) as shown in **Table 7**.

Cmpd	Clp[a]	F%[b]	Vdss[c]	B/P[d]	CYP3A4 IC_{50}[e]	3A4 TDI[f]
15	47.5	33	2.0	0.5	>100μM	Yes
17	61.3	11	4.4	0.4	64 μM	No

Table 7. (a) rat Clp given in ml/min/Kg, 1mg/kg iv dose (b) rat oral bioavailability, 1mg/Kg po dose (c) Vdss given in L/Kg (d) rat brain to plasma ratio obtained after 1mg/kg iv dose administration (e) CyP450s Gentest™ microplated – based fluorimetric assay with recombinant human P450 enzymes: data reported as IC_{50} on 3A4 BFC (f) Time Dependent Inhibition of CYP3A4 enzyme with BFC as substrate was examined by comparing IC_{50} value from experiment with pre-incubation (30 min) to the IC_{50} value from experiment without pre-incubation; a substantial decrease in IC_{50} after pre-incubation (IC_{50} fold shift >1.5) is characteristic of compound showing TDI.

Pyridine derivative **15**, a compound with greatly reduced (2-logs fold) lipophilicity with respect to lead molecule **10**, showed in rats a moderate-high plasma clearance, decent brain penetration and acceptable oral bioavailability together with a very low CyP450s inhibitory profile; this compound however still showed TDI on CYP 3A4 enzyme (**Table 7**). This issue was eventually overcome with compound **17**, which showed slightly higher *in vivo* rat Clp with respect to **15**, low CyP450s inhibitory profile but no TDI on 3A4 enzyme (**Table 7**). This data set was suggesting that the replacement of the first LHS thiazole ring (compound **10** vs. compound **17**) was sufficient to rule out the TDI effect on the 3A4 enzyme. However, when a pyrimidine ring was installed instead of the phenyl moiety on the second LHS ring TDI was again measurable (compound **15** *vs.* compound **17**); therefore, in this molecular context, the pyrimidine ring apparently contributed to the observed TDI behavior of this compound.

In conclusion, starting from an OX_1 selective series, we identified new potent dual OX_1/OX_2 antagonists. Compound **15** showed good *in vitro* and *in vivo* DMPK profile. Further, the CYP3A4 TDI issue was eliminated in this new series by replacing the LHS thiazole ring, used to decorate the spiro-pyrrolidine scaffold, with a pyridine moiety.

Acknowledgments

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22. Compound **15** analytical data ($C_{24}H_{23}F_3N_6O$, Molecular Weight = 468.5): 1HNMR (400MHz, $CDCl_3$) δ ppm 8.6-8.85 (m, 1H), 8.36-8.58 (m, 1H), 8.19-8.33(m, 1H), 7.47-7.50 (m, 1H), 7.27-7.34 (m, 2H), 7.08-7.19 (m, 2H), 6.01-6.50 (m, 1H), 4.73-4.87(m, 1H), 3.64-3.87 (m, 2H), 3.35-3.48 (m, 1H) 3.10-3.13 (m, 1H) 2.56-2.67 (m, 3H) 2.37-2.53 (m, 1H), 1.60-1.66 (m, 1H), 0.45-0.77 (m, 4H); HPLC-MS $[MH]^+ = 469$.
23. Compound **17** analytical data ($C_{26}H_{25}F_3N_4O$, Molecular Weight = 466.5): 1H NMR (400MHz, $CDCl_3$) δ ppm = 8.97-8.55 (m, 2 H), 8.46-8.09 (m, 2 H), 7.60 -7.30 (m, 2 H), 7.25-6.92 (m, 2 H), 6.55 (d, J = 8.8 Hz, 1 H), 4.84 (d, J = 4.9 Hz, 1 H), 4.04 - 2.73 (m, 4 H), 2.29 (dd, J = 8.3, 12.7 Hz, 1 H), 1.63 (d, J = 8.8 Hz, 1 H), 1.03 - 0.03 (m, 4 H); HPLC-MS $[MH]^+ = 468$.

Graphical Abstract

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Discovery, synthesis, selectivity modulation and DMPK characterization of 5-azaspiro[2.4]heptanes as potent orexin receptor antagonists

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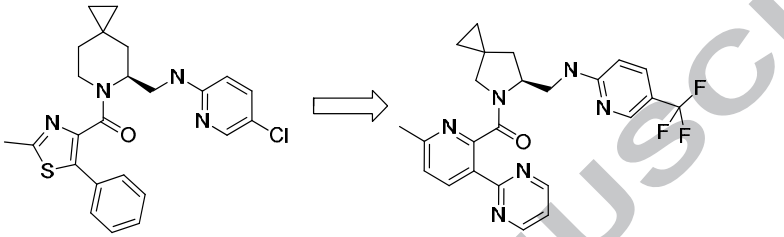

7
*h*OX$_1$ pKb=7.9
*h*OX$_2$ pKb<5.0
cLogP=5.58

15
*h*OX$_1$ pKb=8.4
*h*OX$_2$ pKb=7.5
cLogP=3.09