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Synthesis, structure–activity relationship studies, and identification of novel 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine derivatives as dual orexin receptor antagonists. Part 1

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ABSTRACT

A novel series of non-peptidic OX_1R/OX_2R orexin receptor antagonists was prepared by heterocyclic replacement of the dimethoxyphenyl moiety contained in the tetrahydroisoquinoline core skeleton of almorexant. Introduction of substituted imidazole moieties delivered potent dual orexin receptor antagonists with nanomolar potency for hOX_1R and hOX_2R suitable for further fine-tuning. The preparation of these novel orexin receptor antagonists and the outcome of preliminary structure–activity relationship studies are described in this communication.

The neuropeptides orexin A and orexin B (also named hypocretin-1 and hypocretin-2) were discovered in 1998 by two independent research groups. Both peptides are produced exclusively by a small population of neurons in the lateral hypothalamus.[1,2] Two orphan G-protein-coupled receptors (GPCRs) for these endogenous ligands were as well identified and they are known as orexin 1 (OX_1R) and orexin 2 (OX_2R) receptors. Both receptors are highly conserved across mammalian species. The OX_1 receptor binds orexin A with high affinity and selectivity over orexin B, whereas the OX_2 receptor binds both neuropeptides with comparably high affinity.[2] Since the discovery of the orexin neuropeptides, several studies have highlighted their potential role in the regulation of biological functions including feeding[2] and the sleep/wake cycle.[3,4] During the last decade, several groups within the pharmaceutical industry have developed orexin receptor antagonists in order to identify the physiological role of the orexin receptors and explore the potential of orexin receptor antagonists as therapeutics.[5] We have reported that almorexant, a dual orexin receptor antagonist (DORA),[6] promoted somnolence without cataplexy in rats, dogs, and humans.[7] In the course of our investigations towards the identification of further non-peptidic, low molecular weight orexin receptor antagonists, we were interested in heterocyclic replacements of the dimethoxyphenyl unit contained in the tetrahydroisoquinoline skeleton of almorexant.[8] We reported that the replacement of this moiety by a substituted pyrazole afforded pyrazolo-tetrahydropyridines as potent DORAs.[9] Herein, we describe the synthesis and preliminary structure–activity relationship studies of a novel series of DORAs related to almorexant where the dimethoxyphenyl moiety was replaced by substituted imidazoles (Fig. 1).[10]

For a convenient preparation of the planned 5,6,7,8-tetrahydroimidazo[1,5-*a*]-pyrazine derivatives **9**, it was envisaged to develop a selective synthesis of the key trisubstituted imidazoles **4** (Scheme 1) with the goal to avoid isomeric mixtures due to the issue of tautomerism associated with imidazoles. The developed synthesis started with the diiodination of 2-substituted imidazoles **1**[11] affording 4,5-diiodoimidazoles **2**.[12] Deprotonation of pseudosymmetric **2**, and subsequent N-alkylation (NaH, $Br(CH_2)_2NHBoc$, DMF) furnished the corresponding derivatives **3**. The pivotal step for the selective preparation of 4-iodoimidazoles **4** was a regioselective iodine/magnesium exchange of the 5-iodo moiety in **3** (EtMgBr, THF, −40 °C) followed by trapping of the intermediate carbanion with water.[13,14] The application of this methodology allowed to obtain exclusively the target 4-iodoimidazoles **4**. Boc-deprotection of **4** (4 N HCl in dioxane, CH_2Cl_2) provided quantitatively the corresponding primary amines that reacted with 3-(4-(trifluoromethyl)phenyl)propanal **5** in a subsequent microwave assisted Pictet–Spengler-like reaction (DIPEA, EtOH, microwave).[15] Boc-protection delivered the racemic 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazines **6**, and the

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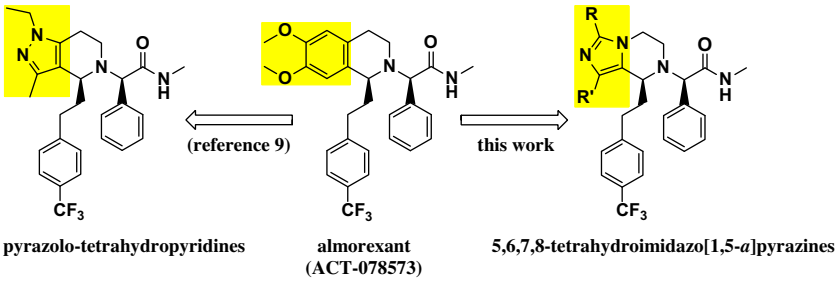
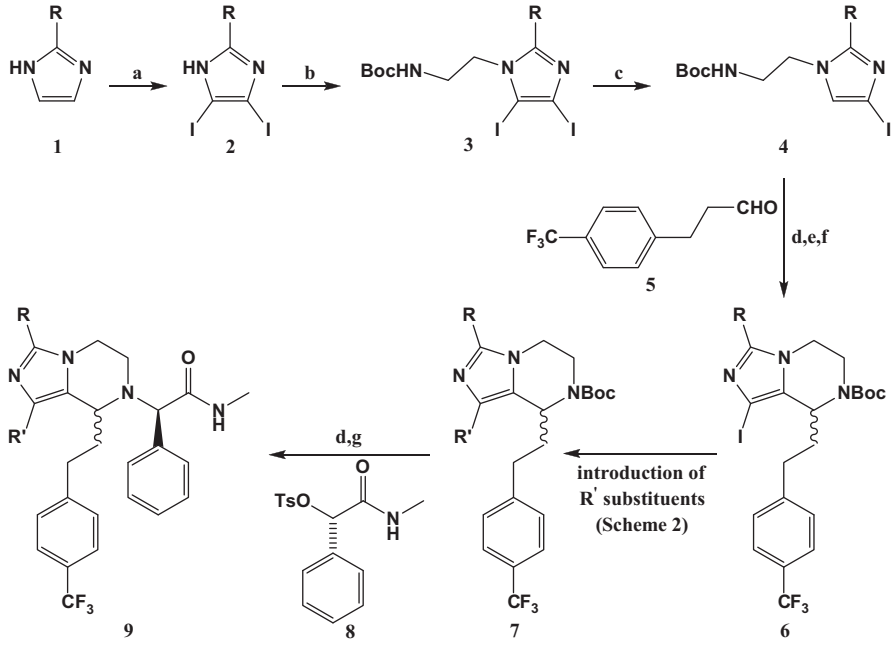


Figure 1. Almorexant, the related pyrazolo-tetrahydropyridines, and the investigated 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazines.

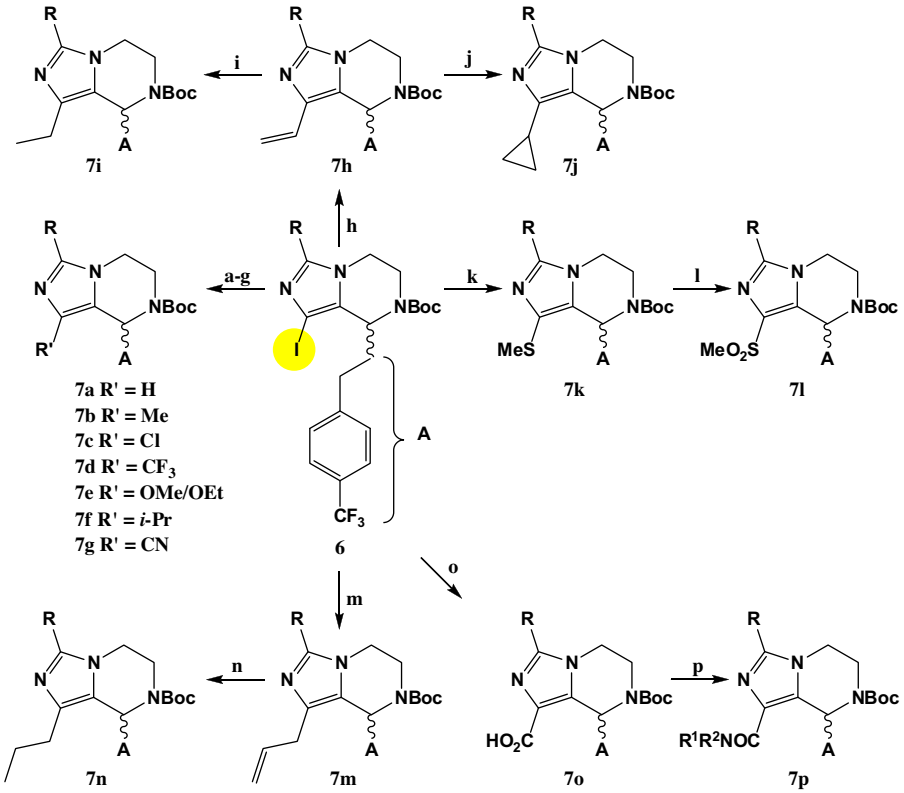


Scheme 1. Preparation of 5,6,7,8-tetrahydroimidazo[1,5-*a*]-pyrazines. Reagents and conditions: (a) I_2, Na_2CO_3, dioxane, H_2O, rt (95–100%); (b) NaH, DMF, rt, then $Br(CH_2)_2NHBoc$, 100 °C (42–77%); (c) (i) 3 M EtMgBr in Et_2O, THF, −40 °C, (ii) H_2O (82–95%); (d) 4 M HCl in dioxane, CH_2Cl_2, 0 °C to, rt (97–100%); (e) aldehyde **5**, DIPEA, EtOH, microwave (50 W; 140 °C; 6 bar; 10 min); (f) Boc_2O, DIPEA, CH_2Cl_2, rt (58–87% over 2 steps); (g) tosylate **8**, DIPEA, 3-methyl-2-butanone, 80 °C (25–60%).

versatility of the iodo-substituent allowed the preparation of a variety of derivatives **7** (Scheme 2). Boc-deprotection of **7** followed by N-alkylation of the resulting secondary amines with the chiral (*S*)-tosylate **8** delivered the target 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazines **9** as diastereoisomeric mixtures that could be further separated into the enantiomers via chromatography.

The versatility of the iodo-substituent in 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazines **6** allowed the straightforward introduction of a variety of substituents R′ (Scheme 2). Several residues could be conveniently introduced with one synthetic operation. Thus, hydrogenolytic cleavage of the iodo-substituent (H_2, 10% Pd/C, K_2CO_3, MeOH) delivered **7a**. Iodine/lithium exchange (*n*-BuLi, THF, −78 °C) or iodine/magnesium exchange (EtMgBr, THF, −30 °C) with **6** and subsequent trapping of the intermediate carbanion with diverse electrophiles proved to be a particularly straightforward synthetic approach allowing the insertion of methyl (**7b**), chloro (**7c**), isopropyl (**7f**), cyano (**7g**), *n*-propyl (**7n**), and carboxylic acid (**7o**) residues. The latter was converted into amides (**7p**) after additional coupling with amines (TBTU, HNR^1R^2, DIPEA, DMF). In another approach, copper-mediated trifluoromethylation[16] ($FSO_2CF_2CO_2Me$, CuI, HMPA, DMF) allowed the introduction of the trifluoromethyl moiety (**7d**). Alkoxy residues (**7e**) could be incorporated by copper-mediated alkoxylations (MeOH or EtOH, CuI, 1,10-phenanthroline, Cs_2CO_3, microwave).[17] A related copper-mediated procedure (MeSNa, CuCl, NMP) allowed the insertion of the thiomethyl residue (**7k**) that was oxidized (*m*-CPBA, CH_2Cl_2) to the corresponding sulfone (**7l**). *Stille* cross-coupling reaction with **6** (tributyl(vinyl)tin, Pd_2dba_3, PPh_3, DMF)[18] smoothly introduced the vinyl moiety (**7h**) that could be either hydrogenated (H_2, 10% Pd/C, MeOH) to the ethyl-substituted derivative (**7i**) or converted into the cyclopropyl moiety (**7j**) using modified cyclopropanation conditions (Et_2Zn, CH_2I_2, CF_3CO_2H).[19]

The antagonistic activity of the 5,6,7,8-tetrahydroimidazo[1,5-*a*]-pyrazines **9** with both orexin receptors was evaluated with a cell-based FLIPR assay (fluorometric imaging plate reader) measuring Ca^{2+} flux as a functional determinant of orexin binding.[20] Preliminary structure–activity relationship studies were devoted to the exploration of the influence of substituent R′ on the potency toward both orexin receptors (Table 1). These initial investigations were performed with derivatives **9** containing the *para*-CF_3-phenyl ring from almorexant, and having ethyl as a fixed substituent R like in the related dual pyrazolo-tetrahydropyridines.[9] Limiting the substituent R′ to hydrogen (diastereoisomers **10**) led to moderate potency toward hOX_2R and absence of affinity for hOX_1R. A methyl group induced a substantial eightfold increase in hOX_2R potency but this alkyl residue could not improve the affinity for hOX_1R as shown with diastereoisomers **11**. Compared to methyl, ethyl afforded an almost equipotent diastereoisomeric mixture (**12**) but

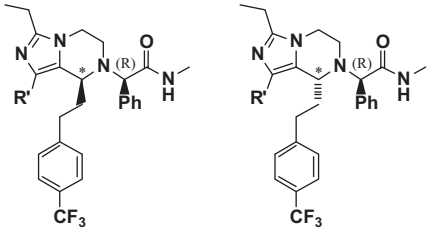


Scheme 2. Versatility of the iodo-substituent in 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazines for the introduction of substituents R′. Reagents and conditions: (a) H_2 (1 atm), 10% Pd/C (10% in weight), K_2CO_3, MeOH, rt (69–98%); (b) *n*-BuLi, MeI, THF, −78 °C (45–70%); (c) *n*-BuLi, hexachloroethane, THF, −78 °C (39–66%); (d) $FSO_2CF_2CO_2Me$, CuI, HMPA, DMF, 80 °C (30–84%); (e) MeOH (R′ = OMe) or EtOH (R′ = OEt), CuI, 1,10-phenanthroline, Cs_2CO_3, microwave (150 W; 150 °C; 13 bar; 90 min) (29–35%); (f) (i) *n*-BuLi, THF, acetone, −78 °C, (ii) Burgess' reagent, THF, 0 °C, (iii) H_2 (1 atm), 10% Pd/C (20% in weight), MeOH, rt (18–20% over 3 steps); (g) *n*-BuLi, *para*-toluenesulfonyl cyanide, THF, −78 °C (27–50%); (h) Pd_2dba_3, PPh_3, tributyl(vinyl)tin, DMF, 90 °C (63–77%); (i) H_2 (1 atm), 10% Pd/C (100% in weight), MeOH, rt (83–97%); (j) (i) Et_2Zn, CH_2I_2, CF_3CO_2H, CH_2Cl_2, 0 °C to rt, (ii) Boc_2O, DIPEA, CH_2Cl_2, rt (34–40% over 2 steps); (k) MeSNa, CuCl, NMP, 140 °C (66–84%); (l) *m*-CPBA, CH_2Cl_2, rt (51–86%); (m) *n*-BuLi, allyl bromide, THF, −78 °C (40–55%); (n) H_2 (1 atm), 10% Pd/C (50% in weight), MeOH, rt (80–95%); (o) 3 M EtMgBr in Et_2O, CO_2, THF, −30 °C to rt (82%); (p) TBTU, HNR^1R^2, DIPEA, DMF, rt (35–65%).

enlarging the alkyl residue to *n*-propyl (**13**) proved to be detrimental for hOX_2R affinity with an almost 10-fold loss in potency. Cyclopropyl was similarly tolerated regarding potency towards hOX_2R (**15**) but this substituent remained ineffective for the interaction with hOX_1R. Compared to ethyl, the unsaturated vinyl moiety triggered an outstanding increase of potency towards hOX_1R while maintaining potency towards hOX_2R (diastereoisomers **16**). We observed a similar trend with the iodo-substituent but to a lower extent regarding the affinity for hOX_1R (diastereoisomers **17**). Further evaluation of halogen atoms indicated the superiority of the chloro moiety that allowed an outstanding improvement of potency towards hOX_1R as shown with the dual orexin receptor antagonist **18**. Previous investigations in the related tetrahydroisoquinoline and pyrazolo-tetrahydropyridine series have shown that the (*S*,*R*)-stereoisomer was the most active isomer in both series (Fig. 1).[9] The influence of the stereochemistry for 5,6,7,8-tetrahydroimidazo[1,5-*a*]-pyrazines was investigated with the chloro-containing derivatives (**18**/**19**). In this new series the (*R*,*R*) isomer **19** was also significantly less potent against both receptors compared to the corresponding (*S*,*R*) stereoisomer **18** (7- and 12-fold decrease, respectively, in hOX_1R and hOX_2R potency with **19**). The additional (*R*,*S*) and (*S*,*S*) isomers were essentially inactive (IC_{50} >1 μM with both orexin receptors), and the importance of the (*R*)-configuration for the phenylglycine moiety was already established with the related tetrahydroisoquinoline and pyrazolo-tetrahydropyridine series. The evaluation of additional substituents R′ indicated that the electron-withdrawing trifluoromethyl moiety was detrimental for the potency toward hOX_1R (stereoisomer **20**). The electron-donating methoxy group afforded appreciable potency towards both orexin receptors but the diastereoisomers **21** remained clearly less potent than the chloro-containing DORA **18**. Lengthening of the alkoxy moiety to ethoxy (diastereoisomers **22**) proved to be highly detrimental for the potency towards both orexin receptors. The influence of a related thiomethyl group was also evaluated (stereoisomer **23**). This moiety induced a twofold decrease in hOX_1R potency compared to the chloro-derivative **18**. Oxidation of the thiomethyl residue to the corresponding sulfone (stereoisomer **24**) resulted in a substantial loss of potency towards hOX_1R while keeping the affinity for hOX_2R almost unaffected. The electron-withdrawing cyano group (diastereoisomers **25**) and amide residues (diastereoisomers **26–28**) were detrimental for the potency towards hOX_1R while the affinity for hOX_2R remained high with a secondary amide (**27**) and especially with the cyano group (**25**).

The evaluation of substituents R′ clearly emphasized the superiority of the chloro moiety for the identification of potent dual orexin receptor antagonists. In an attempt to further improve potency in this series of DORAs, we evaluated the influence of additional substituents R. With this aim in view, specific 2-substituted imidazoles **1** had to be prepared in order to synthesize the corresponding 5,6,7,8-tetrahydroimidazo[1,5-*a*]-pyrazines **9** according to Scheme 1. A variety of 2-substituted imidazoles **1** were conveniently prepared from commercially available nitriles and α-amino-acetaldehyde acetals.[21] Thus, copper(I)-induced addition of 2,2-dimethoxyethanamine **30** to nitriles **29** (CuCl, neat, 85 °C) delivered the corresponding amidines **31** (Scheme 3). After elimi-

Table 1
SAR studies of 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazines: influence of R′

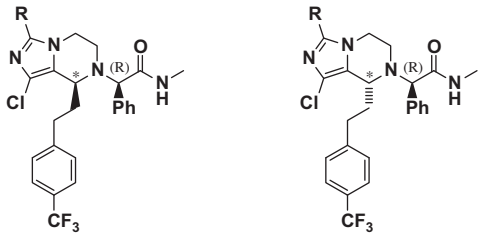


(S;R)-stereoisomer (R;R)-stereoisomer

Compound	Stereochemistry	R′	hOX_1R[a]	hOX_2R[a]
10	(*S*,*R*) + (*R*,*R*)	H	10,000	194
11	(*S*,*R*) + (*R*,*R*)	Me	10,000	24
12	(*S*,*R*) + (*R*,*R*)	Et	10,000	20
13	(*S*,*R*) + (*R*,*R*)	*n*-Pr	10,000	225
14	(*S*,*R*) + (*R*,*R*)	*i*-Pr	10,000	2904
15	(*S*,*R*)	*c*-Pr	4171	29
16	(*S*,*R*) + (*R*,*R*)	$CH{=}CH_2$	150	23
17	(*S*,*R*) + (*R*,*R*)	I	717	23
18	(*S*,*R*)	Cl	40	9
19	(*R*,*R*)	Cl	283	107
20	(*S*,*R*)	CF_3	1066	11
21	(*S*,*R*) + (*R*,*R*)	OMe	134	73
22	(*S*,*R*) + (*R*,*R*)	OEt	3980	2746
23	(*S*,*R*)	SMe	85	14
24	(*S*,*R*)	SO_2Me	1677	25
25	(*S*,*R*) + (*R*,*R*)	CN	537	10
26	(*S*,*R*) + (*R*,*R*)	$CONH_2$	10,000	194
27	(*S*,*R*) + (*R*,*R*)	CONHMe	492	38
28	(*S*,*R*) + (*R*,*R*)	$CONMe_2$	344	111

[a] IC_{50} values in nM (FLIPR assay).

Table 2
SAR studies of 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazines: influence of R



(S;R)-stereoisomer (R;R)-stereoisomer

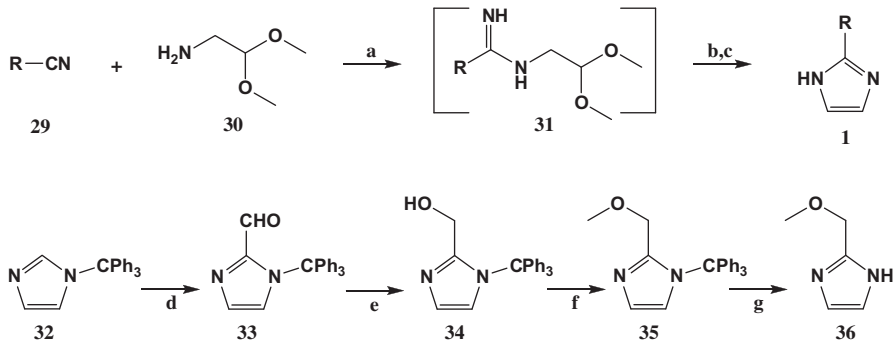
Compound	Stereochemistry	R	hOX_1R[a]	hOX_2R[a]
18	(*S*,*R*)	Et	40	9
37	(*S*,*R*)	Me	90	13
38	(*S*,*R*)	*n*-Pr	459	60
39	(*S*,*R*) + (*R*,*R*)	CH_2OMe	1645	25
40	(*S*,*R*)	*i*-Pr	313	11
41	(*S*,*R*)	*c*-Pr	31	9
42	(*S*,*R*)	*c*-$PrCH_2$	1426	35

[a] IC_{50} values in nM (FLIPR assay).

nation of copper salts (thioacetamide, MeOH, filtration), cyclisation under acidic conditions (12 M HCl, MeOH, 80 °C) led to the desired 2-substituted imidazoles **1**. In another approach, deprotonation of 1-tritylimidazole **32** (*n*-BuLi, THF, −78 °C) afforded selectively the carbanion at C-2 that could be trapped with a variety of electrophiles.[22] For example, quenching with DMF afforded **33** (Scheme 3) that could be converted to the methyl ether **36** after reduction ($NaBH_4$, MeOH), O-alkylation (NaH, MeI, THF), and cleavage of the trityl group (AcOH, MeOH).

The structure–activity relationship studies to investigate the influence of additional substituents R were performed with derivatives **9** containing the *para*-CF_3-phenyl ring from almorexant and a chloro residue as substituent R′ (Table 2). Compared to ethyl (DORA **18**), methyl resulted in an almost twofold loss of potency towards hOX_1R (stereoisomer **37**). Enlargement of the alkyl group to *n*-propyl (stereoisomer **38**) was even more detrimental for the potency towards both orexin receptors, but mainly for hOX_1R with an 11-fold loss in potency. The isosteric methoxymethyl was not better tolerated and induced an even more pronounced loss of potency for hOX_1R (diastereoisomers **39**). Compared to ethyl the branched isopropyl moiety also induced a substantial eightfold decrease of potency towards hOX_1R while keeping similar potency for hOX_2R (**40**). The sterically less demanding cyclopropyl group was however better tolerated (stereoisomer **41**) and similar to ethyl regarding the affinities for both orexin receptors. The enlargement to cyclopropylmethyl (stereoisomer **42**) proved to be highly detrimental for hOX_1R affinity with a 46-fold loss in potency compared to cyclopropyl.

We measured the concentrations of the dual orexin receptor antagonists **18** and **41** in brain and plasma sampled 3 h following oral administration to male Wistar rats (100 mg/kg, po). Total concentrations of the DORA **18** reached 303 nM (153 ng/g) in the brain and 4210 nM (2127 ng/ml) in plasma (brain/plasma ratio = 0.07). When the dual orexin receptor antagonist **41** was orally administered to rats, brain and plasma levels reached 385 nM (199 ng/g) and 6398 nM (3308 ng/ml), respectively (brain/plasma ratio = 0.06). Considering a plasma protein binding of 99% measured for **18** and **41** in human plasma, the concentrations of free **18** and **41** available in the brain at 3 h can be estimated at 3.0 and 3.8 nM, respectively. For a direct comparison with the related tetrahydroisoquinoline series, a similar experiment afforded a five to sixfold higher concentration of free almorexant in brain (20 nM, brain/plasma ratio = 0.32).[7]



Scheme 3. Synthesis of 2-substituted imidazoles. Reagents and conditions: (a) CuCl, neat, 0–85 °C; (b) thioacetamide, MeOH, 0–45 °C; (c) 12 M HCl, MeOH, 0–80 °C (overall yield: 26–35%); (d) *n*-BuLi, DMF, THF, −78 °C (76%); (e) $NaBH_4$, MeOH, 45 °C (99%); (f) NaH, MeI, THF, 0 °C to rt (51%); (g) AcOH, MeOH, 75 °C (99%).

Previous investigations of the corresponding tetrahydroisoquinoline and pyrazolo-tetrahydropyridine series have outlined that brain penetration can be substantially influenced by the substitution of the phenethyl motif and further evaluation of this moiety was envisaged for 5,6,7,8-tetrahydroimidazo[1,5-*a*]-pyrazines.

In summary, we have described the synthesis and the identification of a novel series of dual orexin receptor antagonists based on the heterocyclic replacement of the dimethoxyphenyl moiety, present in the tetrahydroisoquinoline series, by a disubstituted imidazole. Investigations of the imidazole allowed to discover appropriate substituents affording potent dual orexin receptor antagonists **18** and **41** with low nanomolar potency for hOX_1R and hOX_2R. Efforts to further optimize potency and mainly brain penetration by fine-tuning of the pivotal phenethyl motif, and the sleep-promoting activity of leading 5,6,7,8-tetrahydroimidazo[1,5-*a*]-pyrazines with a rat EEG model will be disclosed in due course.

Acknowledgments

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11. 2-Substituted imidazoles **1** used for the investigations are either commercially available or specifically synthesized (Scheme 3). Substituents R corresponding to these 2-substituted imidazoles **1** are listed in Table 2.
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