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Mendeleev Commun., 2021, **31**, 501–503

Mendeleev Communications

Novel medium-sized di(het)areno-fused 1,4,7-(oxa)thiadiazecines as probes for aminergic receptors

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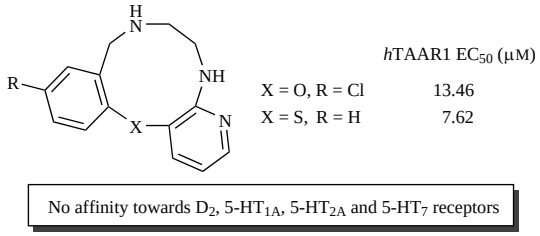
DOI: 10.1016/j.mencom.2021.07.021

Di(het)areno-fused 1,4,7-(oxa)thiadiazecanes were synthesized by the reduction of the corresponding ten-membered lactams obtained, in turn, *via* the 'hydrated imidazoline ring expansion' (HIRE) methodology. Two of them displayed micromolar agonistic activity towards trace amine-associated receptor 1 (TAAR1) and no affinity towards a panel of dopamine (D2) and serotonin (5-HT1A, 5-HT2A and 5-HT7) receptors. These findings validate compounds of this chemotype as scaffolds for the design of selective aminergic receptor modulators.

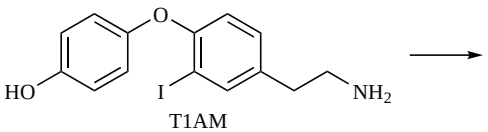


Keywords: medium-sized rings, 1,4,7-thiadiazecines, 1,4,7-oxadiazecines, lactam reduction, dopamine D_2 receptor, serotonin receptors, trace amine-associated receptor 1.

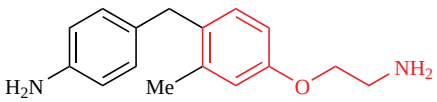
Trace amine-associated receptor 1 (TAAR1) is a G protein-coupled receptor (GPCR, Gαs) that binds endogenous molecules dubbed trace amines (TAs) and is likely involved in the classical monoamine neurotransmitter regulation.[1] Unsurprisingly, therapeutic applications of TAAR1 modulators are anticipated in the treatment of central nervous system disorders, particularly schizophrenia. Recently, compound SEP-363856 co-developed by Sunovion and PsychoGenics received FDA's designation as breakthrough therapy.[2] However, TAAR1 ligands may be useful in other therapeutic areas such as drug addiction[3] and metabolic disease.[4]

Most ligands to TAAR1 have a lot in common with the ligand space of other aminergic GPCRs, as exemplified by *p*-tyramine, octopamine, methamphetamine, amphetamine or synephrine as the receptors' potent ligands. However, considering the structure of ractopamine and, especially, of EPPTB (for the structures, see Online Supplementary Materials, Figure S1), the only potent antagonist of TAAR1 is discovered to date. Therefore, one can conclude that there is a substantial room for medicinal chemistry design beyond the confines of 'aromatic group/two-carbon linker/primary of secondary amine' to which the above-listed ligands conform.[5]

Moreover, over the last decade, the patent literature (mostly by Hoffmann-La Roche AG) described a number of fundamentally new chemotypes.[6] The representatives of these newer-generation chemotypes are chiral, non-racemic nanomolar agonists RO5256390 and RO5263397 of 2-aminooxazoline series (see Figure S1).[7] Particularly relevant to this work, was the modification of the structure of 3-iodothyronamine (T1AM) reported by Chiellini and Rapposelli resulting in the equipotent new compound **1** containing an additional oxygen atom in the linker between the aminoethyl moiety and the aromatic ring.[8]



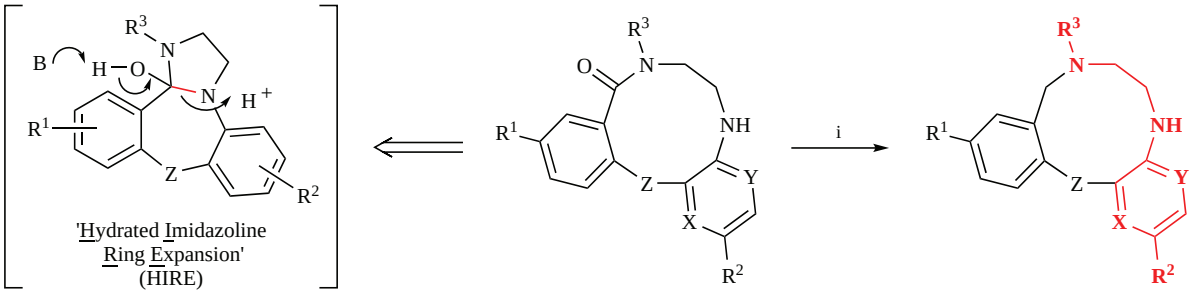
T1AM



1

Recently, we gained access to a wide range of 10-membered di(het)areno-fused lactams **2** (Scheme 1) *via* an approach dubbed 'hydrated imidazoline ring expansion' (HIRE).[9,10] We reasoned that the reduction of their lactam carbonyl group would deliver compounds **3** bearing a pharmacophoric 2-[(het)arylamino]-ethylamine moiety (highlighted in red) which may ensure affinity to TAAR1, in analogy to the oxygen-linked tyramine analogs **1**. Herein, we describe the realization of this idea and the study of agonistic activity of compounds thus obtained with respect to TAAR1.

Compounds **2a**–**i** were synthesized as described previously[9,10] and were reduced with a 2 : 1 mixture of lithium aluminum hydride and $AlCl_3$.† The yields of products **3a**–**i** were generally modest to good throughout (Table 1) and were not further optimized.



a R^1 = H, R^2 = CF_3, R^3 = Et, X = Y = CH, Z = S
b R^1 = R^2 = H, R^3 = 4-$MeC_6H_4CH_2$, X = CH, Y = N, Z = S
c R^1 = R^2 = H, R^3 = Et, X = CH, Y = N, Z = S
d R^1 = H, R^2 = (pyrrolidino)sulfonyl, R^3 = Et, X = CH, Y = N, Z = S
e R^1 = H, R^2 = CO_2Et (in **2e**), CH_2OH (in **3e**), R^3 = Me, X = H, Y = N, Z = S
f R^1 = R^2 = H, R^3 = 2-$FC_6H_4CH_2$, X = Y = N, Z = S
g R^1 = R^2 = R^3 = H, X = CH, Y = N, Z = S
h R^1 = Cl, R^2 = R^3 = H, X = CH, Y = N, Z = O
i R^1 = R^3 = H, R^2 = CF_3, X = CH, Y = N, Z = O

Scheme 1 *Reagents and conditions*: i, $LiAlH_4$ (2 equiv.), $AlCl_3$ (1 equiv.), Et_2O, room temperature, 24 h.

We then tested compounds **2a**–**i** in bioluminescence resonance energy transfer-based *in vitro* assay[11] on HEK293T cells transiently transfected with *h*TAAR1 gene, using tyramine hydrochloride (1 μM) as a positive control. Most of the compounds investigated produced no activation of TAAR1 receptor and thus were deemed inappropriate starting points for further pursuit and optimization. However, two compounds, **3g**,**h**, displayed agonistic activity at the receptor in the micromolar range. As both compound share a fully unsubstituted *N*[1]-(pyridin-2-yl)ethane-1,2-diamine motif and belong to either 6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thia- or oxadiazecine chemotype, this, in our view, defines the TAAR1-agonistic pharmacophore for further optimization (see Table 1). Interestingly, compound **3i** is a differently substituted inactive 1,4,7-oxadiazecine congener of **3h**, which demonstrates that substitutions in the nitrogen-bound aromatic ring are not tolerated.

Table 1 Yields and TAAR1 agonistic activity of di(het)areno-fused 1,4,7-(oxa)thiadiazecanes **3a**–**i**.

Compound	Yield (%)	TAAR1 agonistic activity EC_{50} / [a] μM
3a	44	NA
3b	58	NA
3c	36	NA
3d	27	NA
3e	61[b]	NA
3f	39	NA
3g	61	7.62
3h	57	13.46
3i	43	NA

[a] NA – not active (<20% activity produced at TAAR1 by 1 μM concentration of tyramine). [b] The hydroxymethyl side substituent resulted from reduction of ethoxycarbonyl group in **2e**.

Achieving selective targeting of a specific aminergic receptor is a formidable task considering the similarity of pharmacophores ensuring the affinity to various classes of these biotargets.[12] Therefore, we were curious to see if compounds **3g**,**h** which displayed affinity to TAAR1 would have any affinity to other aminergic receptors. Likewise, it was of interest to verify if compounds devoid of TAAR1 activity would display any affinity towards other aminergic targets. Compounds **3a**–**i** were screened in radioligand binding assays against a small panel of receptors including D_2, 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 as described previously.[13] Rather reassuringly, compounds **3g**,**h** (micromolar TAAR1 agonists) displayed no affinity towards these receptors in the 1–10 μM concentration range thereby manifesting themselves as selective modulators of TAAR1. At the same time, compound **3e** caused 89.9 ± 2.2% and 35.7 ± 6.5% displacement of ^{3}H-ketanserin ligand from 5-HT_{2A} receptor at concentrations 10 and 1 μM, respectively. Compound **3e** appeared to have selective affinity towards 5-HT_{2A} as it was found to possess a much weaker affinity towards other targets. Specifically, it caused only 51.7 ± 1.2%, 18.8 ± 5.8% and 42.0 ± 3.3% displacement of ^{3}H-raclopride from D_2, ^{3}H-8-OH-DPAT (7-dipropylamino-5,6,7,8-tetrahydronaphthalen-1-ol) from 5-HT_{1A} and ^{3}H-5-CT (5-carboxamidotryptamine) from 5-HT_7, respectively, at 10 μM concentration.

In summary, we have described the first example of di(het)-areno-fused 1,4,7-(oxa)thiadiazecanes incorporating a 2-[(het)-arylamino]ethylamine moiety. As speculated based on the presence of the latter, some of the compounds synthesized and investigated (both minimally substituted 6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxa- and thiadiazecines) displayed specific agonistic activity towards trace amine-associated receptor 1 (TAAR1). These compounds displayed no affinity to a panel comprising D_2 receptors and three serotonin receptor subtypes (5-HT_{1A}, 5-HT_{2A} and 5-HT_7). At the same time, compound **3e** featuring a different substitution pattern around the 6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadi-azecine core was found inactive against TAAR1 but displayed selective affinity towards 5-HT_{2A} receptor as measured in radioligand binding assays. Collectively, these findings validate

† *General procedure for the preparation of compounds* **3a**–**i**. A solution of lactam **2** (0.060 mmol) in THF (1 ml) was added dropwise to a solution of $LiAlH_4$ (14 mg, 0.36 mmol) and $AlCl_3$ (24 mg, 0.18 mmol) in diethyl ether (1 ml) at 0 °C. The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was then quenched with cold water (2 ml). The aqueous phase was extracted with CH_2Cl_2, the organic phase was washed with water (4 × 5 ml), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using an appropriate gradient of ethyl acetate in hexanes as the eluent.

the new di(het)areno-fused ten-membered heterocyclic scaffold as a platform for the design of selective modulators of aminergic receptors.

This research was supported by the Russian Science Foundation (grant no. 19-75-30008). We thank the Research Center for Magnetic Resonance, the Center for Chemical Analysis and Materials Research, and Research Resource Center for Molecular and Cell Technologies of Saint Petersburg State University Research Park for obtaining the analytical data.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.07.021.

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Received: 24th February 2021; Com. 21/6462