Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2021, **31**, 488–489

Mendeleev Communications

Rare *cis*-configured 2,4-disubstituted 1-alkylpiperidines: synthesized and tested against trace-amine-associated receptor 1 (TAAR1)

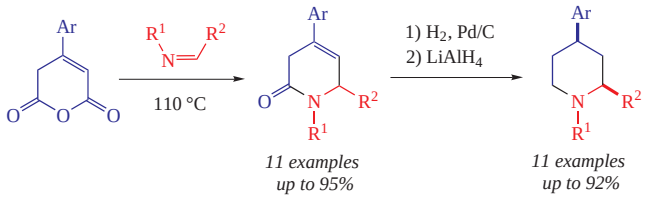
Ekaterina Levashova,[a] Andrey Firsov,[a] Olga Bakulina,[a] Anatoly Peshkov,[a] Evgeny Kanov,[a] Raul R. Gainetdinov[a] and Mikhail Krasavin*[a,b]

[a] *Institute of Chemistry, St. Petersburg State University, 199034 St. Petersburg, Russian Federation. E-mail: m.krasavin@spbu.ru*

[b] *Immanuel Kant Baltic Federal University, 236016 Kaliningrad, Russian Federation*

DOI: 10.1016/j.mencom.2021.07.016

Rare *cis*-configured 2,4-disubstituted 1-alkylpyridines were envisioned as ligands for trace amine associated receptor 1 (TAAR1). They were synthesized in diastereomerically pure form with the decarboxylative Castagnoli–Cushman reaction followed by two reduction events. Despite showing no affinity to TAAR1 as was anticipated, these novel, druglike and CNS-focused compounds will be of much utility in subsequent lead generation pursuits.



Keywords: trace amine associated receptor 1, decarboxylation, Castagnoli–Cushman reaction, stereoselectivity, hydrogenation, lactam reduction, piperidines, bioluminescence resonance energy transfer.

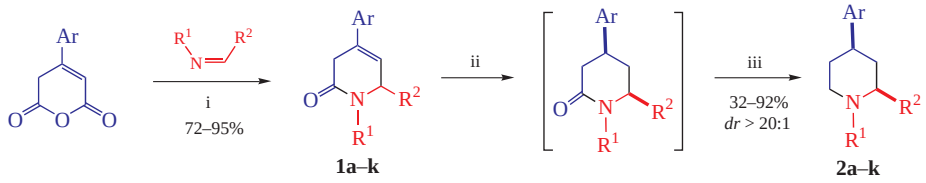
TAAR1 is a G-protein coupled receptor (Gαs) that responds to various endogenous molecules named trace amines (TAs) and is likely related to the classical monoamine neurotransmitter regulation.[1] Therapeutic applications of TAAR1 modulators are thus implicated in the central nervous system disorders, particularly, the treatment of schizophrenia with compound SEP-363856 co-developed by Sunovion and PsychoGenics recently received FDA's breakthrough therapy designation.[2] However, potential benefits of perturbing TAAR1 with a small molecule (ant)agonists are envisioned in areas as vast as drug addiction[3] and metabolic disorders.[4]

The landscape of structural classes endowed with an affinity to TAAR1 is largely reminiscent of that of other aminergic GPCRs, as exemplified by *p*-tyramine, ocotopamine, methamphetamine, amphetamine or syneprine as the receptors' potent ligands. However, the structure of ractopamine and, especially, of EPPTB clearly demonstrated 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 most of the 'classical' aminergic ligands conform.[5] Moreover, over the last decade, the patent literature (primarily originating from Hoffmann-La Roche AG) showcased a resurgence of fundamentally new chemotypes which have been expertly reviewed.[6] Representative of these newer-generation chemotypes are chiral non-racemic nanomolar agonists 2-aminooxazolines RO5256390 and RO5263397 (for the structures, see Online Supplementary Materials, Figure S1).[7]

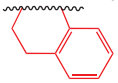
Considering the said flexibility in positioning the lipophilicity centroids relative to the basic centers, which still allows obtaining potent TAAR1 ligands, we were curious to synthesize and test a series of stereodefined *cis*-configured piperidines which have so far not been explored in the context of GPCR modulation (a related scaffold was featured in Merck's β-secretase inhibitors for treatment of the Alzheimer's disease).[8] These compounds, in turn, were envisioned as products of total stereoselective reduction of similarly rare 4,6-disubstituted 1,6-dihydropyridin-2(3*H*)-ones **1** (Scheme 1) which we had earlier found to be the sole products of the decarboxylative variant of the Castagnoli–Cushman reaction (CCR) of imines with either 3-arylglutaconic acids[9] or their anhydrides[10] (see also Online Supplementary Materials, Figure S2). In contrast to the reported multistep approaches[11,12] for stereoselective synthesis of similar compounds, CCR strategy offers advantages of cost-effective, simple and quick experimental procedure, combined with broader substrate scope.

For the preparation of starting 4,6-disubstituted-1,6-dihydropyridin-2(3*H*)-ones **1** in this work, we employed 3-arylglutaconic acid anhydrides[10] which provide significantly improved yields of products **1** compared to *in situ* cyclodehydration of 3-arylglutaconic acids.[9] Indeed, the product yields for the reaction conducted in the two-component format were excellent throughout, including the newly synthesized product **1g** (see Scheme 1).

The intended conversion of compounds **1** to their fully reduced counterparts **2** highly depended on the sequence of steps. Strangely, attempted reduction of the γ,δ-unsaturated lactam ring with $LiAlH_4$ gave massive decomposition while a mild, room-temperature hydrogenation of the double bond removed this liability and rendered the respective piperidin-2-ones (not isolated), the competent substrates for the lactam carbonyl removal. Thus, the yields of compounds **2a**–**k** (obtained as single diastereomers according to ^{1}H NMR spectrum, *dr* > 20 : 1) calculated over two steps were good to excellent (see Scheme 1). The relative stereochemistry of the hydrogenation products was unequivocally established by the combination of DEPT, NOESY and HSQC correlations observable in the tricyclic product **2k** (see Online Supplementary Materials, Figure S3).



a R^1 = Pr, R^2 = 3-FC_6H_4, Ar = 4-FC_6H_4
b R^1 = Bu, R^2 = 4-$F_3CC_6H_4$, Ar = Ph
c R^1 = 4-$MeOC_6H_4(CH_2)_2$, R^2 = 4-MeC_6H_4, Ar = 4-$F_3COC_6H_4$
d R^1 = *c*-C_3H_5, R^2 = 4-$MeOC_6H_4$, Ar = 3,5-$(F_3C)_2C_6H_3$
e R^1 = Bu, R^2 = 4-$MeOC_6H_4$, Ar = 2-$MeOC_6H_4$
f R^1 = Me, R^2 = Ar = Ph
g R^1 = Bu, R^2 = Pr^i, Ar = 4-$MeOC_6H_4$
h R^1 = Bn, R^2 = Pr^i, Ar = Ph
i R^1 = $MeO(CH_2)_2$, R^2 = 4-FC_6H_4, Ar = 2-$MeOC_6H_4$
j R^1 = $Me_2CH(CH_2)_2$, R^2 = 4-MeC_6H_4, Ar = 4-$MeOC_6H_4$
k Ar = Ph, R^1 + R^2 =



Scheme 1 *Reagents and conditions*: i, PhMe, 110 °C, 18 h (*cf.* ref. 10); ii, H_2 (1 atm.), Pd/C, MeOH, room temperature, 48 h; iii, $LiAlH_4$ (3 equiv.), dioxane, 110 °C, 3 h.

Unfortunately, when tested in bioluminescence resonance energy transfer-based *in vitro* assay using HEK293T cells using tyramine hydrochloride (1 μM) as a positive control, none of the compounds investigated produced a promising activation of TAAR1 receptor and thus were deemed inappropriate starting points for further pursuit and optimization.

In conclusion, we have envisaged rare *cis*-configured 1,2,4-trisubstituted piperidines as probes for trace amine associated receptor 1 (TAAR1). Synthesis of the probe series was based on the decarboxylative variant of the Castagnoli–Cushman reaction in two-component format. Stereoselective reduction and lactam carbonyl removal produced the target compounds. Unfortunately, TAAR1 activity prophesied for the series was not detected. Nonetheless, these novel, CNS-focused compounds are available for further drug discovery efforts.

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 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.2021.07.016.

References

1 A. A. Aleksandrov, E. S. Dmitrieva, A. B. Volnova, V. M. Knyazeva, R. R. Gainetdinov and N. V. Polyakova, *Neuroreport*, 2019, **30**, 1004.
2 L. S. Brady, W. Z. Potter and J. A. Gordon, *Exp. Opin. Drug Discov.*, 2019, **14**, 1213.
3 J.-F. Liu and J.-X. Li, *Front. Pharmacol.*, 2018, **9**, 279.
4 E. S. Michael, L. Covic and A. Kuliopulos, *J. Biol. Chem.*, 2019, **294**, 4401.
5 X. Liu, D. K. Grandy and A. Janowski, *Pharmacol. Exp. Ther.*, 2014, **350**, 124.
6 M. Tonelli and E. Cichero, *Expert Opin. Ther. Pat.*, 2020, **30**, 137.
7 G. Galley, A. Beurier, G. Décoret, A. Goergler, R. Hutter, S. Mohr, A. Pähler, P. Schmid, D. Türck, R. Unger, K. G. Zbinden, M. C. Hoener and R. D. Norcross, *ACS Med. Chem. Lett.*, 2016, **7**, 192.
8 K. Liu, S. J. Stachel, C. A. Coburn, T. G. Steele, R. Soll, H. Wu, X. Peng, Y. Cai, X. Du and J. Li, *Patent WO 2010094242 A1*, 2010.
9 A. Firsov, E. Chupakhin, D. Dar'in, O. Bakulina and M. Krasavin, *Org. Lett.*, 2019, **21**, 1637.
10 A. Firsov, O. Bakulina, D. Dar'in, N. Guranova and M. Krasavin, *J. Org. Chem.*, 2020, **85**, 6822.
11 L. Zhang, M. A. Brodney, J. Candler, A. C. Doran, A. J. Duplantier, I. V. Efremov, E. Evrard, K. Kraus, A. H. Ganong, J. A. Haas, A. N. Hanks, K. Jenza, J. T. Lazzaro, N. Maklad, S. A. McCarthy, W. Qian, B. N. Rogers, M. D. Rottas, C. J. Schmidt, J. A. Siuciak, F. D. Tingley, III and A. Q. Zhang, *J. Med. Chem.*, 2011, **54**, 1724.
12 M. Amat, M. Pérez, A. T. Minaglia and J. Bosch, *J. Org. Chem.*, 2008, **73**, 6920.

Received: 24th February 2021; Com. 21/6461