ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett

Letter

Ulotaront: A TAAR1 Agonist for the Treatment of Schizophrenia

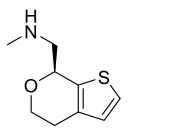
Michele L. R. Heffernan,* Lee W. Herman, Scott Brown, Philip G. Jones, Liming Shao, Michael C. Hewitt, John E. Campbell, Nina Dedic, Seth C. Hopkins, Kenneth S. Koblan, and Linghong Xie

Cite This: *ACS Med. Chem. Lett.* 2022, 13, 92−98

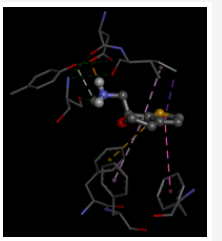
Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Ulotaront (SEP-363856) is a trace-amine associated receptor 1 (TAAR1) agonist with 5-HT1A receptor agonist activity in Phase 3 clinical development, with FDA Breakthrough Therapy Designation, for the treatment of schizophrenia. TAAR1 is a G-protein-coupled receptor (GPCR) that is expressed in cortical, limbic, and midbrain monoaminergic regions. It is activated by endogenous trace amines, and is believed to play an important role in modulating dopaminergic, serotonergic, and glutamatergic circuitry. TAAR1 agonism data are reported herein for ulotaront and its analogues in comparison to endogenous TAAR1 agonists. In addition, a human TAAR1 homology model was built around ulotaront to identify key interactions and attempt to better understand the scaffold-specific TAAR1 agonism structure−activity relationships.



Ulotaront (SEP-363856, **1**)
TAAR1 EC_{50} = 38 nM



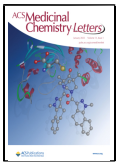
KEYWORDS: *Ulotaront, Trace amine-associated receptor 1 (TAAR1), Trace amines, Schizophrenia*

Ulotaront (SEP-363856) is a TAAR1 agonist with 5-HT1A agonist activity currently in Phase 3 clinical trials, with FDA Breakthrough Therapy Designation, for the treatment of schizophrenia. It has a novel mechanism of action (MOA) compared to antipsychotic drugs, as it is not an antagonist at either the dopamine D2 or the serotonin 5-HT2A receptors.[1,2] Although current antipsychotics demonstrate efficacy against the positive symptoms of schizophrenia, they do not effectively treat the negative or cognitive symptom domains and are associated with substantial adverse effects including movement disorders and metabolic side effects leading to increased cardiovascular risk.[3] Therefore, the urgency to develop new medications with differentiated MOAs is apparent.

Ulotaront has demonstrated efficacy in the treatment of symptoms of an exacerbation of schizophrenia in a large randomized, double-blind placebo-controlled clinical trial, with continued improvement in a 6-month open-label extension study.[1,2] Nonclinical studies support agonism at TAAR1 and 5-HT1A receptors as contributing to the mechanism of action.[4] *In vivo*, ulotaront has demonstrated broad efficacy in nonclinical models of schizophrenia, including phencyclidine (PCP)-induced hyperactivity,[4,5] prepulse inhibition (PPI) of the acoustic startle response,[4] and subchronic PCP-induced deficits in social interaction.[4,5] It also significantly reduced ketamine-induced increases in striatal dopamine synthesis capacity,[6] and it demonstrated inhibitory effects in ventral tegmental area (VTA) neurons in slice and *in vivo* electrophysiology studies,[4] likely mediated via action of TAAR1. Furthermore, Begni *et al.* report that ulotaront upregulates the expression of plasticity-related genes in rats, especially in the prefrontal cortex.[5] Ulotaront also has effects on sleep architecture, likely related to modulation of dopaminergic and serotonergic signaling pathways, with increased latency to rapid-eye movement (REM) sleep and decreased time spent in REM-sleep reported in both rats[4] and humans.[7]

Trace amine-associated receptors (TAARs) are a family of GPCRs, first identified in 2001,[8,9] that are activated predominantly by low abundant (typically <500 nM),[10] trace amines. TAAR1 is expressed in multiple mammalian brain regions, including key dopaminergic (VTA) and serotonergic (dorsal raphe nuclei; DRN) nuclei.[11] Growing evidence supports the potential utility of TAAR1 as a therapeutic target for schizophrenia and other neuropsychiatric disorders through modulation of monoaminergic transmission. In particular, a number of studies utilizing endogenous and synthetic TAAR1 agonists, TAAR1 antagonists, and TAAR1 knockout mice have demonstrated TAAR1 regulation of dopaminergic systems.[12−20] In contrast to postsynaptic D2 receptor blockade, negative regulation of hyperdopaminergic circuits, either through inhibition of dopamine neuronal firing, dopamine release and/or dopamine synthesis capacity, has been proposed to underly the antipsychotic-like effects of TAAR1 agonists.[4,6,10,12,14] In addition, TAAR1 activation also modulates glutamatergic neurotransmission and attenuates hypoglutamatergic activity.[4,10,14,21,22] This is of relevance as both excessive

Received: October 4, 2021
Accepted: November 22, 2021
Published: December 6, 2021



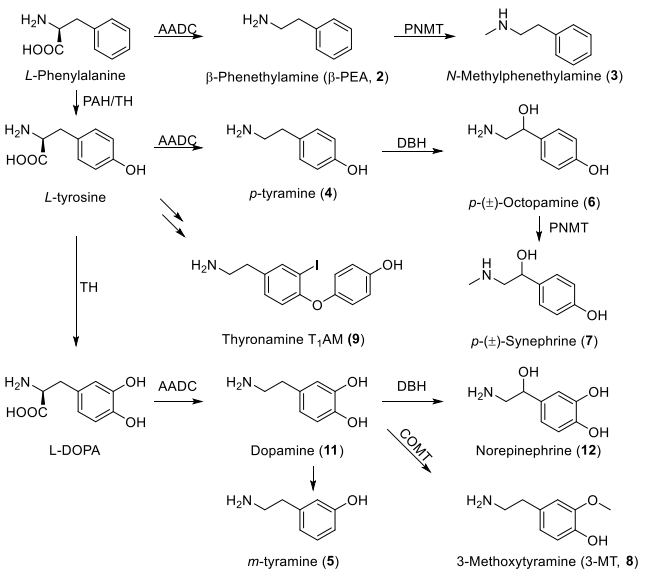
https://doi.org/10.1021/acsmedchemlett.1c00527
ACS Med. Chem. Lett. 2022, 13, 92−98

dopaminergic activity and deficits in cortical glutamatergic neurotransmission have been implicated in the pathophysiology of schizophrenia.[23−26]

Endogenous trace amines are derived from amino acids by biosynthetic pathways involving initial decarboxylation, with subsequent transformations such as *N*-methylation and/or oxidation(s) of the aromatic ring or *β*- to the amine (Scheme 1).[10,27−29] Examples include the most well-known trace amine *β*-phenethylamine (*β*-PEA, **2**), which is derived from L-phenylalanine, as well as other trace amines with the phenethylamine-containing core, such as its *N*-methylated analogue *N*-methylphenethylamine (**3**) as well as various oxygenated analogues derived from *L*-tyrosine such as *p*-tyramine (**4**), *m*-tyramine (**5**), octopamine (**6**), synephrine (**7**), 3-methoxytyramine (3-MT, **8**), and the endogenous 3-iodothyronamine (T1AM, **9**).[10,30] Nonphenethylamine trace amine TAAR1 agonists include tryptamine (**10**), which is derived similarly, from the amino acid *L*-tryptophan (Scheme 2).[10] Interestingly, the trace amines are found in the same brain regions and are synthesized through the same pathways as biogenic amine neurotransmitters with weak TAAR1 agonist activity such as dopamine (**11**), norepinephrine (**12**) and serotonin (**13**),[31] but are in much lower abundance due to tightly controlled, rapid elimination pathways.[10]

In addition to their effects on TAARs, endogenous trace amines have also been shown to exert effects at other targets, including aminergic, non-GPCR targets, and transporters.[10,27]

Scheme 1. Trace Amines and Neurotransmitters Derived from L-Phenylalanine and L-Tyrosine[10a]

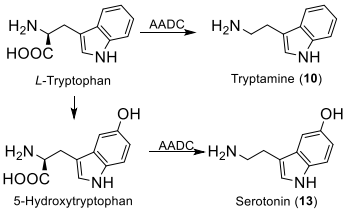


[a]AADC, Aromatic L-amino acid decarboxylase; PAH, phenylalanine hydroxylase; PNMT, phenylethanolamine *N*-methyltransferase; DBH, dopamine-*β*-hydroxylase; COMT, catechol-*O*-methyltransferase; T_1AM, 3-iodothyronamine; TH, tyrosine hydrolase

Thus, the development of selective, small molecule TAAR1 ligands was key to the study of TAAR1-mediated biological effects.

A number of synthetic TAAR1 agonists have also been described (Scheme 3),[32,33] such as Hoffmann-La Roche's reported TAAR1 agonists RO5166017 (**14**),[14,34] RO5256390 (**15**),[21,35] RO5203648 (**16**),[19,35] RO5263397 (**17**),[21,36] and Ralmitaront (**18**).[37,38]

Scheme 2. Trace Amines and Neurotransmitters Derived from L-Tryptophan



Scheme 3. Hoffmann-La Roche's Synthetic TAAR1 Agonists

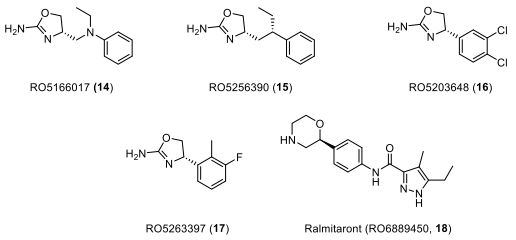


Table 1. Human TAAR1 Agonist Activity of Endogenous Ligands[a]

		EC_{50} (nM)[b]	E_{max} (%)[b]
2	*β*-phenethylamine	15 ± 4	111 ± 3
3	*N*-methylphenethylamine	151 ± 29	111 ± 1
4	*p*-tyramine	76 ± 16	111 ± 1
5	*m*-tyramine	339 ± 72	109 ± 3
9	T_1AM	225 ± 54	105 ± 3
8	3-MT	308 ± 21	101 ± 2
6a	(−)-octopamine	1569 ± 138	116 ± 4
6b	(+)-octopamine	4113 ± 206	108 ± 5
7a	(−)-synephrine	4729 ± 377	113 ± 2
10	tryptamine	2210 ± 180	102 ± 0.3
11	dopamine	1710 ± 160	97 ± 0.5
12	(L)-(−)-norepinephrine	12 200 ± 2,000	99 ± 8
13	serotonin	35 100 ± 12,100	75 ± 8

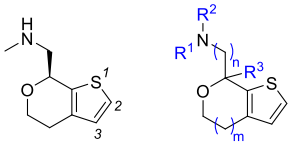
[a]Data shown as mean ± SEM (n = 3). [b]E_{max} is the maximum effect compared to *p*-tyramine control applied to each plate.

While it is now known that ulotaront is a TAAR1 agonist, the efforts that led to the identification of ulotaront were driven by a target-agnostic approach for the discovery of drug candidates with excellent drug-like properties that lack dopamine D2 and serotonin 5-HT2A antagonist activity while demonstrating an *in vivo* phenotypic antipsychotic-like profile.[4,39] Since the medicinal chemistry was not driven by TAAR1 functional activity, it is of interest to retrospectively evaluate the TAAR1 agonism structure−activity relationship (SAR) around this novel TAAR1 agonist chemotype. In this regard, we conducted a single study that measured the human TAAR1 agonist activity, under the same conditions and in triplicate, of known endogenous ligands as well as compounds from the ulotaront chemotype. We then built a human TAAR1 homology model with ulotaront as a bound ligand, in order to identify key interactions and attempt to interpret the SAR of analogues of ulotaront.

The TAAR1 activities of a series of endogenous ligands from this study are summarized in Table 1. Overall, the measured EC_{50}'s tend to be lower in general than those in published

https://doi.org/10.1021/acsmedchemlett.1c00527
ACS Med. Chem. Lett. 2022, 13, 92−98

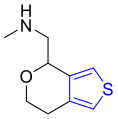
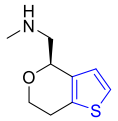
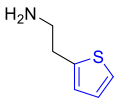
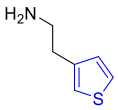
Table 2. Human TAAR1 Agonist Activity of Ulotaront (1) and Analogues



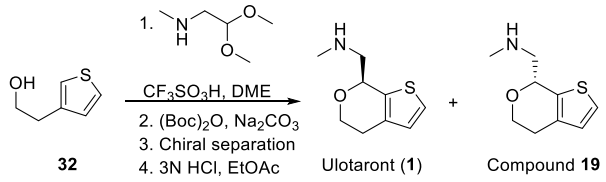
ulotaront (**1**)

	Configuration	m	n	R^1	R^2	R^3	EC_{50} (nM)	Emax (%)
1	*S*	1	1	Me	H	H	38 ± 11	109 ± 3
19	*R*	1	1	Me	H	H	645 ± 169	108 ± 1
20	*RS*	1	1	Me	H	H	51 ± 4	110 ± 4
21	*S*	1	1	Me	H	Me	45,700 ± 5,100	95 ± 4
22	*S*	1	1	H	H	H	3.5 ± 1.2	110 ± 1
23	*S*	1	1	Me	Me	H	203 ± 27	112 ± 1
24	*S*	1	1	-$(CH_2)_4$-		H	7,198 ± 502	113 ± 1
25	*S*	1	2	H	H	H	233 ± 55	105 ± 3
26	*RS*	2	1	Me	H	H	321 ± 65	113 ± 5
27	*RS*	2	1	H	H	H	65 ± 10	111 ± 2

Table 3. Human TAAR1 Agonist Activity of Other Thienyl Analogues

		EC_{50} (nM)	Emax (%)
28		290 ± 50	112 ± 1
29		113 ± 12	110 ± 1
30		8.3 ± 0.5	113 ± 2
31		25 ± 9	112 ± 1

Scheme 4. Synthesis of Ulotaront (1) and its Enantiomer (19) from 2-(Thiophen-3-yl)ethan-1-ol (32)



reports[8,30,31,40] but with similar rank ordering. Trace amine *β*-PEA (**2**) was the most potent endogenous ligand evaluated, with EC_{50} = 15 nM. Its *N*-methyl analogue (**3**) was approximately 10-fold less active. Oxidation of the aromatic ring also reduced TAAR1 potency, with the 4-hydroxylated analogue *p*-tyramine (**4**) and 3-hydroxylated analogue *m*-tyramine (**5**) demonstrating about 5-fold and 23-fold lower activity than *β*-PEA, respectively. Thyronamine T_1AM (**9**), which contains the *β*-PEA core, was less potent, but still submicromolar, with EC_{50} = 225 nM, as was the 3-methoxy, 4-hydroxy analogue 3-MT (**8**), with EC_{50} = 308 nM.

Oxidation of the *β*-phenethylamine scaffold *α*- to the aromatic ring also reduced TAAR1 agonism, with both enantiomers of octopamine (**6a**, **6b**) being 21-fold and 54-fold less active, respectively, than the corresponding non-hydroxylated analogue *p*-tyramine (**4**). As seen with *N*-methylation of *β*-PEA (**2**), *N*-methylation of the more active octopamine isomer (**6a**) to the endogenous trace amine (−)-synephrine (**7a**) reduced activity, in this case by approximately 3-fold compared to **6a**. Tryptamine (**10**), with an indole in place of the phenyl of *β*-PEA, is about 150-fold less active than *β*-PEA, with an EC_{50} = 2.2 *μ*M.

The biogenic amine neurotransmitters tested were all considerably less active than the more potent of the trace amines. For example, dopamine (**11**), which has both the 3-hydroxy group like *m*-tyramine **5** and the 4-hydroxy group as in *p*-tyramine, is 5-fold and 23-fold less active, respectively, than **5** and **4**. Norepinephrine (**12**), which is hydroxylated *α*- to the aromatic group compared to dopamine (**11**), is less active, similarly to the SAR observed with the trace amines. Serotonin (**13**), was the least active (EC_{50} = 23.8 *μ*M), which is consistent with aromatic hydroxylation reducing the potency of the weakly active trace amine tryptamine (**10**).

Human TAAR1 agonists activities for ulotaront and a series of its analogues are shown in Table 2, with ulotaront (**1**) demonstrating full agonist activity (E_{max} = 109%) with an EC_{50} of 38 nM. As with its *in vivo* potency[4] and 5-HT1A potency,[41] ulotaront has more potent (∼17-fold) TAAR1 agonism than its enantiomer (**19**). This absolute TAAR1 agonism stereochemical preference exists for all sets of enantiomers tested (see the Supporting Information for data on other enantiomers). Furthermore, substitution of the chiral carbon of ulotaront with methyl (**21**) reduces TAAR1 potency by >1000-fold.

https://doi.org/10.1021/acsmedchemlett.1c00527
ACS Med. Chem. Lett. 2022, 13, 92−98

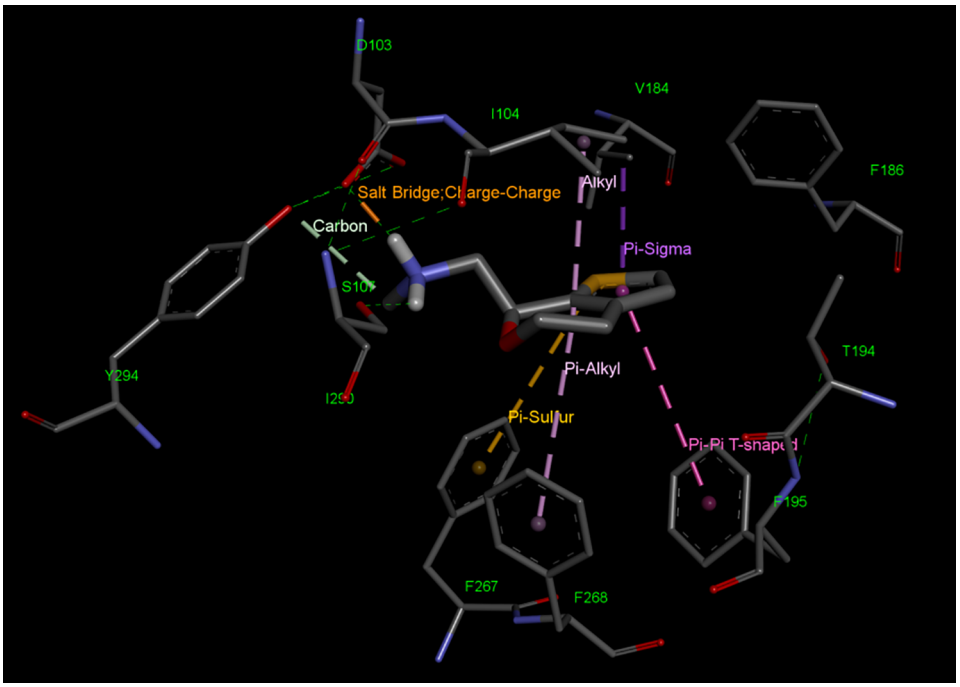


Figure 1. Ulotaront bound to the human TAAR1 receptor binding site. Graphic rendered by Biovia Discovery Studio Visualizer.

SAR around the ulotaront amine was also investigated. Similar to the trace amines β-PEA (**2**) and *N*-methyl PEA (**3**), the *N*-demethylated analogue (**22**) of ulotaront is about 11-fold more potent, with EC_{50} = 3.5 nM. Interestingly, the *N*,*N*-dimethyl analogue **23** is less active, with EC_{50} = 203 nM. When R^1 and R^2 together equal $-(CH_2)_4-$ to form a pyrrolidine ring such as in **24**, TAAR1 agonist potency is further reduced, with an EC_{50} 189-fold less potent than that of ulotaront. Lastly, extending the linker length from one carbon as in ulotaront to a two-carbon linker (**25**) reduced the activity 67-fold compared to the corresponding *N*-demethylated analogue **22**.

Expansion of the dihydropyran ring of ulotaront to the tetrahydrooxepin ring of racemic **26** resulted in an approximately 6-fold decrease in potency (EC_{50} = 321 nM) compared to racemic ulotaront **20**. As with demethylated ulotaront, the corresponding *N*-demethylated analogue (**27**) was about 5-fold more potent (EC_{50} = 65 nM) compared to **26**.

The location of the sulfur in the fused thiophenyl ring is also important. Racemic **28** (Table 3), with the thienyl sulfur shifted to the 2-position in ulotaront, is ∼6-fold less potent than racemic ulotaront (**20**). Similarly, compound **29**, with the thienyl sulfur shifted to the 3-position in ulotaront, is 3-fold less active for TAAR1 than ulotaront.

Considering the shared aryl ethyl amine scaffold of ulotaront with the trace amines such as β-PEA, we also tested the TAAR1 agonist activity of the ring opened analogues **30** and **31**. The thiophen-2-ylethanamine **30** corresponds to the ulotaront thiophene configuration, while the thiophen-3-ylethanamine **31** corresponds to the thieno[3,2-*c*]pyranyl configuration of **29**. Both diethyl amine thiophenes had potent TAAR1 agonism (EC_{50} = 8.3 and 25 nM, respectively), with the thiophene corresponding to the ulotaront configuration being approximately 3-fold more potent than the other.

Ulotaront was synthesized (Scheme 4) by the condensation of 2-(thiophen-3-yl)ethanol (**32**) and *N*-methylaminoacetaldehyde dimethyl acetal in the presence of triflic acid in dimethoxyethane.[39] BOC protection, followed by chiral separation and then deprotection provided ulotaront. Analogous reactions were used to synthesize some of the compounds in Table 2. Thienyl analogues **28** and **29** were synthesized similarly, but from 2-(thiophen-3-yl)ethan-1-ol and 2-(thiophen-2-yl)ethan-1-ol, respectively. Details for the chemical synthesis for ulotaront as well as all the compounds from Tables 2 and 3 can be found in the Supporting Information.

The initial three-dimensional homology model for TAAR1 was obtained from GPCRdb.[42] The starting pose for ulotaront was determined by docking with the program FRED[43] (v4.0). Molecular dynamics calculations reported in this work were all performed using the AMBER[44] (v20) simulation package. Docking, minimization, molecular dynamics, and simulated annealing were performed as described in the Supporting Information. This process produced a TAAR1 homology model (Figure 1) that was used to identify key interactions and attempt to better understand the scaffold-specific TAAR1 agonism SAR reported in Tables 2 and 3.

The primary interaction of ulotaront with TAAR1 is a salt bridge from the amine to the conserved Asp103, a typical interaction in class A GPCRs.[8,45] The aspartate also participates in a hydrogen bond network with Ser107 and Tyr294. The thiophene is sandwiched between Phe198 on one side (with which it makes a $\pi-\pi$ T-interaction) and Ile104 on the other. Phe267 makes a π−sulfur interaction, while Phe268 makes a hydrophobic contact with the pyran ring alkyl carbons. Ulotaront does not interact with Ser 198 that is believed to interact with the catechol in norepinephrine.

Our model shares commonalities with various homology and docking models that previously reported ligand interactions with Asp103, Ser107, Ile104, Phe195, Tyr294, Phe267, and Phe268.[46−52] Recently, a report of a molecular dynamics (MD) study specifically describing the interactions of ulotaront with the TAAR1 receptor was published.[53] Our model agrees with that model with regard to interactions with Asp103, Ser107, Phe195, Phe268, and Ile104 but not for interactions

https://doi.org/10.1021/acsmedchemlett.1c00527
ACS Med. Chem. Lett. 2022, 13, 92−98

with Phe186, Phe199, Thr194, Ser198, and Thr271 that are asserted by the authors of that paper. Furthermore, the published model does not describe a role for Tyr294 and Phe267, which figure prominently in our model.

Our TAAR1 model accounts for a number of the SAR observations made for ulotaront and its related analogues but may not be appropriate for other scaffolds. Compound **21**, a virtually inactive analogue (EC_{50} = 46 μM) with an extra methyl at the tertiary center on the isochroman ring, would make an unfavorable contact with Phe267. Inverting the chiral center, such as in ulotaront's enantiomer **19**, would either prevent the critical salt bridge to Asp103 or force the orientation of the thiophene into unfavorable collisions with the three Phe groups. Extending the amine carbon chain results in less active compound **25**, which would be expected as the lengthened chain would push the thiophene and the pyran ring into an orientation that would allow fewer contacts with the Phe and Ile groups that sandwich the parent compound. Removing the amine methyl (**22**) would enable an additional hydrogen bond to Tyr294, while adding another methyl (**23**) would disrupt the hydrogen bond to Ser107. Incorporating the nitrogen into a ring (**24**) reduces potency, as in the case of adding an additional methyl, as well as adding steric bulk to an already crowded region around Trp264.

It is less obvious why flipping the thiophene ring, as in compounds **28** and **29**, would result in a modest potency reduction, since most of the proposed interactions would be preserved. Perhaps this is due to an electronic effect which would not be captured by the approximations of dynamics simulations. As well, thiophen-2-ylethanamine **30** is extremely potent (EC_{50} = 8.3 nM), even though the number of favorable contacts is reduced. Perhaps this is due to a favorable reorganization of the receptor.

In conclusion, the TAAR1 agonism SAR around the ulotaront scaffold was retrospectively investigated, as ulotaront was discovered through a target-agnostic, *in vivo* phenotypic approach. Evaluation of ulotaront in a TAAR1 homology model identified key binding pocket interactions and was useful to understand the TAAR1 agonism SAR of ulotaront analogues originally evaluated only phenotypically. Ulotaront, currently in Phase 3 clinical development for the treatment of schizophrenia, with its novel (non-D2, non-5-HT2A) mechanism of action, represents a new pharmacological class for the treatment of schizophrenia.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.1c00527.

Supplemental references relating to currently available antipsychotics, mammalian TAAR1 expression, reported synthetic human TAAR1 agonists, endogenous trace amine and neurotransmitter biosynthesis pathways, reported TAAR1 agonist activity of trace amines, and rodent TAAR1 homology models; detailed synthetic, pharmacological, and homologue modeling-related procedures, compound characterization data, and additional TAAR1 agonism data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Michele L. R. Heffernan − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States;* orcid.org/0000-0003-2001-8833; Email: michele.heffernan@sunovion.com

Authors

Lee W. Herman − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States;* orcid.org/0000-0002-9664-9191

Scott Brown − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States*

Philip G. Jones − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States*

Liming Shao − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States*

Michael C. Hewitt − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States*

John E. Campbell − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States*

Nina Dedic − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States*

Seth C. Hopkins − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States*

Kenneth S. Koblan − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States*

Linghong Xie − *Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts 01752, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmedchemlett.1c00527

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

The current research was funded by Sunovion Pharmaceuticals, Inc. All authors were employees of Sunovion Pharmaceuticals, Inc. at the time of their contribution to this work.

Notes

The authors declare the following competing financial interest(s): All Authors were employees of Sunovion Pharmaceuticals, Inc. at the time of their contribution to this work.

■ ACKNOWLEDGMENTS

Sunovion discovered ulotaront in collaboration with PsychoGenics based in part on a mechanism-independent approach using the in vivo phenotypic SmartCube platform and associated artificial intelligence algorithms. We thank Junhui Kang and the ChemPartner chemistry team for compound resynthesis and characterization. TAAR1 agonism data was obtained commercially from Euroscreen Fast, a business unit of Epics Therapeutics. Vibrational Circular Dichroism spectroscopy was obtained commercially from Biotools, Inc. in Juniper, FL.

■ REFERENCES

(1) Correll, C. U.; Koblan, K. S.; Hopkins, S. C.; Kent, J.; Cheng, H.; Goldman, R.; Loebel, A. Safety and Effectiveness of SEP-363856 in

Schizophrenia: Results of a 6-Month, Open-Label Extension Study. *CNS Spectr.* **2021**, *26* (2), 148−149.
(2) Koblan, K. S.; Kent, J.; Hopkins, S. C.; Krystal, J. H.; Cheng, H.; Goldman, R.; Loebel, A. A Non-D2-Receptor-Binding Drug for the Treatment of Schizophrenia. *N. Engl. J. Med.* **2020**, *382* (16), 1497−1506.
(3) Miyamoto, S.; Duncan, G. E.; Marx, C. E.; Lieberman, J. A. Treatments for Schizophrenia: A Critical Review of Pharmacology and Mechanisms of Action of Antipsychotic Drugs. *Mol. Psychiatry* **2005**, *10* (1), 79−104.
(4) Dedic, N.; Jones, P. G.; Hopkins, S. C.; Lew, R.; Shao, L.; Campbell, J. E.; Spear, K. L.; Large, T. H.; Campbell, U. C.; Hanania, T.; Leahy, E.; Koblan, K. S. SEP-363856, a Novel Psychotropic Agent with a Unique, Non-D2 Receptor Mechanism of Action. *J. Pharmacol. Exp. Ther.* **2019**, *371* (1), 1−14.
(5) Begni, V.; Sanson, A.; Luoni, A.; Sensini, F.; Grayson, B.; Munni, S.; Neill, J. C.; Riva, M. A. Towards Novel Treatments for Schizophrenia: Molecular and Behavioural Signatures of the Psychotropic Agent Sep-363856. *Int. J. Mol. Sci.* **2021**, *22* (8), 4119.
(6) Kokkinou, M.; Irvine, E. E.; Bonsall, D. R.; Natesan, S.; Wells, L. A.; Smith, M.; Glegola, J.; Paul, E. J.; Tossell, K.; Veronese, M.; Khadayate, S.; Dedic, N.; Hopkins, S. C.; Ungless, M. A.; Withers, D. J.; Howes, O. D. Reproducing the Dopamine Pathophysiology of Schizophrenia and Approaches to Ameliorate It: A Translational Imaging Study with Ketamine. *Mol. Psychiatry* **2021**, *26*, 2562.
(7) Hopkins, S. C.; Dedic, N.; Koblan, K. S. Effect of TAAR1/5-HT1A Agonist SEP-363856 on REM Sleep in Humans. *Transl. Psychiatry* **2021**, *11* (1), 228.
(8) Borowsky, B.; Adham, N.; Jones, K. A.; Raddatz, R.; Artymyshyn, R.; Ogozalek, K. L.; Durkin, M. M.; Lakhlani, P. P.; Bonini, J. A.; Pathirana, S.; Boyle, N.; Pu, X.; Kouranova, E.; Lichtblau, H.; Ochoa, F. Y.; Branchek, T. A.; Gerald, C. Trace Amines: Identification of a Family of Mammalian G Protein-Coupled Receptors. *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98* (16), 8966−8971.
(9) Bunzow, J. R.; Sonders, M. S.; Arttamangkul, S.; Harrison, L. M.; Zhang, G.; Quigley, D. I.; Darland, T.; Suchland, K. L.; Pasumamula, S.; Kennedy, J. L.; Olson, S. B.; Magenis, R. E.; Amara, S. G.; Grandy, D. K. Amphetamine, 3,4-Methylenedioxymethamphetamine, Lysergic Acid Diethylamide, and Metabolites of the Catecholamine Neurotransmitters Are Agonists of a Rat Trace Amine Receptor. *Mol. Pharmacol.* **2001**, *60* (6), 1181−1188.
(10) Gainetdinov, R. R.; Hoener, M. C.; Berry, M. D. Trace Amines and Their Receptors. *Pharmacol. Rev.* **2018**, *70* (3), 549−620.
(11) Rutigliano, G.; Accorroni, A.; Zucchi, R. The Case for TAAR1 as a Modulator of Central Nervous System Function. *Front. Pharmacol.* **2018**, *8*, 987.
(12) Leo, D.; Mus, L.; Espinoza, S.; Hoener, M. C.; Sotnikova, T. D.; Gainetdinov, R. R. Taar1-Mediated Modulation of Presynaptic Dopaminergic Neurotransmission: Role of D2 Dopamine Autoreceptors. *Neuropharmacology* **2014**, *81*, 283−291.
(13) Bradaia, A.; Trube, G.; Stalder, H.; Norcross, R. D.; Ozmen, L.; Wettstein, J. G.; Pinard, A.; Buchy, D.; Gassmann, M.; Hoener, M. C.; Bettler, B. The Selective Antagonist EPPTB Reveals TAAR1-Mediated Regulatory Mechanisms in Dopaminergic Neurons of the Mesolimbic System. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106* (47), 20081−20086.
(14) Revel, F. G.; Moreau, J.-L.; Gainetdinov, R. R.; Bradaia, A.; Sotnikova, T. D.; Mory, R.; Durkin, S.; Zbinden, K. G.; Norcross, R.; Meyer, C. A.; Metzler, V.; Chaboz, S.; Ozmen, L.; Trube, G.; Pouzet, B.; Bettler, B.; Caron, M. G.; Wettstein, J. G.; Hoener, M. C. TAAR1 Activation Modulates Monoaminergic Neurotransmission, Preventing Hyperdopaminergic and Hypoglutamatergic Activity. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108* (20), 8485−8490.
(15) Espinoza, S.; Ghisi, V.; Emanuele, M.; Leo, D.; Sukhanov, I.; Sotnikova, T. D.; Chieregatti, E.; Gainetdinov, R. R. Postsynaptic D2 Dopamine Receptor Supersensitivity in the Striatum of Mice Lacking TAAR1. *Neuropharmacology* **2015**, *93*, 308−313.
(16) Harmeier, A.; Obermueller, S.; Meyer, C. A.; Revel, F. G.; Buchy, D.; Chaboz, S.; Dernick, G.; Wettstein, J. G.; Iglesias, A.; Rolink, A.; Bettler, B.; Hoener, M. C. Trace Amine-Associated Receptor 1 Activation Silences GSK3β Signaling of TAAR1 and D2R Heteromers. *Eur. Neuropsychopharmacol.* **2015**, *25* (11), 2049−2061.
(17) Lindemann, L.; Meyer, C. A.; Jeanneau, K.; Bradaia, A.; Ozmen, L.; Bluethmann, H.; Bettler, B.; Wettstein, J. G.; Borroni, E.; Moreau, J.-L.; Hoener, M. C. Trace Amine-Associated Receptor 1 Modulates Dopaminergic Activity. *J. Pharmacol. Exp. Ther.* **2008**, *324* (3), 948−956.
(18) Revel, F. G.; Meyer, C. A.; Bradaia, A.; Jeanneau, K.; Calcagno, E.; Andre, C. B.; Haenggi, M.; Miss, M. T.; Galley, G.; Norcross, R. D.; Invernizzi, R. W.; Wettstein, J. G.; Moreau, J. L.; Hoener, M. C. Brain-Specific Overexpression of Trace Amine-Associated Receptor 1 Alters Monoaminergic Neurotransmission and Decreases Sensitivity to Amphetamine. *Neuropsychopharmacology* **2012**, *37* (12), 2580−2592.
(19) Revel, F. G.; Moreau, J. L.; Gainetdinov, R. R.; Ferragud, A.; Velazquez-Sanchez, C.; Sotnikova, T. D.; Morairty, S. R.; Harmeier, A.; Groebke Zbinden, K.; Norcross, R. D.; Bradaia, A.; Kilduff, T. S.; Biemans, B.; Pouzet, B.; Caron, M. G.; Canales, J. J.; Wallace, T. L.; Wettstein, J. G.; Hoener, M. C. Trace Amine-Associated Receptor 1 Partial Agonism Reveals Novel Paradigm for Neuropsychiatric Therapeutics. *Biol. Psychiatry* **2012**, *72* (11), 934−942.
(20) Wolinsky, T. D.; Swanson, C. J.; Smith, K. E.; Zhong, H.; Borowsky, B.; Seeman, P.; Branchek, T.; Gerald, C. P. The Trace Amine 1 Receptor Knockout Mouse: An Animal Model with Relevance to Schizophrenia. *Genes, Brain Behav.* **2007**, *6* (7), 628−639.
(21) Revel, F. G.; Moreau, J. L.; Pouzet, B.; Mory, R.; Bradaia, A.; Buchy, D.; Metzler, V.; Chaboz, S.; Groebke, Z. K.; Galley, G.; Norcross, R. D.; Tuerck, D.; Bruns, A.; Morairty, S. R.; Kilduff, T. S.; Wallace, T. L.; Risterucci, C.; Wettstein, J. G.; Hoener, M. C. A New Perspective for Schizophrenia: TAAR1 Agonists Reveal Antipsychotic- and Antidepressant-like Activity, Improve Cognition and Control Body Weight. *Mol. Psychiatry* **2013**, *18* (5), 543−556.
(22) Espinoza, S.; Lignani, G.; Caffino, L.; Maggi, S.; Sukhanov, I.; Leo, D.; Mus, L.; Emanuele, M.; Ronzitti, G.; Harmeier, A.; Medrihan, L.; Sotnikova, T. D.; Chieregatti, E.; Hoener, M. C.; Benfenati, F.; Tucci, V.; Fumagalli, F.; Gainetdinov, R. R. TAAR1 Modulates Cortical Glutamate NMDA Receptor Function. *Neuropsychopharmacology* **2015**, *40* (9), 2217−2227.
(23) Howes, O. D.; Kambeitz, J.; Kim, E.; Stahl, D.; Slifstein, M.; Abi-Dargham, A.; Kapur, S. The Nature of Dopamine Dysfunction in Schizophrenia and What This Means for Treatment: Meta-Analysisof Imaging Studies. *Arch. Gen. Psychiatry* **2012**, *69* (8), 776−786.
(24) Laruelle, M.; Abi-Dargham, A.; Gil, R.; Kegeles, L.; Innis, R. Increased Dopamine Transmission in Schizophrenia: Relationship to Illness Phases. *Biol. Psychiatry* **1999**, *46* (1), 56−72.
(25) Coyle, J. T.; Basu, A.; Benneyworth, M. Glutamatergic Synaptic Dysregulation in Schizophrenia. *Handb. Exp. Pharmacol.* **2012**, *213*, 267−295.
(26) Javitt, D. C.; Zukin, S. R. Recent Advances in the Phencyclidine Model of Schizophrenia. *Am. J. Psychiatry* **1991**, *148* (10), 1301−1308.
(27) Burchett, S. A.; Hicks, T. P. The Mysterious Trace Amines: Protean Neuromodulators of Synaptic Transmission in Mammalian Brain. *Prog. Neurobiol. (Oxford, U. K.)* **2006**, *79* (5−6), 223−246.
(28) Grandy, D. K. Trace Amine-Associated Receptor 1-Family Archetype or Iconoclast? *Pharmacol. Ther.* **2007**, *116* (3), 355−390. Grandy, D. K. Trace amine-associated receptor 1-Family archetype or iconoclast? *Pharmacol. Ther.* **2007**, *116* (3), 355−390.
(29) Christian, S. L.; Berry, M. D. Trace Amine-Associated Receptors as Novel Therapeutic Targets for Immunomodulatory Disorders. *Front. Pharmacol.* **2018**, *9*, 680.
(30) Cöster, M.; Biebermann, H.; Schoeneberg, T.; Staeubert, C. Evolutionary Conservation of 3-Iodothyronamine as an Agonist at the Trace Amine-Associated Receptor 1. *Eur. Thyroid J.* **2015**, *4* (Suppl. 1), 9−20.
(31) Lindemann, L.; Ebeling, M.; Kratochwil, N. A.; Bunzow, J. R.; Grandy, D. K.; Hoener, M. C. Trace Amine-Associated Receptors

https://doi.org/10.1021/acsmedchemlett.1c00527
ACS Med. Chem. Lett. 2022, 13, 92−98

Form Structurally and Functionally Distinct Subfamilies of Novel G Protein-Coupled Receptors. *Genomics* **2005**, *85* (3), 372−385.
(32) Xu, Z.; Li, Q. TAAR Agonists. *Cell. Mol. Neurobiol.* **2020**, *40* (2), 257−272.
(33) Tonelli, M.; Cichero, E. Trace Amine Associated Receptor 1 (TAAR1) Modulators: A Patent Review (2010-Present). *Expert Opin. Ther. Pat.* **2020**, *30* (2), 137−145.
(34) Galley, G.; Groebke Zbinden, K.; Norcross, R.; Stalder, H. Preparation of Aminooxazoline Derivatives for Use as TAAR1 Ligands. WO 2008/098857 A1, 2008.
(35) Galley, G.; Groebke Zbinden, K.; Norcross, R.; Stalder, H. Preparation of Aminooxazoline Derivatives for Use as Central Nervous System Agents. WO2008092785A1, 2008.
(36) Hoener, M.; Raab, S.; Risterucci, C.; Sewing, S. Pharmaceutical Combination of Trace Amine-Associated Receptor 1 Agonist and an Antipsychotic Drug. US20120028964A2, 2012.
(37) Galley, G.; Hoener, M.; Norcross, R.; Pflieger, P. Preparation of 5-Ethyl-4-Methylpyrazole-3-Carboxamide Having Activity as Agonist of TAAR. WO2017157873A1, 2017.
(38) WHO. International Nonproprietary Names for Pharmaceutical Substances (INN). *WHO Drug Inf.* **2019**, *33* (2), 233−392.
(39) Shao, L.; Campbell, J. E.; Hewitt, M. C.; Campbell, U.; Hanania, T. G. Preparation of Thienopyranylmethanamine Derivatives and Analogs for Use as Nervous System Agents. WO2011069063A2, 2011.
(40) Wainscott, D. B.; Little, S. P.; Yin, T.; Tu, Y.; Rocco, V. P.; He, J. X.; Nelson, D. L. Pharmacologic Characterization of the Cloned Human Trace Amine-Associated Receptor1 (TAAR1) and Evidence for Species Differences with the Rat TAAR1. *J. Pharmacol. Exp. Ther.* **2007**, *320* (1), 475−485.
(41) Ulotaront (**1**) 5-HT1A binding K_i = 284 nM (see ref 4), while ulotaront enantiomer **19** 5-HT1A binding K_i = 10.5 μM (previously unreported result).
(42) Kooistra, A. J.; Mordalski, S.; Pándy-Szekeres, G.; Esguerra, M.; Mamyrbekov, A.; Munk, C.; Keserű, G. M.; Gloriam, D. E. GPCRdb in 2021: Integrating GPCR Sequence, Structure and Function. *Nucleic Acids Res.* **2021**, *49* (D1), D335−D343.
(43) McGann, M. FRED Pose Prediction and Virtual Screening Accuracy. *J. Chem. Inf. Model.* **2011**, *51* (3), 578−596.
(44) Case, D. A.; Aktulga, H. M.; Belfon, K.; Ben-Shalom, I. Y.; Brozell, S. R.; Cerutti, D. S.; Cheatham, T.E., III; Cruzeiro, V. W. D.; Darden, T. A.; Duke, R. E.; Giambasu, G.; Gilson, M. K.; Gohlke, H.; Goetz, A. W.; Harris, R.; Izadi, S.; Izmailov, S. A.; Jin, C.; Kasavajhala, K.; Kaymak, M. C. et al. *Amber20*; University of California, San Francisco, 2020.
(45) Cherezov, V.; Rosenbaum, D. M.; Hanson, M. A.; Rasmussen, S. G. F.; Thian, F. S.; Kobilka, T. S.; Choi, H.-J.; Kuhn, P.; Weis, W. I.; Kobilka, B. K.; Stevens, R. C. High-Resolution Crystal Structure of an Engineered Human B2-Adrenergic G Protein-Coupled Receptor. *Science (Washington, DC, U. S.)* **2007**, *318* (5854), 1258−1265.
(46) Lam, V. M.; Rodriguez, D.; Zhang, T.; Koh, E. J.; Carlsson, J.; Salahpour, A. Discovery of Trace Amine-Associated Receptor 1 Ligands by Molecular Docking Screening against a Homology Model. *MedChemComm* **2015**, *6* (12), 2216−2223.
(47) Cichero, E.; Espinoza, S.; Gainetdinov, R. R.; Brasili, L.; Fossa, P. Insights into the Structure and Pharmacology of the Human Trace Amine-Associated Receptor 1 (HTAAR1): Homology Modelling and Docking Studies. *Chem. Biol. Drug Des.* **2013**, *81* (4), 509−516.
(48) Cichero, E.; Espinoza, S.; Franchini, S.; Guariento, S.; Brasili, L.; Gainetdinov, R. R.; Fossa, P. Further Insights Into the Pharmacology of the Human Trace Amine-Associated Receptors: Discovery of Novel Ligands for TAAR1 by a Virtual Screening Approach. *Chem. Biol. Drug Des.* **2014**, *84* (6), 712−720.
(49) Tan, E. S.; Naylor, J. C.; Groban, E. S.; Bunzow, J. R.; Jacobson, M. P.; Grandy, D. K.; Scanlan, T. S. The Molecular Basis of Species-Specific Ligand Activation of Trace Amine-Associated Receptor 1 (TAAR1). *ACS Chem. Biol.* **2009**, *4* (3), 209−220.
(50) Tonelli, M.; Espinoza, S.; Gainetdinov, R. R.; Cichero, E. Novel Biguanide-Based Derivatives Scouted as TAAR1 Agonists: Synthesis, Biological Evaluation, ADME Prediction and Molecular Docking Studies. *Eur. J. Med. Chem.* **2017**, *127*, 781−792.
(51) Francesconi, V.; Cichero, E.; Kanov, E. V.; Laurini, E.; Pricl, S.; Gainetdinov, R. R.; Tonelli, M. Novel 1-Amidino-4-Phenylpiperazines as Potent Agonists at Human TAAR1 Receptor: Rational Design, Synthesis, Biological Evaluation and Molecular Docking Studies. *Pharmaceuticals* **2020**, *13* (11), 391.
(52) Guariento, S.; Tonelli, M.; Espinoza, S.; Gerasimov, A. S.; Gainetdinov, R. R.; Cichero, E. Rational Design, Chemical Synthesis and Biological Evaluation of Novel Biguanides Exploring Species-Specificity Responsiveness of TAAR1 Agonists. *Eur. J. Med. Chem.* **2018**, *146*, 171−184.
(53) Nair, P. C.; Miners, J. O.; McKinnon, R. A.; Langmead, C. J.; Gregory, K. J.; Copolov, D.; Chan, S. K. W.; Bastiampillai, T. Binding of SEP-363856 within TAAR1 and the 5HT1A Receptor: Implications for the Design of Novel Antipsychotic Drugs. *Mol. Psychiatry* **2021**, 1−7.

https://doi.org/10.1021/acsmedchemlett.1c00527
ACS Med. Chem. Lett. 2022, 13, 92−98