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Highly potent, non-basic 5-HT$_6$ ligands. Site mutagenesis evidence for a second binding mode at 5-HT$_6$ for antagonism

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ABSTRACT

A series of 5-HT$_6$ ligands derived from (*R*)-1-(amino)methyl-6-(phenyl)sulfonyltetralin was prepared that yielded several non-basic analogs having sub-nanomolar affinity. Ligand structure–activity relationships, receptor point mutation studies, and molecular modeling of these novel ligands all combined to reveal a new alternative binding mode to 5-HT$_6$ for antagonism.

The 5-HT$_6$ receptor is a member of the super family of seven trans-membrane G-protein-coupled receptors and the small group of 5-HT receptors that are positively linked to adenylyl cyclase.[1] It occurs almost exclusively in the brain and is most densely localized in those areas of the limbic and cortical regions that are associated with cognition. Although the functional role of 5-HT$_6$ is somewhat controversial, its physiological distribution and binding characteristics to several important tricyclic antidepressants and atypical antipsychotics implicate it in diverse CNS disorders including psychosis,[1] affective disorders,[1b,2] anxiety,[3] epilepsy,[4] obesity,[5] and most compellingly, cognition and memory disorders.[5a,c,6] Animal behavioral and micro-dialysis studies support a regulatory role for 5-HT$_6$ in cholinergic and glutamatergic pathways suggesting 5-HT$_6$ antagonists may have therapeutic utility for the treatment of cognitive deficits in Alzheimer's disease and schizophrenia.[6a,7]

While there has been extensive effort with considerable progress in identifying functional ligands for 5-HT$_6$ since its discovery,[1a] there remains some controversy over the mode by which ligands bind at the receptor site. Indeed, the molecular diversity of active templates[8] for 5-HT$_6$ has caused more conundrum than clarification. To date, the structural features that are most commonly recognized for antagonist binding to 5-HT$_6$ are three main elements: (i) a positive ionizable anchoring group, usually in the form of an amine, that interacts with the receptor at trans-membrane helix 3 aspartic acid 106 (TM3 Asp106) and that is attached by no more than 5-atom distance to (ii) a flat aromatic core ring system. To the core ring system, (iii) a second distal pendant aromatic ring is attached by a linker that must be tetrahedral in geometry and is most effectively accommodated by sulfonyl. As these features are quite simplistic, it is not surprising that so many different active molecular scaffolds have been identified, and yet a model for binding remains nebulous. The first attempt at a binding model was proposed by Bromidge[9] and included an ionic interaction between ligand amine and TM3 Asp106 with additional aromatic π-stacking interactions involving Phe277 and Trp281. Subsequently, Glennon and co-workers[10] proposed two separate binding orientations for agonists and antagonists with both orientations sharing the TM3 Asp106 site for positive ionizable interactions. The other major interactions for antagonism in this model were implied to occur between the pendant arylsulfonyl ring and TM6 Gln291 (H-bond) and TM7 Phe302 (π-stacking). Campillo and co-workers[11] have proposed a similar model to Glennon's with the addition of hydrophobic π-stacking elements between the ligand core ring and TM6 Phe284, and the ligand pendant ring with TM5 Phe188. Until now, all of these models have been well consistent with ligand structure–activity relationships (SAR) and the structural characteristics that are recognized for binding.

A radioligand binding screen of our in house compound libraries turned up the di-substituted tetralin **1** (Fig. 1) as a very potent and selective 5-HT$_6$ antagonist, but with pharmacokinetic (PK) properties that included very poor brain penetration and a CYP2D6 IC$_{50}$ of less than 50 nM, both of which were attributed to the highly polar

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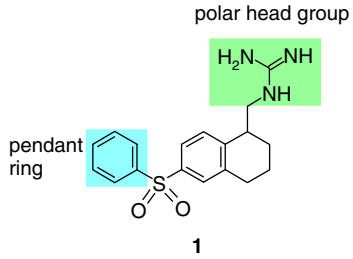
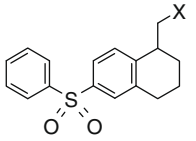


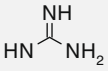
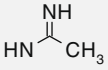
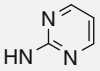
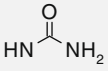
Figure 1. Breakdown of regions of **1** for analog development.

guanidine. With the hope of finding a more PK compatible head group for this template, we prepared a small selected group of analogs (**2**–**6**, Table 1) designed to dissect the importance of the guanidine for binding, and were highly encouraged to find that not only was the guanidine non-essential, but that a simple non-basic urea (**6**) provided comparable activity. Compound **6** was subsequently confirmed to completely inhibit 5-HT evoked response at a recombinately expressed human 5-HT_6 receptor. Herein, we report our efforts to further optimize compound **1** with respect to receptor binding and PK properties, all of which led to the discovery of several non-basic functional ligands having sub-nanomolar affinity. In addition, we offer clear evidence that they bind in a manner separate from the traditional positive ionizable TM3 Asp106 site.

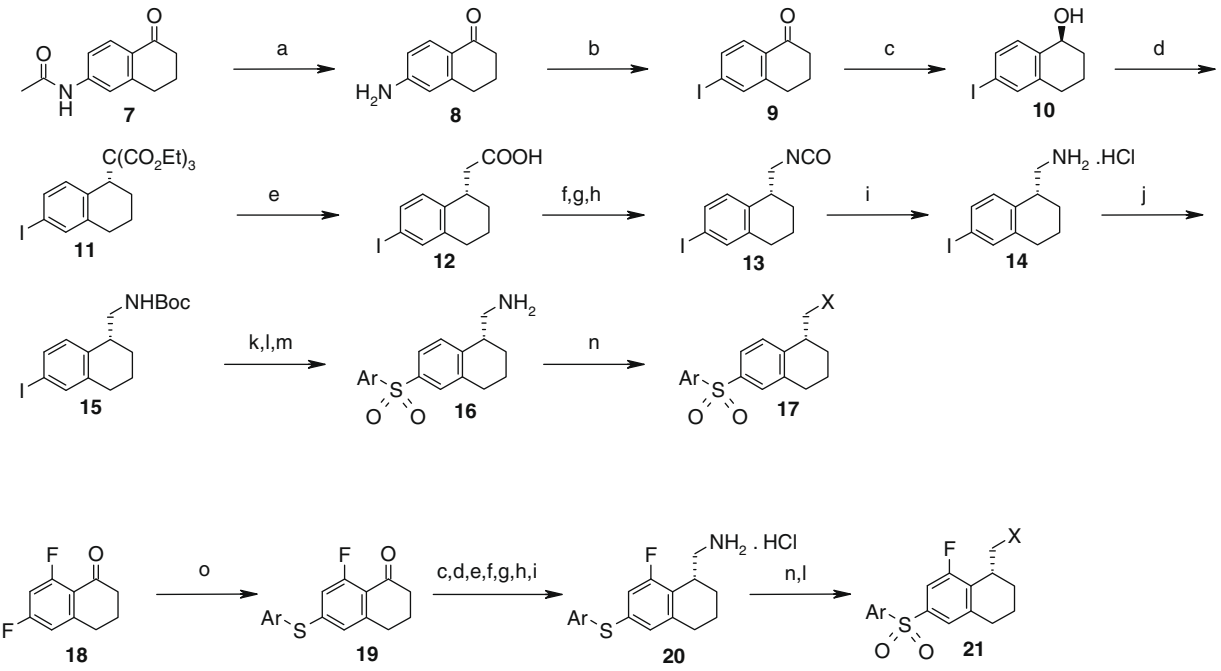
As shown in Figure 1, the lead template was divided into two structural regions for analog development, the pendant ring and the polar head group. A chiral synthesis (Scheme 1) was devised that provided key intermediates as well as a means of determining the absolute configuration of the active enantiomer, which ultimately proved to be R. Thus, starting from the commercially available tetralone **7** (Scheme 1), iodide **9** was obtained in excellent yield and was then converted to the chiral alcohol **10** by way of asymmetric borane reduction using the conditions of Burkhardt and Salunkhe.[12] Key to the sequence was Mitsunobu reaction of **10** with inversion of configuration at the asymmetric center to give tricarboxylate **11** which was hydrolyzed to the chiral acid **12**, all accomplished using the procedure of Hillier et al.[13] Carboxylic acid **12** was then subjected to Curtius rearrangement followed by isocyanate hydrolysis to give amine salt **14** which after recrystallization

Table 1
Binding to h5-HT_6 by selected polar head group analogs of lead tetralin **1**



Compound	X	h5-HT_6[a] (pK_i)
1		9.8
2		9.2
3		9.5
4		10.2
5		7.6
6		9.2

[a] Affinities (pK_i in −log M) were determined by radioligand binding with [^{3}H] LSD in membranes prepared from cells engineered to recombinantly express human 5-HT_6 receptors.



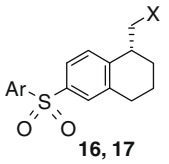
Scheme 1. Reagents and conditions: (a) 20% H_2SO_4, 90 °C, 100%; (b) $NaNO_2$, KI, 94%; (c) (*S*)-2-Me-CBS-oxazaborolidine, $PhNEt_2{\cdot}BH_3$, PhMe, 25 °C, 95%, 98% ee; (d) $HC(CO_2Et)_3$, PMe_3, DIAD, PhMe, −50 °C, 88%; (e) NaOH, MeOH–H_2O, then HOAc, reflux, 84%; (f) oxalyl chloride, cat. DMF; (g) NaN_3, acetone–H_2O; (h) PhMe, 90 °C; (i) concd HCl, 90 °C, then recrystallization from MeOH–EtOAc, 67%, 99.5% ee; (j) Boc_2O, TEA, MeOH, 90%; (k) ArSH, $Pd_2(dba)_3$, xantphos, *i*-Pr_2NEt, THF, 70–90%; (l) *m*-CPBA, CH_2Cl_2, 90–100%; (m) TFA, 100%; (n) electrophile, 70–90%; (o) ArSH, K_2CO_3, DMF, 55 °C, 70–80%.

was upgraded to 99.5% ee. Protection of amine **14** as the *tert*-butyl carbamate served to provide divergent intermediate **15** which was coupled with various aryl thiols under the conditions of Itoh and Mase.[14] Oxidation and deprotection gave pendant ring analogs **16** that were then reacted with various electrophiles to give polar head group analogs **17**. Finally, starting from commercially available di-fluorotetralone **18**, 8-fluoro analogs **21** were prepared using a similar route but with variation in the order of sequence.

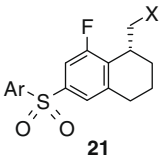
Table 2 lists the binding results to human 5-HT_6 for analogs **16**, **17**, and **21**. Remarkably, out of a total of 54 compounds, only six have pK_i less than 8 or affinity concentration greater than 10 nM. Compounds **16g** and **h** were the only two analogs that were essentially inactive, and both compounds substitute pendant alkylsulfonyl for arylsulfonyl. All previously proposed 5-HT_6 binding models have implied the importance of hydrophobic π-stacking interactions,[9–11] particularly with respect to the ligand pendant ring. Here, the observation that cyclohexyl sulfone **16h** is inactive while the benzyl sulfone **16g** retains only slight activity confirms that aromatic π-stacking by the pendant ring is in fact a critical interaction for binding, and that simple hydrophobic interactions without π-stacking is insufficient. Notably, the hydrophobic 3-fluorophenyl analog **16d** and the efficient π-stacking 3-indolyl analog **16n** have the highest affinities of all. The results for substituted amines **17b–k** indicate that the TM3 Asp106 site is capable of accommodating basic amine substituents with varying size and polarity ranging from a simple methyl ether (**17f**) to a highly polar built in salt bridge (**17g**). These results all support a binding site that is both versatile and accommodating with respect to ligand structure.

The most interesting results in Table 2 are represented by the group of compounds **17l–ad.** This subseries consists of amines that have been acylated or sulfonylated to give non-basic polar head groups. Even though this group of analogs is incapable of ionic interactions under physiological conditions, they maintain for the most part very high binding affinity. These results were surprising and provided the first hint of a change in the ligand–receptor binding interactions. A striking SAR trend that provided a clue into the nature of the non-ionic interactions is noted in the compound parings **17l/17o**, **17q/17r**, and **17z/17aa**. In each of these pairs, methyl is substituted for hydrogen at the same nitrogen of the polar head group, and in each case a corresponding reduction of at least one log unit in affinity occurs. These results are in direct contrast to those for the fully methylated amine **4** (Table 1) which actually

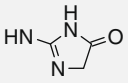
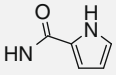
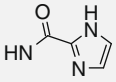
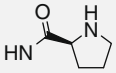
Table 2
Binding to h5-HT_6 for analogs **16**, **17**, and **21**



16, 17



21

Compd	X	Ar	pK_i[a]	Compd	X	Ar	pK_i[a]
16a	NH_2	Ph	9.8	**17u**	$NHCOC(CH_3)_3$	3-F-Ph	8.4
16b	NH_2	3-HO-Ph	9.6	**17v**	$NHCOC(CH_3)_2OH$	3-F-Ph	8.7
16c	NH_2	3-MeO-Ph	9.4	**17w**	$NHSO_2CH_3$	3-F-Ph	9.7
16d	NH_2	3-F-Ph	10.1	**17x**	$N(CH_3)SO_2CH_3$	3-F-Ph	9.4
16e	NH_2	3-$MeSO_2$-Ph	8.4	**17y**	$NHSO_2CF_3$	3-F-Ph	7.5
16f	NH	3-CN-Ph	9.3	**17z**	$NHSO_2NH_2$	3-F-Ph	9.9
16g	NH_2	$PhCH_2$	6.8	**17aa**	$N(CH_3)SO_2NH_2$	3-F-Ph	8.4
16h	NH_2	*c*-C_6H_{11}	<6	**17ab**	$NHSO_2NHCH_3$	3-F-Ph	9.0
16i	NH_2	3-Pyrrolyl	9.5	**17ac**	$NHSO_2N(CH_3)_2$	3-F-Ph	8.7
16j	$NHCH_3$	3-Pyrrolyl	9.8				
16k	NH_2	1-Me-3-pyrrolyl	8.1	**17ad**		3-F-Ph	7.5
16l	NH_2	4-Pyrazolyl	8.7				
16m	NH_2	5-Thiazolyl	9.1				
16n	NH_2	3-Indolyl	10.3	**17ae**		3-F-Ph	10.0
17a	NH_2	6-F-4-benzimidazolyl	8.3				
17b	$NHCH_2CONH_2$	3-F-Ph	10.0				
17c	$N(CH_3)CH_2CONH_2$	3-F-Ph	8.9	**17af**		3-F-Ph	8.3
17d	$NHCH_2CONHCH_3$	3-F-Ph	9.0				
17e	$NHCH_2CH_2OH$	3-F-Ph	9.9				
17f	$NHCH_2CH_2OCH_3$	3-F-Ph	9.6	**17ag**		3-F-Ph	7.8
17g	$NHCH_2CH_2CH_2SO_2OH$	3-F-Ph	8.9				
17h	$NHCOCH_2NH_2$	3-F-Ph	9.5				
17i	$NHCOCH_2NHCH_3$	3-F-Ph	9.8	**17ah**		3-F-Ph	9.2
17j	$NHCOCH_2N(CH_3)_2$	3-F-Ph	9.4				
17k	$CONHC(=NH)NH_2$	3-F-Ph	9.2				
17l	$NHCONH_2$	3-F-Ph	9.7	**17ai**		3-F-Ph	10.0
17m	$NHCONHCH_3$	3-F-Ph	9.4				
17n	$NHCON(CH_3)_2$	3-F-Ph	8.6				
17o	$N(CH_3)CONH_2$	3-F-Ph	7.4	**17aj**		3-F-Ph	8.2
17p	$NHCO_2CH_3$	3-F-Ph	8.8				
17q	$NHCOCH_3$	3-F-Ph	9.9	**21a**	$NHCH_2CH_2OH$	3-F-Ph	9.8
17r	$N(CH_3)COCH_3$	3-F-Ph	8.8	**21b**	$NHCONH_2$	3-F-Ph	9.7
17s	$NHCOCH_2OH$	3-F-Ph	10.0	**21c**	$NHCOCH_2OH$	3-F-Ph	9.6
17t	$NHCOCH_2OCH_3$	3-F-Ph	9.1	**21d**	$NHCOCH_3$	Ph	9.5

[a] Affinities (pK_i in −log M) were determined by radioligand binding with [^{3}H] LSD in membranes prepared from cells engineered to recombinantly express human 5-HT_6 receptors.

gained affinity relative to the less substituted analogs **1–3**. These data again imply a deviation in binding interactions for the non-basic ligands, and that the new interaction involves a H-bond donation from the ligand head group to the receptor.

To gain insight into the binding results at the molecular level, the binding of several analogs to h5-HT_6 receptor point mutations was examined. The results are shown in Table 3 and are tabulated as change in binding pK_i (ΔpK_i) relative to wild type receptor protein. The agonist 5-HT and arylpiperazine SB-258585, a known selective antagonist,[15] are included as reference ligands. As noted in Table 3, SB-258585 and tetralin amines **16d**, **16j**, and **17e** all experienced significant reduction in affinity with mutation D106A, consistent with Asp106 being the anchoring point for basic amine antagonists. Interestingly however, the magnitude of the reduction for the tetralin amines is essentially a full order less than that for the arylpiperazine SB-258585. This implies that the tetralin amines may not depend solely on Asp106 for binding of the head group. In contrast, the neutral polar head group analogs **17l** and **21d** (Table 3) experienced no significant decline in affinity with mutation D106A indicating these analogs to be totally independent of Asp106 for binding. Point mutations C110A, S193A, and T196A, all mutations of polar residues that have been implicated in binding models by other investigators,[11] had in this investigation minimal to no effect on binding. The one point mutation that produced a significant effect with all ligands is F284A. Phe284 is located on helix 6 opposite to TM3 Asp106 and in close sequence with Trp281 and Phe285, all of which make up a region of the receptor that is rich in hydrophobic aromatic residues. The data in Table 3 suggests that this hydrophobic pocket, and in particular Phe284, is probably a critical common site for all 5-HT_6 antagonists to bind via aromatic ring π-stacking. Hence, although the non-basic ligands, unlike the basic amines, bind independent of Asp106, both ligand types still share a common point of interaction of pendant ring with Phe284, *and are therefore most likely oriented at the receptor in a similar manner.* The remaining question is: what receptor residue accepts the H-bond from the non-basic head group?

Considering an orientation within the helix complex that is similar for both basic amine and neutral ligands, it is reasonable to assume that for the neutral ligands to competitively block the receptor, the H-bond donation must be to a residue in helix 3 near the residue with which the amine group of 5-HT interacts,[16] that is, Asp106. Modeling studies of **21d** in the receptor site reveal only one residue in helix 3 capable of fulfilling these requirements, and that is Thr103. Figure 2 shows a graphics model of a view looking down the interior of the helix complex with **21d** docked in the optimum orientation for H-bond donation to Thr103 and hydrophobic π-stacking of pendant ring with Phe284. The positive ionizable binding site for basic amine ligands at TM3 Asp106 is shown at the top of the view for reference. Notably, the model reveals an additional H-bond from TM5 Ser185 to the amide carbonyl of **21d** that occurs as a result of the positioning of the ligand to Thr103. This additional interaction strengthens the binding of the head group and serves to completely block access to the agonist binding site at Asp106. Moreover, the model reveals that the ligand core ring system does not significantly interact with receptor protein, but instead serves primarily as a scaffold to bridge a specific distance across the interior allowing the pharmacophore extremities to make contact points. This, along with dual binding sites for the ligand polar head group, could explain why so many different ring systems have been identified as active templates for 5-HT_6 antagonists.[8]

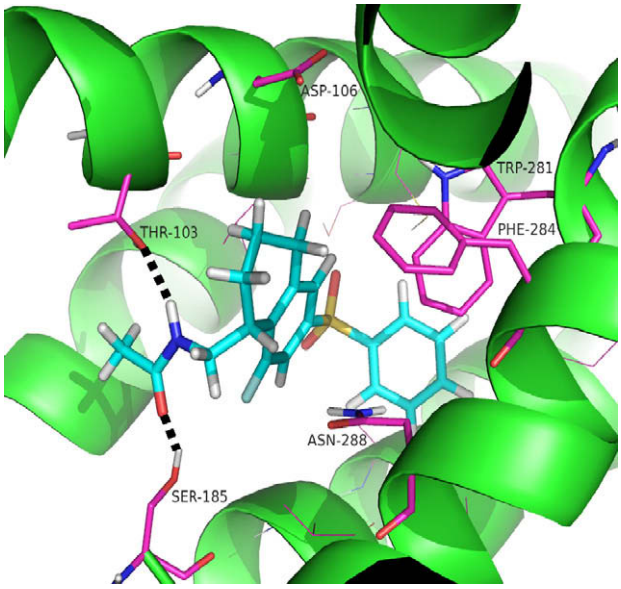


Figure 2. Graphics illustration of non-basic ligand **21d** docked in the 5-HT_6 receptor with new H-bond interactions at TM3 Thr103 and TM5 Ser185 highlighted.

Although rare, non-amine serotonin receptor ligands are not totally unknown. Recently, Ladduwahetty et al.[17] reported a series of acylated and sulfonylated 4-phenethyl-piperidines as non-basic 5-HT_{2A} antagonists demonstrating that a basic amine is not a requirement for 5-HT_{2A} binding. While 5-HT_6 is known to share 40–45% sequence homology with 5-HT_2,[18] the Asp106 residue for forming a salt bridge is conserved in almost all aminergic receptors. Whether a non-amine binding site in other aminergic receptor proteins is conserved or not remains to be determined. Nevertheless, the discovery of non-amine functional ligands for both 5-HT_6 and 5-HT_2 brings the discovery of other such ligands for related receptors into the realm of possibility, and has significant implications from a safety standpoint for therapy areas that target aminergic receptors. A major safety advantage of non-amine ligands is their general tendency to have little to no affinity for inhibiting the IKr potassium channel (hERG), a voltage gated ion channel that is intimately involved in cardio rhythm. In fact, many of the neutral ligands in Table 2 were found to be essentially devoid of IKr channel affinity having IC_{50} values typically >50 μM. In contrast to this, many of the analogs **16** and **17** that incorporate amine functionality, which is believed to be a major contributor to the hERG pharmacophore,[19] were found to have IC_{50}'s in the range 0.5–5 μM. Finally, a PK profile of acetamide **21d** revealed reasonably good brain penetration and a CYP450 panel of IC_{50} values all in excess of 15 μM.

In conclusion, a series of very potent 5-HT_6 antagonists based on the (*R*)-1-(amino)methyl-6-(phenyl)sulfonyltetralin molecular template was prepared. N-acylated and N-sulfonylated derivatives

Table 3
Change in binding pK_i from WT h5-HT_6 to h5-HT_6 amino acid point mutations for selected compounds

	h5-HT_6 point mutations[a] (ΔpK_i)						
	D106A	C110A	S193A	T196A	W281A	F284A	N288A
5-HT	−1.3	−0.5	−0.7	−0.7	−0.5	−1.3	−0.5
SB-258585	−2.4	0.5	−0.3	0.3	−0.5	−1.3	−0.7
16d	−1.1	0.3	0.1	0.2	−2.0	−1.2	−0.7
16j	−1.5	0.4	−0.4	0.4	−0.9	−1.7	−0.7
17e	−0.7	0.4	0.1	0.5	−0.5	−0.7	−0.2
17l	0	0.3	−0.4	0.4	−1.4	−1.5	−0.5
21d	−0.2	0.4	−0.4	0.4	−2.0	−1.5	−0.4

[a] Amino acid abbreviations: D (aspartic acid), A (alanine), C (cysteine), S (serine), T (threonine), W (tryptophan), F (phenylalanine), N (asparagine). Affinities (pK_i in −log M) were determined by radioligand binding in membranes prepared from cells engineered to recombinantly express human 5-HT_6 receptors.

of the series gave functionally active, non-basic analogs having sub-nanomolar binding affinities. Based on SAR, receptor point mutation studies, and molecular modeling, a novel binding orientation for the non-basic antagonists was proposed that does not involve an interaction with Asp106, but instead relies on H-bond interactions of the polar head group with receptor residues Thr103 and Ser185. These results introduce a new alternative binding model for the design of highly potent, non-basic 5-HT_6 antagonists that have very little to no hERG liability.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.03.110.

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