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Mitigating hERG Inhibition: Design of Orally Bioavailable CCR5 Antagonists as Potent Inhibitors of R5 HIV-1 Replication

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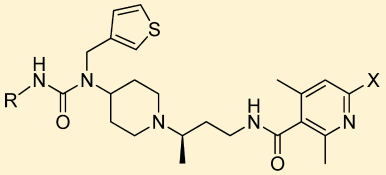
Supporting Information

ABSTRACT: A series of CCR5 antagonists representing the thiophene-3-yl-methyl ureas were designed that met the pharmacological criteria for HIV-1 inhibition and mitigated a human ether-a-go-go related gene (hERG) inhibition liability. Reducing lipophilicity was the main design criteria used to identify compounds that did not inhibit the hERG channel, but subtle structural modifications were also important. Interestingly, within this series, compounds with low hERG inhibition prolonged the action potential duration (APD) in dog Purkinje fibers, suggesting a mixed effect on cardiac ion channels.



KEYWORDS: *HIV-1, hERG, CCR5, chemokine receptor*

The marketing approvals of the first in class chemokine receptor antagonists, maraviroc[1] in 2007 targeting CCR5 and plerixafor[2,3] in 2008 targeting CXCR4, mark an important milestone for chemokine receptor drug development. Although both of these receptors were identified as important coreceptors required by the HIV-1 virus to infect cells,[4] most of the research effort has focused on developing inhibitors of CCR5, since the most commonly transmitted HIV-1 strains (M-tropic) utilize the CCR5 coreceptor.

Recently, we reported[5] on the identification of pyridin-2-ylmethylaminopiperidin-1-ylbutyl amides (**1**) as a novel class of CCR5 antagonists that exhibited potent inhibition of R5 HIV-1 (BaL) replication in PBMC (Figure 1). These compounds were

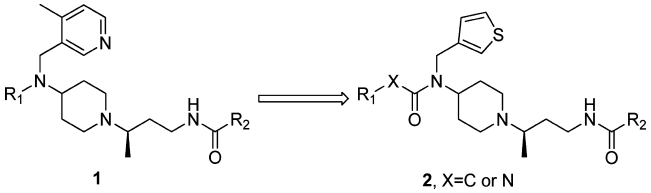


Figure 1. Structure of compounds **1** and **2**.

identified based on our initial redesign efforts of Schering C.[6] Although these compounds met most of the criteria for further development, they were found to have a significant hERG liability (also reported by the GSK[7] and Pfizer[8] groups), which we sought to mitigate by reducing the lipophilicity through the design of compounds **2** (Figure 1). The antiviral activity was used to determine a structure−activity relationship (SAR), and it was measured utilizing the R5 HIV-1 PBMC assay.[9] In addition, we also utilized a gp120/CCR5 cell fusion assay[10] as a first pass screen to select compounds for antiviral screening since the fusion data were found to be a reliable predictor of antiviral activity.

On the basis of the recognition that compound **1a** containing an anilino nitrogen (R^1 = phenyl) had potent antiviral activity, we reasoned that the most expedient way to address the hERG liability was to replace the substituted phenyl group on the left had side with an amide or urea that would reduce the lipophilicity[11] as measured by cLog *P*. Initially, the 4-methyl pyridine moiety on the top left-hand side was retained, but these compounds were substantially less potent than the corresponding thiophene analogues,[5] so the thiophene moiety was utilized for further optimization (Table 1). For example, comparison of the tetrahydropyranyl esters **1b** and **2b** showed that the thiophene **2b** provided a 44-fold enhancement in potency as compared to the 4-methyl pyridine **1b** based on CCR5 fusion inhibition. Similarly, comparison of the pyridinyl ureas **1c** and **2c** showed a 130-fold increase in potency for **2c** as compared to the 4-methyl pyridine **1c**.

Several amide analogues of compound **2** were prepared (Table 2). Aside from maintaining antiviral potency, the important properties that were measured to distinguish the analogues was fusion inhibition shift in the presence of α-1-acid glycoprotein (AGP), human plasma protein binding, and hERG inhibition based on % inhibition and/or IC_{50}. The simple methyl amide **2d** containing the optimum 2-chloro-4,6-

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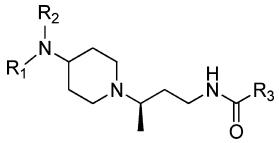
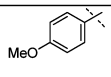
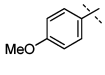
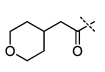
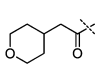
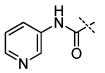
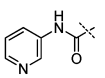
Table 1. Comparative in Vitro Pharmacology and hERG Inhibition of 4-Methyl Pyridine and Thiophene Compounds[a]



Compd	R_1	R_2	R_3	MW/ cLog P	CCR5 Fusion IC_{50}[b] (nM)	Fold AGP fusion shift[c]	HIV-1 PBMC IC_{50}[d] (nM)	PBMC CC_{50}[e] (nM)	Protein Binding[f] %	hERG inhib.[g] %
1a				517/ 3.4	10.9 (n=10)	10.6	1832 (n=2)	>38300	83	58
2a				508/ 4.1	1.2 (n=6)	8.0	65.9 (n=3)	>38700	91	97
1b				570/ 2.2	31.1	na	na	na	na	na
2b				561/ 2.9	0.7 (n=6)	1.1	22.5 (n=3)	>35600	80	67
1c				564/ 3.1	14.3	na	na	na	na	na
2c				555/ 3.8	0.11 (n=4)	4.0	34.4 (n=3)	>32378	46	20

[a]Assays were performed in duplicate, and values represent the mean with standard deviations <30% of the mean. Bracketed values represent the number of experiments. [b]Viral gp120/CCR5 binding was assessed by a cell fusion assay between P4R5 cells expressing CCR5, CD4, and a LTR-β-gal construct (LacZ gene under the control of the HIV-1 LTR promoter) and CHO-tat cells expressing the HIV-1 JRFLenv and HIV-1 Tat. The P4R5/CHO-tat, CCR5/gp120 interaction was assessed by measuring the resultant β-galactosidase activity. IC_{50} is the concentration of compound required to inhibit cell fusion by 50%. [c]Fold AGP fusion shift is the shift in the CCR5 fusion assay in the presence of 1 mg/mL of α-acid glycoprotein. [d]Peripheral blood mononuclear cells (PBMC) were isolated from healthy volunteers and infected by R5 HIV-1 (BaL strain) as reported in ref 9. IC_{50} is the concentration of the compound required to inhibit viral replication by 50% as measured by p-24 HIV-1-specific Ag ELISA. [e]CC_{50} is the concentration required to reduce the viability of PBMC by 50%. [f]Plasma protein binding was calculated by diluting a 25 mM stock solution in DMSO to 1 μM in human plasma, dialyzing for 5 h against PBS (pH 7.4) at 37 °C, and determining the concentration remaining in each compartment by LC. [g]hERG inhibition was measured at 10 μM in CHO cells stably expressing the recombinant human hERG channel subunit (IKr) using an automated patch clamp platform (QPatch-Sophion Biosciences).

dimethyl pyridine amide group[5] demonstrated that activity could still be maintained in the absence of a hydrophobic aromatic group. Extending the amide using a methoxymethyl group **2e** provided an approximate 4-fold enhancement in antiviral activity and a hERG IC_{50} of 8.4 μM. The cyanomethyl moiety (**2f**) further reduced lipophilicity and resulted in a 2-fold increase in potency and a hERG IC_{50} of 16.0 μM as compared to **2e**. Other amide modifications included compounds **2b** and **2g**, **h**. Of these, the cyclic carbamate **2h** had the best overall profile with hERG inhibition of 21% and an anti-HIV-1 activity of 1.6 nM. Interestingly, use of the cyano pyridine amide **2g** provided a 1 Log reduction in cLog *P* as compared to **2b** but only a marginal decrease in hERG inhibition (61 vs 67%), suggesting that discrete structural modifications also played an important role.[12] However, because many of these compounds showed evidence of conformational isomerism around the amide bond, the amide analogues were not further pursued.

As a consequence, we shifted our attention to preparing a series of urea analogues (Table 2). It was encouraging to observe that the methyl urea **2i** was found to have good potency, although the hERG IC_{50} of 1.6 μM (cLog *P* of 2.6) suggested that even in this series other factors were impacting hERG. Interestingly, the dimethyl analogue **2j** was inactive, indicating the importance of NH in binding to CCR5. Incorporation of a hydroxyl urea **2k** was tolerated based on the CCR5 fusion assay, but this did not correlate to anti-HIV-1 activity (IC_{50} = 344 nM). However, the corresponding methoxy urea analogue **2l** provided encouraging in vitro properties including a hERG IC_{50} of 5.5 μM and an anti-HIV-1 activity of 14.8 nM. Additional analogues incorporating the meythoxy methyl urea moiety (**2m**−**p**) were prepared in which the right-hand side pyridyl amide was modified in an attempt to further improve the antiviral potency and hERG inhibition. An 8-fold increase in potency (IC_{50} = 1.9 nM) was achieved using the 2,6-dicholoro-4-methyl pyridine amide **2m** (cLog *P* = 2.6), but this was accompanied by a 20-fold increase in hERG inhibition (IC_{50} = 0.3 μM). However, this liability was overcome by using the corresponding *N*-oxide **2o** that displayed a hERG inhibition of 21% while still maintaining favorable in vitro properties. In addition, using either an *iso*-propyl amide **2n** or a cyano group **2p** in place of the 2-chloro substituent of the pyridyl amide improved the hERG inhibition with IC_{50} values of >30 and 10.8 μM, respectively, and anti-HIV-1 potencies of 3−5 nM. The hERG liability could also be mitigated by modifications to the left-hand side urea moiety. For instance, the methoxyethoxy urea **2q** hERG IC_{50} was >40 μM. On the basis of a combined modeling mutagenesis approach[13] where it was postulated that addition of an appropriately tethered carboxylic acid to the urea would pick up an ionic interaction with Lys^{191}, compound **2r** was prepared in which antiviral potency was maintained at 6.9 nM, but more importantly, the hERG IC_{50} was >50 μM.

The thiophene compounds (Tables 1 and 2) were prepared as outlined in Scheme 1 other than compound **2a**.[5] The

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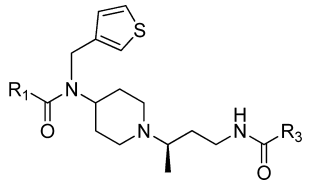
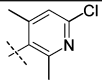
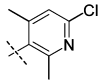
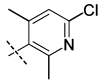
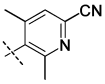
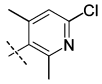
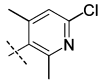
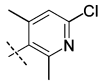
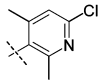
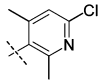
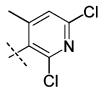
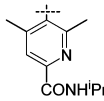
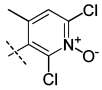
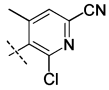
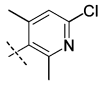
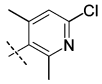
Table 2. In Vitro Pharmacology and hERG Inhibition of Compounds 2[a]



Compd	R_1	R_3	MW/ cLog P	CCR5 Fusion IC_{50} (nM)	Fold AGP fusion shift	HIV-1 PBMC IC_{50} (nM)	PBMC CC_{50} (nM)	Protein Binding %	hERG inhib. %	hERG IC_{50} (μM)
2d	Me		477/ 2.6	0.9 (n=4)	1.4	138 (n=4)	>42000	55	37	na
2e	$MeOCH_2$		507/ 2.8	0.4 (n=7)	1.1	38.0 (n=8)	>38800	63	31	8.4
2f	$NCCH_2$		502/ 2.4	0.4 (n=4)	1.1	17.1 (n=3)	>39800	54	14	16
2g			552/ 1.9	0.8 (n=6)	1.0	16.1 (n=3)	>36200	85	61	na
2h			562/ 2.9	0.1 (n=5)	0.7	1.6 (n=3)	>35600	44	21	na
2i	MeNH		492/ 2.6	0.3 (n=4)	2.5	15.5 (n=4)	>40600	46	73	1.6
2j	Me_2N		506/ 3.3	48.4 (n=1)	na	na	na	na	na	na
2k	HONH		494/ 2.3	0.3 (n=11)	0.7	344 (n=5)	>38500	40	44	na
2l	MeONH		508/ 2.8	0.3 (n=11)	1.7	14.8 (n=10)	>35200	42	60	5.5
2m	MeONH		529/ 2.6	0.08 (n=5)	1.2	1.9 (n=7)	>37800	53	85	0.3
2n	MeONH		559/ 2.7	0.4 (n=7)	1.3	4.8 (n=4)	>35800	42	12	33
2o	MeONH		545/ 0.9	0.4 (n=5)	1.5	7.3 (n=4)	>38500	31	21	na
2p	MeONH		519/ 1.6	0.1 (n=6)	0.9	2.9 (n=3)	>38500	75	44	10.8
2q	$MeO(CH_2)_2$ ONH		551/ 3.2	0.3 (n=5)	3.2	21.3 (n=3)	>34400	43	15	>40
2r	HO_2C-4-$PhCH_2NH$		612/ 1.8	0.5	0.4	6.9 (n=3)	>32200	58	na	>50

[a]See Table 1.

substituted cyano pyridine **4a**, used for the preparation of compounds **2g** and **2p**, was prepared from commercially available 2-chloro-4-methyl nicotinic acid by nucleophilic addition of the cyano group to the corresponding *N*-oxide **3a**. The advanced intermediate **8**, prepared by reductive amination of 3-aminomethyl thiophene **7**[14] with ketone **6**, was used to prepare the analogues **2a**−**r**. Nitrile reduction of enantiomerically pure **5**[5,15] under Raney-Ni-catalyzed hydrogenation conditions followed by Boc protection of the amine afforded **6** in good yield. Installation of the amide moiety was readily accomplished using standard peptide coupling procedures, whereas the urea moiety was installed using

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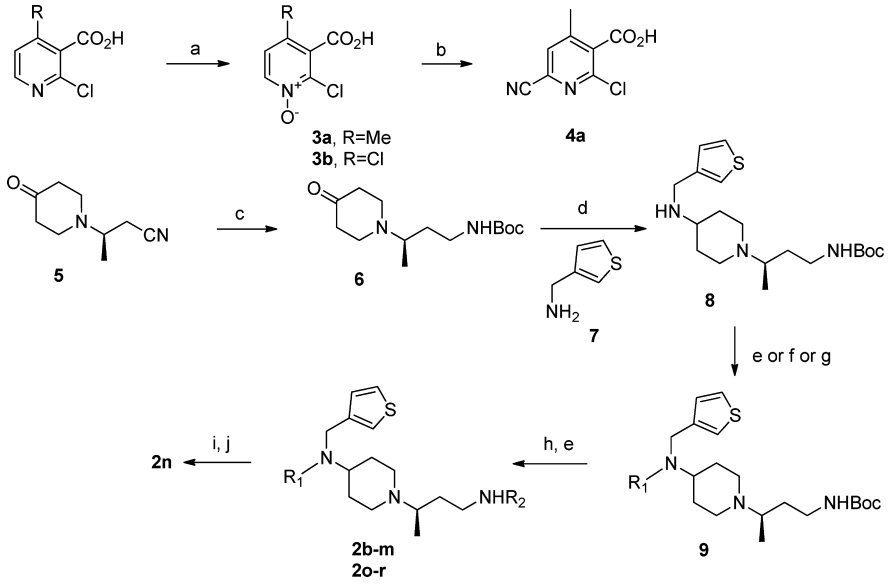
Scheme 1. [a]



[a]Reagents: (a) $CO(NH_2)_2{\cdot}H_2O_2$, TFAA, 1,2-dichloroethane, 65 °C, 18 h, 39%. (b) $(Me)_2NCOCl$, TMSCN, 1,2-dichloroethane/DMF (3:1), 50 °C, 18 h, 43%. (c) H_2 (45 psi), Raney Ni, Boc_2O, NaOH, MeOH, 1 h, 60%. (d) $NaBH(OAc)_3$, CH_2Cl_2, 98%. (e) HOBt, EDCI, DIPEA, RCO_2H, DMF, 74−89%. (f) RNCO, CH_2Cl_2, RT. (g) RNH_2, CDI, Et_3N, CH_2Cl_2 or R_2NCOCl, Et_3N, 1,2-dichloroethane, 60 °C. (h) TFA, CH_2Cl_2, RT, 100%. (i) NaOH (10 N, aq.)/EtOH (1:3), 100 °C, 16 h, 75%. (j) HOBt, EDCI, DIPEA, *i*$PrNH_2$, DMF, 40%.

commercially available isocyanates or amines. Boc deprotection under mildly acidic conditions then afforded the compounds **2b−m** and **2o−r** in good overall yields. The *iso*-Pr amide **2n** was prepared by base hydrolysis of the precursor nitrile followed by standard coupling procedures (Scheme 1).

The pharmacokinetic parameters of some compounds that had an acceptable hERG profile were evaluated in rat and/or dog (Table 3). Many of the ureas that were evaluated in dog

Table 3. Pharmacokinetics of 2e, 2l, and 2n−p in Rat and Dog[a]

compd	species	C_{max} (μM)	$AUC_{0\text{-}inf}$ (h μM)	CL (mL/min/kg)	V (L/kg)	$T_{1/2}$ (h)	F (%)
2e	rat	2.54	5.59	85.0	18.6	2.5	29
2l		3.36	13.40	87.1	53.0	7.0	73
2e		4.9	1.64	89.6	9.8	1.2	72
2l		3.3	5.89	52.6	23.9	5.2	151
2n	dog	2.62	3.71	29.5	7.7	4.1	52
2o		0.26	0.37	40.3	2.6	0.7	7
2p		1.94	3.24	39.2	6.3	1.8	60

[a]Clearance (CL), volume of distribution (V), and half-life ($T_{1/2}$) calculated following a 10 μmol/kg iv dose in rat and 5 μmol/kg iv dose in dog. Oral bioavailability (F) calculated following solution doses of 100 μmol/kg in rat and 12.5 μmol/kg in dog.

PK had good oral bioavailability and exposure other than the *N*-oxide **2o**. Compounds **2e** and **2l** had good oral bioavailability in rat and dog and were selected for further evaluation as were compounds **2n** and **2q** that had good dog PK.

The selectivity of **2e**, **2l**, **2n**, **2q**, and related analogues was evaluated in Ca^{2+} flux assays against a series of other closely related G-protein-coupled receptors (GPCRs), which included CCR1, CCR2b, CCR4, CXCR1, CXCR2, and CXCR4, and were found to be noninhibitory at concentrations of 5 μM. When tested against a panel of five isoforms of CYP 450, these compounds were found to be noninhibitory at concentrations >10 μM. Compounds **2e**, **2l**, and **2q** progressed to a 7 day safety study in rat. The NOAEL for all three compounds was determined to be at ≥400 mg/kg (the highest test dose).

In addition to 7 day safety dog studies (no telemetry studies were conducted), these compounds and others were evaluated in the canine Purkinje fiber assay[16] to further understand the risk for drug-induced arrhythmias (Table 4). Surprisingly, all of the thiophene compounds tested at 10 μM using the three standard stimulation frequencies resulted in significant prolongation of the APD in a reverse rate-dependent fashion, which is consistent with blocking the hERG potassium channel.[17] However, this observation was not supported by the in vitro hERG inhibitory data. For example, compounds **2f**, **2h**, and **2q** inhibited hERG at IC_{50} values of 16 to >40 μM, but the % change in APD_{60} at a basic cycle length (BCL) of 2 s was significant (18−43%). In addition, **2l** and **2n** also showed a significant % change in APD_{60}, 55 and 37%, respectively, with a hERG IC_{50} of 5.5 and >30 μM. There was no occurrence of early after depolarizations (EADs), and as the prolongation of APD_{60} and APD_{90} was similar at every stimulation cycle, there was no evidence of triangulation of the action potential. Given this observed discrepancy between hERG channel inhibition and APD, we postulated that these compounds were likely having a mixed effect on cardiac ion channels. The lack of effect on the resting membrane potential (RMP) or the rate of depolarization (Vmax) suggests that sodium channels are not inhibited at the concentrations tested. In addition to hERG (IKr), there is significant contribution to phase III repolarization provided by the slowly activating delayed rectifier potassium channel (IKs).[18] Inhibition of this channel provides a possible mechanism for the APD observed in this study; however, none of these compounds were specifically tested for inhibition of this channel.

In conclusion, we have described our efforts to mitigate a hERG liability present in a series of compounds by decreasing lipophilicity. Although we were able to identify compounds

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Table 4. Dog Purkinje Fiber Data[a] and hERG Data for Compounds 2f, 2h, 2l, 2n, and 2q

		Δ%		ΔmV			
compd[b]	BCL (s)	APD_{60}	APD_{90}	RMP	APA	V_{max} (Δ%)	hERG IC_{50} (μM)
2f	2	42.9 ± 4.2*	47.6 ± 7.5*	−1.5 ± 1.3	4.3 ± 3.1	29.1 ± 9.5	16
	1	31.5 ± 1.9*	31.9 ± 4.6*	−1.9 ± 1.1	3.4 ± 2.3	21.1 ± 7.0	
	0.5	15.7 ± 0.9*	17.7 ± 2.0*	−0.9 ± 1.6	2.9 ± 1.5	18.4 ± 5.2*	
2h	2	18.4 ± 8.3	14.2 ± 2.1*	−1.8 ± 1.8	13.7 ± 8.2	57.1 ± 42.5	na
	1	14.5 ± 8.4	10.6 ± 2.1*	−2.2 ± 2.9	15.2 ± 7.9	81.7 ± 56.9	
	0.5	7.7 ± 7.1	4.5 ± 1.4	−1.5 ± 3.2	11.3 ± 6.4	48.4 ± 27.4	
2l	2	55.1 ± 4.5*	57.0 ± 6.6*	−0.6 ± 0.7	−3.6 ± 1.8	−8.3 ± 15.2	5.5
	1	42.6 ± 5.6*	42.2 ± 5.5*	−0.5 ± 0.9	−3.8 ± 2.3	−8.0 ± 15.6	
	0.5	24.9 ± 3.0*	27.3 ± 3.3*	−1.3 ± 0.5	−2.5 ± 1.6	−7.4 ± 17.2	
2n	2	37.1 ± 11.2*	34.2 ± 5.9*	−1.4 ± 0.5	1.2 ± 2.6	4.5 ± 13.1	33
	1	34.5 ± 10.5*	31.6 ± 5.5*	−1.9 ± 0.6	2.2 ± 2.1	7.8 ± 11.1	
	0.5	24.8 ± 5.7*	24.2 ± 3.4*	−2.3 ± 0.8	2.6 ± 1.8	9.0 ± 11.5	
2q	2	24.2 ± 4.7*	22.6 ± 3.7*	−2.7 ± 3.1	2.4 ± 2.7	4.0 ± 6.4	>40
	1	18.1 ± 2.7*	16.5 ± 2.7*	−2.8 ± 2.8	1.3 ± 2.3	−4.0 ± 5.4	
	0.5	12.2 ± 3.1	10.5 ± 2.9*	−3.6 ± 3.2	1.2 ± 2.5	−4.1 ± 3.9	

[a]Action potential parameters are reported as means ± SDs percent change (Δ%) increase (+) or decrease (−) in test compound-exposed Purkinje fibers over those measured in time-matched vehicle control. APD_{60} and APD_{90} = action potential duration at 60 and 90% repolarization, respectively; RMP = resting membrane potential; APA = action potential amplitude; V_{max}, maximum velocity of phase 0 depolarization; and BCL = basic cycle length. [b]Compounds tested at 10 μM.

with acceptable hERG inhibition, these compounds prolonged the APD in canine Purkinje fibers, suggesting a more complex mixed cardiac ion channel effect. As a consequence, the development of these compounds was halted, and in due course, we will describe our efforts in redesigning this chemotype.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for the synthesis of compounds **2b**, **2e**,**f**, **2h**, **2j**−**r**, **3a**,**b**, **4a**, **6**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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