Synthesis, Potency, and In Vivo Profiles of Quinoline Containing Histamine H_3 Receptor Inverse Agonists

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A new structural series of histamine H_3 receptor antagonist was developed. The new compounds are based on a quinoline core, appended with a required basic aminoethyl moiety, and with potency- and property-modulating heterocyclic substituents. The analogs have nanomolar and subnanomolar potency for the rat and human H_3R in various in vitro assays, including radioligand competition binding as well as functional tests of H_3 receptor-mediated calcium mobilization and GTPγS binding. The compounds possessed favorable drug-like properties, such as good PK, CNS penetration, and moderate protein binding across species. Several compounds were found to be efficacious in animal behavioral models of cognition and attention. Further studies on the pharmaceutic properties of this series of quinolines discovered a potential problem with photochemical instability, an issue which contributed to the discontinuation of this series from further development.

Introduction

Currently, there are four known major classes of histamine receptors, namely, H_1, H_2, H_3, and H_4.[1] The H_1 and H_2 receptors are involved with the allergic response and gastric acid secretion, respectively,[2] and histamine H_1 and H_2 antagonists such as fexofenadine and famotidine are in clinical use. The recently discovered H_4 receptor is expressed in mast cells, eosinophils, and tissues involved in immune responses and may play a role in mediating inflammation.[3]

The histamine H_3 receptor (H_3R) was identified in 1983 as an autoreceptor controlling the release of histamine.[4] The histamine H_3 receptor subtype has been shown to also be a heteroreceptor, and by virtue of its predominant expression in neurons, it has been shown to be able to regulate the release of other neurotransmitters such as acetylcholine, dopamine, norepinephrine, and serotonin.[5] These neurotransmitters are known to play important roles in modulating vigilance, attention, and cognition enhancement. In addition to in vitro studies, in vivo blockade of the H_3 receptor with synthetic compounds has been demonstrated to increase neurotransmitter release.[6] Overall, the body of research on H_3 supports that antagonism/inverse agonism of the receptor has strong potential for utility in treating a variety of CNS diseases, including ADHD, Alzheimer's disease, mild cognitive impairment, and schizophrenia.[7]

Many of the earliest generations of H_3R antagonists were analogs of the endogenous neurotransmitter histamine and, therefore, contained an imidazole group.[8] In general, these imidazole containing compounds suffered potential liabilities of low CNS penetration[9] and the propensity to inhibit cytochrome P_{450} metabolism.[10] These liabilities appear to be less common with the more recent classes of nonimidazole antagonists, results which have been reviewed.[11]

A propyloxy chain linker group is present in many reported imidazole and nonimidazole H_3R antagonists.[12] A strategy to rigidify this moiety led to the design of a new structural class based on a benzofuran skeleton; compounds in the class retained in vitro activity, as exemplified by analogs such as ABT-239 (**1**; Figure 1).[13] This compound has shown efficacy in several behavioral models of cognition.[13a] To further investigate the SAR and build chemically distinct series of analogs, we carried out a campaign to replace the benzofuran core with other bicyclic moieties.[14] In these derivatives, incorporation of an ethyl group as a linker and of (*R*)-2-methylpyrrolidine as the amine component generated many compounds with high potency. Based on an early hypothesis that compounds with higher lipophilicity would have increased CNS levels, a series of naphthalenes depicted in structure **2** was designed.[15] As anticipated, these more lipophilic naphthalene derivatives were indeed found to have a somewhat higher brain-to-plasma concentration ratio than homologous benzofurans such as **1** and, as an unexpected bonus, were generally more potent in vitro as well.[15] Like the benzofurans, specific naphthalene analogs were tested and found efficacious in cognition models.[16] The favorable properties of these two classes, the benzofuran and naphthylene series, motivated a search for other series that would be able to greatly expand the structural diversity while retaining good drug-like properties overall.

A new series of quinoline-based compounds (**3**) was targeted to address an opportunity highlighted during the SAR investigations of the naphthylene series (**2**), where it was found that the R group had a strong and beneficial effect on increasing the in vitro potency. Analogs of **2** were generated via organometallic coupling reactions (Suzuki, Stille, Ullmann) to install to the R group using as an intermediate compounds of structure **2**, wherein R was a bromine or a borate. The quinoline analogs (**3**) offered a unique opportunity to greatly expand the variety of the R moiety because of the different chemistry used to construct this series.[17] Instead of appending R groups by cross-coupling technologies, as in **2**, the quinolines were synthesized using the Freidlander cyclization between an aminoaldehyde and a methyl ketone (see Scheme 1). Because a large variety of methyl ketones were available from commercial and in-house sources, the Freidlander cyclization allowed for the synthesis

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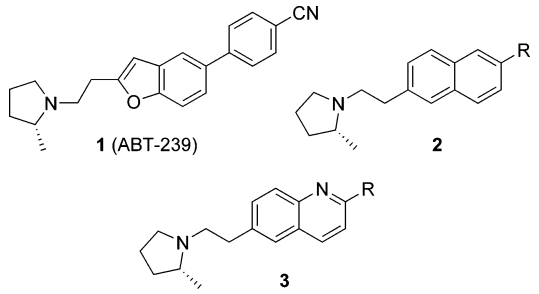
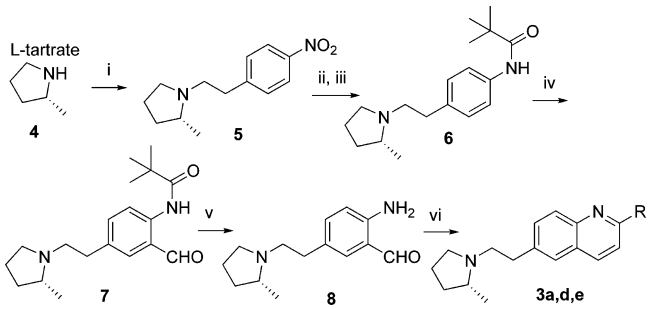


Figure 1.

Scheme 1[a]



[a] Reagents and conditions: (i) 4-nitrophenethyl bromide, K_2CO_3, DMF, 60 °C, 60 h; (ii) H_2, Pd/C, MeOH; (iii) pivaloyl chloride, Et_3N, CH_2Cl_2, 16 h; (iv) 3.3 equiv *n*-BuLi, TMEDA, Et_2O, −78 °C, rt, 4 h, 0 °C; 6 equiv DMF, rt, 16 h (78% for 4 steps); (v) 2 M HCl, Δ; NaOH (60−80% yield); (vi) RCOMe (**9a**, **9d**, **9e**), KOH, EtOH, Δ.

of a wider range of compounds that were not readily accessible via the typical coupling reactions used in the naphthylene series (**2**). As an additional benefit, this facilitated a broader exploration of the SAR and a larger compound set from which to search for agents with high in vitro potency, good PK, and in vivo activity. This report highlights compounds **3a**−**3f** (Table 1) as representative examples of the quinoline series.[14,17b] These compounds all possessed good overall drug-like properties and were subsequently tested in more advanced assays.

Chemistry

The key step in the synthesis of the quinolines was the Friedlander cyclization,[18] wherein we coupled aminoaldehyde **8** with diverse heterocyclic methyl ketones (see Scheme 1). Intermediate **8** was itself synthesized in a five step sequence using as a key starting material the L-tartaric acid salt of (*R*)-2-methylpyrrolidine.[19] In the sequence, the only problematic step was the deprotection of **7**. To obtain good yields, this step required heating a very dilute solution of **7** in aqueous acid for a short period of time. This requirement for high dilution and short reaction time made it difficult to generate intermediate **7** on a large scale because of the heating and cooling of the required large reaction volumes in a timely manner and the large quantities of sodium hydroxide needed to basify the mixture during workup. Extended heating or more concentrated conditions resulted in lower yields of compound **8**, due to the formation of a side product with a lower R_f than compound **8**, with a structure that is believed to be a trimer of compound **8**.[20] In an attempt to circumvent this problem, the pivaloyl amide of compound **6** was replaced by the more easily removable Boc protecting group. Unfortunately, this Boc derivative of **6** was more difficult to synthesize from the intermediate aniline on large scale, and also, the *ortho*-directed metalation step on the Boc analog of **6** was found to require use of *tert*-butyl lithium as a base, and even this provided only modest yields of the corresponding aldehyde.

The problems described above motivated us to develop an alternative synthesis (Scheme 2) using alcohol **13** as the key intermediate. This route was used for resynthesis of target compounds **3b**, **3c**, and **3f** on larger scale. Although the compounds that are reported here only contain (*R*)-2-methylpyrrolidine as the basic amine moiety, in subsequent studies with other amines, **13** was a versatile intermediate because it allows for modification of either the amine or the R group at a late stage in the synthesis. But overall, the route shown in Scheme 1 was considered superior for generating larger quantities of compounds due to its higher overall yield and fewer number of steps.

The scale-up of pyrazole **3e** (see Table 1) demanded larger quantities of methyl ketone **9e**. Initially, we synthesized **9e** using reported literature procedures,[21] but these routes resulted in the desired 1,3-dimethylpyrazole isomer (ketone **9e**) being contaminated with substantial amounts of the unwanted isomer, 1,5-dimethyl-4-acetylpyrazole, which was separable from **9e** only with great difficulty. Therefore, an alternative synthesis was developed as shown in Scheme 3. In this route, 1-methylhydrazine was first protected as the hydrazone, **16**,[22] then reacted with 3-ethoxymethylenepentane-2,4-dione,[23] which generated the key intermediate **17**. Treatment of compound **17** with 1 M HCl in ethanol resulted in deprotection of the hydrazine and subsequent in situ intramolecular cyclization. This process cleanly provided the 1,3-dimethyl isomeric pyrazole **9e** in high yield and without contamination by the 1,5-dimethyl isomer.

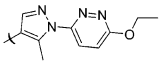
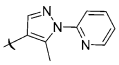
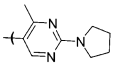
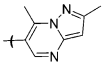
Results

The new compounds **3a**−**3f** were all found to bind potently to the human and rat H_3R in competition binding assays (see Table 1), with the analogs generally 3-fold more potent for the human receptor over the rat H_3R.[24] High potency at the rat H_3R is an especially important attribute because the behavioral models are carried out in rat. These compounds (Table 1) were highly selective for the H_3R over the other histamine subtypes, as well as a battery of other receptors and the hERG channel.[25]

The compounds were also evaluated for their functional blockade of the H_3R in separate in vitro cellular assays that probed for receptor antagonism and inverse agonism. Target compounds **3a**−**3f** blocked agonist-induced ((*R*)-α-methylhistamine, RAMH) increases in intracellular calcium levels in HEK cells expressing the human H_3R. The new compounds were potent, with K_b values ranging from 1.5 to 8.7 nM (see Table 2).[24] In separate assays, H_3R antagonism was also demonstrated through blockade of agonist-induced (RAMH) stimulation of GTPγS binding. As seen in Table 2, the compounds were more potent at the human receptor than the rat H_3R in the functional assays, mirroring the findings in the radioligand displacement assays shown in Table 1. In yet another assay (Table 3), the new compounds were able to potently reduce the basal levels of GTPγS binding to the human and rat H_3 receptor, supporting that **3a**−**3f** are inverse agonists of the H_3 receptor. This inverse agonism is potentially significant, because H_3Rs have been shown to be constitutively active (partly activated in the absence of endogenous agonist histamine) in both in vitro and in vivo studies.[26]

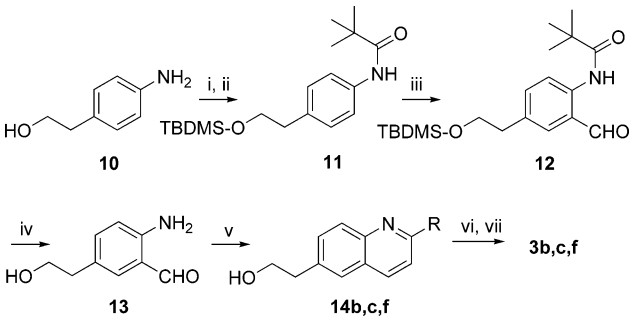
Before testing analogs in rodent behavioral assays in vivo, PK properties were determined in rat, the species ultimately used for behavioral models (see Table 4). The new compounds **3a**−**3f** had very good PK profiles, with moderate half-lives ($t_{1/2}$ = 1.7−8.3 h) and good oral bioavailabilities (F = 30−98%). The reduced volume of distributions (Vβ) for the quinolines compared to **1** may be due to their increased hydrophilic nature,

Table 1. Binding Affinities of Compounds **1** and **3a**−**3f** at Human and Rat H_3R[a]

		human H_3		rat H_3	
cmpd	R	$pK_i \pm SEM$	K_i (nM)	$pK_i \pm SEM$	K_i (nM)
1		9.35 ± 0.04	0.45	8.87 ± 0.04	1.35
3a		9.73 ± 0.13	0.19	9.31 ± 0.08	0.49
3b		9.59 ± 0.03	0.26	9.04 ± 0.05	0.91
3c		9.54 ± 0.12	0.29	9.14 ± 0.04	0.72
3d		9.62 ± 0.09	0.24	9.03 ± 0.10	0.93
3e		9.35 ± 0.12	0.45	8.79 ± 0.08	1.62
3f		9.47 ± 0.03	0.34	8.71 ± 0.11	1.95

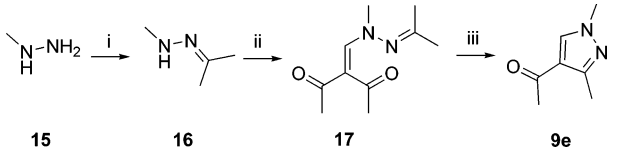
[a] $n \geq 4$. Assessed by displacement of [^{3}H]-*N*-α-methyl histamine from cell membranes isolated from C6 cells expressing cloned rat or human H_3R.[24] The pK_i (−log K_i) ± the standard error of the mean (SEM) are reported.

Scheme 2[a]



[a] Reagents and conditions: (i) pivaloyl chloride, Et_3N, CH_2Cl_2, 16 h (78%); (ii) TBDMSCl, imidazole, CH_2Cl_2 (98%); (iii) 2.3 equiv *n*-BuLi, TMEDA, Et_2O, 0 °C, rt, 2 h, −10 °C; 6 equiv DMF, rt, 16 h (83%); (iv) 2 M HCl in EtOH, Δ (35%); (v) RCOMe (**9b**, **9c**, **9f**), KOH, EtOH, Δ; (vi) MsCl, Et_3N, CH_2Cl_2; (vii) (*R*)-2-Me-pyrrolidine, Cs_2CO_3, MeCN, PhMe, Δ (80% for 2 steps).

Scheme 3[a]



[a] Reagents and conditions: (i) acetone, rt; Δ; then distill (44%); (ii) 3-ethoxymethylenepentane-2,4-dione, Et_2O (84%); (iii) 1 M HCl, EtOH (96%).

consistent with their lower calculated CLogP values (see Table 5). With the exception of the more lipophilic ABT-239 (**1**), lower clearance values (CLb) in the new compounds correlated well with longer $t_{1/2}$.

Brain penetration is of course an important property for agents targeting CNS diseases. Although the processes governing brain entry are multifactorial involving biological processes such as efflux transporters,[27] the physicochemical properties have a very strong influence on CNS penetration. Properties thought favorable to blood−brain barrier (BBB) penetration include weak hydrogen−bonding potential, moderate-to-high lipophilicity

Table 2. In Vitro Functional Antagonism of Compounds **1** and **3a**−**3f** in Calcium Mobilization and GTPγS Binding Assays[a]

			inhibition of [^{35}S]GTPγS binding[b]			
	calcium mobilization[c] (human)		human		rat	
cmpd	$pK_b \pm SEM$	K_b (nM)	$pK_b \pm SEM$	K_b (nM)	$pK_b \pm SEM$	K_b (nM)
1	7.87 ± 0.15	13.49	9.04 ± 0.04	0.91	8.34 ± 0.14	4.57
3a	8.06 ± 0.14	8.71	8.88 ± 0.18	1.32	9.00 ± 0.12	1.00
3b	8.34 ± 0.13	4.57	9.27 ± 0.03	0.54	8.15 ± 0.29	7.08
3c	8.46 ± 0.19	3.47	9.05 ± 0.18	0.89	8.71 ± 0.10	1.95
3d	8.47 ± 0.09	3.39	9.41 ± 0.11	0.39	9.04 ± 0.13	0.91
3e	8.77 ± 0.10	1.70	9.13 ± 0.07	0.74	8.51 ± 0.11	3.09
3f	8.82 ± 0.12	1.51	9.19 ± 0.09	0.65	8.45 ± 0.05	3.55

[a] $n \geq 3$. [b] Inhibition of RAMH-induced binding of [^{35}S]GTPγS.[24] [c] Functional activity determined in HEK-239 cell line, coexpressing hH_3R and Gαq/i5, measuring reduction of 30 nM RAMH-induced increases in intracellular calcium.[24]

Table 3. In Vitro Inverse Agonism of Compounds **1** and **3a**−**3f** in GTPγS Binding Assays[a]

	reduction of basal [^{35}S]GTPγS binding[b]			
	human		rat	
cmpd	$pEC_{50} \pm SEM$	EC_{50} (nM)	$pEC_{50} \pm SEM$	EC_{50} (nM)
1	8.89 ± 0.06	1.29	7.76 ± 0.20	17.4
3a	9.23 ± 0.09	0.59	9.13 ± 0.14	0.74
3b	8.85 ± 0.11	1.41	8.44 ± 0.08	3.63
3c	9.11 ± 0.07	0.78	8.52 ± 0.10	3.02
3d	8.95 ± 0.22	1.12	8.30 ± 0.08	5.01
3e	8.70 ± 0.11	2.00	8.24 ± 0.07	5.75
3f	8.80 ± 0.09	1.58	8.14 ± 0.10	7.24

[a] $n \geq 3$. [b] Reduction of basal [^{35}S]GTPγS binding (efficacy > 20%).[24]

(CLogP), lower polar surface area (PSA), reduced flexibility, and small size.[27,28] Most CNS active drugs that efficiently penetrate the brain have low polar surface areas (<70 Å).[29] However, a caveat is that as lipophilicity rises, there is often a concomitant reduction in the fraction of unbound drug in brain because much of the compound is nonspecifically bound to brain tissue.[30] Optimal design involves finding an appropriate balance

Table 4. PK Properties of Compounds Tested in Rats at 1 mg/kg

	PK[a]			
	i.v.[b]			p.o.[c]
cmpd	$t_{1/2}$ (h)	Vβ	CLb	*F* (%)
1	5.3	11.6	1.50	53
3a	8.3	7.4[d]	0.53	70
3b	2.4	4.1	1.18	75
3c	4.0	8.5	1.45	98
3d	5.3	6.3	0.84	90
3e	1.7	9.0	3.7	58
3f	2.0	9.2[e]	2.54	30[f]

[a] Data expressed as mean; $n = 3$ animals; SEM < 20% of mean unless stated. [b] Compounds dosed intravenously; $n = 3$ animals; Vβ (volume of distribution, L/h); CLb (clearance, $Lh^{-1}kg^{-1}$). [c] Compounds dosed orally; *F* (oral bioavailabilty, %). [d] SEM ± 1.9. [e] SEM ± 3.1. [f] SEM ± 10.

Table 5. Physicochemical Properties and CNS Penetration

				CNS penetration[a]			
				mouse[b]		rat[c]	
cmpd	PSA	CLogP[d]	MW	brain concn (ng/g)	brain-to-blood ratio	brain concn (ng/g)	brain-to-plasma ratio
1	40.2	5.15	330	1728	19×	3082	36−52×
3a	69.0	4.36	443	3242	42×		
3b	46.8	4.20	398	1659	23×		
3c	45.2	4.14	402	718	16×		
3d	46.3	4.12	386	174	1.5×	440	1.6×
3e	34.0	3.44	335			425	1.8×
3f	41.9	4.32	383	0		50[e]	0.4×

[a] All compounds $n \geq 3$. Compounds dosed 1 mg/kg, measured 1 h after dosing, concentrations were determined by HPLC-MS; SEM < 11% of mean unless stated. [b] Dosed i.p. [c] Dosed i.v. [d] Calculated.[47] [e] SEM ± 22.

Table 6. Plasma Protein Binding (% Bound)[a]

cmpd	dog	human	monkey	rat
1	91	97	94	94
3a	83	83	79	89
3b	78	85	81	77
3c	80	81	70	84
3d	60	64	55	70
3e	58	75	50	62
3f	43	56	50	61

[a] Compounds (5 μM) were incubated with plasma, and the mixture was centrifuged in a Microcon membrane filtration unit to separate bound from free compound. Free compound was quantified against a standard curve (LC-MS/MS) and reported as the percent bound. $n = 1$.

of physicochemical properties, lipophilic enough to allow for efficient partitioning into brain tissue, but not too lipophilic so that unbound drug is free to act at the target.

The ability of compounds **3a**−**3f** to enter the brain was evaluated in rodents (see Table 5). In mouse, compound **3a** had exceptionally high brain levels (3242 ng/g/mg of compound dosed) and a large brain-to-blood ratio (42×). Compounds **3d** and **3e** had more modest brain levels in rat, similar to the plasma levels. Surprisingly, compound **3f** had no detectable levels in mouse brain and only low levels in rat. The reason for this finding is undetermined and could not be rationalized on any physicochemical basis such as CLogP, molecular weight, or polar surface area. Instead, we suspect there could be some factor particular to compound **3f** itself such as, for example, the compound might be actively effluxed from the brain.

The plasma protein binding of the analogs was measured in several species (Table 6). Compounds had moderate protein binding (43−89%), which is favorable, indicating that a sizable free fraction of circulating drug is present in the plasma. The moderate degree of plasma protein binding for these agents can be rationalized by their lower lipophilicity as assessed by CLogP values (see Table 5). Compounds **3a**−**3e** had good overall drug-like characteristics and were advanced to behavioral models.

Table 7. In Vivo Results[a]

cmpd	SR[b]	5-trial IA[c]
1	0.01−0.1	0.1−1
3a	0.1[d]	1
3b	0.01[e]	
3c	0.003	
3d	0.003−0.01	0.3−1
3e	0.003−0.01	0.1−1

[a] Activity of compounds in two rodent behavioral assays: the social recognition memory (SR) test in adult rats[31] and the 5-trial inhibitory avoidance (5-trial IA) in spontaneously hypertensive rat (SHR) pups.[32] Efficacious doses are in mg/kg, following i.p. and s.c. administration, respectively. [b] $n \geq 12$ animals; $P < 0.05$, Dunnett's post hoc analysis. [c] $n \geq 9$ animals; $P < 0.05$ Mann−Whitney analysis. [d] $n = 6$. [e] A trend toward efficacy was seen at this dose for compound **3b**, but it did not reach statistical significance, $P > 0.05$, Dunnett's post hoc analysis.

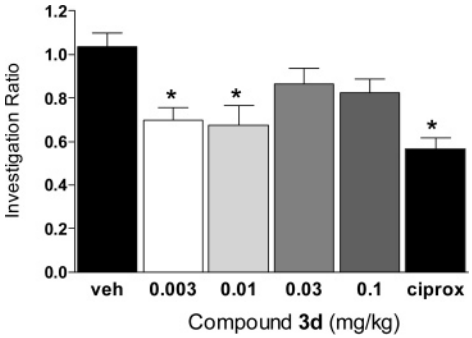


Figure 2. Compound **3d** in SR. The effect of compound **3d** on enhancing SR memory in adult rats is shown graphically as the mean ± SEM.[31] With **3d**, or with the standard reference H_3 antagonist ciproxifan (ciprox, 1.0 mg/kg), recall of the initial social encounter is improved, with a consequent reduction in the time spent reinvestigating the juvenile, expressed as the investigation ratio. *$P < 0.05$, Dunnett's post hoc analysis; $n = 12$ animals, dosed i.p.

Two in vivo behavioral models were used to assess the compounds' ability to facilitate memory and learning in rodents (see Table 7). The social recognition (SR) memory model evaluated the memory enhancing effects by testing the ability of agents to improve the retention of encounters between animals.[31] In this model, an adult rat is allowed to explore a juvenile rat for 5 min during a period of social investigation and then, after a 2 h separation, is reintroduced to the juvenile for a second 5 min period. Test compounds or saline vehicle were administered intraperitoneally (i.p.) to the adult rat immediately after the first 5 min exposure period. The duration of investigation (grooming, sniffing, close following) was recorded over each 5 min period. Social memory was quantified by determining the investigation ratio, which is the ratio of the time the adult rat spends investigating the juvenile in the second encounter divided by the time the adult spends investigating the juvenile during the first encounter. An agent that enhances memory will reduce the exploration time of the second encounter relative to the first and, hence, the investigation ratio. The H_3R antagonist ciproxifan dosed at 1 mg/kg was used as a standard, as this compound reliably enhances SR memory.[31] Compounds **3a** and **3c**−**3e** were clearly effective in this model. A more detailed dose response determination was done for compounds **3d** and **3e**, confirming that they were active over a range of doses (see Figure 2 for the graph of compound **3d**).

The five-trial inhibitory avoidance (5-trial IA) acquisition model assesses aspects of learning as well as impulsive behavior.[32] This model, which uses spontaneously hypertensive

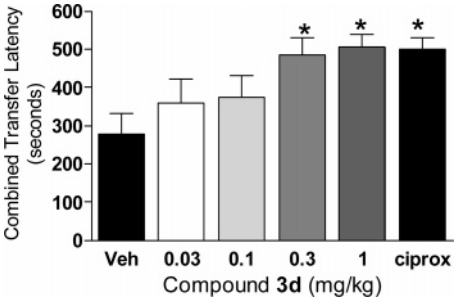


Figure 3. Compound **3d** in 5-trial IA. Compound **3d** improves avoidance acquisition in the five-trial, repeated acquisition, inhibitory avoidance response in SHR pups compared with vehicle.[32] The summed latency shows the improvement in acquisition for trials 2−5 compared to vehicle-treated controls. Compound **3d** or vehicle was dosed s.c. 30 min prior to the first training trials; ciproxifan (ciprox, 3.0 mg/kg) was included as a positive control. Data are expressed as mean ± SEM. *$P < 0.05$ Mann−Whitney analysis. $n \geq 9$ animals.

rat pups, is used as a predictive of efficacy in ADHD.[33] The model evaluates the ability of an agent to improve the rate at which a rat pup learns, during five trials, to avoid entering a darkened chamber where it receives a mild foot shock. Compounds were injected subcutaneously (s.c.) in the scruff of the neck 30 min prior to the training. Behavioral responses are expressed as the combined transfer latency, which is the sum of time over the five trials the rat spends before entering the darkened chamber. Compounds **3a**, **3d**, and **3e** were evaluated in this model and compared to the activity of the standard histamine H_3 antagonist ciproxifan (tested at 3 mg/kg). All three of the new compounds were found to be efficacious in this model (see Figure 3 for graph of compound **3d**). Evaluation of plasma concentrations sampled at the efficacious doses revealed that compounds **3d** and **3e** were very potent, with behavioral efficacy seen at plasma levels of 19.2 ng/mL at the 0.3 mg/kg dose for **3d** and 2.5 ng/mL at the 0.1 mg/kg dose for **3e**.

We were surprised to find that compound **3a** was relatively weak in vivo, despite its excellent potency and PK profile in rat and very high brain levels in mouse. One rationale for this could be that compound **3a** might have a high propensity for nonspecific binding to brain tissue, such as cell membranes and lysosomes, thus accounting for its very high brain levels.[30] However, if there was a very high level of nonspecific binding of **3a** to CNS tissues, the actual amount of free unbound **3a** in the brain may be low compared to compounds such as **3d** and **3e**, which had lower brain penetration but were more potent in vivo.

The overall favorable behavioral profiles of compounds **3d** and **3e** in the SR and 5-trial IA in vivo models led us to assess these agents further. Administered i.p., no untoward CNS side effects were seen for **3d** in rat at doses up to 2.8 mg/kg in a general test for CNS side effects.[31] At higher doses (9.4 mg/kg), mild hypoactivity and piloerection were noted; however, these effects are present at 30-fold above the behaviorally effective dose (0.3 mg/kg in the 5-trial IA). Compound **3e** was free of overt CNS side effects[32] at 2.8 mg/kg and mild tremor and mild hypoactivity were evident at 9.4 mg/kg, 94-fold above its active dose (0.1 mg/kg in the 5-trial IA).

An examination of the off-target binding profile was conducted (Cerep and in-house). Tested at a concentration of 10 μM, **3d** was found to be highly selective for the H_3R. Except for the sigma receptor (96%), only weak binding was seen (% inhibition at 10 μM in parentheses) at adenosine-A3 (69% inhibition), muscarinic-M4 (74%), and L-type calcium channels (63%). For compound **3e**, only sigma receptors (86%) showed significant affinity at 10 μM.

Compounds such as **3d** and **3e** are cationic amphiphiles, so-called because at physiological pH they contain both a protonated hydrophilic domain and a hydrophobic domain. Compounds in this class have been reported to have the potential to bind to and accumulate in the phospholipid bilayers of cells and induce phospholipidosis, a lipid storage disorder in which phospholipids accumulate in endosomes and lysosomes as lamellar bodies in various tissues.[34] While phospholipidosis noted in in vitro assays is in itself not considered a toxic response, it is often associated with toxicity in targeted organs.[35] Compounds **3d** and **3e** were examined in vitro in rat hepatocytes for their phospholipid index (PI),[36,37] a measurement of their potential to induce phospholipidosis as normalized to the standard amiodorane (at 5 μM, PI = 1), a compound with a known propensity to induce phospholipidosis.[38a] Compound **3d** was found to be only a moderate inducer of phospholipidosis, having PIs of 0.66 ± 0.41 and 0.69 ± 0.08 at 44 μM and 88 μM, respectively, while at a lower concentration (22 μM) this compound was an even weaker inducer (PI = 0.21 ± 0.09).[38b] Thus, the compound was considered to have a limited ability to induce phospholipidosis at a concentration below 20 μM. Compound **3e** was a weak inducer of phospholipidosis at 100 μM (PI = 0.39 ± 0.01) and inactive at lower concentrations and was considered unlikely to cause phospholipidosis in vivo.

Testing for genetoxicity found that compounds **3d** and **3e** were nonclastogenic and nonmutagenic.[39] Also, no inhibition of any key CYP−P_{450} enzymes (1A2, 2A6, 2C19, 2C9, 2D6, 2E1, or 3A4) was observed at 10−20 μM, and so it was judged that **3d** and **3e** had low potential for drug−drug related interactions. Further PK studies indicated good bioavailability for **3d** and **3e** in dog ($F = 72 \pm 10$ and 77 ± 10%, respectively). The compounds showed high whole-cell permeability in Caco-2 membranes, supporting an expectation of efficient oral absorption. Both compounds **3d** and **3e** had good water solubility (8.7 and 21 mg/mL, respectively, at pH 7), consistent with their moderate polarity and single positive molecular charge arising from a basic pyrrolidine (measure pK_b of 9.7).

Further studies on the pharmaceutic properties of compounds **3d** and **3e** did uncover an interesting observation: a potential problem with photochemical stability. Stability studies revealed that the free bases of compounds **3d** and **3e** were unstable toward UV light, especially at high pH and in the solid phase.[40] This instability was believed likely to be due to the quinoline moiety because other nonquinoline containing agents (naphthylenes) of otherwise similar structure did not exhibit this instability. Salts of compound **3e** were examined and displayed an improvement in the stability relative to the free base.[41] In cardiovascular studies in the anesthetized dog, the principal side effect seen for compound **3d** was an increase in heart contractility (9 ± 1% increase in dP/dt_{max} at a blood concentration of 108 ± 24 ng/mL).[42] The photo instability of members of the quinoline series and the cardiovascular liabilities of compound **3d** led us to discontinue compounds from this quinoline series for further evaluation as potential clinical candidates.

In summary, a new series of quinoline-containing H_3R antagonists was discovered. The compounds are potent inverse agonists at the rat and human H_3R (K_i 1.95−0.17 nM) and are selective for the H_3R over other histamine subtypes and a variety of other receptors and ion channels. The compounds were found to have desirable drug-like characteristics of cognitive agents such as good PK, moderate protein binding across species and the ability to cross the BBB. Analogs **3d** and **3e** were tested in vivo in two rodent behavioral models and, consistent with profiles previously reported for H_3R antagonists, both **3d** and

3e were efficacious in these in vivo models of learning and attention and may be useful as tool compounds.

Experimental Section

General. Proton NMR spectra were obtained on a Varian Mercury plus 300 or Varian UNITY plus 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as an internal standard. Melting points were determined on a Thomas−Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Quantitative Technologies, Inc. Column chromatography was carried out on silica gel 60 (230−400 mesh). Thin-layer chromatography (TLC) was performed using 250 mm silica gel 60 glass-backed plates with F254 as indicator.

2-[1-(6-Ethoxypyridazin-3-yl)-5-methyl-1*H*-pyrazol-4-yl]-6-[2-(2-(*R*)-methylpyrrolidin-1-yl)ethyl]quinoline L-Tartrate (3a). Compound **8** (0.66 g, 2.9 mmol) and compound **9a** (1.0 g, 4.3 mmol) were treated with a solution of NaOH (0.29 g, 7.2 mmol) in EtOH (80 mL), refluxed overnight, cooled, concentrated, and chromatographed using 1 and 2% (9:1 MeOH/satd NH_4OH) in CH_2Cl_2 to provide 0.32 g (25%) of the title compound, which was converted to the L-tartaric acid salt. ^{1}H NMR (CD_3OD) δ 1.49 (t, J = 7.1 Hz, 3H), 1.48 (d, J = 6.1 Hz, 3H), 1.78 (m, 1H), 2.12 (m, 2H), 2.34 (m, 1H), 2.99 (s, 3 H), 3.17−3.43 (m, 4H), 3.58 (m, 1H), 3.72 (m, 2H), 4.59 (q, J = 7.1 Hz, 2H), 7.37 (d, J = 9.2 Hz, 1H), 7.73 (dd, J = 8.8, 2.0 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 1.7 Hz, 1H), 8.05 (m, 2H), 8.29 (m, 4H); MS (DCI/NH_3) m/z 443 (M + H)$^+$. Anal. ($C_{26}H_{30}N_6O\cdot C_4H_6O_6\cdot 2H_2O$) C, H, N.

2-(5-Methyl-1-pyridin-2-yl-1*H*-pyrazol-4-yl)-6-[2-(2-(*R*)-methylpyrrolidin-1-yl)ethyl]quinoline L-Tartrate (3b). Scheme 2, Step vi: Compound **14b** (3.86 g, 11.7 mmol) was suspended in CH_2Cl_2 (120 mL), treated with Et_3N (2.45 mL, 17.6 mmol), treated with MsCl (1.2 mL, 15.2 mmol), stirred at ambient temperature for 2 h, treated with H_2O (50 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to provide the 4.78 g (100%) of the mesylate (methanesulfonic acid, 2-[2-(5-methyl-1-pyridin-2-yl-1*H*-pyrazol-4-yl)quinolin-6-yl]ethyl ester) as a white solid. ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 3.14 (s, 3H), 3.22 (t, J = 6.6 Hz, 2H), 4.55 (t, J = 6.6 Hz, 2H), 7.45−7.50 (m, 1H), 7.74 (dd, J = 8.6, 1.9 Hz, 1H), 7.86−7.91 (m, 2H), 7.94 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 8.04−8.10 (m, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.41 (s, 1H), 8.57−8.61 (m, 1H); MS (DCI/NH_3) m/z 409 (M + H)$^+$. **Step vii:** (*R*)-2-Methylpyrrolidine L-tartrate[19] (4.1 g, 17.2 mmol) was treated with 50% NaOH soln (5.5 g, 68 mmol), treated with brine (10 mL), and extracted with toluene (15 mL). This solution of (*R*)-2-methylpyrrolidine in toluene was added to a suspension of the mesylate (3.5 g, 8.6 mmol) in CH_3CN (15 mL). The resulting mixture was treated with Cs_2CO_3 (5.6 g, 17 mmol), stirred at 80 °C for 16 h in a sealed flask, cooled, and filtered through diatomaceous earth to remove the solids. The solids were washed with CH_2Cl_2, and the combined filtrates were concentrated and chromatographed using a gradient of EtOAc/HCOOH/H_2O (22:1:1, 10:1:1, 4:1:1, and 3:2:1). The fractions containing the product were concentrated to dryness, treated with 1 M NaOH (100 mL), treated with CH_2Cl_2 (100 mL), filtered through celite, and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (2 × 100 mL). The combined CH_2Cl_2 extractions were dried ($MgSO_4$), filtered, concentrated, and chromatographed using a gradient of 2, 3.5, 4, 4.5, and 5% (9:1 MeOH/satd aq NH_4OH) in CH_2Cl_2 to provide 2.75 g (81%) of the title compound. This free base (2.73 g, 6.87 mmol) was treated with L-tartaric acid (1.03 g, 6.87 mmol), treated with 3 mL of H_2O, concentrated to dryness, and crystallized from MeOH/EtOAc. The crystals were collected by filtration, washed with EtOAc, and dried under vacuum to provide 3.27 g (87%) of the salt. Mp 123−131 °C; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, J = 6.1 Hz, 3H), 1.40−1.57 (m, 1H), 1.77−1.90 (m, 2H), 1.99−2.12 (m, 1H), 3.06 (s, 3H), 2.74−3.14 (m, 5H), 3.31−3.51 (m, 2H), 4.04 (s, 2H), 7.43−7.51 (m, 1H), 7.70 (dd, J = 8.5, 2.0 Hz, 1H), 7.83 (d, J = 1.7 Hz, 1H), 7.88 (dt, J = 8.2, 1.0 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 8.03−8.10 (m, 1H), 8.33 (d, J = 8.1 Hz, 1H), 8.39 (s, 1H), 8.57−8.60 (m, 1H); MS (DCI/NH_3) m/z 398 (M + H)$^+$; Anal. ($C_{25}H_{27}N_5\cdot C_4H_6O_6\cdot H_2O$) C, H, N.

6-{2-[(2*R*)-2-Methyl-pyrrolidin-1-yl]ethyl}-2-(4-methyl-2-pyrrolidin-1-ylpyrimidin-5-yl)quinoline phosphate (3c). The title compound was prepared using the procedure described for compound **14b** and **3b**, substituting 1-(4-methyl-2-pyrrolidin-1-ylpyrimidin-5-yl)ethanone[43] (compound **9c**) for compound **9b**. The free base of the product was treated with 1 molar equiv of a 0.1 M solution of H_3PO_4 in 19:1 MeOH/H_2O and concentrated. Upon addition of CH_3CN, the salt crystallized and was collected by filtration, washed with CH_3CN, and dried under vacuum to provide the corresponding H_3PO_4 salt. Mp 209−212 °C; ^{1}H NMR (DMSO-d_6) δ 1.14 (d, J = 6.1 Hz, 3H), 1.33−1.50 (m, 1H), 1.69−1.83 (m, 2H), 1.88−2.04 (m, 5H), 2.53 (s, 3H), 2.61−2.78 (m, 2H), 2.93−3.14 (m, 2H), 3.17−3.38 (m, 2H), 3.53−3.59 (m, 4H), 7.70 (m, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.85 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 8.33 (d, J = 8.8 Hz, 1H), 8.54 (s, 1H); MS (DCI/NH_3) m/z 402 (M + H)$^+$; Anal. ($C_{25}H_{31}N_5\cdot H_3PO_4\cdot 0.1\ H_2O$) C, H, N.

2-(2,7-Dimethylpyrazolo[1,5-*a*]pyrimidin-6-yl)-6-{2-[(2*R*)-2-methylpyrrolidin-1-yl]ethyl}quinoline maleate (3d). Compound **8** (2.08 g, 8.9 mmol) was treated with EtOH (90 mL), treated with compound **9d** (2.03 g, 10.7 mmol), treated with a satd soln of KOH in EtOH (0.9 mL), heated to 75 °C for 16 h, cooled, concentrated, and chromatographed, using a gradient of 3:1, 1:1, 1:2, and 1:4 EtOAC/[4:1:1 EtOAc/HCOOH/H_2O]. The fractions containing the product were concentrated to dryness, treated with 1 M NaOH (100 mL), treated with CH_2Cl_2, and filtered through celite. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and chromatographed using a gradient of 2 and 3.5% (9:1 MeOH/satd NH_4OH) in CH_2Cl_2 to provide 2.1 g (60%) of the title compound. The free base was converted to the maleic acid salt and crystallized from acetone/EtOAc. Mp 151−153 °C; ^{1}H NMR (DMSO-d_6) δ 1.39 (d, J = 6.1 Hz, 3H), 1.52−1.70 (m, 1H), 1.88−2.07 (m, 2H), 2.16−2.30 (m, 1H), 2.51 (s, 3H), 2.91 (s, 3H), 3.14−3.41 (m, 5H), 3.59−3.75 (m, 2H), 7.82 (dd, J = 8.8, 1.7 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 1.7 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 8.49 (d, J = 8.5 Hz, 1H), 8.74 (s, 1H), 9.22 (bs, 1H); MS (DCI/NH_3) m/z 386 (M + H)$^+$; Anal. ($C_{24}H_{27}N_5\cdot C_4H_4O_4$) C, H, N.

(*R*)-2-(1,3-Dimethyl-1*H*-pyrazol-4-yl)-6-(2-(2-methylpyrrolidin-1-yl)ethyl)quinoline (3e). The title compound was prepared using the procedure described for compound **3d** substituting compound **9e** for compound **9d** as the free base. Mp 133−134 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 6.1 Hz, 3H), 1.46 (m, 1H), 1.65−2.02 (m, 3H), 2.24 (q, J = 8.7 Hz, 1H), 2.32−2.46 (m, 2H), 2.64 (s, 3H), 2.91−3.19 (m, 3H), 3.30 (dt, J = 8.5, 2.71 Hz, 1H), 3.91 (s, 3H), 7.51−7.61 (m, 3H), 7.90 (s, 1H), 7.97 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H); MS (DCI/NH_3) m/z 335 (M + H)$^+$; Anal. ($C_{21}H_{26}N_4$) C, H, N.

2-Methyl-3-{6-[2-([2*R*]-2-methylpyrrolidin-1-yl)-ethyl]quinolin-2-yl}-[1,8]naphthyridine Phosphate (3f). The title compound was prepared using the procedure described for compound **14b** and **3b**, substituting 1-(2-methyl-[1,8]-naphthyridin-3-yl)ethanone[44] (compound **9f**) for compound **9b**. The free base of the product was converted to the H_3PO_4 salt as described for compound **3c**. Mp 142−153 °C; ^{1}H NMR (DMSO-d_6) δ 1.17 (d, J = 6.1 Hz, 3H), 1.45 (m, 1H), 1.79 (m, 2H), 2.00 (m, 1H), 2.54−2.87 (m, 3H), 2.80 (s, 3H), 3.10 (m, 2H), 3.23−3.43 (m, 2H), 7.64 (dd, J = 8.1, 4.4 Hz, 1H), 7.78 (dd, J = 8.6, 1.5 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 8.49 (d, J = 8.8 Hz, 1H), 8.53 (dd, J = 8.1, 1.7 Hz, 1H), 8.60 (s, 1H), 9.10 (dd, J = 4.2, 1.9 Hz, 1H); MS (DCI/NH_3) m/z 383 (M + H)$^+$; Anal. ($C_{25}H_{26}N_4\cdot H_3PO_4\cdot 0.5H_2O\cdot 0.25CH_3CN$) C, H, N.

(2*R*)-2-Methyl-1-[2-(4-nitrophenyl)ethyl]pyrrolidine (5). (*R*)-2-Methylpyrrolidine L-tartrate (**4**;[19] 4.0 g, 17.0 mmol), 1-(2-bromoethyl)-4-nitrobenzene (9.8 g, 43 mmol), and K_2CO_3 (12 g, 85 mmol), were combined in DMF (20 mL) in a sealed tube at 50 °C and stirred vigorously for 16 h. The mixture was allowed to

cool to room temperature, diluted with Et_2O (100 mL), washed with water (2×, 100 mL and then 50 mL), and extracted twice with 1 M HCl (50 mL and 25 mL). The aqueous acidic extractions were combined, washed with Et_2O (50 mL), cooled to 0 °C, adjusted to pH 14 with 50% NaOH solution, and extracted with CH_2Cl_2 (3×, 50 mL). The CH_2Cl_2 extractions were combined, dried ($MgSO_4$), and filtered, and the filtrate was concentrated to provide 3.85 g (97%) of compound **5**. ^{1}H NMR ($CDCl_3$) δ 1.08 (d, $J = 6.1$ Hz, 3H), 1.43 (m, 1H), 1.75 (m, 2H), 1.93 (m, 1H), 2.19 (q, $J = 8.7$ Hz, 1H), 2.34 (m, 2H), 2.91 (m, 2H), 3.03 (m, 1H), 3.22 (td, $J = 8.5$, 3.0 Hz, 1H), 7.38 (m, 2H), 8.15 (m, 2H); MS (DCI/NH_3) m/z 235 $(M + H)^+$.

2,2-Dimethyl-*N*-(4-{2-[(2*R*)-2-methyl-1-pyrrolidinyl]ethyl}-phenyl)propanamide (6). Step ii: Compound **5** (3.85 g, 16.4 mmol) was hydrogenated using 10% Pd/C (0.39 g) in MeOH (20 mL) under 1 atm H_2 for 16 h. After the H_2 was replaced with N_2, the mixture was diluted with MeOH (150 mL), stirred for 15 min, and filtered, and the filtrate was concentrated to provide 3.24 g (97%) of the aniline, (*R*)-4-(2-(2-methylpyrrolidin-1-yl)ethyl)aniline. ^{1}H NMR ($CDCl_3$) δ 1.11 (d, $J = 6$ Hz, 3H), 1.43 (m, 1H), 1.74 (m, 2H), 1.90 (m, 1H), 2.25 (m, 3H), 2.70 (m, 2H), 2.97 (m, 1H), 3.24 (td, $J = 9$, 3 Hz, 1H), 3.55 (s, 2H), 6.63 (d, $J = 8$ Hz, 2H), 7.01 (d, $J = 8$ Hz, 2H); MS (DCI/NH_3) m/z 205 $(M + H)^+$. **Step iii:** The aniline (2.77 g, 14 mmol) was dissolved in anhydrous CH_2Cl_2 (70 mL) under N_2, treated with Et_3N (2.3 mL, 16 mmol), cooled to 0 °C, treated with trimethylacetyl chloride (1.9 mL, 15 mmol), stirred at ambient temperature for 60 h, and treated with 1 M NaOH (40 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated to provide 4.0 g (99%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.10 (d, $J = 6.1$ Hz, 3H), 1.31 (s, 9H), 1.44 (m, 1H), 1.76 (m, 2H), 1.92 (m, 1H), 2.18 (q, $J = 8.8$ Hz, 1H), 2.27 (m, 2H), 2.78 (m, 2H), 2.99 (m, 1H), 3.23 (td, $J = 9.2$, 3.0 Hz, 1H), 7.17 (d, $J = 8.5$ Hz, 2H), 7.44 (d, $J = 8.5$ Hz, 2H); MS (DCI/NH_3) m/z 289 $(M + H)^+$.

***N*-(2-Formyl-4-{2-[(2*R*)-2-methyl-1-pyrrolidinyl]ethyl}phenyl)-2,2-dimethylpropanamide (7).** A mixture of compound **6** (4.0 g, 13.9 mmol) under N_2 in anhydrous Et_2O (140 mL) was treated with TMEDA (6.5 mL, 43 mmol), cooled to 0 °C, treated with *n*-BuLi (16.7 mL of a 2.5 M solution in hexanes, 41.8 mmol) over 10 min, stirred for 4 h at ambient temperature, cooled to 0 °C, treated all at once with anhydrous DMF (6.5 mL, 83 mmol), stirred for 16 h at ambient temperature, diluted with Et_2O (100 mL), washed with water (75 mL), washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 2, 3.5, 5, and 7.5% (9:1 MeOH/concd NH_4OH) in CH_2Cl_2 to provide 3.57 g (81%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.10 (d, $J = 6.1$ Hz, 3H), 1.35 (s, 9H), 1.44 (m, 1H), 1.75 (m, 2H), 1.93 (m, 1H), 2.19 (q, $J = 8.7$ Hz, 1H), 2.31 (m, 2H), 2.85 (m, 2H), 3.01 (m, 1H), 3.23 (td, $J = 8.5$, 3.0 Hz, 1H), 7.47 (dd, $J = 8.6$, 2.2 Hz, 1H), 7.51 (d, $J = 2.4$ Hz, 1H), 8.71 (d, $J = 8.5$ Hz, 1H), 9.92 (s, 1H), 11.31 (s, 1H); MS (DCI/NH_3) m/z 317 $(M + H)^+$.

2-Amino-5-{2-[(2*R*)-2-methyl-1-pyrrolidinyl]ethyl}-benzaldehyde (8). Compound **7** (2.46 g, 7.8 mmol) in 3 M HCl (40 mL) was heated at 80 °C for 4 h, allowed to cool to room temperature, and carefully poured into a mixture of 1 M NaOH (250 mL) and CH_2Cl_2 (75 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The residue was purified by chromatography on silica gel eluting with a gradient of 2, 3.5, and 5% (9:1 MeOH/concd NH_4OH) in CH_2Cl_2 to provide 1.23 g (68%) the title compound. ^{1}H NMR ($CDCl_3$) δ 1.12 (d, $J = 6.1$ Hz, 3H), 1.50 (m, 1H), 1.76 (m, 2H), 1.93 (m, 1H), 2.25 (m, 3H), 2.76 (m, 2H), 2.99 (m, 1H), 3.25 (td, $J = 8.7$, 2.7 Hz, 1H), 5.99 (s, 2H), 6.60 (d, $J = 8.5$ Hz, 1H), 7.19 (dd, $J = 8.3$, 2.2 Hz, 1H), 7.31 (d, $J = 2.4$ Hz, 1H), 9.85 (d, 0.7 Hz, 1H).

1-[1-(6-Chloropyridazin-3-yl)-5-methyl-1*H*-pyrazol-4-yl]ethan-1-one (9a). A mixture of 3-chloro-6-hydrazinopyridazine (2.0 g, 14 mmol) and 3-dimethylaminomethylenepentane-2,4-dione[21b] (2.6 g, 17 mmol) in EtOH (80 mL) was heated to reflux for 3 h and allowed to stand at ambient temperature overnight. The solid was collected by filtration, washed with ethanol, and dried under vacuum to provide the title compound. ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H), 2.85 (s, 3H), 8.17 (d, $J = 9.5$ Hz, 1H), 8.23 (d, $J = 9.2$ Hz, 1H), 8.43 (s, 1H); MS (DCI/NH_3) m/z 237 $(M + H)^+$.

1-(2,7-Dimethylpyrazolo[1,5-*a*]pyrimidin-6-yl)ethanone (9d). A solution of 3-dimethylaminomethylenepentane-2,4-dione[21b] (4 g, 25.8 mmol) and 3-amino-5-methylpyrazole (2.45 g, 24.5 mmol) in EtOH (50 mL) was heated to reflux for 2 h, cooled to ambient temperature, and stirred overnight. The solid precipitate was collected by filtration, washed with cold EtOH (50 mL), and dried under vacuum to provided 3.8 g (82%) of the title compound. ^{1}H NMR (CD_3OD) δ 2.52 (s, 3H), 2.68 (s, 3H), 3.07 (s, 3H), 6.55 (s, 1H), 6.87 (s, 1H); MS (DCI/NH_3) m/z 190 $(M + H)^+$.

1-(1,3-Dimethyl-1*H*-pyrazol-4-yl)ethanone (9e). Compound **17** (9.1 g, 46 mmol) was dissolved in EtOH (20 mL), treated with 1 M HCl (20 mL), stirred at ambient temperature for 15 min, concentrated to approximately 20 mL total volume under vacuum using a rotovap, treated with satd $NaHCO_3$ (45 mL), and extracted with CH_2Cl_2 (4 × 50 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$), filtered, and concentrated to provide 6.2 g (96%) of the title compound as a solid. ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.47 (s, 3H), 3.86 (s, 3H), 7.76, (s, 1H); MS (DCI/NH_3) m/z 139 $(M + H)^+$.

***N*-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]phenyl}-2,2-dimethylpropionamide (11). Step i:** 2-(4-Aminophenyl)ethanol (**10**; 23.24 g, 0.17 mol) was dissolved in CH_2Cl_2 (670 mL), treated with Et_3N (28.1 mL, 0.20 mol), cooled to 0 °C, treated with trimethylacetyl chloride (22.8 mL, 0.185 mol) over 10 min, stirred at ambient temperature for 16 h, and treated with 1 M NaOH (250 mL), and the layers were separated. The NaOH layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was recrystallized from 100 mL of EtOAc, which was treated slowly with 25 mL of hexane while still hot. The resulting solid was collected by filtration, washed with 1:1 hexane/EtOAc, and dried under vacuum to provide 29.1 g (78%) of the alcohol, *N*-[4-(2-hydroxyethyl)phenyl]-2,2-dimethylpropionamide. ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.83 (t, $J = 6.6$ Hz, 2H), 3.83 (t, $J = 6.6$ Hz, 2H), 7.18 (d, 8.5 Hz, 2H), 7.29 (bs, 1H), 7.46 (d, 8.5 Hz, 2H); MS (DCI/NH_3) m/z 222 $(M + H)^+$. **Step ii:** The alcohol from above (30.76 g, 0.14 mol) was treated with CH_2Cl_2 (195 mL), treated with *tert*-butyldimethylchlorosilane (25.1 g, 0.17 mol), treated with imidazole (13.2 g, 0.19 mol), stirred at ambient temperature for 2 h, treated with hexane (195 mL), stirred at ambient temperature for 5 min, and filtered to remove the solid. The solid was washed with 1:1 CH_2Cl_2/hexane. The combined filtrates were concentrated and chromatographed using a gradient of hexane/EtOAc (50:1, 40:1, 20:1, 10:1, 5:1, and 4:1) to provide 45.7 g (98%) of the title compound. ^{1}H NMR ($CDCl_3$) δ −0.01 (s, 6H), 0.88 (s, 9H), 1.32 (s, 9H), 2.79 (t, $J = 7.1$ Hz, 2H), 3.78 (t, $J = 7.0$ Hz, 2H), 7.16 (d, $J = 8.5$ Hz, 2H), 7.28 (bs, 1H), 7.44 (d, $J = 8.5$ Hz, 2H); MS (DCI/NH_3) m/z 336 $(M + H)^+$.

***N*-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-2-formylphenyl}-2,2-dimethylpropionamide (12).** Compound **11** (35.24 g, 105 mmol) was treated with anhydrous Et_2O (1.05 L) under N_2, cooled to 0 °C, treated with anhydrous TMEDA (38.0 mL, 0.25 mol), treated with *n*-BuLi (97 mL of a 2.5 M soln in hexane, 0.24 mol), stirred at ambient temperature for 2 h, cooled to −10 °C, treated all at once with anhydrous DMF (49 mL, 0.63 mol), stirred at ambient temperature for 16 h, washed with H_2O (400 mL and then 250 mL), washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed using a gradient of hexane/EtOAc (40:1, 20:1, and 15:1) to provide 31.87 g (83%) of the title compound. ^{1}H NMR ($CDCl_3$) δ −0.01 (s, 6H), 0.89 (s, 9H), 1.38 (s, 9H), 2.86 (t, $J = 6.4$ Hz, 2H), 3.83 (t, $J = 6.4$ Hz, 2H), 7.48 (dd, $J = 8.7$, 2.2 Hz, 1H), 7.54 (d, $J = 2.0$ Hz, 1H), 8.73 (d, $J = 8.5$ Hz, 1H), 9.93 (s, 1H), 11.33 (bs, 1H); MS (DCI/NH_3) m/z 364 $(M + H)^+$.

2-Amino-5-(2-hydroxyethyl)benzaldehyde (13). Compound **12** (9.0 g, 24.8 mmol) was treated with EtOH (450 mL), treated with 2 M HCl (900 mL), heated to reflux for 30 min, concentrated by removing the EtOH by distillation at atmospheric pressure over a 1.5 h period, cooled to 0 °C, treated with NaOH soln (50% by weight, 150 g), and extracted with CH_2Cl_2 (5 × 250 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$), filtered, concentrated to provide 2.90 g (35%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 2.80 (t, J = 6.4 Hz, 2H), 3.84 (t, J = 6.4 Hz, 2H), 6.03 (bs, 2H), 6.63 (d, J = 8.5 Hz, 1H), 7.20 (dd, J = 8.5, 2.0 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 9.85 (s, 1H); MS (DCI/NH_3) m/z 166 $(M + H)^+$.

2-[2-(5-Methyl-1-pyridin-2-yl-1*H*-pyrazol-4-yl)-quinolin-6-yl]-ethanol (14b). Compound **13** (3.83 g, 23.2 mmol) was treated with 1-(5-methyl-1-pyridin-2-yl-1*H*-pyrazol-4-yl)ethanone[45] (compound **9b**; 6.06 g, 30.1 mmol), treated with EtOH (230 mL), treated with a satd soln of KOH in EtOH (2 mL), heated to reflux for 9 h, stirred at ambient temperature for 7 h, concentrated, and chromatographed using a gradient of EtOAc/CH_2Cl_2 (1:1, 2:1, and 2:0) to provide 4.67 g (61%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 2.93 (t, J = 6.8 Hz, 2H), 3.06 (s, 3H), 3.68−3.78 (m, 2H), 4.71 (t, J = 5.1 Hz, 1H), 7.41−7.52 (m, 1H), 7.64 (dd, J = 8.5, 2.0 Hz, 1H), 7.76 (d, J = 1.4 Hz, 1H), 7.86−7.93 (m, 3H), 8.01−8.12 (m, 1H), 8.31 (d, J = 8.1 Hz, 1H), 8.39 (s, 1H), 8.56−8.62 (m, 1H); MS (DCI/NH_3) m/z 331 $(M + H)^+$.

1-Methyl-2-(propan-2-ylidene)hydrazine (16).[46] Acetone (100 mL) was treated dropwise with methyl hydrazine (**15**; 20 mL, 0.38 mol), stirred at ambient temperature for 45 min, heated to 55 °C for 15 min, cooled to ambient temperature, dried ($MgSO_4$), filtered, concentrated, and distilled (bp 110−116 °C at atmospheric pressure) to provide 14.2 g (44% yield) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H), 1.94 (s, 3H), 2.92 (s, 3H), 3.82 (s, 1H).

3-((1-Methyl-2-(propan-2-ylidene)hydrazinyl)methylene)pentane-2,4-dione (17). 3-(Ethoxymethylene)pentane-2,4-dione[23] (8.6 g, 55 mmol) was dissolved in ether (30 mL), cooled to 0 °C, treated with compound **16** (4.8 g, 55 mmol) dropwise over 5 min, and stirred at ambient temperature overnight. The mixture was directly chromatographed on silica gel using a gradient (1:1:0, 1:2:0, 0:1:0, 0:9:1, and 0:4:1) of hexane/EtOAC/EtOH to provide 9.1 g (84%) of the title compound. ^{1}H NMR ($CDCl_3$) δ1.96 (s, 3H), 2.07 (s, 3H), 2.28 (s, 6H), 3.12 (s, 3H), 7.34 (s, 1H); MS (DCI/NH_3) m/z 197 $(M + H)^+$.

Supporting Information Available: Combustion analysis of compounds **3a**−**3f** and bar graphs of in vivo results from Table 7. This material is available free of charge via the Internet at http://pubs.acs.org.

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(40) Compounds **3d** and **3e** were exposed to (a) visible light and (b) UV + visible light according to ICH guidelines. Compound **3d** was found to be labile to UV + visible light in solution at pH13 and in the solid state (<1 (0.38 ± 0.89) and 72 ± 1 % of compound recovery, respectively, ± standard deviations). Compound **3e** was found to be labile to UV + visible light in solution at pH 1, 6, and 13 and in the solid state (76 ± 1, 3 ± 1, <1 (0.12 ± 0.04), and 83 ± 1% unchanged, respectively). In a separate experiment, the free base of compounds **3d** and **3e** displayed decomposition to 7 days of ambient light exposure (97 ± 1% and 88.0 ± 0.6%).

(41) Salts of compound **3e** were examined in solid state stability studies. All salts examined showed an improved % recovery under UV + visible light: HCl (92 ± 1%), fumarate (97.4 ± 0.2%), phosphate-(93 ± 3%), D-tartrate (97 ± 1%), L-tartrate (94.8 ± 0.3%), trisphosphate (85 ± 1%), napsylate (92 ± 1%), and malate (93.3 ± 0.3%) vs free base (83 ± 1%; % recovery after exposure in parentheses, ±standard deviations). In a separate experiment, the salts of compound **3e** also demonstrated an increased stability to 7 days of ambient light exposure; HCl (98.6 ± 0.6%), fumarate (100.0 ± 0.6%), phosphate (99.4 ± 0.3%), D-tartrate (99.6 ± 0.2%), L-tartrate (99.9 ± 0.5%), trisphosphate (96 ± 1%), napsylate (94 ± 1%), and malate (98 ± 1%) vs free base (88 ± 1%).

(42) Data expressed as mean ± SEM for six animals. Compound **3d** had minimal propensity for QT interval prolongation (only 9 ± 3% increase in QTc in anesthetized dog at 4214 ± 157 ng/mL, 220-fold the efficacious concentration in the 5-trial IA model). QTc was calculated using the Van de Waters correction formula. See the following reference for a description of the cardiovascular dog model: Fryer, R. M.; Preusser, L. C.; Calzadilla, S. V.; Hu, Y.; Xu, H.; Marsh, K. C.; Cox, B. F.; Lin, C. T.; Gopalakrishnan, M.; Reinhart, G. A. (−)-(9*S*)-9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-*b*]quinolin-8(4*H*)-one 1,1-dioxide (A-278637), a novel ATP-sensitive potassium channel opener: Hemodynamic comparison to ZD-6169, WAY-133537, and nifedipine in the anesthetized canine. *J. Cardiovasc. Pharmacol.* **2004**, *44*, 137−147.

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