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Identification of diamino chromone-2-carboxamides as MCHr1 antagonists with minimal hERG channel activity

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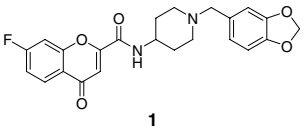
Abstract—A series of potent 2-carboxychromone-based melanin-concentrating hormone receptor 1 (MCHr1) antagonists were synthesized and evaluated for hERG (human Ether-a-go-go Related Gene) channel affinity and functional blockade. Basic dialkylamine-terminated analogs were found to weakly bind the hERG channel and provided marked improvement in a functional patch-clamp assay versus previously reported antagonists of the series.

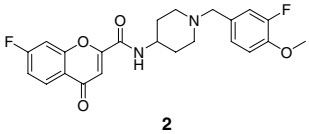
Melanin-concentrating hormone (MCH) is a cyclic 19-amino acid neuropeptide that serves as an important mediator of food intake and energy balance in mammals.[1,2] Various data suggest that interruption of MCH signaling could be an effective anti-obesity therapy. For example, transgenic mice overexpressing the MCH gene are insulin resistant and obese,[3] while mice lacking the gene encoding MCH are hypophagic, lean, and maintain elevated metabolic rates.[4] Additionally, mice lacking the gene for encoding the MCH receptor maintain elevated metabolic rates and remain lean despite hyperphagia on a normal diet.[5,6] Indeed, several reports of orally efficacious small-molecule inhibitors of rodent MCHr1 have recently been published.[7,8]

In the electrocardiogram, the QT interval represents the time during which ventricles depolarize and repolarize. In humans, I_{Kr}, an inwardly rectifying potassium channel encoded by the human Ether-a-go-go Related Gene (hERG), plays an important role in ventricle repolarization.[9] Congenital mutations to the hERG channel (I_{Kr})



1

MCHr1 binding IC_{50} (nM)[a] = 3 ± 1
MCHr1 Ca^{2+} fluxIC$_{50}$ (nM)[b] = 29 ±7
hERG (dof) IC^{50} (μM)[c] = 15.1 ±4.6



2

MCHr1 binding IC_{50} (nM)[a]= 24 ± 6
MCHr1 Ca^{2+} fluxIC$_{50}$ (nM)[b]= 168 ± 12
hERG (dof) IC_{50} (μM)[c]= 8.3 ± 0.92

Chart 1. Chromone-based MCHr1 antagonists. [a]Displacement of [^{125}I]-MCH from MCHr1 expressed in IMR-32 (I3.4.2) cells (MCH binding $K_d = 0.66 \pm 0.25$ nM, $B_{max} = 0.40 \pm 0.08$ picomol/mg).[11] [b]Inhibition of MCH-mediated Ca^{2+} release in whole IMR-32 cells (MCH $EC_{50} = 62.0 \pm 3.6$ nM). [c]Displacement of [^{3}H]-dofetilide from hERG/HEK membrane homogenates at 6 concentrations, $\frac{1}{2}$ log apart, in duplicate, using a 96-well plate design. IC_{50} values calculated using Graphpad Prizm software.

Keywords: MCHr1; Obesity; hERG; Patch-clamp.
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are responsible for QT prolongation, resulting in potentially life-threatening cardiac arrhythmias such as *torsades de pointes*. Moreover, small molecule blockade of the hERG channel has been associated with acquired QT prolongation, which in some instances has led to similar untoward effects and, ultimately, to the removal of the offending agents from the consumer market. Acquired QT prolongation is now considered a significant risk factor for human safety predictions of drug candidates, making hERG channel cross-reactivity a potentially severe liability.

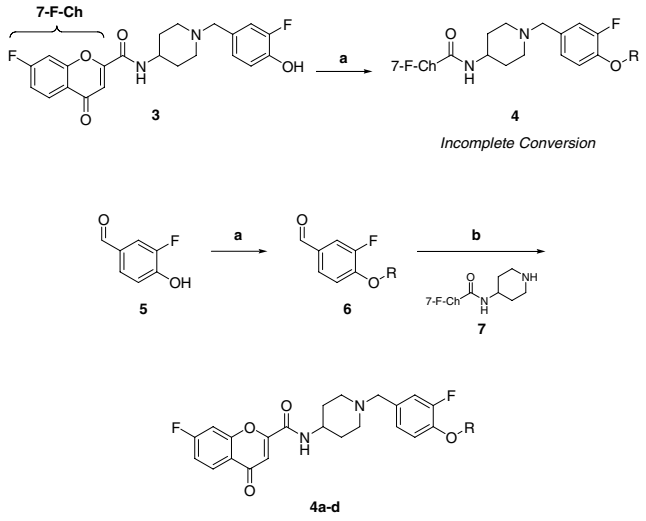
A previous report[10] from these laboratories described the optimization of chromone-based MCHr1 antagonist **1** (Chart 1) and detailed its in vivo weight-loss efficacy in a DIO mouse model of obesity. However, the high therapeutic plasma C_{max} (7.7 μM) required to induce efficacy eroded the observed in vitro selectivity windows and rendered the attainment of a satisfactory safety window impossible. Specifically, **1** showed 90% functional blockade of the hERG tail current in a patch-clamp assay at the efficacious plasma C_{max}. The detrimental effect of the blockade was confirmed in the pentobarbital-anesthetized dog model, where significant QT prolongation at low multiples of the therapeutic plasma C_{max} was observed.

Henceforth, advancement of the chromone series would likely necessitate a decrease in the therapeutic plasma C_{max} and that greater off-target selectivity be engineered into the series, particularly with respect to the hERG channel. In this letter, we disclose the MCHr1- and hERG-related SARs of a chromone-based sub-series. Compounds with excellent MCHr1 binding affinity, good MCHr1 functional activity, weak hERG channel binding affinity, and greatly diminished hERG channel functional blockade relative to **1** are highlighted. Adequate CNS penetration of optimized analogs upon oral dosing prompted their evaluation in a 2-week study in DIO mice.

Previous work[10] detailed the study of the piperidine linker and 2-carboxychromone sub-unit of **1**, wherein the 7-fluoro-substituted permutation was considered optimized with respect to MCHr1 potency, CNS penetration, and hERG selectivity. Our studies have also revealed that incorporation of polar substituents into the benzylamine moiety greatly diminishes the hERG affinity of the resultant analogs, though at the cost of requisite CNS exposure.[10,12] As we considered various alternative 'leads' to the development of hERG-selective[13] MCHr1 antagonists that could efficiently penetrate the brain, our attention was drawn to the previously reported[10] **2**, which carries a 3-fluoro-4-methoxy aryl substituent in place of the piperonyl moiety found in parent **1**. Considering its good functional potency (MCHr1 Ca^{2+} flux IC_{50} = 168 nM) and the potential for rapid modification of the benzyl unit via its ether bond, we selected **2** as the root of a more general analog library.

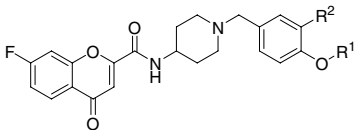
We chose to survey the SAR of ether **2** by means of Mitsunobu reaction-based elaboration of the phenol **3**. However, initial efforts to directly couple **3** with a variety of substituted alcohols under the action of DBAD and PS–Ph_3P in THF were beset by incomplete reaction. While this method variably delivered sufficient quantities of materials **4** for initial in vitro testing, we found the sequence of Mitsunobu reaction of the more acidic hydroxybenzaldehyde **5** (vs **3**) with the appropriate alcohol to generate 4-alkoxybenzaldehydes **6** and subsequent reductive amination with the piperidine **7** to be more efficient and amenable to preparations of **4** on scale (see Scheme 1).

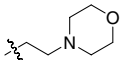
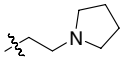
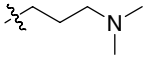
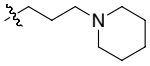
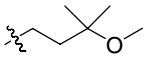
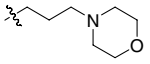
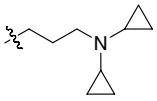
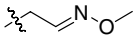
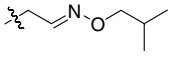
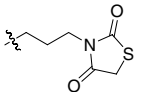
Cognizant of our aforementioned forays into hERG-selective MCHr1 antagonists in which drug distribution was effectively limited or even excluded from the brain,[12] we initially focused on introducing polarity to the benzylamine unit by moieties that would likely maintain high volumes of distribution, such as tethered dialkyl amines. Thus, incorporation of cyclic amines by an ethyl linker was unproductive, as the diamines **4a** and **4b** weakly bound to MCHr1 and had no functional potency in the Ca^{2+} flux assay (see Table 1). Attachment of a dialkyl amine by an *n*-propyl tether in compounds such as **4c** and **4d**, however, had more beneficial results, rescuing both the MCHr1 binding and functional potencies. Indeed, **4d** was approximately twice as functionally potent as the methyl ether **2**. Encouraged by these results, we assayed the compounds in a hERG channel affinity screen (displacement of [^{3}H]-dofetilide, see Table 1). We were intrigued to find that **4c** and **4d** had considerably less hERG channel affinity than the parents **1** and **2**, with the smaller, less lipophilic R^1 group in **4c** seemingly more beneficial in this regard. In contrast, related terminal ethers such as **8** had increased affinity for the hERG channel relative to **1** and **2**, with only modest affinity for MCHr1. In accord with this trend, the lipophilic trifluoroethyl ether **9** was the most potent binder of the hERG channel within this preliminary subset.



Scheme 1. Reagents and conditions: (a) ROH, DBAD, PS–Ph_3P, THF, 50 °C (60–80% for **5** to **6**); (b) $NaBH(OAc)_3$, AcOH, THF, rt (60–70%).

Table 1. Binding affinity and functional potency of MCHr1 antagonists[a]



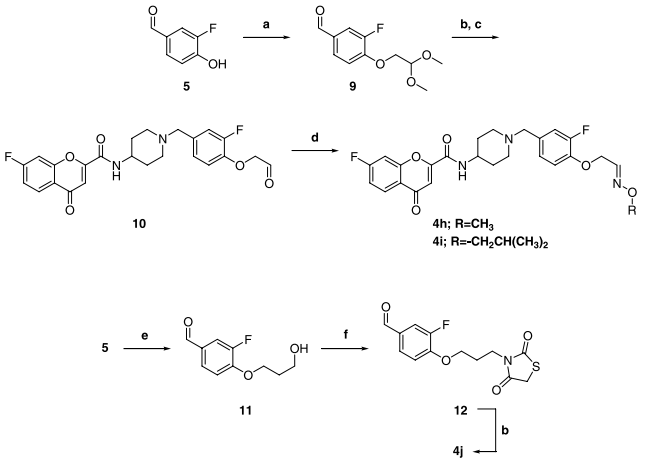
Compound	R^1	R^2	MCHr1 binding IC_{50} (μM)[b,e]	MCHr1 Ca^{2+} flux IC_{50} (μM)[c,e]	hERG (dof) IC_{50} (μM)[d,e]
2	CH_3	F	0.024	0.168	8.3
4a		F	>2	NT[f]	NT[f]
4b		F	1.52	>10	NT[f]
4c		F	0.020	0.773	65
4d		F	0.003	0.086	42
8		H	0.165	1.75	4.3
9	CF_3CH_2-	F	0.064	NT[f]	1.6
4f		F	NT[f]	NT[f]	34
4g		F	0.051	4.01	0.74
4h		F	0.031	0.480	3.2
4i		F	0.015	1.98	0.45
4j		F	0.004	0.545	8.5

[a] All compounds were >95% pure by HPLC and characterized by ^1H NMR and HRMS.
[b] See Chart 1, footnote a.
[c] See Chart 1, footnote b.
[d] See Chart 1, footnote c.
[e] Values represent an average of at least two determinations.
[f] NT, not tested.

To further investigate the requirements for favorable hERG selectivity, we synthesized close structural analogs of **4c** and **4d** having attenuated basicity at the terminal amine. Thus, the morpholino and dicyclopropylamino[14] analogs **4f** and **4g** were synthesized according to the methods outlined in Scheme 1 for similar substrates. We were also interested in the effect of polar non-ionizable termini on the hERG affinity of the sub-series and, therefore, assayed the oxime ethers **4h**, **4i** and the thiazolidinedione **4j**, which were made according to Scheme 2.

The syntheses of **4h** and **4i** commenced with alkylation of benzaldehyde **5** with bromo-acetaldehyde dimethyl acetal to provide the differentiated bis-aldehyde equivalent **9** (Scheme 2). Reductive amination with **7** under standard conditions and subsequent treatment of the adduct with aqueous HCl revealed the aldehyde **10**. Condensation of **10** with *O*-alkylhydroxylamines gave **4h** and **4i**. The thiazolidinedione **4j** was made from phenol **5** by the 3-step sequence of alkylation with 3-bromopropanol, Mitsunobu reaction with thiazolidinedione, and reductive amination.

Evaluation of morpholine **4f** and dicyclopropylamine **4g** (see Table 1) revealed their increased hERG affinity relative to the piperidine **4d**. Notably, inclusion of the weakly basic dicyclopropylamino moiety resulted in a

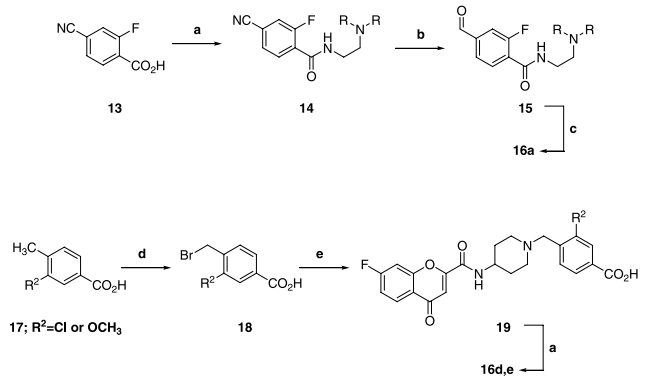


Scheme 2. Reagents and conditions: (a) $(MeO)_2CHCH_2Br$, K_2CO_3, acetone; 50 °C (78%); (b) **7**, MP–$CNBH_3$, AcOH, MeOH, 50 °C (50–80%); (c) acetone, 1N HCl, 70 °C (95%); (d) $RONH_3Cl$, MeOH, rt (80–90%); (e) 3-bromopropanol, K_2CO_3, DMF; 80 °C (77%); (f) thiazolidinedione, DBAD, PS–Ph_3P, THF, 50 °C (65%).

compound (**4g**) with sub-micromolar affinity for the hERG channel and with greatly diminished MCHr1 functional potency. Interestingly, the hERG channel affinities of **4d**, **4f**, and **4g** correlate with the pK_a of the terminal amine's conjugate acid, supporting the notion that increased cationic character at the terminus inhibits hERG channel binding. Compounds with non-ionizable polar oxime ether termini, such as **4h**, were relatively good binders to the hERG channel. The 10-fold increase in hERG channel affinity acquired in the *iso*-butyl for methyl exchange on going from **4h** to **4i** was also particularly striking. Finally, the polar thiazolidinedione **4j** was an exceptional binder to MCHr1, but had very modest MCHr1 functional potency and offered no benefit in terms of hERG selectivity over the parent methyl ether **2**.

Having found that basic 3-propylamino moieties in antagonists such as **4d** retained good MCHr1 potency and deterred hERG channel binding, we next explored modification to the 4-atom tether connecting the phenyl ring to the amine terminus. We hypothesized that a more polar[15] linker would further decrease hERG channel binding and, hence, elected to probe the effect of amide-based tethers on the hERG and MCHr1 affinities of the sub-series.

Representative amides **16** were made according to Scheme 3. The 2-fluoro analog (Table 2 numbering) **16a** was conveniently made from commercially available 2-fluoro-4-cyanobenzoic acid **13**. Thus, EDCI-mediated amide coupling gave **14**, which was partially reduced to the aldehyde **15** with Raney Nickel. Reductive amination with **7** as described previously gave the analog **16a**. Alternatively, 3-chloro-4-methyl- or 3-methoxy-4-methyl benzoic acids were functionalized under radical conditions to give the benzyl bromides **18** (Scheme 3). Alkylation with **7** followed by standard amide formation with 2-aminoethylpyrrolidine yielded the analogs **16d**, **16e**. The 'reversed-amide' **20** was made by acylation

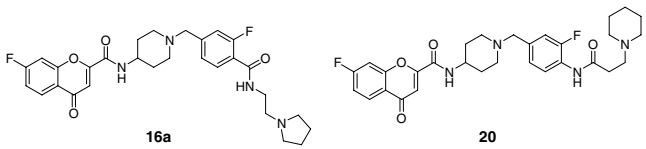


Scheme 3. Reagents and conditions: (a) $R_2NCH_2CH_2NH_2$, EDCI, HOBt, NMM, DMF (65–95%); (b) Ra–Ni, NaH_2PO_2, pyridine, AcOH, H_2O (60–70%); (c) **7**, $NaBH(OAc)_3$, AcOH, THF, rt (67%); (d) NBS, AIBN, CCl_4, 90 °C (30–65%); (e) **7**, K_2CO_3, EtOH (40–75%).

of the corresponding aniline with commercially available 3-piperidine-1-yl propionyl chloride.

To our delight, replacement of the ether tether with a benzamide-type linkage to give **16a** (Chart 2) provided an additional decrease in the hERG channel affinity, as no inhibition of dofetilide binding was seen up to the measured assay concentration. This compound retained excellent MCHr1 binding affinity, but the amido unit was detrimental to the MCHr1 functional potency, resulting in nearly a fourfold decrease with respect to ether **4d**. Conversely, the 'reversed amide' **20** retained much of the MCHr1 binding and functional potency of **4d**. Interestingly, however, **20** had hERG affinity comparable to the methyl ether **2**, ostensibly due, in part, to attenuation of the terminal amine's pK_a by the *beta*-disposed carbonyl group.

Guided by these results, we surveyed the MCHr1 and hERG channel SARs of benzamides related to **16a**. The archetype **16b**, lacking the 2-fluoro substitution, had MCHr1 activity similar to **16a**, but had slightly higher binding affinity for the hERG channel. As with the ether-linked analogs, changes to the basicity and/or lipophilicity of the terminal component directly affected the MCHr1 functional potency and hERG selectivity. For example, the 4,4-difluoropiperidine-substituted analog **16c** was 5-fold less functionally potent at MCHr1 than **16b**, and its binding affinity for the hERG channel increased by 10-fold. Substitution to the phenyl ring also



16a

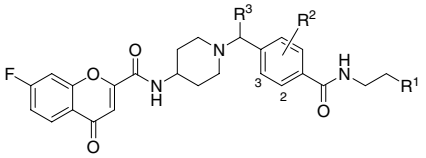
MCHr1 binding IC_{50} (μM)^{a,d} = 0.029
MCHr1 Ca^{2+} flux IC_{50} (μM)^{b,d} = 0.420
hERG (dof) IC_{50} (μM)^{c,d} = > 100

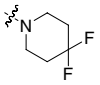
20

MCHr1 binding IC_{50} (μM)^{a,d} = 0.023
MCHr1 Ca^{2+} flux IC_{50} (μM)^{b,d} = 0.120
hERG (dof) IC_{50} (μM)^{c,d} = 9.18

Chart 2. Amide-based MCHr1 antagonists. [a]See Chart 1, footnote a. [b]See Chart 1, footnote b. [c]See Chart 1, footnote c. [d]See Table 1, footnote e.

Table 2. Binding affinity and functional potency of MCHr1 antagonists[a]



Compound	R^1	R^2	R^3	MCHr1 binding IC_{50} (μM)[b, e]	MCHr1 Ca^{2+} flux IC_{50} (μM)[c,e]	hERG (dof) IC_{50} (μM)[d,e]
16a		2-F	H	0.029	0.420	>100
16b		H	H	0.017	0.519	66
16c		H	H	0.086	2.93	6.3
16d		3-Cl	H	0.002	0.136	11
16e		3-OCH_3	H	0.026	0.270	6.6
16f		3-CH_2	CH_2	0.009	1.9	23

[a] All compounds were >95% pure by HPLC and characterized by ^{1}H NMR and HRMS.
[b] See Table 1, footnote b.
[c] See Table 1, footnote c.
[d] See Table 1, footnote d.
[e] See Table 1, footnote e.

greatly affected the affinities for the MCH receptor and hERG channel, as already noted for the 2-fluoro derivative **16a**. Substitution at the 3-position with a chlorine atom or methoxy group provided functionally potent MCHr1 antagonists **16d** and **16e**, but negated the previously observed beneficial effect of the terminal basic amine on hERG affinity. The racemic, constrained indanyl **16f** also lost functional MCHr1 potency and had hERG affinity comparable to the piperonyl **1**.

Several analogs with varying affinities for the hERG channel were chosen for study in a patch-clamp assay of functional hERG current blockade, as summarized in Table 3. Compound **1**, which was previously shown to induce QT prolongation in the anesthetized-dog model at therapeutically relevant plasma concentrations, was chosen as a standard compound and found to cause 100% inhibition of the hERG tail current at 30 μM drug concentration.[16] The ether **4d** induced 57% inhibition at the same concentration, an improvement that roughly correlated with its relative increase in hERG binding IC_{50}. Despite the apparent difference in the hERG binding IC_{50}'s of the amides **16a** and **16b**, the functional assay at 30 μM drug concentration revealed they were nearly equally benign to the hERG tail current, imparting 21% and 13% inhibition, respectively, and thus represented marked improvements to hERG channel cross-reactivity as measured by this parameter.

Table 3. Selected parameters for compounds **1**, **4d**, **16a**, and **16b**

Compound	MCHr1 binding IC_{50} (μM)	hERG (dofetilide) IC_{50} (μM)	Patch-clamp: tail current inhibition at 30 μM[a]
1	0.003	15.1	100%
4d	0.003	42.0	57%
16b	0.013	66.2	13%
16a	0.029	>100	21%

[a] The hERG current was evaluated using HEK 293 cells stably expressing hERG. Drug effects were evaluated based on changes of tail currents measured during 4 s repolarizing test pulses to −50 mV preceded by a 3 s depolarizing conditioning pulse to 0 mV (holding potential of −80 mV, pulses applied once every 15 s). Experiments were conducted at 36.5–37 °C with a 5 mM external K + HEPES-buffered Tyrode's solution.

The fluorinated amide **16a** was chosen for pharmacokinetic (PK) analysis to assess the CNS-penetrating ability of this hERG-selective class of MCHr1 antagonists. Acute oral dosing (10 mpk) of **16a** in DIO mice exposed an interesting PK profile (see Table 4) characterized by a shallow plasma C_{max} (598 ng/mL) and a relatively short (2 h) plasma $t_{1/2}$. Additionally, **16a** showed a long (8 h) half-life in the brain, leading to 12 h drug concentrations in the brain (75 ng/g) superior to those in the plasma (38 ng/mL). We surmised that chronic dosing of an MCHr1-potent compound with this in vivo profile

Table 4. Selected PK parameters of **16a** in DIO mice (10 mg/kg po)[a]

	$AUC_{0-\infty}$[b]	C_{max}[b]	C_{12h}	$t_{1/2}$
Plasma	3154 (ng h/mL)	598 ng/mL	38 ng/mL	2 h
Brain	1378 (ng h/g)	185 ng/g	75 ng/g	8 h

[a] All values are mean values ($n = 3$ unless specified otherwise). Inter-animal variability was less than 30%. Compounds are dosed in DIO mice at 10 mg/kg, po in a vehicle containing 1% Tween 80 and water.

[b] The three mice with highest plasma and brain concentrations were averaged to provide the peak plasma and brain concentrations (C_{max}), respectively. The mean plasma or brain concentration data were submitted to multi-exponential curve fitting using WinNonlin. The area under the mean concentration–time curve from 0 to t h (time of the last measurable concentration) after dosing (AUC_{0-t}) was calculated using the linear trapezoidal rule for the concentration–time profile. The residual area was extrapolated to infinity, determined as the final measured mean concentration (C_t) divided by the terminal elimination rate constant (β), and was added to AUC_{0-t} to produce the total area under the curve ($AUC_{0-\infty}$).

might lead to a steady-state CNS concentration sufficient to induce MCHr1-mediated weight loss while limiting plasma drug exposure.

To test the pharmacokinetic aspect of this hypothesis, compound **16a** was orally dosed at 10 mpk qd to DIO mice fed a high fat diet for 2 weeks.[17] Day 14 drug levels indicated that while the plasma drug concentration cleared from a one-hour concentration of 0.77 μg/mL to a 16-h concentration of 0.10 μg/mL, a constant ($C_{1h} = C_{16h}$) concentration of 0.6 μg/g had been reached in the brain. However, we were concerned by the non-linear relationship between the acute (0.185 μg/g) and chronic brain distributions. Particularly, the static nature of the latter prompted us to analyze more closely the drug distribution in other tissues, where we found significant accumulation in the heart and thigh.[18] As this phenomenon was likely secondary to the di-basic[19] character of **16a**, an aspect of the entire sub-series that was seemingly critical to deliver off-target (hERG channel) selectivity, work in this area was discontinued.

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