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Structure–Activity Relationships, Pharmacokinetics, and in Vivo Activity of CYP11B2 and CYP11B1 Inhibitors

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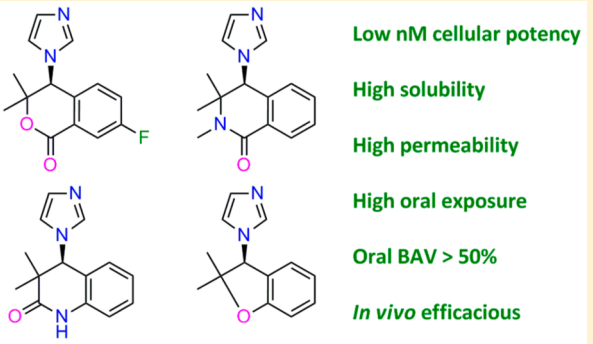
Supporting Information

ABSTRACT: CYP11B2, the aldosterone synthase, and CYP11B1, the cortisol synthase, are two highly homologous enzymes implicated in a range of cardiovascular and metabolic diseases. We have previously reported the discovery of LCI699, a dual CYP11B2 and CYP11B1 inhibitor that has provided clinical validation for the lowering of plasma aldosterone as a viable approach to modulate blood pressure in humans, as well normalization of urinary cortisol in Cushing's disease patients. We now report novel series of aldosterone synthase inhibitors with single-digit nanomolar cellular potency and excellent physicochemical properties. Structure–activity relationships and optimization of their oral bioavailability are presented. An illustration of the impact of the age of preclinical models on pharmacokinetic properties is also highlighted. Similar biochemical potency was generally observed against CYP11B2 and CYP11B1, although emerging structure–selectivity relationships were noted leading to more CYP11B1-selective analogs.



INTRODUCTION

Cytochrome P450s are a class of proteins that occupy a unique place in the battles drug discovery scientists fight to bring safe and effective small molecule therapeutics to patients. As greater than 75% of xenobiotics are metabolically cleared, with a major proportion undergoing CYP450-mediated oxidation,[1] designing compounds with low affinity and/or reactivity toward these heme-containing enzymes is of major concern to the medicinal chemist.[2] On the other hand, targeted inhibition of human cytochrome P450s for therapeutic purposes has historically been the subject of less scrutiny.[3] The efficacy of aromatase (CYP19) inhibitors such as letrozole and anastrozole as adjuvant treatment of estrogen-receptor-positive breast cancers is now well established.[4] More recently, 17α-hydroxylase/C17,20 lyase (CYP17A1) inhibitors have demonstrated their utility, leading to the approval of abiraterone for the treatment of castration-resistant prostate cancer.[5] In this paper we describe efforts targeting two other human steroidogenic CYP450s CYP11B1 and CYP11B2. CYP11B1 converts deoxycortisol to cortisol, while CYP11B2 transforms 11-deoxycorticosterone to aldosterone. Chronic activation of the renin–angiotensin–aldosterone system is central to the pathophysiology of heart failure and hypertension. Elevated serum aldosterone levels predispose subjects to the development of hypertension,[6] and high serum aldosterone is thought to contribute to resistant hypertension.[7] The latter represents a significant medical need; as much as 30% of the hypertensive population may be resistant to treatment, with resulting higher incidence of cardiovascular events.[8] Elevated levels of plasma aldosterone upon prolonged treatment with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, referred to as "aldosterone escape" or "aldosterone breakthrough", have long been noted,[9] and this may be a contributing factor to treatment resistance. Additionally, extensive evidence exists that links aldosterone to proinflammatory states, cardiac and vascular fibrosis, and end-organ failure, independent of blood pressure.[10] Two decades ago, the poor prognosis for heart failure patients with elevated aldosterone was recognized,[11] and subsequently, blockade of the mineralocorticoid receptor (MR) with spironolactone and eplerenone was shown to have profound effects on mortality and morbidity in patients with cardiac dysfunction.[12] However, those steroidal agents have limitations in terms of off-target effects and on-target hyperkalemia, and their mechanism of action does not lead to reduced aldosterone levels. This offers one of several avenues for differentiation of aldosterone synthase inhibitors (ASI) over MR antagonists, as many lines

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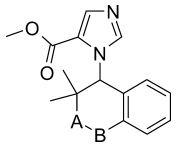
Table 1. Characteristics of Initial Racemic Lead Compounds 1−5



compd	A	B	IC_{50} (μM) H295-R aldosterone	IC_{50} (μM) CYP3A4	% inhibition (10 μM), CYP19	liver microsomes $t_{1/2}$ (min) rat	liver microsomes $t_{1/2}$ (min) human
1	S	CH_2	0.007	0.17	81	<1.5	3
2	CH_2	CH_2	0.007	0.11	59	3	5
3	CH_2	O	0.073	0.29	30	15	20
4	CH_2	CH-(*p*-MeO-Ph)	0.079	<0.07	77	11	2
5	O	C(O)	0.055	0.46	3	86	315

of evidence suggest a pathological role of aldosterone via non-MR mediated pathways.[13] The study of the impact on the aforementioned disease states of modulating aldosterone levels (and those of its precursors) via CYP11B2 inhibition is therefore of clear value. Although concomitant inhibition of highly homologous CYP11B1 in the context of hypertensive population is a potential safety concern, it is intriguing to note that a recent analysis suggested that the predominant MR agonist in the context of cardiomyocyte damage is cortisol.[14]

Our interest in this field was stimulated by the observation that FAD286, the *R*-(+)-enantiomer of the racemic aromatase inhibitor CGS016949A (fadrozole) was a potent inhibitor of aldosterone synthase (CYP11B2).[15] We subsequently showed that chronic administration of FAD286 in rats led to a reduction in cardiac inflammation and fibrosis and resulted in slowing of the progression of heart failure following coronary artery occlusion.[16] Cardiac and renal protection, as well as a reduction in several inflammatory markers, were demonstrated with FAD286 in a study using a double-transgenic rat (dTG rat) overexpressing human renin and angiotensinogen and elevated angiotensin II and aldosterone levels.[17] These and subsequent studies[18] suggested that pharmacological inhibition of aldosterone synthase might be clinically useful, which led us, and others,[19−21] to engage in programs to discover novel CYP11B2 inhibitors. Our initial forays led to the discovery of LCI699, a potent dual inhibitor of CYP11B2 and CYP11B1.[21] Studies with LCI699 confirmed and extended the findings that ASI prevents development of cardiac and renal functional abnormalities and prolonged survival of dTG rats, independent of blood pressure.[21b] LCI699 has proven to be effective in multiple cohorts of hypertensive patients.[22] For instance, an 8-week placebo-controlled dose−response study on patients with essential hypertension reported a decrease in blood pressure with a dose of 1 mg of LCI699 q.d., which had a antihypertensive effect similar to that of 50 mg b.i.d. eplerenone.[22b] This study also revealed that cortisol secretion in response to adrenocorticotropic hormone (ACTH) stimulation was blunted in 21% of patients. These findings were confirmed in a separate ACTH stress test study,[23] precluding exploration of high doses and determination of optimal doses for blood pressure regulation with LCI699. However, recognizing that options to normalize cortisol levels in Cushing's disease patients unwilling or unable to undergo surgery are limited, we conducted a 10-week, 12 patients dose-escalation study (4−100 mg/day), where LCI699 was shown to normalize free urinary cortisol.[24]

The optimization efforts that led to the discovery of LCI699 were recently reported.[21a] As LCI699 illustrates, our initial efforts toward bringing the first ASI to the clinic for human proof-of-concept studies focused on imidazole series derived from FAD286. Although the focus was primarily on pharmacodynamics and selectivity over CYP19, it quickly became apparent that achieving high oral bioavailability was a significant challenge across all imidazole based series. The work presented herein, which was conducted concurrently to the progression of LCI699 to the clinic, describes our successful attempts at identifying potent ASIs devoid of aromatase activity and presents a general solution to the problem of achieving high oral bioavailability. At the time this work was conducted, the impact of modulating levels of mineralocorticoids, corticosteroids, and precursor steroids via inhibition of aldosterone synthase in human was not known, and the relation between in vitro selectivity and human pharmacology had not been established. Moreover, data generated in our ACTH rat model suggested that LCI699, despite low in vitro selectivity for CYP11B2 over CYP11B1, may be selective in vivo, with ED_{50} values 47-fold lower for aldosterone versus corticosterone.[21b] Given this context, we did not set out to achieve selectivity over CYP11B1 for the series described herein. We did nonetheless test these compounds in a human recombinant CYP11B1 assay and found some interesting trends toward CYP11B1 selectivity, which we also report herein.

RESULTS AND DISCUSSION

Compounds **1**−**5** were identified from the Novartis compound collection as potential starting points for lead optimization because of their potent activity in our cellular aldosterone secretion assay[25] (Table 1). This class of racemic imidazole carboxylates had previously been reported to be useful as herbicides and antifungals by disrupting sterol biosynthesis through inhibition of 14α-demethylase ($P450_{14DM}$).[26]

As we embarked on this program, we focused on identifying scaffolds devoid of aromatase activity, good selectivity over CYP3A4 and with generally improved oral bioavailability. In vitro−in vivo pharmacokinetic correlation analysis for 72 imidazole ASIs synthesized in-house prior to this work revealed a clear relationship between rat liver microsome half-life and rat oral bioavailability. Half-lives greater than 20 min were necessary but not always sufficient to achieve oral bioavailability greater than 30% (Figure 1). Hence, our initial investigations focused on lactone **5**, which was not the most potent ASI, but had the best rat liver microsome half-life, and also displayed greater selectivity against CYP19 (aromatase) and CYP3A4. It

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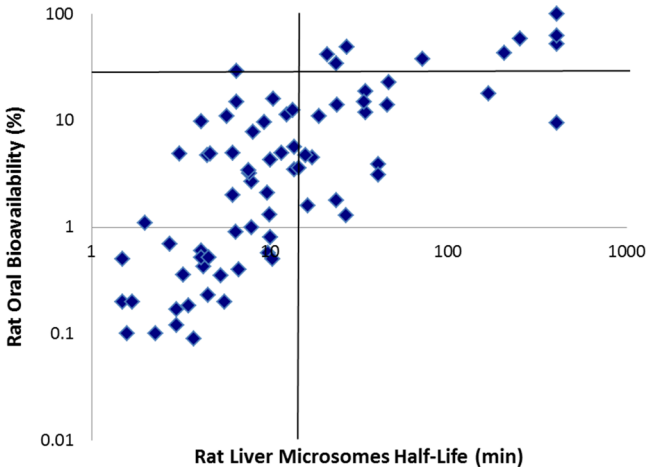

Figure 1. Relationship between rat liver microsome half-life and rat oral bioavailability for compounds prepared prior to selection of **5** as a lead compound (bold lines indicates the 20 min and 30% mark for half-life and bioavailability, respectively).

is intersting to note that for compounds **1**–**5**, structure–metabolic stability relationship followed a trend whereby removing Csp^3–H bonds in the bicyclic ring led to an increase in stability in vitro. Resynthesis of **5** and chiral separation revealed that only one of the two enantiomers, **5E**, was a potent CYP11B2 inhibitor, a finding that proved quite general across the series. Exploration of the SAR for the imidazole side chain is shown in Table 2.

A variety of functionalities at the 4-position of the imidazole were tolerated and gave good on-target potency, with generally only one of the two enantiomers displaying CYP11B2 inhibition.[27] Substitution at C-2 or C-5 obliterated activity (data not shown), consistent with putative binding of N-1 to the heme iron. Excellent selectivity over CYP19 was observed irrespective of the substitution, and good selectivity over CYP3A4 was also generally observed. With the exception of alkyl-substituted imidazole **12** and **13**, all compounds appeared to be more stable in human liver microsomes versus rat. Replacement of the *gem*-dimethyl group with other alkyl substituents (**22**–**25**) revealed a flat structure–activity relationship, save for the tetrahydropyran (**25**), which afforded improved metabolic stability, albeit at the expense of potency (Table 3).

An angiotensin II infusion model[18a] using chronically cannulated Sprague Dawley (SD) rats was used to establish the PK–PD relationship for these compounds. Blood samplings were conducted at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 24 h time points following oral administration, and plasma aldosterone and plasma compound concentrations were measured. Pharmacokinetic parameters for various imidazole substitution as in **5E** (ester), **12** (ethyl), and **16** (alcohol) are shown in Table 4. Consistent with our prior observations, the low observed oral bioavailability of **12** was expected in view of the poor microsomal stability. Breakdown of the correlation between rat liver microsome clearance and oral bioavailability was observed for ester **5E** and alcohol **16**. This is perhaps expected in the case of **16**, as hepatic microsomal clearance grossly underpredict in vivo clearance, and liver microsomes may not adequately model the metabolism that alcohols such as **16** undergo. However, the low bioavailability of **5E**, which exhibited low in vitro and in vivo clearance, was a bit more surprising. Stability in the GI tract, intestinal clearance, or a combination of both might explain the poor oral bioavailability of ester **5E**. With **12** in hand, we sought to better understand how these lactones were metabolized.

Analysis of rat urine and plasma samples collected following po dosing of **12** at 10 mg/kg in this model showed metabolites resulting from transformation of the imidazole moiety only (Figure 2). Consistent with this observation, we found that better oral bioavailability was observed for compound **11**, which has no substitution on the imidazole ring, and also compound **14**, where the difluoromethyl substitution would not be expected to undergo rapid oxidative metabolism (Table 5).

Removing substitution on the imidazole ring to confer good oral bioavailability proved to be a general solution to what had been, in our experience, a vexing problem for ASIs up until then (see Figure 1). Indeed compounds **27**–**29**, where the lactone is replaced by a different heterocycle, also showed excellent oral bioavailability, in all cases superior to the corresponding analogs with additional substitution on the imidazole ring (data not shown). All the compounds described herein are weak bases with high solubility and permeability (see Supporting Information), and it is unlikely that these two parameters significantly limit oral absorption. Metabolic clearance (first-pass extraction) may then be the primary factor influencing oral bioavailability, consistent with the observation that, for these series of compounds, a microsomal half-life greater than 20 min is largely predictive of good oral bioavailability.

As previously mentioned, the angiotensin II infusion model[18a] using SD rats allowed us to establish PK–PD relationships in the same experiment. The PD (plasma aldosterone) data, expressed as time-weighted average (TWA) for the 0–8 h period, are shown in Table 6. As expected, given the good in vitro potency and favorable plasma exposures, all compounds afforded robust lowering of aldosterone secretion in vivo.

Despite the success with optimization of the lactones and validation of our initial hypothesis, we did further evaluate lead compounds **1**–**4**,and in so doing came across an interesting case of age-related metabolism. A curious in vitro–in vivo metabolism correlation, distinct from the compounds described so far, arose with compound **2E** (eutomer of **2**). Extremely low in vivo clearance was measured for **2E** (0.3 mL min^{-1} kg^{-1}), in sharp contrast with rapid clearance in rat liver microsomes ($t_{1/2}$ = 2 min) and marginal oral bioavailability (0.2%). Again, solubility (0.06 g/L, pH 6.8) and permeability (caco-2 A–B 33.10^{-6} cm/s) would not be expected to limit oral absorption. Incubation of **2E** with rat liver microsomes showed a major metabolite **M2** (34% surface area) after 5 min of incubation (Figure 3), the mass of which was consistent with a single hydroxylation.

Ten micrograms of **M2** could be isolated, an amount sufficient to acquire a ^{1}H NMR spectrum, which suggested hydroxylation at the benzylic methylene. This metabolite was synthesized, and the isomers were separated. Considering hydroxylation occurs at the same position as the carbonyl in compounds such as **5**, we reasoned that **M2** may be an active metabolite. This proved to be the case; data for the most potent isomer (**30**) are shown in Table 7 (the eutomer of the trans analog was ~4-fold less potent). With **30** in hand, which affords a desirable in vivo PK profile with an oral bioavailability of 46%, we did not seek to elucidate the sharp disconnect between the extremely low in vivo clearance and low bioavailability of compound **2E**, reminiscent of that observed for structurally related ester **5E**. The good oral bioavailability of **30** was

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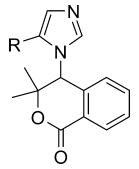
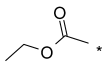
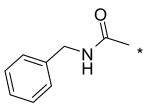
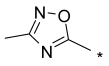
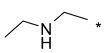
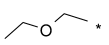
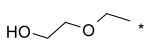
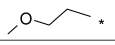
Table 2. Cellular Aldosterone Secretion, CYP3A4, Aromatase and Microsomal Stability Data of ASIs from a Lactone Series



Compd[a]	R	IC$_{50}$ (μM)		%inhibition (10 μM)	liver microsomes $t_{1/2}$ (min)	
		H295-R aldosterone[b]	CYP3A4	CYP19	Rat	Human
5E		0.024 (22)	> 50	0	164	>400
6		0.003 (48)	n.d.	13	2	62
7[c]		> 1	n.d.	n.d.	n.d.	n.d.
8[c]		0.087	18	10	2	8
9		0.036 (0)	n.d.	9	27	77
10[c]		0.187	n.d.	5	29	62
11		0.027 (13)	5.6	17	23	232
12		0.003 (66)	5.0	16	17	23
13		0.015 (20)	n.d.	6	19	21
14		0.001 (40)	n.d.	13	> 400[e]	> 400[e]
15[c]		0.128	n.d.	7	15	383
16		0.004 (89)	20	18	163	183
17[d]		0.013 (7)	> 20	0	35	> 400
18[c]		> 1	n.d.	0	n.d.	n.d.
19		0.002 (16)	n.d.	15	9	30
20[c]		0.137	n.d.	0	143	>400
21		0.028 (24)	1.5	4	5	35

[a]Compounds are single enantiomers (>98% ee), unless otherwise stated. [b]% inhibitory activity at 1 μM distomer is shown in parentheses. [c]Racemate. [d]The eutomer from the other diastereomer (not shown) is 8-fold less potent in the cellular assay. [e]Racemate data.

confirmed in a dose escalation study using water as vehicle, albeit with AUC increasing in a less than dose-proportional manner, i.e., AUC_{last}(0−24 h) of 21, 56, and 90 μM·h at 3, 10, and 30 mg/kg dose, respectively.

However, the disconnect between high predicted hepatic clearance (RLM $t_{1/2}$ = 4 min) and low in vivo clearance (7 mL min^{-1} kg^{-1}) as was observed with **2E** remained, and we sought to investigate this further. We considered the possibility of an age specific metabolic event for **2E** and **30**, since the PK data were generated from 10-months-old cannulated SD rats while the rat liver microsomes were derived from the liver of 10-weeks-old SD rats. Thus, we decided to run PK studies with 10-weeks-old SD rats. What we found was a severe discrepancy between the PK properties of compounds **2E** and **30** in 10-weeks-old versus 10-months-old SD rats (Table 8). Whereas plasma clearance for **2E** was determined to be 0.3 mL min^{-1} kg^{-1} in 10-months-old rats, the clearance in 10-weeks-old rats was found to be 143 mL min^{-1} kg^{-1}, which was indeed consistent with clearance predicted from microsomal data but obviously also indicative of extra-hepatic clearance. No compound was detected in plasma after oral administration, consistent with complete first-pass hepatic extraction. Com-

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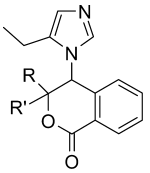
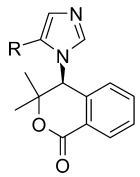
Table 3. Modification of the *gem*-Dimethyl Group



Compd[a]	R	R'	IC_{50} (μM) H295-R aldosterone	IC_{50} (μM) CYP3A4	% inhibition (10 μM) CYP19	liver microsomes $t_{1/2}$ (min) rat	liver microsomes $t_{1/2}$ (min) human
22			0.004 (33)	0.5	38	15	5
23			0.007 (8)	2.3	11	11	19
24			0.010 (16)	1.3	30	5	12
25[b]			0.31	0.9	n.d.	> 400	63

[a]Compounds are single enantiomers (>98% ee), unless otherwise stated. [b]Racemate.

Table 4. Pharmacokinetic Data



5E R= CO_2Me
12 R=Et
16 R=CH_2OH

compd[a]	H295-R aldosterone IC_{50} (μM)[b]	rat liver microsomes $t_{1/2}$ (min)	in vivo rat PK dose (mg/kg): 1 (po), 0.3 (ia) CL (mL min^{-1} kg^{-1})	AUC(0–24 h) (nM·h) po	*F* (%)
5E	0.024	165	2	1024	3
12	0.003	17	25	257	8
16	0.004	163	34	342	19

[a]All compounds are single enantiomers. [b]Distomer data for **12** and **16** as shown in Table 2; the distomer of **5E** shows 22% inhibition at 1 μM.

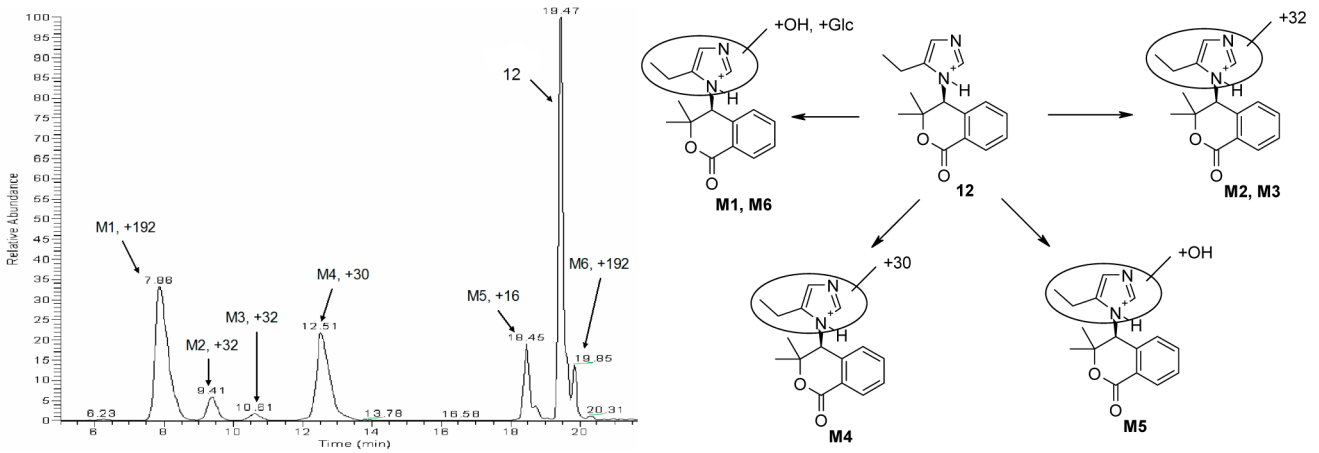


Figure 2. Mass chromatograms of rat urine, 30 min after a 10 mg/kg oral dose of **12**.

pound **30**, the hydroxylated analog of **2E** that had been isolated from liver microsomes incubates, showed much reduced clearance compared to **2E** (35 mL min^{-1} kg^{-1}). Unfortunately in the case of 10-weeks-old SD rats, **30** failed to offer significant benefits over **2E** in terms of oral bioavailability, with GI stability or intestinal metabolism perhaps accounting for the very high first-pass extraction.

As stated in the Introduction, achieving selectivity for CYP11B2 over CYP11B1 was not a specific objective of this program. However, these series of imidazole-containing compounds were profiled in human recombinant CYP11B2 and CYP11B1 assays[28] in order to determine their in vitro selectivity and were found to have no meaningful selectivity for CYP11B2 over CYP11B1. On the other hand, CYP11B1 selectivity was observed, and some SAR data suggest that

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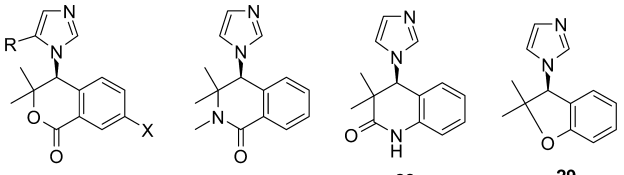
Table 5. Pharmacokinetic Data



14 R=CHF_2, X=H
11 R=H, X=H
26 R=H, X=F

27 **28** **29**

compd[a]	H295-R aldosterone IC_{50} (μM)[b]	rat liver microsomes $t_{1/2}$ (min)	in vivo rat PK, dose (mg/kg): 1 (po), 0.3 (ia)		
			CL (mL min^{-1} kg^{-1})	AUC(0–24 h) (nM·h) po	*F* (%)
14	0.001	>400	4	3446	26
11	0.027	23	30	1031	55
26	0.010	256	28	1479	50
27	0.010	93	23	2253	62
28	0.005	88	20	4040	114
29	0.082	228	8	5442	55

[a]All compounds are single enantiomers. [b]Distomer data for **14** and **11** as shown in Table 2; % inhibitory activity at 1 μM distomer of **26**, **27**, **28**, and **29** are 0%, 23%, 42%, and 27%, respectively.

Table 6. PK/PD Relationships

compd[a]	H295-R aldosterone IC_{50} (μM)	rat recCYP11B2 IC_{50} (μM)	TWA_{0-8h} compd concn (nM)	TWA_{0-8h} % reduction of plasma aldosterone concentration
5E[b]	0.024	nd	110	76
12[c]	0.003	nd	28	87
16	0.004	0.003	22	84
14	0.001	nd	255	75
11	0.027	nd	129	45
26	0.010	0.002	149	64
27	0.010	nd	281	68
28	0.005	0.001	429	77
29[d]	0.082	nd	540	75

[a]All compounds were dosed po at 1 mg/kg using 1.5 equiv of HCl/water as a vehicle except for those compounds where the following vehicles were used. [b]Vehicle: cornstarch. [c]Vehicle: 1.5 equiv of HCl, cornstarch. [d]Vehicle: water.

further optimization of CYP11B1 selectivity is possible (Table 9). For instance, although the unfunctionalized lactone **11** shows no selectivity, ring contraction to either the ether **29** or ketone **31** confers some selectivity for CYP11B1, via loss of potency against CYP11B2. Substituting either the ether oxygen or the lactone for a methylene, as in **32**, rebuilds some of the potency against CYP11B2, with no effect on CYP11B1. Potency on CYP11B2 can also be regained by adding hydroxymethyl substitution to **31** to give **33**. Interestingly, in the case of analogs of **33**, selectivity for CYP11B1 can be increased with judicious choice of substitution on the indanone ring (see **34** versus **35**). Additional strategies for optimization of CYP11B1 selectivity are suggested by compounds **37** and **36** (versus **38**) and compound **39** (versus **11**). Although the selectivities observed here are fairly modest, they suggest that a focused effort on optimization of CYP11B1 selectivity in these series could lead to highly selective CYP11B1 inhibitors,[29] which are expected to be useful for the treatment of Cushing's disease.[24]

CHEMISTRY

The challenges in synthesizing these heterocycle-substituted imidazoles revolved mainly around regisoselective alkylation of the imidazole ring, and several strategies were employed to achieve this, depending on imidazole substitution, as shown in Schemes 1–6. (1*H*-Imidazol-5-yl)methanol **40** was used as starting material for many C5-substituted imidazoles (Scheme 1). N-tritylation of **40** occurs at the least hindered nitrogen, and subsequent TBS protection of the alcohol enables regioselective

Metabolite Designation *m/z* / Modification	RT (min)	Rat Area Response (%)				
		T=0	T=5 min	T=10 min	T=20 min	T=40 min
M1 *m/z* 477 Oxidation & Glucuronidation	6.2	<0.1	5.4	28.0	77.3	72.2
M2 *m/z* 301 Oxidation	7.7	<0.1	34.1	34.4	20.7	0.4
M3 *m/z* 461 Glucuronidation	8.6	<0.1	6.6	11.4	16.6	12.5
M4 *m/z* 299 Dehydrogenation & Oxidation	11.1	0.1	1.1	5.0	21.6	14.5
PARENT *m/z* 285	13.6	100% control	13.7	1.3	0.3	0.3

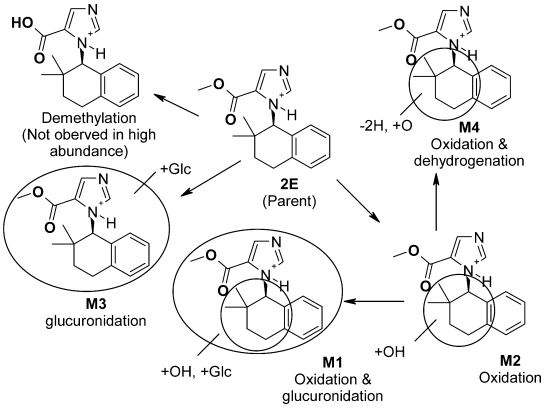


Figure 3. Metabolite identification study for compound **2E** in rat liver microsomes.

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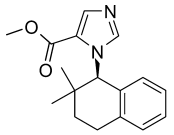
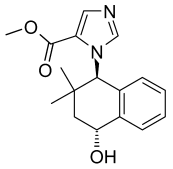
Table 7. Profile of Compounds 2E and 30



2E



30

compd[a]	aldosterone IC_{50} (μM)	rat liver microsomes $t_{1/2}$ (min)	in vivo rat PK dose (mg/kg): 1 (po), 0.3 (ia)		
			CL (mL min^{-1} kg^{-1})	AUC(0–24 h) (nM·h)	F (%)
2E	0.006	2	0.3	467	0.2
30	0.014	4	7	3566	46

[a]All compounds are single enantiomers.

Table 8. Comparison of in Vitro and in Vivo PK Parameters in 10-Weeks-Old and 10-Months-Old SD Rats for 2E and 30

	2E		30	
	10-months old	10-weeks old	10-months old	10-weeks old
RLM $t_{1/2}$ (min)	N/A	2	N/A	4
predicted CLh (mL min^{-1} kg^{-1})	N/A	53	N/A	50
CL (mL min^{-1} kg^{-1})	0.3	143	7	35
V_{Dss} (L/kg)	0.3	1.9	3.8	4.4
$T_{1/2}$ (h)	21	0.2	15	3.4
C_{max} (nM), 1 mpk po	184	BQL	1268	11
AUC(0–24 h) (nM·h), 1 mpk po	467	BQL	3566	11
F (%)	0.2	NR	46	0.3

benzylation at N1 to give **42**. Quenching of the lithium anion derived from **42** with acetone followed by acid-mediated ring closure afforded alcohol **16**, a common precursor to a number of analogs. Alcohol **16** was used to access ethers **19** and **21**, the synthesis of which proved quite challenging, and was best achieved via S_N2 on the primary chloride derived from **16**. Alcohol **16** was also transformed directly to esters **5** and **6** using a one-pot cyanide-mediated oxidation.[30] A similar one-pot methodology was employed to access nitrile **9**,[31] the precursor to acid **7**, amides **8** and **36**–**38**, as well as oxadiazole **10**. Alcohol **16** was oxidized by MnO_2 to give aldehyde **45**, the precursor to **14**, **15**, **17**, **18**, and **20**.

Ethyl- and isopropyl-substituted imidazoles **12**, **13**, and **22**–**25** were synthesized from the iodoimidazole precursor **48**, which was accessed by reacting *N*-Boc-4-iodoimidazole with the triflate derived from alcohol **47**, as depicted in Scheme 2.

Lactone-containing unsubstituted imidazole such as **11**, **26**, and **39** were prepared by reacting the sodium anion of imidazole with 2-cyanobenzyl bromide in DMF at room temperature, followed by the same lithium anion-trapping/acid-catalyzed ring closing sequence as previously described (Scheme 3).

The synthesis of lactam **60** was accomplished via a Beckmann rearrangement of indanone **31**, which was prepared by reacting imidazole with the triflate derived from alcohol **57**, as depicted in Scheme 4. Trapping of the sodium anion of **60** with methyl iodide yielded **27**.

Another method we employed to alkylate imidazole with sterically hindered heterocycles, which was used to prepare reverse lactam **28**, indane **32**, and dihydrobenzofuran **29**, was to react carbonyl-1,1-diimidazole with the corresponding alcohol, as depicted in Scheme 5.

Finally, imidazole carboxylate-containing indanes and tetrahydronaphthalene rings were most efficiently prepared using Mitsunobu conditions (Scheme 6). The nitrogen distal to the carboxylate is the most nucleophilic, and the use of strong bases such as potassium hydroxide or sodium hydride yields the undesired regiochemistry. On the other hand, Mitsunobu conditions typically yield greater than 20:1 ratio for the desired compound under mild conditions when an electron withdrawing group resides at the 5 postion of the imidazole. Compounds **65**, **66**, **67**, and **73** were used as intermediates to prepare **30**, **33**, **34**, and **35**, respectively, as described in Scheme 6.

CONCLUSION

Novel series of soluble and permeable imidazole-based ASIs with single-digit nanomolar cellular potency and high selectivity over aromatase were optimized for oral exposure. A general solution to the problem of low oral bioavailability was found by removing substitution on the imidazole ring. Although these compounds were not optimized for CYP11B2 versus CYP11B1 selectivity, some emerging structure–selectivity relationships were observed leading to more CYP11B1-selective analogs. The combination of highly favorable ADME properties and nascent selectivity for CYP11B1 over CYP11B2 creates an opportunity to further develop these series of imidazole toward the treatment of cortisol-driven disorders.

EXPERIMENTAL SECTION

Pharmacology Studies. Measurement of cellular aldosterone synthase inhibition,[25] aromatase inhibition,[21a] recombinant human CYP11B1, and human and rat CY11B2 inhibition[28] were conducted as previously described.

For in vitro measurement of cellular aldosterone activity, human adrenocortical carcinoma NCI-H295R cells were seeded in NBS 96-well plates at a density of 25 000 cells/well in 100 μL of a growth medium containing DMEM/F12 supplemented with 10% FCS, 2.5% Nu-serum, 1 μg ITS/mL, and 1× antibiotic/antimycotic. The medium was changed after culturing for 3 days at 37 °C under an atmosphere of 5% CO_2/95% air. On the following day, cells were rinsed with 100 μL of DMEM/F12 and incubated with 100 μL of treatment medium containing 1 μM Ang II and a compound at different concentrations in quadruplicate wells at 37 °C for 24 h. At the end of incubation, 50 μL of medium was withdrawn from each well for measurement of aldosterone production by an RIA using mouse anti-aldosterone monoclonal antibodies. Measurement of aldosterone activity could also be performed using a 96-well plate format. Each test sample was incubated with 0.02 μCi of D-[1,2,6,7-3H(N)]aldosterone and 0.3 μg of anti-aldosterone antibody in phosphate buffered saline (PBS) containing 0.1% Triton X-100, 0.1% bovine serum albumin, and 12% glycerol in a total volume of 200 μL at room temperature for 1 h. Anti-

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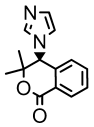
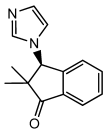
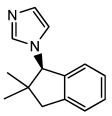
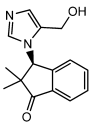
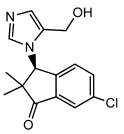
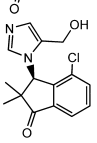
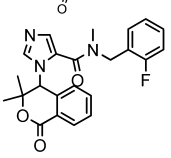
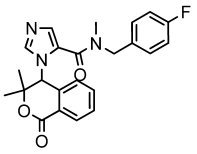
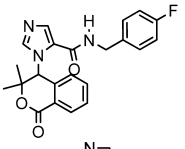
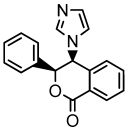
Table 9. Emerging CYP11B1 Selectivity

Compd[a]	Structure	CYP11B2 IC_{50} (nM)	CYP11B1 IC_{50} (nM)	B2/B1 IC_{50} ratio
11		1.3	0.5	2
31		17.3	0.5	36
29		22.3	1.1	21
32		2.1	0.3	8
33		2.8	0.5	5
34		25.3	1.0	25
35		1.5	0.8	1
36[b]		155.7	3.9	40
37[b]		150.8	15.3	9
38[b]		4.6	3.3	1
39		57.2	2.3	25

[a]Compounds are single enantiomers, except otherwise noted. [b]Racemate.

mouse PVT SPA beads (50 μL) were then added to each well and incubated overnight at room temperature prior to counting in a Microbeta plate counter. The amount of aldosterone in each sample is calculated by comparing with a standard curve generated using known quantities of the hormone.

For measurement of recombinant CYP11B2 enzyme activity, material from frozen CYP11B2 preparations was thawed on ice on the day of experiment and then diluted in an ice-cold assay buffer containing 8.5 mM MgCl2, 3.1 mM KCl, 7.6 mM NaCl, and 50 mM Tris/HCl, pH 7.4, to a protein concentration of 1−3 mg/mL. The CYP11B2 assays were performed in 96-well U-bottom non-tissue-culture-treated plates. Depending on the experiment, 5−125 μg of protein (62.5 μg for IC_{50} determinations) in 35 μL was incubated with 75 μL of assay buffer or a compound at the desired concentration and 20 μL of substrate mix (1.08× NADPH regeneration solution A, 6.5× NADPH regeneration solution B, 810 μM NADPH, 6.5 μM 11-deoxycorticosterone in assay buffer) for 2 h at 25 °C in a shaking incubator. The reaction was stopped by adding 10 μL of 1.4% Triton

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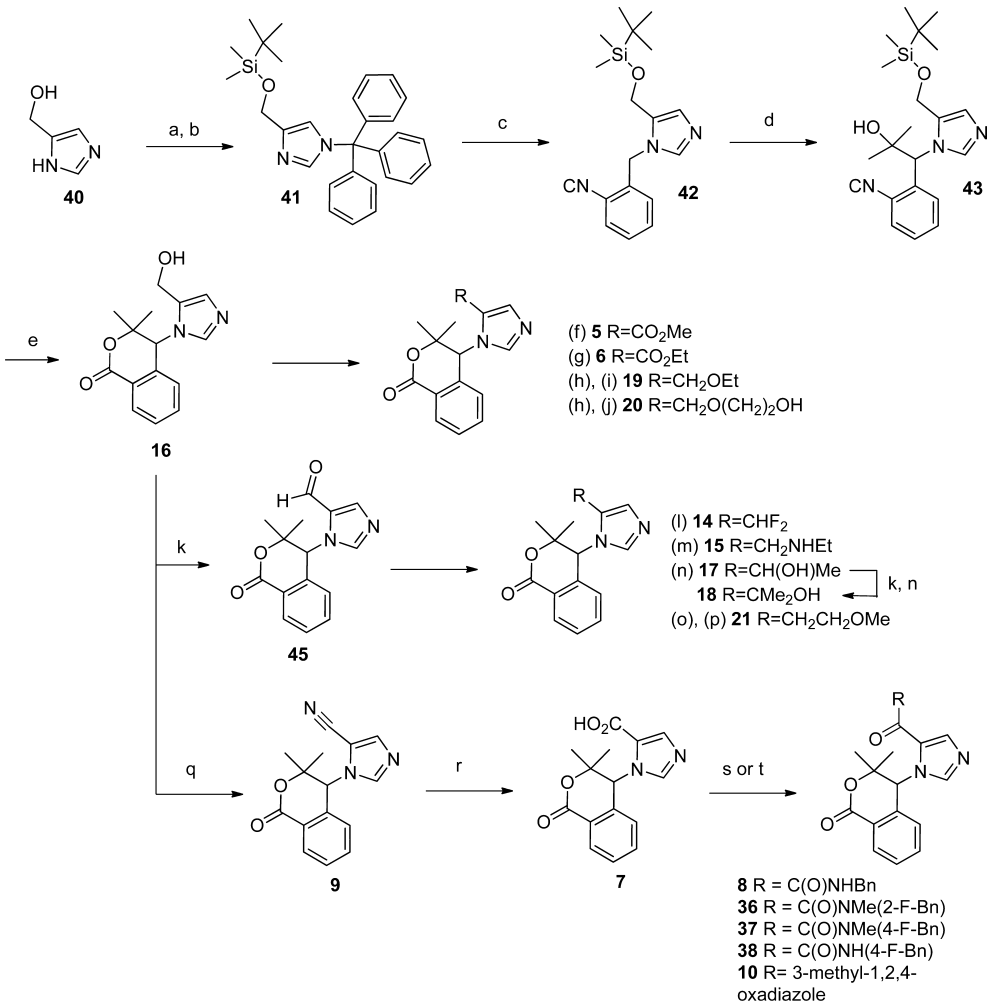
Scheme 1[a]



[a](a) TrCl (1.1 equiv), Et_3N (2.3 equiv), DMF, rt, 16 h; (b) TBSCl (1.1 equiv), imidazole (3 equiv), DMAP (0.1 equiv), DMF, rt, 2 h; (c) 2-cyanobenzyl bromide (1.05 equiv), acetonitrile, 60 °C, 16 h, then Et_2NH, 30 min, then methanol, 30 min; (d) LHMDS, THF, −78 °C, 20 min, then acetone, 40 min; (e) aq H_2SO_4, THF, reflux, 16 h; (f) NaCN (1.1 equiv), MnO_2 (15 equiv), methanol, THF, reflux, 2 days; (g) NaCN (1.1 equiv), MnO_2 (15 equiv), ethanol, THF, reflux, 2 days; (h) thionyl chloride, 60 °C, 2 h; (i) anhydrous ethanol, DIPEA (1.5 equiv), reflux, 16 h; (j) glycol, DIPEA (1.5 equiv), 80 °C, 16 h; (k) MnO_2 (15 equiv), dioxane, 60 °C, 16 h; (l) DAST (5 equiv), DCE, reflux, 16 h; (m) $EtNH_2$ (1.5 equiv), $Na(OAc)_3BH$ (3 equiv), DCE, 50 °C, 5 h; (n) MeMgBr (1.3 equiv), THF/dibutyl ether, −78 °C to rt, 16 h; (o) methoxymethyltriphenylphosphonium chloride (7 equiv), NaHMDS (8 equiv), THF, rt, 15 min, then 45, rt, 1 h; (p) H_2 balloon, Pd/C, methanol, rt, 48 h; (q) $MgSO_4$ (14 equiv), NH_3 (2 M in ^{i}PrOH, 4.5 equiv), MnO_2 (14 equiv), THF, rt, 48 h; (r) aq H_2SO_4, THF, reflux, 16 h; (s) DMF (0.7 equiv), oxalyl chloride (2.5 equiv), DCM, 0 °C to rt, 2 h, then dry in vacuo then amine (3 equiv), DCM, rt, 1 h; (t) oxalyl chloride (2.5 equiv), DCM, 0 °C to rt, 3 h, then dry in vacuo then *N*-hydroxyacetamidine (1.3 equiv), chloroform, reflux, 72 h.

X-100 and briefly shaking the plates. Plates were then centrifuged at 2400 rpm for 6 min, and 80 μL of supernatant was removed for measurement of aldosterone content by scintillation proximity assay (SPA).

Measurement of recombinant CYP11B1 enzyme activity was carried out in a manner similar to that of the CYP11B2 assay except that 50−300 μg of protein from the CYP11B1 preparations and 500 nM 11-deoxycortisol were used as enzyme source and substrate, respectively. The reaction was stopped by adding 10 μL of 1.4% Triton X-100 and briefly shaking the plates. Plates were then centrifuged at 2400 rpm for 6 min, and 50 μL of supernatant was removed for measurement of cortisol content by SPA.

The study protocols for the rat model of Ang II-stimulated aldosterone synthesis have been described.[21b] Briefly, an initial loading dose of 300 ng/kg angiotensin II (Ang II) was followed by 100 ng/kg/min intravenous (iv) infusion for 9 h. After 1 h of Ang II or ACTH infusion, a blood sample was collected for determining the post-Ang II "baseline" (i.e., secretagogue-elevated) plasma aldosterone concentrations. Infusion continued for a further 8 h after test article administration. Blood samples were withdrawn in heparin (final concentration of 15 U/mL) from the arterial cannula at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 24 h postdosing. Plasma aldosterone was determined by radioimmunoassay and test article by liquid chromatography separation coupled with tandem mass spectrometric detection (LC−MS/MS).

Liver Microsomal Stability and Metabolite Identification. The in vitro half-life ($t_{1/2}$) and predicted metabolic clearance (CLh) in rat or human liver microsomes (RLM or HLM) (BD Gentest, Woburn, MA) was determined based on published method.[32] In brief, 1 μM test compound was incubated at 37 °C in pooled RLM or HLM (containing 0.5 mg of microsomal protein per mL) in the presence of 25 μg of alamethacin per mg protein, 1.0 mM NADPH, 1.0 mM UDPGA, and 2 mM $MgCl_2$. The half-life ($t_{1/2}$) was derived by monitoring the disappearance of test compound over a short period of time (e.g., 30 min) by LC/MS/MS. The CLh was calculated using a modified "well-stirred model" that accounted for portal blood flow

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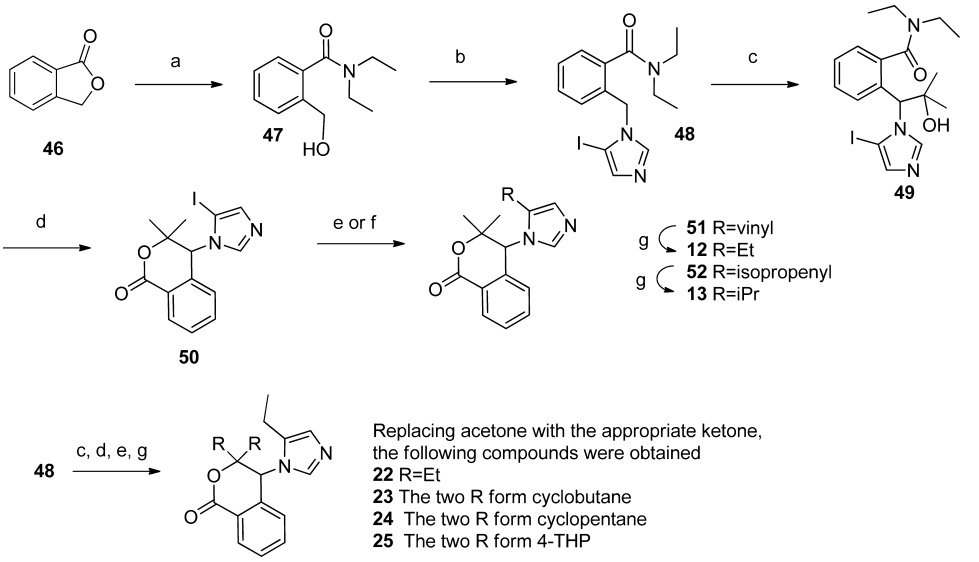
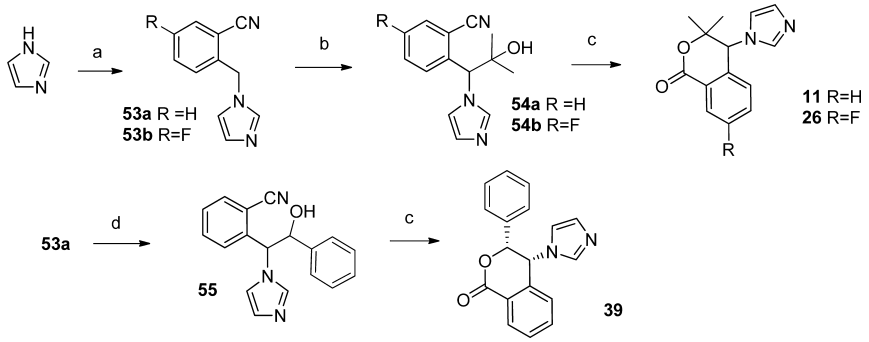
Scheme 2[a]



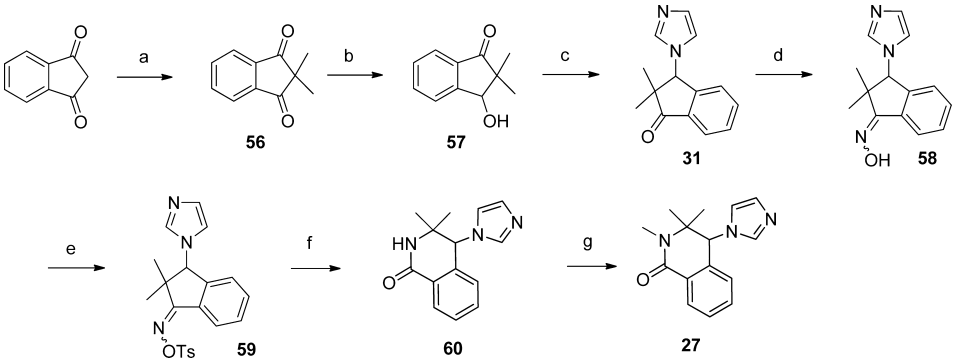
[a](a) $AlCl_3$ (1.3 equiv), Et_2NH (2.5 equiv), DCE, 45 min, rt; (b) Tf_2O (1.1 equiv), $^iPrEt_2N$ (1.2 equiv), DCM, −78 °C, 30 min, then *N*-Boc-4-iodoimidazole (0.7 equiv), −78 °C to rt, 18 h; (c) LDA (1 equiv), THF, −78 °C, 15−30 min, then ketone (5 equiv), 1−2 h; (d) KOH, H_2O/dioxane, 60 °C, 13−30 h, then add conc HCl until pH = 1, then 60 °C, 16−24 h; (e) tributylvinyltin (2 equiv), $Pd_2dba_3{\cdot}CHCl_3$ (0.02 equiv), PPh_3 (0.08 equiv), DMF, 90 °C, 3−6 h; (f) tributylisopropenyltin (2 equiv), $Pd_2dba_3{\cdot}CHCl_3$ (0.1 equiv), trifuran-2-ylphosphane (0.15 equiv), NMP, 90 °C, 24 h; (g) 10% Pd/C (0.05 equiv), H_2, methanol, 3−72 h.

Scheme 3[a]



[a](a) NaH (1.5 equiv), DMF, rt, 30 min, then appropriate 2-cyanobenzyl bromide (1 equiv), 30 min; (b) LHMDS (1.5 equiv), THF, −78 °C, 30 min, then acetone (1.5 equiv), 30 min; (c) aq H_2SO_4, dioxane, reflux, 2−16 h; (d) LHMDS (3.5 equiv), THF, −78 °C, 10 min, then benzaldehyde (4.5 equiv), 1 min.

Scheme 4[a]



[a](a) 50% KF on Celite (~5 equiv), MeI (3 equiv), acetonitrile, 70 °C, 14 h; (b) $NaBH_4$ (0.3 equiv), ethanol, −30 °C, 1 h; (c) Tf_2O (3 equiv), DIPEA (4 equiv), DCM, −78 °C, 10 min, then −10 °C, 10 min, then imidazole (6 equiv), −78 °C to rt; (d) NH_2OH. HCl (2.5 equiv), pyridine (12 equiv), methanol, 55 °C, 14 h; (e) *p*-TsCl (2 equiv), DMAP (0.03 equiv), pyridine, 50 °C, 14 h; (f) pyridine, 190 °C (microwave), 35 min; (g) NaH (1.3 equiv), DMF, −10 °C, 10 min, then MeI (2 equiv), −10 °C to rt, 20 min.

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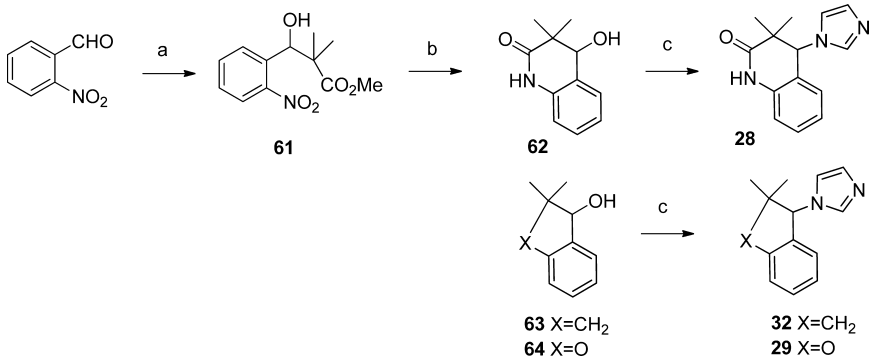
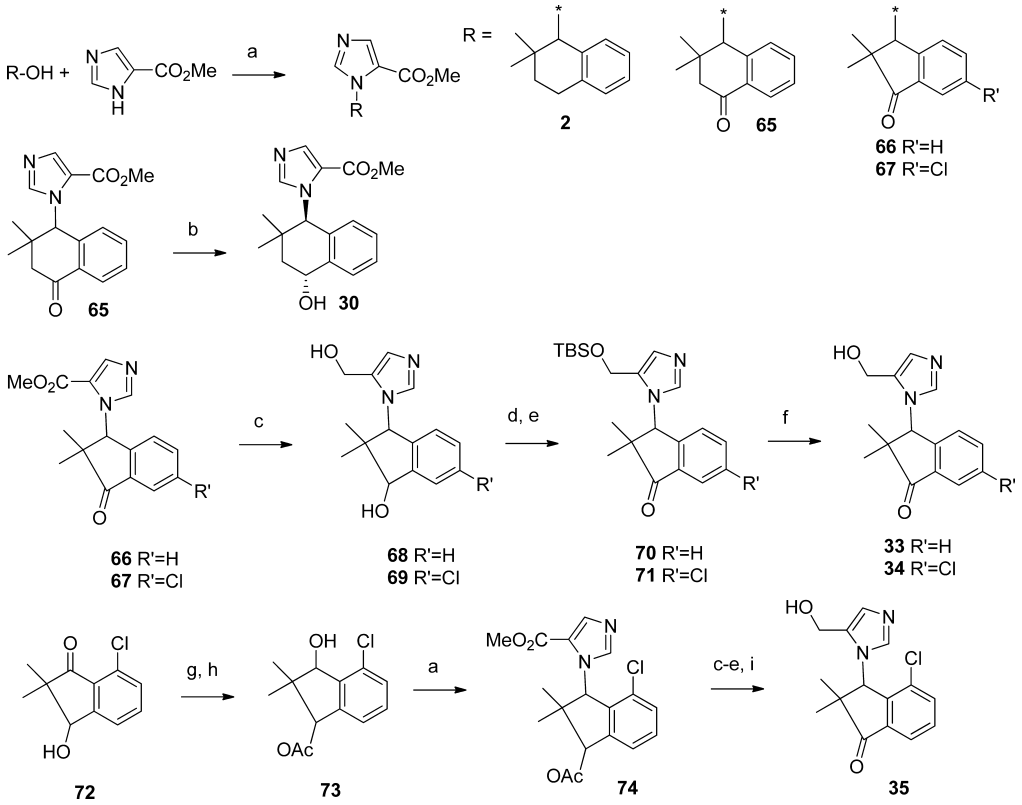
Scheme 5[a]



[a](a) 1-Methoxy-1-(trimethylsiloxy)-2-methyl-1-propene (1.2 equiv), $Sc(OTf)_3$ (0.03 equiv), DCM, −78 to 0 °C, 1 h, then 1 M HCl, 1 h; (b) 10% Pd/C, H_2 (balloon), methanol, 5 h; (c) carbonyl-1,1-di-imidazole (2.0 equiv), acetonitrile, reflux, 5 h.

Scheme 6[a]



[a](a) PPh_3 (1−2 equiv), DMAD or DIAD or DTBAD (1−2 equiv), THF, 0 °C to rt, 1−15 h; (b) $NaBH_4$ (1.5 equiv), MeOH, 0 °C, 10 min; (c) $LiAlH_4$ (1.5 equiv), THF, 0 °C, 30 min; (d) imidazole (1.1 equiv), TBSCl (1 equiv), DMF, rt, 14 h; (e) MnO_2 (20 equiv), 1,4-dioxane, 100 °C, 1−2 h; (f) 4 M HCl in 1,4-dioxane, rt, 2 h; (g) Ac_2O (2 equiv), pyridine (10 equiv), DCM, rt, 1 h.; (h) $NaBH_4$ (3 equiv), EtOH, rt, 2 h; (i) 4 M HCl in 1,4-dioxane, methanol, rt, 30 min.

(Qh) and considered no difference between plasma protein binding and microsomal protein binding of the test compounds. In the metabolite identification, 10 μM test compound was incubated at 37 °C in pooled RLM or HLM (containing 1 mg of microsomal protein per mL) in the presence of 60 μg of alamethacin per mg protein, 2.0 mM NADPH, 4.0 mM UDPGA, and 5 mM $MgCl_2$. Following in vitro incubation and protein precipitation, samples were analyzed by LC/MS/MS for detection and characterization of the metabolites formed.

Rat Pharmacokinetic Studies for 2E and 30. Male Sprague Dawley rats (200−300 g) (Harlan Laboratories Inc., Indianapolis, IN, USA) were used in the experiments. All animal experiments were performed in accordance with IACUC protocol. Two rats received 0.3 mg/1 mL/kg (free base equivalents) by slow intravenous injection via the jugular vein, and three rats received 1 mg/5 mL/kg in solution of suspension via oral gavage. Approximately 0.2 mL of venous whole blood was collected from the jugular vein catheter of each animal at 5 min (iv dose only) and 0.25, 0.5, 1, 2, 4, 6, and 8 h postdose and transferred to a EDTA tube. The blood was centrifuged at 3000 rpm, and the plasma was transferred to a polypropylene tube, capped, and stored frozen (−20 °C) for parent compound analysis. Protein precipitation was employed for sample preparation. A 25 μL aliquot of sample was subjected to protein precipitation using 150 μL of acetonitrile containing 100 ng/mL of internal standard (Glyburide). After vortex and centrifugation for 5 min at 4000 rpm, the supernatant (125 μL) was transferred to a 1 mL 96-well plate, followed by the addition of 50 μL of water. The analysis was conducted by using

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HPLC separation coupled with mass spectrometric detection. All pharmacokinetic (PK) parameters were derived from concentration−time data by noncompartmental analyses. All pharmacokinetic parameters were calculated with the computer program WinNonlin (Enterprise, version 5.2) purchased from Pharsight Corporation (St. Louis, MO).

General Chemical Methods. Starting materials, reagents, and solvents were obtained from commercial sources and used as received. THF and diethyl ether were anhydrous grade. Progress of the reactions was monitored by thin-layer chromatography (TLC) analysis (Merck, 0.2 mm silica gel 60 F254 on glass plates) or by analytical LC−MS using an Agilent 1100 series with UV detection at 214 and 254 nm and an electrospray mode (ESI) coupled with a Waters ZQ single quad mass detector. Purification of intermediates and final products was carried out on normal phase using an ISCO CombiFlash system or an Analogix Intelliflash 280 or a Biotage SP1 system and prepacked SiO_2 cartridges eluted with optimized gradients of either heptane−ethyl acetate mixture or dichloromethane−methanol as described. Preparative high pressure liquid chromatography (HPLC) was performed on Waters or Gilson instruments. Systems were run with either a 5−95% or 10−90% acetonitrile/water gradient with either a 0.1% TFA or 0.1% NH_4OH modifier. All target compounds had purity of >95% as established by analytical HPLC. Resolution of the racemates was carried out by preparative HPLC using the conditions described, and enantiomeric excesses were >98%. NMR spectra were recorded on a Bruker AV400 (Avance 400 MHz) instrument. Chemical shifts (δ) are reported in parts per million (ppm) relative to deuterated solvent as the internal standard ($CDCl_3$ 7.26 ppm, DMSO-d_6 2.50 ppm, CD_3OD 3.31), and coupling constants (J) are in hertz (Hz). Peak multiplicities are expressed as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m), and broad singlet (br s).

4-(*tert*-Butyldimethylsilanyloxymethyl)-1-trityl-1*H*-imidazole (41). Trityl chloride (45.57 g, 0.163 mol), (1*H*-imidazol-4-yl)methanol (20.00 g, 0.148 mol), and triethylamine (37.46 g, 0.370 mol) in DMF (150 mL) were stirred at rt for 16 h, whereupon the mixture was poured into ice-cold water. The precipitate was filtered off and dried under high vacuum to give (1-trityl-1*H*-imidazol-4-yl)methanol as a solid. Crude (1-trityl-1*H*-imidazol-4-yl)methanol (26.4 g, 0.077 mol), imidazole (15.88 g, 0.233 mol), DMAP (0.950 g, 7.7 mmol), and TBSCl (12.89 g, 0.085 mol) in DMF (0.1 L) were stirred at rt for 2 h, whereupon water was added. The mixture was extracted three times with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel flash chromatography (elution with hexanes−ethyl acetate, 7:3) to yield **41** as a white solid; ESI-MS m/z 455 $(M + H)^+$.

2-[5-(*tert*-Butyldimethylsilanyloxymethyl)imidazol-1-ylmethyl]benzonitrile (42). **41** (12.9 g, 28.4 mmol) and 2-cyanobenzyl bromide (6.12 g, 31.2 mmol) in acetonitrile (100 mL) were heated to 60 °C overnight, whereupon diethylamine (30 mL) was added. After 30 min, methanol (2 mL) was added. After 30 min the volatiles were removed in vacuo. The residue was taken up in dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel flash chromatography (elution with dichloromethane−methanol, 49:1) to yield partially purified **42** which was used in the next step without further purification; ESI-MS m/z 328.2 $(M + H)^+$.

2-{1-[5-(*tert*-Butyldimethylsilanyloxymethyl)imidazol-1-yl]-2-hydroxy-2-methylpropyl}benzonitrile (43). Crude **42** (7.6 g) was dried azeotropically with toluene and then dissolved in THF (100 mL) and cooled to −75 °C. LHMDS (1 M in THF, 35 mL, 35 mmol) was added dropwise. Ten minutes after the end of addition, acetone (2.0 g, 35 mmol) was added. Thirty minutes after the end of addition, saturated aqueous sodium bicarbonate (2 mL) was added and the mixture was allowed to warm to rt, then poured into water. After extraction with ethyl acetate the organic phase was dried over Na_2SO_4 and concentrated in vacuo to give crude **43** (3 g), which was used in the next step without further purification; ESI-MS m/z 386.1 $(M + H)^+$.

(*R*)- or (*S*)-4-(5-Hydroxymethylimidazol-1-yl)-3,3-dimethylisochroman-1-one (*R*- and *S*-16). Crude **43** (3 g) was dissolved in THF (80 mL). Water (1.6 mL) and sulfuric acid (1.6 mL) were added, and the mixture was stirred at reflux overnight. After cooling down, the mixture was poured in water. The two phases were separated, and the pH of the aqueous phase was adjusted to ∼9 with aqueous sodium bicarbonate. Extraction with ethyl acetate, drying over Na_2SO_4, and concentration in vacuo gave a solid which is recrystallized from ethyl acetate. 4-(5-Hydroxymethylimidazol-1-yl)-3,3-dimethylisochroman-1-one (1.7 g, 20%, 3 steps) was obtained as a white solid. Resolution of the racemate achieved by chiral HPLC using the ChiralPak IA column with a 7:2:1 heptane−dichloromethane−ethanol mobile phase gave **16**; t_R = 8.3 min (distomer t_R = 7.1 min); ESI-MS m/z 272.9 $(M + H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.29 (s, 3 H), 1.54 (s, 3 H), 4.71 (d, J = 13.6 Hz, 1 H), 4.82 (d, J = 13.9 Hz, 1 H), 5.51 (s, 1 H), 6.89 (s, 1 H), 7.29 (s, 1 H), 7.41 (d, J = 7.6 Hz, 1 H), 7.53−7.58 (m, 1 H), 7.59−7.65 (m, 1 H), 8.25 (dd, J = 7.6, 1.5 Hz, 1 H).

(*R*)- or (*S*)-3-(3,3-Dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carboxylic Acid Ethyl Ester (6). To a solution of **16** (0.56 g, 2.0 mmol) in THF (10 mL) were added ethanol (0.6 mL), sodium cyanide (0.111 g, 2.26 mmol), and manganese dioxide (2.69 g, 30.9 mmol). The mixture was stirred at reflux for 2 days, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (heptane−ethyl acetate, 4:1 to 1:9) to give 3-(3,3-dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carboxylic acid ethyl ester as oil (230 mg, 36%). Resolution of the racemate was achieved by chiral HPLC using the ChiralPak AS-H column with a 4:1 hexanes−isopropanol mobile phase to give **6**; t_R = 12.4 min (distomer t_R = 10.5 min); ESI-MS m/z 315.1355 [$(M + H)^+$, calcd for $C_{17}H_{18}N_2O_4$, 315.1345]; ^1H NMR (400 MHz, CD_3OD) of the HCl salt δ ppm 1.24 (s, 3 H), 1.43 (t, J = 7.1 Hz, 3 H), 1.55 (s, 3 H), 4.46 (q, J = 7.1 Hz, 2 H), 6.83 (s, 1 H), 7.53 (d, J = 7.6 Hz, 1 H), 7.66−7.71 (m, 2 H), 7.78 (td, 1 H), 7.91 (s, 1 H), 8.26 (dd, J = 7.8, 1.3 Hz, 1 H).

(*R*)- or (*S*)- 3-(3,3-Dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carboxylic Acid Methyl Ester (5). Compound **5** was prepared following the same procedure as **6**, using methanol instead of ethanol. Resolution of the racemate was achieved by chiral HPLC using the ChiralPak AS-H column with a 9:1 hexanes−isopropanol mobile phase to give **5**; t_R = 30.9 min (distomer t_R = 22.0 min); ESI-MS m/z 301.0 $(M + H)$; ^1H NMR (400 MHz, CD_3OD) δ ppm 1.26 (s, 3 H), 1.58 (s, 3 H), 4.00 (s, 3 H), 6.81 (s, 1 H), 7.47 (s, 1 H), 7.54 (d, J = 7.6 Hz, 1 H), 7.71 (td, J = 7.8, 1.3 Hz, 1 H), 7.79 (dd, J = 7.6, 1.5 Hz, 1 H), 7.82 (d, J = 1.0 Hz, 1 H), 8.28 (dd, J = 7.7, 1.4 Hz, 1 H).

(*R*)- and (*S*)-4-(5-Ethoxymethylimidazol-1-yl)-3,3-dimethylisochroman-1-one (19). A solution of **16** (1.0 g, 3.6 mmol) in thionyl chloride (50 mL) was heated to 60 °C for 2 h. The volatiles were removed in vacuo to give 4-(5-chloromethylimidazol-1-yl)-3,3-dimethylisochroman-1-one. A portion (0.15 g, 0.52 mmol) was redissolved in anhydrous ethanol (5 mL). Diisopropylethylamine (0.100 g, 0.77 mmol) was added, and the mixture was stirred at reflux overnight. The mixture was purified by semipreparative reverse phase HPLC to give 4-(5-ethoxymethylimidazol-1-yl)-3,3-dimethylisochroman-1-one (70 mg, 44%, 2 steps). Resolution of the racemate was achieved by chiral HPLC using the ChiralPak IA column with a 7:2:1 heptane−dichloromethane−ethanol mobile phase to give **19**; t_R = 8.9 min (distomer t_R = 6.3 min); ESI-MS m/z 301.0 $(M + H)^+$; ^1H NMR (400 MHz, CD_3OD) δ ppm 1.26 (s, 3 H), 1.29 (t, J = 6.1 Hz, 3 H), 1.54 (s, 3 H), 3.62 (br s, 2 H), 4.70 (br s, 2 H), 5.59 (s, 1 H), 7.02 (s, 1 H), 7.29 (br s, 1 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.63 (td, J = 7.8, 1.3 Hz, 1 H), 7.74 (td, J = 7.6, 1.3 Hz, 1 H), 8.21 (dd, J = 7.8, 1.3 Hz, 1 H).

4-[5-(2-Hydroxyethoxymethyl)imidazol-1-yl]-3,3-dimethylisochroman-1-one (20). Compound **20** was prepared following the same procedure as **19**, using glycol instead of ethanol. ESI-MS m/z 317.0 $(M + H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.31 (s, 3 H), 1.55 (s, 3 H), 1.76 (br s, 1 H), 3.55−3.69 (m, 2 H), 3.78−3.86 (m, 2 H), 4.65−4.75 (m, 2 H), 5.46 (s, 1 H), 7.06 (s, 1 H), 7.34 (d, J = 8.3 Hz, 2 H), 7.55 (td, J = 7.6, 1.3 Hz, 1 H), 7.62 (td, J = 7.6, 1.5 Hz, 1 H), 8.25 (dd, J = 7.8, 1.5 Hz, 1 H).

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3-(3,3-Dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carbaldehyde (45). To a solution of racemic **16** (2.72 g, 10 mmol) in dioxane (150 mL) was added manganese dioxide (13 g, 150 mmol), and the reaction mixture was heated to 60 °C overnight. Filtration through Celite and concentration in vacuo gave a residue which was purified by silica gel chromatography (dichloromethane−methanol) to afford **45** (2.5 g, 93%). Crude **45** was of sufficient purity before chromatography and was typically used without purification; ESI-MS m/z 271.1 $(M + H)^+$.

(*R*)- or (*S*)-4-(5-Difluoromethylimidazol-1-yl)-3,3-dimethylisochroman-1-one (14). To a solution of **45** (0.135 g, 0.50 mmol) in dichloroethane (5 mL) under nitrogen was added DAST (0.403 g, 2.5 mmol), and the mixture was heated to reflux overnight. After another 2 h, an additional portion of DAST (0.060 g, 0.372 mmol) was added. The organic phase was shaken with saturated aqueous sodium bicarbonate and filtered through Celite. The organic phase was dried over magnesium sulfate, filtered and the residue was purified by reverse phase HPLC using C18 Xbridge and acetonitrile/NH_4OH gradient to give 4-(5-difluoromethylimidazol-1-yl)-3,3-dimethylisochroman-1-one. Resolution of the racemate was achieved by chiral HPLC using the ChiralPak IA column with a 3:1 heptane−isopropanol mobile phase to give **14** (14 mg, 10%); t_R = 13.3 min (distomer t_R = 21.4 min); ESI-MS m/z 293.0 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.32 (s, 3 H), 1.57 (s, 3 H), 5.50 (s, 1 H), 6.86 (t, J = 52.7 Hz, 1 H), 7.32 (t, J = 2.6 Hz, 1 H), 7.43 (s, 1 H), 7.44 (m, 1 H), 7.54−7.63 (m, 1 H), 7.63−7.71 (m, 1 H), 8.27 (dd, J = 7.7, 1.3 Hz, 1 H).

4-(5-Ethylaminomethylimidazol-1-yl)-3,3-dimethylisochroman-1-one (15). To a solution of **45** (0.133 g, 0.49 mmol) in dichloroethane (2 mL) were added ethylamine (0.37 mL, 0.738 mmol) and sodium triacetoxyborohydride (0.313 g, 1.477 mmol). The reaction mixture was stirred at 50 °C for 5 h. The mixture was cooled to room temperature, washed with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved purified by reverse phase HPLC to give **15** (65 mg, 44%); HR-ESI-MS m/z 300.1705 $[(M + H)^+$, calcd for $C_{17}H_{22}N_3O_2$, 300.1712]; ^{1}H NMR (400 MHz, CD_3OD) of the TFA salt δ ppm 1.27 (s, 3 H), 1.46 (t, J = 6.8 Hz, 3 H), 1.59 (s, 3 H), 3.35−3.40 (m, 2 H), 4.65 (br s, 2 H), 5.82 (s, 1 H), 7.51 (br s, 1 H), 7.64 (d, J = 7.3 Hz, 1 H), 7.75 (td, J = 7.8, 1.0 Hz, 1 H), 7.84 (td, J = 7.6, 1.3 Hz, 1 H), 7.92 (br s, 1 H), 8.30 (dd, J = 7.8, 1.3 Hz, 1 H).

(*R*,*R*)-, (*S*,*S*)-, (*R*,*S*)-, (*S*,*R*)-4-[5-(1-Hydroxyethyl)imidazol-1-yl]-3,3-dimethylisochroman-1-one (17 and Stereoisomers). To a solution of **45** (0.500 g, 1.852 mmol) in THF (20 mL) at −78 °C was added 1 M methyl magnesium bromide in dibutyl ether (2.41 mL, 2.41 mmol). The reaction mixture was stirred at −78 °C for 3 h, whereupon acetone (2 mL) was added. The mixture was allowed to warm to ambient temperature and then poured into water (50 mL). The mixture was extracted with ethyl acetate. The combined organic phase was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (DCM−methanol, 99:1 to 19:1) to give 4-[5-(1-hydroxyethyl)imidazol-1-yl]-3,3-dimethylisochroman-1-one (400 mg, 75%). Resolution of all four stereoisomers was achieved by chiral HPLC. Using a ChiralPak IA column using an 85:15 heptane−isopropanol mobile phase afforded **17**. The remaining three stereoisomers were resolved with a ChiralPak AD using an 85:15 heptane−ethanol mobile phase to give stereoisomer B (t_R = 61.4 min), stereoisomer C (t_R = 76.7 min) and stereoisomer D (t_R = 94.9 min).

17 and stereoisomer D: ESI-MS m/z 287.0 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.26 (s, 3 H), 1.54 (s, 3 H), 1.79 (d, J = 6.6 Hz, 3 H), 1.84 (d, J = 8.6 Hz, 1 H), 4.91−5.01 (m, 1 H), 5.67 (s, 1 H), 7.01 (s, 1 H), 7.24 (s, 1 H), 7.47 (d, J = 8.1 Hz, 1 H), 7.52−7.58 (m, 1 H), 7.59−7.64 (m, 1 H), 8.25 (dd, J = 7.7, 1.4 Hz, 1 H).

Stereoisomers B and C: ESI-MS m/z 287.1 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (s, 3 H), 1.56 (s, 3 H), 1.77 (d, J = 6.6 Hz, 3 H), 1.85 (br s, 1 H), 5.06−5.12 (m, 1 H), 5.60 (s, 1 H), 6.99 (s, 1 H), 7.23 (d, J = 7.6 Hz, 1 H), 7.40 (s, 1 H), 7.54 (td, J = 7.8, 1.3 Hz, 1 H), 7.61 (td, J = 7.6, 1.5 Hz, 1 H), 8.24 (dd, J = 7.7, 1.4 Hz, 1 H).

4-[5-(1-Hydroxy-1-methylethyl)imidazol-1-yl]-3,3-dimethylisochroman-1-one (18). To a solution of **17** and its three stereoisomers (0.100 g, 0.35 mmol) in dioxane (2 mL) was added manganese dioxide (0.46 g, 5.2 mmol), and the reaction mixture was heated to 60 °C overnight. Filtration through Celite and concentration in vacuo gave crude 4-(5-acetylimidazol-1-yl)-3,3-dimethylisochroman-1-one. The crude ketone (0.150 g, 0.50 mmol) was dissolved in THF (2 mL) at −78 °C, 1 M methylmagnesium bromide in dibutyl ether (0.65 mL, 0.65 mmol) was added, and the mixture was allowed to warm to rt overnight. This process was repeated twice before quenching with acetone. The mixture was poured into water and extracted with ethyl acetate. The combined organic phase was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by reverse phase HPLC to give **18** (50 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.30 (dd, J = 7.7, 1.4 Hz, 1H), 7.97−7.90 (m, 1H), 7.75 (td, J = 7.6, 1.5 Hz, 1H), 7.68 (td, J = 7.6, 1.1 Hz, 1H), 7.58 (s, 1H), 7.04 (s, 1H), 6.59 (s, 1H), 3.04 (s, 1H), 1.90 (s, 3H), 1.78 (s, 3H), 1.59 (s, 3H), 1.33 (s, 3H).

(*R*)- or (*S*)-4-[5-(2-Methoxyethyl)imidazol-1-yl]-3,3-dimethylisochroman-1-one (21). To a solution of methoxymethyltriphenylphosphonium chloride (0.914 g, 2.67 mmol) in THF (10 mL) was added lithium hexamethyldisilazide (1 M in THF, 2.9 mL, 2.9 mmol), and the mixture was stirred for 15 min. **45** (0.60 g, 2.22 mmol) in THF (0.2 mL) was then added, and the mixture was stirred for 1 h. It was then quenched with methanol. The organic phase was concentrated to dryness in vacuo. The residue was dissolved in methanol, and 10% Pd/C was added. The reaction vessel was flushed with hydrogen gas and stirred under balloon pressure for 48 h. The mixture was filtered, and the filtrate was concentrated in vacuo to give a residue which was purified by reverse phase HPLC using C18 Xbridge and acetonitrile/NH_4OH gradient to give 4-[5-(2-methoxyethyl)imidazol-1-yl]-3,3-dimethylisochroman-1-one. The racemate was resolved chiral HPLC using the ChiralPak IA column with a 65:35 hexanes−reagent alcohol mobile phase to give **21** (70 mg, 10%, 2 steps); t_R = 11.8 min (distomer t_R = 9.2 min); HR-ESI-MS m/z 301.1555 $[(M + H)^+$, calcd for $C_{17}H_{20}N_2O_3$, 301.1552]; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.25 (s, 3 H), 1.56 (s, 3 H), 3.13 (br s, 2 H), 3.45 (br s, 3 H), 3.70−3.79 (m, 2 H), 5.71 (s, 1 H), 6.90 (s, 1 H), 7.15 (br s, 1 H), 7.52 (d, J = 7.6 Hz, 1 H), 7.60−7.72 (m, 1 H), 7.74−7.86 (m, 1 H), 8.24 (dd, J = 7.8, 1.5 Hz, 1 H).

(*R*)- or (*S*)-3-(3,3-Dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carbonitrile (9). To a solution of **16** (1.0 g, 3.76 mmol) in THF (30 mL) were added magnesium sulfate (4.79 g, 0.055 mol) and ammonia (2 M isopropanol, 9 mL, 0.018 mol). Manganese dioxide (9 mL, 0.055 mol) was then added, and the reaction mixture was stirred at room temperature for 48 h. Filtration through Celite and concentration in vacuo afford a residue, which was purified by reverse-phase HPLC to give 3-(3,3-dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carbonitrile (546 mg, 55%). Resolution of the racemate was achieved by chiral HPLC using the ChiralPak IA column with a 7:3 heptane−ethanol mobile phase to give **9**; t_R = 42.7 min (distomer t_R = 13.5 min); ESI-MS m/z 268.0 $(M + H)^+$; ^{1}H NMR (400 MHz, MeOD) δ ppm 1.33 (s, 3 H), 1.60 (s, 3 H), 5.87 (s, 1 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.67−7.78 (m, 1 H), 7.78−7.98 (m, 3 H), 8.28 (dd, J = 7.7, 1.4 Hz, 1 H).

3-(3,3-Dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carboxylic Acid (7). **9** (0.100 g, 0.374 mmol) was dissolved in a mixture of tetrahydrofuran (2 mL) and water (0.2 mL). Sulfuric acid (0.2 mL, 1.872 mmol) was added, and the mixture was stirred at reflux for 16 h. Concentration in vacuo gave a residue which was purified by reverse phase HPLC to give **7** (45 mg, 41%); ESI-MS m/z 287.0 $(M + H)^+$.

3-(3,3-Dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carboxylic Acid Benzylamide (8). **7** (0.100 g, 0.349 mmol) was dissolved in dichloromethane (2 mL). Catalytic amount of dimethylformamide (0.002 mL,0.0262 mmol) was added to the reaction mixture and cooled to 0 °C. Oxalyl chloride (0.076 mL, 0.874 mmol) was added, and the cooling bath was removed. The mixture was stirred at room temperature for 2 h and then concentrated in vacuo. The residue obtained was redissolved in dichloromethane, and benzylamine (0.114 mL, 1.04 mmol) was added. Reaction mixture was

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stirred at room temperature for 1 h. The mixture was washed with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (dichlromethane−methanol, 19:1) to give **8** (38 mg, 29%); ESI-MS m/z 376.0 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.24 (s, 3 H), 1.53 (s, 3 H), 4.62 (s, 2 H), 6.98 (s, 1 H), 7.26−7.35 (m, 1 H), 7.35−7.46 (m, 5 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.64−7.73 (m, 2 H), 7.74−7.84 (m, 1 H), 8.26 (dd, J = 7.8, 1.5 Hz, 1 H).

3-(3,3-Dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carboxylic Acid (2-Fluorobenzyl)methylamide (36). Compound **36** was prepared using the same procedure as **8**, using *N*-methyl-2-fluorobenzylamine instead of benzylamine. ESI-MS m/z 408.1 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.25 (s, 3 H), 1.52 (s, 3 H), 3.24 (br s, 3 H), 4.93 (br s, 2 H), 6.26 (s, 1 H), 7.17−7.40 (m, 2 H), 7.37−7.53 (m, 4 H), 7.64−7.73 (m, 2 H), 7.80 (td, J = 7.3, 1.3 Hz, 1 H), 8.26 (d, J = 7.8 Hz, 1 H).

3-(3,3-Dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carboxylic Acid (4-Fluorobenzyl)methylamide (37). Compound **37** was prepared using the same procedure as **8**, using *N*-methyl-4-fluorobenzylamine instead of benzylamine. ESI-MS m/z 408.1 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.24 (s, 3 H), 1.53 (s, 3 H), 3.23 (br s, 3 H), 4.82 (br s, 2 H), 6.30 (s, 1 H), 7.18 (t, J = 8.7 Hz, 2 H), 7.38−7.45 (m, 4 H), 7.66 (br d, J = 7.6 Hz, 1 H), 7.70 (td, J = 7.6, 1.3 Hz, 1 H), 7.81 (td, J = 7.6, 1.4 Hz, 1 H), 8.26 (dd, J = 7.6, 1.3 Hz, 1 H).

3-(3,3-Dimethyl-1-oxoisochroman-4-yl)-3*H*-imidazole-4-carboxylic Acid (4-Fluoro)benzylamide (38). Compound **38** was prepared using the same procedure as **8**, using 4-fluorobenzylamine instead of benzylamine. ESI-MS m/z 394.3 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.23 (s, 3 H), 1.53 (s, 3 H), 4.59 (s, 2 H), 6.97 (s, 1 H), 7.07−7.19 (m, 2 H), 7.36 (s, 1 H), 7.40−7.48 (m, 2 H), 7.55 (d, J = 7.6 Hz, 1 H), 7.65−7.73 (m, 1 H), 7.75−7.82 (m, 2 H), 8.26 (d, J = 7.8 Hz, 1 H).

3,3-Dimethyl-4-[5-(3-methyl[1,2,4]oxadiazol-5-yl)imidazol-1-yl]isochroman-1-one (10). 7 (0.538 g, 1.88 mmol) was dissolved in dichloromethane (4 mL) and cooled to 0 °C. Oxalyl chloride (0.41 mL, 4.702 mmol) was added, and the cooling bath was removed. The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo. The residue obtained was redissolved in chloroform, and *N*-hydroxyacetamidine (0.181 g, 2.44 mmol) was added. The reaction mixture was stirred at reflux for 72 h. The mixture was cooled to room temperature, washed with saturated solution of sodium bicarbonate, and extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane−ethyl acetate, 3:7) to give **10** (100 mg, 16%) as a white solid; ESI-MS m/z 325.0 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.26 (s, 3 H), 1.61 (s, 3 H), 2.55 (s, 3 H), 6.94 (s, 1 H), 7.56 (d, J = 7.1 Hz, 1 H), 7.63 (s, 1 H), 7.72 (td, J = 7.6, 1.3 Hz, 1 H), 7.80 (td, J = 7.6, 1.3 Hz, 1 H), 8.01 (s, 1 H), 8.30 (dd, J = 7.8, 1.3 Hz, 1 H).

***N,N*-Diethyl-2-hydroxymethylbenzamide (47).** To a suspension of aluminum trichloride (12.67 g, 94.98 mmol) in dichloroethane (40 mL) was added diethylamine (13.5 g, 182.7 mmol) in dichloroethane (20 mL) while the temperature was maintained below 25 °C with an ice bath. After another 25 min at rt, phthalide (10.00 g, 74.5 mmol) was added in three portions and formation of a precipitate was observed. After 45 min, water and ice were added and the mixture was stirred for 30 min and filtered through Celite. The aqueous phase was extracted with dichloromethane. After drying the combined organic phase over $MgSO_4$ and filtering through a cotton plug, the volatiles were removed in vacuo to give a residue, which was purified by silica gel flash chromatography (dichloromethane−methanol, 49:1 to 97:3 to 19:1) to give **47** as a crude orange oil (12.92 g), which was used in the next step with no further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3 H, t, J = 7.0 Hz), 1.28 (3 H, t, J = 7.0 Hz), 3.24 (2 H, q, J = 7.0 Hz), 3.55 (1 H, t, J = 6.8 Hz), 3.58 (2 H, q, J = 7.0 Hz), 4.52 (2 H, d, J = 6.8 Hz), 7.24 (1 H, dd, J = 7.4, 1.5 Hz), 7.32 (1 H, td, J = 7.4, 1.5 Hz), 7.39 (1 H, td, J = 7.4, 1.5 Hz), 7.44 (1 H, td, J = 7.4, 1.5 Hz).

***N,N*-Diethyl-2-(5-iodoimidazol-1-ylmethyl)benzamide (48).** A flask was charged with dichloromethane (200 mL) and trifluoromethanesulfonic anhydride (19.34 g, 67.20 mmol) and cooled to −78 °C. A solution of diisopropylethylamine (9.57 g, 73.30 mmol) and **47** (12.92 g, 61.09 mmol) in dichloromethane (40 mL) was added over 10 min. After 30 min, a solution of 4-iodoimidazole-1-carboxylic acid *tert*-butyl ester (12.83 g, 42.76 mmol) in dichloromethane (40 mL) was added. The mixture was allowed to gradually warm overnight, and after 18 h, saturated aqueous sodium bicarbonate (100 mL) was added and the mixture was stirred vigorously for 30 min. The aqueous layer was extracted with dichloromethane. The combined organic phase was dried over $MgSO_4$, filtered through a cotton plug, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (dichloromethane−methanol, 49:1) to afford **48** (5.32 g, 32%); ESI-MS m/z 384.1 $(M + H)^+$.

***N,N*-Diethyl-2-[2-hydroxy-1-(5-iodoimidazol-1-yl)-2-methylpropyl]benzamide (49).** To a solution of diisopropylamine (0.97 g, 6.39 mmol) in THF (50 mL) at −78 °C under nitrogen was added *n*-BuLi (2.5 M in hexanes, 3.8 mL, 9.6 mmol), and the mixture was warmed to 0 °C. After 15 min, the LDA solution was cooled to −78 °C and a solution of **48** (2.45 g, 6.39 mmol) in THF (5 mL) was added over 15 min. Thirty minutes after the end of addition, acetone (1.86 g, 31.97 mmol) in THF (5 mL) was added to the brown solution and the mixture was stirred for 1 h, whereupon 10% acetic acid in water was added. The mixture was poured in ethyl acetate, and the two phases were separated. The organic phase was washed with saturated aqueous sodium bicarbonate. The combined aqueous phase was extracted twice with ethyl acetate. The combined organic phase was dried over $MgSO_4$, filtered through a cotton plug, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (elution with dichloromethane−methanol, 49:1 to 97:3 to 24:1) to afford crude **49** as a yellow solid which was used in the next step with no further purification; ESI-MS m/z 442.0 $(M + H)^+$.

4-(5-Iodoimidazol-1-yl)-3,3-dimethylisochroman-1-one (50). Dioxane (22 mL) and 1 M aqueous KOH (22 mL, 22 mmol) were added to **49** (1.65 g), and the mixture was heated to 60 °C. After 13.5 h, the mixture was cooled to 0 °C and acidified to pH 1 with conc HCl. The mixture was heated to 60 °C. After 24 h, the mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate, water, and brine, dried over magnesium sulfate, and filtered through a cotton plug. Concentration in vacuo gave an orange solid, which was purified by silica gel flash chromatography (methylene chloride−methanol, 49:1) to give **50** (1.00 g, 42%, 2 steps) as a yellow solid; ESI-MS m/z 369.0 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.30 (s, 3 H), 1.57 (s, 3 H), 5.39 (s, 1 H), 7.19 (s, 1 H), 7.28 (br d, J = 7.6 Hz, 1 H), 7.39 (s, 1 H), 7.59 (td, J = 7.6, 1.3 Hz, 1 H), 7.66 (td, J = 7.6, 1.3 Hz, 1 H), 8.27 (dd, J = 7.6, 1.4 Hz, 1 H).

4-(5-Vinylimidazol-1-yl)-3,3-dimethylisochroman-1-one (51). DMF (30 mL) was added to **50** (1.62 g, 4.18 mmol), tributylvinyltin (2.40 g, 8.36 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (0.087 g, 0.084 mmol), and triphenylphosphine (0.089 g, 0.334 mmol) under nitrogen. The mixture was heated to 90 °C to give a clear tan solution. After 3 h, the mixture was cooled down, diluted with isopropyl acetate, and washed twice with water and brine. The combined organic phase was dried over magnesium sulfate and filtered through a cotton plug. The residue was purified by silica gel flash chromatography (10 wt % silica gel/KF, elution with dichloromethane−methanol, 49:1 to 24:1) to give **51** as a yellow solid; ESI-MS m/z 269.2 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.20 (s, 3 H), 1.51 (s, 3 H), 5.42 (br s, 1 H), 5.69 (s, 1 H), 5.81 (br s, 1 H), 6.95 (br s, 1 H), 7.14 (br s, 1 H), 7.21 (s, 1 H), 7.42 (d, J = 7.6 Hz, 1 H), 7.58−7.69 (m, 1 H), 7.70−7.80 (m, 1 H), 8.21 (dd, J = 7.8, 1.3 Hz, 1 H).

(*R*)- or (*S*)- 4-(5-Ethylimidazol-1-yl)-3,3-dimethylisochroman-1-one (12). To a solution of **51** (0.049 g, 0.173 mmol) in methanol (1 mL) was added Pd/C (10 wt %, 0.009 g, 0.009 mmol), and the flask was flushed with hydrogen. The mixture was stirred under balloon pressure. After 3 h, another portion of catalyst (0.009 g) was added.

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After 7 h, the mixture was filtered and concentrated in vacuo to give 4-(5-ethylimidazol-1-yl)-3,3-dimethylisochroman-1-one as a white solid. The racemate was resolved by chiral HPLC using the ChiralPak IA column with a 9:1 hexanes−ethanol mobile phase to give **12** (60 mg, 44%) as a white solid; t_R = 23.8 min (distomer t_R = 34.3 min); ESI-MS m/z 271.2 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.25 (s, 3 H), 1.43 (br s, 3 H), 1.56 (s, 3 H), 2.87 (br s, 2 H), 5.55 (br s, 1 H), 6.83 (s, 1 H), 7.17 (br s, 1 H), 7.45 (d, J = 7.6 Hz, 1 H), 7.67 (td, J = 7.6, 1.0 Hz, 1 H), 7.78 (td, J = 7.6, 1.3 Hz, 1 H), 8.24 (dd, J = 7.6, 1.0 Hz, 1 H).

***N*,*N*-Diethyl-2-[(1-hydroxycyclobutyl)-(5-iodoimidazol-1-yl)-methyl]benzamide (75).** To a solution of diisopropylamine (0.38 g, 3.76 mmol) in THF (25 mL) at −78 °C under nitrogen was added *n*-BuLi (2.5 M in hexanes, 1.50 mL, 3.75 mmol), and the mixture was warmed to 0 °C. After 15 min, the LDA solution was cooled to −78 °C and a solution of **48** (1.00 g, 2.51 mmol) in THF (5 mL) was added over 10 min. Fifteen minutes after the end of addition, cyclobutanone (0.90 g, 12.53 mmol) in THF (2 mL) was added to the brown solution. After 1.5 h, 10% acetic acid in water was added. The organic phase was washed with saturated aqueous sodium bicarbonate, and the combined organic phase was dried over $MgSO_4$, filtered through a cotton plug, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (elution with dichloromethane−methanol, 49:1 to 97:3) to afford **75** as a crude product which was used in the next step with no further purification; ESI-MS m/z 454.2 (M + H).

[4-(5-Iodoimidazol-1-yl)isochroman-1-one]-3-spirocyclobutane (76). Dioxane (12 mL) and aqueous KOH (9 mmol) were added to crude **75** (0.61 g), and the mixture was heated to 60 °C. After 30 h, the mixture was cooled to 0 °C and acidified to pH 1 with conc HCl, and the mixture was heated to 65 °C. After 16 h, the mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate, water, and brine. The combined aqueous phase was back-extracted twice with ethyl acetate, and the combined organic phase was dried over magnesium sulfate and filtered through a cotton plug. Concentration in vacuo gave a residue which was purified by silica gel flash chromatography (methylene chloride−methanol, 49:1) to give, after trituration with chloroform, **76** (0.31 g, 32%, 2 steps) as a pale yellow foam; ESI-MS m/z 381.0 (M + H).

[4-(5-Vinylimidazol-1-yl)isochroman-1-one]-3-spirocyclobutane (77). DMF (5 mL) was added to **76** (0.31 g, 0.77 mmol), tributylvinyltin (0.46 g, 1.39 mmol), $Pd_2dba_3.CHCl_3$ (0.016 g, 0.015 mmol), and triphenylphosphine (0.016 g, 0.062 mmol) under nitrogen. The mixture was heated to 90 °C. After 6 h, the mixture was cooled down, diluted with isopropyl acetate, and washed twice with water and brine. The combined organic phase was dried over magnesium sulfate and filtered through a cotton plug. The residue was purified by silica gel flash chromatography (10 wt % KF in silica gel, elution with dichloromethane−methanol, 49:1) to give **77** (0.195 g, 90%) as a pale yellow solid; ESI-MS m/z 281.2 (M + H).

(*R*)- or (*S*)-[4-(5-Ethylimidazol-1-yl)isochroman-1-one]-3-spirocyclobutane (23). To a solution of **77** (0.193 g, 0.654 mmol) in methanol (4 mL) was added Pd/C (10 wt %, 0.035 g, 0.033 mmol), and the flask was flushed with hydrogen. The mixture was stirred under balloon pressure. After 3.5 h, the mixture was filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (elution with dichloromethane−methanol, 49:1) to give [4-(5-ethylimidazol-1-yl)isochroman-1-one]-3-spirocyclobutane (0.165 g, 89%). The racemate was resolved by chiral HPLC using the ChiralPak IA column with a 4:1 heptane−isopropanol mobile phase to give **23** as a faint yellow solid; t_R = 36.0 min (distomer t_R = 15.0 min); mp 178−179 °C; ESI-MS m/z 283.1 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.43 (t, J = 7.5 Hz, 3 H), 1.68−1.80 (m, 1 H), 2.03−2.15 (m, 3 H), 2.36−2.47 (m, 2 H), 2.71−2.86 (m, 2 H), 5.29 (s, 1 H), 6.85 (d, J = 1.3 Hz, 1 H), 7.29−7.35 (m, 1 H), 7.31 (s, 1 H), 7.56 (td, J = 7.6, 1.3 Hz, 1 H), 7.64 (td, J = 7.6, 1.5 Hz, 1 H), 8.22 (dd, J = 7.7, 1.4 Hz, 1 H).

(*R*)- or (*S*)- 4-(5-Ethylimidazol-1-yl)-3,3-diethylisochroman-1-one (22). Compound **22** was prepared from **48** following the same sequence employed to prepare **12**, using diethylketone instead of acetone. Resolution of racemate was achieved by chiral HPLC using the ChiralPak IA column with a 9:1 heptane−isopropanol mobile phase to give **22** as a white solid; t_R = 21.5 min (distomer t_R = 14.8 min); ESI-MS m/z 299.1 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.96 (t, J = 7.3 Hz, 3 H), 0.97 (t, J = 7.3 Hz, 3 H), 1.42 (t, J = 7.3 Hz, 3 H), 1.46 (masked, 1 H), 1.51 (dq, J = 14.6, 7.3 Hz, 1 H), 1.73 (dq, J = 14.6, 7.3 Hz, 1 H), 1.95 (dq, J = 14.8, 7.3 Hz, 1 H), 2.73 (q, J = 7.3 Hz, 2 H), 5.16 (s, 1 H), 6.84 (s, 1 H), 7.18 (d, J = 7.3 Hz, 1 H), 7.24 (s, 1 H), 7.50−7.56 (m, 1 H), 7.61 (dt, J = 7.3, 1.3 Hz, 1 H), 8.23 (dd, J = 7.7, 1.4 Hz, 1 H).

(*R*)- or (*S*)-[4-(5-Ethylimidazol-1-yl)isochroman-1-one]-3-spirocyclopentane (24). Compound **24** was prepared from **48** using the same sequence employed to prepare **12**, using cyclopentanone instead of acetone. Resolution of racemate was achieved by chiral HPLC using the ChiralPak IA column with a 85:15 heptane−isopropanol mobile phase to give **24** as a white solid; t_R = 31.5 min (distomer t_R = 17.7 min); ESI-MS m/z 297.1 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.39 (t, J = 7.5 Hz, 3 H), 1.61−2.05 (m, 8 H), 2.63−2.78 (m, 2 H), 5.12 (s, 1 H), 6.83 (d, J = 1.0 Hz, 1 H), 7.22 (d, J = 7.6 Hz, 1 H), 7.34 (s, 1 H), 7.54 (dt, J = 7.6, 1.3 Hz, 1 H), 7.61 (dt, J = 7.6, 1.3 Hz, 1 H), 8.22 (dd, J = 7.6, 1.3 Hz, 1 H).

[4-(5-Ethylimidazol-1-yl)isochroman-1-one]-3-spiro(4-tetrahydropyran) (25). Compound **25** was prepared from **48** using the same sequence employed to prepare **12**, using tetrahydropyran-4-one instead of acetone. ESI-MS m/z 313.1 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.36−1.45 (m, 4 H), 1.64−1.72 (m, 1 H), 1.81−1.89 (m, 2 H), 2.65−2.80 (m, 2 H), 3.79−3.95 (m, 4 H), 5.03 (s, 1 H), 6.86 (s, 1 H), 7.22 (br s, 1 H), 7.24 (d, J = 7.8 Hz, 1 H), 7.58 (dd, J = 7.6, 1.3 Hz, 1 H), 7.66 (dd, J = 7.3, 1.3 Hz, 1 H), 8.26 (dd, J = 7.7, 1.4 Hz, 1 H).

4-(5-Isopropenylimidazol-1-yl)-3,3-dimethylisochroman-1-one (52). To a solution of **50** (0.700 g, 1.90 mmol) in NMP (5 mL) was added tris(dibenzylideneacetone)dipalladium (0.196 g, 0.19 mmol) and trifuryl-2-ylphospane (0.066 g, 0.285 mmol). Tributylisopropenyltin (1.25g, 3.80 mmol) was added to the reaction mixture, and it was heated to 90 °C for 24 h. The mixture was then allowed to cool to room temperature, washed with water, and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane−methanol, 19:1) to give **52** (0.45 g, 84%) as a white solid; ESI-MS m/z 283.0 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.21 (s, 3 H), 1.50 (s, 3 H), 2.24 (br s, 3 H), 5.31 (br s, 1 H), 5.56 (br s, 1 H), 5.73 (s, 1 H), 7.02 (br s, 1 H), 7.28 (br s, 1 H), 7.51 (d, J = 7.8 Hz, 1 H), 7.69 (td, J = 7.8, 1.0 Hz, 1 H), 7.81 (td, J = 7.6, 1.3 Hz, 1 H), 8.25 (d, J = 7.8 Hz, 1 H).

(*R*)- or (*S*)-4-(5-Isopropylimidazol-1-yl)-3,3-dimethylisochroman-1-one (13). To a solution of **52** (0.225 g, 0.797 mmol) in methanol (5 mL) was added 10% Pd/C (0.225 g). The reaction vessel was flushed with hydrogen gas and stirred under balloon pressure for 72 h. The mixture was filtered and the filtrate concentrated in vacuo to give a 4-(5-isopropylimidazol-1-yl)-3,3-dimethylisochroman-1-one (0.210 g) as a yellow solid. Resolution of the racemate was achieved by chiral HPLC using the ChiralPak IA column with a 9:1 heptane−isopropanol mobile phase to give **13**; t_R = 13.7 min (distomer t_R = 11.3 min); ESI-MS m/z 285.0 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.24 (s, 3 H), 1.41 (d, J = 6.6 Hz, 3 H), 1.45 (d, J = 6.8 Hz, 3 H), 1.56 (s, 3 H), 3.23 (br s, 1 H), 5.60 (br s, 1 H), 6.88 (br s, 1 H), 7.15 (br s, 1 H), 7.44 (d, J = 7.3 Hz, 1 H), 7.68 (td, J = 7.6, 1.1 Hz, 1 H), 7.79 (td, J = 7.6, 1.3 Hz, 1 H), 8.25 (dd, J = 7.8, 1.3 Hz, 1 H).

2-Imidazol-1-ylmethylbenzonitrile (53a). To a solution of imidazole (1.0 g, 14.6 mmol) in DMF (10 mL) was added sodium hydride (60% wt in mineral oil, 0.887 g, 22.17 mmol) at room temperature. The mixture was stirred for 30 min, whereupon 2-cyanobenzyl bromide (2.87 g, 14.6 mmol) was added. After an additional 30 min, water was added and the mixture was extracted with ethyl acetate. The aqueous phase was poured into aqueous sodium bicarbonate and extracted with dichloromethane. The combined organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo to give a residue which was purified by silica gel

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chromatography (dichloromethane−methanol, 19:1) to give **53a** (1.1 g, 41%); ESI-MS *m/z* 184.3 (M + H).

2-(2-Hydroxy-1-imidazol-1-yl-2-methylpropyl)benzonitrile (54a). **53a** (1.0 g, 5.49 mmol) was dissolved in THF (10 mL) and cooled to −75 °C. LHMDS (1 M in THF, 8.24 mL, 8.24 mmol) was added dropwise. Ten minutes after the end of addition, acetone (0.48 g, 8.24 mmol) was added. Thirty minutes after the end of addition, saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was allowed to warm to rt, then poured into water. After extraction with ethyl acetate, the organic phase was dried over Na_2SO_4 and concentrated in vacuo to give **54a** (1.75 g), which was used in the next step without further purification; ESI-MS *m/z* 242.1 (M + H).

(*R*)- or (*S*)-4-(Imidazol-1-yl)-3,3-dimethylisochroman-1-one (11). Crude **54a** (1.75 g) was dissolved in dioxane (15 mL) and water (15 mL). Sulfuric acid (1.5 mL, 29.0 mmol) was added, and the mixture was stirred at reflux for 2 h. After cooling down, the pH was adjusted with solid sodium bicarbonate. The mixture was extracted with ethyl acetate, and the combined organic phase was washed with water, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane−methanol, 19:1) to give 4-(imidazol-1-yl)-3,3-dimethylisochroman-1-one (780 mg, 58%, 2 steps). Resolution of the racemate was achieved by chiral HPLC using the ChiralPak AS-H column with a 9:1 heptane−ethanol mobile phase to give **11**; t_R = 10.1 min (distomer t_R = 16.6 min); ESI-MS *m/z* 242.9 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.30 (s, 3 H), 1.53 (s, 3 H), 5.76 (s, 1 H), 6.98 (s, 1 H), 7.09 (s, 1 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 7.64−7.73 (m, 1 H), 7.76−7.85 (m, 1 H), 7.89 (s, 1 H), 8.25 (dd, *J* = 7.7, 1.4 Hz, 1 H).

(*R*)- or (*S*)-7-Fluoro-4-imidazol-1-yl-3,3-dimethylisochroman-1-one (26). Compound **26** was prepared following the same procedure as **11**, using 2-cyano-4-fluorobenzyl bromide instead of 2-cyanobenzyl bromide. Resolution of the racemate was achieved by chiral HPLC using the Chiralcel OD column with a 9:1 hexanes−ethanol mobile phase to give **26**; t_R = 13.6 min (distomer t_R = 17.4 min); ESI-MS *m/z* 261.3 $(M + H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.28 (s, 3 H), 1.53 (s, 3 H), 5.74 (s, 1 H), 6.91 (s, 1 H), 7.03 (s, 1 H), 7.43−7.61 (m, 2 H), 7.77 (s, 1 H), 7.93 (dd, *J* = 8.3, 2.3 Hz, 1 H).

(3*R*,4*R*)- or (3*S*,4*S*)-4-Imidazol-1-yl-3-phenylisochroman-1-one (39) and (3*R*,4*S*) and (3*S*,4*R*) Isomers. **53** (0.84 g, 4.36 mmol) was dissolved in THF (40 mL) and cooled to −78 °C. LHMDS (1.0 M in THF, 15.2 mL, 15.2 mmol) was added, followed after 10 min with benzaldehyde (2.10 g, 19.60 mmol). After 1 min, the reaction was quenched with 1 M aqueous sodium hydrogen sulfate. The pH was adjusted to 12 with 4 M aqueous sodium hydroxide and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a residue, which was purified by silica gel flash chromatography (dichloromethane−methanol, 1:0 to 23:1 gradient) to give after concentration of the fractions a yellow residue (1.40 g), which was redissolved in dioxane (40 mL). 10 M aqueous H_2SO_4 (2.2 mL, 22 mmol) was added. The mixture was heated to 90 °C. After overnight stirring, the mixture was diluted with ethyl acetate and washed with saturated aqueous bicarbonate and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a gum (1.12 g). Purification and resolution of the four isomers of 4-imidazol-1-yl-3-phenylisochroman-1-one was achieved by chiral HPLC using the ChiralPak OD-RH column with a 7:3 heptane−ethanol mobile phase to give **39** (0.131 g, 10%); t_R = 14.0 min (distomer t_R = 16.7 min); ESI-MS *m/z* 291.0 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.06 (d, *J* = 2.9 Hz, 1 H), 6.29 (d, *J* = 2.9 Hz, 1 H), 6.59 (s, 1 H), 6.72 (s, 1 H), 7.09 (s, 1 H), 7.16−7.22 (m, 2 H), 7.28−7.34 (m, 3 H), 7.60 (d, *J* = 7.1 Hz, 1 H), 7.71 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.81 (td, *J* = 7.6, 1.5 Hz, 1 H), 8.19 (dd, *J* = 7.8, 1.3 Hz, 1 H). The two enantiomers of the trans diastereomer eluted as third (t_R = 23.2 min) and fourth peaks (t_R = 43.2 min); ESI-MS *m/z* 291.0 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.19 (d, *J* = 10.5 Hz, 1 H), 6.36 (d, *J* = 10.5 Hz, 1 H), 6.70 (d, *J* = 7.8 Hz, 1 H), 6.91 (s, 1 H), 7.19 (t, *J* = 1.3 Hz, 1 H), 7.30−7.36 (m, 3 H), 7.37−7.44 (m, 2 H), 7.56−7.64 (m, 2 H), 7.72 (td, *J* = 7.6, 1.4 Hz, 1 H), 8.10 (dd, *J* = 7.7, 1.1 Hz, 1 H).

2,2-Dimethylindan-1,3-dione (56). Potassium fluoride on Celite (50% wt, 24 g, 210 mmol) was heated at 135 °C for 2 h under vacuum (<20 Torr). The solid was then permitted to cool to room temperature and placed under a nitrogen atmosphere at which time a solution of indan-1,3-dione (6.11 g, 42 mmol) in acetonitrile (60 mL) was added followed by iodomethane (7.9 mL, 126 mmol). The reaction was heated in a sealed vessel at 70 °C overnight. The reaction mixture was cooled to room temperature and filtered through a pad of Celite. The resulting residue was purified by silica gel flash chromatography (ethyl acetate−heptane, 0:1 to 1:9) to give **56** (6.11 g, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.30 (s, 6 H), 7.84−7.89 (m, 2 H), 7.96−8.02 (m, 2 H).

3-Hydroxy-2,2-dimethylindan-1-one (57). To a solution of **56** (430 mg, 2.47 mmol) in ethanol (80 mL) at −30 °C was added a solution of $NaBH_4$ (29 mg, 0.74 mmol) in ethanol (3 mL). After 1 h the reaction was quenched with saturated aqueous NH_4Cl and the mixture was brought to room temperature. The reaction mixture was concentrated to approximately half of its original volume and then diluted with ethyl acetate and washed with water. The aqueous layer was then back-extracted twice with ethyl acetate. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (ethyl acetate−heptane, 0:1 to 1:6) to afford **57** (320 mg, 74%); ESI-MS *m/z* 177.0 $(M + H)^+$.

(*R*)- or (*S*)-3-Imidazol-1-yl-2,2-dimethylindan-1-one (31). To a solution of trifluoromethansulfonic anhydride (1.13 mL, 6.75 mmol) in dichloromethane (10 mL) at −78 °C was added, via cannula, a solution of diisopropylethylamine (1.8 mL, 10.1 mmol) and **57** (400 mg, 2.25 mmol) in dichloromethane (5 mL). The reaction was stirred at −78 °C for 10 min and then was placed at −10 °C for 10 min. The reaction was then recooled to −78 °C, and a solution of imidazole (920 mg, 13.5 mmol) in dichloromethane (12 mL) was added via cannula. The reaction was then placed at room temperature for 1 h, at which time it was diluted with saturated aqueous $NaHCO_3$ and ethyl acetate. The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (ethyl acetate−dichloromethane, 1:3 to 1:0) to afford 3-imidazol-1-yl-2,2-dimethylindan-1-one (318 mg, 62%). The resolution of the racemate was achieved by chiral HPLC using a ChiralPak IA column with 4:1 heptane−ethanol to give **31**; t_R = 5.8 min (other enantiomer t_R = 7.7 min); ESI-MS *m/z* 227 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.80 (s, 3 H), 1.41 (s, 3 H), 5.52 (s, 1 H), 6.73 (s, 1 H), 7.12 (s, 1 H), 7.51 (d, *J* = 7.6 Hz, 1 H), 7.56 (s, 1 H), 7.62 (t, *J* = 7.5 Hz, 1 H), 7.70−7.80 (m, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H).

4-Imidazol-1-yl-3,3-dimethyl-3,4-dihydro-2*H*-isoquinolin-1-one (60). To a solution of racemic **31** (350 mg, 1.55 mmol) in methanol (19 mL) were added pyridine (1.6 mL, 19.6 mmol) and then hydroxylamine hydrochloride (270 mg, 3.9 mmol). The reaction was stirred at 55 °C for 14 h and then cooled to room temperature. The reaction was concentrated in vacuo to approximately half of the original volume. The mixture was then diluted with ethyl acetate and 50% saturated aqueous NaCl. The layers were separated, and the aqueous layer was extracted two additional times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was dissolved in pyridine (10 mL) and placed at 0 °C. DMAP (6 mg, 0.05 mmol) and *p*-toluenesulfonyl chloride (615 mg, 3.22 mmol) were added, and the mixture was stirred at room temperature for 1 h. The reaction was then warmed to 50 °C and stirred for 14 h. The reaction was then cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ and ethyl acetate. The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. From the resulting residue 293 mg was dissolved in pyridine (11 mL) and heated by microwave irradiation at 190 °C for 35 min in a sealed vessel. The reaction was cooled to room temperature, quenched with saturated aqueous $NaHCO_3$, and diluted with ethyl acetate. The mixture was then dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography

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(methanol−dichloromethane, 0:1 to 1:10) to provide **60** (47 mg, 27%) (52% BORSM); HRESI-MS *m/z* 242.1293 [(M + H)$^+$, calcd for $C_{14}H_{16}N_3O$, 242.1293]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.15 (s, 3 H), 1.40 (s, 3 H), 5.09 (s, 1 H), 5.73 (br s, 1 H), 6.82 (s, 1 H), 7.04 (s, 1 H), 7.21−7.26 (m, 1 H), 7.50−7.60 (m, 3 H), 8.17−8.26 (m, 1 H).

(*R*)- or (*S*)-4-Imidazol-1-yl-2,3,3-trimethyl-3,4-dihydro-2*H*-isoquinolin-1-one (27). To a solution of **60** (140 mg, 0.58 mmol) in DMF (8 mL) at −10 °C was added NaH (60% dispersion in oil, 30 mg, 0.75 mmol). After 10 min, the reaction was warmed to room temperature for 5 min and then recooled to −10 °C. The reaction was then charged with methyl iodide (0.075 mL, 1.2 mmol) and placed at room temperature. After 20 min, the reaction was cooled to −10 °C, quenched with saturated aqueous NH_4Cl, and diluted with saturated aqueous $NaHCO_3$ and ethyl acetate. The layers were separated, and the aqueous layer was extracted two times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (methanol−dichloromethane, 0:1 to 1:12) to afford 4-imidazol-1-yl-2,3,3-trimethyl-3,4-dihydro-2*H*-isoquinolin-1-one (110 mg, 75%). The resolution of the racemate was achieved by chiral HPLC using a ChiralPak AS-H column with 85:15 heptanes−reagent alcohol to give **27**; t_R = 10.9 min (distomer t_R = 22.9 min); HRESI-MS *m/z* 256.1448 [(M + H)$^+$, calcd for $C_{15}H_{18}N_3O$, 256.1450]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.22 (s, 3 H), 1.33 (s, 3 H), 3.09 (s, 3 H), 5.01 (s, 1 H), 6.78 (s, 1 H), 7.02 (s, 1 H), 7.20 (d, *J* = 3.8 Hz, 1 H), 7.47−7.57 (m, 3 H), 8.20−8.28 (m, 1 H).

(*R*)- or (*S*)-4-Imidazol-1-yl-3,3-dimethyl-3,4-dihydro-1*H*-quinolin-2-one (28). 1-Methoxy-1-(trimethylsiloxy)-2-methyl-1-propene (10.4 g, 60 mmol) was added to a suspension of 2-nitrobenzaldehyde (6.0 g, 40 mmol), scandium(III) trifluoromethanesulfonate (1.0 g, 2.0 mmol) in DCM (150 mL) at −78 °C. The resulting mixture was warmed to 0 °C over 3 h, quenched with 1 M aqueous HCl, and stirred at room temperature for 1 h. The mixture was extracted with ethyl acetate, and the combined organic fraction was washed with brine, dried over Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel flash chromatography to give a yellow oil (7.0 g). A portion (6.55 g) was redissolved in methanol (100 mL). Palladium on carbon (10%, 650 mg) was added, and the mixture was stirred for 5 h under hydrogen at balloon pressure. The mixture was then filtered through a pad of Celite, which was washed with methanol. After concentration the residue was washed with ether to give a solid (4.23 g). A portion (0.20 g, 1.06 mmol) and CDI (0.20 g, 1.27 mmol) were dissolved in acetonitrile (4 mL) and heated to reflux for 3 h. Two additional portions of CDI (69 mg, 0.43 mmol) were added. After another 2 h, the solvent was removed in vacuo. The residue was taken up in dichloromethane and washed with water. The organic phase was dried over Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel flash chromatography (dichloromethane−methanol, 1:0 to 97:3) to give a colorless solid (0.12 g, 46%). The resolution of the racemate was achieved by chiral HPLC using a ChiralPak AS-H column with 9:1 heptane−ethanol to give **28**; t_R = 18.4 min (distomer t_R = 22.5 min); ESI-MS *m/z* 242.1288 [(M + H)$^+$, calcd for $C_{14}H_{15}N_3O$, 242.1293]; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.70 (s, 1 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.10−7.03 (m, 2H), 6.95 (s, 2 H), 5.30 (s, 1 H), 1.26 (s, 3 H), 1.02 (s, 3 H).

(*R*)- or (*S*)-1-(2,2-Dimethyl-2,3-dihydrobenzofuran-3-yl)-1*H*-imidazole (29). To a solution of **64** (260 mg, 1.58 mmol) in acetonitrile (5 mL) was added 1,1′-carbonyldiimidazole (310 mg, 1.90 mmol). The mixture was then heated at reflux overnight. The reaction was cooled to room temperature and concentrated. The resulting residue was dissolved in dichloromethane and washed with saturated aqueous $NaHCO_3$ and brine. The organic solution was dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (ethyl acetate−dichloromethane, 0:1 to 4:1) to furnish 1-(2,2-dimethyl-2,3-dihydrobenzofuran-3-yl)-1*H*-imidazole (176 mg, 52%). Resolution of the racemate was achieved by chiral HPLC using a ChiralPak IA column with 9:1 heptane−ethanol to give **29**; t_R = 13.0 min (distomer t_R = 15.0 min); HRESI-MS *m/z* 215.1187 [(M + H)$^+$, calcd for $C_{13}H_{14}N_2O$, 215.1184]. The HCl salt of **29** was prepared by dissolution in diethyl ether, followed by treatment with an excess of 1 N HCl in diethyl ether and removal of the volatiles in vacuo; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.17 (s, 3 H), 1.55 (s, 3 H), 5.90 (s, 1 H), 6.99 (d, *J* = 8.08 Hz, 1 H), 7.06 (t, *J* = 7.58 Hz, 1 H), 7.25 (s, 1 H), 7.40 (d, *J* = 7.58 Hz, 1 H), 7.42−7.49 (m, 1 H), 7.59 (s, 1 H), 8.81 (s, 1 H).

(*R*)- and (*S*)-1-(2,2-Dimethylindan-1-yl)-1*H*-imidazole (32). Compound **32** was prepared using the same procedure as **29**. Starting from **63** (1.0 g, 6.16 mmol), 1-(2,2-dimethylindan-1-yl)-1*H*-imidazole (0.82 g, 63%) was obtained. Resolution of the racemate was achieved by chiral HPLC using a ChiralPak IA column with 1:4 isopropanol−heptane to give **32**; t_R = 13.7 min (distomer t_R = 15.9 min); ESI-MS *m/z* 213.2 (M + H)$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.75 (s, 3 H), 1.28 (s, 3 H), 2.70−3.03 (m, 2 H), 5.19 (s, 1 H), 6.73 (s, 1 H), 7.07 (s, 1 H), 7.15−7.38 (m, 4 H), 7.46 (s, 1 H);

3-(2,2-Dimethyl-3-oxoindan-1-yl)-3*H*-imidazole-4-carboxylic Acid Methyl Ester (66). To a solution of **57** (3.22 g, 18.3 mmol) in THF (40 mL) were added methyl 4-imidazolecarboxylate (3.22 g, 21.9 mmol) and triphenylphosphine (3.56 g, 13.6 mmol) .The reaction was cooled to 0 °C, and di-*tert*-butyl azodicarboxylate (5.74 g, 21.9 mmol) was added. The reaction was placed at room temperature and permitted to stir for 3 h. The reaction mixture was cooled to 0 °C and quenched with 4 N HCl in dioxane and stirred for 30 min. The reaction was concentrated to near dryness and diluted with ethyl acetate. The organic layer was extracted three times with 1 N aqueous HCl. The aqueous extracts were combined, neutralized with Na_2CO_3, and extracted three times with ethyl acetate. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (ethyl acetate−dichloromethane, 0:1 to 3:7) to furnish **66** (4.02 g, 77%); ESI-MS *m/z* 285.1246 [(M + H)$^+$, calcd for $C_{16}H_{16}N_2O_3$, 285.1239]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.82 (s, 3 H), 1.46 (s, 3 H), 4.02 (s, 3 H), 6.70 (s, 1 H), 7.39 (s, 1 H), 7.47−7.52 (m, 1 H), 7.72 (t, *J* = 7.45 Hz, 1 H), 7.79−7.86 (m, 1 H), 7.93−7.99 (m, 2 H).

***cis*- and *trans*-3-(5-Hydroxymethylimidazol-1-yl)-2,2-dimethylindan-1-ol (68).** To a solution of **66** (4.02 g, 14.1 mmol) in THF (200 mL) at 0 °C was added $LiAlH_4$ (800 mg, 21.2 mmol). The reaction was permitted to stir for 30 min, at which time it was quenched at 0 °C by the consecutive addition of 9:1 THF−H_2O (12 mL), 2 M aqueous NaOH (15 mL), and H_2O (9 mL). The reaction was warmed to room temperature and diluted with THF (100 mL). After addition of $MgSO_4$ (20 g), the heterogeneous mixture was stirred for 15 min and then filtered through a pad of Celite. The pad of Celite was washed with ethyl acetate and the combined filtrate was concentrated to afford an approximately 5.5:1 diastereomeric mixture of **68** (3.8 g) which was used with no further purification; ESI-MS *m/z* 259.0 (M + H)$^+$; ^{1}H NMR (400 MHz, CD_3OD) major diastereomer, δ ppm 0.77 (s, 3 H), 1.25 (s, 3 H), 4.69 (s, 1 H), 4.73 (s, 2 H), 5.43 (s, 1 H), 6.96 (br s, 1 H), 7.18 (d, *J* = 7.6 Hz, 1 H), 7.30−7.57 (m, 4 H); minor diastereomer, δ ppm 0.82 (s, 3 H), 1.14 (s, 3 H), 4.73 (s, 2 H), 4.97 (s, 1 H), 5.59 (s, 1 H), 6.96 (br s, 1 H), 7.23 (d, *J* = 7.3 Hz, 1 H), 7.31−7.57 (m, 4 H).

3-[5-(*tert*-Butyldimethylsilanyloxymethyl)imidazol-1-yl]-2,2-dimethylindan-1-one (70). To a solution of **68** (3.8 g, 14.1 mmol) in DMF (150 mL) was added imidazole (1.05 g, 15.5 mmol), and the reaction was cooled to −20 °C. Then a solution of *tert*-butyldimethylsilyl chloride (2.12 g, 14.1 mmol) in DMF (10 mL) was added. The reaction was allowed to warm to room temperature overnight. The next morning the reaction was concentrated to near dryness and diluted with water and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated to give 3-[5-(*tert*-butyldimethylsilanyloxymethyl)-imidazol-1-yl]-2,2-dimethylindan-1-ol (6.8 g), which was taken up in 1,4-dioxane (120 ml), and manganese(IV) oxide (24.5 g, 282 mmol) was added. The reaction was then heated at 100 °C for 1 h, cooled to room temperature, filtered, and concentrated. The residue was purified by silica gel chromatography (ethyl acetate−dichloromethane, 0:1 to 1:0) to afford **70** (4.35 g, 83%); ESI-MS *m/z* 371.1 (M + H)$^+$.

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(*R*)- or (*S*)- 3-(5-Hydroxymethylimidazol-1-yl)-2,2-dimethylindan-1-one (33). To **70** (370 mg, 1 mmol) was added 4 N HCl in 1,4-dioxane (20 mL). The reaction was permitted to stir for 2 h, at which time it was quenched with saturated aqueous $NaHCO_3$ and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (methanol−dichloromethane, 0:1 to 1:20) to furnish 3-(5-hydroxymethylimidazol-1-yl)-2,2-dimethylindan-1-one (150 mg, 58%). The resolution of the racemate was achieved by chiral HPLC using a ChiralPak IA column with 85:15 heptane−ethanol to give **33**; t_R = 13.6 min (distomer t_R = 15.7 min); ESI-MS *m/z* 257.1295 [(M + H)$^+$, calcd for $C_{15}H_{17}N_2O_2$, 257.1290]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.87 (s, 3 H), 1.46 (s, 3 H), 4.69−4.97 (m, 2 H), 5.93 (s, 1 H), 7.16 (s, 1 H), 7.19 (s, 1 H), 7.54 (d, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 7.5 Hz, 1 H), 7.72−7.82 (m, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H).

(*R*)- or (*S*)- 6-Chloro-3-(5-hydroxymethylimidazol-1-yl)-2,2-dimethylindan-1-one (34). To a solution of **67**, which can be prepared starting from 5-chloroindanone as described for **66** (740 mg, 2.3 mmol) in THF (25 mL) at 0 °C was added lithium aluminum hydride (140 mg, 3.68 mmol) in three portions. The reaction was permitted to stir for 30 min, at which time it was quenched at 0 °C by the consecutive addition of 9:1 THF−H_2O (2.0 mL), 2 M aqueous NaOH (2.3 mL), and H_2O (1.5 mL). The reaction was warmed to room temperature and diluted with THF (15 mL). After addition of $MgSO_4$ (2.2 g), the heterogeneous mixture was stirred for 15 min and then filtered through a pad of Celite. The pad of Celite was washed with ethyl acetate, and the combined filtrate was concentrated. The resulting residue was dissolved in DMF (25 mL) and cooled to 0 °C. To the resulting solution was added imidazole (290 mg, 4.26 mmol) followed by TBSCl (425 mg, 2.8 mmol). The reaction was placed at room temperature and permitted to stir for 2.5 h. The reaction was quenched with ethanol, concentrated to near dryness, and diluted with saturated aqueous $NaHCO_3$ and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (ethyl acetate−heptane, 1:4 to 1:0) to provide 3-[5-(*tert*-butyldimethylsilanyloxymethyl)imidazol-1-yl]-6-chloro-2,2-dimethylindan-1-ol as a diastereomeric mixture; ESI-MS*m/z* 407.2 (M + H)$^+$. The alcohol (400 mg) was dissolved in 1,4-dioxane (15 mL), and manganese(IV) oxide (2.0 g, 20 mmol) was added. The resulting heterogeneous solution was heated at 80 °C for 60 min, cooled to room temperature, filtered, and concentrated. The resulting residue was then dissolved in methanol, cooled to 0 °C, and treated with 4 N hydrochloric acid in 1,4-dioxane (1 mL, 4.0 mmol). The reaction was placed at room temperature and permitted to stir for 3 h, at which time the reaction was cooled to 0 °C and diluted with saturated aqueous $NaHCO_3$. The reaction mixture was then concentrated in vacuo to approximately one-fourth of the original volume and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted two times with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (ethanol−ethyl acetate, 0:1 to 1:10) to furnish 6-chloro-3-(5-hydroxymethylimidazol-1-yl)-2,2-dimethylindan-1-one (250 mg, 37%). Resolution of the racemate was achieved by chiral HPLC using a ChiralPak IA column with 85:15 heptane−ethanol to give **34**; t_R = 8.4 min (distomer t_R = 13.0 min); ESI-MS *m/z* 291.0891 [(M + H)$^+$, calcd for $C_{15}H_{16}N_2O_2Cl$, 291.0900]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.87 (s, 3 H), 1.44 (s, 3 H), 1.89 (br s, 1 H), 4.70−4.92 (m, 2 H), 5.75 (s, 1 H), 6.92 (s, 1 H), 7.07 (s, 1 H), 7.41 (d, *J* = 8.1 Hz, 1 H), 7.69 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.87 (d, *J* = 2.0 Hz, 1 H).

Acetic Acid 4-Chloro-3-hydroxy-2,2-dimethylindan-1-yl Ester (73). To a solution of 7-chloro-3-hydroxy-2,2-dimethylindan-1-one (287 mg, 1.36 mmol) in dichloromethane (15 mL) were added pyridine (1.1 mL, 13.6 mmol) and acetic anhydride (0.26 mL, 2.72 mmol). The reaction was permitted to stir for 1 h and was then diluted with water and extracted twice with dichloromethane. The combined organic extracts were washed successively with 4 N aqueous HCl and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was then diluted with ethanol (10.0 mL) and cooled to −10 °C. The solution was then charged with a solution of $NaBH_4$ (100 mg, 2.63 mmol) in ethanol (6 mL). The reaction was permitted to warm to room temperature over 1 h, at which time additional $NaBH_4$ (50 mg, 1.31 mmol) was added. The reaction was permitted to stir for another 1.5 h and then diluted with saturated aqueous NH_4Cl. The reaction mixture was concentrated to remove the organic volatiles and then extracted three times with ethyl acetate. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (ethyl acetate−heptane, 0:1 to 1:2) to give **73** (235 mg, 70%); ESI-MS *m/z* 237.17 (M−OH)$^+$

3-(3-Acetoxy-7-chloro-2,2-dimethylindan-1-yl)-3*H*-imidazole-4-carboxylic Acid Methyl Ester (74). To a solution of **73** (1.55 g, 6.1 mmol) in THF (30 mL) were added methyl 4-imidazolecarboxylate (1.53 g, 12.2 mmol) and triphenylphosphine (3.2 g, 12.2 mmol). The reaction was cooled to 0 °C, and di-*tert*-butyl azodicarboxylate (2.81 g, 12.2 mmol) was added. The reaction was placed at room temperature and permitted to stir for 12 h and then was heated to 40 °C for 1.5 h. The reaction mixture was cooled to 0 °C, quenched with 4 N HCl in dioxane (20 mL, 80 mmol), and stirred for 30 min. The reaction was concentrated to near dryness and diluted with ethyl acetate. The organic layer was extracted three times with 1 N aqueous HCl. The aqueous extracts were combined, neutralized with Na_2CO_3, and extracted three times with ethyl acetate. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (ethyl acetate−dichloromethane, 0:1 to 1:3) to give **74** (1.4 g, 63%); ESI-MS *m/z* 332.04 (M + H)$^+$.

(*R*)- or (*S*)- 4-Chloro-3-(5-hydroxymethylimidazol-1-yl)-2,2-dimethylindan-1-one (35). To a solution of **74** (1.4 g, 3.86 mol) in THF (30 mL) at 0 °C was added lithium aluminum hydride (290 mg, 7.71 mmol) in three portions. The reaction was permitted to stir for 30 min, at which time it was quenched at 0 °C by the consecutive addition of 9:1 THF−H_2O (4.0 mL), 2 M aqueous NaOH (4.5 mL), and H_2O (3.0 mL). The reaction was warmed to room temperature and diluted with THF (30 mL). $MgSO_4$ (4.5 g) was then added, and the resulting heterogeneous mixture was stirred for 15 min and then filtered through a pad of Celite. The pad of Celite was washed with ethyl acetate, and the combined filtrate was concentrated. The resulting residue was dissolved in DMF (30 mL) and cooled to 0 °C. To the resulting solution was added imidazole (350 mg, 5.1 mmol) followed by TBSCl (640 mg, 4.24 mmol). The reaction was placed at room temperature and permitted to stir for ∼15 h. The reaction was then quenched with ethanol, concentrated to near dryness, and diluted with saturated aqueous $NaHCO_3$ and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated. The resulting residue was dissolved in 1,4-dioxane (30 mL), and manganese(IV) oxide (7.5 g, 75 mmol) was added. The resulting heterogeneous solution was heated at 110 °C for 90 min, cooled to room temperature, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (ethyl acetate−heptane, 0:1 to 1:4) to afford 3-[5-(*tert*-butyldimethylsilanyloxymethyl)imidazol-1-yl]-4-chloro-2,2-dimethylindan-1-one; ESI-MS *m/z* 405.11 (M + H)$^+$. To a solution of 3-[5-(*tert*-butyldimethylsilanyloxymethyl)imidazol-1-yl]-4-chloro-2,2-dimethylindan-1-one (2.4 g, 5.9 mmol) in methanol (40 mL) was added a 4 N solution of HCl in 1,4-dioxane (9 mL, 36 mmol). The reaction was permitted to stir for 30 min, at which time the reaction was cooled to 0 °C and diluted with saturated aqueous $NaHCO_3$. The reaction mixture was then concentrated in vacuo to approximately one-fourth of the original volume and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted two times with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (methanol−dichloromethane, 0:1 to 1:19) to give 4-chloro-3-(5-hydroxymethylimidazol-1-yl)-2,2-dimethylindan-1-

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one (1.34 g, 81%). Resolution of the racemate was achieved by chiral HPLC using a ChiralPak IA column with 90:10 heptane−ethanol to give **35**; t_R = 12.0 min (distomer t_R = 18.2 min); HRESI-MS m/z 291.0909 [$(M + H)^+$, calcd for $C_{15}H_{16}N_2O_2Cl$, 291.0909]; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 0.91 (s, 3 H), 1.40 (s, 3 H), 4.80 (d, J = 4.29 Hz, 2 H), 5.88 (s, 1 H), 6.89 (s, 1 H), 6.97 (s, 1 H), 7.69 (t, J = 7.71 Hz, 1 H), 7.79−7.87 (m, 2 H).

Acetic Acid 2,2-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl Ester (80). To a suspension of 60% NaH in an oil dispersion (20 g, 500 mmol) in THF (600 mL) at 0 °C was added a solution of α-tetralone (24.8 g, 166.5 mmol) in THF (40 mL) via cannula, followed by iodomethane (119 g, 833 mmol). The reaction was permitted to warm to room temperature and after 1 h was quenched with 1 M aqueous sodium bisulfate. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated. The resulting residue was then dissolved in methanol (600 mL) and dichloromethane (100 mL). Sodium borohydride (37.8 g, 262 mmol) was then added in five portions over 20 min. After 1 h the reaction was diluted with water, and the organic solvents were then evaporated in vacuo. The resulting mixture was extracted with ethyl acetate, and the organic extract was dried with magnesium sulfate, filtered, and concentrated. The resulting residue was then dissolved in dichloromethane (300 mL). To the resulting solution was added triethylamine (50 g, 490 mmol) and 4-dimethylaminopyridine (4 g, 33 mmol). The reaction was cooled to 0 °C and charged with acetic anhydride (42 g, 408 mmol). The reaction was permitted to stir for 10 min, then was diluted with ethyl acetate and washed with 1 M aqueous $NaHSO_4$, followed by saturated aqueous $NaHCO_3$. The organic phase was dried with magnesium sulfate, filtered, and concentrated. The resulting oil was then purified by distillation (110 °C at 0.2 Torr) to give **80** (34.6 g, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.95 (s, 3 H), 1.01 (s, 3 H), 1.50−1.63 (m, 1 H), 1.84−1.99 (m, 1 H), 2.10 (s, 3 H), 2.76−2.94 (m, 2 H), 5.74 (s, 1 H), 7.08−7.31 (m, 4 H).

Acetic Acid 2,2-Dimethyl-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl Ester (81). To a solution of **80** (380 mg, 1.71 mmol) in 1,2-dichloroethane (7 mL) was added dirhodium(II) tetrakis-(caprolactam) [$Rh_2(cap)_4$, CAS no. 138984-26-6] (15 mg, 0.017 mmol) followed by a 5.5 M decane solution of *tert*-butyl hydroperoxide [TBHP] (3.1 mL, 17.1 mmol). The reaction mixture was placed at 40 °C. After 4 h the reaction was charged with additional $Rh_2(cap)_4$ (7.5 mg, 0.008 mmol) and TBHP (1.55 mL, 8.53 mmol). After stirring at 40 °C for an additional 20 h, the reaction mixture was charged again with $Rh_2(cap)_4$ (7.5 mg, 0.008 mmol) and TBHP (1.55 mL, 8.53 mmol). After a total of 48 h the reaction was cooled to room temperature, diluted with water, and extracted twice with dichloromethane. The organic extracts were then treated with 1.6 M aqueous $FeSO_4$, and the resulting biphasic solution was permitted to stir for 30 min, at which time the layers were separated and the organic layer was dried with magnesium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel flash chromatography (ethyl acetate−hexanes, 1:9 to 1:4) to provide **81** (0.32 g, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.04 (s, 3 H), 1.09 (s, 3 H), 2.14 (s, 3 H), 2.45−2.53 (m, 1 H), 2.85 (d, J = 17.2 Hz, 1 H), 5.94 (s, 1 H), 7.38−7.49 (m, 2 H), 7.54−7.64 (m, 1 H), 8.05 (dd, J = 7.7, 1.4 Hz, 1 H).

(*R*)- or (*S*)-3-(2,2-Dimethyl-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)-3*H*-imidazole-4-carboxylic Acid Methyl Ester (65). To a solution of **81** (4.03 g, 16.7 mmol) in methanol (50 mL) and dichloromethane (10 mL) was added potassium carbonate (2.33 g, 16.66 mmol). The reaction was permitted to stir for 8 h at which time it was diluted with ethyl acetate, and the resulting solution was washed successively with water and brine. The aqueous phases were then back-extracted with dichloromethane and the organic phases were then combined, dried over magnesium sulfate, filtered, and concentrated to furnish 4-hydroxy-3,3-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one, which was used in the next step with no further purification. To a portion (2.87 g, 13.88 mmol) and methyl 4-imidazolecarboxylate (1.25 g, 9.72 mmol) in THF (80 mL) at 0 °C were added triphenylphosphine (3.68 g, 13.88 mmol) and dimethyl azodicarboxylate (40% in toluene, 5.14 mL, 13.88 mmol), and the cooling bath was removed. After 15 h, the mixture was concentrated and the resulting residue was dissolved in ethyl acetate (250 mL) and was extracted five times with 1 M aqueous HCl (40 mL portions). The acidic aqueous phases were cooled to 0 °C, and the pH was adjusted to ∼12 with 4 M aqueous NaOH at 0 °C. The aqueous phase was then extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$ and filtered and concentrated. The resulting residue was purified by silica gel flash chromatography (dichloromethane−methanol, 49:1) to give 3-(2,2-dimethyl-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)-3*H*-imidazole-4-carboxylic acid methyl ester; ESI-MS m/z 299.0 $(M + H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.97 (s, 3 H), 1.15 (s, 3 H), 2.63 (d, J = 16.8 Hz, 1 H), 2.74 (d, J = 16.8 Hz, 1 H), 3.93 (s, 3 H), 6.79 (s, 1 H), 7.02 (d, J = 7.6 Hz, 1 H), 7.35 (s, 1 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.55 (td, J = 7.6, 1.5 Hz, 1 H), 7.86 (s, 1 H), 8.13 (dd, J = 7.6, 1.5 Hz, 1 H). Resolution of racemic **65** was achieved by chiral HPLC using ChiralPak IA at 14 mL/min using heptane−reagent alcohol, 7:3, to give enantiomer A (14.7 min) (0.53 g, 18%) and enantiomer B (21.1 min) (0.53 g, 18%) as white crystalline powders.

(1*R*)- or (1*S*)-3-(*trans*-4-Hydroxy-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-*r*-1-yl)-3*H*-imidazole-4-carboxylic Acid Methyl Ester (30) and (1*R*)- or (1*S*)-3-(*cis*-4-Hydroxy-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-*r*-1-yl)-3*H*-imidazole-4-carboxylic Acid Methyl Ester (83). To a solution of **65** (enantiomer A, 0.130 g, 0.431 mmol) in methanol (4 mL) at 0 °C was added $NaBH_4$ (0.025 g, 0.647 mmol). After 10 min, aqueous buffer, pH 7, was added and the mixture was extracted with dichloromethane. The organic phase was dried over magnesium sulfate and filtered through a cotton plug to give a residue, which was purified by silica gel flash chromatography (dichloromethane−methanol, 99:1 to 49:1) to give **30** (18 mg, 14%) as a white solid and **83** (12 mg, 10%) as a white solid.

30: ESI-MS m/z 301.0 $(M + H)^+$; ^{1}H NMR (400 MHz, MeOD) δ ppm 0.95 (s, 3 H), 1.09 (s, 3 H), 1.87 (dd, J = 13.5, 8.7 Hz, 1 H), 2.19 (dd, J = 13.5, 5.9 Hz, 1 H), 3.94 (s, 3 H), 5.01 (dd, J = 8.7, 5.9 Hz, 1 H), 6.63 (s, 1 H), 6.70 (d, J = 7.6 Hz, 1 H), 7.26 (t, J = 7.6 Hz, 1 H), 7.39 (t, J = 7.6 Hz, 1 H), 7.55 (s, 1 H), 7.69 (d, J = 7.6 Hz, 1 H), 7.83 (d, J = 1.0 Hz, 1 H).

83: ESI-MS m/z 301.0 $(M + H)^+$; ^{1}H NMR (400 MHz, MeOD) δ ppm 0.77 (s, 3 H), 1.18 (s, 3 H), 1.82 (dd, J = 13.9, 10.4 Hz, 1 H), 1.95 (dd, J = 13.9, 6.8 Hz, 1 H), 3.97 (s, 3 H), 6.32 (s, 1 H), 7.08 (d, J = 7.6 Hz, 1 H), 7.30 (t, J = 7.6 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 1 H), 7.49 (s, 1 H), 7.75 (s, 1 H), 7.78 (d, J = 7.6 Hz, 1 H).

(*R*)- and (*S*)-3-(2,2-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3*H*-imidazole-4-carboxylic Acid Methyl Ester (2). Resolution of racemic **2** (which was obtained from the Novartis compound collection) was achieved by chiral HPLC using a ChiralPak IA column with a 1:4 ethyl acetate−hexanes mobile phase to provide **2E**; t_R =12.7 min (distomer t_R = 14.8 min); ESI-MS m/z 285.1; $(M + H)^+$. ^{1}H NMR (400 MHz, CD_3OD) of the HNO_3 salt: δ ppm 0.87 (s, 3 H), 1.17 (s, 3 H), 1.67−1.74 (m, 1 H), 1.80−1.88 (m, 1 H), 2.97−3.15 (m, 2 H), 4.06 (s, 3 H), 6.57 (s, 1 H), 7.09 (d, J = 7.8 Hz, 1 H), 7.22−7.26 (m, 1 H), 7.32−7.40 (m, 2 H), 8.32 (d, J = 1.3 Hz, 1 H), 8.61 (s, 1 H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Solubility and permeability data for compounds **2E**, **5E**, **11**, **12**, **16**, **26**, and **28**−**30**; experimental procedures for the synthesis of **63**, **64**, and **79**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.5b00407.

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■ ABBREVIATIONS USED

Ac, acetyl; Tr, trityl; DMF, dimethylformamide; TBS, *tert*-butyldimethylsilyl; DMAP, 4-dimethylaminopyridine; LHMDS, lithium hexamethyldisilazide; THF, tetrahydrofuran; DIPEA, *N*-diisopropyl-*N*-ethylamine; DAST, *N*,*N*-diethylaminosulfur trifluoride; DCE, dichloroethane; DCM, dichloromethane; LDA, lithium *N*,*N*-diisopropylamine; dba, dibenzylideneacetone; NMP, *N*-methylpyrrolidine; Tf, trifluoromethylsulfonyl; DMAD, dimethyl azodicarboxylate; DIAD, diisopropyl azodicarboxylate; DTBAD, di-*tert*-butyl azodicarboxylate

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