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Tetrahydrochromenoimidazoles as Potassium-Competitive Acid Blockers (P-CABs): Structure−Activity Relationship of Their Antisecretory Properties and Their Affinity toward the hERG Channel†

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Potassium-competitive acid blockers (P-CABs) constitute a new therapeutic option for the treatment of acid-related diseases that are widespread and constitute a significant economical burden. Enantiomerically pure tetrahydrochromenoimidazoles were prepared using the readily available candidate **4** (BYK 405879) as starting material or the Noyori asymmetric reduction of ketones as key reaction. A comprehensive SAR regarding the influence of the 5-carboxamide and the 8-aryl residue on in vitro activity, acid-suppression in the Ghosh Schild rat, and affinity toward the hERG channel was established. In addition, efficacy and duration of the antisecretory action was examined for the most promising target compounds by 24 h pH-metry in the fistula dog and a significantly different SAR was observed as compared to the Ghosh Schild rat. Several tetrahydrochromenoimidazoles were identified that possessed a comparable profile as the candidate **4**.

1. Introduction

Acid-related disorders are highly prevalent in the developed world. They have a significant impact on patient quality of life and are a major burden on health care systems. Gastric acid was identified as an important pathogenic factor for a variety of common gastrointestinal disorders such as duodenal ulcer and gastresophageal reflux disease (GERD[a]).[7] GERD has emerged as the most important acid-related disorder. Medical treatment of GERD has focused on acid inhibition, specifically maintaining pH > 4 in the esophagus as long as possible.[7]

The principal stimulants of acid secretion are histamine, gastrin, and acetylcholine. These agents interact with receptors coupled to two major signal transduction pathways (adenylate cyclase and intracellular calcium). Both the intracellular cAMP and calcium-dependent signaling systems activate downstream kinases, ultimately leading to fusion and activation of H^+/K^+-ATPase, the proton pump.[7] Because the gastric proton pump is located at the end of the signaling cascade, its inhibition is thought to be especially efficient in controlling gastric acid secretion and the development of H^+/K^+-ATPase inhibitors for the treatment of acid-related diseases has attracted considerable interest.[8]

A variety of heterocyclic structures has been described in literature that inhibit the gastric proton pump either in an irreversible or a reversible manner.[8] Irreversible proton pump inhibitors (PPIs) are acid-activated prodrugs that covalently bind to the gastric H^+/K^+-ATPase on its luminal surface.[9] PPIs are very effective and safe drugs and have revolutionized the treatment of acid-related diseases.[10] Nevertheless, they have some shortcomings including short plasma residence time, a delayed onset of action, incomplete acid suppression in the majority of patients, and the need for ingestion before a meal to achieve maximal efficacy.[10] An estimated 30−40% of GERD patients continue to suffer from symptoms during PPI treatment, which has stimulated the search for even more effective drugs.[11] Various K^+-competitive inhibitors of the pump, acid pump antagonists (APAs), or potassium-competitive acid blockers (P-CABs) are being developed with the

†Design of novel P-CABs, Part VII, see refs 1−6.

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[a] Abbreviations: APA, acid pump antagonist; cAMP, cyclic adenosine monophosphate; CDI, carbonyldiimidazole; cpd; compound; CE, capillary electrophoresis; DAIPEN, 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine; DIAD, diisopropylazodicarboxylate; DIPEA, diisopropylethylamine (Hünig's base); DMAP, 4-dimethylaminopyridine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; ED_{50}, effective dose (50% reduction of maximum effect); EDC-HCl, *N*-(3-dimethylaminocarbonyl)-*N*′-ethylcarbodiimide hydrochloride; ee, enantiomeric excess; equiv, equivalent(s); ESI, electrospray ionization; GERD, gastresophageal reflux disease; h, hour(s); hERG, human ether-a-go-go related gene; H^+/K^+-ATPase, gastric proton pump; logD, distribution coefficient between 1-octanol and aqueous KCl solution (parameter for compound lipophilicity); MIBK, methylisobutyl ketone; min, minute(s); mp, melting point; MsOH, methanesulfonic acid; n.d., not done; P-CAB, potassium competitive acid blocker; pIC_{50}, negative logarithmic value of the compound concentration required to achieve 50% inhibition; pK_a, dissociation constant; PPI, proton pump inhibitor; PVC, polyvinyl chloride; SAR, structure−activity relationship; S/C ratio, substrate to catalyst ratio; SEM, trimethylsilylethoxymethyl; TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; TES, ethyltrimethylsilyl; THF, tetrahydrofuran; TMS, tetramethylsilane; t_M, migration time; t_R, retention time; TdP, torsades de pointes; Xyl-BINAP, 2,2′-bis(di(3,5-dimethylphenyl)phosphanyl)-1,1′-binaphthyl; Xyl-P-Phos, 2,2′,6,6′-tetramethoxy-4,4′-bis[di(3,5-dimethylphenyl)phosphino]-3,3′-bipyridinyl.

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advantage of complete inhibition of acid secretion independent of pump activity and improved acid control.[9] P-CABs already bind to the resting pump, i.e., to its nonphosphorylated form in the absence of ATP.[12] Because of their reversible mode of action, the duration of their antisecretory effect directly depends on the drug's serum concentration. Consequently, P-CABs allow optimum control of pH elevation with respect to both its duration and degree.[13]

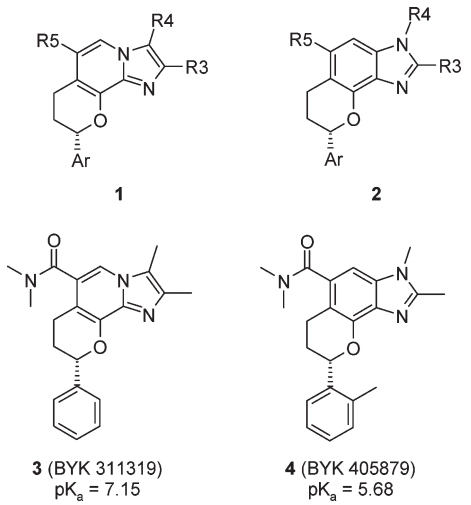
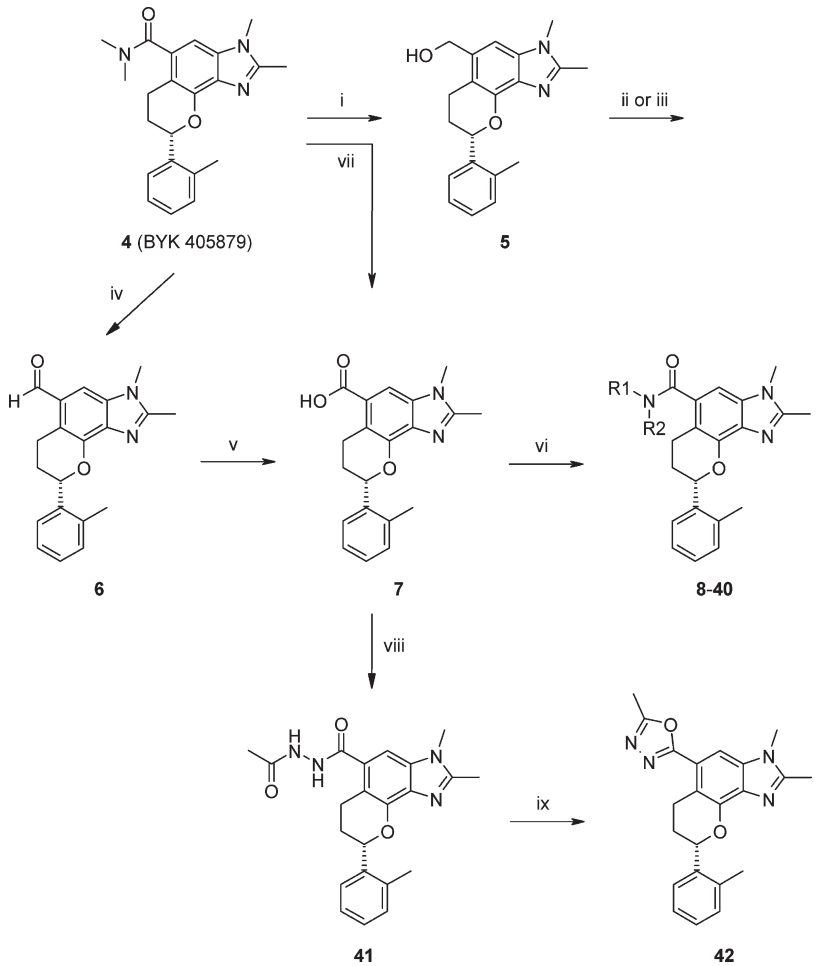


Figure 1

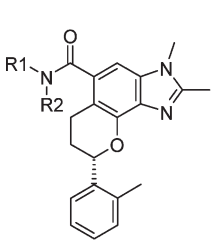
One research area within Nycomed was focused on the development of 3,6,7,8-tetrahydrochromenoimidazoles **2** as potassium-competitive acid blockers (Figure 1). This heterocyclic scaffold emerged from the systematic investigation of possible variations of the well-known imidazo[1,2-*a*]pyridine motif.[5] In comparison to the isomeric imidazo[1,2-*a*]pyridines **1**, represented by **3** (BYK 311319),[5] the respective benzimidazoles **2**, represented by **4** (BYK 405879),[14,15] possess a lower pK_a value, resulting in a more selective accumulation in the parietal cell and a better safety profile. Enantiopure P-CABs belonging to both structural classes can be prepared in an analogous manner (asymmetric reduction of ketones followed by Mitsunobu cyclization of the resulting diols), and the large scale synthesis of the candidate **4** was based on this synthetic strategy.[14−17] Although the tetrahydrochromenoimidazole **4** constitutes a P-CAB with well-balanced properties, we studied the SAR within this lead series in more detail focusing on (a) optimum pharmacological activity in two species (Ghosh

Scheme 1[a]

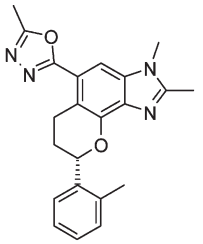


[a] Reagents and conditions: (i) Li[Et_3BH], THF, rt, 2 h, then NaOH, H_2O, then H_2O_2, 100% (crude); (ii) SO_3-pyridine, DMSO, Et_3N, rt, 3 h, 78%; (iii) Dess−Martin periodinane, CH_2Cl_2, rt, 2 h, 49%; (iv) $LiAlH_4$, THF, rt, 1 h, 46%; (v) $NaClO_2$, NaH_2PO_4-H_2O, *t*-BuOH, 2-methylbut-2-ene, H_2O, 40 °C, 5 h, 91%; (vi) amide coupling, method 1, EDC-HCl, DMAP, CH_2Cl_2, HNR1R2 or HNR1R2-HCl, NEt_3, rt, 0.5−18 h, method 2, TBTU, DIPEA, DMF, 40 °C, 0.5−1 h, then HNR1R2 or HNR1R2-HCl, 40 °C, 1−2 h or rt, 17 h, method 3, CDI, CH_2Cl_2, rt, 1−1.5 h, then HNR1R2, HOAc, rt, 4−17 h, method 4, TBTU, DIPEA, HNR1R2 or HNR1R2-HCl, DMF, rt, 2 h, yields reported in Table 1; (vii) NaOH, ethylene glycol, 195 °C, 2 d (distillation of H_2O), 80%; (viii) TBTU, DIPEA, DMF, 40 °C, 1 h, then acetohydrazide, 40 °C, 2 h, 75%; (ix) $POCl_3$, 50 °C, 1 h, 42%.

Table 1. Biological and Pharmacological Evaluation of Target Compounds with Different Carboxamide Residues



4, 8-40



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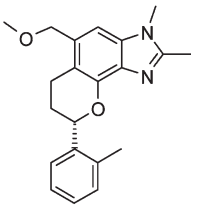

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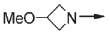
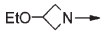
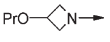
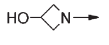
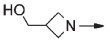
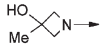
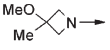
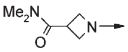
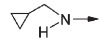
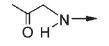
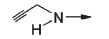
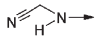
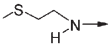
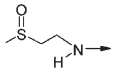
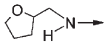
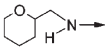
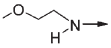
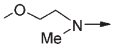
Entry	Cpd.	NR1R2	Yield [%][a]	H^+/K^+-ATPase pIC_{50}[b]	Gastric Glands pIC_{50}[c]	Ghosh Schild rat ED_{50} [μmol/kg][d]	hERG[e] % inhib. @ 10 μM	logD (pH 7.4)[f]	logD[g] (HPLC, pH 7.4)	pK_a[h]
1	**4**		[i]	5.3	6.1	0.23	33	2.52	2.8	5.68
2	**8**		53	5.5	6.1	0.3	14	n. d.	2.8	n. d.
3	**9**		76	5.0	6.0	0.3	28	2.81	3.0	5.54
4	**10**		63	4.7	5.4	0.3	28	3.29	3.3	5.36
5	**11**		57	5.2	6.2	0.3	18	2.79	2.9	5.66
6	**12**		43	4.5	6.1	0.4	70	n. d.	3.0	n. d.
7	**13**		40	4.9	5.9	0.2	94	3.88	3.3	5.62
8	**14**		58	5.0	4.4	1.2	11	n. d.	2.4	n. d.
9	**15**		58	5.0	4.2	1.4	2	n. d.	2.4	n. d.
10	**16**		66	4.7	4.1	3 / 10 %	1	n. d.	2.5	n. d.
11	**17**		28	4.3	5.5	1.0	20	n. d.	3.0	n. d.
12	**18**		41	4.9	4.1	3 / 36 %	6	n. d.	2.5	n. d.
13	**19**		68	4.6	n. d.	3 / 22 %	7	n. d.	2.3	n. d.
14	**20**		90	4.8	5.3	2.0	14	n. d.	2.5	n. d.
15	**21**		[j]	5.1	5.6	0.25	3	2.67	2.7	5.70
16	**22**		76	4.9	6.0	0.12	24	3.29	2.9-3.0	5.71
17	**23**		88	4.7	6.2	<0.3	66	3.40	3.2	5.63
18	**24**		57	4.7	6.2	0.45	30	n. d.	3.1	n. d.
19	**25**		[j]	4.9	6.1	0.3	43	3.10	3.0	5.68
20	**26**		79	4.7	6.3	<0.3	90	3.79	3.3	5.76
21	**27**		70	4.6	6.0	0.3	63	2.48	2.8	5.62
22	**28**		77	4.7	5.7	0.3	83	3.03	3.1	5.58
23	**29**		75	4.7	4.9	3.0	18	n. d.	2.9	n. d.
24	**30**		54	4.8	5.9	1.0	73	n. d.	3.2	n. d.

Table 1. Continued

Entry	Cpd.	NR1R2	Yield [%][a]	H^+/K^+-ATPase pIC_{50}[b]	Gastric Glands pIC_{50}[c]	Ghosh Schild rat ED_{50} [μmol/kg][d]	hERG[e] % inhib. @ 10 μM	logD (pH 7.4)[f]	logD[g] (HPLC, pH 7.4)	pK_a[h]
25	**31**		43[k]	4.6	n. d.	1.4	6	n. d	n. d.	n. d
26	**32**		65	4.6	5.0	2.0	49	n. d.	2.6	n. d.
27	**33**		74	4.3	5.5	1.0	75	n. d.	3.0	n. d.
28	**34**		91	<5.0	5.2	1.2	54	n. d.	3.3	n. d.
29	**35**		36	4.9	5.5	0.8	55	n. d.	2.8	n. d.
30	**36**		41	4.9	5.5	1.2	8	n. d.	2.9	n. d.
31	**37**		30	4.6	5.0	1.8	13	n. d.	2.6	n. d.
32	**38**		64	5.4	5.9	0.15	13	2.59	2.9	5.49
33	**39**		[j]	5.4	6.1	0.7	43	3.50	3.1	5.70
34	**40**		76	4.8	5.3	1.0	4	n. d.	2.8	n. d.
35	**42**			4.6	5.3	0.6	27	3.76	3.3	5.17
36	**43**			5.1	6.0	0.5	34	3.86	3.4	6.24

[a] Yield of the coupling reaction of carboxylic acid **7** with the respective amine HNR1R2. [b] pIC_{50} value of the inhibition of H^+/K^+-ATPase derived from hog gastric mucosa (competitive binding assay). [c] pIC_{50} value of the inhibition of ^{14}C-dimethylaminopyridine accumulation in intact gastric glands isolated from New Zealand rabbits. [d] Pentagastrin-stimulated acid secretion of the perfused rat stomach (Ghosh Schild rat): ED_{50} (μmol/kg) or dose (μmol/kg)/reduction (%). [e] % inhibition of the hERG channel in the presence of 10 μM of the respective API (whole-cell patch-clamp technique). [f] Distribution coefficient between 1-octanol and aqueous KCl solution determined at 25 °C by potentiometric titrations in the range of pH 2.0−11.0. [g] Logarithmic partition coefficient determined at 37 °C by reversed phase HPLC using seven substances with known logD as reference. [h] Determined by potentiometric cosolvent titrations in 0.15 mol/L KCl solutions in the range of pH 2.0−11.0 at 25 °C using methanol as cosolvent. [i] The synthesis of BYK 405879 (**4**) is reported in lit.[15] [j] Synthesis via asymmetric reduction of the respective ketone precursor and subsequent Mitsunobu cyclization of the obtained diol (see Scheme 2, Table 2). [k] Prepared by oxidation of sulfide **30** with sodium periodate (MeOH, H_2O, rt, 1 h).

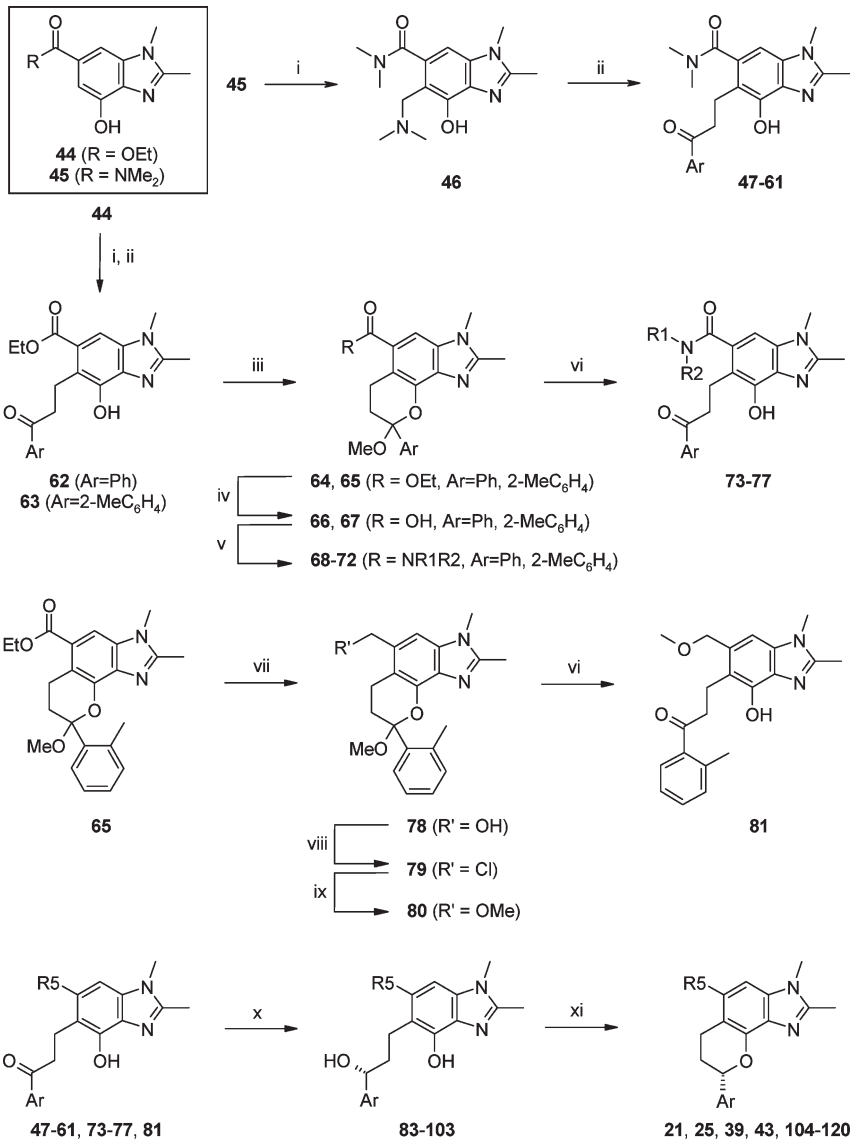
Schild rat and fistula dog) and (b) low affinity toward the hERG channel. The primary objective of the study was to identify P-CABs with a longer duration of action in the fistula dog than the current candidate **4**.

(a) The primary goal of the first pharmacological model, the Ghosh Schild rat, is to determine the ED_{50} value of the respective drug substance.[13] This value reflects the dose by which the maximum amount of pentagastrin-stimulated acid output is reduced by 50%. The acid output is measured for a period of 3.5 h after administration of the P-CAB. A preliminary assessment whether the antisecretory effect of the drug substance is long-lasting is already possible from the analysis of the shape of the titration curve. However, the fistula dog constitutes a more suitable pharmacological model for the determination of the duration of acid suppression. The dogs used for these investigations received special surgery that allows the introduction of a pH-electrode into their stomach and the determination of their intragastric pH value over a period of several hours after administration of the drug substance.[13] The identification of P-CABs which are able to increase the intragastric pH to a value of >5 for at least 6−8 h is a major goal. Such substances should be useful for the treatment of night-time GERD, a phenomenon having a severe impact on patients' quality of life which cannot be treated in a satisfactory manner by the administration of irreversible proton pump inhibitors.[7]

(b) In recent years, a number of drugs have been withdrawn from the market due to cardiovascular toxicity associated with blockade of the hERG channel. The human ether-a-go-go related gene (hERG) potassium channel plays a key role in regulating cardiac excitability and maintenance of normal cardiac rhythm.[18,19] The inhibition of potassium channels encoded by hERG is considered as the main mechanism underlying an acquired long QT syndrome and a potentially fatal arrythmia called "torsades de pointes" (TdP).[19] Although the risk of cardiovascular toxicity cannot be assessed merely on basis of in vitro hERG assays, such assays form a key element in the assessment of TdP liability, with patch-clamp electrophysiology as gold standard.[20,21] hERG channels exhibit a unique susceptibility to pharmacological inhibition by therapeutically and chemically diverse drugs. Despite considerable computational and statistical modeling efforts and studies on hERG, the knowledge of how known ligands bind to hERG remains fragmentary and a structure−activity relationship has to be established within each chemical series.[19,20,22,23]

This publication provides a comprehensive overview over the SAR in the class of tetrahydrochromenoimidazoles **2**

Scheme 2[a]



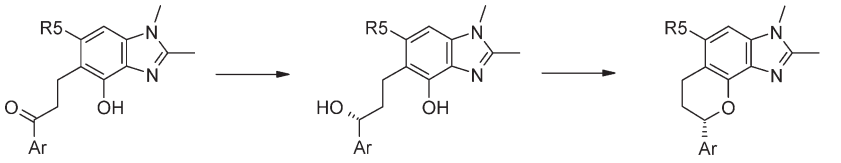
[a] Reagents and conditions: (i) Eschenmoser's salt, CH_2Cl_2, rt, 3 h; (ii) 1-(1-arylvinyl)pyrrolidine, toluene or 1,2-dimethoxyethane, 80−100 °C, 1−6 h, yields reported in Table 2 (method A); (iii) 2,2-dimethoxypropane, MsOH, CH_2Cl_2, rfl., 16 h, **64** (Ar=Ph) 92%, **65** (Ar=2-MeC_6H_4) 96%; (iv) KOH, MeOH, H_2O, 55 °C, 16 h, **66** (Ar=Ph) 99%, **67** (Ar=2-MeC_6H_4) 99%; (v) TBTU, DIPEA, DMF, rt, 1 h, then amine, rt, 2 h; (vi) 1 N HCl, THF, 50 °C, 2−6 h, yields reported in Table 2 (method B); (vii) $LiAlH_4$, THF, rt, 2 h, 90%; (viii) $SOCl_2$, CH_2Cl_2, 0 °C, 1.5 h, 100%; (ix) NaOMe, MeOH, 50 °C, 0.5 h, 95%; (x) $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] (S/C = 100:1 to 500:1), 1.1−2.75 equiv *t*-BuOK (1 M solution in *t*-BuOH), 25−80 bar H_2, 65−80 °C, 16−20 h, yields and optical purities reported in Table 2; (xi) PPh_3, DIAD, THF, rt, 5 min−18 h, yields and optical purities reported in Table 2.

covering their physicochemical and biological properties, their affinity toward the hERG channel, and their pharmacological efficacy in the Ghosh Schild rat and the fistula dog.[24−26]

2. Chemistry

For the synthesis of the first series of target compounds (aryl = 2-methylphenyl), the readily available carboxamide **4** was used as starting material. Hydrolysis of the amide function present in **4** and further transformation of the carboxylic acid intermediate **7** can provide access to tetrahydrochromenoimidazoles bearing a variety of residues NR1R2 (Scheme 1). In the beginning, a suitable method for the direct hydrolysis of the carboxamide residue was not available. However, the carboxylic acid **7** could be prepared in a convenient manner following the indirect approach illustrated in Scheme 1. The reduction of carboxamide **4** using lithium triethylborohydride afforded the corresponding alcohol **5** that was oxidized to the aldehyde **6** using either sulfurtrioxide pyridine complex (Parikh−Doering conditions) or Dess−Martin periodinane.[27] The sulfurtrioxide pyridine complex was the preferred reagent because the product **6** could be isolated by a simple crystallization step. In the case of the Dess−Martin oxidation, the aldehyde **6** had to be purified by column chromatography. Alternatively, aldehyde **6** was prepared by reduction of carboxamide **4** with lithium aluminum hydride. However, the two-step procedure (reduction of carboxamide **4** to alcohol **5** and subsequent oxidation) was preferred because the reactions could be controlled more easily on a larger scale. Finally, the carboxylic acid **7** was obtained in >90% yield using sodium chlorite as oxidizing

Table 2. Synthesis of Target Compounds **21**, **25**, **39**, **43**, **104**−**120**



47-61, **73-77**, **81** **83-103** **21**, **25**, **39**, **43**, **104-120**

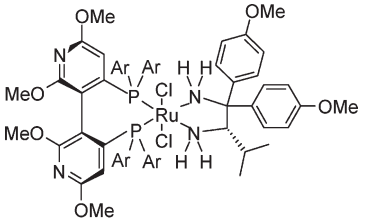
Entry	R5	Ar	Ketone	Yield[a]	Diol	Yield[b]	ee[b]	Target Compound	Yield[c]	ee[c]
1			**73**	B: 71[d]	**83**	30[d]	95[d]	**21**	35	98
2			**74**	B: 84[d]	**84**	45[d]	98[d]	**25**	66	98
3			**75**	B: 57[d]	**85**	94[d]	91[d]	**39**	51	80
4			**81**	B: 70[d]	**86**	71[d]	98[d]	**43**	79	95
5			**47**	A: 42[d]	**87**	70[d]	98[d]	**104**	77[d]	96[d]
6			**76**	B: 76[d]	**88**	52[d]	77[d]	**105**	75	73
7			**77**	B: 47[d]	**89**	32[d]	85[d]	**106**	76	82
8			**48**	A: 36[d]	**90**	49[d]	96[d]	**107**	62	96
9			**49**	A: 45[d]	**91**	48[d]	88[d]	**108**	91	90
10			**50**	A: 41[d]	**92**	51[d]	86[d]	**109**	73	83
11			**51**	A: 52	**93**	61	93	**110**	53	n. d.
12			**52**	A: 39[d]	**94**	66[d]	97[d]	**111**	50	98
13			**53**	A: 44[d]	**95**	35[d]	88[d]	**112**	62	82
14			**54**	A: 32	**96**	90	68-71	**113**	85	60
15			**55**	A: 44[d]	**97**	61[d]	83[d]	**114**	48	83
16			**56**	A: 53	**98**	84	91	**115**	66	95
17			**57**	A: 45	**99**	79	85	**116**	91	n. d.
18			**58**	A: 36	**100**	53	69[e]	**117**	34	95
19			**59**	A: 13	**101**	45	n. d.	**118**	64	39
20			**60**	A: 22[d]	**102**	62[d]	80[d]	**119**	61	77
21			**61**	A: 24[d]	**103**	63[d]	96[d]	**120**	39	n. d.

[a] The reported yields relate to Scheme 2, steps (i) and (ii), method A, or steps (v) and (vi) / step (vi) in the case of ketone **81**, method B. [b] The reported yields and optical purities relate to Scheme 2, step (x). [c] The reported yields and optical purities relate to Scheme 2, step (xi). [d] The synthesis has been described in lit.[14] [e] Increase of optical purity by subsequent crystallization in the presence of mandelic acid.

agent (Kraus oxidation).[28] Later it was found that the direct saponification of the carboxamide residue could be achieved by heating a solution of the substrate **4** and sodium hydroxide in ethylene glycol to 190 °C and removal of water (present in the reagents/solvent) by destillation.[29] A variety of target compounds **8**−**40** was prepared by condensation of the carboxylic acid **7** with different amines using EDC-HCl, TBTU, or CDI as coupling agent (Table 1). The tetrahydrochromenoimidazole, **42**, bearing a 2-methyl-1,3,4-oxadiazole substituent, was obtained in two steps from carboxylic acid **7** (Scheme 1). Condensation of carboxylic acid **7** with acetohydrazide afforded intermediate **41**, which was heated in phosphorus oxychloride, affording the carboxamide isoster **42** in 42% yield.

To examine the influence of the aryl residue on the pharmacological activity and the hERG affinity of the respective benzimidazole derivative, a similar approach was pursued as previously described for the candidate **4** (Scheme 2, Table 2).[14,15] The prochiral ketones **47**−**61** were prepared by transformation of the Mannich base **46** with different 1-(1-arylvinyl)pyrrolidines. Ketones **62** and **63**, containing a carboxylic ester moiety, were used as versatile intermediates for rapid variation of the carboxamide moiety and as starting material for the synthesis of the 5-methoxymethylene-substituted target compound **43**. For these purposes, the oxo function was protected by conversion of the ketones **62** and **63** into their acetals **64** and **65**. The ester moiety of **64** and **65** was saponified and the respective carboxamide residue was introduced by TBTU mediated coupling of the carboxylic acids **66** and **67** with different amines. Finally, the prochiral ketones **73**−**77** were prepared by acid-catalyzed cleavage of their acetal precursors **68**−**72**. Alternatively, the carboxylic ester **65** was reduced with lithium aluminum hydride and the obtained alcohol **78** was activated with thionyl chloride. The methoxymethylene function was installed by nucleophilic substitution of the resulting chloride **79** with sodium methylate. Again, acid-catalyzed cleavage of acetal **80** afforded the required prochiral ketone **81**. Noyori asymmetric hydrogenation of the respective ketones **47**−**61**, **73**−**77**, and **81** in the presence of $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **82** (Figure 2) afforded the alcohols **83**−**103**, typically in 80−98% ee.[14,30−34] The synthesis of the target compounds **21**, **25**, **39**, **43**, and **104**−**120** was then completed by Mitsunobu cyclization of the diols **83**−**103** using triphenylphosphine and DIAD (Table 2). In the 4-chlorophenyl series and in the 4-chloro-2-methylphenyl series, a variation of the carboxamide residue CONR1R2 was performed by applying the methods discussed in Scheme 1 (Scheme 3).

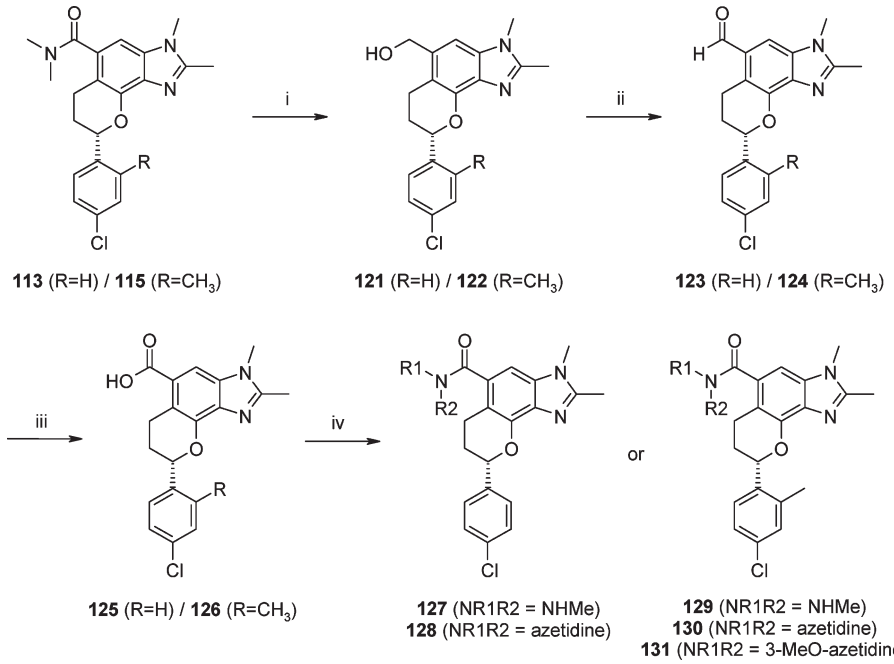
The 2-cyclopropyl-substituted benzimidazole **139** was prepared following the synthetic route described previously for the candidate **4** (Scheme 4).[15] The prochiral ketone **134** was obtained by conversion of Mannich base **132** with ethyl 3-(2-methylphenyl)-3-oxopropanoate and subsequent saponification and decarboxylation of intermediate **133**. To reduce the amount of hydrogenation catalyst and to enhance the optical purity of the alcohol **137**, the phenolic hydroxy group was protected by conversion of hydroxyketone **134** with benzyl bromide. The asymmetric hydrogenation of the



82 (Ar = 3,5-dimethylphenyl)

Figure 2

Scheme 3[a]



113 (R=H) / **115** (R=CH_3) **121** (R=H) / **122** (R=CH_3) **123** (R=H) / **124** (R=CH_3)

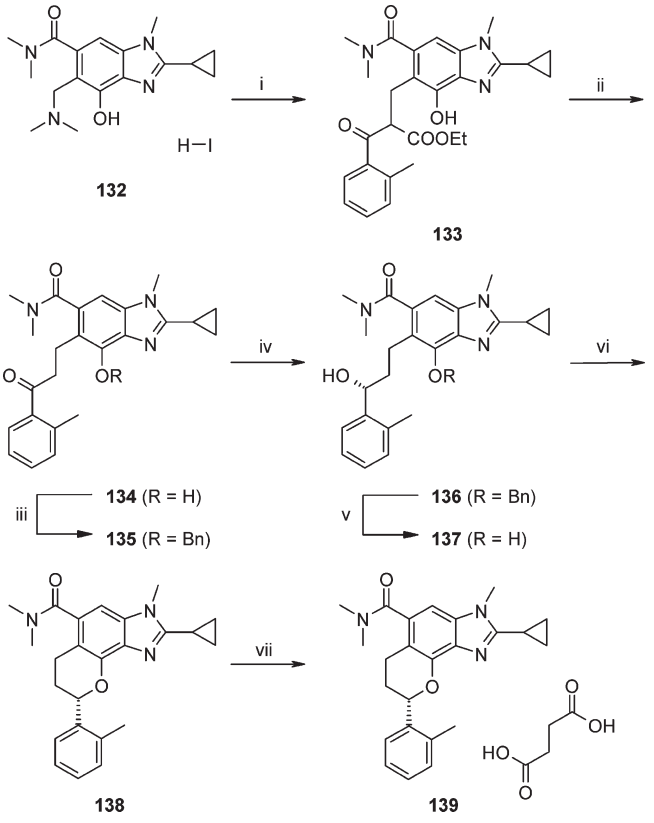
125 (R=H) / **126** (R=CH_3) **127** (NR1R2 = NHMe) **128** (NR1R2 = azetidine) **129** (NR1R2 = NHMe) **130** (NR1R2 = azetidine) **131** (NR1R2 = 3-MeO-azetidine)

[a] Reagents and conditions: (i) Li[Et_3BH], THF, rt, 2 h, then NaOH, H_2O, 0 °C, 20 min, then H_2O_2, 0 °C, 0.75 h, **121** 95% (crude), **122** 72% (crude); (ii) SO_3-pyridine, DMSO, NEt_3, rt, 16−17 h, **123** 96%, **124** 62%; (iii) $NaClO_2$, NaH_2PO_4-H_2O, *t*-BuOH, 2-methyl-2-butene, H_2O, 45 °C, 20 h, **125** 97%, **126** 100% (crude); (iv) TBTU, DIPEA, DMF, 40−45 °C, 0.75−1 h, then **127** methylamine, rt, 16 h, 73%, **128** azetidine, 40 °C, 1 h, 72%, **129** methylamine, rt, 16 h, 53%, **130** azetidine, rt, 16 h, 53%, **131** 3-methoxyazetidine, rt, 16 h, 47%.

benzyl-protected ketone **135** proceeded smoothly at a substrate to catalyst ratio of 1000:1, and the alcohol **136** was isolated in 90% yield and 95.4% ee. Finally, the protecting group was removed by catalytic hydrogenation and the resulting diol **137** transformed to the target compound **138** under Mitsunobu conditions. The chemical purity of the tetrahydrochromenoimidazole **138** was enhanced by crystallization in the presence of succinic acid affording the salt **139**.

The synthesis of the 2-hydroxymethyl analogue **140** of the candidate **4** has been described previously.[35] The corresponding 2-methoxymethyl-substituted benzimidazole derivative **142** was prepared by activation of the hydroxy function of **140** with thionyl chloride and subsequent nucleophilic substitution of the chloro atom of intermediate **141** with methanol (Scheme 5).

Scheme 4[a]



[a] Reagents and conditions: (i) ethyl 3-(2-methylphenyl)-3-oxopropanoate, potassium *tert*-pentylate, DMF, toluene, 60 °C, 5 h; (ii) Cs_2CO_3, MeOH/H_2O, 85 °C, 4 h, Σ37%; (iii) benzyl bromide, K_2CO_3, DMF, 55 °C, 4 h, 51%; (iv) $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] (S/C = 1000:1), *t*-BuOK, H_2 (80 bar), 2-PrOH, *t*-BuOH, 70 °C, 17 h, 90%, 95.4% ee; (v) Pd/C, H_2 (1 bar), EtOH, rt, 18 h, 95%; (vi) PPh_3, DIAD, THF, rt, 0.5 h; (vii) succinic acid, MIBK, 80 °C, 0.75 h, rt, 17 h, Σ74%, 95.6% ee.

The 3-NH analogue **150** of the candidate **4** was also prepared (Scheme 6). The benzimidazole nitrogen atom was protected using the SEM protecting group in an early stage of this synthesis. To this end, building block **143** was alkylated with 2-(trimethylsilyl)ethoxymethyl chloride, furnishing the protected analogue **144** in 39% yield. The carboxamide residue was then introduced by palladium-catalyzed cross coupling of bromobenzimidazole **144** with carbonmonoxide and dimethylamine affording intermediate **145**. The 4-hydroxybenzimidazole **146**, obtained by hydrogenolytic cleavage of the benzyl protecting group present in **145**, was used as starting material for the reaction sequence described earlier (synthesis and asymmetric reduction of ketone **147**, Mitsunobu cyclization of the resulting diol **148** to the tetrahydrochromenoimidazole **149**). The hydrogenation step proceeded with excellent enantioselectivity (96% ee), and the high optical purity was maintained in the course of the Mitsunobu reaction. Finally, the SEM protecting group was removed by treatment of **149** with boron trifluoride and the target compound **150** was obtained in quantitative yield.

3. Biological and Physicochemical Evaluation of the Target Compounds

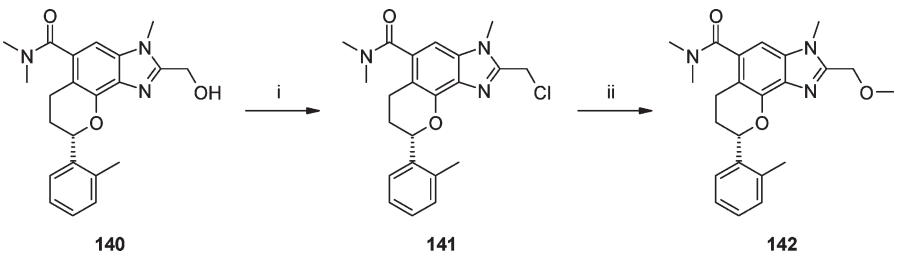
3.1. Assays for the Determination of Biochemical and Pharmacological Activity. The biological and pharmacological activity of the target compounds was determined using the assays described previously.[5,13,36]

First, the inhibitory activity against H^+/K^+-ATPase isolated from hog gastric mucosa was assessed using a competitive binding assay.[5,36] When comparing the pIC_{50} values of the tetrahydrochromenoimidazole target compounds with those obtained for other P-CABs, it has to be considered that the enzymatic activity depends on the pK_a value of the respective inhibitor. Because the assay is conducted at pH 7.4 and the inhibition of the enzyme is caused by the protonated heterocycle, typically lower pIC_{50} values are obtained for the less basic benzimidazoles ($pK_a \sim 5.8$) as compared to their imidazo[1,2-*a*]pyridine analogues ($pK_a \sim 6.8$).

Second, the cellular activity of the respective tetrahydrochromenoimidazole was assessed from the reduction of the accumulation of the weak base ^{14}C-dimethylaminopyridine in intact gastric glands isolated from New Zealand rabbits.[5,36] The pIC_{50} values reported in Tables 1, 3, and 4 constitute the geometric mean from 4 to 5 measurements. The standard deviation amounts to 0.1−0.2 log units.

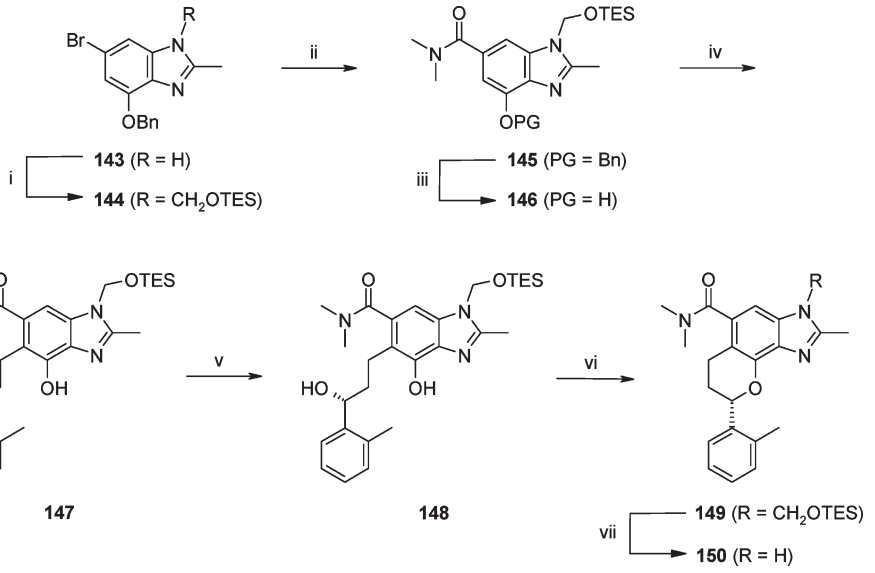
Finally, the reduction of the acid output in the Ghosh Schild rat was determined as a parameter for the in vivo activity of the respective P-CAB.[5,13,36] In this model, fasted female Sprague−Dawley rats were anesthetized with urethane. A PVC tube was inserted into the stomach via the esophagus,

Scheme 5[a]



[a] Reagents and conditions: (i) $SOCl_2$, CH_2Cl_2, rt, 2 h, 98%; (ii) NaOMe, MeOH, 65 °C, 17 h, 45%.

Scheme 6[a]



[a] Reagents and conditions: (i) SEMCl, Et_3N, DMF, CH_2Cl_2, rt, 5 h, 39%; (ii) $Pd(OAc)_2$, PPh_3, $HNMe_2$, CO (6 bar), THF, 120 °C, 60 h, 72%; (iii) Pd/C, H_2 (5 bar), EtOH, rt, 16 h, 93%; (iv) (a) Eschenmoser's salt, CH_2Cl_2, rt, 7 h, (b) 1-[(2-methylphenyl)vinyl]pyrrolidine, 1,2-dimethoxypropane, 85 °C, 3 h, 20%; (v) $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN], *t*-BuOK, H_2 (25 bar), 2-PrOH, *t*-BuOH, 65 °C, 16 h, 70%, 95.8% ee; (vi) PPh_3, DIAD, THF, rt, 10 min, 45% (mixture with $Ph_3P{=}O$); (vii) BF_3-OEt_2, CH_2Cl_2, rt, 3 h, quant, 96.1% ee.

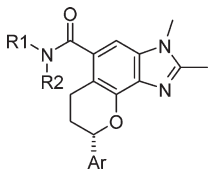
and the stomach was perfused with saline. A second tube draining the pylorus was inserted through the abdominal wall for collection of gastric secretion. Acid secretion was determined at 15 min intervals by titration of the perfusate with NaOH. Gastric secretion was stimulated during a period of 4.5−5 h by an intravenous infusion of pentagastrin starting after determination of 2 basal values of acid secretion (t = 30 min). After 1 additional h, the P-CAB was administered intraduodenally (t = 90 min). The maximum inhibition was defined as the maximum difference between the acid output in the presence of the test drug and in the respective controls. The ED_{50} value reflects the dose of the inhibitor that causes 50% reduction of the pentagastrin-stimulated acid output.

For the most promising target compounds, efficacy and duration of the antisecretory activity was determined in the fasted fistula dog.[13] In this model, surgery was performed on male Beagle dogs and a metallic fistula was placed in the left side of the abdomen of the lowest part of the distal gastric corpus region near the greater curvature. Gastric acid secretion was stimulated one hour after beginning of continuous pH-metry by subcutaneous infusion of pentagastrin covering a 22.5 h period. Drugs or vehicle were administered orally as capsules 2.5 h after the start of the pH-metry (i.e., 1.5 h after onset of pentagastrin infusion). Capsules were used to guarantee that the full dose of the respective inhibitor reached the stomach of the dog. In the stomach, the P-CAB was released over a period of 3−5 min from the capsule. The intragastric pH was continuously recorded for 24 h by means of a combined glass electrode connected to an ambulatory pH meter.

hERG tail currents were recorded from stably transfected CHO-K1 cells using the whole-cell patch-clamp technique to test for a blockade of a test compound at 10 μM. Each compound was applied to three different cells. The relative blockade of the tail current amplitude was calculated and presented as arithmetic mean. In general, the standard deviation of the single compounds did not exceed 7%.

3.2. Influence of the Carboxamide Substituent on hERG Inhibition and Pharmacological Activity. Biological and Pharmacological Activity. In the azetidine series, significant inhibition of the gastric proton pump was observed only for the parent compound **8** (Table 1, entry 2) or if the azetidine ring contained a lipophilic substituent, e.g., fluoro or alkoxy (P-CABs **9**−**13**, entries 3−7). Substitution of the azetidine moiety with a hydrophilic residue, e.g., hydroxy (target compounds **14** and **15**, entries 8 and 9) or carboxamide (benzimidazoles **18** and **19**, entries 12 and 13) or quarternization (compounds **16** and **17**, entries 10 and 11) resulted in a loss of in vitro and in vivo activity. The unsubstituted carboxamide **20** (NR1R2 = NH_2, entry 14) showed little affinity toward H^+/K^+-ATPase. In contrast, significant inhibitory activity was observed for a number of tetrahydrochromenoimidazoles belonging to the alkyl series (**21**−**24**, entries 15−18) and cyclopropyl series (**25**−**26**, entries 19 and 20). Further modifications, including the oxidation (**27**, entry 21, NR1R2 = 2-oxopropyl) or dehydrogenation (**28**, entry 22, NR1R2 = 2-propinyl) of the propyl side chain were also tolerated. Interestingly, the activity of the target compounds **28** and **29** containing the isosteric 2-propinyl and cyanomethyl substituents differed significantly (entries 22 and 23). The incorporation of a sulfur or oxygen heteroatom into the alkyl side chain resulted in compounds with reduced antisecretory properties (**30**−**31**, **35**−**36**, entries 24, 25 and 29, 30). Likewise, the carboxamides **32**−**34** containing heterocyclic residues did not possess a favorable profile (entries 26−28). In the case of the *N*-methoxy-substituted carboxamides **37** and **38**, the alkylation state of the nitrogen atom had a great impact on the P-CAB activity (entries 31 and 32). Whereas the secondary amide **37** only possessed weak antisecretory properties, its tertiary analogue **38** showed noteworthy inhibitory activity in the gastric glands and in the Ghosh Schild rat. Ring extension from azetidine (**8**, entry 2) to pyrrolidine (**39**, entry 33) was tolerated. However, the incorporation of an oxygen atom into the pyrrolidine moiety (morpholine **40**, entry 34) resulted in reduced inhibition of the gastric proton pump. It was also examined briefly whether the

Table 3. Biological and Pharmacological Evaluation of Target Compounds with Different Carboxamide and Aryl Residues



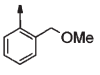
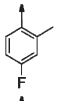
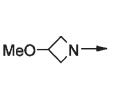
Entry	Cpd.	NR1R2	Ar	H^+/K^+-ATPase pIC_{50}[a]	Gastric Glands pIC_{50}[b]	Ghosh Schild rat ED_{50} [μmol/kg][c]	hERG[d] % inhib. @ 10 μM	logD (pH 7.4)[e]	logD[f] (HPLC, pH 7.4)	pK_a[g]
1	**104**			5.3	5.5	0.26	28	n. d.	2.5	n. d.
2	**4**			5.3	6.1	0.23	33	2.52	2.8	5.68
3	**105**			4.8	5.2	0.5	26	n. d.	2.4	n. d.
4	**21**			5.1	5.6	0.25	3	2.67	2.7	5.70
5	**106**			4.9	5.6	0.3	18	n. d.	2.6	n. d.
6	**8**			5.5	6.1	0.3	14	n. d.	2.8	n. d.
7	**107**			4.9	5.8	0.5	9	2.41	2.7	5.55
8	**108**			n. d.	5.8	0.4	13	2.86	3.0	5.45
9	**109**			5.4	5.9	0.5	11	n. d.	3.0	n. d.
10	**110**			4.8	5.5	1.5	18	3.18	3.1	5.63
11	**111**			4.7	4.8	1.6	7	1.90	2.6	5.61
12	**112**			5.3	6.0	0.1	28	2.36	2.7	5.65
13	**113**			5.1	6.4	0.15	84	2.92	2.9-3.0	5.59
14	**127**			<5.0	5.7	0.3	68	n. d.	2.9	n. d.
15	**128**			5.3	5.9	0.16	84	n. d.	3.0	n. d.
16	**114**			5.6	6.3	<0.3	19	n. d.	2.9	n. d.
17	**115**			6.1	6.7	0.1	-6	3.40	3.2	5.59
18	**129**			4.9	6.1	0.15	45	3.46	3.1	5.60

Table 3. Continued

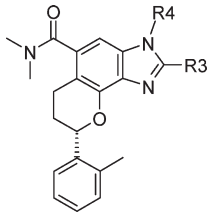
Entry	Cpd.	NR1R2	Ar	H^+/K^+-ATPase pIC_{50}[a]	Gastric Glands pIC_{50}[b]	Ghosh Schild rat ED_{50} [μmol/kg][c]	hERG[d] % inhib. @ 10 μM	logD (pH 7.4)[e]	logD[f] (HPLC, pH 7.4)	pK_a[g]
19	**130**			5.2	6.4	0.15	48	3.43	3.2	5.49
20	**131**			5.4	6.3	0.4	95	3.42	3.2	5.48
21	**116**			5.4	6.1	0.1	33	n. d.	3.0	n. d.
22	**117**			6.0	6.4	<0.3	59	3.66	3.3	5.36
23	**118**			4.1	4.2	3 / 24 %	65	3.37	3.2	5.57
24	**119**			5.0	4.3	2.0	9	n. d.	2.4	n. d.
25	**120**			6.3	6.0	<0.3	18	2.32	2.7	5.66

[a] pIC_{50} value of the inhibition of H^+/K^+-ATPase derived from hog gastric mucosa (competitive binding assay). [b] pIC_{50} value of the inhibition of ^{14}C-dimethylaminopyridine accumulation in intact gastric glands isolated from New Zealand rabbits. [c] Pentagastrin-stimulated acid secretion of the perfused rat stomach (Ghosh Schild rat): ED_{50} (μmol/kg) or dose (μmol/kg)/reduction (%). [d] % inhibition of the hERG channel in the presence of 10 μM of the respective API (whole-cell patch-clamp technique). [e] Distribution coefficient between 1-octanol and aqueous KCl solution determined at 25 °C by potentiometric titrations in the range of pH 2.0−11.0. [f] Logarithmic partition coefficient determined at 37 °C by reversed phase HPLC using seven substances with known logD as reference. [g] Determined by potentiometric cosolvent titrations in 0.15 mol/L KCl solutions in the range of pH 2.0 to pH 11.0 at 25 °C using methanol as cosolvent.

P-CAB properties were maintained if the typical carboxamide residue R5 was replaced by other structural motifs. Target compound **42**, containing a 2-methyl-1,3,4-oxadiazole ring, showed significant cellular activity and possessed an ED_{50} value of 0.6 μmol/kg in the Ghosh Schild rat. Likewise, the ether derivative **43** possessed very favorable antisecretory properties.

hERG Inhibition. The affinity of the respective tetrahydrochromenoimidazole toward the hERG channel strongly depends on the geometry and the lipophilicity of the residue NR1R2 (Table 1). This is reflected by the data obtained for the azetidino series. If the azetidine ring does not contain any substituents at all (**8**, logD(HPLC) = 2.8, entry 2) or a hydrophilic residue (**14**−**16**, **18**−**19**, logD(HPLC) = 2.3−2.5, entries 8−10, 12, and 13), less than 15% hERG inhibition was observed at a dose of 10 μM. The same trend is visible by comparing the alkoxy-substituted azetidines **11** (R = OMe, logD(HPLC) = 2.9, entry 5), **12** (R = OEt, logD(HPLC) = 3.0, entry 6), and **13** (R = OPr, logD(HPLC) = 3.3, entry 7): With increasing size of the alkoxy group, the hERG inhibition observed in the presence of 10 μM of the respective P-CAB increased from 18% to 94%. In the series of the alkyl-substituted carboxamides **20**−**24** (entries 14−18), the hERG inhibition was determined by both, the size (cf. *n*-propyl **23** vs methyl **21** and hydrogen **20**) and the geometry (cf. *i*-propyl **24** vs *n*-propyl **23**) of the alkyl group. Ring closure, i.e., the transition from isopropyl **24** to cyclopropyl **25**, slightly increased the affinity to the hERG channel (compare entries 18 and 19). On the other hand, a strong increase of hERG inhibition occurred when a methylene spacer was introduced between the nitrogen atom and the cyclopropyl ring (**25** vs **26**, entries 19 and 20). The oxidation of the methylene group of the *n*-propyl residue to a carbonyl group showed little influence on the hERG inhibitory activity (**23** vs **27**, entries 17 and 21). Comparison of the hERG data obtained for the isosteric amides **28** (R1 = propinyl) and **29** (R1 = cyanomethyl) clearly illustrates the importance of the lipophilicity of the side chain (entries 22 and 23). The hERG data obtained for the sulfide **30** and the sulfoxide 31 provides further evidence that the lipophilicity of the carboxamide residue plays an important role (entries 24 and 25). At a dose of 10 μM, the lipophilic sulfide **30** (logD(HPLC) = 3.2) causes 73% inhibition of the hERG channel. The hERG affinity is reduced to 6% if the sulfide group is oxidized to the corresponding sulfoxide derivative **31**. The lipophilic tetrahydrofurano- and tetrahydropyrano-substituted carboxamides **33** (logD(HPLC) = 3.0) and **34** (logD(HPLC) = 3.3) also showed high affinity to the hERG channel (entries 27 and 28). The alkylation state of the nitrogen atom of the carboxamide residue also plays a role, e.g., the secondary amide **35** (entry 29) causes significantly stronger inhibition of the hERG channel than its tertiary analogue **36** (entry 30). However, the trend that secondary amides enhance the affinity toward the hERG channel (in comparison to their tertiary analogues) is not general (cf. the secondary amide **37** with its tertiary analogue **38**, entries 31 and 32). The increase of size of the cyclic amine NR1R2 is accompanied by enhanced affinity toward the hERG channel (cf. azetidine **8**, logD(HPLC) = 2.8, and pyrrolidine **39**, logD(HPLC) = 3.1, entries 2 and 33). On the other hand, the hERG inhibition can be reduced by incorporation of a heteroatom into the cyclic residue NR1R2 (cf. pyrrolidine **39**, logD(HPLC) = 3.1, and morpholine **40**, logD(HPLC) = 2.8, entries 33 and 34). Despite the rather high lipophilicity of target compounds **42** (logD(HPLC) = 3.3) and **43** (logD(HPLC) = 3.4), containing a

Table 4. Biological and Pharmacological Evaluation of Target Compounds with Different Substituents Attached to the Imidazole Ring



Entry	Cpd.	R3	R4	H^+/K^+-ATPase pIC_{50}[a]	Gastric Glands pIC_{50}[b]	Ghosh Schild rat ED_{50} [μmol/kg][c]	hERG[d] % inhib @ 10 μM	logD (pH 7.4)[e]	logD[f] (HPLC, pH 7.4)	pK_a[g]
1	**4**	Me	Me	5.3	6.1	0.23	33	2.52	2.8	5.68
2	**139**	c-Pr	Me	n.d.	n.d.	0.1	6	2.84	3.3	5.28
3	**140**	CH_2OH	Me	n.d.	5.93	1.0	12	n.d.	2.5	n.d.
4	**142**	CH_2OMe	Me	4.57	4.34	3.0	7	n.d.	2.9	n.d.
5	**150**	Me	H	5.59	5.71	0.5	11	2.82	2.8	5.66, > 11.8

[a] pIC_{50} value of the inhibition of H^+/K^+-ATPase derived from hog gastric mucosa (competitive binding assay). [b] pIC_{50} value of the inhibition of ^{14}C-dimethylaminopyridine accumulation in intact gastric glands isolated from New Zealand rabbits. [c] Pentagastrin-stimulated acid secretion of the perfused rat stomach (Ghosh Schild rat): ED_{50} (μmol/kg) or dose (μmol/kg)/reduction (%). [d] % inhibition of the hERG channel in the presence of 10 μM of the respective API (whole-cell patch-clamp technique). [e] Distribution coefficient between 1-octanol and aqueous KCl solution determined at 25 °C by potentiometric titrations in the range of pH 2.0−11.0. [f] Logarithmic partition coefficient determined at 37 °C by reversed phase HPLC using seven substances with known logD as reference. [g] Determined by potentiometric cosolvent titrations in 0.15 mol/L KCl solutions in the range of pH 2.0−11.0 at 25 °C using methanol as cosolvent.

2-methyl-1,3,4-oxadiazole ring or a methoxymethylen group in lieu of the carboxamide residue, these derivatives showed a moderate interaction with the hERG channel (comparable to the *N*,*N*-dimethylcarboxamide **4**).

3.3. Influence of the Aryl Substituent on hERG Inhibition and Pharmacological Activity. As in the case of the carboxamide substituent, the choice of the aryl moiety had a significant influence on the biological and pharmacological activity of the target compounds and their affinity toward the hERG channel (Table 3).

The introduction of a methyl substituent in ortho-position of the phenyl moiety consistently increased the cellular activity of the target compounds in a magnitude of 0.5 log units (cf. entries 1−6, **4** vs **104**, **21** vs **105**, and **8** vs **106**). The increase in potency was accompanied by a slight increase in lipophilicity (Δ logD(HPLC) = 0.2−0.3). In two cases, also a higher affinity toward the gastric proton pump enzyme was observed (Δ pIC_{50} = 0.3−0.6). On the other hand, a uniform trend with regard to the pharmacological activity in the Ghosh Schild rat and the inhibition of the hERG channel was not visible.

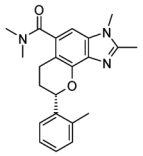
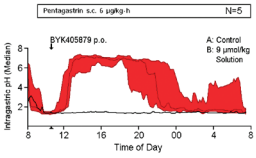
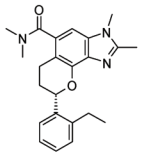
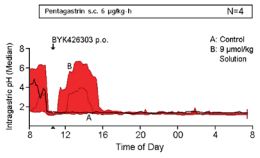
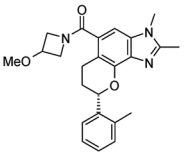
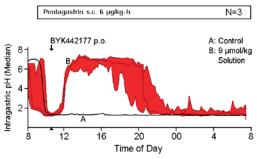
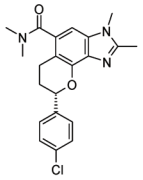
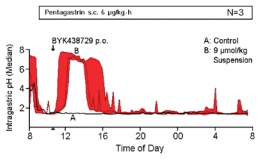
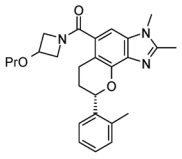
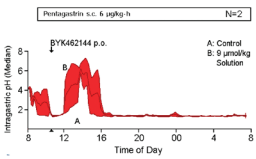
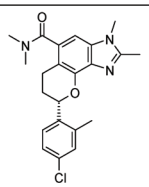
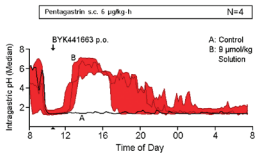
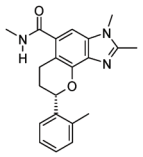
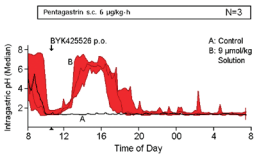
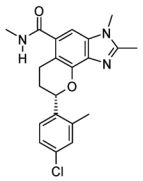
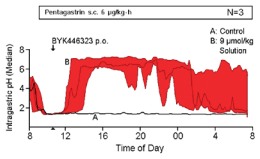
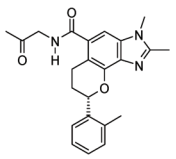
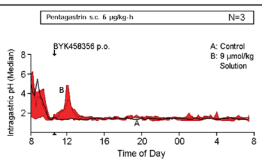
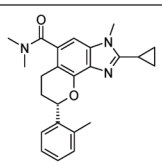
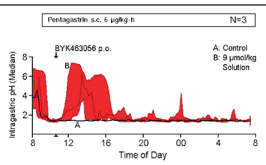
Other substituents (apart from the methyl group) were also tolerated in the ortho position of the phenyl ring. Replacement of the methyl group by a fluoro atom (**107**, entry 7), a chloro atom (**108**, entry 8), or an ethyl group (**109**, entry 9) was accompanied only by a minor loss of cellular activity (Δ pIC_{50} = 0.2−0.3) and a slight change in lipophilicity (Δ logD(HPLC) = −0.1 to 0.2). In the same manner, a small increase in dose (from 0.23 μmol/kg to 0.4−0.5 μmol/kg) was required to achieve 50% reduction of the pentagastrin-stimulated acid output in the Ghosh Schild rat. Bulky alkyl substituents were not tolerated in ortho position of the phenyl ring and caused a reduction of both the in vitro and in vivo efficacy (e.g., cylopropyl derivative **110**, entry 10). Likewise, target compound **111**, possessing an *ortho*-methoxymethylene group, showed little biological and pharmacological activity (entry 11).

Para-substitution of the phenyl moiety with halide atoms turned out to be highly beneficial, especially with regard to cellular activity and in vivo efficacy in the Ghosh Schild rat (**112** and **113**, entries 12 and 13 vs **104**, entry 1). Whereas the introduction of the fluoro atom did not exert any influence on the affinity of the target compound toward the hERG channel (entry 12 vs 1), the presence of the chloro atom resulted in a strongly enhanced inhibition of hERG (entry 13 vs 1).

Interestingly, upon introduction of an additional ortho-methyl substituent, the excellent in vitro and in vivo potency was maintained in both series (**114** and **115**, entries 16 and 17 vs **112** and **113**, entries 12 and 13), whereas a significant reduction of hERG binding was observed, especially in the chloro series. Because the presence of the chloro atom seemed to be highly beneficial for the efficacy of the target compounds as P-CABs further carboxamide residues were studied in the 4-chlorophenyl and the 4-chloro-2-methylphenyl series (**127** and **128**, entries 14 and 15/**129**−**131**, entries 18−20). Although a high degree of cellular activity and in vivo efficacy was maintained upon replacement of the dimethylamine residue by methylamine or azetidine, in some cases a decrease of the pIC_{50} value determined in the competitive binding assay against H^+/K^+-ATPase was observed. On the other hand, the primary goal to reduce hERG binding by variation of the carboxamide residue was not achieved in the 4-chlorophenyl series. In the case of aryl = 4-chloro-2-methylphenyl, the dimethylcarboxamide residue was found to exert an unique influence on the hERG channel because an increase of hERG inhibition was observed for the other carboxamide analogues studied. This effect was especially pronounced for the 3-methoxyazetidine substituent: the respective target compound **131** caused complete inhibition of the hERG channel at a dose of 10 μM. Generally it is thought that changes in lipophilicity can contribute significantly to hERG binding. However, in the present case, the different affinity toward hERG cannot be explained by this parameter because almost identical logD values were determined for all of the target compounds **115** and **129**−**131** prepared in the 4-chloro-2-methyl series (logD = 3.40−3.46, logD(HPLC) = 3.1−3.2).

Target compounds **116** and **117** carrying two halide substituents in ortho- and para-positions of the phenyl moiety were also prepared (entries 21 and 22). These compounds

Table 5. Comparison of the Pharmacological Activity of Selected 3,6,7,8-Tetrahydrochromeno[7,8-*d*]imidazoles in the Ghosh Schild Rat and the Fistula Dog

Compound	Pharmacological activity	Compound	Pharmacological activity
 **4**	 ED_{50} (rat) = 0.23 μmol/kg	 **109**	 ED_{50} (rat) = 0.5 μmol/kg
 **11**	 ED_{50} (rat) = 0.3 μmol/kg	 **113**	 ED_{50} (rat) = 0.15 μmol/kg
 **13**	 ED_{50} (rat) = 0.4 μmol/kg	 **115**	 ED_{50} (rat) = 0.1 μmol/kg
 **21**	 ED_{50} (rat) = 0.25 μmol/kg	 **129**	 ED_{50} (rat) = 0.15 μmol/kg
 **27**	 ED_{50} (rat) = 0.3 μmol/kg	 **139**	 ED_{50} (rat) = 0.1 μmol/kg

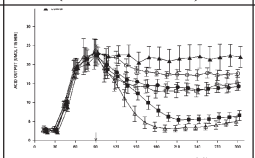
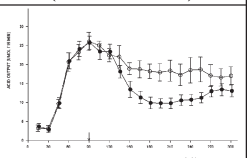
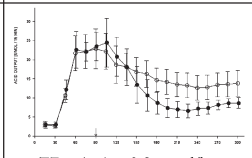
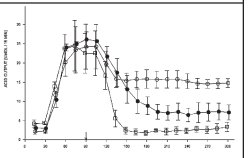
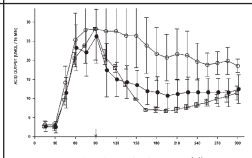
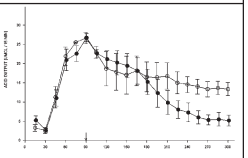
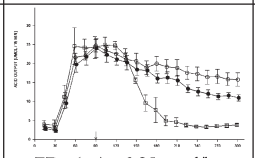
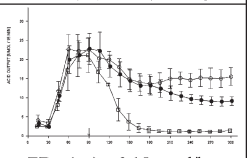
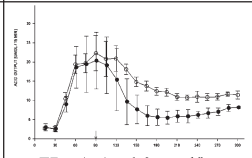
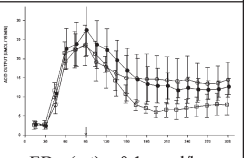
showed high cellular activity and potent antisecretory properties in the Ghosh Schild rat, comparable to their respective 2-methyl analogues (**116**, entry 21 vs **114**, entry 16, **117**, entry 22 vs **115**, entry 17). However, in terms of hERG binding, the *ortho*-methylphenyl motif seemed to offer certain advantages over the *ortho*-chlorophenyl residue (**117**, entry 22 vs **115**, entry 17).

From the data obtained for the naphthyl-substituted target compound **118**, it can be concluded that sterically demanding aryl substituents compromise the biological and pharmacological activity (entry 23). On the other hand, this highly lipophilic moiety (logD = 3.37) might account for the enhanced affinity of tetrahydrochromenoimidazole **118** toward the hERG channel.

The isosteric replacement of the phenyl moiety against a thiophene substituent was also investigated. In the case of the 2-thienyl ring, this modification was accompanied by a strong decrease of the in vitro and in vivo activity of the respective target compound **119** (cf. entries 24 and 1). As exemplified by benzimidazole **120**, the position of the sulfur atom in the aromatic ring seems to be crucial. The replacement of the 2-methylphenyl motif by a 2-methyl-3-thienyl ring was well tolerated, and both compounds **120** and **4** possessed similar cellular activity and pharmacological properties (entry 25 vs 2). In terms of affinity toward the gastric proton pump enzyme and the hERG channel, the thiophene derivative **120** even offered certain advantages over the candidate **4**.

3.4. Influence of the Imidazole Substitution Pattern on hERG Inhibition and Pharmacological Activity. The SAR of the substituents attached in 2- and 3-position of the imidazole ring was also studied briefly. The data reported in Table 4 clearly indicates that this position is highly sensitive toward structural changes. Although the oxidation of the methyl group to the hydroxymethyl analogue **140** only was accompanied by a minor decrease in cellular activity, the pharmacological activity in the Ghosh Schild rat was reduced significantly (**140**, entry 3 vs **4**, entry 1). An even more pronounced decrease in both in vitro and in vivo efficacy was observed for the ether derivative **142** (entry 4 vs entry 1). On the other hand, the replacement of the methyl group by a cyclopropyl substituent was well-tolerated and resulted in a low ED_{50} value of 0.1 μmol/kg in the Ghosh Schild rat (**139**, entry 2 vs **4**, entry 1). The data reported in Table 4 also suggests that the imidazole substitution pattern exerts little influence on hERG binding. The three target compounds **139**, **140**, and **142** did not cause any noteworthy hERG inhibition at a dose of 10 μM. This is an interesting finding because the

Table 6. Titration Curves of Selected 3,6,7,8-Tetrahydrochromeno[7,8-*d*]imidazoles in the Ghosh Schild Rat (*x* Axis: Time [0−300 min]; *y* Axis: Acid Output [0−30 μmol/15 min])

Compound / Dose (μmol/kg)	Pharmacological activity (Ghosh Schild rat)	Compound / Dose (μmol/kg)	Pharmacological activity (Ghosh Schild rat)
4 0.1 (n=6) 0.2 (n=6) 0.3 (n=6) 0.6 (n=6) 1.0 (n=6)	 ED_{50} (rat) = 0.23 μmol/kg	**109** 0.3 (n=5) 1.0 (n=6)	 ED_{50} (rat) = 0.5 μmol/kg
11 0.3 (n=4) 1.0 (n=3)	 ED_{50} (rat) = 0.3 μmol/kg	**113** 0.1 (n=3) 0.3 (n=2) 1.0 (n=2)	 ED_{50} (rat) = 0.15 μmol/kg
13 0.1 (n=3) 0.3 (n=3) 1.0 (n=2)	 ED_{50} (rat) = 0.4 μmol/kg	**115** 0.1 (n=3) 0.3 (n=3)	 ED_{50} (rat) = 0.1 μmol/kg
21 0.1 (n=8) 0.3 (n=8) 1.0 (n=3)	 ED_{50} (rat) = 0.25 μmol/kg	**129** 0.1 (n=4) 0.3 (n=4) 1.0 (n=2)	 ED_{50} (rat) = 0.15 μmol/kg
27 0.3 (n=3) 1.0 (n=2)	 ED_{50} (rat) = 0.3 μmol/kg	**139** 0.1 (n=3) 0.3 (n=4) 1.0 (n=3)	 ED_{50} (rat) = 0.1 μmol/kg

replacement of the methyl group against the cyclopropyl moiety was accompanied by an increase in lipophilicity (logD of **4**: 2.52 vs logD of **139**: 2.84). Whereas in the case of the carboxamide residue lipophilicity constituted an important parameter for hERG binding, this might not be the case for the substituents attached to the imidazole ring.

The replacement of the imidazole N-substituent against a hydrogen atom resulted in an increased affinity toward the H^+/K^+-ATPase and a slight decrease in cellular activity and efficacy in the rat (**150**, entry 5 vs **4**, entry 1). Interestingly, this modification was accompanied by an increase in lipophilicity (logD of **150**: 2.82 vs logD of **4**: 2.52) and a decrease in hERG-binding.

3.5. Influence of the Substitution Pattern on the Basicity of the Target Compounds. The pK_a values of 30 target compounds were determined by potentiometric titration in 0.15 mol/L KCl solutions in the range of pH 2.0−11.0 at 25 °C using methanol as cosolvent. The following conclusions can be drawn from the values reported in Tables 1, 3, and 4: (a) The tetrahydrochromenoimidazole scaffold is very well-suited for the design of weakly basic P-CABs. Most of the target compounds **2** possess pK_a values in the range of 5.6−5.7, i.e., they are significantly less basic than the isomeric 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines **1** ($\Delta pK_a \sim 1.3$).[5] (b) In general, the character of the carboxamide substituent exerts little influence on the pK_a value of the respective target compound. The difluoroazetidine moiety constitutes an exception to this rule, and the introduction of this residue resulted in a P-CAB with reduced basicity (**10**, Table 1, entry 4, pK_a = 5.36). A greater impact on the basicity was observed when the typical carboxamide residue R5 was replaced by other structural motifs. The 1,3,4-oxadiazole substituted target compound **42** (Table 1, entry 35) possesses a lower pK_a value of 5.17, whereas the ether derivative **43** (Table 1, entry 36, pK_a = 6.24) is significantly more basic than the carboxamides listed in Table 1. (c) Likewise, little variation of the pK_a value was observed when the carboxamide residue was kept constant and the aryl moiety was modified (Table 3). Target compounds with halide atoms in the ortho-position (**107** and **108**, Table 3, entries 7 and 8, pK_a = 5.55/5.45) or ortho- and para-positions (**117**, Table 3, entry 22, pK_a = 5.36) of the phenyl ring show somewhat reduced basicity. (d) The preliminary data reported in Table 4 suggests that effective modulation of the basicity might be feasible by modification of the substituent R3 attached to the imidazole ring. The 2-cyclopropyl-substituted tetrahydrochromenoimidazole **139** (Table 4, entry 2, pK_a = 5.28) was found to be significantly less basic than its 2-methyl analogue **4** (entry 1, pK_a = 5.68). (e) The influence of the substituent attached to the nitrogen atom of the imidazole ring on the basicity of the respective P-CAB has to be studied in more detail.

3.6. Species Dependence of Pharmacological Activity (Ghosh Schild Rat versus Fistula Dog). The antisecretory properties of the 29 most promising target compounds (based on the ED_{50} value determined in the Ghosh Schild rat) were assessed in the fasted, pentagastrin-stimulated

fistula dog (Table 5). The pH-curve obtained for the candidate **4** clearly illustrates that the single oral administration of this compound (9 μmol/kg) resulted in fast and strong inhibition of acid output and thus to a pronounced elevation of intragastric pH up to almost neutrality. The lag phase between the oral administration of tetrahydrochromenoimidazole **4** and the onset of the pH-elevating effects is mostly due to a delayed gastric emptying of residual acid.[13] In both species, P-CAB **4** showed good oral bioavailability (rat: 64%, dog: 72%) and moderate clearance (rat: 1.26 L/h/kg, dog: 0.28 L/h/kg).

The study of further 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles in the fistula dog revealed that the pharmacological activity of the respective compound in the dog could not be predicted from its antisecretory activity in the Ghosh Schild rat. Whereas for some compounds (like **4**) the low ED_{50} value (0.23 μmol/kg) determined in the Ghosh Schild rat was reflected in a long lasting increase of the intragastric pH in the fistula dog (pH-elevation to >5 for ~8 h), other 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles were significantly more active in the Ghosh Schild rat than in the fistula dog. For instance, the introduction of a chloro atom into the 2-methylphenyl substituent resulted in an increase of the pharmacological activity in the Ghosh Schild rat (**115**: $ED_{50} = 0.1$ μmol/kg versus **4**: $ED_{50} = 0.23$ μmol/kg). However, the increase of the intragastric pH caused by target compound **115** (Ar = 4-chloro-2-methylphenyl) was of shorter duration (pH-elevation to >5 for ~4 h versus ~8 h). The same trend was visible in the case of the 4-chlorophenyl derivative **113** (Ghosh Schild rat: $ED_{50} = 0.15$ μmol/kg, fistula dog: pH-elevation to >5 for ~2 h). The species difference was even more pronounced for some analogues of **4** that showed a potent antisecretory activity in the Ghosh Schild rat ($ED_{50} < 0.5$ μmol/kg) but did not cause any significant pH elevation in the dog, e.g., the 5-(2-oxopropylcarboxamide) **27**, the 8-(2-ethylphenyl) derivative **109**, or the 3-cyclopropyl analogue **139**. The comparison of the carboxamides **11** and **13** illustrates that small structural changes that are readily tolerated in the Ghosh Schild rat can exert a strong influence on the pharmacological activity in the dog. Comparable ED_{50} values of 0.3 and 0.4 μmol/kg were determined for both alkoxyazetidines **11** (3-methoxy) and **13** (3-propoxy) in the rat. In the case of the methoxy derivative **11**, the recorded pH-metry curve was similar to the one of the candidate **4**, with an increase in pH to a value >5 for 6−8 h. In contrast, administration of the propoxy derivative **13** did not cause a noteworthy rise of the intragastric pH. The analysis of the pH curves obtained for the methylcarboxamides **21** and **129** in comparison to their dimethyl analogues **4** and **115** also indicates that the SAR in the fistula dog is distinct and different to the one observed for the Ghosh Schild rat. Whereas the removal of one methyl group from the dimethylcarboxamide residue present in **4** exerted little influence on the pharmacological activity in the rat (**4** and **21**: ED_{50} values of 0.23 and 0.25 μmol/kg), a significant difference in the duration of pH elevation was observed in the fistula dog (**4**: pH >5 for 8 h vs **21**: 2.5 h). Also in the 4-chloro-2-methylphenyl series, comparable ED_{50} values of 0.1 and 0.15 μmol/kg were determined for both analogues **115** and **129** in the Ghosh Schild rat. Interestingly, in this series, the methylcarboxamide caused a much more potent rise of the intragastric pH than the dimethylcarboxamide (**129**: pH >5 for 8 h vs **115**: 4 h).

Methodological differences between the two models might partly account for the differences observed in SAR. For example, two compounds with a comparable ED_{50} value in the Ghosh Schild rat could have very different inhibition profiles, one being a rapidly inversed inhibition whereas the other is more protracted, with inhibition of the pentagastrin response lasting for a considerable time. Against this background, the comparison of titration curves of selected 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles in the Ghosh Schild rat is of interest (Table 6, the same compounds were selected as in Table 5). As mentioned above, the experiments were conducted over a period of 300 min. Acid secretion was stimulated by iv administration of pentagastrin from $t = 30$ min to $t = 300$ min. Different doses of each P-CAB were administered after $t = 90$ min (2−8 rats/dose). At the highest dose investigated in the Ghosh Schild rat (1.0 μmol/kg), the maximum inhibition of acid output was achieved 60−90 min after administration of the respective P-CAB (*x* axis: 150−180 min, compound **115** was not examined at a dose of 1.0 μmol/kg). In most cases, the maximum inhibition of acid output was maintained until the end of the experiment (*x*-axis: 300 min). For compounds **13** and **27**, a distinct increase in acid output was observed in the period of 240−300 min, suggesting a more rapidly reversed inhibition in these cases. However, most of the investigated compounds showed a reasonable duration of action in the Ghosh Schild rat and the observed species differences cannot be attributed merely to different inhibition profiles. The 4-chloro-derivative **113**, for example, showed a long duration of action in the Ghosh Schild rat (Table 6) but only a short-lasting effect in the fistula dog (Table 5). The mode of administration is another difference between the two models (intraduodenally in the rat, orally in the dog). If any of the compounds was acid-sensitive, then some or most of the test compound might be degraded even before it gets to the gut for absorption. To this end, the stability of two of the target compounds shown in Table 5 in 0.1 N hydrochloric acid was examined at 37 °C over a period of 24 h. The P-CABs **4** and **11** were found to be acid-stable and, based on their chemical structure, it is reasonable to believe that neither of the other target compounds shown in Figure 5 is acid-sensitive.

The acquired in vitro eADME data (microsomal clearance) suggest that the species differences in efficacy cannot be explained by significant differences in stability of the parent compounds in the dog/rat. Kinetic investigations, i.e., the determination of the concentration of the respective P-CAB in the serum of the dog, have not yet been conducted for a satisfactory number of 3,6,7,8-tetrahydrochromeno-[7,8-*d*]imidazoles. The result of such experiments might help to explain the pronounced species dependence of pharmacological activity observed in this structural class. Differences in the amino acid sequence and the 3D structure between the gastric proton pump of the dog and the H^+/K^+-ATPase of the rat might also account for these findings.

In conclusion, although doses of 9 μmol/kg of several target compounds (e.g., the azetidines **8**, **10**, and **11**, the ethylcarboxamide **22**, the cyclopropylcarboxamide **25**, and the 4-chloro-2-methyl derivatives **129**, **130**, and **131**, some pH-metry curves are not depicted in Table 5) were able to increase the intragastric pH to a value >5 for at least 5 h, none of the investigated 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles was more potent than the candidate **4**.

4. Summary

In conclusion, 65 enantiopure tetrahydrochromenoimidazoles were prepared either by hydrolysis of the readily available

candidate **4** or by Noyori asymmetric reduction of the respective ketone precursors and Mitsunobu cyclization of the resulting diols. A clear SAR was established with respect to the in vitro activity of the target compounds, their antisecretory properties in the Ghosh Schild rat, and their affinity toward the hERG channel. In the case of the carboxamide residue, small aliphatic groups and cycloaliphatic rings were found to be most beneficial. Within each series, an increase in lipophilicity resulted in enhanced hERG binding. Regarding the phenyl residue, ortho-/para-substitution or ortho-/para-disubstitution with a methyl group or chloro and fluoro atoms turned out to be most favorable. The presence of a para-chloro atom strongly enhanced both the pharmacological activity of the target compound in the Ghosh Schild rat and its affinity toward the hERG channel. For the most promising target compounds, efficacy and duration of the antisecretory effect was assessed by 24 h pH-metry in the fistula dog and, surprisingly, a different SAR was observed. Further investigations related to the bioavailability of the target compounds in the dog and the structural differences between the gastric proton pump enzyme expressed in both species will offer possible explanations for this finding. Several target compounds possess a profile comparable to the one of the tetrahydrochromenoimidazole **4** and constitute promising candidates for further development as drugs for the treatment of acid-related diseases.

5. Experimental Section

5.1. Chemistry. 5.1.1. General. All chemicals were purchased from the major chemical suppliers as highest purity grade and used without any further purification. The hydrogenation catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **82** was purchased from Johnson Matthey, Cambridge, UK. The progress of the reaction was monitored on Macherey-Nagel HPTLC plates Nano-SIL 20 UV_{254} (0.20 mm layer, nano silica gel 60 with fluorescence indicator UV_{254}) using dichloromethane/methanol as solvent system. Column chromatography was performed with Merck silica gel 60 (70−230 mesh ASTM) with the solvent mixtures specified in the corresponding experiment. Spots were visualized by iodine vapor or by irradiation with ultraviolet light (254 nm). Melting points (mp) were taken in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with Bruker FT-NMR spectrometers (DRX 200, AX 300, AV 400) at frequencies of 200, 300, or 400 MHz, respectively. $CDCl_3$ or DMSO-d_6 were used as solvents. The chemical shifts were reported as parts per million (δ ppm) with tetramethylsilane (TMS) as an internal standard. Elemental analysis was performed on a Carlo Erba 1106 C, H, N analyzer. The identity and the purity of all available title compounds was verified by HPLC/HRMS. High pressure liquid chromatography was performed under the following experimental conditions: Instrument: Agilent Technologies, 1200 series. Column: Agilent Extend C18 column 50 mm × 4.6 mm, 1.8 μm. Eluant for title compounds **8**, **9**, **11**, **12**, **14**−**20**, **22**−**24**, **26**, **27**, **29**, **32**−**35**: A, water/acetonitrile = 95:5 (v/v) + 0.1% of formic acid; B, acetonitrile. Eluant for title compounds **21**, **25**, **28**, **30**, **36**−**40**, **42**, **43**, **105**−**120**, **127**−**131**, **139**, **142**, **150**: A, water/acetonitrile = 90:10 (v/v) + 0.05% of formic acid, B, acetonitrile/water = 95:5 (v/v) + 0.05% of formic acid. Gradient: A/B: 100:0 (0−0.1 min), 100:0 to 0:100 (0.1−4 min), 0:100 to 100:0 (4−5 min), 100:0 (5−6 min). Flow rate: 1.0 mL/min (title compounds **8**, **9**, **11**, **12**, **14**−**20**, **22**−**24**, **26**, **27**, **29**, **32**−**35**), 1.2 mL/min (title compounds **21**, **25**, **28**, **30**, **36**−**40**, **42**, **43**, **105**−**120**, **127**−**131**, **139**, **142**, **150**). Temp: 50 °C. Detection: DAD at 220 nm. All target compounds with the exception of P-CABs **119** (90.8%) and **139** (94.1%) possessed a purity of >95% (see Supporting Information). High resolution mass spectra were obtained on an Agilent MSD-TOF instrument using electrospray ionization (ESI positive).

5.1.2. Conversion of 3,6,7,8-Tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamides into Carboxylic Acids. General Procedure 1 (Reduction of Carboxamides to Alcohols with Lithium Triethylborohydride). At a temperature of 0 °C, lithium triethylborohydride (1 M solution in THF, 3.5 equiv) was slowly added to a suspension of the respective carboxamide in THF (final substrate concentration ~0.15 M). The yellow solution was stirred for 2 h at room temperature. Water (~100 mL/mol carboxamide) and sodium hydroxide (330 g/mol carboxamide) was added to the reaction mixture, and stirring was continued for 20 min. A solution of hydrogen peroxide in water (30 wt %, ~1 L/mol carboxamide) was added slowly and with caution. The biphasic mixture was stirred at room temperature. Dichloromethane and water was added, and the phases were separated. The aqueous phase was extracted with dichloromethane (2×). The combined organic phases were dried over magnesium sulfate, and the solvent was evaporated. The crude title compound was used for the subsequent oxidation step without further purification.

[(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl]methanol (5). Preparation from carboxamide **4** (16.1 g, 44.4 mmol) and lithium triethylborohydride (1 M solution in THF, 155 mL, 155 mmol) according to general procedure 1. Yield: >100% (crude product, 16.6 g of a yellow solid). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.98 (m_c, 1 H), 2.20 (m_c, 1 H), 2.38 (s, 3 H), 2.45 (s, 3 H), 2.89 (m_c, 2 H), 3.66 (s, 3 H), 4.55 (m_c, 2 H), 5.04 (t, 1 H), 5.22 (dd, 1 H), 7.05 (s, 1 H), 7.26 (m_c, 3 H), 7.48 (m_c, 1 H). HRMS calcd for $C_{20}H_{23}N_2O_2$ m/z (MH^+), 323.1754; found, 323.1755.

[(8*S*)-8-(4-Chlorophenyl)-2,3-dimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl]methanol (121). Preparation from carboxamide **113** (9.7 g, 25.3 mmol) and lithium triethylborohydride (1 M solution in THF, 91 mL, 91 mmol) according to general procedure 1. Yield: 35% (crude product, 3.0 g). The aqueous phase was filtered over a pad of silica gel. The silica gel was extracted with a mixture of dichloromethane (600 mL) and methanol (300 mL). Evaporation of the solvent furnished another batch of the title compound (5.2 g, 60% yield). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.04 (m_c, 1 H), 2.26 (m_c, 1 H), 2.46 (s, 3 H), 2.71 (m_c, 1 H), 2.87 (m_c, 1 H), 3.67 (s, 3 H), 4.53 (d, 2 H), 5.02 (t, 1 H), 5.16 (dd, 1 H), 7.04 (s, 1 H), 7.49 (m_c, 4 H).

[(8*S*)-8-(4-Chloro-2-methylphenyl)-2,3-dimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl]methanol (122). Preparation from carboxamide **115** (8.4 g, <21.1 mmol) and lithium triethylborohydride (1 M solution in THF, 64 mL, 64 mmol) according to general procedure 1. Yield: 72% (crude product, 5.4 g of a beige solid). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.95 (m_c, 1 H), 2.25 (m_c, 1 H), 2.38 (s, 3 H), 2.45 (s, 3 H), 2.91 (m_c, 2 H), 3.67 (s, 3 H), 4.56 (bs, 2 H), 5.04 (bt, 1 H), 5.22 (d, 1 H), 7.05 (s, 1 H), 7.33 (m_c, 2 H), 7.49−7.65 (m, 1 H). HRMS calcd for $C_{20}H_{22}ClN_2O_2$ m/z (MH^+), 357.1364; found, 357.1365.

General Procedure 2 (Oxidation of Alcohols to Aldehydes under Parikh−Doering Conditions).[27] Sulfur trioxide pyridine complex (~3.0 equiv) was added portionwise to a suspension of the respective alcohol in DMSO/triethylamine = 3:2 (v/v), substrate concentration ~0.20 M. The reaction mixture was stirred for 3−17 h at room temperature, and water was added. The title compound was isolated by filtration and dried in vacuo.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carbaldehyde (6). *Prepared by reduction of carboxamide **4** with lithium aluminum hydride*: Lithium aluminum hydride (20 mg, 0.54 mmol) was added to a suspension of carboxamide **4** (300 mg, 0.83 mmol) in THF (5 mL). The reaction mixture was stirred for 1 h at room temperature and quenched by addition of water (20 μL), 4 N sodium hydroxide solution (20 μL), and more water (60 μL). The organic phase was dried over sodium sulfate, and the solvent was evaporated. The

residue (190 mg of a colorless foam) was purified by column chromatography (30 g of silica gel, eluant: dichloromethane). Evaporation of the corresponding fractions afforded the title compound in 46% yield (120 mg of a colorless foam). *Prepared by oxidation of alcohol **5** with Dess Martin Periodinane*: A solution of alcohol **5** (300 mg, 0.93 mmol) in dichloromethane (8 mL) was added to a solution of Dess−Martin periodinane (430 mg, 1.01 mmol) in dichloromethane (8 mL). After a reaction time of 2 h at room temperature, 1 N sodium hydroxide solution (10 mL) was added and stirring was continued for 10 min. The phases were separated. The organic phase was washed with 1.5 M sodium hydroxide solution (2×). The aqueous phase was extracted with dichloromethane (1×). The combined organic phases were dried over sodium sulfate, and the solvent was evaporated. The residue was purified by column chromatography [30 g of silica gel, eluant: dichloromethane/methanol = 100:1 (v/v)]. Evaporation of the corresponding fractions afforded the title compound (140 mg of a colorless solid, 49% yield). *Prepared by Parikh−Doering oxidation of alcohol **5***: Preparation from alcohol **5** (8.0 g, 24.8 mmol) and sulfur trioxide pyridine complex (12.8 g, 80.4 mmol) according to general procedure 2. Yield: 78% (6.2 g of a brown solid); mp 216−220 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.98 (m_c, 1 H), 2.29 (m_c, 1 H), 2.39 (s, 3 H), 2.54 (s, 3 H), 3.34 (m_c, 2 H), 3.77 (s, 3 H), 5.32 (dd, 1 H), 7.27 (m_c, 3 H), 7.48 (m_c, 1 H), 7.69 (m_c, 1 H), 10.17 (s, 1 H). HRMS calcd for $C_{20}H_{21}N_2O_2$ m/z (MH^+), 321.1598; found, 321.1598.

(8*S*)-8-(4-Chlorophenyl)-2,3-dimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carbaldehyde (123). Preparation from alcohol **121** (5.1 g, 14.9 mmol) and sulfur trioxide pyridine complex (7.1 g, 44.6 mmol) according to general procedure 2. Yield: 96% (4.86 g of a colorless solid); mp 260−262 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.04 (m_c, 1 H), 2.30 (m_c, 1 H), 2.54 (s, 3 H), 3.26 (m_c, 2 H), 3.78 (s, 3 H), 5.25 (dd, 1 H), 7.50 (m_c, 4 H), 7.70 (s, 1 H), 10.14 (s, 1 H).

(8*S*)-8-(4-Chloro-2-methylphenyl)-2,3-dimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carbaldehyde (124). Preparation from alcohol **122** (5.3 g, 14.9 mmol) and sulfur trioxide pyridine complex (7.1 g, 44.6 mmol) according to general procedure 2. Yield: 28% (1.43 g of a colorless solid). After a period of 3 days, a second batch of the title compound (1.82 g, 34% yield) was isolated by filtration of the mother liquor and washing of the precipitate with water (20 mL); mp 170−172 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.97 (m_c, 1 H), 2.29 (m_c, 1 H), 2.39 (s, 3 H), 2.53 (s, 3 H), 3.32 (m_c), 3.78 (s, 3 H), 5.31 (d, 1 H), 7.34 (m_c, 2 H), 7.49 (m_c, 1 H), 7.71 (s, 1 H), 10.17 (s, 1 H). HRMS calcd for $C_{20}H_{20}ClN_2O_2$ m/z (MH^+), 355.1208; found, 355.1210.

General Procedure 3 (Oxidation of Aldehydes to Carboxylic Acids under Kraus Conditions).[28] A solution of sodium chlorite (1.3−1.7 equiv) and sodium dihydrogen phosphate monohydrate (1.2−2.0 equiv) in water was added to a suspension of the respective aldehyde in *tert*-butanol and 2-methyl-2-butene [final substrate concentration ~0.15 M, ratio of water/*tert*-butanol/2-methyl-2-butene = 15:45:40 (v/v/v)]. After a period of 5−20 h at 40−45 °C, the reaction mixture was diluted with water. Stirring was continued for several minutes, and the title compound was isolated by filtration.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxylic Acid (7). *Prepared by oxidation of aldehyde **6***: Oxidation of aldehyde **6** (6.1 g, 19.1 mmol) according to general procedure 3. Yield: 91% (5.8 g of a colorless solid); mp 297−299 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.93 (m_c, 1 H), 2.26 (m_c, 1 H), 2.39 (s, 3 H), 2.51 (s), 3.24 (m_c, 2 H), 3.72 (s, 3 H), 5.30 (dd, 1 H), 7.26 (m_c, 3 H), 7.47 (m_c, 1 H), 7.64 (s, 1 H), 12.55 (bs, 1 H). *Prepared by hydrolysis of carboxamide **4***: Carboxamide **4** (90.0 g, 0.25 mol) and anhydrous sodium hydroxide beads (100 g, 2.5 mol) were dissolved in ethylene glycol (900 mL). In a three-neck flask equipped with a distillation bridge, the reaction mixture was heated at 195 °C for 2 d. The reaction mixture was cooled to room temperature, transferred into a 20 L vessel, and treated with concentrated hydrochloric acid (adjustment of a pH value of 4−5, approximately 210 mL) and water (9 L). The colorless suspension was stirred for 3 h at room temperature. The title compound (67.0 g of a colorless solid, 80% yield) was isolated by filtration; mp > 285 °C (decomp). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.93 (m_c, 1 H), 2.25 (m_c, 1 H), 2.39 (s, 3 H), 2.50 (s), 3.24 (m_c, 2 H), 3.72 (s, 3 H), 5.30 (dd, 1 H), 7.26 (m_c, 3 H), 7.47 (m_c, 1 H), 7.64 (s, 1 H), 12.56 (bs, 1 H). HRMS calcd for $C_{20}H_{21}N_2O_3$ m/z (MH^+), 337.1547; found, 337.1538.

(8*S*)-8-(4-Chlorophenyl)-2,3-dimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxylic Acid (125). Oxidation of aldehyde **123** (6.1 g, 17.9 mmol) according to general procedure 3. Yield: 97% (6.18 g of a colorless solid); mp 348 °C (decomp). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.00 (m_c, 1 H), 2.26 (m_c, 1 H), 2.50 (s), 3.16 (m_c, 2 H), 3.72 (s, 3 H), 5.23 (dd, 1 H), 7.49 (m_c, 4 H), 7.63 (s, 1 H).

(8*S*)-8-(4-Chloro-2-methylphenyl)-2,3-dimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxylic Acid (126). Oxidation of aldehyde **124** (3.2 g, 9.0 mmol) according to general procedure 3. Yield: > 100% (3.61 g of a colorless solid, presumably due to the presence of inorganic salts). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.92 (m_c, 1 H), 2.26 (m_c, 1 H), 2.40 (s, 3 H), 2.50 (s), 3.23 (m_c, 2 H), 3.72 (s, 3 H), 5.30 (d, 1 H), 7.32 (m_c, 2 H), 7.50 (m_c, 1 H), 7.62 (s, 1 H). HRMS calcd for $C_{20}H_{20}ClN_2O_3$ m/z (MH^+), 371.1157; found, 371.1153.

5.1.3. Conversion of 3,6,7,8-Tetrahydrochromeno[7,8-*d*]imidazole-5-carboxylic Acids into Carboxamides. General Procedure 4 (Conversion of Carboxylic Acids into Carboxamides Using EDC-HCl). *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC-HCl, 1.3−2.0 equiv) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) was added to a suspension of the corresponding carboxylic acid in dichloromethane (10−15 mL). Stirring at room temperature afforded a solution, which was treated with the corresponding amine (1.0−3.0 equiv) or the hydrochloride salt of the corresponding amine (1.0−3.0 equiv) and triethylamine (1.1−6 equiv). After a period of 0.5−18 h at room temperature, the corresponding title compound was isolated as described in workup procedure 1.

General Procedure 5 (Conversion of Carboxylic Acids into Carboxamides Using TBTU). *N*,*N*-Diisopropylethylamine (DIPEA, 2.5 equiv) was added to a suspension of the corresponding carboxylic acid and *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU, 1.5 equiv) in DMF. After heating at 40 °C for 0.5−1 h, a solution was obtained. After addition of the corresponding amine or the hydrochloride salt of the corresponding amine (1.3−3.0 equiv), the reaction mixture was heated at 40 °C for 1−2 h or stirred at room temperature for 17 h and the corresponding title compound was isolated as described in workup procedure 1 or 2.

General Procedure 6 (Conversion of Carboxylic Acids into Carboxamides Using CDI). A solution of the corresponding carboxylic acid and 1,1′-carbonyldiimidazole (CDI, 2.0 equiv) in dichloromethane was stirred for 1−1.5 h at room temperature. The corresponding amine (2.0 equiv) and a drop of acetic acid was added and stirring was continued for 4−17 h at room temperature. The corresponding title compound was isolated as described in workup procedure 3.

General Procedure 7 (Conversion of Carboxylic Acids into Carboxamides Using TBTU). The corresponding amine or the hydrochloride salt of the corresponding amine (2.0 equiv) was added to a solution of the corresponding carboxylic acid (200 mg), *N*,*N*-diisopropylethylamine (DIPEA, 2.5 equiv), and *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU, 1.5 equiv) in DMF (5 mL). The reaction mixture was stirred at room temperature for 2 h, and the corresponding title compound was isolated as described in workup procedure 2.

Workup Procedure 1 (Isolation of Carboxamides). After addition of water, the phases were separated. The organic phase was

washed with sodium bicarbonate solution (1−2×) and water (1×). The combined aqueous phases were extracted with dichloromethane (1−2×). The combined organic phases were dried over magnesium sulfate or sodium sulfate, the solvent was evaporated, and the crude product was purified by column chromatography.

Workup Procedure 2 (Isolation of Carboxamides). The reaction mixture was poured on a mixture of dichloromethane and water. The phases were separated and the aqueous phase was extracted with dichloromethane (2×). The combined organic phases were washed with water, dried over sodium sulfate, and the solvent was evaporated. The crude product was purified by column chromatography on silica gel and crystallization/washing. The solvents employed for column chromatography, crystallization, and washing are specified in the corresponding experiments.

Workup Procedure 3 (Isolation of Carboxamides). The reaction mixture was poured on water and a pH-value of 8 was adjusted by addition of saturated sodium bicarbonate solution. The aqueous phase was extracted with dichloromethane (2×). The combined organic phases were evaporated to dryness. The title compound was purified by column chromatography on silica gel and crystallization/washing. The solvents employed for column chromatography, crystallization, and washing are specified in the corresponding experiments.

(8*S*)-5-[(Azetidin-1-yl)carbonyl]-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (8). Preparation from carboxylic acid **7** (1.0 g, 3.0 mmol) and azetidine (290 μL, 4.23 mmol) according to general procedure 7/workup procedure 1. Eluant for column chromatography: dichloromethane/methanol = 50:1 (v/v). Yield: 53% (600 mg of a colorless solid); mp 177−178 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.96 (m_c, 1 H), 2.22 (m_c, 3 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.81 (m_c, 1 H), 3.04 (m_c, 1 H), 3.69 (s, 3 H), 3.87 (m_c, 1 H), 4.03 (m_c, 3 H), 5.31 (dd, 1 H), 7.03 (s, 1 H), 7.25 (m_c, 3 H), 7.46 (m_c, 1 H). HRMS calcd for $C_{23}H_{26}N_3O_2$ m/z (MH^+), 376.2020; found, 376.2020.

(8*S*)-5-[(3-Fluoroazetidin-1-yl)carbonyl]-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (9). Preparation from carboxylic acid **7** (0.5 g, 1.5 mmol) and 3-fluoroazetidine hydrochloride (418 mg, 3.75 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Solvent for washing: diethyl ether (10 mL)/acetone (0.5 mL). Yield: 76% (450 mg of a colorless solid); mp 130−132 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.96 (m_c, 1 H), 2.22 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s), 2.85 (m_c, 1 H), 3.05 (m_c, 1 H), 3.70 (s, 3 H), 3.90−4.50 (m, 4 H), 5.32, 5.43 (d, bd, 2 H), 7.09 (s, 1 H), 7.25 (m_c, 3 H), 7.46 (m_c, 1 H). HRMS calcd for $C_{23}H_{25}FN_3O_2$ m/z (MH^+), 394.1925; found, 394.1933. Anal. ($C_{23}H_{24}FN_3O_2$): C, H, N.

(8*S*)-5-[(3,3-Difluoroazetidin-1-yl)carbonyl]-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (10). Preparation from carboxylic acid **7** (0.5 g, 1.5 mmol) and 3,3-difluoroazetidine hydrochloride (388 mg, 3.00 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Solvent for washing: diisopropyl ether (5 mL)/diethyl ether (5 mL)/petroleum ether (5 mL). Yield: 63% (390 mg of a colorless solid); mp 202−203 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.95 (m_c, 1 H), 2.22 (m_c, 1 H), 2.39 (s, 3 H), 2.48 (s, 3 H), 2.87 (m_c, 1 H), 3.09 (m_c, 1 H), 3.72 (s, 3 H), 4.46 (m_c, bs, 4 H), 5.32 (d, 1 H), 7.19 (s, 1 H), 7.25 (m_c, 3 H), 7.47 (m_c, 1 H).

(8*S*)-5-[(3-Methoxyazetidin-1-yl)carbonyl]-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (11). Preparation from carboxylic acid **7** (0.9 g, 2.7 mmol) and 3-methoxyazetidine hydrochloride (380 mg, 3.1 mmol) according to general procedure 7/workup procedure 1. Eluant for column chromatography: dichloromethane/methanol = 50:1 (v/v). Yield: 57% (650 mg of a colorless solid); mp 217 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.97 (m_c, 1 H), 2.20 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.79 (m_c, 1 H), 3.03 (m_c, 1 H), 3.21 (d, 3 H), 3.70, 3.83 (s, m_c, 5 H), 4.10, 4.22 (m_c, bs, 3 H), 5.31 (d, 1 H), 7.05 (s, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H). HRMS calcd for $C_{24}H_{28}N_3O_3$ m/z (MH^+), 406.2125; found, 406.2127. Anal. ($C_{24}H_{27}N_3O_3$): C, H, N.

(8*S*)-5-[(3-Ethoxyazetidin-1-yl)carbonyl]-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (12). Preparation from carboxylic acid **7** (500 mg, 1.5 mmol) and 3-ethoxyazetidine (303 mg, 3.00 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: first column, dichloromethane/methanol = 20:1 (v/v); second column, ethyl acetate/methanol = 9:1 (v/v). Yield: 43% (270 mg of a colorless foam). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.13 (m_c, 3 H), 1.95 (m_c, 1 H), 2.22 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.80 (m_c, 1 H), 3.04 (m_c, 1 H), 3.40 (m_c, 2 H), 3.70, 3.68−4.31 (s, m_c, 8 H), 5.31 (d, 1 H), 7.06 (s, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H). HRMS calcd for $C_{25}H_{30}N_3O_3$ m/z (MH^+), 420.2282; found, 420.2290.

(8*S*)-5-[(3-Propoxyazetidin-1-yl)carbonyl]-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (13). Preparation from carboxylic acid **7** (0.5 g, 1.5 mmol) and 3-propoxyazetidine (346 mg, 3.00 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Solvent for crystallization: ethyl acetate (1 mL)/diethyl ether (10 mL). Yield: 40% (260 mg of a colorless solid). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 0.87 (m_c, 3 H), 1.51 (m_c, 2 H), 1.95 (m_c, 1 H), 2.20 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.80 (m_c, 1 H), 3.02 (m_c, 1 H), 3.29 (m_c), 3.70, 3.82, 3.93, 4.02, 4.18, 4.28 (s, 5 m_c, 8 H), 5.31 (d, 1 H), 7.06 (s, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H).

(8*S*)-5-[(3-Hydroxyazetidin-1-yl)carbonyl]-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (14). Preparation from carboxylic acid **7** (0.5 g, 1.5 mmol) and 3-hydroxyazetidine hydrochloride (312 mg, 2.86 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Solvent for washing: acetone (0.5 mL)/diethyl ether (10 mL). Yield: 58% (340 mg of a colorless solid); mp 303 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.96 (m_c, 1 H), 2.21 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.80 (m_c, 1 H), 3.03 (m_c, 1 H), 3.69, 3.73 (s, m_c, 5 H), 4.01, 4.20 (2 m_c, 2 H), 4.49 (m_c, 1 H), 5.32 (d, 1 H), 5.71 (t, 1 H), 7.02 (s, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H). HRMS calcd for $C_{23}H_{26}N_3O_3$ m/z (MH^+), 392.1969; found, 392.1969. Anal. ($C_{23}H_{25}N_3O_3$): C, H, N.

1-{[(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl]carbonyl}-azetidin-3-ylmethanol (15). Preparation from carboxylic acid **7** (0.5 g, 1.5 mmol) and azetidin-3-ylmethanol (synthesis described in the Supporting Information, 260 mg, 2.97 mmol) according to general procedure 6/workup procedure 3. Eluant for column chromatography: toluene/dioxane/methanol = 60:35:5 (v/v/v). Solvent for crystallization: ethyl acetate/*n*-heptane. Yield: 58% (350 mg of colorless crystals); mp 222−225 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.97 (m_c, 1 H), 2.23 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.68 (m_c, 1 H), 2.81 (m_c, 1 H), 3.03 (m_c, 1 H), 3.53 (m_c, 3 H), 3.70, 3.70−4.07 (s, m, 6 H), 4.79 (m_c, 1 H), 5.31 (d, 1 H), 7.03 (s, 1 H), 7.27 (m_c, 3 H), 7.48 (m_c, 1 H). HRMS calcd for $C_{24}H_{28}N_3O_3$ m/z (MH^+), 406.2125; found, 406.2126.

1-{[(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl]carbonyl}-3-methylazetidin-3-ol (16). Preparation from carboxylic acid **7** (0.75 g, 2.2 mmol) and 3-methylazetidin-3-ol (synthesis described in the Supporting Information, 400 mg, 4.44 mmol) according to general procedure 6/workup procedure 3. Eluant for column chromatography: toluene/dioxane/methanol/triethylamine = 60:34:5:1 (v/v/v/v). Solvent for crystallization: ethyl acetate/*n*-heptane. Yield: 66% (590 mg of colorless crystals); mp 279−282 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.40 (d, 3 H), 1.99 (m_c, 1 H), 2.23 (m_c, 1 H), 2.39 (s, 3 H), 2.47 (s, 3 H), 2.81 (m_c, 1 H), 3.04 (m_c, 1 H), 3.69 (s, m_c, 4 H), 3.86 (m_c, 3 H), 5.32 (d, 1 H), 5.64 (d, 1 H), 7.02 (s, 1 H), 7.25 (m_c, 3 H), 7.46 (m_c, 1 H). HRMS calcd for $C_{24}H_{28}N_3O_3$ m/z (MH^+), 406.2125; found, 406.2119.

(8*S*)-5-[(3-Methoxy-3-methylazetidin-1-yl)carbonyl]-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (17). Preparation from carboxylic acid **7** (0.75 g, 2.2 mmol) and 3-methoxy-3-methylazetidine (synthesis described in the Supporting Information, 450 mg, 4.44 mmol) according to general procedure 6/workup procedure 3. Eluant for column chromatography: toluene/dioxane/methanol/triethylamine = 60:35:5:1 (v/v/v/v). Solvent for crystallization: ethyl acetate/*n*-heptane. Yield: 28% (260 mg of colorless crystals); mp 207−208 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.43 (d, 3 H), 1.97 (m_c, 1 H), 2.22 (m_c, 1 H), 2.39 (s, 3 H), 2.47 (s, 3 H), 2.80 (m_c, 1 H), 3.04 (m_c, 1 H), 3.17 (d, 3 H), 3.70, 3.62−4.01 (s, m, 7 H), 5.32 (d, 1 H), 7.07 (s, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H). HRMS calcd for $C_{25}H_{30}N_3O_3$ *m*/*z* (MH^+), 420.2282; found, 420.2282. Anal. ($C_{25}H_{29}N_3O_3$): C, H, N.

1-{[(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl]carbonyl}-*N*,*N*-dimethylazetidine-3-carboxamide (18). Preparation from carboxylic acid **7** (0.5 g, 1.5 mmol) and *N*,*N*-dimethylazetidine-3-carboxamide (synthesis described in the Supporting Information, 380 mg, 2.97 mmol) according to general procedure 6/workup procedure 3. Eluant for column chromatography: first column, toluene/dioxane/methanol = 60:35:5 (v/v/v); second column, dichloromethane/methanol = 100:3 (v/v); third column, toluene/dioxane/methanol = 60:35:5 (v/v/v). Yield: 41% (268 mg of a colorless solid); mp 100−105 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.95 (m_c, 1 H), 2.23 (m_c, 1 H), 2.39 (s, 3 H), 2.47 (s, 3 H), 2.83, 2.83, 2.85 (s, m_c, s, 7 H), 3.70, 3.76 (s, m_c, 4 H), 4.06 (m_c, 4 H), 5.32 (dd, 1 H), 7.03 (s, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H). HRMS calcd for $C_{26}H_{31}N_4O_3$ *m*/*z* (MH^+), 447.2391; found, 447.2394.

(8*S*)-1-[(2,3-Dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl)carbonyl]azetidine-2-carboxamide (19). Preparation from carboxylic acid **7** (0.5 g, 1.5 mmol) and azetidine-2-carboxamide (300 mg, 3.00 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Solvent for washing: acetone (0.5 mL)/diethyl ether (20 mL)/methanol (0.1 mL). Yield: 68% (430 mg of an orange solid); mp 177−179 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, mixture of stereoisomers): δ = 1.95 (m_c, 1 H), 2.19 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, bs), 2.70−3.20 (m, 3 H), 3.70, 3.67−4.06 (s, m, 5 H), 4.71 (m_c, 1 H), 5.31 (m_c, 1 H), 7.01−7.53 (m, 7 H). HRMS calcd for $C_{24}H_{27}N_4O_3$ *m*/*z* (MH^+), 419.2078; found, 419.2086.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (20). Preparation from carboxylic acid **7** (5.0 g, 15.0 mmol) and ammonia (6.5 mL of a 7 M solution in methanol, 45.5 mmol) according to general procedure 5. The reaction mixture was poured on saturated sodium bicarbonate solution (400 mL). The phases were separated and the aqueous phase extracted with dichloromethane (3 × 300 mL). The combined organic phases were dried over sodium sulfate and the solvent was evaporated. The title compound was washed with a mixture of acetone (20 mL) and diethyl ether (30 mL). Yield: 90% (4.5 g of a colorless solid). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.94 (m_c, 1 H), 2.23 (m_c, 1 H), 2.38 (s, 3 H), 2.48 (s, 3 H), 2.95 (m_c, 1 H), 3.16 (m_c, 1 H), 3.69 (s, 3 H), 5.29 (d, 1 H), 7.18 (s, 1 H), 7.26 (m_c, 4 H), 7.47 (m_c, 1 H), 7.62 (bs, 1 H). HRMS calcd for $C_{20}H_{22}N_3O_2$ *m*/*z* (MH^+), 336.1707; found, 336.1709.

(8*S*)-*N*-Ethyl-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (22). Preparation from carboxylic acid **7** (0.75 g, 2.2 mmol) and ethylamine hydrochloride (360 mg, 4.4 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 50:1 (v/v). Solvent for washing: diethyl ether (20 mL). Yield: 76% (610 mg of a colorless solid); mp 258 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.14 (t, 3 H), 1.92 (m_c, 1 H), 2.23 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.85 (m_c, 1 H), 3.11 (m_c, 1 H), 3.23 (q), 3.69 (s, 3 H), 5.29 (d, 1 H), 7.09 (s, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H), 7.99 (t, 1 H). HRMS calcd for $C_{22}H_{26}N_3O_2$ *m*/*z* (MH^+), 364.2020; found, 364.2022.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-*N*-propyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (23). Preparation from carboxylic acid **7** (0.50 g, 1.5 mmol) and propylamine (247 μL, 3.0 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Solvent for washing: diethyl ether/petroleum ether. Yield: 88% (500 mg of a colorless solid); mp 244 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 0.92 (t, 3 H), 1.54 (m_c, 2 H), 1.93 (m_c, 1 H), 2.23 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.85 (m_c, 1 H), 3.10 (m_c, 1 H), (3.20, m_c, 2 H), 3.69 (s, 3 H), 5.28 (d, 1 H), 7.08 (s, 1 H), 7.25 (m_c, 3 H), 7.47 (m_c, 1 H), 8.15 (t, 1 H). HRMS calcd for $C_{23}H_{28}N_3O_2$ *m*/*z* (MH^+), 378.2176; found, 378.2175. Anal. ($C_{23}H_{27}N_3O_2$): H, N. For C: calcd, 73.18; found, 72.34.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-*N*-(propan-2-yl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (24). Preparation from carboxylic acid **7** (0.50 g, 1.5 mmol) and isopropylamine (257 μL, 3.0 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: first column, dichloromethane/methanol = 50:1 (v/v); second column, dichloromethane/methanol = 20:1 (v/v). Solvent for washing: diethyl ether (20 mL). Yield: 57% (320 mg of a colorless solid); mp 249 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.17 (t, 6 H), 1.94 (m_c, 1 H), 2.24 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.84 (m_c, 1 H), 3.10 (m_c, 1 H), 3.70 (s, 3 H), 4.06 (m_c, 1 H), 5.28 (d, 1 H), 7.06 (s, 1 H), 7.26 (m_c, 3 H), 7.47 (m_c, 1 H), 8.00 (d, 1 H). HRMS calcd for $C_{23}H_{28}N_3O_2$ *m*/*z* (MH^+), 378.2175; found, 378.2175. Anal. ($C_{23}H_{27}N_3O_2$): C, H, N.

(8*S*)-*N*-(Cyclopropylmethyl)-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (26). Preparation from carboxylic acid **7** (0.7 g, 2.1 mmol) and 1-cyclopropylmethanamine (200 μL, 162 mg, 2.3 mmol) according to general procedure 5/workup procedure 1. Eluant for column chromatography: dichloromethane/methanol = 50:1 (v/v). Yield: 79% (640 mg of an orange solid); mp 231 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.24 (m_c, 2 H), 0.44 (m_c, 2 H), 1.03 (m_c, 1 H), 1.93 (m_c, 1 H), 2.23 (m_c, 1 H), 2.39 (s, 3 H), 2.48 (s, 3 H), 2.87 (m_c, 1 H), 3.12 (m_c, 3 H), 3.70 (s, 3 H), 5.29 (d, 1 H), 7.10 (s, 1 H), 7.27 (m_c, 3 H), 7.47 (m_c, 1 H), 8.27 (t, 1 H). HRMS calcd for $C_{24}H_{28}N_3O_2$ *m*/*z* (MH^+), 390.2176; found, 390.2172.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-*N*-(2-oxopropyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (27). Preparation from carboxylic acid **7** (0.7 g, 2.1 mmol) and 1-aminoacetone hydrochloride (450 mg, 4.11 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: first column, dichloromethane/methanol = 13:1 (v/v); second column, ethyl acetate/triethylamine = 8:2 (v/v). Solvent for washing: diethyl ether. Yield: 70% (570 mg of a colorless solid, 99.2% ee). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.93 (m_c, 1 H), 2.16 (s, 3 H), 2.23 (m_c, 1 H), 2.39 (s, 3 H), 2.49 (s), 2.93 (m_c, 1 H), 3.14 (m_c, 1 H), 3.70 (s, 3 H), 4.06 (m_c, 2 H), 5.30 (d, 1 H), 7.18 (s, 1 H), 7.26 (m_c, 3 H), 7.47 (m_c, 1 H), 8.43 (t, 1 H). HRMS calcd for $C_{23}H_{26}N_3O_3$ *m*/*z* (MH^+), 392.1969; found, 392.1974. Anal. ($C_{23}H_{25}N_3O_3$): H, N. For C: calcd, 70.57; found, 69.94. HPLC analytical method: column, Chiralpak AD-H 250 mm × 4.6 mm, 5 μm; eluant, ethanol/*n*-heptane = 20:80 (v/v); flow rate, 1 mL/min; temperature, 25 °C; t_R (8*R*) = 15.6 min/0.4 area %; t_R (8*S*) = 28.4 min/99.6 area %.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-*N*-prop-2-yn-1-yl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (28). Preparation from carboxylic acid **7** (0.7 g, 2.1 mmol) and prop-2-yn-1-amine (180 μL, 155 mg, 2.8 mmol) according to general procedure 5/workup procedure 1. Eluant for column chromatography: dichloromethane/methanol = 50:1 (v/v). Yield: 77% (600 mg of a yellow solid); mp 206 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.93 (m_c, 1 H), 2.23 (m_c, 1 H), 2.38 (s, 3 H), 2.49 (s), 2.86 (m_c, 1 H), 3.13 (m_c, 2 H), 3.70 (s, 3 H), 4.03 (m_c, 2 H), 5.30 (d, 1 H), 7.13 (s, 1 H), 7.27 (m_c, 3 H), 7.47 (m_c, 1 H),

8.65 (t, 1 H). HRMS calcd for $C_{23}H_{24}N_3O_2$ *m*/*z* (MH^+), 374.1863; found, 374.1859.

(8*S*)-*N*-(Cyanomethyl)-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (29). Preparation from carboxylic acid **7** (0.5 g, 1.5 mmol) and aminoacetonitrile (168 mg, 3.0 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Solvent for washing: acetone (1 mL)/diethyl ether (10 mL). Yield: 75% (420 mg of a pale-yellow solid); mp 241−242 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.93 (m_c, 1 H), 2.24 (m_c, 1 H), 2.39 (s, 3 H), 2.49 (s), 2.87 (m_c, 1 H), 3.15 (m_c, 1 H), 3.71 (s, 3 H), 4.30 (d, 2 H), 5.31 (d, 1 H), 7.20 (s, 1 H), 7.26 (m_c, 3 H), 7.47 (m_c, 1 H), 8.90 (t, 1 H). HRMS calcd for $C_{22}H_{23}N_4O_2$ *m*/*z* (MH^+), 375.1816; found, 375.1822.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-*N*-[2-(methylsulfanyl)-ethyl]-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (30). Preparation from carboxylic acid **7** (0.8 g, 2.4 mmol) and 2-(methylthio)ethanamine (430 μL, 421 mg, 4.6 mmol) according to general procedure 7/workup procedure 1. Eluant for column chromatography: dichloromethane/methanol = 50:1 (v/v). Yield: 54% (530 mg of an off-white solid); mp 210 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.93 (m_c, 1 H), 2.12 (s, 3 H), 2.23 (m_c, 1 H), 2.38 (s, 3 H), 2.48 (s), 2.67 (t, 2 H), 2.89 (m_c, 1 H), 3.13 (m_c, 1 H), 3.42 (m_c, 2 H), 3.69 (s, 3 H), 5.29 (dd, 1 H), 7.11 (s, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H), 8.27 (t, 1 H). HRMS calcd for $C_{23}H_{28}N_3O_2S$ *m*/*z* (MH^+), 410.1897; found, 410.1898.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-*N*-[2-(methylsulfinyl)-ethyl]-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (31). An aqueous solution of sodium periodate (175 mg, 0.82 mmol, in 1 mL of water) was added to a solution of sulfide **30** (200 mg, 0.60 mmol) in methanol (8 mL). The colorless suspension was stirred for 1 h at room temperature and poured on a mixture of water (12 mL) and dichloromethane (20 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 5 mL). The combined organic phases were washed with water (1×), dried over sodium sulfate, and the solvent was evaporated. The residue (230 mg of a colorless solid) was purified by column chromatography [60 g of silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)] and washed with diethyl ether. The title compound was isolated in 43% yield (90 mg of a colorless solid); mp 150−152 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.94 (m_c, 1 H), 2.23 (m_c, 1 H), 2.38 (s, 3 H), 2.48 (s, 3 H), 2.62 (s, 3 H), 2.91 (m_c, 2 H), 3.11 (m_c, 2 H), 3.61 (m_c, 2 H), 3.69 (s, 3 H), 5.30 (d, 1 H), 7.14 (d, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H), 8.42 (t, 1 H).

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-*N*-oxetan-3-yl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (32). Preparation from carboxylic acid **7** (0.50 g, 1.5 mmol) and oxetan-3-amine hydrochloride (412 mg, 3.76 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Solvent for washing: acetone (0.5 mL)/diethyl ether (10 mL). Yield: 65% (381 mg of a colorless solid); mp 274−275 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.94 (m_c, 1 H), 2.23 (m_c, 1 H), 2.38 (s, 3 H), 2.48 (s, 3 H), 2.85 (m_c, 1 H), 3.12 (m_c, 1 H), 3.71 (s, 3 H), 4.59 (m_c, 2 H), 4.79 (m_c, 2 H), 4.98 (m_c, 1 H), 5.29 (d, 1 H), 7.19 (s, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H), 8.90 (d, 1 H). HRMS calcd for $C_{23}H_{26}N_3O_3$ *m*/*z* (MH^+), 392.1969; found, 392.1969. Anal. ($C_{23}H_{25}N_3O_3$): C, H, N.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-*N*-(tetrahydrofuran-2-ylmethyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (33). Preparation from carboxylic acid **7** (0.7 g, 2.1 mmol) and 1-tetrahydrofuran-2-ylmethanamine (430 μL, 421 mg, 4.2 mmol) according to general procedure 5/workup procedure 1. Eluant for column chromatography: dichloromethane/methanol = 10:1 (v/v). Yield: 74% (650 mg of a yellow solid); mp 201 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, mixture of stereoisomers): δ = 1.63 (m_c, 1 H), 1.84 (m_c, 2 H), 1.94 (m_c, 2 H), 2.22 (m_c, 1 H), 2.38 (s, 3 H), 2.48 (s, 3 H), 2.87 (m_c, 1 H), 3.12 (m_c, 1 H), 3.32 (m_c), 3.65, 3.69 (m_c, s, 4 H), 3.78 (m_c, 1 H), 3.99 (m_c, 1 H), 5.29 (d, 1 H), 7.10 (s, 1 H), 7.26 (m_c, 3 H), 7.47 (m_c, 1 H), 8.19 (m_c, 1 H). HRMS calcd for $C_{25}H_{30}N_3O_3$ *m*/*z* (MH^+), 420.2282; found, 420.2292.

(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-*N*-(tetrahydro-2*H*-pyran-2-ylmethyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (34). Preparation from carboxylic acid **7** (0.7 g, 2.1 mmol) and 1-tetrahydro-2*H*-pyran-2-ylmethanamine hydrochloride (630 mg, 4.2 mmol) according to general procedure 5/workup procedure 1. Eluant for column chromatography: dichloromethane/methanol. Yield: 91% (830 mg of a colorless solid); mp 208 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, mixture of stereoisomers): δ = 1.20 (m_c, 1 H), 1.47 (bs, 3 H), 1.67 (m_c, 1 H), 1.80 (bs, 1 H), 1.93 (m_c, 1 H), 2.22 (m_c, 1 H), 2.38 (s, 3 H), 2.48 (s, 3 H), 2.85 (m_c, 1 H), 3.12 (m_c, 1 H), 3.24 (m_c, 2 H), 3.36, 3.43 (2 m_c, 2 H), 3.78 (s, 3 H), 3.89 (m_c, 1 H), 5.29 (dd, 1 H), 7.10 (m_c, 1 H), 7.26 (m_c, 3 H), 7.47 (m_c, 1 H), 8.13 (m_c, 1 H). HRMS calcd for $C_{26}H_{32}N_3O_3$ *m*/*z* (MH^+), 434.2438; found, 434.2437.

(8*S*)-*N*-(2-Methoxyethyl)-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (35). Preparation from carboxylic acid **7** (0.50 g, 1.5 mmol) and 2-methoxyethylamine (170 μL, 1.9 mmol) according to general procedure 7/workup procedure 1. Eluant for column chromatography: ethyl acetate/ethanol = 10:1 (v/v). Yield: 36% (310 mg of a colorless solid). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.92 (m_c, 1 H), 2.23 (m_c, 1 H), 2.38 (s, 3 H), 2.48 (s, 3 H), 2.86 (m_c, 1 H), 3.12 (m_c, 1 H), 3.31 (s), 3.41 (m_c, 2 H), 3.48 (m_c, 2 H), 3.69 (s, 3 H), 5.29 (d, 1 H), 7.10 (s, 1 H), 7.26 (m_c, 3 H), 7.47 (m_c, 1 H), 8.19 (t, 1 H). HRMS calcd for $C_{23}H_{28}N_3O_3$ *m*/*z* (MH^+), 394.2125; found, 394.2127. Anal. ($C_{23}H_{27}N_3O_3$): C, H, N.

(8*S*)-*N*-(2-Methoxyethyl)-*N*,2,3-trimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (36). Preparation from carboxylic acid **7** (0.70 g, 2.1 mmol) and *N*-(methoxyethyl)methylamine (230 mg, 2.6 mmol) according to general procedure 7/workup procedure 1. Eluant for column chromatography: first column, ethyl acetate/ethanol = 50:1 (v/v); second column, ethyl acetate/ethanol = 150:1 (v/v). Yield: 21% (batch 1 obtained after first column, 180 mg of a colorless foam)/20% (batch 2 obtained after second column, 170 mg of a slightly yellow oil). ^{1}H NMR (DMSO-d_6, 300 MHz, 110 °C): δ = 2.04 (m_c, 1 H), 2.23 (m_c, 1 H), 2.39 (s, 3 H), 2.46 (s, 3 H), 2.69 (m_c, 1 H), 2.87, 2.88 (s, m_c, 7 H), 3.51 (bs, 4 H), 3.66 (s, 3 H), 5.32 (d, 1 H), 6.83 (s, 1 H), 7.21 (m_c, 3 H), 7.45 (m_c, 1 H). HRMS calcd for $C_{24}H_{30}N_3O_3$ *m*/*z* (MH^+), 408.2282; found, 408.2284.

(8*S*)-*N*-Methoxy-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (37). Preparation from carboxylic acid **7** (0.75 g, 2.2 mmol) and *O*-methylhydroxylamine hydrochloride (360 mg, 4.3 mmol) according to general procedure 5/workup procedure 1. Eluant for column chromatography: dichloromethane/methanol = 50:1 (v/v). Subsequent crystallization of the title compound (430 mg of a yellow foam) from 2-propanol. Yield: 30% (240 mg of a colorless solid); mp 160 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.98 (m_c, 1 H), 2.26 (m_c, 1 H), 2.39 (s, 3 H), 2.53 (s, 3 H), 2.88 (m_c, 1 H), 3.13 (m_c, 1 H), 3.74 (s, 6 H), 5.34 (d, 1 H), 7.21 (s, 1 H), 7.27 (m_c, 3 H), 7.46 (m_c, 1 H), 11.41 (bs, 1 H). HRMS calcd for $C_{21}H_{24}N_3O_3$ *m*/*z* (MH^+), 366.1812; found, 366.1811.

(8*S*)-*N*-Methoxy-*N*,2,3-trimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (38). Preparation from carboxylic acid **7** (0.8 g, 2.4 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (700 mg, 7.2 mmol) according to general procedure 7/workup procedure 1. Eluant for column chromatography: dichloromethane/methanol = 50:1 (v/v). Yield: 64% (580 mg of a brown solid); mp 168 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.98 (m_c, 1 H), 2.23 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.68 (m_c, 1 H), 2.97 (m_c, 1 H), 3.22 (s, 3 H), 3.55 (s, 3 H), 3.69 (s, 3 H), 5.31 (dd, 1 H), 7.04 (s, 1 H), 7.25 (m_c, 3 H), 7.47 (m_c, 1 H). HRMS calcd for $C_{22}H_{26}N_3O_3$ *m*/*z* (MH^+), 380.1969; found, 380.1968. Anal. ($C_{22}H_{25}N_3O_3$): C, H, N.

[(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl](morpholin-4-yl)methanone (40). Preparation from carboxylic acid **7** (0.8 g, 2.4 mmol) and morpholine (420 μL, 4.8 mmol) according to general procedure 7/workup procedure 1. Eluant for column chromatography: dichloromethane/methanol. Yield: 76% (740 mg of a colorless solid); mp 212 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.97 (bs, 1 H), 2.22 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.59−3.10 (bm, 2 H), 3.22 (bs, 2 H), 3.44, 3.54, 3.68 (3 bs, 9 H), 5.33 (d, 1 H), 6.96 (s, 1 H), 7.26 (m_c, 3 H), 7.46 (m_c, 1 H). HRMS calcd for $C_{24}H_{28}N_3O_3$ *m*/*z* (MH^+), 406.2125; found, 406.2112. Anal. ($C_{24}H_{27}N_3O_3$): C, H, N.

(8*S*)-*N*′-Acetyl-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carbohydrazide (41). Preparation from carboxylic acid **7** (0.70 g, 2.1 mmol) and acetohydrazide (593 mg, 8.0 mmol) according to general procedure 5/workup procedure 2. Purification: washing with methanol (1 mL) and diethyl ether (10 mL) instead of column chromatography. Yield: 75% (616 mg of a light-yellow solid); mp 240−242 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.93, 1.96 (s, m_c, 4 H), 2.25 (m_c, 1 H), 2.39 (s, 3 H), 2.50 (s), 2.96 (m_c, 1 H), 3.14 (m_c, 1 H), 3.74 (s, 3 H), 5.34 (dd, 1 H), 7.25 (m_c, 4 H), 7.48 (m_c, 1 H), 9.89 (bs, 1 H), 9.98 (bs, 1 H).

(8*S*)-2,3-Dimethyl-5-(5-methyl-1,3,4-oxadiazol-2-yl)-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (42). A solution of carbohydrazide **41** (580 mg, 1.48 mmol) in phosphorus oxychloride (4.8 mL) was heated at 50 °C for 1 h. The reaction mixture was poured on a mixture of ice−water (50 mL) and dichloromethane (50 mL) and a pH value of 8 was adjusted by addition of 6 N sodium hydroxide solution. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic phases were dried over sodium sulfate, and the solvent was evaporated. The residue (530 mg of a yellow oil) was purified by column chromatography [50 g of silica gel, eluant: dichloromethane/methanol = 50:1 (v/v)]. Evaporation of the corresponding fractions afforded a solid residue (240 mg), which was washed with diethyl ether (10 mL). The title compound was isolated in 42% yield (230 mg of a colorless solid); mp 190−192 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.01 (m_c, 1 H), 2.32 (m_c, 1 H), 2.40 (s, 3 H), 2.52 (s, 3 H), 2.60 (s, 3 H), 3.25 (m_c, 2 H), 3.76 (s, 3 H), 5.37 (dd, 1 H), 7.27 (m_c, 3 H), 7.49 (m_c, 1 H), 7.62 (s, 1 H). HRMS calcd for $C_{22}H_{23}N_4O_2$ *m*/*z* (MH^+), 375.1816; found, 375.1816. Anal. ($C_{22}H_{22}N_4O_2$): H, N. For C: calcd, 70.57; found, 69.82.

(8*S*)-8-(4-Chlorophenyl)-*N*,2,3-trimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (127). Preparation from carboxylic acid **125** (750 mg, 2.1 mmol) and methylamine (2 N solution in THF, 2.10 mL, 4.2 mmol) according to general procedure 7. The reaction mixture was concentrated to a volume of 10 mL, and diethyl ether (10 mL) added. After a period of 30 min, the title compound was isolated by filtration: 570 mg of a colorless solid (73% yield); mp 317 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.97 (m_c, 1 H), 2.23 (m_c, 1 H), 2.49 (s), 2.75, 2.78 (d, m_c, 4 H), 3.03 (m_c, 1 H), 3.69 (s, 3 H), 5.22 (dd, 1 H), 7.12 (s, 1 H), 7.49 (m_c, 4 H), 8.08 (q, 1 H). HRMS calcd for $C_{20}H_{21}ClN_3O_2$ *m*/*z* (MH^+), 370.1317; found, 370.1310. Anal. ($C_{20}H_{20}ClN_3O_2$): C, H, N.

Azetidin-1-yl[(8*S*)-8-(4-chlorophenyl)-2,3-dimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl]methanone (128). Preparation from carboxylic acid **125** (750 mg, 2.1 mmol) and azetidine (350 μL, 5.2 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 30:1 (v/v). Slurrying in diethyl ether. Yield: 72% (600 mg of a colorless solid); mp 281 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.01 (m_c, 1 H), 2.22 (m_c, 3 H), 2.48 (s, 3 H), 2.73 (m_c, 1 H), 2.95 (m_c, 1 H), 3.69 (s, 3 H), 3.85 (m_c, 1 H), 4.02 (m_c, 3 H), 5.24 (dd, 1 H), 7.04 (s, 1 H), 7.49 (m_c, 4 H). HRMS calcd for $C_{22}H_{23}ClN_3O_2$ *m*/*z* (MH^+), 396.1473; found, 396.1471.

(8*S*)-8-(4-Chloro-2-methylphenyl)-*N*,2,3-trimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (129). Preparation from carboxylic acid **126** (600 mg, 1.6 mmol) and methylamine (2 N solution in THF, 1.60 mL, 3.2 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Slurrying in acetone (0.5 mL) and diethyl ether (10 mL). Yield: 53% (324 mg of a colorless solid); mp 130−132 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.89 (m_c, 1 H), 2.21 (m_c, 1 H), 2.38 (s, 3 H), 2.48 (s, 3 H), 2.76 (d, 3 H), 2.85 (m_c, 1 H), 3.12 (m_c, 1 H), 3.69 (s, 3 H), 5.28 (d, 1 H), 7.13 (s, 1 H), 7.33 (m_c, 2 H), 7.47 (m_c, 1 H), 8.08 (q, 1 H). HRMS calcd for $C_{21}H_{23}ClN_3O_2$ *m*/*z* (MH^+), 384.1473; found, 384.1483.

Azetidin-1-yl[(8*S*)-8-(4-chloro-2-methylphenyl)-2,3-dimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl]methanone (130). Preparation from carboxylic acid **126** (600 mg, 1.6 mmol) and azetidine (215 μL, 3.2 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Slurrying in acetone (0.5 mL) and diethyl ether (10 mL). Yield: 53% (350 mg of a slightly yellow solid). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.92 (m_c, 1 H), 2.22 (m_c, 3 H), 2.39 (s, 3 H), 2.47 (s, 3 H), 2.80 (m_c, 1 H), 3.04 (m_c, 1 H), 3.69 (s, 3 H), 3.87 (m_c, 1 H), 4.01 (m_c, 3 H), 5.30 (d, 1 H), 7.04 (s, 1 H), 7.33 (m_c, 2 H), 7.47 (m_c, 1 H). HRMS calcd for $C_{23}H_{25}ClN_3O_2$ *m*/*z* (MH^+), 410.1630; found, 410.1636.

(8*S*)-8-(4-Chloro-2-methylphenyl)-5-[(3-methoxyazetidin-1-yl)carbonyl]-2,3-dimethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (131). Preparation from carboxylic acid **126** (500 mg, 1.35 mmol) and 3-methoxyazetidine hydrochloride (334 mg, 2.70 mmol) according to general procedure 5/workup procedure 2. Eluant for column chromatography: dichloromethane/methanol = 50:1 (v/v). Solvent for crystallization: acetone (0.5 mL)/petroleum ether (5 mL). Yield: 47% (280 mg of a pale-yellow solid); mp 193−195 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.92 (m_c, 1 H), 2.22 (m_c, 1 H), 2.39 (s, 3 H), 2.47 (s, 3 H), 2.78 (m_c, 1 H), 3.01 (m_c, 1 H), 3.21 (d, 3 H), 3.70 (s, 3 H), 3.87, 4.01, 4.20 (3 m_c, 5 H), 5.31 (d, 1 H), 7.07 (s, 1 H), 7.33, 7.34 (s, d, 2 H), 7.47 (d, 1 H). HRMS calcd for $C_{24}H_{27}ClN_3O_3$ *m*/*z* (MH^+), 440.1735; found, 440.1740. Anal. ($C_{24}H_{26}ClN_3O_3$): H, N. For C: calcd, 65.52; found, 65.04.

5.1.4. Synthesis and Asymmetric Reduction of Ketones. Mitsunobu Cyclization to 3,6,7,8-Tetrahydrochromeno[7,8-*d*]imidazoles. General Procedure 8 (Transformation of Mannich Bases into Ketones). A suspension of the Mannich base in toluene (0.1−0.5 M) was heated to 100 °C and the respective 1-[1-(aryl)-vinyl]-pyrrolidine (1.4 −2.5 equiv) was added dropwise. The reaction mixture was kept at 100 °C for 2.5−4 h. After cooling to room temperature, the solvent was evaporated in vacuo and the residue was purified as described below. The required 1-[1-(aryl)-vinyl]-pyrrolidines were prepared by titanium tetrachloride mediated condensation of the respective acetophenone derivative with pyrrolidine, see lit.[37]

5-[3-(2-Cyclopropylphenyl)-3-oxopropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (51). The title compound was prepared from Mannich base **46** (12.0 g, 41.3 mmol) and 1-[1-(2-cyclopropylphenyl)vinyl]pyrrolidine (12.1 g, 56.4 mmol) as described in general procedure 8. The crude product was purified by column chromatography [silica gel, eluant: dichloromethane, then dichloromethane/methanol = 20:1 (v/v)] and crystallization from 2-propanol: 8.7 g of an off-white solid (52% yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.64 (m_c, 2 H), 0.91 (m_c, 2 H), 2.22 (m_c, 1 H), 2.50 (s, 3 H), 2.61 (bm_c, 1 H), 2.76 (s, 3 H), 2.98, 3.07 (s, bs, 6 H), 3.66 (s, 3 H), 6.77 (s, 1 H), 7.04 (m_c, 1 H), 7.24 (m_c, 1 H), 7.38 (m_c, 1 H), 7.48 (m_c, 1 H), 9.97 (bs, 1 H). HRMS calcd for $C_{24}H_{28}N_3O_3$ *m*/*z* (MH^+), 406.2125; found, 406.2123.

5-[3-(4-Chlorophenyl)-3-oxopropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (54). The title compound was prepared from Mannich base **46** (31.5 g, 108.5

mmol) and 1-[1-(4-chlorophenyl)vinyl]pyrrolidine (56.0 g, 270.5 mmol) as described in general procedure 8. The crude product was purified by column chromatography [450 g of silica gel, eluant: dichloromethane, then dichloromethane/methanol = 20:1 (v/v)] and crystallization from acetone (50 mL): 14.0 g of a colorless solid (32% yield); mp 258−260 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.53 (s, 3 H), 2.78, 3.00, 3.15 (2 s, bs, 10 H), 3.69 (s, 3 H), 6.79 (s, 1 H), 7.58 (d, 2 H), 7.98 (d, 2 H), 9.95 (bs, 1 H). HRMS calcd for $C_{21}H_{23}ClN_3O_3$ *m*/*z* (MH^+), 400.1422; found, 400.1419. Anal. ($C_{21}H_{22}ClN_3O_3$): C, H, N.

5-[3-(4-Chloro-2-methylphenyl)-3-oxopropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (56). The title compound was prepared from Mannich base **46** (9.4 g, 32.4 mmol) and 1-[1-(4-chloro-2-methylphenyl)vinyl]pyrrolidine (11.5 g, 51.8 mmol) as described in general procedure 8. A suspension of the crude product in diisopropyl ether (100 mL) was stirred for 16 h at room temperature, and the precipitate was isolated by filtration. At a temperature of 50 °C, fumaric acid (1.9 g) was added to a solution of the obtained solid in 2-propanol (100 mL). After a period of 1 h at room temperature, the precipitate was isolated by filtration. The solid was dissolved in dichloromethane and saturated sodium bicarbonate solution. The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was evaporated. The residue was crystallized from a mixture of diisopropyl ether (80 mL) and ethyl acetate (20 mL). The title compound was isolated by filtration and dried in vacuo (7.1 g, 53% yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.41 (s, 3 H), 2.52 (s), 2.77 (s, 4 H), 2.99, 3.06 (s, bs, 5 H), 3.30 (bs), 3.69 (s, 3 H), 6.78 (s, 1 H), 7.37 (m_c, 2 H), 7.74 (d, 1 H), 10.13 (bs, 1 H). HRMS calcd for $C_{22}H_{25}ClN_3O_3$ *m*/*z* (MH^+), 414.1579; found, 414.1577. Anal. ($C_{22}H_{24}ClN_3O_3$): C, H, N.

5-[3-(2-Chloro-4-fluorophenyl)-3-oxopropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (57). The title compound was prepared from Mannich base **46** (41.5 g, 143 mmol) and 1-[1-(2-chloro-4-fluorophenyl)vinyl]pyrrolidine (65.2 g, 289 mmol) as described in general procedure 8 (reaction temperature: 70 °C). The crude product was purified by column chromatography [silica gel, eluant: dichloromethane/methanol = 95:5 (v/v)]. The resulting yellow oil was dissolved in acetone (200 mL), and fumaric acid (16.6 g, 143 mmol) was added. The suspension was stirred for 3 d at room temperature and the precipitate was isolated by filtration. The salt of the title compound with fumaric acid was washed with acetone, dried in vacuo at a temperature of 40 °C, dissolved in dichloromethane, and treated with saturated sodium bicarbonate solution (250 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3×). The combined organic phases were washed with water (80 mL), dried over sodium sulfate, and the solvent was evaporated. This afforded a 80:20 mixture of the title compound with 5-[3-(2-chloro-4-pyrrolidin-1-ylphenyl)-3-oxopropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (46.1 g, 77% yield). The compounds were separated by column chromatography [silica gel, eluant: ethyl acetate/methanol = 95:5 to 9:1 (v/v)] and obtained in 45% yield (26.7 g of title compound) and 9% yield (6.1 g of byproduct), respectively. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.61 (s, 3 H), 2.77, 2.87 (bs, s, 4 H), 3.15 (s, 3 H), 3.35 (m_c, 3 H), 3.66 (s, 3 H), 6.69 (s, 1 H), 6.99 (m_c, 1 H), 7.13 (m_c, 1 H), 7.65 (m_c, 1 H), 11.80 (bs, 1 H). HRMS calcd for $C_{21}H_{22}ClFN_3O_3$ *m*/*z* (MH^+), 418.1328; found, 418.1316. Anal. ($C_{21}H_{21}ClFN_3O_3$): C, H, N.

5-[3-(2,4-Dichlorophenyl)-3-oxopropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (58). The title compound was prepared from Mannich base **46** (13.7 g, 47.0 mmol) and 1-[1-(2,4-dichlorophenyl)vinyl]pyrrolidine (18.2 g, 75.3 mmol) as described in general procedure 8. A suspension of the crude product in diisopropyl ether (200 mL) was stirred for 30 min at reflux and for 17 h at room temperature. The precipitate was isolated by filtration. The crude title compound was suspended in acetone (100 mL), and fumaric acid (5.45 g) was added at reflux temperature. The mixture was stirred for 1 h at reflux and cooled to room temperature. The salt of the title compound with fumaric acid was isolated by filtration and suspended in dichloromethane (150 mL). The title compound was released by treatment with 1 N sodium hydroxide solution (3 × 50 mL). The organic phase was dried over magnesium sulfate, and the solvent was evaporated. The residue was slurried in 2-propanol (40 mL): 7.3 g of an off-white solid (36% yield). ^{1}H NMR (DMSO, 200 MHz): δ = 2.52 (s), 2.77, 2.80 (s, bs, 4 H), 2.98, 3.05 (s, m_c, 6 H), 3.66 (s, 3 H), 6.78 (s, 1 H), 7.54 (m_c, 1 H), 7.65 (m_c, 1 H), 7.73 (m_c, 1 H), 10.03 (bs, 1 H). HRMS calcd for $C_{21}H_{22}Cl_2N_3O_3$ *m*/*z* (MH^+), 434.1033; found, 434.1036.

4-Hydroxy-*N*,*N*,1,2-tetramethyl-5-[3-(naphthalen-2-yl)-3-oxopropyl]-1*H*-benzimidazole-6-carboxamide (59). The title compound was prepared from Mannich base **46** (2.6 g, 9.0 mmol) and 1-(1-naphthalen-2-yl-vinyl)pyrrolidine (3.45 g, 15.4 mmol) as described in general procedure 8. The crude product was dissolved in acetone (100 mL), fumaric acid (1.2 g) was added, and the solution was stirred overnight at room temperature. The precipitate was isolated by filtration and washed with acetone (2 × 20 mL). The salt of the title compound with fumaric acid was dissolved in dichloromethane (100 mL), and aqueous ammonia was added until a pH value of 9 was reached. The phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried over magnesium sulfate and concentrated in vacuo. The title compound was purified by column chromatography [silica gel, eluant: dichloromethane/methanol = 15:1 (v/v)] and crystallization from acetone: 0.48 g of a colorless solid (13% yield); mp 221−225 °C. ^{1}H NMR (DMSO, 200 MHz): δ = 2.54 (s, bs), 2.79, 2.90, 3.00 (s, bs, s, 9 H), 3.69 (s, 3 H), 6.81 (s, 1 H), 7.64 (m_c, 2 H), 8.00 (m_c, 3 H), 8.16 (m_c, 1 H), 8.72 (m_c, 1 H), 10.04 (bs, 1 H). HRMS calcd for $C_{25}H_{26}N_3O_3$ *m*/*z* (MH^+), 416.1969; found, 416.1964.

General Procedure 9 (Asymmetric Hydrogenation of Ketones). In a flask filled with argon, the corresponding ketone was suspended in 2-propanol and potassium *tert*-butylate solution (1 M in *tert*-butanol, 1.1 equiv) was slowly added (final substrate concentration 0.20−0.46 M). At a temperature of 50 °C, the hydrogenation catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **82** (S/C = 100:1) was added and stirring was continued for several minutes. The suspension was transferred into an autoclave, purged with hydrogen (3×), and hydrogenated at 70 °C and 80 bar pressure for 16−20 h. After cooling to room temperature and releasing of the hydrogen pressure, the reaction mixture was poured on saturated ammonium chloride solution. The mixture was extracted with dichloromethane (4×). The combined organic phases were dried over magnesium sulfate or sodium sulfate, and the solvent was evaporated. The residue was slurried in acetone. The title compound was isolated by filtration and dried in vacuo.

The optical purity of the title compound was determined either by HPLC (column: Daicel Chiralpak AD-H, 250 mm × 4.6 mm, 5 μm, flow rate: 1 mL/min, detection wavelength: 218 nm) or by capillary electrophoresis (instrument: Agilent CE-3D; capillary: Agilent 56/64.5 cm × 50 μm bare fused silica bubble; buffer: 50 mM sodium phosphate, pH 2.5; chiral selector: 40 mM heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin; voltage: 30 kV; temperature: 20 °C; detection wavelength: 219/226 nm).

5-[(3*R*)-3-(2-Cyclopropylphenyl)-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (93). The title compound was prepared by asymmetric reduction of ketone **51** (6.7 g, 16.5 mmol) as described in general procedure 9. Purification by column chromatography [silica gel, eluant: dichloromethane/methanol = 10:1 (v/v)] instead of slurrying in acetone: 4 g of a slightly green foam (61% yield, 92.6% ee). HPLC analytical method: t_R (3*R*) = 8.5 min/96.3 area %; t_R

(3*S*) = 11.2 min/3.7 area %. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.57 (m_c, 2 H), 0.83 (m_c, 2 H), 1.60−2.05, 1.92 (bs, m_c, 2 H), 2.50 (s), 2.59 (bs, 1 H), 2.70 (s, 3 H), 2.92 (s, 4 H), 3.65 (s, 3 H), 5.05 (bs, 2 H), 6.71 (s, 1 H), 6.89 (m_c, 1 H), 7.11 (m_c, 2 H), 7.43 (m_c, 1 H), 9.77 (bs, 1 H). HRMS calcd for $C_{24}H_{30}N_3O_3$ *m*/*z* (MH^+), 408.2282; found, 408.2276.

5-[(3*R*)-3-(4-Chlorophenyl)-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (96). The title compound was prepared by asymmetric reduction of ketone **54** (10.0 g, 25.0 mmol) as described in general procedure 9. The diol **96** precipitated when the reaction mixture was poured on a stirred mixture of saturated ammonium chloride solution (100 mL), dichloromethane (100 mL), and methanol (30 mL). The title compound was isolated by filtration and dried in vacuo: 6.0 g (60% yield, 68.0% ee). The organic phase of the filtrate was concentrated, and the sparingly soluble residue was washed with acetone (20 mL). This afforded a second batch of the title compound (30% yield, 70.8% ee). CE analytical method: t_M (3*S*) = 26.4 min/16.0 (14.6) area %; t_M (3*R*) = 26.9 min/84.0 (85.4) area %; mp 290−291 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.55−2.00 (m, 2 H), 2.15−2.50 (m), 2.50 (s), 2.67 (s, m_c, 4 H), 2.88 (s, 3 H), 3.64 (s, 3 H), 4.49 (t, 1 H), 5.24 (bs, 1 H), 6.69 (s, 1 H), 7.34 (m_c, 4 H), 9.75 (bs, 1 H). HRMS calcd for $C_{21}H_{25}ClN_3O_3$ *m*/*z* (MH^+), 402.1579; found, 402.1580.

5-[(3*R*)-3-(4-Chloro-2-methylphenyl)-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (98). The title compound was prepared by asymmetric reduction of ketone **56** (7.0 g, 16.9 mmol) as described in general procedure 9: 5.6 g of a colorless solid (84% yield, 90.6% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 80:20 (v/v); t_R (3*R*) = 19.4 min/95.3 area %; t_R (3*S*) = 25.4 min/4.7 area %. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.50−2.00 (m, 2 H), 2.21 (s, bs, 4 H), 2.50 (s, m_c), 2.69 (s, 3 H), 2.92 (s, 3 H), 3.64 (s, 3 H), 4.67 (bs, 1 H), 5.14 (bs, 1 H), 6.71 (s, 1 H), 7.20 (m_c, 2 H), 7.41 (d, 1 H), 9.80 (bs, 1 H). HRMS calcd for $C_{22}H_{27}ClN_3O_3$ *m*/*z* (MH^+), 416.1735; found, 416.1729. Anal. ($C_{22}H_{26}ClN_3O_3$): C, H. For N: calcd, 10.10; found, 9.54.

5-[(3*R*)-3-(2-Chloro-4-fluorophenyl)-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (99). The title compound was prepared by asymmetric reduction of ketone **57** (3 × 5.0 g, 3 × 12.0 mmol) as described in general procedure 9: 11.85 g of a slightly green solid (79% yield, 84.5% ee). The optical purity of the title compound was determined by capillary electrophoresis using the method described above. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.55−2.10 (m, 2 H), 2.40 (m_c), 2.70 (s, bs, 4 H), 2.91 (s, 3 H), 3.64 (s, 3 H), 4.87 (bt, 1 H), 5.40 (bs, 1 H), 6.71 (s, 1 H), 7.23 (m_c, 1 H), 7.33 (m_c, 1 H), 7.60 (m_c, 1 H), 10.01 (bs, 1 H). HRMS calcd for $C_{21}H_{24}ClFN_3O_3$ *m*/*z* (MH^+), 420.1485; found, 420.1485. Anal. ($C_{21}H_{23}ClFN_3O_3$): C, H, N.

5-[(3*R*)-3-(2,4-Dichlorophenyl)-3-hydroxypropyl]-4-hydroxy-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (100). The title compound was prepared by asymmetric reduction of ketone **58** (6.0 g, 13.8 mmol) as described in general procedure 9: 3.2 g of a colorless solid (53% yield, 69.0% ee). To enhance the optical purity, a mixture of the title compound (3.0 g, 6.9 mmol) and L-(+)-mandelic acid (1.26 g, 8.3 mmol) in acetone (60 mL) was stirred for 1 h at 50 °C and for 18 h at room temperature. The precipitate was isolated by filtration and the title compound released by treatment with saturated sodium bicarbonate solution. A suspension was formed upon addition of dichloromethane. The title compound was isolated by filtration, slurried in water (20 mL), and dried in vacuo (50 °C): 1.9 g, 32% overall yield, ee determined after Mitsunobu cyclization to **117**. CE analytical method: t_M (3*S*) = 25.1 min/15.5 area %; t_M (3*R*) = 26.2 min/84.5 area %. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.73 (bs, 2 H), 2.45 (bs), 2.69 (bs, 4 H), 2.90 (s, 3 H), 3.64 (s, 3 H), 4.86 (bt, 1 H), 5.44 (bs, 1 H), 6.70 (s, 1 H), 7.43 (m_c, 1 H), 7.51 (m_c, 1 H), 7.58 (m_c, 1 H), 9.80 (bs, 1 H). HRMS calcd for $C_{21}H_{24}Cl_2N_3O_3$ *m*/*z* (MH^+), 436.1189; found, 436.1185.

4-Hydroxy-5-[(3*R*)-3-hydroxy-3-(naphthalen-2-yl)propyl]-*N*,*N*,1,2-tetramethyl-1*H*-benzimidazole-6-carboxamide (101). The catalyst $RuCl_2$[(*S*)-Xyl-PPhos][(*S*)-DAIPEN] **82** (12 mg) and ketone **59** (400 mg, 1.0 mmol) were weighed in the glass liner and placed in a Parr microreactor (volume: 25 mL) that was purged with nitrogen (5×) and hydrogen (5×). Potassium *tert*-butylate solution (1 M in *tert*-butanol, 2.75 mL) and 2-propanol (2.5 mL) was added. The autoclave was then purged with hydrogen without stirring (5×) and with stirring (5×). The reaction mixture was stirred at a hydrogen pressure of 25−30 bar and a temperature of 65 °C for 20 h. After cooling to room temperature, the solvent was evaporated. The residue was dissolved in dichloromethane and washed with saturated ammonium chloride solution. The aqueous phase was extracted several times with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated in vacuo, leading to a green solid (340 mg). The conversion (100%) was measured by HPLC. A part of the crude product (300 mg) was purified by column chromatography on silica gel [eluant: dichloromethane/methanol = 15:1 (v/v)]. This afforded the pure title compound (164 mg of a green solid, 39% yield, 45% corrected yield, ee determined after Mitsunobu cyclization to **118**); mp 145−147 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.81 (bs, 1 H), 2.01 (bs, 1 H), 2.50 (s, bs), 2.66 (s, 3 H), 2.78 (s, bs, 4 H), 3.64 (s, 3 H), 4.66 (bs, 1 H), 5.29 (bs, 1 H), 6.69 (s, 1 H), 7.48 (m_c, 3 H), 7.81 (s, 1 H), 7.88 (m_c, 3 H), 9.73 (bs, 1 H). HRMS calcd for $C_{25}H_{28}N_3O_3$ *m*/*z* (MH^+), 418.2125; found, 418.2121.

General Procedure 10 (Mitsunobu Cyclization to Tetrahydrochromenoimidazoles). A solution of the corresponding diol and triphenylphosphine (1.3 to 3.0 equiv) in tetrahydrofuran was treated with DIAD (1.3 to 3.0 equiv), and the mixture was stirred for 5 min to 18 h at room temperature. The title compound was isolated by one of the following workup procedures:

Workup 1. In the course of the reaction a precipitate was formed and the title compound was isolated by filtration.

Workup 2. The reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel and in some cases by crystallization or slurrying in a suitable solvent.

Workup 3. The reaction mixture was concentrated in vacuo in the presence of silica gel, and the residue was purified by column chromatography on silica gel and in some cases by crystallization or slurrying in a suitable solvent.

Workup 4. The reaction mixture was concentrated in vacuo, and the residue was dissolved in dichloromethane and ice−water. A pH value of 2 was adjusted by addition of hydrochloric acid (2 N), and the organic phase was discarded. The aqueous phase was treated with sodium hydroxide solution (2 N) until a pH value of 10 was obtained and extracted with dichloromethane (3×). The combined organic phases were dried over sodium sulfate, and the solvent was evaporated.

The optical purity of the title compound was determined either by HPLC (column: Daicel Chiralpak AD-H, 250 mm × 4.6 mm, 5 μm; flow rate: 1 mL/min; detection wavelength: 218 nm) or by capillary electrophoresis (instrument: Agilent CE-3D; capillary: Agilent 56/64.5 cm × 50 μm barefused silica bubble; buffer: 50 mM sodium phosphate, pH 2.5; chiral selector: 40 mM heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin; voltage: 30 kV; temperature: 20 °C; detection wavelength: 219/226 nm).

(8*S*)-*N*,2,3-Trimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (21). The title compound was prepared by Mitsunobu cyclization of diol **83** (270 mg, 0.73 mmol) as described in general procedure 10 (reaction time: 18 h). Workup 1; 89 mg of a colorless solid (35% yield, 97.5% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 80:20 (v/v) + 0.1% diethylamine; t_R (8*R*) = 6.0 min/1.3 area %; t_R (8*S*) = 7.9 min/98.7 area %; mp 259−260 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.94 (m_c, 1 H), 2.22 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.77, 2.83 (d, m_c, 4 H), 3.12 (m_c, 1 H),

3.69 (s, 3 H), 5.29 (dd, 1 H), 7.12 (s, 1 H), 7.27 (m_c, 3 H), 7.45 (m_c, 1 H), 8.09 (q, 1 H). HRMS calcd for $C_{21}H_{24}N_3O_2$ *m/z* (MH^+), 350.1863; found, 350.1862.

(8*S*)-*N*-Cyclopropyl-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (25). The title compound was prepared by Mitsunobu cyclization of diol **84** (0.32 g, 0.81 mmol) as described in general procedure 10 (reaction time: 10 min). Workup 2; eluant for column chromatography: ethyl acetate, then ethyl acetate/methanol = 9:1 (v/v). Slurrying in diethyl ether: 200 mg of a colorless solid (66% yield, 97.5% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 80:20 (v/v); t_R (8*R*) = 6.0 min/1.2 area %; t_R (8*S*) = 7.9 min/97.5 area %; mp 289 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.64 (m_c, 2 H), 0.90 (m_c, 2 H), 2.08 (m_c, 1 H), 2.26 (m_c, 1 H), 2.37 (s, 3 H), 2.56 (s, 3 H), 2.98 (m_c, 2 H), 3.22 (m_c, 1 H), 3.68 (s, 3 H), 5.39 (dd, 1 H), 6.02 (bs, 1 H), 6.94 (s, 1 H), 7.19 (m_c, 3 H), 7.56 (m_c, 1 H). HRMS calcd for $C_{23}H_{26}N_3O_2$ *m/z* (MH^+), 376.2020; found, 376.2017.

[(8*S*)-2,3-Dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl](pyrrolidin-1-yl)methanone Hydrochloride (39). The title compound (free base) was prepared by Mitsunobu cyclization of diol **85** (750 mg, 1.8 mmol) as described in general procedure 10 (reaction time: 5 h). Workup 2; eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Salt formation by addition of a 2 M solution of hydrochloric acid in diethyl ether to a solution of the free base of the title compound in acetone (rt, 17 h, then removal of the solvent). Crystallization from acetone/diethyl ether: 401 mg of a beige solid (51% yield, 79.8% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 80:20 (v/v); t_R (8*R*) = 12.7 min/10.1 area %; t_R (8*S*) = 20.0 min/89.9 area %; mp 127−128 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.92 (m_c, 5 H), 2.21 (m_c, 1 H), 2.38 (s, 3 H), 2.47 (s, 3 H), 2.66 (m_c, 1 H), 2.93 (m_c, 1 H), 3.07 (m_c, 1 H), 3.21 (m_c, 1 H), 3.48 (m_c, 2 H), 3.68 (s, 3 H), 5.32 (dd, 1 H), 6.98 (s, 1 H), 7.26 (m_c, 3 H), 7.47 (m_c, 1 H). HRMS calcd for $C_{24}H_{28}N_3O_2$ *m/z* (MH^+), 390.2176; found, 390.2172.

(8*S*)-5-(Methoxymethyl)-2,3-dimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole (43). The title compound was prepared by Mitsunobu cyclization of diol **86** (800 mg, 2.26 mmol) as described in general procedure 10 (reaction time: 0.5 h). Workup 3; eluant for column chromatography: first column, ethyl acetate; second column, ethyl acetate/petroleum ether = 3:2 (v/v), then ethyl acetate; 600 mg of a colorless solid (79% yield, 95.4% ee). HPLC analytical method: eluant, *n*-hexane/2-propanol = 95:5 (v/v); t_R (8*R*) = 30.0 min/2.3 area %; t_R (8*S*) = 37.7 min/97.7 area %. ^{1}H NMR (DMSO, 200 MHz): δ = 1.99 (m_c, 1 H), 2.26 (m_c, 1 H), 2.38 (s, 3 H), 2.45 (s, 3 H), 2.94 (m_c, 2 H), 3.33 (s, 3 H), 3.67 (s, 3 H), 4.48 (s, 2 H), 5.24 (dd, 1 H), 7.02 (s, 1 H), 7.27 (m_c, 3 H), 7.49 (m_c, 1 H). HRMS calcd for $C_{21}H_{25}N_2O_2$ *m/z* (MH^+), 337.1911; found, 337.1913. Anal. ($C_{21}H_{24}N_2O_2$): H, N. For C: calcd, 74.97; found, 74.24.

(8*S*)-*N*,2,3-Trimethyl-8-phenyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (105). The title compound was prepared by Mitsunobu cyclization of diol **88** (1.0 g, 2.8 mmol) as described in general procedure 10 (reaction time: 18 h). Workup 2; eluant for column chromatography: dichloromethane/methanol = 10:1 (v/v); 0.79 g of a white solid (75% yield; 73.2% ee). CE analytical method: t_M (8*S*) = 22.0 min/86.6 area %; t_M (8*R*) = 24.4 min/13.4 area %; mp 290−291 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.02 (m_c, 1 H), 2.22 (m_c, 1 H), 2.48 (s), 2.76, 2.80 (d, m_c, 4 H), 3.05 (m_c, 1 H), 3.69 (s, 3 H), 5.19 (dd, 1 H), 7.11 (s, 1 H), 7.42 (m_c, 5 H), 8.08 (q, 1 H). HRMS calcd for $C_{20}H_{22}N_3O_2$ *m/z* (MH^+), 336.1707; found, 336.1698. Anal. ($C_{20}H_{21}N_3O_2$): H, N. For C: calcd, 71.62; found, 71.21.

Azetidin-1-yl[(8*S*)-2,3-dimethyl-8-phenyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazol-5-yl]methanone (106). The title compound was prepared by Mitsunobu cyclization of diol **89** (0.8 g, 2.2 mmol) as described in general procedure 10 (reaction time: 18 h). Workup 1; 0.6 g of a white solid (76% yield; 81.8% ee). CE analytical method: t_M (8*S*) = 21.3 min/90.9 area %; t_M (8*R*) = 23.2 min/9.1 area %; mp 241−242 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.15 (m_c, 4 H), 2.47 (s), 2.74 (m_c, 1 H), 2.96 (m_c, 1 H), 3.69 (s, 3 H), 3.94 (m_c, 4 H), 5.21 (dd, 1 H), 7.03 (s, 1 H), 7.40 (m_c, 5 H). HRMS calcd for $C_{22}H_{24}N_3O_2$ *m/z* (MH^+), 362.1863; found, 362.1857.

(8*S*)-8-(2-Fluorophenyl)-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (107). The title compound was prepared by Mitsunobu cyclization of diol **90** (1.6 g, 4.1 mmol) as described in general procedure 10 (reaction time: 1 h). Workup: The reaction mixture was concentrated in vacuo. The residue was treated with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel [eluant: dichloromethane/methanol = 14:1 (v/v)] and crystallized from acetone to afford 0.8 g (62% yield, 96.1% ee) of the title compound as a white solid. HPLC analytical method: eluant, *n*-heptane/ethanol = 80:20 (v/v) + 0.1% diethylamine; t_R (8*R*) = 12.4 min/1.9 area %; t_R (8*S*) = 13.6 min/96.4 area %; mp 199−201 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.15 (m_c, 2 H), 2.47, 2.55 (s, m_c), 2.79, 2.83 (s, m_c, 4 H), 3.01 (s, 3 H), 3.68 (s, 3 H), 5.44 (dd, 1 H), 6.94 (s, 1 H), 7.27 (t, 2 H), 7.44 (m_c, 1 H), 7.56 (t, 1 H). HRMS calcd for $C_{21}H_{23}FN_3O_2$ *m/z* (MH^+), 368.1769; found, 368.1761.

(8*S*)-8-(2-Chlorophenyl)-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (108). The title compound was prepared by Mitsunobu cyclization of diol **91** (200 mg, 0.50 mmol) as described in general procedure 10 (reaction time: 5 min). Workup 2; Eluant for column chromatography: dichloromethane/methanol = 100:3 (v/v); 175 mg of a colorless foam (91% yield, 89.6% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 90:10 (v/v); t_R (8*R*) = 28.5 min/5.2 area %; t_R (8*S*) = 31.3 min/94.8 area %. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.99 (m_c, 1 H), 2.30 (m_c, 1 H), 2.52 (s), 2.64 (bs, 1 H), 2.80, 2.88 (s, m_c, 4 H), 3.01 (s, 3 H), 3.69 (s, 3 H), 5.47 (dd, 1 H), 6.96 (s, 1 H), 7.46 (m_c, 3 H), 7.63 (m_c, 1 H). HRMS calcd for $C_{21}H_{23}ClN_3O_2$ *m/z* (MH^+), 384.1473; found, 384.1472.

(8*S*)-8-(2-Ethylphenyl)-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (109). The title compound was prepared by Mitsunobu cyclization of diol **92** (130 mg, 0.33 mmol) as described in general procedure 10 (reaction time: 5 min). Workup 2; Eluant for column chromatography: dichloromethane/methanol = 100:3 (v/v); 90 mg of a colorless foam (73% yield, 83.4% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 80:20 (v/v); t_R (8*R*) = 8.3 min/8.3 area %; t_R (8*S*) = 9.5 min/91.7 area %. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.21 (t, 3 H), 1.90−2.30 (m_c, 2 H), 2.46 (s, 3 H), 2.55−2.95, 2.73, 2.82 (m_c, dq, s, 7 H), 3.02 (s, 3 H), 3.67 (s, 3 H), 5.34 (dd, 1 H), 6.92 (s, 1 H), 7.29 (m_c, 3 H), 7.48 (m_c, 1 H). HRMS calcd for $C_{23}H_{28}N_3O_2$ *m/z* (MH^+), 378.2176; found, 378.2173. Anal. ($C_{23}H_{27}N_3O_2$): C, H, N.

(8*S*)-8-(2-Cyclopropylphenyl)-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (110). The title compound was prepared by Mitsunobu cyclization of diol **93** (3.80 g, 9.4 mmol) as described in general procedure 10 (reaction time: 30 min). Workup 4 (extraction with ethyl acetate instead of dichloromethane) and column chromatography [eluant: ethyl acetate, then ethyl acetate/methanol = 50:1 (v/v)]: 1.9 g of a colorless foam (53% yield, no separation of enantiomers accomplished by HPLC). ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 0.69 (m_c, 2 H), 0.94 (m_c, 2 H), 2.08 (m_c, 2 H), 2.30 (m_c, 1 H), 2.47 (s, 3 H), 2.60 (m_c, 1 H), 2.81 (s, 3 H), 2.92 (m_c, 1 H), 3.02 (s, 3 H), 3.68 (s, 3 H), 5.65 (d, 1 H), 6.93 (s, 1 H), 7.07 (m_c, 1 H), 7.26 (m_c, 2 H), 7.49 (m_c, 1 H). HRMS calcd for $C_{24}H_{28}N_3O_2$ *m/z* (MH^+), 390.2176; found, 390.2177.

(8*S*)-8-[2-(Methoxymethyl)phenyl]-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (111). The title compound was prepared by Mitsunobu cyclization of diol **94** (900 mg, 2.19 mmol) as described in general procedure 10

(reaction time: 10 min). Workup 2; eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Slurrying in diethyl ether: 430 mg of a colorless solid (50% yield, 98.0% ee). HPLC analytical method: eluant, *n*-hexane/2-propanol = 90:10 (v/v); t_R (8*R*) = 46.1 min/1.0 area %; t_R (8*S*) = 48.8 min/97.6 area %; mp 200 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.99 (m_c, 1 H), 2.23 (m_c, 1 H), 2.46 (s, 3 H), 2.64 (m_c, 1 H), 2.81, 2.85 (s, m_c, 4 H), 3.02 (s, 3 H), 3.30 (s), 3.68 (s, 3 H), 4.56 (dd, 2 H), 5.36 (dd, 1 H), 6.93 (s, 1 H), 7.38 (m_c, 3 H), 7.65 (m_c, 1 H). HRMS calcd for $C_{23}H_{28}N_3O_3$ *m*/*z* (MH^+), 394.2125; found, 394.2123. Anal. ($C_{23}H_{27}N_3O_3$): C, H, N.

(8*S*)-8-(4-Fluorophenyl)-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide Hydrochloride (112). The free base of the title compound was prepared by Mitsunobu cyclization of diol **95** (1.8 g, 4.7 mmol) as described in general procedure 10 (reaction time: 3 h). Workup 3; eluant for column chromatography: dichloromethane/methanol = 100:0 to 87:13 (v/v). Crystallization from acetone and a saturated solution of HCl in diethyl ether: batch 1, 0.81 g of a colorless solid (43% yield); batch 2, 0.36 g of a colorless solid (19% yield, 81.8% ee). A batch of the free base of the title compound was obtained by purification of the mother liquor [column chromatography on silica gel, eluant: dichloromethane/methanol = 20:1 (v/v)]: 0.50 g of a colorless solid (30% yield). CE analytical method: t_M (8*S*) = 20.1 min/90.1 area %; t_M (8*R*) = 21.0 min/9.0 area %; mp 290−292 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.13 (m_c, 1 H), 2.33 (m_c, 1 H), 2.75, 2.77, 2.79 (m_c, 2 s, 8 H), 3.04 (s, 3 H), 3.89 (s, 3 H), 5.42 (dd, 1 H), 7.28 (t, 2 H), 7.41 (s, 1 H), 7.62 (dd, 2 H). HRMS calcd for $C_{21}H_{23}FN_3O_2$ *m*/*z* (MH^+), 368.1796; found, 368.1796.

(8*S*)-8-(4-Chlorophenyl)-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (113). The title compound was prepared by Mitsunobu cyclization of diol **96** (11.6 g, 28.9 mmol) as described in general procedure 10 (reaction time: 1.5 h). Work up 4 and slurrying in isopropyl acetate (30 mL): 9.4 g of a colorless solid (85% yield, 60.0% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 70:30 (v/v); t_R (8*R*) = 13.2 min/20.0 area %; t_R (8*S*) = 19.1 min/80.0 area %; mp 234−236 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.03 (m_c, 1 H), 2.24 (m_c, 1 H), 2.48, 2.50 (s, m_c), 2.76 (s, m_c, 4 H), 3.00 (s, 3 H), 3.68 (s, 3 H), 5.25 (dd, 1 H), 6.93 (s, 1 H), 7.49 (m_c, 4 H). HRMS calcd for $C_{21}H_{23}ClN_3O_2$ *m*/*z* (MH^+), 384.1473; found, 384.1474. Anal. ($C_{21}H_{22}ClN_3O_2$): H, N, Cl. For C: calcd, 65.71; found, 65.09.

(8*S*)-8-(4-Fluoro-2-methylphenyl)-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (114). The title compound was prepared by Mitsunobu cyclization of diol **97** (630 mg, 1.58 mmol) as described in general procedure 10 (reaction time: 30 min). Workup 2; eluant for column chromatography: dichloromethane/methanol = 100:3 (v/v); 290 mg of a colorless foam (48% yield, 83.0% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 80:20 (v/v); t_R (8*R*) = 12.4 min/8.5 area %; t_R (8*S*) = 17.5 min/91.5 area %. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.99 (m_c, 1 H), 2.21 (m_c, 1 H), 2.40 (s, 3 H), 2.47 (s, 3 H), 2.57−2.74 (m, 1 H), 2.74−2.96, 2.80 (m, s, 4 H), 3.02 (s, 3 H), 3.68 (s, 3 H), 5.30 (dd, 1 H), 6.93 (s, 1 H), 7.09 (m_c, 2 H), 7.49 (m_c, 1 H). HRMS calcd for $C_{22}H_{25}FN_3O_2$ *m*/*z* (MH^+), 382.1925; found, 382.1928.

(8*S*)-8-(4-Chloro-2-methylphenyl)-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (115). The title compound was prepared by Mitsunobu cyclization of diol **98** (5.4 g, 13.0 mmol) as described in general procedure 10 (reaction time: 18 h). The reaction solvent was removed in vacuo and the residue distributed between ethyl acetate and 1 N hydrochloric acid. The phases were separated and the aqueous phase extracted with ethyl acetate (3×) and dichloromethane (1×). The organic extracts were discarded. A basic pH value was adjusted by addition of 25% aqueous ammonia solution and the aqueous phase extracted with ethyl acetate (2×). The combined organic phases were dried over magnesium sulfate, and the solvent was removed in vacuo. The title compound was purified further by crystallization from isopropyl acetate and dried in vacuo at a temperature of 50 °C: 3.43 g of a colorless solid (66% yield, 95.4% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 80:20 (v/v); t_R (8*R*) = 13.8 min/2.3 area %; t_R (8*S*) = 19.2 min/97.7 area %. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.93 (m_c, 1 H), 2.21 (m_c, 1 H), 2.39 (s, 3 H), 2.47 (s, 3 H), 2.62 (m_c, 1 H), 2.80, 2.88 (s, m_c, 4 H), 3.01 (s, 3 H), 3.68 (s, 3 H), 5.32 (d, 1 H), 6.93 (s, 1 H), 7.33 (m_c, 2 H), 7.48 (d, 1 H). HRMS calcd for $C_{22}H_{25}ClN_3O_2$ *m*/*z* (MH^+), 398.1630; found, 398.1631. Anal. ($C_{22}H_{24}ClN_3O_2$): C, H, N.

(8*S*)-8-(2-Chloro-4-fluorophenyl)-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (116). The title compound was prepared by Mitsunobu cyclization of diol **99** (16.5 g, 39 mmol) as described in general procedure 10 (reaction time: 0.5 h). Workup: The reaction mixture was diluted with water and a pH value of 3 was adjusted by addition of 2 N hydrochloric acid (40 mL). The acidic solution was extracted with ethyl acetate (3×), and the organic extracts were discarded. The aqueous phase was treated with concentrated ammonia solution (20 mL) until a pH value of 9.5 was obtained. A precipitate was formed which was collected by filtration, washed with water, and dried in vacuo at temperatures of 50 and 100 °C. This afforded the pure title compound in 91% yield (14.4 g of a colorless solid). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.99 (m_c, 1 H), 2.28 (m_c, 1 H), 2.48 (s, 3 H), 2.63 (m_c, 1 H), 2.80, 2.87 (s, m_c, 4 H), 3.01 (s, 3 H), 3.68 (s, 3 H), 5.43 (dd, 1 H), 6.96 (s, 1 H), 7.34 (m_c, 1 H), 7.53 (m_c, 1 H), 7.66 (m_c, 1 H). HRMS calcd for $C_{21}H_{22}ClFN_3O_2$ *m*/*z* (MH^+), 402.1379; found, 402.1379.

(8*S*)-8-(2,4-Dichlorophenyl)-*N*,*N*,2,3-tetramethyl-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (117). The title compound was prepared by Mitsunobu cyclization of diol **100** (1.90 g, 4.5 mmol) as described in general procedure 10 (temperature: 60 °C, reaction time: 1 h). Workup: The reaction mixture was concentrated. The residue was dissolved in ethyl acetate (50 mL) and 1 N hydrochloric acid (50 mL), and the phases were separated. The acidic aqueous phase was extracted with ethyl acetate (3 × 20 mL), and the organic extracts were discarded. The aqueous phase was treated with 25% ammonia solution and extracted with ethyl acetate (2 × 40 mL). A mixture of the title compound with inorganic salts (690 mg) precipitated from the ethyl acetate phase. The solid was treated with dichloromethane (30 mL) and water (20 mL). The phases were separated and the aqueous phase extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over magnesium sulfate and concentrated in vacuo: 630 mg of a colorless solid (34% yield, 95.2% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 80:20 (v/v); t_R (8*R*) = 14.0 min/2.4 area %; t_R (8*S*) = 20.1 min/97.6 area %. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.96 (m_c, 1 H), 2.29 (m_c, 1 H), 2.48 (s), 2.62 (m_c, 1 H), 2.79, 2.84 (s, m_c, 4 H), 3.01 (s, 3 H), 3.69 (s, 3 H), 5.44 (d, 1 H), 6.98 (s, 1 H), 7.55 (m_c, 1 H), 7.63 (m_c, 1 H), 7.71 (m_c, 1 H). HRMS calcd for $C_{21}H_{22}Cl_2N_3O_2$ *m*/*z* (MH^+), 418.1084; found, 418.1086.

(8*S*)-*N*,*N*,2,3-Tetramethyl-8-(naphthalen-2-yl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide hydrochloride (118). The title compound (free base) was prepared by Mitsunobu cyclization of diol **101** (150 mg, 0.36 mmol) as described in general procedure 10 (reaction time: 4.25 h). Workup 2; eluant for column chromatography: dichloromethane/methanol = 20:1 (v/v). Salt formation by addition of a 2 M solution of hydrochloric acid in diethyl ether to a solution of the free base of the title compound in acetone. The precipitate was isolated by filtration and dried in vacuo: 101 mg of a beige solid (64% yield, 38.6% ee). HPLC analytical method: eluant, *n*-heptane/ethanol = 80:20 (v/v) + 0.1% diethylamine; t_R (8*R*) = 25.3 min/30.4 area %; t_R (8*S*) = 31.2 min/68.7 area %; mp 262−264 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.25 (m_c, 1 H), 2.45 (m_c), 2.72, 2.78, 2.81 (m_c, s, s, 7 H), 3.01, 3.05 (m_c, s, 4 H), 3.90 (s, 3 H), 5.59 (dd, 1 H), 7.43 (s, 1 H), 7.56 (m_c, 2 H), 7.70 (m_c, 1 H), 7.99 (m_c, 3 H),

8.14 (s, 1 H). HRMS calcd for $C_{25}H_{26}N_3O_2$ m/z (MH^+), 400.2020; found, 400.2021.

(8*S*)-*N*,*N*,2,3-Tetramethyl-8-(thiophen-2-yl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (119). The title compound was prepared by Mitsunobu cyclization of diol **102** (450 mg, 1.20 mmol) as described in general procedure 10 (reaction time: 0.75 h). Workup 3; eluant for column chromatography: dichloromethane/methanol = 30:1 (v/v); 260 mg of a colorless foam (61% yield, 77.2% ee). HPLC analytical method: eluant, *n*-hexane/2-propanol = 80:20 (v/v); t_R (8*S*) = 12.3 min/81.5 area %; t_R (8*R*) = 16.9 min/10.5 area %.; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 2.16 (m_c, 1 H), 2.35 (m_c, 1 H), 2.47 (s, 3 H), 2.65 (m_c, 1 H), 2.76, 2.79 (s, m_c, 4 H), 3.01 (s, 3 H), 3.67 (s, 3 H), 5.50 (dd, 1 H), 6.92 (s, 1 H), 7.07 (m_c, 1 H), 7.20 (m_c, 1 H), 7.55 (m_c, 1 H). HRMS calcd for $C_{19}H_{22}N_3O_2S$ m/z (MH^+), 356.1427; found, 356.1428.

(8*S*)-*N*,*N*,2,3-Tetramethyl-8-(2-methylthiophen-3-yl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (120). The title compound was prepared by Mitsunobu cyclization of diol **103** (0.54 g, 1.4 mmol) as described in general procedure 10 (reaction time: 10 min). Workup 2; eluant for column chromatography: ethyl acetate, then ethyl acetate/methanol = 9:1 (v/v). Slurrying in diethyl ether: 200 mg of a colorless solid (39% yield); Mp 233 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.20 (m_c, 2 H), 2.47 (s, 3 H), 2.57 (s, 3 H), 2.88 (s, bs, 5 H), 3.15 (s, 3 H), 3.67 (s, 3 H), 5.27 (dd, 1 H), 6.76 (s, 1 H), 7.03 (m_c, 2 H). HRMS calcd for $C_{20}H_{24}N_3O_2S$ m/z (MH^+), 370.1584; found, 370.1578. Anal. ($C_{20}H_{23}N_3O_2S$): C, H, N.

5.1.5. Variation of the Substituents Attached to the Imidazole Part of the 3,6,7,8-Tetrahydrochromeno[7,8-*d*]imidazole Scaffold. 2-Cyclopropyl-4-hydroxy-*N*,*N*,1-trimethyl-5-[3-(2-methylphenyl)-3-oxopropyl]-1*H*-benzimidazole-6-carboxamide (134). At a temperature of 60 °C, potassium *tert*-pentylate (42.0 mL of a 25% solution in toluene diluted with 22 mL of dry DMF) was added over a period of 40 min to a suspension of the Mannich base **132** (14.0 g, 31.5 mmol) and ethyl 3-(2-methylphenyl)-3-oxopropanoate (8.0 g, 40.0 mmol) in dry toluene (120 mL). The reaction mixture was stirred for 5 h at 60 °C, cooled, and poured on a mixture of saturated ammonium chloride solution (160 mL) and ethyl acetate (350 mL). The phases were separated and the aqueous phase extracted with ethyl acetate (40 mL). The combined organic phases were washed with water (2 × 40 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography [220 g of silica gel, eluant: dichloromethane, then dichloromethane/methanol = 100:2 (v/v)]. A solution of the resulting ketoester **133** (6.2 g, 13.0 mmol) in methanol (100 mL) was heated to 85 °C and treated with cesium carbonate (21.0 g, 65.0 mmol, dissolved in 30 mL of water). After a period of 4 h at 85 °C, the reaction mixture was poured on a mixture of saturated ammonium chloride solution (100 mL) and dichloromethane (250 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (30 mL). The combined organic phases were washed with water (40 mL), dried over sodium sulfate, and concentrated under reduced pressure. This afforded 4.7 g of the crude title compound (37% yield, HPLC purity: 88%). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.06 (d, 4 H), 2.21 (quintet, 1 H), 2.41 (s, 3 H), 2.77 (s, bs, 4 H), 2.99, 3.03 (s, bs, 6 H), 3.78 (s, 3 H), 6.78 (s, 1 H), 7.30 (m_c, 2 H), 7.42 (m_c, 1 H), 7.68 (m_c, 1 H), 9.62 (bs, 1 H). HRMS calcd for $C_{24}H_{28}N_3O_3$ m/z (MH^+), 406.2125; found, 406.2119.

4-(Benzyloxy)-2-cyclopropyl-*N*,*N*,1-trimethyl-5-[3-(2-methylphenyl)-3-oxopropyl]-1*H*-benzimidazole-6-carboxamide (135). Benzyl bromide (2.4 g, 14.0 mmol) was added dropwise to a suspension of ketone **134** (4.5 g, 11.0 mmol) and potassium carbonate (2.0 g, 14.0 mmol) in DMF (70 mL). The reaction mixture was heated to 55 °C, stirred for 4 h at this temperature, and poured on a mixture of saturated ammonium chloride solution (70 mL) and ethyl acetate (180 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with water (2 × 30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography [200 g of silica gel, eluant: dichloromethane, then dichloromethane/methanol = 100:1 (v/v)] and crystallization from diethyl ether (30 mL). The title compound was isolated by filtration, washed with diethyl ether (15 mL), and dried in vacuo: 2.8 g of a colorless solid (51% yield); mp 122−124 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.09 (d, 4 H), 2.24 (quintet, 1 H), 2.36 (s, 3 H), 2.63, 2.73 (bs, s, 4 H), 2.92, 2.99 (bs, s, 6 H), 3.81 (s, 3 H), 5.75 (s, 2 H), 7.00 (s, 1 H), 7.24 (m_c, 5 H), 7.39 (m_c, 3 H), 7.54 (m_c, 1 H). HRMS calcd for $C_{31}H_{34}N_3O_3$ m/z (MH^+), 496.2595; found, 496.2594. Anal. ($C_{31}H_{33}N_3O_3$): C, H, N.

4-(Benzyloxy)-2-cyclopropyl-5-[(3*R*)-3-hydroxy-3-(2-methylphenyl)propyl]-*N*,*N*,1-trimethyl-1*H*-benzimidazole-6-carboxamide (136). In a 100 mL autoclave, the protected ketone **135** (3.0 g, 6.0 mmol) was dissolved in dry 2-propanol (40 mL). Potassium *tert*-butylate (0.6 mL of a 1 M solution in *tert*-butanol, 0.6 mmol) and the hydrogenation catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **82** (8 mg, S/C = 1000:1) were added. The reactor was purged with hydrogen (3×) and subjected to a hydrogen pressure of 80 bar. The hydrogenation was conducted at 70 °C over a period of 17 h. After cooling to room temperature and release of the hydrogen pressure, the reaction mixture was poured on saturated ammonium chloride solution (70 mL) and dichloromethane (130 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic phases were washed with water (2 × 30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue (3.0 g of a foamy solid, 95.0% ee) was purified by column chromatography [100 g of silica gel, eluant: dichloromethane/methanol = 100:2 (v/v)]: 2.8 g of a colorless solid (90% yield, 95.4% ee). HPLC analytical method: column, Daicel Chiralcel OD-H, 250 mm × 4.6 mm, 5 μm; flow rate, 1 mL/min; detection wavelength, 218 nm; eluant, *n*-heptane/ethanol = 90:10 (v/v); t_R (3*R*) = 12.4 min/97.7 area %; t_R (3*S*) = 14.0 min/2.3 area %; mp 109−111 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.08 (d, 4 H), 1.60 (bs, 1 H), 1.79 (bs, 1 H), 2.18 (s, 3 H), 2.24 (quintet, 1 H), 2.55 (bs), 2.66 (s, 3 H), 2.88, 2.93 (bs, s, 4 H), 3.78 (s, 3 H), 4.68 (bs, 1 H), 4.97 (bs, 1 H), 5.67 (s, 2 H), 6.93 (s, 1 H), 7.12 (m_c, 3 H), 7.31 (m_c, 3 H), 7.40 (m_c, 3 H). HRMS calcd for $C_{31}H_{36}N_3O_3$ m/z (MH^+), 498.2751; found, 498.2752.

2-Cyclopropyl-4-hydroxy-5-[(3*R*)-3-hydroxy-3-(2-methylphenyl)-propyl]-*N*,*N*,1-trimethyl-1*H*-benzimidazole-6-carboxamide (137). Palladium on charcoal (0.3 g, 10 wt %) was added to a solution of the benzyl-protected alcohol **136** (2.7 g, 5.4 mmol) in dry ethanol (80 mL). The reaction mixture was hydrogenated (1 bar hydrogen pressure) at room temperature for 18 h. The catalyst was removed by filtration and washed with dichloromethane. Evaporation of the combined filtrates afforded the title compound: 2.1 g of a colorless solid (95% yield, 95.9% ee). HPLC analytical method: column, Daicel Chiralpak AD-H, 250 mm × 4.6 mm, 5 μm; flow rate, 1 mL/min; detection wavelength, 218 nm; eluant, *n*-heptane/ethanol = 85:15 (v/v); t_R (3*R*) = 17.7 min/91.3 area %; t_R (3*S*) = 21.3 min/1.9 area %; mp 148−150 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.05 (d, 4 H), 1.72 (bs, 2 H), 2.19, 2.22 (m_c, s, 4 H), 2.55 (bs), 2.69 (s, 3 H), 2.85, 2.92 (m_c, s, 4 H), 3.76 (s, 3 H), 4.69 (bs, 1 H), 5.03 (bs, 1 H), 6.71 (s, 1 H), 7.08 (m_c, 2 H), 7.15 (m_c, 1 H), 7.40 (m_c, 1 H), 9.43 (bs, 1 H). HRMS calcd for $C_{24}H_{30}N_3O_3$ m/z (MH^+), 408.2282; found, 408.2271.

(8*S*)-2-Cyclopropyl-*N*,*N*,3-trimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide Butanedioate (139). DIAD (1.6 g, 6.0 mmol) was added dropwise to a solution of the diol **137** (1.9 g, 4.6 mmol) and triphenylphosphine (1.6 g, 6.0 mmol) in THF (40 mL). The reaction solution was stirred for 30 min at room temperature and poured on saturated ammonium chloride solution (30 mL) and ethyl acetate (60 mL). The phases were separated, and the aqueous

phase was extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (2 × 20 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue (5.0 g of a green oil) was purified by column chromatography twice [first column, 100 g of silica gel; eluant, ethyl acetate/methanol = 20:1 (v/v); second column, 50 g of silica gel; eluant, ethyl acetate/methanol = 100:1 (v/v)]. The free base of the title compound **138** (1.25 g) was dissolved in methyl isobutyl ketone (10 mL), and succinic acid (480 mg, 4.0 mmol) was added. The suspension was stirred for 45 min at 80 °C and for 17 h at room temperature. The title compound was isolated by filtration, washed with methyl isobutyl ketone (3 mL), and dried in vacuo (50 °C): 1.2 g (74% yield, ratio API/succinic acid = 1:1.5, 95.6% ee). HPLC analytical method: column, Daicel Chiralpak AD-H, 250 mm × 4.6 mm, 5 μm; flow rate, 1 mL/min; detection wavelength, 218 nm; eluant, *n*-heptane/ethanol = 80:20 (v/v); t_R (8*R*) = 9.8 min/2.2 area %; t_R (8*S*) = 12.8 min/97.8 area %; mp 146−148 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 0.99 (m_c, 4 H), 2.00 (m_c, 1 H), 2.18 (m_c, 2 H), 2.37 (s, 3 H), 2.42 (s, 6 H), 2.61 (m_c, 1 H), 2.80, 2.88 (s, bs, 4 H), 3.01 (s, 3 H), 3.79 (s, 3 H), 5.30 (dd, 1 H), 6.92 (s, 1 H), 7.25 (m_c, 3 H), 7.44 (m_c, 1 H), 12.13 (bs, 3 H). HRMS calcd for $C_{24}H_{28}N_3O_2$ *m*/*z* (MH^+), 390.2176; found, 390.2184.

(8*S*)-2-(Chloromethyl)-*N*,*N*,3-trimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (141). A solution of alcohol **140** (450 mg, 1.2 mmol) in dichloromethane (15 mL) was cooled to 0 °C, and thionyl chloride (180 mg, 1.5 mmol) was added dropwise. The reaction mixture was stirred for 2 h at room temperature and poured on a cold mixture of aqueous sodium carbonate solution (15 mL) and dichloromethane (10 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (10 mL). The combined organic phases were washed with water (20 mL), dried over sodium sulfate, and concentrated under reduced pressure. The title compound (480 mg of a colorless solid, 98% yield) was subjected to the next step without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.03 (m_c, 1 H), 2.27 (m_c, 1 H), 2.40 (s, 3 H), 2.67 (m_c, 1 H), 2.83 (s, 3 H), 2.99, 3.04 (m_c, s, 4 H), 3.89 (s, 3 H), 5.11 (s, 2 H), 5.42 (d, 1 H), 7.18 (s, 1 H), 7.28 (m_c, 3 H), 7.49 (m_c, 1 H). HRMS calcd for $C_{22}H_{25}N_3O_2Cl$ *m*/*z* (MH^+), 398.1630; found, 398.1628.

(8*S*)-2-(Methoxymethyl)-*N*,*N*,3-trimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-d]imidazole-5-carboxamide (142). Sodium methylate (3 mL of a 0.5 M solution in methanol) was added portionwise to a solution of the chloro derivative **141** (400 mg, 1.0 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature for 1 h and heated to 65 °C for 17 h. After cooling to room temperature, the reaction mixture was poured on saturated ammonium chloride solution (15 mL) and dichloromethane (25 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were washed with water (2 × 10 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was crystallized from a mixture of acetone (1 mL) and diethyl ether (10 mL). The title compound was isolated by filtration, washed with diethyl ether (5 mL), and dried in vacuo: 180 mg of a colorless solid, 45% yield; mp 178−180 °C.^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.01 (m_c, 1 H), 2.23 (m_c, 1 H), 2.39 (s, 3 H), 2.62 (m_c, 1 H), 2.82, 2.90 (s, bs, 4 H), 3.02 (s, 3 H), 3.29 (s), 3.76 (s, 3 H), 4.64 (s, 2 H), 5.35 (dd, 1 H), 7.00 (s, 1 H), 7.26 (m_c, 3 H), 7.48 (m_c, 1 H). HRMS calcd for $C_{23}H_{28}N_3O_3$ *m*/*z* (MH^+), 394.2125; found, 394.2125. Anal. ($C_{23}H_{27}N_3O_3$): C, H, N.

4-(Benzyloxy)-6-bromo-2-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole (144). To a suspension of benzimidazole **143** (36.5 g, 115 mmol) and triethylamine (17.7 mL, 138 mmol) in a dimethylformamide−dichloromethane mixture (10:1) was added dropwise [2-(chloromethoxy)ethyl](trimethyl)-silane (24.5 mL, 138 mmol) and the suspension was stirred for 5 h at room temperature. The reaction mixture was poured into water and extracted with dichloromethane (3×). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel [eluant: toluene/dioxane = 9:1 (v/v)], affording 19.5 g (39% yield) of the title compound as a white solid; mp 94−95 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = −0.10 (s, 9 H), 0.83 (t, 2 H), 2.50 (s, 3 H), 3.47 (t, 2 H), 5.28 (s, 2 H), 5.47 (s, 2 H), 6.90 (s, 1 H), 7.28 (m_c, 1 H), 7.34 (m_c, 2 H), 7.42 (m_c, 3 H). HRMS calcd for $C_{21}H_{28}N_2O_2BrSi$ *m*/*z* (MH^+), 447.1098; found, 447.1108.

4-(Benzyloxy)-*N*,*N*,2-trimethyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-6-carboxamide (145). The bromo derivative **144** (19.5 g, 43.6 mmol), triphenylphosphine (4.6 g, 17.9 mmol), palladium(II) acetate (1.5 g, 6.5 mmol), and dimethylamine solution (2 M in THF, 218 mL, 436 mmol) were transferred to an autoclave and carbonylated (6 bar CO) for 60 h at 120 °C. The catalyst was filtered off and the filtrate concentrated in vacuo. The residue was purified by column chromatography on silica gel [eluant: toluene/dioxane = 2:1 (v/v)], affording 13.8 g (72% yield) of the title compound as a white solid; mp 118−120 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = −0.10 (s, 9 H), 0.81 (t, 2 H), 2.55 (s, 3 H), 2.90 (s, 6 H), 3.50 (t, 2 H), 5.30 (s, 2 H), 5.59 (s, 2 H), 6.80 (s, 1 H), 7.38 (m_c, 6 H). HRMS calcd for $C_{24}H_{34}N_3O_3Si$ *m*/*z* (MH^+), 440.2364; found, 440.2371.

4-Hydroxy-*N*,*N*,2-trimethyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-6-carboxamide (146). A solution of the benzyl protected benzimidazole **145** (13.7 g, 31.1 mmol) in ethanol (1.2 L) was hydrogenated over 10% Pd/C (1.4 g) in an autoclave (5 bar H_2) for 16 h at room temperature. The catalyst was filtered off and the filtrate concentrated in vacuo. The residue was crystallized from diisopropyl ether to afford 10.1 g (93% yield) of the title compound as a white solid; mp 154−156 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = −0.11 (s, 9 H), 0.80 (t, 2 H), 2.52 (s, 3 H), 2.93 (s, 6 H), 3.50 (t, 2 H), 5.55 (s, 2 H), 6.55 (s, 1 H), 7.10 (s, 1 H), 9.92 (bs, 1 H). HRMS calcd for $C_{17}H_{28}N_3O_3Si$ *m*/*z* (MH^+), 350.1894; found, 350.1894.

4-Hydroxy-*N*,*N*,2-trimethyl-5-[3-(2-methylphenyl)-3-oxopropyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-6-carboxamide (147). A solution of the hydroxybenzimidazole **146** (2.4 g, 6.9 mmol) in dichloromethane (40 mL) was treated with Eschenmoser's salt (1.8 g, 9.8 mmol), and the reaction was stirred for 7 h at room temperature. The reaction mixture was poured into saturated sodium hydrogencarbonate solution, stirred for 30 min at room temperature, and extracted with dichloromethane (3×). The organic layers were dried over magnesium sulfate and concentrated in vacuo. A suspendion of the residue (2.77 g of a beige solid, 6.8 mmol, 99% yield) in 1,2-dimethoxyethane (100 mL) was heated to 85 °C, and a solution of 1-[1-(2-methylphenyl)vinyl]pyrrolidine (2.0 g, 10.7 mmol) was slowly added. The reaction mixture was heated at 85 °C for 3 h, cooled to room temperature, and the solvent was evaporated in vacuo. A column filled with silica gel was loaded with the residue, and the title compound was eluted with a mixture of toluene/1,4-dioxane = 2:1 (v/v). Evaporation of the corresponding fractions afforded a beige solid that was recrystallized from isopropanol. The title compound was obtained in 20% yield (0.67 g of a colorless solid); mp 163−164 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = −0.10 (s, 9 H), 0.83 (t, 2 H), 2.40 (s, 3 H), 2.56 (s, bs, 4 H), 2.75 (s, 3 H), 3.00, 3.05 (s, bs, 6 H), 3.52 (t, 2 H), 5.50 (s, 2 H), 6.90 (s, 1 H), 7.29 (m_c, 2 H), 7.40 (m_c, 1 H), 7.70 (m_c, 1 H), 9.99 (s, 1 H). HRMS calcd for $C_{27}H_{38}N_3O_4Si$ *m*/*z* (MH^+), 496.2626; found, 496.2623.

4-Hydroxy-5-[(3*R*)-3-hydroxy-3-(2-methylphenyl)propyl]-*N*,*N*,2-trimethyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-6-carboxamide (148). Two samples of ketone **147** (223 mg, 0.45 mmol/271 mg, 0.54 mmol) and $RuCl_2$[(*S*)-Xyl-P-Phos]-[(*S*)-DAIPEN] **82** (S/C = 100:1) were weighed in glass liners that were then placed in an Argonaut Endeavor (eight wells pressure parallel reactor, overhead stirrers, and heating block). The vessel was sealed and the wells purged by pressurizing five times with nitrogen to 2 bar and releasing the pressure. The base

(0.5 mL/0.6 mL of a 1 M solution of potassium *tert*-butylate in *tert*-butanol) and 2-propanol (2.0 mL/2.4 mL) were then injected. The wells were purged by pressurizing five times with hydrogen to 25 bar (under stirring) and releasing the pressure. The reaction was then heated to 65 °C and pressurized to 25 bar of hydrogen. After a period of 16 h, the hydrogen pressure was released, and the reaction mixtures were transferred to round bottomed flasks with the help of methanol (10 mL). The solvent was evaporated, and the crude products were analyzed by HPLC (both samples: 100% conversion, 91−92% ee). The combined samples were dissolved in dichloromethane and washed with saturated ammonium chloride solution. The aqueous phase was extracted several times with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated in vacuo furnishing a green solid (390 mg). A part of the crude product (350 mg) was purified by column chromatography on silica gel [eluant: dichloromethane/methanol = 20:1 (v/v)]. This afforded the pure title compound (320 mg of a foamy solid, 64% yield, 70% corrected yield, 95.8% ee). Determination of the optical purity by capillary electrophoresis: instrument, Agilent CE-3D; capillary, Agilent 56/64.5 cm × 50 μm bare fused silica bubble; buffer, 50 mM sodium phosphate, pH 2.5; chiral selector, 40 mM heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin; voltage, 30 kV; temperature, 20 °C; detection wavelength, 219 nm; t_M (3*S*) = 27.5 min/2.1 area %; t_M (3*R*) = 27.9 min/97.9 area %. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = −0.10 (s, 9 H), 0.82 (t, 2 H), 1.78 (bm, 2 H), 2.21 (s, 3 H), 2.55 (s), 2.69 (s, 3 H), 2.92 (s, 4 H), 3.50 (t, 2 H), 4.69 (bs, 1 H), 5.03 (bd, 1 H), 5.50 (s, 2 H), 6.84 (s, 1 H), 7.13 (m_c, 3 H), 7.41 (m_c, 1 H), 9.77 (bs, 1 H). HRMS calcd for $C_{27}H_{40}N_3O_4Si$ *m*/*z* (MH^+), 498.2783; found, 498.2789.

(8*S*)-*N*,*N*,2-Trimethyl-8-(2-methylphenyl)-3-{[2-(trimethylsilyl)ethoxy]methyl}-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (149). To a solution of the diol **148** (300 mg, 0.60 mmol) in tetrahydrofuran (10 mL) was added triphenylphosphine (300 mg, 1.14 mmol) and DIAD (240 μL, 245 mg, 1.21 mmol) and the solution was stirred for 10 min at room temperature. The reaction mixture was concentrated in vacuo and the crude product purified by column chromatography [eluant for first column,: dichloromethane/methanol = 40:1 (v/v); eluant for second column, petroleum ether/ethyl acetate = 1:1 to 1:3 (v/v)]. Evaporation of the corresponding fractions afforded 430 mg of a mixture of the title compound (30 wt %, 45% corrected yield) and triphenylphosphine oxide (70 wt %). ^{1}H NMR (DMSO-d_6, 400 MHz): δ = −0.08 (s, 9 H), 0.83 (t, 2 H), 1.99 (m_c), 2.24 (m_c, 1 H), 2.39 (s, 3 H), 2.50 (s), 2.67 (bs, 1 H), 2.80 (s, 3 H), 2.90 (bs, 1 H), 3.02 (s, 3 H), 3.52 (t, 2 H), 5.35 (dd, 1 H), 5.54 (s, 2 H), 7.06 (s, 1 H), 7.27 (m_c, 3 H), 7.48 (m_c, 1 H); triphenylphospine oxide: 7.59 (m_c).

(8*S*)-*N*,*N*,2-Trimethyl-8-(2-methylphenyl)-3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazole-5-carboxamide (150). At a temperature of 0 °C, borontrifluoride etherate (290 μL, 325 mg, 2.3 mmol) was added dropwise to a solution of the protected benzimidazole **149** (400 mg, 30 wt %, 0.25 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 3 h at room temperature, and the solvent was evaporated in the presence of silica gel. The residue was loaded on top of a column filled with silica gel, and the title compound was eluted with dichloromethane/methanol = 50:1 (v/v). Evaporation of the corresponding fractions afforded the title compound (110 mg, quant yield, 96.1% ee). HPLC analytical method: column, Daicel Chiralpak AD-H, 250 mm × 4.6 mm, 5 μm; eluant, *n*-hexane/2-propanol = 90:10; flow rate, 1 mL/ min; detection wavelength, 218 nm; t_R (8*S*) = 21.9 min/97.7 area %; t_R (8*R*) = 32.5 min/1.9 area %; mp 219 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.04 (m_c, 1 H), 2.26 (m_c, 1 H), 2.40 (s, 3 H), 2.53, 2.63 (s, m_c), 2.81 (s, 3 H), 2.90, 3.02 (m_c, s, 4 H), 5.43 (dd, 1 H), 6.99 (s, 1 H), 7.28 (m_c, 3 H), 7.50 (m_c, 1 H). HRMS calcd for $C_{21}H_{24}N_3O_2$ *m*/*z* (MH^+), 350.1863; found, 350.1857.

5.2. Biological and Pharmacological Investigation of 3,6,7,8-Tetrahydrochromeno[7,8-d]imidazoles. The experimental conditions for the in vitro assays (competitive binding assay for determination of the inhibitory activity against H^+/K^+-ATPase isolated from hog gastric mucosa, reduction of the accumulation of the weak base ^{14}C-dimethylaminopyridine in intact gastric glands) and the pharmacological tests (reduction of the acid output in the Ghosh Schild rat, efficacy and duration of the antisecretory activity in the fasted fistula dog) have been described previously.[5,13,36]

5.3. Effect of a Test Compound on the hERG Tail Current Amplitude in Stably Transfected CHO-K1 Cells Using Patch Clamp Recordings. CHO-K1 cells stably expressing the hERG channel (NMI TT GmbH, Reutlingen, Germany) were continuously maintained and passaged in sterile culture flasks containing DMEM/ HAM F12 + 10% FCS (Invitrogen, Karlsruhe, Germany) with Zeocin (50 μg/mL, Invitrogen, Karlsruhe, Germany) to select for cells transfected with the plasmid containing hERG and Zeocin resistance. For electrophysiological measurements, CHO-K1 cells were seeded onto 12 mm sterile coverslips positioned in 24-well plates containing 0.5 mL of culture medium DMEM/ HAM F12 + 10% FCS at a density of 30000 cells per coverslip. By using this cell density, the cells do not tend to cluster and are not electrically coupled. The medium contained Nocodazol (90 ng/mL, Invitrogen, Karlsruhe, Germany) to arrest the cell cycle in order to generate a polyploide genome. Penicillin/streptomycin (10 μL/ml, Invitrogen, Karlsruhe, Germany) solution was added to the medium. The cells were incubated at 37 °C in a humidified atmosphere with 5% CO_2. Test compounds were dissolved in DMSO to prepare stock solution (in general 1000× of highest final concentration). The final concentration (10 μM, adjusted to 0.1% DMSO) was diluted from the corresponding stock solution shortly prior to the electrophysiological experiments. The extracellular solution was prepared freshly every day and kept at room temperature (19−26 °C). The components of the extracellular solution with an osmolarity of 300−305 mOsm/kg were (in mM): 140 NaCl, 4 KCl, 4 $MgSO_4$, 1.8 $CaCl_2$, 10 HEPES, and 20 glucose. The pH of the extracellular solution was set to 7.4 using NaOH. The intracellular solution was thawed every day from a frozen (−22 °C) aliquot. When in use, the pipet solution was filled into the patch pipettes. The pipet solution with an osmolarity of 290−295 mOsm/kg included the following components (in mM): 115 K-Aspartat, 3 $MgCl_2$, 0.7 $CaCl_2$, 10 HEPES, 12 EGTA, and 5 K_2-ATP. The pH of the intracellular solution was set to 7.2 using KOH. CHO-K1 cells were placed on the dish holder of the microscope and were continuously perfused (at approximately 2 mL/min). A patch clamp amplifier EPC-10 (HEKA, Lambrecht, Germany) connected to a PC using the software Pulse v8.79 (HEKA, Lambrecht, Germany) was used to perform the experiments. Patch electrodes with a pipet resistance ranging from 2 to 5 MΩ were used to form a gigaseal between the patch electrode and individual CHO-K1 cells (seal resistance: > 1 GΩ). The cell membrane under the pipet tip was then ruptured by negative pressure to ensure electrical access to the cell interior (whole-cell configuration). With a leak current larger than 300 pA, the cell was omitted. As soon as a stable seal was established, a voltage protocol was run every 25 s (start-to-start). This voltage protocol consisted of a hyperpolarizing step from −80 to −90 mV to calculate for the membrane resistance, followed by the repolarization to the holding potential of −80 mV. The hERG outward tail currents were measured upon depolarization of the membrane potential to +20 mV for 2750 ms (activation of channels) and subsequent repolarization to −50 mV for 250 ms. A variation of current amplitudes less than 5% was defined as steady-state level. Once the steady-state level of the control recordings had been accomplished at least for five sweeps, cells were continuously perfused with an extracellular solution containing the test compound. During wash-in of the test compound, the voltage protocol indicated above was applied continuously until the effect of the test compound reached a steady-state. Each test compound was tested on three different cells. The tail current amplitude values were generated for each voltage step by subtracting the mean current during the holding

potential at the intermediate step of −80 mV from the tail current peak. The mean of the at least last three current amplitudes at the steady-state in the presence of the test compound was compared to that of control condition of the same cell. The amount of current block was calculated as percentage of control. Data from at least three individual cells were collected.

5.4. Physical Chemistry. 5.4.1. Determination of Dissociation Constants and Distribution Coefficients. The pK_a values and the distribution coefficients between 1-octanol and aqueous KCl solution of the investigated compounds were determined by potentiometric cosolvent titrations as described previously.[5]

5.4.2. Estimation of logD at pH 7.4 by Reversed-Phase HPLC. The logarithmic partition coefficient logD was determined by correlation of the HPLC retention time of an investigated substance to a calibration curve calculated by linear regression of retention times and the known logD values (−0.02, 1.62, 2.06, 2.82, 3.41, 4.00, 5.10) at pH 7.4 of seven substances from the Nycomed compound library. Each substance was investigated in a double injection HPLC experiment. The calibration substances and the sample were dissolved in DMSO to a concentration of 10.0 mM. A sample of the calibration/sample solution (15 μL) per deep well was diluted with acetonitrile (100 μL). This dilution was carried out directly in the deep well plate before each first injection by the HPLC autosampler. Chromatographic conditions: HPLC equipment, Hitachi LaChrom 7000 series; HPLC column, Waters X Terra C18 100 mm × 2.1 mm, particle size 5 μM, equipped with a precolumn of 10 mm length; diode array detection, 230−330 nm; data acquisition time, 18.9 min; column oven temperature, 37 °C; injection volume, 2.0 μL; eluant, 10 mM ammonium acetate buffer (pH 7.4)/acetonitrile; flow rate, 0.5 mL; gradient, 96:4 to 0:100 (0−16 min), 0:100 (16−18.2 min), 0:100 to 96:4 (18.2−18.9 min).

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Supporting Information Available: Synthesis of azetidin-3-ylmethanol, 3-methylazetidin-3-ol, and *N*,*N*-dimethylazetidine-3-carboxamide. Assessment of purity of all target compounds by HPLC/HRMS and/or elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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