Arylcyclopropanecarboxyl Guanidines as Novel, Potent, and Selective Inhibitors of the Sodium Hydrogen Exchanger Isoform-1

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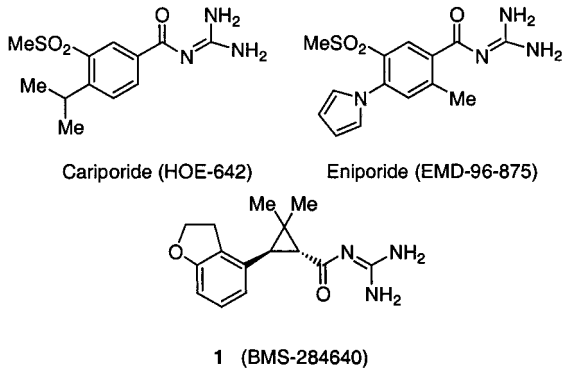
A novel series of arylcyclopropanecarboxyl guanidines was synthesized and evaluated for activity against the sodium hydrogen exchanger isoform-1 (NHE-1). In biological assays conducted in an AP1 cell line expressing the human NHE-1 isoform, the starting cyclopropane **3a** (IC_{50} = 3.5 μM) shows inhibitory activity comparable to cariporide (IC_{50} = 3.4 μM). Structure−activity relationships are used to optimize the affinity of various acyl guanidines for NHE-1 by screening the effect of substituents at both aryl and cyclopropyl rings. It is demonstrated that introduction of appropriate hydrophobic groups at the phenyl ring and a *gem*-dimethyl group at the cyclopropane ring enhances the NHE-1 inhibitory activity by up to 3 orders of magnitude (compound **7f**, IC_{50} = 0.003 μM). In addition, the *gem*-dimethyl series of analogues seem to display improved oral bioavailability and longer plasma half-life in rats. Furthermore, the lead benzodihydrofuranyl analogue **1** (BMS-284640) shows over 380-fold increased NHE-1 inhibitory activity as well as improved selectivity for NHE-1 over NHE-2 compared to cariporide.

Introduction

The sodium hydrogen exchanger (NHE) isoforms are integral plasma membrane proteins which transport sodium ions in exchange for protons.[1] Currently there are six known isoforms of NHE. NHE-1 is ubiquitous and plays a role in maintaining cellular pH, intracellular sodium ion concentration, and cell volume. NHE-2 is present in all three major gastric epithelial cell types and is expressed in the small intestine, colon, and kidney.[2] It is believed to be involved in the regulation of acid secretion by the stomach, because an NHE-2 knockout transgenic mouse shows decreased acid secretion linked to reduced viability of gastric parietal cells.[2] NHE-3 is primarily found in renal epithelia, localized to the apical membrane, where it has been implicated in the absorption of sodium.[4] NHE-4 is found in the stomach[5] and the collecting tubule of the renal inner medulla, where it has been proposed to play a specialized role in volume regulation.[6] NHE-5 is present in several nonepithelial tissues, including brain, spleen, and skeletal muscle, and its role is unknown. NHE-6 is ubiquitous and is believed to be most abundant in mitochondria.

Intracellular pH changes have been implicated in a variety of pathophysiological conditions including hypertension and myocardial ischemia. NHE-1 is the predominant isoform in myocardial cells, and it is believed to be responsible for exchanging intracellular protons generated by anaerobic metabolism for extracellular sodium ions during ischemia.[7] As such, it is implicated in the increase in intracellular sodium that underlies calcium overload and contractile dysfunction observed during ischemia and reperfusion. NHE-1 inhibition limits ischemic damage by indirectly inhibiting calcium overload.[8] A major advantage of an NHE-1 inhibitor is that NHE-1 is believed to be inactive in the normal myocardium, and thus, any effects due to inhibition of NHE-1 should be specific for the ischemic region.



1 (BMS-284640)

Figure 1.

Cariporide (HOE-642) (Figure 1) was the first selective NHE-1 inhibitor discovered, and it is currently in phase II/III clinical trials as a potential treatment for myocardial infarction (MI) and ischemic damage due to angioplasty and reperfusion following thrombolysis.[9] Another NHE-1 inhibitor, EMD-96-875 (eniporide) is also reported to be in phase II clinical trials.[10]

Our objective was to identify a potent and selective NHE-1 inhibitor that is suitable for once or twice daily dosing. Since most known NHE inhibitors are acyl guanidines, we synthesized a series of acyl guanidine analogues from diverse carboxylic acids using high-throughput solution phase chemistry. From this effort, several novel acyl guanidines were identified as potent

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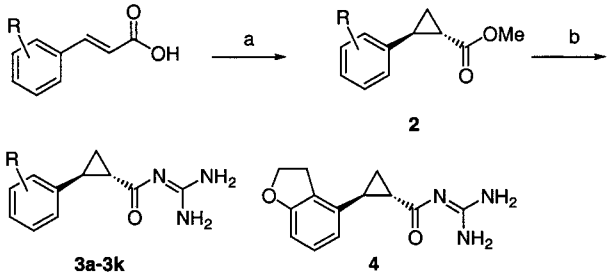
Scheme 1. Synthesis of Arylcyclopropanecarboxyl Guanidines (**3a**−**k** and **4**) via Palladium Catalyzed Cyclopropanation of Cinnamic Acids or Esters[a]



[a] Reagents: (a) $Pd(OAc)_2/CH_2N_2$/ether/THF; (b) guanidine/DMF.

inhibitors of NHE-1, including analogues containing an arylcyclopropane moiety. Herein we report the design, synthesis, and NHE-1 inhibitory activity of a novel series of arylcyclopropanecarboxyl guanidines including compound **1** (BMS-284640, NHE-1 $IC_{50} = 9$ nM), which in our hands is ca. 380-fold more potent than cariporide and orally bioavailable in rats and dogs.[11]

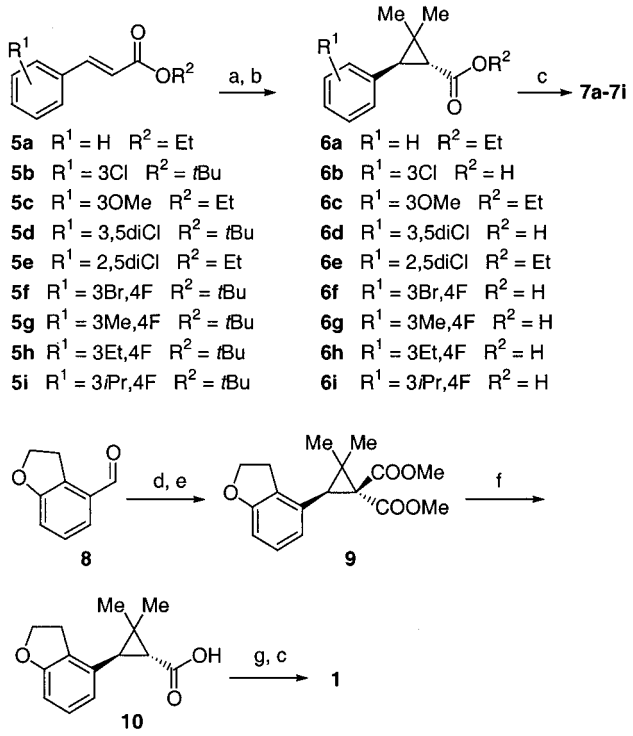
Chemistry

The arylcyclopropanecarboxyl guanidines described herein may be divided into an unsubstituted cyclopropane series and a *gem*-dimethylcyclopropane series. Synthesis of the first series of analogues **3a**−**3k** and **4** was carried out via the sequence of steps outlined in Scheme 1. Most of the cinnamic acids or esters used in the preparation of this series are commercially available. Synthesis of the unsaturated acid required for the preparation of **4** has been described previously by Catt et al.[12]

The various cyclopropanecarboxyl esters **2** were prepared by treatment of a THF solution of the respective *trans*-cinnamic acids (or esters) with an ether solution of diazomethane in the presence of palladium acetate and used as such without further purification.[13] The various esters **2** could be converted to the corresponding acyl guanidines by treatment with excess guanidine (free base) in DMF for 12 h. In each case, the products isolated after workup were subjected to reversed-phase preparative HPLC to isolate pure acyl guanidines as TFA salts. It is noteworthy that the various cyclopropanecarboxyl guanidines described herein exhibited limited stability when they were exposed as free bases to methanol or ethanol yielding the corresponding cyclopropyl esters. However, these compounds could be isolated in pure and stable form as acid salts.

Synthesis of the *gem*-dimethyl series of analogues **7a**−**7i** involved cyclopropanation of ethyl or *tert*-butyl cinnamates (**5a**−**5i**). While some of the cinnamic acids or esters used to prepare this series of analogues could be obtained from commercial sources, most of them were prepared from the corresponding aldehydes via Horner−Emmons or Wittig reactions.[14] Generally a THF or DMF solution of *tert*-butyl diethylphosphonoacetate was treated at low temperature with sodium bistrimethylsilylamide followed by treatment with a solution of the corresponding aldehyde. Alternatively, stirring the aldehydes with (carbethoxymethylene)triphenylphosphorane or (carb-*tert*-butoxymethylene)triphenyl-phosphorane in refluxing dichloromethane also afforded the corresponding cinnamates.

Scheme 2. Synthesis of *gem*-Dimethylcyclopropanecarboxyl Guanidines from Ethyl or *tert*-Butyl Cinnamates via Cyclopropanation with Isopropylidenetriphenyl Phosphorane[a]

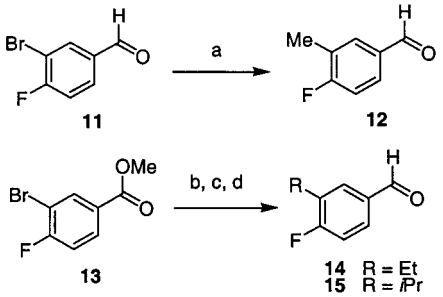


[a] Reagents: (a) isopropyltriphenylphosphonium iodide/*n*-BuLi/THF; (b) TFA−CH_2Cl_2 1:1 (used only for the *tert*-butyl esters); (c) CDI/DMF then guanidine; (d) dimethyl malonate/piperidine/acetic acid; (e) 2-nitropropane/potassium *tert*-butoxide/DMSO; (f) sodium cyanide/DMSO; (g) chiral resolution (see Experimental Section).

The cyclopropanation typically involved treating a THF solution of the cinnamate at −78 °C to room temperature with isopropylidenetriphenylphosphorane (generated by treating a THF solution of isopropyltriphenylphosphonium iodide with *n*-BuLi).[15] In most cases the crude cyclopropyl *tert*-butyl esters thus prepared were converted to the corresponding acids by treatment with excess trifluoroacetic acid in methylene chloride at room temperature (Scheme 2). The yields for the cyclopropanation step ranged from 20 to 95%. In general, the presence of an ortho substituent on the aryl group resulted in reduced yields most likely due to steric hindrance. Nevertheless, the crude products were subjected to the usual acid/base extractive workup to afford acids of sufficient purity. Treatment of a solution of crude carboxylic acids in DMF with stoichiometric quantities of 1,1′-carbonyldiimidazole (CDI) for 1 h at room temperature followed by treatment with guanidine (free base) or guanidine carbonate afforded the various *gem*-dimethylcyclopropanecarboxyl guanidines. Most of the final compounds in this series were purified by reversed phase preparative HPLC and isolated as TFA salts.

The benzodihydrofuranyl analogue **1** was initially prepared in a manner similar to that described above for synthesis of the acyl guanidines **7a**−**7i**. However, this approach was problematic due to poor yields for the cyclopropanation step. An alternate procedure was therefore developed which involved condensation of dimethyl malonate with the known aldehyde **8**[12] to

Scheme 3. Synthesis of Various 3-Alkyl-4-fluorobenzaldehydes[a]



[a] Reagents: (a) methylboronic acid/CsF/$Pd(Ph_3P)_4$/DME/argon; (b) ethyl or isopropyl magnesium chloride/$ZnCl_2PdCl_2$(dppf)/CuI/THF; (c) LAH/THF; (d) Swern oxidation.

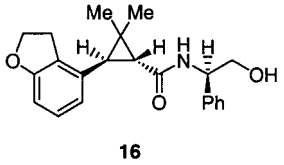


Figure 2.

afford the corresponding unsaturated diester and subsequent cyclopropanation with 2-nitropropane in the presence of potassium *tert*-butoxide to afford **9**. The diester **9** was converted to the acid **10** by treatment with sodium cyanide in dimethyl sulfoxide.

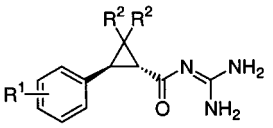
In some instances the aldehydes used to prepare the respective cinnamates also had to be prepared (Scheme 3). Aldehyde **12** was synthesized from the corresponding bromo aldehyde **11** as described by Wright et al.[16] The 3-ethyl- and 3-isopropylbenzaldehydes **14** and **15**, respectively, were prepared from the corresponding 3-bromobenzoate **13** via treatment with ethyl or isopropyl Grignard reagent by using the procedure of Weichert et al.[17] followed by LAH reduction of the resulting benzoates and subsequent Swern oxidation.

Most of the compounds were initially prepared and evaluated as racemates. However, several key compounds including the racemic form of **1** were subsequently resolved via chromatography on a chiral preparative HPLC column, and each enantiomer was independently characterized and evaluated in relevant biological assays. It is noteworthy that in all cases most of the NHE-1 inhibitory activity could be attributed to a single enantiomer.[18] This article enlists physical data only for the enantiomers that exhibited enhanced potencies in the primary screen. Enantiomerically pure forms of **1** and compound **7h** were also prepared by resolving the corresponding racemic acids via chromatography using a chiral column prior to coupling with guanidine. The absolute stereochemistry of **1** was determined to be (*R*,*R*) by a single-crystal X-ray analysis of the (*R*)-phenylglycinol amide **16** (Figure 2) derived from the acid (+)-**10**.

Results and Discussion

NHE inhibitors were screened in an AP1 cell line[19] (devoid of NHE activity) expressing the human NHE isoforms-1, -2, -3, and -5. The IC_{50} values were determined by measuring the ability of compounds to inhibit 50% of the sodium dependent recovery of pH following an imposed acidosis.[20] Using this protocol, IC_{50} values for cariporide and eniporide were measured as 3.4 and 0.38 μM, respectively.

Table 1. Sodium Hydrogen Exchange-1 (NHE-1) Activity of the Various Arylcyclopropanecarboxyl Guanidines[a]



compd no.	R^1	R^2	IC_{50} (μM)[b]
3a	H	H	3.5
3b	2-Cl	H	0.98
3c	3-Cl	H	0.28
3d	4-Cl	H	2.9
3e	4-F	H	1.6
3f	3-OMe	H	0.54
3g	3-NO_2	H	1.6
3h	4-NO_2	H	>30
3i	2,5-diCl	H	0.04 ± 0.0015 [c]
3j	3-Br, 4-F	H	0.09 ± 0.0565
3k	4-^{i}Pr	H	>30
4			0.12 ± 0.0268[c]
7a	H	Me	0.069
7b	3-Cl	Me	0.014 ± 0.0047[c]
7c	3-OMe	Me	0.012 ± 0.0056
7d	3,5-diCl	Me	0.006 ± 0.0004[c]
7e	2,5-diCl	Me	0.005 ± 0.0014[c]
7f	3-Br, 4-F	Me	0.003 ± 0.0014
7g	3-Me, 4-F	Me	0.032
7h	3-Et, 4-F	Me	0.005 ± 0.0003[c]
7i	3-^{i}Pr, 4-F	Me	0.017
1			0.009 ± 0.0013[c]
HOE-642 (cariporide)			3.4 ± 1.19
EMD-96-875 (eniporide)			0.38 ± 0.14

[a] Sodium hydrogen exchange activity is determined in AP1 cells expressing human NHE-1. [b] The IC_{50} values are means ± SEM of 3−6 experiments; single values indicate the results of one experiment. [c] IC_{50} values are reported only for the more active (+)-enantiomers.

The starting acyl guanidine **3a** showed NHE-1 inhibitory potency (IC_{50} = 3.5 μM) similar to cariporide (Table 1). Introduction of a chloro group at the 2- or 3-position of the phenyl group resulted in a modest 3- or 12-fold increase in potency (compounds **3b** and **3c**, respectively), perhaps indicating a role of hydrophobic interactions at the receptor and/or increased affinity resulting from conformational preference. While incorporation of the 4-chloro group (compound **3d**) did not affect the IC_{50} value of the parent compound **3a**, introduction of a smaller fluoro group (compound **3e**) at this site enhanced the NHE-1 inhibitory activity by approximately 2-fold. The 3-methoxy analogue **3f** also showed a ca. 6-fold increase in binding affinity. While the 3-nitro compound **3g** displayed ca. 2-fold enhancement in potency, the 4-nitro analogue **3h** was essentially devoid of NHE-1 inhibitory activity. The 2,5-dichloro and 3-bromo-4-fluoro analogues **3i** and **3j**, with IC_{50} values of 40 and 90 nM respectively, are 87- and 39-fold more potent than the unsubstituted compound **3a**. The 4-isopropyl analogue **3k** did not significantly inhibit NHE-1 at 30 μM concentration. The lack of inhibitory activity of the 4-nitro and 4-isopropyl analogues, **3h** and **3k** respectively, may be attributed to steric restrictions at the binding site. Constraining the 3-methoxy analogue **3f** to afford the more rigid benzodihydrofuran-derived analogue **4** resulted in further 4-fold enhancement in potency.

Table 2. Specificity of **1**, Cariporide, and Eniporide for NHE-1 Isoform vs NHE-2, -3, and -5 Isoforms[a,b]

compd	NHE-1 IC_{50} (μM)	NHE-2 IC_{50} (μM)	NHE-3 IC_{50} (μM)	NHE-5 IC_{50} (μM)
1	0.009 ± 0.0013	1.8 ± 0.44	>30	3.36 ± 0.14
cariporide	3.4 ± 1.19	62 ± 7.00	>30	>30
eniporide	0.38 ± 0.14	17 ± 2.43	>30	>30

[a] Sodium hydrogen exchange activity is determined in AP1 cells expressing human NHE-1−5. [b] The IC_{50} values are means ± SEM of 2−6 experiments.

Efforts were also made to explore substituent effects at the cyclopropyl ring. Table 1 outlines a series of *gem*-dimethylcyclopropyl analogues **1** and **7a**−**7i**. The phenyl analogue **7a** was ca. 50-fold more potent than the lead compound **3a**. The substantial increase in potency of **7a** induced by the *gem*-dimethyl group was also exhibited by a number of additional analogues (Table 1). This may be attributed to further hydrophobic interactions achieved by the inhibitor at the receptor site. Alternatively, the conformational rigidity imposed by introducing steric bulk at the cyclopropane ring may hinder rotation of aryl and acyl guanidine groups relative to the cyclopropane ring, thus optimizing interactions at respective binding sites. Combination of this "*gem*-dimethyl effect" with groups capitalizing on interactions at the phenyl ring resulted in the discovery of some of the most potent NHE-1 inhibitors known to date. For instance, the 3-bromo-4-fluoro-*gem*-dimethyl analogue **7f** (IC_{50} = 3 nM) is ca. 1100-fold more potent than the lead compound **3a** and cariporide. Attempts were made to investigate steric requirements of hydrophobic groups at the 3-position of the phenyl ring as well as to find a replacement for the 3-bromo group of **7f**. The 3-alkyl-4-fluoro analogues **7g**−**7i** were therefore prepared and evaluated for NHE-1 potency. The 3-ethyl-4-fluoro analogue **7h** with an IC_{50} value of 5 nM is 3- and 6-fold more potent than the corresponding isopropyl and methyl analogues, respectively. Introduction of the *gem*-dimethyl group to **4** resulted in 13-fold enhanced potency yielding **1** (IC_{50} = 9 nM).

Selectivity

The selectivity of several acyl guanidines discussed herein for NHE-1 was investigated in cell lines expressing NHE-2, NHE-3, and NHE-5. Table 2 outlines the various IC_{50} values for **1**, cariporide, and eniporide. Compound **1** exhibits improved selectivity for NHE-1. It is ca. 200-fold selective for NHE-1 over NHE-2, nearly an order of magnitude more selective than cariporide, and 4-fold more selective than eniporide. Chronic inhibition of NHE-2 activity may lead to gastric problems, since the NHE-2 knockout transgenic mouse shows decreased acid secretion linked to reduced viability of gastric parietal cells.[3] Loss of parietal cells in man would lead to inhibition of vitamin B12 uptake due to loss of intrinsic factor. None of the compounds show significant inhibition of NHE-3 at concentrations up to 30 μM. Selectivity of **1** against NHE-5 is intermediate to NHE-2 and NHE-3.

Standard electrophysiological techniques were used to measure the effects of various NHE inhibitors on cardiac sodium channel currents.[21] Both compound **1** and eniporide had little effect on sodium current at 100 μM (30% and 15% inhibition, respectively). However, cariporide is only 26-fold selective for NHE-1 vs the cardiac sodium current (IC_{50} = 88 μM).

Table 3. Pharmacokinetic Parameters and Oral Bioavailability of Selected Arylcyclopropanecarboxyl Guanidines in Rats[a]

compd no.	*Vss*[b] (L/kg)	clearance (mL/min/kg)	$t_{1/2}$ (h)	% oral bioavailability
3i	21 ± 7	143 ± 4	3.4 ± 1.7	13 ± 0
7e	23 ± 3	44 ± 12	8 ± 2	47 ± 21
4	6 ± 1	120 ± 4	1.3 ± 0.3	49 ± 9
1	8.6 ± 2.9	74 ± 9	3 ± 2	63 ± 24

[a] Plasma concentrations were determined after a single (10 μmol/kg, n = 3) intra-arterial and oral dose to rats; the vales are means ± SEM of the three experiments. [b] Volume of distribution at steady state.

Pharmacokinetic Properties

Several analogues reported here were evaluated for pharmacokinetic (PK) properties in rats. Various compounds were dosed orally or intra-arterially at 10 μmol/kg (n = 3), and plasma samples were analyzed by LC/MS/MS. Table 3 outlines oral bioavailability and various PK parameters of selected NHE-1 inhibitors. In cases where both the *gem*-dimethyl and the *des*-dimethyl analogues were tested, the dimethyl analogues exhibited longer plasma elimination half-life ($t_{1/2}$) and improved oral bioavailability. For example, after a single intra-arterial and oral dose to rats, the $t_{1/2}$ and oral bioavailability values for the 2,5-dichlorophenyl analogue **3i** and the corresponding dimethyl analogue **7e** were 3.4 h and 13% vs 8 h and 47%. Similarly, **1** with 63% oral bioavailability and a 3 h $t_{1/2}$ showed superior PK profile over the corresponding analogue without the *gem*-dimethyl group (compound **4**).

Conclusion

This report describes the design and synthesis of various novel arylcyclopropanecarboxyl guanidines as potent and selective inhibitors of NHE-1. Systematic structure−activity relationships were used to optimize the inhibition by various cyclopropyl acyl guanidines of NHE-1 by studying the effect of substituents at the aryl ring. In general, introduction of chloro, methoxy, and lower alkyl groups at the meta position and a fluoro group at the para position result in significant enhancement in potency. It was also realized that incorporation of a *gem*-dimethyl group at the cyclopropane ring further improves the NHE-1 inhibitory activity. In addition, the *gem*-dimethyl series of analogues display improved pharmacokinetic properties when compared to the corresponding analogues without the dimethyl group.

Evaluation of cariporide, a compound under investigation in human clinical trials, reveals that this compound exhibits only modest potency against the human NHE-1 (IC_{50} = 3.4 μM) with modest 18-fold selectivity over NHE-2. It has also been shown that compound **1** shows 380- and 40-fold improved potency for NHE-1 over cariporide and eniporide, respectively, as well as improved NHE-1/NHE-2 selectivity. In addition, **1** has a good oral bioavailability (63%) and modest plasma half-life (3 h) in rats. Furthermore, in dogs, the oral bioavailability of **1** is 34% with a 4.4 h half-life. On the basis of the improved selectivity and superior pharmacokinetic profile, compound **1** was selected for further

development. Efforts are underway to evaluate **1** in animal models, and the results of which will be published in due course.

Experimental Section

Reagents and solvents were purchased from Aldrich Chemical Co. and used without further purification. Silica gel 60 (Merck) was used for flash chromatography, and silica gel 60 F_{254} (Merck) was used for thin-layer chromatography (TLC). The mobile systems are indicated in the procedures. TLC spots were examined under UV light at 254 nm. Analytical HPLC analyses were performed under the following conditions: YMC S5 ODS 4.6 × 50 mm column/linear gradient system of H_2O-MeOH-H_3PO_4 90:10:0.2 to 10:90:0.2 over 4 min at a flow rate of 4 mL/min with a 1 min hold time at 10:90:0.2 H_2O−MeOH−H_3PO_4. All final compounds were purified by preparative HPLC on a YMC ODS A 30 × 250 mm column using a water−MeOH−TFA 90:10:0.1 to 10:90:0.1 linear gradient over 30 min at a flow rate of 25 mL/min. Unless otherwise noted, all reactions were monitored by LC/MS (Shimadzu-Micromass system/YMC S5 ODS 4.6 × 50 mm column/water−MeOH−TFA 90:10:0.1 to 10:90:0.1 linear gradient over 4 min followed by a 1 min hold at 10:90:0.1 of water−MeOH−TFA at a flow rate of 4 mL/min. NMR data were obtained using a JEOL CPF-270, Delta Eclipse 270, 400, or 500 spectrometer. Several compounds were resolved by chromatography on a chiral column (CHIRALPAK AD 50 × 500 mm column manufactured by Chiral Technologies, Inc., Exton, PA) to obtain each enantiomer in pure form. Optical rotations were determined by using a Perkin-Elmer 241 polarimeter. All final compounds were of ≥98% purity by the LC/MS and analytical HPLC systems and were characterized by NMR and high-resolution mass spectral (HRMS) analyses.

Procedure A. General Procedure for Preparing Arylcyclopropanecarboxyl Guanidines 3a−k from Cinnamic Acids or Esters.[13] To a solution of the cinnamic acid or ester (0.5 mmol) in THF (10 mL) were added $Pd(OAc)_2$ (5 mg) and a cold (0 °C) ethereal solution of diazomethane (6 mL, freshly prepared from 1-methyl-3-nitro-1-nitrosoguanidine (MNNG, 74 mg, 4.5 mmol)) alternately in small portions with continuous stirring during 10−15 min (the addition of diazomethane was done in small portions just following each addition of the palladium catalyst). It is noteworthy that the analytical HPLC retention times and the TLC R_f values for the cinnamates and the corresponding cyclopropyl esters are almost indistinguishable. Furthermore, we could not observe the molecular ions $(M + H)^+$ for the cyclopropyl esters in LC/MS. Therefore, the progress of these reactions was monitored by ^{1}H NMR. Upon completion of the reaction, a few drops of glacial acetic acid were added to quench excess diazomethane. The reaction mixture was filtered through Celite, and the filtrate was concentrated to give a thick dark brown residue. The crude cyclopropyl esters thus prepared were dissolved in 0.5 mL of DMF and treated with a solution of guanidine (148 mg, 2.5 mmol) in DMF (1 mL). The reaction mixtures were stirred for 12 h at room temperature, diluted with water, and extracted with EtOAc. The organic layer was dried over magnesium sulfate and concentrated, and the residue was subjected to reversed-phase preparative HPLC (ODS column/H_2O−MeOH−TFA, 90:10:0.1 to 10:90:0.1 gradient) to afford the corresponding acyl guanidines as TFA salts. The following compounds (**3a−k**) were prepared by the general procedure A described above.

(±)-*trans*-*N*-(Aminoiminomethyl)-2-phenylcyclopropanecarboxamide (3a): obtained as a white solid (TFA salt, 14% yield, two steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.03 (brs, 1H), 8.58 (brs, 2H), 8.06 (brs, 2H), 7.22 (t, 2H, J = 7.2 Hz, 7.8 Hz), 7.17 (t, 1H, J = 7.8 Hz, 7.2 Hz), 7.05 (d, 2H, 9.1 Hz), 2.60−2.59 (m, 1H), 2.00−1.99 (m, 1H), 1.69−1.66 (m, 1H), 1.43−1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.00, 156.00, 138.00, 128.64, 127.20, 126.36, 28.90, 26.08, 19.10; HRMS (ESI) calcd for $C_{11}H_{13}N_3O$ $(M + H)^+$ 204.1138, found 204.1139; Anal. HPLC t_R = 2.4 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2-(2-chlorophenyl)-cyclopropanecarboxamide (3b): obtained as a white solid (TFA salt, 96% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.29 (brs, 1H), 8.85 (brs, 2H), 7.95 (brs, 2H), 7.38−7.36 (m, 1H), 7.22−7.20 (m, 2H), 7.10−7.08 (m, 1H), 2.85−2.82 (m, 1H), 2.01−1.99 (m, 1H), 1.79−1.77 (m, 1H), 1.53−1.52 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.78, 155.49, 136.68, 135.41, 129.20, 128.47, 127.61, 127.17, 26.23, 24.97, 15.70; HRMS (ESI) calcd for $C_{11}H_{12}ClN_3O$ $(M + H)^+$ 238.0748, found 238.0738; Anal. HPLC t_R = 2.7 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2-(3-chlorophenyl)-cyclopropanecarboxamide (3c): obtained as a gummy solid (TFA salt, 26% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.14 (brs, 1H), 8.57 (brs, 2H), 8.16 (brs, 2H), 7.22−7.21 (m, 2H), 7.12 (s, 1H), 6.99−6.98 (m, 1H), 2.63−2.62 (m, 1H), 2.07−2.04 (m, 1H), 1.76−1.74 (m, 1H), 1.48−1.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.85, 155.96, 140.65, 134.55, 129.90, 127.24, 126.82, 124.44, 28.05, 25.98, 18.58; HRMS (ESI) calcd for $C_{11}H_{12}ClN_3O$ $(M + H)^+$ 238.0748, found 238.0742; Anal. HPLC t_R = 2.9 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2-(4-chlorophenyl)-cyclopropanecarboxamide (3d): obtained as a gummy solid (TFA salt, 38% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.08 (brs, 1H), 8.54 (brs, 2H), 8.16 (brs, 2H), 7.26 (d, 2H, J = 8.2 Hz), 7.04 (d, 2H, J = 8.8 Hz), 2.63−2.61 (m, 1H), 2.04−2.02 (m, 1H), 1.75−1.72 (m, 1H), 1.45−1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.91, 155.90, 137.10, 132.83, 128.74, 127.73, 27.97, 25.98, 18.66; HRMS (ESI) calcd for $C_{11}H_{12}ClN_3O$ $(M + H)^+$ 238.0748, found 238.0748; Anal. HPLC t_R = 2.9 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2-(4-fluorophenyl)-cyclopropanecarboxamide (3e): obtained as a white solid (TFA salt, 47% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.19 (brs, 1H), 8.63 (brs, 2H), 8.09 (brs, 2H), 7.10−7.08 (m, 2H), 6.98 (t, 2H, J = 8.2 Hz, 8.8 Hz), 2.64−2.63 (m, 1H), 2.03−2.01 (m, 1H), 1.68−1.66 (m, 1H), 1.44−1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.13, 161.25, 156.70, 135.00, 128.10, 128.06, 115.50, 115.40, 28.03, 25.92, 18.62; HRMS (ESI) calcd for $C_{11}H_{12}FN_3O$ $(M + H)^+$ 222.1043, found 222.1046; Anal. HPLC t_R = 2.5 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2-(3-methoxyphenyl)-cyclopropanecarboxamide (3f): obtained as a white solid (TFA salt, 98% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.04 (brs, 1H), 8.55 (brs, 2H), 8.15 (brs, 2H), 7.20 (t, 1H, 7.7 Hz, 8.2 Hz), 6.77 (d, 1H, J = 8.2 Hz), 6.69 (d, 1H, J = 7.7 Hz), 6.64 (s, 1H), 3.78 (s, 3H), 2.64−2.63 (m, 1H), 2.07−2.05 (m, 1H), 1.74−1.71 (m, 1H), 1.48−1.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.50, 159.82, 156.20, 140.21, 129.65, 118.57, 112.61, 111.94, 55.16, 28.69, 26.02, 18.89; HRMS (ESI) calcd for $C_{12}H_{15}N_3O_2$ $(M + H)^+$ 234.1243, found 234.1241; Anal. HPLC t_R = 2.6 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2-(3-nitrophenyl)-cyclopropanecarboxamide (3g): obtained as an off-white solid (TFA salt, 68% yield); ^{1}H NMR (500 MHz, CD_3OD) δ 8.10 (d, 1H, J = 8.7 Hz), 8.08 (s, 1H), 7.63 (d, 1H, J = 7.7 Hz), 7.56 (t, 1H, J = 7.7 Hz, 8.3 Hz), 2.80−2.77 (m, 1H), 2.17−2.15 (m, 1H), 1.82−1.80 (m, 1H), 1.67−1.65 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 178.00, 156.0, 149.0, 142.00, 133.40, 130.49, 122.36, 121.73, 27.81, 27.24, 17.88; HRMS (ESI) calcd for $C_{11}H_{12}N_4O_3$ $(M + H)^+$ 249.0988, found 249.0982; Anal. HPLC t_R = 2.3 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2-(4-nitrophenyl)-cyclopropanecarboxamide (3h): obtained as a white solid (TFA salt, 31% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 8.17 (d, 2H, J = 8.8 Hz), 7.42 (d, 2H, J = 8.8 Hz), 2.77−2.74 (m, 1H), 2.24−2.21 (m, 1H), 1.83−1.79 (m, 1H), 1.68−1.64 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.38, 158.50, 149.00, 148.00, 128.65, 125.05, 28.78, 28.48, 19.20; HRMS (ESI) calcd for $C_{11}H_{12}N_4O_3$ $(M + H)^+$ 249.0988, found 249.0989; Anal. HPLC t_R = 2.3 min.

(+)-*trans*-*N*-(Aminoiminomethyl)-2-(2,5-dichlorophenyl)cyclopropanecarboxamide (3i): The title compound was prepared in racemic form (57% yield, white solid) from the corresponding cinnamate **5e** as described in procedure A except that the crude product was purified by flash chromatography (silica gel/ethyl acetate−MeOH−triethylamine 80:20:0.3). The racemic product was submitted to preparative

chromatography on a chiral column (CHIRALPAK AD/92:8:0.3 hexanes−EtOH−triethylamine) to afford **3i** as the faster moving enantiomer (white solid, free base); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.2 Hz, 1H, Ar), 7.09 (dd, 1H, J = 8.2 Hz, 2.2 Hz, Ar), 6.98 (d, 1H, J = 2.2 Hz, Ar), 2.71−2.67 (m, 1H), 1.88−1.84 (m, 1H), 1.62−1.58 (m, 1H), 1.25−1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184, 161.04, 140.57, 133.66, 132.52, 130.24, 127.35, 127.09, 38.98, 24.12, 16.38; $[\alpha]_D$ +220° (c = 0.4, MeOH); MS (ESI) 274 $(M + H)^+$; Anal. HPLC t_R = 3.2 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2-(3-bromo-4-fluorophenyl)cyclopropanecarboxamide (3j): obtained as a white solid (TFA salt, 81% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.25 (brs, 1H), 8.64 (brs, 2H), 8.09 (brs, 2H), 7.34 (d, 1H, J = 5.5 Hz), 7.05−7.04 (m, 1H), 7.03 (s, 1H), 2.64−2.61 (m, 1H), 2.04−2.02 (m, 1H), 1.76−1.73 (m, 1H), 1.46−1.42 (m, 1H); HRMS (ESI) calcd for $C_{11}H_{11}BrFN_3O$ $(M + H)^+$ 300.0149, found 300.0144; Anal. HPLC t_R = 3.0 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2-(4-isopropylphenyl)-cyclopropanecarboxamide (3k): obtained as a white solid (TFA salt, 73% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.09 (brs, 1H), 8.62 (brs, 2H), 8.17 (brs, 2H), 7.15 (d, 2H, J = 8.3 Hz), 7.04 (d, 2H, J = 8.3 Hz), 2.89−2.86(m, 1H), 2.64−2.62 (m, 1H), 2.07−2.03 (m, 1H), 1.72−1.68 (m, 1H), 1.46−1.44 (m, 1H), 1.23 (d, 6H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.37, 155.96, 147.79, 135.92, 126.66, 126.34, 33.73, 28.53, 25.98, 23.94, 18.82; HRMS (ESI) calcd for $C_{14}H_{19}N_3O$ $(M + H)^+$ 246.1607, found 246.1596; Anal. HPLC t_R = 3.3 min.

(+)-*trans*-*N*-(Aminoiminomethyl)-2-(2,3-dihydro-4-benzofuranyl)cyclopropanecarboxamide (4): 1,1′-Carbonyldiimidazole (298 mg, 1.84 mmol) was added to a solution of 2-(2,3-dihydro-4-benzofuranyl)cyclopropanecarboxylic acid[12] (300 mg, 1.47 mmol) in THF (3 mL). The reaction mixture was stirred for 3 h at room temperature followed by the addition of guanidine (434 mg, 7.35 mmol) in DMF (1 mL). After the reaction mixture was stirred at room temperature for 1 h, the solvent was removed in vacuo to afford an off-white residue. The crude product was purified by silica gel flash chromatography as in the case of compound **3i** (white solid, 216 mg, 48%) and submitted to chromatography on a chiral column (CHIRALPAKAD/85:15:0.1 hexanes−ethanol−triethylamine) to afford **4** as the faster moving enantiomer (free base, off-white solid, mp 149−150 °C); ^{1}H NMR (270 MHz, CD_3OD) δ 6.99 (dd, J = 7.62, 8.2 Hz, 1H, Ar), 6.59 (d, J = 8.2 Hz, 1H, Ar), 6.39 (d, J = 7.62 Hz, 1H, Ar), 5.96 (b, 4H, NH), 4.51 (t, 2H, J = 8.8 Hz), 3.56 (d, 2H, J = 8.8 Hz), 2.25−2.35 (m, 1H), 1.82−1.90 (m, 1H), 1.46−1.50 (m, 1H), 1.20−1.22 (m, 1H); $[\alpha]_D$ +136° (c = 0.4, MeOH); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 185.70, 162.07, 160.29, 138.74, 128.87, 127.11, 116.70, 107.73, 71.79, 29.77, 29.31, 24.81, 17.48; HRMS (ESI) calcd for $C_{13}H_{15}N_3O_2$ $(M + H)^+$ 246.1243, found 246.1244; Anal. HPLC t_R = 2.49 min.

***trans*-3-Chlorocinnamic Acid, *tert*-Butyl Ester (5b):** To a solution of 3-chlorocinnamic acid (200 g, 1.095 mol) in 700 mL THF was added di-*tert*-butyl pyrocarbonate ($(Boc)_2O$, 286.8 g, 1.314 mol) at 0 °C followed by the addition of 4-(dimethylamino)pyridine (26.76 g, 0.219 mol) in small portions. The reaction mixture was stirred at room temperature for 14 h, diluted with EtOAc, washed sequentially with water, 2.5% sulfuric acid, and saturated sodium bicarbonate. The organic phase was dried over $MgSO_4$ and concentrated to afford a brown oil which was used as such in the next step without purification (260 g, 99% yield); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67 (d, 1H, J = 18.0 Hz), 7.65 (s, 1H), 7.52−7.40 (m, 3H), 6.51 (d, 1H, J = 18.0 Hz), 1.69 (s, 9H).

***trans*-3,5-Dichlorocinnamic Acid, *tert*-Butyl Ester (5d):** To a solution of *tert*-butyl diethylphosphonoacetate (6.94 g, 27.50 mmol) in THF (50 mL) at 0 °C was added sodium bis(trimethylsilyl)amide (NaHMDS) (1 M in toluene, 27.50 mL, 27.50 mmol) under argon. The resulting solution was warmed to 25 °C and stirred for 30 min. After cooling the reaction mixture to 0 °C, a solution of 3,5-dichlorobenzaldehyde (4.38 g, 25.00 mmol) in THF (25 mL) was slowly added. The reaction mixture was allowed to warm to room temperature, stirred overnight, and poured onto saturated NH_4Cl/EtOAc. The aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude residue by silica gel flash chromatography (9:1 hexanes−ethyl acetate) provided **5d** as a white solid (5.19 g, 77% yield); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.51 (d, 1H, J = 17.8 Hz), 7.31 (s, 1H), 7.29−7.23 (m, 2H), 6.29 (d, 1H, J = 17.8 Hz), 1.48 (s, 9H).

3-Ethyl-4-fluorobenzaldehyde[18] (14): Ethylmagnesium chloride (2.0 M in ether, 17.1 mL, 34.24 mmol) was added slowly to anhydrous zinc chloride (flame dried, 4.67 g, 34.24 mmol) in 50 mL THF under argon. The resulting white slurry was stirred at 50 °C for 3 h. In a separate flask a solution of 3-bromo-4-fluorobenzoic acid methyl ester (5.00 g, 22.83 mmol) in 50 mL of THF was sequentially treated with $PdCl_2$(dppf)[23] (0.835 g,1.14 mmol) and copper(I) iodide (0.261 g, 1.37 mmol) under argon. The alkyl zinc slurry that had been stirring at 50 °C for 3 h was added slowly to the ester mixture at room temperature. The resulting dark brown slurry was stirred in the dark at room temperature for 48 h. The reaction mixture was concentrated in vacuo to give a dark brown residue, which was taken up in EtOAc and washed sequentially with 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to obtain crude methyl 3-ethyl-4-fluorobenzoate as dark brown oil (4.8 g).

The above crude ester (4.80 g, 26.35 mmol) was dissolved in THF (100 mL) under argon followed by the addition of LAH (1.0 M solution in THF, 52.6 mL, 52.6 mmol) dropwise at 0 °C. The reaction was allowed to warm to room temperature over 1 h, quenched with methanol, and filtered. The filtrate was diluted with EtOAc, washed sequentially with saturated $NaHCO_3$ and brine, then dried ($MgSO_4$), and concentrated in vacuo to obtain 3-ethyl-4-fluorobenzyl alcohol as light brown oil (3.5 g).

A solution of DMSO (3.56 mL, 49.94 mmol) in 20 mL of methylene chloride was added dropwise to a stirred solution of oxalyl chloride (2.18 mL, 24.97 mmol) in methylene chloride (50 mL) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 15 min followed by the addition of the crude alcohol from above (3.5 g, 22.7 mmol) in 15 mL of methylene chloride. The reaction mixture was stirred at −78 °C for 45 min followed by the addition of triethylamine (10.44 mL, 75 mmol), and the mixture was allowed to come to room temperature. The mixture was diluted with methylene chloride, washed sequentially with 10% aqueous sulfuric acid, saturated sodium bicarbonate solution, and water. The organic layer was dried over magnesium sulfate and concentrated to give 3-ethyl-4-fluorobenzaldehyde (**14**) as a yellow oil (3.3 g, 95% yield); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.71 (dd, 1H, J = 2.2, 7.47 Hz), 7.69−7.60 (m, 1H), 7.09 (dd, 1H, J = 8.3, 9.2 Hz), 2.66 (q, 2H, J = 7.9 Hz), 1.20 (t, 3H, J = 7.9 H).

***trans*-3-Ethyl-4-fluorocinnamic Acid, *tert*-Butyl Ester (5h):** The aldehyde **14** was converted to **5h** as described for **5d** (brown oil, 65% yield); ^{1}H NMR ($CDCl_3$) δ 7.51 (d, 1H, J = 17.0 Hz), 7.34 (d, 1H, J = 9.1 Hz), 7.31−7.28 (m, 1H), 6.98 (dd, 1H, J = 8.6 Hz, 8.4 Hz), 6.27 (d, 1H, J = 17.0 Hz), 2.66 (q, 2H, J = 7.7 Hz), 1.51 (s, 9H), 1.22 (t, 3H, J = 7.7 Hz).

***trans*-4-Fluoro-3-isopropylcinnamic Acid, *tert*-Butyl Ester (5i):** was prepared from 3-bromo-4-fluorobenzoic acid methyl ester as described for **5h** (35% overall yield); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.54 (d, 1H, J = 15 Hz), 7.50−7.30 (m, 2H), 7.06 (t, 1H, J = 8.2 Hz), 6.29 (d, 1H, J = 15 Hz), 3.25−3.15 (m, 1H), 1.57 (s, 9H), 1.27 (d, 6H, J = 6.4 Hz).

Procedure B. (±)-*trans*-3-(3,5-Dichlorophenyl)-2,2-dimethylcyclopropanecarboxylic Acid (6d): To a suspension of isopropyltriphenylphosphonium iodide (6.48 g, 15 mmol) in THF (45 mL) at −78 °C was added *n*-BuLi (2.5 M in hexane, 6.6 mL, 16.5 mmol). The resulting mixture was warmed to 0 °C and stirred for 30 min. The reaction mixture was cooled to −78 °C followed by the addition of a solution of **5d** (4.11 g, 15 mmol) in THF (30 mL). The reaction mixture was stirred for 2 h at 0 °C, then slowly warmed to 25 °C, and stirred overnight. The reaction mixture was poured onto 10%

H_2SO_4/EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were sequentially washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo. The crude cyclopropyl *tert*-butyl ester was dissolved in 25 mL of trifluoroacetic acid/methylene chloride (1:1), and the resulting solution was stirred for 1 h at room temperature. The reaction mixture was concentrated in vacuo. The residue was partitioned between 10% NaOH and Et_2O. The aqueous layer was washed three times with ether. The aqueous layer was acidified with dilute sulfuric acid and extracted with EtOAc. The EtOAc layer was dried over $MgSO_4$ and concentrated in vacuo to afford a white solid (2.32 g, 71% yield over two steps); ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 1H), 7.30−7.27 (m, 2H), 2.77 (d, 1H, J = 8.9 Hz), 2.20 (d, 1H, J = 8.9 Hz), 1.48 (s, 3H), 1.05 (s, 3H).

(±)-*trans*-2,2-Dimethyl-3-phenylcyclopropanecarboxylic Acid, Ethyl Ester (6a): prepared by cyclopropanation of ethyl cinnamate as described in procedure B (gummy solid, 55% yield); ^{1}H NMR ($CDCl_3$) δ 7.58−7.11 (m, 5H), 4.05 (q, 2H, 7.1 Hz), 2.41 (d, 1H, J = 5.7 Hz), 1.82 (d, 1H, J = 5.7 Hz), 1.29 (s, 3H), 1.19 (t, 3H, 7.1 Hz), 0.79 (s, 3H).

(±)-*trans*-3-(2,5-Dichlorophenyl)-2,2-dimethylcyclopropanecarboxylic Acid, Ethyl Ester (6e): To a solution of 2,5-dichlorobenzaldehyde (165 g, 0.94 mol) in dichloromethane (1300 mL) was added (carbethoxymethylene)triphenylphosphorane (348 g, 1.0 mol) at room temperature. The resulting solution was stirred under reflux for 4 h, cooled to room temperature, and concentrated. The residue was dissolved in 3:7 ethyl acetate:hexanes (200 mL) and filtered through a short bed of silica gel. The silica bed was washed with ethyl acetate−hexanes (3:7). The filtrate was concentrated to give 212 g (91%) of the cinnamate **5e** as pale yellow oil. This compound was converted to **6e** as described in procedure B (white solid, 55% yield); ^{1}H NMR ($CDCl_3$) δ 7.58−7.11 (m, 3H), 4.05 (q, 2 H, 7.1 Hz), 2.41 (d, 1 H, J = 5.7 Hz), 1.82 (d, 1 H, J = 5.7 Hz), 1.29 (s, 3H), 1.19 (t, 3H, 7.1 Hz), 0.79 (s, 3H).

(±)-*trans*-2,2-Dimethyl-3-(3-chlorophenyl)cyclopropanecarboxylic Acid (6b): prepared as described in procedure B (white solid, 65% yield); ^{1}H NMR (270 MHz, CD_3OD) δ 7.42−7.25 (m, 4H), 2.73 (d, 1H, J = 8.1 Hz), 2.13 (d, 1H, J = 8.1 Hz), 1.52 (s, 3H), 1.07 (s, 3H).

(+)-*trans*-2,2-Dimethyl-3-(3-ethyl-4-fluorophenyl)-cyclopropanecarboxylic Acid (6h): prepared from **5h** by the method described in procedure B (pale oil, 95% yield); ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.43 (brs, 1H), 7.07−6.85 (m, 3H), 2.72 (d, 1H, J = 5.8 Hz), 2.63 (q, 2H, J = 7.4 Hz), 1.93 (d, 1H, J = 5.8 Hz), 1.42 (s, 3H), 1.20 (t, 3H, J = 7.4), 0.95 (s, 3H). The racemic acid was separated into the two enantiomers by preparative chromatography on a chiral column (CHIRALPAK AD column/97:3:0.3 hexanes−2-propanol−acetic acid) to give **6h** (faster moving enantiomer); $[\alpha]_D$ +16.9° (c = 1, methanol).

(±)-*trans*-2,2-Dimethyl-3-(4-fluoro-3-isopropylphenyl)-cyclopropanecarboxylic Acid (6i): prepared from **5i** by the method described in procedure B (50% yield); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.18−7.10 (brm, 1H), 7.02−6.90 (brm, 2H), 3.24−3.14 (brm, 1H), 2.68 (d, 1H, J = 2.1 Hz), 1.91 (d, 1H, J = 2.1 Hz), 1.42 (s, 3H), 1.25 (d, 6H, J = 6.5 Hz), 0.94 (s, 3H).

***(1R,3R)*-3-(2,3-Dihydro-4-benzofuranyl)-2,2-dimethylcyclopropanecarboxylic Acid (10):** To a solution of **8**[12] (25 g, 169 mmol) and dimethyl malonate (22.3 g, 169 mmol) in benzene (400 mL) were added piperidine (3 g, 35 mmol) and acetic acid (10 g, 169 mmol). The resulting solution was stirred under reflux for 18 h and then concentrated in vacuo. The residual mixture was taken up in ethyl acetate (200 mL) and washed sequentially with 1 N HCl and saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated to give 33 g (73%) of the corresponding arylidenemalonate as yellow oil.

To a solution of the crude malonate from above (33 g, 126 mmol) in DMSO (300 mL) was added 2-nitropropane (22.4 g, 252 mmol) and potassium *tert*-butoxide (28 g, 252 mmol). The mixture was stirred for 65 h at room temperature, and ethyl acetate (200 mL) was added. The reaction mixture was washed with 1 N HCl, and the organic layer was dried ($MgSO_4$) and concentrated to give 24 g (62% yield) of the corresponding dimethylcyclopropane diester **9** as yellow oil.

A portion of the dimethylcyclopropane intermediate from above (20 g, 65.8 mmol) and sodium cyanide (11.6 g, 237 mmol) in DMSO (125 mL) was heated at 150 °C for 23 h. After cooling, the mixture was diluted with water and made basic by adding 10% aqueous potassium hydroxide. The mixture was washed three times with ether, acidified with dilute sulfuric acid, and extracted with hexanes−ethyl acetate (80:20, needed to filter through Celite to remove emulsion). The organic layer was dried ($MgSO_4$) and concentrated to afford a crude brownish residue, which was treated with activated charcoal in hot ethanol to afford a light yellow solid. This material (ca. 9:1 *trans*−*cis*) was recrystallized from 90:10 acetonitrile−water to afford 5 g (15% corrected yield from **8**) of the racemic form of **10** as a white solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.05 (dd, 1H, J = 7.9, 7.7 Hz), 6.68 (d, 1H, J = 7.9 Hz), 6.58 (d, 1H, J = 7.7 Hz), 4.59 (dd, 2H, J = 9, 9 Hz), 2.9−3.4 (m, 2H), 2.59 (d, 1H, J = 5.9 Hz), 1.98 (d, 1H, J = 5.9 Hz), 1.45 (s, 3H), 0.98 (s, 3H). The racemic acid from above was resolved by preparative chromatography on a chiral column (CHIRALPAK AD column/85:15:1.5 hexanes−2-propanol−acetic acid) to give enantiomerically pure **10** (faster moving) { $[\alpha]_D$ +40° (c = 1, methanol)} as well as the corresponding slower moving (*1S,3S*)-enantiomer {$[\alpha]_D$ −40° (c = 1, methanol)}.

(+)-*trans*-*N*-(Aminoiminomethyl)-3-(3,5-dichlorophenyl)-2,2-dimethylcyclopropanecarboxamide (7d): To a solution of the acid **6d** (425 mg, 1.60 mmol) in DMF (5 mL) at room temperature was added CDI (313 mg, 1.90 mmol), and the resulting solution was stirred for 1 h at room temperature. Guanidine carbonate (609 mg, 3.20 mmol) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with brine, then dried (Na_2SO_4), and concentrated to afford a yellow gum (373 mg, 77% yield). The above crude racemate was resolved (CHIRALPAK AD column/90:10:0.2 hexanes−EtOH−NEt_3) to give the **7d** as the faster moving enantiomer; $[\alpha]_D$ +22.5° (c = 1, isopropyl alcohol). Compound **7d** was converted to the corresponding TFA salt by treatment of the free base in methylene chloride with 1 equiv of TFA; ^{1}H NMR (TFA salt, $CDCl_3$) δ 9.02 (brs, 1H), 7.71 (brs, 2H), 7.37 (s, 1H) 7.30−7.25 (m, 2H), 2.72 (d, 1H, J = 8.9 Hz), 2.18 (d, 1H, J = 8.9 Hz), 1.48 (s, 3H), 1.05 (s, 3H); HRMS (ESI) calcd for $C_{13}H_{15}Cl_2N_3O$ $(M + H)^+$ 300.0671, found 300.0659; Anal. HPLC t_R = 3.71 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2,2-dimethyl-3-phenylcyclopropanecarboxamide (7a): prepared from **6a** via treatment with guanidine and subsequent purification as described in procedure A (white solid, TFA salt, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (brs, 4H), 7.43−7.01 (m, 5H), 2.47 (d, 1H, J = 5.7 Hz), 2.19 (d, 1H, J = 5.7 Hz), 1.21 (s, 3H), 0.82 (s, 3H); HRMS (ESI) calcd for $C_{13}H_{15}N_3O_2$ $(M + H)^+$ 232.1451, found 232.1460; Anal. HPLC t_R = 3.50 min.

(+)-*trans*-*N*-(Aminoiminomethyl)-3-(3-chlorophenyl)-2,2-dimethylcyclopropanecarboxamide (7b): To a solution of the acid **6b** (100 mg, 0.44 mmol) in DMF (2 mL) at 25 °C was added CDI (86 mg, 0.53 mmol). The resulting solution was stirred for 1 h at room temperature followed by the addition of guanidine (52 mg, 0.88 mmol). The reaction mixture was stirred at room temperature for 1 h and partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with brine. The ethyl acetate layer was dried (Na_2SO_4) and concentrated to provide the racemic form of **7b** as a white solid (90 mg, 75% yield). The crude product was separated into its two enantiomers (CHIRALPAK AD column/90:10:0.2 hexanes−EtOH−NEt_3) to give the faster moving enantiomer) {$[\alpha]_D$ −27.0° (c = 1, isopropyl alcohol)} and the title compound **7b** as the slower moving enantiomer {$[\alpha]_D$ +27.1° (c = 1, isopropyl alcohol)}; ^{1}H NMR (TFA salt, CD_3OD) δ 9.05 (brs, 1H), 7.72 (brs, 2H), 7.51−7.42 (m, 3H), 7.32−7.28 (m, 1H), 3.10 (d, 1H, J = 8.1 Hz), 2.34 (d, 1H, J = 8.1 Hz),

1.54 (s, 3H), 1.16 (s, 3H); HRMS (ESI) calcd for $C_{13}H_{16}ClN_3O$ $(M + H)^+$ 266.1061, found 266.1052; Anal. HPLC t_R = 3.48 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2,2-dimethyl-3-(3-methoxyphenyl)cyclopropanecarboxamide (7c): A solution of *m*-anisaldehyde (1.0 g, 7.34 mmol) and carbethoxymethylenetriphenylphosphorane (3.0 g, 8.81 mmol) in dichloromethane (50 mL) was refluxed for 3 h. The reaction mixture was concentrated, and the crude residue was purified by silica gel chromatography using dichloromethane as an eluant to give 1.43 g of the cinnamate **5c** (95%). Crude **5c** was converted to **6c** as described in procedure B. Crude **6c** was converted to **7c** via treatment with guanidine as described in the general procedure A (white solid, TFA salt, 4% overall yield); ^{1}H NMR (400 MHz, CD_3OD) δ 7.24 (t, 1H, J = 7.89 Hz), 6.81 (m, 3H), 3.80 (s, 3H), 2.86 (d, 1H, J = 5.79 Hz), 2.16 (d, 1H, J = 5.76 Hz), 1.39 (s, 3H), 1.01 (s, 3H).

(+)-*trans*-*N*-(Aminoiminomethyl)-3-(2,5-dichlorophenyl)-2,2-dimethylcyclopropanecarboxamide (7e): prepared in racemic form from **6e** as described for **7b** (white solid, 72% yield). The racemic product was subjected to chromatography (CHIRALPAK AD column/95:5:0.2 hexanes−2-propanol−NEt_3) giving **7e** (faster moving enantiomer); $[\alpha]_D$ +22.0° (c = 0.77, isopropyl alcohol); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.10−7.01 (m, 2H), 2.61 (d, 1H, J = 5.86 Hz), 1.94 (d, 1H, J = 5.86 Hz), 1.34 (s, 3H), 0.82 (s, 3H); HRMS (ESI) calcd for $C_{13}H_{15}Cl_2N_3O$ $(M + H)^+$ 300.0671, found 300.0661; Anal. HPLC t_R = 3.567 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-3-(3-bromo-4-fluorophenyl)-2,2-dimethylcyclopropanecarboxamide (7f): 3-Bromo-4-fluorocinnamic acid was converted to the corresponding *tert*-butyl ester **5f** as described for **5b**. The crude ester **5f** was converted to the acid **6f** as described in procedure B**.** Compound **6f** was coupled with guanidine as in the case compound **7b** to afford **7f** after reversed-phase preparative HPLC purification (TFA salt, white solid, 23% overall yield); ^{1}H NMR (270 MHz, CD_3OD) δ 7.52 (brd, 1H, J = 7.5 Hz), 7.25−7.20 (m, 1H), 7.18 (t, 1H, J = 10.5, Hz), 2.84 (d, 1H, J = 7.5 Hz), 2.17 (d, 1H, J = 7.5 Hz), 1.37 (s, 3H), 0.98 (s, 3H); HRMS (ESI) calcd for $C_{13}H_{15}BrFN_3O_2$ $(M + H)^+$ 328.0462, found 328.0453; Anal. HPLC t_R = 3.565 min.

(±)-*trans*-*N*-(Aminoiminomethyl)-2,2-dimethyl-3-(4-fluoro-3-methylphenyl)cyclopropanecarboxamide (7g): To a solution of 3-bromo-4-fluorobenzaldehyde (**11**) (1.00 g, 4.93 mmol) in ethylene glycol dimethyl ether (18 mL) were sequentially added cesium fluoride (1.66 g, 10.96 mmol), methyl boronic acid (0.33 g, 5.48 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.15 mmol) under argon. The reaction mixture was refluxed for 17 h, diluted with EtOAc, and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the crude product was subjected to flash chromatography (silica gel/hexanes−ethyl acetate 96:4) to afford 4-fluoro-3-methylbenzaldehyde (**12**) (0.523 g) contaminated with ca. 25% of **11**.

This mixture was converted to the corresponding cinnamate **5g** as described for **5d**. Crude cinnamate **5g** was subsequently transformed to the cyclopropyl acid **6g** as described in procedure B. In the final step, the acid **6g** was converted to **7g** as described for **7b**. The crude product (still contaminated with ca. 25% of **7f**) was purified by preparative HPLC (C18 column/water−methanol−trifluoroacetic acid 90:10:0.1 to 10:90:0.1 gradient) to afford pure **7g** as a colorless gummy solid (TFA salt, 3% overall yield); ^{1}H NMR (DMSO-d_6) δ 8.35−8.15 (m, 4H), 7.16 (d, 1H, J = 6.8 Hz), 7.09−7.02 (m, 2H), 2.63 (d, 1H, J = 6.3 Hz), 2.23−2.17 (m, 4H), 1.28 (s, 3H), 0.89 (s, 3H); HRMS (ESI) calcd for $C_{14}H_{18}FN_3O$ $(M + H)^+$ 264.1513, found 264.1500; Anal. HPLC t_R = 3.4 min.

(+)-*trans*-*N*-(Aminoiminomethyl)-2,2-dimethyl-3-(3-ethyl-4-fluorophenyl)cyclopropanecarboxamide (7h): Prepared from the acid (+)-**6h** via the procedure described for **7b**. The crude product was purified by preparative HPLC as described in general procedure A giving **7h** as a colorless gum (TFA salt, 74% yield); ^{1}H NMR (270 MHz, $CDCl_3$) δ 11.68 (brs, 1H), 8.51 (brs, 1H), 7.98 (brs, 2H), 6.94 (d, 1H, J = 7.4 Hz), 6.92−6.80 (m, 2H), 2.79 (d, 1H, J = 5.7 Hz), 2.60 (q, 2H, J = 7.4 Hz), 1.99 (d, 1H, J = 5.7 Hz), 1.36 (s, 3H), 1.18 (t, 3H, J = 7.4 Hz), 0.95 (s, 3H); HRMS (ESI) calcd for $C_{15}H_{20}FN_3O$ $(M + H)^+$ 278.1669, found 278.1659; Anal. HPLC t_R = 3.56 min. A portion of **7h** from above (TFA salt) was dissolved in methylene chloride and washed with 5% sodium carbonate, and the methylene chloride layer was treated with 1 equiv of HCl in ether to give HCl salt of **7h**; $[\alpha]_D$ +4.9° (c = 0.3, MeOH).

(±)-*trans*-*N*-(Aminoiminomethyl)-2,2-dimethyl-3-(4-fluoro-3-isopropylphenyl)cyclopropanecarboxamide (7i): prepared from **6i** as described for **7b** (TFA salt, colorless gum, 15% overall yield); ^{1}H NMR ($CDCl_3$) δ 11.75 (brs, 1H), 8.60 (brs, 1H), 7.92 (brs, 2H), 6.98−6.87 (m, 3H), 3.21−3.12 (m, 1H), 2.80 (d, 1H, J = 5.8 Hz), 2.0 (d,1H, J = 5.8 Hz), 1.35 (s, 3H), 1.21 (d, 6H, J = 6.9 Hz), 0.94 (s, 3H); HRMS (ESI) calcd for $C_{16}H_{22}FN_3O$ $(M + H)^+$ 292.1826, found 292.1816; Anal. HPLC t_R = 3.7 min.

(1*R*,3*R*)-*trans*-*N*-(Aminoiminomethyl)-3-(2,3-dihydrobenzofuran-4-yl)-2,2-dimethylcyclopropanecarboxamide (1): This compound was prepared from the corresponding acid **10** as described for **7b** (white solid, HCl salt, 54% yield from **10**); MS m/z 274 $(M + H)^+$; ^{1}H NMR (270 MHz; $CDCl_3$) δ 11.80 (s, 1H); 8.40 (bs, 4H); 7.01 (t, 1H, J = 7.84); 6.67 (d, 1H, J = 7.94); 6.55 (d, 1H, J = 7.65); 4.58 (t, 2H, J = 9.2); 3.28−3.20 (m, 1H); 3.09−3.00 (m, 1H); 2.71 (d, 1H, J = 5.6); 2.12 (d, 1H, J = 5.7); 1.4 (s, 3H); 0.99 (s, 3H); ^{13}C NMR (270 MHz; $CDCl_3$) δ 173.90, 160.30, 156.40, 133.50, 128.50, 127.40, 119.90, 108.60, 71.43, 37.46, 34.43, 33.22, 29.29, 22.21, 20.52; $[\alpha]_D$ +7.3° (c = 1 $CHCl_3$); Anal. ($C_{15}H_{19}N_3O_2$·HCl) C, H, N.

NHE Assays: Stable cell lines expressing four members of the human Na^+/proton exchanger gene family, NHE-1, NHE-2, NHE-3, and NHE-5, were developed for use as screens. All clones were expressed in AP1 cells, a CHO (Chinese hamster ovary) cell derivative that lacks any endogenous NHE activity. cDNA clones for human NHE-1 and NHE-3 were obtained using PCR primers based on the published human sequences.[4,22] A cDNA clone for human NHE-2 was obtained from Dr. K. Ramaswamy at the University of Illinois at Chicago. An AP1 cell line expressing the human NHE-5 isoform was obtained from Dr. J. Orlowski (McGill University, Montreal, Canada).

These cell lines were then used to assay NHE activity. Monolayers grown in 96-well plates were washed twice in NaCl−HEPES buffer (100 mM NaCl, 50 mM HEPES pH 7.3, 10 mM glucose, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$) and incubated at room temperature for 30 min in buffer containing BCECF-AM (Molecular Probes, #B3051), at a final concentration of 5 μM. Cells were then washed once with NaCl-HEPES and acid-loaded by first incubating with NH_4Cl−HEPES (20 mM NH_4Cl, 80 mM NaCl, 50 mM HEPES pH 7.3, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$) for 9 min, then by washing twice with ammonium-free, Na^+-free HEPES buffer (100 mM choline Cl, 50 mM HEPES pH 7.3, 10 mM glucose, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$). Drugs were then preincubated with cells for 7.5 min. NHE activity was initiated by the addition of 450 mM NaCl (final concentration 135 mM). Fluorescence readings were taken 5 min after the addition of NaCl to each microplate, at 444 nm excitation/538 nm emission and also at 485 nm excitation/538 nm emission. Activity in the absence of NaCl was subtracted from the activity in the presence of NaCl, and the ratio of 485 nm/444 nm readings were determined as an index of pH. The IC_{50} values reported in Tables 1 and 2 were determined from an 8-point dose response curve.

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Supporting Information Available: Analytical data for compound **1** and crystallographic data and details of refinement are available for compound **16** and the maleic acid and mesylate salts of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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