(5-Arylfuran-2-ylcarbonyl)guanidines as Cardioprotectives through the Inhibition of Na^+/H^+ Exchanger Isoform-1

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A series of (5-arylfuran-2-ylcarbonyl)guanidines was synthesized and evaluated for the NHE-1 inhibitory activity and cardiprotective efficacy against ischemia-reperfusion injury. Starting with (5-phenylfuran-2-ylcarbonyl)guanidine **47** with a moderate inhibitory effect on NHE-1, the compounds with various substituents at the phenyl ring were investigated with the aim to optimize the potency. In this study, the 2,5-disubstituted compounds appeared to have better activities than the other analogues, and the 2-methoxy-5-chlorophenyl compound **85** was found as a potent inhibitor of NHE-1 ($IC_{50} = 0.081\ \mu M$). Furthermore, **85** showed a marked reduction of infarct size in the rat myocardial infarction model in vivo and significant improvement of cardiac contractile function in the isolated rat heart ischemia model in vitro.

Introduction

Even though early reperfusion has been the best strategy so far to limit infarct size,[1] morbidity and mortality from acute myocardial infarction (AMI) still remain significant. Therefore there is a need to provide better cardioprotection therapy which slows the progression of myocardial ischemic injury and attenuates the detrimental consequences of reperfusion.[2,3] The Na^+/H^+ exchanger type 1 (NHE-1) inhibitors have been found to reduce infarct size, myocardial stunning, arrhythmia, and endothelial dysfunction in animal models of myocardial ischemia and reperfusion.[4−6]

The available experimental evidence suggests that the cardioprotection of NHE-1 inhibitors is likely to arise primarily from the attenuation of intracellular Na^+ accumulation during ischemia, which would attenuate intracellular Ca^{2+} accumulation during both ischemia and subsequent reperfusion.[7,8] Ischemic conditions induce intracellular acidification, which strongly activates the NHE-1.[9] Under these conditions, the NHE-1 plays the crucial role to restore physiological pH by the extrusion of H^+ and the influx of Na^+ with the ischemia-induced inhibition of Na^+/K^+ ATPase which is the primary Na^+ extrusion pathway from the cardiac myocyte. Then intracellular Na^+ is accumulated, which alters the sarcolemmal Na^+/Ca^{2+} exchanger (NCX) to the reversal mode in a manner that inhibits Ca^{2+} efflux and/or enhances Ca^{2+} influx, resulting in a pathologic increase in intracellular Ca^{2+}. This intracellular Ca^{2+} overload is involved in ischemic and reperfusion injuries such as activation of contractile dysfunction, arrhythmia, and cellular death.[10] With a strategy to attenuate the harmful consequences of excessive NHE activation, several NHE-1 inhibitors have been developed as cardioprotective agents.[11]

There have been several trials to replace the acylguanidine moiety known as a key pharmacophoric unit for NHE-1 inhibitors,[12] with its bioisostere such as aminoguanidine[13] and 2-aminoimidazole,[14] but it was quite limited. However, the studies on the template bearing an acylguanidine moiety were diversely performed including the six-membered monocycles such as the phenyl of cariporide[15] and the pyrazine of amiloride,[16] the five-membered monocycles such as the pyrazole of zoniporide (Figure 1),[17] and the bicycles such as a quinoline and an indole.[18]

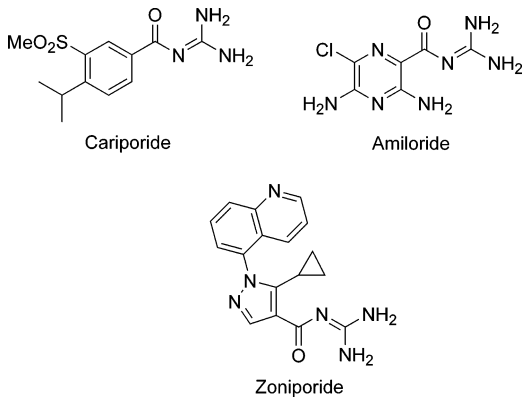

Figure 1. Representative NHE-1 inhibitors.

From our efforts to identify a novel template, especially based on five-membered ring which has not been investigated as intensively as six-membered ring, (5-phenylfuran-2-ylcarbonyl)guanidine **47** was found as an initial lead. Starting with **47**, the activity of this series of compounds was optimized through the introduction of various one or two substituents on the phenyl ring attached to the 5-position of the furan ring (Figure 2). Herein, the synthesis, structure−activity relationships, and pharmacological properties of this analogues are described.

Chemistry. The synthesis of (5-arylfuran-2-ylcarbonyl)guanidines was accomplished by relatively simple procedures. Starting with methyl 5-bromofuran-2-carboxylate, variously substituted phenyl ring was introduced into the 5-position of furan ring by the Pd-

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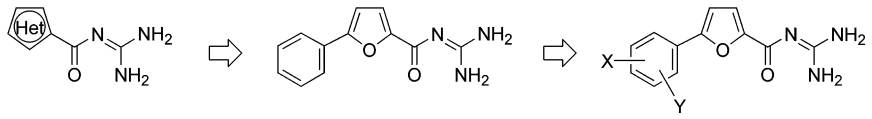
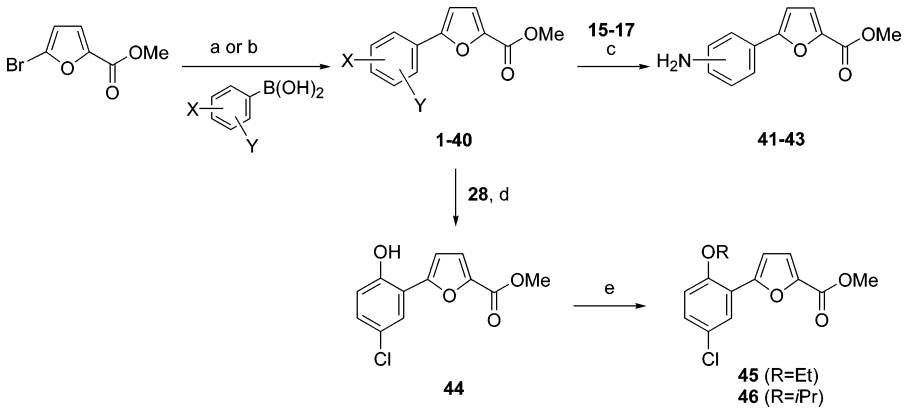


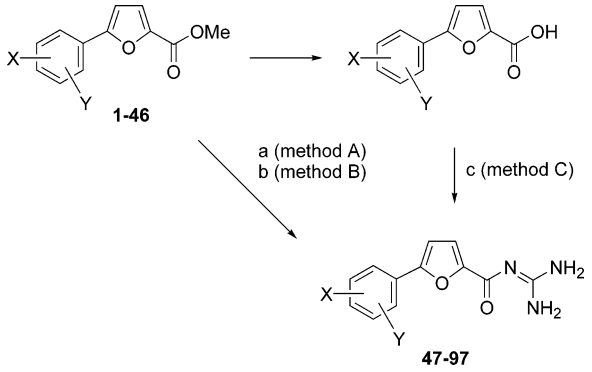
Figure 2. Identification of 5-(arylfuran-2-ylcarbonyl)guanidines.

Scheme 1. Preparation of Methyl 5-Arylfuran-2-carboxylate[a]



[a] Reagents and conditions: (a) Na_2CO_3, $Pd(PPh_3)_4$, toluene, reflux; (b) $Ba(OH)_2$, $Pd(PPh_3)_4$, DME, 80 °C; (c) H_2, Pd/C, MeOH, rt; (d) BBr_3, CH_2Cl_2, rt; (e) RI, K_2CO_3, DMF, rt.

Scheme 2. Preparation of (5-Arylfuran-2-ylcarbonyl)guanidines[a]



[a] Reagents and conditions: (a) guanidine, MeOH, reflux; (b) guanidine, DMF, rt; (c) (i) CDI, THF, rt; (ii) guanidine, rt.

catalyzed Suzuki reaction (Scheme 1).[19] Generally the Suzuki reaction proceeded well using sodium carbonate as a base in toluene in the presence of $Pd(PPh_3)_4$. In some cases, barium hydroxide was used as a base in 1,2-dimethoxyethane (DME). The compounds substituted with amino group (**41**−**43**) were prepared from the corresponding nitro compounds (**15**−**17**) by catalytic hydrogenation. Demethylation of the methoxy group of 5-(2-methoxy-5-chlorophenyl)furan-2-carboxylate **28** using BBr_3 gave the phenol **44**, which was further diversified to the ethoxy compound **45** and isopropoxy compound **46** by *O*-alkylation.

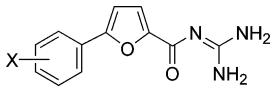
As outlined in Scheme 2, acylguanidines were obtained either from esters by treating with excess guanidine in methanol (method A) or in DMF (method B), or from the corresponding carboxylic acids, first activating with stoichiometric amounts of 1,1′-carbonyldiimidazole (CDI), followed by treating with guanidine (method C). The final acylguanidine compounds were purified by silica gel column chromatography or crystallization as a methanesulfonic acid salt.

Biology. The NHE-1 inhibitory activity was determined by measuring their ability to inhibit the sodium dependent recovery of pH following an imposed acidosis, in PS120 variant cells in which the human NHE-1 was selectively expressed.[20] The cardioprotective efficacy was evaluated using a perfused rat heart model according to Langendorff[21] and an in vivo rat myocardial infarction model.[22] In the heart perfused model, each isolated rat heart was stabilized for 15 min, treated with 10 μM concentration of the compound for 10 min, and subjected to 30 min global ischemia followed by 30 min reperfusion. The % recovery of rate pressure product (RPP = HR × LVDP, heart rate × left ventricular developing pressure) at the end of reperfusion to the preischemic value was measured as an index for cardiac contractile function. Antiischemic in vivo potency was determined by measuring a percentage ratio of myocardial infarction size to the area at risk (IS/AAR, %), using an ischemic myocardium-damaged rat model which was stabilized for 20 min after a left thoracotomy operation and subjected to coronary artery occlusion for 45 min, followed by reperfusion for 90 min. The vehicle or compounds were intravenously administered by bolus injection at 5 min prior to onset of ischemia into the femoral vein.

Results and Discussion

The starting (5-phenylfuran-2-ylcarbonyl)guanidine **47** showed a weaker NHE-1 inhibitory activity (IC_{50} = 3.1 μM) than cariporide (IC_{50} = 1.2 μM). The effect of various substituents at the ortho-, meta-, or para-position of the phenyl ring was primarily investigated (Table 1). Most of the para-substituted analogues (**66**−**72**) were inactive. The activities of the meta-substituted analogues varied in a wide range, from almost inactive compounds (**64**, **65**), to moderately active compounds (**61**, **62**, and **63**), and to quite active compounds (**59**, **60**). The ortho-substituted analogues were generally more active than **47** as shown in **49** (IC_{50} = 1.1 μM), **50** (IC_{50} = 2.3 μM), **52** (IC_{50} = 2.0 μM), and **51** (IC_{50} = 0.34 μM). The compounds with bulkier 2-alkyl or -alkoxy groups such as **55** (IC_{50} = 1.4 μM), **56** (IC_{50} = 2.6 μM), **57** (IC_{50} = 2.4 μM), and **58** (IC_{50} = 1.1 μM) also exhibited good activities.

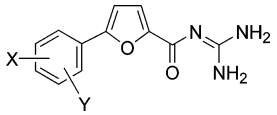
Table 1. Inhibitory Effect on NHE-1 and Cardioprotective Efficacy of Monosubstituted 5-(Arylfuran-2-ylcarbonyl)guanidines



compd	X	IC_{50}[a] (μM)	RPP[b] (%) 10 μM	IS/AAR[c] (%) 0.3 mg/kg	compd	X	IC_{50}[a] (μM)	RPP[b] (%) 10 μM	IS/AAR[c] (%) 0.3 mg/kg
control			13 ± 1	59 ± 1	**59**	3-F	2.4	78 ± 12	38 ± 5
cariporide		1.2	45 ± 4	38 ± 3	**60**	3-Cl	0.75	101 ± 5	45 ± 0
47	H	3.1	49 ± 2	50 ± 2[d]	**61**	3-OMe	7.4		
48	2-F	3.5	43 ± 11	51 ± 3	**62**	3-Me	6.0	75 ± 5	40 ± 2[d]
49	2-Cl	1.1	44 ± 4	37 ± 2[d]	**63**	3-CF_3	9.4		
50	2-OMe	2.3	46 ± 11	33 ± 3[d]	**64**	3-NO_2	>30		
51	2-Me	0.34	93 ± 26	46 ± 1[d]	**65**	3-NH_2	> 30		
52	2-CF_3	2.0	44 ± 4	46 ± 4	**66**	4-F	39		
53	2-NO_2	2.3	40 ± 11	50 ± 3	**67**	4-Cl	27		
54	2-NH_2	20			**68**	4-OMe	> 30		
55	2-Et	1.4	45 ± 9	38 ± 2[d]	**69**	4-Me	> 30		
56	2-OEt	2.6	45 ± 13	41 ± 3[d]	**70**	4-CF_3	> 30		
57	2-O^{i}Pr	2.4	42 ± 21	43 ± 8[d]	**71**	4-NO_2	> 30		
58	2-OPh	1.1			**72**	4-NH_2	> 30		

[a] IC_{50} values resulted from at least two experiments. [b] In vitro cardioprotective effect was evaluated measuring a % RPP (LVDP × HR) at the end of reperfusion to preischemic value in the isolated ischemic rat heart model (10 μM). Value are means ± SEM of at least three determinations. [c] In vivo anti-infarction effect was determined by measuring a % ratio of myocardial infarct size to area at risk (IS/AAR) in rat myocardial infarction model (0.3 mg/kg), $n = 3$ or higher. Values are means ± SEM. [d] Administration of 1.0 mg/kg

Table 2. Inhibitory Effect on NHE-1 and Cardioprotective Efficacy of Disubstituted 5-(Arylfuran-2-ylcarbonyl)guanidines



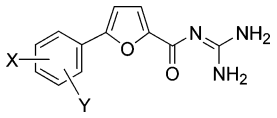
compd	X	Y	IC_{50}[a] (μM)	RPP[b] (%) 10 μM	IS/AAR[c] (%) 0.3 mg/kg	compd	X	Y	IC_{50}[a] (μM)	RPP[b] (%) 10 μM	IS/AAR[c] (%) 0.3 mg/kg
control				13 ± 1	59 ± 2	**85**	2-OMe	5-Cl	0.081	42 ± 6	34 ± 2
cariporide			1.2	45 ± 4	38 ± 3	**86**	2-Cl	5-CF_3	>30		
73	2-F	3-F	7.9			**87**	2-OMe	5-Br	0.093	6 ± 1	50 ± 5
74	2-Cl	3-Cl	1.7	40 ± 13	40 ± 4[d]	**88**	2-F	6-F	>30		
75	2-OMe	3-OMe	>30			**89**	2-Cl	6-F	>30		
76	2-Me	3-Me	4.4			**90**	2-OMe	6-OMe	>30		
77	2-F	4-F	15			**91**	2-Me	6-Me	3.7	38 ± 2	
78	2-F	5-F	1.3	64 ± 22	39 ± 2[d]	**92**	3-F	5-F	1.3	57 ± 6	36 ± 5
79	2-Cl	5-Cl	0.12	22 ± 2	28 ± 3[d]	**93**	3-Cl	5-Cl	0.73	27 ± 4	35 ± 0[d]
80	2-OMe	5-OMe	4.4			**94**	3-Me	5-Me	3.0	50 ± 13	38 ± 4
81	2-Me	5-Me	0.65	31 ± 1		**95**	2-OH	5-Cl	0.14	81 ± 4	42 ± 1
82	2-F	5-Me	1.7	17 ± 1		**96**	2-OEt	5-Cl	0.14	6 ± 3	31 ± 3[d]
83	2-Me	5-F	0.23	41 ± 8	35 ± 3[d]	**97**	2-O^{i}Pr	5-Cl	0.13	4 ± 1	39 ± 3[d]
84	2-OMe	5-F	0.48	27 ± 4	36 ± 3[d]						

[a] IC_{50} values resulted from at least two experiments. [b] In vitro cardioprotective effect was evaluated measuring a % RPP (LVDP × HR) at the end of reperfusion to preischemic value in the isolated ischemic rat heart model (10 μM). Values are means ± SEM of at least three determinations. [c] In vivo anti-infarction effect was determined by measuring a % ratio of myocardial infarct size to area at risk (IS/AAR) in ischemic myocardium damage rat model (0.3 mg/kg), $n = 3$ or higher. Values are means ± SEM. [d] Administration of 1.0 mg/kg.

The compounds showing good NHE-1 inhibitory activity were further investigated for their cardioprotective effects against ischemia-reperfusion injury. In the perfused rat heart model, cariporide significantly improved the recovery of cardiac contractile function (45% RPP) compared with the control (13% RPP). In the in vivo rat myocardial infarct model, cariporide also significantly reduced the infarct size (38% IS/AAR vs 59% of the control) at a dose of 0.3 mg/kg. Most compounds with a good activity on NHE-1 exhibited a good cardioprotective efficacy both in vitro and in vivo. In the isolated rat heart ischemia model, the compounds **51** (93%), **59** (78%), **60** (101%), and **62** (75%) greatly improved the recovery of contractile function against ischemia-reperfusion injury.

Next the effect of disubstituion at the phenyl ring on the activity was examined as shown in Table 2. The 2,6-disubstituted compounds **88**−**90** were almost inactive except the dimethyl compound **91** ($IC_{50} = 3.7$ μM). The 2,3-disubstituted compounds (**73**, **74**, **76**) showed moderate activities except the 2,3-dimethoxy compound **75** ($IC_{50} > 30$ μM). The 3,5-difluoro **92** ($IC_{50} = 1.3$ μM), 3,5-dichloro **93** ($IC_{50} = 0.73$ μM), and 3,5-dimethyl **94** ($IC_{50} = 3.0$ μM) compounds exhibited similar or slightly increased potency compared with the monosubstituted derivatives. The 2,5-disubstitution appeared to be much better for increasing the activity on NHE-1 than the other substitution patterns investigated. Especially the 2-methoxy-5-chloro compound **85** ($IC_{50} = 0.081$ μM) and 2-methoxy-5-bromo compound **87** ($IC_{50} = 0.093$ μM) showed highly improved potency on NHE-1, which were 10 times more potent than cariporide. While the excellent NHE-1 inhibitory activity of **87** was not translated into the efficacy for the improvement of cardiac contractility nor in the reduction of infarct size, the compound **85** greatly reduced the infarct size (34% IS/

Table 3. Dose-Dependent Cardioprotective Efficacies of Selected Compounds



compd	X	Y	IC_{50}[a] (μM)	RPP (%),[b] μM				IS/AAR (%),[c] mg/kg			
				0.3	1	3	10	0.1	0.3	1.0	3.0
control				13				59			
cariporide			1.2		15	33	45	41	38	35	
59	3-F		2.4	25	44	54	78	41	38	32	26
60	3-Cl		0.75		64	67	101	53	45	40	
85	2-OMe	5-Cl	0.081		27	32	42	35	34	27	
92	3-F	5-F	1.3		28	41	57	40	36	30	
94	3-Me	5-Me	3.0	15	37	49	50	43	38		

[a] IC_{50} values resulted from at least two experiments. [b] In vitro cardioprotective effect was evaluated measuring a % RPP (LVDP × HR) at the end of reperfusion to pre-ischemic value in the isolated ischemic rat heart model. Values are means ± SEM (0.3, 1, 3, and 10 μM) of at least three determinations. [c] In vivo anti-infarction effect was determined by measuring a % ratio of myocardial infarct size to area at risk (IS/AAR) in ischemic myocardium damage rat model, $n = 3$ or higher (0.1, 0.3, 1.0, and 3.0 mg/kg iv administration). Values are means ± SEM.

AAR) and significantly recovered the cardiac contractile function (42% RPP). In general the potency on NHE-1 of this series of compounds was well correlated with their cardioprotective efficacy both in vitro and in vivo.

Additionally the activity of the 2-hydroxy-5-chloro compound **95**, which was found as the major metabolite of **85** in our preliminary study on metabolism, was investigated. The compound **85** (50 μM) was incubated with human or rat liver microsomes (1 mg/mL of protein concentration) for 1 h and analyzed using LC/MS/MS including its metabolites; the results indicate that 84−88% of **85** remained, and **95** was identified as a major metabolite. Compound **95** also showed a good NHE-1 inhibitory activity and cardioprotective effect.

The dose-dependent cardioprotective efficacy was further studied for the selected compounds, cariporide, **59**, **60**, **85**, **92**, and **94**, which exhibited the high potency on NHE-1 and good cardioprotective efficacy (Table 3). All tested compounds showed a dose dependency. The most potent compound **85** in the NHE-1 inhibition assay ($IC_{50} = 0.081$ μM), greatly reduced infarct size dose-dependently with a significant improvement of cardiac contractile dysfunction from ischemia-reperfusion injury, which was comparable to cariporide. Further studies on **85** employing various models are in progress.

Conclusion

A series of (5-arylfuran-2-ylcarbonyl)guanidine analogues were synthesized and evaluated for their cardioprotective efficacy against ischemia-reperfusion injury as well as the NHE-1 inhibitory activity. With the aim to optimize the activity of (5-phenylfuran-2-ylcarbonyl)-guanidine **47** having a moderate activity on NHE-1, various substituents were introduced at the phenyl ring. From these studies, [5-(2-methoxy-5-chlorophenyl)furan-2-ylcarbonyl]guanidine **85** was identified as a highly potent NHE-1 inhibitor. In addition, **85** greatly reduced the infarct size in the rat myocardial infarction model in vivo and significantly improved the cardiac contractile dysfunction in the isolated ischemic rat heart model. These findings suggest that **85** could be an attractive therapeutic candidate for myocardial ischemic diseases.

Experimental Section

Chemistry. Melting points were determined on a capillary melting point apparatus and are uncorrected. Anhydrous solvents were dried by conventional methods. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. Analytical TLC was performed on Merck-glass-backed silica gel 60 F_{254} plates. Merck silica gel 60 was used for flash chromatography. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) with TMS as an internal standard. Chemical shifts are reported in δ (ppm). Mass spectra were obtained with a JEOL JMS-DX 303 instrument by using electron impact or chemical ionization techniques. Elemental analyses were performed by Korea Research Institute of Chemical Technology's Analytical Department and C, H, and N values are within ±0.4% of the calculated values.

General Procedures for the Preparation of the Compounds 1−28. To a solution of methyl 5-bromo-2-furoate (300 mg, 1.46 mmol) in toluene (6 mL) were added arylboronic acid (1.76 mmol) in CH_3OH (0.5 mL), 2 M Na_2CO_3 (0.9 mL, 1.8 mmol), and catalytic amounts of $Pd(PPh_3)_4$. The reaction mixture was heated at reflux for 6 h, diluted with water (20 mL), and extracted with ethyl acetate (20 mL × 2). The extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane: ethyl acetate = 6:1) to afford the corresponding 5-aryl-substituted furans.

5-Phenylfuran-2-carboxylic acid methyl ester (1): 72% yield (white solid); mp 90−91 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 6.74 (dd, $J = 3.7$ Hz, 1H), 7.25 (d, $J = 3.7$ Hz, 1H), 7.35−7.46 (m, 3H), 7.81 (m, 2H); MS 202 (M^+).

5-(2-Fluorophenyl)furan-2-carboxylic acid methyl ester (2): 90% yield (white sold); ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 6.93 (dd, $J = 3.2$, 3.3 Hz, 1H), 7.14−7.34 (m, 4H), 7.99 (m, 1H); MS 220 (M^+).

5-(3-Fluorophenyl)furan-2-carboxylic acid methyl ester (3): 79% yield (white solid); mp 82 °C; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 6.69 (d, $J = 3.6$ Hz, 1H), 6.97 (m, 1H), 7.18 (d, $J = 3.6$ Hz, 1H), 7.31 (m, 1H), 7.39 (dd, $J = 2.1$, 8.1 Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H); MS 220 (M^+).

5-(4-Fluorophenyl)furan-2-carboxylic acid methyl ester (4): 75% yield (white solid); mp 70 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 6.68 (d, $J = 3.6$ Hz, 1H), 7.12 (dd, $J = 8.7$, 8.7 Hz, 2H), 7.24 (d, $J = 3.6$ Hz, 1H), 7.76 (dd, $J = 8.7$, 12.0 Hz, 2H); MS 220 (M^+).

5-(2-Chlorophenyl)furan-2-carboxylic acid methyl ester (5): 43% yield (white solid); mp 68 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 7.21 (d, $J = 3.6$ Hz, 1H), 7.28 (m, 2H), 7.34 (ddd, $J = 7.2$, 6.9, 1.2 Hz, 1H), 7.46 (dd, $J = 1.2$, 7.8 Hz, 2H), 7.99 (dd, $J = 1.8$, 7.8 Hz, 2H); MS 236 (M^+).

5-(3-Chlorophenyl)furan-2-carboxylic acid methyl ester (6): 83% yield (white solid); mp 76 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 6.75 (d, $J = 3.3$ Hz, 1H), 7.24 (d, $J = 3.2$ Hz, 1H), 7.33 (m, 2H), 7.65 (dd, $J = 2.0$, 7.1 Hz, 2H), 7.76 (d, $J = 2.0$ Hz, 1H); MS 236 (M^+).

5-(2-Methylphenyl)furan-2-carboxylic acid methyl ester (7): 90% yield (oil); ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 3.91 (s, 3H), 6.63 (d, J = 3.6 Hz, 1H), 7.25−7.29 (m, 4H), 7.76 (m, 1H); MS 216 (M^+).

5-(3-Methylphenyl)furan-2-carboxylic acid methyl ester (8): 78% yield (white solid); mp 85−86 °C; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.94 (s, 3H), 6.74 (d, J = 3.4 Hz, 1H), 7.18 (d, J = 7.7 Hz, 1H), 7.26 (d, J = 3.4 Hz, 1H), 7.33 (dd, J = 7.7, 7.7 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.64 (s, 1H); MS 216 (M^+).

5-(4-Methylphenyl)furan-2-carboxylic acid methyl ester (9): 83% yield (white solid); mp 71−72 °C; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.84 (s, 3H), 6.61 (d, J = 3.5 Hz, 1H), 7.15−7.17 (m, 3H), 7.60 (d, J = 8.2 Hz, 1H); MS 216 (M^+).

5-[2-(Trifluoromethyl)phenyl]furan-2-carboxylic acid methyl ester (10): 94% yield (oil); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 6.79 (d, J = 3.6 Hz, 1H), 7.26 (d, J = 3.6 Hz, 1H), 7.50 (dd, J = 8.7, 8.7 Hz, 1H), 7.62 (dd, J = 8.7, 9.0 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H); MS 270 (M^+).

5-[4-(Trifluoromethyl)phenyl]furan-2-carboxylic acid methyl ester (11): 76% yield (white solid); mp 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.85 (d, J = 3.6 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.4 Hz, 1H); MS 270 (M^+).

5-(2-Methoxyphenyl)furan-2-carboxylic acid methyl ester (12): 67% yield (white solid); mp 63 °C; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 3.95 (s, 3H), 6.97 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 3.9 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 3.6 Hz, 1H), 7.32 (ddd, J = 1.8, 7.5, 8.1 Hz, 1H), 8.01 (dd, J = 1.8, 7.5 Hz, 1H); MS 232 (M^+).

5-(3-Methoxyphenyl)furan-2-carboxylic acid methyl ester (13): 96% yield (white solid); mp 62 °C; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 3.91 (s, 3H), 6.73 (d, J = 3.6 Hz, 1H), 6.91 (ddd, J = 1.5, 1.8, 9.0 Hz, 1H), 7.24 (d, J = 3.6 Hz, 1H), 7.29−7.36 (m, 3H); MS 232 (M^+).

5-(4-Methoxyphenyl)furan-2-carboxylic acid methyl ester (14): 97% yield (white solid); mp 83−83.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 3.91 (s, 3H), 6.61 (d, J = 3.6 Hz, 1H), 6.94 (d, J = 9.0 Hz, 1H), 7.24 (d, J = 3.6 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H); MS 232 (M^+).

5-(2-Nitrophenyl)furan-2-carboxylic acid methyl ester (15): 94% yield (yellow solid); ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 6.70 (d, J = 3.6 Hz, 1H), 7.25 (d, J = 3.6 Hz, 1H), 7.52 (ddd, J = 1.2, 7.5, 8.1 Hz, 1H), 7.65 (ddd, J = 1.2, 7.5, 7.8 Hz, 1H), 7.81 (m, 2H); MS 247 (M^+).

5-(3-Nitrophenyl)furan-2-carboxylic acid methyl ester (16): 51% yield (yellow solid); mp 146 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 6.91 (d, J = 3.6 Hz, 1H), 7.29 (d, J = 3.6 Hz, 1H), 7.71 (dd, J = 7.8, 8.4 Hz, 1H), 7.98 (dd, J = 0.9, 7.8 Hz, 1H), 8.31 (dd, J = 2.1, 8.4 Hz, 1H), 8.51 (d, J = 2.1 Hz, 1H); MS 247 (M^+).

5-(4-Nitrophenyl)furan-2-carboxylic acid methyl ester (17): 99% yield (yellow solid); ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 6.95 (d, J = 3.6 Hz, 1H), 7.29 (d, J = 3.6 Hz, 1H), 7.93 (d, J = 8.7 Hz, 2H), 8.29 (d, J = 8.7 Hz, 2H); MS 247 (M^+).

5-(2-Ethoxyphenyl)furan-2-carboxylic acid methyl ester (18): 67% yield (white solid); mp 74−75 °C; ^{1}H NMR ($CDCl_3$) δ 1.53 (t, J = 7.0 Hz, 3H), 3.91 (s, 3H), 4.17 (q, J = 7.0 Hz, 2H), 6.95 (d, J = 8.3 Hz, 1H), 7.03 (dd, J = 7.5, 7.6 Hz, 1H), 7.07 (d, J = 3.7 Hz, 1H), 7.29 (m, 2H), 8.02 (dd, J = 1.6, 7.8 Hz, 1H); MS 246 (M^+).

5-(2-Isopropoxyphenyl)furan-2-carboxylic acid methyl ester (19): 61% yield (oil); ^{1}H NMR ($CDCl_3$) δ 1.43 (d, J = 7.2 Hz, 6H), 3.91 (s, 3H), 4.71 (m, 1H), 6.99 (m, 2H), 7.08 (d, J = 3.6 Hz, 1H), 7.25 (d, J = 3.6 Hz, 1H), 7.29 (dd, J = 1.7, 8.3 Hz, 1H), 8.02 (dd, J = 1.7, 7.8 Hz, 1H); MS 260 (M^+).

5-(2-Phenoxyphenyl)furan-2-carboxylic acid methyl ester (20): 70% yield (white solid); mp 86 °C; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 6.93 (d, J = 7.7 Hz, 1H), 7.00 (m, 3H), 7.13−7.38 (m, 6H), 8.10 (dd, J = 1.9, 7.7 Hz, 1H).

5-(2,3-Dichlorophenyl)furan-2-carboxylic acid methyl ester (21): 39% yield (white solid); mp 108 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 7.23−7.33 (m, 3H), 7.47 (dd, J = 1.5, 8.1 Hz, 1H), 7.95 (dd, J = 1.5, 7.8 Hz, 1H); MS 270 (M^+).

5-(3,5-Dichlorophenyl)furan-2-carboxylic acid methyl ester (22): 67% yield (white solid); mp 136 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.78 (d, J = 3.6 Hz, 1H), 7.25 (d, J = 3.3 Hz, 1H), 7.33 (dd, J = 1.5, 1.8 Hz, 1H), 7.65 (m, 2H); MS 270 (M^+).

5-(3,5-Dimethylphenyl)furan-2-carboxylic acid methyl ester (23): 71% yield (white solid); mp 105−106 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 6H), 3.92 (s, 3H), 6.70 (d, J = 3.6 Hz, 1H), 6.99 (s, 1H), 7.24 (d, J = 3.6 Hz, 1H), 7.41(s, 2H); MS 230 (M^+).

5-(2,5-Dimethoxyphenyl)furan-2-carboxylic acid methyl ester (24): 47% yield (oil); ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 6.87 (m, 2H), 7.05 (d, J = 3.7 Hz, 1H), 7.25 (d, J = 3.7 Hz, 1H), 7.54 (d, J = 2.7 Hz, 1H); MS 262 (M^+).

5-(2-Fluoro-5-methylphenyl)furan-2-carboxylic acid methyl ester (25): 52% yield (oil); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.93 (s, 3H), 6.91 (dd, J = 3.6, 3.6 Hz, 1H), 7.02 (dd, J = 8.4, 10.9 1H), 7.11 (m, 1H), 7.27 (d, J = 3.6 Hz 1H), 7.78 (d, J = 5.9 Hz, 1H); MS 234 (M^+).

5-(2-Methyl-5-fluorophenyl)furan-2-carboxylic acid methyl ester (26): 91% yield (oil); ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 3.92 (s, 3H), 6.67 (d, J = 3.6 Hz, 1H), 6.94 (ddd, J = 2.9, 8.1, 8.3 Hz, 1H), 7.20 (m, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.49(dd, J = 2.9, 9.8 Hz, 1H); MS 234 (M^+).

5-(2-Methoxy-5-fluorophenyl)furan-2-carboxylic acid methyl ester (27): 63% yield (white solid); mp 94 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 3.93 (s, 3H), 6.90 (dd, J = 4.0, 9.0 Hz, 1H), 7.00 (m, 1H), 7.07 (d, J = 3.6 Hz, 1H), 7.25(d, J = 3.6 Hz, 1H), 7.71 (dd, J = 3.0, 9.3 Hz, 1H); MS 250 (M^+).

5-(2-Methoxy-5-chlorophenyl)furan-2-carboxylic acid methyl ester (28): 54% yield (white solid); mp 128 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 3.94 (s, 3H), 6.90 (d, J = 9.0 Hz, 1H), 7.05 (d, J = 3.7 Hz, 1H), 7.26 (m, 2H), 7.98(d, J = 2.8 Hz, 1H); MS 266 (M^+).

General Procedures for the Preparation of the Compounds 29−40. To a solution of methyl 5-bromo-2-furoate (300 mg, 1.46 mmol) and arylboronic acid (1.76 mmol) in 1,2-dimethoxyethane (8 mL) was added a 2 M aqueous solution of $Ba(OH)_2 \cdot H_2O$ (0.9 mL, 1.8 mmol). After the addition of catalytic amounts of $Pd(PPh_3)_4$, the reaction mixture was stirred at 80 °C for 12 h, diluted with water (20 mL), and extracted with ethyl acetate (20 mL × 2). The extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate = 20:1).

5-(2,3-Difluorophenyl)furan-2-carboxylic acid methyl ester (29): 35% yield (white solid); mp 84−85 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 6.74 (dd, J = 3.6, 3.7 Hz, 1H), 7.18 (m, 2H), 7.28 (m, 1H), 7.75 (m, 1H); MS 238 (M^+).

5-(2,4-Difluorophenyl)furan-2-carboxylic acid methyl ester (30): 71% yield (white solid); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 6.87 (dd, J = 3.6, 3.9 Hz, 1H), 6.90−7.01 (m, 2H), 7.26 (d, J = 3.6 Hz, 1H), 7.97 (m, 1H); MS 238 (M^+).

5-(2,5-Difluorophenyl)furan-2-carboxylic acid methyl ester (31): 65% yield (white solid); mp 73 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.95−7.17 (m, 3H), 7.27 (d, J = 3.6 Hz, 1H), 7.68 (m, 1H); MS 238 (M^+).

5-(3,5-Difluorophenyl)furan-2-carboxylic acid methyl ester (32): 79% yield (white solid); mp 145−147 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.75−6.83 (m, 2H), 7.24−7.32 (m, 3H); MS 238 (M^+).

5-(2,5-Dichlorophenyl)furan-2-carboxylic acid methyl ester (33): 42% yield (white solid); mp 85−86 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 7.21−7.28 (m, 3H), 7.39 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); MS 270 (M^+).

5-(2,6-Dimethylphenyl)furan-2-carboxylic acid methyl ester (34): 57% yield (oil); ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.37 (s, 3H), 3.91 (s, 3H), 6.56 (d, J = 3.5 Hz, 1H), 7.18 (m, 2H), 7.48 (dd, J = 1.8, 7.1 Hz, 1H); MS 230 (M^+).

5-(2,3-Dimethylphenyl)furan-2-carboxylic acid methyl ester (35): 60% yield (oil); ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.37 (s, 3H), 3.91 (s, 3H), 6.55 (d, J = 3.6 Hz, 1H), 7.13−7.21

(m, 2H), 7.27 (d, J = 3.6 Hz, 1H), 7.48 (dd, J = 1.7, 7.3 Hz, 1H); MS 230 (M^+).

5-(2,5-Dimethylphenyl)furan-2-carboxylic acid methyl ester (36): 68% yield (oil); ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.47 (s, 3H), 3.92 (s, 3H), 6.61 (d, J = 3.6 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.59 (s, 1H); MS 230 (M^+).

5-(2,6-Dimethoxyphenyl)furan-2-carboxylic acid methyl ester (37): 53% yield (white solid); ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 6H), 3.89 (s, 3H), 6.60 (m, 3H), 7.29 (m, 2H); MS 262 (M^+).

5-(2,3-Dimethoxyphenyl)furan-2-carboxylic acid methyl ester (38): 95% yield (oil); ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 6.92 (dd, J = 1.5, 6.8 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.13 (dd, J = 6.8, 8.1 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.57 (dd, J = 1.5, 8.1 Hz, 1H); MS 262 (M^+).

5-(2-Chloro-6-fluorophenyl)furan-2-carboxylic acid methyl ester (39): 10% yield (oil) ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.79 (m, 1H), 7.10 (m, 1H), 7.25−7.34 (m, 3H); MS 254 (M^+).

5-(2-Methoxy-5-bromophenyl)furan-2-carboxylic acid methyl ester (40): 38% yield (white solid) mp 140 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 3.94 (s, 3H), 6.85 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 3.6 Hz, 1H), 7.25 (d, J = 3.6 Hz, 1H), 7.39 (dd, J = 2.4, 8.8 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H); MS 311 (M^+).

5-(2-Aminophenyl)furan-2-carboxylic Acid Methyl Ester (41). To a solution of the nitro compound **15** (290 mg, 1.17 mmol) in CH_3OH (10 mL) was added 10% Pd/C (29 mg). The resulting mixture was stirred for 2 h under H_2 (3 atm) at room temperature. After the reaction was completed, the mixture was filtered over a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate = 4:1) to yield a pale yellow solid (239 mg, 94%): ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.67 (d, J = 3.6 Hz, 1H), 6.73−6.80 (m, 2H), 7.15 (ddd, J = 1.5, 7.2, 7.2 Hz, 1H), 7.26 (d, J = 3.6 Hz, 1H), 7.50 (dd, J = 1.5, 7.8 Hz, 1H); MS 217 (M^+).

5-(3-Aminophenyl)furan-2-carboxylic Acid Methyl Ester (42). The compound **42** (101 mg, 51%) was prepared by the same procedure to prepare the compound **41** except using the compound **16** (222 mg, 0. 9 mmol) as a starting material: mp 99−101 °C; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 6.62−6.70 (m, 2H), 7.15 (m, 2H), 7.25 (m, 2H); MS 217 (M^+).

5-(4-Aminophenyl)furan-2-carboxylic Acid Methyl Ester (43). The compound **43** (84 mg, 97%) was prepared by the same procedure to prepare the compound **41** except using the compound **17** (100 mg, 0. 40 mmol) as a starting material: mp 125−126 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 6.53 (d, J = 3.6 Hz, 1H), 6.69 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 3.6 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H); MS 217 (M^+).

5-(2-Hydroxy-5-chlorophenyl)furan-2-carboxylic Acid Methyl Ester (44). To a solution of the compound **28** (200 mg, 0.75 mmol) in CH_2Cl_2 was added an 1 M solution of BBr_3 in CH_2Cl_2 (1.65 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, treated with saturated $NaHCO_3$ solution (20 mL), and extracted with ethyl acetate (30 mL × 2). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate = 20:1) to give the compound **44** (121 mg, 64%): mp 176−177 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.91 (m, 2H), 7.03 (brs, 1H), 7.18 (dd, J = 2.7, 8.7 Hz, 1H), 7.29 (d, J = 3.3 Hz, 1H), 7.68 (d, J = 2.7 Hz, 1H); MS 252 (M^+).

5-(2-Ethoxy-5-chlorophenyl)furan-2-carboxylic Acid Methyl Ester (45). To a solution of the compound **44** (100 mg, 0.4 mmol) in DMF (1.5 mL) were added K_2CO_3 (82 mg, 0.59 mmol) and iodoethane (38 μL, 0.47 mmol). The reaction mixture was stirred at room temperature for 3 h, diluted with water (20 mL), and extracted with ethyl acetate (20 mL × 2). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate = 10:1) to afford the compound **45** (84 mg, 75%): mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 1.54 (t, J = 7.0 Hz, 3H), 3.93 (s, 3H), 4.15 (q, J = 7.0 Hz, 2H), 6.88 (d, J = 8.7 Hz, 1H), 7.09 (d, J = 3.6 Hz, 1H), 7.24 (m, 2H), 7.98 (d, J = 2.7 Hz, 1H); MS 280 (M^+).

5-(2-Isopropoxy-5-chlorophenyl)furan-2-carboxylic Acid Methyl Ester (46). The compound **46** was prepared by the same procedure to synthesize the compound **45**, except using isopropyl iodide as an alkylating agent: mp 68−69 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 6.0 Hz, 6H), 3.92 (s, 3H), 4.67 (m, 1H), 6.89 (d, J = 9.0 Hz, 1H), 7.09 (d, J = 3.6 Hz, 1H), 7.22 (dd, J = 2.7, 9.0 Hz, 1H), 7.25 (d, J = 3.6 Hz, 1H), 7.89 (d, J = 2.7 Hz, 1H); MS 294 (M^+).

General Procedures for the Preparation of (5-Arylfuran-2-ylcarbonyl)guanidines 47−97. Method A. Small pieces of sodium (4.6 g, 0.2 mol) were slowly added to dry CH_3OH (100 mL) with stirring. After the complete dissolution of sodium in CH_3OH, guanidine hydrochloride (19.1 g, 0.2 mol) was added, and the resulting mixture was stirred at room temperature for 1 h. White precipitates were filtered, resulting a 2 M solution of free guanidine in methanol had been stored in a refrigerator for several months. The corresponding ester compound (1.0 mmol) was dissolved CH_3OH (5 mL), and a 2 M methanol solution of guanidine (3.0 mL, 6.0 mmol) was added. The reaction mixture was heated at reflux with stirring for 12 h. Brine (25 mL) was added, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic layer was washed with brine twice, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% methanol in CH_2Cl_2) to yield the (furan-2-ylcarbonyl)guanidines. Otherwise the compounds were purified as mathanesulfonic acid salts. The residue was dissolved in acetone (5 mL), and methanesulfonic acid was added with stirring and cooled to 0 °C. The precipitates were filtered to give the methanesulfonate.

(5-Phenylfuran-2-ylcarbonyl)guanidine methanesulfonate (47): 46% yield (white solid); mp 205 °C; ^{1}H NMR (D_2O) δ 2.81 (s, 3H), 6.97 (d, J = 3.7 Hz, 1H), 7.45 (d, J = 3.7 Hz, 1H), 7.46−7.52 (m, 3H), 7.80−7.85 (m, 2H); MS 229 (M^+); Anal. ($C_{13}H_{15}N_3O_5S$) C, H, N, S.

[5-(2-Fluorophenyl)furan-2-ylcarbonyl]guanidine methanesulfonate (48): 54% yield (white solid); mp 220 °C; ^{1}H NMR (DMSO-d_6) δ 2.39 (s, 3H), 7.14 (dd, J = 3.3, 3.6 Hz, 1H), 7.54 (m, 1H), 7.40−7.46 (m, 2H), 7.69 (d, J = 3.6 Hz, 1H), 8.11 (dd, J = 8.7, 9.0 Hz, 1H), 8.41 (brs, 4H), 11.19 (brs, 1H); M^+ 247;); MS 247 (M^+); Anal. ($C_{13}H_{14}FN_3O_5S$) C, H, N, S.

[5-(2-Chlorophenyl)furan-2-ylcarbonyl]guanidine (49): 94% yield (white solid); mp 201−202 °C; ^{1}H NMR (CD_3OD) δ 7.22 (m, 2H), 7.32 (ddd, J = 1.7, 7.6, 7.9 Hz, 1H), 7.42 (ddd, J = 1.4, 7.6, 7.9 Hz, 2H), 7.50 (dd, J = 1.4, 7.9 Hz, 1H), 8.13 (dd, J = 1.7, 7.9 Hz, 2H); MS 263 (M^+); Anal. ($C_{12}H_{10}ClN_3O_2$) C, H, N.

[5-(2-Methoxyphenyl)furan-2-ylcarbonyl]guanidine (50): 49% yield (pale yellow solid); mp 121−123 °C; ^{1}H NMR (CD_3OD) δ 3.97 (s, 3H), 7.03−7.11 (m, 3H), 7.23 (d, J = 3.5 Hz, 1H), 7.33 (ddd, J = 1.8, 7.0, 7.5 Hz, 2H), 8.10 (d, J = 1.8, 7.6 Hz, 1H); MS 259 (M^+); Anal. ($C_{13}H_{13}N_3O_3$) C, H, N.

[5-(2-Ethylphenyl)furan-2-ylcarbonyl]guanidine (55): 32% yield (white solid); mp 151−153 °C; ^{1}H NMR (CD_3OD) δ 1.22 (t, J = 7.5 Hz, 3H), 2.90 (q, J = 7.5 Hz, 2H), 6.68 (d, J = 3.6 Hz, 1H), 7.23 (d, J = 3.6 Hz, 1H), 7.29 (m, 3H), 7.73 (d, J = 7.3 Hz, 1H); MS 257 (M^+); Anal. ($C_{14}H_{15}N_3O_2$) C, H, N.

[5-(2-Ethoxyphenyl)furan-2-ylcarbonyl]guanidine (56): 40% yield (yellow solid); mp 174−175 °C; ^{1}H NMR (CD_3OD) δ 1.53 (t, J = 7.0 Hz, 3H), 4.20 (q, J = 7.0 Hz, 2H), 7.01−7.09 (m, 3H), 7.21 (d, J = 3.5 Hz, 1H), 7.29 (dd, J = 1.5, 7.4 Hz, 1H), 8.11 (dd, J = 1.7, 7.7 Hz, 1H); MS 273 (M^+); Anal. ($C_{14}H_{15}N_3O_3$) C, H, N.

[5-(2-Isopropoxyphenyl)furan-2-ylcarbonyl]guanidine (57): 95% yield (white solid); mp 178 °C; ^{1}H NMR (CD_3OD) δ 1.42 (d, J = 6.0 Hz, 6H), 4.79 (m, 1H), 7.04−7.09 (m, 3H), 7.20 (d, J = 3.5 Hz, 1H), 7.28 (ddd, J = 1.3, 7.0, 7.4 Hz, 1H), 8.11 (dd, J = 1.7, 6.9 Hz, 1H); MS 287 (M^+); Anal. ($C_{15}H_{17}N_3O_3$) C, H, N.

[5-(2-Phenoxyphenyl)furan-2-ylcarbonyl]guanidine (58): 88% yield (white solid); mp 191−193 °C; ^{1}H NMR (CD_3OD) δ 6.94−7.02 (m, 4H), 7.13 (m, 2H), 7.26−7.38 (m, 4H), 8.22 (dd, J = 1.9, 7.6 Hz, 1H); MS 321 (M^+); Anal. ($C_{18}H_{15}N_3O_3$) C, H, N.

[5-(3-Chlorophenyl)furan-2-ylcarbonyl]guanidine (60): 47% yield (white solid); mp 128 °C; ^{1}H NMR (CD_3OD) δ 6.89 (d, J = 3.6 Hz, 1H), 7.15 (d, J = 3.6 Hz, 1H), 7.22−7.34 (m, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.83 (s, 1H); MS 263 (M^+); Anal. ($C_{12}H_{10}ClN_3O_2$) C, H, N.

[5-(3-Methoxyphenyl)furan-2-ylcarbonyl]guanidine methanesulfonate (61): 4% yield (yellow solid); mp 194−195 °C; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H), 3.85 (s, 3H), 7.06 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 3.6 Hz, 1H), 7.43−7.56 (m, 3H), 7.66 (d, J = 3.6 Hz, 1H), 8.36 (brs, 4H), 11.07 (brs, 1H); MS 259 (M^+); Anal. ($C_{14}H_{17}N_3O_6S$) C, H, N, S.

[5-(3-Nitrophenyl)furan-2-ylcarbonyl]guanidine (64): 63% yield (yellow solid); mp 270 °C; ^{1}H NMR (DMSO-d_6) δ 7.38 (d, J = 3.6 Hz, 1H), 7.45 (d, J = 3.6 Hz, 1H), 7.79 (m, 1H), 8.24 (m, 2H), 8.55 (s, 1H); MS 274 (M^+); Anal. ($C_{12}H_{10}N_4O_4$) C, H, N.

[5-(4-Fluorophenyl)furan-2-ylcarbonyl]guanidine (66): 51% yield (white solid); mp 191 °C; ^{1}H NMR (DMSO-d_6) δ 6.99 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 7.43 (dd, J = 8.6, 8.9 Hz, 2H), 7.67 (dd, J = 5.5, 8.6 Hz, 2H); MS 247 (M^+); Anal. ($C_{12}H_{10}FN_3O_2$) C, H, N.

[5-(4-Methylphenyl)furan-2-ylcarbonyl]guanidine methanesulfonate (69): 14% yield (white solid); mp 245 °C; ^{1}H NMR (DMSO-d_6) δ 2.54 (s, 6H), 7.41 (d, J = 3.6 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 3.6 Hz, 1H), 8.03 (d, J = 8.1 Hz, 2H), 8.53 (brs, 4H); MS 243 (M^+); Anal. ($C_{14}H_{17}N_3O_5S$) C, H, N, S.

[5-[4-(Trifluoromethyl)phenyl]furan-2-ylcarbonyl]guanidine (70): 35% yield (white solid); mp 183−185 °C; ^{1}H NMR (DMSO-d_6) δ 7.22 (d, J = 3.5 Hz, 1H), 7.27 (d, J = 3.5 Hz, 1H), 7.82 (d, J = 8.3 Hz, 2H), 8.03 (d, J = 8.3 Hz, 2H); MS 297 (M^+); Anal. ($C_{13}H_{10}F_3N_3O_2$) C, H, N.

[5-(2,3-Difluorophenyl)furan-2-ylcarbonyl]guanidine (73): 93% yield (white solid); mp 209−210 °C; ^{1}H NMR (CD_3OD) δ 6.96 (dd, J = 3.6, 3.6 Hz, 1H), 7.24 (m, 3H), 7.89 (m, 1H); MS 265 (M^+); Anal. ($C_{12}H_9F_2N_3O_2$) C, H, N.

[5-(2,3-Dichlorophenyl)furan-2-ylcarbonyl]guanidine (74): 84% yield (white solid); mp 227 °C; ^{1}H NMR (DMSO-d_6) δ 7.20 (d, J = 3.6 Hz, 1H), 7.34 (d, J = 3.6 Hz, 1H), 7.59 (dd, J = 7.9, 8.0 Hz, 1H), 7.75 (dd, J = 1.3, 8.0 Hz, 1H), 7.98 (dd, J = 1.3, 7.9 Hz, 1H); MS 297 (M^+); Anal. ($C_{12}H_9Cl_2N_3O_2$) C, H, N.

[5-(2,3-Dimethoxyphenyl)furan-2-ylcarbonyl]guanidine (75): 83% yield (white solid); mp 185 °C; ^{1}H NMR (CD_3OD) δ 3.84 (s, 3H), 3.88 (s, 3H), 7.00 (dd, J = 1.4, 8.2 Hz, 1H), 7.05 (d, J = 3.6 Hz, 1H), 7.13 (dd, J = 8.2, 8.2 Hz, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.66 (dd, J = 1.4, 8.2 Hz, 1H); MS 289 (M^+); Anal. ($C_{14}H_{15}N_3O_4$) C, H, N.

[5-(2,3-Dimethylphenyl)furan-2-ylcarbonyl]guanidine (76): 92% yield (white solid); mp 192−194 °C; ^{1}H NMR (CD_3OD) δ 2.34 (s, 3H), 2.38 (s, 3H), 6.60 (d, J = 3.5 Hz, 1H), 7.11−7.20 (m, 3H), 7.52 (dd, J = 1.7, 9.0 Hz, 1H); MS 257 (M^+); Anal. ($C_{14}H_{15}N_3O_2$) C, H, N.

[5-(2,4-Difluorophenyl)furan-2-ylcarbonyl]guanidine methanesulfonate (77): 81% yield (yellow solid); mp 240 °C; ^{1}H NMR (DMSO-d_6) δ 2.37 (s, 3H), 7.11 (dd, J = 3.6, 3.9 Hz, 1H), 7.34 (m, 1H) 7.51 (ddd, J = 2.1, 8.1, 8.4 Hz, 1H), 7.67 (d, J = 3.9 Hz, 1H), 8.14 (m, 1H), 8.37 (brs, 4H), 11.17 (brs, 1H); MS 265 (M^+); Anal. ($C_{13}H_{13}F_2N_3O_5S$) C, H, N, S.

[5-(2,5-Difluorophenyl)furan-2-ylcarbonyl]guanidine (78): 85% yield (white solid); mp 209 °C; ^{1}H NMR (CD_3OD) δ 6.96 (dd, J = 3.6, 4.2 Hz, 1H), 7.07 (m, 1H), 7.20 (m, 2H), 7.88 (m, 1H); MS 265 (M^+); Anal. ($C_{12}H_9F_2N_3O_2$) C, H, N.

[5-(2,5-Dichlorophenyl)furan-2-ylcarbonyl]guanidine (79): 84% yield (white solid); mp 198−200 °C; ^{1}H NMR (DMSO-d_6) δ 7.09(d, J = 3.5 Hz, 1H), 7.27 (d, J = 3.5 Hz, 1H), 7.43 (dd, J = 2.6, 8.6 Hz, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 2.6 Hz, 1H); MS 297 (M^+); Anal. ($C_{12}H_9Cl_2N_3O_2$) C, H, N.

5-(2,5-Dimethoxyphenyl)furan-2-ylcarbonyl]guanidine (80): 76% yield (white solid); mp 131 °C; ^{1}H NMR (CD_3OD) δ 3.84 (s, 3H), 3.89 (s, 3H), 6.87 (dd, J = 3.0, 9.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 1H), 7.04 (d, J = 3.6 Hz, 1H), 7.18 (d, J = 3.6 Hz, 1H), 7.71 (d, J = 3.0 Hz, 1H); MS 289 (M^+); Anal. ($C_{14}H_{15}N_3O_4$) C, H, N.

[5-(2,5-Dimethylphenyl)furan-2-ylcarbonyl]guanidine (81): 94% yield (white solid); mp 176−177 °C; ^{1}H NMR (CD_3OD) δ 2.35 (s, 3H), 2.46 (s, 3H), 6.68 (d, J = 3.5 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 3.5 Hz, 1H), 7.71 (s, 1H); MS 257 (M^+); Anal. ($C_{14}H_{15}N_3O_2$) C, H, N.

[5-(2-Fluoro-5-methylphenyl)furan-2-ylcarbonyl]guanidine (82): 87% yield (white solid); mp 194 °C; ^{1}H NMR (CD_3OD) δ 2.38 (s, 3H), 6.87 (m, 1H), 7.02−7.14 (m, 2H), 7.19 (d, J = 3.6 Hz, 1H), 7.94 (dd, J = 2.1, 7.5 Hz, 1H); MS 261 (M^+); Anal. ($C_{13}H_{12}FN_3O_2$) C, H, N.

[5-(2-Methyl-5-fluorophenyl)furan-2-ylcarbonyl]guanidine (83): 91% yield (white solid); mp 176 °C; ^{1}H NMR (CD_3OD) δ 2.48 (s, 3H), 6.79 (d, J = 3.5 Hz, 1H), 6.98 (ddd, J = 2.7, 8.3, 8.3 Hz, 1H), 7.20 (d, J = 3.5 Hz, 1H), 7.27 (dd, J = 5.9, 8.3 Hz), 7.68 (dd, J = 2.7, 10.4 Hz); MS 261 (M^+); Anal. ($C_{13}H_{12}FN_3O_2$) C, H, N.

[5-(2-Methoxy-5-fluorophenyl)furan-2-ylcarbonyl]guanidine (84): 87% yield (white solid); mp 195−197 °C; ^{1}H NMR (CD_3OD) δ 3.94 (s, 3H), 7.04 (m, 2H), 7.08 (d, J = 3.5 Hz, 1H), 7.17 (d, J = 3.5 Hz, 1H), 7.87 (dd, J = 2.6, 9.7 Hz, 1H); MS 281 (M^+); Anal. ($C_{13}H_{12}FN_3O_3$) C, H, N.

[5-(2-Methoxy-5-chlorophenyl)furan-2-ylcarbonyl]guanidine (85): 92% yield (white solid); mp 190 °C; ^{1}H NMR (CD_3OD) δ 3.95 (s, 3H), 7.06 (m, 2H), 7.16 (d, J = 3.6 Hz, 1H), 7.27 (dd, J = 2.6, 8.8 Hz, 1H), 8.13 (d, J = 2.6 Hz, 2H); MS 293 (M^+); Anal. ($C_{13}H_{12}ClN_3O_3$) C, H, N.

[5-(2-Methoxy-5-bromophenyl)furan-2-ylcarbonyl]guanidine (87): 89% yield (white solid); mp 145 °C; ^{1}H NMR (CD_3OD) δ 3.96 (s, 3H), 7.04 (m, 2H), 7.16 (d, J = 3.5 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 8.27 (s, 1H); MS 337 (M^+); Anal. ($C_{13}H_{12}BrN_3O_3$) C, H, N.

[5-(2,6-Difluorophenyl)furan-2-ylcarbonyl]guanidine (88): 79% yield (white solid); mp 220 °C; ^{1}H NMR (CD_3OD) δ 6.86 (brs, 1H), 7.09 (m, 2H), 7.21 (brs, 1H), 7.39 (m, 1H); MS 265 (M^+); Anal. ($C_{12}H_9F_2N_3O_2$) C, H, N.

[5-(2-Chloro-6-fluorophenyl)furan-2-ylcarbonyl]guanidine (89): 77% yield (white solid); mp 198 °C; ^{1}H NMR (CD_3OD) δ 6.75 (brs, 1H), 7.20 (m, 2H), 7.42 (m, 2H); MS 281 (M^+); Anal. ($C_{12}H_9ClFN_3O_2$) C, H, N.

[5-(2,6-Dimethoxyphenyl)furan-2-ylcarbonyl]guanidine (90): 53% yield (white solid); mp 122 °C; ^{1}H NMR (CD_3OD) δ 3.77 (s, 6H), 6.49 (d, J = 3.6 Hz, 1H), 6.69 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 3.6 Hz, 1H), 7.35 (t, J = 8.4 Hz, 1H); MS 289 (M^+); Anal. ($C_{14}H_{15}N_3O_4$) C, H, N.

[5-(2,6-Dimethylphenyl)furan-2-ylcarbonyl]guanidine (91): 88% yield (white solid); mp 189 °C; ^{1}H NMR (CD_3OD) δ 2.34 (s, 3H), 2.37 (s, 3H), 6.60 (d, J = 3.5 Hz, 1H), 7.14 (m, 2H), 7.19 (d, J = 3.5 Hz, 1H), 7.52 (t, J = 7.3 Hz, 1H); MS 257 (M^+); Anal. ($C_{14}H_{15}N_3O_2$) C, H, N.

[5-(3,5-Difluorophenyl)furan-2-ylcarbonyl]guanidine (92): 89% yield (white solid); mp 220 °C; ^{1}H NMR (DMSO-d_6) δ 7.04 (d, J = 3.5 Hz, 1H), 7.21 (m, 2H), 7.49 (m, 2H); MS 265 (M^+); Anal. ($C_{12}H_9F_2N_3O_2$) C, H, N.

[5-(3,5-Dichlorophenyl)furan-2-ylcarbonyl]guanidine (93): 75% yield (white solid); mp 216 °C; ^{1}H NMR (DMSO-d_6) δ 7.05 (d, J = 3.5 Hz, 1H), 7.23 (d, J = 3.5 Hz, 1H), 7.52 (d, J = 1.7 Hz, 1H), 7.80 (d, J = 1.8 Hz, 2H); MS 297 (M^+); Anal. ($C_{12}H_9Cl_2N_3O_2$) C, H, N.

[5-(3,5-Dimethylphenyl)furan-2-ylcarbonyl]guanidine (94): 92% yield (white solid); mp 189 °C; ^{1}H NMR (CD_3OD) δ 2.32 (s, 6H), 6.80 (d, J = 3.3 Hz, 1H), 6.96 (s, 1H), 7.14 (d, J = 3.3 Hz, 1H), 7.47 (s, 2H); MS 257 (M^+); Anal. ($C_{14}H_{15}N_3O_2$) C, H, N.

[5-(2-Hydroxy-5-chlorophenyl)furan-2-ylcarbonyl]guanidine methanesulfonate (95): 30% yield (white solid); mp 223 °C; ^{1}H NMR (CD_3OD) δ 2.68 (s, 3H), 6.91 (d, J = 8.7 Hz, 1H), 7.20 (dd, J = 2.6, 8.7 Hz, 1H), 7.27 (d, J = 3.8 Hz, 1H),

7.55 (d, J = 3.8 Hz, 1H), 7.99 (d, J = 2.6 Hz, 1H); MS 279 (M^+); Anal. ($C_{13}H_{14}ClN_3O_6S$) C, H, N, S.

[5-(2-Ethoxy-5-chlorophenyl)furan-2-ylcarbonyl]guanidine (96): 93% yield (white solid); mp 175−177 °C; ^{1}H NMR (CD_3OD) δ 1.54 (t, J = 7.0 Hz, 3H), 4.20 (q, J = 7.0 Hz, 2H) 7.06 (d, J = 8.9 Hz, 1H), 7.12 (d, J = 3.6 Hz, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.27 (dd, J = 2.6, 8.9 Hz, 1H), 8.15 (d, J = 2.6 Hz, 1H); MS 307 (M^+); Anal. ($C_{14}H_{14}ClN_3O_3$) C, H, N.

[5-(2-Isopropoxy-5-chlorophenyl)furan-2-ylcarbonyl]-guanidine (97): 91% yield (white solid); mp 206−207 °C; ^{1}H NMR (CD_3OD) δ 1.43 (d, J = 6.0 Hz, 6H), 4.78 (m, 1H) 7.07 (d, J = 9.0 Hz, 1H), 7.12 (d, J = 3.5 Hz, 1H), 7.19 (d, J = 3.5 Hz, 1H), 7.26 (dd, J = 2.7, 9.0 Hz, 1H), 8.15 (d, J = 2.7 Hz, 1H); MS 321 (M^+); Anal. ($C_{15}H_{16}ClN_3O_3$) C, H, N.

Method B. To a solution of the corresponding ester (1.0 mmol) in DMF (3 mL) was added a 2 M methanol solution of guanidine (3 mL, 6 mmol), and the resulting mixture was stirred at room temperature for 2 h. Brine (20 mL) was added, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic layer was washed with 10% NaCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% methanol in CH_2Cl_2) to yield the (furan-2-ylcarbonyl)-guanidine.

[5-(2-Aminophenyl)furan-2-ylcarbonyl]guanidine (54): 94% yield (pale yellow solid); mp 181 °C; ^{1}H NMR (CD_3OD) δ 6.70−6.75 (m, 2H), 6.83 (dd, J = 0.9, 8.1 Hz, 1H), 7.09 (m, 1H), 7.21 (d, J = 3.6 Hz, 1H), 7.56 (dd, J = 1.5, 7.8 Hz, 1H); MS 244 (M^+); Anal. ($C_{12}H_{12}N_4O_2$) C, H, N.

[5-(3-Fluorophenyl)furan-2-ylcarbonyl]guanidine (59): 89% yield (white solid); mp 211 °C; ^{1}H NMR (CD_3OD) δ 1.43 (d, J = 6.0 Hz, 6H), 4.78 (m, 1H) 7.07 (d, J = 9.0 Hz, 1H), 7.12 (d, J = 3.5 Hz, 1H), 7.19 (d, J = 3.5 Hz, 1H), 7.26 (dd, J = 2.7, 9.0 Hz, 1H), 8.15 (d, J = 2.7 Hz, 1H); MS 247 (M^+); Anal. ($C_{12}H_{10}FN_3O_2$) C, H, N.

[5-(3-Methylphenyl)furan-2-ylcarbonyl]guanidine (62): 39% yield (white solid); mp 131−133 °C; ^{1}H NMR (CD_3OD) δ 2.41 (s, 3H), 6.86 (d, J = 3.5 Hz, 1H), 7.15 (m, 1H), 7.18 (d, J = 3.5 Hz, 1H), 7.31 (dd, J = 7.5, 7.9 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.73 (s, 1H); MS 243 (M^+); Anal. ($C_{13}H_{13}N_3O_2$) C, H, N.

[5-(3-Aminophenyl)furan-2-ylcarbonyl]guanidine (65): 81% yield (yellow solid); mp 200 °C; ^{1}H NMR (CD_3OD) δ 6.69 (m, 1H), 6.78 (d, J = 3.6 Hz, 1H), 6.78 (d, J = 3.6 Hz, 1H), 7.11−7.22 (m, 4H); MS 244 (M^+); Anal. ($C_{12}H_{12}N_4O_2$) C, H, N.

[5-(4-Aminophenyl)furan-2-ylcarbonyl]guanidine (72): 84% yield (yellow solid); mp 208 °C; ^{1}H NMR (CD_3OD) δ 6.59 (d, J = 3.6 Hz, 1H), 6.73 (dd, J = 2.0, 6.7 Hz, 2H), 7.15 (d, J = 3.6 Hz, 1H), 7.60 (dd, J = 2.0, 6.7 Hz, 2H); MS 244 (M^+); Anal. ($C_{12}H_{12}N_4O_2$) C, H, N.

Method C. To a solution of the corresponding furan-2-carboxylic acid (1.0 mmol) in THF (5 mL) was added 1,1′-carbonyldiimidazole (182 mg, 1.12 mmol), and the reaction mixture was stirred at room temperature for 30 min, followed by an addition of a 2 M methanol solution of guanidine (3.0 mL, 6.0 mmol) and continuous stirring at room temperature for 12 h. Brine (20 mL) was added, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic layer was washed with 10% NaCl twice, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was dissolved in acetone (4 mL), and methanesulfonic acid (0.2 mL) was added. The resulting solution was cooled to 0 °C, and the precipitates were filtered to yield the acylguanidine methanesulfonate.

[5-(2-Methylphenyl)furan-2-ylcarbonyl]guanidine methanesulfonate (51): 94% yield (white solid); mp 190 °C; ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H), 2.51 (s, 3H), 7.05 (d, J = 3.9 Hz, 1H), 7.38 (m, 3H), 7.65 (m, 1H), 7.84 (m, 1H), 8.31 (brs, 4H), 11.01 (brs, 1H); MS 243 (M^+); Anal. ($C_{14}H_{17}N_3O_5S$) C, H, N, S.

[5-[2-(Trifluoromethyl)phenyl]furan-2-ylcarbonyl]guanidine methanesulfonate (52): 62% yield (yellow solid); mp 229 °C; ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3H), 7.07 (d, J = 3.6 Hz, 1H), 7.69 (d, J = 3.6 Hz, 1H), 7.75 (dd, J = 8.7, 9.0 Hz, 1H), 7.87 (dd, J = 8.7, 9.0 Hz, 1H), 7.94 (m, 2H), 8.34 (brs, 4H), 11.25 (brs, 1H); MS 297 (M^+); Anal. ($C_{14}H_{14}F_3N_3O_5S$) C, H, N, S.

[5-(2-Nitrophenyl)furan-2-ylcarbonyl]guanidine methanesulfonate (53): 94% yield (yellow solid); mp 229−231 °C; ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H), 7.13 (d, J = 3.6 Hz, 2H), 7.70 (d, J = 3.6 Hz, 1H), 7.79 (dd, J = 8.7, 9.0 Hz, 1H), 7.96 (m, 2H), 7.99 (d, J = 9.0 Hz, 1H), 8.36 (brs, 4H), 11.84 (brs, 1H); MS 274 (M^+); Anal. ($C_{13}H_{14}N_4O_7S$) C, H, N, S.

[5-[3-(Trifluoromethyl)phenyl]furan-2-ylcarbonyl]guanidine methanesulfonate (63): 69% yield (yellow solid); mp 238 °C; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H), 7.54 (d, J = 3.6 Hz, 1H), 7.67 (d, J = 3.6 Hz, 1H), 7.76−7.84 (m, 2H), 8.27 (m, 2H), 8.34 (brs, 4H); MS 297 (M^+); Anal. ($C_{14}H_{14}F_3N_3O_5S$) C, H, N, S.

[5-(4-Chlorophenyl)furan-2-ylcarbonyl]guanidine methanesulfonate (67): 70% yield (off white solid); mp 252−253 °C; ^{1}H NMR (DMSO-d_6) δ 2.38 (s, 3H), 6.81(d, J = 3.6 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 8.36 (brs, 3H), 11.01 (brs, 1H); MS 263 (M^+); Anal. ($C_{13}H_{14}ClN_3O_5S$) C, H, N, S.

[5-(4-Methoxyphenyl)furan-2-ylcarbonyl]guanidine methanesulfonate (68): 71% yield (yellow solid); mp 212 °C; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H), 3.84 (s, 3H), 7.10 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 3.6 Hz, 1H), 7.62 (d, J = 3.6 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 8.33 (brs, 4H), 11.01 (brs, 1H); M^+ 259; Anal. ($C_{14}H_{17}N_3O_6S$) C, H, N, S.

[5-(4-Nitrophenyl)furan-2-ylcarbonyl]guanidine (71): 99% yield (yellow solid); mp 193−195 °C; ^{1}H NMR (DMSO-d_6) δ 7.08 (d, J = 3.6 Hz, 1H), 7.33 (d, J = 3.6 Hz, 1H), 8.01 (dd, J = 2.1, 7.0 Hz, 1H), 7.96 (dd, J = 2.1, 7.0 Hz, 2H); MS 274 (M^+); Anal. ($C_{12}H_{10}N_4O_4$) C, H, N.

[5-[2-Chloro-5-(trifluoromethyl)phenyl]furan-2-ylcarbonyl]guanidine methanesulfonate (86): 90% yield (white solid); mp 243 °C; ^{1}H NMR (D_2O) δ 2.74 (s, 3H), 7.50 (d, J = 3.7 Hz, 1H), 7.64 (d, J = 3.7 Hz, 1H), 7.72−7.74 (m, 2H), 8.38 (s, 1H); MS 331 (M^+); Anal. ($C_{14}H_{13}ClF_3N_3O_5S$) C, H, N, S.

Biology. Inhibitory Effect on NHE-1. Na^+/H^+-exchanger (NHE-1) inhibitory activity was used as our primary screen and measured by the rate of NHE-1-mediated recovery of intracellular pH (pHi) in a 96-well microplate using a pH sensitive fluorescent dye, 2′,7′-bis-2-carboxyethyl-5(6)-carboxyfluorescein acetoxymethyl ester (BCECF-AM, Sigma-Aldrich Co., MO).[23,24] PS120 Fibroblast cells expressing human NHE-1 were obtained from Professor J. Pouyssegur (Nice, France)[20] and maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 1% penicillin/streptomycin (100X solution), 1% l-glutamine (200 mM solution), and 10% fetal bovine serum at 37 °C, in a humidified atmosphere of 5% CO_2 and 95% air. Cells were grown to confluency and then harvested from 100 mm culture dishes using trypsin−EDTA solution. Cells were washed twice with Na-free buffer (138.2 mM choline chloride, 4.9 mM KCl, 1.5 mM $CaCl_2 \cdot 2H_2O$, 1.2 mM $MgSO_4 \cdot 7H_2O$, 1.2 mM KH_2PO_4, 15 mM D-glucose, 20 mM HEPES, at pH 7.4) and incubated with 10 μM of BCECF-AM and 20 mM NH_4Cl at 37 °C for 30 min. The BCECF- and NH_4Cl-loaded cells were then washed, resuspended in Na-free buffer, and kept on ice.

The 10 μL of the BCECF- and acid-loaded cells (2.5×10^4 cells) was added to 180 μL of HBS buffer containing NaCl (137 mM NaCl, 4.9 mM KCl, 1.5 mM $CaCl_2 \cdot 2H_2O$, 1.2 mM $MgSO_4 \cdot 7H_2O$, 1.2 mM KH_2PO_4, 15 mM D-glucose, 20 mM HEPES, pH 7.4) with 10 μL of DMSO or compounds in 96-well microplate. NHE activity was initiated by NaCl, and fluorescence readings were taken 4 min after the addition of acidified cell to each microplate containing NaCl, at 444 nm excitation/535 nm emission and also at 485 nm excitation/535 nm emission using a spectrofluorometer (GEMINI-XS, Molecular Device, CA) at room temperature. Activity in the absence of NaCl was subtracted from the activity in the presence of NaCl. The initial increase in pHi in response to NaCl was taken as an estimate of Na^+/H^+-exchange activity, and the inhibitory effect of the compounds was evaluated as IC_{50} value (concentration required to inhibit pHi recovery by 50%). Calibration of pHi was accomplished using the high K^+-nigericin method.[25] The

BCECF fluorescence ratio (485/444) was plotted against pH*i* and fitted by linear regression.

Cardioprotective Activity in Isolated Ischemic Rat Heart Model. The anti-ischemic effects of the compounds on isolated rat hearts were determined, according to our previously reported paper.[26] Briefly male Sprague−Dawley rats (400−450 g) were anesthetized with sodium pentobarbital, and their hearts were then excised and quickly moved to a Langendorff apparatus (H.S.E., Germany), where they were perfused with oxygenated modified Krebs−Henseleit bicarbonate buffer at a constant perfusion pressure (85 mmHg). After stabilization for 15 min, the hearts were pretreated for 10 min with compounds (10 μM, 0.04% DMSO) before onset of global ischemia. Then the hearts were subjected to global ischemia by completely shutting off the perfusate for 30 min, followed by reperfusion. Contractile function (rate pressure product, RPP) was measured as LVDP (left ventricular developing pressure) × HR (heart rate) at 30 min after reperfusion.

In Vivo Cardioprotective Activity in Ischemic Myocardium Rat Model. To measure cardioprotective potencies in vivo, we determined the % ratio of myocardial infarction size to area at risk (IS/AAR, %) in ischemic myocardium rat model.[27] Experimental details of method are described in previous our report.[28] In brief, the left coronary artery was occluded according to the Selye H. method.[29] The rats underwent a left thoracotomy operation and were allowed to stabilize for 20 min. The PE tube was pressed on the surface of the heart directly above the coronary artery and a hemostatic pincette was applied to clamp the tube and ligature for 45 min, resulting in coronary artery occlusion. Reperfusion was allowed for 90 min by the removal of the hemostatic pincette. Vehicle or test compounds were intravenously administered by bolus injection at 5 min prior to ischemia via the catheter inserted into the femoral vein. After injection of a 1% Evans blue, rats were then sacrificed by iv injection of pentobarbital, and the heart was removed. The left ventricle was cut horizontally to the heart apex into five or six slices, which were weighed. These slices were analyzed using a Hi-scope installed with an image analyzing program (Image Pro Plus). The area at risk (AAR) obtained from each slice was summed for all slices, and the total AAR was divided by the total weight of the left ventricle to yield % AAR. The heart slices were then stained with 2,3,5-triphenyltetrazolium chloride (TTC). The viable portion of the slice is stained red by TTC, whereas the TTC stain is absent in the area of infarct. The infarct size of each slice was summed for all slices and the resulting summed infarct sized was divided by total AAR weight or total left ventricle weight to yield % IS.

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Supporting Information Available: Elemental analysis data. These materials are available free of charge via the Internet at http://pubs.acs.org.

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