Bromobenzofuran-Based Non-peptide Antagonists of Angiotensin II: GR138950, a Potent Antihypertensive Agent with High Oral Bioavailability

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We have identified GR138950, a potent antagonist of the angiotensin II receptor with high oral bioavailability, as our second drug candidate to GR117289. Using GR117289, a compound with moderate bioavailability (20%) in man as a lead, we pursued a strategy aimed at enhancing bioavailability. The strategy was based on SAR established around the diacid GR117289, and from this, it was proposed that a monoacid, in particular a trifluoromethanesulfonamide, should be better absorbed after oral administration and have enhanced oral bioavailability. This led to the identification of GR138950, a potent antihypertensive agent in the renal hypertensive rat, causing sustained falls in blood pressure after oral administration. Oral bioavailability of GR138950 in rats and dogs is high, confirming that GR138950 is well absorbed after oral administration. Moreover, the low plasma clearance and long plasma half-life suggest that this compound will be suitable for once a day administration. Furthermore, the preliminary data indicate that the high bioavailability of GR138950 seen in rats and dogs translates to man. These results demonstrate clearly that GR138950 has the potential to be a clinically effective antihypertensive agent. Further studies are in progress to evaluate GR138950 in the treatment of hypertension.

Introduction

There is good clinical evidence that attenuation of the activity of the renin angiotensin system by inhibiting the production of angiotensin II or by blocking the action of angiotensin II at its receptor is an effective method for treating hypertension[2] and may also be useful in the treatment of heart failure.[3] Angiotensin II, an octapeptide (AspArgValTyrIleHisProPhe), is a potent vasoconstrictor agent and is produced *in vivo* from angiotensin I by angiotensin converting enzyme (ACE). Inhibitors of ACE such as Enalapril and Captopril are effective treatments for hypertension and are widely used in the clinic. ACE is not, however, a selective enzyme for the conversion of angiotensin I into angiotensin II, as it degrades other peptides such as bradykinin,[4] substance P,[5] and enkephalins.[5] Some of the side effects of ACE inhibitors such as angioedema[6] and cough[7] have been attributed to the resulting elevated levels of bradykinin.

Angiotensin II exerts its actions through specific receptors,[8] and a potentially advantageous approach to interrupt the renin angiotensin system is to specifically block the actions of angiotensin II at its receptor. Early antagonists of angiotensin II such as saralasin[9] are peptoid in nature and are partial agonists. Like most peptides, they have poor oral absorption and are rapidly cleared from the plasma.

The discovery of Losartan (DuP753) (**1**), a potent and selective non-peptide antagonist of angiotensin II,[10] has stimulated much interest in this area of research. Recent clinical studies with **1**[11] have demonstrated the potential of antagonists of angiotensin II in the treatment of hypertension. In particular, one study[11a] has demonstrated that after 5 days of treatment with **1**, at doses of 50, 100, and 150 mg, a similar antihypertensive effect to that of Enalapril is observed, with a lower incidence of adverse events.

Our own work in this area led to the identification of the bromobenzofuran GR117289 (**2**),[12–14] a potent and selective antagonist of angiotensin II, which lowers blood pressure in renal hypertensive rats after oral administration.[15] However, in man **2** has only moderate bioavailability (20%), which is due to poor absorption from the gastrointestinal tract rather than to first pass metabolism. As part of our continued research in this area, we set ourselves the objective of identifying a compound with improved oral bioavailability by addressing the issue of absorption. We attributed the poor absorption of **2** and related compounds to the fact that they are diacids. We therefore adopted a strategy of restricting ourselves to the design and synthesis of monoacidic antagonists of angiotensin II.

This strategy led to the identification of the triflamide GR138950 (**3**),[16] a potent and selective antagonist of angiotensin II with good oral bioavailability, low plasma clearance, and potent oral antihypertensive activity in renal hypertensive rats. Furthermore, **3** is currently being evaluated in the clinic for the treatment of hypertension.

Background and Strategy

Our overall objective has been to identify compounds which have the potential to be potent orally active antihypertensive agents in man. We believe that in

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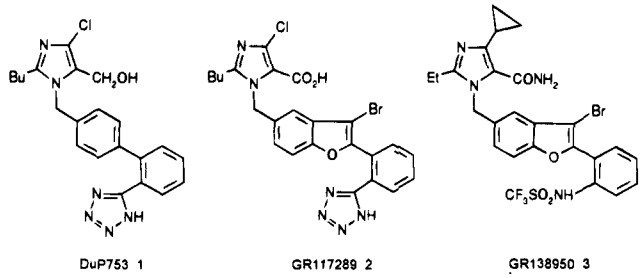


order to compete successfully with other forms of treatment for hypertension, such compounds will have to be suitable for once a day oral administration. To achieve this objective in addition to exhibiting good oral antihypertensive activity, any clinical candidate must have high bioavailability and low plasma clearance.

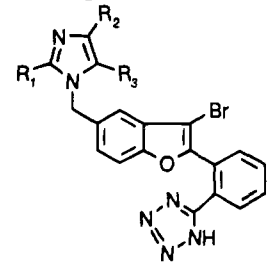
Bioavailability is generally considered to be the fraction or percentage of a drug which reaches the circulation following administration. It reflects the quantity and rate at which a drug is absorbed into the blood and the removal of the drug from it. High oral bioavailability is desirable in any clinical candidate to ensure good systemic exposure to a given dose of drug. Where the bioavailability of a drug is low, factors such as age, health, lifestyle, and simple biological variation can give rise to different levels of systemic exposure after a given oral dose, in a given subpopulation.[17] This variability in exposure can lead to either ineffective treatment or undesirable side effects.

Although there is no defined lower limit for bioavailability, we aimed to identify a compound with an improved bioavailability over **2**. In our early work[12] with **2** and its analogues, the majority of which were diacids, we found that few compounds exhibited oral activity in the renal hypertensive rat,[15] and we attributed this to poor oral absorption. This conclusion was supported by the observation that the antihypertensive activities of diacids closely related to **2** were considerably less effective after oral administration than after systemic administration. Furthermore, the diacid **2** has low plasma clearance in rats and dogs (Table 1), again suggesting that the low bioavailability is due to poor oral absorption.

In contrast, we had found that a number of monoacids exhibited good bioavailability. For example, the oral bioavailability of the monoacid ethyl ester **5**[18] in the dog is 70% compared to that of only 8% for the diacid parent **4** (Table 1). Although the ethyl ester **5** is well absorbed, it is only poorly converted *in vivo* into the active diacid **4** and consequently proved inadequate as a drug candidate. Attempts to develop the prodrug approach further using more labile double esters, which have been used in antibacterials,[19] resulted in compounds which suffered significant ester cleavage prior to absorption. This highlights one of the inherent problems associated with the design of prodrugs.

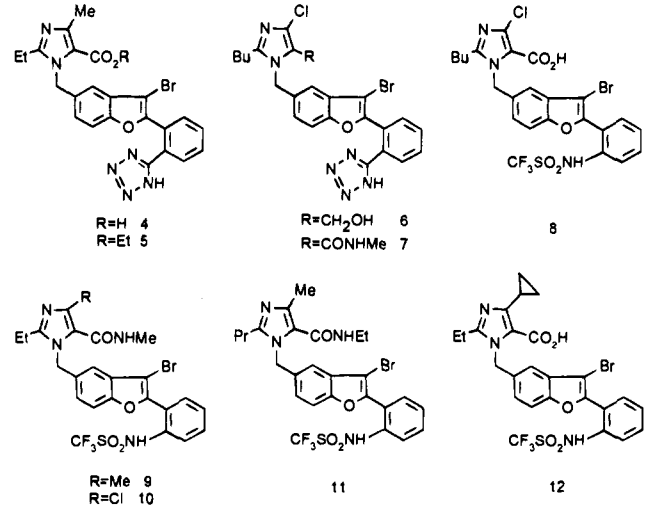
Two other examples of monoacids with acceptable bioavailability are the imidazolemethanol **6**[12] and *N*-methylimidazolecarboxamide **7**[18] analogues of **2** (Table 1). Both of these compounds (**6**, **7**) are potent antagonists of angiotensin II *in vitro* and lower blood pressure in the renal hypertensive rat. However, the duration of their pharmacodynamic effect is short, probably as a result of their high plasma clearance. Consequently, neither compound fulfilled the requirement of a potential drug candidate. Nevertheless, in the light of the above observations, we concluded that, in this series of compounds, a monoacid might be better absorbed than a diacid. We therefore adopted the strategy of working exclusively with monoacidic antagonists of angiotensin II, in order to achieve our objective of improved absorption and higher bioavailability. Furthermore, because of the inherent problems associated with the plasma kinetics of prodrugs, we excluded them from this study.

Table 1. Pharmacokinetic Parameters of Selected Tetrazole Derivatives in Rat and Dog at doses of 3–10 mg/kg



no.	R_1	R_2	R_3	$t_{1/2}$[a] (h)	Clp[a] (mL/min/kg)	V_d[a] (L/kg)	F[a] (%)	species
2	Bu	Cl	CO_2H	8	0.8	0.5	3	rat
2	Bu	Cl	CO_2H	2.5	6	1.2	9	dog
4	Et	Me	CO_2H	4.0	6	2.0	8	dog
5	Et	Me	CO_2Et	0.2	~100	2.0	70	dog
6	Bu	Cl	CH_2OH	1.0	18	1.3	37	rat
7	Bu	Cl	CONHMe	0.5	11	0.3	36	dog

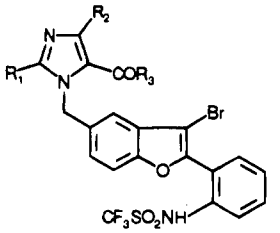
[a] F = bioavailability; Clp = plasma clearance; V_d = volume of distribution; $t_{1/2}$ = plasma half-life.



Our initial targets following this strategy were the triflamides **9** and **10**. This choice was based on three key aspects of the SAR we had established around **2** and on the crucial observation of unexpectedly high oral activity in a compound with relatively low potency *in vitro*.

SAR studies around **2**[12,18] had demonstrated that an acidic group in the pendant aromatic ring is crucial for high potency *in vitro*. In contrast, the carboxylic acid in the imidazole ring, although important, is not crucial for high potency *in vitro*. Clearly, under our monoacid strategy, the imidazolecarboxylic acid should be replaced by a neutral group. In this context, we favored a secondary carboxamide as our previous work[16] had shown the *N*-methylimidazolecarboxamide **7** retained the highest potency *in vitro* relative to the carboxylic

Table 2. Antagonists of Angiotensin II; Imidazolecarboxamide Variants *in Vitro* and Antihypertensive Effects



					RHR (0.5 mg/kg po)[b]				
no.	R_1	R_2	R_3	pK_i[a]	5h	7h	24 h	anal.[c]	mp (°C)
48	Et	Me	NH_2	8.9 ± 0.09	−40 ± 7	−61 ± 9	−3 ± 7	MS	118–124
9	Et	Me	NHMe	8.5 ± 0.03	−43 ± 9	−54 ± 10	−6 ± 3	CHN	170–3
49	Et	Me	NHEt	8.9 ± 0.15	−17 ± 4	−33 ± 6	4 ± 3	MS	110–5
50	Et	Cl	NH_2	8.5 ± 0.09	−57 ± 12	−55 ± 12	−12 ± 6	MS	68–70 dec
10	Et	Cl	NHMe	8.6 ± 0.14	−30 ± 9	−31 ± 5	−4 ± 5	CHN	105–6 dec
51	Et	Cl	NHEt	8.7 ± 0.18	−37 ± 12	−43 ± 10	−12 ± 8	CHN[d]	104–6
52	Pr	Cl	NH_2	8.7 ± 0.09	−19 ± 6	−28 ± 7	9 ± 5	CHN	198–200
53	Pr	Cl	NHMe	8.9 ± 0.20	−67 ± 9	−61 ± 7	−19 ± 9	CHN	78–80 dec
54	Pr	Cl	NHEt	9.0 ± 0.13	−40 ± 6	−54 ± 6	−13 ± 5	CHN	172
55	Pr	Me	NH_2	9.1 ± 0.13	−38 ± 9	−37 ± 7	−8 ± 6	MS	250 dec
56	Pr	Me	NHMe	9.0 ± 0.14	−30 ± 13	−50 ± 13	−12 ± 16	CHN	164–70
11	Pr	Me	NHEt	9.5 ± 0.03	−33 ± 8	−48 ± 5	−30 ± 10	CHN	187–90
57	Me	Me	NHMe	7.5 ± 0.05	6 ± 5	0 ± 6	−3 ± 3	CHN[e]	208–10
58	Bu	Cl	NHMe	8.8 ± 0.10	−40 ± 12[f]	−45 ± 13[f]	7 ± 5[f]	CHN	156–8

[a] *In vitro* activity in rat liver.[13] [b] Renal hypertensive rat: $n = 4$, 95% confidence limits given.[15] [c] For full details, see additional data; MS = high-resolution mass spectrum. [d] N: calcd, 8.84; found, 8.15. [e] N: calcd, 8.3; found, 9.0. [f] Evaluated at 1 mg/kg.

acid **2**. Furthermore, the carboxamide would serve as a versatile functional group for structural modification. Additionally we felt that any drop in potency associated with replacing the carboxylic acid by a carboxamide could be offset by replacing the butyl group with the potency-enhancing ethyl group.[18] We thus anticipated that incorporation of a 2-ethylimidazole-5-carboxamide would afford a monoacid retaining good potency *in vitro*.

The key advance toward improved bioavailability was serendipitous. As part of our biological strategy, we had adopted a policy of evaluating all our compounds in renal hypertensive rats[15] *via* the oral route. The triflamide analogue (**8**) of **2**, although only weakly active *in vitro*,[18] exhibited good oral activity in this model. These results, which have been reported in a preliminary publication,[16] indicated that a triflamide might be better absorbed than a tetrazole.

Taking these observations together, i.e. the necessary position of a single acid substituent, the imidazole SAR, and the enhanced absorption of a triflamide, we identified the triflamides (**9**, **10**) as initial targets, anticipating good oral absorption and undiminished potency *in vitro*.

Results and Discussion

The triflamides (**9**, **10**) have a similar profile of activity, as each other, both *in vitro*[13] and *in vivo* (Table 2) and come close to satisfying our criteria for a drug candidate. The profile of action of these compounds is illustrated by **9**. In the renal hypertensive rat, it is as effective after oral administration as after systemic administration (Figure 1), indicating good oral absorption. Indeed, subsequent pharmacokinetic studies in the rat with this compound showed it to have high bioavailability (Table 5) and thus good oral absorption. However, the high plasma clearance of this compound is consistent with its shorter pharmacodynamic effect in the renal hypertensive rat relative to **2**, precluding the development of this compound as a drug candidate.

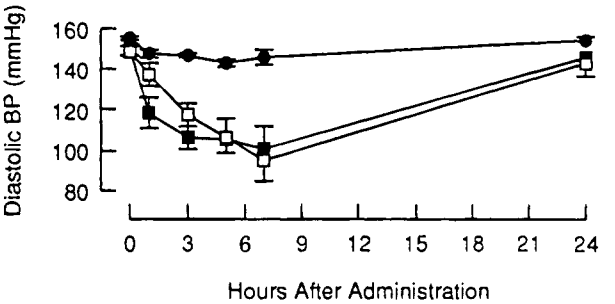
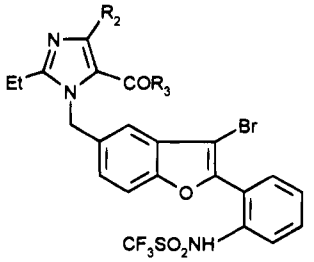


Figure 1. Effect of the administration of oral vehicle (●, 0.1 mL/100 g) or intra-arterial (■, 0.5 mg/kg) and oral administration (□, 0.5 mg/kg) of the triflamide **9** on the diastolic blood pressure of renal hypertensive rats ($n = 4$).

The relative contributions of renal, metabolic, and/or biliary clearance to the plasma clearance of the triflamide **9** were not investigated. Nevertheless, we chose to use the compound as a lead. Structural changes were made to the imidazolecarboxamide substituents with the aim of identifying compounds with good oral absorption and, in addition, lower plasma clearance. Initially compounds were evaluated in the renal hypertensive rat after oral administration. Subsequently those compounds with good oral antihypertensive activity and a longer duration of action than **9** were selected for pharmacokinetic evaluation to establish if they had the required profile.

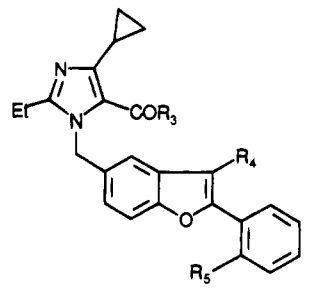
Initially we investigated compounds with alternative alkyl groups at both the 2-position of the imidazole and the nitrogen of the carboxamide while maintaining a methyl or chloro group at the 4-position (Table 2). The compounds (**9–11**, **48–58**) have similar binding affinities for the angiotensin AT_1 receptor (rat liver membranes)[13] with the exception of the 2-methyl derivative **57**, which was only weakly active *in vitro* and is inactive *in vivo*. The compounds with high binding affinity were

Table 3. Antagonists of Angiotensin II; Imidazolecarboxamide Variants *in Vitro* and Antihypertensive Effects



				RHR (0.5 mg/kg po)[b]				
no.	R_2	R_3	pK_i[a]	5 h	7 h	24 h	anal.[c]	mp (°C)
3	cC_3H_5	NH_2	9.3 ± 0.20	−66 ± 8	−76 ± 10	−38 ± 8	CHN	202–3
59	cC_3H_5	NHMe	9.4 ± 0.10	−60 ± 12	−52 ± 8	−9 ± 5	MS	147–52
60	cC_3H_5	NHEt	9.2 ± 0.13	−53 ± 12	−63 ± 10	−14 ± 6	CHN	222–4
61	cC_3H_5	NHiBu	9.9 ± 0.18	−63 ± 3	−70 ± 14	−47 ± 12	CHN	180–1
62	Me	NMe_2	8.6 ± 0.06	1 ± 4	2 ± 4	1 ± 6	MS	156–8
63	Et	NH_2	9.1 ± 0.13	−35 ± 8	−38 ± 12	−17 ± 6	CHN	130–45
64	iPr	NH_2	8.4 ± 0.23	−21 ± 5	−22 ± 5	−13 ± 7	MS	185–6
65	iBu	NH_2	7.7 ± 0.20	−4 ± 9	−19 ± 9	−8 ± 10	MS	200–1

Table 4. Antagonists of Angiotensin II; Phenylbenzofuranyl Variants *in Vitro* and Antihypertensive Effects



					RHR (1.0 mg/kg po)[b]				
no.	R_3	R_4	R_5	pK_i[a]	5 h	7 h	24 h	anal.[c]	mp (°C)
3	NH_2	Br	$NHSO_2CF_3$	9.3 ± 0.20	−65 ± 6	−66 ± 5	−52 ± 6	CHN	202–3
66	NH_2	H	$NHSO_2CF_3$	7.0 ± 0.12	−18 ± 6	−16 ± 4	7 ± 7	CHN	230–1
67	NH_2	Cl	$NHSO_2CF_3$	8.9 ± 0.14	−57 ± 6	−60 ± 11	−42 ± 18	MS	186–8
68	NH_2	CF_3	$NHSO_2CF_3$	9.0 ± 0.23	−48 ± 5	−49 ± 3	−17 ± 17	MS	183–6
69	NH_2	Et	$NHSO_2CF_3$	8.8 ± 0.23	−37 ± 6	−42 ± 6	−2 ± 8	MS	130–5
38	NHEt	Br	CO_2H	8.6 ± 0.07	6 ± 6	0 ± 7	4 ± 13	CHN	182–4
41	NHEt	Br	tetrazol-5-yl	9.4 ± 0.23	−8 ± 4	−9 ± 6	−1 ± 5	MS	155–60 dec
1	DuP753 (Losartan)			7.5 ± 0.20	−30 ± 6	−41 ± 12	−36 ± 11		

[a] *In vitro* activity in rat liver.[13] [b] Renal hypertensive rat: $n = 4$, 95% confidence limits given.[15] [c] For full details, see additional data; MS = high-resolution mass spectrum.

also potent antagonists against angiotensin II-induced contractions in the rabbit isolated aorta (data not shown).

We chose the 2-propyl-4-methyl-*N*-ethyl analogue **11** from this initial set of compounds for pharmacokinetic evaluation. Unlike other compounds of the series, this compound has an extended duration of action in the renal hypertensive rat with significant antihypertensive activity at 24 h (Table 2). Disappointingly, however, although the oral bioavailability in rats of this compound was good (90%) and the plasma clearance was lower (29 mL/min/kg) than for the 2-ethyl-*N*,4-dimethylimidazole-5-carboxamide **9** (42 mL/min/kg) (Table 5), the extended duration of action in the renal hypertensive rat is primarily due to its high volume of distribution.

We next investigated whether varying the substiuents at the 4-position of the imidazole would lead to compounds with improved plasma clearance. From these studies (Table 3), the 4-cyclopropyl primary amide analogue **3** emerged as another compound with an extended duration of action in the renal hypertensive rat (Figure 2) and was selected for pharmacokinetic evaluation. The isobutylamide derivative **61** which has a similar hemodynamic profile to **3** in the renal hypertensive rat was identified at a later date. It offers no significant advantage over **3**.

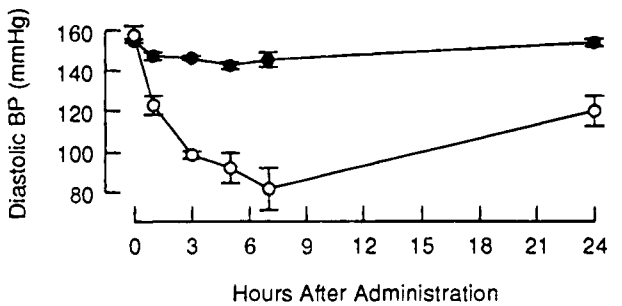
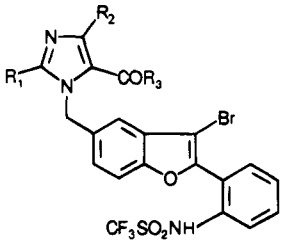


Figure 2. Effects of the administration of oral vehicle (●, 0.1 mL/100 g) and oral administration of **3** (○, 0.5 mg/kg) on the diastolic blood pressure of renal hypertensive rats ($n = 4$).

Table 5. Pharmacokinetic Parameters of Selected Triflamide Derivatives in Rat and Dog



no.	R_1	R_2	R_3	$t_{1/2}$[a] (h)	Clp[a] (mL/min/kg)	V_d[a] (L/kg)	F[a] (%)	species
9	Et	Me	NHMe	1.2	42	4.3	95	rat
11	Pr	Me	NHEt	4.5	29	11	90	rat
3	Et	cC_3H_5	NH_2	3.2	8.9	2.4	79	rat
3	Et	cC_3H_5	NH_2	9.3	1.6	0.9	complete	dog

[a] F = bioavailability; Clp = plasma clearance; V_d = volume of distribution; $t_{1/2}$ = plasma half-life.

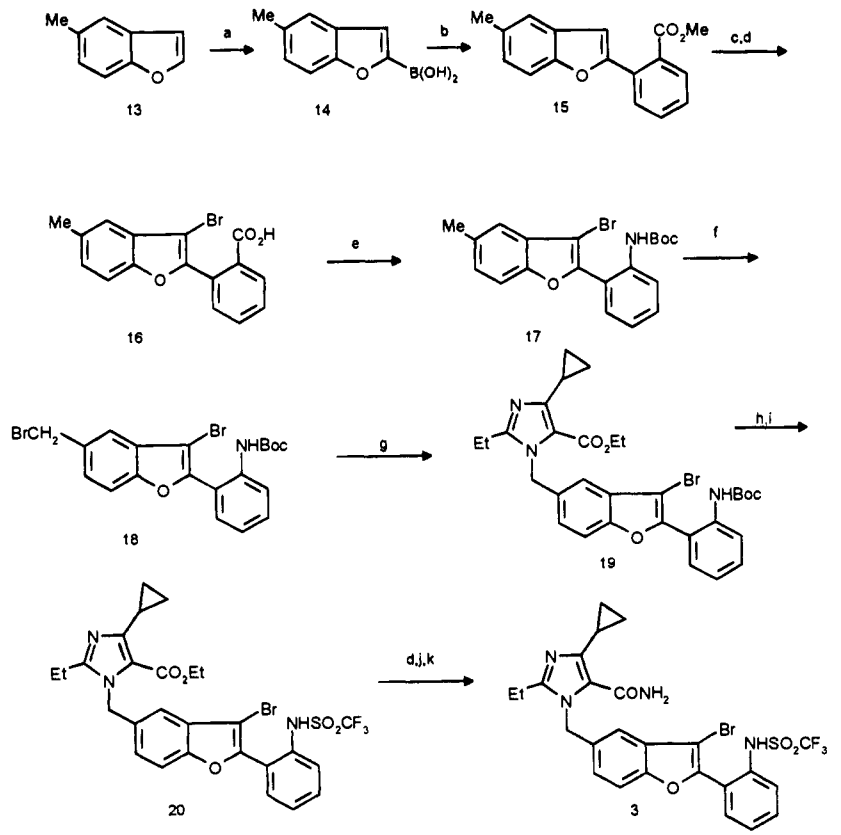
The pharmacokinetic studies on **3** revealed good bioavailability in rats (79%), indicating good absorption. Moreover, the extended duration in the renal hypertensive rat was now attributable to a significantly lower plasma clearance (8.9 mL/min/kg) (Table 5) rather than to a high volume of distribution. In addition, HPLC analysis of the plasma samples indicated that **3** was not acting as a prodrug for the carboxylic acid **12**, which is also a potent antagonist of the angiotensin receptor. The pharmacokinetic profile of **3** was also evaluated in dogs, where it displayed high bioavailability and low plasma clearance. Thus, **3** satisfied our criteria for a potential drug candidate and is currently undergoing evaluation in man for the treatment of hypertension. Furthermore, the preliminary data indicate that the high bioavailability of GR138950 (**3**) seen in rats and dogs translates to man.

In addition, **3** has high affinity for angiotensin AT_1 binding sites in rat liver ($pK_i = 9.3$; $n = 6$) and is a weak competitor for AT_2 binding sites in bovine cerebellum ($pK_i = <6$; $n = 6$).[13] Furthermore, **3** is a potent antagonist of angiotensin II-induced contractions in the isolated rabbit aorta ($pK_b = \sim 9.0$; $n = 6$) and does not affect 5-HT- or phenylephrine-induced tone in this preparation.[13]

Although **3** satisfied the criteria for a clinical candidate, a limited investigation of analogues modified at the 3-position of the benzofuran was carried out. We have previously described the SAR around the benzofuran 3-substituent of **2**.[18] This has suggested that potency *in vitro* increases with increasing σ-electron-withdrawing power (σ^i) of the benzofuran 3-substituent. In the triflamide series related to **3** (Table 4), the general trend is again followed. However, in contrast to the series related to **2**, in which only the 3-chloro and 3-bromo derivatives retain significant oral activity, in the series related to **3**, all of the 3-substituted compounds (**67**–**69**) are active after oral administration. As these compounds did not offer any advantage over **3**, they were not investigated any further.

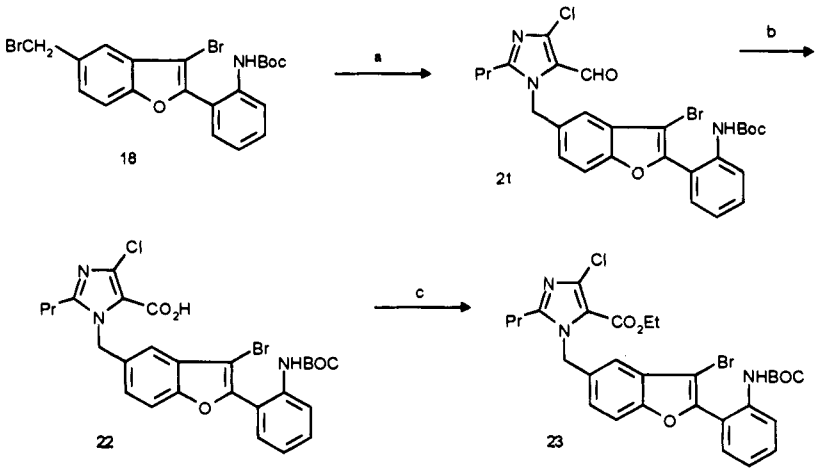
Finally, we reinvestigated the effect on oral activity of replacing the triflamide group in the pendant phenyl ring with a carboxylic acid or tetrazole group. These compounds (**38**, **41**) have high binding affinity but are devoid of oral antihypertensive activity in the renal

Scheme 1[a]



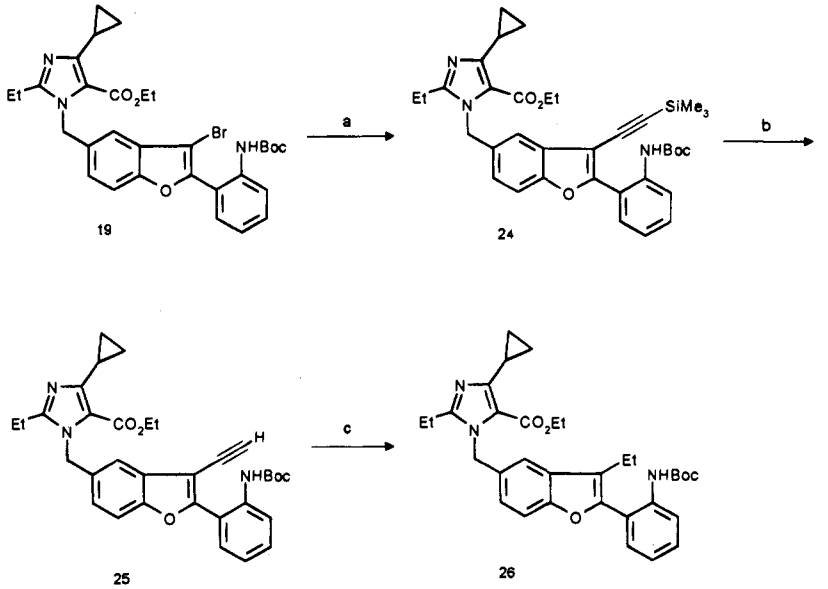
[a] (a) BuLi, TMEDA, $B(OiPr)_3$; (b) methyl 2-bromobenzoate, $(Ph_3P)_4Pd(0)$, DME, Na_2CO_3, 6.5 h, △; (c) Br_2, CCl_4, 0–5 °C, 40 min; (d) NaOH, MeOH, △, 3 h; (e) DPPA, Et_3N, tBuOH, 1,4-dioxane, △, 20 h; (f) NBS, CCl_4, $(PhCO_2)_2$; (g) K_2CO_3, DMF, **43**; (h) TFA, CH_2Cl_2; (i) $(CF_3SO_2)_2O$, CH_2Cl_2, Et_3N, −70 °C; (j) CDI, THF; (k) NH_3 (0.88), EtOH, 3 h.

Scheme 2[a]



[a] (a) DMF, K_2CO_3, **47**; (b) NaOCl, $(CH_3)_2C{=}CHCH_3$, NaH_2PO_4, THF, tBuOH; (c) EtOH, DEAD, Ph_3P, THF.

Scheme 3[a]



[a] (a) $HC{\equiv}CSiMe_3$, $(Ph_3P)_4Pd(0)$, CuI, Et_2NH, 90 °C; (b) NaOH, H_2O, MeOH, THF; (c) Pd/C, H_2.

hypertensive rat (Table 4). These results confirmed that in the benzofuran series of antagonists of angiotensin II, the triflamide moiety enhances oral activity over the tetrazole or carboxylic acid group.

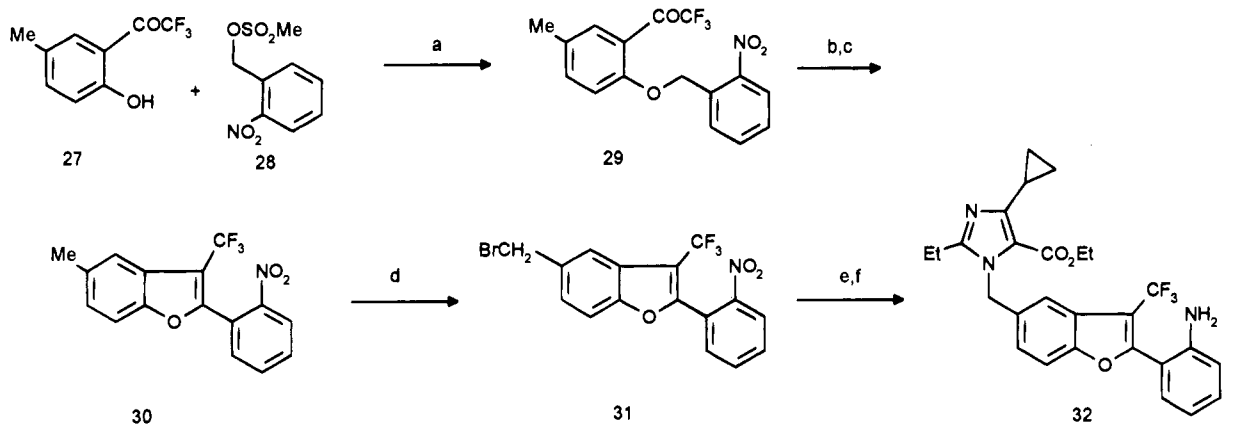
Thus, although our monoacid strategy was successful in obtaining a compound with high bioavailability, it was crucially dependent on the characteristics of the pendant acid moiety. Furthermore, we have recently described a series of diacid antagonists of angiotensin II[20] that possess excellent oral bioavailability. Clearly there is still much to understand about the factors that are important for oral absorption and consequently bioavailability.

In conclusion, our goal was to identify an antagonist of angiotensin II which has improved bioavailability over **2**. By following a strategy of working exclusively with monoacids, in particular trifluoromethanesulfonamides, we have identified **3** as our second drug candidate which is a potent and selective non-peptide antagonist of angiotensin II. Furthermore, **3** is a potent antihypertensive agent in the renal hypertensive rat, causing sustained falls in blood pressure after oral administration. The oral bioavailability of **3** in rats is high (79%) and in dogs is complete, confirming that it is well absorbed after oral administration. Moreover, its low plasma clearance suggests that this compound will be suitable for once a day administration. Preliminary data indicate that the high bioavailability of **3** seen in rats and dogs translates to man. These results demonstrate that **3** has the potential to be a clinically effective antihypertensive agent. Further studies are in progress to evaluate **3** in the treatment of hypertension.

Chemistry

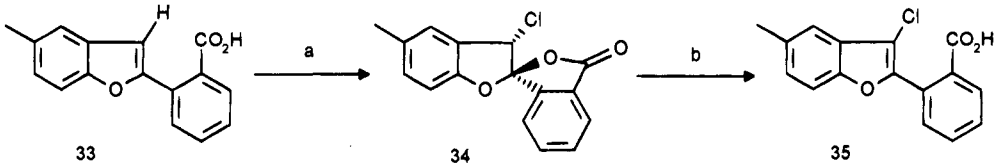
Triflamides (**11**, **55–57**, **59–61**, **63–65**) were prepared using a general procedure which is illustrated with the synthesis of **3** (Scheme 1). A palladium(0)-catalyzed coupling of the boronic acid **14** with methyl 2-bromobenzoate gave the 2-arylbenzofuran **15**. Bromination and subsequent saponification of the ester followed by a Curtius rearrangement of the resulting carboxylic acid **16** afforded the carbamate **17**. Radical bromination of the methyl group gave the (bromomethyl)benzofuran **18** which on alkylation with the imidazole ester **43** (Scheme 8) afforded **19** with no evidence of the

Scheme 4[a]



[a] (a) K_2CO_3, NaI, DMA, room temperature, 18 h; (b) NaOMe, DMA, 0–25 °C, 2 h; (c) Ac_2O, cH_2SO_4, △, 4.5 h; (d) NBS, CCl_4, $(PhCO_2)_2$; (e) DMF, NaH, **43**; (f) Pd/C, HCl, THF, H_2.

Scheme 5[a]



[a] (a) NCS, 1,4-dioxane, H_2O, △; (b) DBU, PhMe, 45 °C.

regioisomer. Removal of the *tert*-butyl carbamate protecting group followed by trifluoromethanesulfonylation gave the triflamide **20**. Saponification of the ester **20** and subsequent amide formation completed the synthesis to afford **3**.

For compounds **52–54**, a variant of the above procedure was utilized (Scheme 2). The intermediate dibromide **18** was reacted with an imidazolecarboxaldehyde (**47**) (Scheme 8). The aldehyde was oxidized and the resultant acid (**22**) esterified to give the intermediate imidazole-5-carboxylic acid ester **23** which was then converted into the required compounds (**52–54**) using the same procedure described above for **3**. Compounds **9**, **10**, **48–51**, **58**, and **62** were prepared in an analogous manner using the requisite imidazolecarboxaldehyde.

Alternative substituents were introduced into the 3-position of the benzofuran as described in Schemes 3–5.

The 3-ethyl group was introduced into the benzofuran by a three-stage process. Palladium(0)-catalyzed coupling of **19** with (trimethylsilyl)acetylene followed by silyl cleavage gave the 3-ethynyl derivative **25** which under hydrogenation conditions gave the 3-ethylbenzofuran intermediate **26** (Scheme 3). This was then converted into the required compound (**69**) using the established procedures (as for **3**, Scheme 1).

The 3-trifluoromethyl intermediate **32** was prepared as shown in Scheme 4. Benzylation of the *o*-(trifluoroacetyl)phenol **27** with the mesylate **28** gave the ether **29** which on base treatment followed by dehydration afforded **30**. Radical bromination afforded **31**, and subsequent alkylation and deprotection gave the aniline **32**, which was converted into **68** by an analogous procedure to that described above (Scheme 1).

The 3-chlorobenzofuran intermediate **35** was prepared as described in Scheme 5. Chlorination of the acid **33** with *N*-chlorosuccinimide resulted in the stable chlorolactone **34**, which only rearomatized on treatment with DBU to give the intermediate chlorobenzofuran **35**. Conversion of **35** into **67** was accomplished as described for **3** (Scheme 1).

The carboxylic acid analogue **38** was prepared from intermediate **16** (Scheme 6). Protection of **16** as a *tert*-butyl ester followed by radical bromination gave **36**. Alkylation with the imidazole **43** gave the *tert*-butyl ester **37**, with the final deprotection being effected with trifluoroacetic acid to afford **38**.

The tetrazole derivative **41** was prepared from the bromomethyl derivative **39**[12] using established methodology (Scheme 7).

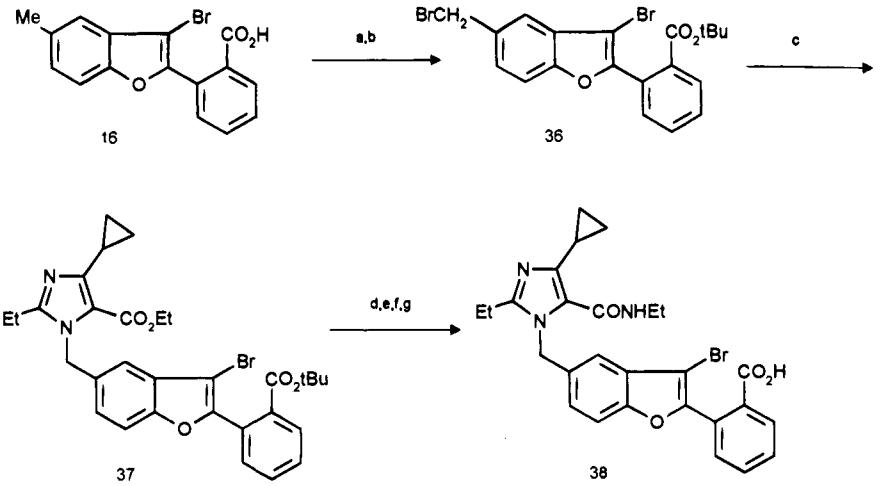
The imidazoles required for the synthesis of **3**, **38**, **41**, **57**, **59–61**, and **63–69** were prepared as depicted for **43** in Scheme 8. The imidazolecarboxaldehydes required for **9**, **11**, **48**, **49**, **55**, and **56** were obtained using literature procedures.[21] However, the 3-chloro derivatives (**46**, **47**) were prepared by treatment of **44** and **45**[21] with *N*-chlorosuccinimide and subsequent oxidation with manganese oxide. 2-Butyl-4-chloro-1*H*-imidazole-5-carboxaldehyde was prepared following a literature procedure.[10]

Experimental Section

^1H NMR spectra were measured ($SiMe_4$ internal standard) on a Bruker WM 250 (250 MHz) or a Varian Unity (400 MHz) spectrometer. All melting points were measured using an Electrothermal 9200 apparatus and are uncorrected. Column chromatography was performed using Merck Kieselgel 60 (Art. No. 9385; flash chromatography). Solvents were dried according to standard procedures.[22] Solutions were dried over $MgSO_4$ before evaporation under reduced pressure. Abbreviations include *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA), dimethoxyethane (DME), *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), and diethyl azodicarboxylate (DEAD).

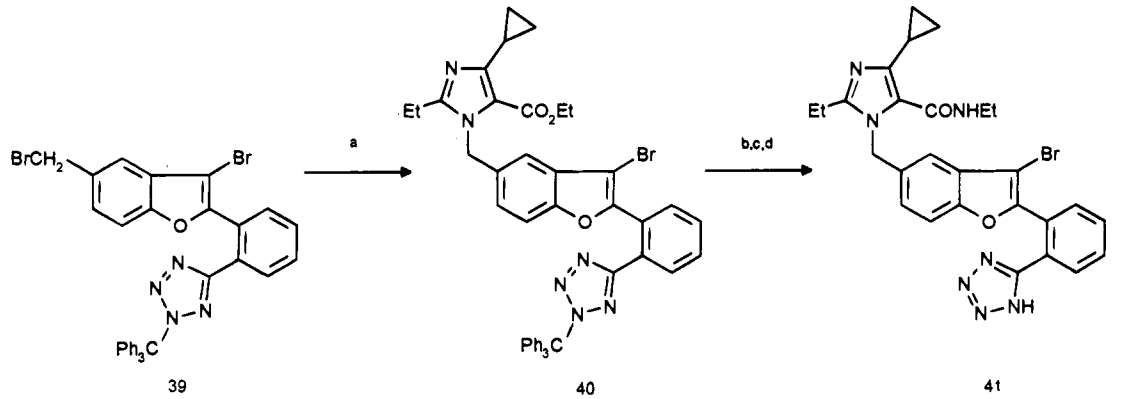
5-Methylbenzofuran-2-boronic Acid (14). *n*-Butyllithium (88.3 mL; 1.6 M; 0.14 mol) was added dropwise to a stirred solution of TMEDA (22.6 mL; 0.15 mol) and **13** (20 g; 0.15 mol) in Et_2O (300 mL) under an atmosphere of N_2, maintaining the temperature below −60 °C throughout. The solution was

Scheme 6[a]



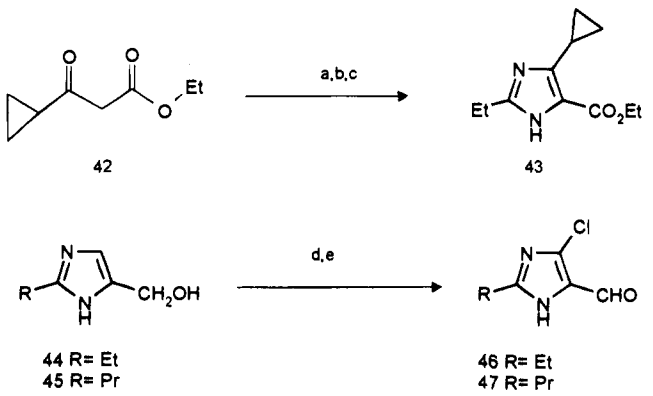
[a] (a) $(tBuO)_2CHNMe_2$; (b) NBS, CCl_4; (c) K_2CO_3, DMF, **43**; (d) NaOH, MeOH; (e) CDI, CH_2Cl_2; (f) $EtNH_2$; (g) TFA.

Scheme 7[a]



[a] (a) K_2CO_3, DMF, **43**; (b) NaOH, MeOH; (c) CDI; (d) $EtNH_2$.

Scheme 8[a]



[a] (a) AcOH, $NaNO_2$; (b) AcCl, EtOH, H_2, Pd/C; (c) EtCH(=NH)OEt, EtOH, Et_3N; (d) NCS, $MeOCH_2CH_2OH$, 1,4-dioxane; (e) MnO_2, CH_2Cl_2.

warmed to −10 °C over 45 min and stirred at this temperature for 30 min. A precipitate formed on warming. The suspension was cooled and triisopropyl borate (43 mL; 0.19 mol) was added, maintaining the temperature below −60 °C. The solution was warmed gradually to room temperature before the reaction was quenched with 2 M HCl (75 mL). The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were washed with 2 M HCl (4 × 100 mL) and water (2 × 30 mL) and dried before evaporation to give the title compound as a white solid (13.8 g; 56%), mp 244−6 °C, which was used without further purification. Anal. ($C_9H_9BO_3$) C, H.

Methyl 2-(5-Methyl-2-benzofuranyl)benzoate (15). A solution of methyl 2-bromobenzoate (11.70 g, 54 mmol), **14** (12.75 g, 72 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.5 g) in DME (300 mL) and aqueous Na_2CO_3 (2M, 60 mL) was heated to reflux with vigorous stirring under an atmosphere of N_2. After 1.5 h, a further 500 mg of catalyst was added and stirring at reflux under nitrogen continued. After 5 h, the reaction mixture was cooled to room temperature and diluted with Et_2O (300 mL). The organic layer was separated, washed with water (3 × 100 mL), and dried. Evaporation under reduced pressure gave a yellow oily, suspension which was purified by chromatography eluting with Et_2O/hexane (1:9) to give a yellow oil. This was further purified by Kugelrohr distillation to give the title compound (4.31 g, 30%). Anal. ($C_{17}H_{14}O_3$) C, H.

Methyl 2-(3-Bromo-5-methyl-2-benzofuranyl)benzoate (70). A solution of **15** (46.8 g, 0.176 mol) in CCl_4 (500 mL) was cooled to 5 °C and treated dropwise with Br_2 in CCl_4 (1 M, 190 mL, 0.19 mol) while maintaining a temperature of 0−5 °C. Stirring at 0−5 °C was then continued for 40 min, and then the solution was cautiously poured into aqueous sodium thiosulfate solution (10%, 500 mL). The organic solution was washed with water (200 mL), dried, and evaporated to give the title compound as an orange oil which crystallized on standing (62.15 g, quantitative), mp 68−9 °C. Anal. ($C_{17}H_{13}BrO_3$) C: calcd, 59.15; found, 57.97.

2-(3-Bromo-5-methyl-2-benzofuranyl)benzoic Acid (16). A solution of **70** (25 g, 0.07 mol) in MeOH (200 mL) was treated with aqueous NaOH (2 M, 50 mL) and the solution heated under reflux for 3 h. The solvent was removed *in vacuo* and the residue diluted with water (50 mL). The aqueous solution was washed with Et_2O (3 × 300 mL) and then acidified to pH 2 using 2 M HCl. The aqueous solution was extracted with Et_2O (4 × 200 mL), and the extracts were combined, dried,

and evaporated to give the title compound as a pale yellow solid (22 g, 92%): mp 183–4 °C; NMR ($CDCl_3$) δ 8.04 (1H, dd, CH), 7.78 (1H, dd, CH), 7.65 (1H, dt, CH), 7.54 (1H, dt, CH), 7.37–7.3 (2H, brs + d, 2 × CH), 7.14 (1H, dd, CH), 2.48 (3H, s, CH_3).

1,1-Dimethylethyl [2-(3-Bromo-5-methyl-2-benzofuranyl)phenyl]carbamate (17). A solution of **16** (9 g, 0.027 mol) in dry 1,4-dioxane (210 mL) was treated with diphenyl phosphorazidate (5.85 mL, 0.032 mol), triethylamine (3.78 mL, 0.027 mol), and *tert*-butyl alcohol (3.85 mL, 0.04 mol) before heating to reflux under an atmosphere of N_2. After 20 h, the reaction mixture was cooled and solvent evaporated to give an orange oil. Purification by column chromatography, eluting with Et_2O/hexane (5:95), afforded the title compound as a white solid (1.95 g, 18%): mp 130–1 °C; NMR ($CDCl_3$) δ 8.19 (1H, brd, CH), 7.65 (1H, dd, CH), 7.50–7.38 (3H, m, 2 × CH + NH), 7.25–7.16 (3H, m, 3 × CH), 2.52 (3H, s, CH_3), 1.48 (9H, s, 3 × CH_3).

1,1-Dimethylethyl [2-[3-Bromo-5-(bromomethyl)-2-benzofuranyl]phenyl]carbamate (18). A solution of **17** (4.29 g, 10.7 mmol), NBS (1.9 g, 10.7 mmol), and benzoyl peroxide (30 mg) in dry CCl_4 (100 mL) was heated at reflux while being irradiated with a 200 W lamp for 1.5 h. The mixture was filtered, and the filtrate was washed with water (2 × 100 mL). The organic solution was dried, filtered, and evaporated to give the title compound (5 g, 97% 70% pure) which was used directly in the next reaction.

Ethyl 1-[[3-Bromo-2-[2-[[(1,1-dimethylethoxy)carbonyl]amino]phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxylate (19). A mixture of **18** (36 g, 70% pure, 0.052 mol), **43** (16 g, 0.0769 mol), and K_2CO_3 (14 g, 0.1 mol) in DMF (600 mL) was stirred at room temperature under an atmosphere of N_2 for 16 h. The suspension was poured into brine (600 mL) and extracted with EtOAc (1 L, 500 mL). The extracts were washed with aqueous LiCl (10%, 400 mL) and water (400 mL). The combined extracts were dried and concentrated *in vacuo* to give an oil which was purified by flash chromatography eluting with Et_2O/hexane (1:2) to give the title compound (19.7 g, 62%) as a pale yellow foam; NMR ($CDCl_3$) δ 8.19 (1H, brd, CH), 7.63 (1H, dd, CH), 7.5–7.42 (2H, m, 2 × CH), 7.25 (1H, brs, CH), 7.2–7.1 (2H, m, CH + NH), 7.01 (1H, dd, CH), 5.65 (2H, s, CH_2), 4.28 (2H, q, CH_2), 2.73–2.58 (3H, q + m, CH_2 + CH), 1.48 (9H, s, 3 × CH_3), 1.33 (3H, t, CH_3), 1.25 (3H, t, CH_3), 1.1–0.9 (4H, m, 2 × CH_2). Anal. ($C_{31}H_{34}BrN_3O_5$) C, H, N.

Ethyl 1-[[3-Bromo-2-(2-aminophenyl)-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxylate (71). Trifluoroacetic acid (30 mL) was added to a stirred solution of **19** (19.7 g, 32.4 mmol) in CH_2Cl_2 (250 mL) at 3 °C under an atmosphere of N_2. The mixture was stirred at room temperature for 16 h, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (250 mL), washed with aqueous $NaHCO_3$ (8%, 40 mL), dried, and concentrated *in vacuo* to afford a dark yellow viscous oil. Purification by chromatography eluting with Et_2O afforded the title compound (16.2 g, 98%) as a white foam: NMR ($CDCl_3$) δ 7.59 (1H, dd, CH), 7.40 (1H, d, CH), 7.3–7.2 (2H, m, 2 × CH), 6.95 (1H, dd, CH), 6.88–6.77 (2H, m, 2 × CH), 5.63 (2H, s, CH_2), 4.36–4.2 (4H, q + brs, CH_2 + NH_2), 2.7–2.58 (3H, q + m, CH_2 + CH), 1.3 (3H, t, CH_3), 1.2 (3H, t, CH_3), 1.1–0.9 (4H, m, 2 × CH_2).

Ethyl 1-[[3-Bromo-2-[2-[[(trifluoromethyl)sulfonyl]amino]phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxylate (20). A 1 M solution of trifluoromethanesulfonic anhydride in CH_2Cl_2 (16 mL) was added dropwise to a stirred solution of **71** (8 g, 15.7 mmol) in CH_2Cl_2 (100 mL) containing triethylamine (2.8 mL, 0.02 mol) at −70 °C under an atmosphere of N_2. After stirring for 45 min at −70 °C, further trifluoromethanesulfonic anhydride (1 M in CH_2Cl_2, 2 mL) was added dropwise. After 15 min, water (20 mL) was added and the cooling bath removed. The solution was warmed to room temperature, and further water (200 mL) was added. The organic phase was dried and evaporated to give the title compound as an off-white solid (10 g, 100%): mp 81–3 °C; NMR ($CDCl_3$) δ 7.84 (1H, dd, CH), 7.70 (1H, dd, CH), 7.58–7.40 (3H, dt, dt, d, 3 × CH), 7.25 (1H, d, CH), 7.05 (1H, dd, CH), 6.5 (1H, brs, NH), 5.63 (2H, s, CH_2), 4.28 (2H, q, CH_2), 2.7–2.55 (3H, q + m, CH_2 + CH), 1.30 (3H, t, CH_3), 1.2 (3H, t, CH_3), 1.1–0.9 (4H, m, 2 × CH_2). Anal. ($C_{27}H_{25}BrF_3N_3O_5S$) C, H, N.

1-[[3-Bromo-2-[2-[[(trifluoromethyl)sulfonyl]amino]phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxylic Acid (12). A mixture of **20** (20.3 g, 31 mmol) in MeOH (300 mL) and aqueous NaOH (2 M, 250 mL) was heated at 50 °C for 3 h. The MeOH was removed *in vacuo*, and the aqueous residue was acidified with HCl (2 M, 265 mL) to pH 3 at 5 °C. The solid which precipitated was collected by filtration and dissolved in EtOAc (500 mL). After washing with water (300 mL), the solution was dried and evaporated *in vacuo* to give the title compound as an off-white solid (18.5 g, 95%): mp 138–140 °C; NMR ($CDCl_3$) δ 7.68 (1H, dd, CH), 7.53–7.30 (4H, m, 4 × CH), 7.2 (1H, d, CH), 7.0 (1H, dd, CH), 5.61 (2H, s, CH_2), 2.72–2.58 (3H, q + m, CH_2 + CH), 1.17 (3H, t, CH_3), 1.0–0.8 (4H, m, 2 × CH_2). Anal. ($C_{25}H_{21}BrF_3N_3O_5S$·0.061H_2O) C, H, N.

1-[[3-Bromo-2-[2-[[(trifluoromethyl)sulfonyl]amino]phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxamide (3). CDI (0.17 g, 1.05 mmol) was added in one portion to a solution of **12** (0.514 g, 0.84 mmol) in dry THF (30 mL) at room temperature under an atmosphere of N_2. The mixture was stirred for 3 h and then ammonia (1 mL, 0.88 g/mL) and EtOH (2 mL) were added and the mixture then stirred for 16 h followed by heating under reflux for 4 h. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in a mixture of EtOAc and CH_2Cl_2 (1:3, 30 mL). Water (30 mL) was added, and the pH was adjusted to 6 with dilute HCl (0.25 M). The organic extract was dried and evaporated, and the residue was crystallized from MeOAc and hexane to give the title compound as a white solid (0.33 g, 64%): mp 202–3 °C; NMR (400 MHz, DMSO-d_6) δ 7.9 (1H, brs, CH), 7.56 (1H, brd, CH), 7.46 (1H, brd, CH), 7.43–7.3 (2H, m, 2 × CH), 7.18 (1H, brd, CH), 7.04 (1H, brd, CH), 5.68 (2H, s, CH_2), 2.92 (2H, brs, CH_2), 2.15 (1H, m, CH), 1.16 (3H, t, CH_3), 1.08–0.8 (4H, m, 2 × CH_2). Anal. ($C_{25}H_{22}BrF_3N_4O_4S$) C, H, N.

1-[[3-Bromo-2-[2-[[(1,1-dimethylethoxy)carbonyl]amino]phenyl]-5-benzofuranyl]methyl]-4-chloro-2-propyl-1*H*-imidazole-5-carboxaldehyde (21). A mixture of **18** (5.5 g, 70% pure, 0.008 mol), **47** (1.72 g, 0.01 mol), and K_2CO_3 (1.67 g, 0.012 mol) in DMF (20 mL) was stirred at room temperature under an atmosphere of N_2 for 20 h. The suspension was diluted with water (40 mL) and extracted with Et_2O (3 × 50 mL). The combined extracts were dried and concentrated *in vacuo* to give an oil which was purified by flash chromatography eluting with Et_2O/hexane (3:7) to give the title compound (2.9 g, 63%) as a white solid: mp 75–6 °C; NMR ($CDCl_3$) δ 9.8 (1H, s, CHO), 8.17 (1H, brd, CH), 7.63 (1H, dd, CH), 7.53–7.42 (2H, m, 2 × CH), 7.29 (1H, d, CH), 7.2–7.08 (3H, m, 2 × CH + NH), 5.7 (2H, s, CH_2), 2.69 (2H, t, CH_2), 1.80 (2H, m, CH_2), 1.48 (9H, s, 3 × CH_3), 0.99 (3H, t, CH_3). Anal. ($C_{27}H_{27}BrClN_3O_4$) C, H, N.

1-[[3-Bromo-2-[2-[[(1,1-dimethylethoxy)carbonyl]amino]phenyl]-5-benzofuranyl]methyl]-4-chloro-2-propyl-1*H*-imidazole-5-carboxylic Acid (22). A solution of **21** (2.9 g, 5 mmol) and 2-methyl-2-butene (30 mL, 2 M in THF) in dry THF (85 mL) and *tert*-butyl alcohol (19 mL), under an atmosphere of N_2, was treated with a solution of sodium chlorite (80%, 4.52 g, 40 mmol) and sodium dihydrogen phosphate dihydrate (4.52 g, 29 mmol) in water (65 mL). The mixture was stirred at room temperature for 20 h. The layers were separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined extracts were washed with water (150 mL), dried, and concentrated *in vacuo* to give a foam. This material was dissolved in 2 M NaOH solution (50 mL) and then washed with Et_2O (50 mL). The basic layer was acidified to pH 3 using 2 M HCl and extracted with Et_2O (3 × 80 mL). The extracts were dried and evaporated to give the title compound (2.7 g, 91%) as a white solid: mp 104–5 °C; NMR (400 MHz, DMSO-d_6) δ 13.0 (1H, brs, COOH), 9.0 (1H, brs, NH), 7.68–7.45 (4H, m, 4 × CH), 7.28 (1H, dt, CH), 7.22 (1H, brs, CH), 7.13 (1H, dd, CH), 5.78 (2H, s, CH_2), 2.64 (2H, t, CH_2), 1.6 (2H, m, CH_2), 1.3 (9H, s, 3 × CH_3), 0.89 (3H, t, CH_3). Anal. ($C_{27}H_{27}BrClN_3O_5$) C, H, N.

Ethyl 1-[[3-Bromo-2-[2-[[(1,1-dimethylethoxy)carbonyl]amino]phenyl]-5-benzofuranyl]methyl]-4-chloro-2-propyl-1*H*-imidazole-5-carboxylate (23). A solution of DEAD (1.09 mL, 6.9 mmol) in dry THF (10 mL) was added, dropwise, at room temperature under an atmosphere of N_2 to **22** (2.7 g, 4.6 mmol) and triphenylphosphine (1.8 g, 6.9 mmol) in EtOH (0.81 mL, 13.8 mmol) and dry THF (120 mL). The resulting solution was stirred at room temperature for 20 h and then concentrated *in vacuo*. The residue was purified by flash chromatography eluting with Et_2O/hexane (3:7) to give the title compound (2.45 g, 88%) as a white solid: mp 68–70 °C; NMR ($CDCl_3$) δ 8.18 (1H, brd, CH), 7.63 (1H, brdd, CH), 7.53–7.4 (2H, m, 2 × CH), 7.27–7.0 (4H, m, 3 × CH + NH), 5.7 (2H, s, CH_2), 4.3 (2H, q, CH_2), 2.68 (2H, t, CH_2), 1.78 (2H, m, CH_2), 1.5 (9H, s, 3 × CH_3), 1.35 (3H, t, CH_3), 0.98 (3H, t, CH_3). Anal. ($C_{29}H_{31}BrClN_3O_5$) C, H, N.

Ethyl 4-Cyclopropyl-1-[[2-[2-[[(1,1-dimethylethoxy)carbonyl]amino]phenyl]-3-[(trimethylsilyl)ethynyl]-5-benzofuranyl]methyl]-2-ethyl-1*H*-imidazole-5-carboxylate (24). (Trimethylsilyl)acetylene (8 mL) followed by bis(triphenylphosphine)palladium dichloride (0.86 g, 1.2 mmol) and copper(I) iodide (0.26 g, 1.4 mmol) was added to a solution of **19** (7.05 g, 12 mmol) in diethylamine (40 mL). The contents were heated at 90 °C in a sealed vessel under pressure for 29 h. After cooling, the residue was diluted with EtOAc (300 mL) and washed with water (300 mL). The dried organic extract was concentrated *in vacuo* and the residue purified by flash chromatography eluting with Et_2O/hexane (1:3) to give the title compound as a yellow solid (2.4 g, 32%): mp 74–8 °C; NMR ($CDCl_3$) δ 8.15 (1H, brd, CH), 7.92 (1H, dd, CH), 7.88 (1H, brs, NH), 7.5–7.38 (2H, m, 2 × CH), 7.33 (1H, brs, CH), 7.15 (1H, t, CH), 6.95 (1H, dd, CH), 5.64 (2H, s, CH_2), 4.28 (2H, q, CH_2), 2.72–2.58 (3H, m, q, CH + CH_2), 1.5 (9H, s, 3 × CH_3), 1.32 (3H, t, CH_3), 1.23 (3H, t, CH_3), 1.07 (2H, m, CH_2), 0.95 (2H, m, CH_2), 0.25 (9H, s, 3 × CH_3). Anal. ($C_{36}H_{43}N_3O_5Si$) C, H, N.

Ethyl 4-Cyclopropyl-1-[[2-[2-[[(1,1-dimethylethoxy)carbonyl]amino]phenyl]-3-ethynyl-5-benzofuranyl]methyl]-2-ethyl-1*H*-imidazole-5-carboxylate (25). Aqueous sodium hydroxide (2 M, 60 mL) was added to a stirred solution of **24** (2.38 g, 3.8 mmol) in a mixture of MeOH (40 mL) and THF (15 mL) and stirring continued for 16 h at ambient temperature. The resulting mixture was concentrated *in vacuo* and partitioned between dilute HCl (pH 4) and EtOAc. The dried organic extract was concentrated *in vacuo* and the residue purified by flash chromatography eluting with Et_2O/hexane (3:7) to give the title compound as a yellow foam (1.51 g, 72%): mp 77–80 °C; NMR ($CDCl_3$) δ 8.18 (1H, brd, CH), 7.95 (1H, dd, CH), 7.68 (1H, brs, NH), 7.5–7.38 (3H, m, 3 × CH), 7.16 (1H, t, CH), 6.98 (1H, dd, CH), 5.62 (2H, s, CH_2), 4.28 (2H, q, CH_2), 3.42 (1H, s, CH), 2.72–2.57 (3H, m, q, CH + CH_2), 1.5 (9H, s, 3 × CH_3), 1.32 (3H, t, CH_3), 1.22 (3H, t, CH_3), 1.07 (2H, m, CH_2), 0.96 (2H, m, CH_2). Anal. ($C_{33}H_{35}N_3O_5$) C, H, N.

Ethyl 4-Cyclopropyl-1-[[2-[2-[[(1,1-dimethylethoxy)carbonyl]amino]phenyl]-3-ethyl-5-benzofuranyl]methyl]-2-ethyl-1*H*-imidazole-5-carboxylate (26). A solution of **25** (600 mg, 1.08 mmol) in EtOH (35 mL) containing 10% Pd/C (300 mg) was hydrogenated at room temperature and pressure for 20 min. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to give the title compound as a white solid (530 mg, 88%): mp 75–83 °C; NMR ($CDCl_3$) δ 8.2 (1H, brd, CH), 7.48–7.3 (3H, m, 3 × CH), 7.27 (1H, brs, CH), 7.2 (1H, brs, NH), 7.11 (1H, t, CH), 6.95 (1H, dd, CH), 5.63 (2H, s, CH_2), 4.28 (2H, q, CH_2), 2.75–2.55 (5H, m, q, CH + 2 × CH_2), 1.48 (9H, s, 3 × CH_3), 1.31 (3H, t, CH_3), 1.3-1.2 (6H, t, 2 × CH_3), 1.08 (2H, m, CH_2), 0.95 (2H, m, CH_2). Anal. ($C_{33}H_{39}N_3O_5$) C, H, N.

2,2,2-Trifluoro-1-[5-methyl-2-[(2-nitrophenyl)methoxy]phenyl]ethanone (29). Methanesulfonyl chloride (2.45 mL, 31.6 mmol) in dry 1,4-dioxane (10 mL) was added dropwise to a stirred solution of 2-nitrobenzyl alcohol (4.57 g, 29.8 mmol) and triethylamine (4.62 mL, 33.1 mmol) in 1,4-dioxane (50 mL) while maintaining the temperature at 15–25 °C. Stirring was continued for 1.5 h when the mixture was filtered and the solid washed thoroughly with 1,4-dioxane (50 mL). This filtrate was added to a mixture of 2,2,2-trifluoro-1-(2-hydroxy-5-methylphenyl)ethanone (**27**)[23] (6.23 g, 30.5 mmol), sodium iodide (0.458 g, 3.05 mmol), and K_2CO_3 (4.64 g, 33.6 mmol) in *N*,*N*-dimethylacetamide (60 mL). The mixture was stirred vigorously under an atmosphere of N_2 for 18 h. Distilled water (500 mL) was added over 5 min at ambient temperature and the resultant slurry stirred for 2 h. The solid was collected by filtration, washed with 1,4-dioxane/water (1:1) (300 mL) and water (3 × 50 mL), and dried to give the title compound as a pale yellow solid (7.37 g, 72%): mp 94–100 °C; NMR ($CDCl_3$) δ 8.22 (1H, dd, CH), 8.1 (1H, dd, CH), 7.78 (1H, dt, CH) 7.6-7.48 (2H, brs, brt, 2 × CH), 7.43 (1H, dd, CH), 7.03 (1H, d, CH), 5.58 (2H, s, CH_2), 2.38 (3H, s, CH_3).

2,3-Dihydro-5-methyl-2-(2-nitrophenyl)-3-(trifluoromethyl)-3-benzofuranol (cis and trans diastereoisomers) (72). Sodium methoxide (246 mg, 4.5 mmol) was added at 0 °C to a solution of **29** (4.36 g, 12.9 mmol) in *N*,*N*-dimethylacetamide (40 mL) and stirred for 3 h. Distilled water (100 mL) was added and the aqueous layer extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with water (80 mL) and 10% aqueous LiCl solution (2 × 100 mL) and dried and the solvent removed *in vacuo* to give an oil. Purification by flash column chromatography eluting initially with Et_2O/hexane (10:1 and then 3:1) gave a mixture of the epimeric alcohols as pale yellow solids. First epimer (1.33 g, 30%): mp 120–2 °C; NMR ($CDCl_3$) δ 8.16 (1H, brd, CH), 7.9 (1H, brd, CH), 7.71 (1H, brt, CH), 7.58 (1H, brt, CH), 7.33 (1H, brs, CH), 7.23 (1H, brd, CH), 6.9 (1H, d, CH), 6.38 (1H, s, CH), 4.4 (1H, brs, OH), 2.38 (3H, s, CH_3). Anal. ($C_{16}H_{12}F_3NO_4$) C, H, N. Other epimer (2.11 g, 48%): mp 128–130 °C; NMR ($CDCl_3$) δ 7.81 (1H, dd, CH), 7.64 (1H, dt, CH), 7.58–7.48 (2H, m, 2 × CH), 7.31 (1H, brs, CH), 7.23 (1H, brd, CH), 6.84 (1H, d, CH), 6.2 (1H, s, CH), 3.75 (1H, s, OH), 2.37 (3H, s, CH_3). Anal. ($C_{16}H_{12}F_3NO_4$) C, H, N.

5-Methyl-2-(2-nitrophenyl)-3-(trifluoromethyl)benzofuran (30). A solution of **72** (5.73 g, 16.9 mmol) in Ac_2O (50 mL) and concentrated sulfuric acid (5 drops) was heated at reflux for 4.5 h. After cooling, the solution was concentrated *in vacuo*, diluted with EtOAc (100 mL), washed with 8% $NaHCO_3$ (2 × 100 mL), and dried. The solvent was removed *in vacuo* to give the title compound as a brown solid (5.69 g, quantitative): mp 90–2 °C; NMR ($CDCl_3$) δ 8.2 (1H, dd, CH), 7.81–7.63 (3H, m, 3 × CH), 7.54 (1H, brs, CH), 7.4 (1H, d, CH), 7.25 (1H, dd, CH), 2.5 (3H, s, CH_3). Anal. ($C_{16}H_{10}F_3NO_3$) C, H, N.

5-(Bromomethyl)-2-(2-nitrophenyl)-3-(trifluoromethyl)benzofuran (31): from **30** according to the method of **18** and used directly in the next reaction.

Ethyl 4-Cyclopropyl-2-ethyl-1-[[2-(2-nitrophenyl)-3-(2,2,2-trifluoromethyl)-5-benzofuranyl]methyl]-1*H*-imidazole-5-carboxylate (73). Sodium hydride (60% dispersion, 0.5 g 12.5 mmol) was added to a stirred slightly cloudy solution of **43** (2.4 g, 11.5 mmol) in DMF (100 mL). After the solution was stirred for 45 min under an atmosphere of N_2, a solution of **31** (4g, 70% assumed purity, 7 mmol) in DMF (50 mL) was added dropwise. The reaction mixture was stirred at room temperature for 12 h before being diluted with water (800 mL) and extracted with EtOAc (500 mL). The organic extract was washed with aqueous LiCl (3 × 200 mL), dried, and concentrated *in vacuo*. The residue was purified by column chromatography using CH_2Cl_2/MeOH (30:1) as eluant affording the title compound (1.6 g, 43%) as a brown foam: NMR ($CDCl_3$) δ 8.2 (1H, dd, CH), 7.8–7.6 (3H, m, 3 × CH), 7.5–7.4 (2H, brs, d, 2 × CH), 7.0 (1H, dd, CH), 5.63 (2H, s, CH_2), 4.29 (2H, q, CH_2), 2.7–2.58 (3H, q + m, CH_2 + CH), 1.31 (3H, t, CH_3), 1.22 (3H, t, CH_3), 1.1–0.9 (4H, m, 2 × CH_2).

Ethyl 1-[[2-(2-Aminophenyl)-3-(2,2,2-trifluoromethyl)-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxylate (32). A mixture of prereduced 10% palladium on carbon (1 g), water (30 mL), concentrated hydrochloric acid (30 mL), and a solution of **73** (1.4 g, 2.65 mmol) in THF (90 mL) was hydrogenated at atmospheric pressure and 20 °C for 2 h. The mixture was filtered through hyflo, and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL), washed with aqueous Na_2CO_3 (2 M, 500 mL), dried, and evaporated. The residue was

purified by chromatography using CH_2Cl_2/MeOH (75:1) to give the title compound as an off-white solid (1.03 g, 78%): mp 136–8 °C; NMR ($CDCl_3$) δ 7.48–7.42 (2H, brd, d, 2 × CH), 7.3–7.24 (2H, m, 2 × CH), 6.96 (1H, dd, CH), 6.88–6.76 (2H, dd + dt, 2 × CH), 5.62 (2H, s, CH_2), 4.28 (2H, q, CH_2), 4.13 (2H, brs, NH_2), 2.7–2.58 (3H, q + m, CH_2 + CH), 1.31 (3H, t, CH_3), 1.2 (3H, t, CH_3), 1.1–0.9 (4H, m, 2 × CH_2). Anal. ($C_{27}H_{26}F_3N_3O_3$) C, H, N.

2-(5-Methyl-2-benzofuranyl)benzoic acid (33): from **15** using the method of **16**. Anal. ($C_{16}H_{12}O_3$) C, H.

(±)-3-Chloro-5-methylspiro[benzofuran-2(3*H*),1′(3′*H*)-isobenzofuran]-3′-one (34). A solution of **33** (10 g, 40 mmol) in 1,4-dioxane (300 mL) and water (4 mL) was treated with NCS (7.67 g, 0.058 mol), and the mixture was heated at reflux for 1.5 h. The cooled reaction mixture was diluted with EtOAc (300 mL) and washed with brine (3 × 300 mL). The organic solution was concentrated *in vacuo*, and the residue was triturated with MeOH to give the title compound as a white solid (7.22 g, 63%): NMR ($CDCl_3$) δ 7.99–7.90 (2H, m, 2 × CH), 7.83–7.68 (2H, 2 × dt, 2 × CH), 7.32 (1H, brs, CH), 7.18 (1H, dd, CH), 6.91 (1H, d, CH), 5.48 (1H, s, CH), 2.4 (3H, s, CH_3).

2-(3-Chloro-5-methyl-2-benzofuranyl)benzoic Acid (35). A suspension of **34** (7.135 g, 24.9 mmol) in toluene (250 mL) was treated with DBU (4.58 g, 30 mmol) over 5 min. The suspension was heated at 45 °C for 45 min and then at reflux for 1 h. After cooling, the reaction mixture was diluted with toluene (300 mL) and washed with dilute HCl (250 mL) and brine (250 mL). The organic layer was dried and concentrated *in vacuo* to afford the title compound (6.78 g, 95%) as a yellow solid: NMR (DMSO-d_6) δ 13.0 (1H, vbrs, COOH), 7.96 (1H, brd, CH), 7.8–7.6 (3H, 2 × m, 3 × CH), 7.56 (1H, d, CH), 7.44 (1H, brs, CH), 7.28 (1H, dd, CH), 2.48 (3H, s, CH_3). Anal. ($C_{16}H_{11}ClO_3$) H; C: calcd, 67.03; found, 67.53.

1,1-**Dimethylethyl 2-(3-Bromo-5-methyl-2-benzofuranyl)benzoate (74).** A suspension of **16** (33.78 g, 0.102 mol) in dry toluene (200 mL) was heated to 80 °C and *N*,*N*-dimethylformamide di-*tert*-butyl acetal (83 g, 0.408 mol) was added dropwise over 20 min. The solution was heated for 1 h, cooled, and washed with water (200 mL), saturated $NaHCO_3$ (2 × 150 mL), and aqueous LiCl (10% w/v; 200 mL). The organic solution was dried and evaporated *in vacuo* to give the title compound as an off-white solid (37.18 g, 94%): mp 69–70 °C; NMR ($CDCl_3$) δ 7.93 (1H, dd, CH), 7.7 (1H, dd, CH), 7.63–7.48 (2H, 2 × dt, 2 × CH), 7.37–7.31 (2H, brs + d, 2 × CH), 7.17 (1H, dd, CH), 2.5 (3H, s, CH_3), 1.27 (9H, s, 3 × CH_3). Anal. ($C_{20}H_{19}BrO_3$) C, H, N.

1,1-**Dimethylethyl 2-[3-Bromo-5-(bromomethyl)-2-benzofuranyl]benzoate (36).** A mixture of **74** (8.8 g; 22.7 mmol) and NBS (4.04 g; 22.7 mmol) in dry CCl_4 (300 mL) was heated at reflux for 3 h while being illuminated with a 200 W lamp. The cooled reaction mixture was filtered and then washed with water (2 × 150 mL), dried, and evaporated to give the title compound as an oily residue (10.6 g, quantitative, 70% pure) which was used in the next step without purification.

Ethyl 1-[[3-Bromo-2-[2-[(1,1-dimethylethoxy)carbonyl]-phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxylate (37). A mixture of the impure **36** (6 g, 8.9 mmol), the imidazole **43** (1.6 g, 7.7 mmol), and anhydrous K_2CO_3 (1.5 g, 10.8 mmol) in dry DMF (50 mL) was stirred at ambient temperature for 40 h. The reaction mixture was diluted with EtOAc (200 mL), and the organic solution was washed with aqueous LiCl solution (10% w/v, 400 mL) and water (50 mL), dried, and evaporated *in vacuo*. The residue was purified by flash chromatography using CH_2Cl_2 changing to CH_2Cl_2/MeOH (9:1) as eluant to give the title compound as a yellow foam (1.37 g, 30%): NMR ($CDCl_3$) δ 7.93 (1H, dd, CH), 7.69 (1H, dd, CH), 7.65–7.5 (2H, 2 × dt, 2 × CH), 7.38 (1H, d, CH), 7.24 (1H, d, CH), 6.98 (1H, dd, CH), 5.63 (2H, s, CH_2), 4.28 (2H, q, CH_2), 2.64 (3H, q + m, CH_2 + CH), 1.32 (3H, t, CH_3), 1.25 (9H, s, 3 × CH_3), 1.18 (3H, t, CH_3), 1.1–0.9 (4H, m, 2 × CH_2). Anal. ($C_{31}H_{33}BrN_2O_5$) C, H, N.

1-[[3-Bromo-2-[2-[(1,1-dimethylethoxy)carbonyl]-phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxylic Acid (75). A mixture of **37** (0.3 g, 0.505 mmol) and aqueous NaOH (5 M, 1 mL) in MeOH (4 mL) was stirred at reflux for 3 h. The cooled reaction mixture was carefully acidified to pH 3 with HCl (2 M), and the product was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was dried and evaporated. The residue was purified by flash chromatography using CH_2Cl_2/MeOH (20:1) as eluant to give the title compound as a white solid (0.168 g, 59%): mp 118–121 °C; NMR ($CDCl_3$) δ 7.92 (1H, dd, CH), 7.68 (1H, dd, CH), 7.62–7.5 (2H, 2 × dt, 2 × CH), 7.36 (1H, d, CH), 7.25 (1H, d, CH), 6.97 (1H, dd, CH), 5.65 (2H, s, CH_2), 2.68–2.6 (3H, q + m, CH_2 + CH), 1.25 (9H, s, 3 × CH_3), 1.15 (3H, t, CH_3), 1.1–0.9 (4H, m, 2 × CH_2). Anal. ($C_{29}H_{29}BrN_2O_5$·0.5H_2O) C, H, N.

1,1-**Dimethylethyl 2-[3-Bromo-5-[[4-cyclopropyl-2-ethyl-5-[(ethylamino)carbonyl]-1*H*-imidazol-1-yl]methyl]-2-benzofuranyl]benzoate (76).** A mixture of **75** (0.3 g, 0.53 mmol) and CDI (0.12 g, 0.74 mmol) in dry CH_2Cl_2 (6 mL) was stirred at ambient temperature for 1 h. $EtNH_2$ (0.5 mL, 7.6 mmol) was added, and the mixture was stirred at ambient temperature for 20 h and heated at reflux for 4 h. The mixture was poured into water (50 mL) and the product extracted with EtOAc (2 × 50 mL). The organic extract was dried, filtered, and evaporated. The residue was purified by column chromatography using Et_2O/hexane (4:1) as eluant to give the title compound as a white solid (0.195 g, 62%): mp 132–3 °C; NMR ($CDCl_3$) δ 7.93 (1H, dd, CH), 7.68 (1H, dd, CH), 7.63–7.5 (2H, 2 × dt, 2 × CH), 7.37 (1H, d, CH), 7.25 (1H, d, CH), 7.08 (1H, dd, CH), 6.4 (1H, brt, NH), 5.67 (2H, s, CH_2), 3.46 (2H, m, CH_2), 2.64 (2H, q, CH_2), 2.0 (1H, m, CH), 1.26 (9H, s, 3 × CH_3), 1.18 (6H, 2 × t, 2 × CH_3), 1.08–0.96 (4H, m, 2 × CH_2). Anal. ($C_{31}H_{34}BrN_3O_4$) C, H, N.

2-[3-Bromo-5-[[4-cyclopropyl-2-ethyl-5-[(ethylamino)carbonyl]-1*H*-imidazol-1-yl]methyl]-2-benzofuranyl]benzoic Acid (38). A solution of **76** (0.175 g, 0.295 mmol) in dry TFA (4 mL) was stirred at ambient temperature for 1.5 h. The solvent was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL), water was added, and the pH of the aqueous solution was adjusted to 5 with aqueous Na_2CO_3 (2 M). The organic extract was dried and evaporated to give a solid residue which was crystallized from MeOAc/hexane to give the title compound as a white solid (0.12 g, 75%): mp 182–4 °C; NMR (DMSO-d_6) δ 13.0 (1H, brs, COOH), 8.15 (1H, brt, NH), 7.97 (1H, brd, CH), 7.77–7.63 (3H, m, 3 × CH), 7.62 (1H, d, CH), 7.32 (1H, d, CH), 7.17 (1H, dd, CH), 5.55 (2H, s, CH_2), 3.25 (2H, m, CH_2), 2.63 (2H, q, CH_2), 2.06 (1H, m, CH), 1.18–1.05 (6H, 2 × t, 2 × CH_3), 0.88–0.78 (4H, m, 2 × CH_2). Anal. ($C_{27}H_{26}BrN_3O_4$) C, H, N.

Ethyl 1-[[3-Bromo-2-[2-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxylate (40). A mixture of **43** (3 g, 14.4 mmol) and **39**[12] (16.71 g, 70% pure, ~24 mmol) and anhydrous K_2CO_3 (2.59 g, 18.7 mmol) in dry DMF (200 mL) was stirred at ambient temperature for 72 h. Water (400 mL) was added, and the product was extracted with EtOAc (3 × 300 mL). The combined extracts were washed with aqueous LiCl solution (3 × 300 mL, 10%), dried, and evaporated. The residue was purified by flash chromatography using Et_2O/hexane (1:2) as eluant to give the title compound as a white foam (6.21 g, 54%): NMR ($CDCl_3$) δ 8.2 (1H, dd, CH), 7.72–7.54 (3H, m, 3 × CH), 7.27 (3H, brt, 3 × CH), 7.13 (7H, brt + brs, 7 × CH), 6.92 (1H, d, CH), 6.82 (6H, brd, 6 × CH), 6.76 (1H, dd, CH), 5.6 (2H, s, CH_2), 4.22 (2H, q, CH_2), 2.7–2.53 (3H, m + q, CH + CH_2), 1.28 (3H, t, CH_3), 1.18 (3H, t, CH_3), 1.12–0.92 (4H, m, CH_2). Anal. ($C_{46}H_{39}BrN_6O_3$) C, H, N.

1-[[3-Bromo-2-[2-(1*H*-tetrazol-5-yl)phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxylic Acid (77). A mixture of the ester **40** (7.7 g, 9.6 mmol) and aqueous NaOH (2 M, 140 mL) in MeOH (50 mL) was heated at reflux for 7 h. The solvent was evaporated, and the aqueous residue was washed with Et_2O (2 × 100 mL). The aqueous solution was acidified (pH 3) with hydrochloric acid (2 M) and extracted with EtOAc (3 × 300 mL). The organic extract was dried and evaporated to give the title compound as a white solid (5.058 g, 98%): mp 188–191 °C; NMR ($CDCl_3$/MeOH-d_4) δ 7.94 (1H, dd, CH), 7.85 (1H, dd, CH), 7.75–7.63 (2H, m, 2 × CH), 7.3 (1H, d, CH), 7.19 (1H, brd, CH), 7.01 (1H, dd, CH), 5.69 (2H, s, CH_2), 2.8–2.62 (3H, m + q, CH +

CH_2), 1.18 (3H, t, CH_3), 1.03–0.96 (4H, m, 2 × CH_2). Anal. ($C_{25}H_{21}BrN_6O_3 \cdot 0.4H_2O$) C, H, N.

1-[[3-Bromo-2-[2-(1*H*-tetrazol-5-yl)phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2,*N*-diethyl-1*H*-imidazole-5-carboxamide (41). A suspension of **77** (198 mg, 0.37 mmol) and CDI (188 mg, 1.2 mmol) in dry CH_2Cl_2 was stirred at ambient temperature under an atmosphere of N_2 for 2 h. The solvent was removed *in vacuo* to give the imidazolide as a white foam. $EtNH_2$ (70% in aqueous solution, 1 mL) was added to a stirred solution of the imidazolide in THF (10 mL) and the mixture heated at reflux for 18 h. After cooling, water was added to the organic solution, and the aqueous layer was acidified (~pH 4) and separated. The aqueous layer was further extracted with EtOAc (20 mL). The combined organic phases were dried and the solvents removed *in vacuo*. The residue was purified by flash chromatography using CH_2Cl_2/MeOH/AcOH (900:30.6) as the eluant to give the title compound as a white solid (90 mg, 43%): mp 155–160 °C; NMR (DMSO-d_6) δ 8.10 (1H, t, NH), 8.0–7.94 (1H, m, CH), 7.88–7.80 (1H, m, CH), 7.8–7.7 (2H, m, 2 × CH), 7.5 (1H, d, CH), 7.28 (1H, brs, CH), 7.15 (1H, dd, CH), 5.5 (2H, s, CH_2), 3.25 (2H, m, CH_2), 2.62 (2H, q, CH_2), 2.05 (1H, m, CH), 1.18–1.0 (6H, 2 × t, 2 × C_3), 0.85–0.75 (4H, m, 2 × CH_2). Accurate mass found: 560.140806 (± 0.3 ppm).

1-[[2-[2-[[(Trifluoromethyl)sulfonyl]amino]phenyl]-5-benzofuranyl]methyl]-4-cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxamide (66). A mixture of Pd/C (10% w/w, 0.15 g), anhydrous K_2CO_3 (0.1 g, 0.75 mmol), and **3** (0.3 g, 0.49 mmol) in EtOAc (15 mL) was hydrogenated for 4 h. The mixture was filtered, and the filtrate was acidified with HCl to pH 4. The resulting precipitate was crystallized from a mixture of EtOAc/MeOH to give the title compound as a white solid (0.15 g, 57%): mp 230–1 °C; NMR (DMSO-d_6) δ 8.05 (2H, brs, CH + NH), 7.88–7.82 (2H, dd + s, 2 × CH), 7.59 (1H, d, CH), 7.49 (1H, d, CH), 7.39 (1H, s, CH), 7.18 (1H, dt, CH), 6.96 (1H, t, CH), 5.66 (2H, s, CH_2), 2.97 (2H, q, CH_2), 2.19 (1H, m, CH), 1.15 (3H, t, CH_3), 1.08 (2H, m, CH_2), 0.90 (2H, m, CH_2). Anal. ($C_{25}H_{23}F_3N_4O_4S$) C, H, N.

4-Chloro-2-ethyl-1*H*-imidazole-5-methanol (78). A solution of **44**[21] (19.66 g, 0.156 mol) in 2-methoxyethanol (175 mL) and 1,4-dioxane (175 mL) was stirred with NCS (21.23 g, 0.156 mol) in the dark at room temperature for 18 h. The solvent was removed *in vacuo* and the residue partitioned between water (200 mL), brine (200 mL), and EtOAc (300 mL). The organic extract was washed with water (50 mL) and brine (50 mL), dried, and concentrated *in vacuo* to a yellow solid. This was triturated twice with CH_2Cl_2 to give the title compound as a white solid (11.49 g, 46%): NMR (MeOH-d_4) δ 4.45 (2H, s, CH_2O), 2.62 (2H, q, CH_2), 1.2 (3H, t, CH_3).

4-Chloro-2-ethyl-1*H*-imidazole-5-carboxaldehyde (46). A solution of **78** (11.35 g, 70.6 mmol) in CH_2Cl_2 (240 mL) was treated with manganese dioxide (30.59 g, 0.35 mol), and the mixture was heated at reflux for 3.5 h. The warm mixture was filtered and the filtrate concentrated *in vacuo* to a yellow solid. Trituration with hexane followed by washing with Et_2O gave the title compound as a white solid (6.41 g, 57%): NMR ($CDCl_3$) δ 11.60 (1H, brs, NH), 9.68 (1H, s, CHO), 2.90 (2H, q, CH_2), 1.40 (3H, t, CH_3). Anal. ($C_6H_7ClN_2O$) C, H; N: calcd, 17.66; found, 17.12.

4-Chloro-2-propyl-1*H*-imidazole-5-carboxaldehyde (47) was prepared from **45**[21] using a similar method to **46**: NMR (DMSO-d_6) δ 12.20 (1H, brs, NH), 5.15 (1H, t, OH), 2.51 (2H, t, CH_2), 1.62 (2H, m, CH_2) 0.85 (3H, t, CH_3). Anal. ($C_7H_9ClN_2O$) C, H, N.

Ethyl α-Amino-β-oxocyclopropanepropanoate Hydrochloride (79). A solution of **42**[24] (23.5 g, 0.15 mol) in glacial acetic acid (28 mL) was treated with sodium nitrite (13.8 g, 0.2 mol) in water (33 mL) added dropwise over 1.5 h at ambient temperature. The mixture was stirred for 2 h, water (110 mL) was added, and stirring was continued for 2 h. The product was extracted with Et_2O (3 × 250 mL), and the ethereal solution was washed with water (100 mL), aqueous $NaHCO_3$ (100 mL), and brine (100 mL), dried, and evaporated to give a yellow oil (20 g, 72%) which was used directly in the next reaction. Acetyl chloride (15.35 mL, 0.215 mol) was added to a cooled solution of the above yellow oil (20 g, 0.108 mol) in absolute EtOH (250 mL) before being added to a suspension of 5% Pt/C (1.85 g) in absolute EtOH (150 mL). The stirred mixture was then hydrogenated at room temperature and pressure for 5 h. The catalyst was filtered off through a pad of hyflo and the filtrate concentrated *in vacuo* to give, after azeotroping with toluene (2 × 80 mL), an off-white solid. This was tritrated with Et_2O (500 mL) to give the title compound (14.5 g, 60%) as a white solid: mp 196–7 °C; NMR (DMSO-d_6) δ 9.0 (3H, brs, NH_3^+), 5.53 (1H, s, CH), 4.3 (2H, m, CH_2), 2.48 (1H, m, CH), 1.28 (3H, t, CH_3), 1.2–0.9 (4H, m, 2 × CH_2). Anal. ($C_8H_{13}NO_3 \cdot HCl$) C: calcd, 46.27; found, 45.34.

Ethyl 4-Cyclopropyl-2-ethyl-1*H*-imidazole-5-carboxylate (43). A solution of **79** (14.5 g, 0.07 mol) in EtOH (110 mL) was added dropwise over 1 h to a stirred suspension of ethyl propanimidate hydrochloride (25.1 g, 0.18 mol) and triethylamine (32 mL, 0.23 mol) in absolute EtOH (200 mL). After stirring overnight under an atmosphere of N_2, the gray suspension was concentrated *in vacuo* to afford a gray residue which was partitioned between EtOAc (250 mL), EtOH (50 mL), water (200 mL), and brine (100 mL). The aqueous phase was further extracted with EtOAc (2 × 100 mL), and the combined organic extracts were dried and concentrated *in vacuo* to afford a gray solid (31 g). Purification by chromatography eluting with hexane/Et_2O (1:3 increasing to 1:1) gave the title compound (3.5 g, 24%) as a white solid: mp 154–5 °C; NMR (MeOH-d_4) δ 4.32 (2H, q, CH_2), 2.7–2.52 (3H, q + m, CH_2 + CH), 1.36 (3H, t, CH_3), 1.23 (3H, t, CH_3), 1.0–0.85 (4H, 2 × m, 2 × CH_2). Anal. ($C_{11}H_{16}N_2O_2$) C, H, N.

Pharmacokinetic Studies. Rats and dogs were fasted overnight prior to dosing and received either a single oral or an intravenous dose (nominally 3 mg/kg). Rats were anesthetized (isoflurane, Abbot), and blood samples were taken at 30 min intervals up to 2.5 h and then at 2 h intervals up to 12 h and at 18 and 24 h postdose (~10 mL dorsal aorta/cardiac puncture). The blood was transfered to heparinized tubes and centrifuged (Hereaus Sepatech); the plasma was removed and stored at −20 °C prior to analysis. Blood samples were taken from dogs at 30 min intervals up to 2.5 h and then at 2 h intervals up to 12 h and at 18 and 24 h postdose, and plasma was obtained as described above.

Plasma samples were prepared for HPLC by either of the following methods. (a) Plasma samples (0.5 mL) were acidified with HCl (1 M, 0.1 mL) and diluted with aqueous TFA (0.055 v/v) to 1 mL. Samples were centrifuged (Heraeus Sepatech), and the supernatant fractions (0.5 mL) were applied onto 500 mg C18 Bond Elut cartridges (Jones Chromatography) preconditioned with MeOH (3 mL)/water (3 mL). The cartridges were washed with aqueous TFA (3 mL 0.05% v/v) and the compounds eluted with MeOH (3 mL). The MeOH eluant was evaporated (Savant Speedvac) and resuspended in HPLC, mobile phase (150–200 μL). (b) Plasma samples were diluted with glycine buffer (pH 2.5, 1.5 mL, 0.05 M) and applied to 100 mg C2 Bond Elut cartridges preconditioned with CH_3CN (1 mL)/water (1 mL). The cartridges were washed with water (1 mL) and glycine buffer/CH_3CN (8:2 v/v, 1 mL), and compounds were eluted with glycine buffer/CH_3CN (3:7 v/v, 400 μL). HPLC was performed using either (a) 5 μm ODS1 Spherisorb column (15 cm × 0.46 cm i.d.) eluting with aqueous TFA (0.05% v/v)/CH_3CN, mobile phase, at 1 mL/min or (b) 4 μm Nova-pak ODS column (10 cm × 0.5 cm i.d.) eluting with glycine buffer (pH 2.5)/CH_3CN, mobile phase, at 1 mL/min. The parameters were determined using Siphar. The oral bioavailability was determined by AUC po/AUC iv × 100.

Pharmacological Studies. The binding assay was performed and the antagonist activity in the rabbit isolated aorta was assessed following the method of Robertson et al.[13]

The antihypertensive activity was assessed using the renal artery-ligated hypertensive rat model of Cangiano et al.[15]

Samples were prepared for administration by dissolving ~3 mg in a mixture of EtOH (0.1 mL) and Na_2CO_3 (2 M, 0.1 mL) or EtOH (0.1 mL) and $NaHCO_3$ (8%, 0.1 mL) and then making up to the desired final concentration with saline.

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