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Design, Synthesis, and Biological Activity of Novel Factor Xa Inhibitors: 4-Aryloxy Substituents of 2,6-Diphenoxypyridines†

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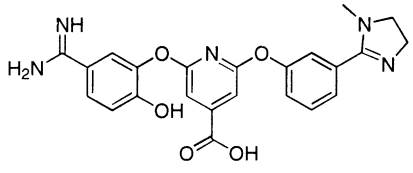
Abstract—A novel series of triaryloxypyridines have been designed to inhibit factor Xa, a serine protease strategically located in the coagulation cascade. Inhibitor **5e** has a K_I against factor Xa of 0.12 nM and is greater than 8000- and 2000-fold selective over two related serine proteases, thrombin and trypsin, respectively. The 4-position of the central pyridine has been identified as a site that tolerates various substitutions without deleterious effects on potency and selectivity. This suggests that the 4-position of the pyridine ring is an ideal site for chemical modifications to identify inhibitors with improved pharmacokinetic characteristics. This investigation has resulted in inhibitor **5d**, which has an oral availability of 6% in dogs. The synthesis, in vitro activity, and in vivo profile of this class of inhibitors is outlined.

Introduction

There remains an unmet clinical need for orally active antithrombotics. To this end, we have been involved in the search for novel inhibitors of factor Xa (fXa), a trypsin-like serine protease in the coagulation cascade.[2] FXa occupies the strategic juncture of the two arms of the coagulation cascade, the intrinsic (surface activated) and extrinsic (vessel injury-tissue factor) pathways.[3] Potential clinical indications for an antithrombotic such as a fXa inhibitor include myocardial infarction, deep vein thrombosis following orthopedic surgery, complications following transient ischemic attack, and unstable angina. Since many of these conditions require long term administration, an orally available inhibitor would be preferred. A number of small molecule fXa inhibitors have been disclosed,[4] but clinical results have not been published.



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In an earlier report, we described the discovery and characterization of a series of pyridine based fXa inhibitors exemplified by **1**.[5] Compound **1** is a potent inhibitor of fXa with selectivity over both thrombin and trypsin, but suffers from pharmacokinetic liabilities. While we had extensively explored substitution on either of the phenyl moieties, alternate substitution of the pyridine had not been investigated for the more advanced inhibitors. In previous studies, we observed that amidine-containing 2,6-diphenoxypyridines with a C4 carboxylic acid moiety had improved although still low oral availability compared to related inhibitors. For this reason we concentrated our efforts on inhibitors with an acidic moiety. The 4-position of the pyridine is the focus of this study, due in part to the synthesis and the resulting redundancy of the 2- and 6-positions and

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the lack of regioisomeric mixtures. Herein, we describe a novel series of inhibitors with carboxy-substituted aryloxy groups in the 4-position of the pyridine, which potently and selectively inhibit fXa as well as demonstrate good in vivo duration of action in rats.

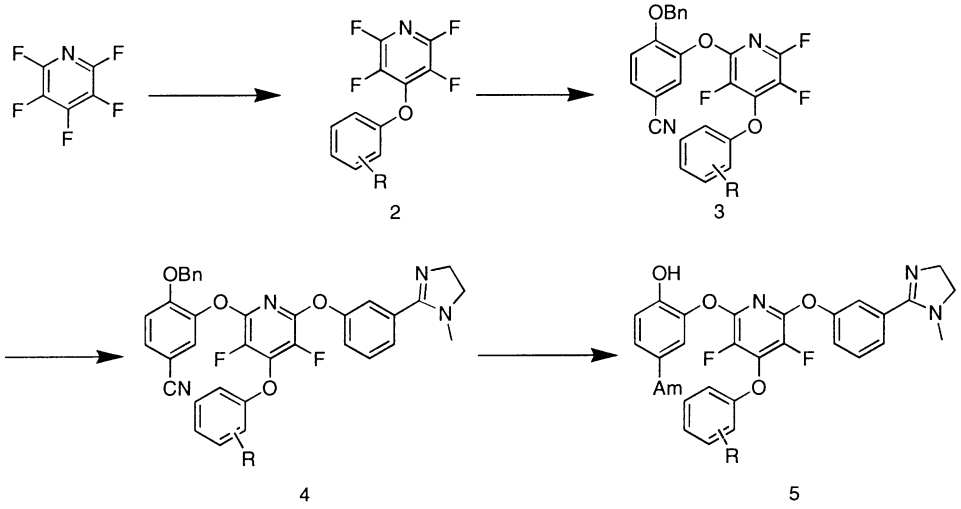
Chemistry

The inhibitors were prepared by sequential addition of the appropriately substituted phenols to pentafluoropyridine (Scheme 1).[6] Addition of the first phenol occurs regioselectively at the C-4 position, allowing the order of the next two additions to be determined by the more valuable starting material. Additions were typically high yield and multiple additions could often be accomplished in a single reaction vessel. Standard conditions were used for converting the nitrile to the amidine. Hydrolyses of acids were accomplished by heating esters in acidic solutions. Except for the unsubstituted guanidine-containing rings, all compounds were prepared by the sequential addition of the fully substituted aromatic moiety. Guanidine-containing inhibitors were prepared by reacting aniline intermediate **6** at the nitrile stage with cyanamide (Scheme 2).

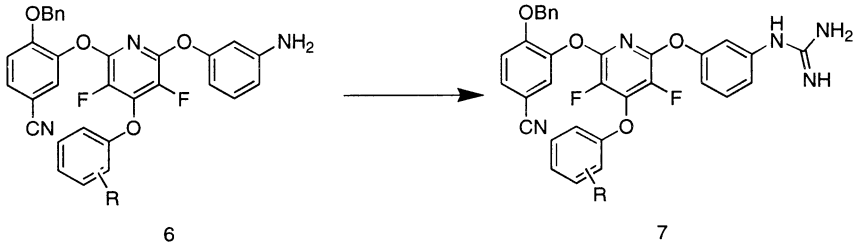
Results and Discussion

The screening tree to determine the best inhibitors began with the potency determination against human fXa. Subsequent screening against human thrombin (fIIa) for selectivity within the coagulation cascade and bovine trypsin for general specificity against serine proteases was carried out for the more potent inhibitors (fXa K_i < 1 μM). The activities of the three serine proteases were determined as the initial rate of the cleavage of peptide p-nitroanilide by the enzyme. All substrate concentrations used are equal to their K_m values under the present assay conditions. A modification of the Morrison equation was used for inhibitors with K_i less than 3 nM to correct for the proportion of inhibitor bound to the enzyme relative to the free inhibitor.[7]

Studies were initiated by examining substituted benzoic acid derivatives and the intermediate esters that were isolated (Table 1). The carboxylic acids were approximately 10-fold more potent than the corresponding ethyl ester (e.g., **5a** vs **5b**). Additionally there was a tendency for the methyl ester to be more potent than the corresponding ethyl ester (**5f/5g** and **5ff/5gg**). There was no significant difference when varying the regiochemistry of the carboxylic acid moiety (**5b** and **5t**), but the carboxylic acid moiety was important for activity (**5kk** vs **5d** or **5v**, **5nn** vs **5j**). On the other hand, substitution of the benzoic acid moiety did not significantly affect potency (**5d**, **5e**, **5h**, **5j**, and **5k** vs **5b**, and **5v**, **5x**, **5z**, and **5aa** vs **5t**) with the exception of **5dd**, which was less potent than the unsubstituted inhibitor **5t**. Extending the length of the acid chain also had little effect on activity (**5n** and **5ii**), but when the chain was unsaturated, some decreases in potency were noted (**5p**, **5q**, and **5hh**). Replacement of an acid with an amide gave an inhibitor intermediate in potency to the acid and ethyl

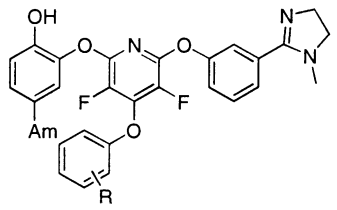


Scheme 1.



Scheme 2.

Table 1. Activity of compounds **5** against human FXa, human thrombin and bovine trypsin



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Compd	R	K_i (nM)		
		FXa	fIIa	trypsin
a	4-$CO_2CH_2CH_3$	1.6	440	510
b	4-CO_2H	0.19	790	340
c	2-OCH_3-4-$CO_2CH_2CH_3$	1.4	340	460
d	2-OCH_3-4-CO_2H	0.33	600	310
e	2-OH-4-CO_2H	0.12	990	280
f	2,6-OCH_3-4-CO_2CH_3	0.89	350	280
g	2,6-OCH_3-4-$CO_2CH_2CH_3$	1.6	460	370
h	2,6-OCH_3-4-CO_2H	0.18	650	180
i	2-Cl-4-$CO_2CH_2CH_3$	5.8	380	760
j	2-Cl-4-CO_2H	0.30	570	310
k	2,6-CH_3-4-CO_2H	0.25	1200	270
l	2,6-CH_3-4-$CO_2CH_2CH_3$	6.3	1000	960
m	2-OCH_3-4-$CH_2CO_2CH_2CH_3$	0.56	530	290
n	2-OCH_3-4-CH_2CO_2H	0.14	570	250
o	2,6-OCH_3-4-CH=$CHCO_2CH_2CH_3$	3.5	510	480
p	2,6-OCH_3-4-CH=$CHCO_2H$	0.59	720	230
q	4-CH=$CHCO_2H$	0.15	300	210
r	4-CH=$CHCO_2CH_3$	1.1	340	430
s	3-$CO_2CH_2CH_3$	1.2	480	380
t	3-CO_2H	0.11	590	240
u	2-OCH_3-5-$CO_2CH_2CH_3$	0.56	300	310
v	2-OCH_3-5-CO_2H	0.18	340	200
w	2,3-OCH_3-5-$CO_2CH_2CH_3$	1.0	240	300
x	2,3-OCH_3-5-CO_2H	0.21	250	220
y	3-$CONH_2$-5-$CO_2CH_2CH_3$	0.52	140	260
z	3-$CONH_2$-5-CO_2H	0.22	230	180
aa	3,5-CO_2H	0.13	660	180
bb	3-CO_2H-5-$CO_2CH_2CH_3$	0.42	260	220
cc	3-$CH_2CH_2CO_2CH_2CH_3$	1.1	530	340
dd	2-$OCH_2CH_2N(CH_3)_2$-5-CO_2H	0.68	130	290
ee	3-$CHCHCONH_2$	0.93	370	390
ff	3-$CHCHCO_2CH_3$	1.4	580	520
gg	3-$CHCHCO_2CH_2CH_3$	2.3	520	400
hh	3-$CHCHCO_2H$	0.32	470	250
ii	3-$CH_2CH_2CO_2H$	0.19	620	290
jj	2-OCH_3-5-(1*H*-tetrazol-5-yl)	0.37	320	240
kk	2-OCH_3	0.56	550	320
ll	2-OCH_3-5-$NHSO_2CF_3$	0.36	410	140
mm	3-(1-Methyl-1*H*-imdazolin-2-yl)	0.94	140	180
nn	2-Cl	0.98	680	380
oo	2-Cl-4-$CONHSO_2Ph$	0.69	590	560
pp	2-Cl-4-$CONHSO_2CH_3$	0.24	300	350

ester (**5ee** vs **5hh** and **5gg**) in one case, and equipotent to the acid in two others (**5z** vs **5aa** and **5y** vs **5bb**). Inhibitors with acidic groups that are not carboxylic acids such as tetrazole, trifluoromethansulfonylamide, and phenylsulfonylamide (**5jj**, **5ll**, and **5oo**) were less potent than their carboxylic acid counterparts, but the methanesulfonylamide **5pp** was equipotent.

Molecular modeling studies indicate that the substitutents off of the 4-position of the pyridine are outside of the enzyme pocket and extended into the solvent. A possible explanation for the fact that the acids are more potent than the esters, even though there does not seem to be direct binding of this moiety with the enzyme, is that the acids are better able to solvate in the aqueous environment surrounding the enzyme, resulting in a non-specific potency increase over the corresponding esters. This is supported by a comparison of the inhibitors with the non-carboxylate acidic substituents, **5oo** and **5pp**, with the more lipophilic **5oo** being less potent.

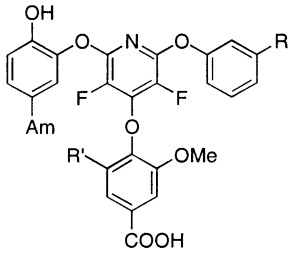
Substitution had little effect on the activity against fIIa or trypsin. Except for seven inhibitors (**5b**, **5e**, **5k**, **5l**, **5p**, **5dd**, and **5mm**) the activity against fIIa was within 180–700 nM. The data for trypsin was even less variable in that only three inhibitors fell outside of the range of 180–600 nM (**5i**, **5l**, and **5ll**). It is not surprising that these substitutents have little effect on the activity in other serine proteases since the groups are outside of the binding pocket.

Substitutions were made on the phenyl at the 6-position of the pyridine (distal position) and were found to be consistent with our earlier findings (Table 2).[8] Structural findings from crystal structures of related compounds bound to fXa indicate that this portion of the molecule is in the S4 pocket.[9] Typically, highly basic substituents are preferred in this pocket and consistent with this, the compounds with the basic 1-methyl-2-imidazoline were found to be the most potent inhibitors (**5d** and **5h**). Additionally, the inhibitors containing less basic groups (**8b**, **8d**, and **8f**) were less active and the acid **8g** was much less active. Contrary to the norm, the non-basic dimethylamide **8c** was comparable to **5d**. A series of guanidines (**8h–k**) was prepared to investigate the effects of these highly basic groups. All three substituted guanidines (**8i–k**) were significantly less potent than the unsubstituted **8h**. As opposed to the cyclic amidine series where a significant difference was noted between the unsubstituted and methyl substituted imidazoline, the two inhibitors were equipotent in the cyclic guanidine series (**8j** vs **8k**).

Substitution at the distal position had profound effects on fIIa selectivity. All of the guanidine containing inhibitors had K_i's > 4 μM against fIIa and the acid was essentially inactive against both fIIa and trypsin. The guanidine **8e** is the most selective inhibitor from this series reported to date. The imidazole **8f** and aniline **8b** were more potent against fIIa. Trypsin activity was less affected by changes in substitution at this position.

Selected inhibitors were further evaluated for their half-life and plasma levels after intravenous and oral dosing in rats (Table 3). Rats were dosed via oral gavage at 10 mg/kg or iv at 1 mg/kg with homogeneous solutions. Inhibitor plasma concentrations were determined at various time points by comparing the fXa inhibitory activity of a plasma sample with the activity of a plasma sample with exogenously added inhibitor.[10] In general, inhibitors tended to have a short duration when dosed iv with $t_{1/2}$ less than 1 h. In rats dosed intravenously, plasma concentrations tend to be higher with an increasing number of methoxy groups (**5x** vs **5v** vs

Table 2. Activity of compounds **8** against human FXa, human thrombin and bovine trypsin



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Compd	R	R′	K_i (nM)		
			FXa	fIIa	Trypsin
5d	1-Methyl-1*H*-imidazolin-2-yl	H	0.23	460	240
8a	$C(NH)NH_2$	H	0.47	1900	520
8b	$N(CH_3)_2$	H	1.2	140	570
8c	$CON(CH_3)_2$	H	0.66	790	870
8d	$CH_2N(CH_3)_2$	H	3.6	2600	580
8e	$NHC(NH)NH_2$	H	0.13	4200	560
8f	1-methyl-1*H*-imidazol-2-yl	H	3.2	50	880
8g	COOH	H	27	>5000	>5000
5h	1-methyl-1*H*-imidazolin-2-yl	OCH_3	0.18	650	180
8h	$NHC(NH)NH_2$	OCH_3	0.17	4100	550
8i	(pyrrolidin-1-yl)(imino)methylamino	OCH_3	35	4300	1200
8j	(1*H*-imidazolin-2-yl)amino	OCH_3	6.8	4000	650
8k	(1-methyl-1*H*-imidazolin-2-yl)amino	OCH_3	6.6	3800	1200

Table 3. Inhibitor plasma concentrations after iv or po dosing in rats[a]

Compd	iv		po		
	30 min	60 min	30 min	60 min	90 min
5b	2.4	1.0	0.01	nd	nd
5d	8.4	4.7	<0.9	2.2	2.4
5e	1.5	1.0			
5h	11	7.7	0.03	>0.06	0.04
5j	1.7	1.4			
5n	1.1	0.5	0.3	0.8	0.2
5p	12	9.4			
5t	2.1	0.9	0.05	<0.02	<0.02
5v	9.1	6.4	0.06	0.04	0.08
5x	13	11	0.04	0.05	0.1
8a	7.9	5.0			
8b	0.8	0.3			
8d	1.3	0.4			
8e	12	7.5			

[a]Reported values are the plasma levels in μM.

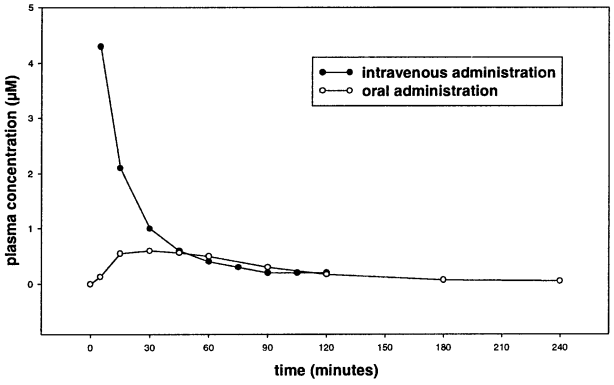

Figure 1. Plasma concentrations of **5d** after oral and iv administration.

5t and **5d** vs **5b**). Although structurally similar to other compounds tested, when dosed orally, only **5d** showed significant plasma concentrations.

The pharmacokinetic parameters of inhibitor **5d** looked promising in the rat and it was further evaluated in dogs (Fig. 1). Conscious beagles were dosed via oral gavage at 10 mg/kg or intravenously at 1 mg/kg with homogeneous aqueous solutions of **5d**. Inhibitor concentrations were determined at various time points with the same methods as those determined in the rat. The half-life after oral dosing was >1.5 h and the maximum plasma concentration was 0.6 μM. As was typically seen with these inhibitors, after intravenous administration the maximum plasma concentrations are much higher. The calculated oral availability of **5d** is 6% in dogs and was not considered adequate for further development of this inhibitor or series.

Conclusion

A novel series of potent inhibitors of human fXa have been designed and prepared with subnanomolar potencies and greater than 30,000-fold selectivity over

human fIIa and greater than 2000-fold selectivity over bovine trypsin, two related serine proteases. Substitution of the distal phenyl ring with guanidine containing substituents significantly improved fIIa selectivity. Although the inhibitors demonstrated poor oral availability, the four position of the pyridine has been identified as a site for substitution that does not negatively affect either the fXa potency or selectivity. A future publication will further explore the 4-position of the pyridine and the effect of those substitutents on potency, selectivity, and oral availability.

Experimental

All starting materials not described below were purchased from commercial sources. All reagents and solvents were used as received from commercial sources without additional purification. Elemental analyses were performed by Robertson Microlit Laboratories; Madison, NJ and results were within ±0.4% of the calculated values. NMR spectra were recorded with a Varian XL-300 spectrometer and were consistent with the assigned structures. HPLC were performed with a Rainin SD-1 Dynamax system and a C-18 reverse-phase Dynamax 60A column using a gradient of acetonitrile (0.1% TFA) in water (0.1% TFA).

Human fXa and human fIIa were from Enzyme Research Lab., South Bend, IN, USA and bovine trypsin was from Boehringer Mannheim Corp., Indianapolis, IN, USA. All peptide-*p*-nitroanilide substrates were purchased from Pharmacia Hepar Inc., Franklin, OH, USA. Tris–HCl, NaCl and $CaCl_2$ were from J. T. Baker Inc., Jackson, TN, USA and polyethylene glycol 6000 was from BDH Laboratory Supplies, Poole, UK.

4-(2,3,5,6-Tetrafluoropyridin-4-yl)-3-methoxybenzoic acid, ethyl ester (2, R = 2-OCH_3, 4-$COOCH_2CH_3$). Pentafluoropyridine (0.75 mL, 6.8 mmol) was added to an ice cooled solution of 2-methoxy-4-hydroxybenzoic acid (1.34 g, 6.8 mmol), and cesium carbonate (2.9 g, 8.8 mmol) in acetonitrile (60 mL). The solution was warmed to ambient temperature. After stirring for 12 h the mixture was partitioned with water and EtOAc. The organic layer was separated, dried ($MgSO_4$), and the solvent was removed in vacuo to give 2.38 g (100%) of an orange solid that was used without further purification. NMR ($CDCl_3$) δ 7.7 (d, 1H), 7.7 (s, 1H), 7.2 (d, 1H), 4.4 (q, 2H), 3.9 (s, 3H), 1.4 (t, 3H).

4-[2-[5-Cyano-2-(phenylmethoxy)phenoxy]-3,5,6-trifluoropyridin-4-yl]-3-methoxybenzoic acid, ethyl ester (3, R = 2-OCH_3, 4-$COOCH_2CH_3$). 4-(2,3,5,6-Tetrafluoropyridin-4-yl)-3-methoxybenzoic acid, ethyl ester (2.35 g, 6.8 mmol) was dissolved in CH_3CN (60 mL) and 3-hydroxy-4-(phenylmethoxy)benzonitrile (1.53 g, 6.8 mmol) and cesium carbonate (2.9 g, 8.8 mmol) were added. After stirring for 15 h starting material remained. After heating at 35 °C for 5 h, the mixture was partitioned with EtOAc and 1 N KOH. The organic layer was separated, dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by chromatography on silica with hexane/CH_2Cl_2 (1/4) gave 3.21 g (86%) of a white amorphous solid. NMR ($CDCl_3$) δ 7.66 (d, 1H), 7.63 (dd, 1H), 7.54 (dd, 1H), 7.49 (d, 1H), 7.34 (m, 3H), 7.2 (m, 2H), 7.08 (d, 1H), 6.92 (d, 1H), 5.1 (s, 2H), 4.4 (q, 2H), 3.85 (s, 3H), 1.4 (t, 3H).

4-[2-[5-Cyano-2-(phenylmethoxy)phenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]-3-methoxybenzoic acid, ethyl ester (4, R = 2-OCH_3, 4-$COOCH_2CH_3$). 4-[2-[5-Cyano-2-(phenylmethoxy)phenoxy]-3,5,6-trifluoropyridin-4-yl]-3-methoxybenzoic acid, ethyl ester (1.0 g, 1.8 mmol) was dissolved in DMSO (20 mL) and 4,5-dihydro-3-(hydroxyphenyl)-1-methylimidazole (0.47 g, 1.8 mmol) and cesium carbonate (1.5 g, 4.5 mmol) were added. After stirring for 15 h, starting material remained. After heating at 35 °C for 2 h, the mixture was partitioned with EtOAc and 0.1 N aq KOH. The organic layer was separated, washed with 0.5 N aq KOH and brine, dried ($MgSO_4$), and the solvent was removed in vacuo to give 1.18 g (84%) of a white amorphous solid that was used without further purification. NMR ($CDCl_3$) δ 7.7 (s, 1H), 7.65 (d, 1H), 7.1–7.4 (m, 10H), 6.9 (m, 3H), 5.0 (s, 2H), 4.4 (q, 2H), 3.9 (s, 3H), 3.9 (m, 2H), 3.45 (t, 2H), 2.7 (s, 3H), 1.4 (t, 3H).

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-3-methoxybenzoic acid, ethyl ester, trifluoroacetic acid salt (5c). 4-[2-[5-Cyano-2-(phenylmethoxy)phenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]-3-methoxybenzoic acid, ethyl ester (1.1 g, 1.4 mmol) was dissolved in absolute EtOH (6 mL) and cooled in a dry ice/acetone bath. HCl (g) was bubbled into the solution to saturate and the reaction was sealed. After stirring for 15 h at ambient temperature, the solvent was removed in vacuo to give 1.55 g of a white foam. The material was dissolved in EtOH (6 mL) and cooled in a dry ice/acetone bath. Ammonia was condensed in the tube and the tube was sealed. After heating at 75 °C for 1.5 h, the solvent was removed in vacuo. The residue was redissolved in EtOH (20 mL) and Pd/C (10%, 250 mg) was added. After shaking under 55 psi of H_2 for 3 h, the solid was removed by filtration and the solvent removed in vacuo. A portion of the residue was purified by HPLC using a Dynamax column and a gradient of CH_3CN in H_2O with 0.1% TFA. The resulting fractions were combined and the solvent was removed by lyophylization to give 530 mg of **5c**. NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.1 (s, 2H), 9.05 (s, 2H), 7.6 (m, 5H), 7.4 (m, 4H), 7.0 (d, 1H), 4.35 (q, 2H), 4.1 (m, 2H), 3.95 (s, 3H), 3.95 (m, 2H), 3.0 (s, 3H), 1.35 (t, 3H). Anal. ($C_{32}H_{29}F_2N_5O_7$·2.4 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-3-methoxybenzoic acid, trifluoroacetic acid salt (5d). A portion of the residue prior to purification from the procedure for **5c** was dissolved in 6 N aq HCl (30 mL). After heating at 85 °C for 4 h, the solvent

was removed in vacuo. The residue was purified by HPLC using a Dynamax column and a gradient of CH_3CN in H_2O with 0.1% TFA. The resulting fractions were combined and the solvent was removed by lyophylization to give 170 mg of 5c as a white solid. NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.1 (s, 2H), 9.0 (s, 2H), 7.6 (m, 5H), 7.4 (m, 4H), 7.05 (d, 1H), 4.1 (m, 2H), 3.95 (s, 3H), 3.95 (m, 2H), 3.0 (s, 3H). Anal. ($C_{30}H_{25}F_2N_5O_7$·2.5 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzoic acid, ethyl ester, trifluoroacetic acid salt (5a). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.1 (s, 2H), 9.0 (s, 2H), 8.1 (d, 1H), 7.7 (s, 1H), 7.6 (m, 1H), 7.5 (m,1H), 7.4 (m, 5H), 7.05 (d, 1H), 4.35 (q, 2H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H), 1.35 (t, 3H). Anal. ($C_{31}H_{27}F_2N_5O_6$·2.4 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzoic acid, trifluoroacetic acid salt (5b). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.04 (s, 2H), 8.84 (s, 2H), 8.04 (d, 1H), 7.66 (s, 1H), 7.58 (m, 1H), 7.5 (m, 2H), 7.4 (m, 2H), 7.32 (d, 2H), 7.03 (d, 1H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H). Anal. ($C_{29}H_{23}F_2N_5O_6$·2.5 TFA·H_2O) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-3-hydroxybenzoic acid, trifluoroacetic acid salt (5e). NMR (DMSO-d_6) δ 11.15 (s, 1H), 10.5 (s, 3H), 10.25 (s, 1H), 9.1 (s, 2H), 8.9 (s, 2H), 7.6 (m, 3H), 7.4 (m, 4H), 7.3 (m, 1H), 7.05 (d, 1H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H). Anal. ($C_{29}H_{23}F_2N_5O_7$·2.5 TFA·H_2O) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-3,5-dimethoxybenzoic acid, methyl ester, trifluoroacetic acid salt (5f). NMR (DMSO-d_6) δ 11.2 (s, 1H), 10.3 (s, 1H), 9.04 (s, 2H), 8.96 (s, 2H), 7.64 (m, 1H), 7.5 (m, 2H), 7.4 (m, 5H), 7.04 (d, 1H), 4.1 (m, 2H), 3.95 (m, 2H), 3.9 (s, 9H), 3.0 (s, 3H). Anal. ($C_{32}H_{29}F_2N_5O_8$·2.5 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-3,5-dimethoxybenzoic acid, ethyl ester, trifluoroacetic acid salt (5g). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.05 (s, 2H), 9.0 (s, 2H), 7.6 (m, 3H), 7.4 (m, 5H), 7.05 (d, 1H), 4.35 (q, 2H), 4.1 (m, 2H), 3.95 (m, 2H), 3.9 (s, 6H), 3.0 (s, 3H), 1.35 (t, 3H). Anal. ($C_{33}H_{31}F_2N_5O_8$·2.8 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-3,5-dimethoxybenzoic acid, trifluoroacetic acid salt (5h). NMR (DMSO-d_6) δ 10.25 (s, 1H), 9.01 (s, 2H), 8.84 (s, 2H), 7.62 (d, 1H), 7.57 (d, 1H), 7.50 (t, 1H), 7.36 (m, 5H), 7.02 (d, 1H), 4.05 (m, 2H), 3.95 (m, 2H), 3.9 (s, 6H), 3.0 (s, 3H). Anal. ($C_{31}H_{27}F_2N_5O_8$·2.5 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-3-chlorobenzoic acid, ethyl ester, trifluoroacetic acid salt (5i). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.1 (s, 2H), 8.95 (s, 2H), 8.2 (s, 1H), 8.0 (d, 1H), 7.4–7.7 (m, 7H), 7.05 (d, 1H), 4.35 (q, 2H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H), 1.35 (t, 3H). Anal. ($C_{31}H_{26}F_2N_5O_6$·2.5 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-3-chlorobenzoic acid, trifluoroacetic acid salt (5j). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.1 (s, 2H), 8.95 (s, 2H), 8.2 (s, 1H), 7.95 (d, 1H), 7.4–7.7 (m, 7H), 7.05 (d, 1H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H). Anal. ($C_{29}H_2F_2N_5O_6$·2.5 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-3,5-dimethylbenzoic acid, trifluoroacetic acid salt (5k). NMR (DMSO-d_6) δ 11.2 (s, 1H), 10.3 (s, 1H), 9.05 (s, 2H), 8.95 (s, 2H), 7.8 (s, 2H), 7.65 (s, 1H), 7.5 (m, 2H), 7.4 (m, 3H), 7.05 (d, 1H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H), 2.3 (s, 6H). Anal. ($C_{31}H_{27}F_2N_5O_6$·2.7 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-3,5-dimethylbenzoic acid, ethyl ester, trifluoroacetic acid salt (5l). NMR (DMSO-d_6) δ 11.2 (s, 1H), 10.3 (s, 1H), 9.04 (s, 2H), 8.94 (s, 2H), 7.82 (s, 2H), 7.65 (d, 1H), 7.58 (dd, 1H), 7.52 (dd, 1H), 7.4 (m, 3H), 7.02 (d, 1H), 4.35 (q, 2H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H), 2.3 (s, 6H), 1.35 (t, 3H). Anal. ($C_{33}H_{31}F_2N_5O_6$·2.7 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-3-methoxybenzeneacetic acid, ethyl ester, trifluoroacetic acid salt (5m). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.1 (s, 2H), 8.95 (s, 2H), 7.65 (s, 1H), 7.6 (m, 2H), 7.4 (m, 3H), 7.2 (d, 1H), 7.15 (s, 1H), 7.0 (d, 1H), 6.9 (d, 1H), 4.15 (q, 2H), 4.1 (m, 2H), 3.95 (m, 2H), 3.85 (s, 3H), 3.7 (s, 2H), 3.0 (s, 3H), 1.25 (t, 3H). Anal. ($C_{33}H_{31}F_2N_5O_6$·2.4 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-3-methoxybenzeneacetic acid, trifluoroacetic acid salt (5n). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.05 (s, 4H), 7.65 (s, 1H), 7.6 (m, 2H), 7.4 (m, 3H), 7.2 (d, 1H), 7.15 (s, 1H), 7.05 (d, 1H), 6.9 (d, 1H), 4.1 (m, 2H), 3.95 (m, 2H), 3.8 (s, 3H), 3.6 (s, 2H), 3.0 (s, 3H). Anal. ($C_{31}H_{27}F_2N_5O_7$·2.4 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-3,5-dimethoxybenzene-3-propenoic acid, ethyl ester, trifluoroacetic acid salt (5o). NMR (DMSO-d_6) δ 11.1 (br, 1H), 10.25 (s, 1H), 9.0 (s, 2H), 8.9 (s, 2H), 7.6 (m, 3H), 7.5 (m, 1H), 7.35 (m, 3H), 7.25 (s, 2H), 7.0 (d, 1H), 6.75 (d, 1H), 4.2 (q, 2H), 4.05 (m, 2H), 3.9 (m,

2H), 3.8 (s, 6H), 2.95 (s, 3H), 1.25 (t, 3H). Anal. ($C_{35}H_{33}F_2N_5O_8$·2.7 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]-3,5-dimethoxybenzene-3-propenoic acid, trifluoroacetic acid salt (5p). NMR (DMSO-d_6) δ 11.2 (br, 1H), 10.25 (s, 1H), 9.05 (s, 2H), 8.95 (s, 2H), 7.6 (m, 3H), 7.5 (m, 1H), 7.35 (m, 3H), 7.2 (s, 2H), 7.0 (d, 1H), 6.65 (d, 1H), 4.05 (m, 2H), 3.9 (m, 2H), 3.8 (s, 6H), 2.95 (s, 3H). Anal. ($C_{33}H_{29}F_2N_5O_8$·2.5 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]benzene-3-propenoic acid, trifluoroacetic acid salt (5q). NMR (DMSO-d_6/TFA) δ 10.25 (s, 1H), 9.05 (s, 2H), 8.95 (s, 2H), 7.75 (d, 2H), 7.4–7.6 (m, 7H), 7.25 (d, 2H), 7.0 (d, 1H), 6.5 (d, 1H), 4.05 (m, 2H), 3.9 (m, 2H), 2.95 (s, 3H). Anal. ($C_{31}H_{25}F_2N_5O_6$·2.5 TFA.0.5 H_2O) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridin-4-yl]benzene-3-propenoic acid, methyl ester, trifluoroacetic acid salt (5r). NMR (DMSO-d_6/TFA) δ 10.25 (s, 1H), 9.05 (s, 2H), 8.95 (s, 2H), 7.75 (d, 2H), 7.4–7.6 (m, 7H), 7.25 (d, 2H), 7.0 (d, 1H), 6.5 (d, 1H), 4.05 (m, 2H), 3.9 (m, 2H), 3.7 (s, 3H), 2.95 (s, 3H). Anal. ($C_{32}H_{27}F_2N_5O_6$·2.5 TFA) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzoic acid, ethyl ester, trifluoroacetic acid salt (5s). NMR (DMSO-d_6) δ 11.3 (br, 1H), 10.3 (s, 1H), 9.1 (s, 4H), 7.85 (s, 1H), 7.75 (d, 1H), 7.4–7.7 (m, 8H), 7.05 (d, 1H), 4.35 (q, 2H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H), 1.35 (t, 3H). Anal. ($C_{31}H_{27}F_2N_5O_6$·2.4 TFA) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzoic acid, trifluoroacetic acid salt (5t). NMR (DMSO-d_6) δ 11.2 (s, 1H), 10.3 (s, 1H), 9.05 (s, 2H), 9.0 (s, 2H), 7.85 (d, 1H), 7.4–7.7 (m, 9H), 7.05 (d, 1H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H). Anal. ($C_{29}H_{23}F_2N_5O_6$·2.7 TFA) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-4-methoxybenzoic acid, ethyl ester, trifluoroacetic acid salt (5u). NMR (DMSO-d_6) δ 11.2 (s, 1H), 10.3 (s, 1H), 9.05 (s, 2H), 8.95 (s, 2H), 7.9 (dd, 1H), 7.78 (d, 1H), 7.66 (dd, 1H), 7.59 (dd, 1H), 7.5 (m, 1H), 7.4 (m, 3H), 7.04 (d, 1H), 4.35 (q, 2H), 4.1 (m, 2H), 3.95 (s, 3H), 3.95 (m, 2H), 3.0 (s, 3H), 1.35 (t, 3H). Anal. ($C_{32}H_{29}F_2N_5O_7$·2.4 TFA) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-4-methoxybenzoic acid, trifluoroacetic acid salt (5v). NMR (DMSO-d_6) δ 11.35 (s, 1H), 10.4 (s, 1H), 9.2 (s, 2H), 9.04 (s, 2H), 7.88 (dd, 1H), 7.72 (d, 2H), 7.66 (d, 1H), 7.56 (m, 1H), 7.44 (m, 3H), 7.36 (d, 1H), 7.14 (d, 1H), 4.1 (m, 2H), 3.95 (s, 3H), 3.95 (m, 2H), 3.0 (s, 3H). Anal. ($C_{30}H_{25}F_2N_5O_7$·2.5 TFA) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-4,5-dimethoxybenzoic acid, ethyl ester, trifluoroacetic acid salt (5w). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.05 (s, 2H), 9.0 (s, 2H), 7.65 (s, 1H), 7.6 (d, 1H), 7.4–7.6 (m, 6H), 7.05 (d, 1H), 4.35 (q, 2H), 4.1 (m, 2H), 3.95 (s, 3H), 3.95 (m, 2H), 3.85 (s, 3H), 3.0 (s, 3H), 1.35 (t, 3H). Anal. ($C_{33}H_{31}F_2N_5O_8$·2.4 TFA) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-4,5-dimethoxybenzoic acid, trifluoroacetic acid salt (5x). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.1 (s, 2H), 9.05 (s, 2H), 7.65 (s, 1H), 7.6 (d, 1H), 7.4-7.6 (m, 6H), 7.05 (d, 1H), 4.1 (m, 2H), 3.95 (s, 3H), 3.95 (m, 2H), 3.85 (s, 3H), 3.0 (s, 3H). Anal. ($C_{31}H_{27}F_2N_5O_8$·2.5 TFA) C, H, N.

3-Aminocarbonyl-5-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzoic acid, ethyl ester, trifluoroacetic acid salt (5y). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.1 (s, 2H), 8.95 (s, 2H), 8.35 (m, 2H), 8.0 (s, 1H), 7.9 (s, 1H), 7.4–7.8 (m, 7H), 7.05 (d, 1H), 4.35 (q, 2H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H), 1.35 (t, 3H). Anal. ($C_{32}H_{28}F_2N_6O_7$·2.5 TFA·H_2O) C, H, N.

3-Aminocarbonyl-5-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzoic acid, trifluoroacetic acid salt (5z). NMR (DMSO-d_6) δ 11.25 (s, 1H), 10.3 (s, 1H), 9.16 (s, 2H), 8.98 (s, 2H), 8.36 (m, 1H), 8.32 (m, 1H), 7.96 (s, 1H), 7.88 (s, 1H), 7.72 (m, 2H), 7.61 (dd, 1H), 7.4–7.6 (m, 4H), 7.05 (d, 1H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H). Anal. ($C_{30}H_{24}F_2N_6O_7$·2.7 TFA) C, H, N.

5-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzene-1,3-dicarboxylic acid, trifluoroacetic acid salt (5aa). NMR (DMSO-d_6) δ 11.2 (s, 1H), 10.3 (s, 1H), 9.06 (s, 2H), 8.97 (s, 2H), 8.3 (m, 1H), 7.97 (m, 2H), 7.68 (d, 1H), 7.60 (dd, 1H), 7.4–7.6 (m, 4H), 7.05 (d, 1H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H). Anal. ($C_{30}H_{23}F_2N_5O_8$·2.4 TFA·H_2O) C, H, N.

5-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzene-1,3-dicarboxylic acid, ethyl ester, trifluoroacetic acid salt (5bb). NMR (DMSO-d_6) δ 11.2 (s, 1H), 10.3 (s, 1H), 9.06 (s, 2H), 8.98 (s, 2H), 8.36 (m, 1H), 8.02 (m, 1H), 8.0 (m, 1H), 7.68 (d, 1H), 7.60 (dd, 1H), 7.4–7.6 (m, 4H), 7.06 (d, 1H), 4.4 (q, 2H), 4.1 (m, 2H), 3.95 (m, 2H), 3.0 (s, 3H), 1.35 (t, 3H). Anal. ($C_{32}H_{27}F_2N_5O_6$·2.8 TFA) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzene-3-propanoic acid, ethyl ester, trifluoroacetic acid salt (5cc). NMR (DMSO-d_6/TFA) δ 11.22 (s, 1H), 10.3 (s, 1H), 9.08 (s, 2H), 8.95 (s, 2H), 7.5

(m, 7H), 7.1 (m, 4H), 4.0 (m, 6H), 3.05 (s, 3H), 2.92 (t, 2H). 2.68 (t, 2H), 1.15 (t, 3H). Anal. ($C_{33}H_{31}F_2N_5O_6$·2.4 TFA) C, H, N.

5-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-4-(2-dimethylaminoethoxy)benzoic acid, trifluoroacetic acid salt (5dd). NMR (DMSO-d_6) δ 9.70 (brs, 2), 8.95 (brs, 2), 7.92 (d, 1), 7.75–7.40 (m, 8), 7.15 (d, 1), 4.60 (m, 2), 4.20–3.90 (m, 4), 3.63 (m, 2), 3.05 (s, 3), 2.95 (brs, 6). Anal. ($C_{33}H_{32}F_2N_6O_7$·3.3 TFA·1.9 H_2O) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzene-3-propenamide, trifluoroacetic acid salt (5ee). NMR (DMSO-d_6/TFA) δ 10.3 (s, 1H), 9.05 (s, 2H), 8.85 (s, 2H), 7.7 (s, 1H), 7.6 (d, 1H), 7.5 (m, 8H), 7.25 (m, 1H), 7.05 (d, 1H), 6.65 (d, 1H), 4.05 (m, 2H), 3.9 (m, 2H), 2.95 (s, 3H). Anal. ($C_{31}H_{26}F_2N_6O_6$·2.5 TFA) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzene-3-propenoic acid, methyl ester, trifluoroacetic acid salt (5ff). NMR (DMSO-d_6/TFA) δ 10.25 (s, 1H), 9.05 (s, 2H), 8.85 (s, 2H), 7.4–7.7 (m, 10H), 7.3 (m, 1H), 7.05 (d, 1H), 6.7 (d, 1H), 4.05 (m, 2H), 3.9 (m, 2H), 3.7 (s, 3H), 3.0 (s, 3H). Anal. ($C_{32}H_{27}F_2N_5O_6$·2.2 TFA) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzene-3-propenoic acid, ethyl ester, trifluoroacetic acid salt (5gg). NMR (DMSO-d_6/TFA) δ 10.3 (s, 1H), 9.05 (s, 2H), 8.85 (s, 2H), 7.4–7.7 (m, 10H), 7.3 (m, 1H), 7.05 (d, 1H), 6.7 (d, 1H), 4.2 (q, 2H), 4.05 (m, 2H), 3.9 (m, 2H), 3.0 (s, 3H), 1.25 (t, 3H). Anal. ($C_{33}H_{29}F_2N_5O_6$·2 TFA·H_2O) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzene-3-propenoic acid, trifluoroacetic acid salt (5hh). NMR (DMSO-d_6/TFA) δ 10.25 (s, 1H), 9.05 (s, 2H), 8.85 (s, 2H), 7.4–7.7 (m, 10H), 7.3 (m, 1H), 7.05 (d, 1H), 6.6 (d, 1H), 4.05 (m, 2H), 3.9 (m, 2H), 3.0 (s, 3H). Anal. ($C_{31}H_{25}F_2N_5O_6$·2.5 TFA) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]benzene-3-propanoic acid, trifluoroacetic acid salt (5ii). NMR (DMSO-d_6/TFA) δ 10.25 (s, 1H), 9.05 (s, 2H), 8.8 (s, 2H), 7.6 (s, 1H), 7.55 (d, 1H), 7.3–7.5 (m, 4H), 7.0–7.2 (m, 4H), 4.05 (m, 2H), 3.0 (s, 3H), 2.85 (t, 2H), 2.55 (m, 2H). Anal. ($C_{31}H_{27}F_2N_6O_6$·2.5 TFA) C, H, N.

3-[3,5-Difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]-4-[2-methoxy-5-(1*H*-tetrazol-5-yl)phenoxy]-pyridin-2-yl]-4-hydroxycarboximidamide, trifluoroacetic acid salt (5jj). NMR (DMSO-d_6/TFA) δ 9.08 (s, 2H), 8.95 (s, 2H), 7.95 (s, 2H), 7.5 (m, 7H), 7.1 (d, 1H), 4.08 (m, 7H), 3.05 (s, 3H). Anal. ($C_{30}H_{25}F_2N_9O_5$·2.5 TFA) C, H, N.

3-[3,5-Difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]-4-(2-methoxyphenoxy)pyridin-2-yl]-4-hydroxycarboximidamide, trifluoroacetic acid salt (5kk). NMR (DMSO-d_6/TFA) δ 10.35 (s, 1H), 9.0 (s, 2H), 8.8 (s, 2H), 7.65 (s, 1H), 7.55 (m, 2H), 7.4 (m, 3H), 7.2 (m, 2H), 7.0 (m, 2H), 4.1 (m, 4H), 3.95 (m, 2H), 3.8 (s, 3H), 3.0 (s, 3H). Anal. ($C_{29}H_{25}F_2N_5O_5$·2.5 TFA) C, H, N.

3-[3,5-Difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]-4-[2-methoxy-5-(trifluoromethylsulfonylamino)phenoxy]pyridin-2-yl]-4-hydroxycarboximidamide, trifluoroacetic acid salt (5ll). NMR (DMSO-d_6) δ 10.26 (s, 1H), 9.0 (s, 2H), 8.8 (s, 2H), 7.1–7.7 (m, 9H), 7.0 (d, 1H), 4.0 (m, 4H), 3.8 (s, 3H), 2.94 (s, 3H). Anal. ($C_{30}H_{25}F_5N_6O_7S$·3 TFA) C, H, N.

3-[3,5-Difluoro-4,6-bis[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-2-yl]-4-hydroxycarboximidamide, trifluoroacetic acid salt (5mm). NMR (DMSO-d_6) δ 11.4 (br, 1H), 10.45 (s, 1H), 10.35 (s, 1H), 9.1 (br, 4H), 7.4–7.8 (m, 10H), 7.05 (d, 1H), 4.1 (m, 4H), 3.95 (m, 2H), 3.05 (s, 3H), 3.0 (s, 3H). Anal. ($C_{32}H_{28}F_2N_7O_4$·4.7 TFA) C, H, N.

3-[4-(2-Chlorophenoxy)-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-2-yl]-4-hydroxycarboximidamide, trifluoroacetic acid salt (5nn). NMR (DMSO-d_6) δ 11.3 (s, 1H), 10.45 (s, 1H), 9.2 (s, 2H), 9.0 (s, 2H), 7.7 (s, 1H), 7.6 (m, 2H), 7.5 (m, 1H), 7.4 (m, 5H), 7.25 (m, 1H), 7.1 (d, 1H), 4.05 (m, 2H), 3.9 (m, 2H), 3.0 (s, 3H). Anal. ($C_{28}H_{22}ClF_2N_5O_4$·2.3 HCl·H_2O) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-3-chloro-*N*-phenylsulfonylbenzamide, trifluoroacetic acid salt (5oo). NMR (DMSO-d_6) δ 10.26 (s, 1H), 9.01 (s, 2H), 8.84 (s, 2H), 8.2 (d, 1H), 8.0 (m, 2H), 7.9 (dd, 1H), 7.3–7.7 (m, 10H), 7.0 (d, 1H), 4.0 (m, 4H), 2.94 (s, 3H). Anal. ($C_{35}H_{27}ClF_2N_6O_7S$·2.5 TFA·1.5 H_2O) C, H, N.

3-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-3-chloro-N-methylsulfonylbenzamide, trifluoroacetic acid salt (5pp). NMR (DMSO-d_6) δ 10.26 (s, 1H), 9.0 (s, 2H), 8.8 (s, 2H), 8.26 (d, 1H), 7.96 (dd, 1H), 7.4–7.7 (m, 7H), 7.02 (d, 1H), 4.0 (m, 4H), 3.36 (s, 3H), 2.95 (s, 3H). Anal. ($C_{30}H_{25}ClF_2N_6O_7S$·2.5 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]phenoxy]-2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoropyridin-4-yl]-3-methoxybenzoic acid, trifluoroacetic acid salt (8a). NMR (DMSO-d_6) δ 11.2 (s, 1H), 9.3 (s, 2H), 9.2 (s, 2H), 9.05 (s, 2H), 8.95 (s, 2H), 7.4–7.7 (m, 8H), 7.4 (d, 1H), 7.05 (d, 1H), 3.95 (s, 3H). Anal. ($C_{27}H_{21}F_2N_5O_7$·2.6 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-(3-dimethylamino)phenoxy]pyridin-4-yl]oxy]-2-methoxybenzoic acid, trifluoroacetic acid salt (8b). NMR (DMSO-d_6) δ 11.05 (s, 1H), 9.05 (s, 2H), 8.8 (s, 2H), 7.7 (m, 2H), 7.6 (m, 2H), 7.35 (d, 1H), 7.05 (m,

2H), 6.45 (d, 1H), 6.3 (m, 2H), 3.95 (s, 3H), 2.85 (s, 6H). Anal. ($C_{28}H_{24}F_2N_4O_7$·2.5 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[(3-dimethylaminocarbonyl)phenoxy]pyridin-4-yl]-oxy]-2-methoxybenzoic acid, trifluoroacetic acid salt (8c). NMR (DMSO-d_6) δ 11.05 (br, 1H), 9.05 (s, 2H), 8.75 (s, 2H), 7.6 (m, 4H), 7.35 (m, 2H), 7.1 (m, 4H), 3.95 (s, 3H), 3.0 (s, 3H), 2.8 (s, 3H). Anal. ($C_{29}H_{24}F_2N_4O_8$·1.1 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[(3-dimethylaminomethyl)phenoxy]pyridin-4-yl]-oxy]-2-methoxybenzoic acid, trifluoroacetic acid salt (8d). NMR (DMSO-d_6) δ 9.05 (s, 2H), 9.0 (s, 2H), 7.7 (m, 2H), 7.6 (m, 2H), 7.35 (m, 2H), 7.1 (m, 3H), 7.05 (d, 1H), 4.2 (s, 2H), 3.95 (s, 3H), 2.7 (s, 6H). Anal. ($C_{29}H_{26}F_2N_4O_7$·2.4 TFA) C, H, N.

4-[2-[3-[Amino(imino)methyl]amino]phenoxy]-6-[5-cyano-2-(phenylmethoxy)phenoxy]-3,5-difluoropyridin-4-yl]oxy]-3-methoxybenzoic acid, ethyl ester, trifluoroacetic acid salt (7, R = 2-OCH_3-4-$COOCH_2CH_3$). To 4-[2-(3-aminophenoxy)-6-[5-cyano-2-(phenylmethoxy)phenoxy]-3,5-difluoropyridin-4-yl]oxy]-3-methoxybenzoic acid, ethyl ester (0.50 g, 0.80 mmol) dissolved in EtOH (15 mL) was added cyanamide (0.6 g, 14 mmol) and 6 M aq HCl (0.7 mL). After refluxing for 16 h, cyanamide (1.2 g, 28 mmol) and 6 M aq HCl (0.1.4 mL) was added. After stirring for 56 h, the reaction mixture was concentrated. The residue was purified by HPLC using a Dynamax column and a gradient of CH_3CN in H_2O with 0.1% TFA. The resulting fractions were combined and the solvent was removed by lyophylization to give 0.42 g of the title compound.

4-[2-[3-[Amino(imino)methyl]amino]phenoxy]-6-[5-[amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoropyridin-4-yl]oxy]-3-methoxybenzoic acid, 2.0 trifluoroacetic acid salt, 1.0 hydrate, (8e). NMR (DMSO-d_6) δ 11.2 (s, 1H), 9.9 (s, 1H), 9.07 (s, 2H), 8.9 (s, 2H), 7.7 (m, 2H), 7.6 (m, 5H), 7.36 (d, 1H), 7.28 (t, 1H), 7.1 (d, 1H), 6.95 (m, 2H), 3.95 (s, 3H). Anal. ($C_{27}H_{22}F_2N_6O_7$·2.0 TFA) C, H, N, F.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-(1-methyl-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]-3-methoxybenzoic acid, trifluoroacetic acid salt (8f). NMR (DMSO-d_6) δ 8.90 (brs, 2), 8.70 (brs, 2), 7.77–7.31 (m, 10), 7.21 (d, 1), 6.85 (d, 1), 3.85 (s, 3), 3.78 (s, 3). Anal. ($C_{30}H_{23}F_2N_5O_7$·2.0 TFA·1.7 H_2O) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[(3-hydroxycarbonyl)phenoxy]pyridin-4-yl]oxy]-2-methoxybenzoic acid, trifluoroacetic acid salt (8g). NMR (DMSO-d_6) δ 11.05 (s, 1H), 9.05 (s, 2H), 8.95 (s, 2H), 7.6 (m, 6H), 7.35 (m, 3H), 7.05 (d, 1H), 3.95 (s, 3H). Anal. ($C_{27}H_{19}F_2N_3O_9$·1.3 TFA) C, H, N.

4-[2-[3-[Amino(imino)methyl]amino]phenoxy]-6-[5-[amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoropyridin-4-yl]oxy]-3,5-dimethoxybenzoic acid, 2.0 trifluoroacetic acid salt, 1.0 hydrate, (8h). NMR (DMSO-d_6) δ 9.8 (s, 1H), 9.03 (s, 2H), 8.8 (s, 2H), 6.8–7.7 (m, 10H), 3.86 (s, 6H). Anal. ($C_{28}H_{24}F_2N_6O_8$·2.0 TFA·H_2O) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[[3-pyrolidin-1-yl(imino)methyl]amino]phenoxy]-pyridin-4-yl]oxy]-2,6-dimethoxybenzoic acid, 2.7 trifluoroacetic acid (8i). NMR (DMSO-d_6) δ 9.16 (s, 1H), 9.04 (s, 2H), 8.86 (s, 2H), 7.5–7.7 (m, 4H), 7.36 (s, 2H), 7.28 (t, 1H), 7.07 (d, 1H), 6.8–7.0 (m, 3H), 3.9 (s, 6H), 3.5 (br, 4H), 1.9 (br, 4H). Anal. ($C_{32}H_{30}F_2N_6O_8$·2.7 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-[(4,5-dihydro-1*H*-imidazol-2-yl)amino]phenoxy]pyridin-4-yl]oxy]-3,5-dimethoxybenzoic acid, 2.5 trifluoroacetic acid salt (8j). NMR (DMSO-d_6) δ 10.48 (s, 1H), 9.0 (s, 2H), 8.8 (s, 2H), 8. 4 (s, 2H), 7.62 (d, 1H), 7.55 (dd, 1H), 7.32 (s, 2H), 7.22 (t, 1H), 7.02 (d, 1H), 6.8–6.9 (m, 3H), 3.84 (s, 6H), 3.62 (s, 4H). Anal. ($C_{30}H_{26}F_2N_6O_8$·2.5 TFA) C, H, N.

4-[2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-6-[3-[(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)amino]phenoxy]pyridin-4-yl]oxy]-3,5-dimethoxybenzoic acid, 2.5 trifluoroacetic acid salt (8k). NMR (DMSO-d_6) δ 9.98 (s, 1H), 9.0 (s, 2H), 8.8 (s, 2H), 8.24 (s, 1H), 7.65 (d, 1H), 7.58 (dd, 1H), 7.35 (s, 2H), 7.26 (t, 1H), 7.03 (d, 1H), 6.9–7.0 (m, 3H), 3.85 (s, 6H), 3.6 (m, 4H), 3.0 (s, 3H). Anal. ($C_{31}H_{28}F_2N_6O_8$·2.5 TFA) C, H, N. Enzyme assay procedures.[11] The activities of human fXa, human fIIa, and bovine trypsin were determined as the initial rate of the cleavage of peptide *p*-nitroanilide by the enzyme. The assay was performed at room temperature in flat-bottom microtiter plates in a final volume of 200 μL. The reaction mixture consisted of 50 mM TrisHCl (pH 7.5), 150 mM NaCl, 2.5 mM $CaCl_2$, and 0.1% polyethylene glycol 6000, with enzyme and substrate at the following concentrations: (1) FXa assay: 1 nM fXa and 164 μM S2222, (2) FIIa assay: 16 nM fIIa and 300 μM S2302, and (3) trypsin assay: 16 nM bovine trypsin and 127 μM S2266. All substrate concentrations used are equal to their K_m values under the present assay conditions. Controls without the test inhibitors or with a reference compound were also run in each assay plate. Enzyme was incubated with test compounds for 10 min, the reaction was then started by the addition of the substrate. Reaction rates were determined by measuring the rate of the absorbance change at 405 nm in a ThermoMax microplate reader (Molecular Devices Corp., Sunnyvale, CA, USA).

Data analysis methods

IC_{50} values for inhibitors were obtained by log-logit analysis with a computer spreadsheet. For inhibitors with K_i less than 3 nM, IC_{50} values were determined by fitting data to a modification of the Morrison equation to correct for the proportion of inhibitor bound to the enzyme relative to the free inhibitor.[7] Since the inhibition mechanism is competitive, K_i values were then obtained by dividing the IC_{50} values by a factor of $1 + [S]/K_m$. K_i values are the mean of multiple determinations ($n \geq 2$). Standard deviations are $< 30\%$ of the mean.

References and Notes

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