Design, Synthesis, and Activity of a Novel Series of Factor Xa Inhibitors: Optimization of Arylamidine Groups[1,2]

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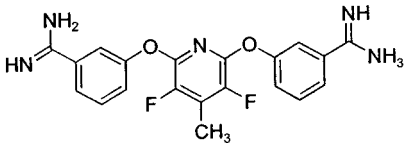
A novel series of diaryloxypyridines have been designed as selective nanomolar factor Xa (fXa) inhibitors for use as anticoagulants. In this paper, we describe our efforts to identify an additional interaction and a replacement for the distal amidine group that binds in the S3/S4 pocket of fXa. Introduction of a hydroxyl group para to the proximal amidine group increases the potency vs fXa by 1−2 orders of magnitude, which is the result of a hydrogen bond to Ser195 of the catalytic triad. A methyl imidazoline and a dimethylamide are good alternatives for the second amidine. These substitutions have increased the selectivity vs the related serine proteases trypsin and thrombin. The synthesis, in vitro activity, and hypothetical modes of binding to fXa based on trypsin crystallographic data are outlined.

Introduction

Factor Xa (fXa) plays a strategic role in the coagulation pathway at the juncture of the intrinsic and extrinsic pathways. The discovery of a novel class of potent, selective fXa inhibitors provides the opportunity to develop a new anticoagulant with greatly reduced bleeding risk.[3,4] An early lead structure in our fXa inhibitors program, **1**, bears two arylamidine groups, which have been associated with poor oral bioavailability. Therefore, the next phase of our drug discovery effort was focused on modifying one of the arylamidine groups. We had evidence from earlier studies that at least one amidine is necessary for activity, and we expected potency to decrease significantly on replacement of one of the amidines. For that reason, we expected that once a monoamidine was found, an additional binding site would be required to regain the lost potency. Herein, we report on the results of those studies that conclude with potent, selective, and novel monoamidine inhibitors of fXa.



1

Chemistry

Compounds were prepared as previously described[1−3,5] and as outlined in Scheme 1. Unsymmetrical bisaryloxypyridines were prepared by reaction of 1 equiv of a 3-cyanophenol with 2,3,5,6-tetrafluoro-4-methylpyridine to give the desired monoaddition adduct **3**. Addition of a second phenol using higher temperatures in dimethyl sulfoxide (DMSO) gave compounds **4a**−**ss** after conversion of the nitrile to the amidine under standard Pinner conditions.[6] Both phenol additions could be carried out in a single reaction vessel by controlling the number of equivalents of phenol and the reaction temperature and using sequential addition.

Compounds substituted on the dimethylbenzamide, **5a**−**l**, or dimethyl aniline, **4 cc** and **5m**−**r** were prepared in a similar manner, with a series of appropriately substituted phenols added to give **2**. Compounds substituted on the benzamidine aromatic moiety, **6a**−**p**, were prepared in a similar manner, with a series of appropriately substituted cyanophenols added to the monoaddition product. Hydroxy compounds were prepared as the appropriate methoxy compound and deprotected with boron tribromide. Typically, the amino-substituted compounds were prepared from the corresponding nitro compounds by reduction. The 6-amino-substituted compounds (**6g**,**m**) were purified by high-performance liquid chromatography (HPLC) after the final step and were found to isomerize on reapplication to the reaction conditions (see Figure 1). Compounds **7a**−**n** bearing a carboxylic acid group at C-4 were prepared typically by addition of phenols to 2,6-dichloropyridine-4-carboxylic acid using higher temperatures and longer reaction times.

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).

A series of diaryloxypyridines bearing an arylamidine group and a 3-substituted aromatic group were prepared to explore the structure−activity relationships (SAR) for fXa binding (Table 1). The importance of the distal amidine group to binding to fXa can be seen in the loss of potency by replacing the amidine, **1**, with hydrogen, **4a**. The difficulty in identifying a significant interaction between the S3/S4 pocket of fXa and the ligand is

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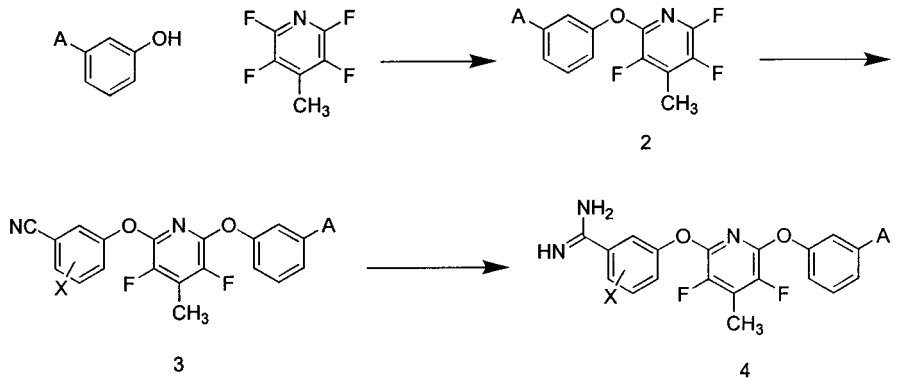
Scheme 1



demonstrated by the fact that most of the modifications showed a greater than 2 orders of magnitude loss in activity. Acidic functional groups as in analogues **4d** and **4q** were not tolerated by any of the proteases assayed. However, three substituents, the weak bases dimethylaniline (**4cc**) and imidazole (**4kk**) and the neutral dimethylamide (**4f**), showed interesting activity.

A SAR was developed around the most potent analogue in the series, dimethylcarboxamide-bearing inhibitor **4f**. The slightly larger diethylcarboxamide analogue, **4g**, is 8-fold less potent than the dimethyl analogue indicating that the amide binding site may be limited in size. Removal of the methyl groups from the amide resulted in inhibitors that were 15- and 3-fold less potent against fXa **4b** and **4e**, respectively. A similar steric trend is observed with the cyclic amides; the smaller **4i** is more potent than **4j**−**l**. Systematic SAR efforts also revealed the important components of the amide functional group. As shown in Table 1, a decrease in potency is observed upon removal of the carbonyl group, **4nn**, just the carbonyl oxygen, **4y**,**z**, or removal of the nitrogen, **4v** or **4w**. Substitution of the amide for a sulfonamide, **4x**, also resulted in a decrease in potency against fXa. Introduction of a methylene carbon between the aromatic and the amide groups resulted in a 3-fold decrease in activity in the dimethylcarboxamide series, **4f** vs **4n**, but had little effect on the unsubstituted amide, **4b** vs **4o**. With the introduction of a two carbon linker, **4t** vs **4u**, potency decreased about 10-fold from **4f**. A similar result was seen upon introduction of a hydroxymethylene group, **4r**,**s**, with the dimethylcarboxamide about 6-fold less active than the unsubstituted amide and 27-fold less potent than **4f**. We hypothesized that the potency of the dimethylcarboxamide analogues is due to the amide adopting a nonplanar configuration with respect to the phenyl ring rather than the planar configuration predicted for less potent inhibitors such as the unsubstituted amide (**4b**) and *N*-methylamide (**4e**).

In the base-substituted analogue series, anilines have a similar SAR to the amides, with the dimethylaniline **4cc** the most potent compound of the series (**4bb**−**ff**,**jj**). Substitution of the aniline to give a sulfonamide, amide, or urea (**4gg**−**ii**) caused at least a 20-fold decrease in activity. The imidazole, **4kk**, also showed interesting potency, and further elaboration of the imidazole will be discussed in a later series. The binding of these compounds within the S3/S4 pocket is consistent with the increase in potency with increased tendency for adopting a nonplanar configuration with respect to the phenyl ring.

Additional substitutions on the phenyl rings were made in the hope of regaining the potency lost upon replacing the second amidine functionality. Initially, substitutions were made on the distal phenyl ring, using **4f** or **4cc** as parents from the most potent monoamidines found (Table 2). No improvements in activity were found with any substitution. Substitution at the 6-position of the aromatic ring decreased potency (**5e**−**f**,**j**−**l**,**o**−**r**) in both the aniline and the dimethylcarboxamide series. Similar loss in potency was seen upon substitution in the 2- and 4-position in the dimethylaniline series (**5m**,**n**) and in the dimethylcarboxamide series (**5a**−**d**). Substitution at the 5-position was tolerated in the dimethylcarboxamide series (**5g**,**i**) by fXa and selective against other proteases. However, the selectivity was reversed with the 5-hydroxy analogue, **5h**, which was at least 8-fold more potent against thrombin and trypsin than fXa.

Substitutions on the amidine-bearing phenyl ring yielded more interesting results. To make proper comparisons, the distal phenyl group was kept constant with a dimethylcarboxamide or dimethylaniline as in **4f**,**cc** (Table 3). One of the first compounds prepared in this series was the para-amino analogue, **6m**, which was 2−3-fold more potent than unsubstituted **4cc**. The enhanced potency of a *para*-aminobenzamidine over *para*-hydroxybenzamidine and benzamidine had been observed previously against trypsin and fXa.[7] In contrast to the simple substituted benzamidine case, in our series, the para-hydroxy analogue, **6o**, was about 20-fold more potent than the corresponding amino ana-

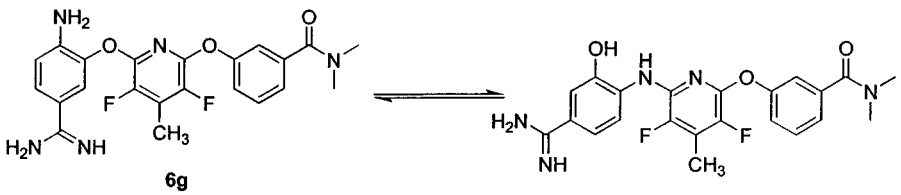
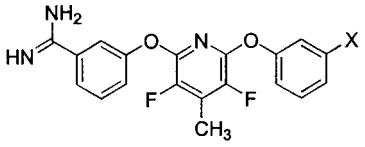


Figure 1. N and O Interconversion.

Table 1. Activity of Analogues of **1** Containing One Amidine

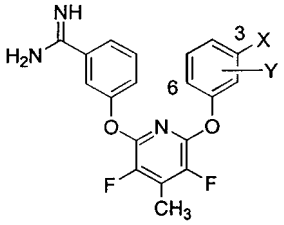


4

		K_i (nM)		
no.	X	Xa	IIa	trypsin
1	$C(NH)NH_2$	13	22 000	810
4a	H	>5000	>5000	>5000
4b	$CONH_2$	280	>5000	>5000
4c	CO_2Et	5200	>5000	>5000
4d	COOH	5000	>5000	>5000
4e	CONHMe	1200		
4f	$CONMe_2$	80	>5000	2700
4g	$CONEt_2$	690		
4h	CONMeBn	2400		
4i	COPyrrolidine	220	>5000	2800
4j	COMorpholine	1400	>5000	>5000
4k	COPiperidine	820	>5000	3000
4l	COPiperazineMe	>5000		
4m	CONHPh	>5000	>5000	
4n	CH_2CONMe_2	460	>5000	4200
4o	CH_2CONH_2	280	>5000	>5000
4p	CH_2COOEt	810	>5000	>5000
4q	CH_2COOH	>5000	>5000	>5000
4r	$CHOHCONMe_2$	2200	>5000	3300
4s	$CHOHCONH_2$	370		
4t	$(CH_2)_2CONMe_2$	1300	>5000	4900
4u	$(CH_2)_2CONH_2$	700		>5000
4v	COMe	1400	>5000	
4w	$COCHMe_2$	2100	>5000	3800
4x	$SONMe_2$	720	>5000	2400
4y	CH_2NH_2	1400	>5000	2900
4z	CH_2NMe_2	640		
4aa	NO_2	2500	>5000	>5000
4bb	NH_2	3300	>5000	>5000
4cc	NMe_2	160	2600	1900
4dd	NHEt	530	>5000	2700
4ee	NEt_2	400	730	2100
4ff	NHPh	1800	3800	>5000
4gg	$NHSO_2Me$	3804	4900	1900
4hh	NHAc	5800		
4ii	$NHCONH_2$	4000	>5000	>5000
4jj	Morpholine	650	>5000	2000
4kk	Imidazole	125	>5000	4800
4ll	OMe	1350	1800	
4mm	OCF_3	1800	>5000	>5000
4nn	$OCHMe_2$	620	5300	2900
4oo	F	3200		
4pp	Cl	1700	>5000	
4qq	OH	5000		
4rr	CF_3	1600	>5000	
4ss	CH_2OH	1300		

logue, **6m**, and about 50-fold more potent than the unsubstituted analogue, **4cc**.[2,3] A similar difference in potency was seen in the dimethylcarboxamide series of analogues, **4f** and **6g**,**i**. Since our first report on the enhanced potency of the *para*-hydroxybenzamidine group, researchers at Aventis have reported a 20-fold increase in potency upon introduction of a para-hydroxyl group on their pyrrolidinone template.[8] In addition, we have reported an 8-fold increase in potency for a similar change to the *N*-propenylbenzamidine-aminophenol template[9] and a 4-fold decrease in potency in the *N*-propenylbenzamidine-benzimidazole template.[10] These results suggest that there is an optimum binding orientation for a *para*-hydroxybenzamidine substituent in the S1 pocket. The corresponding methoxy-containing compounds, **6d**−**f**,**j**−**k**,**p**, which are hydrogen bond

Table 2. Activity of Compounds Substituted on the Distal S3/S4 Binding Ring



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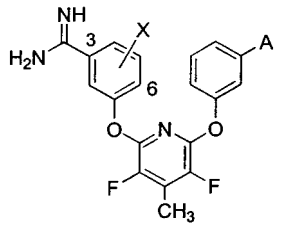
			K_i (nM)		
no.	X	Y	Xa	IIa	trypsin
4f	$CONMe_2$	H	80	>5000	2700
5a	$CONMe_2$	2-OH	4500		
5b	$CONMe_2$	2-OMe	2400		
5c	$CONMe_2$	4-OH	2000		
5d	$CONMe_2$	4-OMe	1400	3000	450
5e	$CONMe_2$	5,6-OH	>5000	>5000	3400
5f	$CONMe_2$	5,6-OMe	>5000		
5g	$CONMe_2$	5-$CONMe_2$	160	>5000	1600
5h	$CONMe_2$	5-OH	>5000	740	1900
5i	$CONMe_2$	5-OMe	140	>5000	750
5j	$CONMe_2$	6-Me	>5000		
5k	$CONMe_2$	6-OH	>5000	>5000	3700
5l	$CONMe_2$	6-OMe	>5000	>5000	2100
4cc	NMe_2	H	160	2600	1900
5m	NMe_2	2-Me	320	950	5000
5n	NMe_2	4-Cl	500	5300	1000
5o	NMe_2	6-COOEt	>5000	>5000	>5000
5p	NMe_2	6-COOH	2400		
5q	NMe_2	6-Me	>5000	>5000	>5000
5r	NMe_2	6-OMe	>5000	2200	>5000

Table 3. Activity of Compounds Substituted on the Proximal or S1 Binding Ring and Substitution on the Distal Aromatic Ring



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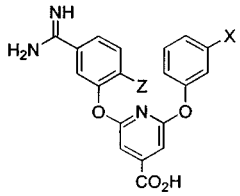
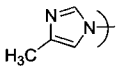
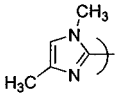
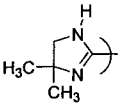
			K_i (nM)		
no.	A	X	Xa	IIa	trypsin
4f	$CONMe_2$	H	80	>5000	2700
6a	$CONMe_2$	2-OH	>5000	>5000	>5000
6b	$CONMe_2$	2-OH-5-OMe	>5000	>5000	>5000
6c	$CONMe_2$	5,6-OH	23	1200	1100
6d	$CONMe_2$	5,6-OMe	180	>5000	>5000
6e	$CONMe_2$	5-OH-6-OMe	160	>5000	>5000
6f	$CONMe_2$	5-OMe	2700		
6g	$CONMe_2$	6-NH_2	14	2300	550
6h	$CONMe_2$	6-$NHSO_2CF_3$	>5000		
6i	$CONMe_2$	6-OH	1.8	1100	1100
6j	$CONMe_2$	6-OMe	720	>5000	4300
4cc	NMe_2	H	160	2600	1900
6k	NMe_2	2,6-OMe	>5000		
6l	NMe_2	6-Me	1200		
6m	NMe_2	6-NH_2	64	300	400
6n	NMe_2	6-$NHSO_2Me$	5500	>5000	>5000
6o	NMe_2	6-OH	3	190	1000
6p	NMe_2	6-OMe	1400		

acceptors and electron-donating substituents, were over 9-fold less active than the unsubstituted analogue. Similarly, sulfonamides **6h**,**n**, which are hydrogen bond

Table 4. Activity of Compounds Substituted on the Distal or S3/S4 Binding Ring



7

No	X	Z	K_i (nM) Xa	IIa	Trypsin
7a	Am	H	59	27000	570
7b	Am	OH	6	5100	520
7c	$CONMe_2$	H	263	>5000	730
7d	$CONMe_2$	OH	3.1	490	150
7e	NMe_2	OH	12	120	750
7f		OH	26	1400	1200
7g		OH	8	680	580
7h		OH	13	650	160
7i		OH	9	180	650
7j		OH	8.4	880	470
7k		OH	85	>5000	1400
7l		OH	2.4	810	220
7m		OH	810	>5000	1400
7n	$NCCNH_2$	OH	78	3400	350

donors and electron-donating substituents, were over 30-fold less active than the unsubstituted analogue. The methyl-containing compound, **6l**, which has a similar steric bulk and weak electron-donating properties, is 7-fold less active. Other substituents caused no increase in potency. On the basis of these results, we concluded that potency against fXa can be dramatically increased with a small electron-donating substituent at C-6 capable of forming a hydrogen bond with the serine of the catalytic triad.

The SAR for the substituents on the distal ring in the 4-carboxylic acid series of analogues was explored as shown in Table 4. Interestingly, the hydroxy substituent does not have as large an effect on the bisamidine (**7b** vs **7a**) as it does on the monoamidine (**7d** vs **7c**) resulting in the monoamidine having similar potency to the bisamidine (**7d** vs **7b**). Analogues bearing the optimized dimethylcarboxamide (**7d**) or a dimethylamine (**7e**) substitutent and a carboxylic acid group were potent inhibitors of fXa. In contrast to the amide and amine series, the SAR in the imidazole series had not yet been explored fully and was examined with a carboxylic acid at C-4.

In general agreement with observations in the amide and amine series (Table 1), substitution of the imidazole at C-2 with a methyl caused a 3-fold increase in potency over the unsubstituted compound (**7f** vs **7g**). Reversal of the point of attachment and the methyl subsituent did not affect potency but did decrease selectivity vs thrombin (**7g** vs **7i**). Partial saturation of the *N*-methyl imidazole to the *N*-methyl-imidazoline ring produced one of the most potent compounds in this series, **7l**. In general agreement with observations in the amide, amino, and imidazole series (Tables 1 and 4), a methyl group dramatically increased the potency of the analogue (**7l** vs **7k**), which can be explained by the preferred out-of-plane orientation of the phenyl and imidazoline rings mentioned earlier. Additional SAR evidence for the importance of the methyl substituent on the orientation of the phenyl ring and the substituent is the loss of potency seen in the dimethyl substitution at C-4 (**7m**). In the trypsin crystal structure of **7k** (Figure 2),[11] the imidazoline ring is in the plane of the phenyl, but in the trypsin crystal structure of **7l**, the ring is forced out of the plane of the phenyl ring by the methyl group.[13]

A parallel activity to the search for positive interactions between the inhibitor and fXa is the development of a SAR for negative interactions with thrombin (fIIa) and trypsin. The active sites of serine proteases have distinct differences,[12] which we were only partially successful in exploiting. Compound **1** has excellent selectivity vs thrombin and good selectivity vs trypsin. However, replacement of the distal or S3/S4 binding amidine group resulted in reduced selectivity for both thrombin and trypsin (Table 1). The failure to identify an additional interaction for the distal ring with fXa (Table 2) also failed to provide a negative interaction with thrombin or trypsin. The influence of the basic amidine replacements described in Table 4 is seen in the 30-fold variation in the selectivity ratio of fXa to thrombin (**7e**−**l**) and the 8-fold variation in the corresponding ratio of fXa vs trypsin (**7h** vs **7l**). The increase in selectivity is due to methyl substituent and partial saturation of the imidazole ring but is limited by steric bulk as in **7m**.

The crystal structure of bovine trypsin complexed with **7k** has been refined at 1.8 Å to an *R* factor of 15.5% and a R_{free} of 21.7% in space group $P3_121$. The inhibitor is bound at the active site of trypsin in an L-shaped conformation similar to the binding mode of an earlier inhibitor from the same series (Figure 2)[11] and is similar to the binding of a pyrrolidinone inhibitor to Trypsin[8] and fXa.[14] The proximal benzamidine ring is bound in the S1 pocket, with the amidine making hydrogen bonds to Asp189, Ser190, Gly218, and a water molecule. The hydroxyl group para to the amidine is also hydrogen-bonded to a water molecule, which in turn is hydrogen-bonded to the hydroxyl of the catalytic triad Ser195. The pyridine ring has no interactions with the primary trypsin molecule. The imidazoline moiety binds in the S3/S4 pocket in an extended conformation. One of the

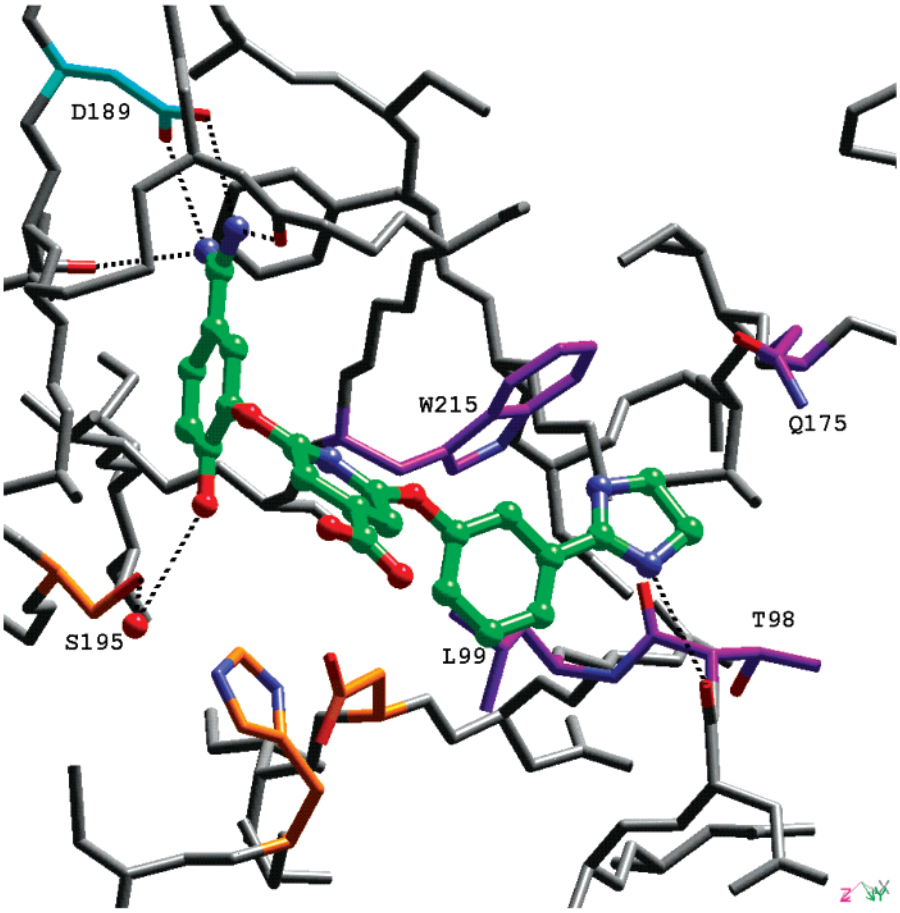


Figure 2. Crystal structure of **7k** in bovine trypsin. The carbon atoms of the inhibitor are colored green. Carbon atoms of specific residues have been colored. Asp189 at the bottom of the S1 pocket is blue. The catalytic triad Ser195, His57, and Asp102 is orange. Residues that form the S4 pocket, Thr98, Leu99, Gln175, and Trp215, are purple. Hydrogen bonds are depicted as dashed lines.

imidazoline nitrogens makes a long hydrogen bond to the carbonyl oxygen on Asn97. The C-4 carboxylate is solvent-exposed and makes no interactions with trypsin.

Selectivity vs the serine proteases, thrombin and trypsin, is strongly affected by the introduction of the 6-hydroxyl group on the proximal or S1 binding amidine group (**6i**,**o** vs **4f**,**cc**). This increase in potency against fXa and selectivity vs thrombin and trypsin is thought to be the result of variation in the binding of ligand to the serine proteases, rather than the introduction of selective negative interactions. The differential interaction of the 6-hydroxyl group on the proximal ring and with different proteases is at least partly explained by a hydrogen bond to the O^{γ} Ser195 of the catalytic triad. The distance between the 6-hydroxyl group of **7k** and the Ser195 in trypsin (Figure 2) is 3.61 Å, which requires a bridging water molecule to form a hydrogen bond. The corresponding distance between the 6-hydroxyl group of a closely related analogue of **7k** and fXa is 2.4 Å, which allows for a stronger direct hydrogen bond.[13]

In addition to potency and selectivity, we evaluated the pharmacokinetic profile of our inhibitors in the rat. The plasma concentrations after intravenous administration (1 mg/kg, $n = 3$) for **1** at 30 min was 0.1 μM as compared to a concentration of 0.8 μM for **7a**. The pharmacokinetic profile of the inhibitors was further improved with the introduction of the para-hydroxy group, **7b**, which gave a plasma concentration of 1.9 μM at 30 min (rat, 1 mg/kg, $n = 3$). Replacement of the amidine group with an imidazoline group, as in **7k**, further increased the comparable plasma concentration at 30 min to 3.0 μM with a 1.4 μM concentration at 1 h. Unfortunately, introduction of the *N*-methyl group on **7k** to give the more potent **7l** resulted in a 3-fold decrease in plasma concentrations after intravenous administration to the rat with 1.1 μM at 30 min and 0.4 μM at 60 min. The pharmacokinetic profile of **7l** was expanded to include oral dosing in the rat at 10 mg/kg. Plasma concentrations of 1.4, 0.2, and 0.1 μM were measured at 1, 2, and 4 h, respectively. Although the 4-carboxylic acid group was able to improve the pharmacokinetic profile of the pyridine-based fXa inhibitors, alternative substitutents at C-4 of the pyridine ring were explored to improve the profile.[3]

Conclusion

A novel series of potent inhibitors of human fXa have been designed and prepared with low nanomolar potencies and 400-fold selectivity over the related serine protease human fIIa and 100-fold selectivity over bovine trypsin. The second amidine of the original inhibitors has been replaced with less basic or neutral substituents. An additional binding site has been identified between Ser195 of the catalytic triad and a hydroxy group on the amidine-bearing ring via a bridging water molecule. Future papers will describe the exploration of substitution on the 4-position of the pyridine and the

effect of those substitutents on potency, selectivity, and oral bioavailability.[15]

Experimental Section

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. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian XL-300 spectrometer and were consistent with the assigned structures. HPLC was performed with a Rainin SD-1 Dynamax system and a C-18 reverse phase Dynamax 60A column using a gradient of acetonitrile (0.1% trifluoroacetyl (TFA)) in water (0.1% TFA).

Human FXa and human fIIa were from Enzyme Research Lab., South Bend, IN, and bovine trypsin was from Boehringer Mannheim Corp., Indianapolis, IN. All peptide-*p*-nitroanilide substrates were purchased from Pharmacia Hepar Inc., Franklin, OH. TrisHCl, NaCl, and $CaCl_2$ were from J. T. Baker Inc., Jackson, TN, and poly(ethylene glycol) 6000 was from BDH Laboratory Supplies, Poole, England.

2,6-Dichloropyridine-4-carboxylic Acid, Ethyl Ester. To a solution of 2,6-dichloropyridine-4-carbonyl chloride (8.19 g, 38.09 mmol, 1 equiv) in 70 mL of methylene chloride at 0 °C was added triethylamine (7 mL, 50.6 mmol, 1.3 equiv) followed by ethanol (3.0 mL, 50.6 mmol, 1.3 equiv). The reaction was allowed to warm to room temperature overnight. The reaction was diluted with water, and the layers were separated. The organic layer was washed with water, saturated sodium bicarbonate, and 10% aqueous HCl and then dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford the ester (8.1 g, 95%) as a yellow solid. ^{1}H NMR ($CDCl_3$): 1.41 (t, 3), 4.42 (q, 2), 7.80 (s, 2) ppm.

2-Chloro-6-(5-cyano-2-benzyloxyphenoxy)pyridine-4-carboxylic Acid, Ethyl Ester. To a solution of 2,6-dichloropyridine-4-carboxylic acid, ethyl ester (6.35 g, 28.9 mmol 1 equiv) in 300 mL of DMSO were added cesium carbonate (12.2 g, 37.5 mmol, 1.3 equiv) and 5-cyano-2-benzyloxyphenol (6.5 g, 28.9 mmol, 1 equiv). The reaction was allowed to stir overnight at room temperature. The reaction was poured into water (1 L) and adjusted to pH 7 with 10% HCl. The resultant mixture was extracted into ethyl acetate (3 × 300 mL), and the combined organic layers were washed with 10% HCl, water, and brine. After it was dried over anhydrous Na_2SO_4, the solution was evaporated in vacuo to afford crude material (13.1 g). Purification by flash chromatography through silica gel with 2/1 hexanes−ethyl acetate as eluent afforded pure ether (7.6 g 64%) as a white solid. ^{1}H NMR ($CDCl_3$): 1.40 (t, 2), 4.41 (q, 2), 5.10 (s, 2), 7.00 (m, 1), 7.15 (m, 2), 7.28 (m, 3), 7.40−7.58 (m, 4) ppm.

2-(5-Cyano-2-benzyloxyphenoxy)-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridine-4-carboxylic Acid, Ethyl Ester. To a solution of 2-chloro-6-(5-cyano-2-benzyloxyphenoxy)pyridine-4-carboxylic acid, ethyl ester (1.60 g, 3.9 mmol, 1 equiv) in 40 mL of DMSO were added cesium carbonate (1.65 g, 5.1 mmol, 1.3 equiv), imidazoline phenol (1.3 g, 3.9 mmol, 1 equiv), and potassium fluoride (0.23 g, 3.9 mmol, 1 equiv). The reaction was heated at 100 °C for 19 h. The mixture was diluted with 0.1 N NaOH (120 mL) and ethyl acetate (120 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with 10% HCl, water, and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. Purification by flash chromatography through silica gel with 20:1:0.1 methylene chloride:methanol:ammonium hydroxide afforded pure ether (131 mg, 6%). ^{1}H NMR ($CDCl_3$): 1.18 (t, 3), 2.64 (s, 3), 3.40 (t, 2), 3.81 (t, 2), 4.39 (q, 2), 495 (s, 2), 6.93−7.40 (m, 14) ppm.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-(4,5-dihydro-1-methyl-1H-imidazol-2-yl)phenoxy]pyridine-4-carboxylic Acid, 2.2 Trifluoroacetic Acid Salt, 0.9 Hydrate (7l). Hydrogen chloride gas was bubbled through a solution of **3** (340 mg, 0.62 mol) in 5 mL of ethanol at 0 °C in a pressure tube for 15 min. The tube was sealed and allowed to warm to room temperature overnight. The tube was opened, and the imidate was precipitated by addition of ether and hexanes. The precipitate was collected and dissolved in ethanol. Hydrogen chloride gas was bubbled through the solution at 0 °C in a pressure tube for 15 min. The tube was sealed and heated at 65 °C for 2.5 h. The solution was evaporated in vacuo, and the residue was heated in 8 mL of 6 N HCl for 1 h. The reaction mixture was purified by reversed-phase preparative HPLC to afford 174 mg of pure **7l**. ^{1}H NMR (DMSO-d_6): 10.35 (br s, 1), 9.05 (br s, 2), 8.83 (br s, 2), 7.40−7.71 (m, 6), 7.07 (m, 3), 3.82−4.20 (m, 4), 3.00 (s, 3). Anal. C, H, N.

3-[(3,5-Difluoro-4-methyl-6-phenoxypyridin-2-yl)oxy]-benzenecarboximidamide, Acetic Acid Salt (4a). ^{1}H NMR (300 MHz, DMSO): δ 10.3 (br s, 4H), 7.5 (m, 4H), 7.3 (m, 2H), 7.1 (m, 3H), 2.4 (s, 3 H), 1.75 (s, 3 H). Anal. ($C_{19}H_{15}F_2N_3O_2\cdot C_2H_4O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzamide, 1.1 Trifluoroacetic Acid (4b). NMR (DMSO-d_6): δ 9.3 (s, 2H), 9.05 (s, 2H), 8.0 (s, 1H), 7.5 (m, 6 H), 7.42 (t, 1H), 7.22 (d, 2H), 2.4 (m, 3H). Anal. ($C_{20}H_{16}N_4O_3F_2\cdot 1.1$TFA) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzoic Acid Ethyl Ester, Acetic Acid Salt (4c). NMR (DMSO-d_6): δ 10.2 (br, 4 H), 7.75 (d, 1 H), 7.7 (s, 1 H), 7.5 (m, 6 H), 4.35 (q, 2 H), 2.4 (s, 3 H), 1.75 (s, 3 H), 1.35 (t, 3 H). Anal. ($C_{22}H_{19}F_2N_3O_4\cdot C_2H_4O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]3,5-difluoro-4-methylpyridin-2-yl]oxy]benzoic Acid, 0.25 Hydrate (4d). NMR (DMSO-d_6): δ 9.3 (s, 2H), 9.1 (s, 2 H), 7.75 (d, 1 H), 7.5 (m, 7 H), 2.4 (s, 3 H). Anal. ($C_{20}H_{15}F_2N_3O_4\cdot 0.25H_2O$) C, H, N.

3-[[6-[3-Amino(imino)methyl]phenoxy]3,5-difluoro-4-methylpyridin-2-yl]oxy]*n*-methyl-benzamide, Acetic Acid Salt, 0.2 Hydrate (4e). NMR (DMSO-d_6): δ 10.3 (br, 4H), 8.5 (m, 1H), 7.6 (m, 1 H), 7.58 (m, 3 H), 7.4 (m, 4 H), 7.3 (m, 1 H), 2.8 (d, 3 H), 2.4 (s, 3H), 1.75 (s, 3 H). Anal. ($C_{21}H_{18}F_2N_4O_3\cdot C_2H_4O_2\cdot 0.2H_2O$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzamide, Acetic Acid Salt, Hemihydrate (4f). NMR (DMSO-d_6): δ 10.3 (br, 4 H), 7.5 (m, 5 H), 7.2 (m, 3 H), 3.0 (s, 3 H), 2.8 (s, 3 H), 2.4 (s, 3 H), 1.75 (s, 3 H). Anal. ($C_{22}H_{20}F_2N_4O_3\cdot 0.5H_2O\cdot C_2H_4O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-diethylbenzamide, Acetic Acid Salt, Hemihydrate (4g). NMR (DMSO-d_6): δ 10.1 (br, 4 H), 7.5 (m, 3 H), 7.4 (m, 2 H), 7.2 (d, 1H), 7.1 (m, 4 H), 3.4 (br, 2 H), 3.0 (br, 2 H), 2.4 (s, 3 H), 1.75 (s, 3 H), 1.15 (br, 3 H), 0.95 (br, 3 H). Anal. ($C_{24}H_{24}F_2N_4O_3\cdot C_2H_4O_2\cdot 0.5H_2O$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]3,5-difluoro-4-methylpyridin-2-yl]oxy]-*n*-methyl-*n*-phenylmethylbenzamide, Acetic Acid Salt, Hemihydrate (4h). NMR (DMSO-d_6): δ (mixture of rotamers) 10.1 (br, 4 H), 7.6 (m, 3 H), 7−7.6 (m, 13), 4.6 and 4.25 (2s, 2 H), 2.85 and 2.65 (2s, 3H), 2.4 (s, 3 H), 1.75 (s, 3 H). Anal. ($C_{28}H_{24}F_2N_4O_3\cdot C_2H_4O_2\cdot 0.5H_2O$) C, H, N.

1-[3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzoyl]pyrrolidine, Acetic Acid Salt, 0.9 Hydrate (4i). NMR (DMSO-d_6): δ 10.3 (br, 4 H), 7.3−7.6 (m, 5 H), 7.2 (m, 3 H), 3.4 (t, 2 H), 3.2 (t, 2 H), 2.4 (s, 3 H), 2.1 (s, 6 H), 1.8 (m, 4 H), 1.75 (s, 3 H). Anal. ($C_{24}H_{22}F_2N_4O_3\cdot C_2H_4O_2\cdot 0.9H_2O$) C, H, N.

4-[3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzoyl]morpholine, Acetic Acid Salt (4j). NMR (DMSO-d_6): δ 10.1 (br, 4 H), 7.3−7.6 (m, 5 H), 7.2 (m, 3 H), 3.1−3.8 (m, 8 H), 2.4 (s, 3 H), 1.75 (s, 3 H). Anal. ($C_{24}H_{22}F_2N_4O_4\cdot C_2H_4O_2$) C, H, N.

1-[3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyredin-2-yl]oxy]benzoyl]piperidine, Acetic Acid Salt, 0.75 Hydrate (4k). NMR (DMSO-d_6): δ 10.25 (br, 4H), 7.6 (m, 3 H), 7.4 (m, 2 H), 7.2 (m, 1 H), 7.15 (m, 2 H), 3.45 (br, 2 H), 3.15 (br, 2 H), 2.4 (s, 3H), 1.8 (s, 3 H), 1.3−1.6 (m, 6 H). Anal. ($C_{25}H_{24}F_2N_4O_3\cdot C_2H_4O_2\cdot 0.75H_2O$) C, H, N.

1-[3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzoyl]-4-methylpiperazine, Acetic Acid Salt, Hydrate (4l). NMR (DMSO-d_6): δ 10.5 (br, 4H), 7.6 (m, 3 H), 7.4 (m, 2 H), 7.2 (m, 1 H), 7.15 (m, 2 H), 3.17−3.7 (m, 4 H), 2.4 (s, 3H), 2.4 (m, 4 H), 2.2 (s, 3 H), 1.8 (s, 3 H). Anal. ($C_{25}H_{25}F_2N_5O_3 \cdot C_2H_4O_2 \cdot H_2O$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*-phenylbenzamide, Acetic Acid Salt (4m). NMR (DMSO-d_6): δ 10.3 (br, 4 H), 7.8 (m, 4 H), 7.3−7.6 (m, 8 H), 7.15 (t, 1 H), 2.4 (s, 3 H), 1.75 (s, 3 H). Anal. ($C_{26}H_{20}F_2N_4O_3 \cdot C_2H_4O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzeneacetamide, 0.1 Hydrate, 1.6 Trifluoroacetic Acid Salt (4n). NMR (300 MHz, DMSO): δ 7.52 (m, 2H), 7.25 (m, 2H), 6.95 (m, 4H), 3.64 (s, 2H), 2.95 (s, 3H), 2.75 (s, 3H), 2.37 (s, 3H). Anal. ($C_{23}H_{22}F_2N_4O_3 \cdot 0.1H_2O \cdot 1.6C_2HF_3O_2$) C, H, N, F.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzeneacetamide, 1.25 Hydrate, 1.12 Trifluoroacetic Acid Salt (4o). NMR (300 MHz, DMSO): δ 9.36 (s, 2H), 9.2 (s, 2H), 7.58 (m, 4H), 7.25 (m, 1H), 6.95 (m, 3H), 3.64 (s, 2H), 2.37 (s, 3H). Anal. ($C_{21}H_{18}F_2N_4O_3 \cdot 1.25H_2O \cdot 1.12C_2HF_3O_2$) C, H, N, F.

3-[[6-[3-[Amino(imino)methyl]phenoxy]3,5-difluoro-4-methylpyridin-2-yl]oxy]benzeneacetic Acid Ethyl Ester, Acetic Acid Salt (4p). NMR (300 MHz, DMSO): δ 7.58 (m, 4H), 7.25 (m, 1H), 6.95 (m, 3H), 4.1 (q, 2H), 3.64 (s, 2H), 2.37 (s, 3H), 1.2 (t, 3H). Anal. ($C_{23}H_{21}F_2N_3O_4 \cdot C_2H_4O_2$) C, H, N, F.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzeneacetic Acid, 1.1 Hydrate, Trifluoroacetic Acid Salt (4q). NMR (300 MHz, DMSO): δ 9.36 (s, 2H), 9.2 (s, 2H), 7.58 (m, 4H), 7.25 (m, 1H), 6.95 (m, 3H), 3.4 (s, 2H), 2.37 (s, 3H). Anal. ($C_{21}H_{17}F_2N_3O_4 \cdot 1.1H_2O \cdot C_2HF_3O_2$) C, H, N, F.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethyl-a-hydroxy-benzeneacetamide, Acetic Acid Salt, 0.5 Hydrate (4r). NMR (300 MHz, DMSO): δ 7.5 (m, 4H), 7.19 (t, 1H), 7.09 (m, 3H), 5.35 (m, 1H), 2.82 (s, 6H), 2.37 (s, 3H). Anal. ($C_{23}H_{21}F_2N_4O_4 \cdot 0.5H_2O \cdot C_2H_4O_2$) C, H, N, F.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-α-methoxybenzeneacetamide, Acetic Acid Salt, 0.5 Hydrate (4s). NMR (300 MHz, DMSO): δ 7.5 (m, 4H), 7.25 (m, 1H), 7.09 (m, 3H), 4.55 (m, 1H), 3.25 (s, 3H), 2.37 (s, 3H). Anal. ($C_{22}H_{20}F_2N_4O_4 \cdot 0.5H_2O \cdot C_2H_4O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3, 5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzenepropanamide, 1.8 Trifluoroacetic Acid Salt (4t). NMR (300 MHz, DMSO): δ 9.33 (d, 2H), 7.56 (m, 4H), 7.23 (m, 1H), 6.9 (m, 3H), 2.95 (s, 3H), 2.85 (s, 3H), 2.75 (t, 2H), 2.53 (t, 2H), 2.37 (s, 3H). Anal. ($C_{24}H_{24}F_2N_4O_3 \cdot 1.8C_2HF_3O_2$) C, H, N, F.

3-[[6-[3[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzenepropanamide, 0.5 Hydrate, 1.5 Trifluoroacetic Acid Salt (4u). NMR (300 MHz, DMSO): δ 9.33 (s, 2H), 9.14 (s, 2H), 7.6 (m, 3H), 7.34 (s, 1H), 7.2 (m, 1H), 6.95 (m, 2H), 6.85 (s, 1H), 2.8 (t, 2H), 2.37 (s, 3H), 2.3 (t, 2H). Anal. ($C_{22}H_{20}F_2N_4O_3 \cdot 0.5H_2O \cdot 1.5C_2HF_3O_2$) C, H, N, F.

3-[[6-(3-Actylphenoxy)-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt (4v). NMR (300 MHz, DMSO): δ 7.5 (m, 8H), 2.41 (s, 3H), 1.72 (s, 3H). Anal. ($C_{21}H_{17}F_2N_3O_3 \cdot C_2H_4O_2$) C, H, N, F.

3-[[3,5-Difluoro-4-methyl-6-[3-(2-methyl-1-oxopropyl)-phenoxy]pyridin-2-yl]oxy]benzenecarboximidamide, 0.9 Acetic Acid Salt, Hydrochloride (4w). NMR (300 MHz, DMSO): δ 10.4 (br, 4H), 7.5 (m. 8H), 2.5 (s, 6H), 2.4 (s, 3H), 1.75 (s, 3H). Anal. ($C_{23}H_{21}F_2N_5O_3 \cdot HCl \cdot 0.9C_2H_4O_2$) C, H, N, F.

3-[[6-[3-[Amino(imino)methyl]phenoxy-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzenesulfonamide, Acetic Acid Salt, 0.5 Hydrate (4x). NMR (300 MHz, DMSO): δ 7.5 (m, 8H), 3.42 (m, 1H), 2.37 (s, 3H), 1.14 (d, 6H). Anal. ($C_{21}H_{20}F_2N_4O_4S \cdot C_2H_4O_2 \cdot 0.5H_2O$) C, H, N.

3-[[6-[3-(Aminomethyl)phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, 2 Trifluoroacetic Acid Salt (4y). NMR (300 MHz, DMSO): δ 9.03 (s, 2H), 8.25 (br s, 2H), 7.6 (m, 4H), 7.3 (m, 1H), 7.2 (m, 3H), 4.05 (s, 2H), 2.37 (s, 3H). Anal. ($C_{20}H_{18}F_2N_4O_2 \cdot 0.5H_2O \cdot 0.2C_2HF_3O_2$) C, H, N, F.

3-[3,5-Difluoro-6-[3-(dimethylaminomethy)phenoxy]-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt, 0.5 Hydrate (4z). NMR (DMSO): δ 10.4 (br, 4 H), 7.5 (m, 4 H), 7.25 (t, 1 H), 7.0 (m, 3 H), 3.3 (s, 2 H), 2.4 (s, 3 H), 2.1 (s, 6 H), 1.75 (s, 3 H). Anal. ($C_{22}H_{22}F_2N_4O_2 \cdot C_2H_4O_2 \cdot 0.5H_2O$) C, H, N.

3-[3,5-Difluoro-6-(3-nitrophenoxy)-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt, 0.9 Hydrate (4aa). NMR (DMSO-d_6): δ 10.1 (br, 4 H), 8.05 (m, 2 H), 7.65 (m, 2 H), 7.55 (m, 2 H), 7.45 (m, 2 H), 2.4 (s, 3 H), 1.75 (s, 3 H). Anal. ($C_{19}H_{14}F_2N_4O_4 \cdot C_2H_4O_2 \cdot 0.9H_2O$) C, H, N.

3-[[6-(3-Aminophenoxy)-3,5-difluoro-4-methylpyridin-2-yl]oxy]benxenecarboximidamide, 0.7 Hydrate, 2 Trifluoroacetic Acid Salt (4bb). NMR (DMSO-d_6): δ 9.3 (s, 2 H), 9.2 (s, 2 H), 7.8 (m, 3 H), 7.75 (m, 1 H), 7.0 (t, 1 H), 6.4 (d, 1 H), 6.3 (m, 2 H), 2.4 (s, 3 H). Anal. ($C_{19}H_{16}F_2N_4O_2 \cdot 0.7H_2O \cdot 2C_2HF_3O_2$) C, H, N.

3-[[3,5-Difluoro-6-[3-(dimethylamino)phenoxy]-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt (4cc). ^{1}H NMR (300 MHz, DMSO): δ 10.3 (br s, 4H), 7.5 (m, 4H), 7.1 (t, 1H), 6.45 (d, 1H), 6.40 (s, 1H), 6.3 (d, 1 H), 2.85 (s, 6 H), 2.4 (s, 3 H), 1.75 (s, 3 H). Anal. ($C_{21}H_{20}F_2N_4O_2 \cdot C_2H_4O_2$) C, H, N.

3-[[3,5-Difluoro-6-[3-(ethylamino)phenoxy]-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt, 0.3 Hydrate (4dd). NMR (DMSO-d_6): δ 10.2 (br, 4 H), 7.5 (m, 4 H), 7.0 (t, 1 H), 6.35 (d, 1 H), 6.2 (m, 2 H), 5.7 (s, 1 H), 3.0 (m, 2 H), 2.4 (s, 3 H), 1.8 (s, 3 H), 1.15 (t, 3 H). Anal. ($C_{21}H_{20}F_2N_4O_2 \cdot 0.3H_2O \cdot C_2H_4O_2$) C, H, N.

3-[[6-[-3-(Dimethylamino)phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt (4ee). NMR (DMSO-d_6): δ 10.2 (br, 4 H), 7.5 (m, 4 H), 7.1 (t, 1 H), 6.4 (d, 1 H), 6.35 (s, 1 H), 6.25 (d, 1 H), 3.25 (q, 4 H), 2.4 (s, 3 H), 1.75 (s, 3 H), 1.0 (t, 6 H). Anal. ($C_{23}H_{24}F_2N_4O_3 \cdot C_2H_4O_2$) C, H, N.

3-[[3,5-Difluoro-4-methyl-6-[3-(phenylamino)phenoxy]-pyridin-2-yl]oxy]benzenecarboximidamide, 0.6 Acetic Acid Salt, 0.5 Hydrate, 0.4 Hydrochloride (4ff). NMR (DMSO-d_6): δ 10 (br, 4H), 8.4 (s, 1H), 7.5 (m, 4 H), 7.25 (t, 2H), 7.15 (m, 3 H), 6.9 (m, 2 H), 6.8 (s, 1 H), 6.55 (d, 1H), 2.4 (s, 3H), 1.8 (s, 1.8 H). Anal. ($C_{25}H_{20}F_2N_4O_3 \cdot 0.6C_2H_4O_2 \cdot 0.5H_2O \cdot 0.4HCl$) C, H, N.

3-[[3,5-Difluoro-6-[3-(methylsulfonylamino)phenoxy]-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt (4gg). NMR (DMSO-d_6): δ 10.2 (br, 4 H), 7.5 (m, 3 H), 7.40 (dt, 1 H), 7.15 (t, 1 H), 6.85 (dd, 1 H), 6.80 (t, 1H), 6.66 (dd, 1 H), 2.83 (s, 3 H), 2.36 (s, 3 H), 1.74 (s, 3 H). Anal. ($C_{20}H_{18}F_2N_4O_4S \cdot C_2H_4O_2$) C, H, N.

***N*-[3-[[6-[3-[Amino(imino)methyl]phenoxy]3,5-difluoro-4-methylpyridin-2-yl]oxy]phenyl]acetamide, 0.25 Hydrate, Acetic Acid Salt (4hh).** NMR (DMSO-d_6): δ 10.3 (br, 4 H), 10.1 (s, 1 H), 7.5 (m, 5 H), 7.2 (m, 2 H), 6.8 (m, 1 H), 2.4 (s, 3 H), 2.05 (s, 3 H), 1.75 (s, 3 H). Anal. ($C_{21}H_{18}F_2N_4O_3 \cdot C_2H_4O_2 \cdot 0.25H_2O$) C, H, N.

1-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]phenyl]urea, 0.1 Ammonium Chloride, Hydrochloride (4ii). NMR (DMSO-d_6): δ 9.4 (s, 2 H), 9.2 (s, 2 H), 9.1 (s, 1 H), 7.6 (m, 4 H), 7.4 (s, 1 H), 7.15 (t, 1 H), 7.0 (d, 1 H), 6.65 (d, 1 H), 6.1 (s, 2 H), 2.4 (s, 3 H). Anal. ($C_{20}H_{16}F_2O_3N_5 \cdot 0.1NH_4Cl \cdot HCl$) C, H, N.

3-[3,5-Difluoro-6-[3-(morpholine-4-yl)phenoxy]-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid, 0.6 Hydrate (4jj). NMR (DMSO-d_6): δ 10.2 (br, 4 H), 7.3−7.6 (m, 4 H), 7.15 (t, 1 H), 6.7 (m, 2 H), 6.5 (d, 1 H), 3.7 (s, 4 H), 3.0 (s, 4H), 2.4 (s, 3 H), 1.75 (s, 3 H). Anal. ($C_{23}H_{22}N_4F_2O_3 \cdot C_2H_4O_2 \cdot 0.6H_2O$) C, H, N.

3-[[3,5-Difluoro-6-[3-(1H-imidazol-1-yl)phenoxy]-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Hy-

drochloride, 0.9 Hydrate (4kk). NMR (DMSO-d_6): δ 9.9 (br, 4 H), 8.3 (s, 1 H), 7.8 (s, 1 H), 7.5 (m, 6 H), 7.3 (t, 1 H), 7.15 (m, 2 H), 2.4 (s, 3 H). Anal. ($C_{22}H_{17}F_2N_5O_2 \cdot HCl \cdot 0.9H_2O$) C, H, N.

3-[[3,5-Difluoro-4-methyl-6-[3-(trifluoromethyl)phenoxy]-pyredin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt (4ll). NMR (300 MHz, DMSO): δ 10.1 (br. s, 4H), 7.61−7.55 (m, 2H), 7.51 (m, 1H), 7.46 (m, 1H), 7.23 (m, 1H), 6.74−6.65 (m, 3H), 3.71 (s, 3H), 2.39 (s, 3H). Anal. ($C_{20}H_{17}F_2N_3O_3 \cdot 0.7C_2H_4O_2 \cdot 0.1C_4H_{10}O \cdot 0.6HCl$) C, H, N.

3-[[6-[(3-Trifluoromethoxy)phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt (4mm). NMR (300 MHz, DMSO): δ 2.37 (s, 3H), 7.15 (m, 3H), 7.55 (m, 5H). Anal. ($C_{20}H_{14}F_5N_3O_3 \cdot C_2H_4O_2$) C, H, N, F.

3-[[[6-[3-(Methylethoxy)phenoxy]-3,5-difluoro-4-methyl-pyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt (4nn). NMR (300 MHz, DMSO): δ 7.58 (m, 4H), 7.19 (t, 1H), 6.65 (m, 3H), 4.52 (m, 1H), 2.37 (s, 3H), 1.21 (d, 6H). Anal. ($C_{22}H_{21}F_2N_3O_3 \cdot C_2HF_3O_2$) C, H, N, F.

3-[[3,5-Difluoro-6-(3-fluorophenoxy)-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, 1.1 Acetic Acid Salt (4oo). NMR (300 MHz, DMSO): δ 10.4 (br. s, 4H), 7.59−7.48 (m, 3H), 7.44 (m, 1H), 7.34 (m, 1H), 7.06 (d, 1H), 7.00−6.94 (m, 2H), 2.38 (s, 3H). Anal. ($C_{19}H_{14}F_3N_3O_2 \cdot 1.1C_2H_4O_2$) C, H, N.

3-[[6-(3-Chlorophenoxy)-3,5-difluoro-4-methylpyredin-6-yl]oxy]benzenecarboximidamide, 1.25 Acetic Acid Salt (4pp). NMR (300 MHz, DMSO): δ 10.4 (br. s, 4H), 7.62−7.47 (m, 4H), 7.35 (t, 1H), 7.31 (t, 1H), 7.21 (dd, 1H), 7.12 (dd, 1H), 2.40 (s, 3H). Anal. ($C_{19}H_{14}ClF_2N_3O_2 \cdot 1.25C_2H_4O_2$) C, H, N.

3-[[3,5-Difluoro-6-(3-hydroxyphenoxy)-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt, Diethyl ether (4qq). NMR (300 MHz, DMSO): δ 7.58 (m, 4H), 2.37 (s, 3H), 7.1 (m, 1H), 6.55 (m, 3H). Anal. ($C_{19}H_{15}F_2N_3O_3 \cdot C_2H_4O_2 \cdot C_4H_{10}O$) C, H, N, F.

3-[[3,5-Difluoro-4-methyl-6-[3-(trifluoromethyl)phenoxy]-pyredin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt (4rr). NMR (300 MHz, DMSO): δ 10.4 (br. s, 4H), 7.59−7.53 (m, 5H), 7.5−7.4 (m, 3H), 2.41 (s, 3H). Anal. ($C_{20}H_{14}F_5N_3O_2 \cdot 1.0C_2H_4O_2$) C, H, N.

3-[[3,5-Difluoro-6-[3-(hydroxymethyl)phenoxy]-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, 0.4 Hydrate, 1.1 Trifluoroacetic Acid Salt (4ss). NMR (300 MHz, DMSO): δ 9.33 (s, 2H), 7.56 (m, 4H), 7.23 (m, 1H), 7.02 (m, 3H), 4.45 (s, 2H), 2.37 (s, 3H). Anal. ($C_{20}H_{17}F_2N_3O_3 \cdot 0.4H_2O \cdot 1.1C_2HF_3O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-2-hydroxy-*N*,*N*-dimethylbenzamide, 1.5 Trifluoroacetic Acid Salt (5a). NMR (DMSO-d_6): δ 9.6 (s, 1), 9.2 (s, 2), 9.0 (s, 2), 7.5 (m, 3), 7.4 (d, 1), 7.1 (d, 1), 6.9 (d, 1), 6.8 (t, 1), 3.7 (br s, 6), 2.4 (s, 3). Anal. ($C_{22}H_{20}F_2N_4O_4 \cdot 1.5C_2HF_3O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-2-methoxy-*N*,*N*-dimethylbenzamide, 1.35 Trifluoroacetic Acid Salt (5b). NMR (DMSO-d_6): δ 9.2 (s, 2), 9.0 (s, 2), 7.5 (dd, 3), 7.4 (d, 1), 7.2 (d, 1), 7.1 (t, 1), 7.0 (d, 1), 3.5 (br s, 6), 3.0 (s, 3), 2.4 (s, 3). Anal. ($C_{23}H_{22}F_2N_4O_4 \cdot 1.35C_2HF_3O_2$) C, H, N.

5-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethyl-2-methoxybenzenecarboxamide, Hydrate, 1.2 Trifluoroacetic Acid Salt (5c). NMR (DMSO-d_6): δ 9.8 (br s, 1), 9.3 (s, 2), 9.2 (s, 2), 7.5 (m, 4), 7.0 (dd, 1), 6.9 (s, 1), 6.8 (d, 1), 2.9 (br s, 3), 2.7 (br s, 3), 2.4 (s, 3). Anal. ($C_{22}H_{20}F_2N_4O_4 \cdot 1.2C_2HF_3O_2 \cdot 1.0H_2O$) C, H, N.

5-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethyl-2-methoxybenzenecarboxamide, Hydrate, 1.25 Trifluoroacetic Acid Salt (5d). NMR (DMSO-d_6): δ 9.3 (s, 2), 9.0 (s, 2), 7.5 (m, 3), 7.4 (d, 1), 7.1 (d, 1), 6.9 (m, 2), 3.7 (s, 3), 2.9 (s, 3), 2.6 (s, 3), 2.4 (s, 3). Anal. ($C_{23}H_{22}F_2N_4O_4 \cdot 1.25C_2HF_3O_2 \cdot 1.0H_2O$) C, H, N.

5-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-3,4-dihydroxy-*N*,*N*-dimethylbenzamide, 0.9 Ammonium Chloride, 2.0 Trifluoroacetic Acid Salt (5e). NMR (DMSO-d_6): δ 9.3 (s, 2), 9.0 (s, 2), 7.4 (m, 4), 6.7 (s, 1), 6.5 (s, 1), 2.8 (br s, 6), 2.4 (s, 3). Anal. ($C_{22}H_{20}F_2N_4O_4 \cdot 2.0C_2HF_3O_2 \cdot 0.9NH_4Cl$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-4,5-dimethoxy-*N*,*N*-dimethylbenzamide, 1.2 Hydrate, Trifluoroacetic Acid Salt (5f). NMR (DMSO-d_6): δ 9.3 (s, 2), 9.1 (s, 2), 7.9 (s, 1), 7.4 (m, 7), 3.9 (s, 3), 3.6 (s, 3), 2.4 (s, 3). Anal. ($C_{22}H_{20}F_2N_4O_5 \cdot C_2HF_3O_2 \cdot 1.2H_2O$) C, H, N.

5-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*,*N*′,*N*′-tetramethylbenzene-1,3-dicarboxamide, 1.75 Trifluoroacetic Acid Salt (5g). NMR (DMSO-d_6): δ 9.3 (s, 2), 9.1 (s, 2), 7.5 (m, 4), 7.25 (s, 2), 7.15 (s, 1), 3.0 (br s, 6), 2.8 (br s, 6), 2.4 (s, 3). Anal. ($C_{25}H_{25}F_2N_5O_4 \cdot 1.75C_2HF_3O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-5-hydroxy-*N*,*N*-dimethylbenzamide, 1.6 Trifluoroacetic Acid Salt (5h). NMR (DMSO-d_6): δ 9.3 (s, 2), 9.0 (s, 2), 7.5 (m, 4), 6.5 (m, 3), 2.9 (s, 3), 2.7 (s, 3), 2.4 (s, 3). Anal. ($C_{22}H_{20}F_2N_4O_4 \cdot 1.41C_2HF_3O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-5-methoxy-*N*,*N*-dimethylbenzamide, 1.1 Trifluoroacetic Acid Salt (5i). NMR (DMSO-d_6): δ 9.3 (s, 2), 9.1 (s, 2), 7.6 (m, 4), 6.8 (s, 1), 6.7 (d, 2), 3.7 (s, 3), 2.9 (s, 3), 2.8 (s, 3), 2.4 (s, 3). Anal. ($C_{23}H_{22}F_2N_4O_4 \cdot 1.1C_2HF_3O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethyl-4-methylbenzamide, 1.65 Trifluoroacetic Acid Salt (5j). NMR (DMSO-d_6): δ 9.3 (s, 2), 9.1 (s, 2), 7.5 (m, 4), 7.3 (d, 1), 7.1 (m, 2), 2.9 (br s, 3), 2.7 (br s, 3), 2.4 (s, 3), 2.1 (s, 3). Anal. ($C_{23}H_{22}F_2N_4O_3 \cdot 1.65C_2HF_3O_2$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-4-hydroxy-*N*,*N*-dimethylbenzamide, 1.2 Trifluoroacetic Acid Salt, 0.5 Hydrate (5k). NMR (DMSO-d_6): δ 9.2 (s, 2), 8.9 (s, 2), 7.4 (m, 4), 7.0 (m, 2), 6.9 (d, 1), 2.8 (br s, 6), 2.4 (s, 3). Anal. ($C_{22}H_{20}F_2N_4O_4 \cdot 1.2C_2HF_3O_2 \cdot 0.5H_2O$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]phenoxy]3,5-difluoro-4-methylpyridin-2-yl]oxy]-4-methoxy-*N*,*N*-dimethylbenzamide, 1.55 Trifluoroacetic Acid Salt (5l). NMR (DMSO-d_6): δ 9.3 (s, 2), 9.1 (s, 2), 7.5 (m, 3), 7.3 (d, 1), 7.2 (m, 2), 7.1 (d, 1), 3.8 (s, 3), 2.9 (br s, 3), 2.8 (br s, 3), 2.4 (s, 3). Anal. ($C_{23}H_{22}F_2N_4O_4 \cdot 1.55C_2HF_3O_2$) C, H, N.

3-[[3,5-Difluoro-6-(3-(dimethylamino)-2-methylphenoxy)-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, 1.75 Hydrate, 2 Trifluoroacetic Acid Salt (5m). NMR (DMSO-d_6): δ 9.3 (s, 2H), 9.2 (s, 2H), 7.55 (m, 3 H), 7.4 (d, 1H), 7.1 (t, 1H), 6.9 (d, 1H), 6.75 (d, 1H), 2.65 (s, 6H), 2.4 (s, 3H), 2.05 (s, 3H). Anal. ($C_{22}H_{22}F_2N_4O_2 \cdot 1.75H_2O \cdot 2C_2HF_3O_2$) C, H, N.

3-[[6-(4-Chloro-3-dimethylaminophenoxy)-3,5-difluoro-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Hydrate, 2.2 Trifluoroacetic Acid Salt (5n). NMR (DMSO-d_6): δ 9.3 (s, 2H), 9.14 (s, 2H), 7.6 (m, 3H), 7.5 (m, 1 H), 7.28 (d, 1H), 6.88 (d, 1H), 6.74 (dd, 1H), 2.65 (s, 6H), 2.4 (m, 3H). Anal. ($C_{22}H_{19}ClF_2N_4O \cdot 2.2C_2HF_3O_2 \cdot H_2O$) C, H, N.

2-[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]-4-dimethylaminobenzenecarboxylic Acid, Ethyl Ester, Acetic Acid Salt, 1.1 Hydrate (5o). NMR (DMSO-d_6): δ 9.2 (s, 2H), 8.95 (s, 2H), 7.67 (d, 1 H), 7.46 (d, 3H), 7.35 (m, 2H), 7.15 (d, 1H), 6.48 (d,1H), 6.35 (s, 1H), 4.0 (q, 2H), 2.95 (s, 6H), 2.35 (s, 3H), 1.85 (s, 3H), 1.05 (t, 3H). Anal. ($C_{26}H_{28}F_2N_4O_6 \cdot 1.1H_2O$) C, H, N.

2-[[6-[3-[Amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-4-dimethylaminobenzoic Acid, 1.5 Trifluoroacetic Acid Salt (5p). NMR (DMSO-d_6): δ 9.25 (s, 2H), 9.0 (s, 2H), 7.68 (d, 1 H), 7.45 (m, 3H), 7.22 (d, 1H), 6.5 (d, 1H), 6.4 (m, 1H), 3.05 (s, 6H), 2.4 (s, 3H). Anal. ($C_{22}H_{20}F_2N_4O_4 \cdot 1.5C_2HF_3O_2$) C, H, N.

3-[[3,5-Difluoro-6-[5-(dimethylamino)-2-methylphenoxy]-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, 1.2 Hydrate, 2 Trifluoroacetic Acid Salt (5q). NMR (DMSO-d_6): δ 9.2 (s, 2H), 9.05 (s, 2H), 7.45 (m, 3 H),

7.3 (m, 4H), 3.05 (s, 6H), 2.35 (s, 3H), 2.05 (s, 3H). Anal. ($C_{22}H_{22}F_2N_4O_2 \cdot 1.2H_2O \cdot 2C_2HF_3O_2$) C, H, N.

3-[[3,5-Difluoro-6-(5-(dimethylamino)-2-methoxyphenoxy)-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, Acetic Acid Salt, 0.2 Hydrate (5r). NMR (DMSO-d_6): δ 9.25 (s, 2H), 9.05 (s, 2H), 7.5 (m, 2 H), 7.45 (m, 3H), 7.25 (d, 1H), 7.1 (d, 1H), 3.65 (s, 3H), 3.05 (s, 6H), 2.35 (s, 3H), 1.95 (s, 3H). Anal. ($C_{22}H_{22}F_2N_4O_3 \cdot C_2H_4O_2 \cdot 0.2H_2O$) C, H, N.

3-[[6-[3-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzamide, Hydrate, Trifluoroacetic Acid (6a). NMR (300 MHz, DMSO): δ 9.03 (s, 2H), 8.75 (s, 2H), 7.5 (m, 1H), 7.3 (m, 5H), 2.97 (s, 3H), 2.92 (s, 3H), 2.37 (s, 3H). Anal. ($C_{22}H_{20}F_2N_4O_4 \cdot H_2O \cdot C_2HF_3O_2$) C, H, N, F.

3-[[3,5-Difluoro-6-[3-(dimethylamino)phenoxy]-4-methylpyridin-2-yl]oxy]-2-hydroxy-4-methoxybenzenecarboximidamide, 1.2 Hydrate, 2 Trifluoroacetic Acid Salt (6b). NMR (300 MHz, DMSO): δ 8.88 (s, 2H), 8.67 (s, 2H), 7.45 (d, 1H), 7.02 (t, 1H), 6.75 (d, 1H), 6.41 (d, 1H), 6.24 (s, 1H), 6.02 (d, 1H), 2.85 (s, 6H), 2.37 (s, 3H).

(**6b**): Anal. ($C_{21}H_{20}F_2N_4O_4 \cdot 1.2H_2O \cdot 2C_2HF_3O_2$) C, H, N, F.

3-[[6-[5-[Amino(imino)methyl]-2,3-dihydroxyphenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzamide, Hydrate, 1.5 Trifluoroacetic Acid Salt (6c). NMR (300 MHz, DMSO): δ 10.2 (br s, 2H), 9.03 (s, 2H), 8.75 (s, 2H), 7.3 (m, 1H), 7.1 (m, 5H), 2.95 (s, 3H), 2.75 (s, 3H), 2.37 (s, 3H). Anal. ($C_{22}H_{20}F_2N_4O_5 \cdot H_2O \cdot 1.5C_2HF_3O_2$) C, H, N, F.

3-[[6-[5-[Amino(imino)methyl]-2,3-dimethoxyphenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzamide, 0.3 Hydrogen Bromide, 1.3 Trifluoroacetic Acid Salt (6d). NMR (300 MHz, DMSO): δ 9.19 (s, 4H), 9.07 (s, 4H), 7.3 (m, 3H), 7.1 (m, 3H), 3.89 (s, 3H), 3.65 (s, 3H), 2.95 (s, 3H), 2.75 (s, 3H), 2.37 (s, 3H). Anal. ($C_{24}H_{24}F_2N_4O_5 \cdot 0.3HBr \cdot 1.3C_2HF_3O_2$) C, H, N, F.

3-[[6-[5-[Amino(imino)methyl]-3-hydroxy-2-methoxyphenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzamide, 0.1 Hydrogen Bromide, 1.15 Trifluoroacetic Acid Salt (6e). NMR (300 MHz, DMSO): δ 10.3 (s, 1H), 9.03 (s, 2H), 8.75 (s, 2H), 7.3 (m, 3H), 7.1 (m, 3H), 3.89 (s, 3H), 2.95 (s, 3H), 2.75 (s, 3H), 2.37 (s, 3H). Anal. ($C_{23}H_{22}F_2N_4O_5 \cdot 0.1HBr \cdot 1.15C_2HF_3O_2$) C, H, N, F.

3-[[6-[5-[Amino(imino)methyl]-3-methoxyphenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzamide, 2 Trifluoroacetic Acid Salt (6f). NMR (300 MHz, DMSO): δ 9.25 (s, 2 H), 9.2 (s, 2H), 7.4 (t, 1 H), 7.2 (m, 6H), 3.8 (s, 3H), 2.95 (s, 3H), 2.75 (s, 3 H), 2.4 (s, 3 H) ppm. Anal. ($C_{23}H_{22}F_2N_4O_4 \cdot 2C_2HF_3O_2$) C, H, N.

3-[[6-[2-Amino-5-[amino(imino)methyl]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzamide, 1.6 Hydrate, 0.17 Trifluoroacetic Acid Salt, 0.8 Acetic Acid Salt (6g). NMR (300 MHz, DMSO): δ 8.8 (s, 4H), 7.49 (dd, 1H), 7.47 (s, 1H), 7.33 (t, 1H), 7.16−7.11 (m, 2H), 7.06 (s, 1H), 6.76 (d, 1H), 6.19 (s, 2H), 2.98 (s, 3H), 2.79 (s, 3H), 2.40 (s, 3H). Anal. ($C_{22}H_{21}F_2N_5O_3 \cdot 1.6H_2O \cdot 0.8C_2H_4O_2 \cdot 0.17C_2HF_3O_2$) C, H, N.

3-[[6-[[5-[Amino(imino)methyl]-2-trifluoromethylsulfonylamino]phenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzamide, 0.2 Hydrochloride (6h). NMR (300 MHz, DMSO): δ 8.93 (s, 2H), 8.52(s, 2H), 7.49−7.47 (m, 3H), 7.26 (t, 1H), 7.10−7.03 (m, 2H), 6.98 (m, 1H), 2.95 (s, 3H), 2.78 (s, 3H), 2.34 (s, 3H). Anal. ($C_{23}H_{20}F_5N_5O_5S \cdot 0.2HCl$) C, H, N.

3-[[6-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzamide, 0.1 Hydrate, 0.9 Trifluoroacetic Acid Salt, 0.76 Acetic Acid Salt (6i). NMR (300 MHz, DMSO): δ 9.03 (s, 2H), 8.75 (s, 2H), 7.6 (m, 2H), 7.3 (m, 1H), 7.1 (m, 4H), 2.95 (s, 3H), 2.75 (s, 3H), 2.37 (s, 3H). Anal. ($C_{22}H_{20}F_2N_4O_4 \cdot 0.1H_2O \cdot 0.9C_2HF_3O_2 \cdot 0.76C_2H_4O_2$) C, H, N, F.

3-[[6-[5-[Amino(imino)methyl]-2-methoxyphenoxy]-3,5-difluoro-4-methylpyridin-2-yl]oxy]-*N*,*N*-dimethylbenzamide, 0.5 Hydrate, 1.5 Trifluoroacetic Acid Salt (6j). NMR (300 MHz, DMSO): δ 9.10 (s, 4H), 8.94 (s, 4H), 7.7 (m, 2H), 7.3 (m, 2H), 7.1 (m, 3H), 2.95 (s, 3H), 2.75 (s, 3H), 2.37 (s, 3H). Anal. ($C_{23}H_{22}F_2N_4O_4 \cdot 0.5H_2O \cdot 1.5C_2HF_3O_2$) C, H, N, F.

2,4-Dimethoxy-3-[[3,5-difluoro-6-[3-(dimethylamino)-phenoxy]-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, 0.6 Acetic Acid Salt, 2 Hydrate, 0.1 Trifluoroacetic (6k). NMR (300 MHz, DMSO): δ 7.45 (d, 1H), 7.07 (m, 2H), 6.44 (d, 1H), 6.24 (s, 1H), 6.05 (d, 1H), 3.78 (s, 6H), 2.85 (s, 6H), 2.37 (s, 3H). Anal. ($C_{23}H_{24}F_2N_4O_4 \cdot 0.6C_2H_4O_2 \cdot 0.2H_2O \cdot 0.1C_2HF_3O_2$) C, H, N, F.

3-[[3,5-Difluoro-6-[3-(dimethylamino)phenoxy]-4-methylpyridine-2-yl]oxy]-4-methylbenzenecarboximidamide, 0.95 Acetic Acid Salt, 0.3 Hydrate, 0.05 Trifluoroacetic Acid Salt (6l). NMR (300 MHz, DMSO): δ 10.1 (br. s, 4H), 7.55 (d, 1H), 7.48 (d, 1H), 7.42 (d, 1H), 7.02 (t, 1H), 6.43 (dd, 1H), 6.30 (t, 1H), 6.22 (dd, 1H), 2.81 (s, 6H), 2.37 (s, 3H), 2.19 (s, 3H). Anal. ($C_{22}H_{22}N_4O_2F_2 \cdot 0.95C_2H_4O_2 \cdot 0.05C_2HF_3O_2 \cdot 0.3H_2O$) C, H, N.

4-Amino-3-[[3,5-difluoro-6-[3-(dimethylamino)phenoxy]-4-methylpyridin-2-yl]oxy]benzenecarboximidamide, 1.5 Hydrate, 0.18 Trifluoroacetic Acid Salt, 0.8 Acetic Acid Salt (6m). NMR (300 MHz, DMSO): δ 12.0 (br. s, 1H), 8.78 (br. s, 2H), 8.63 (br. s, 2H), 7.49 (dd, 1H), 7.48 (s, 1H), 7.00 (t, 1H), 6.78 (d, 1H), 6.41 (dd, 1H), 6.30 (t, 1H), 6.25 (dd, 1H), 6.22 (br. s, 2H), 2.81 (s, 6H), 2.36 (s, 3H). Anal. ($C_{21}H_{21}F_2N_5O_2 \cdot 0.8C_2H_4O_2 \cdot 0.18C_2HF_3O_2 \cdot 1.5H_2O$) C, H, N.

3-[[[3,5-Difluoro-6-(3-dimethylamino)phenoxy]-4-methylpyridin-2-yl]oxy]-4-(methylsulfonylamino)benzenecarboximidamide, 1.5 Hydrate, 0.1 Trifluoroacetic Acid Salt, 0.8 Acetic Acid Salt (6n). NMR (300 MHz, DMSO): δ 9.3 (br. s, 4H), 7.50 (d, 1H), 7.21 (t, 1H), 7.15−7.12 (m, 2H), 6.60 (dd, 1H), 6.53−6.47 (m, 2H), 3.00 (s, 3H), 2.90 (s, 6H), 2.21 (s, 3H). Anal. ($C_{22}H_{23}F_2N_5O_4S \cdot 0.8C_2H_4O_2 \cdot 0.1C_2HF_3O_2 \cdot 1.5H_2O$) C, H, N.

3-[[[3,5-Difluoro-6-(3-dimethylamino)phenoxy]-4-methylpyridin-2-yl]oxy]-4-hydroxybenzenecarboximidamide, 2.2 Trifluoroacetic Acid Salt, 0.2 Hydrogen Bromide (6o). NMR (300 MHz, DMSO): δ 11 (br s, 1H), 9.07 (s, 2H), 8.75 (s, 2H), 7.65 (s, 1H), 7.57 (d, 1H), 7.08 (d, 1H), 6.95 (t, 1H), 6.4 (d, 1H), 6.27 (s, 1H), 6.15 (d, 1H), 2.85 (s, 6H), 2.37 (s, 3H). Anal. ($C_{21}H_{20}F_2N_4O_3 \cdot 2.2C_2HF_3O_2 \cdot 0.2HBr$) C, H, N, F.

3-[[3,5-Difluoro-6-[3(dimethylamino)phenoxy]-4-methylpyridin-2-yl]oxy]-4-methoxybenzenecarboximidamide, 0.5 Acetic Acid Salt, 0.2 Methylene Chloride, Hydrate (6p). NMR (300 MHz, DMSO): δ 7.75 (d, 1H), 7.7 (s, 1H), 7.28 (d, 1H), 7.05 (t, 1H), 6.45 (d, 1H), 6.3 (s, 1H), 6.15 (d, 1H), 2.85 (s, 6H), 2.37 (s, 3H). Anal. ($C_{22}H_{22}F_2N_4O_3 \cdot H_2O \cdot 0.5C_2HF_3O_2 \cdot 0.2CH_2Cl_2$) C, H, N, F.

2-[3-[Amino(imino)methyl]phenoxy]-6-[5-[amino(imino)methyl]-2-hydroxyphenoxy]pyridine-4-carboxylic Acid, Dihydrate, 3.2 Trifluoroacetic Acid Salt (7b). NMR (300 MHz, DMSO): δ 11.17 (s, 1H), 9.38 (s, 2H), 9.23 (s, 2H), 9.14 (s, 2H), 8.95 (s, 2H), 7.65 (m, 5H), 7.1 (m, 4H). Anal. ($C_{20}H_{17}N_5O_5 \cdot 2H_2O \cdot 3.2C_2HF_3O_2$) C, H, N.

2-[5-[Amino(imino)methyl]phenoxy]-6-[3-[(dimethylamino)carbonyl]phenoxy]pyridine-4-carboxylic Acid, 4 Hydrate, 3 Hydrochloric Acid Salt (7c). NMR (300 MHz, DMSO): δ 9.35 (s, 2H), 9.2 (s, 2H), 8.5 (br, 1H), 7−7.8 (m. 10H), 3.0 (s, 3H), 2.8 (s, 3H). Anal. ($C_{22}H_{20}N_4O_5 \cdot 4H_2O \cdot 3HCl$) C, H, N.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-[(dimethylamino)carbonyl]phenoxy]pyridine-4-carboxylic Acid, 0.9 Hydrate, 1.3 Trifluoroacetic Acid Salt (7d). NMR (300 MHz, DMSO): δ 11.21 (s, 1H), 9.16 (s, 2H), 9.04 (s, 2H), 7.7 (m, 2H), 7.43 (m, 1H), 7.1 (m, 6H), 3.05 (s, 3H), 2.85 (s, 3H). Anal. ($C_{22}H_{20}N_4O_6 \cdot 0.9H_2O \cdot 1.3C_2HF_3O_2$) C, H, N.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-(dimethylamino)phenoxy]pyridine-4-carboxylic Acid, 0.5 Hydrate, 2.2 Trifluoroacetic Acid Salt (7e). NMR (DMSO-d_6): δ 9.1 (s, 2), 8.8 (s, 2), 7.6 (m, 2), 7.4 (t, 1), 7.0 (m, 6), 3.0 (s, 6). Anal. ($C_{21}H_{20}N_4O_5 \cdot 2.2C_2HF_3O_2 \cdot 0.5H_2O$) C, H, N.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-(1H-imidazol-1-yl)phenoxy]pyridine-4-carboxylic Acid, Hydrate, 2.1 Trifluoroacetic Acid Salt (7f). NMR (DMSO-d_6): δ 9.7 (s, 1), 9.0 (s, 2), 8.7 (s, 2), 8.2 (s, 1), 7.9 (s, 1), 7.6 (m,

3), 7.3 (d, 1), 7.1 (s, 1), 7.0 (d, 1). Anal. ($C_{22}H_{17}N_5O_5 \cdot 2.1C_2HF_3O_2 \cdot H_2O$) C, H, N.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-(2-methyl-1H-imidazol-1-yl)phenoxy]pyridine-4-carboxylic Acid, 2.5 Trifluoroacetic Acid Salt, 1.5 Hydrate (7g). NMR (300 MHz, DMSO): δ 9.02 (br s, 2), 8.78 (br s, 2), 7.80 (d, 1), 7.72 (d, 1), 7.52−7.64 (m, 3), 7.31−7.46 (m, 3), 7.09 (d, 2), 7.0 (d, 1), 2.46 (s, 3). Anal. ($C_{23}H_{19}N_5O_5 \cdot 1.9H_2O \cdot 1.8C_2HF_3O_2$) C, H, N.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-(4-methyl-1H-imidazol-1-yl)phenoxy]pyridine-4-carboxylic Acid, 3 Hydrate, 1.9 Trifluoroacetic Acid Salt (7h). NMR (300 MHz, DMSO): δ 2.10 (s, 3), 6.93 (d, 1), 7.08 (m, 2), 7.23 (m, 1), 7.30−7.60 (m, 6), 7.85 (s, 3), 8.70 (br s, 2), 8.95 (br s, 2). Anal. ($C_{23}H_{19}N_5O_5 \cdot 3H_2O \cdot 1.9C_2HF_3O_2$) C, H, N.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-(1-methyl-1H-imidazol-2-yl)phenoxy]pyridine-4-carboxylic Acid, 2.1 Trifluoroacetic Acid Salt, 0.9 Hydrate (7i). NMR (300 MHz, DMSO): δ 3.79 (s, 3), 6.90 (d, 1), 7.08 (m, 2), 7.36−7.42 (m, 1), 7.46−7.62(m, 5), 7.68 (d, 1), 7.73 (d, 1), 8.63 (br s, 2), 8.95 (br s, 2). Anal. ($C_{23}H_{19}N_5O_5 \cdot 0.9H_2O \cdot 2.1C_2HF_3O_2$) C, H, N.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-(2,4-dimethyl-1H-imidazol-1-yl)phenoxy]pyridine-4-carboxylic Acid, 1.5 Trifluoroacetic Acid Salt, 2.5 Hydrate (7j). NMR (300 MHz, DMSO): δ 2.21 (s, 3), 2.40 (s, 3), 6.95 (d, 1), 7.08 (s, 2), 7.20−7.34 (m, 4), 7.41−7.60 (m, 3), 8.15 (br s, 2), 8.90 (br s, 2). Anal. ($C_{24}H_{19}N_5O_5 \cdot 2.5H_2O \cdot 1.5C_2HF_3O_2$) C, H, N.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-(4,5-dihydro-1H-imidazol-2-yl)phenoxy]pyridine-4-carboxylic Acid, 1.7 Trifluoroacetic Acid Salt, 2.6 Hydrate (7k). NMR (300 MHz, DMSO): δ 3.95 (br s, 4), 7.05 (d, 2), 7.08 (d, 2), 7.40−7.75 (m, 7), 8.80 (br s, 2), 9.03 (br s, 2), 10.50 (br s, 2). Anal. ($C_{22}H_{18}N_5O_5 \cdot 2.6H_2O \cdot 1.7C_2HF_3O_2$) C, H, N, F.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-(4,5-dihydro-4,4-dimethyl-1H-imidazol-2-yl)phenoxy]pyridine-4-carboxylic Acid, 2 Trifluoroacetic Acid Salt, Hydrate (7m). NMR (300 MHz, DMSO): δ 1.40 (s, 6), 3.75 (s, 2), 7.04−7.09 (m, 3), 7.46−7.76 (m, 6), 8.80 (br s,2), 9.05 (br s, 2), 10.45 (br s, 1), 10.75 (br s, 1). Anal. ($C_{24}H_{23}N_5O_5 \cdot 1.1H_2O \cdot 2C_2HF_3O_2$) C, H, N.

2-[5-[Amino(imino)methyl]-2-hydroxyphenoxy]-6-[3-[(2-aminoethyl)amino]phenoxy]pyridine-4-carboxylic Acid, 1.5 Trifluoroacetic Acid Salt (7n). NMR (300 MHz, DMSO): δ 2.95 (m, 2), 3.31 (m, 2), 6.32−6.42 (m, 2), 6.46−6.56 (m, 1), 6.80 (s, 1), 6.90 (s, 1), 7.06−7.18 (m, 2), 7.61−7.90 (m, 4), 8.78 (br s, 2), 9.10 (br s, 2). Anal. ($C_{21}H_{21}N_5O_5 \cdot 2H_2O \cdot 1.5C_2HF_3O_2$) C, H, N.

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