Design, Synthesis, and Biological Activity of 4-[(4-Cyano-2-arylbenzyloxy)-(3-methyl-3*H*-imidazol-4-yl)methyl]benzonitriles as Potent and Selective Farnesyltransferase Inhibitors

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A novel series of 4-[(4-cyano-2-arylbenzyloxy)-(3-methyl-3*H*-imidazol-4-yl)methyl]benzonitriles have been synthesized as selective farnesyltransferase inhibitors using structure-based design. X-ray cocrystal structures of compound **20**-FTase-HFP and A313326-FTase-HFP confirmed our initial design. The decreased interaction between the aryl groups and Ser 48 in GGTase-I binding site could be one possible reason to explain the improved selectivity for this new series of FTase inhibitors. Medicinal chemistry efforts led to the discovery of compound **64** with potent cellular activity (EC_{50} = 3.5 nM) and outstanding pharmacokinetic profiles in dog (96% bioavailable, 18.4 h oral $t_{1/2}$, and 0.19 L/(h·kg) plasma clearance).

Mutated Ras proteins, found in over 30% of human cancers, and particularly in 50% of colon and over 95% of pancreatic cancers, are constitutively activated and lead to uncontrolled cell division due to the loss of their normal GTPase functions. Among several post-translational modifications, the S-farnesylation of the C-terminal cysteine residue of Ras proteins catalyzed by a zinc metalloenzyme farnesyltransferase (FTase) is the critical step that enables the Ras proteins to participate in the transduction of extracellular mitogenic signals to the nucleus.[1] It has been shown that inhibitors of FTase can stop protein farnesylation and suppress the growth of Ras-dependent tumor cells both in cell culture and in rodents.[2] Recently, there has been growing evidence that Ras may not be the only substrate of FTase associated with oncogenesis. RhoB, for example, another member of the class of small GTPases that regulates receptor trafficking, was proposed as a potential target for FTase inhibitor.[3] There is also evidence suggesting that CENP-E and CENP-F, centromere-associated proteins, are the pertinent targets of FTase inhibitors, since functional association of CENP-E with microtubles seems to require farnesylation.[4] While the exact mechanism by which FTase inhibitors exert their antitumor activity still remains controversial, FTase inhibitors are promising agents in cancer therapy because of their excellent efficacy and low systemic toxicity in preclinical animal models.

FTase inhibitor design has evolved from early thiol-containing peptidimimetics to recent non-thiol, non-peptidic, and imidazole-containing chemical entities. This is highlighted by the advancement of several potent inhibitors, most of which have an imidazole moiety that interacts with zinc in the FTase binding site, to clinical trials (Chart 1).[5] Compounds R115777, SCH66366, and BMS-214662 are reported to be highly selective inhibitors of FTase vs geranylgeranyltransferase-I (GGTase-

Chart 1

SCH66336
FTase IC_{50} 2 nM

R115777
FTase IC_{50} 0.9 nM

L-778,123
FTase IC_{50} 2 nM

BMS-214662
FTase IC_{50} 0.7 nM

A315493: X=N
IC_{50} 0.4 nM (FTase), 24 nM (GGTase I)
A313326: X=CH
IC_{50} 0.3 nM (FTase), 18 nM (GGTase I)

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I), while L-778,123 is a dual inhibitor with an inhibitory activity of 98 nM against GGTase-I.

In our continuing effort to identify novel FTase inhibitors,[6] compound A315493 was discovered to have a strong inhibitory activity against FTase (IC_{50} = 0.4 nM) with potent cellular activity (EC_{50} = 8 nM). It exhibits good pharmaockinetic properties in dog and monkey.[7] However, A315493 is a potent GGTase-I inhibitor as well (IC_{50} = 24 nM). It has been documented that a far great number of proteins are post-translationally modified with geranylgeranyl groups while about 50 mammalian proteins are the substrates of FTase.[8] Although inhibitors of GGTase-I have shown in vivo efficacy,[9] they are likely to cause severe, nonspecific side effects resulting from inhibition of other critical cellular processes. Indeed, in a recently published paper, Lobell and co-workers demonstrated that using either a combination of an FTase inhibitor and a GGTase inhibitor or a dual prenyltransferase inhibitor, although eliciting a greater apoptotic response in vitro, significantly shortened the duration of treatment in mouse because of toxicity. They concluded that the therapeutic benefit offered by inhibiting oncogenic Ki-Ras through dual prenyltransferase inhibitor therapy is then limited.[10]

To solve the selectivity issue with A315493, we took a close look at R115777, a selective FTase inhibitor. It is worthwhile to point out that both A315493 and R115777 share quite a few common binding characteristics. Both of them have an *N*-methylimidazole ring that presumably interacts with the zinc ion in the catalytic site of FTase. From a 3-D model, it appears that the 5-cyano-2-pyridyl group of A315493 occupies the same site as the *N*-methylquinolin-2-one of R115777. The cyano group next to the 1-naphthyl of A315493 and the 4-chlorophenyl group of R115777 point into the same region. However, 1-naphthyl of A315493 and 3-chlorophenyl of R115777 clearly bind differently in the active site. We suspect that this binding difference may contribute to the potent GGTase-I activity for A315493 in that both A315493 and R115777 have comparable inhibitory activity against FTase. On the basis of the analysis above, we decided to move the 1-naphthyl group in the upper phenyl ring of A315493 to its lower phenyl ring, leading to compounds with a general structure **1** shown in Chart 1. In doing so, we hoped that analogues of compound **1** would not have the FTase/GGTase selectivity problem that was found for A315493 yet still maintain potent enzymatic and cellular activity and good pharmacokinetic properties. In this report, the synthesis, SAR study, and pharmacokinetic evaluation of the derivatives of compound **1** are described.

Chemistry

The synthesis of secondary alcohols **4a**−**i** is described in Scheme 1. Thus, *N*-methylimidazole was sequentially treated with *n*-BuLi and triethylsilyl chloride to afford 2-triethylsilyl *N*-methylimidazole **3a**. Lithiation of **3a** with *t*-BuLi followed by addition of substituted benzaldehydes provided the alcohols **4a**−**f**. Alcohol **4g** was prepared in a way similar to that of **4a** starting from the thiazole **2b**. 2-Methyl-*N*-methylimidazole **3c** was lithiated with *t*-BuLi and then quenched with 4-cyanobenzaldehyde to give alcohol **4h**. Treatment of 4-chororpyridine **3d** with LDA followed by addition of 4-cyanobenzaldehyde generated the alcohol **4i**.

Scheme 1[a]

2a: X=NCH$_3$
2b: X=S
3a: X=NCH$_3$
3b: X=S
4a: R_1=CN, R_2=H, R_3=H, X=NCH$_3$
4b: R_1=Cl, R_2=H, R_3=H, X=NCH$_3$
4c: R_1=CF$_3$, R_2=H, R_3=H, X=NCH$_3$
4d: R_1=CN, R_2=Cl, R_3=H, X=NCH$_3$
4e: R_1=CN, R_2=F, R_3=H, X=NCH$_3$
4f: R_1=CN, R_2=H, R_3=F, X=NCH$_3$
4g: R_1=CN, R_2=H, R_3=H, X=S

[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; (b) TESCl; (c) *t*-BuLi, THF, −78 °C; (d) ArCHO; (e) HCl(aq); (f) LDA, THF, −78 °C, then 4-CN-PhCHO.

Scheme 2[a]

[a] Reagents and conditions: (a) NBS, AIBN, CCl_4; (b) Ag_2O, **4a**, CH_2Cl_2; (c) $Pd(PPh_3)_4$, $ArB(OH)_2$, Na_2CO_3, toluene, H_2O.

The synthesis of compounds **7**−**11** proceeded as shown in Scheme 2. 2-Iodo-4-chlorotoluene **5** was brominated with NBS and AIBN in CCl_4 to give the corresponding benzyl bromide, which then reacted with the alcohol **4a** to afford benzyl ether **6**. Suzuki coupling between various arylboronic acids and **6** provided compounds **7**−**11**. The synthesis of compounds **15**−**19** and **22**−**30** is described in Scheme 3. Cyanation of 4-bromo-2-aminotoluene **12** with $Zn(CN)_2$ and $Pd(PPh_3)_4$ in DMF followed by the treatment with $NaNO_2$, HCl, and KI afforded 4-cyano-2-iodotoluene **13**. The preparation of compounds **15**−**19** and **22**−**30** from **13** was conducted in a manner similar to that of compounds **7**−**11**. Scheme 4 details the preparation of compounds **33**−**36**. Suzuki coupling of 2-bromo-4-nitrotoluene **31** with 3-methoxybenzene boronic acid gave the biaryl compound **32** in high yield. Bromination of **32** with NBS and AIBN in CCl_4 afforded the corresponding benzyl bromide, which was coupled with the alcohol **4a** to form benzyl ether **33**. Reduction of the nitro group of **33** with $SnCl_2$ and HCl gave the corresponding amino compound **34**. Reac-

Scheme 3[a]

[a] Reagents and conditions: (a) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 110 °C; (b) $NaNO_2$, HCl, KI; (c) NBS, CCl_4, AIBN; (d) Ag_2O, CH_2Cl_2, **4a**; (i) $Pd(PPh_3)_4$, $ArB(OH)_2$, Na_2CO_3, toluene, H_2O.

Scheme 4[a]

[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, H_2O, toluene, 3-$CH_3OPhB(OH)_2$; (b) NBS, CCl_4, AIBN; (c) Ag_2O, CH_2Cl_2, **4a**; (d) $SnCl_2$, HCl, EtOH; (e) CH_3SO_2Cl, CH_2Cl_2, pyridine; (f) EDC, HOBt, $HO_2CCH_2N(CH_3)_2$, DMF.

tion of **34** with either CH_3SO_2Cl or $(CH_3)_2NCH_2CO_2H$ generated the sulfonamide **35** or amide **36**, respectively.

The synthesis of **39**, **40**, and **45** is depicted in Scheme 5. Compound **39** was prepared in a manner similar to the synthesis of **33**. Hydrolysis of **39** gave compound **40**. Aniline **42** was prepared by Suzuki coupling between **41** and 3-methoxybenzene boronic acid followed by reduction with $SnCl_2$ and HCl in methanol. Conversion of aniline **42** to its corresponding iodo derivative with $NaNO_2$ in HCl followed by cyanation with $Zn(CN)_2$ and $Pd(PPh_3)_4$ in DMF gave the corresponding cyano compound **43**. Benzyl alcohol **44** was obtained from the reaction of **43** with DIBAl in toluene. Treatment of **44** with PBr_3 and LiBr in DMF provided the corresponding benzyl bromide, which was then coupled with the alcohol **4a** to afford compound **45**.

Compounds **47**−**55** were prepared as shown in Scheme 6. Biaryl compounds **46a**−**c** were synthesized by Suzuki coupling of 4-cyano-2-iodotoluene **13** with the corresponding arylboronic acids in excellent yields. Bromination of **46a**−**c** with NBS and AIBN followed by the coupling with various alcohols (**4b**−**i**) in the presence of Ag_2O gave compounds **47**−**55**.

Scheme 5[a]

[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, H_2O, toluene, 3-$CH_3OPhB(OH)_2$; (b) NBS, CCl_4, AIBN; (c) Ag_2O, CH_2Cl_2, **4a**; (d) LiOH, H_2O; (e) $SnCl_2$·$2H_2O$, HCl, MeOH, room temp; (f) $NaNO_2$, HCl, KI; (g) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF; (h) DIBAL, toluene; (i) PBr_3, LiBr, DMF.

Scheme 6[a]

[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, $ArB(OH)_2$, Na_2CO_3, toluene, H_2O; (b) NBS, CCl_4, AIBN; (c) Ag_2O, CH_2Cl_2, **4b**−**f** and **4i**; (d) NaH, DME, **4g**,**h**.

Scheme 7 describes the preparation of compounds **60a**−**c**, **61**, and **62**. Amino compound **58** was synthesized in a manner similar to the preparation of compound **34**. Reaction of **58** with various arylsulfonyl chlorides afforded sulfonamides **59a**−**d**, which were converted to the corresponding cyano derivatives **60a**−**d** with $Zn(CN)_2$ and $Pd(PPh_3)_4$ in DMF. Reductive amination of **58** with 3,5-difluorobenzaldehyde followed by cyanation gave compound **61**. Similarly, amidation of **58** with benzoic chloride followed by cyanation generated compound **62**.

Compounds **64** and **65** were prepared as shown in Scheme 8. Methoxy carbonylation of 4-cyano-2-iodotoluene **13** afforded 4-cyano-4-carbomethoxyltoluene, which was converted to its corresponding benzyl bro-

Scheme 7[a]

[a] Reagents and conditions: (a) NBS, CCl_4, AIBN; (b) Ag_2O, CH_2Cl_2; (c) $SnCl_2{\cdot}2H_2O$, HCl, ethanol, room temp; (d) CH_2Cl_2, Py, $ArSO_2Cl$; (e) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 80 °C; (f) $NaCNH_3$, AcOH, 3,5-di-F-PhCHO; (g) PhCOCl, CH_2Cl_2, pyridine.

Scheme 8[a]

[a] Reagents and conditions: (a) $Pd(dppf)_2$, CO, MeOH, Et_3N; (b) NBS, CCl_4, AIBN; (c) Ag_2O, CH_2Cl_2, **4a**; (d) LiOH, $MeOH/H_2O$; (e) EDC, HOBt, $ArNH_2$.

mide with NBS and AIBN in CCl_4 and coupled with the alcohol **4a** to produce benzyl ether **63**. Compounds **64** and **65** were obtained from reaction of the acid, obtained by hydrolysis of **63**, with various arylamines.

Results and Discussion

We first examined the effects of various aryl groups on the activities of FTase and GGTase-I and the inhibition of farnesylation of Ras protein in NIH3T3 cells (EC_{50}). The results are summarized in Table 1. It was gratifying to see that by moving the 1-naphthyl group from the upper benzene ring of A315493 to the lower benzene ring ortho to the benzyl ether, we have successfully obtained a potent FTase inhibitor **16** with a much improved selectivity profile compared to that of A315493, although its cellular activity is somewhat less potent. It is necessary to point out that placing an aryl group ortho to the cyano group of the lower benzene ring resulted in significant loss in biological activities (data not shown).

With this encouraging result, we started a systematic SAR study that led to several interesting findings (Table 1). It appeared that the substitution pattern on the aryl group is important for enzymatic and cellular activity, especially when R = Cl. The substituent at the 3-position of the aryl group resulted in the best enzymatic activity against FTase as shown by compounds **7**–**9**. When R = CN, however, the difference in enzymatic activity against FTase resulting from 3- and 4-substituted aryl groups became indistinguishable as demonstrated by compounds **20**, **24**, **26**, and **27**. The cellular activity is a different case. It is clear that compounds with 3-substitued aryl groups exhibit much better activity than those with 4-substituted aryl groups in the whole-cell assay, demonstrated by compounds **19**, **24**, **26**, and **27**.

Although, with the exception of compound **25**, different substituents at the 3-position on the aryl group have little effect on the enzymatic activity against FTase, they show profound influence on the cellular activity when R is either a chlorine or a cyano group. For example, compound **11** bearing a 3-ethoxyphenyl shows more than 80-fold improvement in cellular activity over the 3-chlorophenyl. A similar observation was also noted when R = CN, as demonstrated by compounds **18** and **24**. Compared to A315493, most of the compounds have demonstrated better cellular activity when R = CN. This was another pleasant surprise for this new series of FTase inhibitors.

Among many factors that affect the activity of compounds in the cell-based assay, a compound's ability to penetrate the cell membrane is certainly important. Both compounds bearing a 3-methoxyphenyl (**10**, CLogP = 4.17; **19**, CLogP = 2.93)[11] show a reduction in lipophilicity compared to compounds with 3-chlorophenyl (**8**, CLogP = 4.94; **18**, CLogP = 3.66), as suggested by their ClogP values. Compound **26** (CLogP = 2.93), which is 14-fold more potent than compound **29** (CLogP = 3.44) in the whole-cell assay, also has a lower CLogP value. This reduced lipophilicity, which stems from the introduction of both cyano and methoxy groups, may be contributing to cellular activity via improved cell penetration. It is worthwhile to point out that several compounds exhibit cellular activity exceeding their intrinsic activity against FTase. Though rare, this phenomenon has been reported by other researchers.[12]

Chirality is important for activity as demonstrated by compounds **20** and **21**. The *R* enantiomer **20** is 60-fold more potent than the corresponding *S* enantiomer **21** in the enzymatic assay against FTase. **21** is essentially inactive in the whole-cell assay. Similar observations have also been documented in other FTase inhibitor research programs.[13]

It is apparent that this new series of FTase inhibitors has shown much better selectivity behavior, with inhibitory activity against GGTase-I largely in the micromolar range. Depending on the aryl groups, the improvements in selectivity range from 30- to more than 410-fold compared to that of A315493. Given their activities against GGTase-I, it is unlikely for these compounds to

Table 1. Structure–Activity Relationship of Substitution on the A-Ring[a]

compd	R	Ar	FTase (nM)	GGTase (nM)	EC_{50} (nM)
7	Cl	2-Cl-Ph	8.9	1800	>1000
8	Cl	3-Cl-Ph	0.80 (4)	1400 (2)	390
9	Cl	4-Cl-Ph	4.8	>1000	525 (2)
10	Cl	3-OMe-Ph	0.91	2000	100
11	Cl	3-OEt-Ph	1.1	1700	4.6
15	CN	Ph	1.3	3500	140
16	CN	1-naphthyl	0.94 (2)	7600(2)	14
17	CN	8-quinolinyl	5.2 (2)	>10000 (2)	15
18	CN	3-Cl-Ph	0.87 (2)	1300 (2)	5.2 (2)
19	CN	3-OMe-Ph	0.75 (2)	4300 (2)	0.75 (2)
20	CN	3-OMe-Ph (*R*)	0.35	1800	0.14
21	CN	3-OMe-Ph (*S*)	21	>10000	>100
22	CN	3,4-OCH_2O-Ph	0.87 (2)	3100	<1 (2)
23	CN	3,4-OCF_2O-Ph	1.1	2000	9.1
24	CN	3-OEt-Ph	0.69 (2)	2100 (2)	0.19
25	CN	3-CH_2OCH_3-Ph	0.19 (2)	1800 (2)	1.0
26	CN	4-OMe-Ph	0.96	2900	7
27	CN	4-OEt-Ph	1.2	750	13
28	CN	4-OCF_3-Ph	0.84	1100	5.1
29	CN	4-CH_3-Ph	1.1	2200	>100
30	CN	3,5-DiF-Ph	0.98	1500	96
33	NO_2	3-OMe-Ph	1.1	903	0.81
34	NH_2	3-OMe-Ph	40	>10000	>100
35	$NHSO_2CH_3$	3-OMe-Ph	35	>10000	>100
36	$NHCOCH_2OMe$	3-OMe-Ph	11	>10000	>100
39	CO_2Me	3-OMe-Ph	13	>10000	>100
40	CO_2H	3-OMe-Ph	83	ND[b]	ND[b]
45	CHO	3-OMe-Ph	1.6	ND[b]	>100

[a] All the compounds were assayed once unless indicated by the number of the replicates shown in parentheses. [b] ND: not determined.

inhibit protein geranylgeranylation efficiently at the concentration required for the inhibition of farnesylation.

Several other R groups attached to the A-ring were also investigated as shown in Table 1. Only compounds **33** and **45**, bearing a strongly electron-withdrawing nitro and formyl group, respectively, show potent intrinsic activity against FTase. Although compound **33** exhibits potent cellular activity, it is less selective than the rest of the compounds.

Once we optimized the substituents for the A-ring, we moved our attention to the B-ring. The results are listed in Table 2. It appears that the cyano group at the R_1 position is very important for cellular activity, although both a chloride and a trifluoromethyl group, bioisosteres of the cyano group, gave comparable enzymatic activity against FTase. Again, this may be a reflection of the fact that the presence of a cyano group lowers the lipophilicity of the compounds. Substitution at the R_2 position has significant effect on the selectivity and cellular activity. Even a small group such as a fluorine atom causes an increased GGTase-I activity and a decreased cellular activity (compare compounds **18**, **19**, **48**, and **49**). This observation reinforced our suspicion that the poor selectivity associated with A315493 originates from the location of the 1-naphthaly group. However, a fluorine atom at the R_3 position has little effect on biological activity.

Table 2. Structure–Activity Relationship of Substitution on the B-Ring[a]

compd	R	R_1	R_2	R_3	FTase (nM)	GGTase (nM)	EC_{50} (nM)
47	OMe	Cl	H	H	2.0	3300	17.7
48	OMe	CN	Cl	H	0.97	170	130
49	Cl	CN	F	H	0.44	630 (2)	36
50	Cl	CN	H	F	0.77	1600	3.3
51	Cl	CF_3	H	H	1.1	2100	>100

[a] All the compounds were assayed once unless indicated by the number of the replicates shown in parentheses.

The imidazole ring is a very important moiety of FTase inhibitors, since its basic nitrogen has a strong interaction with the zinc atom in the FTase catalytic binding site. Different heterocycles such as 1,2-dimethylimidazole and 5-thiazole were examined as replacements. The results are listed in Table 3. It seems that *N*-methylimidazole-4-yl is the best for enzymatic and cellular activity. Although the introduction of a methyl group at the 2-position of the imidazole ring results in

Table 3. Structure–Activity Relationship of Aryl Heterocycles[a]

Compound No.	Ar'	Ar	FTase (nM)	GGTase I (nM)	EC_{50} (nM)
52			2.0	1200	154
53			1.6	4700	9.8
54			4.0	>10,000	ND[b]
55			15	>10,000	>100

[a] All the compounds were assayed once. [b] Not determined.

minimum change in the enzymatic activity, it has a negative impact on the cellular activity. Using other heterocycles yields significant losses in activity due to their attenuated basicity or unfavorable bulk.

Last, we explored the effect of a linker inserted between the aryl group and the A-ring on biological activity. The results are summarized in Table 4. In general, the different linkers have little effect on the enzymatic activity against FTase except for compound **62**, which shows a decreased activity compared to its retroinverted amide **64**. However, the selectivity and cellular activity may be significantly changed depending on the linker inserted. For example, compounds **60a–c** bearing a sulfonamide linker show significant losses in selectivity. This may be due to the fact that a $NHSO_2$ bond adopts a cis configuration different from other linkers, projecting the aryl groups to an area where a better contact between the GGTase-I and the inhibitors can be made. In addition, neither the $NHSO_2$ bond nor the $NHCH_2$ bond is helpful for the cellular activity. Only the amide linker in which the carbonyl group is attached to the A-ring is well tolerated. Indeed, in addition to its potent intrinsic activity against FTase, compound **64** exhibits an excellent selectivity over GGTase-I and a strong cellular inhibition of Ras processing activity.

Pharmacokinetic studies of selected compounds were conducted in dog. The results are listed in Table 5. It is interesting to note that the electronic nature of the substituents on the A-ring plays an important role in the pharmacokinetics. Chlorine, an electron-withdrawing group, provides a much better pharmacokinetic profile for compound **18** compared to compound **19**, which has an electron-donating methoxy group. Other electron-donating groups such as OEt and CH_2OMe give similarly poor results, which may arise from the benzylic oxidation of the benzyl ether facilitated by these electron-donating groups. On the other hand, when there is an amide bond with the carbonyl group directly attached to the A-ring and ortho to the benzyl ether, the benzylic oxidation of the benzyl ether was suppressed because of the strong electron-withdrawing nature of the carbonyl group, resulting in a much improved pharmacokinetic behavior (low plasma clearance rate, long oral half-life, and excellent oral bioavailablity) as demonstrated by compound **64**. It is worthwhile to note that better pharmacokinetic profiles were observed for the compounds bearing the fluorine-containing alkoxy groups as demonstrated by compounds **22**, **23**, and **28**, although to a lesser extent. This probably results from the slower dealkylation associated with fluorine-containing alkoxy groups. The introduction of a methyl group at the 2-position of the imidazole ring proved to be detrimental to the pharmacokinetic behavior because compound **56** shows a dramatic decrease in oral AUC and bioavailablity compared to compound **22**. Replacement of the cyano group of the A-ring with a chlorine atom or substitution of the hydrogen with a fluorine atom ortho to the cyano group of the B-ring gives little change in pharmacokinetic behavior.

X-ray Crystallography. To further elucidate the binding mode of this new series of FTase inhibitors to FTase catalytic binding site and answer the question why this series of compounds possesses much better selectivity than A315493, compound **19** was cocrystallized with hydroxylfarnesyl phosphate (HFP) and FTase for X-ray crystallographic determination. Figure 1 illustrates the X-ray structure of **20**, the more active enantiomer of **19**, bound to the FTase active site. As

Table 4. Structure–Activity Relationship of the Linker X–Y[a]

Compound No.	X-Y	Ar	FTase (nM)	GGTase I (nM)	EC_{50} (nM)
60a	$NHSO_2$	S	0.88	220	>100
60b	$NHSO_2$	H_3C	1.0	65	13
60c	$NHSO_2$		2.6	100	>100
61	$NHCH_2$	F, F	0.61	1,400	150
62	NHCO		5.0	3,100	Nd[b]
64	CONH		2.2	12,000	12
65	CONH	Cl	0.75	5,700	3.5 (2)[c]

[a] All the compounds were assayed once. [b] Nd: not determined. [c] Compound **65** was assayed twice.

expected, the imidazole shows a strong interaction with the zinc ion with a distance of 2.3 Å. The B-ring is on the top of the HFP iosprenoid. The nitrile nitrogen of the B-ring is about 3.4 Å away from the side chain of Arg202 in the β-subunit, the closest amino acid side chain, making reasonable van der Waals contact. The van der Waals nature of the interaction between the cyano group and the protein may explain why the replacement of the cyano group with either a chloride or a trifluoromethyl group resulted in little change in enzymatic activity against FTase. The cyano group of the A-ring is in a pocket defined by lipophilic side chains of amino acids Tyr36, Tyr93, Leu96, and Try106. Again, strong van der Waals interaction between the nitrile nitrogen and the amino acid side chains and main chains was observed, explaining why either a chlorine atom or a nitro group is tolerated. It is interesting to point out that the 3-methoxyphenyl and the B-ring are stacking on top of each other at a distance of 4.5 Å, suggesting a strong $\pi-\pi$ interaction.

Figure 2 shows the superimposed X-ray structures of **20** and A313326, a close analogue of A315493 (Chart 1) bound to the FTase active binding site. It is clear that compound **20** shares a lot of similarities with A313326 in the FTase binding site except the locations of the aryl rings. For example, both compounds show the same distances between the unsubstituted nitrogen of imidazole and the zinc. The similar distances were also observed in the X-ray cocrystal structures with FTase for a couple of close analogues of compound **20**.[14] It is noticeable that the A-ring of compound **20** and the 4-cyanobenzyl ethyl of A313326 are slightly shifted because of the naphthalene ring, but making very similar interaction with the 360's loop. This supported our initial hypothesis that the poor selectivity associated with A313495 stems from the alteration of the inhibitor binding mode caused by the location of the naphthalene ring.

It is difficult to pinpoint the origin of the poor selectivity associated with A313326 without X-ray cocrystal structures of compound **20** and A313326 in the GGTase-I active binding site. It should be noted, however, that Trp102 is not found in the GGTase-I active binding site but is replaced by Ser 48.[15] One possible explanation would be that 3-methoxyphenyl group of compound **20** may have a reduced interaction with Ser 48 in the GGTase-I active binding site compared to 1-naphthyl of A313326 because these two aryl groups bind differently. Therefore, compound **20**'s activity against GGTase-I would be significantly reduced.

Conclusion

A novel series of potent, selective FTase inhibitors, the design of which is based on the 3-D model of A315493, have been developed. X-ray crystallography determination of **19** subsequently confirmed our initial design. The decreased interaction between the aryl groups and Ser 48 in GGTase-I active binding site could be one possible reason to explain the selectivity for this new series of FTase inhibitors. Medicinal chemistry efforts revealed that among different substitutents at the para positions of both A and B rings the cyano group

Table 5. Pharmacokinetic Evaluation of Selected Compounds in Dog

Compd.	Structure	Clp (L/h•kg)	$t_{1/2}$ (oral) (h)	AUC (oral) (μg•h/ml)	F (%)
7		UC[a]	UC[a]	9.85	65[b]
18		0.4	4.7	9.89	76[b]
22		0.6	2.7	3.66	45.4[b]
64		0.19	18.4	5.72	96[c]
19		1.0	2.5	1.73	35[b]
24		1.0	2.2	1.13	23.2[b]
25		0.51	2.2	0.26	13.1[b]
53		1.87	0.9	0.1	15.2[b]
23		0.31	1.3	2.76	82[b]
28		0.44	6.7	1.53	66[b]
49		0.48	8.7	1.58	71[b]
26		0.73	3.6	0.76	54[b]

[a] Unable to calculate. [b] At least three animals were used for each dosing group (oral and iv, 5 mg/kg); the PK parameters reported here were the averages of the animals. [c] Four animals used, cross-over fashion (oral and iv, 1 mg/kg, four different compounds were dosed simultaneously); the PK parameters reported here were the averages of the animals.

is optimal, providing these compounds with potent cellular activity. A wide range of aryl groups can be used without compromising enzymatic or cellular activity and selectivity. Pharmacokinetic studies in dog showed that either 3-chlorophenyl or fluorine-containing alkoxyphenyl groups are the aryl substiuents of choice and that

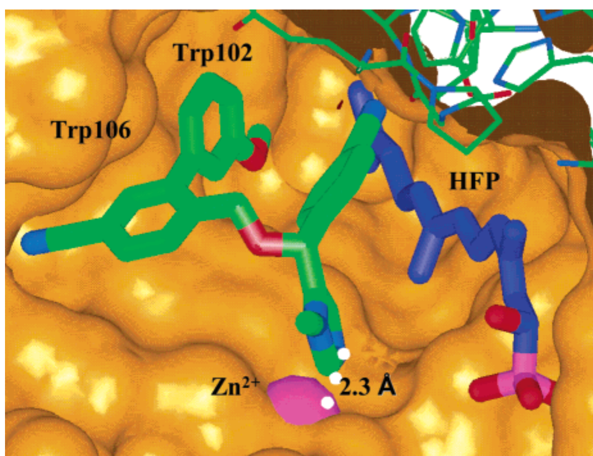

Figure 1. X-ray structure of **20** (green) bound to FTase active site. The isoprenoid group of HFP is shown in blue. The zinc ion is shown in purple.

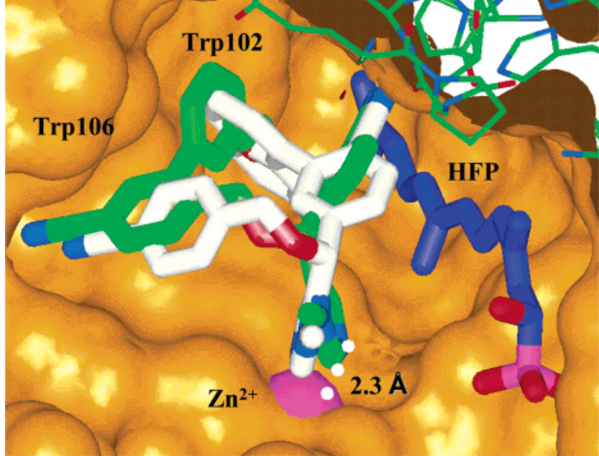

Figure 2. Superimposed X-ray crystal structure of **20** (green) and A313326 (white). The isoprenoid group of HFP is shown in blue, and the zinc ion is shown in purple.

an amide bond is the linker of choice. Particularly, in conjunction with its potent cellular activity and good selectivity, compound **64** showed outstanding pharmacokinetic profiles as demonstrated by its long oral half-life, good oral AUC value, and excellent oral bioavailability.

Experimental Section

All commercially available solvents and reagents were used without further treatment as received unless otherwise noted. DMF, DMA, methylene chloride, toluene, and THF were commercial anhydrous solvents from Aldrich. FT-NMR spectra were obtained on Bruker 250 MHz (62.5 MHz for ^{13}C), 300 MHz (75 MHz for ^{13}C), and 400 MHz (100 MHz for ^{13}C) spectrometers. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., of Madison, NJ. Thin-layer chromatography (TLC) was performed on Kiesegel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed on Merck silica gel 60 (230−400 mesh) using reagent grade solvents. All reactions were performed under a nitrogen atmosphere.

General Procedure for Preparation of the Secondary Alcohols 4a−f. *N*-Methylimidazole **2** (46 mL, 0.577 mol) in 400 mL of anhydrous THF was cooled to −78 °C. To this solution was slowly added 2.5 M *n*-BuLi in hexane (250 mL, 0.625 mol) via an addition funnel to maintain the internal temperature below −60 °C. After the addition of *n*-BuLi was complete, the solution was warmed to −10 °C briefly, cooled to − 78 °C again, and slowly treated with chlorotriethylsilane (111 mL, 0.661 mol) via a cannula to keep the internal temperature below −60 °C. The reaction mixture was gradually warmed to room temperature overnight. The solid was removed by filtration under a stream of nitrogen, and the filtrate was concentrated in vacuo. The resulting liquid was purified with vacuum distillation to give 98 g of 1-methyl-2-triethylsilanyl-1*H*-imidazole as a clear liquid (88%).

1-Methyl-2-triethylsilanyl-1*H*-imidazole (4.32 g, 22 mmol) in 100 mL of anhydrous THF was cooled to −78 °C. To this solution was added 1.7 M *t*-BuLi in hexane (14 mL, 24 mmol) over 5 min. The solution was stirred at −78 °C for additional 1 h and treated dropwise with 4-cyanobenzaldehyde in 20 mL of THF via a cannula. The solution was stirred at −78 °C for 3 h and treated with 20 mL of MeOH. After it warmed to room temperature, the solution was treated with 50 mL of 10% HCl and stirred overnight. The solution was neutralized to pH 7−8 using saturated aqueous $NaHCO_3$, partitioned between EtOAc and H_2O, and extracted with additional EtOAc three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using 20:1 EtOAc/MeOH to provide 2.52 g of 4-[hydroxy(3-methyl-3*H*-imidazol-4-yl)-methyl]benzonitrile **4a** (59%). ^{1}H NMR ($CDCl_3$): δ 7.64−7.67 (dd, *J* = 6.7, 2.3 Hz, 2H), 7.54−7.52 (dd, *J* = 7.8, 0.7 Hz, 2H), 6.31 (s, 1H), 6.56 (s, 1H), 5.89 (s, 1H), 3.53 (s, 3H). MS/ESI (+), *m/z*: 214 (M + H)$^+$, 231 (M + NH_4)$^+$.

(4-Chlorophenyl)-(3-methyl-3*H*-imidazol-4-yl)methanol (4b). Compound **4b** was prepared in a similar manner as described in the preparation of **4a** from 1-methyl-2-triethylsilanyl-1*H*-imidazole. ^{1}H NMR (DMSO-d_6): δ 7.53 (s, 1H), 7.37−7.44 (m, 4H), 6.39 (s, 1H), 6.01 (d, *J* = 5.09 Hz, 1H), 5.79 (d, *J* = 4.4 Hz, 1H), 3.54 (s, 3H). MS/ESI (+), *m/z*: 223 (M + H)$^+$, 240 (M + NH_4)$^+$.

(4-Trifluoromethylphenyl)-(3-methyl-3*H*-imidazol-4-yl)methanol (4c). Compound **4c** was prepared in a similar manner as described in the preparation of **4a** from 1-methyl-2-triethylsilanyl-1*H*-imidazole. ^{1}H NMR (DMSO-d_6): δ 7.72−7.75 (d, *J* = 8.1 Hz, 2H), 7.60−7.62 (d, *J* = 8.1 Hz, 2H), 7.55 (s, 1H), 6.40 (s, 1H), 6.11 (d, *J* = 5.1 Hz, 1H), 5.90 (d, *J* = 5.1 Hz, 1H), 3.55 (s, 3H). MS/ESI (+), *m/z*: 257 (M + H)$^+$, 274 (M + NH_4)$^+$.

2-Chloro-4-[hydroxy(3-methyl-3*H*-imidazol-4-yl)methyl]benzonitrile (4d). Compound **4d** was prepared in a similar manner as described in the preparation of **4a** from 1-methyl-2-triethylsilanyl-1*H*-imidazole. ^{1}H NMR ($CDCl_3$): δ 7.50−7.54 (m, 1H), 7.28−7.39 (m, 2H), 7.28 (s, 1H), 6.72 (s, 1H), 5.95 (s, 1H), 3.55 (s, 3H). MS/ESI (+), *m/z*: 247 (M + H)$^+$, 265 (M + NH_4)$^+$.

(3-Fluoro-4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methanol (4e). Compound **4e** was prepared in a similar manner as described in the preparation of **4a** from 1-methyl-2-triethylsilanyl-1*H*-imidazole. ^{1}H NMR ($CDCl_3$): δ 7.60−7.64 (m, 1H), 7.28−7.39 (m, 2H), 7.28 (s, 1H), 6.72 (s, 1H), 5.95 (s, 1H), 3.55 (s, 3H). MS/ESI (+), *m/z*: 232 (M + H)$^+$, 249 (M + NH_4)$^+$.

(2-Fluoro-4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methanol (4f). Compound **4f** was prepared in a similar manner as described in the preparation of **4a** from 1-methyl-2-triethylsilanyl-1*H*-imidazole. ^{1}H NMR (DMSO-d_6): δ 7.77−7.85 (m, 3H), 7.57 (s, 1H), 6.28 (s, 1H), 6.22 (d, *J* = 5.8 Hz, 1H), 6.04 (d, *J* = 5.2 Hz, 1H), 3.65 (s, 3H). MS/ESI (+), *m/z*: 232 (M + H)$^+$, 249 (M + NH_4)$^+$.

(4-Cyanophenyl)thiazol-5-ylmethanol (4g). Compound **4g** was prepared in a similar manner as described in the preparation of **4a** from thiazole **2b**. ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 1H), 7.67−7.72 (m, 3H), 7.57 (d, *J* = 8.1 Hz, 1H), 6.21 (s, 1H). MS/ESI (+), *m/z*: 217 (M + H)$^+$.

(4-Cyanophenyl)-(2,3-dimethyl-3*H*-imidazol-4-yl)methanol (4h). Compound **4h** was prepared in a similar manner as described in the preparation of **4a** from 2,3-dimethylimidazole **3c**. ^{1}H NMR (DMSO-d_6): δ 7.83 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 6.17 (s, 1H), 6.21 (s, 1H), 6.09 (d, *J*

= 5.1 Hz, 1H), 5.83 (d, J = 4.8 Hz, 1H), 3.43 (s, 3H), 2.23 (s, 3H). MS/ESI (+), m/z: 228 $(M + H)^+$.

(4-Cyanophenyl)-(4-chloropyridin-3-yl)methanol (4i). A solution of LDA, which was generated from diisopropylamine (9.20 mL, 65.64 mmol) and n-BuLi (2.5 M in hexane, 27.0 mL, 67.5 mmol) in THF (100 mL) at −78 °C, was added to a mixture of 4-chloropyridine (6.77 g, 59.63 mmol) in THF (15 mL) at −78 °C. The mixture was stirred at −78 °C for 1.5 h. To this mixture at −78 °C was added a solution of 4-cyanobenzaldehyde (8.60 g, 65.58 mmol) in THF (50 mL). The reaction mixture was stirred overnight while the temperature gradually warmed to room temperature. Saturated NH_4Cl solution was added, and the mixture was extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified on silica gel, eluting with methylene chloride/methanol/NH_4OH (100:5:0.5, v/v/v) to give the title compound (12.04 g, 82.5%). ^1H NMR ($CDCl_3$): δ 8.74 (s, 1 H), 8.44 (d, J = 5.43 Hz, 1 H), 7.66 (m, 2 H), 7.54 (m, 2 H), 7.31 (d, J = 5.43 Hz, 1 H), 6.27 (d, J = 3.05 Hz, 1 H), 2.98 (d, J = 4.07 Hz, 1 H). MS (DCI/NH_3) m/z: 245, 247 $(M + H)^+$.

General Procedure for Preparation of Benzyl Bromide. A mixture of 2-chloro-4-iodotoluene (3.95 g, 15.6 mmol), NBS (3.10 g, 17.2 mmol), and benzoyl peroxide (0.5 g, 2.1 mmol) in 100 mL of CCl_4 was heated to reflux for 2 days. After it cooled to room temperature, the solid was removed by filtration. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography using 25:1 hexanes/EtOAc to provide 3.24 g of 4-chloro-2-iodobenzyl bromide. ^1H NMR ($CDCl_3$): δ 7.85 (d, J = 2.0 Hz, 1H), 7.39 (m, 1H), 7.31 (m, 1H), 4.55 (s, 2H). MS/ESI (+), m/z: 332 $(M + H)^+$.

General Procedure for Preparation of Benzyl Ether. A 100 mL round-bottom flask was charged with (4-cyanophenyl)-(3-methyl-3H-imidazol-4-yl)methanol **4a** (0.50 g, 2.34 mmol), 4-chloro-2-iodobenzyl bromide (1.16 g, 3.5 mmol), silver oxide (1.60 g, 6.9 mmol), and 30 mL of methylene chloride. The flask was wrapped by aluminum foil, and the reaction mixture was stirred at room temperature for 12 h. The insoluble material was filtered off through a pack of Celite, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography using 100:5:0.3 EtOAc/MeOH/NH_4OH to give 0.7 g of 5-[(4-chloro-2-iodobenzyloxy)-(4-cyanophenyl)methyl]-1-methyl-1H-imidazole **6** (70%). ^1H NMR ($CDCl_3$): δ 7.85 (s, 1H), 7.68−7.66 (m, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.47 (m, 1H), 7.34−7.32 (m, 2H), 6.95 (s, 1H), 5.65 (s, 1H), 4.52 (m, 2H), 3.41 (s, 3H). MS/ESI, m/z: 464 $(M + H)^+$.

General Procedure for Suzuki Coupling to Prepare Diaryl Compounds. A 50 mL round-bottom flask was charged with 5-[(4-chloro-2-iodobenzyloxy)-(4-cyanophenyl)methyl]-1-methyl-1H-imidazole **6** (0.080 g, 0.177 mmol), 2-chlorophenylboronic acid (0.055 g, 0.35 mmol), sodium carbonate (0.042 g, 0.531 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.01 g, 0.0089 mmol). To the flask was added 3 mL of toluene, 3 mL of ethanol, and 1 mL of water. The reaction mixture was heated to reflux for 12 h. After it cooled to room temperature, the reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with additional EtOAc, and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography using 100:5:0.3 EtOAc/MeOH/NH_4OH to give 0.048 g of 5-[(4-cyanophenyl)-(5,2′-dichlorobiphenyl-2-ylmethoxy)methyl]-1-methyl-1H-imidazole **7** (62%). ^1H NMR ($CDCl_3$): δ 7.62−7.56 (m, 2H), 7.48−7.16 (m, 11H), 6.78 and 6.69 (s, 1H), 5.38 (s, 1H), 4.40−4.18 (m, 2H), 3.32 and 3.24 (s, 3H) (two rotomers). MS/ESI, m/z: 449 $(M + H)^+$. Anal. ($C_{25}H_{19}Cl_2N_3O\cdot HCl\cdot 0.8H_2O$) C, H, N.

5-[(4-Cyanophenyl)-(5,3′-dichlorobiphenyl-2-ylmethoxy)methyl]-1-methyl-1H-imidazole (8). Compound **8** was prepared from compound **6** in a similar manner as described for the preparation of compound **7**. ^1H NMR ($CDCl_3$): δ 7.61 (d, J = 6.8 Hz, 2H), 7.43 (s, 1H), 7.38−7.27 (m, 8H), 7.13−7.16 (m, 2H), 6.82 (s, 1H), 5.45 (s, 1H), 4.43 (d, J = 11.2 Hz, 1H), 4.33 (d, J = 11.2 Hz, 1H), 3.30 (s, 3H). MS/ESI, m/z: 449 $(M + H)^+$. Anal. ($C_{25}H_{19}Cl_2N_3O\cdot HCl\cdot 1.15H_2O$) C, H, N.

5-[(4-Cyanophenyl)-(5,4′-dichlorobiphenyl-2-ylmethoxy)methyl]-1-methyl-1H-imidazole (9). Compound **9** was prepared from compound **6** in a similar manner as described for the preparation of compound **7**. ^1H NMR ($CDCl_3$): δ 7.63 (d, J = 8.5 Hz, 2H), 7.40−7.18 (m, 11H), 6.81 (s, 1H), 5.45 (s, 1H), 4.45 (d, J = 11.2 Hz, 1H), 4.33 (d, J = 11.2 Hz, 1H), 3.27 (s, 3H). MS/ESI, m/z: 449 $(M + H)^+$. Anal. ($C_{25}H_{19}Cl_2N_3O\cdot HCl\cdot 0.9H_2O$) C, H, N.

5-[(5-Chloro-3′-methoxybiphenyl-2-ylmethoxy)-(4-cyanophenyl)methyl]-1-methyl-1H-imidazole (10). Compound **10** was prepared from compound **6** in a similar manner as described for the preparation of compound **7**. ^1H NMR ($CDCl_3$): δ 7.61 (d, J = 8.5 Hz, 2H), 7.41−7.28 (m, 7H), 6.92 (m, 1H), 6.80−6.85 (m, 2H), 6.76 (s, 1H), 5.43 (s, 1H), 4.46 (d, J = 11 Hz, 1H), 4.39 (d, J = 11 Hz, 1H), 3.79 (s, 3H), 3.30 (s, 3H). MS/ESI, m/z: 444 $(M + H)^+$. Anal. ($C_{26}H_{22}ClN_3O_2\cdot 1.4TFA$) C, H, N.

5-[(5-Chloro-3′-ethoxybiphenyl-2-ylmethoxy)-(4-cyanophenyl)methyl]-1-methyl-1H-imidazole (11). Compound **11** was prepared from compound **6** in a similar manner as described for the preparation of compound **7**. ^1H NMR ($CDCl_3$): δ 7.61 (d, J = 8.5 Hz, 2H), 7.41−7.28 (m, 7H), 6.92 (m, 1H), 6.80−6.85 (m, 2H), 6.76 (s, 1H), 5.43 (s, 1H), 4.46 (d, J = 11 Hz, 1H), 4.39 (d, J = 11 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.30 (s, 3H), 1.47 (t, J = 6.8 Hz, 3H). MS/ESI, m/z: 458 $(M + H)^+$. Anal. ($C_{26}H_{22}ClN_3O_2\cdot 1.4TFA$) C, H, N.

General Procedure for Palladium-Catalyzed Cyanation of Aryl Halides (Bromide or Iodide). A mixture of 2-amino-4-iodotoluene (5.0 g, 21.4 mmol), $Zn(CN)_2$ (1.51 g, 12.9 mmol), and $Pd(PPh_3)_4$ (1.24 g, 1.07 mmol) in 25 mL of DMF was degassed via vacuum/nitrogen cycles. The reaction mixture was heated at 80 °C for 2 h. After it cooled to room temperature, the reaction mixture was partitioned between H_2O and EtOAc. The aqueous layer was extracted with additional EtOAc, and the combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by flash column chromatography using 3:7 EtOAc/hexane to give 2.38 g of 2-amino-4-cyanotoluene (84%).

2-Iodo-4-cyanotoluene (13). 2-Amino-4-cyanotoluene (2.15 g, 16.3 mmol) in 20 mL of acetone was treated with 100 mL of concentrated HCl at room temperature. The solution was cooled to 0 °C and treated dropwise with $NaNO_2$ (1.46 g, 21.4 mmol) dissolved in 10 mL of H_2O. The solution was stirred at 0 °C for 2 h, then treated with KI (8.12 g, 48.9 mmol) in 20 mL of H_2O. After 6 h, the solution was extracted with Et_2O several times. The combined ether layers were washed with brine, dried, filtered, and concentrated. The residue was purified by flash column chromatography using 1:9 EtOAc/hexane to give 2.65 g of 2-iodo-4-cyanotoluene (70%). ^1H NMR ($CDCl_3$): δ 8.08 (d, J = 1.7 Hz, 1H), 75.2−7.55 (m, 2H), 7.32 (d, J = 7.8 Hz, 1H), 2.50 (s, 3H). MS/ESI, m/z: 234 $(M + H)^+$.

5-[(4-Cyano-2-iodobenzyloxy)-(4-cyanophenyl)methyl]-1-methyl-1H-imidazole (14). Compound **14** was prepared from 2-iodo-4-cyanotoluene in a similar manner as described for the preparation of compound **6**. ^1H NMR ($CDCl_3$): δ 8.11 (d, J = 1.7 Hz, 1H), 7.66−7.72 (m, 3H), 7.53−7.58 (m, 4H), 6.99 (s, 1H), 5.70 (s, 1H), 4.50−4.61 (m, 2H), 3.43 (s, 3H). MS/ESI, m/z: 455 $(M + H)^+$.

5-[(5-Cyanobiphenyl-2-ylmethoxy)-(4-cyanophenyl)methyl]-1-methyl-1H-imidazole (15). Compound **15** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^1H NMR (DMSO-d_6): δ 8.96 (s, 1H), 7.89 (m, 1H), 7.86 (d, J = 8.05 Hz, 2H), 7.81 (d, J = 8.05 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 7.48 (d, J = 8.42 Hz, 2H), 7.42−7.44 (m, 3H), 7.33 (dd, J = 6.6, 2.9 Hz, 2H), 7.23 (s, 1H), 5.94 (s, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 3.63 (s, 3H). MS/ESI, m/z: 405 $(M + H)^+$. Anal. ($C_{26}H_{20}N_4O\cdot 1.5$ TFA) C, H, N.

5-[(4-Cyano-2-naphthalen-1-yl-benzyloxy)-(4-cyanophenyl)methyl]-1-methyl-1*H*-imidazole (16). Compound **16** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. Compound **16** exists as a mixture of two rotatomers. ^{1}H NMR (DMSO-d_6): δ 8.94 (s, 0.5 H), 8.90 (s, 0.5 H), 8.00–8.04 (m, 3H), 7.87–7.91 (m, 1H), 7.75–7.78 (m, 2H), 7.51–7.67 (m, 4H), 7.28–7.44 (m, 4H), 7.14–7.24 (m, 2H), 7.08 (s, 0.5 H), 7.04 (s, 0.5H), 5.74 (s, 1H), 4.34 (dd, J = 11.5, 1.4 Hz, 1H), 4.13 (dd, J = 11.4, 6.6 Hz, 1H), 3.58 (s, 1.5H), 3.46 (s, 1.5H). MS/ESI, m/z: 455 (M + H)$^+$. Anal. ($C_{30}H_{22}N_4O\cdot0.4H_2O$) C, H, N.

4-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3-quinolin-8-ylbenzonitrile (17). Compound **17** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR (DMSO-d_6): δ 9.03 (s, 1 H), 8.75 (s, 1H), 8.47 (d, J = 7.2 Hz, 1H), 8.09–8.11 (m, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.68–7.75 (m, 5H), 7.57 (d, J = 4.1 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1 H), 7.21 (d, J = 7.5 Hz, 1H), 7.14 (s, 1H), 5.73 (s, 1H), 4.45 (d, J = 11.5 Hz, 1H), 4.12 (d, J = 11.4 Hz, 1H), 3.58 (s, 3H). MS/ESI, m/z: 456 (M + H)$^+$. Anal. ($C_{29}H_{21}N_5O\cdot1.8HCl$) C, H, N.

3′-Chloro-6-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]biphenyl-3-carbonitrile (18). Compound **18** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR (HCl salt, MeOH-d_4): δ 8.92 (s, 1 H), 7.75–7.80 (m, 4H), 7.64 (s, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.39–7.44 (m, 2H), 7.34 (s, 1H), 7.22–7.25 (m, 1H), 7.19 (s, 1 H), 7.21 (d, J = 7.5 Hz, 1H), 7.14 (s, 1H), 5.87 (s, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 3.72 (s, 3H). MS/ESI, m/z: 439 (M + H)$^+$. Anal. ($C_{26}H_{19}ClN_4O\cdot HCl\cdot0.65H_2O$) C, H, N.

(*R,S*)-6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′-methoxybiphenyl-3-carbonitrile (19). Compound **19** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR ($CDCl_3$): δ 7.69–7.54 (m, 6H), 7.39–7.26 (m, 3H), 6.96 (m, 1H), 6.80–6.75 (m, 3H), 5.47 (s, 1H), 4.53 (d, J = 12.2 Hz, 1H), 4.46 (d, J = 12.2 Hz, 1H), 3.81 (s, 3H), 3.34 (s, 3H). MS/ESI, m/z: 435 (M + H)$^+$, 567 (M + Na)$^+$. Anal. ($C_{27}H_{22}N_4O_2\cdot HCl\cdot H_2O$) C, H, N.

(*R*)-6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′-methoxybiphenyl-3-carbonitrile (20) and (*S*)-6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′-methoxybiphenyl-3-carbonitrile (21). Compounds **20** and **21** were separated by preparative HPLC using column Chiralcel (4.6 mm × 250 mm), eluting with 60:40 hexane/ethanol.

3-Benzo[1,3]dioxol-5-yl-4-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]benzonitrile (22). Compound **22** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR ($CDCl_3$): δ 7.67–7.55 (m, 6H), 7.41 (d, J = 8.1 Hz, 2H), 6.83 (m, 2H), 6.70–6.51 (m, 2H), 6.04 (s, 2H), 5.51 (s, 1H), 4.53 (d, J = 12.2 Hz, 1H), 4.46 (d, J = 12.2 Hz, 1H), 3.38 (s, 3H). MS/(DCI/NH_3) m/z: 449 (M + H)$^+$. Anal. ($C_{27}H_{20}N_4O_3\cdot HCl\cdot0.8H_2O$) C, H, N.

4-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3-(2,2-difluorobenzo[1,3]dioxol-5-yl)-benzonitrile (23). Compound **23** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR ($CDCl_3$): δ 7.69–7.71 (m, 1H), 7.62–7.66 (m, 3H), 7.54 (d, J = 1.6 Hz, 1H), 7.46 (m, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 1.6 Hz, 1H), 6.94 (dd, J = 8.1, 1.6 Hz, 1H), 6.88 (s, 1H), 5.52 (s, 1H), 4.50 (d, J = 12.2 Hz, 1H), 4.41 (d, J = 12.2 Hz, 1H), 3.33 (s, 3H). MS/(DCI/NH_3) m/z: 485 (M + H)$^+$. Anal. ($C_{27}H_{18}F_2N_4O_3$) C, H, N.

6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′-ethoxybiphenyl-3-carbonitrile (24). Compound **24** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR ($CDCl_3$): δ 7.69–7.54 (m, 6H), 7.39–7.27 (m, 3H), 6.94 (m, 1H), 6.80–6.75 (m, 3H), 5.47 (s, 1H), 4.53 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 3.36 (s, 3H), 1.42 (t, J = 6.8 Hz, 3H). MS/ESI, m/z: 449 (M + H)$^+$. Anal. ($C_{28}H_{24}N_4O_2\cdot HCl\cdot0.5H_2O$) C, H, N.

6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′-methoxymethylbiphenyl-3-carbonitrile (25). Compound **25** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR (HCl salt, DMSO-d_6): δ 9.04 (s, 1H), 7.80–7.91 (m, 4H), 7.74 (d, J = 1.7 Hz, 1H), 7.36–7.47 (m, 5H), 7.25–7.27 (m, 3H), 5.95 (s, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.41–4.47 (m, 3H), 3.62 (s, 3H), 3.27 (s, 3H). MS/ESI, m/z: 449 (M + H)$^+$. Anal. ($C_{28}H_{24}N_4O_2\cdot HCl\cdot1.35H_2O$) C, H, N.

6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-4′-methoxybiphenyl-3-carbonitrile (26). Compound **26** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR (HCl salt, DMSO-d_6): δ 9.04 (s, 1H), 7.84–7.88 (m, 3H), 7.80 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.24–7.27 (m, 3H), 6.95–6.98 (m, 2H), 5.96 (s, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 3.81 (s, 3H), 3.65 (s, 3H). MS/ESI, m/z: 435 (M + H)$^+$. Anal. ($C_{27}H_{22}N_4O_2$) C, H, N.

6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-4′-ethoxybiphenyl-3-carbonitrile (27). Compound **27** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR (HCl salt, DMSO-d_6): δ 9.04 (s, 1H), 7.84–7.87 (m, 3H), 7.79 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 1.5 Hz, 1H), 7.60–7.64 (m, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.26 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 6.93–6.95 (m, 2H), 5.95 (s, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.45 (d, J = 11.4 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 3.66 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H). MS/ESI, m/z: 449 (M + H)$^+$. Anal. ($C_{28}H_{24}N_4O_2\cdot0.1H_2O$) C, H, N.

6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-4′-trifluoromethoxybiphenyl-3-carbonitrile (28). Compound **28** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR (HCl salt, DMSO-d_6): δ 8.94 (s, 1H), 7.88–7.92 (m, 2H), 7.85 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 1.8 Hz, 1H), 7.46–7.50 (m, 4H), 7.40 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 7.7 Hz, 1H), 7.20 (s, 1H), 5.93 (s, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.41 (d, J = 11.7 Hz, 1H), 3.64 (s, 3H). MS/ESI, m/z: 489 (M + H)$^+$. Anal. ($C_{27}H_{19}F_3N_4O_2$) C, H, N.

6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-4′-methylbiphenyl-3-carbonitrile (29). Compound **29** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR (HCl salt, DMSO-d_6): δ 9.00 (s, 1H), 7.85–7.87 (m, 3H), 7.79 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 1.3 Hz, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.26 (s, 1H), 7.21–7.22 (m, 4H), 5.94 (s, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 3.63 (s, 3H), 2.37 (s, 3H). MS/ESI, m/z: 419 (M + H)$^+$. Anal. ($C_{27}H_{22}N_4O\cdot1.4TFA$) C, H, N.

6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′,5′-difluorobiphenyl-3-carbonitrile (30). Compound **30** was prepared from compound **14** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR (TFA salt, DMSO-d_6): δ 8.99 (s, 1H), 7.91–7.93 (m, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.29–7.32 (m, 2H), 7.86 (d, J = 8.3 Hz, 2H), 7.29–7.32 (m, 1H), 7.27 (s, 1H), 7.13 (d, J = 6.4 Hz, 2H), 5.96 (s, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 3.64 (s, 3H). MS/ESI, m/z: 441 (M + H)$^+$. Anal. ($C_{26}H_{18}F_2N_4O\cdot C_2HF_3O_2\cdot0.9H_2O$) C, H, N.

3′-Methoxy-2-methyl-5-nitrobiphenyl (32). Compound **32** was prepared via Suzuki coupling from compound **31** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR ($CDCl_3$): δ 8.09–8.11 (m, 2H), 7.40–7.43 (m, 1H), 7.35 (d, J = 8.1 Hz, 1H), 6.93–6.97 (m, 1H), 6.89 (d, J = 7.46 Hz, 1H), 6.83–6.85 (m, 1H), 3.85 (s, 3H), 2.37 (s, 3H). MS/(DCI) m/z: 244 (M + H)$^+$.

4-[(3′-Methoxy-5-nitrobiphenyl-2-ylmethoxy)-(3-methyl-3*H*-imidazol-4-yl)methyl]benzonitrile (33). Compound **33** was prepared from compound **32** in a similar manner as described for the preparation of compound **6**. ^{1}H NMR

($CDCl_3$): δ 8.23 (dd, *J* = 8.3, 2.5 Hz, 1H), 8.15 (d, *J* = 2.4 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.56 (s, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 6.96 (dd, *J* = 7.5, 2.4 Hz, 1H), 6.79–6.84 (m, 3H), 5.50 (s, 1H), 4.48–4.60 (m, 2H), 3.82 (s, 3H), 3.35 (s, 3H). MS/(DCI) *m/z*: 455 (M + H)$^+$. Anal. ($C_{26}H_{22}N_4O_4$·HCl·0.5H_2O) C, H, N.

4-[(5-Amino-3′-methoxybiphenyl-2-ylmethoxy)-(3-methyl-3*H*-imidazol-4-yl)methyl]benzonitrile (34). A mixture of compound **33** (1.0 g, 2.2 mmol) and $SnCl_2$·2H_2O (1.98 g, 8.8 mmol) in 20 mL of EtOH and 10 mL of concentrated HCl was stirred at room temperature overnight. The solution was diluted with 100 mL of H_2O, neutralized with 10% NaOH, and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography using 100:4:0.4 EtOAc/MeOH/NH_4OH to give 0.78 g of compound **34** (84%). ^1H NMR ($CDCl_3$): δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.38 (s, 1H), 7.23–7.28 (m, 1H), 7.19 (d, *J* = 8.14 Hz, 1H), 6.85–6.90 (m, 3H), 6.66–6.69 (m, 2H), 6.61 (d, *J* = 2.3 Hz, 1H), 5.40 (s, 1H), 4.29–4.41 (m, 2H), 3.77 (s, 3H), 2.39 (s, 3H). MS/ESI, *m/z*: 425 (M + H)$^+$. Anal. ($C_{26}H_{24}N_4O_2$·2HCl·0.9H_2O) C, H, N.

***N*-{6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′-methoxybiphenyl-3-yl}methanesulfonamide (35).** Compound **34** (64 mg, 0.15 mmol) in 5 mL of CH_2Cl_2 was treated with CH_3SO_2Cl (17 mg, 0.15 mmol) and Et_3N (0.10 g, 0.6 mmol) at room temperature. The solution was stirred overnight. The solvent was removed in vacuo, and the residue was purified by flash column chromatography using 100:4:0.4 EtOAc/MeOH/NH_4OH to give 0.02 g of compound **35** (27%). ^1H NMR ($CDCl_3$): δ 7.58–7.61 (m, 2H), 7.34–7.43 (m, 4H), 7.24–7.31 (m, 3H), 7.10 (d, *J* = 2.3 Hz, 1H), 6.91 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.80–6.85 (m, 2H), 6.74 (s, 1H), 5.44 (s, 1H), 4.38–4.49 (m, 2H), 3.79 (s, 3H), 3.32 (s, 3H), 3.06 (s, 3H). MS/ESI, *m/z*: 5.0 (M + H)$^+$. Anal. ($C_{27}H_{26}N_4O_4S$·TFA·0.7H_2O) C, H, N.

***N*-{6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′-methoxybiphenyl-3-yl}-2-methoxyacetamide (36).** A mixture of compound **34** (60 mg, 0.14 mmol), methoxyacetic acid (15 mg, 0.17 mmol), HATU (66 mg, 0.17 mmol), and Et_3N (34 mg, 0.34 mmol) in 5 mL of CH_2Cl_2 was stirred overnight. The solution was diluted with EtOAc, washed with H_2O and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography using 100:4:0.4 EtOAc/MeOH/NH_4-OH to give 53 mg of compound **36** (77%). ^1H NMR (CH_3OH-d_4): δ 8.84 (s, 1H), 7.67–7.74 (m, 3H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.09 (s, 1H), 6.95 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.83–6.87 (m, 2H), 5.75 (s, 1H), 4.48–4.59 (m, 2H), 4.04 (s, 2H), 3.79 (s, 3H), 3.65 (s, 3H), 3.48 (s, 3H). MS/ESI, *m/z*: 496 (M + H)$^+$. Anal. ($C_{29}H_{28}N_4O_4$·HCl·H_2O) C, H, N.

3′-Methoxy-6-methylbiphenyl-3-carboxylic Acid Methyl Ester (38). Compound **38** was prepared via the Suzuki coupling from compound **37** in a similar manner as described for the preparation of compound **7**. ^1H NMR ($CDCl_3$): δ 7.91–7.93 (m, 2H), 7.31–7.36 (m, 2H), 6.85–6.93 (m, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 2.32 (s, 3H). MS/(DCI) *m/z*: 257 (M + H)$^+$.

6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′-methoxybiphenyl-3-carboxylic Acid Methyl Ester (39). Compound **39** was prepared from compound **38** in a similar manner as described for the preparation of compound **6**. ^1H NMR ($CDCl_3$): δ 8.04 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.91 (d, *J* = 1.7 Hz, 1H), 7.56–7.62 (m, 3H), 7.36–7.40 (m, 3H), 7.28 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.8, 2.0 Hz, 1H), 6.81–6.85 (m, 2H), 6.77 (s, 1H), 5.46 (s, 1H), 4.46–4.67 (m, 2H), 3.92 (s, 3H), 3.80 (s, 3H), 3.31 (s, 3H). MS/ESI, *m/z*: 468 (M + H)$^+$. Anal. ($C_{28}H_{25}N_3O_4$·0.5H_2O) C, H, N.

6-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′-methoxybiphenyl-3-carboxylic Acid (40). A mixture of compound **39** (0.58 g, 1.23 mmol) and LiOH (59 mg, 2.46 mmol) in 10 mL of H_2O and 5 mL of methanol was stirred at room temperature for 2 days. The pH value of the solution was adjusted to 6 using 1 M $NaHSO_4$. The solution was extracted with EtOAc several times. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to give 0.44 g of compound **40**. ^1H NMR (TFA salt, DMSO-d_6): δ 8.96 (s, 1H), 7.90 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.18 (s, 1H), 6.90 (dd, *J* = 8.3 1.4 Hz, 1H), 6.80–6.81 (m, 2H), 5.88 (s, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 3.68 (s, 3H), 3.57 (s, 3H). MS/ESI, *m/z*: 454 (M + H)$^+$. Anal. ($C_{27}H_{23}N_3O_4$·0.9TFA) C, H, N.

5-Amino-3′-methoxybiphenyl-2-carboxylic Acid Methyl Ester (42). A mixture of 2-chloro-4-nitrobenzoic acid methyl ester (0.42 g, 2 mmol), 3-methoxyphenyl boronic acid (0.375 g, 2.4 mmol), $Pd(PCy_3)_2Cl_2$ (0.074 g, 0.1 mmol), and Na_2CO_3 (0.64 g, 6 mmol) in 10 mL of toluene, 10 mL of dioxane, and 4 mL of EtOH was heated at reflux overnight. After the reaction mixture was cooled to room temperature, it was partitioned between H_2O and EtOAc. The aqueous layer was extracted with additional EtOAc. The combined organic layers were washed with H_2O and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography using 10:90 EtOAc/hexane to give 0.58 g of 5-nitro-3′-methoxybiphenyl-2-carboxylic acid methyl ester. ^1H NMR ($CDCl_3$): δ 8.27 (dd, *J* = 8.4, 2.3 Hz, 1H), 8.23 (d, *J* = 2.4 Hz, 1H), 7.98 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.38–7.41 (m, 2H), 7.34–7.36 (m, 1H), 7.19–7.23 (m, 1H), 3.72 (s, 3H). MS/ESI, *m/z*: 292 (M + H)$^+$.

Compound **42** was prepared from 5-nitro-3′-methoxybiphenyl-2-carboxylic acid methyl ester using $SnCl_2$·2H_2O in a similar manner described for the preparation of compound **34**.

5-Cyano-3′-methoxybiphenyl-2-carboxylic Acid Methyl Ester (43). 5-Iodo-3′-methoxybiphenyl-2-carboxylic acid methyl ester was prepared from compound **42** in a similar manner as described in the preparation of compound **13**. ^1H NMR ($CDCl_3$): δ 7.75–7.76 (m, 2H), 7.51–7.54 (m, 1H), 7.26–7.33 (m, 2H), 6.83–6.93 (m, 3H), 3.83 (s, 3H), 3.63 (s, 3H). MS/ESI, *m/z*: 369 (M + H)$^+$.

Compound **43** was prepared using the general procedure of cyanation of aryl iodides from 5-iodo-3′-methoxybiphenyl-2-carboxylic acid methyl ester. ^1H NMR ($CDCl_3$): δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.67–7.71 (m, 2H), 7.31–7.36 (m, 1H), 6.93–6.97 (m, 1H), 6.82–6.88 (m, 2H), 3.84 (s, 3H), 3.68 (s, 3H). MS/ESI, *m/z*: 268 (M + H)$^+$.

6-Hydroxymethyl-3′-methoxybiphenyl-3-carbaldehyde (44). Compound **43** (0.67 g, 2.51 mmol) in 20 mL of toluene was treated with 1.5 M DIBAL in toluene (4.2 mL, 6.3 mmol) at −78 °C. The solution was stirred at −78 °C for 2 h and warmed to room temperature gradually. The reaction mixture was treated with 10 mL of concentrated HCl and partitioned between H_2O and EtAOc. The aqueous layer was extracted with additional EtOAc. The combined organic layers were washed with H_2O and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography using 30:70 EtOAc/hexane to give 0.59 g of 6-hydroxymethyl-3′-methoxybiphenyl-3-carbaldehyde **42** (95%). MS/(DCI) *m/z*: 243 (M + H)$^+$.

4-[(5-Formyl-3′-methoxybiphenyl-2-ylmethoxy)-(3-methyl-3*H*-imidazol-4-yl)methyl]benzonitrile (45). A mixture of compound **42** (0.61 g, 2.54 mmol), LiBr (0.254 g, 2.92 mmol) in 5 mL of DMF was treated with PBr_3 (0.25 mL, 2.63 mmol) at 0 °C. The solution was stirred at 0 °C for 2 h, poured into water, and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography using 10:90 EtOAc/hexane to give 0.63 g of 6-bromomethyl-3′-methoxybiphenyl-3-carbaldehyde **42** (82%). ^1H NMR ($CDCl_3$): δ 10.05 (s, 1H), 7.63–7.90 (m, 3H), 7.37–7.42 (m, 1H), 6.95–7.03 (m, 3H), 4.47 (s, 2H), 3.87 (s, 3H). MS/(DCI) *m/z*: 306 (M + H)$^+$.

A mixture of 6-bromomethyl-3′-methoxybiphenyl-3-carbaldehyde (0.23 g, 0.75 mmol), compound **4a** (0.106 g, 0.5 mmol), and Ag_2O (0.34 g, 1.5 mmol) in 10 mL of CH_2Cl_2 was stirred at room temperature overnight while the flask was covered with aluminum foil. The solution was filtered through a pack

of Celite, and the filtrate was purified by flash column chromatography using 100:5:0.5 EtOAc/methanol/NH_4OH to give 0.133 g of **45** (60%). ^{1}H NMR ($CDCl_3$): δ 10.05 (s, 1H), 7.88–7.92 (m, 2H), 7.80 (d, J = 1.7 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.50 (s, 1H), 7.38 (d, J = 81. Hz, 2H), 7.29–7.34 (m, 1H), 6.94 (dd, J = 7.8, 2.0 Hz, 1H), 6.80–6.85 (m, 3H), 5.48 (s, 1H), 4.48–4.59 (m, 2H), 3.81 (s, 3H), 3.34 (s, 3H). MS/ESI, *m/z*: 438 (M + H)$^+$. Anal. ($C_{27}H_{23}N_3O_3$·0.4 H_2O) C, H, N.

3′-Chloro-6-methylbiphenyl-3-carbonitrile (46a). Compound **46a** was prepared via Suzuki coupling from compound **13** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR ($CDCl_3$): δ 7.54–7.57 (m, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.36–7.39 (m, 3H), 7.27–7.29 (m, 1H), 7.14–7.18 (m, 1H), 2.31 (s, 3H). MS/ESI, *m/z*: 228 (M + H)$^+$.

3′-Methoxy-6-methylbiphenyl-3-carbonitrile (46b). Compound **46b** was prepared via Suzuki coupling from compound **13** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR ($CDCl_3$): δ 7.52–7.55 (m, 2H), 7.33–7.38 (m, 2H), 6.93 (dd, J = 7.5, 2.7 Hz, 1H), 6.85 (m, 1H), 6.79–6.80 (m, 1H), 3.84 (s, 3H), 2.32 (s, 3H). MS/ESI, *m/z*: 224 (M + H)$^+$.

3-Benzo[1,3]dioxol-5-yl-4-methylbenzonitrile (46c). Compound **46c** was prepared via Suzuki coupling from compound **13** in a similar manner as described for the preparation of compound **7**. ^{1}H NMR ($CDCl_3$): δ 7.48–7.52 (m, 2H), 7.34 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.70–6.75 (m, 2H), 6.02 (s, 2H), 2.32 (s, 3H). MS/ESI, *m/z*: 238 (M + H)$^+$.

6-[(4-Chlorophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]-3′-methoxybiphenyl-3-carbonitrile (47). Compound **47** was prepared from compound **46b** in a similar manner as described for the preparation of compound **6**. ^{1}H NMR (HCl salt, MeOH-d_4): δ 8.84 (s, 1H), 7.75–7.76 (m, 2H), 7.62 (s, 1H), 7.38–7.41 (m, 2H), 7.27–7.35 (m, 3H), 7.10 (s, 1H), 6.97–7.00 (m, 1H), 6.81–6.84 (m, 2H), 5.70 (s, 1H), 4.51–4.63 (m, 2H), 3.79 (s, 3H), 3.69 (s, 3H). MS/ESI, *m/z*: 429 (M + H)$^+$. Anal. ($C_{26}H_{22}ClN_3O_2$·HCl·0.9H_2O) C, H, N.

6-[(3-Chloro-4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]-3′-methoxybiphenyl-3-carbonitrile (48). Compound **48** was prepared from compound **46b** in a similar manner as described for the preparation of compound **6**. ^{1}H NMR ($CDCl_3$): δ 7.66–7.69 (m, 1H), 7.58–7.63 (m, 3H), 7.42 (d, J = 8.5 Hz, 2H), 7.30–7.35 (m, 1H), 7.2 (dd, J = 8.8, 1.7 Hz, 1H), 6.95 (dd, J = 8.0, 2.2 Hz, 1H), 6.86 (s, 1H), 6.76–6.81 (m, 2H), 5.43 (s, 1H), 4.44–4.57 (m, 2H), 3.81 (s, 3H), 3.29 (s, 3H). MS/ESI, *m/z*: 469 (M + H)$^+$. Anal. ($C_{27}H_{21}ClN_4O_2$·0.55H_2O) C, H, N.

3′-Chloro-6-[(4-cyano-3-fluorophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]biphenyl-3-carbonitrile (49). Compound **49** was prepared from compound **46a** in a similar manner as described for the preparation of compound **6**. ^{1}H NMR (HCl salt, MeOH-d_4): δ 7.69–7.71 (m, 1H), 7.57–7.61 (m, 3H), 7.33–7.43 (m, 3H), 7.27 (d, J = 3.8 Hz, 1H), 7.10–7.19 (m, 3H), 6.91 (s, 1H), 7.21–7.22 (m, 4H), 5.47 (s, 1H), 4.41–4.54 (m, 2H), 3.30 (s, 3H). MS/ESI, *m/z*: 457 (M + H)$^+$. Anal. ($C_{26}H_{18}ClFN_4O$·HCl·0.7H_2O) C, H, N.

3′-Chloro-6-[(4-cyano-2-fluorophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]biphenyl-3-carbonitrile (50). Compound **50** was prepared from compound **46a** in a similar manner as described for the preparation of compound **6**. ^{1}H NMR ($CDCl_3$): δ 7.68–7.70 (m, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.57–7.60 (m, 1H), 7.55 (s, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.40–7.42 (m, 2H), 7.32–7.35–7.22 (m, 2H), 7.23–7.25 (m, 1H), 7.10 (d, J = 7.5 Hz, 1H), 5.72 (s, 1H), 4.39–4.49 (m, 2H), 3.50 (s, 3H). MS/ESI, *m/z*: 456 (M + H)$^+$. Anal. ($C_{26}H_{18}ClFN_4O$·HCl·0.7H_2O) C, H, N.

3′-Chloro-6-[(3-methyl-3*H*-imidazol-4-yl)-(4-trifluoromethylphenyl)methoxymethyl]biphenyl-3-carbonitrile (51). Compound **51** was prepared from compound **45a** in a similar manner as described for the preparation of compound **6**. ^{1}H NMR ($CDCl_3$): δ 7.56–7.70 (m, 5H), 7.26–7.41 (m, 6H), 7.12 (d, J = 7.1 Hz, 1H), 6.83 (s, 1H), 5.50 (s, 1H), 4.40–4.62 (m, 2H), 3.34 (s, 3H). MS/ESI, *m/z*: 483 (M + H)$^+$. Anal. ($C_{26}H_{19}ClF_3N_3O$) C, H, N.

3′-Chloro-6-[(4-cyanophenyl)-(2,3-dimethyl-3*H*-imidazol-4-yl)methoxymethyl]biphenyl-3-carbonitrile (52). A mixture of compound **4h** (0.113 g, 0.5 mmol) and 6-bromomethyl-3′-chlorobiphenyl-3-carbonitrile (0.153 g, 0.5 mmol), which was prepared from compound **46a** using the general procedure for the preparation of benzyl bromide, in 5 mL of DME was treated with 60% NaH in mineral oil (40 mg, 1 mmol) at 0 °C. The solution was stirred at room temperature overnight, poured into H_2O, and extracted with EtOAc several times. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography using 100:5:0.5 EtOAc/methanol/NH_4OH to give 0.108 g of compound **52** (48%). ^{1}H NMR ($CDCl_3$): δ 7.67–7.71 (m, 1H), 7.60–7.65 (m, 3H), 7.56 (d, J = 1.7 Hz, 1H), 7.32–7.42 (m, 4H), 7.27–7.28 (m, 1H), 7.11–7.14 (m, 1H), 6.70 (s, 1H), 5.43 (s, 1H), 4.39–4.53 (m, 2H), 3.19 (s, 3H), 2.33 (s, 3H). MS/ESI, *m/z*: 453 (M + H)$^+$. Anal. ($C_{27}H_{21}ClN_4O$·HCl·1.3H_2O) C, H, N.

3-Benzo[1,3]dioxol-5-yl-4-[(4-cyanophenyl)-(2,3-dimethyl-3*H*-imidazol-4-yl)methoxymethyl]benzonitrile (53). Compound **53** was prepared from compound **46c** in a similar manner as described for the preparation of compound **52**. ^{1}H NMR ($CDCl_3$): δ 7.63–7.65 (m, 4H), 7.55 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.66–6.71 (m, 3H), 6.03 (s, 2H), 5.45 (s, 1H), 4.43–4.56 (m, 2H), 3.22 (s, 3H), 2.34 (s, 3H). MS/ESI, *m/z*: 463 (M + H)$^+$. Anal. ($C_{28}H_{22}N_4O_3$·0.55H_2O) C, H, N.

3′-Chloro-6-[(4-cyanophenyl)thiazol-5-ylmethoxymethyl]biphenyl-3-carbonitrile (54). Compound **54** was prepared from compound **46a** in a similar manner as described for the preparation of compound **52**. ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 7.63–7.71 (m, 5H), 7.56 (d, J = 1.7 Hz, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.27–7.39 (m, 3H), 7.10–7.13 (m, 1H), 5.86 (s, 1H), 4.39–4.49 (m, 2H). MS/ESI, *m/z*: 442 (M + H)$^+$. Anal. ($C_{25}H_{16}ClN_3OS$·0.5TFA) C, H, N.

3′-Chloro-6-[(4-chloropyridin-3-yl)-(4-cyanophenyl)-methoxymethyl]biphenyl-3-carbonitrile (55). Compound **55** was prepared from compound **46c** in a similar manner as described for the preparation of compound **52**. ^{1}H NMR ($CDCl_3$): δ 8.68 (s, 1H), 8.44–8.46 (m, 1H), 7.60–7.65 (m, 4H), 7.54 (s, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.30–7.33 (m, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.63–6.67 (m, 2H), 6.03 (s, 2H), 5.78 (s, 1H), 4.49 (s, 2H). MS/ESI, *m/z*: 472 (M + H)$^+$. Anal. ($C_{28}H_{18}ClN_3O_3$·2HCl·0.6H_2O) C, H, N.

4-[(4-Iodo-2-nitrobenzyloxy)-(3-methyl-3*H*-imidazol-4-yl)methyl]benzonitrile (57). Compound **57** was prepared from compound **56** in a similar manner as described for the preparation of compound **33**. ^{1}H NMR ($CDCl_3$): δ 8.38 (d, J = 1.7 Hz, 1H), 7.97 (dd, J = 8.1, 1.7 Hz, 1H), 7.69 (d, J = 8.1 Hz, 2H), 7.45–7.51 (m, 4H), 6.89 (s, 1H), 5.67 (s, 1H), 4.76–4.92 (m, 2H), 3.43 (s, 3H). MS/(DCI) *m/z*: 475 (M + H)$^+$.

4-[(2-Amino-4-iodobenzyloxy)-(3-methyl-3*H*-imidazol-4-yl)methyl]benzonitrile (58). Compound **58** was prepared from compound **57** in a similar manner as described for the preparation of compound **34**. ^{1}H NMR ($CDCl_3$): δ 7.66 (d, J = 8.5 Hz, 2H), 7.51 (s, 1H), 7.45 (d, J = 8.1, Hz, 2H), 7.03–7.07 (m, 2H), 6.95 (s, 1H), 6.68 (d, J = 7.5 Hz, 1H), 5.54 (s, 1H), 4.41–4.54 (m, 2H), 3.37 (s, 3H). MS/(DCI) *m/z*: 445 (M + H)$^+$.

Thiophene-2-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]-5-iodophenyl}-amide (59a). A mixture of compound **58** (0.10 g, 0.23 mmol), thiophene-2-sulfonyl chloride (0.043 g, 0.24 mmol), and 0.2 mL of pyridine in 5 mL of CH_2Cl_2 was stirred at room temperature overnight. The solution was poured into water and extracted with additional CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated. The residue was purified by flash column chromatography using 100:5:0.5 EtOAc/methanol/NH_4OH to give 0.110 g of compound **59a** (81%). ^{1}H NMR ($CDCl_3$): δ 7.68–7.82 (m, 5H), 7.56 (dd, J = 5.1, 1.4 Hz, 1H), 7.50 (dd, J = 8.0, 1.5 Hz, 1H), 7.42–7.49 (m, 3H), 7.14 (s, 1H), 7.00–7.03 (m, 1H), 6.91 (d, J = 9.1 Hz, 1H), 5.56 (s, 1H), 4.30–4.51 (m, 2H), 3.40 (s, 3H). MS/ESI, *m/z*: 591 (M + H)$^+$.

Thiophene-2-sulfonic Acid {5-Cyano-2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]phenyl}-amide (60a). Compound **60a** was prepared from compound **59a** using the general procedure of cyanation of aryl halides (bromide or iodide). ^{1}H NMR ($CDCl_3$): δ 7.69–7.73 (m, 3H), 7.69 (s, 1H), 7.58 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.42–7.47 (m, 4H), 7.31 (s, 1H), 7.26–7.28 (m, 1H), 7.01–7.06 (m, 2H), 5.58 (s, 1H), 4.42–4.59 (m, 2H), 3.37 (s, 3H). MS/ESI, *m*/*z*: 489 (M + H)$^+$. Anal. ($C_{24}H_{19}N_5O_3S_2$·1.28TFA·0.4H_2O) C, H, N.

***N*-{5-Cyano-2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]phenyl}-4-methylbenzenesulfonamide (60b).** Compound **60b** was prepared from compound **59b** in a similar manner as described for the preparation of compound **60a**. ^{1}H NMR ($CDCl_3$): δ 7.69–7.72 (m, 3H), 7.50–7.53 (m, 3H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.37 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.19–7.24 (m, 3H), 7.00 (s, 1H), 5.55 (s, 1H), 4.34–4.51 (m, 2H), 3.36 (s, 3H), 2.39 (s, 3H). MS/ESI, *m*/*z*: 498 (M + H)$^+$. Anal. ($C_{27}H_{23}N_5O_3S$·HCl·1.6H_2O) C, H, N.

Naphthalene-1-sulfonic Acid {5-Cyano-2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]phenyl}-amide (60c). Compound **60c** was prepared from compound **59c** in a similar manner as described for the preparation of compound **60a.** ^{1}H NMR ($CDCl_3$): δ 8.43 (d, *J* = 8.8 Hz, 1H), 8.23 (d, *J* = 7.5 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.47–7.63 (m, 7H), 7.30 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 5.48 (s, 1H), 4.25–4.45 (m, 2H), 3.35 (s, 3H). MS/ESI, *m*/*z*: 533 (M + H)$^+$. Anal. ($C_{30}H_{23}N_5O_3S$·HCl·0.5H_2O) C, H, N.

4-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]-3-(3,5-difluorobenzylamino)benzonitrile (61). A mixture of compound **58** (0.150 g, 0.34 mmol), 3,5-difluorobenzaldehyde (0.096 g, 0.68 mmol), acetic acid (0.122 g, 2.054 mmol), and $NaBH(OAc)_3$ (0.432 g, 2.04 mmol) in 10 mL of 1,2-dichloroethane was stirred overnight. The reaction mixture was partitioned between water and EtOAc. The aqueous layer was extracted with additional EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography using 100:5:0.5 EtOAc/methanol/NH_4OH to give 0.100 g of 4-[[2-(3,5-difluorobenzylamino)-4-iodobenzyloxy]-(3-methyl-3*H*-imidazol-4-yl)methyl]benzonitrile (52%). ^{1}H NMR ($CDCl_3$): δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.37–7.44 (m, 3H), 7.06 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.98 (s, 1H), 6.89 (d, *J* = 1.7 Hz, 1H), 6.69–6.78 (m, 4H), 5.55 (s, 1H), 4.98 (d, *J* = 5.4 Hz, 1H), 4.45–4.63 (m, 2H), 4.30 (d, *J* = 5.8 Hz, 2H), 3.29 (s, 3H). MS/ESI, *m*/*z*: 571 (M + H)$^+$.

Compound **61** was prepared from 4-[[2-(3,5-difluorobenzylamino)-4-iodobenzyloxy]-(3-methyl-3*H*-imidazol-4-yl)methyl]benzonitrile using the general procedure for the cyanation of aryl iodide. ^{1}H NMR (HCl salt, MeOH-*d*$_4$): δ 8.93 (s, 1H), 7.79–7.81 (m, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.36 (s, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 6.82–6.98 (m, 4H), 6.73 (s, 1H), 5.97 (s, 1H), 4.74 (s, 2H), 4.44 (s, 2H), 3.74 (s, 3H). MS/ESI, *m*/*z*: 458 (M + H)$^+$. Anal. ($C_{27}H_{21}F_2N_5O$·1.5TFA) C, H, N.

***N*-{5-Cyano-2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]phenyl}benzamide (62).** A mixture of compound **58** (0.10 g, 0.23 mmol), benzoyl chloride (0.042 g, 0.30 mmol), and Et_3N (0.040 g, 0.38 mmol) in 3 mL of CH_2Cl_2 was stirred overnight. The reaction mixture was partitioned between H_2O and EtOAc. The aqueous layer was extracted with additional EtOAc. The combined organic layers were washed with brine, dried, and concentrated in vacuo. The residue was purified by flash column chromatography using 100:3:0.3 EtOAc/methanol/NH_4OH to give 0.073 g of *N*-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]-5-iodophenyl}benzamide (58%). ^{1}H NMR ($CDCl_3$): δ 9.08 (s, 1H), 8.77 (d, *J* = 1.7 Hz, 1H), 7.69 (d, *J* = 7.1 Hz, 2H), 7.57–7.61 (m, 3H), 7.39–7.49 (m, 6H), 6.99 (s, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.61 (s, 1H), 4.58–4.72 (m, 2H), 3.32 (s, 3H). MS/ESI, *m*/*z*: 548 (M + H)$^+$.

Compound **62** was prepared from *N*-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]-5-iodophenyl}-benzamide using the general procedure for the cyanation of aryl iodide. ^{1}H NMR ($CDCl_3$): δ 9.25 (s, 1H), 8.75 (d, *J* = 1.7 Hz, 1H), 7.69 (d, *J* = 6.8 Hz, 2H), 7.56–7.63 (m, 3H), 7.40–7.45 (m, 6H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.00 (s, 1H), 5.64 (s, 1H), 4.68–4.81 (m, 2H), 3.33 (s, 3H). MS/ESI, *m*/*z*: 548 (M + H)$^+$. Anal. ($C_{27}H_{21}N_5O_2$·0.5H_2O) C, H, N.

5-Cyano-2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]benzoic Acid Methyl Ester (63). A mixture of 3-iodo-4-methylbenzonitrile (**13**) (2.92 g, 12.01 mmol), Pd(dppf)Cl_2 (0.33 g, 0.45 mmol), triethylamine (2.5 g, 24 mmol), and 40 mL of MeOH in an autoclave was charged with carbon monoxide to 450 psi. The autoclave was heated at 120 °C for 20 h. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography, eluting with 15:85 EtOAc/hexane to give 1.33 g of 5-cyano-2-methylbenzoic acid methyl ester as a white solid (62%). ^{1}H NMR ($CDCl_3$): δ 8.21 (d, *J* = 1.7 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 3.93 (s, 3H), 2.68 (s, 3H). MS (DCI/NH_3) *m*/*z*: 193 (M + NH_4)$^+$.

Compound **63** was prepared from 5-cyano-2-methylbenzoic acid methyl ester in a similar manner as described for the preparation of compound **6**. ^{1}H NMR ($CDCl_3$): δ 8.28 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.48 (s, 1H), 6.89 (s, 1H), 5.72 (s, 1H), 5.01 (m, 2H), 3.89 (s, 3H), 3.45 (s, 3H). MS (DCI/NH_3) *m*/*z*: 387 (M + H)$^+$.

5-Cyano-2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]-*N*-phenylbenzamide (64). A solution of 5-cyano-2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)-methoxymethyl]benzoic acid methyl ester (**63**) (0.426 g, 1.10 mmol) in THF/methanol (12 mL/4 mL) at 0 °C was treated with a solution of LiOH·H_2O (0.139 g, 3.30 mmol) in water (1 mL), warmed to room temperature, stirred for about 18 h, and concentrated. The residue was dissolved in water, adjusted to pH 5 with 1 N HCl, and extracted three times with dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to provide 0.349 g of 5-cyano-2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]benzoic acid hydrochloride that was used directly without further purification (78%). ^{1}H NMR ($CDCl_3$): δ 9.11 (br s, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.81–7.79 (m, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.35 (s, 1H), 5.77 (s, 1H), 5.07 (m, 2H), 3.37 (s, 3H).

A mixture of of 5-cyano-2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]benzoic acid hydrochloride (25.0 mg, 0.0611 mmol), aniline (8.5 mg, 0.0917 mmol), EDC (17.6 mg, 0.0917 mmol), HOBT (12.4 mg, 0.0917), and diisopropylethylamine (24 mg, 0.183 mmol) in DMF (1.5 mL) was stirred at room temperature for 24 h. The solution was poured into water and extracted with EtOAc three times. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with ethyl acetate/methanol/NH_4OH (10:0.2:0.02 to 10:1:0.1) to provide 13.0 mg of the desired product as an off-white solid (48%). ^{1}H NMR ($CDCl_3$): δ 8.38 (s, 1H), 7.89 (s, 1H), 7.74 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.50–7.55 (m, 4H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.34–7.37 (m, 3H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.79 (s, 1H), 7.09–7.08 (m, 1H), 6.69 (s, 1H), 5.62 (s, 1H), 4.79–4.89 (m, 2H), 3.34 (s, 3H). MS ESI, *m*/*z* 448 (M + H)$^+$. Anal. ($C_{27}H_{21}N_5O_2$·0.5H_2O) C, H, N.

***N*-(3-Chlorophenyl)-5-cyano-2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-yl)methoxymethyl]benzamide (65).** Compound **65** was prepared in a similar manner as described for the preparation of compound **64** from compound **63**. ^{1}H NMR ($CDCl_3$): δ 8.70 (s, 1H), 7.81 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.57 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.29–7.26 (m, 1H), 7.21–7.18 (m, 2H), 7.09–7.08 (m, 1H), 6.69 (s, 1H), 5.55 (s, 1H), 4.76–4.86 (m, 2H), 3.28 (s, 3H). MS ESI, *m*/*z* 482.0 (M + H)$^+$. Anal. ($C_{27}H_{20}ClN_5O_2$·1.45TFA) C, H, N.

In Vitro Enzyme Assays. The in vitro activity of compounds inhibiting FTase or GGTase-I was determined by using scintillation proximity assay (SPA) technology.[16] Briefly, the

assays were performed with recombinant human FTase or purified bovine brain FTase or GGTase-I [^{3}H]-FPP (NEN) and a biotin conjugated K-ras (B) decapeptide (KKSKTKCVIM) in 50 mM Hepes, 30 mM $MgCl_2$, 20 mM KCl, 5 mM DDT, 0.01% Triton X-100, pH 7.0. After 30 min of incubation, stop/streptandin coated bead reagent was added and the counts associated with the beads were determined using a Packard TopCount scintillation plate reader (Packard).

Ras Processing Assay. Western blot assay was performed to determine the activity of compounds in blocking Ras post-translational processing in intact cells.[16] The processed and unprocessed Ras proteins were separated by gel electrophoresis and immunoblotted with a Pan-Ras antibody (Transduction Laboratories, Lexington, KY) and quantified by densitometry using an image analysis program Image-Pro Plus (Media Cybernetics, Silver Spring, MD).

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