2-Amino-3-substituted-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo-[1,2-*a*]pyridines as a Novel Class of Inhibitors of Human Rhinovirus: Stereospecific Synthesis and Antiviral Activity

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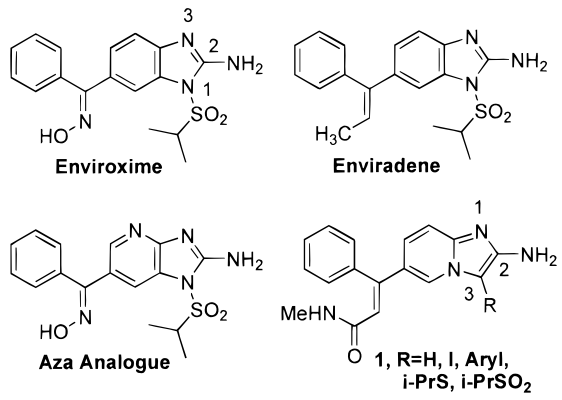
A series of 2-amino-3-substituted-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]-pyridines **1a**−**i**, structurally related to Enviroxime and its analogous benzimidazoles, was designed and prepared for testing as antirhinovirus agents. The imidazo ring in this class of compounds was constructed starting from the aminopyridine after tosylation and subsequent treatment with the appropriate acetamides. The key steps in the synthesis include the development and use of a new Horner−Emmons reagent for the direct incorporation of methyl vinylcarboxamide. The reaction was stereospecific in the substrates **5a**−**f** leading exclusively to the desired *E*-isomer and avoiding the use of reverse-phase preparative HPLC for the separation of both possible isomers before antiviral activity evaluation. The isopropylsulfonyl group, known as the best substituent at the 1-position in the benzimidazole SAR in terms of activity, was introduced in this new series of imidazo[1,2-*a*]pyridines via halogen−metal exchange and subsequent treatment with isopropyl isopropanethiolsulfonate. Compounds **1a**−**i** were evaluated in plaque reduction assay and in a cytopathic effect assay. Compounds **1b**−**d**,**h** exhibited a strong antirhinovirus activity, and no apparent cellular toxicity was visible. The substitution at the 3-position was required for activity. Surprisingly the isopropylsulfonyl in this family of compounds did not enhance the activity as in the case of benzimidazoles. Instead, compound **1i** was 4 times less active than its phenyl and sulfide partners. The chemistry as well as the biological evaluation are discussed.

Introduction

The human rhinoviruses are a group of more than 110 serotypes that are recognized as the most important etiologic agents of the common cold in adults and children.[1] In addition to causing the common cold, these viruses also typically precipitate or exacerbate several chronic conditions such as bronchitis, otitis media, sinusitis, emphysema, and asthma. Because of their significant association with disease, the search for an effective treatment for rhinovirus infections has attracted considerable attention in the scientific community. Since the large number of serotypes makes the development of a broad-spectrum vaccine unlikely, most effort has focused on the development of effective antivirals. Several antiviral drugs have been studied for the treatment of rhinovirus colds. Among compounds that have been studied are those that bind directly to the virus and inhibit virus uncoating and compounds that block the attachment of rhinovirus to ICAM-1. A wide range of compounds have been found to have antirhinovirus activity. However, despite good in vitro activity, the majority of the compounds have been ineffective when given in a manner that would be acceptable for the treatment of colds, namely, by either oral or intranasal administration. Others have been rejected as clinical candidates because of problems with toxicity, unfavorable pharmacology, or insufficient potency. Thus the treatment of the common cold remains an elusive goal.

Chart 1



Enviroxime (Chart 1), a benzimidazole derivative with strong in vitro antirhinoviral activity, is one of the more extensively studied synthetic agents.[2] Enviroxime and related benzimidazoles[3] showed potent broad-spectrum antiviral activity against a range of both rhinoviruses and enteroviruses. Noncytotoxic concentrations of Enviroxime are associated with complete inhibition of replication of 81 rhinovirus sereotypes. The 50% inhibitory concentration (IC_{50}) ranges from 0.05 to 0.12 μg/mL for different serotypes. Although the mechanism of action of Enviroxime is not completely understood, it is believed that the drug inhibits the formation of the viral RNA polymerase replication complex.[4]

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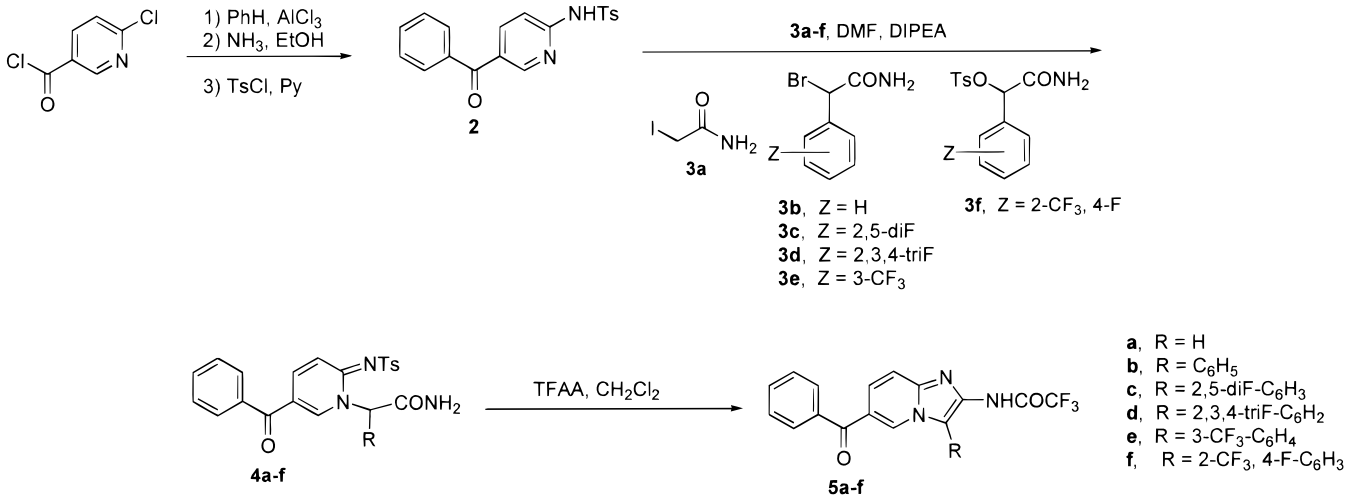
Scheme 1



The major handicaps of Enviroxime are the poor oral bioavailability and undesirable side effects. Studies of oral Enviroxime showed low levels in blood and nasal secretions and an unacceptably high frequency of nausea and vomiting.[5] Thus, despite its potent in vitro antirhinovirus activity, significant therapeutic benefit was not found with either oral or intranasal administration, and Enviroxime clinical studies were terminated. Enviradene, a related benzimidazole, showed improved pharmacokinetics in dogs and caused no emesis.[6] However, the peak plasma levels did not surpass the antiviral IC_{50} value, and the studies on Enviradene were also discontinued. Although the origins of the poor oral bioavailability and emetic side effect found in this class of antirhinoviral agents are not completely understood, considerable efforts are still devoted to this family of benzimidazoles with the aim of finding an analogue with improved oral plasma levels and a better safety profile.[7]

On the other hand, in an effort to identify structurally related analogues of Enviroxime that do not belong to the benzimidazole family, an aza analogue (Chart 1) was designed and synthesized by Kelley et al. [8] However, the new compound was found to be devoid of antiviral activity by the plaque reduction assay.

Here we describe the design, execution, and antiviral activity evaluation of a new class of compounds from the imidazo[1,2-*a*]pyridine family which are structurally related to Enviroxime. The key step of the synthesis is based on a successful application of a new Horner−Emmons reagent for the stereospecific incorporation of methyl vinylcarboxamide.

Chemistry

We decided to transfer the information that was gained from the benzimidazole structure−activity relationship (SAR) to the imidazo[1,2-*a*]pyridine family. From the considerable amount of SAR that was performed around the Enviroxime nucleus, it was concluded that an sp^2 carbon between aromatic rings was a key element for activity. Various substituted olefins and oximes gave active compounds; however, there is a correlation between double-bond geometry and activity, and compounds with *E*-double bonds are much more active and have a better therapeutic index than compounds with *Z*-double bonds. Our sp^2 target was therefore an (*E*)-methyl vinylcarboxamide that would be expected to participate in the hydrogen-bond formation with virus-specific target in an analogous way as the oximes.[9] On the other hand, the substitution at the 1-position of benzimidazoles greatly increases the activity, and both the electron-rich nitrogen at the 3-position and the free amino group at C-2 were key elements for activity. On the basis of this information, we undertook the synthesis of 2-amino-3-substituted-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridines **1a**−**i** that would offer the following potential advantages: (a) maintained potency (structurally related to benzimidazoles) and (b) enhanced oral bioavailability and fewer side effects (new nucleus and new sp^2 carbon between aromatic rings).

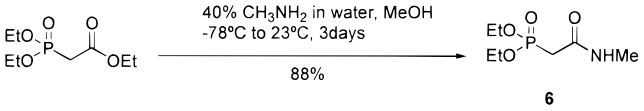
The synthetic approach to the intermediates **5a**−**f** is based on classical transformations[10] as outlined in Scheme 1. Friedel−Crafts acylation of benzene with 6-chloronicotinyl chloride and subsequent treatment with ammonia in ethanol leads to the desired aminopyridine. Reaction of the aminopyridine with *p*-toluenesulfonyl chloride in pyridine and subsequent reaction with the appropriate acetamides in the presence of Hünig's base in DMF provided the corresponding carbamides **4a**−**f** in good yield. The 2-bromo-2-arylacetamides **3b**−**e** required for the latter transformations were prepared from their corresponding 2-bromo-2-arylacetic acids after bromination in the presence of *N*-bromosuccinimide and subsequent amidation. On the other hand, the reagent **3f**, where the leaving group is a tosyl, was prepared from the corresponding aryl aldehyde after treatment with trimethylsilyl cyanide, hydrolysis, acetylation of the resulting hydroxy acid, amidation, removal of the acetyl group, and tosylation. Conversion of **4a**−**f** to the desired 2-(*N*-trifluoracetylamino)imidazopyridines **5a**−**f** was accomplished by treatment with trifluoroacetic anhydride.

As was mentioned above, the detailed analysis of the sp^2 carbon between aromatic rings in the reported benzimidazole SAR had illustrated the importance of the geometry of the double bond. These reports also stressed the difficulties encountered in the separation and purification of the desired *E*-isomer. In most of the cases purification by reverse-phase preparative HPLC

Table 1. Reaction of **5a**−**f** with Diethyl [(*N*-Methylcarbamoyl)methyl]phosphonate (**6**)

substr	R	base	solvent	time (h)	compd	yield (%)	*E:Z*
5a	H	NaH	THF	60	**7a**	0	0
5a	H	KH	THF	24	**7a**	80	1:1
5a	H	LiHMDS	THF	24	**7a**		1.4:1
5a	H	KHMDS	DMF	18	**7a**	63	1:0
5a	H	KHMDS	Tol−THF	60	**7a**	52	1:0
5b	C_{6H4}	KHMDS	Tol−THF	24	**7b**	75	1:0
5c	2,5-diF-C_6H_3	KHMDS	Tol−THF	18	**7c**	86	1:0
5d	2,3,4-triF-C_6H_2	KHMDS	Tol−THF	15	**7d**	50	1:0
5e	3-CF_3-C_6H_4	KHMDS	Tol−THF	15	**7e**	57	1:0
5f	2-CF_3-4-F-C_6H_3	KHMDS	Tol−THF	18	**7f**	79	1:0

Scheme 2



was required before antiviral activity evaluation.[3] We therefore felt the need of having a stereospecific method that allows to convert compounds **5a,b** to our target structures 2-amino-3-substituted-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridines **1a**−**i**. Peterson olefination was tried unsuccessfully in our hands. On the other hand, the only known method for a direct and stereospecific generation of the (*E*)-(*N*-methylcarbamoyl)vinyl function was reported recently by Mitchell et al.[11] They used palladium-catalyzed hydroarylation of arylpropiolamides to prepare stereospecifically (*E*)-3,3-diarylacrylamides. Since this method was not applicable to our substrates, we turned to the Horner−Emmons reaction. Although this reaction is widely used for the preparation of unsaturated esters, to our knowledge there has been no application of this method for the direct preparation of unsaturated carboxamides. Diethyl [(*N*-methylcarbamoyl)methyl]phosphonate (**6**) for the Horner−Emmons reaction was readily prepared in large scale from triethyl phosphonoacetate and methylamine in 88% yield (Scheme 2).

The parameters for the Horner−Emmons reaction using the reagent **6**, which include the nature of base, the solvent, the temperature, and the concentration, were first studied with substrate **5a**. The most significant results are summarized in Table 1. Regarding the stereospecificity, the best results were achieved using KHMDS as base either in DMF or in a mixture of toluene−THF (diluted solution). Under both conditions compound **7a** was isolated in moderate to good yield. ^{1}H NMR analysis of the crude showed only the *E*-isomer of the desired product whose geometry was established by NOE experiments. Because of the low solubility of **5a** in the mixture of toluene−THF, DMF turned out to be the solvent of choice in terms of the chemical yield. The problem of solubility was not encountered in substrates **5b**−**f** where the 3-position was occupied by an aromatic ring. Hence compounds **5b**−**f** were subjected to the Horner−Emmons reaction with **6** using KHMDS as base and toluene−THF as solvent to give the corresponding [(*N*-methylcarbamoyl)vinyl]imidazo-[1,2-*a*]pyridines **7b**−**f** with *E*-selectivity higher than 95% and moderate to good yield (Table 1). With the exception of compound **7a**[12] where the trifluoroacetamide group was hydrolyzed using 0.5 N NaOH, the conversion of **7b**−**f** to their corresponding final products was performed using Hünig's base.

During the benzimidazole SAR exploration of the 1-position with a variety of substituents, the authors came to the conclusion that the isopropylsulfonyl was the best candidate selected because of its significant improvement in activity.[2,3] In fact, it was suggested that the presence of internal hydrogen bonding between the amine hydrogen and the sulfonyl oxygen is important for enhanced activity. In an attempt to transfer this information to imidazopyridine SAR, our next target was 2-amino-3-isopropylsulfonyl-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (**1i**) and its isopropyl sulfide analogue **1h**.

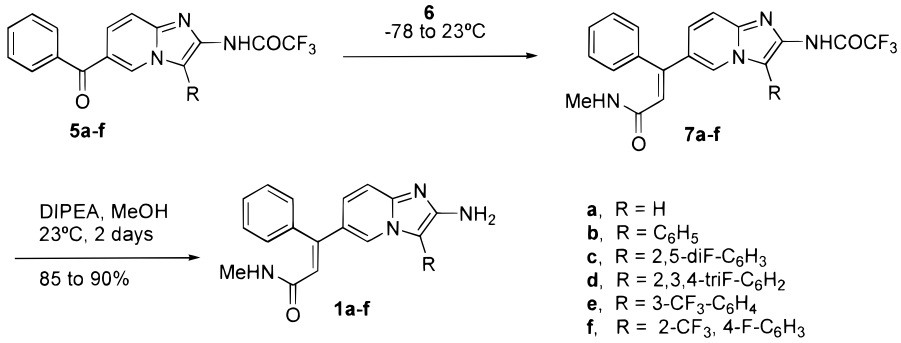
The synthesis of these compounds is outlined in Scheme 4. 2-Trifluoroacetamido-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (**7a**) was chemoselectively iodinated at the 3-position using *N*-iodosuccinimide in acetonitrile at 0 °C in 98% yield. The trifluoroacetamide group of the resulting iodo derivative **7g** could be hydrolyzed when being supported on silica gel and kept with MeOH/CH_2Cl_2 (2:98) to give **1g** in 45% yield. Compound **7g** was first deprotonated with PhLi and then subjected to a halogen−metal exchange reaction with *t*-BuLi, and the resulting trianion was reacted with isopropyl isopropanethiolsulfonate to give compound **7h**, which was mixed with silica gel in MeOH/CH_2Cl_2. The cake was stirred for 2 days yielding the desired 2-amino-3-isopropylthio-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (**1h**) in 73% overall yield from **7g**.

The synthesis of 2-amino-3-isopropylsulfonyl-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]-pyridine (**1i**) was achieved beginning with similar reaction sequences. The resulting crude of **7h** was subjected to MCPBA oxidation to give the corresponding sulfone in 63% yield and subsequent hydrolysis of the trifluoroacetamide group on silica gel support to provide **1i** in 89% yield.

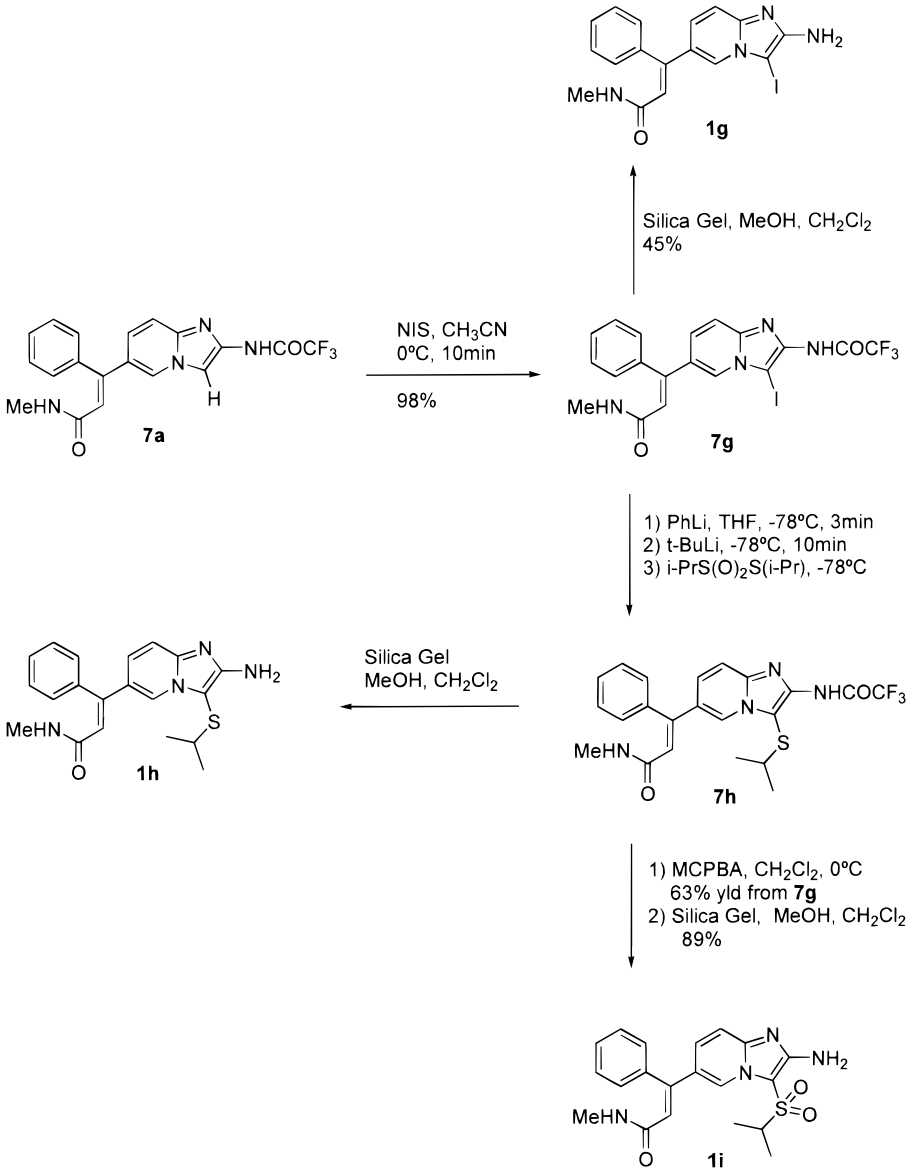
SAR Analysis

[(Methylcarbamoyl)vinyl]imidazopyridines **1a**−**i** were subjected to biological evaluation following the procedures described in the Experimental Section. The compounds were tested taking Enviroxime as a reference. Human rhinovirus-14 was selected as the routine and initial virus for testing due to the amount of information known about this serotype. The plaque reduction assays were run in order to determine the antiviral activity IC_{50} (Table 2). Compounds **1a** with hydrogen and **1g** with iodine at the 3-position did not show antiviral activity. However the substitution of this position by an aryl, sulfenyl, or sulfonyl group resulted

Scheme 3



Scheme 4



in moderate to potent compounds. Hence, it appears that the substitution at the 3-position is a key element for activity. In contrast to the results of the benzimidazole SAR[2] studies where *N*-sulfonyl compounds have generally shown the highest activity with the isopropylsulfonyl being the group of choice, this is just the reverse. The internal hydrogen bonding between the amine hydrogen and the sulfonyl oxygen does not seem to enhance the activity as in the case of benzimidazoles.[3] Instead, a considerable loss of activity was observed when the sulfide in compound **1h** was replaced with its corresponding sulfone. Even the phenyl and substituted fluorophenyl analogues turned out to be more active. Thus, in this new family of compounds the isopropylsulfonyl is apparently not required for antirhinovirus activity and could be replaced by an aromatic ring. Di- and trifluorophenyl analogues **1c**,**d** were found to be slightly more active than their phenyl partners. This

Table 2. Antiviral Activity Evaluation of Imidazopyridines **1a**−**i**

		IC_{50} (μg/mL)		TC_{50} (μg/mL)	
compd	R	PRA[a]	CPE/XTT[b]	CPE/XTT[b]	TC_{50}[b]:IC_{50}[b,c]
1a	H	>10			
1b	C_6H_5	0.27	0.30	5.03	17
1c	2,5-diF-C_6H_3	0.18	0.16	4.87	30
1d	2,3,4-triF-C_6H_2	0.17	0.21	6.98	33
1f	2-CF_3-4-F-C_6H_3	0.44	0.48	>10	>21
1g	I	>3.2			
1h	−S(*i*-Pr)	0.17	0.21	10	48
1i	−$S(O)_2$(*i*-Pr)	0.64			

[a] PRA assay using rhinovirus-14, IC_{50} (mg/mL). [b] CPE/XTT assay using rhinovirus 14. [c] Ratio of TC_{50} over IC_{50}.

suggests the importance of the electronic effect on the antiviral activity.

The active compounds were selected for evaluation in a cytopathic effect assay in order to determine the general cellular toxicity TC_{50}. In general these compounds do not exhibit an apparent cellular toxicity as could be seen by their ratio of TC_{50} over IC_{50}, and no relationship between cellular toxicity and antiviral activity was visible in these experiments.

Conclusion

Benzimidazoles with potent broad-spectrum anti-rhino/enteroviral activity have been studied quite extensively. These compounds have not yet met the requirements for a drug to treat the common cold: (1) potent broad-spectrum antiviral activity, (2) limited potential for the development of resistance, (3) oral bioavailability, (4) safety, and (5) human efficacy. Therefore, the identification of non-benzimidazole structurally related analogues with good antirhinoviral activity is highly desired. We have designed and synthesized a series of 2-amino-3-substituted-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridines, structurally related to Enviroxime. The design of the new class of compounds was based on information that was gained from benzimidazole structure−activity relationships. The development of new Horner−Emmons methodology for the direct incorporation of methyl vinylcarboxamide permitted the construction of the sp^2 region in a stereospecific manner avoiding the use of reverse-phase preparative HPLC for the separation of both possible isomers before antiviral activity evaluation. Most of these compounds (**1b**−**d**,**h**) exhibited a strong antirhinovirus activity, and no apparent cellular toxicity was found. The isopropylsulfonyl, which was the best substituent in the benzimidazole series, did not enhance the activity in this case. Instead, compound **1i** was 4 times less active than its phenyl and sulfide partners. Finally, compounds **1c**,**d**,**h** exhibited a potency comparable to that of Enviradene (0.15 μg/mL), a related benzimidazole that failed in the clinic.

Since the antirhinoviral activity found in this new class of compounds was promising, more biological evaluations that include broad-spectrum activity and oral bioavailability will be worthwhile.

Experimental Section

General Methods. All reagents were purchased from Aldrich and used without further purification unless stated otherwise. Column chromatography was carried out on flash silica gel (Merck 230−400 mesh). TLC analysis was conducted on silica gel plates (Whatman). ^1H and ^{13}C NMR spectra were recorded at 200 or 300 MHz with Bruker instruments. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. Mass spectra and high-resolution mass spectra were recorded at an ionizing voltage of 70 eV on a VG-AutoSpec spectrometer. Mass spectra, elemental analyses, and some NMR spectra were provided by the Servicio Interdepartamental de Investigación (SIdI) at UAM (Madrid).

1,2-Dihydro-2-toluenesulfonimido-5-benzoylpyridine (2). Step 1: 2-Chloro-5-benzoylpyridine. Aluminum chloride (100 g, 0.73 mol) was suspended in 200 mL of benzene under N_2. A solution of chloronicotinoyl chloride (53 g, 0.30 mol) in 100 mL of benzene was added to the rapidly stirring suspension and then refluxed overnight. The reaction was cooled to room temperature. Ethyl acetate (1 L) was added, and the pH was adjusted to 8.5 with 5 N NaOH. Aluminum salts precipitated and were filtered away. The filtrate was washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was recrystallized from Et_2O/hexane (3:2) yielding 54.6 g (83%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, 1H, J = 2.2), 8.09 (dd, 1H, J = 2.6, 8.4), 7.78 (d, 2H, J = 6.7), 7.65 (t, 1H, J = 7.3), 7.53 (d, 2H, J = 7.8), 7.48 (d, 1H, J = 8.4); MS (EI^+) m/z 220 (42), 219 (23), 218 (100), 182 (3), 140 (2), 105 (4).

Step 2: 1,2-Dihydro-2-amino-5-benzoylpyridine. 2-Chloro-5-benzoylpyridine (50 g, 0.23 mol) was dissolved in 250 mL of ethanol and 200 mL of anhydrous ammonia, placed in a reactor, and then heated at 145 °C for 16 h. The solvents were removed in vacuo, and the remaining solid was recrystallized from EtOH/H_2O yielding 38 g (85%) of product as a white solid.

Step 3: 1,2-Dihydro-2-toluenesulfonimido-5-benzoylpyridine (2). 1,2-Dihydro-2-amino-5-benzoylpyridine (77.0 mmol) was dissolved in dry pyridine (60 mL). *p*-Toluenesulfonyl chloride (85.6 mmol) was added, and the solution was heated at 80−90 °C under Ar overnight. Pyridine was removed in vacuo to give a solid. Water (1.5 L) was added, and the mixture was stirred for 90 min. The white solid was collected, dried, and crystallized from ethyl acetate (200 mL) to give **2** (91%) as a white solid: mp 207−209 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H, H_6), 8.06 (d, 1H, J = 8.8, H_3), 7.84 and 7.52 (AA′BB′ system, 4H, J = 7.5, tol), 7.70−7.23 (m, 10H, Ar), 2.31 (s, 3H, Ar); ^{13}C NMR (DMSO-d_6) δ 192.7, 155.0, 148.0, 143.4, 140.4, 138.3, 136.9, 132.9, 129.7, 129.6, 128.8, 127.2, 125.4, 112.5, 21.2; MS (EI^+) m/z 352 M^+ (1), 287 (100), 115 (5), 105 (10), 77 (17), 65 (12); HRMS calcd for $C_{19}H_{16}N_2O_3S$ 352.0882, found 352.0882.

2-Bromo-2-phenylacetamide (3b). Step 1: 2-Bromo-2-phenylacetic Acid. Phenylacetic acid (0.13 mol), benzoyl peroxide (0.54 mmol), and *N*-bromosuccinimide (0.13 mol) were combined in 500 mL of carbon tetrachloride under N_2 and refluxed under UV radiation for 5 h. The reaction was cooled to room temperature, and the succinimide filtered away. The carbon tetrachloride was removed in vacuo and the remaining oil recrystallized from hexane yielding the desired product as a yellow solid (82%).

Step 2: 2-Bromo-2-phenylacetamide (3b). 2-Bromo-2-phenylacetic acid (21 g, 100 mmol) in 170 mL of dry CH_2Cl_2 and 3 drops of DMF were cooled in an ice bath under N_2. Oxalyl chloride (200 mmol) in 25 mL of dry CH_2Cl_2 was added dropwise over 25 min. The ice bath was removed and the reaction stirred for 3 h. The solvents were removed in vacuo and then azeotroped with toluene (3 × 25 mL). The remaining

oil was dissolved in 300 mL of toluene and 300 mL of hexane and stirred vigorously with a mechanical stirrer. Ammonia gas was then blown through a gas dispersion tube over the top of this solution for 1 h. The resulting solid was filtered, and the solvents were removed in vacuo. The solid was dissolved in EtOAc/H_2O and the organic layer washed with 1 N HCl, saturated $NaHCO_3$, and brine and then dried over Na_2SO_4. The solvent was removed in vacuo, and the remaining solid was recrystallized from EtOAc/hexane to yield 16.8 g (68%) of the desired product: mp 138−141 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.80 (br s, 1H, CONH), 7.54 (dd, J = 7.8, 2.3, 2H, ArH), 7.41 (br s, 1H, CONH), 7.41−7.30 (m, 3H, ArH), 5.54 (s, 1H, ArCHBrCONH$_2$); ^{13}C NMR (DMSO-d_6) δ 169.1, 133.8, 128.9, 128.8, 128.7, 49.9; MS (EI$^+$) m/z 213 M$^+$ (1), 169 (15), 134 (89), 91 (100).

2-Bromo-2-(2,5-difluorophenyl)acetamide (3c): prepared according to the procedure for **3b**; 18.5 g (68%); mp 102−104 °C; ^{1}H NMR (300 MHz, DMSO-d_6 δ 7.95 (br s, 1H), 7.61 (br s, 1H), 7.60−7.52 (m, 1H), 7.38−7.28 (m, 2H), 5.80 (s, 1H); FDMS (MeOH) m/z 249 (M$^+$).

2-Bromo-2-(2,3,4-trifluorophenyl)acetamide (3d): prepared according to the procedure for **3b**; 10.2 g (76%); mp 82−84 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85 (br s, 1H), 7.6 (br s, 1H), 7.4−7.3 (m, 2H), 5.80 (s, 1H); FDMS (MeOH) m/z 267 (M$^+$).

2-Bromo-2-(3-trifluoromethylphenyl)acetamide (3e): prepared according to the procedure for **3b**; 14.25 g (52%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (br s, 2H), 7.52−7.82 (m, 3H), 7.50 (s, 1H), 5.66 (s, 1H); FDMS (MeOH) m/z 281 (M$^+$).

2-*O*-Toluenesulfonimido-2-(2-trifluoromethyl-4-fluorophenyl)acetamide (3f). Step 1: 2-Trifluoromethyl-4-fluoromandelic Acid. 2-Trifluoromethyl-4-fluorobenzaldehyde (48.4 g, 252 mmol) and a catalytic amount of zinc iodide (15 mg) were combined under N_2. Trimethylsilyl cyanide (25 g, 252 mmol) was added dropwise over 20 min, and the reaction was stirred overnight; 75 mL of 9 N HCl was then added dropwise over 20 min and reaction refluxed overnight. The cooled solution was then extracted with diethyl ether (3 × 500 mL). The combined ether layers were extracted with saturated $NaHCO_3$ (4 × 200 mL). The combined $NaHCO_3$ layers were acidified to pH 1 with 5 N HCl and extracted with diethyl ether (3 × 500 mL). The combined ether extracts were dried over Na_2SO_4 and concentrated in vacuo. The resulting white solid was recrystallized from $CHCl_3$/hexanes yielding 50.1 g of a white solid (84%): mp 82−84 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70−7.66 (m, 1H), 7.57−7.52 (m, 2H), 5.20 (s, 1H); FDMS (MeOH) m/z 238 (M$^+$). Anal. ($C_9H_6F_4O_3$) C, H.

Step 2: *O*-Acetyl-2-trifluoromethyl-4-fluoromandelic Acid. 2-Trifluoromethyl-4-fluoromandelic acid (49.4 g, 207.6 mmol) was dissolved in 150 mL of 30% HBr/HOAc and stirred overnight. The reaction was then poured onto 3 L of ice and immediately extracted with diethyl ether (3 × 500 mL). The combined ether extracts were then dried over Na_2SO_4 and removed in vacuo yielding 58 g of a white solid (quantitative): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.80−7.60 (m, 3H), 6.12 (s, 1H), 2.13 (s, 3H); FDMS (MeOH) m/z 280 (M$^+$). Anal. ($C_{11}H_8F_4O_4$) C, H.

Step 3: *O*-Acetyl-2-trifluoromethyl-4-fluoromandelic Amide. *O*-Acetyl-2-trifluoromethyl-4-fluoromandelic acid (58 g, 207.6 mmol) in 150 mL of dry CH_2Cl_2 and 3 drops of DMF were cooled in an ice bath under N_2. Oxalyl chloride (500 mmol) in 25 mL of dry CH_2Cl_2 was added dropwise over 25 min. The ice bath was removed and the reaction stirred for 3 h. The solvents were removed in vacuo and then azeotroped with toluene (3 × 25 mL). The remaining oil was dissolved in 100 mL of toluene and 600 mL of hexane and stirred vigorously with a mechanical stirrer. Ammonia gas was then blown through a gas dispersion tube over the top of this solution for 1 h. The resulting solid was filtered, and the solvents were removed in vacuo. The solid was dissolved in EtOAc/H_2O and the organic layer washed with 1 N HCl, saturated $NaHCO_3$, and brine and then dried over Na_2SO_4. The solvent was removed in vacuo, and the remaining solid was recrystallized from EtOAc/hexane to yield 52.36 g (90%) of the desired product: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.78 (br s, 1H), 7.67−7.58 (m, 4H), 6.07 (s, 1H), 2.06 (s, 3H); FDMS (MeOH) m/z 279 (M$^+$). Anal. ($C_{11}H_9F_4NO_4$) C, H, N.

Step 4: 2-Trifluoromethyl-4-fluoromandelic Amide. *O*-Acetyl-2-trifluoromethyl-4-fluoromandelic amide (50.44 g, 180.8 mmol) was dissolved in 250 mL of MeOH and 84 mL of diisopropylethylamine and then refluxed under N_2 for 3 h. Solvents were removed in vacuo, and the remaining solid was recrystallized from EtOAc/hexanes yielding 40.9 g (95%) of a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.62−7.49 (m, 4H), 7.40 (br s, 1H),), 6.40 (d, 1H, J = 5), 5.07 (d, 1H, J = 5); FDMS (MeOH) m/z 237 (M$^+$). Anal. ($C_9H_7F_4NO_2$) C, H, N.

Step 5: 2-*O*-Toluenesulfonimido-2-(2-trifluoromethyl-4-fluorophenyl)acetamide (3f). 2-Trifluoromethyl-4-fluoromandelic amide (11.85 g, 50 mmol) was suspended in 400 mL of CH_2Cl_2 under N_2. Dimethylaminopyridine (500 mg, catalytic), DIPEA (9.6 mL, 55 mmol), and *p*-toluenesulfonyl chloride (10.5 g, 55 mmol) were added, and the reaction was stirred overnight. Solvents were removed in vacuo and remaining solids dissolved in EtOAc. EtOAc was then washed with saturated $NaHCO_3$ (3 × 150 mL) and brine (3 × 150 mL) and dried over Na_2SO_4. EtOAc was removed in vacuo and remaining solid recrystallized from EtOAc/hexane yielding 17.8 g (91%) of a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (br s, 1H), 7.71−7.66 (m, 2H), 7.66 (d, 2H, J = 8.2), 7.52−7.48 (m, 1H), 7.50 (dd, 1H, J = 9.3, 2.6), 7.34 (d, 2H, J = 8.2), 5.81 (s, 1H), 2.33 (s, 3H); FDMS (MeOH) m/z 392 (M + H). Anal. ($C_{16}H_{13}F_4NO_4S$) C, H, N.

1-Carbamoylmethyl-1,2-dihydro-2-*p*-toluenesulfonimido-6-benzoylpyridine (4a). To a stirred suspension of **2** (11.65 g, 32.10 mmol) in 100 mL of dry DMF was added DIPEA (6.34 mL, 34.20 mmol). After 15 min, the solution turned clear. Iodoacetamide (6.74 g, 34.2 mmol) was added. The mixture was stirred for 24 h and then poured onto water (2 L) and stirred for an additional hour. Solid was collected and air-dried yielding 13.15 g (97%) of a white solid: mp 210−212 °C; ^{1}H NMR (200 MHz DMSO-d_6) δ 8.54 (d, 1H, J = 2.0, H_6), 8.06 (dd, 1H, J = 9.5, 2.0, H_4), 7.79−7.64 (m, 5H, Ar), 7.57 (AA′BB′ system, 2H, J = 7.6, tol), 7.47 (d, 1H, J = 9.5, H_3), 7.30 (AA′BB′ system, 2H, J = 7.8, tol), 4.91 (s, 2H, CH_2), 2.35 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 191.0, 167.5, 156.1, 147.4, 142.0, 140.4, 136.6, 133.1, 129.6, 129.5, 129.0, 126.1, 119.9, 115.9, 54.8, 21.1; MS (EI$^+$) m/z 409 M$^+$ (18), 345 (24), 328 (28), 287 (11), 254 (6), 209 (36), 182 (19), 155 (9), 105 (66), 91 (100), 77 (58); HRMS calcd for $C_{19}H_{21}N_3O_4S$ 409.1096, found 409.1105.

1,2-Dihydro-2-toluenesulfonimido-5-benzoyl-*N*-(1-phenylcarbamoylmethyl)pyridine (4b): prepared according to the procedure for **4a**; 14.0 g (96%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17 (br s, 1H), 8.05 (dd, 1H, J = 9.5, 2.2), 7.78 (s, 1H), 7.76 (d, 2H, J = 8.2), 7.69 (s, 1H), 7.56 (d, 1H, J = 9.6), 7.55−7.53 (m, 1H), 7.43−7.28 (m, 11H), 6.84 (s, 1H), 2.34 (s, 3H); FDMS (MeOH) m/z 485 (M$^+$). Anal. ($C_{27}H_{23}N_3O_4S$) C, H, N.

1,2-Dihydro-2-toluenesulfonimido-5-benzoyl-*N*-[1-(2,5-difluorophenyl)carbamoylmethyl]pyridine (4c): prepared according to the procedure for **4a**; 14.9 g (95%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (br s, 1H), 8.11 (dd, 1H, J = 9.4, 2.3), 7.92 (br s, 1H), 7.81 (s, 1H), 7.75 (d, 2H, J = 9.5), 7.64−7.60 (m, 2H), 7.53−7.42 (m, 6H), 7.36 (d, 2H, J = 9.5), 7.12 (s, 1H), 7.06 (m, 1H), 2.38 (s, 3H); FDMS (MeOH) m/z 521 (M$^+$). Anal. ($C_{27}H_{21}F_2N_3O_4S$) C, H, N.

1,2-Dihydro-2-toluenesulfonimido-5-benzoyl-*N*-[1-(2,3,4-trifluorophenyl)carbamoylmethyl]pyridine (4d): prepared according to the procedure for **4a**; 11.3 g (78%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (br s, 1H), 8.05 (dd, 1H, J = 9.4, 2.1), 7.90 (br s, 1H), 7.74−7.69 (m, 1H), 7.70 (d, 2H, J = 8.1), 7.62−7.40 (m, 4H), 7.38−7.35 (m, 3H), 7.31 (d, 2H, J = 7.4), 7.13 (s, 1H), 7.10 (m, 1H), 2.33 (s, 3H). Anal. ($C_{27}H_{20}F_3N_3O_4S$) C, H, N.

1,2-Dihydro-2-toluenesulfonimido-5-benzoyl-*N*-[1-(3-trifluoromethylphenyl)carbamoylmethyl]pyridine (4e): prepared according to the procedure for **4a**; 12.7 g (76%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17 (br s, 1H), 8.07 (dd, 1H, J = 8.0, 3.0), 7.81−7.53 (m, 10H), 7.43−7.40 (m, 2H), 7.36−

7.29 (m, 4H), 6.87 (s, 1H), 2.33 (s, 3H); FDMS (MeOH) *m/z* 553 (M^+). Anal. ($C_{28}H_{22}F_3N_3O_4S$) C, H, N.

1,2-Dihydro-2-toluenesulfonimido-5-benzoyl-*N*-[1-(2-trifluoromethyl-4-fluorophenyl)carbamoylmethyl]-pyridine (4f): prepared according to the procedure for **4a**; 14.46 g (84%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (br s, 1H), 8.06 (dd, 1H, J = 9.5, 2.1), 7.92 (br s, 1H), 7.83 (dd, 1H, J = 9.1, 2.6), 7.64 (d, 2H, J = 8.2), 7.58−7.53 (m, 3H), 7.48−7.36 (m, 6H), 7.28 (d, 2H, J = 8.1), 7.00 (s, 1H), 2.32 (s, 3H); FDMS (MeOH) *m/z* 571 (M^+). Anal. ($C_{28}H_{21}F_4N_3O_4S$) C, H, N.

2-Trifluoroacetamido-6-benzoylimidazo[1,2-*a*]pyridine (5a). To a suspension of **4a** (7.15 g, 17.46 mmol) in 85 mL of dry CH_2Cl_2 was added trifluoroacetic anhydride (62 mL). The mixture was stirred for 2.5 h at 30 °C under Ar. The solvents were removed in vacuo, and the foam was taken up in EtOAc (600 mL) and washed with $NaHCO_3$ (2 × 250 mL) and brine (1 × 250 mL). The organic layer was dried (Na_2SO_4), and solvents were removed in vacuo to afford 5.5 g (92%) of product as a white solid: mp 233−235 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.80 (br s, 1H, NH), 8.66 (s, 1H, H_5), 8.24 (s, 1H, H_3), 7.83−7.78 (m, 3H, Ar), 7.71−7.51 (m, 4H, Ar); ^{13}C NMR (DMSO-d_6) δ 192.8, 141.8, 140.6, 137.0, 133.3, 133.1, 132.6, 129.5, 129.3, 128.6, 125.0, 122.5, 115.5, 104.3; MS (EI$^+$) *m/z* 333 M^+ (100), 314 (9), 264 (49), 256 (37), 236 (7), 228 (7), 209 (8), 159 (8), 146 (6), 105 (52), 77 (53); HRMS calcd for $C_{16}H_{10}N_3O_2F_3$ 333.0725, found 333.0725.

2-Trifluoroacetamido-3-phenyl-6-benzoylimidazo[1,2-*a*]pyridine (5b): prepared according to the procedure for **5a**; 9.75 g (94%); mp 202−204 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.9 (br s, 1H, NH), 8.69 (s, 1H, H_3), 7.78−7.42 (m, 12H, Ar); ^{13}C NMR ($CDCl_3$) δ 192.9, 155.7, 154.9, 142.6, 136.6, 136.3, 133.0, 129.6, 129.4, 128.7, 128.6, 128.1, 127.0, 126.1, 124.3, 118.7, 116.2, 113.0; MS (EI$^+$) *m/z* 409 M^+ (100), 349 (73), 312 (7), 206 (11), 105 (61), 77 (76); HRMS calcd for $C_{22}H_{14}F_3N_3O_2$ 409.1038, found 409.1037. Anal. ($C_{22}H_{14}F_3N_3O_2$) C, H, N.

2-Trifluoroacetamido-3-(2,5-difluorophenyl)-6-benzoylimidazo[1,2-*a*]pyridine (5c): prepared according to the procedure for **5a**; 12.05 g (95%); mp 116−118 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.1 (br s, 1H, NH), 8.50 (s, 1H, H_5), 7.87−7.78 (m, 3H, Ar), 7.70−7.49 (m, 5H, Ar), 7.30−7.11 (m, 2H, Ar); ^{13}C NMR (CD_3OD) δ 194.4, 162.8, 160.0, 158.0, 155.1, 145.1, 138.9, 138.2, 134.1, 131.0, 130.8, 129.7, 127.7, 125.6, 120.2, 119.7, 119.5, 119.2, 119.0, 118.8, 118.5, 118.3, 118.6; MS (EI$^+$) *m/z* 445 M^+ (100), 376 (66), 348 (5), 242 (5), 105 (30), 77 (36); HRMS calcd for $C_{22}H_{12}F_5N_3O_2$ 445.0850, found 445.0859. Anal. ($C_{22}H_{12}F_5N_3O_2$) C, H, N.

2-Trifluoroacetamido-3-(2,3,4-trifluorophenyl)-6-benzoylimidazo[1,2-*a*]pyridine (5d): prepared according to the procedure for **5a**; 8.43 g (87%); mp 78−80 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.31 (br s, 1H), 8.42 (s, 1H), 7.87−7.03 (m, 9H, Ar); ^{13}C NMR ($CDCl_3$) δ 192.5, 162.5, 143.2, 140.4, 137.9, 136.4, 133.3, 130.8, 129.7, 129.1, 128.7, 128.3, 127.1, 124.7, 116.2, 113.3, 113.0; MS (EI$^+$) *m/z* 463 M^+ (100), 374 (71), 359 (10), 260 (6), 105 (49), 77 (52); HRMS calcd for $C_{22}H_{11}F_6N_3O_2$ 463.0755, found: 463.0760. Anal. ($C_{22}H_{11}F_6N_3O_2$) C, H, N.

2-Trifluoroacetamido-3-(3-trifluoromethylphenyl)-6-benzoylimidazo[1,2-*a*]pyridine (5e): prepared according to the procedure for **5a**; 10.17 g (93%); mp 217 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.23 (br s, 1H, NH), 8.63 (s, 1H), 7.89−7.52 (m, 11H, Ar); ^{13}C NMR (DMSO-d_6) δ 191.5, 155.7, 142.2, 136.2, 132.2, 131.7, 129.9, 129.8, 129.7, 129.3, 129.0, 128.0, 127.7, 125.0, 124.8, 124.7, 124.6, 124.5, 122.4, 117.7, 116.3; MS (EI$^+$) *m/z* 477 M^+ (100), 408 (69), 105 (36), 77(43); HRMS calcd for $C_{23}H_{13}F_6N_3O_2$ 477.0912, found 477.0915. Anal. ($C_{23}H_{13}F_6N_3O_2$) C, H, N.

2-Trifluoroacetamido-3-(2-trifluromethyl-4-fluorophenyl)-6-benzoylimidazo[1,2-*a*]pyridine (5f): prepared according to the procedure for **5a**; 11.0 g (88%); mp 189−191 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.2 (br s, 1H, NH), 8.06 (s, 1H, H_5), 7.80−7.40 (m, 10H, Ar); MS (EI$^+$) *m/z* 495 M^+ (100), 426 (62), 329 (9), 105 (26), 77 (35); HRMS calcd for $C_{23}H_{12}F_7N_3O_2$ 495.0818, found 495.0817. Anal. ($C_{23}H_{12}F_7N_3O_2$) C, H, N.

Diethyl [(*N*-Methylcarbamoyl)methyl]phosphonate (6). A solution of 4.12 mL of methylamine in 8.30 mL of methanol was cooled to −78 °C; 8.85 mL of triethyl phosphonoacetate was added dropwise over a 10-min period. The reaction mixture was allowed to warm to room temperature, and then stirred at this temperature for 29 h (TLC: MeOH/CH_2Cl_2, 1:9). The solvents were removed in vacuo at 35 °C, and the resulting colorless liquid was used without further purification for the Horner−Emmons reactions. The preparation of the Horner reagent was repeated on a 30-g scale. The time required was 3 days. The colorless liquid was purified by distillation (0.5 mmHg/130 °C), 87% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.05 (br s, 1H, NH), 4.07 (quintet, 4H, J = 7.0, 2 × CH_2O), 2.79 (d, 2H, J = 24.9, CH_2P), 2.74 (s, 3H, CH_3), 1.22 (t, 6H, J = 7.0, 2 × CH_3−CH_2O); ^{13}C NMR ($CDCl_3$) δ 164.5, 62.7, 62.6, 36.0, 33.5, 26.5, 16.2, 16.1.

2-Trifluoroacetamido-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (7a). Method A: Diethyl [(*N*-methylcarbamoyl)methyl]phosphonate (**6**) (1.88 g, 9 mmol) in 250 mL of dry THF was placed in a flame-dried flask under Ar. The solution was cooled to −78 °C before the dropwise addition of KHMDS (30 mL, 15 mmol; 0.5 M in toluene). The mixture was stirred for 2 h at −78 °C. A solution of 2-trifluoroacetamido-6-benzoylimidazo[1,2-*a*]pyridine (**5a**) (2.0 g, 6.0 mmol) in 100 mL of dry THF was added dropwise. The reaction mixture was stirred at −78 °C for 2 h and then allowed to warm to room temperature. The resulting brown solution was stirred at room temperature for 60 h. The THF was evaporated in vacuo, and the mixture was diluted with 400 mL of EtOAc and washed with saturated NH_4Cl (2 × 100 mL) and once with brine. After drying over $MgSO_4$, the solvents were removed in vacuo to give a red oil. The crude was purified by column chromatography CH_3CN/CH_2Cl_2 (2:1) to give pure vinyl carboxamide **7a** in 52% yield.

Method B: KHMDS (3 g, 15 mmol; solid) was dissolved in 40 mL of dry DMF under Ar at 0 °C. A solution of the diethyl [(*N*-methylcarbamoyl)methyl]phosphonate (**6**) (1.12 g, 5.4 mmol) in 10 mL of dry DMF was added. The reaction mixture was stirred at 0 °C for about 1 h. A solution of 2-trifluoroacetamido-6-benzoylimidazo[1,2-*a*]pyridine (**5a**) (1.5 g, 4.5 mmol) in 10 mL of dry DMF was transferred via cannula. The bath was removed, and the resulting clear brown solution was allowed to warm to room temperature. After 18 h the reaction mixture was quenched with saturated NH_4Cl (30 mL) and extracted with EtOAc (3 × 100 mL). The organic layers were combined and washed with saturated NH_4Cl and then with brine. After drying over $MgSO_4$, the solvent was removed in vacuo. ^{1}H NMR analysis of the crude showed only the desired *E*-isomer along with traces of starting material. The crude was purified by column chromatography (CH_3CN/CH_2Cl_2, 1:2 then 1:1 then 2:1) to give 1.1 g (63% yield) of pure vinyl carboxamide **7a** and 300 mg (20% yield) of recovered ketone: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (s, 1H, H_3), 7.81 (s, 1H, H_5), 7.49−7.27 (m, 7H, Ar), 6.42 (s, 1H, CH=C), 5.29 (br d, 1H, J = 5.0, NHMe), 2.63 (d, 3H, J = 4.9, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.5, 162.2, 154.2, 138.6, 136.8, 129.3, 129.1, 128.5, 127.2, 126.1, 125.1, 123.0, 118.1, 116.0, 106.3, 103.3, 26.3; MS (EI$^+$) *m/z* 388 M^+ (100), 358 (36), 319 (42), 288 (13), 260 (20), 209 (13), 181 (8), 159 (7), 151 (8), 105 (11), 77 (18), 69 (16); HRMS calcd for $C_{19}H_{15}N_4O_2F_3$ 388.1147, found 388.1144.

No isomerization of the double bound was noticed when compound **7a** was kept in the presence of a catalytic amount of TFA overnight or in $CDCl_3$ for several weeks.

2-Trifluoroacetamido-3-phenyl-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (7b). Trifluoroacetamido-3-phenyl-6-benzoylimidazo[1,2-*a*]pyridine (**5b**) (618 mg, 1.27 mmol) was converted to the desired product **7b** in a substantially analogous manner to **7a** to yield 526 mg (75%) after column chromatography (CH_3CN/CH_2Cl_2, 1:1). ^{1}H NMR analysis of the crude showed only the *E*-isomer of the desired product whose geometry was established by NOE experiments: mp 225−227 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (s, 1H, H_5), 7.58−7.23 (m, 12H, Ar), 6.34 (s, 1H, CH=C), 5.17 (br d, J = 5.0, NHMe), 2.64 (d, 3H, J = 5.0, CH_3); ^{13}C NMR (acetone-d_6) δ 170.8, 166.3, 145.3, 142.7, 142.2, 138.2, 135.6, 133.0, 129.8, 129.4, 129.0, 128.8, 128.6, 128.7, 126.9,

125.4, 123.6, 123.3, 117.0, 25.5; MS (EI^+) *m/z* 464 M^+ (100), 395 (50), 365 (44), 338 (36), 235 (26), 209 (15), 166 (17), 104 (13), 77 (16); HRMS calcd for $C_{25}H_{19}N_4O_2F_3$ 464.1460, found 464.1464.

2-Trifluoroacetamido-3-(2,5-difluorophenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (7c). Trifluoroacetamido-3-(2,5-difluorophenyl)-6-benzoylimidazo[1,2-*a*]pyridine (**5c**) (500 mg, 1.15 mmol) was converted to the desired product **7c** in a substantially analogous manner to **7a** to yield 483 mg (86%) after column chromatography (CH_3CN/CH_2Cl_2, 1:1). ^1H NMR analysis of the crude showed only the *E*-isomer of the desired product whose geometry was established by NOE experiments: mp 134−136 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.87 (s, 1H, H_5), 7.62 (AA′BB′ system, 2H, J = 9.2, H_6 and H_7), 7.40−7.28 (m, 8H, Ar), 6.56 (s, 1H, CH=C), 2.65 (s, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 169.4, 161.2, 148.1, 144.2, 140.3, 138.8, 134.2, 130.5, 129.7, 129.5, 129.4, 128.8, 127.5, 125.6, 123.4, 119.3, 119.0, 118.9, 118.6, 118.1, 117.6, 117.3; MS (EI^+) *m/z* 500 M^+ (100), 470 (42), 431 (26), 403 (16), 400 (17), 237 (11), 215 (9), 152 (9), 105 (11), 102 (10), 77 (11); HRMS calcd for $C_{25}H_{17}N_4O_2F_5$ 500.1272, found 500.1279.

2-Trifluoroacetamido-3-(2,3,4-trifluorophenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]-pyridine (7d). The 2-trifluoroacetamido-3-(2,3,4-trifluorophenyl)-6-benzoylimidazo[1,2-*a*]pyridine (**5d**) (303 mg, 0.67 mmol) was converted to the desired product **7d** in a substantially analogous manner to **7a** to give 168 mg (50%) after column chromatography (CH_3CN/CH_2Cl_2, 1:1). ^1H NMR analysis of the crude showed only the *E*-isomer of the desired product whose geometry was established by NOE experiments: mp 115−117 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.71−7.15 (m, 10H, Ar), 6.48 (s, 1H, CH=C), 5.21 (m, 1H, NHMe), 2.65 (d, 3H, CH_3). Anal. ($C_{25}H_{16}F_6N_4O_2$) C, H, N.

2-Trifluoroacetamido-3-(3-trifluoromethylphenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (7e). 2-Trifluoroacetamido-3-(3-trifluoromethylphenyl)-6-benzoylimidazo[1,2-*a*]pyridine (**5e**) (228 mg, 0.49 mmol) was converted to the desired product **7e** in a substantially analogous manner to **7a** to give 228 mg (57%) after column chromatography (CH_3CN/CH_2Cl_2, 1:1). ^1H NMR analysis of the crude showed only the *E*-isomer of the desired product whose geometry was established by NOE experiments: mp 243 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.03−7.23 (m, 11H, Ar), 6.57 (s, 1H, CH=C), 3.51 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 164.9, 160.2, 152.6, 141.5, 137.7, 137.0, 131.4, 129.8, 129.5, 128.8, 128.5, 128.2, 127.9, 127.3, 126.5, 125.2, 123.2, 122.7, 121.1, 116.8, 113.6, 24.8; MS (EI^+) *m/z* 532 M^+ (100), 463 (41), 433 (79), 406 (47), 235 (52), 166 (25), 69 (14); HRMS ($M^+ - 2$) 530.115540.

2-Trifluoroacetamido-3-(2-trifluoromethyl-4-fluorophenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]-imidazo[1,2-*a*]pyridine (7f). 2-Trifluoroacetamido-3-(2-trifluoromethyl-4-fluorophenyl)-6-benzoylimidazo[1,2-*a*]pyridine (**5f**) (500 mg, 1.04 mmol) was converted to the desired product **7f** in substantially analogous manner to **7a** to give 439 mg (79%) after column chromatography (CH_3CN/CH_2Cl_2, 1:1). ^1H NMR analysis of the crude showed only the *E*-isomer of the desired product whose geometry was established by NOE experiments: mp 144−146 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 11.2 (br s, 1H, NH), 7.59−7.34 (m, 7H, Ar), 7.20−7.15 (m, 4H, Ar), 6.23 (s, 1H, CH=C), 5.18 (br d, 1H, J = 4.8, NHMe), 2.60 (d, 3H, J = 4.8, CH_3−NH); ^{13}C NMR ($CDCl_3$) δ 166.4, 165.4, 160.4, 155.1, 145.2, 141.8, 137.4, 136.6, 136.5, 136.3, 129.2, 129.1, 128.8, 128.5, 127.9, 126.1, 123.1, 122.8, 122.2, 119.9, 119.4, 115.9, 114.7, 114.4, 111.4, 26.2; MS (EI^+) *m/z* 550 M^+ (100), 520 (37), 492 (10), 481 (14), 450 (11), 422 (12), 209 (6), 191 (6), 178 (9), 105 (7), 102 (7); HRMS calcd for $C_{26}H_{17}N_4O_2F_7$ 550.1239, found 550.1237.

2-Amino-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]-imidazo[1,2-*a*]pyridine (1a). 2-Trifluoroacetamido-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (**7a**) (300 mg, 0.77 mmol) was stirred in the presence of 0.5 N NaOH (17 mL) at room temperature for 5 h. The solution was neutralized to pH 7 with HCl (5% aqueous solution) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed at reduced pressure to yield 130 mg (58%) as a light-brown solid: mp 97−99 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.61 (d, 1H, J = 1.4, H_5), 7.47−7.41 (m, 3H, Ar), 7.33−7.27 (m, 3H, Ar), 7.12 (dd, 1H, J = 9.3, 1.8, H_7 or H_8), 6.77 (s, 1H, H_3), 6.36 (s, 1H, CH=C), 5.13 (br d, 1H, J = 4.9, NHMe), 3.90 (br s, 2H, NH_2), 2.62 (d, 3H, J = 4.9, CH_3NH); ^{13}C NMR ($CDCl_3$) δ 166.8, 151.0, 146.2, 142.4, 137.4, 129.2, 128.7, 128.6, 125.5, 124.6, 122.5, 121.4, 114.1, 94.4, 26.1; MS (EI^+) *m/z* 292 M^+ (100), 262 (32), 234 (20), 223 (15), 215 (13), 178 (8), 160 (10), 117 (6), 105 (9), 77 (9); HRMS calcd for $C_{17}H_{16}ON_4$ 292.1324, found 292.1328.

2-Amino-3-phenyl-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (1b). 2-Trifluoroacetamido-3-phenyl-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]-imidazo[1,2-*a*]pyridine (**7b)** (0.13 g, 0.26 mmol) was dissolved in MeOH/DIPEA (4 mL, 1:1) and refluxed under Ar for 2 days. The solvents were removed in vacuo, and the mixture was purified by column chromatography (CH_2Cl_2/CH_3CN/MeOH 55:40:5) affording **1b** as a yellow solid in 87% yield: mp 187−189 °C; ^1H NMR (200 MHz, CD_3OD) δ 2.60 (s, 3H), 6.44 (s, 1H), 7.20−7.42 (m, 12H), 7.91 (br s, 1H). Anal. ($C_{23}H_{20}N_4O$) C, H, N.

2-Amino-3-(2,5-difluorophenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (1c). The 2-trifluoroacetamido-3-(2,5-difluorophenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine **(7c)** was converted to the desired product **1c** in manner substantially analogous to **1b**. After column chromatography (CH_3CN/CH_2Cl_2, 1:1), **1c** was isolated as a yellow solid in 82% yield: mp 162−164 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.62 (dd, 1H, J = 2.1, 1.2, H_5), 7.45−6.99 (m, 10H, Ar), 6.35 (s, 1H, H vinyl), 5.19 (d, 1H, J = 4.9, NH), 4.18 (br s, 2H, NH_2), 2.63 (d, 3H, J = 5.0, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.8, 156.5, 149.6, 146.0, 143.0, 137.1, 129.2, 128.7, 128.1, 125.9, 124.0, 123.1, 121.8, 118.1, 117.9, 117.4, 116.1, 115.6, 114.2, 99.6, 26.2; MS (EI^+) *m/z* 404 M^+ (100), 374 (17), 345 (12), 207 (9), 152 (7), 140 (7), 105 (7), 77 (11); HRMS calcd for $C_{23}H_{18}N_4OF_2$ 404.1449, found 404.1448.

2-Amino-3-(2,3,4-trifluorophenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (1d). 2-Trifluoroacetamido-3-(2,3,4-trifluorophenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (**7d**) was converted to the desired product **1d** in a manner substantially analogous to **1b**. After column chromatography (CH_3CN/CH_2Cl_2, 1:1), compound **1d** was isolated as a yellow solid in 91% yield: ^1H NMR (200 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.44−7.00 (m, 9H, Ar), 6.63 (s, 1H, CH=C), 5.20 (br s, 1H, NH−CH_3) 4.13 (br s, 2H, NH_2), 2.62 (d, J = 4.9, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.7, 149.6, 137.1, 129.2, 129.1, 128.8, 128.6, 128.1, 128.0, 127.7, 126.1, 125.7, 123.9, 123.8, 123.6, 123.5, 123.1, 122.7, 122.6, 121.9, 121.8, 118.4, 114.4, 114.2, 112.7, 26.2; MS (EI^+) *m/z* 423 M^+ (6), 422 (25), 392 (6), 353 (14), 259 (14), 105 (16), 84 (100); HRMS: ($M^+ - 1$) 422.135830.

2-Amino-3-(3-trifluoromethylphenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (1e). 2-Trifluoroacetamido-3-(3-trifluoromethylphenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (**7e**) was converted to the desired product **1e** in a manner substantially analogous to **1b**. After column chromatography (CH_3CN/CH_2Cl_2, 1:1), compound **1e** was isolated as a yellow solid in 85% yield: mp 205 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.64 (m, 11H, Ar), 6.42 and 6.38 (s, 1H, CH=C), 5.13 (br s, 1H, NH−CH_3) 4.11 (br s, 2H, NH_2), 2.62 (d, J = 4.9, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 169.4, 150.6, 148.2, 143.6, 142.1, 139.0, 132.4, 131.3, 130.3, 129.4, 129.3, 127.7, 124.9, 123.4, 121.8, 118.7, 114.7, 26.1; MS (EI^+) *m/z* 437 M^+ (36), 436 (100), 406 (18), 377 (16), 279 (10), 77 (6); HRMS ($M^+ - 1$) 436.151580.

2-Amino-3-(2-trifluoromethyl-4-fluorophenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (1f). 2-Trifluoroacetamido-3-(2-trifluoromethyl-4-fluorophenyl)-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]-

pyridine (**7f**) was converted to the desired product **1f** in a manner substantially analogous to **1b**. After column chromatography (CH_3CN/CH_2Cl_2, 1:1), compound **1f** was isolated as a green solid in 78% yield: mp 168−170 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 (dd, 1H, J = 8.4, H_7 or H_8), 7.47−7.16 (m, 9H, Ar), 6.94 (d, 1H, J = 8.9, H_7 or H_8), 6.16 (s, 1H, CH=C), 5.39 (br d, 1H, J = 4.6, NHMe), 3.92 (br s, 2H, NH_2), 2.55 (d, 3H, J = 4.7, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.7, 165.3, 160.3, 149.3, 146.2, 142.3, 137.1, 129.1, 128.5, 125.6, 123.7, 121.9, 121.7, 120.3, 119.9, 115.5, 114.9, 113.9, 100.4, 26.1; MS (EI^+) m/z 454 M^+ (100), 424 (19), 395 (12), 356 (7), 279 (10), 209 (11), 77 (9); HRMS calcd for $C_{24}H_{18}N_4OF_4$ 454.1416, found 454.1407.

2-Trifluoroacetamido-3-iodo-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (7g). To a solution of 2-trifluoroacetamido-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (**7a)** (423 mg, 1.22 mmol) in 20 mL of dry CH_3CN cooled at 0 °C was added *N*-iodosuccinimide (302 mg, 1.34 mmol) portionwise, and the mixture was stirred for 10 min. The desired product precipitated as a white solid which was filtered and air-dried affording 375 mg of crude product. CH_3CN was evaporated in vacuo and the residue dissolved in EtOAc (50 mL) and washed with (40% p/v) $NaHSO_3$ (2 × 50 mL) and $NaHCO_3$ (2 × 50 mL). The organic layer was dried (Na_2SO_4) and EtOAc removed at reduced pressure, affording 240 mg (98% overall yield) of **7g** as a white solid: mp 232−234 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.52 (br s, 1H, $NHCOCF_3$), 7.83 (d, 1H, J = 1.4, H_5), 7.49−7.22 (m, 7H, Ar), 6.37 (s, 1H, CH=C), 5.21 (br d, 1H, J = 4.9, NHMe), 2.65 (d, 3H, J = 4.9, CH_3); ^{13}C NMR (DMSO-d_6) δ 165.2, 155.5, 154.8, 144.5, 144.1, 142.0, 137.7, 129.4, 128.3, 127.9, 125.7, 123.5, 118.8, 116.7, 113.0, 107.3, 25.4; MS (EI^+) m/z 514 M^+ (49), 484 (11), 445 (7), 388 (100), 358 (54), 319 (18), 288 (23), 260 (37), 233 (6), 205 (16), 179 (16), 159 (14), 126 (13), 105 (13), 77 (15), 69 (18); HRMS calcd for $C_{19}H_{14}N_4O_2F_3I$ 514.0114, found 514.0117.

2-Amino-3-iodo-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)-vinyl]imidazo[1,2-*a*]pyridine (1g). Iodoimidazopyridine **7g** (135 mg, 0.46 mmol) was dissolved in CH_2Cl_2/MeOH (98:2, 15 mL). SiO_2 was added to the solution, and the mixture was stirred vigorously for 1 day. The conversion to the amine was followed by TLC (CH_2Cl_2/CH_3CN, 4:1). The residue was filtered and the silica gel washed with CH_3CN (10 mL). Removal of the solvents gave the unstable compound **1g** as a green-yellow solid in 45% yield: mp 186−188 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, 1H, J = 1.7, H_5), 7.47−7.41 (m, 3H, Ar), 7.35−7.24 (m, 3H, Ar), 7.06 (dd, 1H, J = 9.3, 1.9, H_7 or H_8), 6.40 (s, 1H, CH=C), 5.25 (br s, 1H, J = 4.9, NH), 4.40−3.70 (br s, 2H, NH_2), 2.64 (d, 3H, J = 4.9, CH_3).

2-Amino-3-isopropylthio-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (1h). To a solution of 2-trifluoroacetamido-3-iodo-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (**7g**) (72 mg, 0.15 mmol) in 5 mL of THF cooled to −78 °C was added phenyllithium (230 μL, 0.33 mmol) under Ar. The reaction mixture was stirred for 3 min before injecting *t*-BuLi (310 μL, 0.38 mmol). After the mixture stirred for a 10-min period, a solution of isopropyl isopropanethiolsulfonate (109 mg, 0.60 mmol) in 5 mL of THF was added. The reaction mixture was stirred for 30 min at −78 °C and then quenched with 2 drops of H_2O and 10 mL of THF. EtOAc (15 mL) was added, and the mixture was allowed to warm to room temperature. The solution was filtered through Celite, and the solvents were removed in vacuo. Radial chromatography afforded the isopropyl sulfide **1h** with the trifluoroacetyl group cleaved and the intermediate **7h** in pure form. The ratio of intermediate/product depends on the speed of the radial chromatography. The fraction of trifluoroacetyl material **7h** was mixed with silica gel in MeOH/CH_2Cl_2 and the cake was stirred for 2 days. After filtration the desired product **1h** was obtained in 73% overall yield: mp 112−114 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, 1H, J = 1.5, H_5), 7.47−7.20 (m, 7H, Ar), 6.40 (s, 1H, CH=C), 5.20 (br s, 1H, J = 4.9, NHMe), 4.26 (br s, 2H, NH_2), 2.97 (heptet, 1H, J = 6.8, $CH(CH_3)_2$), 2.65 (d, 3H, J = 4.9, CH_3), 1.13 (d, 6H, J = 6.8, $(CH_3)_2CH$); MS (EI^+) m/z 366 M^+ (33), 323 (100), 293 (18), 237 (15), 196 (10), 178 (7), 102 (6); HRMS calcd for $C_{20}H_{22}N_4OS$ 366.1514, found 366.1520.

2-Trifluoroacetamido-3-isopropylsulfonyl-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (7i). To a solution of 2-trifluoroacetamido-3-iodo-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (**7g**) (70 mg, 0.15 mmol) in 5 mL of THF cooled to −78 °C was added PhLi (230 μL, 0.33 mmol) under Ar. The reaction mixture was stirred for 3 min before injecting *t*-BuLi (310 μL, 0.38 mmol). After stirring for a 10-min period, a solution of isopropyl isopropanethiolsulfonate (109 mg, 0.60 mmol) in 5 mL of THF was added. The reaction mixture was stirred for 30 min at −78 °C and then quenched with 2 drops of water and 10 mL of not dried THF. EtOAc (15 mL) was added; the mixture was allowed to warm to room temperature. The solution was filtered through Celite, and the solvents were removed in vacuo. The residue was then dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C. Previously dried *m*-CPBA (208 mg, 5 equiv excess calculated over 100% theoretical yield of sulfide coupling product) dissolved in CH_2Cl_2 (40 mL) was then added dropwise until the complete oxidation to sulfone had finished (monitored by TLC). The solution was washed with Na_2SO_3 (50 mL) and $NaHCO_3$ (2 × 50 mL). The organic layers were dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was purified by flash chromatography in silica gel (CH_3CN/CH_2Cl_2, 1:1) to give 47 mg of **7i** as a white solid (63% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.81 (br s, 1H, $NHCOCF_3$), 8.47 (s, 1H, H_5), 7.76 (d, 1H, J = 8.8, H_7 or H_8), 7.50−7.23 (m, 6H, Ar), 6.42 (s, 1H, H vinyl), 5.28 (br d, 1H, J = 4.8, NHMe), 3.28 (heptet, 1H, J = 6.8, $CH(CH_3)_2$), 1.29 (d, 6H, J = 6.8, CH_3-CH); MS (EI^+) m/z 494 M^+ (33), 425 (33), 388 (100), 358 (59), 319 (24), 292 (57), 288 (19), 260 (23), 237 (21), 205 (18), 178 (18), 105 (17), 83 (16), 58 (24); HRMS calcd for $C_{22}H_{21}N_4O_4F_3S$ 494.1235, found 494.1229.

No isomerization of the double bound was noticed when **7h** was kept in the presence of a catalytic amount of TFA overnight or for several weeks in $CDCl_3$.

2-Amino-3-isopropylsulfonyl-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo [1,2-*a*]pyridine (1i). 2-Trifluoroacetamido-3-isopropylsulfonyl-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]imidazo[1,2-*a*]pyridine (**7i**) (45 mg, 0.09 mmol) was dissolved in a 1:1 mixture of MeOH/CH_2Cl_2, and silica gel was added until a cake was obtained. The cake was vigorously stirred for 2 days. After filtration through Celite, the compound **1i** was obtained as a white solid (33 mg, 89%): mp 207−209 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.46 (s, 1H, H_5), 7.53−7.30 (m, 7H, Ar), 6.41 (s, 1H, CH=C), 5.30 (d, 1H, J = 4.8, NHMe), 5.17 (br s, 2H, NH_2), 3.26 (heptet, 1H, J = 7.0, $CH(CH_3)_2$), 2.12 (d, 3H, J = 4.8, CH_3NH), 1.34 (d, 6H, J = 7.0, $(CH_3)_2CH$); MS (EI^+) m/z 398 M^+ (44), 292 (100), 262 (27), 233 (15), 215 (9), 205 (8), 178 (7), 77 (6), 58 (8); HRMS calcd for $C_{20}H_{22}N_4O_3S$ 398.1413, found 398.1413.

Drug Solutions for Biological Assays. Compounds were dissolved in DMSO at 1000× concentrations and diluted 1/1000 into culture media (final concentration of DMSO = 0.1%). Although DMSO had no detectable effect on virus replication, 0.1% DMSO was added to all no-drug control samples.

Cytopathic Effect Assay. The cytopathic effect (CPE) assay was performed as described previously[13] with a modification to the method of the quantification of the cytopathic effect of virus on the cells. Instead of using crystal violet staining, XTT (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide) was used as substrate to quantify the surviving host cells.[14]

Plaque Reduction Assay. Susceptible H-HeLa cells were grown in 60-mm diameter tissue culture dishes at 37 °C in minimum essential medium with 10% newborn calf serum and 1% nonessential amino acids (medium A). When confluent monolayers were formed, growth medium was removed, and 0.2 mL of medium A containing approximately 150 plaque-forming units of rhinovirus-14 was added. After adsorption for 30 min at room temperature, the infected cell sheet was

overlaid with equal parts of 1.6% sterile agarose solution and a 2-fold concentration of medium A supplemented with $MgSO_4$ (final concentration, 12 mM). Overlay media also contained varying concentrations of the compounds to be tested. Plaque assays were incubated at 35 °C for 48 h. A solution of 10% formalin was added to each dish to inactivate the virus and fix the cell sheet to the plastic surface. The fixed cell sheets were stained with 0.5% crystal violet, and the plaques were counted. Results from duplicate wells at each concentration were averaged and compared with DMSO control wells. The inhibition of plaque formation by 50% (IC_{50}) was calculated from the linear region of the inhibition−concentration curve using the method of Reed and Muench.[15]

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