Design, Synthesis, and Structure−Activity Relationship of Pyridyl Imidazolidinones: A Novel Class of Potent and Selective Human Enterovirus 71 Inhibitors

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Received November 26, 2001

When skeletons of Win compounds were used as templates, computer-assisted drug design led to the identification of a novel series of imidazolidinone derivatives with significant antiviral activity against enterovirus 71 (EV 71), the infection of which had resulted in about 80 fatalities during the 1998 epidemic outbreak in Taiwan. In addition to inhibiting all the genotypes (A, B, and C) of EV 71 in the submicromolar to low micromolar range, compounds **1** and **8** were extensively evaluated against a variety of viruses, showing potent activity against coxsackievirus A9 (IC_{50} = 0.47−0.55 μM) and coxsackievirus A24 (IC_{50} = 0.47−0.55 μM) as well as moderate activity against enterovirus 68 (IC_{50} = 2.13 μM) and echovirus 9 (IC_{50} = 2.6 μM). Our SAR studies revealed that imidazolidinone analogues with an aryl substituent at the para position of the phenoxyl ring, such as compounds **20**, **21**, **27**, **57**, **58**, and **61**, in general exhibited the highest activity against EV 71. Among them, compound **20** and its corresponding hydrochloride salt **57**, in terms of potency and selectivity index, appear to be the most promising candidates in this series for further development of anti-EV-71 agents. Preliminary results of the study on the mode of action by a time-course experiment suggest that test compounds **1** and **8** can effectively inhibit the virus replication at the early stages, referring to virus attachment or uncoating. This indicates that the surface protein may be the target for this type of compounds.

Background and Significance

Enteroviruses comprise nearly 70 distinct serotypes within the family of *piconaviridae*. The subgroups include the polioviruses, coxsackieviruses A and B, echoviruses, and the newer "numbered enteroviruses".[1] Well-documented clinical manifestations associated with enterovirus infection range from the mild "common cold" to fatal neurological and cardiovascular disorders. To date, there is no effective antiviral agent available for the treatment or prevention of enterovirus disease.[2]

Since April 1998, many children in Taiwan fell victim to hand-foot-and-mouth disease, aseptic meningitis/encephalitis, or acute flaccid paralysis, which resulted in almost 80 fatalities.[3] Several independent laboratories have isolated enteroviruses from different specimens taken from the above patients, including fatal cases; enterovirus 71 (EV 71) was identified as a major factor in the etiology of the aforementioned cases.[3] After the 1998 epidemic outbreak of EV 71 infection, EV 71 has been continually isolated throughout the whole island all year round, and many severe cases caused by EV 71 have also been reported. This highlights the urgency and significance for developing anti-EV-71 agents.

Enterovirus consists of a simple virus capsid and a single strand of positive-sense RNA. The capsid contains 60 copies each of four coat proteins, namely, VP1, VP2, VP3, and VP4. Variations within capsid proteins VP1 to VP3 are responsible for the antigenic diversity among the enteroviruses, and neutralization sites are most densely clustered on VP1.[4] Replication of RNA viruses is directed by viral RNA polymerase of relatively low fidelity with characteristic error frequencies of 10^{-3} to 10^{-4} misincorporated nucleotides per round of replication.[5,6] This means that the replication of the enterovirus genome, consisting of about 7500 nucleotides, results in a population of molecules having, on the average, at least one mutation. Moreover, recombination occurs with very high frequency in picornaviruses.[7] Because of the prevalent multiple serotypes and the genetic heterogeneity, development of antiviral agents for regional enterovirus infection is therefore warranted.

Pleconaril (Figure 1), a capsid-binding molecule, has been shown to have a broad spectrum of activities against rhinoviruses and enteroviruses by interfering with the capsid-receptor binding site, resulting in the inhibition of the virus attachment to the cells and uncoating of viral RNA.[8−13] This potential drug candidate is currently undergoing clinical trials, and its successful phase III results for the treatment of viral respiratory infection (VRI),[8] often referred to as the common cold, were announced by Viropharma, Inc.

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10.1021/jm010536a CCC: $22.00 © 2002 American Chemical Society
Published on Web 03/13/2002

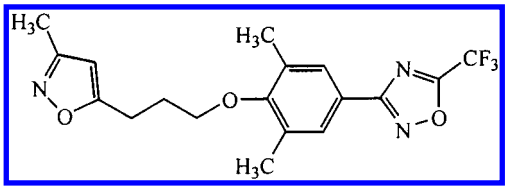


Figure 1. Structure of pleconaril.

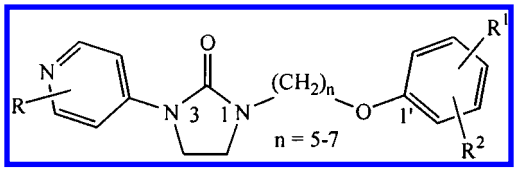


Figure 2. General structure of imidazolidinones.

Unfortunately, we observed that pleconaril could not neutralize the cytopathic effect (CPE) of cultured cells induced by enterovirus isolates from the 1998 outbreak in Taiwan.[14] Presumably, this is due to the fact that pleconaril is deficient in specificity toward the local strain of enterovirus. This fact further reinforces an argument of developing the antienterovirus agents using materials from local strains.

When the skeletons of pleconaril and its related molecules, so-called WIN compounds, are used as templates, the rational design, synthesis, and structure–activity relationship (SAR) studies led to the development of a novel class of imidazolidinones with significant antiviral activity, the general structure of which is illustrated in Figure 2. These synthetic compounds were evaluated for anti-EV-71 activity. Some analogues were found, in addition to inhibiting all of the genotypes of EV 71, to possess antiviral activity against coxsackieviruses A9, A24, B1, B3, and B5, echovirus 9, and enterovirus 68. Details of this investigation will be described herein.

Chemistry

1. Design. It is well recognized that the capsid structures between rhinoviruses and enteroviruses are relatively conserved,[8,15–18] although it is highly conceivable that subtle differences in the sizes and shapes of their hydrophobic VP1 pockets do exist. This, along with the fact that Win compounds are good VP1-binding molecules, made us begin our studies on the development of anti-EV-71 agents based on the backbone of Win compounds.

Closer examination of Win compounds[19–24] and other antipicornavirus agents[25–29] that also exhibit an inhibitory effect on the early stages of viral replication revealed that a structural feature of two terminal aromatic rings linked by an aliphatic chain was constantly recurrent. This structural feature may be critical for the inhibitors to fit into the hydrophobic VP1 pocket, which has a "socklike" shape. Although this property is quite obvious, how to bring it into effect is problematic in practice. Therefore, for the purpose of simplicity and feasibility, we adopted a fixed theme with a terminal phenoxyl moiety linked to an alkyl chain of five to seven carbon atoms to generate a virtual library. The computer was asked to create a library of virtual molecules by ending the linker with an aromatic ring-containing group; this terminal group, however, was elaborated as a functionality possessing a certain degree of complexity

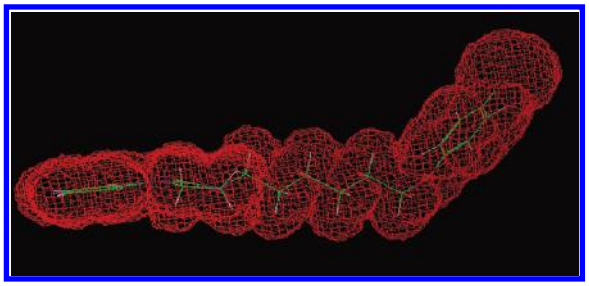
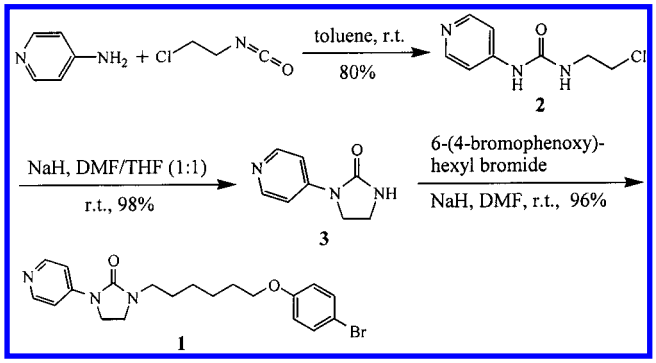


Figure 3. Molecular volume of compound **1**.

Scheme 1



and geometrical rigidity, like fusing a heteroaryl or aryl group to a monocyclic, bicyclic, spiro, or cage system.

A vast number of virtual compounds were generated on the basis of the above design, the structures of which were further optimized by the semiempirical method AM1. Three-dimensional molecular volumes of these compounds were then estimated by calculating van der Waals' radii. This calculation process disclosed, unexpectedly, a series of virtual compounds with molecular pictures extremely similar to the shape of the VP1 cavity of picornaviruses. Interestingly, a common feature of these virtual compounds was the presence of a pyridyl imidazolidinone functionality as the terminal. A typical molecular volume picture of these derivatives, which we refer to as "socklike" molecules, is illustrated by compound **1** as shown in Figure 3. According to Giranda,[30] a molecule with this structural feature might be an ideal receptor-binding inhibitor in that not only can it insert into the hydrophobic pocket within the capsid protein VP1 but it can also extend outside the pocket to the canyon floor, which is the binding site of cellular receptors. This statement along with the discovery of these "socklike" molecules strongly motivated us to realize the synthesis of this class of virtual compounds.

2. Synthesis. The above computer-generated pyridyl imidazolidinone compounds were experimentally realized according to a general synthetic method shown in Scheme 1 with compound **1** as a specific example.[31,32] 4-Aminopyridine was first coupled with 2-chloroethyl isocyanate to give the corresponding urea intermediate **2** in 80% yield. Subsequent intramolecular cyclization of intermediate **2** by treatment with sodium hydride in the THF/DMF (1:1) cosolvent system at room temperature resulted in the formation of cyclic urea **3**[32] in virtually quantitative yield (98%). Compound **3** thus obtained was allowed to react with 6-(4-bromophenoxy)-hexyl bromide in DMF using sodium hydride as a base to afford the expected product **1** in excellent yield (96%). Serving as a key synthetic intermediate, compound **3** underwent substitution reactions with a variety of

Scheme 2

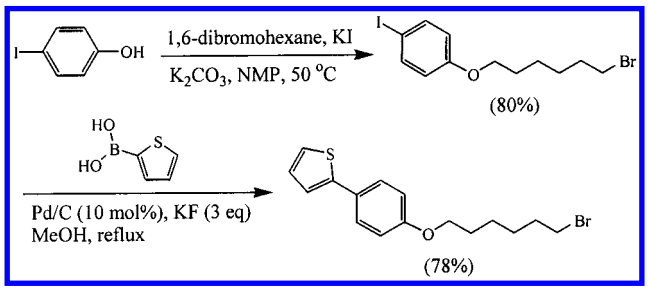
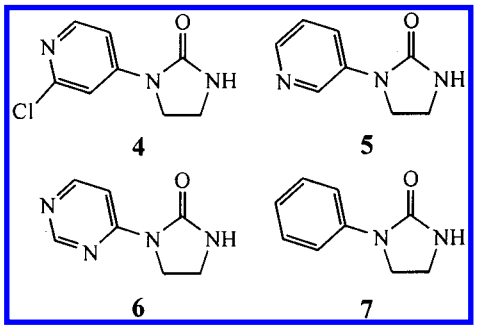


Chart 1



alkylating agents to provide compounds **8**−**35** (Table 2) in high to excellent yields. Alkylating agents employed in the alkylation reactions were readily prepared by use of commercially available phenols as well as dibromoalkanes via nucleophilic substitution reactions under standard conditions.[24,33−35] Alternatively, where necessary, the alkylating agents were prepared via a two-step procedure making use of the Suzuki coupling process as a key operation.[36,37] This is demonstrated by a typical experiment shown in Scheme 2.

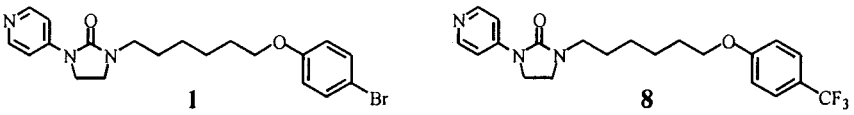
In a similar fashion, starting with various aromatic amines including aniline, 2-chloro-4-aminopyridine, 3-aminopyridine, and 4-aminopyrimidine, a series of key intermediates **4**, **5**, **6**, and **7**[32,38] have also been synthesized (see Chart 1). These intermediates were then individually subjected to alkylation reactions to give the corresponding imidazolidinone derivatives **36**−**56** in good to high yields. Their structures as well as biological activity evaluation are illustrated in Table 3.

To improve water solubility, pyridyl imidazolidinones **20**−**24**, containing a biphenyl moiety, were converted to their corresponding hydrochloride salts **57**−**61**, respectively, in almost 100% yield by treatment with an excess of hydrochloric acid (Aldrich, 1.0 M solution in diethyl ether). As far as the structure is concerned, the most likely protonation site should be the nitrogen in the pyridine ring.

Results and Discussion

Antiviral activity testing was initiated with "socklike" molecules **1** and **8**. The compounds were individually subjected to evaluation against a variety of viruses, including coxsackieviruses (10 serotypes), echoviruses (2 serotypes), human enteroviruses 68 and 71, influenza A and B viruses, herpes simplex virus 1 (HSV-1), and human rhinoviruses 2 (HRV 2) and 14 (HRV 14). The results of this extensive biological evaluation are illustrated in Table 1.[39] As shown, compounds **1** and **8** exhibit significant activities against human enterovirus 68 (IC_{50} = 2.13−4.67 μM), human enteroviruses 71 (IC_{50} = 0.30−1.37 μM), echovirus 9 ($IC_{50} \approx$ 2.6 μM), coxsackievirus A24 (IC_{50} = 0.47−0.55 μM) as well as coxsackievirus A9 (IC_{50} = 0.77−1.44 μM). However, they show weak potency ($IC_{50} \approx$ 11 μM) against HRV 14 and no activity against HRV 2, influenza viruses A and B, HSV-1, and coxsackieviruses B1−B6 up to the concentration tested (25 μM). In comparison with the Win series, a distinct difference in antiviral activity was observed. As

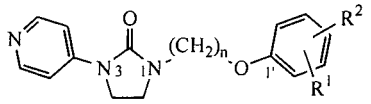
Table 1. Antiviral Activity of Compounds **1** and **8** against Various Viruses



virus	compound **1** IC_{50} [a] (μM)	compound **8** IC_{50} [a] (μM)
EV 71(2086) genotype C	0.31 ± 0.023	0.51 ± 0.003
EV 71(2231) genotype C	1.15 ± 0.052	1.35 ± 0.038
EV 71(BrCr) genotype A	1.26 ± 0.052	1.37 ± 0.069
EV 71(1743) genotype B	0.60 ± 0.016	0.75 ± 0.005
enterovirus 68	2.13 ± 0.190	4.67 ± 0.046
echovirus 9	2.82 ± 0.013	2.61 ± 0.130
echovirus 29	>25	>25
coxsackievirus A9	0.77 ± 0.049	1.44 ± 0.009
coxsackievirus A10	5.88 ± 0.340	15.71 ± 0.770
coxsackievirus A16	>25	>25
coxsackievirus A24	0.55 ± 0.063	0.47 ± 0.120
coxsackievirus B1	5.10 ± 0.045	5.60 ± 0.034
coxsackievirus B2	>25	>25
coxsackievirus B3	>25	>25
coxsackievirus B4	>25	>25
coxsackievirus B5	>25	>25
coxsackievirus B6	>25	>25
human rhinovirus 14	11.60 ± 0.120	>12.5
human rhinovirus 2	>25	>25
influenza A (WSN)	>25	>25
influenza B (WSN)	>25	>25
herpes simplex virus 1	>25	>25

[a] Mean of triplicate well values. All experiments were performed at least twice. Plaque reduction assay was employed.

Table 2. Anti-EV-71 Activity and Cytotoxicity of 3-(4-Pyridyl)-2-imidazolidinones



Compound	n	R^1	R^2	mp(°C)	$IC_{50}(\mu M)^a$	$CC_{50}(\mu M)^b$
1	6	H	4'-Br	98-100	0.35±0.018	>25
8	6	H	4'-CF_3	95-97	0.58±0.002	>25
9	5	H	4'-CF_3	89-90	1.35±0.028	12.50± 0.320
10	7	H	4'-CF_3	81-83	0.61±0.006	6.25±0.096
11	5	H	4'-Br	123-125	0.50±0.010	>25
12	7	H	4'-Br	125-127	0.56±0.026	>25
13	5	H	4'-Cl	132-134	1.35±0.006	>25
14	6	H	4'-Cl	87-89	1.50±0.013	>25
15	7	H	4'-Cl	128-130	0.66±0.042	>25
16	6	H	4'-F	87-89	3.01±0.130	>25
17	6	H	4'-CH_3	89-91	6.36±0.351	>25
18	6	H	4'-OCH_3	93-95	5.43±0.184	>25
19	6	H	4'-SCH_3	100-102	4.96±0.463	>25
20	5	H	4'- 	139-141	0.04±0.001	>25
21	5	H	4'- 	167-169	0.06±0.001	6.25±0.350
22	5	H	4'- 	198-199	ND[c]	ND[c]
23	5	H	4'- 	157-158	ND[c]	ND[c]
24	5	H	4'- 	144-146	0.33±0.017	>25
25	5	H	4'- 	156-158	2.66±0.145	>25
26	5	H	4'- 	198-200	0.58±0.036	>25
27	6	H	4'- 	137-139	0.30±0.011	>25
28	6	H	4'- 	146-148	0.58±0.031	>25
29	6	H	4'-CN	106-108	>0.39	0.39±0.013
30	6	H	3'-Br	81-83	>25	>25
31	6	H	3'-$N(CH_3)_2$	48-50	>25	>25
32	6	2'-Cl	6'-Cl	91-93	>25	>25
33	6	2'-Cl	4'-OCH_3	70-72	>25	>25
34	6			121-123	>6.25	6.25±0.272
35	6			ND[d]	>25	>25

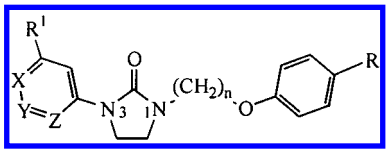
[a] Mean of triplicate well values. All experiments were performed at least twice. Neutralization test was employed. [b] Mean of triplicate well values. All experiments were performed at least twice. [c] Not determined because of poor solubility. [d] Not determined because of amorphous solid.

in the case of pleconaril,[8−10] it exhibits effective antiviral activities against an equal number of serotypes of rhinoviruses and enteroviruses with a slight preference, if any, for inhibiting the former. However, compounds **1** and **8** provide remarkable evidence that they are much more specific for human enteroviruses, in particular, enterovirus 71 (EV 71). Both of these compounds are highly active against EV 71 with IC_{50} values for three genotypes (A, B, and C) of EV 71 in the submicromolar to low micromolar range and also possess a very low cytotoxic effect on the uninfected rhabdomyosarcoma (RD) host cells with IC_{50} values of more than 25 μM (Table 2). Therefore, for our purposes, imidazolidinones **1** and **8** are well qualified to serve as lead compounds for the further development of anti-EV-71 agents.

On the basis of these encouraging results, a series of structurally related imidazolidinones were thus synthesized according to Scheme 1. The resulting compounds **9**−**56** were then submitted for anti-EV-71 testing as well as cytotoxicity evaluation in the RD cell line, results of which are compiled in Tables 2 and 3.

Table 2 summarizes the structure−activity relationship study of the phenyl ring and methylene linker portions of the molecule. It was found that with the exception of compound **29**, para-monosubstituted derivatives (**1**, **8**−**28**) showed moderate to high anti-EV-71 activity (0.04−6.4 μM), irrespective of the electronic character of the substituent. Compound **29** with a cyano group located at the para position was found to be devoid of anti-EV-71 activity but instead exhibited a potent cytotoxic effect (0.39 μM) on the host cells. The underlying cause of this effect is not fully understood and worthy of further study. Biaryl analogues **20**, **21**, and **27** with either a phenyl or thienyl moiety at the para position bestowed the best potency to this class of compounds, results of which are quite similar to those observed for the Win compounds.[23,24] This is probably due to the fact that the strongest hydrophobic interac-

Table 3. Anti-EV-71 Activity and Cytotoxicity of 3-Heteroaryl-2-imidazolidinones and 3-Aryl-2-imidazolidinones: Modification of Pyridine Ring



compd	*n*	X	Y	Z	R	R^1	mp (°C)	IC_{50} [a] (μM)	CC_{50} [b] (μM)
36	6	N	C	C	Br	Cl	83−85	>25	>25
37	6	N	C	C	CF_3	Cl	77−79	>25	>25
38	5	N	C	C	Br	Cl	126−128	>25	>25
39	6	N	C	C	SCH_3	Cl	81−83	>25	>25
40	5	C	N	C	Cl	H	121−123	4.65 ± 0.170	>25
41	6	C	N	C	Cl	H	76−78	2.52 ± 0.175	>25
42	7	C	N	C	Cl	H	116−118	1.43 ± 0.025	>25
43	6	C	N	C	CF_3	H	74−76	2.10 ± 0.410	>25
44	6	C	N	C	F	H	81−83	9.33 ± 0.192	>25
45	6	C	N	C	Br	H	84−86	2.07 ± 0.573	>25
46	6	C	N	C	CH_3	H	73−75	>25	>25
47	6	C	N	C	t-Bu	H	53−55	>25	>25
48	5	N	C	N	CF_3	H	77−79	>25	>25
49	6	N	C	N	CF_3	H	72−74	>25	>25
50	6	N	C	N	Cl	H	125−127	>25	>25
51	6	N	C	N	Br	H	93−95	>25	>25
52	7	N	C	N	Br	H	81−83	>25	>25
53	5	C	C	C	Br	H	90−92	10.66 ± 0.731	>25
54	6	C	C	C	Br	H	73−75	10.60 ± 0.480	>25
55	6	C	C	C	Cl	H	72−74	10.83 ± 1.842	>25
56	6	C	C	C	CF3	H	59−62	12.04 ± 0.776	>25

[a] Mean of triplicate well values. All experiments were performed at least twice. Neutralization test was employed. [b] Mean of triplicates well values. All experiments were performed at least twice.

tion could be provided by an aryl or heteroaryl ring at this position in the binding site. Moreover, in addition to exhibiting the most potent antiviral activity (IC_{50} = 0.04 μM), compound **20** also has an excellent selectivity index of greater than 1250, 1250, and 625 for the D551, WI38, and RD cell lines, respectively (Table 4). Accordingly, further studies based on this biaryl motif are currently under active investigation in our laboratories. For the series of imidazolidinone compounds illustrated in Table 2, para substitution seems to play an essential role in antiviral activity, and this is also evidenced by the fact that compounds with substitution at the meta and/or ortho position such as compounds **30**−**35** lead to a complete loss of antiviral activity.

As exemplified by compounds **1**, **11**, and **12**, the length of the alkyl linker does not appear to contribute significantly to antiviral activity. As such, all subsequently synthesized derivatives were maintained at these lengths (n = 5, 6, or 7).

With the para substitution of the phenoxyl ring maintained, modifications of the other aryl functionality were carried out. As shown in Table 3, compared to their parent compounds **1**, **8**, **11**, and **19**, the corresponding 2-chloro derivatives **36**−**39** showed a decrease in activity by about 100-fold! This effect might be due to a strict steric requirement on the 4-pyridyl moiety or a reduction of the basicity of the pyridine nitrogen resulting from the electron-withdrawing effect of the 2-chloro group. Such a dramatic decrease in activity as a result of a minor modification motivated us to further explore the apparent profound effect of the pyridine ring on antiviral activity in this series.

3-(3-Pyridyl)-2-imidazolidinones **40**−**45**, when compared to their corresponding 4-pyridyl isomers, showed a reduction in antiviral activity by 3- to 7-fold. 4-Pyrimidyl derivatives **48**−**52** were also synthesized and tested but found to be devoid of any antiviral activity. Interestingly, phenyl derivatives **53**−**56** were found to exhibit weak antiviral activity against EV 71. These observations appear to indicate that, apart from a required hydrophobic interaction provided by the aromatic unit itself, a suitably placed hydrogen bonding acceptor is necessary for effective antiviral activity. As for the 4-pyrimidyl derivatives **48**−**52**, the presence of the N-3 nitrogen apparently counteracts the hydrogen bonding acceptor capability of the N-1 nitrogen to such an extent as to render these compounds completely inactive against EV 71.

Compounds with unsatisfactory or poor water solubility such as **20**−**24** were acidified to form their corresponding hydrochloride salts **57**−**61**. The results of their antiviral activity and selectivity index calculated for RD, D551, and WI38 cell lines are outlined in Table 4. It is worth noting that when compared to their neutral parent compounds **20**, **21**, and **24**, compounds **57**−**59**, with lower lipophilicity and weaker ability to penetrate the cells, not only retained antiviral potency against EV 71 but also exhibited lower cytotoxicity. This suggests that the surface protein may be the target for this type of compound. This is consistent with the observation of our preliminary mechanistic studies in which inhibition of the virus replication at the early stages, referring to attachment or uncoating, by the test compounds **1** and **8** can be demonstrated by a time-course experiment.[39] In all cases examined, imidazolidinone **20** and its corresponding salt **57**, in terms of potency and selectivity index, appear to be the most promising candidates for further development as anti-EV-71 agents.

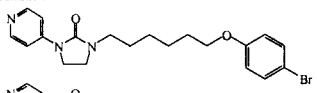
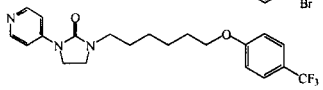
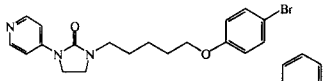
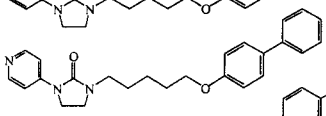
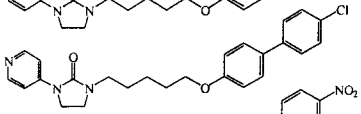
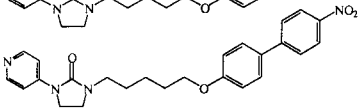
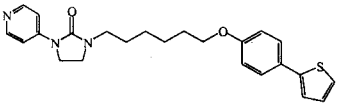
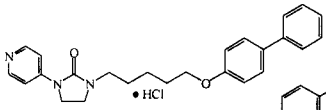
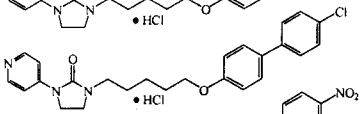
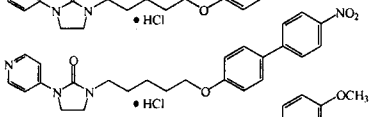
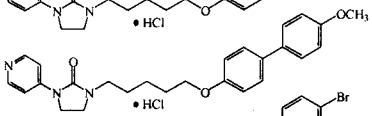
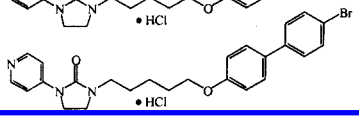
In summary, on the basis of the skeleton of Win compounds, the computer-assisted drug design has resulted in the discovery and experimental realization of a novel series of imidazolidinone derivatives showing significant anti-EV-71 activity. According to an SAR investigation, an aryl substituent at the para position and a pyridine-containing imidazolidinone ring are two key structural requirements for potency and selectivity. Some of the compounds described, such as **20**, **57**, **58**, and **61**, exhibit high antiviral potency and have an excellent selectivity index. Further SAR studies as well as pharmacokinetic and mechanistic studies on this class of compounds are currently under active investigation and will be reported in due course.

Experimental Section

A. Chemistry. For anhydrous reactions, glassware was dried overnight in an oven at 120 °C and cooled in a desiccator over anhydrous $CaSO_4$ or silica gel. Reagents were purchased from Aldrich, Sigma Chemical Co., and Life Technology. Solvents, including dry ether and tetrahydrofuran (THF), were obtained by distillation from the sodium ketyl of benzophenone under nitrogen. Other solvents, including chloroform, dichloromethane, ethyl acetate, and hexane were distilled over CaH_2 under nitrogen. Absolute methanol and ethanol were purchased from Merck and used as received.

Melting points were obtained with a Yanaco (MP-500D) melting point apparatus. Infrared (IR) spectra were recorded on a Perkin-Elmer (Spectrum RX1) spectrophotometer. The wavenumbers reported are referenced to the 1601 cm^{-1}

Table 4. Selectivity Index of Imidazolidinones with Potent Anti-EV-71 Activity

Compound	Structure	IC_{50} (μM)[a]	CC_{50} (μM)[a]			Selectivity Index		
		EV 71	RD[b]	D551[c]	WI38[d]	RD/ EV71	D551/ EV71	WI38/ EV71
1		0.35±0.018	>25	46±0.3	50±3.1	>71	148	161
8		0.58±0.002	>25	55±0.6	36±4.1	>43	108	71
11		0.50±0.010	>25	50±1.9	65±3.5	>50	100	130
20		0.04±0.001	>25	>50	>50	>625	>1250	>1250
21		0.06±0.001	6.25 ± 0.35	6±1.7	32±0.9	104	100	533
24		0.33±0.017	>25	66±4.2	70±3.3	>76	200	212
27		0.30±0.011	>25	46±1.1	60±1.8	>83	153	200
57		0.07±0.001	>25	>100	>100	>357	>1428	>1428
58		0.05±0.009	12.5 ± 0.47	13±0.7	48±2.1	250	260	960
59		0.59±0.017	>25	>100	>100	>42	>169	>169
60		0.34±0.078	>25	>100	>100	>74	>294	>294
61		0.14±0.004	>25	>100	>100	>179	>714	>714

[a] Mean of triplicate well values. All experiments were performed at least twice. Neutralization test was employed. [b] RD: human rhabdomyosarcoma cells. [c] D551: human normal skin fibroblast cells. [d] WI38: human normal lung fibroblast cells.

absorption of polystyrene. The proton NMR spectra were obtained on a Varian Mer-Vx-300 (300 MHz) spectrometer. Chloroform-*d* and dimethyl sulfoxide-d_6 were used as solvent; Me_4Si (δ 0.00 ppm) was used as an internal standard. All NMR chemical shifts are reported as δ values in parts per million (ppm), and coupling constants (J) are given in hertz (Hz). The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, unresolved multiplet due to the field strength of the instrument; and dd, doublet of doublet. Mass spectra were carried out on a Hewlett-Packard (model 1100 MSD) mass spectrometer. Microanalyses were performed on a Heraeus CHN−O rapid microanalyzer.

Purification on silica gel refers to flash column chromatography on Merck silica gel 60 (particle size 230−400 mesh). Analytical TLC was performed on precoated plates purchased from Merck (silica gel 60 F_{254}). Compounds were visualized by using UV light, I_2 vapor, or 2.5% phosphomolybdic acid in ethanol with heating.

A.1. General Procedure for the Synthesis of Compounds 3−6. 1-(4-Pyridyl)-2-imidazolidinone (3). To a solution of 4-aminopyridine (3.00 g, 31.9 mmol) in 15 mL of toluene cooled in an ice bath was added 2-chloroethyl isocyanate (5.31 g, 47.9 mmol) dropwise over 30 min. The mixture was stirred at room temperature for 5 h. The precipitate was collected by filtration and washed with toluene (10 mL) to afford *N*-(2-chloroethyl)-*N*′-(4-pyridyl)urea **2** (5.08 g, 80%).

N-(2-chloroethyl)-*N*′-(4-pyridyl)urea **2** (5.08 g, 0.26 mmol) was dissolved in a mixed solvent of dry tetrahydrofuran (20 mL) and dimethylformamide (20 mL) and cooled in an ice bath. NaH (60% dispersion in mineral oil, 1.07 g, 0.27 mmol) was then added slowly. The resulting mixture was stirred at room temperature for 2 h followed by addition of MeOH (10 mL) to quench the reaction. The solvent was removed under reduced pressure, and the crude residue thus obtained was extracted with chloroform (2 × 30 mL) and washed with brine (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting solid was recrystallized from MeOH to give compound **3** as a white solid (4.07 g, 98%). IR ν_{max} (KBr): 1709, 1483, 1266 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.44 (d, J = 5.4 Hz, 2H), 7.45 (d, J = 5.4 Hz, 2H), 3.91 (t, J = 7.2 Hz, 2H), 3.61 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 159.0, 150.2, 146.6, 111.1, 40.0, 37.1. ESMS m/z: 164.4 (MH^+).

1-(2-Chloro-4-pyridyl)-2-imidazolidinone (4). Yield: 72%. White solid. IR ν_{max} (KBr): 1714, 1592, 1476, 1261 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.20 (d, J = 6.6 Hz, 1H), 7.47 (d, J = 6.6 Hz, 1H), 7.46 (S, 1H), 3.90 (t, J = 7.2 Hz, 2H), 3.63 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 158.2, 152.3, 149.8, 148.7, 110.8, 110.2, 42.6, 37.0. ESMS m/z: 198.5 (MH^+).

1-(3-Pyridyl)-2-imidazolidinone (5). Yield: 76%. White solid. IR ν_{max} (KBr): 1706, 1476, 1264 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.58 (d, J = 2.7 Hz, 1H), 8.27 (dd, J = 4.5, 1.2 Hz, 1H), 8.15 (ddd, J = 8.7, 2.7, 1.2 Hz, 1H), 7.25 (dd, J = 8.7, 4.5 Hz, 1H), 7.12 (br, 1H), 3.95 (t, J = 7.2 Hz, 2H), 3.60 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 159.7, 143.5, 138.5, 136.7, 124.9, 123.3, 44.4, 37.5. ESMS m/z: 164.1 (MH^+).

1-(4-Pyrimidinyl)-2-imidazolidinone (6). Yield: 78%. White solid. IR ν_{max} (KBr): 1693, 1495, 1277 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.82 (s, 1H), 8.44 (d, J = 6.3 Hz, 1H), 8.21 (d, J = 6.3 Hz, 1H), 5.45 (br, 1H), 4.15 (t, J = 8.1 Hz, 2H), 3.60 (t, J = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 158.1, 157.6, 156.2, 109.0, 43.2, 37.2. ESMS m/z: 165.2 (MH^+).

A.2. General Procedure for the Synthesis of 1 and 8−35. 1-[6-(4-Bromophenoxy)hexyl]-3-(4-pyridyl)-2-imidazolidinone (1). To a solution of 1-(4-pyridyl)-2-imidazolidinone (0.10 g, 0.62 mmol) in 10 mL of dimethylformamide was added NaH (60% dispersion in mineral oil, 27.2 mg, 0.68 mmol) in one portion at 0 °C. The resulting mixture was stirred at room temperature for an additional 30 min and then cooled in an ice bath. 1-Bromo-6-(4-bromophenoxy)hexane (0.21 g, 0.62 mmol) was added, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with MeOH (3 mL), and the solvent was pumped off. Saturated NH_4Cl aqueous solution (5 mL) and dichloromethane (20 mL) were added to the residue. The dichloromethane layer was separated and dried over $MgSO_4$, filtered, and evaporated to give the crude residue, which was subjected to purification by flash chromatography on silica gel (EA/MeOH = 10:1) to give compound **1** as a white solid (0.25 g, 96%). IR ν_{max} (KBr): 1708, 1594, 1500, 1269 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J = 6.3 Hz, 2H), 7.45 (d, J = 6.3 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 3.89 (t, J = 6.3 Hz, 2H), 3.78 (t, J = 9.0 Hz, 2H), 3.51 (t, J = 9.0 Hz, 2H), 3.30 (t, J = 7.5 Hz, 2H), 1.78−1.71 (m, 2H), 1.64−1.38 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 158.2, 156.8, 150.3, 147.0, 132.2, 116.3, 112.7, 110.8, 68.0, 43.7, 41.4, 41.3, 29.0, 27.3, 26.4, 25.7. ESMS m/z: 418.4 (MH^+). Anal. ($C_{20}H_{24}BrN_3O_2$) C, H, N.

1-(4-Pyridyl)-3-{6-[4-(trifluoromethyl) phenoxy]hexyl}-2-imidazolidinone (8). Yield: 89%. White solid. IR ν_{max} (KBr): 1709, 1593, 1328, 1110 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J = 6.3 Hz, 2H), 7.49 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 6.3 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 3.97 (t, J = 6.6 Hz, 2H), 3.79 (t, J = 7.2 Hz, 2H), 3.51 (t, J = 7.2 Hz, 2H), 3.31 (t, J = 7.2 Hz, 2H), 1.82−1.75 (m, 2H), 1.64−1.37 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 161.5, 156.8, 150.3, 147.0, 126.9, 126.8, 114.4, 110.8, 68.0, 43.7, 41.4, 41.3, 28.9, 27.3, 26.4, 25.7. ESMS m/z: 408.5 (MH^+). Anal. ($C_{21}H_{24}F_3N_3O_2$) C, H, N.

1-(4-Pyridyl)-3-{5-[4-(trifluoromethyl)phenoxy]pentyl}-2-imidazolidinone (9). Yield: 91%. White solid. IR ν_{max} (KBr): 1711, 1594, 1329, 1259, 1110 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J = 6.3 Hz, 2H), 7.52−7.49 (m, 4H), 6.90 (d, J = 8.7 Hz, 2H), 3.98 (t, J = 6.0 Hz, 2H), 3.80 (t, J = 7.4 Hz, 2H), 3.55 (t, J = 7.4 Hz, 2H), 3.34 (t, J = 6.6 Hz, 2H), 1.86−1.79 (m, 2H), 1.67−1.48 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 161.4, 156.6, 149.0, 147.8, 126.9, 114.4, 111.0, 67.8, 43.7, 41.1, 29.7, 28.7, 27.0, 23.2. ESMS m/z: 394.1 (MH^+). Anal. ($C_{20}H_{22}F_3N_3O_2$) H, N; C: calcd, 61.06; found, 60.43.

1-(4-Pyridyl)-3-{7-[4-(trifluoromethyl)phenoxy]heptyl}-2-imidazolidinone (10). Yield: 92%. Yellow solid. IR ν_{max} (KBr): 1713, 1593, 1329, 1260, 1110 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.41 (d, J = 6.3 Hz, 2H), 7.59 (d, J = 6.3 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 3.96 (t, J = 6.3 Hz, 2H), 3.84 (t, J = 7.4 Hz, 2H), 3.55 (t, J = 7.4 Hz, 2H), 3.31 (t, J = 7.2 Hz, 2H), 1.80−1.73 (m, 2H), 1.60−1.36 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 161.5, 156.2, 148.8, 147.4, 126.9, 114.4, 111.1, 68.8, 43.9, 41.5, 41.3, 29.0, 27.2, 26.6, 25.9. ESMS m/z: 422.2 (MH^+). Anal. ($C_{22}H_{26}F_3N_3O_2$) C, H, N.

1-[5-(4-Bromophenoxy)pentyl]-3-(4-pyridyl)-2-imidazolidinone (11). Yield: 95%. White solid. IR ν_{max} (KBr): 1701, 1598, 1474, 1248 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.41 (d, J = 5.7 Hz, 2H), 7.72 (d, J = 5.7 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 9.0 Hz, 2H), 3.91 (d, J = 6.0 Hz, 2H), 3.84 (d, J = 7.5 Hz, 2H), 3.55 (d, J = 7.5 Hz, 2H), 3.36 (t, J = 7.2 Hz, 2H), 1.84−1.79 (m, 2H), 1.68−1.60 (m, 2H), 1.53−1.47 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 158.0, 156.7, 150.0, 146.9, 132.1, 116.2, 112.6, 110.7, 67.7, 43.6, 41.3, 41.2, 28.6, 27.0, 23.1. ESMS m/z: 404.4 (MH^+). Anal. ($C_{19}H_{22}BrN_3O_2$) C, H, N.

1-[7-(4-Bromophenoxy)heptyl]-3-(4-pyridyl)-2-imidazolidinone (12). Yield: 88%. White solid. IR ν_{max} (KBr): 1698, 1598, 1480, 1243 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.41 (d, J = 5.7 Hz, 2H), 7.46 (d, J = 5.7 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 3.88 (t, J = 6.3 Hz, 2H), 3.77 (t, J = 7.5 Hz, 2H), 3.50 (t, J = 7.5 Hz, 2H), 3.28 (t, J = 7.2 Hz, 2H), 1.79−1.68 (m, 2H), 1.60−1.55 (m, 2H), 1.50−1.24 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 158.2, 156.7, 149.9, 147.2, 132.2, 116.2, 112.6, 110.8, 68.2, 43.8, 41.3, 29.0, 28.9, 27.2, 26.6, 25.9. ESMS m/z: 432.5 (MH^+). Anal. ($C_{21}H_{26}BrN_3O_2$) C, H, N.

1-[5-(4-Chlorophenoxy)pentyl]-3-(4-pyridyl)-2-imidazolidinone (13). Yield: 93%. Yellow solid. IR ν_{max} (KBr): 1699, 1595, 1480, 1252 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.41 (d, J = 6.3 Hz, 2H), 7.46 (d, J = 6.3 Hz, 2H), 7.18 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 3.90 (t, J = 6.3 Hz, 2H), 3.77 (t, J = 9.0 Hz, 2H), 3.51 (t, J = 9.0 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H), 1.84−1.75 (m, 2H), 1.64−1.53 (m, 2H), 1.52−1.46 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 157.5, 156.7, 149.9, 147.1, 129.2, 125.4, 115.7, 110.8, 67.8, 43.6, 41.4, 41.6, 28.7, 27.0, 23.2. ESMS m/z: 360.4 (MH^+). Anal. ($C_{19}H_{22}ClN_3O_2$) C, H, N.

1-[6-(4-Chlorophenoxy)hexyl]-3-(4-pyridyl)-2-imidazolidinone (14). Yield: 94%. White solid. IR ν_{max} (KBr): 1699, 1480, 1252 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J = 5.7 Hz, 2H), 7.51 (d, J = 5.7 Hz, 2H), 7.18 (d, J = 6.6 Hz, 2H), 6.78 (d, J = 6.6 Hz, 2H), 3.90 (t, J = 6.3 Hz, 2H), 3.80 (t, J = 7.5 Hz, 2H), 3.53 (t, J = 7.5 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 1.81−1.71 (m, 2H), 1.63−1.35 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 157.6, 156.5, 148.9, 147.8, 129.3, 125.4, 115.7, 110.9, 68.4, 43.8, 41.4, 41.3, 29.2, 27.2, 26.4, 25.7. ESMS m/z: 374.5 (MH^+). Anal. ($C_{20}H_{24}ClN_3O_2$) C, H, N.

1-[7-(4-Chlorophenoxy)heptyl]-3-(4-pyridyl)-2-imidazolidinone (15). Yield: 84%. White solid. IR ν_{max} (KBr): 170, 1600, 1479, 1243 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.40 (d, J = 6.6 Hz, 2H), 7.46 (d, J = 6.6 Hz, 2H), 7.18 (d, J = 6.9 Hz, 2H), 6.77 (d, J = 6.9 Hz, 2H), 3.87 (t, J = 6.3 Hz, 2H), 3.76 (t, J = 7.2 Hz, 2H), 3.49 (t, J = 7.2 Hz, 2H), 3.27 (t, J = 7.2 Hz, 2H), 1.76−1.71 (m, 2H), 1.57−1.52 (m, 2H), 1.43−1.35 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 157.6, 156.5, 149.8, 147.2, 129.2, 125.2, 115.7, 110.8, 68.1, 43.7, 41.3, 29.0, 28.9, 27.2, 26.6, 25.8. ESMS m/z: 388.3 (MH^+). Anal. ($C_{21}H_{26}ClN_3O_2$) C, H, N.

1-[6-(4-Fluorophenoxy)hexyl]-3-(4-pyridyl)-2-imidazolidinone (16). Yield: 90%. White solid. IR ν_{max} (KBr): 1707, 1595, 1505, 1268 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J = 6.0 Hz, 2H), 7.46 (d, J = 6.0 Hz, 2H), 6.96−6.90 (m, 2H), 6.81−6.77 (m, 2H), 3.89 (t, J = 6.3 Hz, 2H), 3.79 (t, J = 7.2 Hz, 2H), 3.51 (t, J = 7.2 Hz, 2H), 3.30 (t, J = 6.9 Hz, 2H), 1.78−1.73 (m, 2H), 1.61−1.23 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 158.7, 156.8, 150.3, 147.0, 115.9, 115.6, 115.3, 110.8, 68.4, 43.7, 41.4, 41.3, 29.1, 27.3, 26.4, 25.7. ESMS m/z: 358.4 (MH^+). Anal. ($C_{20}H_{24}FN_3O_2$) C, H, N.

1-[6-(4-Methylphenoxy)hexyl]-3-(4-pyridyl)-2-imidazolidinone (17). Yield: 93%. White solid. IR ν_{max} (KBr): 1713, 1593, 1509, 1269 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J = 6.3 Hz, 2H), 7.45 (d, J = 6.3 Hz, 2H), 7.04 (d, J = 8.1 Hz, 2H), 6.76 (d, J = 8.1 Hz, 2H), 3.91 (t, J = 6.3 Hz, 2H), 3.78 (t, J = 10.2 Hz, 2H), 3.51 (t, J = 10.2 Hz, 2H), 3.30 (t, J = 7.5 Hz, 2H), 2.26 (s, 3H), 1.78−1.30 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 156.9, 156.8, 150.3, 147.0, 129.9, 129.8, 114.4, 110.9, 67.8, 43.8, 41.4, 27.3, 26.5, 25.8, 23.8. ESMS m/z: 354.5 (MH^+). Anal. ($C_{21}H_{27}N_3O_2$) C, H, N.

1-[6-(4-Methoxyphenoxy)hexyl]-3-(4-pyridyl)-2-imidazolidinone (18). Yield: 94%. White solid. IR ν_{max} (KBr): 1711, 1594, 1508, 1231 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.41 (d, J = 5.7 Hz, 2H), 7.48 (d, J = 5.7 Hz, 2H), 6.79 (s, 4H), 3.87 (t, J = 6.3 Hz, 2H), 3.78 (t, J = 7.2 Hz, 2H), 3.73 (s, 3H), 3.51 (t, J = 7.2 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 1.79−1.70 (m, 2H), 1.63−1.23 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 156.8, 153.7, 153.2, 150.1, 147.4, 115.4, 114.6, 110.9, 68.4, 55.7, 43.8, 41.3, 29.2, 27.3, 26.5, 25.8. ESMS m/z: 370.2 (MH^+). Anal. ($C_{21}H_{27}N_3O_3$) C, H, N.

1-{(6-[4-(Methylsulfanyl)phenoxy]hexyl}-3-(4-pyridyl)-2-imidazolidinone (19). Yield: 88%. White solid. IR ν_{max} (KBr): 1698, 1600, 1495, 1252 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.40 (d, J = 6.6 Hz, 2H), 7.50 (d, J = 6.6 Hz, 2H), 7.21 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 3.90 (t, J = 6.3 Hz, 2H), 3.79 (t, J = 7.4 Hz, 2H), 3.51 (t, J = 7.4 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 2.41 (s, 3H), 1.80−1.71 (m, 2H), 1.63−1.34 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 157.6, 156.5, 148.9, 147.7, 130.1, 128.6, 115.2, 110.9, 67.9, 43.7, 41.4, 41.3, 29.1, 27.2, 26.4, 25.7, 18.0. ESMS *m*/*z*: 386.5 (MH^+).

1-[5-(Biphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one (20). Yield: 88%. White solid. IR ν_{max} (KBr): 1701, 1628, 1474, 1268 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.43 (br, 2H), 7.54−7.47 (m, 6H), 7.39 (t, J = 7.2 Hz, 2H), 7.29 (d, J = 7.2 Hz, 1H), 6.93 (d, J = 7.2 Hz, 2H), 4.00 (t, J = 6.3 Hz, 2H), 3.79 (t, J = 7.2 Hz, 2H), 3.53 (t, J = 7.2 Hz, 2H), 3.34 (t, J = 6.9 Hz, 2H), 1.89−1.80 (m, 2H), 1.70−1.50 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 158.6, 156.8, 149.9, 147.2, 140.8, 133.7, 128.7, 128.1, 126.7, 114.8, 110.9, 67.7, 43.8, 41.5, 41.4, 28.9, 27.1, 23.3. ESMS *m*/*z*: 402.5 (MH^+). Anal. ($C_{25}H_{27}N_3O_2$) C, H, N.

1-[5-(4′-Chlorobiphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one (21). Yield: 92%. White solid. IR ν_{max} (KBr): 1702, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.41 (d, J = 5.7 Hz, 2H), 7.60 (d, J = 5.7 Hz, 2H), 7.44 (dd, J = 8.7, 1.5 Hz, 4H), 7.34 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 3.99 (t, J = 6.3 Hz, 2H), 3.85 (t, J = 7.2 Hz, 2H), 3.57 (t, J = 7.2 Hz, 2H), 3.35 (t, J = 6.9 Hz, 2H), 1.89−1.80 (m, 2H), 1.72−1.51 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 158.7, 156.2, 148.9, 147.2, 139.2, 132.7, 132.5, 128.8, 128.0, 127.9, 114.8, 111.0, 67.6, 43.8, 41.4, 41.3, 28.8, 27.0 23.3. ESMS *m*/*z*: 436.1 (MH^+). Anal. ($C_{25}H_{26}ClN_3O_2$) C, H, N.

1-[5-(4′-Bromobiphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one (22). Yield: 91%. White solid. IR ν_{max} (KBr): 1706 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.43 (br, 2H), 7.50 (d, J = 8.4 Hz, 4H), 7.44 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 3.99 (t, J = 6.3 Hz, 2H), 3.81 (t, J = 7.2 Hz, 2H), 3.55 (t, J = 7.2 Hz, 2H), 3.34 (t, J = 6.3 Hz, 2H), 1.93−1.80 (m, 2H), 1.70−1.49 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 158.8, 156.6, 149.3, 147.6, 139.4, 132.8, 132.4, 131.8, 128.2, 128.0, 120.8, 114.8, 110.9, 67.7, 43.7, 41.4, 28.8, 27.1, 23.3. ESMS *m*/*z*: 480.5 (MH^+). Anal. ($C_{25}H_{26}BrN_3O_2$) C, H, N.

1-[5-(4′-Methoxybiphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one (23). Yield: 91%. White solid. IR ν_{max} (KBr): 1711, 1606, 1501, 1273 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.43 (br, 2H), 7.54 (d, J = 5.1 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 6.92 (t, J = 8.7 Hz, 4H), 3.99 (t, J = 6.0 Hz, 2H), 3.82 (t, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.55 (t, J = 7.2 Hz, 2H), 3.35 (t, J = 7.2 Hz, 2H), 1.87−1.52 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 158.7, 158.1, 156.4, 148.2, 133.4, 127.7, 114.7, 114.2, 67.6, 55.3, 43.8, 41.4, 41.3, 28.9, 27.0, 23.3. ESMS *m*/*z*: 432.5 (MH^+). Anal. ($C_{26}H_{29}N_3O_3$) C, H, N.

1-[5-(4′-Nitrobiphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one (24). Yield: 86%. Yellow solid. IR ν_{max} (KBr): 1708, 1594, 1512, 1342, 1253 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.43 (br, 2H), 8.24 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 5.1 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 4.00 (t, J = 6.3 Hz, 2H), 3.80 (t, J = 8.6 Hz, 2H), 3.54 (t, J = 8.6 Hz, 2H), 3.34 (t, J = 6.9 Hz, 2H), 1.88−1.83 (m, 2H), 1.68−1.53 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 159.8, 156.8, 149.9, 147.2, 147.1, 146.5, 130.9, 128.5, 127.0, 124.1, 115.1, 110.9, 67.8, 43.7, 41.4, 41.3, 28.8, 27.0, 23.3. ESMS *m*/*z*: 447.5 (MH^+). Anal. ($C_{25}H_{26}N_4O_4$) C, H, N.

4′-[5-(2-Oxo-3-pyridin-4-yl-imidazolidin-1-yl)pentyloxy]-biphenyl-4-carbonitrile (25). Yield: 92%. White solid. IR ν_{max} (KBr): 1704, 1601, 1494, 1267 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.44 (br, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 4H), 6.95 (d, J = 8.4 Hz, 2H), 4.00 (t, J = 6.0 Hz, 2H), 3.82 (t, J = 7.2 Hz, 2H), 3.54 (t, J = 7.2 Hz, 2H), 3.35 (t, J = 6.9 Hz, 2H), 1.90−1.83 (m, 2H), 1.69−1.51 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 159.6, 156.7, 149.4, 147.4, 145.2, 132.6, 131.4, 128.3, 127.1, 119.1,1 115.1, 111.1, 110.0, 67.8, 43.7, 41.4, 28.8, 27.1, 23.3. ESMS *m*/*z*: 427.5 (MH^+).

1-(4-Pyridyl)-3-{5-[4-(2-thienyl)phenoxy]pentyl}-2-imidazolidinone (26). Yield: 84%. White solid. IR ν_{max} (KBr): 1709, 1589, 1501, 1255 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J = 4.8 Hz, 2H), 7.51−7.46 (m, 4H), 7.24−7.16 (m, 2H), 7.02 (dd, J = 5.1, 3.6 Hz, 1H), 6.86 (d, J = 6.6 Hz, 2H), 3.97 (t, J = 6.3 Hz, 2H), 3.79 (t, J = 8.9 Hz, 2H), 3.52 (t, J = 8.9 Hz, 2H), 3.33 (t, J = 6.9 Hz, 2H), 1.86−1.77 (m, 2H), 1.65−1.50 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 158.6, 156.8, 150.3, 150.1, 147.1, 144.3, 127.9, 127.2, 123.8, 122.0, 114.8, 110.9, 67.7, 43.7, 41.4, 41.3, 28.8, 27.1, 23.3. ESMS *m*/*z*: 408.4 (MH^+).

1-(4-Pyridyl)-3-{6-[4-(2-thienyl)phenoxy]hexyl}-2-imidazolidinone (27). Yield: 88%. Yellow solid. IR ν_{max} (KBr): 1706, 1608, 1522, 1404 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.41 (d, J = 6.6 Hz, 2H), 7.50−7.45 (m, 4H), 7.19−7.15 (m, 2H), 7.02 (dd, J = 5.1, 3.9 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 3.96 (t, J = 6.3 Hz, 2H), 3.77 (t, J = 7.5 Hz, 2H), 3.50 (t, J = 7.5 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 1.81−1.75 (m, 2H), 1.59−1.39 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 158.6, 156.7, 150.0, 147.2, 144.3, 127.9, 127.2, 123.8, 122.0, 114.8, 110.9, 67.8, 43.7, 41.3, 29.1, 27.3, 26.4, 25.7. ESMS *m*/*z*: 422.5 (MH^+).

1-{5-[4-(3-Furyl)phenoxy]pentyl}-3-(4-pyridyl)-2-imidazolidinone (28). Yield: 87%. Yellow solid. IR ν_{max} (KBr): 1702, 1592, 1480, 1271 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.39 (d, J = 6.3 Hz, 2H), 7.60 (dd, J = 1.5, 0.9 Hz, 1H), 7.46 (d, J = 6.3 Hz, 2H), 7.41 (t, J = 1.5 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.01 (dd, J = 1.5, 0.9 Hz, 1H), 3.94 (t, J = 6.3 Hz, 2H), 3.75 (t, J = 7.5 Hz, 2H), 3.49 (t, J = 7.5 Hz, 2H), 3.30 (t, J = 6.9 Hz, 2H), 1.83−1.75 (m, 2H), 1.65−1.46 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 158.1, 156.7, 149.8, 147.1, 143.4, 138.1, 137.5, 126.9, 126.0, 124.9 114.7, 110.8, 108.7, 67.6,43.6, 41.3, 28.8, 27.0, 23.2. ESMS *m*/*z*: 392.4 (MH^+).

4-{6-[2-Oxo-3-(4-pyridyl)-1-imidazolidinyl]hexyl}oxy)-benzonitrile (29). Yield: 88%. White solid. IR ν_{max} (KBr): 1697, 1605, 1511, 1427, 1269 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J = 6.6 Hz, 2H), 7.54 (d, J = 9.0 Hz, 2H), 7.50 (d, J = 6.6 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.97 (t, J = 6.3 Hz, 2H), 3.81 (t, J = 7.5 Hz, 2H), 3.53 (t, J = 7.5 Hz, 2H), 3.31 (t, J = 7.2 Hz, 2H), 1.84−1.75 (m, 2H), 1.64−1.36 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 162.3, 156.6, 149.2, 147.6, 133.9, 119.2, 115.4, 110.9, 103.8, 68.1, 43.7, 41.4, 41.3, 28.9, 27.2, 26.4, 25.6. ESMS *m*/*z*: 365.1 (MH^+).

1-[6-(3-Bromophenoxy)hexyl]-3-(4-pyridyl)-2-imidazolidinone (30). Yield: 95%. White solid. IR ν_{max} (KBr): 1712, 1592, 1479, 1269 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.42 (d, J = 6.3 Hz, 2H), 7.46 (d, J = 6.3 Hz, 2H), 7.12−7.01 (m, 3H), 6.78 (d, J = 8.1 Hz, 1H), 3.91 (t, J = 6.3 Hz, 2H), 3.79 (t, J = 7.7 Hz, 2H), 3.52 (t, J = 7.7 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 1.81−1.72 (m, 2H), 1.64−1.36 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 159.8, 156.8, 150.2, 147.0, 130.5, 123.6, 122.7, 117.7, 113.5, 110.8, 67.9, 43.7, 41.2, 28.9, 27.2, 26.4, 25.7. ESMS *m*/*z*: 418.2 (MH^+). Anal. ($C_{20}H_{24}BrN_3O_2$) C, H, N.

1-{6-[3-(Dimethylamino)phenoxy]hexyl}-3-(4-pyridyl)-2-imidazolidinone (31). Yield: 82%. White solid. IR ν_{max} (KBr): 1709, 1595, 1479, 1426, 1268 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.41 (d, J = 6.0 Hz, 2H), 7.47 (d, J = 6.0 Hz, 2H), 7.09 (t, J = 8.7 Hz, 1H), 6.31 (d, J = 8.7 Hz, 1H), 6.25−6.23 (m,2H), 3.92 (t, J = 6.3 Hz, 2H), 3.77 (t, J = 7.2 Hz, 2H), 3.50 (t, J = 7.2 Hz, 2H), 3.27 (t, J = 6.9 Hz, 2H), 2.90 (s, 6H), 1.78−1.61 (m, 2H), 1.61−1.38 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 160.1, 156.7, 152.0,149.9, 147.2, 129.7, 110.9, 105.7, 102.0, 99.7, 67.5, 43.8, 41.3, 40.5, 29.2, 27.3, 26.5, 25.8. ESMS *m*/*z*: 383.5 (MH^+). Anal. ($C_{22}H_{30}N_4O_2$) C, H, N.

1-[6-(2,6-Dichlorophenoxy)hexyl]-3-(4-pyridyl)-2-imidazolidinone (32). Yield: 91%. Yellow solid. IR ν_{max} (KBr): 1713, 1595, 1439, 1269 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.41 (br, 2H), 7.50 (d, J = 5.7 Hz, 2H), 7.25 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 6.95 (t, J = 8.1 Hz, 1H), 3.99 (t, J = 6.3 Hz, 2H), 3.80 (t, J = 7.5 Hz, 2H), 3.54 (t, J = 7.5 Hz, 2H), 3.32 (t, J = 7.2 Hz, 2H), 1.86−1.81 (m, 2H), 1.64−1.43 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 156.6, 151.7, 149.2, 147.7, 129.5, 128.9, 124.9, 110.9, 73.4, 43.8, 41.3, 29.9, 27.2, 26.5, 25.6. ESMS *m*/*z*: 408.1 (MH^+). Anal. ($C_{20}H_{23}Cl_2N_3O_2$) C, H, N.

1-[6-(2-Chloro-4-methoxyphenoxy)hexyl]-3-(4-pyridyl)-2-imidazolidinone (33). Yield: 93%. White solid. IR ν_{max} (KBr): 1712, 1591, 1499, 1281 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.33 (d, J = 5.1 Hz, 2H), 7.37 (d, J = 5.1 Hz, 2H), 6.83 (d, J = 3.0

Hz, 1H), 6.75 (d, J = 9.0 Hz, 1H), 6.63 (dd, J = 9.0, 3.0 Hz, 1H), 3.86 (t, J = 6.3 Hz, 2H), 3.69−3.63 (m, 5H), 3.41 (t, J = 7.0 Hz, 2H), 3.21 (t, J = 7.2 Hz, 2H), 1.76−1.67 (m, 2H), 1.56−1.41 (m, 4H), 1.37−1.29 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 156.5, 153.6, 149.8, 148.6, 146.8, 123.4, 115.7, 114.8, 112.6, 110.6, 69.7, 55.6, 43.4, 41.4, 28.9, 27.0, 26.2, 25.5. ESMS m/z: 404.1 (MH^+). Anal. ($C_{21}H_{26}ClN_3O_3$) C, H, N.

1-[6-(1-Naphthyloxy)hexyl]-3-(4-pyridyl)-2-imidazolidinone (34). Yield: 88%. Yellow solid. IR ν_{max} (KBr): 1713, 1594, 1427, 1270 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.39 (d, J = 6.0 Hz, 2H), 8.26−8.21 (m, 1H), 7.78−7.74 (m, 1H), 7.45−7.29 (m, 6H), 6.75 (dd, J = 7.2, 0.9 Hz, 1H), 4.10 (t, J = 6.3 Hz, 2H), 3.67 (t, J = 7.1 Hz, 2H), 3.43 (t, J = 7.1 Hz, 2H), 3.29 (t, J = 7.2 Hz, 2H), 1.95−1.86 (m, 2H), 1.65−1.54 (m, 4H), 1.48−1.40 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 156.5, 154.7, 149.2, 147.4, 134.4, 127.4, 126.2, 125.9, 125.6, 125.0, 121.9, 120.0, 110.8, 104.5, 67.8, 43.7, 41.2, 29.1, 27.2, 26.4, 25.9. ESMS m/z: 390.5 (MH^+). Anal. ($C_{24}H_{27}N_3O_2$) H, N; C: calcd, 74.01; found, 73.20.

1-(4-Pyridyl)-3-[6-(8-quinolyloxy)hexyl]-2-imidazolidinone (35). Yield: 89%. Yellow solid. IR ν_{max} (KBr): 1716, 1598, 1428 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.90 (dd, J = 4.2, 1.8 Hz, 1H), 8.40 (d, J = 4.2 Hz, 2H), 8.09 (dd, J = 8.4, 1.8 Hz, 1H), 7.45−7.32 (m, 5H), 7.01 (dd, J = 7.5, 1.2 Hz, 1H), 4.21 (t, J = 6.6 Hz, 2H), 3.75 (t, J = 7.2 Hz. 2H), 3.48 (t, J = 7.2 Hz, 2H), 3.29 (t, J = 6.9 Hz, 2H), 2.06−1.97 (m, 4H), 1.64−1.40 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 156.7, 154.8, 149.6, 149.2, 147.4, 136.0, 129.5, 126.7, 121.5, 119.4, 111.2, 110.9, 108.7, 68.8, 43.7, 41.3, 28.9, 27.2, 26.5, 25.8. ESMS m/z: 391.2 (MH^+).

A.3. General Procedure for the Synthesis of 36−39. 1-[6-(4-Bromophenoxy)hexyl]-3-(2-chloro-4-pyridyl)-2-imidazolidinone (36). To a solution of 1-(2-chloro-4-pyridyl)-2-imidazolidinone **4** (0.11 g, 0.55 mmol) dissolved in 10 mL of dimethylformamide cooled in ice bath was added NaH (75% dispersion in mineral oil, 26.6 mg, 0.83 mmol) in one portion. The mixture was stirred at room temperature for 30 min and then was cooled in ice bath. 1-Bromo-6-(4-bromophenoxy)-hexane (0.18 g, 0.55 mmol) was added, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with MeOH, and the solvents were pumped off. Saturated NH_4Cl aqueous solution (5 mL) and dichloromethane (10 mL) were added to the residue. The dichloromethane layer was dried over $MgSO_4$, filtered, evaporated, and purified by column chromatography to give **36** as a yellow solid (0.23 g, 92%). IR ν_{max} (KBr): 1714, 1590, 1488, 1245 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.18 (d, J = 5.7 Hz, 1H), 7.48 (dd, J = 5.4, 1.8 Hz, 1H), 7.43 (d, J = 1.8 Hz, 1H), 7.32 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 9.0 Hz, 2H), 3.89 (t, J = 6.3 Hz, 2H), 3.77 (t, J = 7.2 Hz, 2H), 3.52 (t, J = 7.2 Hz, 2H), 3.30 (t, J = 6.9 Hz, 2H), 1.81−1.71 (m, 2H), 1.61−1.35 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 158.1, 156.2, 152.0, 149.5, 149.0, 132.1, 116.2, 112.6, 110.3, 109.8, 67.9, 43.7, 41.4, 41.2, 28.9, 27.1, 26.4, 25.6. ESMS m/z: 452.0 (MH^+). Anal. ($C_{20}H_{23}BrClN_3O_2$) C, H, N.

1-(2-Chloro-4-pyridyl)-3-{6-[4-(trifluoromethyl)phenoxy]hexyl}-2-imidazolidinone (37). Yield: 88%. White solid. IR ν_{max} (KBr): 1719, 1593, 1477, 1257 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.14 (d, J = 5.4 Hz, 1H), 7.50−7.41 (m, 4H), 6.89 (d, J = 8.4 Hz, 2H), 3.95 (t, J = 6.3 Hz, 2H), 3.74 (t, J = 8.4 Hz, 2H), 3.50 (t, J = 8.4 Hz, 2H), 3.28 (t, J = 6.9 Hz, 2H), 1.80−1.60 (m, 2H), 1.57−1.37 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 161.4, 156.2, 152.0, 149.5, 149.1, 126.8, 126.7, 114.3, 110.3, 109.7, 67.9, 43.6, 41.4, 41.2, 28.9, 27.1, 26.3, 25.6. ESMS m/z: 442.5 (MH^+). Anal. ($C_{21}H_{23}ClF_3N_3O_2$) C, H; N: calcd, 9.51; found, 9.04.

1-[5-(4-Bromophenoxy)pentyl]-3-(2-chloro-4-pyridyl)-2-imidazolidinone (38). Yield: 91%. Yellow solid. IR ν_{max} (KBr): 1707, 1597, 1479 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.19 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H), 7.46 (s, 1H), 7.33 (d, J = 9.0, 2H), 6.73 (d, J = 9.0 Hz, 2H), 3.91 (t, J = 6.3 Hz, 2H), 3.78 (t, J = 7.2 Hz, 2H), 3.53 (t, J = 7.2 Hz, 2H), 3.32 (t, J = 6.9 Hz, 2H), 1.83−1.76 (m, 2H), 1.66−1.49 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 158.5, 156.6, 149.7, 132.7, 116.7, 113.2, 110.9, 110.3, 68.2, 44.2, 41.9, 41.7, 30.1, 29.2, 27.4. ESMS m/z: 438.0 (MH^+).

1-(2-Chloro-4-pyridyl)-3-{6-[4-(methylsulfanyl)phenoxy]hexyl}-2-imidazolidinone (39). Yield: 86%. Yellow solid. IR ν_{max} (KBr): 1714, 1590, 1493, 1243 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.18 (d, J = 6.0 Hz, 1H), 7.49−7.47 (m, 2H), 7.23 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 3.92 (t, J = 6.3 Hz, 2H), 3.77 (t, J = 8.4 Hz, 2H), 3.53 (t, J = 8.4 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 2.42 (s, 3H), 1.81−1.72 (m, 2H), 1.64−1.38 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 157.9, 156.5, 152.1, 149.6, 149.5, 130.4, 128.9, 115.4, 110.6, 110.1, 68.1, 44.0, 41.7, 41.5, 29.3, 27.4, 26.6, 25.9, 18.3. ESMS m/z: 420.4 (MH^+). Anal. ($C_{21}H_{26}ClN_3O_2S$) C, H; N: calcd, 10.01; found, 9.59.

A.4. General Procedure for the Synthesis of 40−47. 1-[5-(4-Chlorophenoxy)pentyl]-3-(3-pyridyl)-2-imidazolidinone (40). To a solution of 1-(3-pyridyl)-2-imidazolidinone (73.4 mg, 0.45 mmol) in 10 mL of dimethylformamide was added NaH (75% dispersion in mineral oil, 21.8 mg, 0.68 mmol) in one portion at 0 °C. The mixture was stirred at room temperature for 30 min and then was cooled in ice bath. 1-[(5-Bromopentyl)oxy]-4-chlorobenzene (124.9 mg, 0.45 mmol) was added, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with MeOH (2 mL), and the solvent was concentrated in vacuo. Saturated NH_4Cl aqueous solution (5 mL) and dichloromethane (15 mL) were added to the residue. The dichloromethane layer was separated and dried over $MgSO_4$, filtered, evaporated, and purified by flash chromatography (MeOH/EtOAc = 1:10) to give compound **40** as a white solid (136.2 mg, 84%). IR ν_{max} (KBr): 1710, 1488, 1431, 1245 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.56 (bs, 1H), 8.21 (bs, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.20−7.11 (m, 1H), 7.15 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 9.0 Hz, 2H), 3.85 (t, J = 6.3 Hz, 2H), 3.74 (t, J = 7.2 Hz, 2H), 3.45 (t, J = 7.2 Hz, 2H), 3.25 (t, J = 6.9 Hz, 2H), 1.80−1.71 (m, 2H), 1.60−1.42 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 157.5, 157.4, 143.0, 137.9, 137.1, 129.1, 125.1, 124.2, 123.2, 115.6, 67.8, 43.6, 41.6, 41.5, 28.6, 27.0, 22.5. ESMS m/z: 360.4 (MH^+). Anal. ($C_{19}H_{22}ClN_3O_2$) C, H, N.

1-[6-(4-Chlorophenoxy)hexyl]-3-(3-pyridyl)-2-imidazolidinone (41). Yield: 85%. Yellow solid. IR ν_{max} (KBr): 1703, 1492, 1433, 1244 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.56 (s, 1H), 8.25 (d, J = 4.2 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.26−7.21 (m, 1H), 7.18 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 3.89 (t, J = 6.3 Hz, 2H), 3.82 (t, J = 7.4 Hz, 2H), 3.52 (t, J = 7.4 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 1.80−1.71 (m, 2H), 1.61−1.36 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 157.5, 157.3, 142.9, 137.9, 137.1, 129.0, 125.1, 124.2, 123.2, 115.8, 67.9, 43.6, 41.6, 41.5, 28.9, 27.1, 26.3, 25.5. ESMS m/z: 374.5 (MH^+). Anal. ($C_{20}H_{24}ClN_3O_2$) C, H, N.

1-[7-(4-Chlorophenoxy)heptyl]-3-(3-pyridyl)-2-imidazolidinone (42). Yield: 83%. Yellow solid. IR ν_{max} (KBr): 1704, 1494, 1246 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.56 (bs, 1H), 8.16 (d, J = 3.3 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.25−7.22 (m, 1H), 7.18 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 3.79 (t, J = 6.3 Hz, 2H), 3.69 (t, J = 6.9 Hz, 2H), 3.39 (t, J = 6.9 Hz, 2H), 3.18 (t, J = 7.2 Hz, 2H), 1.68−1.64 (m, 2H), 1.49−1.30 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 157.4, 157.2, 142.7, 137.8, 137.1, 128.9, 124.9, 124.0, 123.0, 115.5, 67.9, 43.6, 41.4, 41.4, 28.8, 28.7, 27.0, 26.4, 25.6. ESMS m/z: 388.5 (MH^+). Anal. ($C_{21}H_{26}ClN_3O_2$) C, H, N.

1-(3-Pyridyl)-3-{6-[4-(trifluoromethyl)phenoxy]hexyl}-2-imidazolidinone (43). Yield: 91%. White solid. IR ν_{max} (KBr): 1705, 1615, 1484, 1329, 1260, 1110 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.56 (bs, 1H), 8.25 (d, J = 4.2 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.23 (dd, J = 8.7, 4.2 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 3.83 (t, J = 6.6 Hz, 2H), 3.66 (t, J = 7.2 Hz, 2H), 3.36 (t, J = 7.2 Hz, 2H), 3.19 (t, J = 6.9 Hz, 2H), 1.84−1.77 (m, 2H), 1.64−1.39 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 161.2, 157.0, 142.4, 137.8, 137.3, 126.3, 123.8, 123.6, 122.9, 114.0, 67.6, 43.3, 41.2, 41.1, 28.5, 26.5, 26.0, 25.4. ESMS m/z: 408.5 (MH^+). Anal. ($C_{21}H_{24}F_3N_3O_2$) C, H, N.

1-[6-(4-Fluorophenoxy)hexyl]-3-(3-pyridyl)-2-imidazolidinone (44). Yield: 88%. White solid. IR ν_{max} (KBr): 1695, 1484, 1250 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.54 (d, J = 2.7 Hz, 1H), 8.11 (d, J = 4.8 Hz, 1H), 7.95 (dd, J = 8.4, 2.7 Hz, 1H), 7.08 (dd, J = 8.4, 4.8 Hz, 1H), 6.82 (d, J = 9.0 Hz, 2H), 6.66 (d, J = 9.0 Hz, 2H), 3.74 (t, J = 6.3 Hz, 2H), 3.62 (t, J = 7.4 Hz, 2H), 3.31 (t, J = 7.4 Hz, 2H), 3.14 (t, J = 7.2 Hz, 2H), 1.67−1.57 (m, 2H), 1.47−1.22 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 158.2, 157.0, 155.0, 154.8, 142.5, 137.7, 137.0, 123.8, 122.9, 114.9,

67.9, 43.4, 41.3, 41.2, 28.7, 26.9, 26.0, 25.3. ESMS *m/z*: 358.5 (MH^+). Anal. ($C_{20}H_{24}FN_3O_2$) C, H, N.

1-[6-(4-Bromophenoxy)hexyl]-3-(3-pyridyl)-2-imidazolidinone (45). Yield: 89%. Yellow solid. IR ν_{max} (KBr): 1703, 1578, 1481, 1242 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.55 (s, 1H), 8.18 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 9.3 Hz, 2H), 7.14 (dd, J = 8.4, 4.5 Hz, 1H), 6.65 (d, J = 9.3 Hz, 2H), 3.80 (t, J = 6.3 Hz, 2H), 3.69 (t, J = 8.1 Hz, 2H), 3.41 (t, J = 8.1 Hz, 2H), 3.20 (t, J = 7.2 Hz, 2H), 1.72−1.63 (m, 2H), 1.55−1.27 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 157.9, 157.2, 142.8, 137.9, 137.4, 131.9, 124.0, 123.1, 116.0, 112.3, 67.8, 43.6, 41.5, 41.4, 28.8, 27.1, 26.2, 25.4. ESMS *m/z*: 418.1 (MH^+). Anal. ($C_{20}H_{24}BrN_3O_2$) C, H, N.

1-[6-(4-Methylphenoxy)hexyl]-3-(3-pyridyl)-2-imidazolidinone (46). Yield: 85%. White solid. IR ν_{max} (KBr): 1707, 1488, 1248 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.57 (bs, 1H), 8.19 (d, J = 3.3 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.15 (dd, J = 8.4, 3.3 Hz, 1H), 6.97 (d, J = 8.1 Hz, 2H), 6.70 (d, J = 8.1 Hz, 2H), 3.84 (t, J = 6.3 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 3.39 (t, J = 7.2 Hz, 2H), 3.22 (t, J = 7.2 Hz, 2H), 2.19 (s, 3H), 1.72−1.65 (m, 2H), 1.54−1.30 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 157.1, 156.6, 142.7, 137.8, 137.0, 129.5, 129.3, 123.9, 123.0, 114.0, 67.5, 43.5, 41.4, 41.3, 29.3, 27.1, 26.2, 25.6, 20.1. ESMS *m/z*: 354.5 (MH^+). Anal. ($C_{21}H_{27}N_3O_2$) C, H, N.

1-{6-[4-(*tert*-Butyl)phenoxy]hexyl}-3-(3-pyridyl)-2-imidazolidinone (47). Yield: 82%. Yellow solid. IR ν_{max} (KBr): 1699, 1513, 1484, 1431 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.60 (bs, 1H), 8.24−8.21 (m, 2H), 7.29−7.25 (m, 3H), 6.81 (d, J = 6.9 Hz, 2H), 3.93 (t, J = 6.3 Hz, 2H), 3.82 (t, J = 8.6 Hz, 2H), 3.51 (t, J = 8.6 Hz, 2H), 3.30 (t, J = 6.9 Hz, 2H), 1.80−1.73 (m, 2H), 1.62−1.37 (m, 6H), 1.28 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 157.2, 156.5, 142.8, 142.7, 137.8, 137.6, 125.9, 124.2, 123.1, 113.6, 67.4, 43.6, 41.5, 33.7, 31.3, 28.9, 27.1, 26.2, 25.5. ESMS *m/z*: 396.5 (MH^+). Anal. ($C_{24}H_{33}N_3O_2$) C, H, N.

A.5. General Procedure for the Synthesis of 48−52. 1-(4-Pyrimidinyl)-3-{5-[4-(trifluoromethyl)phenoxy]pentyl}-2-imidazolidinone (48). To a solution of 1-(4-pyrimidinyl)-2-imidazolidinone (106.7 mg, 0.65 mmol) in 10 mL of dimethylformamide was added NaH (75% dispersion in mineral oil, 0.98 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min and then was cooled in ice bath. 1-[(5-Bromopentyl)oxy]-4-(trifluoromethyl)benzene (202.2 mg, 0.65 mmol) was added, and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched with MeOH (3 mL), and the solvent was concentrated in vacuo. Saturated NH_4Cl aqueous solution (5 mL) and dichloromethane (20 mL) were added to the residue. The dichloromethane layer was separated and dried over $MgSO_4$, filtered, and evaporated. The crude product thus obtained was purified by flash chromatography on silica gel (MeOH/EtOAc = 1:6) to give compound **48** as a yellow solid (231.1 mg, 90%). IR ν_{max} (KBr): 1714, 1583, 1479 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.80 (s, 1H), 8.41 (d, J = 6.0 Hz, 1H), 8.23 (d, J = 6.0 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.06−3.96 (m, 4H), 3.51 (t, J = 7.2 Hz, 2H), 3.34 (t, J = 7.2 Hz, 2H), 1.88−1.79 (m, 2H), 1.67−1.48 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 161.4, 157.8, 156.1, 155.7, 126.9, 126.8, 123.0, 114.4, 108.8, 67.8, 43.6, 41.5, 40.5, 28.7, 27.0, 23.2. ESMS *m/z*: 395.1 (MH^+).

1-(4-Pyrimidinyl)-3-{6-[4-(trifluoromethyl)phenoxy]hexyl}-2-imidazolidinone (49). Yield: 88%. Yellow solid. IR ν_{max} (KBr): 1722, 1584, 1475, 1402 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.81 (d, J = 1.2 Hz, 1H), 8.42 (d, J = 6.3 Hz, 1H), 8.25 (dd, J = 6.3, 1.2 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 4.06−3.95 (m, 4H), 3.51 (t, J = 7.7 Hz, 2H), 3.32 (t, J = 7.2 Hz, 2H), 1.84−1.72 (m, 2H), 1.65−1.37 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 161.5, 157.3, 155.9, 154.8, 126.8, 122.7, 122.5, 114.4, 108.8, 68.0, 43.7, 41.4, 40.5, 29.0, 27.2, 26.6. ESMS *m/z*: 409.1 (MH^+).

1-[6-(4-Chlorophenoxy)hexyl]-3-(4-pyrimidinyl)-2-imidazolidinone (50). Yield: 92%. White solid. IR ν_{max} (KBr): 1718, 1581, 1474, 1244 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.80 (s, 1H), 8.42 (d, J = 5.7 Hz, 1H), 8.23 (d, J = 5.7 Hz, 1H), 7.18 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 4.02 (t, J = 7.8 Hz, 2H), 3.90 (t, J = 8.1 Hz, 2H), 3.50 (t, J = 8.1 Hz, 2H), 3.31 (t, J = 7.2 Hz, 2H), 1.81−1.72 (m, 2H), 1.64−1.39 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 157.9, 157.8, 156.1, 155.8, 129.4, 129.3, 125.4, 115.8, 108.8, 68.1, 43.7, 41.5, 40.5, 29.1, 27.2, 26.4, 25.9. ESMS *m/z*: 375.1 (MH^+).

1-[6-(4-Bromophenoxy)hexyl]-3-(4-pyrimidinyl)-2-imidazolidinone (51). Yield: 89%. White solid. IR ν_{max} (KBr): 1714, 1583, 1487, 1244 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.79 (s, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.22 (d, J = 5.1 Hz, 1H), 7.31 (d, J = 7.8 Hz, 2H), 6.72 (d, J = 7.8 Hz, 2H), 4.01 (t, J = 7.5 Hz, 2H), 3.89 (t, J = 7.8 Hz, 2H), 3.49 (t, J = 7.8 Hz, 2H), 3.30 (t, J = 6.9 Hz, 2H), 1.78−1.72 (m, 2H), 1.64−1.36 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 158.1, 158.0, 156.2, 156.0, 132.2, 132.1, 116.2, 112.6, 108.8, 68.0, 43.6, 41.4, 40.4, 29.0, 27.2, 26.4, 25.7. ESMS *m/z*: 419.1 (MH^+).

1-[7-(4-Bromophenoxy)heptyl]-3-(4-pyrimidinyl)-2-imidazolidinone (52). Yield: 83%. White solid. IR ν_{max} (KBr): 1720, 1581, 1488, 1244 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.80 (s, 1H), 8.40 (d, J = 6.0 Hz, 1H), 8.25 (d, J = 6.0 Hz, 1H), 7.32 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 4.02 (t, J = 7.5 Hz, 2H), 3.87 (t, J = 6.3 Hz, 2H), 3.49 (t, J = 6.3 Hz, 2H), 3.29 (t, J = 6.9 Hz, 2H), 1.74−1.71 (m, 2H), 1.58−1.25 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 158.1, 157.9, 157.5, 155.9, 155.1, 132.1, 116.2, 112.5, 108.7, 68.1, 43.7, 41.4, 40.4, 29.0, 28.9, 27.1, 26.6, 25.9. ESMS *m/z*: 433.1 (MH^+). Anal. ($C_{20}H_{25}BrN_4O_2$) C, H, N.

A.6. General Procedure for the Synthesis of 53−56. 1-[5-(4-Bromophenoxy)pentyl]-3-phenyl-2-imidazolidinone (53). To a solution of 1-phenyl-2-imidazolidinone (94.1 mg, 0.58 mmol) in 10 mL of dimethylformamide cooled in an ice bath was added NaH (75% dispersion in mineral oil, 27.8 mg, 0.87 mmol). The mixture was stirred at room temperature for 30 min and then was cooled in ice bath. 1-Bromo-4-[(5-bromopentyl)oxy]benzene (186.8 mg, 0.58 mmol) was added, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with MeOH, and the solvent was pumped off. Saturated NH_4Cl aqueous solution (5 mL) and dichloromethane (15 mL) were added to the residue. The dichloromethane layer was dried over $MgSO_4$, filtered, evaporated, and purified by flash chromatography to furnish compound **53** as a white solid (215.1 mg, 92%). IR ν_{max} (KBr): 1701, 1599, 1487, 1244 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.50 (d, J = 7.2 Hz, 2H), 7.31−7.26 (m, 4H), 6.97 (t, J = 7.2 Hz, 1H), 6.70 (d, J = 9.3 Hz, 2H), 3.85 (t, J = 6.6 Hz, 2H), 3.69 (t, J = 7.8 Hz, 2H), 3.37 (t, J = 7.8 Hz, 2H), 3.25 (t, J = 6.9 Hz, 2H), 1.81−1.72 (m, 2H), 1.60−1.43 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 158.0, 157.7, 140.4, 132.0, 128.5, 122.0, 117.0,116.1, 112.4, 67.7, 43.6, 42.2, 41.5, 28.7, 27.0, 23.0. ESMS *m/z*: 403.1 (MH^+). Anal. ($C_{20}H_{23}BrN_2O_2$) C, H, N.

1-[6-(4-Bromophenoxy)hexyl]-3-phenyl-2-imidazolidinone (54). Yield: 90%. White solid. IR ν_{max} (KBr): 1697, 1489, 1246 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.53 (d, J = 7.5 Hz, 2H), 7.33−7.26 (m, 4H), 7.01 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 3.85 (t, J = 6.3 Hz, 2H), 3.69 (t, J = 7.2 Hz, 2H), 3.37 (t, J = 7.2 Hz, 2H), 3.25 (t, J = 6.9 Hz, 2H), 1.76−1.72 (m, 2H), 1.57−1.37 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 158.0, 157.6, 140.5, 131.9, 128.5, 121.8, 116.9, 116.1, 112.3, 67.8, 43.6, 42.1, 41.5, 28.8, 27.2, 26.2, 25.5. ESMS *m/z*: 418.1 (MH^+). Anal. ($C_{21}H_{25}BrN_2O_2$) C, H, N.

1-[6-(4-Chlorophenoxy)hexyl]-3-phenyl-2-imidazolidinone (55). Yield: 93%. White solid. IR ν_{max} (KBr): 1701, 1597, 1492, 1245 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.53 (d, J = 7.5 Hz, 2H), 7.28 (t, J = 7.5 Hz, 2H), 7.18 (d, J = 9.3 Hz, 1H), 6.99 (t, J = 7.5 Hz, 2H), 6.78 (d, J = 9.3 Hz, 2H), 3.87 (t, J = 6.3 Hz, 2H), 3.69 (t, J = 7.4 Hz, 2H), 3.39 (t, J = 7.4 Hz, 2H), 3.26 (t, J = 6.9 Hz, 2H), 1.80−1.70 (m, 2H), 1.61−1.35 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 157.7, 157.5, 140.5, 129.1, 128.6, 125.1, 122.0, 117.0, 115.6, 67.9, 43.7, 42.2, 41.5, 28.9, 27.2, 26.3, 25.6. ESMS *m/z*: 373.1 (MH^+). Anal. ($C_{21}H_{25}ClN_2O_2$) C, H, N.

1-Phenyl-3-{6-[4-(trifluoromethyl)phenoxy]hexyl}-2-imidazolidinone (56). Yield: 89%. White solid. IR ν_{max} (KBr): 1703, 1615, 1329, 1260 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.50 (d, J = 7.2 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 7.27 (t, J = 7.2 Hz, 2H), 6.99 (t, J = 7.2 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 3.93 (t, J = 6.3 Hz, 2H), 3.72 (t, J = 7.5 Hz, 2H), 3.39 (t, J = 7.5 Hz, 2H), 3.25 (t, J = 6.9 Hz, 2H), 1.78−1.73 (m, 2H), 1.57−

1.37 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 161.5, 157.8, 140.6, 128.7, 126.8, 126.7, 122.1, 117.1, 114.4, 68.0, 43.8, 42.3, 41.6, 28.9, 27.3, 26.4, 25.6. ESMS *m/z*: 407.3 (MH^+). Anal. ($C_{22}H_{25}F_3N_2O_2$) C, H, N.

A.7. General Procedure for the Synthesis of 57−61. 1-[5-(Biphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one Hydrochloride (57). To a solution of 1-[5-(biphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one (92.3 mg, 0.23 mmol) in 10 mL of tetrahydrofuran was added HCl·Et_2O (1.0 M solution in diethyl ether, 1.2 mmol) dropwise. The resulting mixture was stirred at room temperature for 30 min and then was filtered. The white precipitate was washed with Et_2O (3 × 7 mL) and dried in vacuo to give compound **57** as a white solid (90.8 mg, 98%). Mp > 200 °C. IR ν_{max} (KBr): 1715, 1636, 1571, 1269 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.59 (d, J = 7.2 Hz, 2H), 8.00 (br, 2H), 7.58 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 4.02−3.95 (m, 4H), 3.59 (t, J = 7.5 Hz, 2H), 3.32−3.27 (m, 2H), 1.79−1.74 (m, 2H), 1.63−1.58 (m, 2H), 1.49−1.1.40(m, 2H). ^{13}C NMR (DMSO-d_6): δ 158.3, 154.9, 153.0, 141.0, 139.8, 132.4, 128.8, 127.7, 126.7, 114.9, 111.3, 67.3, 43.0, 41.6, 28.2, 26.1, 22.6. ESMS *m/z*: 402.5 (M^+).

1-[5-(4′-Chlorobiphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one Hydrochloride (58). Yield: 98%. Mp > 208 °C. White solid. IR ν_{max} (KBr): 1715, 1636, 1571, 1269 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.59 (d, J = 7.2 Hz, 2H), 8.00 (br, 2H), 7.58 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 4.02−3.95 (m, 4H), 3.59 (t, J = 7.5 Hz, 2H), 3.32−3.27 (m, 2H), 1.79−1.74 (m, 2H), 1.63−1.58 (m, 2H), 1.49−1.1.40 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 158.5, 155.0, 153.0, 141.2, 138.6, 131.5, 131.0, 128.8, 127.5, 115.0, 111.4, 67.4, 43.0, 41.6, 28.2, 26.1, 22.7. ESMS *m/z*: 436.4 (M^+).

1-[5-(4′-Nitrobiphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one Hydrochloride (59). Yield: 97%. Mp > 199 °C. Yellow solid. IR ν_{max} (KBr): 1718, 1628, 1509, 1265 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.59 (d, J = 8.7 Hz, 2H), 8.25 (d, J = 8.7 Hz, 2H), 8.00 (br, 2H), 7.90 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 8.7 Hz, 2H), 7.05 (t, J = 9.0 Hz, 2H), 4.06−3.95 (m, 4H), 3.59 (t, J = 7.2 Hz), 3.41−3.27 (m, 2H), 1.80−1.73 (m, 2H), 1.64−1.56 (m, 2H), 1.49−1.41 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 159.6, 155.0, 153.0, 146.3, 146.0, 141.0, 130.0, 128.6, 127.0, 124.1, 115.2, 111.4, 67.5, 43.0, 41.6, 28.2, 26.1, 22.6. ESMS *m/z*: 447.5 (M^+).

1-[5-(4′-Methoxybiphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one Hydrochloride (60). Yield: 98%. Mp > 204 °C. White solid. IR ν_{max} (KBr): 1719, 1628, 1497, 1238 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.59 (d, J = 7.5 Hz, 2H), 8.00 (br, 2H), 7.52 (d, J = 3.6 Hz, 2H), 7.48 (d, J = 3.6 Hz, 2H), 6.99 (d, J = 3.0 Hz, 2H), 6.95 (d, J = 3.0 Hz, 2H), 4.01−3.94 (m, 4H), 3.59 (t, J = 7.2 Hz), 3.46−3.39 (m, 2H), 1.87−1.71 (m, 2H), 1.66−1.56 (m, 2H), 1.48−1.40 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 158.4, 155.4, 153.2, 148.5, 146.3, 141.5, 134.2, 134.1, 127.2, 114.8, 114.3, 111.3, 65.0, 54.9, 45.6, 41.3, 28.2, 26.1, 22.3. ESMS *m/z*: 432.5 (M^+).

1-[5-(4′-Bromobiphenyl-4-yloxy)pentyl]-3-pyridin-4-yl-imidazolidin-2-one Hydrochloride (61). Yield: 99%. Mp > 196 °C. White solid. IR ν_{max} (KBr): 1720, 1628, 1479, 1264 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.60 (d, J = 6.3 Hz, 2H), 8.00 (br, 2H), 7.58−7.56 (m, 6H), 7.00 (d, J = 8.1 Hz, 2H), 4.00−3.95 (m, 4H), 3.64−3.61 (m, 2H), 3.36−3.29 (m, 2H), 1.76−1.74 (m, 2H), 1.61−1.58 (m, 2H), 1.46−1.43 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 157.9, 154.7, 153.0, 141.0, 138.7, 131.7, 128.2, 127.7, 120.4, 115.0, 111.4, 67.4, 43.0, 41.6, 28.2, 26.1, 22.6. ESMS *m/z*: 480.4 (M^+).

B. Biological Evaluation. The following test methods were followed in generating the data in Tables 1−4.

B.1. Cells and Viruses. EV 71 isolates in 1998 outbreak were obtained from Clinical Virology Laboratory in Chang Gung Children's Hospitals (Taipei, Taiwan). BrCr, the prototype of EV 71, was obtained from the American Type Culture Collection (ATCC accession no. VR 784). EV 71-2231 and EV 71-1743 were isolated from throat swabs, while EV 71-2086 was isolated from the skin lesion of an implicated HFMD (hand-foot-and-mouth disease) patient. RD cells (rhabdomyosarcoma cells), Vero cells (African green monkey kidney cells; ATCC accession no. CCL-81), and MRC-5 cells (normal fetal lung cells; ATCC accession no. CCL-171) were used for virus isolation and propagation.

B.2. Neutralization Test.[41] This assay measured the ability of a test compound to inhibit the cytopathic effect induced by a picornavirus on RD cells. The 96-well tissue culture plates were seeded with 200 μL of RD cells at a concentration of 3 × 10^5 cells/mL in DMEM with 10% FBS. The plates were incubated for 24−30 h at 37 °C and were used at about 90% confluency. Virus (100 $TCID_{50}$) mixed with different concentrations of test compounds was added to the cells and incubated at 37 °C for 1 h. After adsorption, the infected cell plates were overlayed with 50 μL of DMEM plus 5% FBS and 2% DMSO. The plate was wrapped in Parafilm and incubated at 37 °C for 64 h. At the end of incubation, the plates were fixed by the addition of 100 μL of 0.5% glutaraldehyde for 1 h at room temperature. After the removal of glutaldehyde, the plates were stained with 0.1% crystal violet for 15 min at room temperature. The plates were washed and dried, and the density of the well was measured at 570 nm. The concentration required for a test compound to reduce the virus-induced cytopathic effect (CPE) by 50% relative to the virus control was expressed as IC_{50}. All assays were performed in triplicate and at least twice.

B.3. Plaque Reduction Assay.[20] Antiviral activity of test compounds was determined by a standard plaque reduction assay. In brief, Vero cells in monolayers were infected at a virus concentration to give approximately 50−100 plaques per monolayer in the virus control containing no test compound. Test compounds were diluted and included in the agar-medium overlay. Plates were incubated at 35 °C for 96 h and then stained with crystal violet and plaques counted. All assays were performed in triplicate and at least twice. The concentration required for a test compound to reduce the number of plaques by 50% relative to the virus control was expressed as IC_{50}.

B.4. Cytotoxicity Assay.[42] Test compounds at various concentrations were added to four different cell lines, including RD, Vero, D551 (human normal skin fibroblast cells), and WI38 (human normal lung fibroblast cells). The cells were then incubated at 37 °C for 96 h. After incubation, the cells were harvested and viable cells were counted by trypan blue staining. All experiments were performed in triplicate and at least twice. The concentration of a test compound required to reduce cell viability to 50% of the tested control culture was expressed as CC_{50}.

Acknowledgment. We are grateful to the National Health Research Institutes of the Republic of China for financial support.

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JM010536A