Selection of a Respiratory Syncytial Virus Fusion Inhibitor Clinical Candidate, Part 1: Improving the Pharmacokinetic Profile Using the Structure−Property Relationship

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We previously reported the discovery of substituted benzimidazole fusion inhibitors with nanomolar activity against respiratory syncytial virus (Andries, K.; et al. *Antiviral Res.* **2003**, *60*, 209−219). A lead compound of the series was selected for preclinical evaluation. This drug candidate, JNJ-2408068 (formerly R170591, **1**), showed long tissue retention times in several species (rat, dog, and monkey), creating cause for concern. We herein describe the optimization program to develop compounds with improved properties in terms of tissue retention. We have identified the aminoethyl-piperidine moiety as being responsible for the long tissue retention time of **1**. We have investigated the replacement or the modification of this group, and we suggest that the pK_a of this part of the molecules influences both the antiviral activity and the pharmacokinetic profile. We were able to identify new respiratory syncytial virus inhibitors with shorter half-lives in lung tissue.

Introduction

Respiratory syncytial virus (RSV[a]), isolated for the first time in humans in 1957,[2] is a cause of respiratory tract infections in all ages. The virus is transmitted from person to person through droplets and close contact with infected individuals or via contaminated surfaces. In healthy adults, RSV infection provokes symptoms similar to the common cold. However, in infants, immunosupressed, and elderly people, infection can be more severe, leading to bronchiolitis, pneumonia, and even mortality in severe cases. Studies have shown that severe RSV infections in the first year of life are a risk factor for the development of asthma later in life.[3,4] Attempts to develop a vaccine have been unsuccessful to date.[5,6] Current treatment options include prophylactic treatment with a monoclonal antibody (Synagis) and therapeutic intervention with the nucleoside analog Ribavirin[7] (Figure 1). These agents have significant limitations, and better therapies are needed to decrease the burden of acute RSV disease in all age populations. During the past decade, several small molecules inhibiting the RSV fusion have been discovered,[8−11] but no trial results have been reported so far for any of them.

In a preceding paper,[1] we described the discovery of substituted benzimidazoles with nanomolar activity against RSV.

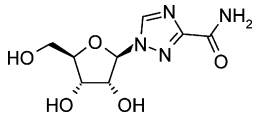

Figure 1. Ribavirin (virazole).

Based on the isolation of escape mutants with point mutations in the fusion protein of RSV,[1] we assumed that these inhibitors act through direct binding to a putative site located in the core domain of the RSV fusion protein. This binding site has been described as a potential target for small-molecule inhibitors,[12] including our lead compound JNJ-2408068 (**1**, Table 1).[13] Compound **1** was selected for preclinical development.

In pharmacokinetic (PK) studies, after intravenous administration, **1** was rapidly eliminated from plasma but showed long tissue retention times in several species (rat, dog, and monkey), creating cause for concern. The terminal half-life in lung tissue was estimated to be between 3 and 4 months.[14] A detailed description of the experiment in rats is given in the Experimental Section. Throughout this paper, retention times in lung tissue are discussed. Lung tissue is taken as representative for other tissues, retention times in other tissues being of the same order. A similar PK profile was found for a close analogue of **1** (**3**, Table 1) endowed with a similar antiviral potency. A somewhat shorter half-life in lung tissue was measured for an aminopropyl derivative (**2**, Table 1), but the tissue retention profile was still not satisfactory.

These findings made **1** less attractive for further preclinical development. The objective of a subsequent discovery program was to design analogs of **1** with an improved PK profile in terms of tissue retention ($T_{1/2\ (24-96h)}$ in lung around 24 h), while keeping the high antiviral potency.

Identification of Substructure Responsible for Tissue Retention. The strategy we used to improve the PK profile of the lead compound aimed to link the tissue retention to a substructure of **1**. As a result, PK studies on different substruc-

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[a] Abbreviations: PK, pharmacokinetic; LC, liquid chromatography; MS, mass spectroscopy; SAR, structure−activity relationship; rt, room temperature; EDTA, ethylenediaminetetraacetic acid; DIPE, diisopropylether.

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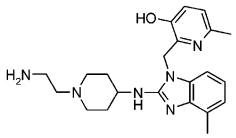
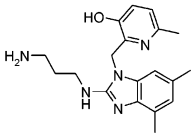
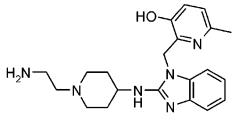
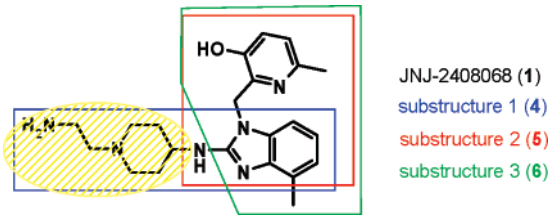
Table 1. In Vitro RSV Inhibitory Activities and PK Profiles of **1** and Analogs in Rat

Compound no	Structure[15]	pEC_{50}	pCC_{50}	$T_{1/2\ (24\text{-}96h)}$ in lung (h)
1		9.6 ± 0.4	< 4	153
2		9.6 ± 0.3	< 4	68
3		9.5 ± 0.4	< 4	211

Scheme 1. Substructures of **1** Used in PK Studies



tures of the lead compound were performed, as depicted in Scheme 1. Three overlapping entities, that is, substructures 1 (**4**), 2 (**5**), and 3 (**6**), which combined make-up compound **1**, were administered in a cassette-dosing PK study to rats. At different time intervals after dosing, plasma and lung homogenate concentrations of the different substructures were determined using LC-MS/MS.

The results of the different experiments are shown in Table 2 together with results obtained for **1**. Compounds **5** and **6** showed levels that were very low or below quantifiable limits, indicating a fast elimination from plasma and absence of tissue retention. Compound **4** showed rapid distribution to the tissues followed by a slow elimination, with a similar rate to that of **1**. Based on the above findings, the aminoethyl-piperidine moiety (highlighted in yellow in Scheme 1) was suspected to play a role in the distribution and the tissue retention observed for **1**.

We replaced the aminoethyl or the aminoethyl-piperidine (as in **2**) moieties in **1** in an attempt to reduce tissue retention.

Synthetic Chemistry. The piperidine derivatives were obtained from different synthetic routes, depending on the nature of the new chain introduced to replace the aminoethyl moiety.

In Scheme 2, the free piperidine intermediate **7**[15] was used as the common core starting material. A simple *N*-alkylation reaction with the corresponding chloro-propane-sulfonamide chains afforded compounds **8** and **9**. The ester intermediate **10,** obtained analogously, served to synthesize carboxamide and carboxylic acid analogs. Addition of ammonia in methanol in a sealed vessel led to compound **11**. Compound **12** was obtained by heating the ester derivative under reflux in HCl (3 N). The reaction of bromopinacolone with the piperidine derivative **7** afforded intermediate **13**. Thereafter, the alcohol function was formed by reduction with $NaBH_4$ to yield the expected *tert*-butyl hydroxyethyl analog **14**. A reductive amination using *para*-formaldehyde and $NaBH_3CN$ allowed us to synthesize the *N*-methyl analog **15** in one step. Finally, we wanted to introduce a chain containing both a basic moiety and a hydroxyl group. This was afforded by utilization of epichlorohydrin. Epichlorohydrin underwent a nucleophilic substitution with intermediate **7**. Next, the nonisolated intermediate was reacted with dimethylamine to give final compound **16**.

To introduce a hydroxyethyl chain, we started from *N*-carbethoxy piperidine derivative **17**[15] (Scheme 3). We protected the hydroxyl of the pyridine moiety with benzylbromide to avoid side reactions. Restoration of the free piperidine and subsequent alkylation with ethyl-chloro acetate afforded intermediate **20**. Reduction of the carboxylic ester with $LiAlH_4$ and, finally, deprotection of the hydroxyl-pyridine gave the expected hydroxyethyl derivative **22**. Compound **22** was used to synthesize derivative **27**, after chlorination of the primary hydroxyl group with $SOCl_2$ and substitution of the thus formed leaving group with pyrrolidine in the presence of K_2CO_3 in CH_3CN. Scheme 3 also describes the synthesis of morpholinoethyl analog **25**. First, the alcohol in the benzyl-protected intermediate **21** was activated with methanesulfonyl chloride. Reaction of the unstable mesylate with morpholine using K_2CO_3 as a base and subsequent hydrogenolysis of the benzyl moiety, led to the expected final compound. Protection of the hydroxyl group located on the pyridine moiety was again required when introducing an isopentyl chain. The two-step synthetic pathway consisted of an alkylation reaction with isopentyl bromide, followed by debenzylation, to provide compound **29**.

As mentioned earlier, we also considered the synthesis of compound **1** analogs in which we replaced the entire aminoethyl-piperidine moiety with new chains. To this end, we chose two different synthetic approaches. A first one (Scheme 4) utilized the chlorobenzimidazole **33**, already bearing the hydroxypyridine moiety, as key intermediate. Protection of the hydroxyl group was required to prevent intramolecular displacement of the chloro-leaving group. This first approach allowed us to obtain *N*-methylpiperazinylpropyl (**41**), *N*-methylpropyl (**42**), *N*-acetylethyl (**43**), and *N*-phenylethyl (**44**) analogs. To obtain diol derivative **36**, we had to use an isopropylidene-protecting group, which was removed afterward in acidic medium.

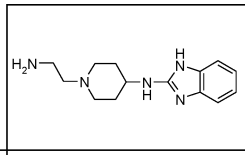
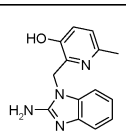
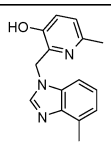
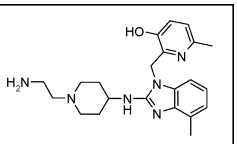
In the second approach, the protection of the hydroxyl group was not required (Scheme 5). We first melted the different amino chains with the chloro-benzimidazole starting material **32**[16] and the hydroxyl-pyridine "head part" was then introduced with the already mentioned method (see Scheme 4) to afford desired compounds **49**−**52**. Butyl (**49**), morpholinopropyl (**50**), phenethyl (**51**), and ethoxycarbonylethyl (**52**) derivatives were synthesized in this way. Ester analog **52** was subsequently reduced in the presence of $LiAlH_4$ in THF to obtain the hydroxypropyl derivative **53**.

Results and Discussions

The PK studies performed with the substructures of compound **1** suggested that the aminoethyl-piperidine moiety could play a role in the observed tissue retention. To confirm this assumption, we modulated the suspected group and analyzed the impact on antiviral activities and PK properties. The structure−activity relationship (SAR) data are summarized in Table 3 for the piperidine derivatives and in Table 4 for the analogs without piperidine moiety. To understand the SAR, we calculated the pK_a[17] for the different inhibitors to predict their possible protonation at physiological pH.

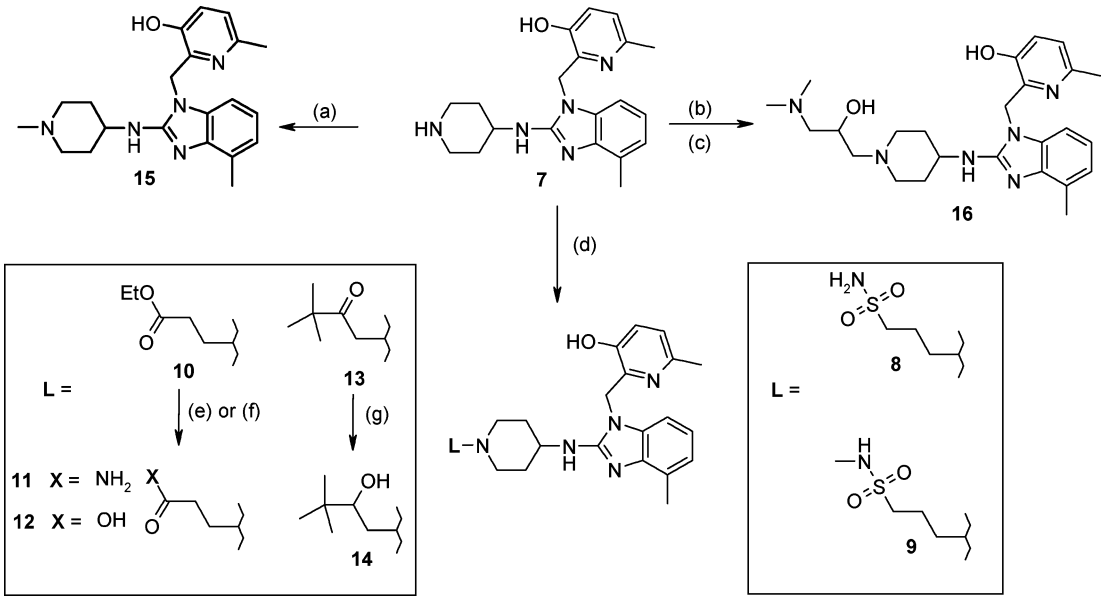
For compounds still bearing the piperidine group (Table 3), the importance of the aminoethyl chain became clear by the reduction of antiviral activity upon modification of this group.

Table 2. Plasma and Lung Levels in Rat at 4, 24, 96, and 168 h for **4**, **5**, **6**, and **1**[a]

					
	Time	**4 (ng/ml)**	**5 (ng/ml)**	**6 (ng/ml)**	**1 (ng/ml)**
Plasma	**4h**	11.8	BLQ*	BLQ	0.97
	24h	6.1	BLQ	BLQ	0.33
	96h	BLQ	BLQ	BLQ	BLQ
	168h	BLQ	BLQ	BLQ	BLQ
Lung	**4h**	247	BLQ	3.9	576.3
	24h	295.3	BLQ	BLQ	559
	96h	83.7	BLQ	BLQ	439
	168h	37.8	BLQ	BLQ	387

[a] BLQ: below limit of quantification.

Scheme 2[a]



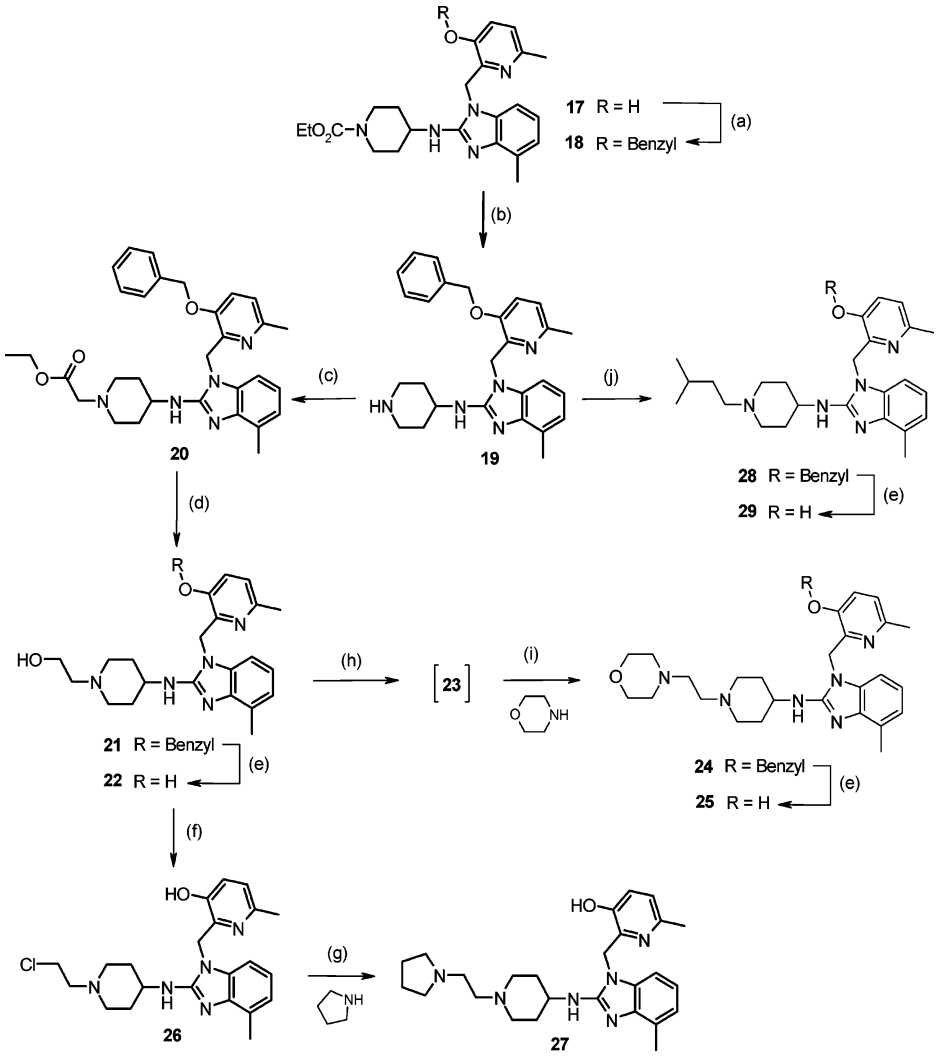
[a] Reagents and conditions (a) HCHO, $NaBH_3CN$, acetic acid, CH_3CN, rt, 12 h; (b) epichlorohydrin, EtOH, rt, 8 h; (c) $NHMe_2$, K_2CO_3, CH_3CN, 80 °C, 8 h; (d) L-Cl, Et_3N, DMF, 75 °C, 12 h or L-Br, Et_3N, KI (cat.), DMF, 60 °C, 4 h or L-Br, Et_3N, DMF, 50 °C, 12 h; (e) NH_3/CH_3OH 7 N, 40 °C, 3 h; (f) HCl 3 N, reflux, 18 h; (g) $NaBH_4$, THF, CH_3OH, rt, 8 h.

In the nonmodified compound, the amino group is protonated at physiological pH and may form a H-bond or an ionic interaction with the target fusion protein. Replacement of the aminoethyl with a simple methyl group (**15**) led to a marked decrease of the activity ($pEC_{50} = 6.8$). This may be due to a lower interaction of the protonated piperidine moiety as compared to the protonated amino group in **1**. Nonbasic chains containing groups that can form a hydrogen bond in addition to the piperidine interaction, gave reasonably potent molecules (**8**, **9**, **11**, and **22**, $7.3 \leq pEC_{50} \leq 7.9$). On the other hand, a hydrophobic chain (**29**) or a *tert*-butyl group in the α position of the OH in compound **22** (**14**) led to reduced potency ($pEC_{50} = 6.2$ and 6.1, respectively). Hydrophobic groups seem to affect the binding of the left part of our RSV inhibitors with the fusion protein. When the used chains were more polar but did not permit additional hydrogen bonds, derivatives were found equipotent to the *N*-methyl piperidine analog **15** (**12** and **25**, $pEC_{50} = 6.8$). With an ethyl-pyrrolidine chain (**27**), protonated at physiological pH, activity was increased again but not to the level of compound **1** ($pEC_{50} = 8$). This difference may be explained by the steric hindrance caused by the basic group. In compound **16**, combination of a protonated amino function and a H-bond donor afforded a further increase of potency ($pEC_{50} = 8.5$).

Comparable results were obtained, with the compounds not bearing a piperidine group (Table 4). SAR around **2** showed that in the compounds without piperidine, the addition of a second methyl on the benzimidazole moiety led to an increase of the activity. We, therefore, applied this modification to our compounds.

The introduction of the most basic groups led to the most potent molecules (**41** and **42**, $pEC_{50} = 7.6$ and 9.2, respectively).

Scheme 3[a]



[a] Reagents and conditions (a) BnCl, K_2CO_3, CH_3CN, DMF, THF, 60 °C, 24 h; (b) KOH, 2-propanol, reflux, 4 h; (c) chloro-acetic acid ethyl ester, K_2CO_3, CH_3CN, 60 °C, 12 h; (d) $LiAlH_4$, THF, 5 °C, 2 h; (e) H_2, Pd/C 10%, CH_3OH, 40 °C, 3−5 bar, 3-4 h; (f) $SOCl_2$, CH_2Cl_2, rt, 5 h; (g) K_2CO_3, CH_3CN, 70 °C, 12 h; (h) Et_3N, CH_3SO_2Cl, CH_2Cl_2, rt, 2 h; (i) K_2CO_3, CH_3CN, 60 °C, 12 h; (j) 1-bromo-3-methyl-butane, Et_3N, DMF, 50 °C, 12 h.

Replacement of the above-mentioned groups with a less basic morpholine (**50**) resulted in somewhat reduced potency (pEC_{50} = 6.9).

Compounds containing poorly basic chains (**43** and **44**) are weak RSV inhibitors. Hydrophobic derivatives showed activity below threshold (**49** and **51**). The only nonbasic moieties that showed antiviral activity were the hydroxyl chains. The presence of two hydroxyl groups was more favorable (pEC_{50} = 7.4 for **36** compared to pEC_{50} = 6.8 for **53**).

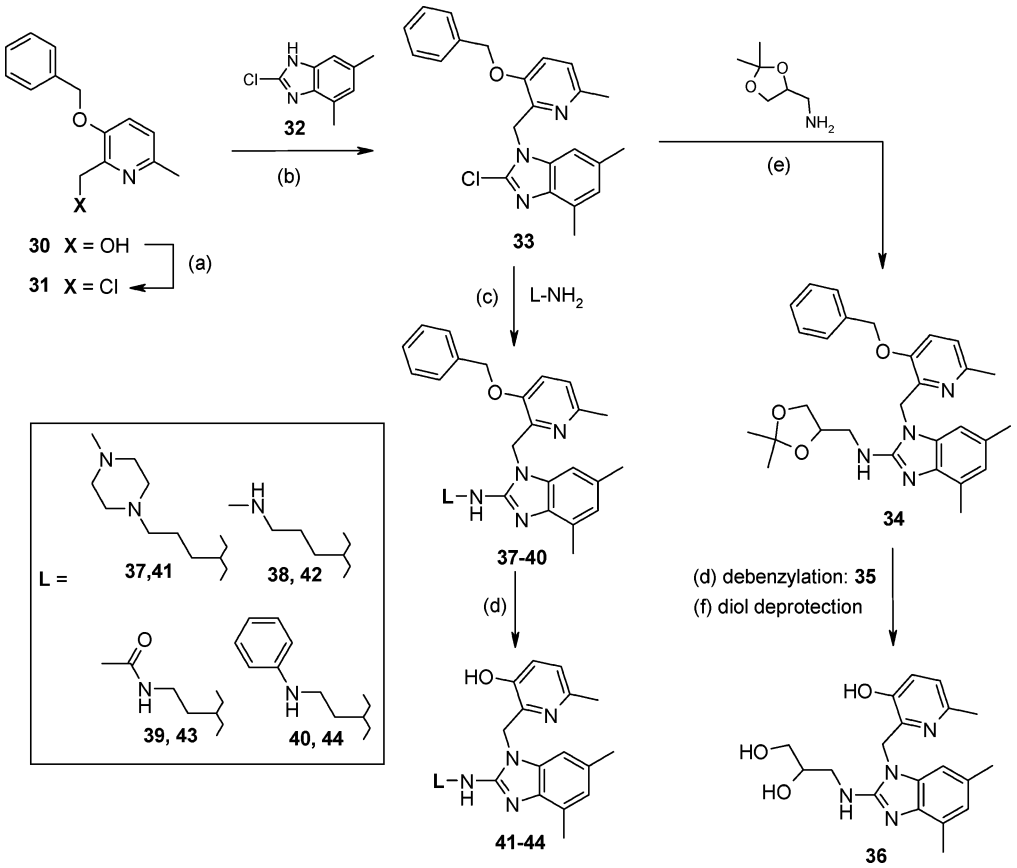
The information learnt from the SAR around these two series of RSV inhibitors is that there may be a polar and/or a charged environment on the target fusion protein in contact with the left part of our molecules. This polar environment would favor hydrogen bonding and ionic interactions.

It is well-established in the literature that the basicity of an amine has a major impact on physicochemical properties and PK parameters.[18,19] A direct link between basicity and tissue retention has been reported. The presence of a basic aminoalkyl group in the antitumor podophyllotoxin derivative TOP-53, has been linked to its predisposition to accumulate in lung tissue.[20] The authors suggest a possible specific interaction with phospholipids as an explanation to this phenomenon. In another publication, the relationship between the physicochemical characteristics of drug candidates and their distribution and retention into the uveal tract was examined, concluding that compounds with strongly basic functionalities are more likely to be distributed and ultimately retained at high concentrations.[21]

In addition to the calculation,[17] we also measured the maximum pK_a[22] of the basic moiety for most of the compounds that underwent in vivo PK studies (Table 5). With this set of compounds, the calculation was less accurate for the piperidine derivatives. The difference between calculated and measured pK_a does not challenge the SAR described earlier, as the latter was established on the putative protonation of the most basic moiety at physiological pH. More accuracy, however, was needed to understand the data from Table 5. Hence, in this case, we based our structure−property relationship analysis on the measured pK_a.

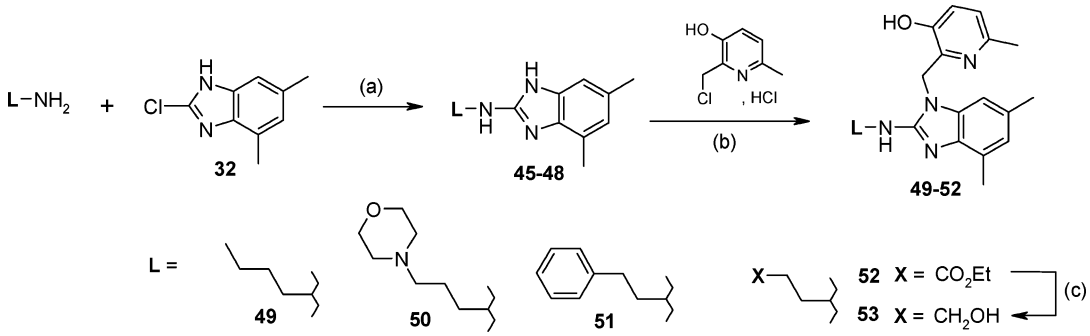
As expected, modulation of the aminoethyl-piperidine moiety led to a modification of the PK profile and we clearly saw an improvement in terms of tissue retention. A reduction of the pK_a below 8 seems to contribute to shorter half-lives in lung tissue. The probability of a multifactorial explanation for the tissue retention makes the interpretation of the results difficult. Nevertheless, we observed that compounds having a maximum pK_a around or above 9 showed tissue retention (compounds **1**, **27**, **41**, and **42**, 80 h $\leq T_{1/2} \leq$ 206 h), while compounds with a maximum pK_a below 8 had shorter half-lives (**8**, **11**, **25**, **36**,

Scheme 4[a]



[a] Reagents and conditions (a) $SOCl_2$, rt, 3 h; (b) K_2CO_3, DMF, rt, 24 h; (c) melting, 130−160 °C, 2 h; (d) H_2, Pd/C 10%, CH_3OH, rt, 3 bar, 1 h; (e) melting, 130 °C to 160 °C, 5 h; (f) HCl 3 N, THF, rt, 3 h.

Scheme 5[a]



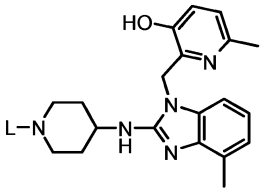
[a] Reagents and conditions (a) melting, 130 °C, 12 h; (b) K_2CO_3, DMF, 70 °C, 4 h; (c) $LiAlH_4$, THF, 5 °C to rt, 4 h.

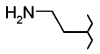
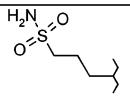
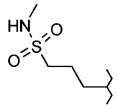
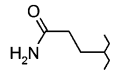
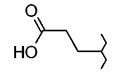
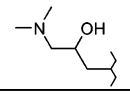
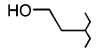
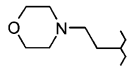
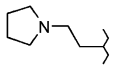
and **50**, $T_{1/2} \leq 57$ h). The only exception to this general rule was compound **22** ($pK_a = 8.9$, $T_{1/2} = 29$ h). Interestingly, two of the latter compounds bear a morpholine group as the basic moiety. In compound **25**, the presence of the morpholine lowered the basicity of the piperidine moiety ($pK_a = 7.6$). In compound **50**, the morpholine group itself was the most basic function with a pK_a below 8 ($pK_a = 7.2$). These basicity levels appear to be a good compromise: enough basicity to be at least partially protonated at physiological pH and to be able to make a H-bond or an ionic interaction, and a lower pK_a preventing tissue retention.

Conclusion

We have identified the aminoethyl-piperidine moiety as being responsible for the long tissue retention time of compound **1**, the former lead of our RSV inhibition program. We have investigated the replacement or the modification of this group and the consequences on antiviral activity and PK properties. We suggest that the basicity of the substituted group influences both the antiviral activity and the PK profile. We were able to identify molecules with shorter half-lives in lung tissue. In the piperidine series, the ethanol chain gave the best result (**22**, $T_{1/2} = 29$ h). In the series omitting piperidine, the most promising candidates were found to be the morpholinopropyl (**50**, $T_{1/2} = 14$ h) and dihydroxypropyl (**36**, $T_{1/2} < 24$ h) derivatives. The improvement of the PK profile was accompanied with a drop in RSV inhibitory activity. Further optimization of these compounds is therefore needed to identify a clinical candidate showing in vivo activity in the animal model using different routes of administration (intravenous, oral, inhalation). A molecular modeling approach will be used in this new optimization program.[23]

Table 3. In Vitro RSV Inhibitory Activities of Piperidine Derivatives



Compound no	L	pEC_{50}	pCC_{50}	Maximum pK_a
1		9.6 ± 0.4	< 4	10.2 ± 0.1 (L chain)
8		7.9 ± 0.1	< 4	9.0 ± 0.4 (piperidine)
9		7.3 ± 0.4	4.1	9.0 ± 0.4 (piperidine)
11		7.3 ± 0.3	< 4	8.7 ± 0.4 (piperidine)
12		6.8 ± 0.6	< 4	9.0 ± 0.4 (piperidine)
14		6.1	4.4	8.9 ± 0.4 (piperidine)
15		6.8 ± 0.3	4.3	9.2 ± 0.4 (piperidine)
16		8.5 ± 0.1	< 4	9.0 ± 0.28 (L chain)
22		7.7 ± 0.2	< 4	8.3 ± 0.4 (piperidine)
25		6.8 ± 0.3	4.2	7.9 ± 0.4 (piperidine)
27		8	4.4	8.7 ± 0.2 (L chain)
29		6.2 ± 0.4	< 4	9.3 ± 0.4 (piperidine)

Experimental Section

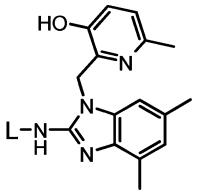
Biology. A HeLaM cell-based assay using a low amount of virus as the inoculum was developed to obtain a multicycle replication experiment.[1] This ensures that compounds interfering with any of the many molecular targets that are important for virus replication in vitro will be detected. RSV was added to HeLaM cells, an epithelial-like cell line, in the presence and absence of various compound concentrations. The viability of treated and untreated cells was assessed by the addition of Tiazolyl blue (MTT) after an incubation period of one week. pEC_{50} values were calculated from the optical density (OD) values, which were measured spectrophotometrically. Virus controls, cell controls, and cytotoxicity controls were included in each plate. Reference compounds were included in each test. Tests in which the virus/cell/compound controls did not meet the objectives were disapproved.

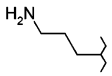
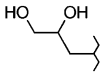
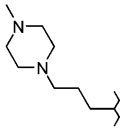
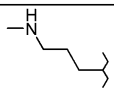
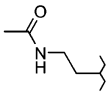
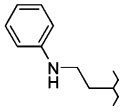
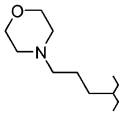
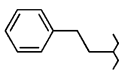
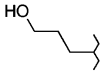
The in vitro model was validated using ribavirin and palivizumab as controls. Both substances produced EC_{50} values in the range of published data. Ribavirin together with **1** was included as positive control in each test.

Pharmacokinetic Determination. Male Sprague−Dawley rats (250 − 300 grams, Charles River, Germany) were used in the present studies (three animals per time group).

Each individual compound was dissolved in a 10% hydroxypropyl-β-cyclodextrin solution at an individual concentration of 1 mg/mL. For some compounds, HCl was added to obtain their total dissolution. An equal volume of each individual solution was added together with an equal volume of demineralized water to make a formulation with a final concentration of 0.25 mg compound/mL. The osmolarity was measured and brought to 283 mosmol/kg with NaCl. The final pH of the formulation was 5.35. Before dosing,

Table 4. In Vitro RSV Inhibitory Activities of Derivatives without Piperidine



Compound no	L	pEC_{50}	pCC_{50}	Maximum pK_a
2		9.6 ± 0.3	< 4	10.0 ± 0.1 (L chain)
36		7.4 ± 0.2	4.3	7.1 ± 0.5 (aminobenzimidazole)
41		7.6 ± 0.1	4.3	8.2 ± 0.42 (L chain)
42		9.2 ± 0.1	4.3	10.4 ± 0.1 (L chain)
43		5.3 ± 0.4	4.9	7.2 ± 0.5 (aminobenzimidazole)
44		< 4	5.5	7.1 ± 0.5 (aminobenzimidazole)
49		< 4	5.1	7.3 ± 0.5 (aminobenzimidazole)
50		6.9 ± 0.4	4.3	7.6 ± 0.1 (L chain)
51		< 4	5.2	7.2 ± 0.5 (aminobenzimidazole)
53		6.8 ± 0.4	4.2	7.2 ± 0.5 (aminobenzimidazole)

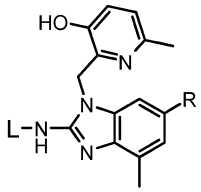
the formulation was stored at room temperature (rt) and protected from light. Immediately after dosage, the formulation was frozen and stored at ≤−18 °C until analysis. All animals were dosed by a 10 min infusion in the tail vein, to provide a final dose of 1 mg compound/kg body weight. The exact infusion speed was calculated taking the exact body weight of the individual animals into account.

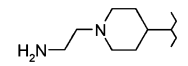
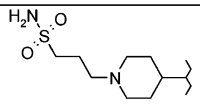
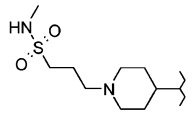
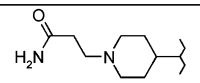
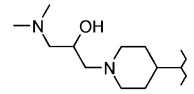
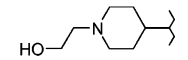
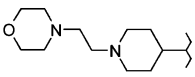
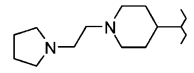
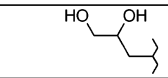
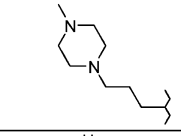
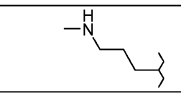
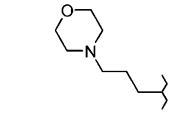
At 4, 24, 96, and 168 h after dose administration, three individual animals per time group were sacrificed by decapitation for blood collection and dissection of lung, liver, and kidney. Blood was collected on EDTA K3 in 10 mL BD Vacutainer tubes. Plasma was obtained following centrifugation at 4 °C. Individual tissue samples were dissected, blotted on filter paper, and weighed immediately. Individual tissue homogenates were prepared in demineralized water (1/9 w/v). Plasma and tissue homogenate samples were stored at ≤−18 °C prior to analysis.

Individual plasma and tissue samples were analyzed using a qualified research bioanalytical method (LC-MS/MS), that is, a bioanalytical method that takes into account all scientific features of a method, as stipulated in the FDA guidelines with respect to stability, accuracy, and precision, but not fully validated.

Chemistry. All analytically pure compounds were dried under vacuum in a drying pistol using a Buchi glass oven B-580 apparatus. Melting points were determined using a Leica VMHB apparatus and are uncorrected. TLC analyses were run on silica gel 60 F_{254} plates (Merck) using a variety of solvent systems and a fluorescent indicator for visualization. Spots were visualized under 254 nm

Table 5. PK Profiles in Rat of the New Derivatives as Compared to JNJ-2408068



Compound no	L	R	$T_{1/2\ (24\text{-}96h)}$ in lung (h)	Maximum pK_a	
				Measured[22]	Calculated[17]
1		H	153	9.4 (L chain)	10.2 ± 0.1 (L chain)
8		H	57	7.3 (piperidine)	9.0 ± 0.4 (piperidine)
9		H	32	Not measured	9.0 ± 0.4 (piperidine)
11		H	46	7.5 (piperidine)	8.7 ± 0.4 (piperidine)
16		H	556	Not measured	9.0 ± 0.28 (L chain)
22		H	29	8.9 (piperidine)	8.3 ± 0.4 (piperidine)
25		H	35	7.6 (piperidine)	7.9 ± 0.4 (piperidine)
27		H	206	9.3 (L chain)	8.7 ± 0.2 (L chain)
36		CH_3	< 24	6.7 (aminobenzimidazole)	7.1 ± 0.5 (aminobenzimidazole)
41		CH_3	80	8.7 (L chain)	8.2 ± 0.42 (L chain)
42		CH_3	93	10.3 (L chain)	10.4 ± 0.1 (L chain)
50		CH_3	14	7.2 (L chain)	7.6 ± 0.1 (L chain)

UV illumination. Column chromatography was performed with silica gel 60 (Merck; 0.015−0.040 mm) or Kromasil (Akzo Nobel; 0.010 mm). Proton NMR spectra were recorded on a Bruker Avance 300 (300 MHz) and a Bruker Avance 400 (400 MHz) spectrometer using internal deuterium lock. Chemical shifts are reported to internal DMSO (δ 2.54) in ppm and coupling constants (J) in Hz. Exact mass spectra (TOF) were recorded with a Micromass LCT instrument. Elemental analyses were performed with a Thermo Electron Corporation instrument EA 1110 or EA 1108 for C, H, N, and the results were within ±0.4% of the theoretical values. Chemicals and solvents were purchased from either Acros Co. or Aldrich Chemical Co. Yields refer to purified products and are not optimized.

3-{4-[1-(3-Hydroxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-ylamino]-piperidin-1-yl}-propane-1-sulfonic Acid Amide (8). A mixture of **7** (0.4 mmol), 3-chloropropane-1-sulfonic acid amide (0.5 mmol), and NEt_3 (0.6 mmol) in DMF (15 mL) was stirred at 75 °C for 12 h, poured into ice water, saturated with K_2CO_3 powder, and extracted with CH_2Cl_2/CH_3OH. The organic layer was separated, dried (over $MgSO_4$), and

filtered, and the solvent was evaporated until dryness. The residue (0.3 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 92/8/0.8). The pure fractions were collected, and the solvent was evaporated. The residue (0.054 g) was crystallized from diethyl ether. The precipitate was filtered off and dried (0.04 g, 24%, melting point: 250 °C); ^{1}H NMR (DMSO-d_6) δ 1.55 (qd, 2 H, J = 10.2 Hz), 1.85 (qt, 2 H, J = 7.7 Hz), 2.00−2.20 (m, 4 H), 2.35 (s, 6 H), 2.40 (t, 2 H, J = 7.7 Hz), 2.82 (d, 2 H, J = 10.2 Hz), 3.02 (t, 2 H, J = 7.7 Hz), 3.75−3.85 (m, 1 H), 5.10 (s, 2 H), 6.65−6.80 (m, 5 H), 7.05−7.12 (m, 2 H), 7.15 (d, 1 H, J = 7.7 Hz), 10.25 (brs, 1 H); HRMS (ESI) calcd for $C_{23}H_{33}N_6O_3S$, 473.2343; found $[MH]^+$, 473.2335.

3-{4-[1-(3-Hydroxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-ylamino]-piperidin-1-yl}-propane-1-sulfonic Acid Methylamide (9). A mixture of **7** (0.4 mmol), 3-chloropropane-1-sulfonic acid methylamide (0.5 mmol), and NEt_3 (0.6 mmol) in DMF (15 mL) was stirred at 75 °C for 12 h, poured into ice water, saturated with K_2CO_3, and extracted with CH_2Cl_2/CH_3OH. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated until dryness. The residue (0.3 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.5). The pure fractions were collected and the solvent was evaporated. The residue (0.052 g) was crystallized from diethyl ether. The precipitate was filtered off and dried (0.031 g, 15%, melting point: 217 °C); ^{1}H NMR (DMSO-d_6) δ 1.52 (qd, 2 H, J = 10.2 Hz), 1.80 (qt, 2 H, J = 7.7 Hz), 2.00−2.20 (m, 4 H), 2.35 (s, 6 H), 2.42 (t, 2 H, J = 7.7 Hz), 2.60 (d, 3 H, J = 5.1 Hz), 2.82 (d, 2 H, J = 10.2 Hz), 3.05 (t, 2 H, J = 7.7 Hz), 3.75−3.85 (m, 1 H), 5.10 (s, 2 H), 6.65−6.80 (m, 3 H), 6.92 (qd, 1 H, J = 5.1 Hz), 7.05−7.10 (m, 2 H), 7.15 (d, 1 H, J = 7.7 Hz), 10.20 (brs, 1 H); HRMS (ESI) calcd for $C_{24}H_{35}N_6O_3S$, 487.2491; found $[MH]^+$, 487.2491.

3-{4-[1-(3-Hydroxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-ylamino]-piperidin-1-yl}-propionic Acid Ethyl Ester (10). A mixture of **7** (2.8 mmol), 3-bromo-propionic acid ethyl ester (3.1 mol), NEt_3 (4.2 mol), and KI (catalytic amount) in DMF (10 mL) was stirred at 60 °C for 4 h, poured into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.6 g) was crystallized from CH_3CN. The precipitate was filtered off and dried (0.45 g, 35%, melting point: 226 °C); ^{1}H NMR (DMSO-d_6) δ 1.19 (t, 3 H, J = 6.8 Hz), 1.50 (qd, 2 H, J = 10.2 Hz), 2.05 (d, 2 H, J = 10.2 Hz), 2.15 (t, 2 H, J = 10.2 Hz), 2.35 (s, 6 H), 2.45 (t, 2 H, J = 6.4 Hz), 2.60 (t, 2 H, J = 6.4 Hz), 2.85 (d, 2 H, J = 10.2 Hz), 3.70−3.80 (m, 1H), 4.07 (qd, 2 H, J = 6.8 Hz), 5.10 (s, 2 H), 6.68−6.82 (m, 3 H), 7.05 (d, 1 H, J = 7.7 Hz), 7.08 (d, 1 H, J = 7.7 Hz), 7.15 (d, 1 H, J = 7.7 Hz), 10.25 (brs, 1 H).

3-{4-[1-(3-Hydroxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-ylamino]-piperidin-1-yl}-propionamide (11). A mixture of **10** (0.4 mmol) in NH_3/CH_3OH 7N (20 mL) was stirred at 40 °C for 3 h, then cooled down to rt, and stirred for 12 h. The solvent was evaporated until dryness. The residue (0.3 g) was purified by column chromatography over kromasil (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/1). The pure fractions were collected, and the solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried (0.096 g, 50%, melting point: 258 °C); ^{1}H NMR (DMSO-d_6) δ 1.50 (qd, 2 H, J = 10.2 Hz), 2.05 (d, 2 H, J = 10.2 Hz), 2.15 (t, 2 H, J = 10.2 Hz), 2.20 (t, 2 H, J = 7.7 Hz), 2.35 (s, 6 H), 2.55 (t, 2 H, J = 7.7 Hz), 2.80 (d, 2 H, J = 10.2 Hz), 3.70−3.80 (m, 1 H), 5.10 (s, 2 H), 6.65−6.80 (m, 4 H), 7.00−7.10 (m, 2 H), 7.15 (d, 1 H, J = 7.7 Hz), 7.4 (s, 1 H), 10.3 (brs, 1 H); HRMS (ESI) calcd for $C_{23}H_{31}N_6O_2$, 423.2524; found $[MH]^+$, 423.2508; Anal. ($C_{23}H_{30}N_6O_2$, 0.2 H_2O) C, H, N.

3-{4-[1-(3-Hydroxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-ylamino]-piperidin-1-yl}-propionic Acid (12). A mixture of **10** (0.9 mmol) in a 3 N solution of HCl in water (5 mL) was stirred and refluxed for 18 h and then cooled down to rt. The precipitate was filtered, washed with diethyl ether, and dried (0.18 g, 31%, melting point: 245 °C); ^{1}H NMR (DMSO-d_6) δ 2.15 (qd, 2 H, J = 10.2 Hz), 2.20 (d, 2 H J = 10.2 Hz), 2.40 (s, 3 H), 2.60 (s, 3 H), 2.90 (t, 2 H, J = 7.7 Hz), 3.10 (t, 2 H, J = 10.2 Hz), 3.30 (t, 2 H, J = 7.7 Hz), 3.60 (d, 2 H, J = 10.2 Hz), 4.40−4.50 (m, 1 H), 5.60 (s, 2 H), 7.05−7.20 (m, 5 H), 7.25 (d, 1 H, J = 7.7 Hz), 7.45 (d, 1 H, J = 7.7 Hz), 10.9 (brs, 1 H); HRMS (ESI) calcd for $C_{23}H_{30}N_5O_3$, 424.2349; found $[MH]^+$, 424.2349; Anal. ($C_{23}H_{29}N_5O_3$, 3 HCl) C, H, N.

1-{4-[1-(3-Hydroxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-ylamino]-piperidin-1-yl}-3,3-dimethyl-butan-2-one (13). A mixture of **7** (1.4 mmol), 1-bromopinacolone (1.7 mmol), and NEt_3 (8.5 mol) in DMF (90 mL) was stirred at 50 °C for 12 h. The solvent was evaporated until dryness. H_2O/EtOAc was added. The aqueous layer was saturated with K_2CO_3 and extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue was taken up in CH_2Cl_2/CH_3OH and crystallized from DIPE. The precipitate was filtered off and dried (0.205 g, 32%, melting point: 230 °C).

2-{2-[1-(2-Hydroxy-3,3-dimethyl-butyl)-piperidin-4-ylamino]-4-methyl-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (14). $NaBH_4$ (0.2 mmol) was added portionwise at 5 °C to a solution of **13** (0.2 mmol) in THF (2 mL) and MeOH (2 mL). The mixture was stirred at rt for 8 h. $NaBH_4$ was added again at 5 °C, and the reaction was stirred at rt for 4 h. H_2O/K_2CO_3 10% was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.12 g) was taken up in CH_2Cl_2/CH_3OH and purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 89/10/1). The pure fractions were collected, and the solvent was evaporated (0.052 g, 45%, melting point: 255 °C); ^{1}H NMR (DMSO-d_6) δ 0.85 (s, 9 H), 1.50 (qd, 2 H, J = 10.2 Hz), 2.10−2.20 (m, 4 H), 2.20 (s, 6 H), 2.20−2.30 (m, 2 H), 2.80 (d, 2 H, J = 10.2 Hz), 3.70−3.85 (m, 2 H), 5.10 (s, 2 H), 6.65−6.85 (m, 3 H), 7.02 (d, 1 H, J = 7.7 Hz), 7.10 (d, 1 H, J = 7.7 Hz), 7.18 (d, 1 H, J = 7.7 Hz), 10.30 (br s, 1 H); HRMS (ESI) calcd for $C_{26}H_{38}N_5O_2$, 452.3032; found $[MH]^+$, 452.3026; Anal. ($C_{26}H_{37}N_5O_2 \cdot 1H_2O$) C, H, N.

6-Methyl-2-[4-methyl-2-(1-methyl-piperidin-4-ylamino)-benzoimidazol-1-ylmethyl]-pyridin-3-ol (15). Formaldehyde 37% in water (1.7 mmol) and $NaBH_3CN$ (1 mmol) were added at rt to a mixture of **7** (0.8 mmol) in CH_3CN (1 mL). Acetic acid (0.3 mL) was added dropwise. The mixture was stirred at rt for 12 h. The solvent was evaporated until dryness. EtOH (3 mL) and a saturated solution of HCl in 2-propanol (1 mL) were added. The mixture was stirred at 80 °C for 2 h, water was added, and the solution was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.21 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/0.1 to 80/20/3). The pure fractions were collected and the solvent was evaporated (0.1 g, 32%, melting point: 210 °C); ^{1}H NMR (DMSO-d_6) δ 1.55 (qd, 2 H, J = 10.2 Hz), 1.95−2.10 (m, 4 H), 2.17 (s, 3 H), 2.32 (s, 3 H), 2.37 (s, 3 H), 2.70 (d, 2 H, J = 10.2 Hz), 3.65−3.75 (m, 1 H), 5.07 (s, 2 H), 6.72 (d, 2 H, J = 7.7 Hz), 6.78 (t, 1 H, J = 7.7 Hz), 6.95 (d, 1 H, J = 7.7 Hz), 7.07 (d, 1 H, J = 7.7 Hz), 7.15 (d, 1 H, J = 7.7 Hz), 10.30 (br s, 1 H); HRMS (ESI) calcd for $C_{21}H_{28}N_5O$, 366.2290; found $[MH]^+$, 366.2294; Anal. ($C_{21}H_{27}N_5O \cdot 1.1HCl \cdot 0.3H_2O \cdot 0.2i$-PrOH) C, H, N.

2-{2-[1-(3-Dimethylamino-2-hydroxy-propyl)-piperidin-4-ylamino]-4-methyl-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (16). A mixture of **7** (1.1 mmol) and epichlorohydrin (1.3 mmol) in EtOH (6 mL) was stirred at rt for 8 h. The solvent was evaporated until dryness (0.53 g, 100%). CH_3CN (5 mL), dimethylamine hydrochloride (1.4 mmol), and K_2CO_3 (9.5 mol) were added, and the mixture was stirred at 80 °C for 8 h. Next, K_2CO_3 10% and H_2O were added, and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.45 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 83/15/2). The pure fractions were collected and the solvent was evaporated (0.1 g, 18%, melting point: 180

°C); ^{1}H NMR (DMSO-d_6) δ 1.55 (qd, 2 H, J = 10.2 Hz), 2.05 (d, 2 H, J = 10.2 Hz), 2.18 (s, 6 H), 2.20−2.30 (m, 5 H), 2.20−2.30 (m, 7 H), 2.70−2.80 (m, 2 H), 3.70−3.85 (m, 2 H), 5.10 (s, 2 H), 6.70−6.80 (m, 3 H), 7.00−7.20 (m, 3 H); HRMS (ESI) calcd for $C_{25}H_{37}N_6O_2$, 453.2973; found $[MH]^+$, 453.2978.

4-[1-(3-Benzyloxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-ylamino]-piperidine-1-carboxylic Acid Ethyl Ester (18). A mixture of **17** (23.6 mmol), benzyl bromide (26 mmol), and K_2CO_3 (0.0354 mol) in a mixture of CH_3CN (50 mL), DMF (50 mL), and THF (100 mL) was stirred at 60 °C for 24 h. The solvent was evaporated until dryness. The residue was taken up in H_2O. The precipitate was filtered on celite, the pad was washed with H_2O, and the filtrate was extracted with diethyl ether. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated until dryness. The residue (12 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/NH_4OH 98/2/0.1). Three fractions were collected and the solvent was evaporated (5 g, 41%); ^{1}H NMR (DMSO-d_6) δ 1.20 (t, 3 H, J = 7.7 Hz), 1.40 (d, 2 H, J = 10.2 Hz), 2.02 (d, 2 H, J = 10.2 Hz), 2.37 (s, 6 H), 3.00−3.12 (m, 2 H), 3.88 (d, 2 H, J = 10.2 Hz), 3.95−4.02 (m, 1 H), 4.06 (qd, 2 H, J = 7.7 Hz), 5.17 (s, 4 H), 6.62 (t, 1 H, J = 7.7 Hz), 6.68 (d, 1 H, J = 7.7 Hz), 6.73 (d, 1 H, J = 7.7 Hz), 6.82 (d, 1 H, J = 7.7 Hz), 7.18 (d, 1 H, J = 7.7 Hz), 7.35−7.50 (m, 6 H).

[1-(3-Benzyloxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-yl]-piperidin-4-yl-amine (19). A mixture of **18** (9.5 mmol) and KOH (9.5 mmol) in 2-propanol (60 mL) was stirred and refluxed for 4 h. The solvent was evaporated until dryness. The residue was taken up in CH_2Cl_2. The organic layer was washed with H_2O, dried (over $MgSO_4$), and filtered, and the solvent was evaporated until dryness (4.19 g, 100%, melting point: 182 °C); ^{1}H NMR (DMSO-d_6) δ 1.35 (qd, 2 H, J = 10.2 Hz), 1.95 (d, 2 H, J = 10.2 Hz), 2.35 (s, 3 H), 2.40 (s, 3 H), 2.55 (t, 2 H, J = 10.2 Hz), 2.95 (d, 2 H, J = 10.2 Hz), 3.75−3.85 (m, 1 H), 5.15 (s, 2 H), 5.18 (s, 2 H), 6.60 (t, 1 H, J = 7.7 Hz), 6.70 (d, 1 H, J = 7.7 Hz), 6.80 (d, 1 H, J = 7.7 Hz), 7.20 (d, 1 H, J = 7.7 Hz), 7.38−7.52 (m, 6 H).

{**4-[1-(3-Benzyloxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-ylamino]-piperidin-1-yl**}**-acetic Acid Ethyl Ester (20).** A mixture of **19** (30.7 mmol), ethyl chloro-acetate (37 mmol), and K_2CO_3 (0.046 mol) in CH_3CN (150 mL) was stirred at 60 °C for 12 h. The solvent was evaporated until dryness. The residue was taken up in CH_2Cl_2. The organic layer was washed with H_2O, dried (over $MgSO_4$), and filtered, and the solvent was evaporated until dryness. The residue was crystallized from 2-propanone/CH_3CN. The precipitate was filtered off and dried (14.5 g, 90%, melting point: 116 °C); ^{1}H NMR (DMSO-d_6) δ 1.20 (t, 3 H, J = 6.8 Hz), 1.52 (qd, 2 H, J = 10.2 Hz), 2.00 (d, 2 H, J = 10.2 Hz), 2.30−2.40 (m, 8 H), 2.85 (d, 2 H, J = 10.2 Hz), 3.24 (s, 2 H), 3.70−3.80 (m, 1 H), 4.09 (qd, 2 H, J = 6.8 Hz), 5.14 (s, 2 H), 5.18 (s, 2 H), 6.60 (t, 1 H, J = 7.7 Hz), 6.68 (d, 1 H, J = 7.7 Hz), 6.72 (d, 1 H, J = 7.7 Hz), 6.79 (d, 1 H, J = 7.7 Hz), 7.20 (d, 1 H, J = 7.7 Hz), 7.35−7.50 (m, 6 H).

2-{**4-[1-(3-Benzyloxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-ylamino]-piperidin-1-yl**}**-ethanol (21).** $LiAlH_4$ (47 mmol) was added portionwise at 5 °C to a mixture of **20** (23 mmol) in THF (250 mL) under a N_2 flow. The mixture was stirred at 5 °C for 2 h. H_2O was added. The mixture was extracted with EtOAc and filtered over celite. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated until dryness (8 g, 72%, melting point: 159 °C); ^{1}H NMR (DMSO-d_6) δ 1.50 (qd, 2 H, J = 10.2 Hz), 2.00 (d, 2 H, J = 10.2 Hz), 2.15 (t, 2 H, J = 10.2 Hz), 2.35 (s, 3 H), 2.40−2.48 (m, 5 H), 2.85 (d, 2 H, J = 10.2 Hz), 3.50 (qd, 2 H, J = 5.1 Hz), 3.70−3.80 (m, 1 H), 4.38 (t, 1 H, J = 5.1 Hz), 5.15 (s, 2 H), 5.19 (s, 2 H), 6.60 (t, 1 H, J = 7.7 Hz), 6.65 (d, 1 H, J = 7.7 Hz), 6.72 (d, 1 H, J = 7.7 Hz), 6.79 (d, 1 H, J = 7.7 Hz), 7.20 (d, 1 H, J = 7.7 Hz), 7.35−7.50 (m, 6 H); MS (ESI^+) found for $C_{29}H_{35}N_5O_2$ $[MH]^+$, 486.

2-{**2-[1-(2-Hydroxy-ethyl)-piperidin-4-ylamino]-4-methyl-benzoimidazol-1-ylmethyl**}**-6-methyl-pyridin-3-ol (22).** A mixture of **21** (0.4 mmol) and Pd/C 10% (0.1 g) in CH_3OH (20 mL) was hydrogenated at 40 °C for 3 h under a 5 bar pressure, then cooled down to rt, and filtered over celite. The filtrate was evaporated until dryness, yielding 0.16 g (100%). This fraction was crystallized from 2-propanone/DIPE. The precipitate was filtered off and dried (0.07 g, 43%, melting point: 258 °C); ^{1}H NMR (DMSO-d_6) δ 1.55 (qd, 2 H, J = 10.2 Hz), 2.05 (d, 2 H J = 10.2 Hz), 2.20 (t, 2 H, J = 10.2 Hz), 2.35 (s, 6 H), 2.45 (t, 2 H, J = 6.4 Hz), 2.85 (d, 2 H, J = 10.2 Hz), 3.50 (t, 2 H, J = 6.4 Hz), 3.70−3.82 (m, 1 H), 4.40 (br s, 1 H), 5.10 (s, 2 H), 6.65−6.82 (m, 3 H), 7.00−7.15 (m, 2 H), 10.3 (brs, 1 H); HRMS (ESI) calcd for $C_{22}H_{30}N_5O_2$, 396.2409; found $[MH]^+$, 396.2400; Anal. ($C_{22}H_{29}N_5O_2 \cdot 0.3H_2O$) C, H, N.

Methanesulfonic Acid 2-{**4-[1-(3-Benzyloxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-ylamino]-piperidin-1-yl**}**-ethyl Ester (23).** Triethylamine (3.1 mmol) was added at 5 °C to a mixture of **21** (2 mmol) in CH_2Cl_2 (40 mL) under a N_2 flow. Methanesulfonyl chloride (3.1 mmol) was added dropwise. The mixture was stirred at 5 °C for 1 h and then at rt for 2 h and poured into H_2O. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated until dryness (1.2 g, 100%). The crude compound was used directly in the next reaction step.

[1-(3-Benzyloxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-yl]-[1-(2-morpholin-4-yl-ethyl)-piperidin-4-yl]-amine (24). A mixture of **23** (2 mmol), morpholine (2.5 mmol), and K_2CO_3 (3.1 mmol) in CH_3CN (50 mL) was stirred at 80 °C for 2 h, then stirred at 60 °C for 12 h. The solvent was evaporated until dryness. The residue was taken up in CH_2Cl_2/H_2O. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was concentrated under reduced pressure. The residue (2 g) was purified by column chromatography over silica gel (eluent: toluene/2-propanol/NH_4OH 80/20/1). The pure fractions were collected, and the solvent was evaporated. The residue (0.6 g, 53%) was crystallized from CH_3CN. The precipitate was filtered off and dried (0.17 g, 15%, melting point: 183 °C); ^{1}H NMR (DMSO-d_6) δ 1.47 (qd, 2 H, J = 10.2 Hz), 2.00 (d, 2 H, J = 10.2 Hz), 2.13 (t, 2 H, J = 10.2 Hz), 2.35 (s, 3 H), 2.37−2.47 (m, 8 H), 2.85 (d, 2 H, J = 10.2 Hz), 3.55 (t, 4 H, J = 5.1 Hz), 3.70−3.80 (m, 1 H), 5.15 (s, 2 H), 5.19 (s, 2 H), 6.60 (t, 1 H, J = 7.7 Hz), 6.65 (d, 1H, J = 7.7 Hz), 6.72 (d, 1 H, J = 7.7 Hz), 6.80 (d, 1 H, J = 7.7 Hz), 7.20 (d, 1 H, J = 7.7 Hz), 7.35−7.52 (m, 6 H); MS (ESI^+) found for $C_{33}H_{43}N_6O_2$ $[MH]^+$, 555.

6-Methyl-2-{**4-methyl-2-[1-(2-morpholin-4-yl-ethyl)-piperidin-4-ylamino]-benzoimidazol-1-ylmethyl**}**-pyridin-3-ol (25).** A mixture of **24** (0.5 mmol) and Pd/C 10% (0.1 g) in MeOH (20 mL) was hydrogenated at rt for 4 h under a 5 bar pressure. The mixture was filtered over celite. The filtrate was evaporated. The residue (0.2 g) was purified by column chromatography over kromasil (eluent: CH_2Cl_2/CH_3OH/NH_4OH 90/10/1). The pure fractions were collected and the solvent was evaporated. The residue (0.13 g, 54%) was crystallized from CH_3CN/DIPE. The precipitate was filtered off and dried (0.122 g, 49%, melting point: 238 °C); ^{1}H NMR (DMSO-d_6) δ 1.55 (qd, 2 H, J = 10.2 Hz), 2.05 (d, 2 H, J = 10.2 Hz), 2.15 (t, 2 H, J = 10.2 Hz), 2.35 (s, 6 H), 2.35−2.45 (m, 8 H), 2.85 (d, 2 H, J = 10.2 Hz), 3.55 (t, 4 H, J = 5.1 Hz), 3.70−3.80 (m, 1 H), 5.10 (s, 2 H), 6.70−6.82 (m, 3 H), 7.00−7.10 (m, 2 H), 7.15 (d, 1H, J = 7.7 Hz), 10.2 (brs,1 H); HRMS (ESI) calcd for $C_{26}H_{37}N_6O_2$, 465.2980; found $[MH]^+$, 465.2978; Anal. ($C_{26}H_{36}N_6O_2 \cdot 1.5H_2O$) C, H, N.

2-{**2-[1-(2-Chloro-ethyl)-piperidin-4-ylamino]-4-methyl-benzoimidazol-1-ylmethyl**}**-6-methyl-pyridin-3-ol (26).** $SOCl_2$ (21.4 mmol) was added dropwise to a solution of **22** in CH_2Cl_2 at 0 °C. The reaction was stirred at rt for 5 h. The precipitate was filtered off, rinsed with DIPE, and dried. The crude compound was used directly in the next reaction step.

6-Methyl-2-{**4-methyl-2-[1-(2-pyrrolidin-1-yl-ethyl)-piperidin-4-ylamino]-benzoimidazol-1-ylmethyl**}**-pyridin-3-ol (27).** A mixture of **26** (1.1 mmol), K_2CO_3 (0.0038 mol), and pyrrolidine (1.3 mmol) in CH_3CN (10 mL) was stirred at 70 °C for 12 h. H_2O was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent

was evaporated. The residue (0.27 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 88/11/1). The pure fractions were collected and the solvent was evaporated. The residue (0.14 g) was crystallized from CH_3CN/2-propanone. The precipitate was filtered off and dried (0.105 g, 28%, melting point: 225 °C); ^{1}H NMR (DMSO-d_6) δ 1.55 (qd, 2 H, J = 10.2 Hz), 1.80−2.02 (m, 4 H), 2.05 (d, 2 H, J = 10.2 Hz), 2.15 (t, 2 H, J = 10.2 Hz), 2.35 (s, 6 H), 2.36−2.55 (m, 8 H), 2.85 (d, 2 H, J = 10.2 Hz), 3.70−3.80 (m, 1 H), 5.10 (s, 2 H), 6.70−6.80 (m, 3 H), 7.05−7.15 (m, 2 H), 7.20 (d, 1 H, J = 7.7 Hz), 10.30 (br s, 1H); HRMS (ESI) calcd for $C_{26}H_{37}N_6O$, 449.3043; found $[MH]^+$, 449.3029; Anal. ($C_{26}H_{36}N_6O\cdot 1.2H_2O$) C, H, N.

[1-(3-Benzyloxy-6-methyl-pyridin-2-ylmethyl)-4-methyl-1*H*-benzoimidazol-2-yl]-[1-(3-methyl-butyl)-piperidin-4-yl]-amine (28). A mixture of **19** (0.6 mmol), 1-bromo-3-methylbutane (0.8 mmol), and NEt_3 (1 mmol) in DMF (20 mL) was stirred at 50 °C for 12 h, poured into H_2O, and extracted with EtOAc. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.1 to 90/10/0.1). The pure fractions were collected and the solvent was evaporated (0.108 g, 31%).

6-Methyl-2-{4-methyl-2-[1-(3-methyl-butyl)-piperidin-4-ylamino]-benzoimidazol-1-ylmethyl}-pyridin-3-ol (29). A mixture of **28** (0.2 mmol) and Pd/C 10% (0.033 g) in MeOH (15 mL) was hydrogenated at rt for 3 h under a 3 bar pressure, then filtered over celite. Celite was washed with CH_3OH/THF. The filtrate was concentrated under reduced pressure. The residue (0.081 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 89/10/1). The pure fractions were collected and the solvent was evaporated (0.044 g, 49.4%, melting point: 230 °C); ^{1}H NMR (DMSO-d_6) δ 0.9 (d, 6 H, J = 7.7 Hz), 1.35 (qd, 2 H, J = 7.7 Hz), 1.45−1.65 (m, 3 H), 2.00−2.15 (m, 4 H), 2.25−2.52 (m, 2 H), 2.45 (s, 6 H), 2.82 (d, 2 H, J = 10.2 Hz), 3.73−3.82 (m, 1 H), 5.10 (s, 2 H), 6.65−6.80 (m, 3 H), 7.05 (d, 1 H, J = 7.7 Hz), 7.10 (d, 1 H, J = 7.7 Hz), 7.15 (d, 1 H, J = 7.7 Hz), 10.25 (brs, 1 H); HRMS (ESI) calcd for $C_{25}H_{36}N_5O$, 422.2928; found $[MH]^+$, 422.2920; Anal. ($C_{25}H_{35}N_5O\cdot 0.8H_2O$) C, H, N.

3-Benzyloxy-2-chloromethyl-6-methyl-pyridine (31). $SOCl_2$ (14 mL) was added dropwise to a solution of (3-benzyloxy-6-methyl-pyridin-2-yl)-methanol **30** (60.6 mmol) in CH_2Cl_2 at 5 °C. The reaction mixture was stirred at rt for 3 h. The solvent was evaporated under reduced pressure. The residue was taken up in diethyl ether. The precipitate was filtered off and dried (16.9 g, 98%, melting point: 182 °C); ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3 H), 4.88 (s, 2 H), 5.31 (s, 2 H), 7.32−7.51 (m, 6 H), 7.83 (d, 1 H, J = 7.7 Hz).

1-(3-Benzyloxy-6-methyl-pyridin-2-ylmethyl)-2-chloro-4,6-dimethyl-1*H*-benzoimidazole (33). A mixture of 2-chloro-4,6-dimethyl-1*H*-benzimidazole **32** (83 mmol), **31** (91.3 mmol), and K_2CO_3 (332 mmol) in DMF (100 mL) was stirred at rt for 24 h. H_2O was then added. The mixture was extracted three times with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated at 30 °C under reduced pressure. The residue was taken up in CH_3CN/DIPE. The precipitate was filtered off and dried (16.8 g, 52%, melting point: 155 °C); ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3 H), 2.28 (s, 3 H), 2.44 (s, 3 H), 5.21 (s, 2 H), 5.47 (s, 2 H), 6.84 (s, 1H), 7.02 (s, 1 H), 7.12 (d, 1 H, J = 7.7 Hz), 7.30−7.48 (m, 6 H).

[1-(3-Benzyloxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1*H*-benzoimidazol-2-yl]-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-amine (34). A mixture of **33** (1.4 mmol) and *C*-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methylamine (1.2 mmol) was stirred at 130 °C for 3 h, then stirred at 160 °C for 2 h, cooled down to rt, and taken up in CH_2Cl_2. The organic layer was washed with a 10% solution of K_2CO_3, dried (over $MgSO_4$), and filtered, and the solvent was evaporated until dryness. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.1). The pure fractions were collected and the solvent was evaporated (0.55 g, 81%).

2-{2-[(2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-amino]-4,6-dimethyl-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (35). A mixture of **34** (1.1 mmol) and Pd/C 10% (0.18 g) in CH_3OH (10 mL) was hydrogenated for 1 h under a 3 bar pressure and then filtered over celite. Celite was rinsed with CH_3OH. The filtrate was concentrated under reduced pressure. The residue (0.47 g) was crystallized from CH_3CN. The precipitate was filtered off and dried (0.27 g, 60%, melting point: 225 °C); ^{1}H NMR (DMSO-d_6) δ 1.29 (s, 3 H), 1.38 (s, 3 H), 2.28 (s, 3 H), 2.32 (s, 3H), 2.36 (s, 3 H), 3.44−3.58 (m, 2 H), 3.78 (t, 2 H, J = 7.7 Hz), 4.04 (t, 2 H, J = 7.7 Hz), 4.37 (qt, 1H, J = 5.7 Hz), 5.04 (dd, 2 H, J = 3.6, 11 Hz), 6.59 (s, 1 H), 6.89 (br s, 2 H), 7.03 (d, 1 H, J = 7.7 Hz), 7.15 (d, 1 H, J = 7.7 Hz), 10.18 (s, 1 H).

3-[1-(3-Hydroxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1*H*-benzoimidazol-2-ylamino]-propane-1,2-diol (36). A mixture of **35** (0.5 mmol) in a 3 N solution of HCl (15 mL) and THF (15 mL) was stirred for 4 h. THF was evaporated under reduced pressure. The aqueous layer was saturated with K_2CO_3 (powder). A solution of CH_2Cl_2/CH_3OH (90/10) was added. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.17 g, 88%) was crystallized from CH_3CN/DIPE. The precipitate was filtered off and dried (0.085 g, melting point: 205 °C); ^{1}H NMR (DMSO-d_6) δ 2.20 (s, 3 H), 2.23 (s, 3 H), 2.28 (s, 3 H), 3.20−3.30 (m, 2 H), 3.60−3.75 (m, 2 H), 4.25−4.35 (m, 1 H), 5.08 (s, 2 H), 5.18−5.25 (m, 2 H), 5.65−5.75 (m, 1 H), 6.54−6.60 (m, 2 H), 6.92 (s, 1 H), 7.03 (d, 1 H, J = 7.7 Hz), 7.20 (d, 1 H, J = 7.7 Hz), 10.30 (br s, 1 H); HRMS (ESI) calcd for $C_{19}H_{25}N_4O_3$, 357.1927; found $[MH]^+$, 357.1935.

2-{4,6-Dimethyl-2-[3-(4-methyl-piperazin-1-yl)-propylamino]-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (41). A mixture of **33** (0.7 mmol) and 3-(4-methyl-piperazin-1-yl)-propylamine (7.6 mmol) was stirred at 160 °C for 2 h. H_2O was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.5 g) was purified by Combiflash column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.5 to 90/10/0.5). The pure fractions were collected, and the solvent was evaporated (**37**, 0.277 g, 70%).

A mixture of **37** (0.5 mmol) and Pd/C 10% (0.1 g) in CH_3OH (15 mL) was hydrogenated at rt for 1 h under a 3 bar pressure, then filtered over celite. The filtrate was evaporated. The residue (0.24 g) was crystallized from 2-propanone/CH_3CN. The precipitate was filtered off and dried (0.17 g, 75%, melting point: 225 °C); ^{1}H NMR (DMSO-d_6) δ 1.79 (qt, 2 H, J = 5.8 Hz), 2.12 (s, 3 H), 2.28 (s, 3 H), 2.30−2.34 (m, 14 H), 2.40 (t, 2 H, J = 5.8 Hz), 3.40 (t, 2 H, J = 5.8 Hz), 5.07 (s, 2 H), 6.56 (s, 1 H), 6.60−6.75 (m, 1H), 6.83 (s, 1 H), 7.03 (d, 1 H, J = 7.7 Hz), 7.13 (d, 1 H, J = 7.7 Hz), 10.30 (br s, 1 H); HRMS (ESI) calcd for $C_{24}H_{35}N_6O$, 423.2872; found $[MH]^+$, 423.2874; Anal. ($C_{24}H_{34}N_6O\cdot 0.5H_2O$) C, H, N.

2-[4,6-Dimethyl-2-(3-methylamino-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (42). Compound **42** was obtained according to the procedure described for compound **41** (0.089 g, 33% (2 steps), melting point: 175 °C); ^{1}H NMR (DMSO-d_6) δ 1.90 (qt, 2 H, J = 5.8 Hz), 2.26 (s, 3 H), 2.29 (s, 3 H), 2.32 (s, 3 H), 2.49 (s, 3 H), 2.88 (t, 2 H, J = 5.8 Hz), 3.49 (t, 2 H, J = 5.8 Hz), 5.10 (s, 2 H), 6.59 (s, 1 H), 6.81 (s, 1 H), 7.01 (d, 1 H, J = 7.7 Hz), 7.15 (d, 1 H, J = 7.7 Hz); HRMS (ESI) calcd for $C_{20}H_{28}N_5O$, 354.2294; found $[MH]^+$, 354.2291.

***N*-{2-[1-(3-Hydroxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1*H*-benzoimidazol-2-ylamino]-ethyl}-acetamide (43).** Compound **43** was obtained according to the procedure described for compound **41** (0.105 g, 37% (2 steps), melting point: 245 °C); ^{1}H NMR (DMSO-d_6) δ 2.20 (s, 3 H), 2.23 (s, 3 H), 2.28 (s, 3 H), 2.35 (s, 3 H), 3.20−3.30 (m, 2 H), 3.70−3.80 (m, 2 H), 5.10 (s, 2 H), 6.52−6.60 (m, 2 H), 6.90 (s, 1 H), 7.05 (d, 1 H, J = 7.7 Hz), 7.17 (d, 1 H, J = 7.7 Hz), 9.82 (br s, 1 H), 10.30 (br s, 1 H); HRMS (ESI) calcd for $C_{20}H_{26}N_5O_2$, 368.2087; found, $[MH]^+$ 368.2094; Anal. ($C_{20}H_{25}N_5O_2\cdot 0.5H_2O$) C, H, N.

2-[4,6-Dimethyl-2-(2-phenylamino-ethylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (44). Compound **44** was obtained according to the procedure described for compound **41**

(0.120 g, 43% (2 steps), melting point: 205 °C); ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3 H), 2.29 (s, 3 H), 2.38 (s, 3 H), 3.29−3.34 (m, 2 H), 3.54−3.62 (m, 2 H), 5.09 (s, 2 H), 5.92 (t, 1H, J = 5.1 Hz), 6.52 (t, 1 H, J = 7.7 Hz), 6.59 (s, 1 H), 6.70 (d, 2 H, J = 7.7 Hz), 6.83 (s, 1 H), 6.90 (br s, 1 H), 7.01 (d, 1 H, J = 7.7 Hz), 7.08 (t, 2 H, J = 7.7 Hz), 7.13 (d, 1H, J = 7.7 Hz), 10.18 (br s, 1 H); HRMS (ESI) calcd for $C_{24}H_{28}N_5O$, 402.2294; found $[MH]^+$, 402.2297; Anal. ($C_{24}H_{27}N_5O$) C, H, N.

2-[(2-Butylamino-4,6-dimethyl-benzoimidazol)-1-ylmethyl]-6-methyl-pyridin-3-ol (49). A mixture of **32** (1.1 mmol) and butylamine (4.8 mmol) was stirred at 120 °C for 3 h and 30 min. Next, H_2O was added, and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated (0.2 g of butyl-(4,6-dimethyl-1*H*-benzoimidazol-2-yl)-amine) **45**. This crude fraction was used directly in the next reaction step.

A mixture of butyl-(4,6-dimethyl-1*H*-benzoimidazol-2-yl)-amine **45** (1.1 mmol), 2-chloromethyl-6-methyl-pyridin-3-ol·HCl (1.1 mmol), and K_2CO_3 (3.8 mmol) in DMF (3 mL) was stirred at 70 °C for 24 h. H_2O and EtOAc were added. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.29 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/NH_4OH 97/3/0.5). The pure fractions were collected and the solvent was evaporated, yielding 0.136 g. This fraction was purified by column chromatography over silica gel (eluent: toluene/*i*-PrOH/NH_4OH 92/8/0.5). The pure fractions were collected and the solvent was evaporated, yielding 0.061 g. The resulting oil was crystallized from DIPE/diethyl ether. The precipitate was filtered off and dried (0.037 g, 10%, melting point: 210 °C); ^{1}H NMR (DMSO-d_6) δ 0.93 (t, 3 H, J = 7.4 Hz), 1.42 (qt, 2 H, J = 7.0 Hz), 1.63 (qt, 2 H, J = 7.0 Hz), 2.28 (s, 3 H), 2.31 (s, 3 H), 2.33 (s, 3 H), 3.38 (t, 2 H, J = 6.6 Hz), 5.06 (s, 2 H), 6.53−6.63 (m, 2 H), 6.88 (s, 1 H), 7.04 (d, 1 H, J = 7.7 Hz), 7.14 (d, 1 H, J = 7.7 Hz), 10.22 (br s, 1 H); HRMS (ESI) calcd for $C_{20}H_{27}N_4O$, 339.2185; found $[MH]^+$, 339.2180; Anal. ($C_{20}H_{26}N_4O$·0.3H_2O) C, H, N.

2-[4,6-Dimethyl-2-(3-morpholin-4-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (50). A mixture of **32** (1.1 mmol) and 3-morpholin-4-yl-propylamine (4.4 mmol) was stirred at 130 °C for 4 h and then cooled down to rt, taken up in H_2O, and extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.328 g) was purified by column chromatography over kromasil (eluent: CH_2Cl_2/CH_3OH/NEt_3 99/1/0.1 to 90/10/1). The pure fractions were collected, and the solvent was evaporated ((4,6-dimethyl-1*H*-benzoimidazol-2-yl)-(3-morpholin-4-yl-propyl)-amine **46**, 0.216 g, 68%). This crude fraction was used directly in the next reaction step.

A mixture of (4,6-dimethyl-1*H*-benzoimidazol-2-yl)-(3-morpholin-4-yl-propyl)-amine **46** (0.7 mmol), 2-chloromethyl-6-methyl-pyridin-3-ol·HCl (0.8 mmol), and K_2CO_3 (3 mmol) in DMF (6 mL) was stirred at 70 °C for 12 h, then cooled down to rt, taken up in H_2O, and extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated. The residue (0.5 g) was purified by column chromatography over kromasil (eluent: CH_2Cl_2/CH_3OH/NH_4OH 93/7/0.5 then toluene/*i*-PrOH/NH_4OH 80/20/1). The pure fractions were collected and the solvent was evaporated. The residue (0.13 g) was taken up in DIPE. The precipitate was filtered off and dried (0.1 g, 33%, melting point: 228 °C); ^{1}H NMR (DMSO-d_6) δ 1.69 (qt, 2 H, J = 7.0 Hz), 2.28 (s, 3 H), 2.30−2.40 (m, 12 H), 3.41 (t, 2 H, J = 5.6 Hz), 3.55 (t, 4 H, J = 3.8 Hz), 5.05 (s, 2 H), 6.56 (s, 1 H), 6.88 (s, 1 H), 7.00 (d, 1 H, J = 7.7 Hz), 7.11 (d, 1 H, J = 7.7 Hz), 10.45 (br s, 1H); HRMS (ESI) calcd for $C_{23}H_{32}N_5O_2$, 410.2556; found $[MH]^+$, 410.2566; Anal. ($C_{23}H_{31}N_5O_2$·1.4H_2O) C, H, N.

2-(4,6-Dimethyl-2-phenethylamino-benzoimidazol-1-ylmethyl)-6-methyl-pyridin-3-ol (51). Compound **51** was obtained according to the procedure described for compound **50** (0.06 g, 14% (2 steps), melting point: 232 °C); ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3 H), 2.29 (s, 3 H), 2.34 (s, 3 H), 2.98 (t, 2 H, J = 7.1 Hz), 3.62 (t, 2 H, J = 7.1 Hz), 5.04 (s, 2 H), 6.58 (s, 1 H), 6.78 (br s, 1 H), 6.85 (s, 1 H), 7.04 (d, 1 H, J = 7.7 Hz), 7.14 (d, 1 H, J = 7.7 Hz), 7.18−7.32 (m, 5 H), 10.11 (br s, 1 H); HRMS (ESI) calcd for $C_{24}H_{27}N_4O$, 387.2185; found $[MH]^+$, 387.2181; Anal. ($C_{24}H_{26}N_4O$·0.5H_2O) C, H, N.

3-[1-(3-Hydroxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1*H*-benzoimidazol-2-ylamino]-propionic Acid Ethyl Ester (52). Compound **52** was obtained according to the procedure described for compound **50** (0.12 g, 8% (2 steps), melting point: 180 °C).

2-[2-(3-Hydroxy-propylamino)-4,6-dimethyl-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (53). $LiAlH_4$ (0.3 mmol) was added portionwise at 5 °C to a mixture of **52** (0.1 mmol) in THF (10 mL) under a N_2 flow. The mixture was stirred at 5 °C for 1 h and then at rt for 3 h. EtOAc and H_2O were added. The mixture was extracted with EtOAc. The organic layer was separated, dried (over $MgSO_4$), and filtered, and the solvent was evaporated until dryness. The residue was crystallized from 2-propanone/CH_3CN/DIPE. The precipitate was filtered off and dried (0.025 g, 73%, melting point: 170 °C); ^{1}H NMR (DMSO-d_6) δ 1.75 (qt, 2 H, J = 5.8 Hz), 2.27 (s, 3 H), 2.29−2.32 (m, 6 H), 3.43−3.53 (m, 4 H), 5.02−5.20 (m, 3 H), 6.57 (s, 1 H), 6.71 (br s, 1 H), 6.83 (s, 1 H), 7.02 (d, 1 H, J = 7.7 Hz), 7.14 (d, 1 H, J = 7.7 Hz), 10.19 (br s, 1 H); HRMS (ESI) calcd for $C_{19}H_{25}N_4O_2$, 341.1978; found $[MH]^+$, 341.1966; Anal. ($C_{19}H_{24}N_4O_2$·0.5H_2O) C, H, N.

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Supporting Information Available: Elemental analyses of the target compounds. This material is available free of charge via the Internet at http://pubs.acs.org/

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