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Synthesis and Characterization of *para*-Substituted *N*,*N*′-Dihydroxybenzamidines and Their Derivatives as Model Compounds for a Class of Prodrugs

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A synthetic strategy for previously unknown *para*-substituted *N*,*N*′-dihydroxybenzamidines and their *O*-monosubstituted and *O*,*O*′-disubstituted methyl, benzyl, and tetrahydropyranyl derivatives is described. The procedure starts with the corresponding hydroxamic acid chlorides, which after dehydrohalogenation give nitrile oxides. These intermediates in turn react with *O*-substituted hydroxylamines to afford the desired *N*,*N*′-dihydroxybenzamidines after workup. This new class of potential prodrugs was characterized by ^{15}N NMR spectroscopy. The chemical shifts show significant correlations with Hammett σ values, especially for the oxime-type nitrogen with $r^2 > 0.99$. The Hammett σ parameter reliably correlates with electron density in molecules. The presented results thus allow predictions relating to π-electron density and basicity in this functional group, and these are important parameters for the discussion of substrate enzyme interactions.

Introduction

Amidine and guanidine structures are popular functional groups in pharmaceutical agents because they act as bioisosteres to the amino acid arginine. The charged basic side chain of arginine can itself participate in strong interactions (ionic, hydrogen bridge linkage) with target molecules and be responsible for pharmacological effects. Many groups of drugs, including inhibitors of blood coagulation[1] and antiparasitics such as pentamidine, contain essential amidine groups.

Amidines are very strong bases, with pK_a values of around 11.6,[2] because of the highly mesomerically stabilized cations formed after protonation at the double bonded nitrogen atom. This leads to the main disadvantage of charged functional groups such as amidines: the poor oral bioavailability due to the inability of charged molecules to pass through membranes. For that reason, one desirable feature would be to keep the highly effective structure in active ingredients but initially to mask the basic character in order to increase oral bioavailability. Electron-withdrawing substituents such as hydroxy groups accomplish this prodrug principle, leading to amidoximes,[3] with pK_a values of around 4.8;[2] these are then enzymatically reduced in vivo to the amidine functional group by "mitochondrial Amidoxime Reducing Component" (mARC), newly discovered in our lab.[4] One current example for decreasing the basic character while increasing oral bioavailability through hydroxylation of one amidine nitrogen atom is to be found in the new small-molecule serine protease inhibitor Upamostat.[5]

To decrease the basic character of amidines further, thus improving oral bioavailability, one goal was to hydroxylate the functional group at both nitrogen atoms; this further reduces the pK_a to 3.8,[6] so the molecules should remain completely uncharged under physiological conditions. In theory, gastrointestinal reduction of the prodrug to the corresponding amidine with loss of membrane permeability should be reduced because of the longer times needed for the two-step reduction, to the benefit of absorption (Scheme 1).

This has been achieved in the case of *N*,*N*′-dihydroxybenzamidine.[7] In vitro tests have already demonstrated the activation of the prodrug by porcine and human kidney and liver microsomes and mitochondria. As was observed for benzamidoximes, *N*-reduction through the action of mARC is the predominant reaction of *N*,*N*′-dihydroxybenzamidine in vitro and in vivo. In the case of amidoximes, rapid enzymatic degradation to amidines occurs after oral application prior to total absorption from the gastrointestinal tract. The presence of an additional hydroxy group delays the degradation to amidines because one more reaction step is necessary. This was confirmed in vitro with porcine hepatocytes: reduction of benzamidoxime to benzamidine, with a rate of 337 ± 68 pmol min^{-1} (mg of protein)$^{-1}$, is prolonged by the reduction of *N*,*N*′-dihydroxybenzamidine to benzamidoxime with a rate of about 1560 ± 540 pmol min^{-1} (mg

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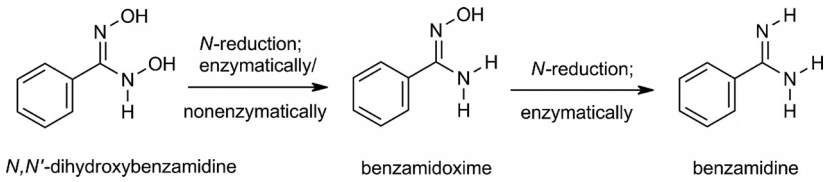


Scheme 1. In vivo biotransformations of *N*,*N*′-dihydroxybenzamidine.

of protein)$^{-1}$.[7] In vivo tests confirm the assumption in terms of extended bioavailability. Oral application of *N*,*N*′-dihydroxybenzamidine to pigs showed rapid metabolism after absorption such that no prodrug could be detected in plasma samples. Instead, benzamidine was found, thus confirming the compatibility of the theoretical prodrug considerations with in vivo data (Scheme 1).[8] The results suggest a demand for *N*,*N*′-dihydroxyamidine prodrugs replacing already existing amidine prodrugs, thus increasing oral bioavailability.

The rate of enzymatic activity towards a molecule depends on the electron density in the functional groups of a molecule interacting with the active site. The Hammett σ value is an established parameter for π-electron distribution in agents allowing forecasting of quantitative structure–activity relationships.[9] We thus undertook an investigation into the synthesis and stability of these hitherto unknown substituted dihydroxybenzamidines bearing various substituents in the aromatic ring and also on their hydroxy groups. Different aromatic *para* substituents with appropriate Hammett σ values are listed in Table 1.[10] The higher the Hammett σ value, the more electron-withdrawing is the substituent.

Table 1. *para*-Substituents in the synthesized derivatives of *N*,*N*′-dihydroxybenzamidines **4**–**9** (Scheme 2), together with Hammett σ values.

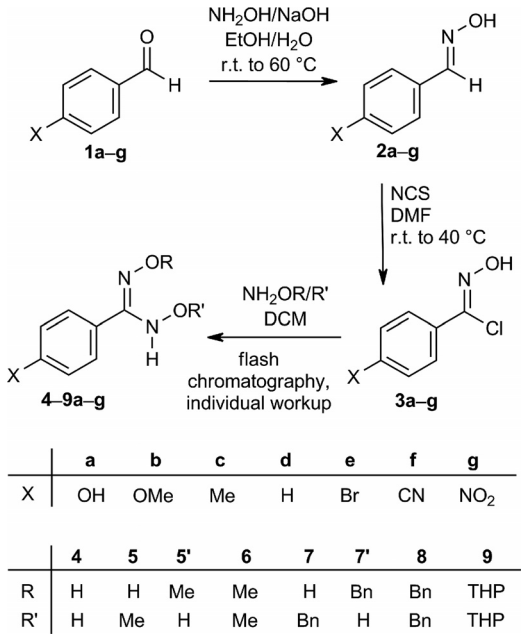
	a	**b**	**c**	**d**	**e**	**f**	**g**
p-X	OH	OMe	Me	H	Br	CN	NO_2
Hammett σ	–0.38	–0.28	–0.14	0	0.26	0.70	0.81

Recent data confirmed a significant relationship between ^{15}N NMR chemical shifts in different *p*-substituted benzamidoximes and benzamidinium salts and the Hammett σ parameters. Consequently, ^{15}N NMR allows forecasts for kinetics of biological reactions of substances of this class.[11] No systematic ^{15}N NMR investigation of *N*,*N*′-dihydroxybenzamidines has yet been performed. Rare examples of *N*,*N*′-dihydroxybenzamidine derivatives have been described in the literature (**4d**, **7**/**7**′**d**, **10**),[12–14] but no NMR spectroscopic data are available.

Results and Discussion

Synthesis

N-Chlorosuccinimide was added to the *para*-substituted benzaldoximes **2** (Scheme 2), obtained from benzaldehydes **1**,[15] to give the corresponding benzhydroxamic acid chlorides **3** by a standard literature procedure.[16] This intermediate was treated with different commercially available hydroxylamine derivatives in diethyl ether or dichloromethane to afford the corresponding *O*-unsubstituted, *O*-monosubstituted, or *O*,*O*′-disubstituted *N*,*N*′-dihydroxybenzamidines **4**–**9** (Scheme 2; see also Table 3, below). Generally, three equivalents of hydroxylamine, acting both as a reagent and as a base for generated hydrogen chloride, were employed. The *O*,*O*′-disubstituted derivatives were preferentially formed with use of a greater excess of substituted hydroxylamine. In the course of this investigation it turned out to be necessary to analyze and isolate the *O*-monosubstituted *N*,*N*′-dihydroxybenzamidine reaction products **5**/**5**′ and **7**/**7**′ immediately, due to decomposition (Table 2).



	a	**b**	**c**	**d**	**e**	**f**	**g**
X	OH	OMe	Me	H	Br	CN	NO_2

	4	**5**	**5'**	**6**	**7**	**7'**	**8**	**9**
R	H	H	Me	Me	H	Bn	Bn	THP
R'	H	Me	H	Me	Bn	H	Bn	THP

Scheme 2. General reaction steps leading to a new class of prodrugs: *para*-substituted *N*,*N*′-dihydroxybenzamidines **4**–**9**.

In contrast to gravimetric liquid chromatography, with fast flash chromatography no products of degradation of **4**–**9** during the chromatographic process were detected. Generally, cleaner products were obtained in larger yields when hydroxylamines were employed as free bases, so derivatives **4**, **7**/**7**′, **8**, and **9** required a simpler workup. Use of hydroxylamine hydrochlorides, which were treated with triethylamine in situ to produce the free bases (products **5**/**5**′, **6**), was also possible, but *p*-nitro- and *p*-hydroxy-substituted reaction products could not be detected when the hydroxylamine/triethylamine protocol was used.

Table 2. Calculated degradation slopes for *O*-monosubstituted *N*,*N*′-dihydroxybenzamidines **5/5**′ and **7/7**′ based on ^{1}H NMR spectra integrals (% h^{-1}).

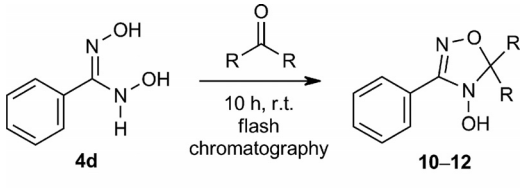
	a	b	c	d	e	f	g
5/5′[a]	–	–0.29	–0.73	–0.26	–2.10	–3.45	–
7/7′[a]	–1.26[b]	–0.35	–0.45	–0.62	–0.53	–1.66	–16.31

[a] Freshly dissolved spectra integrals were set to 100% at t = 0 h. Second ^{1}H spectra integrals were recorded t = 5 to t = 40 h later and gave a proportion of the first recorded integrals. Linear regression led to the listed slopes. Strongly negative slopes indicate fast degradation. [b] Compound is unstable at room temperature even without DMSO.

None of the compounds with the substituents given in Table 1 has been described in the literature except for **4d**,[12,13] **7/7**′**d**[17] (without information about tautomer ratios and NMR spectroscopic data), and **10**[14] (synthesized from the appropriate nitrile oxide and oxime with the aid of BF_3).

Instability in neutral and basic media leads to rapid disproportionation of **4d** to the appropriate amidoxime and nitrosolic acid, which in turn decomposes to the benzonitrile.[18] In acidic media compounds **4**–**9** slowly degrade to hydroxamic acids by hydrolysis, as has been described previously for **4d**;[13] this results in the need for a fast chromatographic purification with acidic solid-phase silica. At room temperature all of the synthesized compounds **4**–**12** except for **7/7**′**a** are stable for about two weeks. In the cases of **4a**–**f** the decomposition product amidoximes were detectable after heating above 35 °C or prolonged storage at ambient temperature, so storage at –18 °C and below was necessary for all substances. No detailed investigation into stability was performed for **5**–**9**, but the *O*,*O*′-disubstituted derivatives **6**, **8**, and **9** turned out to be much more stable, with no further amidoxime formation being detected after purification.

In consideration of the objective of producing different dihydroxybenzamidines as possible prodrugs, further functionalization of **4** was accomplished. Representatively, condensation between *p*-unsubstituted **4d** (Scheme 3) and ketones led to three new cyclic *N*,*N*′-dihydroxybenzamidine derivatives. The desired compounds **10**–**12** decomposed after 1–2 h on storage as the concentrated crude product mixtures. However, immediate flash chromatography led to pure substances **10**–**12**, and these are stable at room temperature for at least about one week.



10: R,R = Me, **11**: R,R = -(CH$_2$)$_4$-, **12**: R,R = -(CH$_2$)$_5$-

Scheme 3. Synthesis of cyclic dihydroxybenzamidines **10**, **11**, and **12**.

General Spectroscopic Analysis

All NMR spectra were recorded in [D$_6$]DMSO because of improved stability and solubility relative to D_2O and $CDCl_3$. One set of signals was observed in every case except for that of **9**; this gave two diastereomeric sets of signals, so there is no evidence for mixtures of *E*/*Z* isomers. All compounds **4**–**9** exist in the *Z* configuration, which is energetically favored, as demonstrated by Barassin et al. for the unsubstituted derivative **4d**.[19] With regard to *N*-substituted benzamidoximes we also assume the exclusive presence of the *Z* isomer if a single-bonded nitrogen has at least one covalent bond to a hydrogen atom.[20] *O*-Monosubstituted *N*,*N*′-dihydroxybenzamidines **5/5**′ and **7/7**′ occur as mixtures of two tautomers, which – unlike the unsubstituted and *O*,*O*′-disubstituted derivatives (**4**, **6**, **8**, **9**) – are not identical. We therefore observe mixtures of two compounds in a ratio of approximately 50:50 for all NMR spectra recorded (Figure 1).

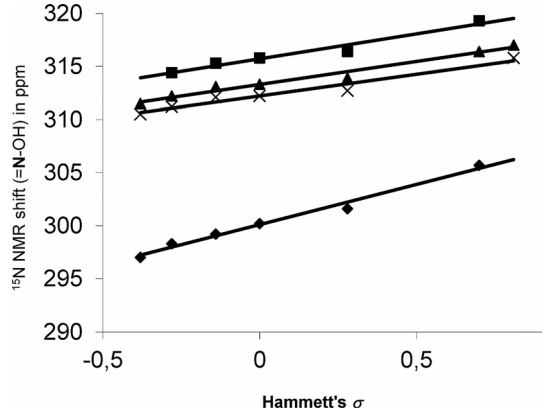


Figure 1. Correlation of ^{15}N NMR chemical shifts of oxime-type nitrogen atoms of (♦) **4a**–**f**, (■) **6b**–**f**, (▲) **8a**–**g**, and (×) **9a**–**e** and **9g** with the corresponding Hammett values (see Table 3 and Table 4 for data).

The observation of two sets of signals for the unsymmetrically substituted *N*,*N*′-dihydroxybenzamidines shows the presence of two tautomeric forms, which in cases of symmetrical substitution are identical. However, there is a slight tendency for *O*-monomethylated derivatives predominantly to contain tautomers of type **5**, whereas in *O*-monobenzylated derivatives tautomers **7**′ prevail (Scheme 4). Katritzky et al. stated that derivative **7d** was more stable,[21] basing this on a 1914 publication by Ley et al.[17] Unfortunately, Ley never studied the stability of the pure substance at room temperature but analyzed complex salts of **7/7**′**d** with metals. Moreover, Katritzky et al. misunderstood the abbreviation "Me" used by Ley et al. for metal and not for methyl. Katritzky et al. stated that rapid tautomerism would lead to only one ^{15}N NMR signal.[21] We, however, observed four nitrogen signals in total for one mixture of tautomers, because two differently hybridized nitrogen atoms appear in each tautomeric form (Scheme 4, Figure 2). Symmetrical substitution affords identical tautomers (Scheme 5), leading to a ^{15}N NMR spectrum showing two chemically different nitrogen signals. The spectroscopic data

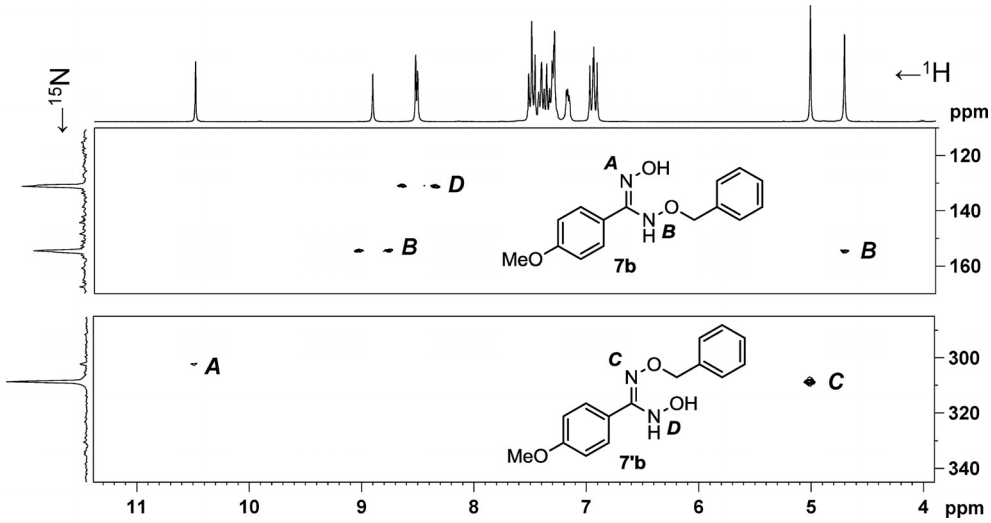
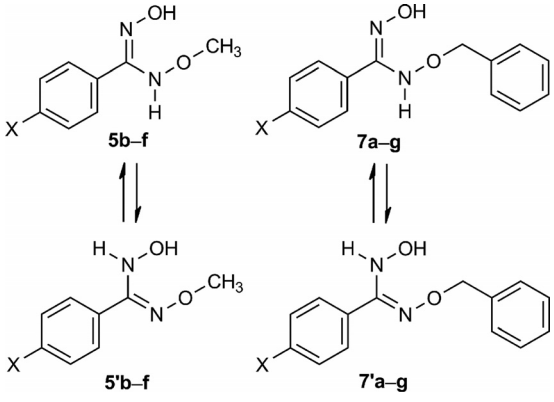


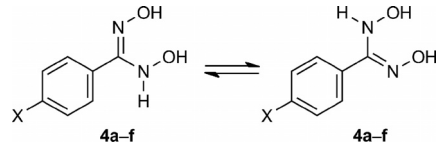
Figure 2. ^{15}N HMBC of the mixture of tautomers of *p*-methoxy-*O*-benzyl-*N*,*N*′-dihydroxybenzamidine (**7b** and **7′b**). Four nitrogen signals can be detected. The hydroxy proton couples over two bonds to nitrogen ***A***. Each *O*-benzylated nitrogen atom (***B*** and ***C***) shows a ^3J coupling to the methylene group. The two split signals ***B*** and ***D*** indicate ^1J NH coupling.

hence give no reason to conclude the existence of only one tautomeric form of **4d**, as claimed by Katritzky.[21] NMR measurements in DMSO display NH groups (large splitting of signals, of the order of 80–90 Hz, in the decoupled HMBC spectrum), showing the presence of one NH group for each tautomeric structure (Figure 2, Table 3). Although there is an equilibrium between the two tautomeric forms, NMR spectroscopy is able to observe two different nitrogen atoms and the NH coupling, so we consider the tautomerization to be slow on the NMR timescale. In most cases ^{15}N HMBC gives better results than direct ^{15}N NMR measurement: ^{15}N chemical shifts can be detected indirectly through coupling with nearby functional groups with sharp ^1H signals [–CH_3 of **5**/**5′** and **6**, –CH_2(–Ph) of **7**/**7′** and **8**] by coupling over two or three bonds, and smaller amounts of substance are acquired (Figure 2).



Scheme 4. Different tautomeric forms of *p*-substituted *O*-monosubstituted *N*,*N*′-dihydroxybenzamidines **5** and **7** (**5**/**5′** 52:48; **7**/**7′** 47:53, calculated from integrals in ^1H NMR spectra).

Unfortunately, compounds **5**/**5′** and **7**/**7′** turned out to decompose in DMSO even at room temperature, and much more rapidly upon heating. The rates of degradation were



Scheme 5. Tautomeric forms of compound **4a**–**f** (also **6b**–**f**, **8a**–**g**, **9a**–**g**) are identical and each give two ^{15}N NMR signals, due in each case to the presence of two differently bonded nitrogen atoms.

estimated from the integrals of the ^1H NMR spectra of freshly dissolved samples and those recorded after a timespan. This decomposition shows the stability to be generally less in cases of electron-withdrawing substituents in the *p*-position, and thus with higher Hammett σ values (Tables 1 and 2). The very fast and complete decay of the *p*-nitro derivative **7**/**7′g** is remarkable.

The degradation products are the corresponding *O*-unsubstituted and *O*-monosubstituted benzamidoximes. As would be expected for *O*,*O*′-bis(tetrahydropyranyl)-*N*,*N*′-dihydroxybenzamidines **9a**–**g**, splitting of NMR peaks due to the presence of diastereomers was observed.

^{15}N NMR Shift Data and Correlations with Hammett σ Values

For the prediction of kinetics in biological systems on the basis of the obtained data, water would be the best solvent. The low solubilities of some compounds, however, together with the need for the same solvent for all derivatives, necessitate the use of [D_6]DMSO. For reliable interpretation we assume similar correlations in both solvents. Linear correlations of chemical shifts with Hammett σ values deliver slopes that describe the sensitivities of the atoms to changes in electron distribution. The intercepts represent the shift

Table 3. Relevant ^{15}N,[a] ^{1}H, and ^{13}C chemical shifts (δ, ppm) and $^{1}J_{N,H}$ couplings (Hz)[b] of the functional groups of *para*-substituted *N*,*N*′-dihydroxybenzamidines and derivatives **4**–**12**[c] in [D_6]DMSO.

	R	R′	Yield [%]	M.p. [°C]	δ (=**N**–)	δ [–**N**(H)–]	$^{1}J_{N,H}$	δ (=NO)**H**	δ (N)**H**	δ (NHO)**H**	δ **C**=NOH (NHOH)
4a	H	H	33	112.2	297.0	128.2	–[d]	10.09	8.08	8.30	156.9
4b	H	H	41	118.3	298.3	128.2	82	10.20	8.13	8.40	156.6
4c	H	H	72	124.2	299.2	128.3	83	10.26	8.16	8.37	156.9
4d	H	H	43	119.8	300.2	128.3	84	10.36	8.22	8.40	157.0
4e	H	H	48	116.7	301.6	128.3	84	10.45	8.27	8.43	155.9
4f	H	H	28	118.6	305.7	128.4	84	10.71	8.40	8.52	155.6
5b	H	Me	12	94.5[e]	–[d]	158.4	–[d]	10.39	8.92	*[f]	154.6
5c	H	Me	10	85.6[e]	–[d]	158.4	–[d]	10.47	8.96	*[f]	154.8
5d	H	Me	21	105.2[e]	–[d]	158.4	–[d]	10.55	9.02	*[f]	154.9
5e	H	Me	37	72.8[e]	–[g]	158.4	82	10.66	9.08	*[f]	153.9
5f	H	Me	23	133.7[e]	309.5	158.1	82	10.95	9.21	*[f]	153.6
5′b	Me	H	12	94.5[e]	311.5	130.7	87	*[f]	8.40	8.48	156.6
5′c	Me	H	9	85.6[e]	312.6	131.1	85	*[f]	8.43	8.48	157.0
5′d	Me	H	18	105.2[e]	312.2	131.1	88	*[f]	8.49	8.50	157.1
5′e	Me	H	35	72.8[e]	313.2	130.6	88	*[f]	8.59	8.56	156.1
5′f	Me	H	22	133.7[e]	316.4	131.2	88	*[f]	8.74	8.66	155.7
6b	Me	Me	56	oil	314.4	160.2	85	*[f]	9.21	*[f]	154.7
6c	Me	Me	18	85.6	315.3	160.3	85	*[f]	9.26	*[f]	155.0
6d	Me	Me	36	oil	315.8	160.4	85	*[f]	9.33	*[f]	155.1
6e	Me	Me	13	oil	316.4	160.3	85	*[f]	9.40	*[f]	154.1
6f	Me	Me	8	83.6	319.3	160.2	86	*[f]	9.53	*[f]	153.7
7a[h]	H	Bn	21	oil	–[d]	154.5	–[d]	10.39	8.85	*[f]	154.9
7b	H	Bn	13	103.0[e]	302.2	154.4	81	10.48	8.91	*[f]	154.5
7c	H	Bn	9	114.2[e]	303.7	154.7	81	10.55	8.94	*[f]	154.8
7d	H	Bn	19	109.2[e]	304.3	155.0	82	10.62	9.01	*[f]	154.9
7e	H	Bn	22	109.0[e]	–[d]	155.6	85	10.74	9.07	*[f]	153.9
7f	H	Bn	18	oil	–[d]	154.7	–[d]	10.95	9.21	*[f]	153.7
7g[i]	H	Bn	42	121.2[e]	–[d]	154.9	82	11.10	9.25	*[f]	153.3
7′a[h]	Bn	H	24	oil	308.3	130.9	88	*[f]	8.44	8.49	157.4
7′b	Bn	H	15	103.0[e]	308.7	131.2	87	*[f]	8.51	8.52	157.1
7′c	Bn	H	11	114.2[e]	309.8	131.3	88	*[f]	8.54	8.52	157.3
7′d	Bn	H	20	109.2[e]	310.4	131.4	88	*[f]	8.62	8.55	157.3
7′e	Bn	H	25	109.0[e]	310.5	131.3	91	*[f]	8.70	8.61	156.3
7′f	Bn	H	21	oil	313.6	131.6	–[d]	*[f]	8.74	8.66	156.0
7′g[i]	Bn	H	44	121.2[e]	314.2	131.8	–[d]	*[f]	8.91	8.75	155.6
8a	Bn	Bn	19	oil	311.5	157.0	86	*[f]	9.23	*[f]	155.5
8b	Bn	Bn	7	oil	312.2	157.1	85	*[f]	9.29	*[f]	155.1
8c	Bn	Bn	29	oil	313.1	157.1	86	*[f]	9.34	*[f]	155.4
8d	Bn	Bn	48	oil	313.3	157.3	86	*[f]	9.44	*[f]	155.5
8e	Bn	Bn	45	70.5	313.9	157.1	88	*[f]	9.50	*[f]	154.5
8f	Bn	Bn	11	89.9	316.4	157.3	87	*[f]	9.64	*[f]	154.1
8g[i]	Bn	Bn	12	oil	317.0	157.2	87	*[f]	9.69	*[f]	153.8
9a[k]	THP	THP	90	oil	310.5; 19	149.4; 36	85	*[f]	8.78; 3.3	*[f]	155.6
9b[k]	THP	THP	47	oil	311.2; 17	149.9; 38	87	*[f]	8.86; 3.8	*[f]	155.3
9c[k]	THP	THP	49	oil	312,1; 21	149.7; 39	84	*[f]	8.87; 4.2	*[f]	155.6
9d[k]	THP	THP	59	oil	312.2; 23	150.6; 33	86	*[f]	8.99; 5.3	*[f]	155.7
9e[k]	THP	THP	56	oil	312.7; 25	150.6; 35	85	*[f]	9.05; 5.2	*[f]	154.7
9f[k]	THP	THP	59	124.6	–[g]	151.3; 33	87	*[f]	9.20; 6.6	*[f]	154.4
9g[k][l]	THP	THP	53	119.7	315.8; 34	151.2; 33	85	*[f]	9.25; 5.5	*[f]	154.1
10			16	130.1	324.0	161.4	*[f]	*[f]	*[f]	9.36	158.8
11			24	132.8	328.6	158.3	*[f]	*[f]	*[f]	9.50	159.4
12			43	71.9	326.7	159.0	*[f]	*[f]	*[f]	9.29	158.9

[a] CH_3NO_2 as external standard in [D_6]DMSO (381.6 ppm). [b] Coupling constants determined from signal splitting in HMBC spectra, precision ± 1 Hz. [c] Measured as 0.6 M solutions in 0.5 mL [D_6]DMSO at 300 K and 30.4 MHz. [d] Signals not detectable. Measurement time limited due to decomposition of compounds **5**/**5**′ and **7**/**7**′. [e] Melting points of the tautomeric mixtures of **5**/**5**′ and **7**/**7**′ are given. [f] Functional group is not part of the compound in question. [g] Maximum solubility of 0.2 M in DMSO is too low. [h] Unstable at room temperature, degradation. [i] δ (NO_2) = 370.1 ppm. [k] Chemical shifts with diastereomeric splitting (ppm, Hz) are given for **9a**–**g**. [l] δ (NO_2) = 369.9 ppm.

values without any additional effect from the substituents (X = H, σ = 0). Both parameters are given for structures **4**–**9** in Table 4, Entries 1–39.

For the unsubstituted *N*,*N*′-dihydroxybenzamidines **4** (Entry 1) the signals of the oxime-type nitrogen atoms are observed at around δ = 300 ppm. The presence of an alkyl

Table 4. ^{15}N and ^{1}H NMR chemical shift (δ, ppm) correlations with Hammett σ values.

Entry	Functional group	Compound	Equation	r^2
1	oxime-type nitrogen =**N**(OH)	**4a–f**	δ[= **N**(OH)] = 7.6 σ + 300.1	0.990 (n = 6)
2		**7b–d**	δ[= **N**(OH)] = 7.5 σ + 304.5	0.942 (n = 3)
3	oxime type nitrogen =**N**(OR)	**5′b–f**	δ[= **N**(OMe)] = 4.7 σ + 312.7	0.913 (n = 5)
4		**6b–f**	δ[= **N**(OMe)] = 4.7 σ + 315.7	0.968 (n = 5)
5		**7′a–g**	δ[= **N**(OBn)] = 4.8 σ + 310.1	0.968 (n = 7)
6		**8a–g**	δ[= **N**(OBn)] = 4.3 σ + 313.3	0.980 (n = 7)
7		**9a–e, g**	δ[= **N**(OTHP)] = 4.1 σ + 312.2	0.961 (n = 6)
8	hydroxylamine-type nitrogen –**N**(HOH)[a]	**4a–f**	δ[–**N**(HOH)] = 0.17 σ + 128.3	0.853 (n = 6)
9		**5b–f**	δ[–**N**(HOMe)] = –0.30 σ + 158.4	0.734 (n = 5)
10		**5′b–f**	δ[–**N**(HOH)] = 0.23 σ + 130.9	0.110 (n = 5)
11		**6b–f**	δ[–**N**(HOMe)] = –0.05 σ + 160.3	0.058 (n = 5)
12		**7a–g**	δ[–**N**(HOBn)] = 0.33 σ + 154.8	0.148 (n = 7)
13		**7′a–g**	δ[–**N**(HOH)] = 0.56 σ + 131.3	0.832 (n = 7)
14		**8a–g**	δ[–**N**(HOBn)] = 0.15 σ + 157.1	0.407 (n = 7)
15		**9a–g**	δ[–**N**(HOTHP)] = 1.48 σ + 150.2	0.891 (n = 7)
16	oxime hydrogen (=NO)**H**	**4a–f**	δ[(= NO)**H**] = 0.54 σ + 10.33	0.987 (n = 6)
17		**5b–f**	δ[(= NO)**H**] = 0.56 σ + 10.54	0.994 (n = 5)
18		**7a–g**	δ[(= NO)**H**] = 0.54 σ + 10.62	0.987 (n = 7)
19	substituted oxime (=NOCR_x)**H**$_y$	**5′b–f**	δ[(= NOCR_x)**H**$_y$] = 0.053 σ + 3.74	0.905 (n = 5)
20		**6b–f**	δ[(= NOCR_x)**H**$_y$] = 0.048 σ + 3.77	0.891 (n = 5)
21		**7′a–g**	δ[(= NOCR_x)**H**$_y$] = 0.057 σ + 5.02	0.893 (n = 7)
22		**8a–g**	δ[(= NOCR_x)**H**$_y$] = 0.057 σ + 5.06	0.910 (n = 7)
23		**9a–g**	δ[(= NOCR_x)**H**$_y$] = 0.042 σ + 5.14	0.599 (n = 7)
24	hydroxylamine O**H** hydrogen	**4a–f**	δ[(–NHO)**H**] = 0.17 σ + 8.40	0.857 (n = 6)
25		**5′b–f**	δ[(–NHO)**H**] = 0.20 σ + 8.51	0.967 (n = 5)
26		**7′a–g**	δ[(–NHO)**H**] = 0.19 σ + 8.56	0.946 (n = 7)
27	substituted hydroxylamine (–NHOCR_x)**H**$_y$	**5b–f**	δ[(–NHOCR_x)**H**$_y$] = 0.025 σ + 3.46	0.690 (n = 5)
28		**6b–f**	δ[(–NHOCR_x)**H**$_y$] = 0.031 σ + 3.44	0.924 (n = 5)
29		**7a–g**	δ[(–NHOCR_x)**H**$_y$] = 0.045 σ + 4.72	0.862 (n = 7)
30		**8a–g**	δ[(–NHOCR_x)**H**$_y$] = 0.043 σ + 4.69	0.891 (n = 7)
31		**9a–g**	δ[(–NHOCR_x)**H**$_y$] = 0.053 σ + 4.79	0.820 (n = 7)
32	hydroxylamine N**H** hydrogen	**4a–f**	δ[–N**H**(OH)] = 0.29 σ + 8.20	0.991 (n = 6)
33		**5b–f**	δ[–N**H**(OMe)] = 0.29 σ + 9.01	0.995 (n = 5)
34		**5′b–f**	δ[–N**H**(OH)] = 0.36 σ + 8.49	0.997 (n = 5)
35		**6b–f**	δ[–N**H**(OMe)] = 0.32 σ + 9.31	0.991 (n = 5)
36		**7a–g**	δ[–N**H**(OBn)] = 0.32 σ + 8.99	0.994 (n = 7)
37		**7′a–g**	δ[–N**H**(OH)] = 0.33 σ + 8.59	0.925 (n = 7)
38		**8a–g**	δ[–N**H**(OBn)] = 0.37 σ + 9.40	0.984 (n = 7)
39		**9a–g**	δ[–N**H**(OTHP)] = 0.38 σ + 8.95	0.982 (n = 7)
40	oxime hydrogen (= NO)**H**	**BAO**[b] **a–g**	δ[(= NO)**H**] = 0.63 σ + 9.59	0.995 (n = 7)
41	amine hydrogen N**H$_2$**	**BAO**[b] **a–g**	δ(–N**H$_2$**) = 0.34 σ + 5.77	0.988 (n = 7)
42		**BA**[c] **a,c–g**	δ(–N**H$_2$**) = 0.42 σ + 9.11	0.884 (n = 6)

[a] Correlations are not significant, so chemical shifts are independent of σ. [b] *p*-Substituted benzamidoximes.[22] [c] *p*-Substituted benzamidines.[22]

substituent on the oxime-type oxygen increases the shift by about 12 ppm (Entries 3 and 5). An alkyl substituent on the hydroxylamine oxygen effects a further deshielding by about 3 ppm (Entries 4, 6, 7).

The ^{15}N NMR chemical shift of the hydroxylamine-type nitrogen is found at about δ = 128 ppm (Entry 8). Alkyl substitution at the corresponding oxygen shifts this signal paramagnetically by about 30 ppm (Entries 9, 12), whereas the presence of an alkyl substituent at the vicinal oxime oxygen leads to a smaller effect with a deshielding of about 2 ppm (Entries 10 and 13). Substituent effects at oxygen on ^{15}N NMR shifts are additive (Entries 4, 6, 7 and 11, 14, 15).

The cyclic compounds **10**–**12** show remarkable paramagnetic ^{15}N NMR chemical shifts, especially of the oxime-type nitrogen atoms. The difference of about 25–30 ppm relative to **4d** represents a much broader effect of cyclization than of *para*-substitution or *O*-substitution without cyclization, for which the differences are smaller for every derivative of type **4**–**9**. The spiro substitution in **11** and **12** leads to increases in the ^{15}N NMR shifts of the oxime-type nitrogen atoms relative to **10**, whereas the hydroxylamine-type nitrogen shifts decrease.

There is a strong correlation of ^{15}N NMR chemical shifts of the oxime-type nitrogen atoms with the Hammett constants, similar to the sensitivity of the ^{15}N NMR shifts to the Hammett σ values in benzamidinium salts,[11] and also to their sensitivity in the case of the oxime-type nitrogen atoms in benzamidoximes,[11] benzamides,[23] and benzonitriles.[24] The slopes of the regression lines are in the 5–10 ppm range. These nitrogen atoms are at least partially sp^2- or sp-hybridized and show electronic interactions with the aromatic systems. The greater the electron-withdrawing effect of the *p*-substituent, the more the ^{15}N NMR signal is

shifted paramagnetically (Figure 1). In the oxime-oxygen-substituted derivatives (Entries 3–7), sensitivity is slightly reduced, by a factor of about 2. In contrast, hydroxylamine-type nitrogen ^{15}N NMR shifts are not susceptible, or are only slightly susceptible, to the effects of substituents in the *para*-position. For this nitrogen atom type there is no significant correlation (Entries 8–15). No further correlation with, for example, the $^{1}J_{N,H}$ coupling constants of hydroxylamine-type nitrogen atoms (Table 3) or the splitting of the diastereomeric signals for derivatives **9a**–**g** (Table 3) was observed. Generally, diastereomeric chemical shift differences for the hydroxylamine-type-nitrogen atoms of **9a**–**g** are larger than those for the oxime-type nitrogen atoms of the same compounds.

^{13}C NMR Spectroscopic Data

The ^{13}C NMR chemical shifts of the dihydroxyamidine functional groups in the aromatic derivatives are observed at δ = 153–159 ppm. There is no significant correlation with σ. Alkyl substitution at the hydroxylamine-type oxygen atoms (**5**, **7**) shifts the signals diamagnetically by 2 ppm relative to those for *O*,*O*′-unsubstituted derivatives **4**, whereas an alkyl substituent at the oxime oxygen atom shifts the carbon shift paramagnetically by about 0.3 ppm (**5**′, **7**′). Additional alkyl substitution of compounds **10**–**12** at the hydroxylamine nitrogen further increases the corresponding ^{13}C NMR chemical shifts: the carbon resonance of the functional group of 159 ppm represents a paramagnetical shift of 2 ppm. Substituent effects at oxygen on ^{13}C NMR shifts also seem to be additive. The ^{13}C chemical shifts of the functional groups of *O*,*O*′-disubstituted derivatives **6** and **8** are thus between those of the monosubstituted compounds **5**/**5**′ and **7**/**7**′.

^{1}H NMR Shifts

Correlations of all ^{1}H NMR chemical shifts of the dihydroxyamidine functional groups in **4**–**9** with Hammett σ values afford significant results. For the oxime hydroxy protons (Entries 16–18), the hydroxylamine hydroxy protons (Entries 24–26), and the hydroxylamine NH protons (Entries 32–39) correlations are in most cases excellent, with $r > 0.99$. Even for protons of the alkyl substituents next to the ether linkages in **5**–**9**, small but significant effects can be observed (Entries 19–23, 27–31). Comparison of the shifts of **4**–**9** with the corresponding shifts of benzamidoximes (BAOs) and benzamidinium chlorides (BAs),[22] the metabolic follow-up products (Scheme 1), is of interest. Appropriate regression lines of proton chemical shifts in [D_6]DMSO with σ are also given in Table 4 (Entries 40–42).

It can be seen that the oxime hydroxy protons in dihydroxyamidines (Entries 16–18) are paramagnetically shifted by about 1 ppm relative to benzamidoxime hydroxy protons (Entry 40). Alkyl substitution of the vicinal hydroxylamine OH groups (**5**, **7**, Entries 17–18) increases ^{1}H NMR chemical shifts by about 0.3 ppm relative to the unsubstituted derivative **4** (Entry 16). The oxime protons show the greatest susceptibility to electronic interactions of all the protons of **4**, **5**, and **7**. The slope of the Hammett plot is in the 0.6 ppm range and similar to the slopes found for the benzamidoxime hydroxy groups and the benzamidinium amino groups (Entries 40, 42). The hydroxylamine NH proton chemical shifts of about 8.5 ppm for **4**–**9** (Entries 32–39) are similar to those for benzamidinium salts (Entry 42). Alkyl substitution of the vicinal oxime hydroxy groups in **5**′ and **7**′ results in increases of about 0.3 ppm in the chemical shifts of the amine protons. Substitution of the hydroxylamine OH groups in **5** and **7** shifts the signals paramagnetically by about 0.8 ppm. *O*,*O*′-Disubstituted derivatives **6**, **8**, and **9** show these effects to be additive. The slope for the correlation of the amino protons of dihydroxybenzamidines **4**–**9** is half the magnitude, with a value of 0.3 ppm (Entries 32–39), as is also found for the amino protons of benzamidoximes (Entry 41). The ^{1}H chemical shifts of the hydroxylamine OH protons of **4** are about 8.4 ppm and shift paramagnetically by about 0.15 ppm if the vicinal oxime group is substituted (Entries 24–26). Cyclic *N*,*O*-disubstituted dihydroxyamidine derivatives **10**–**12** show significant deshielding of the hydroxylamine hydrogen chemical shift signals of 9.5 ppm, 0.5–1 ppm above those of all other derivatives **4**–**9**. Correlation of the hydroxylamine OH protons with σ leads to a relatively small slope of about 0.2 ppm, due to the greater distance to the *para*-effector. The shifts of the protons of the alkyl substituents (i.e., methyl groups, methylene protons of benzyl groups, and methine protons of THP residues) are also influenced significantly by the substituents on the aromatic rings, with slopes of about 0.02 to 0.06 ppm (Entries 19–23 and 27–31). It has to be clearly stated that these protons are already nine bonds away from the *para*-substituent.

Therefore, for the interaction of compounds **4**–**9** with enzymes, not only is the influence of substituents of the aromatic system on the electron density at the nitrogen atoms of importance, but the strength of hydrogen bonding also needs to be discussed.

Conclusions

We have established versatile synthetic approaches to different previously unknown *para*-substituted *N*,*N*′-dihydroxybenzamidines and derivatives representing a new class of prodrugs. All of the reactions start with the intermediate **3** and different hydroxylamine derivatives. This method can also be adapted to the synthesis of other dihydroxybenzamidine compounds, so a route to a variety of new potential prodrugs is created. Properties relating to instability of the compounds have been analyzed, so conditions leading to decomposition can be prevented. NMR chemical shifts of oxime-type nitrogen atoms and all hydrogen atoms of dihydroxyamidine functional groups correlate strongly with Hammett σ values, so *para*-substitution has a significant influence on electron density in the functional group. Mono- and disubstitution of oxygen also leads to predicta-

ble effects in the electron density at the corresponding N, H, and C atoms. Cyclization of the dihydroxyamidine functional group decreases electron density massively. With the obtained data, kinetics of reactions with biological structures can be predicted. Quantitative structure–activity correlation of mARC activity with the Hammett σ values, for example, results in a relationship of mARC kinetics with NMR spectroscopic data, which will be part of further investigations.

Experimental Section

General: *para*-Substituted benzaldehydes were commercially available (Merck, Aldrich) and were used without purification. Melting points were measured with a Stuart Scientific melting-point apparatus SMP3 and are uncorrected. For TCL, silica plates (Polygram SIL G/UV$_{254}$ 0.25 mm) were used. All NMR spectra were recorded in concentrations of 0.1–0.3 M for ^{1}H, ^{13}C, and ^{15}N HMBC and 0.5 to 0.7 M in the case of direct ^{15}N detection. ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded at 300 K with a Bruker Avance III 300 instrument and a multinuclear probe head, with use of the manufacturer's pulse programs. The solvent for all spectra was [D$_6$]DMSO. For ^{15}N NMR measurements, between 50 and 150 mg of **4**–**12** in 0.5 mL solvent or saturated solutions were used. ^{1}H (300 MHz), ^{13}C (75.4 MHz), and ^{15}N (30.4 MHz) spectra were referenced to internal [D$_5$]DMSO (^{1}H NMR δ = 2.50 ppm), internal [D$_6$]DMSO (^{13}C NMR δ = 39.5 ppm), and external standard nitromethane (^{15}N NMR δ = 0.0 ppm), which was corrected to ammonia scale by addition of 381.6 ppm. All coupling constants (J values) are quoted in Hz; ds stands for diastereomeric shift. ^{15}N data were obtained by direct measurement or indirect detection of proton resonances. For the recording of ^{1}H, ^{15}N gradient-enhanced HSQC spectra a sweep width of 550 ppm and 512 t_1 increments, an acquisition time of 0.24 s, an interpulse delay of 1.5 s, and two repetitions per t_1 increment were used. Resolution enhancement was achieved through linear prediction. For recording of gradient-enhanced HMBC spectra without decoupling with 512 t_1 increments an acquisition time of 0.12 s, an interpulse delay of 1.5 s, and 16 or 24 repetitions per t_1 increment were necessary. A ^{15}N sweep rate of 550 ppm and resolution improvement through linear prediction were also employed. Direct detection of ^{15}N shifts was achieved with conventional composite pulse decoupling, a sweep width of 550 ppm, a 30° flip angle acquisition of 32 K data points, and a delay of 2 s. Only for derivatives **10**–**12** was it necessary to record ^{15}N spectra by inverse gated decoupling with a very short acquisition time of about 0.5 s and a relaxation delay of 8 s to detect N–2. Mass spectrometry was carried out with a Bruker Esquire ~ LC instrument under ESI conditions in the positive ionization mode. Samples were applied after chromatographic separation with a RP 8 column and a 0.1% aqueous acetic acid/acetonitrile gradient. IR spectra were recorded with a Perkin–Elmer Spectrum 100 FTIR instrument with ATR attachment. Elemental analyses were measured by the Department of Inorganic Chemistry, Christian Albrechts University of Kiel with a CHNS Analyzer (HEKAtech GmbH).

General Synthesis of *para*-Substituted Benzaldoximes 2a–g: The syntheses were carried out by a literature procedure.[25] Hydroxylamine hydrochloride (4.17 g, 60 mmol) was dissolved in water (40 mL) and neutralized with aqueous sodium hydroxide solution (10%). A solution of an aldehyde **1** (50 mmol) in ethanol was added slowly to this mixture with stirring in a water bath at 20 °C. The suspension was stirred at room temperature with monitoring by TLC (cyclohexane/ethyl acetate 8:2; 2% aqueous $FeCl_3$ solution with heat colored oximes **2a**–**g** brown). After completion of the reaction about 1 h later, ethanol was evaporated. The residue was diluted with water and extracted three times with dichloromethane. The combined organic phase was washed with brine and dried with anhydrous sodium sulfate. After evaporation of the solvent, the compound **2** (one out of **2a**–**g**) was obtained in 90–100% yield. Products were used for further reactions without additional purification. The obtained characterizing data are consistent with literature information.

General Synthesis of *para*-Substituted Benzhydroxamic Acid Chlorides 3a–g: The syntheses were carried out by a literature procedure.[16] The benzaldoxime (one out of **2a**–**g**, 30 mmol) was dissolved in dimethylformamide (50 mL) with stirring, and *N*-chlorosuccinimide (30 mmol) was added in two portions at room temperature. Initiation of the reaction was accelerated by use of a slight increase in the temperature to 40 °C for 20 min and UV light. The reaction was monitored by TLC (cyclohexane/ethyl acetate 8:2; 2% aqueous $FeCl_3$ solution colored **3a**–**g** red-brown after heating). After about 12 h the reaction was complete. An ice/water mixture was added and extracted twice with diethyl ether. The organic phase was washed twice with ice/water, dried with anhydrous sodium sulfate, and concentrated to give 95–100% **3a**–**g**. The products were stored at –18 °C because of slow decomposition at room temperature. The obtained characterizing data were consistent with literature information.

General Synthesis of *para*-Substituted *N*,*N*′-Dihydroxybenzamidines 4a–f: The syntheses were based on a literature procedure describing the synthesis of **4d**.[12] The appropriate hydroxamic acid chloride (one out of **3a**–**f**, 3 mmol) was dissolved in diethyl ether (5–10 mL), and the solution was poured into a dropping funnel. Hydroxylamine (9 mmol, 297 mg, 3 equiv.) as free base was dissolved in ethanol and the solution was cooled down in an ice-bath with stirring in a flask. The hydroxamic acid chloride (**3a**–**f**) was added slowly with stirring. The reaction was monitored by TLC (cyclohexane/ethyl acetate 1:1; 2% aqueous $FeCl_3$ solution colored **4a**–**f** blue). If TLC still indicated **3a**–**f** after 7 h, further hydroxylamine (2 equiv.) dissolved in ethanol was added to the reaction mixture. After completion of the reaction (about 15–20 h) the formed suspension was filtered. Flash chromatography of the concentrated crude filtrate (max. 30 °C) on silica as solid phase and with cyclohexane/ethyl acetate gradient as mobile phase resulted in the desired product **4a**–**f**. Additional workup gave pure products **4a**–**f**.

***p*-Hydroxy-*N*,*N*′-dihydroxybenzamidine (4a):** Starting compound **3a** (515 mg, 3 mmol) was used. After flash chromatography, the compound was triturated with dichloromethane and filtered to give product **4a** (165 mg, 0.98 mmol, 32.7%) as a beige powder, m.p. 112.2 °C. R_f (cyclohexane/ethyl acetate 1:1): 0.13. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.74 (d, 2 H, Ar-H), 7.39 (d, 2 H, Ar-H), 8.08 (s, 1 H, NH), 8.30 [s, 1 H, (NHO)H], 9.58 (s, 1 H, *p*-OH), 10.09 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 114.5 (Ar-C-3), 122.7 (Ar-C-1), 129.1 (Ar-C-2), 156.9 [C$_q$(NN)], 158.0 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 128.2 (NH), 297.0 (=NOH) ppm.

***p*-Methoxy-*N*,*N*′-dihydroxybenzamidine (4b):** Starting compound **3b** (928 mg, 5 mmol) was used. After flash chromatography, the compound was triturated with dichloromethane and filtered to give product **4b** (373 mg, 2.05 mmol, 41.2%) as a white solid, m.p. 118.3 °C. R_f (cyclohexane/ethyl acetate 1:1): 0.28. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.77 (s, 3 H, *p*-OCH$_3$), 6.92 (d, 2 H, Ar-H), 7.52 (d, 2 H, Ar-H), 8.13 (s, 1 H, NH), 8.40 [s, 1 H, (NHO)-

H], 10.20 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.1 (*p*-OCH$_3$), 113.2 (Ar-C-3), 124.3 (Ar-C-1), 129.1 (Ar-C-2), 156.6 [C$_q$(NN)], 159.7 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]-DMSO): δ = 128.2 ($^1J_{N,H}$ = 82 Hz, NH), 298.3 (=NOH) ppm.

***p*-Methyl-*N*,*N*′-dihydroxybenzamidine (4c):** Starting compound **3c** (339 mg, 2 mmol) was used. After flash chromatography, the compound was triturated with dichloromethane and filtered to give product **4c** (238 mg, 1.43 mmol, 71.7%) as a white solid, m.p. 124.2 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.13. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.31 (s, 3 H, *p*-CH$_3$), 7.17 (d, 2 H, Ar-H), 7.47 (d, 2 H, Ar-H), 8.16 (s, 1 H, NH), 8.37 [s, 1 H, (NHO)H], 10.26 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.9 (*p*-CH$_3$), 127.6 (Ar-C-2), 128.3 (Ar-C-3), 129.2 (Ar-C-1), 138.1 (Ar-C-4), 156.9 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]-DMSO): δ = 128.3 ($^1J_{N,H}$ = 83 Hz, NH), 299.2 (=NOH) ppm.

***N*,*N*′-Dihydroxybenzamidine (4d):** Starting compound **3d** (778 mg, 5 mmol) was used. After flash chromatography, the compound was dissolved in a small amount of ethyl acetate, precipitated with petroleum ether, and cooled overnight to give product **4d** (324 mg, 2.13 mmol, 42.6%) as a white solid, m.p. 119.8 °C; m.p.[26] 112–113 °C; m.p.[12] 115 °C. R_f (cyclohexane/ethyl acetate 6:4): 0.31. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.40 (m, 3 H, Ar-H), 7.58 (m, 2 H, Ar-H), 8.22 (s, 1 H, NH), 8.40 [s, 1 H, (NHO)H], 10.36 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 127.8 (Ar-C-2), 127.8 (Ar-C-3), 128.8 (Ar-C-4), 132.2 (Ar-C-1), 157.0 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 128.3 ($^1J_{N,H}$ = 84 Hz, NH), 300.2 (=NOH) ppm.

***p*-Bromo-*N*,*N*′-dihydroxybenzamidine (4e):** Starting compound **3e** (680 mg, 2.9 mmol) was used. After flash chromatography, the compound was triturated with dichloromethane and filtered to give product **4e** (320 mg, 1.39 mmol, 47.8%) as a white solid, m.p. 116.7 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.12. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.50 (d, 2 H, Ar-H), 7.57 (d, 2 H, Ar-H), 8.27 (s, 1 H, NH), 8.43 [s, 1 H, (NHO)H], 10.45 [s, 1 H, (=NO)-H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 122.0 (Ar-C-4), 129.7 (Ar-C-2), 130.7 (Ar-C-3), 131.3 (Ar-C-1), 155.9 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 128.3 ($^1J_{N,H}$ = 84 Hz, NH), 301.6 (=NOH) ppm.

***p*-Cyano-*N*,*N*′-dihydroxybenzamidine (4f):** Starting compound **3f** (361 mg, 2 mmol) was used. After flash chromatography, the compound was triturated with dichloromethane and filtered to give product **4f** (100 mg, 0.56 mmol, 28.2%) as a pale yellow solid, m.p. 118.6 °C. R_f (cyclohexane/ethyl acetate 1:1): 0.33. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.73 (d, 2 H, Ar-H), 7.84 (d, 2 H, Ar-H), 8.40 (s, 1 H, NH), 8.52 [s, 1 H, (NHO)H], 10.71 [s, 1 H, (=NO)-H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 111.2 (Ar-C-4), 118.7 (*p*-CN), 128.4 (Ar-C-2), 131.8 (Ar-C-3), 136.8 (Ar-C-1), 155.6 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 128.4 ($^1J_{N,H}$ = 84 Hz, NH), 305.7 (=NOH) ppm.

General Synthesis of *para*-Substituted *O*-Methyl-*N*,*N*′-dihydroxybenzamidines 5/5′b–f: The starting compound (one out of **3b**–**f**) was dissolved in diethyl ether or dichloromethane with stirring in a flask. *O*-Methylhydroxylamine hydrochloride (2 equiv.) and triethylamine (2 equiv.) were added successively. The mixture was stirred at room temperature and monitored by TLC (cyclohexane/ethyl acetate 6:4, 2% aqueous $FeCl_3$ solution indicating **5/5′b**–**f** as blue spots). After 20–25 h reaction was stopped. Precipitated byproduct was filtered off. The filtrate was concentrated under reduced pressure at max. 30 °C and applied to silica for flash chromatography with cyclohexane/ethyl acetate gradient as mobile phase and silica as solid phase to give **5/5′b**, **5/5′d**, and **5/5′e** as pure products. Additional workup was required for **5/5′c** and **5/5′f** and led to pure compounds.

***p*-Methoxy-*O*-methyl-*N*,*N*′-dihydroxybenzamidine (5/5′b):** Compound **3b** (371 mg, 2 mmol) was dissolved in diethyl ether (7 mL). Methylhydroxylamine hydrochloride and triethylamine were dissolved in ethanol and added slowly to the reaction mixture with stirring. After flash chromatography, the compound was triturated with cyclohexane and filtered to give pure product **5/5′b** [78 mg, 0.40 mmol, 24.2% (**5b**: 12.4%; **5′b**: 11.8%)] as a white solid, m.p. 94.5 °C. R_f (cyclohexane/ethyl acetate 1:1): 0.50.

Tautomer 5b: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.45 (s, 3 H, OCH$_3$), 3.77 (s, 3 H, *p*-OCH$_3$), 6.93 (m, 2 H, Ar-H), 7.47 (m, 2 H, Ar-H), 8.92 (s, 1 H, NH), 10.39 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.1 (*p*-OCH$_3$), 62.4 (NHOCH$_3$), 113.2–113.4 (Ar-C-3), 123.9 (Ar-C-1), 128.7–129.5 (Ar-C-2), 154.6 [C$_q$(NN)], 159.9 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 158.4 (NH) ppm.

Tautomer 5′b: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.72 (s, 3 H, OCH$_3$), 3.77 (s, 3 H, *p*-OCH$_3$), 6.93 (m, 2 H, Ar-H), 7.47 (m, 2 H, Ar-H), 8.40 (s, 1 H, NH), 8.48 [s, 1 H, (NHO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.1 (*p*-OCH$_3$), 61.0 (=NOCH$_3$), 113.2–113.4 (Ar-C-3), 123.2 (Ar-C-1), 128.7–129.5 (Ar-C-2), 156.6 [C$_q$(NN)], 159.9 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 130.7 ($^1J_{N,H}$ = 87 Hz, NH), 311.5 (=NOCH$_3$) ppm.

***p*-Methyl-*O*-methyl-*N*,*N*′-dihydroxybenzamidine (5/5′c):** Compound **3c** (339 mg, 2 mmol) was dissolved in diethyl ether (5 mL). Methylhydroxylamine hydrochloride and triethylamine were dissolved in ethanol and added slowly to the reaction mixture with stirring. Flash chromatography gave pure product **5/5′c** [67 mg, 0.37 mmol, 18.6% (**5c**: 9.5%, **5′c**: 9.1%)] as a white solid, m.p. 85.6 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.29.

Tautomer 5c: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.32 (s, 3 H, *p*-CH$_3$), 3.46 (s, 3 H, OCH$_3$), 7.19 (m, 2 H, Ar-H), 7.43 (m, 2 H, Ar-H), 8.96 (s, 1 H, NH), 10.47 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.8 (*p*-CH$_3$), 62.5 (NHOCH$_3$), 127.3–128.0 (Ar-C-2), 128.3–128.5 (Ar-C-3), 129.0 (Ar-C-1), 138.5 (Ar-C-4), 154.8 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 158.4 (NH) ppm.

Tautomer 5′c: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.32 (s, 3 H, *p*-CH$_3$), 3.74 (s, 3 H, OCH$_3$), 7.19 (m, 2 H, Ar-H), 7.43 (m, 2 H, Ar-H), 8.43 (s, 1 H, NH), 8.48 [s, 1 H, (NHO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.8 (*p*-CH$_3$), 61.0 (=NOCH$_3$), 127.3–128.0 (Ar-C-2), 128.1 (Ar-C-1), 128.3–128.5 (Ar-C-3), 138.5 (Ar-C-4), 157.0 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 131.1 ($^1J_{N,H}$ = 85 Hz, NH), 312.6 (=NOCH$_3$) ppm.

***O*-Methyl-*N*,*N*′-dihydroxybenzamidine (5/5′d):** Compound **3d** (311 mg, 2 mmol) was dissolved in dichloromethane (5 mL). Methylhydroxylamine hydrochloride and triethylamine were then added to the reaction mixture with stirring. Flash chromatography gave pure product **5/5′d** [127 mg, 0.77 mmol, 38.3% (**5d**: 20.7%, **5′d**: 17.6%)] as a white solid, m.p. 105.2 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.37.

Tautomer 5d: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.47 (s, 3 H, OCH$_3$), 7.39 (m, 3 H, Ar-H), 7.53 (m, 2 H, Ar-H), 9.02 (s, 1 H, NH), 10.55 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 62.5 (NHOCH$_3$), 127.4–127.7 (Ar-C-2), 127.9–128.1 (Ar-C-3), 129.0 (Ar-C-4), 131.8 (Ar-C-1), 154.9 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 158.4 (NH) ppm.

Tautomer 5′d: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.75 (s, 3 H, OCH$_3$), 7.39 (m, 3 H, Ar-H), 7.53 (m, 2 H, Ar-H), 8.49 (s, 1 H,

NH), 8.50 [s, 1 H, (NHO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 61.1 (=NOCH$_3$), 127.4–127.7 (Ar-C-2), 127.9–128.1 (Ar-C-3), 129.0 (Ar-C-4), 131.2 (Ar-C-1), 157.1 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 131.1 ($^1J_{N,H}$ = 88 Hz, NH), 312.2 (=NOCH$_3$) ppm.

***p*-Bromo-*O*-methyl-*N*,*N*′-dihydroxybenzamidine (5/5′e):** Compound **3e** (469 mg, 2 mmol) was dissolved in dichloromethane (10 mL). Methylhydroxylamine hydrochloride and triethylamine were then added to the reaction mixture with stirring. Flash chromatography gave pure product **5/5′e** [352 mg, 1.44 mmol, 71.9% (**5e**: 37.2%, **5′e**: 34.7%)] as a white solid, m.p. 72.8 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.35.

Tautomer 5e: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.46 (s, 3 H, OCH$_3$), 7.47 (m, 2 H, Ar-H), 7.59 (m, 2 H, Ar-H), 9.08 (s, 1 H, NH), 10.66 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 62.5 (NHOCH$_3$), 122.3 (Ar-C-4), 129.4–130.1 (Ar-C-2), 130.7–131.0 (Ar-C-3), 131.2 (Ar-C-1), 153.9 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 158.4 (NH, $^1J_{N,H}$ = 82 Hz) ppm.

Tautomer 5′e: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.75 (s, 3 H, OCH$_3$), 7.47 (m, 2 H, Ar-H), 7.59 (m, 2 H, Ar-H), 8.56 [s, 1 H, (NHO)H], 8.59 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 61.2 (=NOCH$_3$), 122.4 (Ar-C-4), 129.4–130.1 (Ar-C-2), 130.4 (Ar-C-1), 130.7–131.0 (Ar-C-3), 156.1 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 130.6 ($^1J_{N,H}$ = 88 Hz, NH), 313.2 (=NOCH$_3$) ppm.

***p*-Cyano-*O*-methyl-*N*,*N*′-dihydroxybenzamidine (5/5′f):** Compound **3f** (542 mg, 3 mmol) was dissolved in dichloromethane (15 mL). Methylhydroxylamine hydrochloride and triethylamine were then added to the reaction mixture with stirring. After flash chromatography, the compound was triturated successively with cyclohexane and dichloromethane and filtered to give pure product **5/5′f** [257 mg, 1.35 mmol, 45.1% (**5f**: 23.3%, **5′f**: 21.8%)] as a white solid, m.p. 133.7 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.21.

Tautomer 5f: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.48 (s, 3 H, OCH$_3$), 7.70 (m, 2 H, Ar-H), 7.86 (m, 2 H, Ar-H), 9.21 (s, 1 H, NH), 10.95 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 62.6 (NHOCH$_3$), 111.6 (Ar-C-4), 118.6 (*p*-CN), 128.1–128.9 (Ar-C-2), 131.8–132.0 (Ar-C-3), 136.9 (Ar-C-1), 153.6 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 158.1 (NH, $^1J_{N,H}$ = 82 Hz), 309.5 (=NOH) ppm.

Tautomer 5′f: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.78 (s, 3 H, OCH$_3$), 7.70 (m, 2 H, Ar-H), 7.86 (m, 2 H, Ar-H), 8.66 [s, 1 H, (NHO)H], 8.74 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 61.5 (=NOCH$_3$), 111.6 (Ar-C-4), 118.6 (*p*-CN), 128.1–128.9 (Ar-C-2), 131.8–132.0 (Ar-C-3), 135.9 (Ar-C-1), 155.7 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 131.2 ($^1J_{N,H}$ = 88 Hz, NH), 316.4 (=NOCH$_3$) ppm.

General Synthesis of *para*-Substituted *O*,*O*′-Dimethyl-*N*,*N*′-dihydroxybenzamidines 6b–f: The starting compound (one out of **3b**–**f**) was dissolved in dichloromethane with stirring in a flask. Two equivalents of methylhydroxylamine hydrochloride and (2 equiv.) of triethylamine were added successively. The mixture was stirred at room temperature and monitored by TLC (cyclohexane/ethyl acetate 7:3, with 2% aqueous $FeCl_3$ solution indicating **6b**–**f** as yellow spots and disappearance of **3b**–**f**). After 24 h further methylhydroxylamine hydrochloride (2 equiv.) and triethylamine (2 equiv.) were added if **3b**–**f** was still detectable. The procedure was repeated after 48 h. Usually the reaction was complete after 48–72 h and the precipitated byproduct was filtered off. The filtrate was concentrated under reduced pressure at max. 30 °C and applied onto silica for flash chromatography with cyclohexane/ethyl acetate gradient as mobile phase and silica as solid phase to give **6b**–**f** as pure products.

***p*-Methoxy-*O*,*O*′-dimethyl-*N*,*N*′-dihydroxybenzamidine (6b):** Compound **3b** (742 mg, 4 mmol) was dissolved in diethyl ether (15 mL). Methylhydroxylamine hydrochloride and triethylamine were dissolved in ethanol and slowly added to the reaction mixture with stirring. Flash chromatography gave pure product **6b** (473 mg, 2.25 mmol, 56.3%) as a colorless oil. R_f (cyclohexane/ethyl acetate 1:1): 0.50. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.43 [s, 3 H, (NHO)CH$_3$], 3.75 [s, 3 H, (=NO)CH$_3$], 3.78 (s, 3 H, *p*-OCH$_3$) 6.95 (d, 2 H, Ar-H), 7.43 (d, 2 H, Ar-H), 9.21 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.1 (*p*-OCH$_3$), 61.1 (=NOCH$_3$), 62.7 (NHOCH$_3$), 113.4 (Ar-C-3), 122.9 (Ar-C-1), 129.1 (Ar-C-2), 154.7 [C$_q$(NN)], 160.1 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]-DMSO): δ = 160.2 ($^1J_{N,H}$ = 85 Hz, NH), 314.4 (=NOCH$_3$) ppm.

***p*-Methyl-*O*,*O*′-dimethyl-*N*,*N*′-dihydroxybenzamidine (6c):** Compound **3c** (339 mg, 2 mmol) was dissolved in dichloromethane (5 mL). Methylhydroxylamine hydrochloride and triethylamine were then added to the reaction mixture with stirring. Flash chromatography gave pure product **6c** (83 mg, 0.43 mmol, 21.4%) as a pale yellow oil. R_f (cyclohexane/ethyl acetate 8:2): 0.52. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.33 (s, 3 H, *p*-CH$_3$), 3.43 [s, 3 H, (NHO)CH$_3$], 3.76 [s, 3 H, (=NO)CH$_3$], 7.20 (d, 2 H, Ar-H), 7.39 (d, 2 H, Ar-H), 9.26 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.8 (*p*-CH$_3$), 61.2 (=NOCH$_3$), 62.7 (NHOCH$_3$), 127.7 (Ar-C-2), 127.9 (Ar-C-1), 128.5 (Ar-C-3), 138.9 (Ar-C-4), 155.0 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 160.3 ($^1J_{N,H}$ = 85 Hz, NH), 315.3 (=NOCH$_3$) ppm.

***O*,*O*′-Dimethyl-*N*,*N*′-dihydroxybenzamidine (6d):** Compound **3d** (622 mg, 4 mmol) was dissolved in diethyl ether (8 mL). Methylhydroxylamine hydrochloride and triethylamine were dissolved in ethanol and added slowly to the reaction mixture with stirring. Flash chromatography gave pure product **6d** (262 mg, 1.46 mmol, 36.4%) as a yellow oil. R_f (cyclohexane/ethyl acetate 7:3): 0.59. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.44 [s, 3 H, (NHO)CH$_3$], 3.78 [s, 3 H, (=NO)CH$_3$], 7.41 (m, 3 H, Ar-H), 7.50 (m, 2 H, Ar-H), 9.33 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 61.3 (=NOCH$_3$), 62.8 (NHOCH$_3$), 127.8 (Ar-C-2), 128.0 (Ar-C-3), 129.4 (Ar-C-4), 130.9 (Ar-C-1), 155.1 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 160.4 ($^1J_{N,H}$ = 85 Hz, NH), 315.8 (=NOCH$_3$) ppm.

***p*-Bromo-*O*,*O*′-dimethyl-*N*,*N*′-dihydroxybenzamidine (6e):** Compound **3e** (469 mg, 2 mmol) was dissolved in dichloromethane (10 mL). Methylhydroxylamine hydrochloride and triethylamine were then added to the reaction mixture with stirring. Flash chromatography gave pure product **6e** (62 mg, 0.25 mmol, 12.7%) as a colorless oil. R_f (cyclohexane/ethyl acetate 7:3): 0.60. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.44 [s, 3 H, (NHO)CH$_3$], 3.78 [s, 3 H, (=NO)CH$_3$], 7.45 (d, 2 H, Ar-H), 7.61 (d, 2 H, Ar-H), 9.40 [s, 1 H, (NHO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 61.3 (=NOCH$_3$), 62.7 (NHOCH$_3$), 122.8 (Ar-C-4), 129.8 (Ar-C-2), 130.0 (Ar-C-1), 131.0 (Ar-C-3), 154.1 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 160.3 ($^1J_{N,H}$ = 85 Hz, NH), 316.4 (=NOCH$_3$) ppm.

***p*-Cyano-*O*,*O*′-dimethyl-*N*,*N*′-dihydroxybenzamidine (6f):** Compound **3f** (361 mg, 2 mmol) was dissolved in dichloromethane (10 mL). Methylhydroxylamine hydrochloride and triethylamine were then added to the reaction mixture with stirring. Flash chromatography gave pure product **6f** (32 mg, 0.16 mmol, 7.8%) as a white solid, m.p. 83.6 °C. R_f (cyclohexane/ethyl acetate 8:2): 0.53. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.46 [s, 3 H, (NHO)CH$_3$], 3.80 [s, 3 H, (=NO)CH$_3$], 7.67 (d, 2 H, Ar-H), 7.87 (d, 2 H, Ar-H),

9.53 [s, 1 H, (NHO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 61.6 (=NOCH$_3$), 62.8 (NHOCH$_3$), 112.0 (Ar-C-4), 118.5 (*p*-CN), 128.6 (Ar-C-2), 132.0 (Ar-C-3), 135.4 (Ar-C-1), 153.7 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 160.2 ($^1J_{N,H}$ = 86 Hz, NH), 319.3 (=NOCH$_3$) ppm.

General Synthesis of *para*-Substituted *O*-Benzyl-*N*,*N*′-dihydroxybenzamidines 7/7′a–g: Benzylhydroxylamine (2 equiv.) was added to a solution of **3** (one out of **3a**–**g**) in dichloromethane, diethyl ether, or dichloromethane/diethyl ether. The reaction mixture was stirred at room temperature and monitored by TLC (cyclohexane/ethyl acetate 6:4, with 2% aqueous $FeCl_3$ solution indicating **7/7′a**–**g** as blue spots). After 20–25 h the reaction was stopped. Precipitated byproduct was filtered off. The filtrate was concentrated under reduced pressure at max. 30 °C and transferred to silica for flash chromatography with cyclohexane/ethyl acetate gradient as mobile phase and silica as solid phase. Compound **7/7′f** was obtained as a pure product. Additional workup was required for **7/7′a**–**e** and **g** and led to pure compounds.

***p*-Hydroxy-*O*-benzyl-*N*,*N*′-dihydroxybenzamidine (7/7′a):** Compound **3a** (343 mg, 2 mmol) was dissolved in a mixture of diethyl ether and dichloromethane (1:1, 15 mL). Flash chromatography gave pure product **7/7′a** [227 mg, 0.88 mmol, 44.0% (**7a**: 20.5%, **7′a**: 23.5%)] as a colorless oil, which turns from orange to black during storage at room temperature within five hours (decomposition). R_f (cyclohexane/ethyl acetate 1:1): 0.44.

Tautomer 7a: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.70 (s, 2 H, OCH$_2$-), 6.77 (m, 2 H, Ar-H), 7.29 (m, 5 H, Bn-Ar-H), 7.36 (m, 2 H, Ar-H), 8.85 (s, 1 H, NH), 9.69 (s, 1 H, *p*-OH), 10.39 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 76.6 (OCH$_2$-), 114.6–114.8 (Ar-C-3), 122.3 (Ar-C-1), 127.6–129.0 (Bn-Ar-C), 129.0–129.6 (Ar-C-2), 154.9 [C$_q$(NN)], 158.4 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 154.5 (NH) ppm.

Tautomer 7′a: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 5.00 (s, 2 H, OCH$_2$-), 6.77 (m, 2 H, Ar-H), 7.29 (m, 5 H, Bn-Ar-H), 7.36 (m, 2 H, Ar-H), 8.44 (s, 1 H, NH), 8.49 [s, 1 H, (NHO)H], 9.69 (s, 1 H, *p*-OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 74.7 (OCH$_2$-), 114.6–114.8 (Ar-C-3), 121.7 (Ar-C-1), 127.6–129.0 (Bn-Ar-C), 129.0–129.6 (Ar-C-2), 157.4 [C$_q$(NN)], 158.4 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 130.9 ($^1J_{N,H}$ = 88 Hz, NH), 308.3 (=NOBn) ppm.

***p*-Methoxy-*O*-benzyl-*N*,*N*′-dihydroxybenzamidine (7/7′b):** Compound **3b** (742 mg, 4 mmol) was dissolved in dichloromethane (20 mL). After flash chromatography, the compound was dissolved in ethyl acetate, precipitated with cyclohexane, and filtered to give pure product **7/7′b** [300 mg, 1.10 mmol, 27.6% (**7b**: 12.5%, **7′b**: 15.1%)] as a white solid, m.p. 103.0 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.28.

Tautomer 7b: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.77 (s, 3 H, *p*-OCH$_3$), 4.71 (s, 2 H, OCH$_2$-), 6.94 (m, 2 H, Ar-H), 7.29 (m, 5 H, Bn-Ar-H), 7.49 (m, 2 H, Ar-H), 8.91 (s, 1 H, NH), 10.48 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.1 (*p*-OCH$_3$), 76.6 (OCH$_2$-), 113.2–113.3 (Ar-C-3), 123.9 (Ar-C-1), 127.5–128.9 (Bn-Ar-C), 128.9–129.5 (Ar-C-2), 154.5 [C$_q$(NN)], 159.9 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 154.4 ($^1J_{N,H}$ = 81 Hz, NH), 302.2 (=NOH) ppm.

Tautomer 7′b: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.77 (s, 3 H, *p*-OCH$_3$), 5.01 (s, 2 H, OCH$_2$-), 6.94 (m, 2 H, Ar-H), 7.29 (m, 5 H, Bn-Ar-H), 7.49 (m, 2 H, Ar-H), 8.51 (s, 1 H, NH), 8.52 [s, 1 H, (NHO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.1 (*p*-OCH$_3$), 74.8 (OCH$_2$-), 113.2–113.3 (Ar-C-3), 123.3 (Ar-C-1), 127.5–128.9 (Bn-Ar-C), 128.9–129.5 (Ar-C-2), 157.1 [C$_q$(NN)], 160.0 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 131.2 ($^1J_{N,H}$ = 87 Hz, NH), 308.7 (=NOBn) ppm.

***p*-Methyl-*O*-benzyl-*N*,*N*′-dihydroxybenzamidine (7/7′c):** Compound **3c** (509 mg, 3 mmol) was dissolved in dichloromethane (7 mL). After flash chromatography, the compound was dissolved in ethyl acetate, precipitated with petroleum ether, and filtered to give pure product **7/7′c** [150 mg, 0.59 mmol, 19.5% (**7c**: 9.0%, **7′c**: 10.5%)] as a white solid, m.p. 114.2 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.37.

Tautomer 7c: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.33 (s, 3 H, *p*-CH$_3$), 4.71 (s, 2 H, OCH$_2$-), 7.31 (m, 9 H, Ar-H), 8.94 (s, 1 H, NH), 10.55 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 20.9 (*p*-CH$_3$), 76.6 (OCH$_2$-), 127.4–128.1 (Ar-C-2), 128.2–128.7 (Bn-Ar-C), 128.5–128.7 (Ar-C-3), 128.9 (Ar-C-1), 138.4 (Ar-C-4), 154.8 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]-DMSO): δ = 154.7 ($^1J_{N,H}$ = 81 Hz, NH), 303.7 (=NOH) ppm.

Tautomer 7′c: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.33 (s, 3 H, *p*-OCH$_3$), 5.02 (s, 2 H, OCH$_2$-), 7.31 (m, 9 H, Ar-H), 8.52 [s, 1 H, (NHO)H], 8.54 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 20.9 (*p*-CH$_3$), 74.8 (OCH$_2$-), 127.4–128.1 (Ar-C-2), 128.2–128.7 (Bn-Ar-C), 128.3 (Ar-C-1), 128.5–128.7 (Ar-C-3), 138.6 (Ar-C-4), 157.3 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]-DMSO): δ = 131.3 ($^1J_{N,H}$ = 88 Hz, NH), 309.8 (=NOBn) ppm.

***O*-Benzyl-*N*,*N*′-dihydroxybenzamidine (7/7′d):** Compound **3d** (778 mg, 5 mmol) was dissolved in diethyl ether (7 mL). Benzylhydroxylamine was dissolved in ethanol (5 mL), and the mixture was dropped slowly into the reaction mixture. After flash chromatography, the compound was dissolved in ethyl acetate, precipitated with petroleum ether, and filtered to give pure product **7/7′d** [474 mg, 1.96 mmol, 39.2% (**7d**: 18.8%, **7′d**: 20.4%)] as a white solid, m.p. 109.2 °C; m.p.[17] 109–110 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.31.

Tautomer 7d: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.72 (s, 2 H, OCH$_2$-), 7.27 (m, 5 H, Bn-Ar-H), 7.42 (m, 5 H, Ar-H), 9.01 (s, 1 H, NH), 10.62 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 76.7 (OCH$_2$-), 127.7 (Ar-C-2), 127.9–128.7 (Bn-Ar-C), 128.1–128.2 (Ar-C-3), 129.1 (Ar-C-4), 131.7 (Ar-C-1), 154.9 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 155.0 ($^1J_{N,H}$ = 82 Hz, NH), 304.3 (=NOH) ppm.

Tautomer 7′d: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 5.03 (s, 2 H, OCH$_2$-), 7.27 (m, 5 H, Bn-Ar-H), 7.42 (m, 5 H, Ar-H), 8.55 [s, 1 H, (NHO)H], 8.62 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 74.9 (OCH$_2$-), 127.7 (Ar-C-2), 127.9–128.7 (Bn-Ar-C), 128.1–128.2 (Ar-C-3), 129.4 (Ar-C-4), 131.2 (Ar-C-1), 157.3 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 131.4 ($^1J_{N,H}$ = 88 Hz, NH), 310.4 (=NOBn) ppm.

***p*-Bromo-*O*-benzyl-*N*,*N*′-dihydroxybenzamidine (7/7′e):** Compound **3e** (469 mg, 2 mmol) was dissolved in dichloromethane (10 mL). After flash chromatography, the compound was triturated with cyclohexane and filtered to give pure product **7/7′e** [300 mg, 0.93 mmol, 46.7% (**7e**: 21.8%, **7′e**: 24.9%)] as a white solid, m.p. 109.0 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.46.

Tautomer 7e: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.71 (s, 2 H, OCH$_2$-), 7.29 (m, 5 H, Bn-Ar-H), 7.47 (m, 2 H, Ar-H), 7.58 (m, 2 H, Ar-H), 9.07 (s, 1 H, NH), 10.74 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 76.7 (OCH$_2$-), 122.4 (Ar-C-4), 127.5–128.8 (Bn-Ar-C), 129.5–130.1 (Ar-C-2), 130.8–130.9 (Ar-C-3), 130.9 (Ar-C-1), 153.9 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]-DMSO): δ = 155.6 ($^1J_{N,H}$ = 85 Hz, NH) ppm.

Tautomer 7′e: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 5.02 (s, 2 H, OCH$_2$-), 7.29 (m, 5 H, Bn-Ar-H), 7.47 (m, 2 H, Ar-H), 7.58 (m, 2

H, Ar-H), 8.61 [s, 1 H, (NHO)H], 8.70 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 75.0 (OCH_2-), 122.5 (Ar-C-4), 127.5–128.8 (Bn-Ar-C), 129.5–130.1 (Ar-C-2), 130.8–130.9 (Ar-C–), 130.4 (Ar-C-1), 156.3 [C_q(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 131.3 ($^1J_{N,H}$ = 91 Hz, NH), 310.5 (=NOBn) ppm.

***p*-Cyano-*O*-benzyl-*N*,*N*′-dihydroxybenzamidine (7/7′f):** Compound **3f** (542 mg, 3 mmol) was dissolved in dichloromethane (15 mL). Flash chromatography gave pure product **7/7′f** [310 mg, 1.16 mmol, 38.7% (**7f**: 18.1%, **7′f**: 20.6%)] as a pale yellow oil. R_f (cyclohexane/ethyl acetate 7:3): 0.42.

Tautomer 7f: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.75 (s, 2 H, OCH_2-), 7.29 (m, 5 H, Bn-Ar-H), 7.71 (m, 2 H, Ar-H), 7.84 (m, 2 H, Ar-H), 9.21 (s, 1 H, NH), 10.95 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 76.8 (OCH_2-), 111.6 (Ar-C-4), 118.6 (*p*-CN), 127.5–128.9 (Bn-Ar-C), 128.3–129.0 (Ar-C-2), 131.8–131.9 (Ar-C-3), 138.1 (Ar-C-1), 153.9 [C_q(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 154.7 (NH) ppm.

Tautomer 7′f: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 5.06 (s, 2 H, OCH_2-), 7.29 (m, 5 H, Bn-Ar-H), 7.71 (m, 2 H, Ar-H), 7.84 (m, 2 H, Ar-H), 8.66 [s, 1 H, (NHO)H], 8.74 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 75.3 (OCH_2-), 111.7 (Ar-C-4), 118.6 (*p*-CN), 127.5–128.9 (Bn-Ar-C), 128.3–129.0 (Ar-C-2), 131.8–131.9 (Ar-C-3), 137.6 (Ar-C-1), 156.0 [C_q(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 131.6 (NH), 313.6 (=NOBn) ppm.

***p*-Nitro-*O*-benzyl-*N*,*N*′-dihydroxybenzamidine (7/7′g):** Compound **3g** (401 mg, 2 mmol) was dissolved in dichloromethane (10 mL). After flash chromatography, the compound was triturated with dichloromethane and filtered to give pure product **7/7′g** [494 mg, 1.72 mmol, 86.1% (**7g**: 41.9%, **7′g**: 44.2%)] as a yellow solid, m.p. 121.2 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.34.

Tautomer 7g: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.76 (s, 2 H, OCH_2-), 7.30 (m, 5 H, Bn-Ar-H), 7.78 (m, 2 H, Ar-H), 8.23 (m, 2 H, Ar-H), 9.25 (s, 1 H, NH), 11.10 [s, 1 H, (=NO)H] ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 76.8 (OCH_2-), 123.0–123.1 (Ar-C-3), 127.5–128.9 (Bn-Ar-C), 128.9–129.3 (Ar-C-2), 137.7 (Ar-C-1), 147.6 (Ar-C-4), 153.3 [C_q(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]-DMSO): δ = 154.9 ($^1J_{N,H}$ = 82 Hz, NH), 370.1 (*p*-NO_2) ppm.

Tautomer 7′g: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 5.08 (s, 2 H, OCH_2-), 7.30 (m, 5 H, Bn-Ar-H), 7.78 (m, 2 H, Ar-H), 8.23 (m, 2 H, Ar-H), 8.75 [s, 1 H, (NHO)H], 8.91 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 75.3 (OCH_2-), 123.0–123.1 (Ar-C-3), 127.5–128.9 (Bn-Ar-C), 128.9–129.3 (Ar-C-2), 138.1 (Ar-C-1), 147.6 (Ar-C-4), 155.6 [C_q(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]-DMSO): δ = 131.8 (NH), 314.2 (=NOBn), 370.1 (*p*-NO_2) ppm.

General Synthesis of *para*-Substituted *O*,*O*′-Dibenzyl-*N*,*N*′-dihydroxybenzamidines 8a–g: Benzylhydroxylamine (2 equiv.) was added to a stirred solution of **3** (one out of **3a–g**) in dichloromethane, diethyl ether, or dichloromethane/diethyl ether. The reaction mixture was stirred at room temperature and monitored by TLC (cyclohexane/ethyl acetate 7:3, with 2% aqueous $FeCl_3$ solution indicating **8a–g** as yellow spots). Disappearance of **3a–g** was monitored. After 24 h, further benzylhydroxylamine (2 equiv.) was added if **3a–g** was still detectable. The procedure was repeated after 48 h. Usually the reaction was complete after 48–72 h and the precipitated byproduct was filtered off. The filtrate was concentrated under reduced pressure at max. 30 °C and transferred to silica for flash chromatography with cyclohexane/ethyl acetate gradient as mobile phase and silica as solid phase; this led to **8a–g** as pure products.

***p*-Hydroxy-*O*,*O*′-dibenzyl-*N*,*N*′-dihydroxybenzamidine (8a):** Compound **3a** (343 mg, 2 mmol) was dissolved in a mixture of diethyl ether and dichloromethane (1:1, 15 mL). Flash chromatography after 48 h gave pure product **8a** (129 mg, 0.37 mmol, 18.5%) as a light yellow oil. R_f (cyclohexane/ethyl acetate 1:1): 0.63. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.67 [s, 2 H, (NHO)CH_2-], 5.03 [s, 2 H, (=NO)CH_2-], 6.78 (d, 2 H, Ar-H), 7.27 (m, 5 H, Bn-Ar-H), 7.28 (d, 2 H, Ar-H), 9.23 (s, 1 H, NH), 9.73 (s, 1 H, *p*-OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 74.9 (=$NOCH_2$-), 76.9 ($NHOCH_2$-), 114.7 (Ar-C-3), 121.2 (Ar-C-1), 127.5–128.8 (Bn-Ar-C), 129.4 (Ar-C-2), 155.5 [C_q(NN)], 158.6 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 157.0 ($^1J_{N,H}$ = 86 Hz, NH), 311.5 (=NOBn) ppm.

***p*-Methoxy-*O*,*O*′-dibenzyl-*N*,*N*′-dihydroxybenzamidine (8b):** Compound **3b** (742 mg, 4 mmol) was dissolved in dichloromethane (20 mL). Flash chromatography after 24 h gave pure product **8b** (107 mg, 0.30 mmol, 7.4%) as a light yellow oil. R_f (cyclohexane/ethyl acetate 7:3): 0.64. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.78 (*p*-OCH_3), 4.67 [s, 2 H, (NHO)CH_2-], 5.04 [s, 2 H, (=NO)CH_2-], 6.95 (d, 2 H, Ar-H), 7.25 (m, 5 H, Bn-Ar-H), 7.44 (d, 2 H, Ar-H), 9.29 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.2 (*p*-OCH_3), 75.0 (=$NOCH_2$-), 76.9 ($NHOCH_2$-), 113.3 (Ar-C-3), 122.8 (Ar-C-1), 127.5–128.8 (Bn-Ar-C), 129.4 (Ar-C-2), 155.1 [C_q(NN)], 160.2 (Ar-C-4) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 157.1 ($^1J_{N,H}$ = 85 Hz, NH), 312.2 (=NOBn) ppm.

***p*-Methyl-*O*,*O*′-dibenzyl-*N*,*N*′-dihydroxybenzamidine (8c):** Compound **3c** (339 mg, 2 mmol) was dissolved in diethyl ether (10 mL). Flash chromatography after 96 h gave pure product **8c** (200 mg, 0.58 mmol, 28.9%) as a light yellow oil. R_f (cyclohexane/ethyl acetate 8:2): 0.66. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.33 (*p*-CH_3), 4.69 [s, 2 H, (NHO)CH_2-], 5.05 [s, 2 H, (=NO)CH_2-], 7.27 (m, 14 H, Ar-H), 9.34 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.9 (*p*-CH_3), 75.1 (=$NOCH_2$-), 76.9 ($NHOCH_2$-), 127.5 (Ar-C-1), 127.6–128.8 (Bn-Ar-C), 127.9 (Ar-C-2), 128.1 (Ar-C-3), 139.0 (Ar-C-4), 155.4 (C_q(NN)) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 157.1 ($^1J_{N,H}$ = 86 Hz, NH), 313.1 (=NOBn) ppm.

***O*,*O*′-Dibenzyl-*N*,*N*′-dihydroxybenzamidine (8d):** Compound **3d** (622 mg, 4 mmol) was dissolved in diethyl ether (5 mL). Benzylhydroxylamine was dissolved in ethanol (10 mL), and the mixture was dropped slowly into the reaction mixture. Flash chromatography after 24 h gave pure product **8d** (640 mg, 1.93 mmol, 48.2%) as a colorless oil. R_f (cyclohexane/ethyl acetate 8:2): 0.63. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.69 [s, 2 H, (NHO)CH_2-], 5.07 [s, 2 H, (=NO)CH_2-], 7.29 (m, 15 H, Ar-H), 9.44 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 75.1 (=$NOCH_2$-), 77.1 ($NHOCH_2$-), 127.6–128.8 (Bn-Ar-C), 127.9 (Ar-C-2), 128.2 (Ar-C-3), 129.5 (Ar-C-4), 130.8 (Ar-C-1), 155.5 [C_q(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 157.3 ($^1J_{N,H}$ = 86 Hz, NH), 313.3 (=NOBn) ppm.

***p*-Bromo-*O*,*O*′-dibenzyl-*N*,*N*′-dihydroxybenzamidine (8e):** Compound **3e** (469 mg, 2 mmol) was dissolved in dichloromethane (10 mL). Flash chromatography after 120 h gave pure product **8e** (367 mg, 0.89 mmol, 44.7%) as a white solid, m.p. 70.5 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.63. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 4.69 [s, 2 H, (NHO)CH_2-], 5.06 [s, 2 H, (=NO)-CH_2-], 7.25 (m, 10 H, Bn-Ar-H), 7.42 (d, 2 H, Ar-H), 7.59 (d, 2 H, Ar-H), 9.50 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 75.2 (=$NOCH_2$-), 77.1 ($NHOCH_2$-), 122.8 (Ar-C-4), 127.6–128.8 (Bn-Ar-C), 129.9 (Ar-C-1), 130.0 (Ar-C-2), 130.9 (Ar-C-3), 154.5 [C_q(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 157.1 ($^1J_{N,H}$ = 88 Hz, NH), 313.9 (=NOBn) ppm.

***p*-Cyano-*O*,*O*′-dibenzyl-*N*,*N*′-dihydroxybenzamidine (8f):** Compound **3f** (542 mg, 3 mmol) was dissolved in dichloromethane (15 mL). Flash chromatography after 96 h gave pure product **8f** (116 mg, 0.32 mmol, 10.8%) as a white solid, m.p. 89.9 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.64. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.71 [s, 2 H, (NHO)CH$_2$-], 5.09 [s, 2 H, (=NO)CH$_2$-], 7.26 (m, 10 H, Bn-Ar-H), 7.62 (d, 2 H, Ar-H), 7.84 (d, 2 H, Ar-H), 9.64 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 75.5 (=NOCH$_2$-), 77.2 (NHOCH$_2$-), 111.9 (Ar-C-4), 118.5 (*p*-CN), 127.7–128.9 (Bn-Ar-C), 128.8 (Ar-C-2), 131.9 (Ar-C-3), 137.8 (Ar-C-1), 154.1 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 157.3 ($^1J_{N,H}$ = 87 Hz, NH), 316.4 (=NOBn) ppm.

***p*-Nitro-*O*,*O*′-dibenzyl-*N*,*N*′-dihydroxybenzamidine (8g):** Compound **3g** (401 mg, 2 mmol) was dissolved in dichloromethane (10 mL). Flash chromatography after 96 h gave pure product **8g** (90 mg, 0.24 mmol, 11.9%) as a yellow oil. R_f (cyclohexane/ethyl acetate 8:2): 0.48. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.73 [s, 2 H, (NHO)CH$_2$-], 5.11 [s, 2 H, (=NO)CH$_2$-], 7.27 (m, 10 H, Bn-Ar-H), 7.71 (d, 2 H, Ar-H), 8.23 (d, 2 H, Ar-H), 9.69 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 75.5 (=NOCH$_2$-), 77.2 (NHOCH$_2$-), 123.1 (Ar-C-3), 127.7–129.0 (Bn-Ar-C), 129.2 (Ar-C-2), 137.1 (Ar-C-1), 147.8 (Ar-C-4), 153.8 [C$_q$(NN)] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 157.2 ($^1J_{N,H}$ = 87 Hz, NH), 317.0 (=NOBn), 370.1 (*p*-NO$_2$) ppm.

General Synthesis of *para*-Substituted *O*,*O*′-Bis(tetrahydropyran-2-yl)-*N*,*N*′-dihydroxybenzamidines 9a–g: Tetrahydropyranylhydroxylamine (2 equiv.) was added to a solution of the starting compound **3** (one out of **3a**–**g**) in dichloromethane. The reaction mixture was stirred at room temperature and monitored by TLC (cyclohexane/ethyl acetate 7:3, with 2% aqueous $FeCl_3$ solution and heat indicating **9a**–**g** as blue spots). Occasionally further treatment was necessary to ensure full consumption of **3a**–**g**. After 24 h further tetrahydropyranylhydroxylamine (2 equiv.) was added if **3a**–**g** was still detectable. The procedure was repeated after 48 h. Usually the reaction was complete after 48–72 h and precipitated byproduct was filtered off. The filtrate was concentrated under reduced pressure at 30 °C or below and transferred to silica for flash chromatography with cyclohexane/ethyl acetate gradient as mobile phase and silica as solid phase to give **9a**–**e** as pure products. Additional workup was required for **9f** and **9g** and led to pure compounds.

***p*-Hydroxy-*O*,*O*′-bis(tetrahydropyran-2-yl)-*N*,*N*′-dihydroxybenzamidine (9a):** Compound **3a** (189 mg, 1.1 mmol) was dissolved in a mixture of diethyl ether and dichloromethane (1:1, 10 mL). Flash chromatography after 96 h gave pure product **9a** (334 mg, 0.99 mmol, 90.4%) as a light yellow oil. R_f (cyclohexane/ethyl acetate 1:1): 0.41. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.56 [m, 12 H, (NHO)THP, (=NO)THP], 3.42 [m, 2 H, (NHO)THP, (=NO)THP], 3.74 [m, 1 H, (NHO)THP], 4.56 [m, 1 H, (=NO)THP], 4.76 {m, 1 H, O-CH-O [(NHO)THP]}, 5.10 {m, 1 H, O-CH-O [(=NO)THP]}, 6.77 (d, 2 H, Ar-H), 7.37 (d, *J* = Ar-H, ds = 3.4 Hz, 2 H), 8.78 (s, *J* = NH, ds = 3.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 18.8–19.5 (2 C, 2 × THP-C-4), 24.1–25.0 (2 C, 2 × THP-C-5), 28.0–28.7 (2 C, 2 × THP-C-3), 61.4–61.9 (2 C, 2 × THP-C-6), 99.7–99.9 [1 C, (=NO)THP-C-2], 101.4–101.7 [1 C, (NHO)THP-C-2], 114.7 (Ar-C-3, ds = 0.7 Hz), 120.9 (Ar-C-1, ds = 4.3 Hz), 129.5 (Ar-C-2, ds = 4.7 Hz), 155.6 [C$_q$(NN), ds = 0.7 Hz], 158.7 (Ar-C-4, ds = 2.8 Hz) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 149.4 ($^1J_{N,H}$ = 85 Hz, ds = 36 Hz, NH), 310.5 (=NOTHP, ds = 19 Hz) ppm. For each value the mean of the chemical shift and diastereomeric shift (ds) – if present – of both isomers are given.

***p*-Methoxy-*O*,*O*′-ditetrahydropyran-2-yl-*N*,*N*′-dihydroxybenzamidine (9b):** Compound **3b** (557 mg, 3 mmol) was dissolved in dichloromethane (15 mL). Flash chromatography after 48 h gave pure product **9b** (488 mg, 1.40 mmol, 46.5%) as a colorless oil. R_f (cyclohexane/ethyl acetate 7:3): 0.41. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.57 [m, 12 H, (NHO)THP, (=NO)THP], 3.48 [m, 2 H, (NHO)THP, (=NO)THP], 3.69 [m, 1 H, (NHO)THP], 3.80 [m, 1 H, (=NO)THP], 4.77 {m, 1 H, O-CH-O [(NHO)THP]}, 5.13 {m, 1 H, O-CH-O [(=NO)THP]}, 6.96 (d, 2 H, Ar-H), 7.49 (d, *J* = Ar-H, ds = 3.5 Hz, 2 H), 8.86 (s, 1 H, NH, ds = 3.8 Hz) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 18.7–19.2 (2 C, 2 × THP-C-4), 24.6–24.9 (2 C, 2 × THP-C-5), 27.9–28.7 (2 C, 2 × THP-C-3), 55.1 (*p*-OCH$_3$), 61.4–61.8 (2 C, 2 × THP-C-6), 99.8–100.0 [1 C, (=NO)-THP-C-2], 101.4–101.7 [1 C, (NHO)THP-C-2], 113.3 (Ar-C-3, ds = 0.8 Hz), 122.5 (Ar-C-1, ds = 5.3 Hz), 129.5 (Ar-C-2, ds = 4.8 Hz), 155.3 [C$_q$(NN), ds = 0.6 Hz], 160.2 (Ar-C-4, ds = 4.8 Hz) ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 149.9 (NH, $^1J_{N,H}$ = 87 Hz, ds = 38 Hz), 311.2 (=NOTHP, ds = 17 Hz) ppm. For each value the mean of the chemical shift and diastereomeric shift (ds) – if present – of both isomers are given.

***p*-Methyl-*O*,*O*′-bis(tetrahydropyran-2-yl)-*N*,*N*′-dihydroxybenzamidine (9c):** Compound **3c** (339 mg, 2 mmol) was dissolved in dichloromethane (10 mL). Flash chromatography after 48 h gave pure product **9c** (340 mg, 0.99 mmol, 49.4%) as a colorless oil. R_f (cyclohexane/ethyl acetate 7:3): 0.40. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.58 [m, 12 H, (NHO)THP, (=NO)THP], 3.49 [m, 2 H, (NHO)THP, (=NO)THP], 3.70 [m, 1 H, (NHO)THP], 3.81 [m, 1 H, (=NO)THP], 4.80 {m, 1 H, O-CH-O [(NHO)THP]}, 5.16 {m, 1 H, O-CH-O [(=NO)THP]}, 7.21 (d, 2 H, Ar-H), 7.46 (d, 2 H, Ar-H, ds = 3.7 Hz), 8.87 (s, *J* = NH, ds = 4.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 18.7–19.2 (2 C, 2 × THP-C-4), 20.8 (*p*-CH$_3$), 24.6–24.9 (2 C, 2 × THP-C-5), 27.9–28.7 (2 C, 2 × THP-C-3), 61.4–61.8 (2 C, 2 × THP-C-6), 99.9–100.1 [1 C, (=NO)THP-C-2], 101.5–101.8 [1 C, (NHO)THP-C-2], 127.6 (Ar-C-1, ds = 5.5 Hz), 128.0 (Ar-C-2, ds = 4.7 Hz), 128.5 (Ar-C-3, ds = 0.7 Hz), 139.1 (Ar-C-4, ds = 4.1 Hz), 155.6 [C$_q$(NN), ds = 0.8 Hz], ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 149.7 (NH, $^1J_{N,H}$ = 84 Hz, ds = 39 Hz), 312.1 (=NOTHP, ds = 21 Hz) ppm. For each value the mean of the chemical shift and diastereomeric shift (ds) – if present – of both isomers are given.

***O*,*O*′-Bis(tetrahydropyran-2-yl)-*N*,*N*′-dihydroxybenzamidine (9d):** Compound **3d** (171 mg, 1.1 mmol) was dissolved in dichloromethane (10 mL). Flash chromatography after 120 h gave pure product **9d** (209 mg, 0.65 mmol, 59.4%) as a colorless oil. R_f (cyclohexane/ethyl acetate 7:3): 0.44. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.56 [m, 12 H, (NHO)THP, (=NO)THP], 3.47 [m, 2 H, (NHO)THP, (=NO)THP], 3.68 [m, 1 H, (NHO)THP], 3.82 [m, 1 H, (=NO)-THP], 4.80 {m, 1 H, O-CH-O [(NHO)THP]}, 5.15 {m, 1 H, O-CH-O [(=NO)THP]}, 7.43 (m, 3 H, Ar-H), 7.55 (m, 2 H), 8.99 (s, 1 H, NH, ds = 5.3 Hz) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 18.6–19.2 (2 C, 2 × THP-C-4), 24.6–24.9 (2 C, 2 × THP-C-5), 27.9–28.7 (2 C, 2 × THP-C-3), 61.5–61.8 (2 C, 2 × THP-C-6), 100.0–100.1 [1 C, (=NO)THP-C-2], 101.6–101.9 [1 C, (NHO)THP-C-2], 127.9 (Ar-C-3, ds = 0.7 Hz), 128.1 (Ar-C-2, ds = 4.4 Hz), 129.5 (Ar-C-4, ds = 3.3 Hz), 130.5 (Ar-C-1, ds = 4.2 Hz), 155.7 [C$_q$(NN), ds = 4.2 Hz] ppm. ^{15}N NMR (30 MHz, [D$_6$]DMSO): δ = 150.6 ($^1J_{N,H}$ = 86 Hz, ds = 33 Hz, NH), 312.2 (=NOTHP, ds = 23 Hz) ppm. For each value the mean of the chemical shift and diastereomeric shift (ds) – if present – of both isomers are given.

***p*-Bromo-*O*,*O*′-bis(tetrahydropyran-2-yl)-*N*,*N*′-dihydroxybenzamidine (9e):** Compound **3e** (258 mg, 1.1 mmol) was dissolved in dichloromethane (10 mL). Flash chromatography after 120 h gave pure product **9e** (245 mg, 0.61 mmol, 55.8%) as a colorless oil. R_f (cyclohexane/ethyl acetate 7:3): 0.52. ^{1}H NMR (300 MHz,

[D_6]DMSO): δ = 1.57 [m, 12 H, (NHO)THP, (=NO)THP], 3.46 [m, 2 H, (NHO)THP, (=NO)THP], 3.63 [m, 1 H, (NHO)THP], 3.79 [m, 1 H, (=NO)THP], 4.79 {m, 1 H, O-CH-O [(NHO)THP]}, 5.14 {m, 1 H, O-CH-O [(=NO)THP]}, 7.49 (d, 2 H, Ar-H, ds = 3.0 Hz), 7.62 (d, 2 H, Ar-H), 9.05 (s, 1 H, NH, ds = 5.2 Hz) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 18.7–19.1 (2 C, 2×THP-C-4), 24.6–24.8 (2 C, 2×THP-C-5), 27.9–28.6 (2 C, 2×THP-C-3), 61.4–61.9 (2 C, 2×THP-C-6), 100.0–100.2 [1 C, (=NO)THP-C-2], 101.7–102.0 [1 C, (NHO)THP-C-2], 123.0 (Ar-C-4, ds = 3.2 Hz), 129.8 (Ar-C-1, ds = 6.1 Hz), 130.2 (Ar-C-2, ds = 4.8 Hz), 131.0 (Ar-C-3, ds = 0.6 Hz), 154.7 [C_q(NN), ds = 2.3 Hz], ppm. ^{15}N NMR (30 MHz, [D_6]DMSO): δ = 150.6 ($^1J_{N,H}$ = 85 Hz, ds = 35 Hz, NH), 312.7 (=NOTHP, ds = 25 Hz) ppm. For each value the mean of the chemical shift and diastereomeric shift (ds) – if present – of both isomers are given.

***p*-Cyano-*O*,*O*′-bis(tetrahydropyran-2-yl)-*N*,*N*′-dihydroxybenzamidine (9f):** Compound **3f** (542 mg, 3 mmol) was dissolved in dichloromethane (15 mL). Flash chromatography after 7 d gave pure product **9f** (614 mg, 1.78 mmol, 59.3%) as a white solid, m.p. 124.6 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.45. ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 1.58 [m, 12 H, (NHO)THP, (=NO)THP], 3.45 [m, 2 H, (NHO)THP, (=NO)THP], 3.59 [m, 1 H, (NHO)THP], 3.79 [m, 1 H, (=NO)THP], 4.82 {m, 1 H, O-CH-O [(NHO)THP]}, 5.16 {m, 1 H, O-CH-O [(=NO)THP]}, 7.73 (d, 2 H, Ar-H, ds = 2.0 Hz), 7.88 (d, 2 H, Ar-H), 9.20 (s, 1 H, NH, ds = 6.6 Hz) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 18.7–19.0 (2 C, 2×THP-C-4), 24.5–24.8 (2 C, 2×THP-C-5), 27.9–28.5 (2 C, 2×THP-C-3), 61.3–62.0 (2 C, 2×THP-C-6), 100.2–100.3 [1 C, (=NO)THP-C-2], 101.9–102.4 [1 C, (NHO)THP-C-2], 112.0 (Ar-C-4, ds = 2.2 Hz), 118.4 (*p*-CN),129.0 (Ar-C-2, ds = 4.1 Hz), 131.9 (Ar-C-3, ds = 0.4 Hz), 135.2 (Ar-C-1, ds = 5.9 Hz), 154.4 [C_q(NN), ds = 3.3 Hz] ppm. ^{15}N NMR (30 MHz, [D_6]DMSO): δ = 151.3 ($^1J_{N,H}$ = 87 Hz, ds = 25 Hz, NH) ppm. For each value the mean of the chemical shift and diastereomeric shift (ds) – if present – of both isomers are given.

***p*-Nitro-*O*,*O*′-bis(tetrahydropyran-2-yl)-*N*,*N*′-dihydroxybenzamidine (9g):** Compound **3g** (602 mg, 3 mmol) was dissolved in dichloromethane (15 mL). Flash chromatography after 120 h gave pure product **9g** (578 mg, 1.58 mmol, 52.8%) as a pale yellow solid, m.p. 119.7 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.42. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.58 [m, 12 H, (NHO)THP, (=NO)-THP], 3.46 [m, 2 H, (NHO)THP, (=NO)THP], 3.60 [m, 1 H, (NHO)THP], 3.80 [m, 1 H, (=NO)THP], 4.84 {m, 1 H, O-CH-O [(NHO)THP]}, 5.18 {m, 1 H, O-CH-O [(=NO)THP]}, 7.82 (d, 2 H, Ar-H, ds = 2.8 Hz), 8.27 (d, 2 H, Ar-H), 9.25 (s, 1 H, NH, ds = 5.5 Hz) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 18.7–18.9 (2 C, 2×THP-C-4), 24.5–24.8 (2 C, 2×THP-C-5), 27.9–28.5 (2 C, 2×THP-C-3), 61.5–62.0 (2 C, 2×THP-C-6), 100.3 [1 C, (=NO)-THP-C-2], 102.0–102.3 [1 C, (NHO)THP-C-2], 123.1 (Ar-C-3),129.5 (Ar-C-2, ds = 3.0 Hz), 137.0 (Ar-C-1, ds = 8.4 Hz), 147.9 (Ar-C-4, ds = 1.9 Hz), 154.1 [C_q(NN)], ppm. ^{15}N NMR (30 MHz, [D_6]DMSO): δ = 151.2 ($^1J_{N,H}$ = 85 Hz, ds = 33 Hz, NH), 315.8 (=NOTHP, ds = 34 Hz), 369.9 (*p*-NO_2) ppm. For each value the mean of the chemical shift and diastereomeric shift (ds) – if present – of both isomers are given.

General Synthesis of 5,5-Dialkyl-4-hydroxy-3-phenyl-4,5-dihydro-1,2,4-oxadiazoles 10–12: Compound **4d** was dissolved in the appropriate ketone (5 mL), and the solution was stirred at room temperature for about 10 h. During the reaction the color of the mixture turned red, indicating the progress of the reaction. Additionally, the reaction was monitored by TLC (cyclohexane/ethyl acetate 7:3, with 2% aqueous $FeCl_3$ solution indicating **10**–**12** as red spots). Excessively long reaction times resulted in complete decomposition of **10**–**12**, which could be related to the observation of the loss of red color. After 10 h the reaction mixture was evaporated under reduced pressure at room temperature. For **11** and **12** high vacuum and long evaporation times were required. The crude product was transferred to silica for flash chromatography with cyclohexane/ethyl acetate gradient as mobile phase and silica solid phase, which led to pure products **10**–**12** without further purification.

4-Hydroxy-5,5-dimethyl-3-phenyl-4,5-dihydro-1,2,4-oxadiazole (10): Synthesized **4d** (760 mg, 5 mmol) was dissolved in acetone (5 mL) with stirring. Flash chromatography after 10 h gave pure product **10** (246 mg, 1.28 mmol, 25.6%) as a white solid, m.p. 130.1 °C; m.p.[13] 120–122 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.38. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.45 (s, 6 H, 2×CH_3), 7.48 (m, 3 H, Ar-H), 7.79 (m, 2 H, Ar-H), 9.36 [s, 1 H, (NRO)H] ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 22.2 (CH_3), 101.0 (C-5), 126.4 (Ar-C-1), 127.1 (Ar-C-2), 128.6 (Ar-C-3), 130.4 (Ar-C-4), 158.8 (C-3) ppm. ^{15}N NMR (30 MHz, [D_6]DMSO): δ = 161.4 (-NROH), 324.0 (=NOR) ppm.

4-Hydroxy-3-phenyl-1,2,4-oxadiazaspiro[4.4]non-2-ene (11): Synthesized **4d** (304 mg, 2 mmol) was dissolved in cyclopentanone (5 mL) with stirring. Flash chromatography after 10 h gave pure product **11** (105 mg, 0.48 mmol, 24.1%) as a white solid, m.p. 132.8 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.36. ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 1.77 (m, 6 H, 3×-CH_2-), 2.13 (m, 2 H, -CH_2-), 7.48 (m, 3 H, Ar-H), 7.80 (m, 2 H, Ar-H), 9.50 [s, 1 H, (NRO)H] ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 23.2 (C-5, C-8), 32.8 (C-6, C-7), 111.1 (C-9), 126.3 (Ar-C-1), 127.1 (Ar-C-2), 128.6 (Ar-C-3), 130.5 (Ar-C-4), 159.4 (C-3) ppm. ^{15}N NMR (30 MHz, [D_6]-DMSO): δ = 158.3 (-NROH), 328.6 (=NOR) ppm.

4-Hydroxy-3-phenyl-1,2,4-oxadiazaspiro[4.5]dec-2-ene (12): Synthesized **4d** (152 mg, 1 mmol) was dissolved in cyclohexanone (3 mL) with stirring. Flash chromatography after 10 h gave pure product **12** (101 mg, 0.43 mmol, 43.3%) as a white solid, m.p. 71.9 °C. R_f (cyclohexane/ethyl acetate 7:3): 0.35. ^{1}H NMR (300 MHz, [D_6]-DMSO): δ = 1.67 (m, 10 H, 5×-CH_2-), 7.46 (m, 3 H, Ar-H), 7.82 (m, 2 H, Ar-H), 9.29 [s, 1 H, (NRO)H] ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 23.0 (C-5, C-9), 24.6 (C-7), 31.3 (C-6, C-8), 101.7 (C-10), 126.8 (Ar-C-1), 127.2 (Ar-C-2), 128.7 (Ar-C-3), 130.5 (Ar-C-4), 158.9 (C-3) ppm. ^{15}N NMR (30 MHz, [D_6]DMSO): δ = 159.0 (-NROH), 326.7 (=NOR) ppm.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra, elemental analysis, ESI mass spectra values and IR absorption bands are given.

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