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The Synthesis of Vinylogous Amidine Heterocycles

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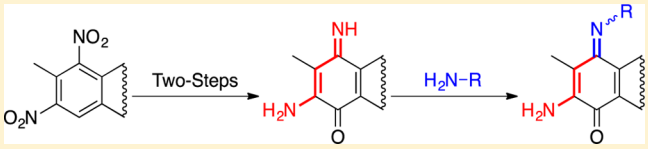
Supporting Information

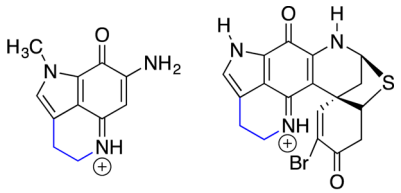
ABSTRACT: We report herein a convenient synthetic methodology for the conversion of *meta*-dinitro heterocyclic rings to iminoquinones with vinylogous amidine functionality. These structures are found in nature, particularly in marine organisms, and may be important for the pigments and biological activity observed with such marine secondary metabolites. Using benzimidazole and indole ring systems we show the versatility of these vinylogous amidines for organic synthesis, including the following: transamination substitution reactions with virtually any primary amine, regional control of the substitution with substituents between the vinylogous amidine, and hydrolytic properties that can be controlled or optimized based on the properties of the chosen ring system. Taken together, this versatile chemistry and functionalization of organic molecules may be useful in the preparation of a variety of chemical products such as drug pharmacophores or assembling macromolecular structures.



INTRODUCTION

The vinylogous amidine functionality, also referred to as an extended amidine, is present in alkaloid secondary metabolites from marine sponges such as the *Latrunculia* and *Zyzzya* species.[1−3] Examples of these include makaluvamine A and Discorhabdin A shown in Chart 1. Initially, the discorhabdins were isolated and found to possess cytotoxic antitumor properties,[4,5] and a number of naturally occurring analogues were later identified that display similar antitumor activity.[6−12] The vinylogous amidine functionality is responsible for the red to purple pigments of the pyrroloiminoquinone natural products and may contribute to their cytotoxic properties. In two previous publications,[13,14] we reported the synthesis and biological evaluation of benzimidazole analogues of the pyrroloiminoquinone alkaloids, Chart 1.

Chart 1. Indole and Benzimidazole Iminoquinones with Extended Amidine Functionality



We reasoned that these analogues could exhibit cytotoxicity due to the presence of both the vinylogous amidine functionality and the purine-like benzimidazole ring. Thus far, we have not identified the exact molecular target(s) for the imidazoquinoxalinones; however, National Cancer Institute (NCI) 60-cell line screening in combination with COMPARE[15] analysis suggest that some of the benzimidazole-based analogues may be promoting cancer cell apoptosis by inhibiting the phosphorylation of BAD (BCL-2 associated death promoter).[13,16] In contrast, the pyrroloiminoquinone natural products have been reported to induce DNA damage via topoisomerase IIα inhibition, though the exact mode by which they inhibit topoisomerase IIα is still unknown.[1,3,17]

As a result of these studies we discovered that the vinylogous amidine functionality could be substituted with virtually any primary alkyl amine via a transamination reaction. Intrigued by our findings, we designed a streamlined synthesis to study the utility of the extended amidine chemistry sans the ethylene tether (Chart 1, blue bonds) illustrated in Scheme 1.[18−23] In this article, we describe the synthetic methodology for the efficient conversion of *meta*-dinitro benzimidazoles and indoles to vinylogous amidines, their substitution chemistry, and hydrolytic stability.

Synthesis starts with readily available *meta*-dinitro derivatives of benzimidazoles and indoles, which were prepared and then reduced to the corresponding diamino derivatives. Without purification, diamines can be converted to iminoquinone based extended amidines in good yield using the method of Fremy's

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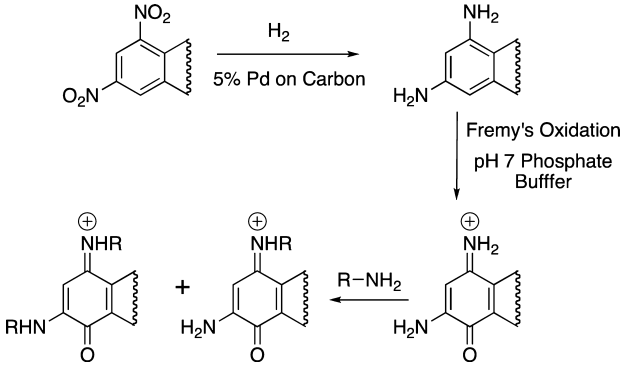
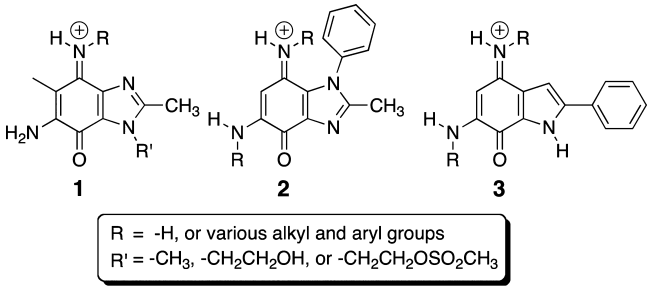
Scheme 1. General Synthesis of Iminoquinone Extended Amidines



salt oxidation.[13,14,24,25] The extended amidines could then be derivatized using primary amines via a transamination reaction. The three broad classes of extended amidines addressed in this report are shown in Chart 2.

Chart 2. Extended Amidines Series 1−3



Finally, hydrolytic stability studies were conducted and a pH-rate profile revealed that the imonoquinone functionality is stable to hydrolysis at neutrality but hydrolyzed slowly to form aminoquinones at pH values >9. Our hydrolysis studies concluded that resonance stabilization of the protonated extended amidine is responsible for the hydrolytic stability at neutrality.

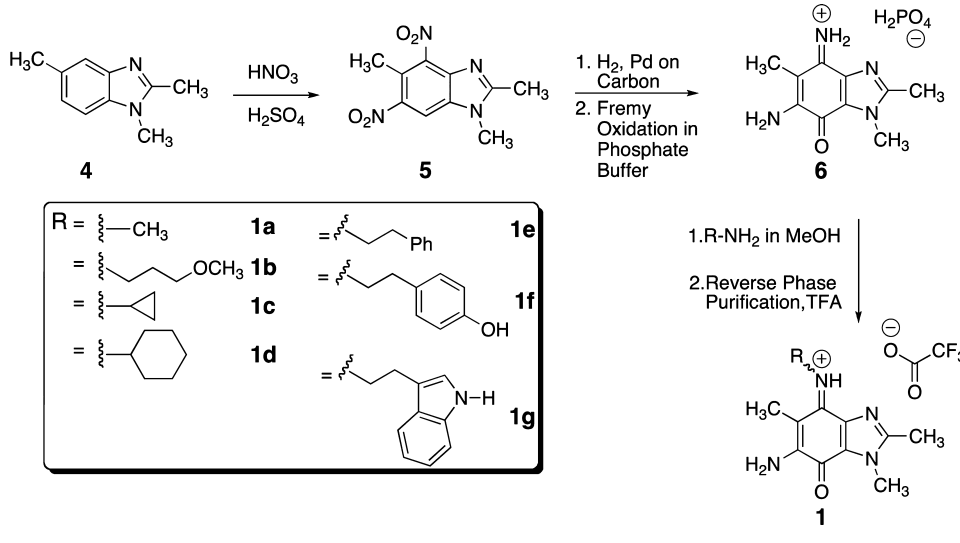
RESULTS AND DISCUSSION

Synthesis of Series 1 Extended Amidines. First, we studied simple analogues of series **1** (Scheme 2) to explore the chemistry of the iminoquinone based extended amidines and the versatility of the transamination reactions with various primary amines. Dinitration of 1,2,5-trimethyl benzimidazole **4**, with 90% nitric acid and concentrated sulfuric acid, afforded **5** in 83% yield as pale yellow crystals from ethanol. The dinitro intermediate **5** was catalytically reduced without isolation of the amine intermediate, followed by Fremy's oxidation to give **6** as a purple crystalline phosphate salt in 70% yield upon reversed phase purification. Key intermediate **6** was substituted using 5 equiv of various amines stirred in methanol at 30 °C, to give extended amidines **1a−g** in ∼50% yields. The substitution occurs at the 4-position based on 2D-NMR studies, which are later discussed in detail.

Once we were successful in elaborating simple analogues of **1**, we then introduced more complicated and potentially labile R′ substituents (Scheme 3). The extended amidines **1h** and **1i** were synthesized in five steps from **7** and **8**. Nitration of **7** and **8** with 90% nitric acid and concentrated sulfuric acid provided trinitro derivatives (∼70% yields), including nitration at the 4 and 6 position of the benzimidazole ring and formation of a nitrate ester of the side chain alcohol. To our benefit, compound **8** was *O*-demethylated under these nitration conditions and the resulting alcohol was converted to the nitrate ester *in situ*. The trinitro intermediates were catalytically reduced to give the diamino intermediates that were isolated as hydrochloride salts, an ∼90% yield as tan crystals. These salts were then oxidized with Fremy's salt to afford **9** and **10** as purple crystalline phosphate salts in ∼98% yield. Subsequent sulfonation with methane sulfonyl chloride in pyridine followed by treatment with 5 equiv of 40% aqueous methylamine gave **1h** and **1i** in 50% yield as blue crystalline TFA salts.

Synthesis of Series 2 Extended Amidines. The synthesis of series **2** was achieved in four steps from picryl chloride (Scheme 4). Picramides **11a** and **11b** were catalytically reduced in the presence of acetic anhydride to give peracetylated tetra-amino intermediates. Subsequently, refluxing in 48% HBr resulted in both deacetylation and formation of 4,6-diaminobenzimidazoles, and then Fremy's oxidation produced

Scheme 2. Synthesis of Series 1 Extended Amidines 1a−1g



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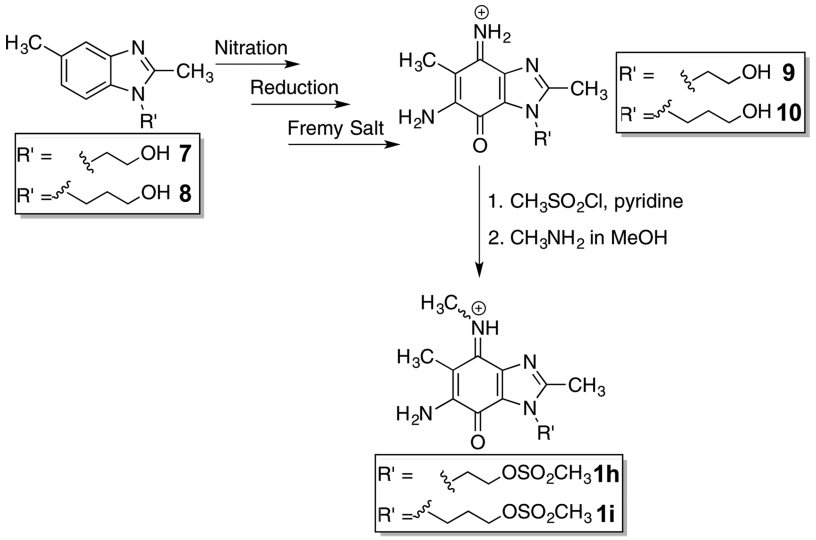
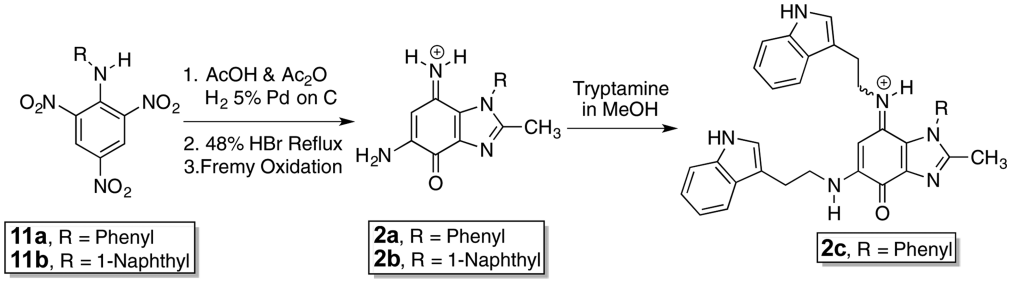
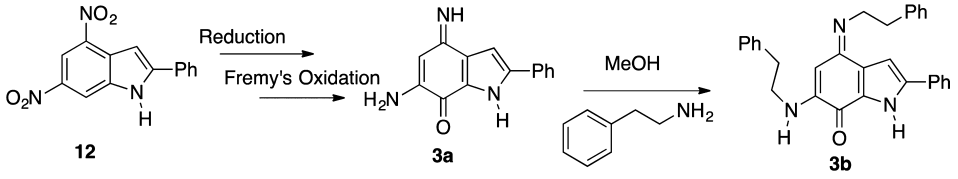
Scheme 3. Synthesis of Series 1 Extended Amidines 1h and 1i



Scheme 4. Synthesis of Series 2 Extended Amidines 2a, b, and c



Scheme 5. Synthesis of Series 3 Extended Amidines 3a and b



2a and **2b**. Finally, transamination of **2a** with tryptamine afforded disubstituted **2c**.

Synthesis of Series 3 Extended Amidines. There are numerous examples of different heterocyclic marine natural products containing the extended amidine moiety.[26] Since various benzimidazole extended amidines could be easily substituted via the transamination reaction we hypothesized that we could apply this versatile reaction to other heterocyclic rings. We chose to explore extended amidine chemistry with the indole ring system because of its prevalence in nature and in synthetic drug pharmacophores.[27] From a synthetic standpoint, starting with a dinitroindole ring was ideal and it was also necessary that the nitro substituents were positioned meta to each other. The nitration of indoles has been well studied, primarily by Noland, Smith, and Rush.[28−31] From these studies it was clear that the desired 4,6-dinitroindole is not possible via direct nitration of indole.

However, this indole could be achieved in three steps by the condensation reaction of trinitrotoluene and benzaldehyde, using a catalytic amount of piperidine.[32,33] The resulting stilbene ortho nitro group was then selectively substituted with sodium azide in dimethylformamide. Thermolysis of the azide derivative in nitrobenzene gave a nitrene intermediate that provided 4,6-dinitro-2-phenylindole (**12**) by an insertion reaction (Scheme 5). Like the benzimidazoles, indole based extended amidines of series **3** were obtained by catalytic reduction of **12** with subsequent Fremy's oxidation giving **3a**, and reaction of **3a** with phenethylamine gave only the disubstituted extended amidine **3b**.

Transamination Regioselectivity, and Tautomeric Equilibria of Extended Amidines. The synthetic studies cited above indicate that series **1** extended amidines exhibit regioselective transamination at the 4-position. In contrast, series **2** and **3** undergo transamination at both the 4- and 6-positions. In this section, we present HMBC spectroscopic data that confirm transamination at the 4-position in series **1**. We also provide calculations that explain the substitution regioselectivity in series **1**, and the lack thereof in series **2** and **3**. We utilized Heteronuclear Multiple Bond Coherence (HMBC) to obtain proton−carbon long distance couplings over 2 to 4 bonds allowing regioselectivity for series **1** to be established. HMBC spectroscopy of **1a** where the delay in pulse

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sequence was optimized for 8 Hz shows both two- and three-bond coupling cross peaks, which could not distinguish between transamination at the 4 and 6 positions (Supporting Information). However, when the pulse sequence delay was optimized at 4 Hz we could easily discern the 2-, 3-, and 4-bond coupling of the methyl amino protons (H13) and the 2-methyl protons (H11) to the C9 carbon, shown as red colored peaks in Figure 1. These cross peaks clearly indicate that transamination

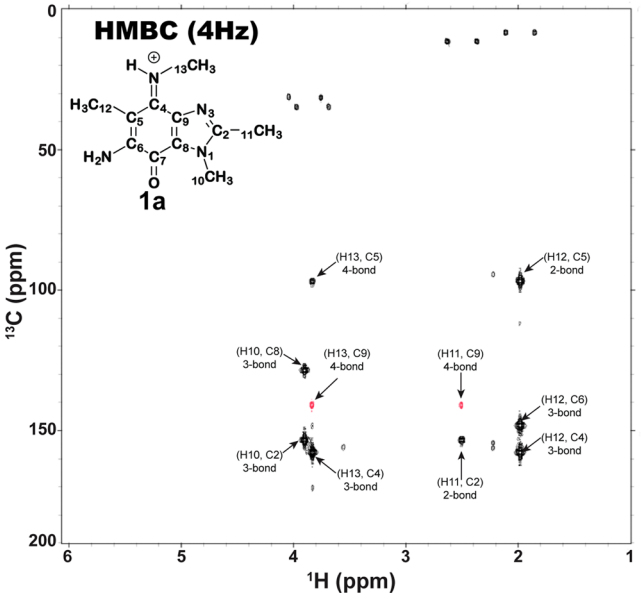


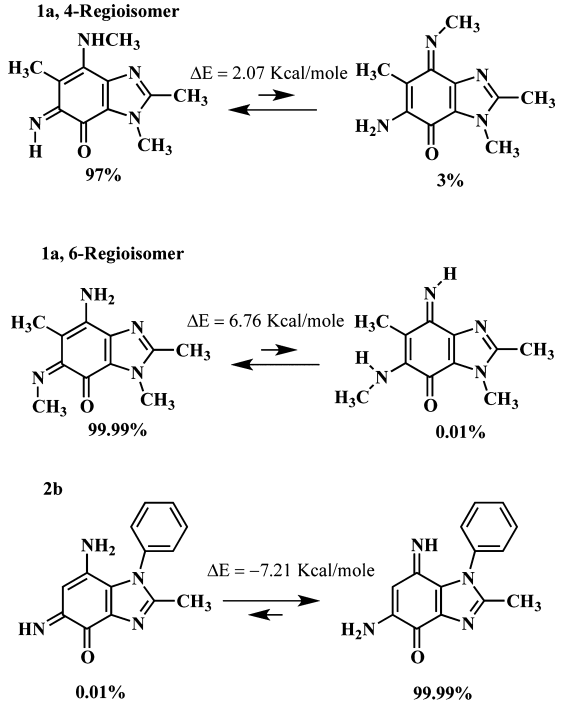
Figure 1. HMBC connectivity spectrum of **1a** at 4 Hz (key correlation peaks are colored red).

occurred at the 4-position rather than at the 6-position. In contrast, a methyl amino group at the 6-position would exhibit 4-bond coupling to the C-7 carbonyl and not C-8. With the transamination product unambiguously assigned to the 4-position, we used three-bond HMBC couplings to assign the ^{13}C chemical shifts of C-4 (157 ppm) and C-6 (149 ppm). All series **1** products display 3-bond coupling to C-4 confirming substitution at the 4-position.

The origins of transamination regioselectivity in series **1** are the apparent steric differences between the 4-position and the 6-position. The 5-methyl and the 7-carbonyl groups prevent substitution by flanking the 6-position. Consistent with this interpretation, transamination regioselectivity is no longer observed in series **2** and **3**, with neither possessing the 5-methyl group. The steric interpretation of regioselectivity was validated with Hartree−Fock calculations carried out using the 3-21G basis set (SpartanModel 2006, Wavefunction, Inc.).[34] These calculations revealed that the 6-methylamino derivative is 1.9 kcal/mol higher in energy compared to that observed with the 4-aminomethyl derivative. The steric differences between the 4-position and the 6-position also influence the tautomeric equilibrium of the extended amidine functional group (Scheme 6). The 4-aminomethyl regioisomer exists predominately as the 6-imino tautomer (*o*-iminoquinone) because steric congestion does not favor the 6-amino tautomer (*p*-iminoquinone). If the 6-aminomethyl regioisomer is considered, the increased steric congestion due to the methyl group favors the 6-imino tautomer to an even greater degree.

In contrast, **2b**, which does not have the 5-methyl group, exists predominately as the *p*-iminoquinone tautomer (favored

Scheme 6. Calculated Δ*E* Values for *o*-Iminoquinone ⇄ *p*-Iminoquinone Tautomeric Equilibria



by −7.21 kcal/mol). We conclude that the 5-methyl group of series **1** causes steric hindrance and 4-amino tautomer predominance, enforcing 4-regiospecificity for transamination.

Hydrolysis Studies of Benzimidazole and Indole Based Extended Amidines. We studied the reaction of extended amidines in aqueous buffers (μ = 1.0 KCl) over a pH range of 0 to 11 and thermostatted to 30 °C. These reactions were accompanied by a substantial color change (purple-colored extended amidine to red-colored aminoquinone) that was monitored at 500 nm with a UV−visible spectrophotometer. These studies provided mechanisms of hydrolysis for both the benzimidazole and indole based extended amidines along with associated rate constants and pK_a values. The hydrolysis of **6** provides a mixture of aminoquinone products **13** and **14** (Scheme 7), which were identified by ^1H NMR and mass spectroscopy.

The pH-rate profile shown in Figure 2 indicates the presence of two mechanisms for hydrolysis: the addition of hydroxide to **6H**$^+$ (k_{HO}) and the addition of hydroxide to neutral **6** (k'_{OH}), Scheme 7. We interpreted the plateau at pH > pK_a as the addition of hydroxide to **6H**$^+$ (k_{OH}) rather than the kinetically equivalent addition of water to neutral **6** based on the stability of **6H**$^+$ toward hydrolysis in moderate to strong acidic aqueous media. Surely, the addition of water to **6H**$^+$ would occur at a larger rate constant than the addition of water to neutral **6**. In fact, we purified **6H**$^+$ and the series **1** and **2** compounds by reversed phase chromatography using 1 M hydrochloric acid as the eluent.

The pH-rate profile shown in Figure 2 was computer-fit to eq 1 (R^2 = 0.98), where a_H is the proton activity determined with a pH meter, K_W is the autoprotolysis constant of water ($10^{-13.86}$ at 30 °C), k_{H2O} = 1.17 × 10^{-3} M^{-1} s^{-1}, K_a = 2.047 × 10^{-8} (pK_a = 7.69), k_{OH} = 7346 M^{-1} s^{-1}, and k'_{OH} = 5.21 × 10^{-13} M^{-1} s^{-1}. The activity of water is considered to be 1 for second-order rate

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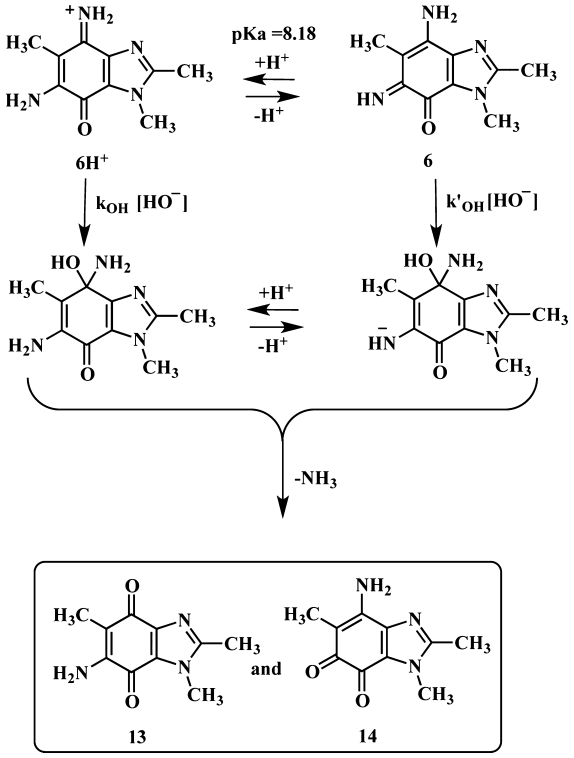
Scheme 7. Hydrolysis Mechanism of 6 in Aqueous Buffer



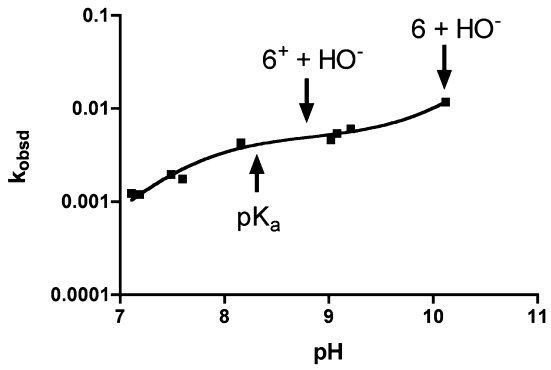


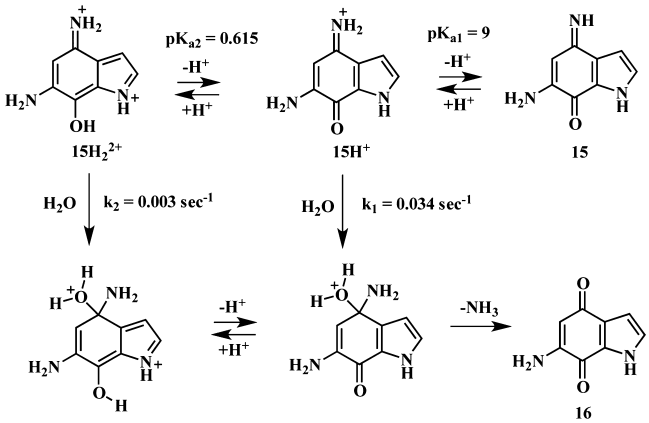
Figure 2. pH-Rate profile for the hydrolysis of compound **6**.

constant calculations. The variable a_H and these constants were used to generate the solid line in Figure 2.

$$k_{obsd} = \frac{K_W k_{OH}}{a_H + K_a} + \frac{K_W k'_{OH}}{a_H} \quad (1)$$

The indole-based extended amidine compounds of series **3** were too insoluble in aqueous media for kinetic studies of hydrolysis, so we studied the hydrolysis of the unsubstituted analogue **15** (Scheme 8). Compound **15** was prepared from 4,6-dinitroindole[35] employing the synthetic methodology shown in Scheme 5. The pH-rate profile shown in Figure 3 indicates the presence of two mechanisms for hydrolysis: the addition of water to protonated **15**, **15H**$^+$ (k_1), and the addition of water to diprotonated **15**, **15H$_2$**$^{2+}$ (k_2). The pH-rate profile data shown in Figure 3 were computer-fit to eq 2 (R^2 = 0.99), where a_H is the proton activity determined with a pH meter, k_1 = 3.06 × 10^{-3} M^{-1} s^{-1}, K_{a1} = 1.0 × 10^{-9} (pK_{a1} = 9.00), k_2 = 0.034 M^{-1} s^{-1}, and K_{a2} = 0.24 (pK_{a2} = 0.615). The activity of water is considered to be 1 for second-order rate constant

Scheme 8. Hydrolysis Mechanism of 15 in Aqueous Buffer



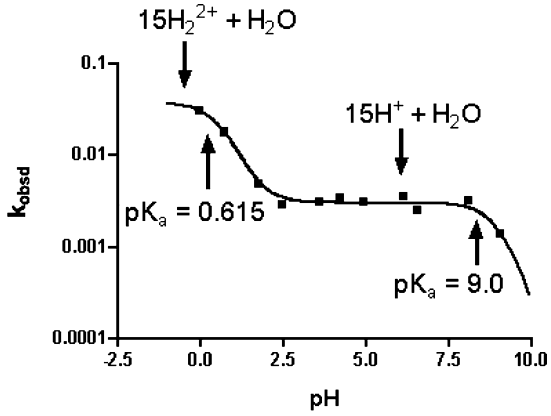


Figure 3. pH-Rate profile for the hydrolysis of **15**.

calculations. The variable a_H and these constants were used to generate the solid line in Figure 3.

$$k_{obsd} = \frac{a_H k_2}{a_H + K_{a2}} + \frac{a_H k_1}{a_H + K_{a1}} \quad (2)$$

From the results cited above, the hydrolysis of **15** involves water addition to either the protonated and diprotonated species. The formation of the dication **15H$_2$**$^{2+}$ is attributed to carbonyl *O*-protonation, which has been documented in our hydrolytic studies of the A-ring of CC-1065[36] and of aziridinyl quinones.[37] However, the electron-rich indole ring of **15** precludes hydroxide addition to the neutral species as observed for more electron-deficient benzimidazole **6**. Our hydrolytic studies of **6** indicate that the benzimidazole-based extended amidines (series **1** and **2**) will have half-lives (~10 min). In contrast, the unsubstituted indole based extended amidine **15** is rapidly hydrolyzed (~ 3 min half-life) at neutrality.

CONCLUSION

Versatile late stage functionalization of organic molecules is a sought after attribute in the preparation of useful chemical products, whether it is the derivatization of a drug pharmacophore or assembling macromolecular structures such as nanoparticles. In this report we have demonstrated such versatility using heterocyclic rings commonly found in nature and clinically used drug pharmacophores. Specifically, benzimidazole and indole based extended amidines can be readily prepared in high yield from *meta*-dinitro derivatives by catalytic reduction and subsequent Fremy's oxidation. These

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highly functionalized compounds can be further derivatized via transamination reactions with virtually any primary amine. Furthermore, substitution can be regioselectively controlled depending on the functional group directly between the extended amidine nitrogen atoms. For example, the series **1** benzimidazole scaffold can be substituted at the 4-position when a 5-methyl substituent is present, due to steric hindrance at the 6-position.

Hydrolysis studies of unsubstituted series **1** and **3** scaffolds indicate that the hydrolytic stability of the extended amidine is dependent on the properties of the ring. For example, the electron deficient benzimidazole series **1** compounds are stable in dilute solutions of strong acids. The base-catalyzed hydrolysis to aminoquinones was only observed in solutions at pH > 8. Such properties are suitable for use in complex biological systems. In contrast, the electron rich indole based extended amidine rapidly hydrolyzed over the pH range of 0 to 9.5 by water addition to both the mono- and diprotonated species. Therefore, depending on the desired application of the extended amidine compound, hydrolytic stability may be controlled or optimized based on the properties of the chosen ring system. Finally, we have demonstrated the utility and versatility of the transamination reaction with three different heterocyclic extended amidine scaffolds, indicating that this chemistry is not limited and could be conceivably applied to any ring system containing the extended amidine moiety.

EXPERIMENTAL SECTION

4,6-Dinitro-1,2,5-trimethyl-1*H*-benzimidazole (5). To a solution consisting of 25 mL of 90% nitric acid and 10 mL of concentrated sulfuric acid was added 1 g (6.25 mmol) of 1,2,5-trimethylbenzimidazole[38] **4** in small portions at room temperature. The solution was warmed to 90 °C and maintained at that temperature with stirring for 24 h. The reaction solution was cooled to room temperature and poured over cracked ice followed by neutralization with 30% aqueous sodium hydroxide solution. The resulting precipitate was filtered, washed with water, dried in the air, and recrystallized with ethanol to give 1.3 g of pale yellow needles, 83% yield: mp, 161−163 °C; TLC (ethyl acetate), R_f = 0.26; FTIR (KBr pellet), 725, 879, 1155, 1251, 1330, 1446, 1531, 2951, 3094 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.09 (1H, s), 3.83 (3H, s), 2.67 (3H, s), 2.54 (3H, s); ^{13}C NMR ($CDCl_3$) δ 159.3, 144.2, 141.2, 137.8, 134.6, 119.8, 109.0, 30.8, 14.7, 14.2. Anal. C, H, N, Calcd for $C_{10}H_{10}N_4O_4 \cdot 0.09\ H_2O$: C, 47.69; H, 4.07; N, 22.25. Found: C, 47.29; H, 3.95; N, 22.23.

6-Amino-4-imino-1,2,5-trimethyl-1*H*-benzimidazole-7-one (6). A mixture consisting of 200 mg (0.8 mmol) of **5**, 100 mg of 5% Pd on carbon in 20 mL of methanol was hydrogenated under 50 psi of H_2 for 3h. The catalyst was filtered through a bed of Celite and washed with methanol, and the filtrate was concentrated *in vacuo* to give a white residue that was immediately taken up into 15 mL of monobasic phosphate buffer (pH = 2.1). To this solution were added, in one portion, 429 mg (1.6 mmol) of Fremy's salt, with subsequent stirring at room temperature for 10 min. The resulting dark purple solution was immediately loaded on a nitrogen push reversed phase column (Phenyl BakerBond) set at 20 psi and eluted with water. The water elution removes any buffer or salts remaining from the reaction. After the initial water elution, the eluent is changed to methanol and the dark purple band is collected, further acidified with a few drops of phosphoric acid, and concentrated *in vacuo* to give **6** as a purple phosphate salt that was recrystallized with methanol and ethyl acetate, yielding 134 mg, 56%. Note: by eluting the band with TFA/methanol or HCl/methanol, the TFA and HCl salts are obtained in 55% and 70% respectively: mp 190−191 °C; TLC (5:3:2 butanol: water: acetic acid) R_f = 0.37; FTIR (KBr pellet): 796, 906, 1041, 1377, 1506, 1626, 1780, 3491 cm^{-1}; ^1H NMR (CD_3OD) δ 3.79 (3H, s), 2.43 (3H, s), 1.89 (3H, s); ^{13}C NMR (D_2O) δ 168.3, 156.5, 155.6, 151.1, 140.9, 125.3, 95.6, 32.2, 12.0, 8.2; (see Supporting Information for 2D-NMR: HMBC and HMQC); HRMS (MALDI-TOF) *m/z*: [M]+ Calcd for $C_{10}H_{13}N_4O$ 205.108, Found 205.109. Anal. C, H, N, Calcd for $C_{10}H_{12}N_4O \cdot TFA \cdot 0.5\ H_2O$: C, 44.04; H, 4.31; N, 17.12. Found: C, 44.10; H, 4.20; N, 16.90.

General Transamination Procedure. To a solution of 0.24 mmol of iminoquinone (e.g., **6*phosphate,** 72.5 mg) dissolved in 10 mL of methanol were added 5 equiv of a primary alkyl amine. For example, 40% aqueous methylamine was used to prepare **1a**. The resulting red solution was heated between 30 and 40 °C and stirred until complete by TLC (1:1 ethyl acetate/acetone). The solvent was removed *in vacuo*, giving a red residue that was taken up in ethyl acetate and chromatographed on silica gel using an eluent of (1:1) acetone/ethyl acetate. The fractions containing product were acidified with a few drops of TFA, concentrated *in vacuo*, and crystallized from ethyl acetate and hexanes to afford the 4-alkylimino derivatives as brownish-purple-to-purple solids **1a−g** in 40−60% yield.

6-Amino-4-methylimino-1,2,5-trimethyl-1*H*-benzimidazole-7-one (1a). 48 mg (60%); mp 196−197 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.43; FTIR (KBr pellet) 1134, 1194, 1373, 1460, 1525, 1593, 1672, 2285, 3103, 3412, cm^{-1}; ^1H NMR (CD_3OD) δ 3.91 (3H, s), 3.84 (3H, s), 2.50 (3H, s), 1.99 (3H, s); ^{13}C NMR (D_2O) δ 170.6, 157.2, 154.4, 146.9, 139.4, 128.3, 114.8, 97.7, 35.2, 32.1, 11.9, 8.9; (see Supporting Information for 2D NMR: HMBC); HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{15}N_4O$ 219.124, Found 219.119. Anal. C, H, N, Calcd for $C_{11}H_{14}N_4O \cdot TFA \cdot 0.6\ CH_2Cl_2$: C, 42.62; H, 4.26; N, 14.62. Found: C, 42.25; H, 3.94; N, 14.89.

6-Amino-4-(3-methoxypropylimino)-1,2,5-trimethyl-1*H*-benzimidazole-7-one (1b). 56 mg (60%); mp, 168−169 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.39; FTIR (KBr pellet) 1132, 1172, 1381, 1527, 1593, 1637, 1697, 2980, 3090, 3412 cm^{-1}; ^1H NMR (CD_3OD): δ 4.56 (2H, t, J = 6.6 Hz) 3.90 (3H, s) 3.60 (2H, t, J = 6.6 Hz) 3.35 (3H, s) 2.49 (3H, s) 2.07 (2H, q, J = 5.7 Hz), 1.90 (3H, s); ^{13}C NMR (D_2O) δ 170.6, 156.8, 154.3, 147.3, 139.5, 128.3, 97.6, 70.2, 69.7, 57.9, 57.8, 45.6, 32.1, 28.7, 12.0, 8.9; (see Supporting Information for 2D NMR: HMBC, HMQC, and TOCSY); (HRMS) MALDI-TOF *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{21}N_4O_2$ 277.166, Found 277.165. Anal. C, H, N, Calcd for $C_{14}H_{20}N_4O_2 \cdot TFA$: C, 49.23; H, 5.42; N, 14.35. Found: C, 48.89; H, 5.28; N, 14.16.

6-Amino-4-cyclopropylimino-1,2,5-trimethyl-1*H*-benzimidazole-7-one (1c). 52 mg (60%); mp dec >260 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.30; FTIR (KBr pellet) 800, 1072, 1384, 1525, 1577, 1639, 3121, 3414 cm^{-1}; ^1H NMR (CD_3OD): δ 4.79 (1H, m), 3.91(3H, s), 2.49 (3H, s), 2.01 (3H, s), 1.15 (4H, m, cyclopropyl methylenes); ^{13}C NMR (DMSO-d_6) δ 170.4, 157.7, 154.3, 151.9, 141.7, 140.1, 126.3, 95.5, 32.7, 13.2, 13.1, 11.5; (see Supporting Information for 2D NMR: HMBC); HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{17}N_4O$ 245.140, Found 245.142.

6-Amino-4-cyclohexylimino-1,2,5-trimethyl-1*H*-benzimidazole-7-one (1d). 48 mg (50%); mp 249−250 °C; TLC (5:3:2 butanol/water/acetic acid), R_f = 0.44; FTIR (KBr pellet) 1296, 1359, 1527, 1583, 1624, 1680, 2930, 3068, 3364 cm^{-1}; ^1H NMR (CD_3OD): δ 5.72 (1H, m), 3.90 (3H, s), 2.49 (3H, s), 1.97 (3H, s), 2.05−1.21 (10H, m, cyclohexyl methylenes); ^{13}C NMR (DMSO-d_6) δ 171.1, 155.5, 153.4, 148.8, 140.0, 128.7, 97.4, 57.0, 32.7, 32.0, 25.1; HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{23}N_4O$ 287.187, Found 287.190.

6-Amino-4-phenethylimino-1,2,5-trimethyl-1*H*-benzimidazole-7-one (1e). 41 mg (40%); mp 179−180 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.50; FTIR (KBr pellet) 1134, 1201, 1379, 1527, 1593, 1689, 3088, 3410 cm^{-1}; ^1H NMR (CD_3OD): δ 7.31 (5H, m), 4.65 (2H, t, J = 7.2 Hz), 3.91 (3H, s), 3.10 (2H, t, J = 7.8 Hz), 2.54 (3H, s), 1.97 (3H, s) (see Supporting Information for 2D NMR: HMBC); ^{13}C NMR (DMSO-d_6) δ 170.4, 157.0, 153.4, 148.0, 139.8, 137.8, 128.7, 128.3, 128.2, 126.4, 97.0, 48.6, 36.0, 31.4, 11.5, 8.5; HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}N_4O$ 309.171, Found 309.168. Anal. C, H, N, Calcd for $C_{18}H_{20}N_4O \cdot TFA$: C, 56.87; H, 5.01; N, 13.26. Found: C, 56.75; H, 4.99; N, 13.17.

6-Amino-4-[2-(4-hydroxyphenyl)-ethylimino]-1,2,5-trimethyl-1*H*-benzimidazole-7-one (1f). 42 mg (40%); mp; dec >170 °C;

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TLC (5:3:2 butanol/water/acetic acid) R_f = 0.47; FTIR (KBr pellet) 1383, 1516, 1593, 2184, 3418, cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.19 (2H, d, J = 8 Hz), 6.74 (2H, d, J = 8 Hz), 4.68 (2H, t, J = 7.2 Hz), 3.91 (3H, s) 3.06 (2H, t, J = 7.8 Hz), 2.45 (3H, s), 2.08 (3H, s); ^{13}C NMR (DMSO-d_6) δ 171.0, 157.0, 156.3, 154.0, 148.8, 139.9, 130.1, 128.6, 128.3, 115.7, 97.1, 49.1, 35.5, 32.7, 13.3, 10.5 (see Supporting Information for 2D NMR: HMBC and HMQC); HRMS (FAB+) m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}N_4O_2$ 325.1664; Found 325.1658.

6-Amino-4-[2-(1*H*-indol-3-yl)-ethylimino]-1,2,5-trimethyl-1*H*-benzimidazole-7-one (1g). 44 mg (40%); mp 191−192 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.37; FTIR (KBr pellet) 746, 800, 1128, 1199, 1371, 1525, 1599, 1689, 3254 cm^{-1}; ^1H NMR (CD_3OD) δ 7.65 (1H, d, J = 8.1 Hz), 7.29 (1H, d, J = 8.1 Hz), 7.09−6.97 (3H, m), 4.78 (2H, t, J = 7.2 Hz), 3.79 (3H, s), 3.23 (2H, t, J = 7.2 Hz), 2.41 (3H, s), 1.94 (3H, s); ^{13}C NMR (DMSO-d_6) δ 171.0, 158.4, 158.1, 156.4, 153.5, 148.6, 140.0, 136.7, 128.4, 127.6, 123.9, 121.5, 119.0, 111.9, 110.8, 97.2, 48.4, 32.6, 26.6, 13.1, 10.6; (see Supporting Information for 2D NMR: HMBC); HRMS (FAB+) m/z: $[M+H]^+$ Calcd for $C_{20}H_{22}N_5O$ 348.1824, Found 348.1819. Anal. C, H, N, Calcd for $C_{20}H_{21}N_5O{\cdot}1.5\ H_2O{\cdot}1.7$TFA: C, 46.82; H, 4.32; N, 11.67. Found: C, 46.98; H, 3.96; N, 12.08.

Nitration of 7 To Afford 4,6-Dinitro-1-(2-nitrooxyethyl)-2,5-dimethyl-1*H*-benzimidazole. To a solution consisting of 10 mL of 90% nitric acid and 5 mL of concentrated sulfuric acid were added 200 mg (1.1 mmol) of **7** (prepared as previously described[14]) in small portions over 5 min at rt. After the addition, the reaction was heated to 90 °C and maintained at that temperature for 24 h. The reaction was cooled to rt and neutralized with 30% aqueous sodium hydroxide with the addition of ice to keep the solution cool. The resulting pale yellow precipitate was filtered, washed with water, air-dried, and recrystallized from ethanol to give 202 mg of pale yellow needles, 69% yield: mp 165−166 °C; TLC (ethyl acetate) R_f = 0.43; FTIR (KBr pellet) 754, 852, 885, 1039, 1278, 1332, 1527, 1641, 3059, 3443 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (1H, s), 4.82 (2H, t, J = 5 Hz), 4.58 (2H, t, J = 5 Hz), 2.74 (3H, s), 2.62 (3H, s). Anal. C, H, N, Calcd for $C_{11}H_{11}N_5O_7{\cdot}0.5\ H_2O$: C, 39.53, H, 3.62; N, 20.95. Found: C, 39.59; H, 3.33; N, 20.74.

6-Amino-1-(2-hydroxyethyl)-4-imino-2,5-dimethyl-1*H*-benzimidazole-7-one (9). A mixture consisting of 500 mg (1.5 mmol) of the nitration product of **7**, 500 mg of 5% Pd on carbon, and 30 mL of methanol was hydrogenated under 50 psi of H_2 for 3 h at rt. The catalyst was filtered off through a pad of Celite, and the filtrate was acidified with 5 drops of conc HCl. Concentration of the solvent *in vacuo* gave the HCl salt of *4,6-diamino-1-(2-hydroxyethyl)-2,5-dimethyl-1H-benzimidazole* from ethyl acetate and methanol as tan crystals, 366 mg, 81% yield.

This HCl salt, 250 mg, was then added to a solution consisting of 688 mg (3 equiv) of Fremy's salt in 25 mL of monobasic phosphate buffer (pH = 2.1) and stirred for 30 min. The resulting dark purple solution was immediately loaded on a nitrogen push reversed phase column (phenyl BakerBond) set at 20 psi and eluted with water. The water elution removes any buffer or salts remaining from the reaction. After the initial water elution the eluent is changed to 100% methanol, and the dark purple band is collected and further acidified with a few drops of phosphoric acid. The purple methanolic solution was concentrated *in vacuo* resulting in a purple solid that was recrystallized from methanol and ethyl acetate with cooling at 4 °C for 12 h to afford **9** as a dark purple crystalline phosphate salt, 350 mg, 95% yield: mp dec >145 °C; TLC (5:3:2 butanol/water/acetic acid), R_f = 0.38; FTIR (KBr pellet) 617, 742, 1107, 1400, 1508, 1624, 3095, 3373 cm^{-1}; ^1H NMR (CD_3OD) δ 4.38 (2H, t, J = 6 Hz), 3.86 (2H, t, J = 6 Hz), 3.54 (3H, s) 1.99 (3H, s); ^{13}C NMR (DMSO-d_6) δ 168.5, 156.7, 155.8, 151.2, 141.4, 125.1, 95.5, 59.8, 47.9, 12.6, 8.3; HRMS (MALDI-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{15}N_4O_2$ 235.119, Found 235.119.

6-Amino-4-methylimino-2,5-dimethyl-1-[2-(methylsulfonyl-oxy)ethyl]-1*H*-benzimidazole-7-one (1h). To a solution consisting of 205 mg (0.62 mmol) of **9** in 10 mL of dry pyridine were added 100 μL of methane sulfonyl chloride (2.1 equiv) under nitrogen at rt, and the solution was stirred for 12 h. Pyridine was removed *in vacuo*, and the resulting blue residue was purified by reversed phase chromatography in the same manner as described for **6**, giving the methylsulfonyl derivative as a blue solid that was pure by NMR: ^1H NMR (CD_3OD) δ 4.62 (4H, m), 3.05 (3H, s), 2.55 (3H, s), 1.99 (3H, s).

To 19 mg of the methylsulfonyl derivative dissolved into 1.5 mL of methanol were added 24 μL of 40% aqueous methylamine. The solution, which turns red upon addition of the amine, was stirred for 24 h in a stoppered round-bottom flask at rt. The reaction was concentrated *in vacuo* giving a red colored residue, which was purified in the same manner as **6**. The methanolic eluent was first acidified with a few drops of TFA to aid in the elution. The resulting blue solid was recrystallized with methanol and ethyl acetate affording **1h** as a blue TFA crystalline salt: mp 158−160 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.35; FTIR (KBr pellet): 1180, 1354, 1533, 1602, 1676, 3200, 3369, cm^{-1}; ^1H NMR (CD_3OD) δ 4.65 (2H, t, J = 5 Hz), 4.59 (2H, t, J = 5 Hz), 3.86 (3H, s), 3.04 (3H, s), 2.56 (3H, s), 2.00 (3H, s); ^{13}C NMR (DMSO-d_6) δ 171.0, 158.9, 158.6. 156.8, 153.6, 148.4, 148.3, 140.8, 128.3, 97.3, 68.5, 45.1, 37.2, 36.0, 13.5, 10.5; (see Supporting Information for 2D NMR: HMBC and HMQC); HRMS (FAB+) m/z: $[M+H]^+$ Calcd for $C_{13}H_{19}N_4O_4S$ 327.1127, Found 327.1119. Anal. C, H, N, Calcd for $C_{13}H_{18}N_4O_4S{\cdot}TFA\cdot 0.7\ H_2O$: C, 39.77; H, 4.54; N, 12.37. Found: C, 39.59; H, 4.30; N, 12.16.

2,5-Dimethyl-1-(3-methoxypropyl)-1*H*-benzimidazole (8). A solution consisting of 5 mL (6.5 g, 38 mmol) of 3-nitro-4-chlorotoluene and 10 mL of methoxypropyl amine was refluxed under nitrogen until the reaction was complete by TLC (DCM). The reaction solution was concentrated *in vacuo*, and the resulting residue was taken up in water and extracted with DCM 3× (50 mL). The organic extracts were washed with aqueous saturated sodium chloride 2× (50 mL), dried with sodium sulfate, and concentrated to give an orange oil that was purified by silica gel column chromatography (DCM).

The oil was dissolved in 50 mL of methanol and hydrogenated with 1 g of 5% Pd on carbon under 50 psi of H_2 for 3 h. The catalyst was filtered through a pad of Celite and washed with methanol, and the filtrate was concentrated *in vacuo* to give the diamine, 4.75 g, 65% yield. The diamine was dissolved in a solution consisting of 15 mL of acetic acid and 15 mL of acetic anhydride and refluxed for 1 h. The reaction was concentrated *in vacuo* to give diacetamide in quantitative yield. The diacetamide (1 g) was refluxed in 25 mL of 4 N HCl for 2 h, cooled to rt, and neutralized with concentrated ammonium hydroxide (pH = 8), extracted with DCM 3× (50 mL), dried with sodium sulfate, and concentrated to give **8** as an amber colored oil that was pure by NMR: ^1H NMR ($CDCl_3$): δ 7.46 (1H, s), 7.17, (1H, d, J = 8 Hz), 7.05 (1H, d, J = 8 Hz), 4.21 (2H, t, J = 6 Hz), 3.32 (3H, s), 3.28 (2H, t, J = 6 Hz), 2.56 (3H, s), 2.46 (3H, s), 2.02 (2H, q, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 151.5, 142.6, 133.0, 131.4, 123.3, 118.7, 68.4, 58.5, 40.3, 28.5, 21.4, 13.5; HRMS (FAB+) m/z: $[M+H]^+$ calcd for $C_{13}H_{19}N_2O^+$ 219.149, Found 219.150.

Nitration of 8 To Afford 2,5-Dimethyl-4,6-dinitro-1-(3-nitrooxypropyl)-1*H*-benzimidazole. Compound **8** was dissolved in 10 mL of concentrated sulfuric acid and cooled on ice. To the cooled sulfuric acid solution 10 mL of 90% nitric acid were added dropwise. The reaction was stirred at rt for 12 h. TLC analysis (ethyl acetate) showed two nitration products. The reaction was then heated to 50 °C until TLC showed one product. The reaction was poured over ice and neutralized with sodium bicarbonate. The neutral solution was extracted 3× (50 mL) with DCM, dried with sodium sulfate, and concentrated giving a yellow residue. The residue was recrystallized with hot ethyl acetate and hexane to yield 500 mg of yellow needles, 41% for two steps: mp; 140−142 °C; TLC (ethyl acetate) R_f = 0.43; FTIR (KBr pellet): 657, 723, 856, 1020, 1168, 1327, 1440, 1529, 1639, 3101 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.13 (1H, s), 4.49 (2H, t, J = 5.4 Hz), 4.37 (2H, t, J = 5.4 Hz), 2.70 (3H, s), 2.59 (3H, s), 2.31(2H, q, J = 6 Hz). Nitrated **8** was used to synthesize **10** without any further purification and characterization.

6-Amino-1-(3-hydroxypropyl)-4-imino-2,5-dimethyl-1*H*-benzimidazole-7-one (10). A solution of 0.5 g (1.47 mmol) of the nitration product of **8** in 100 mL of methanol was reduced under 50 psi H_2 in the presence of 150 mg of 5% Pd on carbon for 12 h. The catalyst was filtered off through a pad of Celite, and the filtrate was

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acidified with 5 drops of conc HCl. Concentration of the solvent *in vacuo* and crystallization from ethyl acetate and methanol gave the HCl salt *4,6-diamino-1-(3-hydroxypropyl)-2,5-dimethyl-1H-benzimidazole* as tan crystals, 395 mg, 87% yield.

The HCl salt, 223 mg (0.823 mmol), was then added to a solution consisting of 663 mg (3 equiv) of Fremy's salt in 25 mL of monobasic phosphate buffer (pH = 2.1) and stirred for 30 min. The resulting dark purple solution was immediately loaded onto a nitrogen push reversed phase column (phenyl BakerBond) set at 20 psi and eluted with water. The water elution removes any buffer or salts remaining from the reaction. After the initial water elution, the eluent was changed to 10% methanol acidified with a few drops of phosphoric acid and the dark purple band was collected. The purple fraction was concentrated *in vacuo* resulting in a purple solid that was recrystallized from methanol and ethyl acetate with cooling at 4 °C for 12 h to afford **10** as a dark purple crystalline phosphate salt, 246 mg, 86% yield: mp dec >200 °C; TLC (5:3:2 butanol/water/acetic acid), R_f = 0.5; ^{1}H NMR (CD_3OD) δ 4.23 (2H, t, J = 6 Hz), 3.48 (2H, t, J = 6 Hz), 2.44 (3H, s), 1.8 (2H, m), 1.87 (3H, s); ^{13}C NMR (D_2O) δ 171.7, 159.8, 157.4, 154.0, 144.2, 127.9, 98.2, 60.9, 45.7, 33.8, 14.7, 10.8; HRMS (FAB+) m/z: $[M+H]^+$ calcd for $C_{12}H_{17}N_4O_2^+$, 249.1351; Found 249.135.

6-Amino-4-methylimino-2,5-dimethyl-1-[2-(methylsulfonyl-oxy)propyl]-1*H*-benzimidazole-7-one (1i). To a solution consisting of 100 mg (0.288 mmol) of **10** and 5 mL of dry pyridine were added 100 μL of methanesulfonyl chloride (4.5 equiv) under nitrogen at rt, and the solution was stirred for 12 h. Pyridine was removed *in vacuo*, and the resulting blue residue was purified by reversed phase chromatography in the same manner as described for **10** to give the methanesulfonoxypropyl derivative as a blue solid, 57 mg (46% yield) that was pure by TLC (5:3:2 butanol/water/acetic acid), R_f = 0.42, and NMR.

A solution of the methanesulfonylpropyl derivative (57 mg) in 5 mL of methanol was combined with 75 μL of 40% aqueous methylamine in a stoppered flask and stirred for 18 h at rt. The reaction was concentrated *in vacuo* to give a red colored residue, which was purified in the same manner as **10** except 100% methanol acidified with a few drops of TFA was used to elute the product. The resulting blue solid was recrystallized with methanol and ethyl acetate affording **1i** as a blue TFA crystalline salt: mp dec >200 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.3; ^{1}H NMR (CD_3OD) δ 4.36 (2H, t, J = 6 Hz), 3.74 (3H, s), 3.54 (2H, t, J = 6 Hz), 2.87 (3H, s), 2.46 (3H, s), 2.10 (3H, s); ^{13}C NMR (D_2O) δ 170.9, 156.9, 153.0, 148.5, 140.8, 128.3, 97.2, 68.0, 42.6, 37.1, 36.0, 29.0, 13.2, 10.4; HRMS (FAB+) m/z: $[M+H]^+$ calcd for $C_{14}H_{21}N_4O_4S^+$, 341.1283; Found 341.1276

Synthesis of *N*-(2,4,6-Trinitrophenyl)aniline (11a) and *N*-(2,4,6-Trinitrophenyl)-1-naphthylamine (11b). To a solution consisting of 1 g of picryl chloride dissolved in methanol were added 2 mol equiv of arylamine, and the mixture was stirred at rt until complete. The product crystallized from the reaction in high purity and in quantitative yield when water was added to the reaction mixture followed by chilling on an ice bath. The melting points of **11a**[39] and **11b**[40] matched those reported in the literature.

Synthesis of 5-Amino-1-aryl-2-methyl-7-imino-1*H*-benzimidazole-4-one (2a and 2b). To a solution consisting of 100 mL of acetic acid, 10 mL of acetic anhydride, and 1.8 mmol of **11a** or **11b** were added 300 mg of 5% Pd on carbon. This mixture was shaken under 50 psi of H_2 for 12 h, and the catalyst was removed by filtration through Celite. Evaporation of the acetic acid and acetic anhydride afforded the peracetylated tetra-amine intermediate as a light yellow oil. This oil was dissolved in 50 mL of 48% HBr and refluxed for 1 h to facilitate both deacetylation and benzimidazole formation. The 48% HBr was removed *in vacuo*, and the product crystallized from methanol ethyl acetate: 5,7-diamino-1-1-aryl-2-methyl-1*H*-benzimidazole·2HBr was obtained as a light tan solid in 79% yield. This product was dissolved in 50 mL of phosphate buffer (pH = 7) and combined with 3 equiv of Fremy's salt. After the reaction was stirred for 10 min, the neutral product was extracted with DCM 3× (50 mL). The organic extracts were washed 3× (50 mL) with 0.5 N HCl to extract **2** as the HCl salt. The acidic aqueous fractions were then washed with 50 mL of DCM and concentrated *in vacuo* to give **2a** and **2b** as purple HCl salts (60% yield).

5-Amino-7-imino-2-methyl-1-phenyl-1*H*-benzimidazole-4-one (2a). Mp dec >205 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.42; FTIR (KBr pellet): 617, 862, 1035, 1172, 1421, 1496, 1637, 3161, 3408 cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.77 (3H, m), 7.65 (2H, m), 5.85 (1H, s), 2.26 (3H, s); ^{13}C NMR (DMSO-d_6) δ 174.9, 155.6, 153.6, 153.5, 137,9, 133.6, 131.8, 131.5, 131.1, 129.8, 129.0 127.5, 89.5, 13.7; HRMS (FAB+) m/z: calcd for $C_{14}H_{13}N_4O^+$, 253.1089; Found 253.1098.

5-Amino-7-imino-2-methyl-1-napthyl-1*H*-benzimidazole-4-one (2b). Mp dec >200 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.21; FTIR (KBr pellet): 584, 829, 1199, 1462, 1612, 3076, cm^{-1}; ^{1}H NMR (CD_3OD): δ 8.32 (1H, d, J = 8 Hz), 8.18 (1H, d, J = 8 Hz), 7.85−7.65 (4H, m), 7.38 (1H, d, J = 8 Hz), 5.78 (1H, s), 2.13 (3H, s); ^{13}C NMR (D_2O) δ 175.1, 155,3, 153.9, 153.7, 138.5, 134.9, 132.5, 131.7, 129.4, 129.3, 129.2, 128.9, 128,0, 127.3, 126.9, 121.4, 89.5, 13.3; HRMS (FAB+) m/z: calcd for $C_{18}H_{15}N_4O^+$ 303.1246; Found 303.1254.

5, 7-Di-[2-(1*H*-indol-3-yl)-ethylimino]-2-methyl-1-phenyl-1*H*-benzimidazole-4-one (2c). To a solution consisting of 50 mg of **2a** dissolved in methanol were added 5 equiv of tryptamine, and the reaction was stirred at rt for 12 h. The reaction was concentrated *in vacuo* and chromatographed on silica gel (1:1 ethyl acetate/acetone) to give 39.8 mg (42% yield) of **2c**: ^{1}H NMR (CD_3OD): δ 7.65 (1H, d, J = 8 Hz), 7.42−6.98 (14H, m), 6.67 (1H, s), 3.76−3.73 (3H, m), 3.18−3.15 (2H, t), 3.02−2.90 (2H, t), 2.65−2.18 (2H, t), 2.07 (3H, s); ^{13}C NMR (Methanol-d_4) δ 173.9, 155.1, 153.7, 153.3, 138.4, 138.3, 137.5, 133.8, 133.0, 132.9, 132.1, 131.9, 128.7, 128.5, 127.8, 125.0, 123.8, 123.0, 122.8, 120.3, 120.1, 119.2, 119.2, 112.7, 112.3, 110.3, 84.8, 46.1, 45.1 26.3, 24.5, 13.1 (see Supporting Information for HMBC 2D NMR); HRMS (FAB+) m/z: calcd for $C_{34}H_{31}N_6O^+$ 539.2559; Found 539.2552.

6-Amino-4-imino-2-phenyl-1*H*-indole-7-one (3a). A mixture consisting of 150 mg (0.53 mmol) of **12** (4,6-dinitro-2-phenyl-1*H*-indole[32,33]) and 75 mg of 5% Pd on carbon, in 15 mL of methanol, was hydrogenated for 3 h under 50 psi of H_2. The catalyst was filtered through a pad of Celite and washed with methanol, and the filtrate was acidified with a few drops of conc HCl and dried *in vacuo* to yield the HCl salt. This salt was immediately dissolved in 10 mL of pH 7 phosphate buffer containing 3 equiv of Fremy's salt (426 mg, 1.6 mmol). The solution was stirred for 10 min, and the resulting amorphous brown solid was filtered off, washed with water, and dried to give 113 mg (90%) of **3a**: mp dec 260 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.63; FTIR (KBr pellet): 584, 829, 1199, 1462, 1612, 3076, cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 13.50 (1H, br s), 10.1−9.9 (1H, br s), 9.06 (1H, br s), 8.43 (1H, br s), 7.84−7.35 (6H, m), 5.71 (1H, s); ^{13}C NMR (DMSO-d_6) δ 169.3, 161.4, 154.6, 142.0, 130.1, 129.5, 129.4, 128.3, 126.2, 125.3, 107.7, 89.6, 39.0, 38.0; HRMS (MALDI-TOF) m/z: calcd for $C_{14}H_{12}N_3O^+$ 238.097; Found 238.095.

4,6-Di(phenethylamino)-2-phenyl-1*H*-indole-7-one (3b). The general procedure for transamination was employed: dec 260 °C; TLC (5:3:2 butanol/water/acetic acid) R_f = 0.70; ^{1}H NMR (d_6-DMSO): δ 7.92 (2H, d, J = 7.5 Hz), 7.43 (3H, t, J = 7.5 Hz), 7.32−7.20 (10H, m), 7.03 (1H, s), 5.51(1H, s), 3.88 (2H, t, 7.5), 3.40 (2H, t, J = 7 Hz), 3.02 (2H, t, J = 7.5 Hz), 2.92 (2H, t, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 169.0, 142.2, 138.9, 138.5, 137.8, 129.9, 129.6, 129.4, 129.3, 129.2, 129.1, 129.04, 129.0, 128.9, 128.9, 127.9, 127.7, 127.3, 127.1, 127.1, 127.0, 126.9, 126.2, 126.1, 126.0, 86.1, 46.0, 44.8, 33.4, 26.3; (see Supporting Information for 2D NMR: COSY and HMBC); HRMS (FAB+) m/z: calcd for $C_{30}H_{28}N_3O^+$ 446.2232; Found 446.2227.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General methods and materials as well as supporting NMR and MS spectra for series **1**−**3** compounds are provided, including ^{1}H, ^{13}C, COSEY, TOCSY, HMQC, and HMBC NMR; high resolution electron impact bombardment MS, MALDI-TOF

MS, and FAB MS. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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