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Oligophenylenaminones as Scaffolds for α-Helix Mimicry

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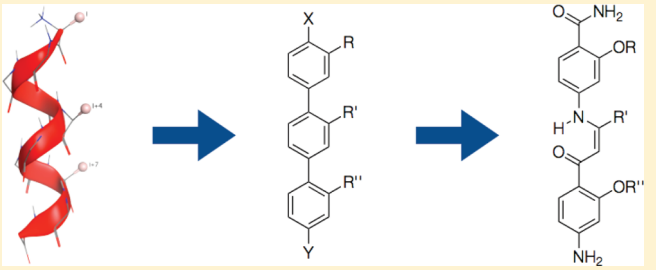
Supporting Information

ABSTRACT: The design and synthesis of small molecule α-helix mimetics has been a productive field over the past decade. These compounds have performed well in a variety of biological systems as functional disruptors of α-helix-mediated protein−protein interactions. In our studies we have continued to develop novel, more biologically compatible scaffolds, which are often easier to assemble and capable of mimicking longer and/or more diverse helices. To this end, we have constructed a new series of *i*, *i*+4, *i*+7 α-helix mimics based on the enaminone scaffold. These molecules represent a step forward in the pursuit of idealized monofacial α-helix mimetics.



INTRODUCTION

α-Helices are the most commonly observed secondary structure in proteins. This important motif not only plays a large role in the higher order structure of many proteins but also frequently comprises key elements of the interfacing domains in protein−protein interactions.[1,2]

Synthetic chemists have long been intrigued by the challenge of developing synthetic α-helix mimetics not only as a tool to study their properties outside of a larger protein but also for utilization as potential therapeutic agents and/or biological probes. Strategies for helix mimicry include helical β-peptides,[3−5] covalently bonded peptide helices,[6−9] and nonpeptidic small molecules.[10−13]

Work in our lab and others over the past decade has produced nonpeptidic small molecules capable of imitating the structure and function of α-helices. Over time, these structures have evolved from small, bicyclic indanes[14] to elongated, rigid terphenyls,[15−17] to more easily assembled and biocompatible structures such as benzoylureas.[18−20]

One crucial goal in the design of helix mimetics is the ease of their synthesis. Ideally, readily accessible monomer units should be linked together in a mild, direct manner, allowing for a variety of mimics of different length and side-chain composition to be synthesized directly.

The challenge of the synthetic accessibility of rod-like aryl oligomers (such as the terphenyls) led us to develop scaffolds that were not composed entirely of aryl subunits. Others have reported helicomimetic molecules which feature six-membered covalently bonded rings in lieu of one of the aryl constituents of the fundamental helix-mimetic framework.[21,22] These systems offer attractive options to the previously developed methods of helix mimicry, especially in regard to the increased ability of these scaffolds to conform to induced-fit models of protein−protein interaction inhibition.

We have recently reported the use of a hydrogen-bonded ring as an arene surrogate in α-helix mimetic scaffolds. Structures of

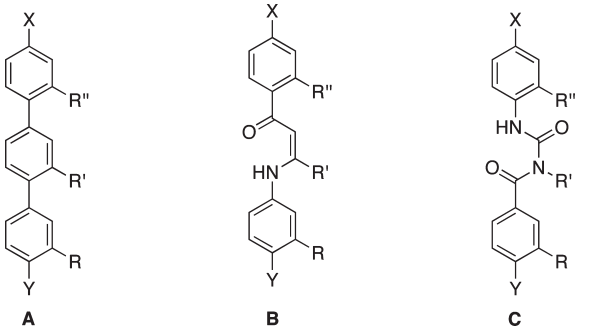


Figure 1. Scaffolds for α-helix mimicry.

this type offer the potential for a more extendable synthesis of a broader range of substrates with increased structural flexibility. Our first example in this category was a simple enaminone derivative (Figure 1B),[23] which established the structural integrity of the intramolecular hydrogen bond and the analogy to α-helix structure.

We have further assembled and investigated a number of benzoylurea compounds (Figure 1C), which, due to their facile synthesis, allowed for the construction of α-helix mimics of extended lengths. These oligobenzoylureas have been shown to adopt conformationally biased structures that are able to project peptidomimetic side chains with the distance and angular projection similar to an α-helix[19,20] and furthermore are able to successfully mimic α-helical protein function in a biological environment.[18]

The success of the benzoylureas prompted us to pursue other α-helix mimics of this type. A replacement of the acylurea with a

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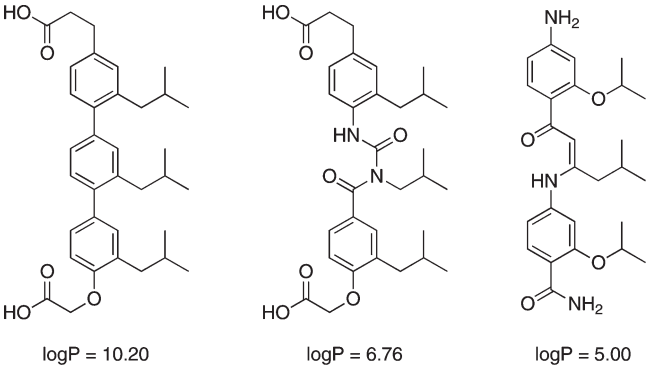


Figure 2. Representative examples of *i*, *i*+4, *i*+7 α-helix mimetics with their respective logP values as calculated by MOE.

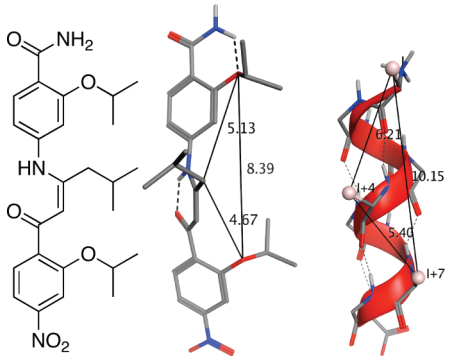


Figure 3. Lowest energy conformation of representative α-helix mimetic enaminone **23** as determined by MOE.

vinylogous amide would not only maintain planarity in the six-membered hydrogen-bonded arene surrogate[24] but also potentially provide an even stronger noncovalent interaction due to its electronically conjugated and dipolar nature. We herein explore the scope and limitations of using an enaminone within α-helix mimetic scaffolds.

RESULTS AND DISCUSSION

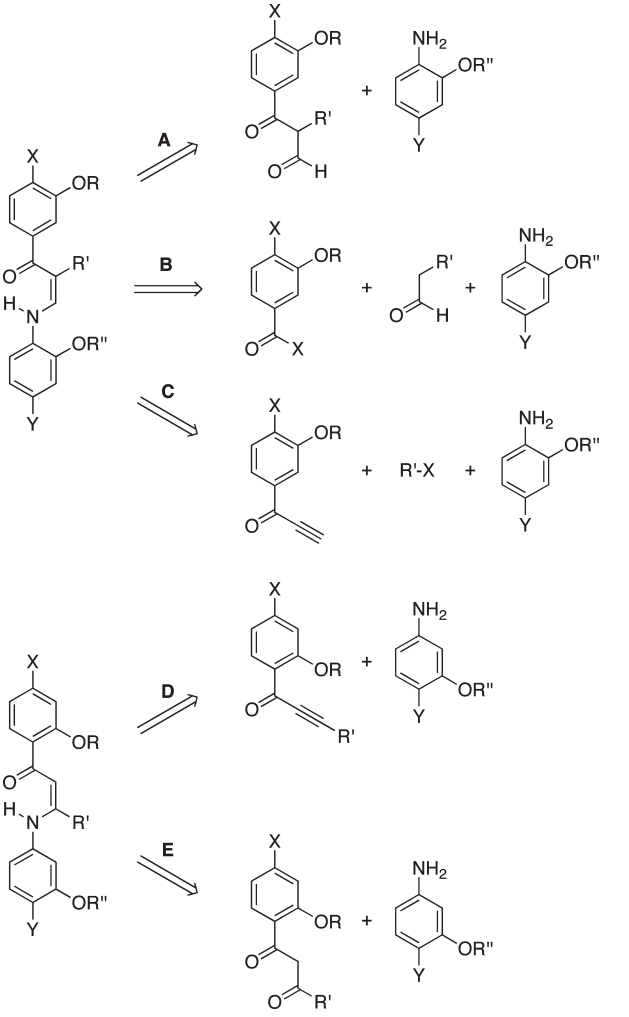
Retrosynthetic Analysis and Modeling Studies. The design of the enaminones was guided not only by synthetic accessibility but also by the optimization of their physical properties. For example, the calculated logP of the proposed structures indicated that they would offer improved solubility over our earlier scaffolds (Figure 2).

Modeling studies performed using MOE (MMFF94, 10 000 iterations, default settings) suggest that the lowest energy conformation of nitroenaminone **23** possesses an intact intramolecular hydrogen bond, and places the three isopropyl groups on a single face of the mimetic (Figure 3). The inter-side-chain distances that the model predicts are in close agreement to those of an idealized α-helix model.

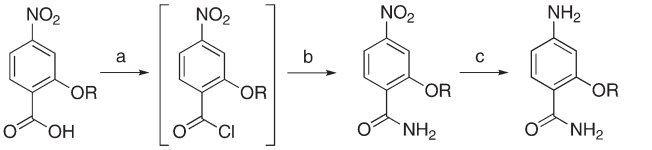
A number of ways to approach the synthesis of helix mimetic enaminones were explored (Scheme 1); however, route **D** involving the conjugate addition of an aniline to an ynone was deemed to be the simplest and thus was investigated.

Synthesis. The synthesis of both the terminal monomers **10**−**12** and the extending monomer units **16**−**18** began with the bis-alkylation and subsequent ester hydrolysis of 2-hydroxy-4-nitrobenzoic acid. Terminal segments **10**−**12** were obtained by

Scheme 1. Retrosynthetic Analyses of Enaminones



Scheme 2. Synthesis of Terminal Monomer Units[a]



1 (R=Me)
2 (R=iPr)
3 (R=Bn)

4 (R=Me)
5 (R=iPr)
6 (R=Bn)

7 (R=Me), 38%
8 (R=iPr), 90%
9 (R=Bn), 90%

10 (R=Me), quant.
11 (R=iPr), quant.
12 (R=Bn), quant.

[a] a. oxalyl chloride, DMF, CH_2Cl_2; b. NH_4OH, CH_2Cl_2; c. PtO_2, K_2CO_3, H_2, MeOH.

conversion to the terminal amide via the acid chloride followed by reduction of the nitrobenzene to the aniline (Scheme 2). Nitrobenzamide **7** was significantly soluble in water; this was detrimental to the obtained yield of this compound due to loss during workup.

Assembly of the extending monomers (Scheme 3) was also achieved via the acid chlorides, which were converted to Weinreb amides **13**−**15** before monoaddition of a lithiated alkyne. The resulting ynone subunit (**16**−**18**) contains two groups which will eventually mimic helix side chains and facilitate the elongation of these *i*, *i*+4, *i*+7 α-helix mimetics.

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The two subunits were joined via a conjugate addition of an aniline (**10**−**12**) to an ynone (**16**−**18**) (Scheme 4). A range of solvents (including water, isopropanol, acetonitrile, dimethyl sulfoxide, and dimethylformamide), additives (including K_2CO_3, $KHCO_3$, 1,4-diazabicyclo[2.2.2]octane, $MgSO_4$, and silica gel), and conditions (various temperatures using both conventional heating and microwave irradiation for various periods of time) were explored. The reported conditions were ultimately chosen due to the rapid manner in which they could afford appreciable amounts of product.

The final nitroenaminones (**19**−**27**) proved to be stable under the reaction conditions. When the reactions were performed at elevated temperatures in alcoholic solvent, the remaining ynone was recovered as the enolone ether (**37**). Isolation of this material and exposure to the aniline under the same conditions led to the generation of more product, while the nitroenaminone was unaffected after re-exposure to the original reaction conditions (Scheme 5).

Reduction with Adams' catalyst afforded the final aminoenaminones (**28**−**36**). While these products proved to be acid-sensitive, they could be purified by flash column chromatography using untreated commercially available silica gel (or via HPLC).

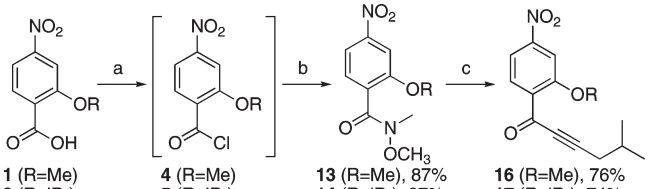
These derivatives were characterized by NMR spectroscopy and mass spectrometry. The structure-stabilizing intramolecular hydrogen bond is evident in solution, as the NH proton of the enaminone portion invariably displayed a chemical shift near 13 ppm in chlorinated solvents; non-hydrogen bonded protons of similar nature have been observed in $CDCl_3$ near 11.5 ppm. Unchanging shifts of the enaminone NH proton during dilution studies in $CDCl_3$ over 3 orders of magnitude (1 mM to 100 mM) and small upfield chemical shift during titration of d_6-DMSO into a 10 mM solution of nitroenaminone **23** in $CDCl_3$ supported the presence of an intramolecular hydrogen (Figure 4).

Additional evidence for the existence of this intramolecular hydrogen bond in solution was provided by a variable temperature ^{1}H NMR study performed in d_6-DMSO. This investigation showed the temperature-dependent coefficient ($\Delta\delta/\Delta K$) of the enaminone proton to be −0.8 ppb/K, which compares favorably to the result of a similar study on the benzoylureas (−2.9 ppb/K for the hydrogen-bonded proton).[19,20]

A single-crystal of nitroenaminone **23** was obtained by slow evaporation of CH_2Cl_2 at 4 °C, and a crystal structure was subsequently obtained (Figure 5). This confirmed that the hydrogen-bond-stabilized six-membered ring was intact in the solid state; the interatomic distance between the ketone oxygen and the aniline proton (1.88 Å) was significantly less than the sum of their respective van der Waals radii (2.72 Å). Also noteworthy is the presence of a hydrogen bond, with an interatomic distance of 2.00 Å, between one of the NH protons of the terminal amide and the oxygen of the alkoxy substituent that is *ortho* to that amide.

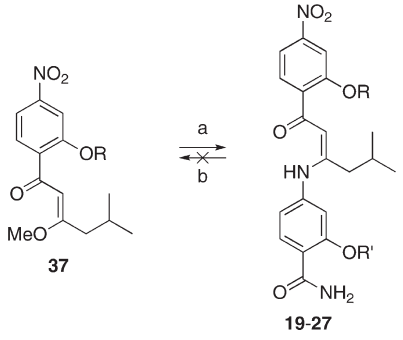
Comparison to a crystal structure of a terphenyl species showed the general size and shape of the enaminone portion of the molecule to be a fine arene surrogate, and suggested that the enaminone scaffold is indeed a viable one for helix mimicry. The distances between the groups that serve as side chain mimics for the *i*, *i*+4, and *i*+7 residues of a helix (5.45, 4.83, and 9.17 Å, as depicted in Figure 5) are comparable to those of an idealized

Scheme 3. Synthesis of Extending Monomer Units[a]



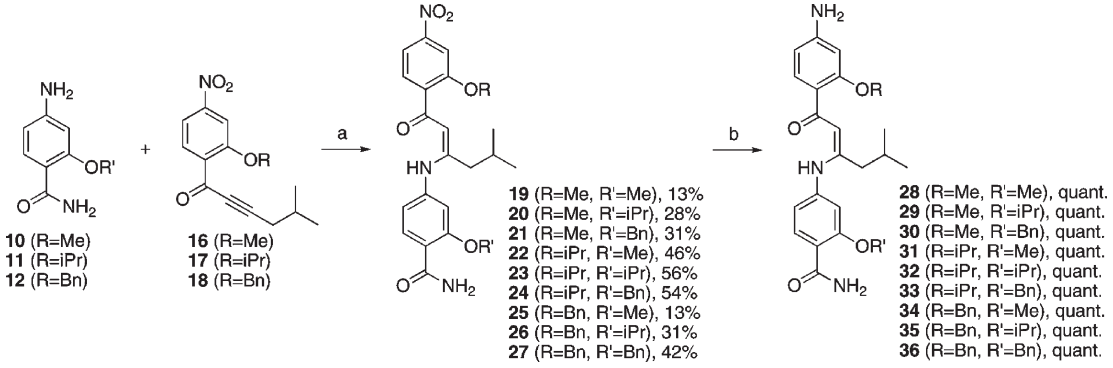
[a] a. oxalyl chloride, DMF, CH_2Cl_2; b. $HNOCH_3CH_3 \cdot HCl$, Et_3N, CH_2Cl_2; c. 4-methyl-1-propyne, nBuLi, THF.

Scheme 5. Conversion of Recovered Enolone Ether to the Desired Nitroenaminone[a]



[a] (R, R′ = Me, iPr, Bn) a. Δ, **10**/**11**/**12**, MeOH; b. Δ, MeOH.

Scheme 4. Synthesis of Final Aminoenaminones 28−36[a]



[a] a. Δ, MeOH; b. PtO_2, K_2CO_3, H_2, MeOH.

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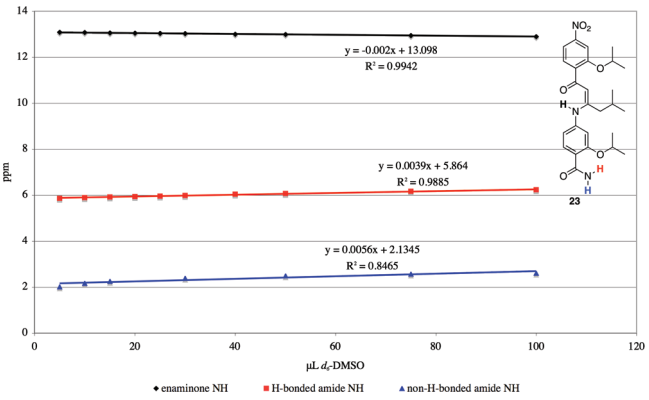

Figure 4. ^{1}H NMR titration study data, performed on compound **23**.

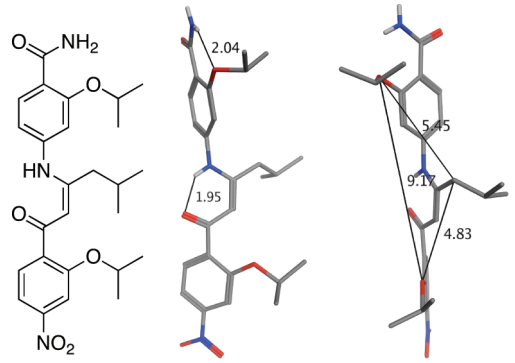

Figure 5. Crystal structure of nitroenaminone **23**.

helix (6.21, 5.40, 10.15 Å) and a crystalographically analyzed terphenyl compound (6.28, 5.10, and 8.83 Å).[17]

CONCLUSIONS

This paper describes the synthesis of a series of α-helix mimetics based on the enaminone scaffold. The reported compounds, which are assembled via a facile and mild conjugate addition of an aniline to an ynone, are structurally reliant on intramolecular hydrogen bonds. Work on assessing the biological activity of helix mimics based on this scaffold is ongoing.

EXPERIMENTAL SECTION

General Notes. All air- and/or moisture-sensitive reactions were carried out under a positive pressure of argon in flame-dried glassware. Dichloromethane (DCM), tetrahydrofuran (THF), and dimethylformamide (DMF) were obtained from commercial sources and dried on an MB-SPS-800 dry solvent system. Column chromatography was performed using silica gel (400−600 mesh). ^{1}H and ^{13}C NMR data were recorded at 500 and 125 MHz, respectively, at room temperature. ^{1}H chemical shifts are reported relative to residual $CHCl_3$ (δ 7.24 ppm for ^{1}H, δ 77.23 ppm for ^{13}C), DMSO (δ 2.50, 39.52 ppm), or CH_2Cl_2 (δ 5.32, 53.80 ppm). Coupling constants (J) are reported in Hz. Purification by reverse phase HPLC was performed using a dual λ UV detector (254 and 365 nm) with a binary pump using a 5 μ C18(2) 250 × 21.2 mm column run at 10 mL/minute using gradient mixtures of water with 0.1% triethylamine and methanol with 0.1% triethylamine.

General Method for the Synthesis of Alkoxybenzoic Acids (1−3). To a pressure vessel containing a magnetic stirbar was added sequentially 1 mmol of 2-hydroxy-4-nitrobenzoic acid, 2.5 mL of *N*,*N*-dimethylformamide, 2.5 mmol of K_2CO_3, and 2.5 mmol of the appropriate alkyl halide (**1**, methyl iodide; **2**, 2-iodopropane; **3**, benzyl bromide). The vessel was then sealed and stirred at 80 °C for 16 h. After being allowed to cool to room temperature, the mixture was diluted with ethyl acetate and washed with distilled water twice followed by an aqueous saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, filtered, and then concentrated. This material was taken up in 1 mL tetrahydrofuran, to which was added 2 mL of ethanol and 2 mL of a 45% aqueous NaOH solution. This mixture was allowed to stir at 80 °C for 15 h. The resulting solution was allowed to cool to ambient temperature and then diluted with distilled water and washed twice with ethyl acetate. The aqueous solution was then acidified using 1 M aqueous HCl and extracted twice with diethyl ether. The combined organic layers were washed with an aqueous saturated sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated as pure product.

*2-Methoxy-4-nitrobenzoic Acid (**1**) (88%).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 13.36 (bs, 1H), 7.87−7.80 (m, 3H), 3.95 (s, 1H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 166.3, 157.9, 149.9, 130.9, 128.1, 115.1, 107.2, 56.5; HRMS (ESI) m/z calculated for $C_8H_7NO_5Na$ [NaM$^+$] 220.0216, found 220.0216.

*2-Isopropoxy-4-nitrobenzoic Acid (**2**) (72%).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 13.30 (bs, 1H), 7.85 (d, J = 2.0, 1H), 7.81 (dd, J = 2.0, 8.4, 1H), 7.76 (d, J = 8.4), 4.84 (septet, J = 6.0, 1H), 1.30 (d, J = 6.0, 6H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 166.6, 155.9, 149.7, 130.7, 129.7, 115.0, 109.4, 71.8, 21.6; HRMS (ESI) m/z calculated for $C_{10}H_{11}NO_5Na$ [NaM$^+$] 248.0529, found 248.0529.

*2-(Benzyloxy)-4-nitrobenzoic Acid (**3**) (83%).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 13.39 (bs, 1H), 7.97 (d, J = 1.8, 1H), 7.87 (dd, J = 1.9, 8.4, 1H), 7.84 (d, J = 8.4, 1H), 7.51 (d, J = 7.4, 2H), 7.41 (t, J = 7.5, 2H), 7.34 (t, J = 7.3, 1H), 5.35 (s, 2H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 166.4, 156.8, 149.7, 136.2, 131.0, 128.6, 128.5, 128.0, 127.2, 115.4, 108.5, 70.3; HRMS (ESI) m/z calculated for $C_{14}H_{11}NO_5Na$ [NaM$^+$] 296.0529, found 296.0527.

General Method for the Synthesis of Terminal Nitroamides (7−9). To a flame-dried round-bottomed flask containing a magnetic stirbar and under an atmosphere of argon was sequentially added 1 mmol benzoic acid, 2 mL CH_2Cl_2, 2 mmol oxalyl chloride, and 2 drops (~100 μL) of *N*,*N*-dimethylformamide. This mixture was stirred at ambient temperature for 1 h, upon which it was concentrated. The resulting material was taken up in 10 mL CH_2Cl_2 and added slowly to a round-bottomed flask containing 15 mL CH_2Cl_2 and 15 mL ammonium hydroxide stirring vigorously. The mixture was diluted with CH_2Cl_2 and washed twice with distilled water and once with an aqueous saturated sodium chloride solution, then dried over magnesium sulfate. Filtration and concentration gave pure products.

*2-Methoxy-4-nitrobenzamide (**7**) (38%).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.87−7.85 (m, 3H), 7.81 (s, 1H), 7.78 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 165.4, 157.1, 149.4, 131.0, 130.3, 115.3, 106.9, 56.6; HRMS (EI) m/z calculated for $C_8H_8N_2O_4Na$ [NaM$^+$] 219.0376, found 219.0375.

*2-Isopropoxy-4-nitrobenzamide (**8**) (90%).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.87 (d, J = 8.4, 1H), 7.85 (d, J = 2.0, 1H), 7.82 (dd, J = 2.1, 8.4, 1H), 7.79 (s, 1H), 7.67 (s, 1H), 4.89 (septet, J = 6.0, 1H), 1.35 (d, J = 6.1, 6H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 165.5, 155.3, 149.4, 131.3, 131.0, 115.1, 108.9, 72.2, 21.4; HRMS (EI) m/z calculated for $C_{10}H_{12}N_2O_4Na$ [NaM$^+$] 247.0689, found 247.0690.

*2-(Benzyloxy)-4-nitrobenzamide (**9**) (90%).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.96 (d, J = 2.0, 1H), 7.88 (dd, J = 2.0, 8.4, 1H), 7.83 (d, J = 8.4, 1H), 7.81 (s, 1H), 7.79 (s, 1H), 7.53 (d, J = 7.2, 2H), 7.42 (t, J = 7.4, 2H), 7.36 (t, J = 7.3, 1H), 5.37 (s, 2H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 165.7, 155.9, 149.1, 136.0, 131.3, 130.8, 128.6, 128.2, 127.7,

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115.6, 108.1, 70.6; HRMS (EI) m/z calculated for $C_{14}H_{12}N_2O_4Na$ [NaM$^+$] 295.0689, found 295.0690.

General Method for the Synthesis of Aminobenzamides (10−12). To a round-bottomed flask containing a magnetic stirbar and 1 mmol of the nitrobenzamide was sequentially added 40 mg of K_2CO_3, 40 mg of PtO_2, and 40 mL of methanol. The flask was sealed and flushed with hydrogen three times using a balloon filled with hydrogen and a vacuum. The mixture was then stirred vigorously under an atmosphere of hydrogen for 45 min. Filtration through Celite and concentration afforded the target aniline in quantitative yield.

*4-Amino-2-methoxybenzamide (**10**).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.62 (d, J = 8.5, 1H), 7.32 (s, 1H), 7.03 (s, 1H), 6.22 (d, J = 1.9, 1H), 6.18 (dd, J = 1.9, 8.5, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 166.2, 159.3, 153.5, 132.9, 108.7, 106.0, 95.9, 55.3; HRMS (EI) m/z calculated for $C_8H_{10}N_2O_2Na$ [NaM$^+$] 189.0634, found 189.0632.

*4-Amino-2-isopropoxybenzamide (**11**).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.64 (d, J = 8.5, 1H), 6.25 (d, J = 1.9, 1H), 6.17 (dd, J = 1.9, 8.5, 1H), 4.60 (septet, J = 6.0, 1H), 3.16 (s, 1H), 1.33 (d, J = 6.0, 6H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 166.3, 157.4, 153.3, 132.9, 109.5, 106.2, 97.9, 70.6, 21.9; HRMS (EI) m/z calculated for $C_{10}H_{14}N_2O_2Na$ [NaM$^+$] 217.0947, found 217.0944.

*4-Amino-2-(benzyloxy)benzamide (**12**).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.64 (d, J = 8.5, 1H), 7.49 (d, J = 7.1, 2H), 7.42 (dd, J = 7.1, 7.3, 2H), 7.37 (d, J = 7.3, 1H), 7.26 (s, 1H), 7.03 (s, 1H), 6.32 (d, J = 1.9, 1H), 6.20 (dd, J = 1.9, 8.5, 1H), 5.14 (s, 2H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 166.2, 158.3, 153.4, 136.5, 132.9, 128.7, 128.2, 127.9, 109.0, 106.4, 97.1, 69.7; HRMS (EI) m/z calculated for $C_{14}H_{14}N_2O_2Na$ [NaM$^+$] 265.0947, found 265.0946.

General Method for the Synthesis of Weinreb Amides (13−15). To a flame-dried round-bottomed flask containing a magnetic stirbar and under an atmosphere of argon was sequentially added 1 mmol benzoic acid, 2 mL CH_2Cl_2, 2 mmol oxalyl chloride, and 2 drops (∼100 μL) of *N*,*N*-dimethylformamide. This mixture was stirred at ambient temperature for 1 h, upon which it was concentrated. The resulting material was placed under an atmosphere of argon, and to this was sequentially added 10 mL CH_2Cl_2, 3 mmol triethylamine, and 1.5 mmol *N*-methoxy-*N*-methylammonium chloride. The reaction was allowed to stir at room temperature for 2.5 h, at which time it was quenched with a saturated aqueous $NaHCO_3$ solution. This was extracted twice with diethyl ether. The combined organic layers were washed with aqueous saturated sodium chloride solution and then dried over magnesium sulfate. Filtration and concentration afforded pure products.

*N,2-Dimethoxy-N-methyl-4-nitrobenzamide (**13**) (87%).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.87 (d, J = 8.2, 1H), 7.85 (s, 1H), 7.55 (d, J = 8.2, 1H), 3.93 (s, 3H), 3.44 (s, 3H), 3.32 (s, 3H), 3.27 (s, 3H).; ^{13}C NMR (125 MHz, d_6-DMSO) δ 166.2, 155.9, 148.8, 132.1, 127.9, 115.5, 106.3, 61.1, 56.4, 31.7; HRMS (ESI) m/z calculated for $C_{10}H_{12}N_2O_5Na$ [NaM$^+$] 263.0638, found 263.0640.

*2-Isopropoxy-N-methoxy-N-methyl-4-nitrobenzamide (**14**) (97%).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 1.9, 8.2, 1H), 7.73 (d, J = 1.9, 1H), 7.37 (d, J = 8.2, 1H), 4.66 (m, 1H), 3.43 (s, 3H), 3.34 (s, 3H), 1.35 (d, J = 5.9, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 155.2, 149.4, 133.2, 128.1, 115.5, 108.3, 77.5, 72.2, 61.6, 32.5, 22.0; HRMS (EI) m/z calculated for $C_{12}H_{16}N_2O_5Na$ [NaM$^+$] 291.0951, found 291.0952.

*2-(Benzyloxy)-N-methoxy-N-methyl-4-nitrobenzamide (**15**) (90%).* ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.94 (s, 1H), 7.89 (d, J = 8.2, 1H), 7.60 (d, J = 8.2, 1H), 7.42 (m, 4H), 7.34 (t, J = 7.0, 1H), 5.33 (s, 2H), 3.45 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 166.3, 154.9, 148.6, 136.1, 132.5, 128.5, 128.0, 127.2, 115.8, 107.6, 70.1, 61.3, 31.8; HRMS (EI) m/z Ccalculated for $C_{16}H_{16}N_2O_5Na$ [NaM$^+$] 339.0951, found 339.0952.

General Method for the Synthesis of Ynones (16−18). To a flame-dried round-bottomed flask under an atmosphere of argon and containing a magnetic stirbar was added 3 mL tetrahydrofuran and 1.05 mmol 4-methyl-1-propyne via syringe. While stirring, the solution was cooled to −78 °C, at which time 0.72 mL of a 1.45 M solution of nBuLi (1.05 mmol) was added dropwise via syringe. The solution was stirred at −78 °C for 10 min, then the dry ice/acetone bath was removed and the solution was stirred and allowed to warm for an additional 15 min. The flask was then again cooled to −78 °C, and then 1 mmol of the Weinreb amide in 3 mL tetrahydrofuran was added to the mixture dropwise via syringe. The solution was stirred at −78 °C for 15 min, at which point it was allowed to return to ambient temperature over a period of 1 h while stirring continued. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$. This mixture was then extracted with ethyl acetate, which was subsequently washed with aqueous saturated sodium chloride solution and dried over magnesium sulfate. Filtration, concentration, and flash column chromatography using 5:1 hexane/ethyl acetate as the eluent afforded the desired ynone.

*1-(2-Methoxy-4-nitrophenyl)-5-methylhex-2-yn-1-one (**16**) (76%).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.5, 1H), 7.84 (dd, J = 2.0, 8.5, 1H), 7.80 (d, J = 2.0, 1H), 3.99 (s, 3H), 2.36 (d, J = 6.5, 2H), 2.00−1.91 (m, 1H), 1.04 (d, J = 6.7, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 159.7, 151.3, 132.9, 132.2, 115.2, 107.4, 97.2, 82.7, 56.7, 28.6, 28.0, 22.3; HRMS (EI) m/z calculated for $C_{14}H_{15}O_4Na$ [NaM$^+$] 284.0893, found 284.0894.

*1-(2-Isopropoxy-4-nitrophenyl)-5-methylhex-2-yn-1-one (**17**) (74%).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 9.1, 1H), 7.78−7.75 (m, 2H), 4.73 (septet, J = 6.1, 1H), 2.32 (d, J = 6.6, 2H), 1.98−1.90 (m, 1H), 1.42 (d, J = 6.1, 6H), 1.01 (d, J = 6.7, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 158.0, 151.1, 133.5, 132.4, 114.9, 109.2, 96.9, 83.0, 72.5, 28.7, 28.0, 22.4, 22.0; HRMS (EI) m/z calculated for $C_{16}H_{19}NO_4Na$ [NaM$^+$] 312.1206, found 312.1204.

*1-(2-(Benzyloxy)-4-nitrophenyl)-5-methylhex-2-yn-1-one (**18**) (77%).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.5, 1H), 7.85 (d, J = 2.0, 1H), 7.83 (dd, J = 2.0, 8.4, 1H), 7.48 (d, J = 7.4, 2H), 7.40−7.35 (m, 2H), 7.34−7.30 (m, 1H), 5.24 (s, 2H), 2.14 (d, J = 6.6, 2H), 1.83−1.75 (m, 1H), 0.93 (d, J = 6.7, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 158.6, 151.1, 135.3, 132.7, 132.6, 128.9, 128.6, 127.6, 115.5, 108.6, 97.5, 82.8, 71.4, 28.4, 27.8, 22.2; HRMS (EI) m/z calculated for $C_{20}H_{19}NO_4Na$ [NaM$^+$] 360.1206, found 360.1207.

General Method for the Synthesis of Nitroenaminones (19−27). To a pressure vessel containing a stirbar was added 1 mmol of the aminobenzamide, followed by 1 mmol of the ynone in 1 mL of methanol. The vessel was sealed and then stirred at 120 °C for 3 h. After cooling, the solution was directly purified using flash column chromatography (2:1 ethyl acetate/hexane).

*(Z)-2-Methoxy-4-((1-(2-methoxy-4-nitrophenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)benzamide (**19**) (13%).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.14 (s, 1H), 8.20 (d, J = 8.4, 1H), 7.86 (dd, J = 2.0, 8.4, 1H), 7.79 (d, J = 2.0, 1H), 7.73 (d, J = 8.4, 1H), 7.61 (s, 1H), 6.90 (d, J = 8.4, 1H), 6.75 (s, 1H), 5.81 (s, 1H), 3.97 (s, 3H), 3.97 (s, 3H), 2.38 (d, J = 7.2, 2H), 1.88−1.78 (m, 1H), 0.91 (d, J = 6.6, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.8, 166.4, 165.3, 158.7, 157.6, 149.7, 143.4, 136.6, 133.9, 130.6, 118.3, 117.1, 116.0, 107.7, 106.8, 100.4, 56.54, 56.47, 41.7, 27.7, 22.6; HRMS (EI) m/z calculated for $C_{22}H_{25}N_3O_6Na$ [NaM$^+$] 450.1636, found 450.1635.

*(Z)-2-Isopropoxy-4-((1-(2-methoxy-4-nitrophenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)benzamide (**20**) (28%).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.07 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.86 (dd, J = 8.4, 2.1 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.76−7.75 (m, 1H), 7.76 (d, J = 8.4 Hz, 1H), 6.89 (dd, J = 8.4, 1.9 Hz, 1H), 6.81 (d, J = 1.9 Hz, 1H), 5.87 (s, 1H), 5.78 (s, 1H), 4.75 (septet, J = 6.1 Hz, 1H), 3.98 (s, 3H), 2.40 (d, J = 7.3 Hz, 2H), 1.89−1.78 (m, 1H), 1.45 (d, J = 6.1 Hz, 6H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 187.5, 166.3, 165.4, 157.8, 157.3, 149.8, 143.3, 136.9, 133.7, 130.8, 119.6, 117.5, 115.9, 110.5, 107.0, 100.3, 72.8, 56.6, 41.7, 27.9, 22.4, 22.2; HRMS (EI) m/z calculated for $C_{24}H_{29}N_3O_6Na$ [NaM$^+$] 478.1949, found 478.1950.

*(Z)-2-(Benzyloxy)-4-((1-(2-methoxy-4-nitrophenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)benzamide (**21**) (31%).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.08 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.86 (dd, J = 8.4, 2.1 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H), 7.50−7.37 (m, 5H), 6.94 (dd, J = 8.4, 1.7 Hz, 1H), 6.88 (d, J = 1.8 Hz, 1H), 5.87 (s, 1H), 5.70 (s, 1H), 5.23 (s, 2H), 3.97 (s, 3H), 2.34 (d, J = 7.3 Hz, 2H), 1.79 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 187.6, 166.0, 165.3, 158.0, 157.8, 149.8, 143.5, 136.8, 135.8, 133.8, 130.8, 129.3, 129.1, 128.1, 118.9, 117.7, 115.9, 109.6, 107.0, 100.5, 71.8, 56.6, 41.7, 27.9, 22.4; HRMS (EI) m/z calculated for $C_{28}H_{29}N_3O_6$Na [NaM$^+$] 526.1949, found 526.1942.

*(Z)-4-((1-(2-Isopropoxy-4-nitrophenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-methoxybenzamide (**22**) (46%).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.14 (s, 1H), 8.20 (d, J = 8.4, 1H), 7.85−7.74 (m, 3H), 7.61 (s, 1H), 6.90 (d, J = 8.4, 1H), 6.74 (s, 1H), 5.97 (s, 1H), 5.81 (s, 1H), 4.78−4.68 (m, 1H), 3.97 (s, 3H), 2.38 (d, J = 7.2, 2H), 1.90−1.78 (m, 1H), 1.41 (d, J = 6.0, 6H), 0.91 (d, J = 6.6, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 166.4, 164.6, 158.7, 155.9, 149.6, 143.6, 137.3, 133.9, 131.3, 118.2, 117.0, 115.6, 109.0, 107.6, 100.9, 77.5, 77.2, 77.0, 72.0, 56.5, 41.8, 27.7, 22.7, 22.1; HRMS (EI) m/z calculated for $C_{24}H_{29}N_3O_6$Na [NaM$^+$] 478.1949, found 478.1925.

*(Z)-2-Isopropoxy-4-((1-(2-isopropoxy-4-nitrophenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)benzamide (**23**) (56%).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.09 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.82−7.75 (m, 3H), 6.89 (dd, J = 8.4, 1.8 Hz, 1H), 6.81 (d, J = 1.8 Hz, 1H), 5.99 (s, 1H), 5.79 (s, 1H), 4.77 (septet, J = 6.0 Hz, 2H), 2.39 (d, J = 7.3 Hz, 2H), 1.85 (m, 1H), 1.45 (d, J = 6.1 Hz, 6H), 1.43 (d, J = 6.0 Hz, 6H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 187.6, 166.4, 165.0, 157.3, 156.1, 149.8, 143.5, 137.6, 133.7, 131.3, 119.5, 117.4, 115.5, 110.5, 109.1, 100.6, 72.8, 72.3, 41.8, 27.9, 22.5, 22.22, 22.00; HRMS (EI) m/z calculated for $C_{26}H_{33}N_3O_6$Na [NaM$^+$] 506.2262, found 506.2239.

*(Z)-2-(Benzyloxy)-4-((1-(2-isopropoxy-4-nitrophenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)benzamide (**24**) (54%).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.10 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.82−7.78 (m, 2H), 7.60 (s, 1H), 7.50−7.36 (m, 5H), 7.33 (s, 1H), 6.93 (dd, J = 8.4, 1.8 Hz, 1H), 6.88 (d, J = 1.8 Hz, 1H), 5.99 (s, 1H), 5.85 (s, 1H), 5.23 (s, 2H), 4.77 (septet, J = 6.1 Hz, 1H), 2.33 (d, J = 7.3 Hz, 2H), 1.86−1.76 (m, 1H), 1.43 (d, J = 6.1 Hz, 6H), 0.88 (d, J = 6.6 Hz, 6H).; ^{13}C NMR (125 MHz, CD_2Cl_2) δ 187.7, 166.1, 164.9, 158.0, 156.1, 149.8, 143.6, 137.5, 135.8, 133.7, 131.3, 129.3, 129.1, 128.1, 118.9, 117.6, 115.5, 109.5, 109.1, 100.8, 72.3, 71.8, 41.8, 27.8, 22.5, 22.0; HRMS (EI) m/z calculated for $C_{30}H_{33}N_3O_6$Na [NaM$^+$] 554.2262, found 554.2236.

*(Z)-4-((1-(2-(Benzyloxy)-4-nitrophenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-methoxybenzamide (**25**) (13%).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.17 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.92−7.86 (m, 2H), 7.58 (s, 1H), 7.51 (d, J = 7.2 Hz, 2H), 7.45−7.34 (m, 3H), 6.89 (dd, J = 8.4, 1.8 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.01 (s, 1H), 5.24 (s, 1H), 3.97 (s, 3H), 2.30 (d, J = 7.3 Hz, 2H), 1.71−1.58 (m, 1H), 0.77 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 186.9, 166.1, 165.5, 158.9, 156.9, 149.8, 143.6, 136.7, 136.0, 133.6, 131.3, 129.1, 128.8, 128.4, 118.5, 117.4, 116.1, 108.2, 108.2, 100.6, 71.7, 56.6, 41.6, 27.8, 22.3; HRMS (EI) m/z calculated for $C_{28}H_{29}N_3O_6$Na [NaM$^+$] 526.1949, found 526.1949.

*(Z)-4-((1-(2-(Benzyloxy)-4-nitrophenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-isopropoxybenzamide (**26**) (31%).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.14 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.92−7.85 (m, 3H), 7.76 (s, 1H), 7.51 (d, J = 7.3 Hz, 2H), 7.46−7.35 (m, 3H), 6.86 (dd, J = 8.4, 1.8 Hz, 1H), 6.78 (d, J = 1.8 Hz, 1H), 6.01 (s, 1H), 5.85 (s, 1H), 5.24 (s, 2H), 4.74 (septet, J = 6.1 Hz, 1H), 2.28 (d, J = 7.4 Hz, 2H), 1.68−1.59 (m, 1H), 1.44 (d, J = 6.1 Hz, 6H), 0.76 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 186.8, 166.4, 165.6, 157.2, 156.9, 149.7, 143.3, 136.7, 136.0, 133.7, 131.3, 129.1, 128.8, 128.3, 119.6, 117.5, 116.1, 110.6, 108.2, 100.4, 72.8, 71.7, 41.6, 27.9, 22.3, 22.2; HRMS (EI) m/z calculated for $C_{30}H_{33}N_3O_6$Na [NaM$^+$] 554.2262, found 554.2263.

*(Z)-2-(Benzyloxy)-4-((1-(2-(benzyloxy)-4-nitrophenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)benzamide (**27**) (42%).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.15 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.91−7.84 (m, 3H), 7.58 (s, 1H), 7.54−7.35 (m, 10H), 6.90 (dd, J = 8.4, 1.8 Hz, 1H), 6.85 (d, J = 1.8 Hz, 1H), 6.01 (s, 1H), 5.80 (s, 1H), 5.24 (s, 2H), 5.22 (s, 2H), 2.22 (d, J = 7.4 Hz, 2H), 1.64−1.55 (m, 1H), 0.73 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 186.8, 166.0, 165.5, 158.0, 156.9, 149.8, 143.5, 136.7, 136.0, 135.8, 133.7, 131.3, 129.3, 129.08, 129.05, 128.8, 128.3, 128.1, 119.0, 117.8, 116.1, 109.7, 108.2, 100.5, 71.8, 71.7, 41.5, 27.9, 22.3; HRMS (EI) m/z calculated for $C_{34}H_{33}N_3O_6$Na [NaM$^+$] 602.2262, found 602.2260.

General Method for the Synthesis of Aminoenaminones (28−36). To a round-bottomed flask containing a magnetic stirbar and 1 mmol of the nitroenaminone was sequentially added 40 mg of K_2CO_3, 40 mg of PtO_2, and 40 mL of methanol. The flask was sealed and flushed with hydrogen three times using a balloon filled with hydrogen and a vacuum. The mixture was then stirred vigorously under an atmosphere of hydrogen for 45 min. After filtration through Celite and concentration, the crude product mixture was taken up in a small amount of methanol and purified via reverse-phase HPLC, and product was obtained in quantitative yield.

*(Z)-4-((1-(4-Amino-2-methoxyphenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-methoxybenzamide (**28**).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.14 (s, 1H), 8.09 (d, J = 8.4, 1H), 7.60 (d, J = 8.3, 1H), 7.59−7.54 (m, 1H), 6.86 (d, J = 8.5, 1H), 6.75 (s, 1H), 6.29 (d, J = 8.4, 1H), 6.23 (s, 1H), 6.11 (s, 1H), 5.73−5.64 (m, 1H), 4.05 (s, 2H), 3.97 (s, 3H), 3.84 (s, 3H), 2.42 (d, J = 7.2, 2H), 1.89−1.78 (m, 1H), 0.92 (d, J = 6.6, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 188.9, 166.3, 161.6, 160.1, 159.0, 151.3, 144.9, 133.5, 132.6, 120.6, 117.0, 116.1, 107.2, 106.9, 101.6, 97.8, 56.5, 55.8, 42.2, 27.6, 22.5; HRMS (EI) m/z calculated for $C_{22}H_{27}N_3O_4$Na [NaM$^+$] 420.1894, found 420.1893.

*(Z)-4-((1-(4-Amino-2-methoxyphenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-isopropoxybenzamide (**29**).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.09 (s, 1H), 8.10 (d, J = 8.5, 1H), 7.76 (bs, 1H), 7.60 (d, J = 8.3, 1H), 6.83 (d, J = 8.5, 1H), 6.75 (s, 1H), 6.29 (d, J = 8.4, 1H), 6.23 (s, 1H), 6.09 (s, 1H), 5.67 (bs, 1H), 4.80−4.69 (m, 1H), 4.04 (s, 2H), 3.84 (s, 3H), 2.40 (d, J = 7.3, 2H), 1.87− 1.78 (m, 1H), 1.44 (d, J = 6.1, 6H), 0.91 (d, J = 6.6, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 188.8, 166.6, 161.8, 160.1, 157.3, 151.3, 144.7, 133.6, 132.6, 120.6, 118.2, 116.4, 109.4, 107.1, 101.3, 97.8, 72.6, 55.8, 42.2, 27.6, 22.5, 22.3; HRMS (EI) m/z calculated for $C_{24}H_{31}N_3O_4$Na [NaM$^+$] 448.2207, found 448.2208.

*(Z)-4-((1-(4-Amino-2-methoxyphenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-(benzyloxy)benzamide (**30**).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.12 (s, 1H), 8.12 (d, J = 8.5, 1H), 7.61 (d, J = 8.4, 1H), 7.57 (bs, 1H), 7.47 (d, J = 7.2, 2H), 7.43 (t, J = 7.2, 2H), 7.40 (d, J = 7.1, 1H), 6.88 (dd, J = 2.0, 8.5, 1H), 6.83 (d, J = 2.0, 1H), 6.29 (dd, J = 2.1, 8.4, 1H), 6.22 (d, J = 2.0, 1H), 6.10 (s, 1H), 5.63 (bs, 1H), 5.21 (s, 2H), 3.84 (s, 3H), 2.36 (d, J = 7.2, 2H), 1.87−1.72 (m, 1H), 0.89 (d, J = 6.6, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 188.9, 166.3, 161.7, 160.1, 158.1, 151.4, 144.8, 136.0, 133.6, 132.6, 129.3, 129.0, 128.2, 120.6, 117.5, 116.5, 108.3, 107.1, 101.5, 97.8, 71.8, 55.8, 42.1, 27.6, 22.5; HRMS (EI) m/z calculated for $C_{28}H_{31}N_3O_4$Na [NaM$^+$] 496.2207, found 496.2206.

*(Z)-4-((1-(4-Amino-2-isopropoxyphenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-methoxybenzamide (**31**).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.16 (s, 1H), 8.09 (d, J = 8.5, 1H), 7.64 (d, J = 8.4, 1H), 7.58 (bs, 1H), 6.86 (dd, J = 1.9, 8.5, 1H), 6.75 (d, J = 1.9, 1H), 6.28 (dd, J = 2.3, 8.2, 1H), 6.27 (s, 1H), 6.21 (d, J = 2.0, 1H), 5.74 (s, 1H), 4.59 (septet, J = 6.0, 1H), 4.02 (s, 2H), 3.97 (s, 3H), 2.42 (d, J = 7.2, 2H), 1.91−1.79 (m, 1H), 1.62 (s, 1H), 1.38 (d, J = 6.0, 6H), 0.92 (d, J = 6.6, 6H).; ^{13}C NMR (125 MHz, CD_2Cl_2) δ 188.9, 166.4, 161.3, 159.0, 158.4, 151.2, 145.0, 133.5, 132.9, 121.4, 117.0, 116.0, 107.4, 106.9, 101.9, 100.1, 71.1, 56.5, 42.4, 27.5, 22.6, 22.3; HRMS (EI) m/z calculated for $C_{24}H_{31}N_3O_4$Na [NaM$^+$] 448.2207, found 448.2208.

*(Z)-4-((1-(4-Amino-2-isopropoxyphenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-isopropoxybenzamide (**32**).* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.12 (s, 1H), 8.10 (d, J = 8.5, 1H), 7.77 (bs, 1H), 7.64 (d,

J = 8.4, 1H), 6.84 (dd, J = 1.9, 8.5, 1H), 6.75 (d, J = 1.8, 1H), 6.28 (dd, J = 2.1, 8.4, 1H), 6.26 (s, 1H), 6.21 (d, J = 2.0, 1H), 5.77 (s, 1H), 4.75 (septet, J = 6.1, 1H), 4.59 (septet, J = 6.0, 1H), 4.02 (bs, 2H), 2.40 (d, J = 7.3, 2H), 1.90−1.78 (m, 1H), 1.63 (s, 1H), 1.44 (d, J = 6.1, 6H), 1.38 (d, J = 6.0, 6H), 0.91 (d, J = 6.6, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 188.9, 166.6, 161.5, 158.4, 157.3, 151.2, 144.7, 133.5, 132.9, 121.5, 118.1, 116.4, 109.3, 107.4, 101.6, 100.1, 72.6, 71.1, 42.3, 27.6, 22.6, 22.32, 22.25; HRMS (EI) m/z calculated for $C_{26}H_{35}N_3O_4Na$ [NaM$^+$] 476.2520, found 476.2519.

(Z)-4-((1-(4-Amino-2-isopropoxyphenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-(benzyloxy)benzamide (**33**). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.14 (s, 1H), 8.12 (d, J = 8.5, 1H), 7.64 (d, J = 8.4, 1H), 7.58 (bs, 1H), 7.49−7.37 (m, 5H), 6.88 (dd, J = 1.9, 8.5, 1H), 6.82 (d, J = 1.8, 1H), 6.29−6.26 (m, 2H), 6.21 (d, J = 2.0, 1H), 5.66 (bs, 1H), 5.21 (s, 2H), 4.59 (septet, J = 6.1, 1H), 4.01 (bs, 2H), 2.35 (d, J = 7.2, 2H), 1.87−1.76 (m, 1H), 1.38 (d, J = 6.0, 6H), 0.89 (d, J = 6.6, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 188.9, 166.3, 161.4, 158.4, 158.1, 151.2, 144.9, 136.0, 133.6, 132.9, 129.3, 129.0, 128.2, 121.4, 117.4, 116.5, 108.3, 107.4, 101.9, 100.1, 71.8, 71.1, 42.3, 27.6, 22.6, 22.3; HRMS (EI) m/z calculated for $C_{30}H_{35}N_3O_4Na$ [NaM$^+$] 524.2520, found 524.2522.

(Z)-4-((1-(4-Amino-2-(benzyloxy)phenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-methoxybenzamide (**34**). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.17 (s, 3H), 8.07 (d, J = 8.5, 1H), 7.71 (d, J = 8.3, 1H), 7.57 (bs, 1H), 7.50 (d, J = 7.2, 2H), 7.41 (t, J = 7.3, 2H), 7.37 (d, J = 7.3, 1H), 6.82 (dd, J = 2.0, 8.5, 1H), 6.72 (d, J = 2.0, 1H), 6.33 (dd, J = 2.0, 8.3, 1H), 6.31 (d, J = 2.0, 1H), 6.23 (s, 1H), 5.65 (bs, 1H), 5.09 (s, 2H), 4.06 (bs, 2H), 3.95 (s, 3H), 2.25 (d, J = 7.3, 2H), 1.63−1.54 (m, 1H), 0.74 (d, J = 6.6, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 188.2, 166.3, 161.9, 159.4, 158.9, 151.4, 144.9, 137.1, 133.5, 133.0, 128.9, 128.5, 128.4, 120.4, 117.0, 116.2, 107.6, 107.0, 101.6, 98.9, 71.0, 56.5, 42.0, 27.5, 22.3; HRMS (EI) m/z calculated for $C_{28}H_{31}N_3O_4Na$ [NaM$^+$] 496.2207, found 496.2209.

(Z)-4-((1-(4-Amino-2-(benzyloxy)phenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-isopropoxybenzamide (**35**). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.13 (s, 1H), 8.08 (d, J = 8.5, 1H), 7.75 (bs, 1H), 7.71 (d, J = 8.3, 1H), 7.50 (d, J = 7.2, 1H), 7.41 (t, J = 7.3, 1H), 7.37 (d, J = 7.3, 1H), 6.80 (dd, J = 2.0, 8.5, 1H), 6.72 (d, J = 2.0, 1H), 6.33 (dd, J = 2.0, 8.3, 1H), 6.31 (d, J = 2.0, 1H), 6.22 (s, 1H), 5.65 (bs, 1H), 5.09 (s, 2H), 4.72 (septet, J = 6.0, 1H), 4.06 (bs, 2H), 2.23 (d, J = 7.4, 2H), 1.62−1.52 (m, 1H), 1.42 (d, J = 6.1, 6H), 0.73 (d, J = 6.6, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 188.2, 166.6, 162.1, 159.4, 157.3, 151.3, 144.6, 137.1, 133.5, 132.9, 128.9, 128.5, 128.4, 120.4, 118.2, 116.5, 109.5, 107.6, 101.3, 98.9, 72.6, 71.0, 41.9, 27.5, 22.3, 22.2; HRMS (EI) m/z calculated for $C_{30}H_{34}N_3O_4$ [(M-H)$^-$] 500.2555, found 500.2552.

(Z)-4-((1-(4-Amino-2-(benzyloxy)phenyl)-5-methyl-1-oxohex-2-en-3-yl)amino)-2-(benzyloxy)benzamide (**36**). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 13.15 (s, 1H), 8.10 (d, J = 8.4, 1H), 7.71 (d, J = 8.3, 1H), 7.57 (bs, 1H), 7.52−7.34 (m, 10H), 6.84 (dd, J = 2.0, 8.5, 1H), 6.79 (d, J = 1.8, 1H), 6.33 (dd, J = 2.0, 8.5, 1H), 6.31 (d, J = 2.0, 1H), 6.22 (s, 1H), 5.65 (bs, 1H), 5.19 (s, 2H), 5.09 (s, 2H), 4.08 (bs, 2H), 2.18 (d, J = 7.3, 2H), 1.58−1.47 (m, 1H), 0.71 (d, J = 6.6, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 188.2, 166.3, 161.9, 159.4, 158.1, 151.4, 144.8, 137.1, 136.0, 133.6, 133.0, 129.3, 129.0, 128.9, 128.5, 128.4, 128.2, 120.4, 117.5, 116.6, 108.4, 107.6, 101.6, 98.8, 71.7, 71.0, 41.9, 27.5, 22.3; HRMS (EI) m/z calculated for $C_{34}H_{34}N_3O_4$ [(M-H)$^-$] 548.2555, found 548.2551.

Dilution Experiment. Samples of **23** in $CDCl_3$ were prepared at three different concentrations (1, 10, and 100 mM). The ^{1}H NMR spectrum of each sample was acquired and compared; the chemical shift of the enaminone NH peak remained unchanged (relative to the solvent peak) at all concentrations (δ 13.10 ppm).

Titration Experiment. Ten NMR tubes were each charged with 1 mL of a 10 mM solution of **23** in $CDCl_3$. To these tubes was added 5, 10, 15, 20, 25, 30, 40, 50, 75, and 100 μL, respectively, of d_6-DMSO. The samples were shaken and then allowed to stand for 30 min, and then the ^{1}H NMR spectrum of each sample was acquired. The chemical shifts of all NH peaks were recorded and plotted.

VT-NMR Experiment. A 10 mM solution of **23** in d_6-DMSO was prepared and loaded into an NMR tube. The ^{1}H NMR spectrum at 10 K intervals (from 300 to 380 K) was acquired. The chemical shift of the enaminone NH proton at each 10 K interval was recorded and plotted. The slope of the plot of ppm vs T gave the temperature-dependent coefficient ($\Delta\delta/\Delta K$) of the enaminone NH proton (−0.8 ppb/K).

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR Spectra for Compounds **1**−**3** and **7**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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