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(*Z*)-Stereoselective Synthesis of *Mono*- and *Bis*-heterocyclic Benzimidazol-2-ones via Cascade Processes Coupled with the Ugi Multicomponent Reaction

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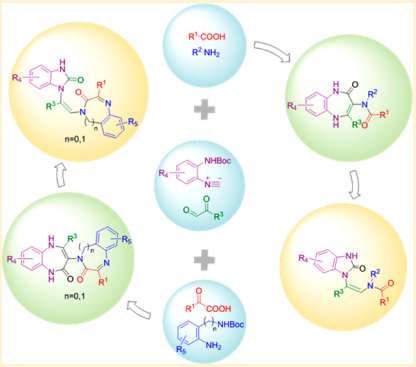
Supporting Information

ABSTRACT: Several novel cascade reactions are herein reported that enable access to a variety of unique *mono*- and *bis*-heterocyclic scaffolds. The sequence of cascade events are mediated through acid treatment of an Ugi adduct that affords 1,5-benzodiazepines which subsequently undergo an elegant rearrangement to deliver (*E*)-benzimidazolones, which through acid-promoted tautomerization convert to their corresponding (*Z*)-isomers. Moreover, a variety of heterocycles tethered to (*Z*)-benzimidazole-2-ones are also accessible through similar domino-like processes, demonstrating a general strategy to access significantly new scaffold diversity, each containing four points of potential diversification. Final structures of five scaffolds have been definitively proven by X-ray crystallography.



INTRODUCTION

Isocyanide-based multicomponent reactions (IMCRs) enable access to complex and diverse molecular scaffolds that are generated in a single step.[1] Indeed when used in conjunction, with cascade processes they prove even more powerful promoting a variety of mechanistically nonobvious, library compatible transformations to new molecular structures.[2] The venerable Ugi IMCR[3] delivers adducts with four points of diversity derived from the reaction of aldehydes or ketones, primary amines, isonitriles, and carboxylic acids in a single operational step with high atom economy,[4] affording products with high iterative efficiency potential (IEP)[5] for optimization in drug discovery campaigns. Moreover, the Ugi adduct is amenable to a large variety of postcondensation modifications, representing a branching point to a wealth of molecular diversity which has been exploited by a plethora of groups in both academic and industrial settings.[6]

Of particular interest to this laboratory and others is the strategic positioning of masked internal amino-nucleophiles relative to complementary electrophilic sites, which upon activation (via *N*-Boc deprotection,[7] azide to amine conversion,[8] or NO_2 reduction[9]) promotes rigidification of the Ugi skeleton to a variety of often pharmacologically relevant scaffolds.[10] Indeed, coupling this strategy to stage cascade reactions proves to be a particularly expeditious and value-adding endeavor in the search of new chemical space.[2] In this context, we herein describe recent results utilizing IMCR/cascade methodology that afford a variety of unique *mono*- and *bis*-heterocyclic scaffolds containing a (*Z*)-benzimidazole-2-one, often thought of as a privileged motif in ligand−receptor interactions.[11] The chemistry is also optimized to access intermediary 1,5-benzodiazpines, which have well documented pharmacological relevance.[12]

RESULTS AND DISCUSSION

Initial studies focused on the generic Ugi reaction of 2-(*N*-Boc-amino)-phenyl-isocyanide **1**, a particularly versatile isonitrile,[13] a carboxylic acid **2**, glyoxaldehyde **3**, and an amine **4** which under methanolic conditions at room temperature gives the desired Ugi adduct **5**, Scheme 1. The crude material was then treated with a solution of 10% trifluoracetic acid (TFA) in DCE and subjected to microwave irradiation (80 °C, 10 min). As expected, this removed the Boc group from the aniline moiety and promoted cyclization of the amine onto the ketone originally derived from the glyoxaldehyde **3** to garner a series of 1,5-benzodiazepines (**7a**−**7f**) in yields ranging from 46% to 65%, Table 1. The structure of the benzodiazepine **7a** was unambiguously confirmed by X-ray crystallography (Figure S1, Supporting Information).[14] It was hoped that continued heating in the TFA/DCE solution at higher temperatures would promote rearrangement of **7** to the corresponding (*E*)-benzimidazole-2-one **8**. However, rearrangement only pro-

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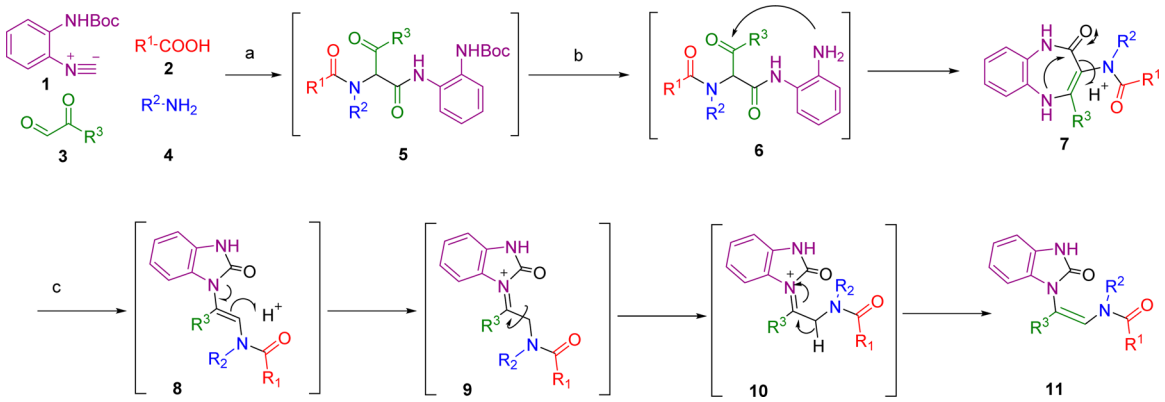
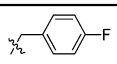
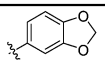
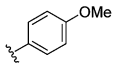
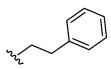
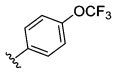
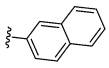
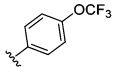
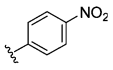
Scheme 1. Reaction Sequence toward 1,5-Benzodiazepines 7 and (*Z*)-Benzimidazole-2-ones 11[a]



[a]Conditions: [a] MeOH, rt overnight; [b] 10% TFA/DCE, microwave irradiation at 80 °C, 10 min; [c] 300 °C neat, 10 min.

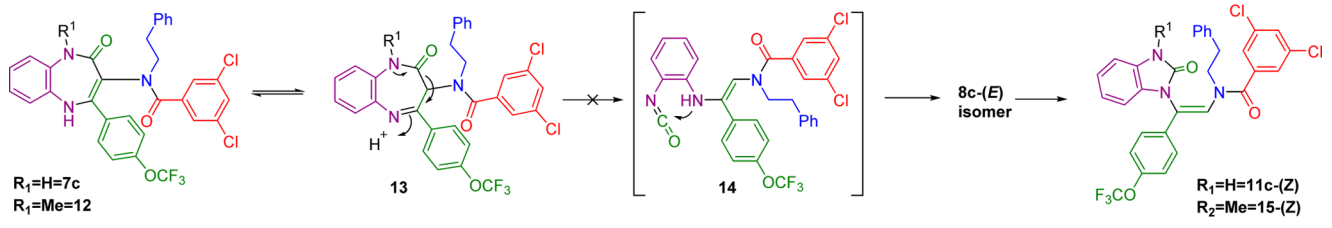
Table 1. Representative Examples of 1,5-Benzodiazepines 7 and (*Z*)-Benzimidazole-2-ones 11

Entry	R^1	R^2	R^3	Comp. **7** [%] yield[b]	Comp. **11** [%] yield[c]
1				**7a**: 63	**11a**: 86
2				**7b**: 65	**11b**: 91
3				**7c**: 62	**11c-(*Z*)**: 72 **8c**: 24
4		H		**7d**: 58	**11d**: 83
5		H		**7e**: 46	**11e**: 88
6		H		**7f**: 47	**11f**: 93
7		H		NI[a]	**11g**: 79

[a]NI: not isolated. [b]Isolated yields of **7** are derived from the start of the one-pot sequence. [c]Isolated yields of **11** are derived from the 1,5-benzodiazepine **7**.

ceeded effectively after exposure of neat, solid product to strong thermal conditions in a sand bath (300 °C), albeit in good final isolated yield (**11a**–**11g**, 79–93%). To our surprise, after final product characterization and definitive structural determination by crystallography of **11g** (Figure S2, Supporting Information[14]), it was found that benzodiazepine ring contraction to the corresponding (*E*)-benzimidazole-2-one **8** had taken place, but in an extended sequence, the (*E*)-form had isomerized to its corresponding (*Z*)-isomer **11**. Noteworthy, the preference for (*Z*)-stereoselectivity was independent of R^2 (the diversity element derived from the amine **4**), being compatible with both aromatic (**11b**) and aliphatic groups (**11a**, **11c**). Moreover, in products (**11d**–**g**), the ammonia surrogate 2,4-dimethoxybenzylamine was employed in the initial Ugi reaction, being cleaved upon acid treatment to leave a free NH. Further evidence of the isomerization was observed with entry 3, Table 1, where heating of the benzodiazepine **7c** was stopped prematurely, enabling isolation of both the (*E*)-stereoisomer (**8c**, 24% yield) and the (*Z*)-stereoisomer (**11c**-(*Z*), 72% yield). Subsequently, exposure of the isolated (*E*)-stereoisomer (**8c**) to the same thermal conditions (300 °C, sand bath, 10 min) demonstrated clean conversion to the corresponding (*Z*)-stereoisomer. Note that this transformation was conducted on the solid form of (**8c**) to mimic the cascade reaction conditions. Indeed, the isomerization is facile in solution where quantitative conversion is witnessed upon standing overnight in $CDCl_3$. A tentative mechanism of 1,5-benzodiazepine rearrangement and subsequent isomerization is depicted, Scheme 1. [Note: studies on what was thought an alternate mechanism are depicted in Scheme 2]. A somewhat similar rearrangement of a less elaborate 1,5-benzodiazepine with an exocyclic double bond, produced from the reaction of phenylenediamine and acetonedicarboxylate, was reported during the course of this work,[15] and previously we have exploited a similar rearrangement of fused tricyclic 1,5-benzodiazepines to afford pyridinone-3-yl-benzimidazol-2-ones.[16] However, this is the first sequential

Scheme 2. Alternate Ring Fragmentation Mechanistic Studies via Isocyanate 14



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multicomponent approach toward (*Z*)-benzimidazol-2-ones with multiple points of diversification. The (*E*)-olefin **8** is in essence an *N*-acyl-enamide, further sensitized to the presence of adventitious acid by the benzimidazole-2-one. Protonation yields the *N*-acyliminium ion[17] intermediate **9** enabling free rotation around the central C−C bond, followed by proton loss from **10** giving the observed thermodynamic (*Z*)-isomer, **11**.

Despite similar 1,5-benzodiazepine rearrangements[15,16] being reported, we envisioned an alternate ring fragmentation mechanism involving isomerization to **13** and ring opening to afford the intermediate isocyanate **14**, with subsequent trapping to give the (*E*)-benzimidazol-2-one **8c**-(*E*) followed by isomerization to the (*Z*)-isomer, **11c**-(*Z*), Scheme 2.

The methylated-1,5-benzodiazepine **12** was thus prepared[12d] (R_1 = methyl) on the assumption this would prohibit isocyanate formation and hence ring fragmentation. Indeed, on subjecting **12** to similar conditions, the (*Z*)-benzimidazol-2-one **15** was formed in good yield, implying mechanistic involvement of the isocyanate **14** was unlikely. Moreover, the 1,5-benzodiazepine **7c** was subject to ring fragmentation conditions in the presence of excess phenethylamine and clean conversion to the (*Z*)-benzimidazol-2-one **11c**-(*Z*) was observed with no detection of a urea derived from intermolecular trapping of isocyanate **14** (94% as judged by LC/MS, UV254 nm). Collectively, these observations negate an isocyanate-based fragmentation sequence and lend some credence to the ring fragmentation mechanism proposed herein and in previous reports.

In regard to the (*E*)- to (*Z*)-benzimidazol-2-one isomerization, it is noted that (*E*)-olefins are generally the thermodynamic isomer; however, it has been shown that in certain cases the (*Z*)-isomer may be favored due to additional intramolecular van der Waals, hydrogen bonding interactions, or dipole−dipole interactions.[18] In order to gain some insight regarding the difference in stability of the two stereoisomers, MMF49 molecular dynamics calculations were performed on **11c**-(*Z*) and **8c**. In agreement with the experimental results, the *Z*-isomer was found to be slightly energetically more stable (86.038 kcal/mol) than the *E*-isomer (91.949 kcal/mol).[19] However, more convincingly one resonance form of **11c** (Figure 1) clearly shows charge−charge stabilization between the positively charged oxygen of the benzimidazolone and the negatively charged amide nitrogen. Indeed, MMF49 molecular dynamic calculations of the resonance forms of **11c** and **8c** show that the (*Z*)-congener is ∼9.1 kcal/mol more stable than the (*E*)-isomer.[19]

With a robust preliminary protocol in place, we thus examined the feasibility of expanding accessible chemotypes to *bis*-heterocyclic scaffolds which we envisioned would also provide additional information surrounding the scope of Scheme 1. As such, a second Boc-protected internal nucleophile and complementary electrophilic carbonyl were incorporated into the Ugi adduct **18** via the use of glyoxylic acids **16** and *ortho*-*N*-Boc anilines **17** respectively, Scheme 3. It was envisioned acid treatment of the adduct **18** would afford the 1,5-benzodiazepine-quinoxalinone **20** through removal of two Boc groups and concomitant closure of two rings. To our delight, after formation of the Ugi product **18** (not isolated), simple acid treatment and microwave irradiation at 180 °C (30 min) afforded the (*Z*)-benzimidazolone **22** in a single step in good yields (**22a**−**22h**, 50−58% Table 2), representing the combination of an MCR and a theoretical six-step one-pot domino process: (1) Boc removal; (2) Boc removal; (3) ring

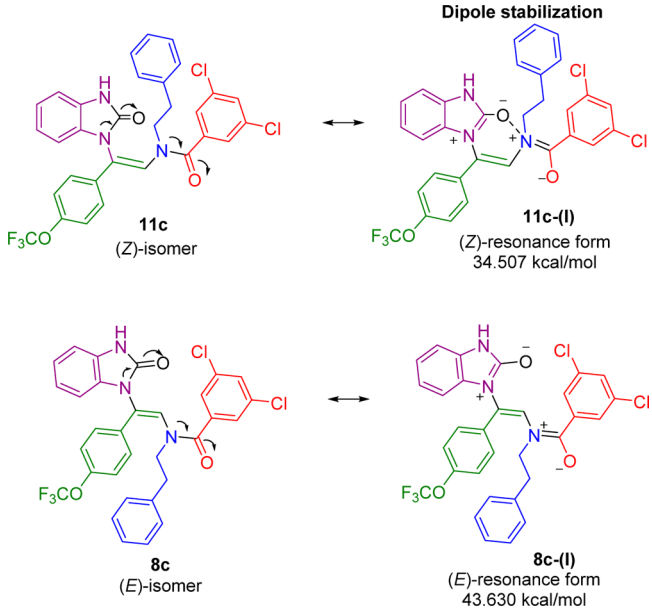

Figure 1. A plausible explanation for the observed formation (*Z*)-benzimidazol-2-ones based on enhanced dipole−dipole interactions in the (*Z*)-resonance form relative to the (*E*)-isomer, supported by MMF49 calculations.

closure to 1,5-benzodiazepine; (4) ring closure to quinoxalin-2-one; (5) 1,5-benzodiazepine rearrangement to (*E*)-benzimidazol-2-one; and (6) isomerization to (*Z*)-benzimidazol-2-one. Note that the relative order of two ring closing events was not ascertained. Final product structures with preferred stereochemistry were fully elucidated via X-ray crystallography of **22c** and **22e** respectively (Figures S3 and S4, Supporting Information).[14] It was subsequently found that with application of milder conditions (100 °C, 10 min, 10% TFA/DCE) the 1,5-benzodiazepine **20** could be isolated, confirmed with the solved X-ray of **20i** (Figure S5, Supporting Information).[14] Interestingly, close analysis of the structure of **20i** revealed that the two substituents of the 1,5-benzodiazepine (the aryl ring and the quinoxalin-2-one) exhibit higher torsional strain (O−C−C−C, 166°) than benzodiazepine **7a** (150°), Figure S3 (Supporting Information), suggesting that steric repulsion is promoting the observed increased rate of 1,5-benzodiazepine **20** rearrangement to (*Z*)-benzimidazol-2-one **22**.

Applying the same rationale behind the design of the *bis*-heterocyclic scaffold **22**, the *mono*-Boc protected benzylic diamine **23** was employed to evaluate access to scaffolds **26** and **27**, Scheme 4. Optimal conditions were found to be similar to those employed in Scheme 1 with a stepwise approach used to initially prepare the *bis*-heterocyclic 1,5-benzodiazepine-1,4-benzodiazepine **26** via exposure to 10% TFA/DCE (microwave, 100 °C) followed by heating at 300 °C (sand bath) to promote rearrangement to the expected (*Z*)-benzimidazol-2-ones **27**. A small set of compounds **26a**−**d** (54−66% yield) and **27a**−**d** (93−96% yield) were prepared containing various aromatic and heteroaromatic substituents in acceptable yields for the double *N*-Boc deprotection/double ring closing step and 1,5-benzodiazepine to (*Z*)-benzimidazol-2-one rearrangement/isomerization, respectively (Table 3). Despite the known atropoisomerism (axial chirality) of benzodiazepines,[20] no further studies were conducted to detect atropoisomeric ratios since interconversion rates tend to be slow in benzodiazepines (e.g., telenzepine atropoisomeric interconversion at 20 °C has a

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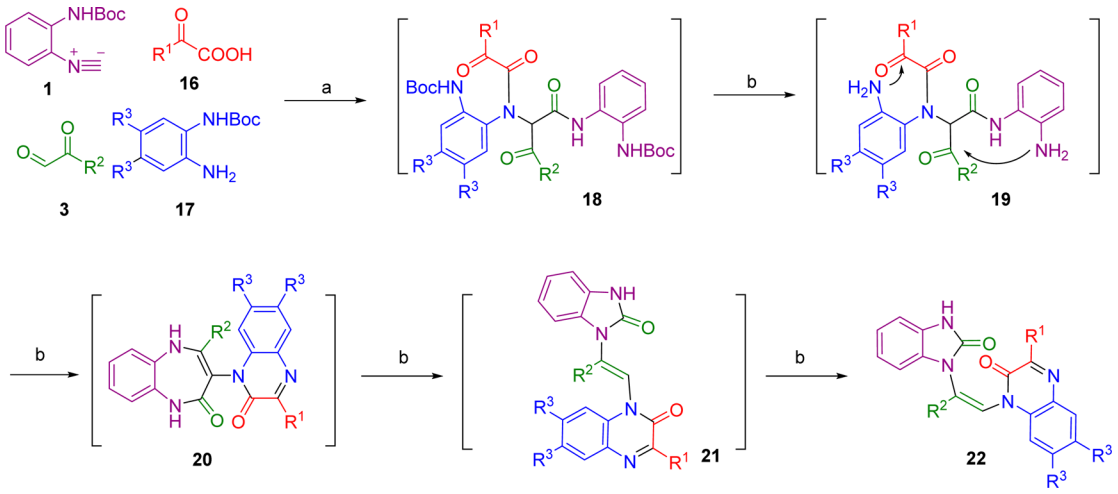
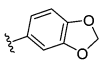
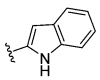
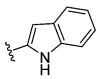
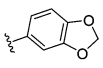
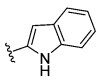
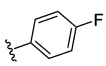
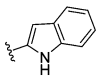
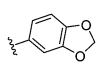
Scheme 3. One-Pot Reaction Sequence toward Benzimidazol-2-one-quinoxalin-2-ones 22[a]



[a]Conditions: [a] MeOH, rt overnight; [b] 10% TFA/DCE, microwave irradiation, 180 °C, 30 min.

Table 2. Benzimidazole-2-one-quinoxalin-2-ones 22a through 22h and 1,5-Benzodiazepine 20i

Entry	R^1	R^2	R^3	Comp. **20** [%] yield[a]	Comp. **22** [%] yield[b]
1			H	-	**22a**: 58
2			H	-	**22b**: 53
3			Me	-	**22c**: 52
4			Me	-	**22d**: 56
5			H	-	**22e**: 55
6			H	-	**22f**: 50
7			H	-	**22g**: 54
8			Me	-	**22h**: 55
9			H	**20i**: 55	**22i**: 95

[a]Conditions to isolate 1,5-benzodiazepine **20i**: 10% TFA/DCE microwave irradiation 100 °C, 10 min. [b]Conditions to afford (*Z*)-benzimidazol-2-ones **22** in a one-pot fashion: 10% TFA/DCE microwave irradiation, 180 °C, 30 min. Isolated yields of **22a–h** are derived from the starting materials **1**, **3**, **16**, **17**. The reported yield for **22i** is based on conversion from **20i**.

$t_{1/2}^{rac}$ = 1000 years), although the reader must be cognizant of this often overlooked form of drug chirality.[20c]

In summary, three novel cascade reactions are herein reported that enable access to a variety of unique *mono*- and *bis*-heterocyclic scaffolds. The cascade events are mediated via acid treatment of an Ugi adduct decorated with strategically positioned Boc-protected primary amines and electrophilic carbonyl centers. The sequences may be stopped to afford pharmacologically relevant *mono*- or *bis*-heterocyclic 1,5-benzodiazepines[12] or prolonged through a thermally induced rearrangement to (*E*)-benzimidazolones which isomerize to their (*Z*)-congener in one pot. The latter uncommon (*Z*)-stereoselectivity is adequately explained through dipole stabilization phenomena, Figure 1. Scaffolds generated through these nonobvious transformations are unique, contain three or four points of diversity, and are worthy of pharmacological evaluation, considering they contain both embedded benzimidazolones, quinoxalinones, and 1,4-benzodiazepines. Moreover, the unique, succint route to the intermediary but isolatable 1,5-benzodiazepine is also of high value.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR were recorded on a 400 MHz NMR spectrometer. ^{1}H NMR data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz), relative intensity (integration). ^{13}C NMR data are reported as follows: chemical shift in ppm (δ). HPLC-MS analyses were performed on an LC-MS instrument using the following conditions: Ultra C18 column (reversed phase, 3 μm, 50 mm × 2.1 mm); a linear gradient from 10% water and 90% acetonitrile to 95% acetonitrile and 5% water over 4.0 min; flow rate of 1 mL/min; UV photodiode array detection from 200 to 300 nm. High resolution mass spectra were obtained using the positive ESI method for all the compounds obtained in an ICR (Ion Cyclotron Resonance analyzer) spectrometer. The products were purified by automated flash chromatography and *n*-hexane/EtOAc or DCM/MeOH solvent systems. All reagents and solvents were obtained from commercial sources and used without further purification. All microwave irradiation experiments were carried out in a BiotageInitiator60 microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 220 W maximum power, using an external sensor of temperature. The reactions were carried out in 10 mL glass tubes, sealed with a Teflon septum and placed in the microwave cavity. The reaction was irradiated at a required ceiling temperature using maximum power for the stipulated time. Then it was cooled to 40 °C with gas jet cooling.

General Procedure for Compounds 7a–7c. A solution of the glyoxaldehyde **3** (0.50 mmol) and amine **4** (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 5 min, followed by addition of 2-(*N*-Boc-amino)-phenyl-isocyanide **1** (0.50 mmol) and the

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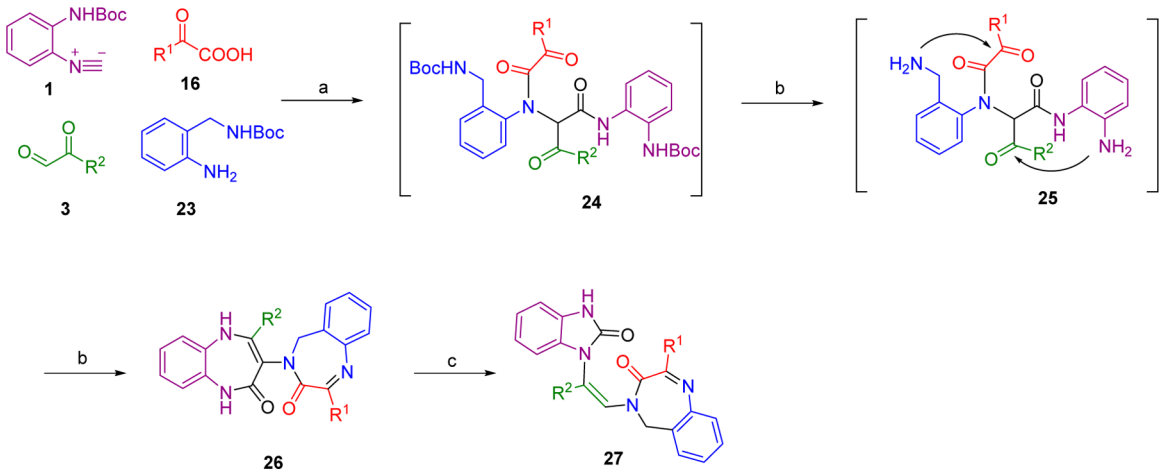
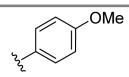
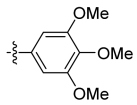
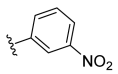
Scheme 4. Reaction Sequence towards 27[a]



[a]Conditions: [a] MeOH, rt overnight; [b] 10% TFA/DCE microwave irradiation, 100 °C, 10 min; [c] 300 °C neat, 10 min.

Table 3. Synthesis of 1,5-Benzodiazepines 26 and (*Z*)-Benzimidazole-2-ones 27

Entry	R^1	R^2	Comp. **26** [%] Yield	Comp. **27** [%] Yield[a]
1			**26a**: 66	**27a**: 94
2			**26b**: 58	**27b**: 95
3			**26c**: 58	**27c**: 93
4			**26d**: 54	**27d**: 96

[a]Isolated yields represent the one-step conversion of **26** to **27**.

carboxylic acid **2** (0.50 mmol). The reaction was monitored by TLC overnight, and on complete disappearance of 2-(*N*-Boc-amino)-phenyl-isocyanide, the solvent was evaporated *in vacuo*. 10% TFA/DCE (5 mL) was then added to the crude mixture and irradiated in a Biotage Initiator60 at 80 °C for 10 min. After cooling to room temperature, the solvent was evaporated *in vacuo*, and crude material was dissolved in EtOAc (15 mL) and washed with a saturated aqueous solution of Na_2CO_3 (1 × 15 mL) followed by brine (2 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated. The product was purified by automated flash chromatography (hexane/EtOAc 10–100%).

*N-(4-(Benzo[d][1,3]dioxol-5-yl)-2-oxo-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)-N-(4-fluorobenzyl)furan-2-carboxamide (**7a**).* Yellow solid, 156 mg, 63%, mp 223–224 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 8.81 (s, 1H), 8.30 (s, 1H), 8.22 (s, 1H), 7.69 (s, 1H), 7.14–7.05 (m, 2H), 7.02–7.00 (m, 1H), 6.92–6.78 (m, 6H), 6.44–6.45 (m, 2H), 6.44 (d, *J* = 1.7 Hz, 1H), 6.03 (d, *J* = 0.9 Hz, 1H), 5.98 (d, *J* = 0.9 Hz, 1H), 4.37–4.24 (m, 2H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 167.1, 162.2, 160.7, 159.8, 154.5, 148.6, 147.7, 146.7, 144.6, 135.0, 133.5, 130.9, 130.4, 130.1, 124.8, 123.6, 121.5, 120.8, 120.4, 115.7, 114.1, 113.9, 111.4, 107.9, 101.3, 79.1, 53.6. HRMS calculated for $C_{28}H_{20}FN_3O_5$ $[M + H]^+$ = 498.1460; found 498.1468.

*N-(4-(4-Methoxyphenyl)-2-oxo-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)-N-phenylquinoline-4-carboxamide (**7b**).* Yellow solid, 159 mg, 65%, mp >260 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 8.90 (s, 1H), 8.66 (d, *J* = 4.3 Hz, 1H), 8.62 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.13 (m, 3H), 7.07 (d, *J* = 4.1 Hz, 1H), 6.99–6.90 (m, 4H), 6.87 (m, 1H), 6.79–6.72 (m, 4H), 6.39–6.28 (m, 2H), 3.86 (s, 3H).[13]C NMR (100 MHz, *d*-DMSO) δ 169.0, 166.7, 160.7, 156.9, 149.4, 147.4, 143.4, 134.2, 131.3, 129.6, 129.1, 128.9, 128.7, 128.1, 126.8, 126.2, 125.8, 125.2, 123.5, 121.2, 120.6, 118.9, 114.1, 113.7, 109.9, 55.5. HRMS calculated for $C_{32}H_{25}N_4O_3$ $[M + H]^+$ = 513.1921; found 513.1922.

*3,5-Dichloro-N-(2-oxo-4-(4-(trifluoromethoxy)phenyl)-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)-N-phenethylbenzamide (**7c**).* Light yellow solid, 189 mg, 62%, 165–166 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 9.23 (s, 1H), 8.40 (s, 1H), 7.54–7.40 (m, 3H), 7.33–7.17 (m, 7H), 6.99–6.75 (m, 6H), 3.63–3.56 (m, 1H), 3.36–3.15 (m, 2H), 2.84–2.77 (m, 1H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 168.5, 167.4, 155.2, 149.0, 140.1, 139.8, 135.2, 133.5, 130.7, 129.9, 128.9, 128.6, 128.4, 128.3, 126.0, 125.7, 125.3, 124.1, 121.1, 120.8, 120.7, 113.9, 55.8, 33.1. HRMS calculated for $C_{31}H_{23}Cl_2F_3N_3O_3$ $[M + H]^+$ = 612.1063; found 612.1065.

General Procedure for Compounds 7d–7f. A solution of 2,4-dimethoxybenzylamine (84 mg, 75 μL, 0.50 mmol) and the glyoxaldehyde **3** (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 5 min, followed by addition of 2-(*N*-Boc-amino)-phenyl-isocyanide **1** (0.50 mmol) and the carboxylic acid **2** (0.50 mmol). The reaction was monitored by TLC overnight, and on complete disappearance of 2-(*N*-Boc-amino)-phenyl-isocyanide, the solvent was evaporated *in vacuo*. 10% TFA/DCE (5 mL) was added to the crude mixture, and the solution was irradiated in a microwave at 100 °C for 10 min. After cooling to room temperature, the solvent was evaporated *in vacuo* and the crude product was dissolved in EtOAc (15 mL) and washed with sat. Na_2CO_3 (1 × 15 mL) and brine (2 × 15 mL). The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*, and the product was purified by automated flash chromatography (hexane/EtOAc 10–100%).

*N-(4-(Benzo[d][1,3]dioxol-5-yl)-2-oxo-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)isonicotinamide (**7d**).* Light yellow solid, 116 mg, 58%, mp >260 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 11.04 (s, 1H), 10.48 (d, *J* = 10.1 Hz, 1H), 8.75–8.62 (m, 2H), 7.67–7.58 (m, 2H), 7.55 (d, *J* = 10.1 Hz, 1H), 7.11–6.94 (m, 2H), 6.93–6.75 (m, 3H), 6.62–6.58 (m, 1H), 6.49 (d, *J* = 7.7 Hz, 1H), 6.02 (s, 2H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 163.9, 152.9, 150.0, 147.8, 147.1, 140.6, 129.9, 129.5, 129.3, 121.8, 121.3, 120.4, 120.2, 118.6, 117.1, 108.9, 108.8, 108.5, 105.1, 101.3. HRMS calculated for $C_{22}H_{17}N_4O_4$ $[M + H]^+$ = 401.1244; found 401.1245.

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*4-Bromo-N-(2-oxo-4-phenyl-2,5-dihydro-1H-benzo[b][1,4]-diazepin-3-yl)benzamide (**7e**).* White solid, 100 mg, 46%, mp 208−210 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 11.11 (s, 1H), 8.77 (s, 1H), 7.81 (d, J = 5.2 Hz, 2H), 7.68−7.36 (m, 8H), 7.35−7.19 (m, 3H), 4.88 (s, 1H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 165.2, 161.3, 138.6, 136.0, 132.2, 131.2, 129.9, 129.5, 129.1, 128.4, 128.0, 127.5, 127.0, 126.3, 125.3, 124.8, 122.0, 56.8. HRMS calculated for $C_{22}H_{17}BrN_3O_2$ $[M + H]^+$ = 434.0499; found 434.0502 and 436.0501.

*N-(2-Oxo-4-(4-(trifluoromethoxy)phenyl)-2,5-dihydro-1H-benzo-[b][1,4]diazepin-3-yl)-2-naphthamide (**7f**).* White solid, 115 mg, 47%, mp 218−220 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 11.18 (s, 1H), 8.81 (d, J = 4.6 Hz, 1H), 8.27 (s, 1H), 8.07−7.84 (m, 4H), 7.66−7.48 (m, 4H), 7.46−7.29 (m, 5H), 4.97 (s, 1H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 166.7, 165.2, 149.8, 138.9, 135.7, 134.7, 132.4, 131.1, 130.8, 130.2, 129.6, 129.3, 128.3, 128.0, 127.6, 127.2, 127.1, 125.4, 124.4, 122.6, 120.9, 119.1, 57.4. HRMS calculated for $C_{27}H_{19}F_3N_3O_3$ $[M + H]^+$ = 490.1373; found 490.1375.

General Procedure for Compounds 11a−11g and 15. Compound **7** was placed in a culture tube and heated to 300 °C for 10 min in a sand bath. After cooling to room temperature, the product was purified by automated flash chromatography (hexane/EtOAc 10−100%) to afford **11**-(*Z*). A small fraction of compound **8c** was obtained if the reaction was stopped after 5 min and followed by immediate purification. *N*-Methylated product **15** was prepared via the same procedure from starting material **12**.

*(Z)-N-(4-Fluorobenzyl)-N-(2-(furan-2-yl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)vinyl)benzo[d][1,3]dioxole-5-carboxamide (**11a**).* Beige solid, 27 mg, 86%, mp 133−135 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.57 (s, 1H), 7.28−7.13 (m, 1H), 7.05−7.00 (m, 4H), 6.85−6.65 (m, 7H), 6.51−6.49 (m, 2H), 5.92 (s, 2H), 2.04 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 163.2, 160.8, 160.3, 154.1, 148.7, 148.4, 147.0, 145.7, 132.3, 129.1, 124.4, 122.6, 121.6, 120.2, 119.4, 119.3, 115.1, 111.9, 111.8, 110.1, 108.7, 106.3, 101.6, 49.7. HRMS calculated for $C_{28}H_{21}FN_3O_5$ $[M + H]^+$ = 498.1459; found 498.1456.

*(Z)-N-(2-(4-Methoxyphenyl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)vinyl)-N-phenylquinoline-4-carboxamide (**11b**).* Brown solid, 144 mg, 91%, mp 124−126 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.67−8.45 (m, 1H), 8.12−7.89 (m, 3H), 7.77−7.48 (m, 2H), 7.31 (s, 1H), 7.06−6.74 (m, 6H), 6.56 (s, 5H), 3.78 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 160.5, 153.8, 149.0, 148.3, 141.2, 139.2, 129.9, 129.8, 129.5, 128.4, 128.2, 127.7, 127.3, 127.1, 126.8, 125.7, 125.3, 125.0, 124.5, 122.3, 122.2, 121.3, 119.2, 114.5, 109.7, 55.41. HRMS calculated for $C_{32}H_{24}N_4O_3$ $[M + H]^+$ = 513.1921; found 513.1927.

*(Z)-3,5-Dichloro-N-(2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2-(4-(trifluoromethoxy)phenyl)vinyl)-N-phenethylbenzamide [**11c**-(Z)].* White solid, 36 mg, 72%, mp 82−84 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H), 7.58 (s, 1H), 7.33−7.31 (m, 1H), 7.29−7.22 (m, 4H), 7.16−7.02 (m, 6H), 6.97−6.89 (m, 3H), 6.50 (s, 1H), 6.20 (s, 1H), 3.86 (br, s, 1H), 3.62−3.58 (m, 1H), 3.04−3.01 (m, 1H), 2.80−2.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 153.8, 149.8, 138.4, 137.9, 135.0, 132.6, 130.7, 129.1, 128.6, 128.5, 128.1, 127.5, 126.9, 126.7, 123.1, 122.6, 121.8, 121.1, 119.0, 110.4, 110.0, 49.5, 33.9. HRMS calculated for $C_{31}H_{23}Cl_2F_3N_3O_3$ $[M + H]^+$ = 612.1063; found 612.1066.

*(E)-2,6-Dichloro-N-(2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2-(4-(trifluoromethoxy)phenyl)vinyl)-N-phenethylbenzamide [**8c**].* Colorless oil, 12 mg, 24%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 7.39−7.19 (m, 6H), 7.13−7.08 (m, 5H), 7.04−7.02 (m, 1H), 6.99−6.82 (m, 3H), 6.65 (s, 1H), 6.29 (d, J = 7.8 Hz, 1H), 4.03−3.99 (m, 2H), 3.20−3.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 155.6, 149.4, 137.9, 137.3, 134.4, 131.1, 130.2, 130.0, 129.5, 129.1, 128.9, 128.7, 127.8, 126.9, 126.6, 122.5, 121.6, 121.3, 121.2, 119.0, 110.0, 109.8, 50.0, 33.7. HRMS calculated for $C_{31}H_{23}Cl_2F_3N_3O_3$ $[M + H]^+$ = 612.1063; found 612.1065.

*(Z)-N-(2-(2-Oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2-(pyridin-4-yl)vinyl)benzo[d][1,3]dioxole-5-carboxamide (**11d**).* Yellow solid, 96 mg, 83%, mp 99−101 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 11.06 (s, 1H), 10.49 (d, J = 10.1 Hz, 1H), 8.76−8.69 (m, 1H), 7.68−7.53 (m, 3H), 7.32−7.18 (m, 1H), 7.10−6.97 (m, 2H), 6.98−6.78 (m, 3H), 6.63−6.57 (m, 1H), 6.49 (d, J = 7.8 Hz, 1H), 6.03 (s, 2H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 163.9, 153.0, 150.5, 150.0, 147.9, 147.1, 144.36, 140.1, 129.9, 129.3, 121.8, 121.3, 120.4, 120.2, 118.6, 117.2, 110.7, 109.0, 108.9, 108.5, 105.1, 101.3. HRMS calculated for $C_{22}H_{17}N_4O_4$ $[M + H]^+$ = 401.1244; found 401.1241.

*(Z)-4-Bromo-N-(2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2-phenylvinyl)benzamide (**11e**).* Brown solid, 87 mg, 88%, mp 107−108 °C, ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 10.21 (s, 1H), 9.89 (d, J = 10.2 Hz, 1H), 7.83 (d, J = 10.3 Hz, 1H), 7.77−7.71 (m, 2H), 7.59−7.53 (m, 2H), 7.37−7.27 (m, 5H), 7.12 (d, J = 7.7 Hz, 1H), 7.05−7.03 (m, 1H), 6.93−6.91 (m, 1H), 6.57 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 174.5, 164.0, 146.0, 143.2, 141.9, 140.6, 140.3, 139.9, 139.3, 138.1, 137.2, 136.6, 135.5, 135.4, 132.3, 132.2, 131.5, 127.5, 120.2, 119.8, 119.8. HRMS calculated for $C_{22}H_{17}BrN_3O_2$ $[M + H]^+$ = 434.0498; found 434.0497.

*(Z)-N-(2-(2-Oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2-(4-(trifluoromethoxy)phenyl)vinyl)-2-naphthamide (**11f**).* Yellow solid, 107 mg, 93%, mp 94−96 °C, ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 10.17 (s, 1H), 9.99−9.96 (m, 1H), 8.35 (s, 1H), 7.99−7.92 (m, 5H), 7.48−7.46 (m, 2H), 7.47 (d, J = 8.9 Hz, 2H), 7.31 (s, 1H), 7.17−7.13 (m, 1H), 7.07 (d, J = 1.2 Hz, 1H), 6.99−6.97 (m, 1H), 6.69−6.66 (m, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 165.8, 149.1, 135.9, 135.8, 129.8, 129.4, 129.0, 128.9, 128.6, 127.7, 127.4, 125.1, 123.7, 122.7, 122.2, 121.9, 116.1, 110.3, 110.2. HRMS calculated for $C_{27}H_{19}F_3N_3O_3$ $[M + H]^+$ = 490.1373; found 490.1370.

*(Z)-N-(2-(4-Bromophenyl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)vinyl)-4-nitrobenzamide (**11g**).* Brown solid, 189 mg, 79%, mp 108−109 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 11.15 (s, 1H), 10.67 (d, J = 10.5 Hz, 1H), 8.29−8.09 (m, 2H), 8.03 (d, J = 10.4 Hz, 1H), 7.69 (s, 4H), 7.54−7.36 (m, 2H), 7.16−6.96 (m, 2H), 6.92−6.88 (m, 1H), 6.54−6.52 (m, 1H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 164.8, 153.0, 146.1, 142.3, 132.1, 131.3, 130.3, 129.6, 129.5, 126.1, 125.9, 125.1, 124.2, 121.6, 120.6, 114.2, 109.2, 108.5. HRMS calculated for $C_{22}H_{16}BrN_4O_4$ $[M + H]^+$ = 479.0349; found 479.0351.

*(Z)-3,5-Dichloro-N-(2-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)-2-(4-(trifluoromethoxy)phenyl)vinyl)-N-phenethylbenzamide (**15**).* Brown solid, 58 mg, 85%, mp 91−93 °C, ^{1}H NMR (400 MHz, DMSO-d6) δ 7.82−7.65 (m, 1H), 7.56−7.52 (m, 4H), 7.40−7.38 (m, 2H), 7.30−7.17 (m, 6H), 7.11−7.09 (m, 1H), 6.88−6.75 (m, 2H), 6.18 (s, 1H), 4.02−4.01 (m, 1H), 3.22−3.18 (m, 1H), 3.08−3.02 (m, 1H), 2.89−2.88 (m, 1H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 172.6, 167.8, 139.9, 139.5, 139.1, 135.5, 133.7, 131.7, 131.5, 129.8, 126.6, 125.6, 122.2, 121.5, 129.8, 115.7, 108.4, 53.7, 34.0, 30.3. HRMS calculated for $C_{32}H_{24}Cl_2F_3N_3O_3$ $[M]^+$ = 626.1220; found 626.1217.

General Procedure for the Preparation of 12. Benzodiazepine **7a** (0.25 mmol, 1.0 equiv) was dissolved in DMF (2 mL), followed by addition of cesium carbonate (0.3 mmol, 1.2 equiv). The mixture was stirred for 10 min at room temperature. Subsequently, methyl iodide (0.25 mmol, 1.0 equiv) was added and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated *in vacuo*, and the crude material was dissolved in EtOAc (5 mL) and washed with brine (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The product **12** was purified by automated flash chromatography (hexane/EtOAc 0−20%).

*3,5-Dichloro-N-(1-methyl-2-oxo-4-(4-(trifluoromethoxy)phenyl)-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)-N-phenethylbenzamide (**12**).* Yellow solid, 68 mg, 44%, mp 229−231 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (m, 3H), 7.30−7.28 (m, 1H), 7.25−7.22 (m, 2H), 7.22−7.19 (m, 2H), 7.18−7.14 (m, 1H), 7.08−7.06 (m, 2H), 7.03−7.00 (m, 2H), 6.80−6.79 (m, 2H), 6.60−6.57 (m, 1H), 5.55 (s, 1H), 3.85−3.78 (m, 1H), 3.55−3.47 (m, 1H), 3.42 (s, 3H), 3.41−3.34 (m, 1H), 3.12−3.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.9, 154.3, 150.69, 150.67, 140.1, 140.0, 139.4, 135.6, 129.5, 129.29, 129.27, 129.0, 128.5, 128.4, 126.6, 126.3, 126.0, 125.6, 123.1, 121.2, 120.9, 119.9, 118.2, 57.4, 37.0, 33.8. HRMS calculated for $C_{32}H_{24}Cl_2F_3N_3O_3Na$ $[M + Na]^+$ = 648.1039; found 648.1037.

General Procedure for the Synthesis of Compound 20i. A solution of glyoxaldehyde **3** (0.50 mmol) and amine **17** (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 5 min, followed

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by addition of the 2-(*N*-Boc-amino)-phenyl-isocyanide **1** (0.50 mmol) and the glyoxylic acid **16** (0.50 mmol). The reaction was monitored by TLC overnight, and on complete disappearance of 2-(*N*-Boc-amino)-phenyl-isocyanide, the solvent was evaporated *in vacuo*. 10% TFA/DCE (5 mL) was added to the mixture, and the solution was irradiated in a microwave at 100 °C for 10 min. Solvent was evaporated *in vacuo*, and the product purified by automated flash chromatography (hexane/EtOAc, 10−100%).

*4-(4-(Benzo[d][1,3]dioxol-5-yl)-2-oxo-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)-2-(thiophen-2-yl)-4,5-dihydro-3H-benzo[e][1,4]diazepin-3-one (**20i**).* Yellow solid, 143 mg, 55%, mp 236−238 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 8.91−8.34 (m, 2H), 7.76 (d, J = 16.5 Hz, 2H), 7.39−6.31 (m, 12H), 6.08−5.63 (m, 2H), 4.45−3.87 (m, 2H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 166.0, 162.8, 156.1, 148.0, 146.1, 144.9, 134.4, 132.8, 131.6, 131.0, 129.5, 128.0, 125.6, 125.0, 123.6, 121.3, 120.5, 107.8, 107.4, 101.0, 52.8. HRMS calculated for $C_{29}H_{21}N_4O_4S$ $[M + H]^+$ = 521.1278; found 521.1278.

General Procedure for Compounds 22a−22i. A solution of glyoxaldehyde **3** (0.50 mmol) and amine **17** (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 5 min, followed by addition of the 2-(*N*-Boc-amino)-phenyl-isocyanide **1** (0.50 mmol) and the glyoxylic acid **16** (0.50 mmol). The reaction was monitored by TLC overnight, and on complete disappearance of 2-(*N*-Boc-amino)-phenyl-isocyanide, the solvent was evaporated *in vacuo*. 10% TFA/DCE (5 mL) was added to the crude mixture and irradiated in a Biotage Initiator60 at 180 °C for 30 min. After cooling to room temperature, the solvent was evaporated *in vacuo* and the crude material was dissolved in EtOAc (15 mL) and washed with sat. Na_2CO_3 (1 × 15 mL) and brine (2 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated, and the product was purified by automated flash chromatography (hexane/EtOAc 10−100%, EtOAc/MeOH 0−40%).

*(Z)-1-(2-(2-Oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2-phenylvinyl)-3-phenyl Quinoxalin-2(1H)-one (**22a**).* Yellow solid, 132 mg, 58%, mp 247−249 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 10.91 (s, 1H), 8.05 (d, J = 7.0 Hz, 2H), 7.74 (d, J = 8.2 Hz, 1H), 7.65−7.11 (m, 12H), 6.83−6.76 (m, 3H), 6.51 (s, 1H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 153.4, 153.1, 135.3, 133.4, 132.1, 130.7, 130.4, 129.8, 129.5, 129.0, 128.9, 128.7, 127.9, 126.4, 124.2, 121.8, 120.3, 115.3, 109.1. HRMS calculated for $C_{29}H_{21}N_4O_2$ $[M + H]^+$ = 457.1659; found 457.1661.

*(Z)-3-(3-Bromophenyl)-1-(2-(2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)-2-phenylvinyl)quinoxalin-2(1H)-one (**22b**).* Yellow solid, 142 mg, 53%, mp >260 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 9.05 (s, 1H), 8.90 (s, 1H), 8.27 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.78−7.65 (m, 2H), 7.63−7.52 (m, 2H), 7.47−7.43 (m, 1H), 7.37−7.05 (m, 6H), 7.05−6.81 (m, 4H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 164.6, 156.5, 154.4, 151.4, 137.7, 135.3, 134.8, 133.7, 132.9, 131.7, 131.3, 131.0, 130.2, 129.4, 127.9, 127.8, 125.9, 125.4, 123.8, 123.6, 121.2, 120.7, 116.0, 101.5. HRMS calculated for $C_{29}H_{20}BrN_4O_2$ $[M + H]^+$ = 535.0764; found 535.0761 and 537.0763.

*(Z)-3-(3-Bromophenyl)-6,7-dimethyl-1-(2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2-phenylvinyl)quinoxalin-2(1H)-one (**22c**).* Yellow solid, 146 mg, 52%, mp >260 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.36−8.00 (m, 2H), 7.69 (d, J = 7.9 Hz, 1H), 7.62−7.02 (m, 8H), 6.85−6.77 (m, 3H), 6.50 (s, 1H), 1.97−1.73 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 150.0, 137.7, 133.4, 132.8, 131.3, 130.4, 130.3, 129.9, 129.6, 129.0, 128.8, 127.8, 126.4, 121.9, 121.3, 120.5, 109.2, 79.2, 18.6. HRMS calculated for $C_{31}H_{24}BrN_4O_2$ $[M + H]^+$ = 563.1077; found 563.1079.

*(Z)-1-(2-(Benzo[d][1,3]dioxol-5-yl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)vinyl)-6,7-dimethyl-3-phenylquinoxalin-2(1H)-one (**22d**).* Yellow solid, 148 mg, 56%, mp >260 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.36−8.26 (m, 2H), 7.63 (s, 2H), 7.50−7.44 (m, 3H), 7.06−7.00 (m, 2H), 6.99−6.92 (m, 1H), 6.88−6.83 (m, 2H), 6.82−6.80 (m, 1H), 6.69 (d, J = 1.7 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 5.82 (s, 2H), 2.34 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 154.7, 152.6, 148.9, 148.0, 140.7, 136.2, 136.0, 133.3, 131.6, 130.2, 130.1, 129.4, 128.1, 127.6, 125.9, 122.5, 122.1, 121.9, 116.2, 110.8, 109.5, 108.7, 107.5, 101.4, 20.6, 19.2. HRMS calculated for $C_{32}H_{25}N_4O_4$ $[M + H]^+$ = 529.1870; found 529.1868.

*(Z)-1-(2-(3-Bromophenyl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)vinyl)-3-(1H-indol-2-yl)quinoxalin-2(1H)-one (**22e**).* Yellow solid, 158 mg, 55%, 231−233 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 11.77 (s, 1H), 10.90 (s, 1H), 8.76−8.70 (m, 2H), 7.87−7.66 (m, 3H), 7.63−7.11 (m, 9H), 6.81 (t, J = 7.9 Hz, 2H), 6.74−6.63 (m, 1H), 6.54 (s, 1H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 136.2, 133.0, 132.8, 132.4, 131.0, 128.7, 128.6, 128.3, 127.6, 126.0, 125.5, 124.0, 122.8, 122.6, 122.2, 121.9, 121.1, 120.4, 115.1, 111.9, 111.0, 109.2. HRMS calculated for $C_{31}H_{21}BrN_5O_2$ $[M + H]^+$ = 574.0873; found 574.0877.

*(Z)-1-(2-(Benzo[d][1,3]dioxol-5-yl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)vinyl)-3-(1H-indol-2-yl)quinoxalin-2(1H)-one (**22f**).* Yellow solid, 135 mg, 50%, mp 237−238 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 11.77 (s, 1H), 10.83 (s, 1H), 8.74−8.70 (m, 2H), 7.74 (d, J = 9.1 Hz, 1H), 7.57−7.08 (m, 7H), 6.97−6.77 (m, 2H), 6.84−6.23 (m, 5H), 6.11 (s, 2H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 153.1, 148.6, 147.9, 136.3, 133.0, 132.8, 128.3, 127.7, 126.1, 122.9, 122.6, 121.7, 121.1, 120.3, 111.9, 109.0, 108.6, 101.7. HRMS calculated for $C_{32}H_{22}N_5O_4$ $[M + H]^+$ = 540.1666; found 540.1671.

*(Z)-1-(2-(4-Fluorophenyl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)vinyl)-3-(1H-indol-2-yl)quinoxalin-2(1H)-one (**22g**).* Light yellow solid, 139 mg, 54%, mp >260 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 11.80 (s, 1H), 10.90 (s, 1H), 8.87−8.59 (m, 2H), 7.75 (d, J = 8.6 Hz, 1H), 7.67−7.00 (m, 10H), 6.72 (m, 5H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 164.2, 161.7, 153.1, 150.5, 136.3, 133.1, 132.8, 130.1, 128.7, 128.3, 127.6, 126.1, 124.0, 122.9, 122.7, 121.8, 121.1, 120.4, 116.0, 115.8, 115.1, 112.0, 111.0, 109.1. HRMS calculated for $C_{31}H_{21}FN_5O_2$ $[M + H]^+$ = 514.1674; found 514.1673.

*(Z)-3-(1H-Indol-2-yl)-6,7-dimethyl-1-(2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2-phenylvinyl)quinoxalin-2(1H)-one (**22h**).* Light yellow solid, 144 mg, 55%, mp >260 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 11.73 (s, 1H), 10.93 (s, 1H), 8.78−8.73 (m, 2H), 7.55−7.14 (m, 10H), 6.93−6.24 (m, 5H), 2.29−2.25 (m, 5H), 1.65 (s, 1H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 153.3, 136.2, 133.7, 132.5, 131.1, 129.6, 129.0, 128.5, 126.1, 122.9, 122.5, 121.7, 120.9, 120.4, 115.4, 111.9, 111.2, 109.1, 18.6. HRMS calculated for $C_{33}H_{26}N_5O_2$ $[M + H]^+$ = 524.2081; found 524.2079.

*(Z)-4-(2-(Benzo[d][1,3]dioxol-5-yl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)vinyl)-2-(thiophen-2-yl)-4,5-dihydro-3H-benzo[e][1,4]diazepin-3-one (**22i**).* Light yellow solid, 48 mg, 95%, mp 120−123 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.79−7.77 (m, 1H), 7.57−7.53 (m, 1H), 7.49−7.36 (m, 2H), 7.21−7.11 (m, 2H), 7.10−6.87 (m, 6H), 6.83−6.74 (m, 2H), 6.66 (d, J = 7.8 Hz, 1H), 5.96 (d, J = 1.5 Hz, 2H), 4.36 (d, J = 14.8 Hz, 1H), 4.16 (d, J = 15.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 155.2, 148.7, 148.5, 146.6, 142.5, 132.4, 131.6, 130.7, 129.7, 128.3, 127.7, 127.4, 127.0, 126.7, 126.5, 126.2, 122.7, 122.3, 121.8, 109.9, 109.5, 109.1, 108.3, 101.6, 50.7. HRMS calculated for $C_{29}H_{21}N_4O_4S$ $[M + H]^+$ = 521.1278; found 521.1277.

General Procedure for Compounds 26a−26d. A solution of glyoxaldehyde **3** (0.50 mmol) and amine **23** (0.50 mmol) in MeOH (1 mL) was stirred at room temperature for 5 min, followed by addition of the 2-(*N*-Boc-amino)-phenyl-isocyanide **1** (0.50 mmol) and the glyoxylic acid **16** (0.50 mmol). The reaction was monitored by TLC overnight, and on complete disappearance of 2-(*N*-Boc-amino)-phenyl-isocyanide, the solvent was evaporated *in vacuo*. 10% TFA/DCE (5 mL) was added to the crude mixture, which was subsequently irradiated in a Biotage Initiator60 at 100 °C for 10 min. After the mixure cooled to room temperature, the solvent was evaporated *in vacuo* and the crude material was dissolved in EtOAc (15 mL) and washed with sat. Na_2CO_3 (1 × 15 mL) and brine (2 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated, and the product was purified by automated flash chromatography (hexane/EtOAc 10−100%, EtOAc/MeOH 0−40%).

*2-(Furan-2-yl)-4-(4-(4-methoxyphenyl)-2-oxo-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)-4,5-dihydro-3H-benzo[e][1,4]diazepin-3-one (**26a**).* Light yellow solid, 162 mg, 66%, mp 194−195 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 8.57 (m, 2H), 7.90−7.85 (m, 1H), 7.55−6.31 (m, 14H), 4.35−4.32 (m, 1H), 3.93−3.87 (m, 1H), 3.66−

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3.60 (m, 3H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 163.1, 152.0, 150.5, 147.1, 135.0, 131.6, 130.0, 129.6, 129.3, 126.7, 126.1, 124.6, 121.8, 121.3, 118.4, 114.5, 113.5, 113.0, 55.9, 55.5. HRMS calculated for $C_{29}H_{23}N_4O_4$ $[M + H]^+$ = 491.1714; found 491.1715.

4-(2-Oxo-4-(3,4,5-trimethoxyphenyl)-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)-2-(thiophen-2-yl)-4,5-dihydro-3H-benzo[e][1,4]diazepin-3-one (**26b**). Yellow solid, 164 mg, 58%, mp 242−244 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 8.93−8.35 (m, 2H), 7.77 (m, 2H), 7.50−6.71 (m, 9H), 6.58 (s, 2H), 4.36 (d, *J* = 14.9 Hz, 1H), 3.99−3.91 (m, 1H), 3.87−3.34 (m, 9H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 166.5, 163.6, 156.9, 152.3, 145.3, 143.1, 138.5, 134.9, 133.4, 132.1, 131.6, 131.4, 128.9, 128.6, 128.1, 125.8, 125.6, 125.3, 124.0, 121.7, 121.0, 111.1, 105.5, 60.0, 56.0, 53.5. HRMS calculated for $C_{31}H_{27}N_4O_5S$ $[M + H]^+$ = 567.1697; found 567.1697.

4-(2-Oxo-4-phenyl-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)-2-phenyl-4,5-dihydro-3H-benzo[e][1,4]diazepin-3-one (**26c**). Yellow solid, 136 mg, 58%, mp 195−197 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 11.20 (s, 1H), 8.82−8.80 (m, 1H), 8.47−8.45 (m, 1H), 8.11−6.56 (m, 18H), 4.48−4.01 (m, 2H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 166.3, 165.5, 163.8, 161.6, 161.2, 160.9, 160.6, 160.3, 160.0, 156.9, 156.1, 152.5, 152.1, 146.1, 145.8, 144.9, 137.4, 137.1, 136.6, 136.1, 134.7, 134.5, 134.1, 131.4, 131.2, 130.9, 130.4, 129.5, 129.3, 128.8, 128.4, 127.9, 127.4, 126.6, 126.0, 125.6, 124.9, 124.2, 123.7, 123.4, 121.9, 120.9, 120.5, 110.0, 109.4, 109.0, 53.8, 52.9. HRMS calculated for $C_{30}H_{22}N_4O_2$ $[M + H]^+$ = 471.1816; found 471.1824.

4-(4-(3-Nitrophenyl)-2-oxo-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)-2-phenyl-4,5-dihydro-3H-benzo[e][1,4]diazepin-3-one (**26d**). Light yellow solid, 139 mg, 54%, mp 202−204 °C, ^{1}H NMR (400 MHz, *d*-DMSO) δ 9.08 (s, 1H), 8.73 (s, 1H), 8.36−7.58 (m, 5H), 7.58−6.48 (m, 12H), 4.55−4.06 (m, 2H). ^{13}C NMR (101 MHz, *d*-DMSO) δ ^{13}C NMR (100 MHz, *d*-DMSO) δ 166.3, 164.5, 161.6, 154.5, 147.0, 145.4, 137.8, 137.4, 134.7, 134.4, 131.2, 131.0, 129.5, 129.3, 128.9, 128.5, 128.2, 125.9, 125.8, 125.6, 124.6, 124.2, 123.4, 121.6, 121.2, 111.4, 52.8. HRMS calculated for $C_{30}H_{22}N_5O_4$ $[M + H]^+$ = 516.1666; found 516.1657.

General Procedure for Compounds 27a−d. **26** (50 mg) was heated directly to 300 °C for 10 min in a sand bath. After the culture tube cooled to room temperature, the product was purified by automated purification (hexane/EtOAc 10−100%) to yield the desired product **27**.

(Z)-2-(Furan-2-yl)-4-(2-(4-methoxyphenyl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)vinyl)-4,5-dihydro-3H-benzo[e][1,4]diazepin-3-one (**27a**). Light yellow solid, 47 mg, 94%, mp 134−136 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.69−7.68 (m, 1H), 7.53−7.51 (m, 1H), 7.44−7.40 (m, 1H), 7.35−7.27 (m, 2H), 7.24 (d, *J* = 2.3 Hz, 1H), 7.18−7.16 (m, 1H), 7.06−6.97 (m, 4H), 6.92−6.83 (m, 3H), 6.64−6.56 (m, 2H), 4.34 (d, *J* = 14.8 Hz, 1H), 4.13 (d, *J* = 14.4 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 154.9, 150.8, 146.4, 130.6, 129.7, 127.7, 127.6, 126.9, 126.7, 126.5, 125.6, 122.2, 121.6, 118.4, 114.8, 112.6, 109.9, 109.6, 55.3, 50.7. HRMS calculated for $C_{29}H_{23}N_4O_4$ $[M + H]^+$ = 491.1714; found 491.1713.

(Z)-4-(2-(2-Oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2-(3,4,5-trimethoxyphenyl)vinyl)-2-(thiophen-2-yl)-4,5-dihydro-3H-benzo-[e][1,4]diazepin-3-one (**27b**). Light yellow solid, 48 mg, 95%, mp 238−240 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.81−7.80 (m, 1H), 7.58−7.56(m, 1H), 7.51−7.35 (m, 2H), 7.17−6.99 (m, 5H), 6.91−6.95 (m, 1H), 6.84 (d, *J* = 7.4 Hz, 1H), 6.67−6.43 (m, 3H), 4.46 (d, *J* = 14.9 Hz, 1H), 4.16 (d, *J* = 15.2 Hz, 1H), 3.92−3.80 (m, 3H), 3.61 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 154.9, 153.8, 146.4, 142.4, 139.1, 132.1, 131.8, 130.4, 129.7, 128.5, 128.2, 127.7, 127.3, 126.8, 126.5, 122.3, 121.8, 110.1, 109.5, 105.6, 60.9, 56.1, 51.4. HRMS calculated for $C_{31}H_{27}N_4O_5S$ $[M + H]^+$ = 567.1697; found 567.1701.

(Z)-4-(2-(2-Oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2-phenylvinyl)-2-phenyl-4,5-dihydro-3H-benzo[e][1,4]diazepin-3-one (**27c**). Light yellow solid, 47 mg, 93%, mp 102−105 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.12−8.07 (m, 2H), 7.58−7.42 (m, 7H), 7.41−7.32 (m, 3H), 7.17−7.19 (m, 1H), 7.14−7.08 (m, 2H), 7.04−6.99 (m, 2H), 6.92−6.89 (m, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 4.30 (d, *J* = 14.9 Hz, 1H), 4.09 (d, *J* = 15.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 160.7, 154.6, 146.9, 135.7, 133.7, 131.5, 130.7, 129.8, 129.6, 129.3, 128.8, 128.6, 128.3, 127.7, 127.5, 126.6, 126.3, 122.2, 121.7, 109.8, 109.5, 50.9. HRMS calculated for $C_{30}H_{23}N_4O_2$ $[M + H]^+$ = 471.1816; found 471.1817.

(Z)-4-(2-(3-Nitrophenyl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]-imidazol-1-yl)vinyl)-2-phenyl-4,5-dihydro-3H-benzo[e][1,4]-diazepin-3-one (**27d**). Light yellow solid, 48 mg, 96%, mp 110−112 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.29 (t, *J* = 1.9 Hz, 1H), 8.22−8.19 (m, 1H), 8.04−7.96 (m, 2H), 7.70−7.68 (m, 1H), 7.56−7.45 (m, 6H), 7.19−7.17 (m, 1H), 7.11−7.05 (m, 4H), 6.98−6.91 (m, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 4.45 (d, *J* = 14.9 Hz, 1H), 4.06 (d, *J* = 14.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 160.5, 154.1, 148.8, 146.8, 135.7, 135.4, 133.9, 131.7, 130.4, 130.1, 129.5, 128.7, 128.7, 127.5, 126.8, 125.8, 124.2, 123.1, 122.8, 122.1, 109.8, 109.4, 51.5. HRMS calculated for $C_{30}H_{22}N_5O_4$ $[M + H]^+$ = 516.1666; found 516.1664.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00955.

^{1}H and ^{13}C NMR spectra for compounds of generic structure **7**, **11**, **20**, **22**, **26**, and **27** and ORTEP diagrams for compounds **7a**, **11g**, **20i**, **22c**, and **22e** (Figures S1−S5 respectively) (PDF)

Crystallographic files for compounds **7a**, **11g**, **20i**, **22c**, and **22e** (CIF)

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Notes

The authors declare no competing financial interest.

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(19) Molecular dynamics calculations were executed on ChemBio3D Ultra 14.0.0.117. MMF94 minimization was performed on **11c**-(**Z**) and **8c** with a maximum number of iterations of 5000 and minimum RMS gradient of 0.100, followed by energy and gradient calculations. Lastly, MMF94 molecular dynamics were done at a step interval of 2 fs, frame interval of 10 fs, with a number of interactions of 10 000 steps, a heating/cooling rate of 1 kcal/atom/ps, and a target temperature of 300 K. Upon completion, MMF94 energy minimizations were repeated and energy and gradient values were calculated. The energy values for **11c**-(**Z**) and **8c** were 86.038 and 91.949 kcal/mol, respectively. Using the same parameters the energy of resonance forms of **11c** and **8c** shown in Figure 1 were calculated. The energy values for **11c**-(**I**) and **8c**-(**I**) were 34.507 and 43.630 kcal/mol, respectively.

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