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Modular and Stereoselective Approach to Highly Substituted Indole/Pyrrole-Fused Diazepanones

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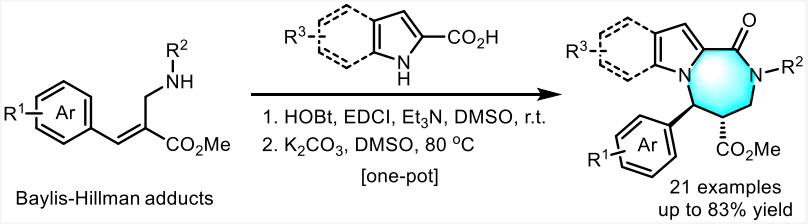

ABSTRACT: A one-pot synthetic method for indole/pyrrole-fused 1,4-diazepanone scaffolds has been developed. This method involves a sequential amide coupling/intramolecular aza-Michael addition of 1*H*-indole/pyrrole-2-carboxylic acids with Morita−Baylis−Hillman-derived allylamines. The readily available starting materials, good stereoselectivity, and gram-scale synthesis make this method valuable for the construction of highly substituted fused heterocycles containing the 1,4-diazepanone moiety.

INTRODUCTION

1,4-Diazepanones make up a highly attractive class of privileged scaffolds in drug discovery and constitute the core structures of many significant pharmaceuticals, including benzodiazepine anxiolytics (e.g., Diazepam, Mexazolam, etc.),[1] the non-nucleoside reverse transcriptase inhibitor Nevirapine,[2] and benzodiazepine receptor antagonist Flumazenil.[3] Consequently, a diversity of polycyclic fused heterocycles containing a 1,4-diazepanone moiety have been developed.[4] In particular, indole/pyrrole-1,2-fused 1,4-diazepinones and their derivatives, which contain privileged indole/pyrrole and 1,4-diazepinone skeletons, have attracted particular attention due to their potential bioactivities. For instance, they have been reported to exhibit activities as myeloid cell leukemia-1 (Mcl-1) inhibitors,[5] ribosomal S6 kinase (RSK) inhibitors,[6] and non-nucleoside HIV-1 reverse transcriptase inhibitors[7] (Figure 1).

Despite their bioactive significance, only a few synthetic methods have been developed to access these scaffolds over the past several decades. In 2018, Uchuskin's group reported a one-pot synthetic method for pyrrole-fused 1,4-diazepanones based on the condensation of *N*-Boc amino acids with furans containing aminoalkyl groups.[8] Recently, Xiao's group developed an *N*-alkylation-initiated redox-neutral [5+2] annulation of 3-alkylindoles with *o*-aminobenzaldehydes via a cascade *N*-alkylation/dehydration/[1,5]-hydride transfer/Friedel−Crafts alkylation sequence to access indole-1,2-fused 1,4-benzodiazepines.[9] Despite this progress, more efficient and straightforward synthetic strategies for such heterocyclic scaffolds are still highly desirable.

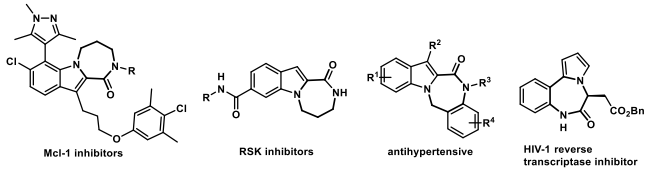

Figure 1. Selected bioactive compounds containing indole/pyrrole-fused 1,4-diazepinone frameworks.

Aza-Michael addition is one of the most important tools for the construction of the C−N bond.[10] In particular, domino or cascade reactions involving intramolecular aza-Michael additions are well developed and have been applied to the construction of various *N*-containing heterocycles.[11] The chemo- and stereoselective intermolecular aza-Michael additions of indoles or pyrroles to electron-deficient alkenes have been reported by several groups.[12] Compared with intermolecular reactions, intramolecular aza-Michael addition of indoles or pyrroles seems more valuable for the construction of fused polycyclic scaffolds. However, only a few examples of such reactions have been reported so far. Bandini[13] and You[14] reported base- or acid-catalyzed intramolecular aza-Michael

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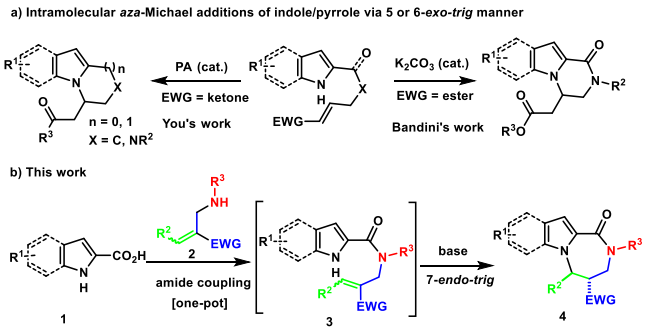
additions of indoles or pyrroles with tethered α,β-unsaturated esters or ketones as Michael acceptors, and these reactions proceeded through a 5- or 6-*exo-trig* cyclization to give five- or six-membered rings (Scheme 1a). 7-*endo-trig* cyclization with a

Scheme 1. Synthesis of Indole/Pyrrole-Fused Heterocycles



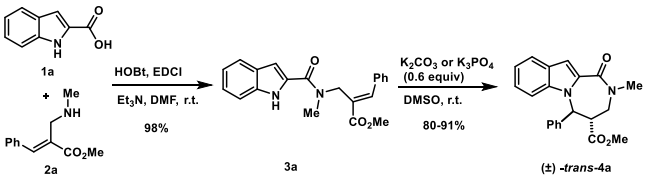
nitrogen as the nucleophile to form seven-membered *N*-containing heterocycles is still underdeveloped.[15] To the best of our knowledge, there have been no reports to date about the intramolecular aza-Michael additions of indoles/pyrroles through a 7-*endo-trig* cyclization to form fused seven-membered *N*-containing polycycles.

Morita−Baylis−Hillmann (MBH) adducts have been extensively used as synthons to construct highly functionalized carbo- or heterocycles.[16] Of these MBH adduct derivatives, allylamines **2**, which can be easily prepared from cheap and readily available starting materials such as aldehydes, activated alkenes, primary amines, etc., are very attractive as versatile synthons due to their diversified functional groups. In our previous work, we have developed an intramolecular iminium ion cyclization reaction of MBH-derived allylamines with aldehydes for the facile synthesis of dihydropyrroles.[17] As a continuation of this work, here we will report a simple one-pot strategy for indole/pyrrole-1,2-fused 1,4-diazepanone scaffolds via a sequential amide coupling/intramolecular aza-Michael addition starting from 1*H*-indole/pyrrole-2-carboxylic acids **1** and MBH allylamines **2** (Scheme 1b). We envisioned that this strategy would provide a modular and straightforward approach for highly substituted indole/pyrrole-fused polycycles.

RESULTS AND DISCUSSION

First, we investigated the stepwise synthesis conditions for the construction of indole-fused 1,4-diazepanone derivatives. The coupling of 1*H*-indole-2-carboxylic acid **1a** and allylamine **2a** (*E*-configured) under the conventional conditions (HOBt, EDCI, and Et_3N in DMF at room temperature) afforded amide intermediate **3a** in 98% yield (Scheme 2). Furthermore, the intramolecular cyclization of **3a** was explored and various organic or inorganic bases and solvents were screened (see the Supporting Information for details). After tedious attempts, we found that both K_2CO_3 and K_3PO_4 were suitable bases for this reaction. Using 0.6 equiv of K_2CO_3 or K_3PO_4 and DMSO as the solvent, the cyclization reaction proceeded smoothly at room temperature to afford the desired product **4a** as the single isomer in 80% (10 h, with K_2CO_3) or 91% (3 h, with K_3PO_4) yield, respectively. Other bases such as Cs_2CO_3, Na_2CO_3, and DBU were not efficient for this reaction. It was also found that the solvents had a strong influence on the reaction. The nonprotonic polar solvent DMSO was key to the successful reaction. Other solvents such as THF, CH_3CN, and CH_2Cl_2 failed to afford any products, which was in agreement with the reported results from Bandini's group.[13] As a result, K_2CO_3 and K_3PO_4 were identified as the suitable bases while DMSO was identified as the key solvent to promote this cyclization reaction.

Scheme 2. Stepwise Investigation of the Synthesis of Indole-Fused 1,4-Diazepanone 4a

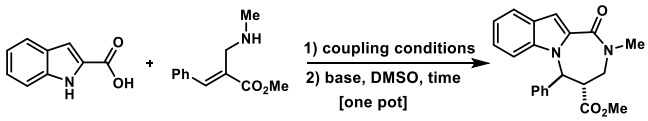


The structure of compound **4a** was clearly characterized by NMR spectra, HRMS spectra, and single-crystal X-ray analysis. Furthermore, X-ray analysis of **4a** showed that the phenyl and ester substituent are in a *trans* configuration, which exhibited the high stereoselectivity of this intramolecular cyclization reaction (see the Supporting Information).

To simplify the experimental operation and make our strategy more efficient and practical, a one-pot procedure for the desired products **4** was carried out on the basis of the aforementioned conditions. Thus, the coupling of 1*H*-indole-2-carboxylic acid **1a** with allylamine **2a** was performed in DMSO following the conditions in Scheme 2. Compound **1a** was completely converted into intermediate **3a** after being stirred at room temperature for 2.5 h (monitored by TLC). Then base was added into the reaction mixture under a nitrogen atmosphere without any other treatment. However, no desired product **4a** formed when the reaction was performed for 24 h at room temperature with 0.6 equiv of K_2CO_3, which was different from the result in the stepwise reaction (Table 1, entry 1).

Therefore, the base amount as well as reaction temperature was further examined. The results showed that an increased temperature and a higher loading of base could promote this

Table 1. Optimization of the One-Pot Reaction Conditions[a]



entry	base (equiv)	t (°C)	time (h)	yield (%)[b]
1	K_2CO_3 (0.6)	rt	24	0[c]
2	K_2CO_3 (1.5)	rt	24	0[c]
3	K_2CO_3 (1.5)	80	20	trace
4	K_2CO_3 (2.0)	80	7.5	75
5	K_2CO_3 (3.0)	80	3	83
6	K_2CO_3 (3.0)	50	17	trace
7	K_2CO_3 (4.0)	80	3	75
8	K_3PO_4 (3.0)	80	4	0[c]
9	Cs_2CO_3 (3.0)	80	3	54

[a]Reaction conditions: (1) **1a** (0.2 mmol), **2a** (0.24 mmol), HOBt (0.24 mmol), EDCI (0.24 mmol), and Et_3N (0.3 mmol) in anhydrous DMSO (2 mL) at room temperature for 3 h; (2) base added and the mixture stirred at the indicated temperature under a N_2 atmosphere. [b]Isolated yields. [c]Only intermediate **3a** could be observed by TLC.

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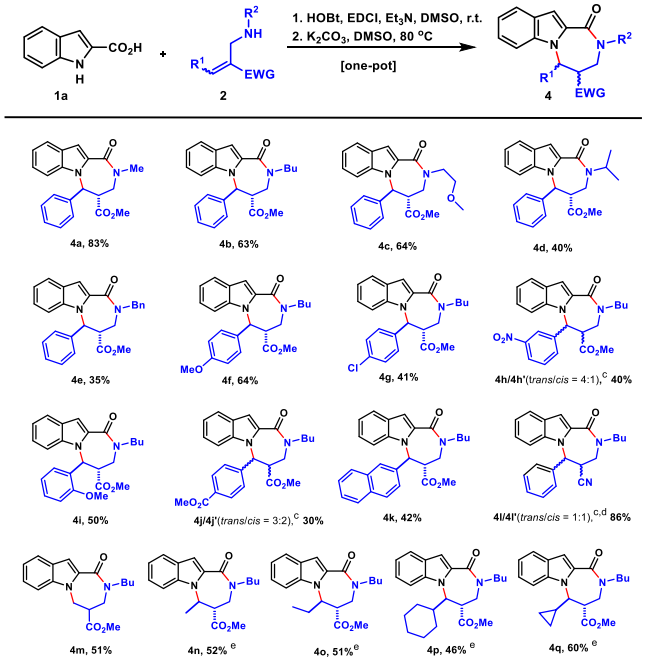
cyclization. The reaction performed at 80 °C with 3.0 equiv of K_2CO_3 gave the best result, and product **4a** was obtained in 83% yield (Table 1, entry 5). It was also found that K_3PO_4 was not efficient in the one-pot reactions while Cs_2CO_3 led to a lower yield (Table 1, entries 8 and 9). With the optimized conditions (Table 1, entry 5) in hand, we next investigated the general applicability of the one-pot amide coupling/intramolecular aza-Michael cyclization reaction. At first, the substrate scope of allylamines **2** was explored (Scheme 3). A

Scheme 3. Substrate Scope of MBH-Derived Allylamines[a,b]



[a]All reactions were carried out with **1a** (0.2 mmol) and **2** (0.24 mmol) in anhydrous DMSO (2 mL) under the optimized conditions. The *E* configuration of allylamines **2** was used unless indicated otherwise. [b]Isolated yields. [c]*trans/cis* ratios based on isolated products. [d]*Z*-configured allylamine **2l** was used. [e]A mixture of *E*- and *Z*-configured allylamine with different ratios was used.

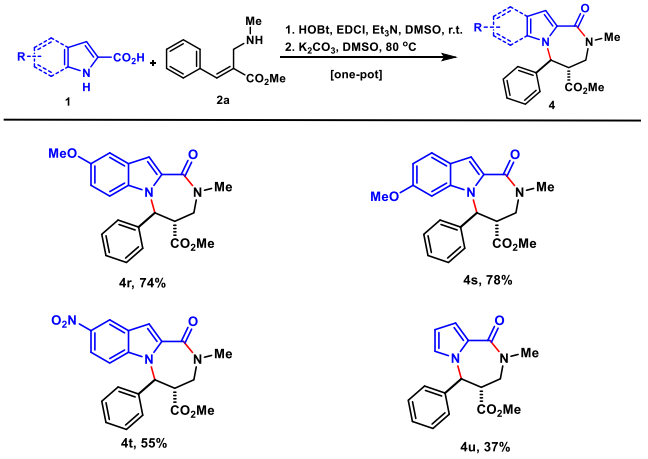
variety of allylamines **2** bearing diverse substituents at R^1 and R^2 could precede the cyclization reactions with 1*H*-indole-2-carboxylic acid **1a**, giving the desired indole-fused 1,4-diazepanones **4** in moderate to good yields with excellent *trans* stereoselectivities in most cases. Alkyl substituents on the nitrogen atom at R^2, including Bu, 2-methoxylethlyl, *i*-Pr, and Bn, were compatible with the reaction, affording the corresponding products **4b**−**4e**, respectively, in 35−64% yields with exclusive *trans* stereoselectivity. Notably, the reaction yields were significantly affected by the steric hindrance of the substituents on allylamine **2** at R^2. For example, bulky substituents such as *i*-Pr or Bn groups gave lower yields of products compared with less hindered Me, Bu, or 2-methoxyethyl groups. The low yields were presumably ascribed to the steric hindrance that decreased the reactivity in the first amide coupling step. In fact, allylamines with a more hindered *t*-Bu or inert Ph group at R^2 failed to give any products under the current conditions (the results are not listed).

Then the electronic effect of the substituents on the phenyl ring at R^1 was studied. The results show that both electron-donating and -withdrawing substituents were compatible with the reaction. Electron-donating substituents on the phenyl ring led to better yields compared with those for electron-withdrawing substituents (e.g., **4f** and **4i** vs **4g**, **4h**, and **4j**). Additionally, it was also found that the substituents could affect the stereoselectivity of products. The electron-donating groups gave the *trans* single isomer (e.g., **4f** and **4i**), while strong electron-withdrawing groups such as NO_2 or ester led to a mixture of *trans* and *cis* isomers (e.g., **4h**/**4h′** and **4j**/**4j′**). Allylamine **2** bearing a 2-naphthyl group at R^1 was also suitable for the reaction, producing *trans* isomer **4k** in 42% yield. For *Z*-configured allylamine **2l** (EWG = -CN), the desired cyclized products were obtained in 86% total yield as a mixture of *anti* and *syn* diastereoisomers (**4l** and **4l′**, 1:1 ratio), which could be separated by column chromatography.

In addition to aromatic groups, aliphatic aldehyde-derived allylamines **2** (R^1 = H, alkyl, or cycloalkyl) were also suitable substrates for this one-pot reaction, affording the desired products in moderate to good yields (e.g., **4m**−**4q**). It was interesting that in these reactions only *trans* isomers were obtained as the single products despite the substrates with a *Z*- and *E*-configured mixture. We envision that it is probably because the unstable *cis* products formed in the reactions can convert *in situ* into the more stable *trans* isomers under basic conditions.

Then the substrate scope of indole-2-carboxylic acid derivatives was explored to undergo the cyclization reaction with allylamine **2a** (Scheme 4). The electron-donating MeO

Scheme 4. Substrate Scope of Indole 2-Carboxylic Acids[a,b]



[a]All reactions were carried out with **1** (0.2 mmol) and **2a** (0.24 mmol) in anhydrous DMSO (2 mL) under the optimized conditions. [b]Isolated yields.

group at the C5 or C6 position on 1*H*-indole-2-carboxylic acids did not influence the reaction, and desired products **4r** and **4s** could be obtained in good yields (74% and 78%, respectively). The electron-withdrawing NO_2 group at the C5 position was also compatible with this reaction but with a slightly decreased yield (**4t**, 55%). In addition, we further expanded the substrate scope by replacing the indole unit with pyrrole-2-carboxylic acid, and desired cyclized product **4u** could also be obtained, although in a lower yield. Likewise, all of the indicated products in Scheme 4 were determined to be in the *trans* configuration by comparison of the NMR spectra data with those of **4a**, which indicated this reaction had excellent stereoselectivities.

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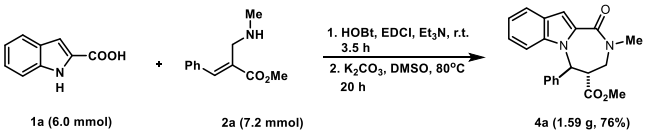
To demonstrate the synthetic practicability of this current methodology, a gram-scale reaction of indole-2-carboxylic acid **1a** and allylamine **2a** was carried out under the optimized conditions, and desired product **4a** was obtained in 76% yield (Scheme 5). This indicated that the one-pot reaction was easy to scale up to give the annulated products without significant decreases in the yields.

Scheme 5. Gram-Scale Synthesis of 4a



1a (6.0 mmol) 2a (7.2 mmol) 4a (1.59 g, 76%)

CONCLUSIONS

In conclusion, we have developed a one-pot method to construct indole/pyrrole-fused 1,4-diazepanone scaffolds. This method involves a sequential amide coupling/intramolecular aza-Michael reaction starting from 1*H*-indole/pyrrole-2-carboxylic acids and MBH-derived allylamines, which can be accessed via aldehydes, activated alkenes, and primary amines. Readily available and cheap starting materials, good stereoselectivity, and gram-scale synthesis make this method useful for the preparation of highly substituted fused 1,4-diazepanone derivatives.

EXPERIMENTAL SECTION

General Experimental Information. Allylamines **2a**, **2b**, and **2d**−**2i** as known compounds were prepared according to the procedure reported by our group.[17] Anhydrous DMSO was applied, and other solvents and reagents were used as supplied by commercial sources without further purification. Flash column chromatography was carried out on silica gel G (200−300 mesh). All reactions were monitored by TLC, which was performed on precoated aluminum sheets of silica gel 60 (F_{254}). Melting points were measured using a SGW X-4 apparatus and were uncorrected. NMR spectra were recorded on a Varian spectrometer (300 MHz for ^{1}H NMR and 75 MHz for $^{13}C\{^1H\}$ NMR). The chemical shifts are reported in parts per million (δ) with TMS as the internal standard and $CDCl_3$ or DMSO-d_6 as the solvent. Multiplicities are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doubled doublet; br.s, broad singlet. Coupling constants (J values) where noted are in hertz. The HRMS spectra were recorded using a quadrupole time-of-flight mass spectrometer and ESI positive ionization source.

General Experimental Procedure for the Synthesis of Allylamines (2c and 2j−2q). The allylamines were prepared by three-step continuous reactions via a modified reported procedure[17] as follows. In step 1, a mixture of the aldehyde (10.0 mmol, 1.0 equiv), methyl acrylate or acrylonitrile (10.5 mmol, 1.05 equiv), and DABCO (1.12 g, 10.0 mmol, 1.0 equiv) without solvent was stirred at 0 °C to room temperature for 7−14 days. After the reaction had reached completion, the mixture was diluted with diethyl ether (25 mL) and then washed with a 0.5 M HCl solution (3 × 30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the Baylis−Hillman alcohol without further purification. In step 2, to a solution of Et_3N (695 μL, 5.0 mmol, 1.0 equiv), Ac_2O (473 μL, 5.0 mmol, 1.0 equiv), and 4-dimethylaminopyridine (DMAP) (61 mg, 0.5 mmol, 0.1 equiv) in 25 mL of dichloromethane was added the crude Baylis−Hillman alcohol (5.0 mmol, 1.0 equiv) prepared as described above at 0 °C, and the resulting mixture was stirred for 30 min. After the reaction had reached completion, the mixture was washed with 20 mL of an aqueous saturated solution of $NaHCO_3$. The organic phase was removed, dried using anhydrous Na_2SO_4, filtered, and concentrated to yield the Baylis−Hillman acetate, which was directly used in the next step. In step 3, to the solution of the crude Baylis−Hillman acrylate (2.5 mmol, 1.0 equiv) in THF (3 mL) was added dropwise over 15 min a stirred solution of amine (5.0 mmol, 2.0 equiv) in THF (12 mL) at 0 °C, and then the mixture was warmed to room temperature and stirred for 30 min. The volatiles was removed in vacuo, and saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined EtOAc layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography on silica gel afforded the desired products.

The alkene configurations of the allylamines described above were determined by comparing the shift value of the β-vinylic proton in ^{1}H NMR spectra with reported values. Among them, allylamines **2b**−**2k** (R^1 = aryl groups, and EWG = -CO_2Me) deriving from aromatic aldehydes were *E*-configured.[18] **2l** (R^1 = Ph, and EWG = -CN) was *Z*-configured.[19] **2n**−**2q** (R^1 = alkyl or cycloalkyl groups) derived from aliphatic aldehydes were inseparable mixtures of *Z*- and *E*-configured isomers, and the ratios were determined on the basis of ^{1}H NMR spectra.[20]

Spectral Data. *Methyl (E)-2-{[(2-Methoxyethyl)amino]methyl}-3-phenyl-acrylate (**2c**).* This compound was prepared via the general procedure as a pale yellow oil (418 mg, 67% total yield), eluting with petroleum ether/ethyl acetate (5:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.52−7.43 (m, 2H), 7.39−7.30 (m, 3H), 3.82 (s, 3H), 3.62 (s, 2H), 3.48 (t, J = 5.7 Hz, 2H), 3.34 (s, 3H), 2.79 (t, J = 5.4 Hz, 2H), 2.01 (br.s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.1, 141.5, 134.8, 130.5, 129.3, 128.5, 128.2, 71.6, 58.4, 51.7, 48.5, 45.4; HRMS (ESI-TOF) calcd for $C_{14}H_{20}NO_3^+$ $[M + H]^+$ 250.1438, found 250.1439.

*Methyl (E)-4-{2-[(Butylamino)methyl]-3-methoxy-3-oxoprop-1-en-1-yl}benzoate (**2j**).* This compound was prepared via the general procedure as a pale yellow oil (344 mg, 45% total yield), eluting with petroleum ether/ethyl acetate (8:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.80 (s, 1H), 7.57 (d, J = 8.1 Hz, 2H), 3.93 (s, 3H), 3.84 (s, 3H), 3.54 (s, 2H), 2.60 (t, J = 6.9 Hz, 2H), 1.66 (br.s, 1H), 1.51−1.41 (m, 2H), 1.40−1.25 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.2, 166.6, 140.4, 140.3, 139.7, 132.7, 130.1, 129.6, 129.4, 52.1, 49.2, 45.9, 32.0, 20.4, 13.9; HRMS (ESI-TOF) calcd for $C_{17}H_{24}NO_4^+$ $[M + H]^+$ 306.1700, found 306.1691.

*Methyl (E)-2-[(Butylamino)methyl]-3-(naphthalen-2-yl)acrylate (**2k**).* This compound was prepared via the general procedure as a pale yellow oil (394 mg, 53% total yield), eluting with petroleum ether/ethyl acetate (10:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.96 (s, 1H), 7.86−7.81 (m, 3H), 7.59 (dd, J = 8.5, 1.2 Hz, 1H), 7.51−7.48 (m, 2H), 3.85 (s, 3H), 3.65 (s, 2H), 2.66 (t, J = 7.0 Hz, 2H), 1.76 (br.s, 1H), 1.55−1.44 (m, 2H), 1.42−1.32 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.6, 141.8, 133.2, 133.1, 132.7, 131.1, 129.5, 128.4, 128.0, 127.6, 126.9, 126.8, 126.4, 52.0, 49.4, 46.1, 32.1, 20.5, 14.0; HRMS (ESI-TOF) calcd for $C_{19}H_{24}NO_2^+$ $[M + H]^+$ 298.1802, found 298.1805.

*(Z)-2-[(Butylamino)methyl]-3-phenylacrylonitrile (**2l**).*[19] This compound was prepared via the general procedure as a pale yellow oil (391 mg, 73% total yield), eluting with petroleum ether/ethyl acetate (10:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.74 (m, 2H), 7.47−7.34 (m, 3H), 7.10 (s, 1H), 3.57 (d, J = 1.4 Hz, 2H), 2.64 (t, J = 6.9 Hz, 2H), 1.61 (br.s, 1H), 1.55−1.42 (m, 2H), 1.43−1.22 (m, 2H), 0.91 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 143.7, 133.3, 130.2, 128.8, 128.7, 118.4, 110.6, 53.7, 48.1, 32.1, 20.3, 13.9; HRMS (ESI-TOF) calcd for $C_{14}H_{19}N_2^+$ $[M + H]^+$ 215.1543, found 215.1533.

*Methyl 2-[(Butylamino)methyl]acrylate (**2m**).* This compound was prepared via the general procedure as a pale yellow oil (86 mg, 20% total yield), eluting with petroleum ether/ethyl acetate (1:1). It was found to be unstable and was used for the next reaction immediately after silica gel chromatography purification. The NMR spectra were not measured.

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*Methyl-2-[(butylamino)methyl]but-2-enoate (**2n**).* An inseparable mixture of *E*- and *Z*-configured isomers (2:1 *E*:*Z* based on ^{1}H NMR spectra) was obtained via the general procedure as a pale yellow oil (264 mg, 57% total yield), eluting with petroleum ether/ethyl acetate (2:1). NMR data for the *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (q, J = 7.2 Hz, 1H), 3.74 (s, 3H), 3.46 (s, 2H), 2.63−2.47 (m, 2H, overlapped), 1.88 (d, J = 7.2 Hz, 3H), 1.72 (br.s, 1H), 1.54−1.19 (m, 4H, overlapped), 0.91 (t, J = 7.2 Hz, 3H, overlapped); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.9, 140.1, 131.0, 51.6, 48.6, 44.5, 32.1, 20.4, 14.3, 13.9. Selected NMR data for the *Z* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (q, J = 7.3 Hz, 0.49H), 4.35 (t, J = 7.0 Hz, 0.36H), 3.78 (s, 1.5H), 3.46 (s, 2H), 3.41−3.34 (m, 1H), 2.02 (d, J = 7.2 Hz, 1.5H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 139.4, 130.7, 53.1, 51.1, 48.4, 15.6; HRMS (ESI-TOF) calcd for $C_{10}H_{20}NO_2^+$ $[M + H]^+$ 186.1489, found 186.1491.

*Methyl-2-[(butylamino)methyl]hex-2-enoate (**2o**).* An inseparable mixture of *E*- and *Z*-configured isomers (5:3 *E*:*Z* based on ^{1}H NMR spectra) was obtained via the general procedure as a pale yellow oil (174 mg, 35% total yield), eluting with petroleum ether/ethyl acetate (3:1). NMR data for the *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (t, J = 7.6 Hz, 1H), 3.75 (s, 3H), 3.45 (s, 2H), 2.54 (t, J = 6.9 Hz, 2H, overlapped), 2.32−2.22 (m, 2H), 1.72 (br.s, 1H, overlapped), 1.52−1.39 (m, 2H), 1.38−1.26 (m, 2H, overlapped), 1.07 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H, overlapped); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.1, 146.8, 129.4, 51.6, 48.6, 44.8, 32.1, 21.9, 20.4, 13.9, 13.3. Selected NMR data for the *Z* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (t, J = 7.4 Hz, 1H), 3.76 (s, 3H), 3.38 (m, 1H), 2.55 (t, J = 7.2 Hz, 2H, overlapped), 2.53−2.44 (m, 2H, overlapped), 1.72 (br.s, 1H), 1.52−1.39 (m, 2H), 1.38−1.26 (m, 2H, overlapped), 1.04 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H, overlapped); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 129.2, 53.1, 51.2, 48.4, 32.1, 22.9, 13.8; HRMS (ESI-TOF) calcd for $C_{11}H_{22}NO_2^+$ $[M + H]^+$ 200.1645, found 200.1654.

*Methyl-2-[(butylamino)methyl]-3-cyclohexyl-acrylate (**2p**).* An inseparable mixture of *E*- and *Z*-configured isomers (1:1 *E*:*Z* based on ^{1}H NMR spectra) was prepared via the general procedure as a pale yellow oil (133 mg, 25% total yield), eluting with petroleum ether/ethyl acetate (5:1). NMR data for the *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, J = 10.1 Hz, 1H), 3.74 (s, 3H), 3.45 (s, 2H), 2.57−2.51 (t, J = 6.9 Hz, 3H, overlapped), 1.81−1.57 (m, about 7H, overlapped), 1.51−1.02 (m, about 8H, overlapped), 0.90 (t, J = 7.2 Hz, 3H, overlapped). Selected NMR data for the *Z* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (d, J = 9.7 Hz, 1H), 3.75 (d, J = 4.2 Hz, 3H), 3.37 (d, J = 1.1 Hz, 2H). NMR data for the isomer mixture: ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.3, 167.9, 150.1, 149.8, 127.9, 127.5, 53.0, 51.5, 51.1, 48.3, 48.0, 44.9, 38.0, 37.5, 32.6, 32.2, 32.0, 31.9, 25.8, 25.6, 25.5, 25.3, 20.3, 13.8; HRMS (ESI-TOF) calcd for $C_{15}H_{28}NO_2^+$ $[M + H]^+$ 254.2115, found 254.2109.

*Methyl-2-[(butylamino)methyl]-3-cyclopropyl-acrylate (**2q**).* An inseparable mixture of *E*- and *Z*-configured isomers (4:3 *E*:*Z* based on ^{1}H NMR spectra) was prepared via the general procedure as a pale yellow oil (264 mg, 50% total yield), eluting with petroleum ether/ethyl acetate (3:1). NMR data for the *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (d, J = 10.8 Hz, 1H), 3.72 (s, 3H), 3.57 (s, 2H), 2.60 (t, J = 6.9 Hz, 2H), 1.80 (br.s, 1H, overlapped), 1.80−1.69 (m, 1H, overlapped), 1.53−1.32 (m, 4H, overlapped), 1.02−0.88 (m, 5H, overlapped), 0.67−0.62 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.9, 150.6, 127.5, 51.5, 48.6, 45.2, 32.1, 20.5, 13.9, 11.6, 8.8. Selected NMR data for the *Z* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (d, J = 10.7 Hz, 1H), 3.78 (s, 3H), 3.36 (s, 2H), 2.54 (t, J = 6.9 Hz, 2H), 1.80−1.69 (m, 1H, overlapped), 1.53−1.32 (m, 4H, overlapped), 1.02−0.88 (m, 5H, overlapped), 0.53−0.49 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 151.0, 126.9, 53.0, 51.2, 48.4, 32.1, 20.4, 13.9, 12.1, 8.7; HRMS (ESI-TOF) calcd for $C_{12}H_{22}NO_2^+$ $[M + H]^+$ 212.1645, found 212.1647.

Preparation of Indole Amide Intermediate 3a. To a solution of 1*H*-indole-2-carboxylic acid (161 mg, 1.0 mmol, 1.0 equiv) in DMF (10 mL) were added HOBt (162 mg, 1.2 mmol, 1.2 equiv) and EDCI (230 mg, 1.2 mmol, 1.2 equiv). After the mixture had been stirred at room temperature for 25 min, the prepared MBH-derived allylamine **2a** (243 mg, 1.2 mmol, 1.2 equiv) and triethylamine (208 μL, 1.5 mmol, 1.5 equiv) were then added immediately. After the addition, the reaction mixture was stirred for an additional 3 h. The reaction mixture was diluted with EtOAc (30 mL), washed successively with a 1 N HCl solution, saturated $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. After the solvent had been removed in vacuo, the crude product was purified by column chromatography on silica gel (2:1 petroleum ether/ethyl acetate) to provide amide intermediate **3a** (0.314 g, 98% yield) as a white solid: mp 115−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (br.s, 1H), 7.98 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.44−7.30 (m, 7H), 7.12 (t, J = 7.4 Hz, 1H), 6.76 (s, 1H), 4.86 (s, 2H), 3.81 (s, 3H), 3.11 (br.s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 167.2, 163.1, 142.3, 135.8, 134.1, 130.2, 129.4, 129.1, 128.6, 128.0, 126.9, 123.2, 121.4, 119.6, 112.0, 104.5, 52.1, 52.1, 45.3; HRMS (ESI-TOF) calcd for $C_{21}H_{21}N_2O_3^+$ $[M + H]^+$ 349.1547, found 349.1551.

Synthesis of Indole-Fused 1,4-Diazepanone (4a) in a Stepwise Manner. To a solution of amide intermediate **3a** (70 mg, 0.2 mmol, 1.0 equiv) in 2 mL of DMSO was added K_2CO_3 (17 mg, 0.12 mmol, 0.6 equiv). The reaction mixture was stirred at room temperature for 10 h under a nitrogen atmosphere. After the reaction had reached completion, the resulting solution was diluted with EtOAc (20 mL), washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography and eluted with petroleum ether/ethyl acetate (2:1) to furnish the desired product **4a** (56 mg, 80% yield).

When K_3PO_4 (0.6 equiv) was used instead of K_2CO_3, the reaction reached completion in 3 h, and a 91% yield of product **4a** was obtained.

General Procedure for the One-Pot Amide Coupling/Intramolecular Aza-Michael Addition for the Synthesis of Compounds 4. A nitrogen-flushed Schlenk flask, equipped with a magnetic stirring bar and a rubber septum, was charged with 1*H*-indole/pyrrole-2-carboxylic acid **1** (0.2 mmol, 1.0 equiv), HOBt (32 mg, 0.24 mmol, 1.2 equiv), and EDCI (46 mg, 0.24 mmol, 1.2 equiv) in dried DMSO (2 mL). After the mixture had been stirred at room temperature for 25 min, the prepared MBH-derived allylamine **2** (0.24 mmol, 1.2 equiv) and triethylamine (42 μL, 0.3 mmol, 1.5 equiv) were added immediately to the mixture. After the addition, the reaction mixture was stirred for an additional 3 h to form the amide intermediate. Under a nitrogen atmosphere, K_2CO_3 (83 mg, 0.6 mmol, 3.0 equiv) was added directly to the reaction mixture. The mixture was heated in an oil bath to 80 °C and reacted until amide intermediate **3** had been completely consumed as judged by TLC. After completion, the resulting solution was diluted with EtOAc (20 mL), washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography, and elution with petroleum ether/ethyl acetate or petroleum ether/diethyl ether furnished the desired product **4**.

*(±)-trans-Methyl 2-Methyl-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4a**).* This compound was prepared via the general procedure as a white solid (58 mg, 83% yield), eluting with petroleum ether/ethyl acetate (2:1): mp 188−189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.27−7.16 (m, 5H), 6.79 (d, J = 7.8 Hz, 2H), 6.68 (s, 1H), 4.07−4.01 (m, 1H), 3.94−3.85 (m, 1H), 3.78 (s, 3H), 3.62 (dd, J = 14.7, 5.0 Hz, 1H), 2.92 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.7, 163.8, 140.6, 138.3, 133.6, 128.8, 127.5, 126.8, 124.8, 124.4, 122.2, 120.8, 110.1, 109.2, 56.8, 52.7, 49.9, 49.5, 34.6; HRMS (ESI-TOF) calcd for $C_{21}H_{21}N_2O_3^+$ $[M + H]^+$ 349.1547, found 349.1541.

*(±)-trans-Methyl 2-Butyl-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4b**).* This compound was prepared via the general procedure as a white solid (49 mg, 63% yield), eluting with petroleum ether/ethyl acetate (10:1): mp 105−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.39−7.10 (m, 6H), 6.81 (d, J = 7.4 Hz, 2H), 6.69 (s, 1H), 3.97−3.87 (m, 1H), 3.86−3.77 (m, 1H), 3.79 (s, 3H),

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3.64 (dd, J = 14.5, 4.9 Hz, 1H), 3.41−3.30 (m, 1H), 3.26−3.17 (m, 1H), 1.55−1.30 (m, 2H), 1.25−1.05 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.8, 163.7, 140.9, 138.1, 134.0, 128.8, 127.4, 126.8, 124.9, 124.4, 122.1, 120.8, 110.1, 109.2, 56.7, 52.8, 51.6, 47.8, 47.3, 30.1, 20.0, 13.8; HRMS (ESI-TOF) calcd for $C_{24}H_{27}N_2O_3^+$ $[M + H]^+$ 391.2016, found 391.2016.

*(±)-trans-Methyl 2-(2-Methoxyethyl)-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4c**).* This compound was prepared via the general procedure as a pale yellow oil (50 mg, 64% yield), eluting with petroleum ether/ethyl acetate (2:1): ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.37−7.14 (m, 6H), 6.82 (d, J = 8.1 Hz, 2H), 6.73 (s, 1H), 4.22−4.16 (m, 1H), 4.04−3.96 (m, 1H), 3.91−3.70 (m, 2H), 3.77 (s, 3H), 3.34−3.27 (m, 1H), 3.17 (s, 3H), 3.15−3.05 (m, 1H), 2.97−2.90 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.3, 164.0, 141.2, 138.1, 133.7, 128.7, 127.2, 126.7, 124.9, 124.4, 122.1, 120.8, 110.0, 108.9, 71.4, 58.6, 56.6, 52.6, 51.4, 49.7, 47.8; HRMS (ESI-TOF) calcd for $C_{23}H_{25}N_2O_4^+$ $[M + H]^+$ 393.1809, found 393.1812.

*(±)-trans-Methyl 2-Isopropyl-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4d**).* This compound was prepared via the general procedure as a white solid (30 mg, 40% yield), eluting with petroleum ether/ethyl acetate (10:1): mp 148−149 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.34−7.14 (m, 6H), 6.81 (d, J = 8.0 Hz, 2H), 6.72 (s, 1H), 4.57−4.43 (m, 1H), 3.87−3.78 (m, 1H), 3.81 (s, 3H), 3.76−3.69 (m, 1H), 3.61−3.52 (m, 1H), 1.10 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.9, 163.8, 141.1, 138.0, 134.2, 128.8, 127.3, 126.7, 124.8, 124.4, 122.1, 120.8, 110.0, 109.3, 56.6, 53.3, 52.8, 45.0, 41.7, 19.7, 19.6; HRMS (ESI-TOF) calcd for $C_{23}H_{25}N_2O_3^+$ $[M + H]^+$ 377.1860, found 377.1852.

*(±)-trans-Methyl 2-Benzyl-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino-[1,2-a]indole-4-carboxylate (**4e**).* This compound was prepared via the general procedure as a white solid (30 mg, 35% yield), eluting with petroleum ether/ethyl acetate (10:1): mp 185−186 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 7.34−7.28 (m, 1H), 7.27−7.14 (m, 7H), 6.99 (dd, J = 7.7, 1.8 Hz, 2H), 6.75−6.71 (m, 2H), 6.67 (s, 1H), 4.66 (d, J = 14.6 Hz, 1H), 4.34 (d, J = 14.6 Hz, 1H), 3.82−3.72 (m, 1H), 3.71 (s, 3H), 3.67−3.54 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.8, 164.0, 141.0, 138.2, 136.4, 133.6, 128.9, 128.7, 128.4, 127.6, 127.4, 126.8, 124.9, 124.6, 122.2, 121.0, 110.1, 109.7, 56.7, 52.7, 51.3, 50.3, 47.0; HRMS (ESI-TOF) calcd for $C_{27}H_{25}N_2O_3^+$ $[M + H]^+$ 425.1860, found 425.1861.

*(±)-trans-Methyl 2-Butyl-5-(4-methoxyphenyl)-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4f**).* This compound was prepared via the general procedure as a pale yellow oil (54 mg, 64% yield), eluting with petroleum ether/ethyl acetate (8:1): ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 7.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.33−7.26 (m, 2H), 7.17 (t, J = 7.8 Hz, 1H), 6.80−6.69 (m, 4H), 6.63 (s, 1H), 3.95−3.78 (m, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 3.66 (dd, J = 14.4, 4.5 Hz, 1H), 3.40−3.22 (m, 2H), 1.58−1.32 (m, 2H), 1.30−1.15 (m, 2H), 0.87 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.9, 163.7, 158.7, 138.1, 134.0, 132.9, 126.8, 126.1, 124.3, 122.1, 120.8, 114.1, 110.1, 109.2, 56.3, 55.1, 52.7, 51.3, 47.8, 47.4, 30.1, 20.0, 13.8; HRMS (ESI-TOF) calcd for $C_{25}H_{29}N_2O_4^+$ $[M + H]^+$ 421.2122, found 421.2117.

*(±)-trans-Methyl 2-Butyl-5-(4-chlorophenyl)-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4g**).* This compound was prepared via the general procedure as a white solid (35 mg, 41% yield), eluting with petroleum ether/ethyl acetate (8:1): mp 131−132 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.36−7.30 (m, 1H), 7.29 (s, 1H), 7.23−7.15 (m, 3H), 6.73 (dd, J = 8.8, 0.9 Hz, 2H), 6.65 (s, 1H), 3.99−3.76 (m, 2H), 3.80 (s, 3H), 3.68−3.60 (m, 1H), 3.39−3.20 (m, 2H), 1.55−1.30 (m, 2H), 1.30−1.05 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.6, 163.5, 139.6, 138.0, 133.7, 133.4, 129.0, 126.8, 126.3, 124.6, 122.3, 121.1, 110.0, 109.6, 56.2, 52.9, 51.6, 47.8, 47.4, 30.2, 20.0, 13.8; HRMS (ESI-TOF) calcd for $C_{24}H_{26}ClN_2O_3^+$ $[M + H]^+$ 425.1626, found 425.1619.

*(±)-trans-Methyl 2-Butyl-5-(3-nitrophenyl)-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4h**) and (±)-cis-Methyl 2-Butyl-5-(3-nitrophenyl)-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4h′**).* They were prepared via the general procedure and purified by flash column chromatography (2:1 petroleum ether/diethyl ether). The total yield was 40%. The more polar *trans* isomer, **4h**, was obtained as a pale yellow oil (28 mg, 32% yield), and the less polar *cis* isomer, **4h′**, as a pale yellow oil (7 mg, 8% yield).

Spectral data for *trans* isomer **4h**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, J = 8.2, 1.2 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.51−7.49 (m, 1H), 7.39−7.26 (m, 2H), 7.20−7.15 (m, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.84 (s, 1H), 6.30 (d, J = 1.9 Hz, 1H), 4.19−4.05 (m, 1H), 3.87 (s, 3H), 3.81−3.71 (m, 1H), 3.16−2.92 (m, 2H), 2.07 (dd, J = 14.5, 5.1 Hz, 1H), 1.71−1.54 (m, 2H), 1.41−1.30 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.8, 160.9, 147.5, 139.3, 134.6, 132.0, 131.9, 131.5, 128.9, 124.5, 123.9, 123.0, 121.4, 121.2, 109.7, 98.7, 70.9, 52.9, 50.0, 40.6, 29.8, 28.5, 19.9, 13.7; HRMS (ESI-TOF) calcd for $C_{24}H_{26}N_3O_5^+$ $[M + H]^+$ 436.1867, found 436.1872.

Spectral data for *cis* isomer **4h′**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, J = 8.1, 1.2 Hz, 1H), 7.92−7.90 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.35−7.25 (m, 2H), 7.27−7.18 (m, 1H), 7.15 (dd, J = 8.3, 1.0 Hz, 1H), 6.97 (s, 1H), 6.26 (d, J = 1.5 Hz, 1H), 4.16−4.00 (m, 1H), 3.90 (s, 3H), 3.50−3.39 (m, 1H), 3.13−2.99 (m, 1H), 2.77 (dd, J = 14.5, 9.0 Hz, 1H), 2.43 (dd, J = 14.5, 4.5 Hz, 1H), 1.82−1.60 (m, 2H), 1.48−1.31 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.2, 160.4, 148.2, 140.1, 135.0, 133.2, 132.2, 132.0, 129.4, 124.4, 123.8, 123.4, 121.8, 121.3, 110.6, 99.0, 72.1, 53.1, 48.6, 40.0, 29.9, 28.7, 20.0, 13.6; HRMS (ESI-TOF) calcd for $C_{24}H_{26}N_3O_5^+$ $[M + H]^+$ 436.1867, found 436.1865.

*(±)-trans-Methyl 2-Butyl-5-(2-methoxyphenyl)-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4i**).* This compound was prepared via the general procedure as a white solid (42 mg, 50% yield), eluting with petroleum ether/ethyl acetate (8:1): mp 133−134 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.34−7.26 (m, 2H), 7.21−7.13 (m, 2H), 6.87−6.83 (m, 2H), 6.74 (t, J = 7.5 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.70−3.60 (m, 1H), 3.58−3.45 (m, 2H), 3.40−3.26 (m, 1H), 1.59−1.42 (m, 1H), 1.40−1.26 (m, 2H), 1.21−1.06 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.3, 163.7, 155.3, 138.0, 134.7, 129.8, 128.8, 126.8, 125.3, 124.2, 121.9, 121.0, 120.7, 110.5, 110.3, 109.2, 55.3, 54.0, 52.5, 52.1, 48.4, 47.5, 30.0, 19.9, 13.8; HRMS (ESI-TOF) calcd for $C_{25}H_{29}N_2O_4^+$ $[M + H]^+$ 421.2122, found 421.2122.

*(±)-trans-Methyl 2-Butyl-5-[4-(methoxycarbonyl)phenyl]-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4j**) and (±)-cis-Methyl 2-Butyl-5-[4-(methoxycarbonyl)phenyl]-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4j′**).* The compounds were prepared via the general procedure and purified by flash column chromatography (4:1 petroleum ether/diethyl ether). The total yield was 30%. The more polar *trans* isomer, **4j**, was obtained as a pale yellow oil (16 mg, 18% yield), and the less polar *cis* isomer, **4j′**, as a pale yellow oil (11 mg, 12% yield).

Spectral data for *trans* isomer **4j**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (dt, J = 8.0, 0.9 Hz, 1H), 7.70−7.65 (m, 2H), 7.45−7.38 (m, 1H), 7.37−7.31 (m, 1H), 7.26−7.19 (m, 1H), 6.92 (s, 1H), 6.79−6.72 (m, 2H), 6.25 (d, J = 1.8 Hz, 1H), 4.19−4.04 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.72−3.64 (m, 1H), 3.11−2.93 (m, 2H), 1.96 (dd, J = 14.1, 3.6 Hz, 1H), 1.69−1.53 (m, 2H), 1.44−1.29 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.9, 166.7, 160.9, 143.3, 132.2, 132.1, 131.8, 129.4, 128.6, 128.1, 124.3, 124.0, 121.3, 109.8, 98.6, 71.0, 52.7, 51.9, 50.5, 40.5, 29.8, 28.7, 19.9, 13.7; HRMS (ESI-TOF) calcd for $C_{26}H_{29}N_2O_5^+$ $[M + H]^+$ 449.2071, found 449.2070.

Spectral data for *cis* isomer **4j′**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.31 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H), 7.20 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.20−7.07 (m, 3H), 6.97 (s, 1H), 6.20 (d, J = 1.5 Hz, 1H), 4.16−3.99 (m, 1H), 3.89

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(s, 3H), 3.83 (s, 3H), 3.47−3.37 (m, 1H), 3.09−2.94 (m, 1H), 2.77 (d, J = 14.4, 8.7 Hz, 1H), 2.37 (dd, J = 14.4, 4.6 Hz, 1H), 1.71−1.63 (m, 2H), 1.44−1.35 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.4, 166.7, 160.5, 143.7, 133.1, 132.3, 131.9, 129.8, 128.6, 128.6, 124.3, 123.7, 121.2, 110.6, 98.7, 72.0, 52.9, 52.0, 49.0, 39.9, 29.8, 29.1, 19.9, 13.6; HRMS (ESI-TOF) calcd for $C_{26}H_{29}N_2O_5^+$ $[M + H]^+$ 449.2071, found 449.2071.

*(±)-trans-Methyl 2-Butyl-5-(naphthalen-2-yl)-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4k**).* This compound was prepared via the general procedure as a pale yellow solid (37 mg, 42% yield), eluting with petroleum ether/ethyl acetate (5:1): mp 139−140 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77−7.63 (m, 4H), 7.55 (d, J = 8.4 Hz, 1H), 7.44−7.37 (m, 2H), 7.45−7.26 (m, 3H), 7.22−7.13 (m, 1H), 6.93 (dd, J = 8.7, 2.1 Hz, 1H), 6.84 (s, 1H), 4.08−4.00 (m, 1H), 3.92−3.82 (m, 1H), 3.80 (s, 3H), 3.67 (dd, J = 15.0, 4.8 Hz, 1H), 3.40−3.15 (m, 2H), 1.30−1.10 (m, 2H), 1.05−0.84 (m, 2H), 0.73 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.9, 163.7, 138.3, 138.2, 134.1, 133.1, 132.5, 129.0, 128.2, 127.4, 126.9, 126.5, 126.2, 124.5, 123.8, 123.1, 122.3, 120.9, 110.2, 109.5, 57.0, 52.9, 51.5, 47.9, 47.5, 30.2, 20.0, 13.7; HRMS (ESI-TOF) calcd for $C_{28}H_{29}N_2O_3^+$ $[M + H]^+$ 441.2173, found 441.2165.

*(±)-trans-2-Butyl-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-[1,4]-diazepino[1,2-a]indole-4-carbonitrile (**4l**) and (±)-cis-2-Butyl-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carbonitrile (**4l′**).* The compounds were prepared via the general procedure and purified by flash column chromatography (2:1 petroleum ether/diethyl ether). The total yield was 86%. The more polar *trans* isomer, **4l**, was obtained as a colorless oil (31 mg, 43% yield), and the less polar *cis* isomer, **4l′**, as a colorless oil (31 mg, 43% yield).

Spectral data for *trans* isomer **4l**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.1 Hz, 1H), 7.47−7.35 (m, 2H), 7.30−7.25 (m, 1H), 7.23−7.08 (m, 3H), 6.99 (s, 1H), 6.91−6.81 (m, 2H), 6.06 (d, J = 1.6 Hz, 1H), 4.31−4.05 (m, 1H), 3.85−3.67 (m, 1H), 3.58−3.48 (m, 1H), 2.60 (dd, J = 13.8, 11.1 Hz, 1H), 1.95 (dd, J = 13.7, 3.9 Hz, 1H), 1.90−1.68 (m, 2H), 1.48−1.40 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.8, 134.9, 132.4, 132.2, 131.8, 128.8, 128.6, 127.5, 124.9, 124.4, 121.8, 117.9, 109.6, 99.5, 69.8, 41.2, 37.8, 30.3, 30.0, 20.0, 13.7; HRMS (ESI-TOF) calcd for $C_{23}H_{24}N_3O^+$ $[M + H]^+$ 358.1914, found 358.1913.

Spectral data for *cis* isomer **4l′**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.4, 1.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.41 (ddd, J = 8.4, 7.1, 1.2 Hz, 1H), 7.34−7.22 (m, 4H), 7.15−7.05 (m, 2H), 7.01 (s, 1H), 5.98 (s, 1H), 4.15−4.00 (m, 1H), 3.50 (ddd, J = 10.6, 4.5, 1.3 Hz, 1H), 3.20−3.15 (m, 1H), 2.58 (dd, J = 13.9, 4.5 Hz, 1H), 2.29 (dd, J = 13.9, 10.6 Hz, 1H), 1.82−1.60 (m, 2H), 1.50−1.35 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.5, 135.0, 133.3, 132.0, 131.6, 129.0, 128.6, 127.7, 125.1, 123.7, 121.7, 118.9, 111.9, 99.7, 71.3, 40.5, 37.1, 30.3, 30.0, 20.0, 13.6; HRMS (ESI-TOF) calcd for $C_{23}H_{24}N_3O^+$ $[M + H]^+$ 358.1914, found 358.1914.

*Methyl 2-Butyl-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4m**).* This compound was prepared via the general procedure as a pale yellow oil (32 mg, 51% yield), eluting with petroleum ether/ethyl acetate (5:1): ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.31 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.15−7.11 (m, 1H), 7.10 (d, J = 0.9 Hz, 1H), 4.77 (dd, J = 14.7, 4.5 Hz, 1H), 4.37 (dd, J = 14.7, 6.6 Hz, 1H), 3.74 (s, 3H), 3.75−3.63 (m, 1H), 3.65−3.44 (m, 2H), 3.53−3.37 (m, 1H), 3.32−3.24 (m, 1H), 1.71−1.59 (m, 2H), 1.48−1.34 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.5, 164.6, 136.9, 134.3, 126.7, 124.1, 122.1, 120.3, 109.7, 107.0, 52.4, 47.6, 47.4, 45.8, 41.9, 30.4, 20.2, 13.8; HRMS (ESI-TOF) calcd for $C_{18}H_{23}N_2O_3^+$ $[M + H]^+$ 315.1703, found 315.1705.

*(±)-trans-Methyl 2-Butyl-5-methyl-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4n**).* This compound was prepared via the general procedure as a colorless oil (34 mg, 52% yield), eluting with petroleum ether/ethyl acetate (5:1): ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.35−7.30 (m, 1H), 7.19 (s, 1H), 7.16−7.11 (m, 1H), 5.52 (q, J = 7.3 Hz, 1H), 3.73 (s, 3H), 3.70−3.66 (m, 1H), 3.65−3.59 (m, 2H), 3.57−3.47 (m, 1H), 3.17 (dd, J = 11.1, 6.3 Hz, 1H), 1.76−1.58 (m, 2H), 1.46 (d, J = 7.2 Hz, 3H), 1.50−1.37 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.8, 164.2, 137.3, 132.5, 126.8, 124.1, 122.1, 120.5, 109.8, 109.2, 52.6, 50.8, 49.8, 48.0, 47.3, 30.3, 24.2, 20.3, 13.8; HRMS (ESI-TOF) calcd for $C_{19}H_{25}N_2O_3^+$ $[M + H]^+$ 329.1860, found 329.1852.

*(±)-trans-Methyl 2-Butyl-1-oxo-5-propyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4o**).* This compound was prepared via the general procedure as a white solid (36 mg, 51% yield), eluting with petroleum ether/ethyl acetate (10:1): mp 77−78 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.35−7.28 (m, 1H), 7.20 (s, 1H), 7.16−7.10 (m, 1H), 5.24 (dd, J = 10.4, 6.0 Hz, 1H), 3.73 (s, 3H), 3.68−3.60 (m, 2H), 3.60−3.44 (m, 2H), 3.22 (dd, J = 11.7, 8.7 Hz, 1H), 1.98−1.77 (m, 2H), 1.74−1.56 (m, 2H), 1.48−1.35 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H), 0.52 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.9, 164.2, 138.6, 132.3, 126.4, 124.2, 122.1, 120.4, 110.0, 109.2, 56.1, 52.5, 49.9, 47.9, 47.3, 32.1, 30.3, 20.3, 13.8, 11.0; HRMS (ESI-TOF) calcd for $C_{20}H_{27}N_2O_3^+$ $[M + H]^+$ 343.2016, found 343.2020.

*(±)-trans-Methyl 2-Butyl-5-cyclohexyl-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4p**).* This compound was prepared via the general procedure as a pale yellow oil (36 mg, 46% yield), eluting with petroleum ether/ethyl acetate (10:1): ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.33−7.28 (m, 1H), 7.17 (s, 1H), 7.15−7.10 (m, 1H), 4.93 (d, J = 11.0 Hz, 1H), 3.72 (s, 3H), 3.68−3.52 (m, 4H), 3.48−3.40 (m, 1H), 1.99 (d, J = 11.9 Hz, 1H), 1.85−1.56 (m, 6H), 1.49−1.11 (m, 6H), 0.99 (t, J = 7.5 Hz, 3H), 0.54−0.46 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 164.2, 138.8, 132.8, 126.3, 124.1, 122.1, 120.4, 110.2, 108.7, 59.9, 52.5, 48.1, 47.2, 46.6, 44.5, 30.9, 30.3, 29.5, 26.0, 25.8, 25.3, 20.3, 13.9; HRMS (ESI-TOF) calcd for $C_{24}H_{33}N_2O_3^+$ $[M + H]^+$ 397.2486, found 397.2480.

*(±)-trans-Methyl 2-Butyl-5-cyclopropyl-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4q**).* This compound was prepared via the general procedure as a white solid (77 mg, 60% yield), eluting with petroleum ether/ethyl acetate (10:1): mp 144−145 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 7.9 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.20 (s, 1H), 7.12 (t, J = 7.5 Hz, 1H), 4.46 (d, J = 10.5 Hz, 1H), 3.71 (s, 3H), 3.70−3.50 (m, 4H), 1.81−1.60 (m, 2H), 1.48−1.38 (m, 2H), 1.36−1.24 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H), 0.69−0.56 (m, 1H), 0.43−0.32 (m, 2H), 0.22−0.15 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.8, 164.5, 137.9, 132.8, 126.7, 124.2, 122.1, 120.4, 109.5, 108.8, 60.1, 52.6, 50.6, 47.7, 47.3, 30.3, 20.3, 19.3, 13.9, 5.3, 4.2; HRMS (ESI-TOF) calcd for $C_{21}H_{27}N_2O_3^+$ $[M + H]^+$ 355.2016, found 355.2019.

*(±)-trans-Methyl 9-Methoxy-2-methyl-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4r**).* This compound was prepared via the general procedure as a white solid (56 mg, 74% yield), eluting with petroleum ether/ethyl acetate (2:1): mp 71−72 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 9.1 Hz, 1H), 7.31−7.15 (m, 4H), 7.12 (d, J = 2.5 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 7.4 Hz, 2H), 6.59 (s, 1H), 4.10−3.91 (m, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.61 (dd, J = 14.2, 4.4 Hz, 1H), 2.92 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.8, 163.8, 154.8, 140.7, 133.9, 133.6, 128.9, 127.5, 127.1, 124.8, 115.6, 111.1, 108.8, 102.7, 57.0, 55.7, 52.8, 49.9, 49.5, 34.7; HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_4^+$ $[M + H]^+$ 379.1652, found 379.1651.

*(±)-trans-Methyl 8-Methoxy-2-methyl-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4s**).* This compound was prepared via the general procedure as a white solid (59 mg, 78% yield), eluting with petroleum ether/ethyl acetate (2:1): mp 62−63 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 8.7 Hz, 1H), 7.32−7.14 (m, 4H), 6.92 (s, 1H), 6.87−6.80 (m, 3H), 6.57 (s, 1H), 4.10−3.87 (m, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.61 (dd, J = 14.5, 4.9 Hz, 1H), 2.90 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.8, 163.9, 158.3, 140.4, 139.4, 132.6, 128.9, 127.5, 124.9, 122.9, 121.0, 111.6, 109.6, 93.1, 56.8, 55.5, 52.8, 49.6, 49.5, 34.6; HRMS

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(ESI-TOF) calcd for $C_{22}H_{23}N_2O_4^+$ [M + H]$^+$ 379.1652, found 379.1647.

*(±)-trans-Methyl 2-Methyl-9-nitro-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-4-carboxylate (**4t**).* This compound was prepared via the general procedure as a light yellow solid (43 mg, 55% yield), eluting with petroleum ether/ethyl acetate (2:1): mp 222−223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 2.3 Hz, 1H), 8.21 (dd, J = 9.3, 2.3 Hz, 1H), 7.60 (d, J = 9.3 Hz, 1H), 7.40 (s, 1H), 7.33−7.20 (m, 3H), 6.82 (d, J = 7.3 Hz, 2H), 6.70 (s, 1H), 4.16−4.03 (m, 1H), 3.88−3.82 (m, 1H), 3.80 (s, 3H), 3.71 (dd, J = 15.0, 5.4 Hz, 1H), 2.93 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.4, 162.7, 142.6, 140.5, 139.1, 136.8, 129.1, 128.0, 125.9, 124.7, 119.6, 119.3, 119.3, 110.5, 57.4, 53.0, 49.4, 49.1, 34.7; HRMS (ESI-TOF) calcd for $C_{21}H_{20}N_3O_5^+$ [M + H]$^+$ 394.1397, found 394.1405.

*(±)-trans-Methyl 2-Methyl-1-oxo-5-phenyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepine-4-carboxylate (**4u**).* This compound was prepared via the general procedure as a white solid (22 mg, 37% yield), eluting with petroleum ether/ethyl acetate (2:1): mp 141−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.30 (m, 3H), 7.18−7.15 (m, 2H), 6.87 (dd, J = 3.9, 1.8 Hz, 1H), 6.43 (dd, J = 3.0, 1.8 Hz, 1H), 6.11 (dd, J = 3.9, 2.7 Hz, 1H), 5.85 (d, J = 7.5 Hz, 1H), 3.80−3.63 (m, 3H), 3.71 (s, 3H), 3.03 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.8, 164.4, 137.4, 129.0, 128.7, 128.6, 127.4, 124.5, 115.7, 108.3, 61.0, 52.5, 51.1, 50.4, 35.0; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O_3^+$ [M + H]$^+$ 299.1390, found 299.1383.

Gram-Scale Synthesis of Compound 4a. A sealed bottle was charged with 1*H*-indole-2-carboxylic acid **1a** (967 mg, 6.0 mmol, 1.0 equiv), HOBt (973 mg, 7.2 mmol, 1.2 equiv), and EDCI (1.38 g, 7.2 mmol, 1.2 equiv) in dried DMSO (30 mL). After the mixture had been stirred at room temperature for 25 min, the prepared MBH-derived allylamine **2a** (1.48 g, 7.2 mmol, 1.2 equiv) and triethylamine (1.25 mL, 9.0 mmol, 1.5 equiv) were added immediately. After the addition, the reaction mixture was stirred for an additional 3 h to form the amide intermediate. Under a nitrogen atmosphere, K_2CO_3 (2.49 g, 18 mmol, 3.0 equiv) was added directly to the reaction mixture. The mixture was heated in an oil bath to 80 °C and stirred for 20 h. After the reaction had reached completion, the resulting solution was diluted with EtOAc (100 mL), washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by column chromatography, using 2:1 petroleum ether/ethyl acetate as the eluent to afford the desired product **4a** as a white solid (1.59 g, 76% yield).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00303.

Experimental details, characterization data for all new compounds, copies of NMR spectra, and X-ray crystallographic analysis of **4a** (PDF)

Accession Codes

CCDC 2060030 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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