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Synthesis of Iodo-Indoloazepinones in an Iodine-Mediated Three-Component Domino Reaction via a Regioselective 7-*endo-dig* Iodo-Cyclization Pathway[±]

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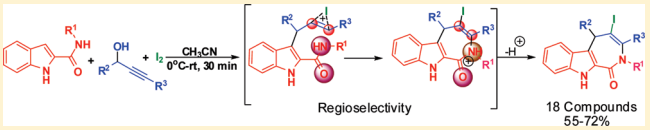
Supporting Information

ABSTRACT: An efficient and rapid synthetic strategy for the naturally occurring indoloazepinone scaffold via a three-component reaction of indole-2-carboxamides, 1,3-disubstituted propargyl alcohols, and I_2 is described. The strategy involves a C−H functionalization−alkyne activation−intramolecular hydroamidation−deprotonation domino sequence. The salient feature of this sequence is regioselective electrophilic 7-*endo-dig* iodo-cyclization during the intramolecular hydroamidation to afford a seven-membered azepinone ring annulated to the indole.



INTRODUCTION

In recent years, multicomponent domino reactions (MCRs)[1] involving condensation of three or more reactants to furnish polyheterocyclic frameworks have received increasing attention, due to their high importance in drug discovery.[2] Unlike traditional multistep processes, these reactions allow formation of several bonds via a cascade of irreversible chemical reactions in a single step without the isolation of intermediate(s). The attractive features of these reactions are simplicity, efficiency, atom economy, shortened reaction times, and diversity-oriented synthesis in one pot.[3] Although the strategy has been successfully applied to the synthesis of five-, six-, and seven-membered heterocycles,[4] the design of new multicomponent domino reactions continues to remain a challenge for organic chemists. As part of our continuing effort on the development of new routes for the synthesis of indole-based natural products[5] as well as polyheterocycles, via multicomponent[6]/multistep reaction formats,[7] we embarked on a search for a three-component domino reaction involving indole-2-carboxamides and 1,3-disubstituted propargyl alcohols as two of the reactants for the generation of indole-annulated azepine rings. In recent years, although multicomponent domino reactions for the synthesis of polyheterocycles using alkynes as one of the participating components[8] have received much attention, the use of 1,3-disubstituted propargyl alcohols, despite their versatility as building blocks,[9] has remained underexplored.[6b] Similarly, in case of the second reactant, although the synthesis of indoles[10] and C-3-functionalized indoles[11] has been extensively carried out in multicomponent format, reports on the use of functionalized indoles for the synthesis of polyheterocycles in multicomponent format are scarce,[12,6] despite being a privileged[13] pharmaceutical template.

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The motivation for our endeavor stemmed from the fact that internal alkynes tethered to an intramolecular nucleophilic center tend to undergo electrophilic 5-, 6-, or 7-endo/exo cyclizations[14] following Baldwin's cyclization principles.[15] The strategy generally involves initial activation of the alkyne either in the presence of iodine-derived electrophilic reagents[16] or in the presence of Brønsted acids/Lewis acids[17]/metals as a catalyst[18], which is then followed by the attack of a nucleophile on the electron-deficient carbon of the alkyne to afford polycyclic structures. Indeed, most of these reactions have been carried out in multistep format and their application to a multicomponent format remains limited to electrophilic 5-/6-*endo-dig* pathways.[19] To the best of our knowledge, there is no report available on the application of electrophilic 7-*endo-dig* format[20] to multicomponent domino reactions.

RESULTS AND DISCUSSION

In our endeavor to develop a three-component strategy involving an electrophilic 7-*endo-dig* cyclization pathway, we envisaged that treating bifunctional indole-2-carboxamide (with C-3 and amidic N as nucleophilic options) with the three-carbon 1,3-disubstituted propargyl alcohol derivatives in the presence of an electrophilic reagent as a third component may lead to a seven-membered ring annulated to the indole via a C−H functionalization−alkyne activation−intramolecular hydroamidation[21]−deprotonation domino sequence. To effect this one-pot domino sequence, we proposed the use of molecular iodine instead of metal catalyst, as the former may not only serve as an electrophile but also act as the third component in the multicomponent format. Such iodo-cyclizations leave an iodine atom attached to

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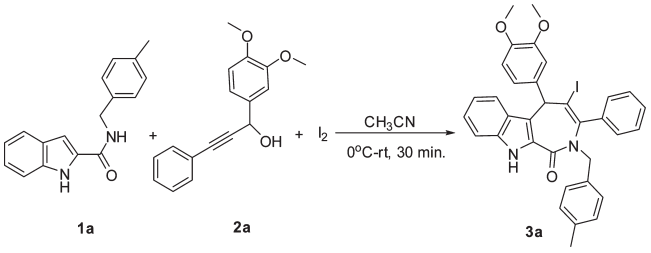
the product that is amenable to further manipulation using palladium-catalyzed coupling reactions (Scheme 1).

In this report, we describe a rapid three-component domino reaction comprising indole-2-carboxamides/1,3-disubstituted propargyl alcohols/I_2 leading to the synthesis of indoloazepinones, a skeleton present in the natural product hymenialdisine (HMD) and its annulated derivatives, which exhibit kinase-inhibiting properties.[22] In addition, the synthetically generated seven-membered azepinone templates are ubiquitously present in natural products as well as in clinically used drugs associated with diverse CNS/CVS activities and thus remain target structures of interest to synthetic chemists.[23]

In our initial experiments, we treated the mixture of *N*-(4-methylbenzyl)-1*H*-indole-2-carboxamide (**1a**; 1.0 equiv) and 1-(3,4-dimethoxyphenyl)-3-phenylprop-2-yn-1-ol (**2a**; 1.0 equiv) with molecular iodine (5.0 equiv) in acetonitrile at room temperature. The progress of the reaction was monitored by TLC, and within 30 min we observed the complete disappearance of **1a** and **2a** followed by the appearance of a fast-moving new spot on TLC. After workup and purification by column chromatography, we isolated a new product with a molecular weight of 640.9 Da in 58% isolated yield. The structure of the product was elucidated by the combined use of various homo- and heteronuclear two-dimensional NMR experiments coupled with the presence of a CO band in the FTIR at 1673 cm^{-1} that led to the identification of the 4-iodoindoloazepinone **3a** as the product arising from intramolecular hydroamidation via 7-*endo-dig* iodo-cyclization pathway. As envisaged, the halo reactant not only acted as an electrophile but also became part of the cyclized product. Recently, the synthesis of 3-benzazepinones, analogous to **3a**, has been reported[24] in multistep format via Au/Ag cocatalyzed intramolecular hydroamidation of 2-(1-alkynyl)phenylacetamide; however, the strategy involved harsh reaction conditions such as high temperature and long reaction times. Figure 1 depicts a few selected HMBC and NOESY correlations required for the confirmation of structure **3a**.

Scheme 1. MCR Involving Indole-2-carboxamide, 1,3-Disubstituted Propargyl Alcohol, and I_2



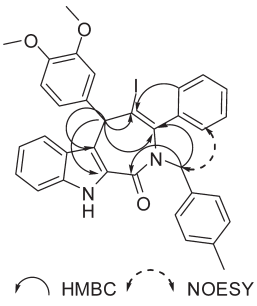


Figure 1. Some important HMBC and NOESY correlations for the confirmation of **3a**.

Mechanistically, formation of **3a** via a three-component domino process may have occurred initially via iodine-catalyzed nucleophilic substitution[6b,25] of 1-(3,4-dimethoxyphenyl)-3-phenylprop-2-yn-1-ol at the alcoholic carbon by the nucleophilic C-3 of the indole to afford the C-3 functionalized intermediate **4** (Figure 2).

The alkyne in **4** then forms an iodonium complex by coordinating with I^+, thereby enhancing the electrophilicity of the alkyne to generate intermediate **5**. The activated (electron-deficient) triple bond then undergoes nucleophilic attack by the amidic nitrogen (intramolecular hydroamidation) to form the protonated intermediate **6** via electrophilic 7-*endo-dig* iodo-cyclization. This is then followed by deprotonation of the amidic proton in the intermediate **6** to afford **3a**. Thus, the internal alkyne in the intermediate **4**, instead of undergoing 6-*exo-dig* cyclization (E1 carbon; Figure 2), preferred the 7-*endo-dig* cyclization format (E2 carbon; Figure 2) to furnish indoloazepinone **3a** as a single regioisomer. Thus, the three-component reaction proceeds via a C−H functionalization−alkyne activation−intramolecular hydroamidation−deprotonation domino sequence in one pot.

In addition, it is interesting to note that regioselectivity was also observed during the intramolecular iodo-cyclization of the intermediate **4** despite the availability of each of the two electrophilic (E1 and E2 alkyne carbons) and nucleophilic centers (O and N). In addition to **3a**, the other three possible regioisomers are structures **7** and **8**, expected to arise from 6-*exo-dig* cyclization by involving carbon E1 of the alkyne and the amidic O and N as nucleophiles and in cyclization, respectively, whereas structure **9** is likely to arise from 7-*endo* cyclization with the involvement of O as the nucleophile and alkyne carbon E2 as an electrophile (Figure 3). In contrast, **3a** is formed as a result of preferential nucleophilic attack by the amidic nitrogen at the alkyne carbon E2 instead of nucleophilic oxygen in the 7-*endo-dig* format.

Once regioselectivity and a probable mechanism were established, we then proceeded to optimize the reaction conditions with a view to enhance the yield of **3a**, and the results have been

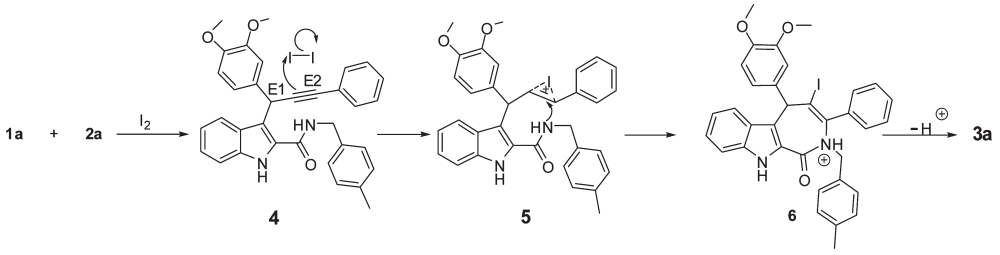


Figure 2. Plausible mechanism for the formation of **3a** from iodine-mediated three-component domino reaction.

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summarized in Table 1. Carrying out MCR at 0 °C for 30 min had a negligible effect on the yield (60%, entry 2) in comparison to the reaction carried out at room temperature (entry 1); however, increasing the reaction time to 45 min enhanced the yield to 68% (entry 3). On the basis of the observation of a slow reaction rate at lower temperatures, initiating reaction at 0 °C and then proceeding to room temperature marginally enhanced the yield to 71% (entry 4). Switching the solvent from acetonitrile to DCM, MeOH, THF, and nitromethane furnished the product in reduced yield (entries 5−8). Replacing molecular iodine with other iodo-based electrophiles such as NIS and ICl failed to furnish title compounds (entries 9 and 10), as these strongly electrophilic iodo reagents may be leading to the formation of 3-iodoindole and thus interfering with the functionalization of C-3. This gets further support from the observation that reducing the concentration of molecular iodine to 2.5 equiv from 5 equiv furnished **3a** in reduced yield (entry 11). Thus, the optimal reaction conditions could be either carrying out the reaction at 0 °C for 45 min or initiating the reaction at 0 °C and then proceeding to room temperature for 30 min. It is interesting to note that molecular iodine played an important role in our multicomponent domino reaction with three-tier involvement: (1) it catalyzed nucleophilic substitution of propargyl alcohol at the alcoholic carbon by the nucleophilic carbon C-3 of the indole,

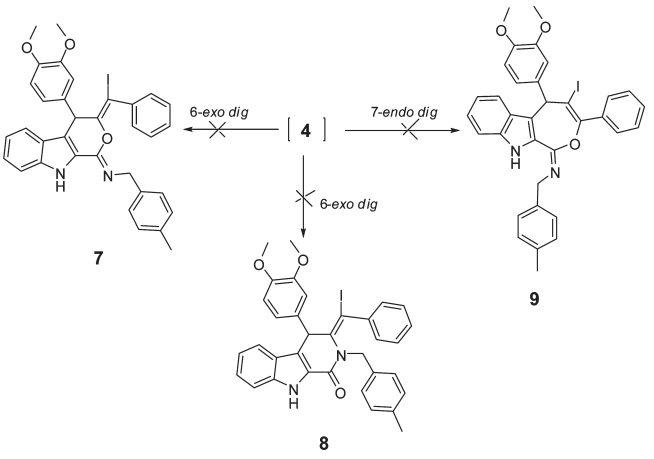

Figure 3. Three other alternatives for the formation of regioisomeric products (**7**−**9**) from the intermediate **4** via either 6-*exo*- or 7-*endo-dig* iodo-cyclizations.

(2) it acted as an electrophile and activated the alkyne in the intermediate **4** by forming an iodonium complex, thereby allowing hydroamidation, and (3) it acted as a third component in the multicomponent format and became part of the final product to afford 4-iodoindoloazepinone **3a**. The scope and limitation of the optimized reaction conditions were examined by studying the effect of different substituents on the amidic nitrogen (R^1; **1a**−**f**) and on the propargyl alcohols (R^2 and R^3; **2a**−**f**). The substrates **1a**−**f** were subjected to multicomponent reactions by treating them with the structurally diverse propargyl alcohol derivatives **2a**−**f** and I_2. The requisite propargyl derivatives can be readily prepared in quantitative yields using a procedure published in the literature.[26] In all cases, the substrates underwent electrophilic 7-*endo-dig* iodo-cyclization to furnish 18 compounds as single regioisomers in 55−72% yields (Table 2). In general, reactions were not sensitive to the electronic properties of the aliphatic amines used for derivatizing the 1*H*-indole-2-carboxylic acid. The synthesis of indole-2-carboxamides using aliphatic amines was carried out by using the standard DCC/HOBt method. Replacing aliphatic amine with aromatic amine in the 2-indolecarboxamide failed to initiate cyclization, probably due to the electronic nature of the substituent. Further, use of a substituted phenyl ring such as R^2 in **2** with both electron-donating and -withdrawing groups had no effect on the yield of 4-iodoindoloazepinone **3**; however, when aliphatic moiety was employed as R^2, the resulting propargyl alcohol derivatives **2** failed to undergo nucleophilic substitution by C-3 of the indole 2-carboxamide **1**. Similarly, employing a phenyl ring with both electron-donating and -withdrawing substituents such as R^3 had no effect on the yield but employing an aliphatic moiety as R^3 led to a slight reduction in the yield of **3** (entries 9, 11, 14, and 18). As described elsewhere,[25] propargyl alcohol ($R^2 = R^3 = H$) failed to undergo nucleophilic substitution by C-3 of the indoles to afford **3**.

CONCLUSION

In conclusion, we have developed an efficient synthetic strategy toward the synthesis of the naturally occurring indoloazepinone scaffold via a three-component reaction involving indole-2-carboxamide, 1,3-disubstituted propargyl alcohols, and I_2 under mild conditions. The strategy follows an iodine-mediated C−H functionalization−alkyne activation−intramolecular hydroamidation−deprotonation domino sequence to afford 4-iodoindoloazepinones. The salient feature of the strategy

Table 1. Optimization of Reaction Conditions for the Formation of 3a

entry	electrophilic reagent	temp (°C)	time (min)	yield of **3a** (%)[a]
1	iodine (5 equiv) in CH_3CN	room temp	30	58
2	iodine (5 equiv) in CH_3CN	0	30	60
3	iodine (5 equiv) in CH_3CN	0	45	68
4	iodine (5 equiv) in CH_3CN	0−room temp	30	71
5	iodine (5 equiv) in DCM	0−room temp	45	55[b]
6	iodine (5 equiv) in CH_3OH	0−room temp	30	27[b]
7	iodine (5 equiv) in THF	0−room temp	30	41[b]
8	iodine (5 equiv) in CH_3NO_2	0−room temp	30	20[b]
9	*N*-iodosuccinimide (5 equiv) in CH_3CN	0−room temp	60	0
10	ICl (5 equiv) in CH_3CN	0−room temp	60	0
11	iodine (2.5 equiv) in CH_3CN	0−room temp	30	30[b]

[a] Isolated yields. [b] Yields based on HPLC.

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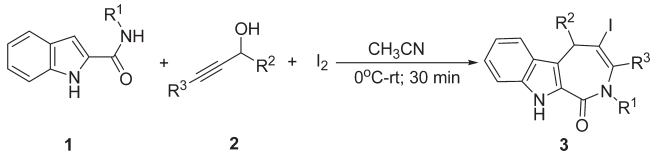
Table 2. Synthesis of 4-Iodoindoloazepinone 3 from 1, 2, and I_2 in Three-Component Domino Format



1 2 3

entry	1	R^1	2	R^2	R^3	product	yield (%)[a]
1	**1a**	4-$CH_3C_6H_4CH_2$	**2a**	3,4-$(CH_3O)_2C_6H_4$	C_6H_5	**3a**	71
2	**1a**	4-$CH_3C_6H_4CH_2$	**2b**	4-$C_2H_5OC_6H_4$	4-$CH_3C_6H_4$	**3b**	63
3	**1b**	4-$CH_3OC_6H_4CH_2$	**2c**	4-$CH_3C_6H_4$	C_6H_5	**3c**	72
4	**1b**	4-$CH_3OC_6H_4CH_2$	**2a**	3,4-$(CH_3O)_2C_6H_4$	C_6H_5	**3d**	66
5	**1b**	4-$CH_3OC_6H_4CH_2$	**2d**	4-ClC_6H_4	4-$CH_3C_6H_4$	**3e**	68
6	**1c**	C_6H_5 CH_2	**2a**	3,4-$(CH_3O)_2C_6H_4$	C_6H_5	**3f**	68
7	**1c**	$C_6H_5CH_2$	**2b**	4-$C_2H_5OC_6H_4$	4-$CH_3C_6H_4$	**3g**	64
8	**1c**	$C_6H_5CH_2$	**2d**	4-ClC_6H_4	4-$CH_3C_6H_4$	**3h**	67
9	**1c**	$C_6H_5CH_2$	**2e**	4-$C_2H_5OC_6H_4$	C_6H_9	**3i**	57
10	**1d**	$(CH_3)_3C$	**2a**	3,4-$(CH_3O)_2C_6H_4$	C_6H_5	**3j**	60
11	**1d**	$(CH_3)_3C$	**2e**	4-$C_2H_5OC_6H_4$	C_6H_9	**3k**	55
12	**1e**	C_5H_9	**2a**	3,4-$(CH_3O)_2C_6H_4$	C_6H_5	**3l**	69
13	**1e**	C_5H_9	**2b**	4-$C_2H_5OC_6H_4$	4-$CH_3C_6H_4$	**3m**	62
14	**1e**	C_5H_9	**2e**	4-$C_2H_5OC_6H_4$	C_6H_9	**3n**	56
15	**1e**	C_5H_9	**2d**	4-ClC_6H_4	4-$CH_3C_6H_4$	**3o**	63
16	**1f**	C_3H_5	**2f**	4-$C_2H_5OC_6H_4$	4-$(CH_3)_3C_6H_4$	**3p**	59
17	**1f**	C_3H_5	**2d**	4-ClC_6H_4	4-$CH_3C_6H_4$	**3q**	55
18	**1f**	C_3H_5	**2e**	4-$C_2H_5OC_6H_4$	C_6H_9	**3r**	52

[a] Isolated yields.

involves regioselective electrophilic 7-*endo-dig* iodo-cyclization wherein a nitrogen nucleophile from the amidic moiety preferentially attacks the activated alkyne rather than the oxygen nucleophile. Haloheterocycles have been documented to play an important role as intermediates, due to their ability to undergo numerous palladium-catalyzed reactions for the substitution of the halide atom. Further studies are in progress to extend the iodine-mediated MCR format to the synthesis of other haloheterocycles.

EXPERIMENTAL SECTION

I. General Information. All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with 200 and 300 MHz spectrometers for ^{1}H NMR and 50 and 75 MHz spectrometers for ^{13}C NMR. Chemical shifts δ are given in ppm relative to the residual signals of tetramethylsilane in $CDCl_3$ or deuterated solvent $CDCl_3$/DMSO-d_6 for ^{1}H and ^{13}C NMR. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m). High-resolution mass spectra were taken with a mass spectrometer. Column chromatography was performed using silica gel (100−200 mesh) as the stationary phase. All reactions were monitored by thin-layer chromatography (TLC). The purity and characterization of these compounds were further established using HR/ESI (+ve) mass spectroscopy. Melting points were measured on a capillary melting point apparatus and are uncorrected.

II. General Experimental Procedure for Indole-2-carboxamides 1a−f. To a stirred solution of indole-2-carboxalic acid (1.0 mmol) in THF at 0 °C was added DCC (1.0 mmol) and HOBT (1.0 mmol), and the reaction mixture was stirred for 30 min. This was followed by addition of the corresponding amine (1.0 mmol) to the reaction mixture, and stirring was continued at room temperature for 24 h. After this the reaction mixture was passed through a bed of Celite, and the filtrate was evaporated to dryness. The oily residue was extracted with EtOAc (50 mL × 3) and sequentially washed with 5% $NaHCO_3$ and 5% $KHSO_4$ and finally with brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The crude product so obtained was purified by triturating with ethanol to afford **1a**−**f**.

N-(4-Methylbenzyl)-1H-indole-2-carboxamide (***1a***): white solid; yield 93%; mp >250 °C; FT-IR (KBr) 2926, 1637, 1564, 1413, 1309, 1012 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.63 (s, 1H), 9.02 (s, 1H), 7.63−7.04 (m, 9H), 4.50 (s, 2H), 2.27 (s, 3H), ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ 161.2, 136.6, 135.9, 131.8, 128.9, 127.3, 123.3, 121.5, 119.8, 112.4, 102.7, 42.0, 20.7 ppm; exact mass for $C_{17}H_{16}N_2O$ 264.13 [M], HR-MS (ESI) found 265.134 07 [M + H]$^+$.

N-(4-Methoxybenzyl)-1H-indole-2-carboxamide (***1b***): white solid; yield 89%; mp >250 °C; FT-IR (KBr) 3281, 1628, 1546, 1512, 1244, 1028 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.58 (s, 1H), 8.96 (t, J = 5.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.29−7.13 (m, 4H), 7.06−6.96 (m, 1H), 6.88 (d, J = 8.6 Hz, 2H), 4.43 (d, J = 5.9 Hz, 2H), 3.72 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.2, 158.4, 136.6, 131.8, 131.7, 128.7, 127.3, 123.5, 121.6, 119.9, 113.8, 112.4, 102.8, 55.2, 41.8 ppm; exact mass for $C_{17}H_{16}N_2O_2$ 280.12 [M], HR-MS (ESI) found 281.129 00 [M + H]$^+$.

N-Benzyl-1H-indole-2-carboxamide (***1c***): white solid; yield 95%; mp 194−196 °C (lit.[27] mp 192−193 °C); FT-IR (KBr) 3269, 2933, 1633, 1545, 1418, 1312 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.61 (s, 1H), 9.05 (t, J = 6.0 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.35−7.14 (m, 7H), 7.03 (t, J = 7.2 Hz, 1H), 4.53 (d, J = 6.0 Hz,

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2H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ 161.2, 139.7, 136.6, 131.7, 128.4, 127.3, 127.2, 126.8, 123.4, 121.4, 119.8, 112.4, 102.7, 42.3 ppm; exact mass for $C_{16}H_{14}N_2O$ 250.11 [M], HR-MS (ESI) found 251.118 44 $[M + H]^+$.

*N-(tert-Butyl)-1H-indole-2-carboxamide (**1d**):* white solid; yield 78%; mp 108−110 °C; FT-IR (KBr) 3230, 2829, 1635, 1542, 1452 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.44 (s, 1H), 7.71 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.19−7.11 (m, 2H), 7.05−6.97 (m, 1H), 1.40 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.8, 136.3, 132.7, 127.1, 123.1, 121.4, 119.6, 112.2, 102.8, 50.9, 28.8 ppm; exact mass for $C_{13}H_{16}N_2O$ 216.13 [M], HR-MS (ESI) found 217.13409 $[M + H]^+$.

*N-Cyclopentyl-1H-indole-2-carboxamide (**1e**):* white solid; yield 86%; mp 220−224 °C; FT-IR (KBr) 3252, 2951, 1619, 1558, 1417, 1310, 1225 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.55 (s, 1H), 8.29 (d, J = 7.4 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.41−7.39 (m, 1H), 7.20−7.11 (m, 2H), 7.05−6.97 (m, 1H), 4.30−4.20 (m, 1H), 1.98−1.52 (m, 8H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ 160.7, 136.4, 132.1, 127.1, 123.1, 121.4, 119.6, 112.3, 102.7, 50.6, 32.2, 23.4 ppm; exact mass for $C_{14}H_{16}N_2O$ 228.13 [M], HR-MS (ESI) found 229.13409 $[M + H]^+$.

*N-Cyclopropyl-1H-indole-2-carboxamide (**1f**):* white solid; yield 83%; mp 220−224 °C; FT-IR (KBr) 3416, 2926, 1626, 1539, 1420, 1310, 1267 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.51 (s, 1H), 8.43 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.18−6.99 (m, 3H), 2.87−2.84 (m, 1H), 0.72 (d, J = 4.7 Hz, 2H), 0.60 (d, J = 4.7 Hz, 2H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ 162.5, 136.5, 131.8, 127.2, 123.4, 121.6, 119.8, 112.4, 102.7, 22.8, 5.9 ppm; exact mass for $C_{12}H_{12}N_2O$ 200.09 [M], HR-MS (ESI) found 201.10279 $[M + H]^+$.

III. General Experimental Procedure for 1,3-Disubstituted Propargyl Alcohols 2a−f. To a degassed solution of terminal alkyne (1.0 mmol) in dry THF at −78 °C under a nitrogen atmosphere was added *n*-BuLi (1.6 M solution in hexane, 2.0 mmol), and the reaction mixture was stirred for 0.5 h at −78 °C. Next the corresponding aldehyde (1.0 mmol) was added to the reaction mixture, and after completion of the reaction as analyzed by TLC, the reaction mixture was diluted with an aqueous solution of ammonium chloride. The mixture was extracted with EtOAc (20 mL × 3), and the separated organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. The crude product so obtained was purified on a silica gel column using hexane/ethyl acetate (1/19, v/v) as eluent to afford **2a−f**.

*1-(3,4-Dimethoxyphenyl)-3-phenylprop-2-yn-1-ol (**2a**):* orange solid; yield 83%; mp 82−83 °C; FT-IR (KBr) 3429, 2959, 1514, 1263, 1141, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.45 (m, 2H), 7.33−7.31 (s, 3H), 7.17−7.15 (m, 2H), 6.89−6.86 (m, 1H), 5.64 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.27 (brs, 1H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149, 133.5, 131.8, 128.7, 128.4, 122.6, 119.2, 111.1, 110.1, 89.0, 86.6, 64.9, 56.0, 55.9 ppm; exact mass for $C_{17}H_{16}O_3$ 268.11 [M], HR-MS (ESI) found 269.12807 $[M + H]^+$.

*1-(4-Ethoxyphenyl)-3-(4-methylphenyl)prop-2-yn-1-ol (**2b**):* white oil; yield 76%; FT-IR (neat) 3452, 2835, 1761, 1612, 1011 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.60 (s, 1H), 4.01 (q, J = 6.9 Hz, 2H), 2.52 (s, 1H), 2.32 (s, 3H), 1.39 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.0, 138.6, 133.1, 131.7, 129.1, 128.2, 119.6, 114.6, 88.5, 86.6, 64.7, 63.6, 21.5, 14.8 ppm; exact mass for $C_{18}H_{18}O_2$ 266.13 [M], HR-MS (ESI) found 267.01272 $[M + H]^+$.

*1-(4-Methylphenyl)-3-phenylprop-2-yn-1-ol (**2c**):* white oil; yield 78%; FT-IR (neat) 3401, 3021, 1632, 1444, 1291, 1215, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.1 Hz, 1H), 7.72−7.69 (m, 1H), 7.51−7.33 (m, 7H), 5.68 (s, 1H), 2.39 (s, 3H), 2.37 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.9, 131.7, 129.3, 128.7. 128.3, 126.8, 122.6, 89.2, 86.4, 64.8, 21.2 ppm; exact mass for $C_{16}H_{14}O$ 222.10 [M], HR-MS (ESI) found 223.10226 $[M + H]^+$.

*1-(4-Chlorophenyl)-3-(4-methylphenyl)prop-2-yn-1-ol (**2d**):* white solid; yield 80%; mp 78−80 °C; FT-IR (KBr) 3032, 2923, 1489, 1091, 1016, 818 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.36−7.33 (m, 4H), 7.53 (d, J = 8.2 Hz, 2H), 5.64 (s, 1H), 2.40 (brs, 1H), 2.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 138.9, 134.1, 131.7, 129.2, 128.7, 128.2, 119.2, 87.8, 87.2, 64.4, 21.5 ppm; exact mass for $C_{16}H_{13}ClO$ 256.07 [M], HR-MS (ESI) found 257.14505 $[M + H]^+$.

*3-Cyclohex-1-en-1-yl-1-(4-ethoxyphenyl)prop-2-yn-1-ol (**2e**):* white oil; yield 76%; FT-IR (neat) 2914, 1737, 1413, 1012 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.15 (s, 1H), 5.50 (d, J = 5.6 Hz, 1H), 4.01 (q, J = 6.9 Hz, 2H), 2.18−2.08 (m, 5H), 1.62−1.57 (m, 4H), 1.40 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ 158.9, 135.5, 133.4, 128.1, 120.2, 114.5, 114.4, 88.3, 86.5, 64.6, 63.6, 29.2, 25.7, 22.3, 21.5, 14.8 ppm; exact mass for $C_{17}H_{20}O_2$ 256.15 [M], HR-MS (ESI) found 257.15415 $[M + H]^+$.

*3-[4-(tert-Butyl)phenyl]-1-(3,4-dimethoxyphenyl)prop-2-yn-1-ol (**2f**):* white oil; yield 85%; FT-IR (neat) 3032, 2923, 1489, 1091, 1016, 818 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.32 (m, 4H), 7.17−7.13 (s, 1H), 6.88−6.81 (s, 2H), 5.63 (s, 1H), 3.83 (s, 3H), 3.87 (s, 3H), 1.79 (s, 1H), 1.30 (s, 9H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 149.2, 131.5, 125.4, 119.2, 118.3, 111.1, 111.0, 110.9, 110.1, 109.1, 88.4, 86.6, 64.9, 56.0, 55.9, 34.8, 31.2 ppm; exact mass for $C_{21}H_{24}O_3$ 324.17 [M], HR-MS (ESI) found 325.02504 $[M + H]^+$.

IV. General Procedure for Synthesis of the Iodo-Indoloazepinone Derivatives 3a−r. To a solution of indole-2-carboxamide **1** (0.200 g, 0.73 mmol) and 1,3-diphenylprop-2-yn-1-ol **2** (0.73 mmol) in acetonitrile (10 mL) was added iodine (5.0 mmol) at 0 °C, and the reaction mixture was stirred for 30 min at room temperature. After completion of the reaction as analyzed by TLC, the reaction mixture was diluted with saturated sodium thiosulfate solution and extracted with EtOAc (20 mL × 3). The separated organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. The crude product so obtained was purified on a silica gel column using hexane/ethyl acetate (1/19, v/v) as eluent to afford 4-iodoindoloazepinones **3a−r**.

*2-(4-Methylbenzyl)-3-phenyl-4-iodo-5-(3,4-dimethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (**3a**):* yellow solid; yield 71%; mp 96−98 °C; FT-IR (KBr) 3054, 2931, 1673, 1510, 1449, 1325, 1258, 1022 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (brs, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.31−7.21 (m, 7H), 7.12−6.93 (m, 7H), 6.78 (d, J = 8.3 Hz, 1H), 5.87 (s, 1H), 4.26 (q, J = 14.8 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 2.30 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 149.2, 148.4, 145.8, 140.2, 138.0, 136.8, 136.2, 132.3, 129.7, 129.0, 128.3, 128.2, 127.8, 125.3, 124.8, 123.9, 120.6, 120.1, 119.9, 118.4, 112.2, 111.3, 110.8, 84.2, 55.9, 55.8, 49.5, 44.5, 21.2 ppm; exact mass for $C_{34}H_{29}IN_2O_3$ 640.12 [M], HR-MS (ESI) found 641.1393 $[M + H]^+$.

*2-(4-Methylbenzyl)-3-(4-methylphenyl)-4-iodo-5-(4-ethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (**3b**):* yellow solid; yield 63%; mp 104−106 °C; FT-IR (KBr) 3289, 2928, 1605, 1438, 1245, 1174, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (brs, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.39−7.35 (m, 4H), 7.24−7.07 (m, 5H), 6.98 (s, 4H), 6.82−6.79 (m, 2H), 5.60 (s, 1H), 4.48 (q, J = 14.8 Hz, 2H), 3.98 (q, J = 6.9 Hz, 2H), 2.36 (s, 3H), 2.27 (s, 3H), 1.40 (t, J = 8.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 151.1, 148.2, 139.1, 136.6, 136.3, 136.1, 135.6, 132.6, 129.2, 128.9, 128.8, 128.2, 127.9, 126.7, 125.8, 124.9, 121.2, 120.3, 119.2, 114.5, 111.8, 90.6, 63.4, 53.5, 50.6, 21.4, 21.1, 14.9 ppm; exact mass for $C_{35}H_{31}IN_2O_2$ 638.14 [M], HR-MS (ESI) found 639.1474 $[M + H]^+$.

*2-(4-Methoxybenzyl)-3-phenyl-4-iodo-5-(4-methylphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (**3c**):* yellow solid; yield 72%; mp 102−104 °C; FT-IR (KBr) 3056, 2946, 1680, 1544, 1231, 1120, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (brs, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.42−7.36 (m, 4H), 7.31−7.21 (m, 5H), 7.11−7.07 (m,

3H), 6.96 (d, J = 8.6 Hz, 2H), 6.73 (d, J = 8.6 Hz, 2H), 5.88 (s, 1H), 4.28 (s, 2H), 3.74 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.5, 158.1, 145.9, 140.2, 138.1, 137.1, 136.8, 131.9, 129.7, 129.6, 129.1, 128.3, 128.2, 127.6, 125.4, 123.7, 120.7, 120.2, 118.8, 112.3, 84.3, 55.4, 49.1, 44.7, 21.2 ppm; exact mass for $C_{33}H_{27}IN_2O_2$ 610.11 [M], HR-MS (ESI) found 611.1179 $[M + H]^+$.

2-(4-Methoxybenzyl)-3-phenyl-4-iodo-5-(3,4-dimethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3d***): yellow solid; yield 66%; mp 103−105 °C; FT-IR (KBr) 3031, 2924, 1663, 1442, 1224, 1046 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.67 (brs, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.44−7.22 (m, 7H), 7.14−7.07 (m, 2H), 6.98−6.90 (m, 3H), 6.78−6.70 (m, 3H), 5.88 (s, 1H), 4.26 (s, 2H), 3.77 (s, 3H), 3.74 (s, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.7, 149.3, 149.3, 148.5, 147.8, 139.9, 138.6, 131.8, 130.8, 129.5, 129.2, 128.4, 128.3, 126.2, 124.4, 122.3, 120.9, 120.3, 119.9, 113.8, 112.6, 111.4, 110.7, 85.3, 55.9, 55.3, 48.5, 44.4 ppm; exact mass for $C_{34}H_{29}IN_2O_4$ 656.12 [M], HR-MS (ESI) found 657.1264 $[M + H]^+$.

2-(4-Methoxybenzyl)-3-(4-methylphenyl)-4-iodo-5-(4-chlorophenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3e***): yellow solid; yield 68%; mp 95−97 °C; FT-IR (KBr) 3330, 2924, 1659, 1437, 1245, 1081 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.22 (brs, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.36−7.27 (m, 7H), 7.15 (d, J = 7.9 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 5.92 (s, 1H), 4.28 (d, J = 14.5 Hz, 2H), 3.76 (s, 3H), 2.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 150.2, 147.7, 139.3, 138.9, 137.4, 136.4, 133.7, 129.6, 129.5, 129.2, 129.1, 129.0, 128.9, 128.8, 127.3, 123.9, 121.5, 120.3, 113.9, 113.1, 87.9, 55.3, 47.8, 44.3, 21.4 ppm; exact mass for $C_{33}H_{26}ClIN_2O_2$ 644.07 [M], HR-MS (ESI) found 645.0809 $[M + H]^+$.

2-Benzyl-3-phenyl-4-iodo-5-(3,4-dimethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3f***): brown solid; yield 68%; mp 112−114 °C; FT-IR (KBr) 3058, 2934, 1673, 1509, 1447, 1257, 1138, 1076 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (brs, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.44−7.18 (m, 10H), 7.14−7.00 (m, 4H), 6.96−6.93 (m, 1H), 6.77 (d, J = 8.2 Hz, 1H), 5.88 (s, 1H), 4.30 (q, J = 14.8 Hz, 2H), 3.83 (s, 3H), 3.78 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.2, 149.2, 148.5, 145.8, 140.2, 139.9, 138.0, 132.3, 129.7, 129.3, 128.4, 128.2, 127.9, 126.7, 125.4, 124.8, 123.9, 120.7, 120.2, 120.0, 118.5, 112.2, 111.3, 110.9, 84.3, 55.9, 49.8, 44.5 ppm; exact mass for $C_{33}H_{27}IN_2O_3$ 626.11 [M], HR-MS (ESI) found 627.1111 $[M + H]^+$.

2-Benzyl-3-(4-methylphenyl)-4-iodo-5-(4-ethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3g***): yellow solid; yield 64%; mp 101−103 °C; FT-IR (KBr) 3270, 2925, 1604, 1440, 1244, 1173, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (brs, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.41−7.13 (m, 14H), 6.82 (d, J = 8.7 Hz, 2H), 5.60 (s, 1H), 4.50 (q, J = 15.3 Hz, 2H), 3.98 (q, J = 6.9 Hz, 2H), 2.37 (s, 3H), 1.38 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.1, 151.2, 148.1, 139.8, 139.2, 136.3, 135.7, 132.6, 129.3, 128.9, 128.4, 128.3, 127.9, 126.8, 126.7, 125.9, 125.1, 121.2, 120.4, 119.4, 114.6, 111.8, 90.6, 63.5, 53.6, 50.9, 21.5, 15.0 ppm; exact mass for $C_{34}H_{29}IN_2O_2$ 624.13 [M], HR-MS (ESI) found 625.1324 $[M + H]^+$.

2-Benzyl-3-(4-methylphenyl)-4-iodo-5-(4-chlorophenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3h***): brown solid; yield 67%; mp 109−111 °C; FT-IR (KBr) 2925, 1676, 1488, 1218, 1155, 1087 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (brs, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.39−7.30 (m, 4H), 7.28−7.24 (m, 1H), 7.21−7.10 (m, 6H), 7.08−6.99 (m, 5H), 5.82 (s, 1H), 4.28 (s, 2H), 2.26 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 150.8, 148.7, 147.4, 138.9, 138.4, 138.0, 136.8, 133.4, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.4, 127.9, 126.9, 124.4, 121.0, 120.0, 112.6, 86.2, 49.3, 44.4, 21.4 ppm; exact mass for $C_{32}H_{24}ClIN_2O$ 614.06 [M], HR-MS (ESI) found 615.0688 $[M + H]^+$.

2-Benzyl-3-cyclohex-1-enyl-4-iodo-5-(4-ethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3i***): yellow solid; yield 57%; mp 113−115 °C; FT-IR (KBr) 2927, 1660, 1487, 1440, 1218, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.94 (brs, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.52 (t, J = 8.0 Hz, 2H), 7.43−7.38 (m, 2H), 7.31−7.23 (m, 3H), 7.19−7.16 (m, 3H), 6.75 (d, J = 8.7 Hz, 2H), 5.93 (s, 1H), 5.58 (s, 1H), 4.74 (s, 2H), 3.99 (q, J = 6.9 Hz, 2H), 2.13−1.62 (s, 8H), 1.40 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 153.2, 148.7, 139.9, 136.5, 136.3, 132.8, 132.1, 128.4, 128.1, 127.9, 126.8, 126.7, 125.8, 124.9, 121.5, 120.3, 119.3, 114.8, 114.5, 111.8, 88.6, 63.4, 52.8, 50.6, 25.9, 24.9, 22.4, 21.8, 14.9 ppm; exact mass for $C_{33}H_{31}IN_2O_2$ 614.14 [M], HR-MS (ESI) found 615.1493 $[M + H]^+$.

2-tert-Butyl-3-phenyl-4-iodo-5-(3,4-dimethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3j***): brown solid; yield 60%; mp 106−108 °C; FT-IR (KBr) 3071, 2926, 1598, 1517, 1260, 1134, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (brs, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.32−7.20 (m, 7H), 7.11−6.96 (m, 3H), 6.77 (d, J = 8.3 Hz, 1H), 5.85 (s, 1H), 3.83 (s, 6H), 0.97 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 149.1, 148.2, 142.2, 141.2, 137.6, 132.9, 129.7, 129.3, 128.3, 128.1, 128.0, 124.8, 124.7, 124.6, 120.3, 119.9, 119.8, 117.0, 111.9, 111.2, 110.5, 81.9, 55.8, 54.0, 44.1, 29.7 ppm; exact mass for $C_{30}H_{29}IN_2O_3$ 592.12 [M], HR-MS (ESI) found 593.1291 $[M + H]^+$.

2-tert-Butyl-3-cyclohex-1-enyl-4-iodo-5-(4-ethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3k***): yellow solid; yield 55%; mp 98−100 °C; FT-IR (KBr) 3253, 2928, 1718, 1631, 1505, 1442, 1244, 1075 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (brs, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.47−7.40 (m, 1H), 7.34−7.25 (m, 4H), 7.11−7.06 (m, 1H), 6.80 (d, J = 8.6 Hz, 2H), 5.84 (s, 1H), 5.72 (s, 1H), 3.98 (q, J = 7.0 Hz, 2H), 2.29−2.09 (m, 4H), 1.74−1.72 (m, 4H), 1.58−1.44 (s, 9H), 1.38 (t, J = 7.0 Hz, 2H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 148.4, 143.4, 137.7, 137.5, 136.6, 132.5, 128.5, 127.9, 125.4, 124.8, 124.7, 122.5, 120.3, 120.0, 117.8, 114.8, 114.6, 112.0, 89.3, 63.4, 54.3, 43.6, 30.3, 29.0, 27.6, 25.3, 22.3, 14.9 ppm; exact mass for $C_{30}H_{33}IN_2O_2$ 580.16 [M], HR-MS (ESI) found 581.1667 $[M + H]^+$.

2-Cyclopentyl-3-phenyl-4-iodo-5-(3,4-dimethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3l***): yellow solid; yield 69%; mp 99−101 °C; FT-IR (KBr) 3257, 2938, 1638, 1568, 1447, 1261, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (brs, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.40−7.21 (m, 7H), 7.13−7.08 (m, 2H), 6.93 (dd, J = 8.2, 1.8 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 5.85 (s, 1H), 3.83 (s, 7H), 1.76−1.57 (m, 2H), 2.29−2.09 (m, 4H), 1.74−1.72 (m, 2H), ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.4, 149.2, 148.4, 144.9, 140.3, 137.9, 132.5, 129.7, 128.0, 127.9, 125.1, 124.8, 124.0, 120.0, 119.8, 117.9, 112.2, 111.3, 110.9, 83.6, 56.5, 55.9, 44.4, 34.2, 34.0, 24.2, 24.1 ppm; exact mass for $C_{31}H_{29}IN_2O_3$ 604.12 [M], HR-MS (ESI) found 605.1272 $[M + H]^+$.

2-Cyclopentyl-3-(4-methylphenyl)-4-iodo-5-(4-ethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3m***): yellow solid; yield 62%; mp 107−109 °C; FT-IR (KBr) 3342, 2944, 2589, 1672, 1535, 1053, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (brs, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.6 Hz, 2H), 7.29−7.19 (m, 4H), 7.11−7.03 (m, 3H), 6.80 (d, J = 8.6 Hz, 2H), 5.84 (s, 1H), 3.99−3.86 (m, 3H), 2.33 (s, 3H), 1.77−1.44 (s, 5H). 1.35 (t, J = 6.9 Hz, 3H), 1.25−1.19 (m, 2H), 0.89−0.85 (m, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.3, 149.5, 147.5, 138.5, 138.1, 137.1, 131.5, 129.4, 128.6, 125.9, 124.4, 122.2, 120.8, 120.3, 114.8, 112.5, 85.2, 63.4, 56.5, 44.0, 33.7, 33.4, 24.0, 21.3, 14.9 ppm; exact mass for $C_{32}H_{31}IN_2O_2$ 602.14 [M], HR-MS (ESI) found 603.1529 $[M + H]^+$.

2-Cyclopentyl-3-cyclohex-1-enyl-4-iodo-5-(4-ethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3n***): yellow solid; yield 56%; mp 103−105 °C; FT-IR (KBr) 3248, 2926, 1630, 1507, 1245, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (brs, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.36−7.25 (m, 5H), 6.82 (d, J = 8.7 Hz, 2H), 5.90 (s, 1H), 5.49 (s, 1H), 4.42-.4.35 (m, 1H), 4.00 (q, J = 6.9 Hz, 2H), 2.32−2.17 (m, 4H), 1.76−1.00 (m, 13H), 0.96−0.89 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 153.4, 147.0, 136.5, 136.1, 132.8, 131.8, 128.2, 126.9, 126.1, 124.8, 120.9, 119.3, 114.5, 111.7, 88.6, 63.4,

56.9, 52.9, 34.9, 34.3, 29.8, 25.9, 25.0, 22.5, 21.9, 14.9 ppm; exact mass for $C_{31}H_{33}IN_2O_2$ 592.16 [M], HR-MS (ESI) found 593.1519 $[M + H]^+$.

2-Cyclopentyl-3-(4-methylphenyl)-4-iodo-5-(4-chlorophenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3o***): white solid; yield 63%; mp 110−112 °C; FT-IR (KBr) 3212, 2921, 1656, 1489, 1331, 1219, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (brs, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.45−7.38 (m, 4H), 7.34−7.28 (m, 4H), 7.16−7.11 (m, 3H), 5.89 (s, 1H), 3.85−3.84 (m, 1H), 2.37 (s, 3H), 1.81−0.85 (m, 8H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.3, 145.4, 138.5, 138.2, 138.0, 137.1, 133.3, 129.6, 129.1, 129.0, 128.6, 128.3, 125.5, 124.6, 123.6, 120.8, 119.9, 117.9, 112.3, 85.1, 56.3, 44.3, 34.0, 33.8, 24.1, 24.0, 21.4 ppm; exact mass for $C_{30}H_{26}ClIN_2O$ 592.08 [M], HR-MS (ESI) found 593.1496 $[M + H]^+$.

2-Cyclopropyl-3-(4-tert-butylphenyl)-4-iodo-5-(3,4-dimethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3p***): yellow oil; yield 59%; FT-IR (neat) 3342, 2944, 2589, 1672, 1535, 1053, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (brs, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.43−7.20 (m, 7H), 7.13 (t, J = 7.2 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.88 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.05 (s, 1H), 1.30 (s, 9H), 0.71 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.2, 150.0, 149.1, 148.4, 147.0, 137.9, 136.9, 132.2, 129.5, 125.3, 124.9, 124.7, 123.6, 120.7, 120.1, 119.8, 118.1, 112.1, 111.3, 111.1, 84.9, 55.9, 55.8, 44.3, 34.6, 31.3, 28.3, 8.5, 8.4 ppm; exact mass for $C_{33}H_{33}IN_2O_3$ 632.15 [M], HR-MS (ESI) found 633.1590 $[M + H]^+$.

2-Cyclopropyl-3-(4-methylphenyl)-4-iodo-5-(4-chlorophenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3q***): yellow solid; yield 55%; mp 116−118 °C; FT-IR (KBr) 3192, 2923, 1623, 1486, 1443, 1270, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.29 (brs, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.47−7.28 (m, 7H), 7.23−7.13 (m, 4H), 5.88 (s, 1H), 3.09−3.05 (s, 1H), 2.37 (s, 3H), 0.88−0.60 (s, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.2, 146.8, 138.4, 138.1, 137.9,136.9,133.3. 131.8, 129.8, 129.1, 129.0, 128.6, 125.5, 124.7, 123.7, 120.8, 119.9, 117.5, 112.3, 85.8, 44.6, 29.8, 21.4, 8.8, 8.7 ppm; exact mass for $C_{28}H_{22}ClIN_2O$ 564.05 [M], HR-MS (ESI) found 565.0527 $[M + H]^+$.

2-Cyclopropyl-3-cyclohex-1-enyl-4-iodo-5-(4-ethoxyphenyl)-5,10-dihydroazepino[3,4-b]indol-1(2H)-one (***3r***): yellow oil; yield 52%; FT-IR (neat) 3247, 2927, 1662, 1503, 1441, 1244, 1174, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.54 (brs, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.39−7.25 (m, 4H), 7.09 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 8.6 Hz, 2H), 5.86 (s, 1H), 5.70 (s, 1H), 2.95 (q, J = 6.9 Hz, 2H), 3.51 (t, J = 5.2 Hz, 2H), 2.19−2.06 (m, 4H), 1.70−1.57 (m, 4H), 1.36 (t, J = 6.9 Hz, 2H), 0.86−0.85 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 148.5, 138.2, 136.9, 131.8, 128.7, 125.5, 124.8, 123.2, 120.7, 120.2, 119.2, 114.7, 112.4, 90.3, 63.5, 43.6, 29.8, 28.4, 28.0, 25.6, 22.8, 22.1, 14.9, 8.4 ppm; exact mass for $C_{29}H_{29}IN_2O_2$ 564.13 [M], HR-MS (ESI) found 565.1327 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information. Figures giving ^1H and ^{13}C NMR and HRMS spectra of all final compounds and 2D spectra of **3a**,**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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