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Gold-catalyzed Rapid Construction of Nitrogen-containing Heterocyclic Compound Library with Scaffold Diversity and Molecular Complexity

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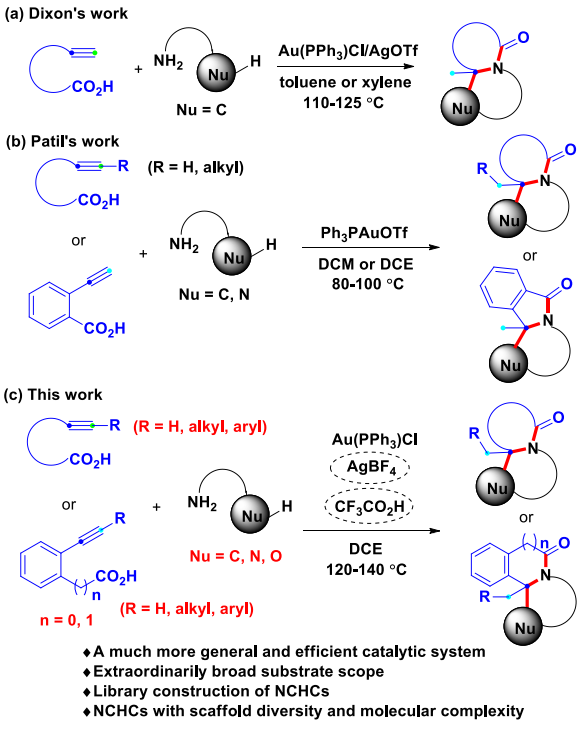
Abstract. 1,3-unsubstituted 2-(1*H*-indol-2-yl)ethanamines were employed for the first time to react with alkynoic acids (AAs) to achieve gold-catalyzed highly selective cascade reactions to furnish novel indole-fused skeletons. Furthermore, with this powerful gold catalytic system, a library of indole/pyrrole/thiophene/benzene/naphthalene/pyridine-based nitrogen-containing heterocyclic compounds (NCHCs) with scaffold diversity and molecular complexity was constructed rapidly using various amine nucleophiles (ANs) and diverse AAs as the building blocks. This general protocol features excellent selectivity, extraordinarily broad substrate scope, readily available inputs, good to high yields, high bond-forming efficiency, and step economy, thus providing a facile and efficient access to a variety of valuable nitrogen-containing heterocycles.

Keywords: Alkynes; Amines; Cascade reaction; Compound library; Gold; Scaffold diversity.

Introduction

Gold catalysts have attracted considerable attention[1] in cascade reactions because of their outstanding performance in activating alkynes,[2] alkenes,[3] allenes,[4] *etc*. Remarkably, alkynoic acids (AAs) are widely employed as building blocks in gold-catalyzed cascade reactions to construct nitrogen-containing heterocyclic compounds (NCHCs) since Dixon's pioneering work (Scheme 1a).[5] They revealed that linear aliphatic AAs underwent a cascade reaction smoothly with amine nucleophiles (ANs) carrying a nucleophilic C atom to provide indole- or pyrrole-fused heterocycles under the catalysis of $AuPPh_3Cl/AgOTf$. Soon afterwards, the group of Patil further broadened the substrate scope of this cascade reaction using a similar catalytic system (Scheme 1b).[6] They proved cyclic aromatic AA, namely 2-ethynylbenzoic acid, and ANs carrying a nucleophilic N atom were also suitable substrates. In our ongoing efforts to develop facile approaches for the construction of nitrogen-containing heterocyclic scaffolds *via* gold catalysis,[7] we herein extensively study the cascade reaction between diverse AAs and ANs, and develop a much more general and efficient



Scheme 1. Cascade reactions between AAs and ANs.

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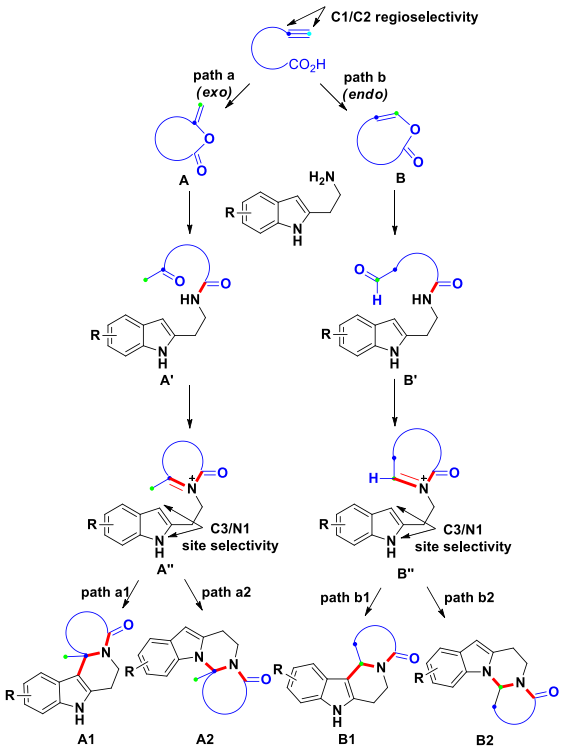
catalytic system, which tolerates a much more broader substrate scope of AAs and ANs, and therefore allows the rapid construction of NCHC library with scaffold diversity and molecular complexity (Scheme 1c). We found the combination of $Au(PPh_3)Cl$, which acts as a Lewis acid catalyst to activate the carbon-carbon triple bonds of AAs, and a Brønsted acid, namely CF_3CO_2H, allows diverse linear aliphatic AAs as well as various cyclic aromatic AAs react well with a broader ANs carrying a nucleophilic C/N/O atom to assemble indole/pyrrole/thiophene/benzene/naphthalene/pyridine-based NCHCs with a large diverse scaffolds. The extraordinarily broad substrate scope of this catalytic system significantly widens the application of the cascade reactions between AAs and ANs in the assembly of nitrogen-containing heterocycles.

On the other hand, indole-fused skeletons are highly valuable scaffolds because they are widely found in bioactive natural products[8] and pharmaceutical agents[9]. Hence, they are considered as one of the most prominent privileged structures[10] in drug development. As a result, methods for the generation of indole-fused frameworks have captured wide attention, and tremendous efforts have been made[11,12] to develop efficient protocols to assemble these frameworks to provide potentially useful scaffolds for drug screening. Apparently, one-pot cascade reactions featuring simple operation and multiple bond formation in a single one chemical process are much more efficient and convenient for the furnishment of these complex scaffolds as compared with multistep synthesis. Despite the remarkable achievements made, the construction of indole-fused heterocyclic multi-ring architectures in high selectivity and efficiency from simple starting materials through a one-pot cascade process still represents a significant synthetic challenge. As part of our interests in the synthesis of indole-fused heterocycles,[13] here we aim to develop a highly selective cascade reaction between 1,3-unsubstituted 2-(1*H*-indol-2-yl)ethanamines and AAs to assemble novel indole-fused skeletons. As shown in Scheme 2, we expected that AAs could undergo intramolecular cyclization motivated by proper metal catalysts to give the enol lactone **A** (path a) or **B** (path b) due to the C1/C2 regioselectivity of the AAs,[5] and the following aminolysis of **A** or **B** by 1,3-unsubstituted 2-(1*H*-indol-2-yl)ethanamines could produce **A'** or **B'**. Then **A'** or **B'** would undergo an iminium ion formation/nucleophilic cyclization sequence to provide four possible scaffolds **A1** (path a1), **A2** (path a2), **B1** (path b1), and **B2** (path b2) owing to the C3/N1 site selectivity of the indole ring. The main challenge of this method is to achieve high levels of chemoselectivity including C1/C2 regioselectivity and C3/N1 site selectivity to generate a single skeleton in high efficiency. In this paper, we report the highly selective and efficient construction of the novel **A1** scaffold through gold catalysis. To the best of our knowledge, 1,3-unsubstituted 2-(1*H*-indol-2-yl)ethanamines are employed for the first time to react with AAs to achieve highly selective tandem reactions, thus affording the novel indole-fused framework **A1**. More importantly, the gold catalytic system was proved to be compatible with various ANs and diverse AAs, and was successfully employed for the rapid construction of an indole/pyrrole/thiophene/benzene/naphthalene/pyridine-based nitrogen-containing heterocyclic compound (NCHC) library with scaffold diversity and molecular complexity.



Scheme 2. Possible reaction pathways.

The hit rates of most of current combinatorial libraries in high-throughput screening (HTS) are far from satisfactory. This is because the scaffold diversity of these libraries, which contain similar molecular skeletons decorated with different substituents, is too limited to possess a wide chemical space. In recent years, skeletal diversity of a compound library is well recognized to be much more important than the appendices in HTS. Since compound libraries featuring a high degree of scaffold diversity can effectively improve the occupation of chemical space to increase the hit rates for various biological targets.[14] Apart from scaffold diversity, drug-like properties are equally important, as a library created with little consideration of drug-like properties may suffer from more absorption, distribution, metabolism, excretion, and toxicity (ADMET) problems during the drug development process.[15] Therefore, a high-quality and valuable compound library should display scaffold diversity as well as good drug-like properties. Undoubtfully, privileged-substructure-based diversity-oriented synthesis (pDOS) offers a powerful strategy to construct high-quality compound libraries because privileged structures exhibit inherent affinity for diverse biological targets and ubiquitously exist in

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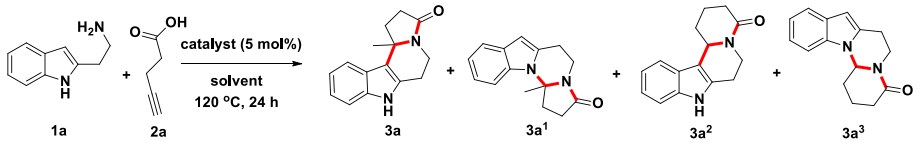
Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	Yield of **3a** (%)[b]	**3a**/**3a**^{1}/**3a**^{2}/**3a**^{3}[c]
1	$Pd(OAc)_2$	Toluene	15	–
2	$Cu(OAc)_2$	Toluene	22	–
3	$AgSbF_6$	Toluene	53	–
4	AgOTf	Toluene	44	–
5	$Ni(OTf)_2$	Toluene	18	–
6	$NiCl_2$	Toluene	15	–
7	$Co(acac)_2$	Toluene	47	–
8	$Co(OAc)_2$	Toluene	36	–
9	$PtCl_2$	Toluene	10	–
10	$PtCl_4$	Toluene	12	–
11	AuCl	Toluene	85	90:10:0:0
12	$AuCl_3$	Toluene	79	92:8:0:0
13	$Au(PPh_3)OTf$[d]	Toluene	88	>99:1:0:0
14	$Au(PPh_3)Cl$	Toluene	90	>99:1:0:0
15	Au catalyst X[e]	Toluene	77	84:16:0:0
16	Au catalyst Y[f]	Toluene	82	>99:1:0:0
17	Au catalyst Z[g]	Toluene	85	80:20:0:0
18	$Au(PPh_3)Cl$	THF	78	>99:1:0:0
19	$Au(PPh_3)Cl$	DCE	96	>99:1:0:0
20	$Au(PPh_3)Cl$	1,4-dioxane	84	>99:1:0:0
21	$Au(PPh_3)Cl$	CH_3CN	75	>99:1:0:0
22	$Au(PPh_3)Cl$	DMF	55	–
23	$Au(PPh_3)Cl$	CH_3OH	41	–
24	HOAc	DCE	0/0[h]	–
25	TFA	DCE	0/0[h]	–
26	HOTf	DCE	0/0[h]	–
27	–	DCE	0	–

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), catalyst (0.0125 mmol), solvent (2.0 ml), 120 °C, 24 h. [b] Isolated yield of **3a**. [c] The ratio was determined by HPLC. [d] $Au(PPh_3)OTf$ was prepared *in situ* by the reaction of $Au(PPh_3)Cl$ and AgOTf. [e] Au catalyst X = Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I); [f] Au catalyst Y = Chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]gold(I); [g] Au catalyst Z = (Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate; [h] 0.25 mmol acid was used.

natural and pharmaceutical products.[16] However, the development of robust processes to generate diverse scaffolds embedded with privileged structures remains a challenge and is highly demanding for drug screening. We herein introduce an efficient protocol, which allows the rapid access to the pDOS library of NCHCs encompassing molecular complexity, scaffold diversity, and drug-like properties. More importantly, two potent compounds with good antiproliferative activities were identified from this library.

Results and Discussion

Initial screening experiments were carried out with 2-(1*H*-indol-2-yl)ethanamine (**1a**) and 4-pentynoic acid (**2a**) as model substrates to optimize the reaction conditions including catalysts and solvents (Table 1). A variety of metal complexes (5 mol%) as Lewis acid catalysts were screened in toluene in a sealed tube at 120 °C for 24 h at first, and it turned out that AuCl was more effective than other metal species such as Pd, Cu, Ag, Ni, Co, and Pt catalysts (entries 1-11). A high yield of **3a** (85%) with excellent C1/C2 regioselectivity and high C3/N1 site selectivity (90:10) were obtained with AuCl. Then a series of Au catalysts were explored (entries 12-17). Isomers **3a** and **3a**^{3}, which derive from the 6-*endo* ring closure intermediate of **2a**, were not observed in these cases. Among them, $Au(PPh_3)Cl$ showed the highest catalytic performance and C3/N1 site selectivity (>99:1) (entry 14). Subsequently, a further screening of solvents (entries 18-23) revealed the transformation was strongly influenced by the solvents used, and DCE turned out to be the best choice for this reaction resulting in almost quantitative yield (96%) with excellent C1/C2 regioselectivity and C3/N1 site selectivity (>99:1) (entry 19). In addition, Brønsted acids such as HOAc,

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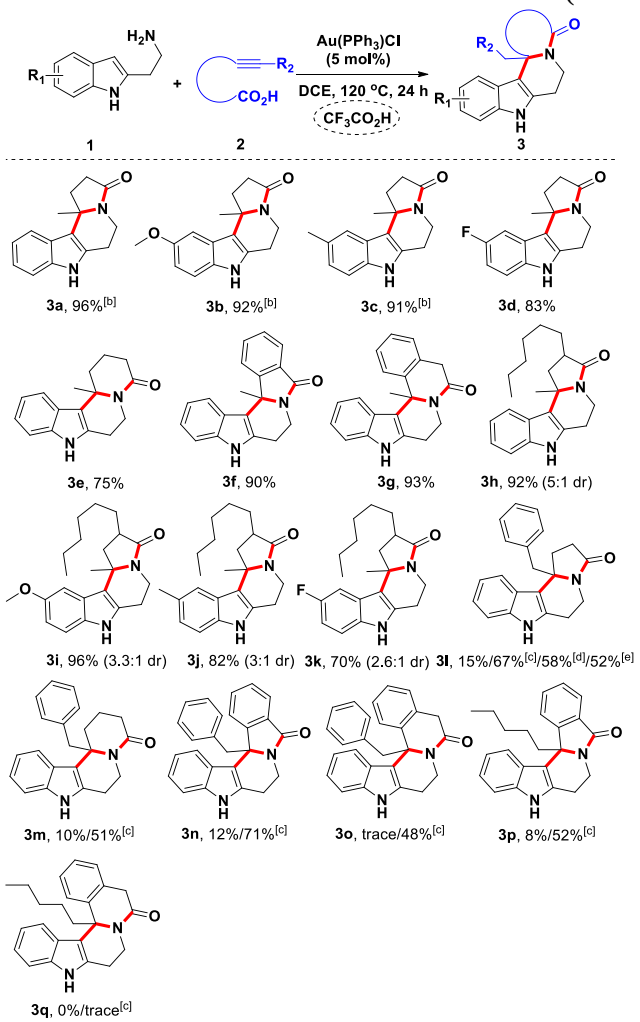
TFA and HOTf were also tested as the catalysts (entries 24-26), but none of them could catalyze this transformation. They also could not promote this reaction even when a stoichiometric amount (1 equivalent) of them was used. By contrast, control experiments showed that $Au(PPh_3)Cl$ played a crucial and indispensable role in this cascade reaction (entry 27). In this way, the optimum results were obtained when 2-(1*H*-indol-2-yl)ethanamine (0.25 mmol) and 4-pentynoic acid (0.3 mmol) were treated with 5 mol% of $Au(PPh_3)Cl$ in DCE in a sealed tube at 120 °C for 24 h.

With the optimal conditions established, we then investigated the scope of this method. Firstly, we examined the reactions of various substituted 2-(1*H*-indol-2-yl)ethanamines **1** with 4-pentynoic acid **2a**. As shown in Scheme 3, the reactions of 2-(1*H*-indol-2-yl)ethanamines bearing electron-donating (5-OMe, 5-Me) or electron-withdrawing group (5-F) appeared to be reactive and afforded the corresponding products **3b-3d** in high yields. It should be noted that the reaction of 2-(5-fluoro-1*H*-indol-2-yl)ethanamine with **2a** was sluggish under standard conditions because the C3 nucleophilicity was weakened by the fluorine. An improved two-step one-pot procedure, in which a Brønsted acid, namely CF_3CO_2H, was added to accelerate the formation of iminium ion, well addressed this issue. Similar results were also observed when the reactions were carried out with other AAs such as 5-hexynoic acid, 2-ethynylbenzoic acid, 2-(2-ethynylphenyl)acetic acid and 2-hexyl-4-pentynoic acid, and this may be attributed to the relatively lower reactivities of these AAs. Nevertheless, these AAs underwent the tandem reactions smoothly to produce the desired products **3e-3k** in 70-96% yields under improved conditions. In addition to terminal AAs, internal AAs were also tested as the reaction substrates. However, we found the reaction between 5-phenylpent-4-ynoic acid and 2-(1*H*-indol-2-yl)ethanamine **1a** was not active, and the desired product **3l** was obtained in a low yield (15%). This may be ascribed to the lower reactivities of internal carbon-carbon triple bonds caused by steric hindrance as compared with terminal ones. We hypothesized the addition of silver salts, which can increase the catalytic activity of $Au(PPh_3)Cl$,[10] would be able to activate the internal carbon-carbon triple bonds of terminally substituted AAs to solve this problem. Therefore, several silver complexes such as $AgBF_4$, AgOTf, and $AgSbF_6$ were added and screened. Pleasingly, $AgBF_4$ was found to be the most efficient silver additive, with which product **3l** was produced in a good yield (67%) at a higher temperature. Similarly, other internal AAs such as 6-phenylhex-5-ynoic acid, 2-(phenylethynyl)benzoic acid, 2-(2-(phenylethynyl)phenyl)acetic acid or 2-(hex-1-yn-1-yl)benzoic acid also reacted well with 2-(1*H*-indol-2-yl)ethanamine **1a** under the catalysis of $Au(PPh_3)Cl/AgBF_4/CF_3CO_2H$ to afford the desired products **3m-3p** in moderate to good yields. We also made our efforts to achieve the synthesis of **3q** from 2-(2-(hex-1-yn-1-yl)phenyl)acetic acid. Unfortunately, a complex reaction mixture was obtained and only a trace amount of **3q** was detected by LC-MS. Notably, excellent C1/C2 regioselectivity of AAs and C3/N1 site selectivity of the indole ring were observed in all examples, providing the corresponding novel indole-fused scaffolds presented by **3a-3p** with high efficiency. The excellent C3/N1 site selectivity of the indole ring may be attributed to the stronger nucleophilicity of C3 than that of N1, whose nucleophilicity is reduced by the aromatic ring.[17,18] As a result, indole C3 instead of indole N1 attacked the iminium ion intermediate in priority to give the C3-cyclization products selectively.

Further experiments under the standard or improved reaction conditions demonstrated that the



Scheme 3. Substrate scope of 2-(1*H*-indol-2-yl)ethanamines and AAs. [a] Unless noted, reactions were performed through a two-step one-pot process: (i) **1** (0.25 mmol), **2** (0.3 mmol), $Au(PPh_3)Cl$ (0.0125 mmol), DCE (2.0 ml), 120 °C, 20 h; (ii) after the first step, CF_3CO_2H (0.25 mmol) was added, and then 120 °C, 4 h; [b] **1** (0.25 mmol), **2** (0.3 mmol), $Au(PPh_3)Cl$ (0.0125 mmol), DCE (2.0 ml), 120 °C, 24 h; [c] (i) **1** (0.25 mmol), **2** (0.3 mmol), $Au(PPh_3)Cl$ (0.0125 mmol), $AgBF_4$ (0.0125 mmol), DCE (2.0 ml), 140 °C, 20 h; (ii) after the first step, CF_3CO_2H (0.25 mmol) was added, and then 140 °C, 4 h; [d] AgOTf was used as the silver additive; [e] $AgSbF_6$ was used as the silver additive.

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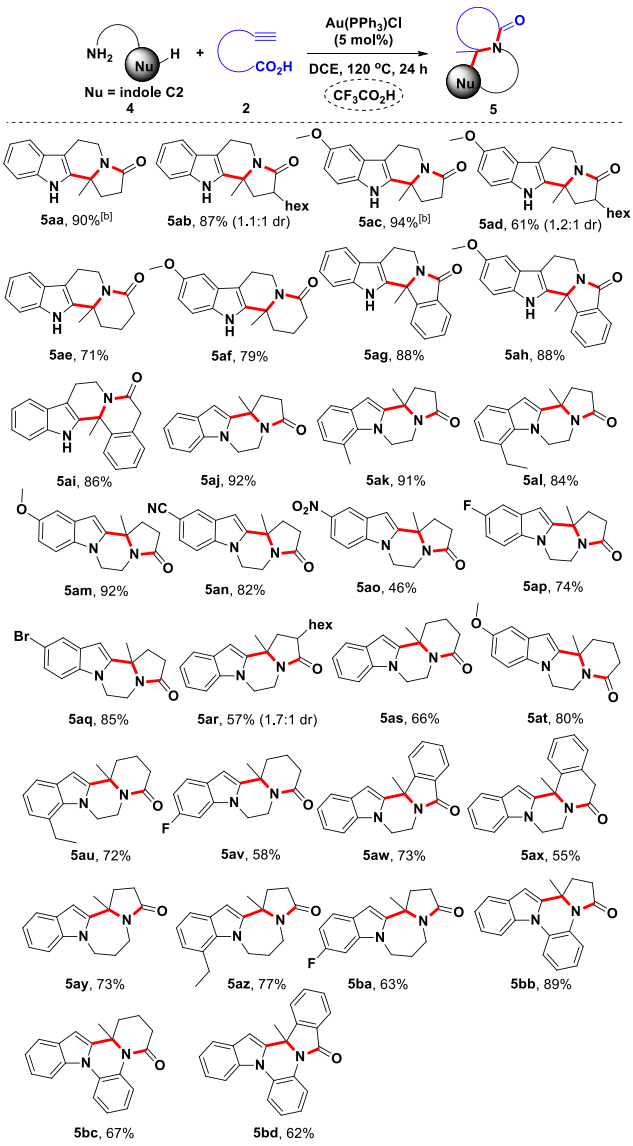
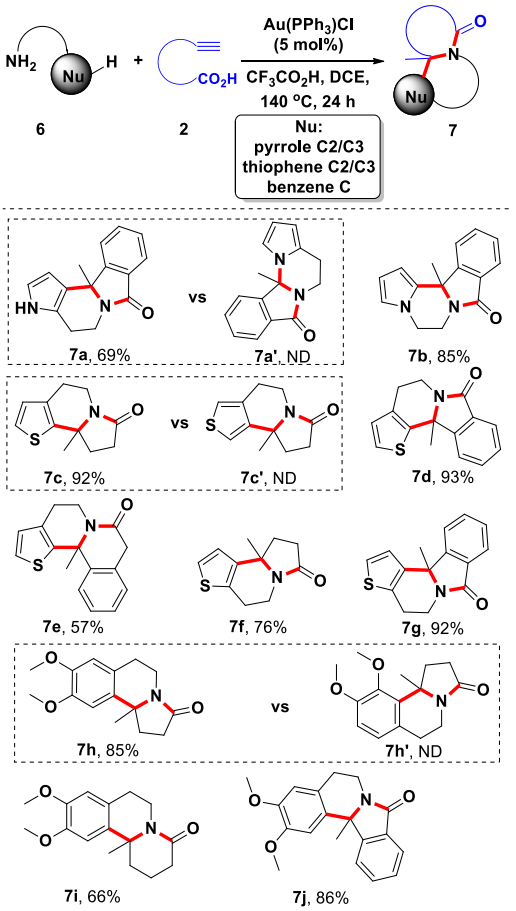


Scheme 4. Substrate scope of ANs and AAs. [a] Unless noted, reactions were performed through a two-step one-pot process: (i) **4** (0.25 mmol), **2** (0.3 mmol), Au(PPh$_3$)Cl (0.0125 mmol), DCE (2.0 ml), 120 °C, 20 h; (ii) after the first step, CF_3CO_2H (0.25 mmol) was added, and then 120 °C, 4 h; [b] **4** (0.25 mmol), **2** (0.3 mmol), Au(PPh$_3$)Cl (0.0125 mmol), DCE (2.0 ml), 120 °C, 24 h.

protocol could be extended to the reactions of various AAs with diverse ANs containing an indole moiety, such as 2-(1*H*-indol-3-yl)ethanamines, 2-(1*H*-indol-1-yl)ethanamines, 3-(1*H*-indol-1-yl)propan-1-amines and 2-(1*H*-indol-1-yl)anilines, to generate a variety of indole-fused scaffolds. In general, all the corresponding NCHCs embedded with an indole motif were obtained in moderate to high yields (Scheme 4). Specifically, 2-(1*H*-indol-3-yl)ethanamines reacted smoothly with anyone of 4-pentynoic acid, 5-hexynoic acid, 2-ethynylbenzoic acid, 2-(2-ethynylphenyl)acetic acid and 2-hexyl-4-pentynoic acid, providing the desired products **5aa**-**5ai** in 61-94% yields. Similarly, 2-(1*H*-indol-1-yl)ethanamines were also found to be suitable substrates, their reactions with various AAs worked well to afford the corresponding products **5aj**-**5ax** in 46-92% yields. To our delight, 3-(1*H*-indol-1-yl)propan-1-amines were well tolerated and converted into the polycyclic products embedded with a seven-membered ring in good yields (**5ay**-**5ba**). This further highlights the efficiency of this approach because the generation of seven-membered ring analogues is less favored on energetics and dynamics in cascade reactions. Gratifyingly, this process could also be applicable to 2-(1*H*-indol-1-yl)anilines, which underwent this transformation successfully to give more rigid compounds **5bb**-**5bd** in 62-89% yields. It should be noticed that the indole-fused polycyclic scaffolds presented by **3a**-**3q** and **5aa**-**5bd** are considered as valuable heterocycles in view of their frequent occurrence in biologically active natural products and drugs.[19]

Pleasingly, other 2-aryl-ethanamines such as 2-(1*H*-pyrrol-2-yl)ethanamine, 2-(1*H*-pyrrol-1-yl)ethanamine, 2-(thiophen-3-yl)ethanamine, 2-(thiophen-2-yl)ethanamine and 2-(3,4-dimethoxyphenyl)ethanamine also turned out to be suitable substrates for this cascade process. They reacted well with AAs to afford the desired NCHCs



Scheme 5. Substrate scope of ANs and AAs. [a] Reactions were performed through a two-step one-pot process: (i) **6** (0.25 mmol), **2** (0.3 mmol), Au(PPh$_3$)Cl (0.0125 mmol), DCE (2.0 ml), 140 °C, 20 h; (ii) after the first step, CF_3CO_2H (0.25 mmol) was added, and then 140 °C, 4 h. ND = Not detected.

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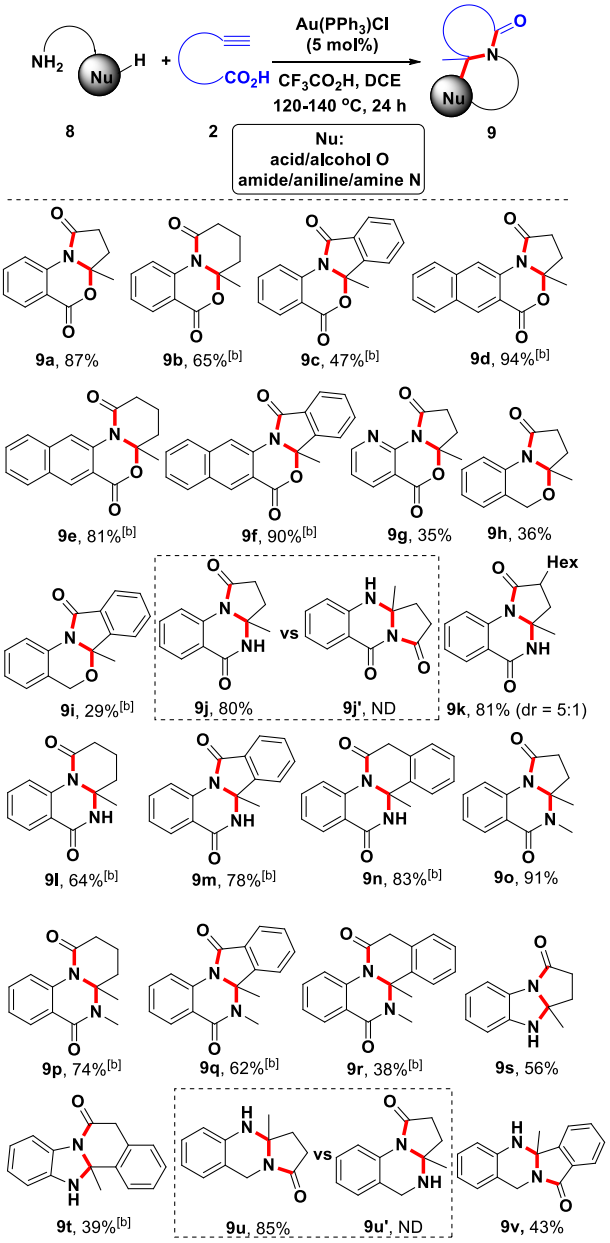
with high selectivity and moderate to high yields (Scheme 5). For example, the reaction of 2-(1*H*-pyrrol-2-yl)ethanamine with 2-ethynylbenzoic acid took place smoothly and selectively, producing the C3 ring closure product **7a** instead of N1 ring closure product **7a'**. Likewise, 2-(thiophen-3-yl)ethanamine underwent this transformation with various AAs in a highly selective manner, providing the C2 ring closure products rather than C4 closure ones (**7c-7e**). Similarly, the ring closure site occurred at the less-hindered position selectively in the reactions between 2-(3,4-dimethoxyphenyl)ethanamine and AAs (**7h-7j**). Based on these results, we could conclude that, when two or more nucleophilic sites exist in the final

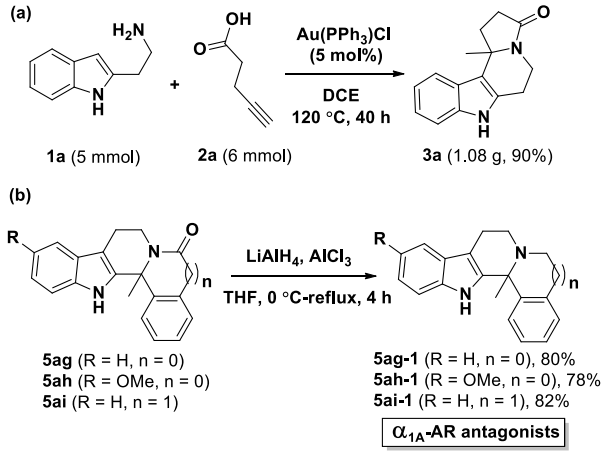


Scheme 6. Substrate scope of ANs and AAs. [a] Unless noted, reactions were performed through the two-step one-pot process with the following conditions: (i) **8** (0.25 mmol), **2** (0.3 mmol), $Au(PPh_3)Cl$ (0.0125 mmol), DCE (2.0 ml), 120 °C, 20 h; (ii) after the first step, CF_3CO_2H (0.25 mmol) was added, and then 120 °C, 4 h. [b] The reaction was performed at 140 °C. ND = Not detected.

cyclization step, the stronger and less-hindered nucleophilic site tends to attack the iminium ion with strict priority to afford the corresponding ring closure products in this cascade process.

The applicability of this cascade reaction in ANs **8** bearing another nucleophilic heteroatom (O, N) was also well studied and established. As shown in Scheme 6, the reactions of 2-aminobenzoic acid/3-amino-2-naphthoic/2-aminonicotinic acid with diverse AAs worked smoothly to give the desired products **9a-9g** in 35-94% yields. Even (2-aminophenyl)methanol could react with AAs to provide the products **9h-9i**, albeit with lower yields. It is worth noting that the aniline N played as the nucleophile which attacked the enol lactone intermediate, and the amide N played as the nucleophile which attacked the iminium ion when 2-aminobenzamide was employed as the bisnucleophile to react with 4-pentynoic acid, thus leading to the formation of **9j** selectively instead of **9j'**. Similar results have been observed in the reactions of 2-aminobenzamide with other AAs such as 2-hexyl-4-pentynoic acid, 5-hexynoic acid, 2-ethynylbenzoic acid, and 2-(2-ethynylphenyl)acetic acid, affording the single kind of products with high selectivity (**9k-9n**). To our delight, positive results were also observed when 2-amino-*N*-methylbenzamide and AAs were subjected to the reaction conditions, and the corresponding products **9o-9r** were obtained in 38-91% yields. Despite the lower yields, benzene-1,2-diamine was also found to be a suitable substrate, which could be converted into the desired products **9s-9t**. Interestingly, in the reaction of 2-(aminomethyl)aniline with 4-pentynoic acid, the more nucleophilic amine N rather than the aniline N displayed as the nucleophile to attack the enol lactone intermediate in the first step. As a result, the aniline N could only display as the nucleophile to attack the iminium ion in the final cyclization step, thus affording **9u** selectively instead of **9u'**. Similarly, **9v** was obtained as the only product in 43% yield when 2-(aminomethyl)aniline and 2-ethynylbenzoic acid were used as the starting materials. From the above results, we could come to a conclusion that the more nucleophilic N is generally involved in the first ring-opening of enol lactone intermediate, while the less nucleophilic N is normally involved in the final cyclization step when bisnucleophiles carrying two nitrogen atoms are employed as the substrates. Briefly, these findings further broadened the substrate scope of the methodology.

Thus, the cascade reactions between various ANs and diverse AAs rapidly created a library of indole/pyrrole/thiophene/benzene/naphthalene/pyridine-based NCHCs with scaffold diversity and molecular complexity. It should be noted that two rings and three new bonds were formed efficiently in a single one step to give the NCHCs bearing a quaternary carbon center. It is also worth noting that lots of the scaffolds in this paper are reported for the first time and turn out to be novel nitrogen-containing heterocyclic frameworks. Such a divergent synthesis



Scheme 7. Gram-scale cascade reaction and derivatization.

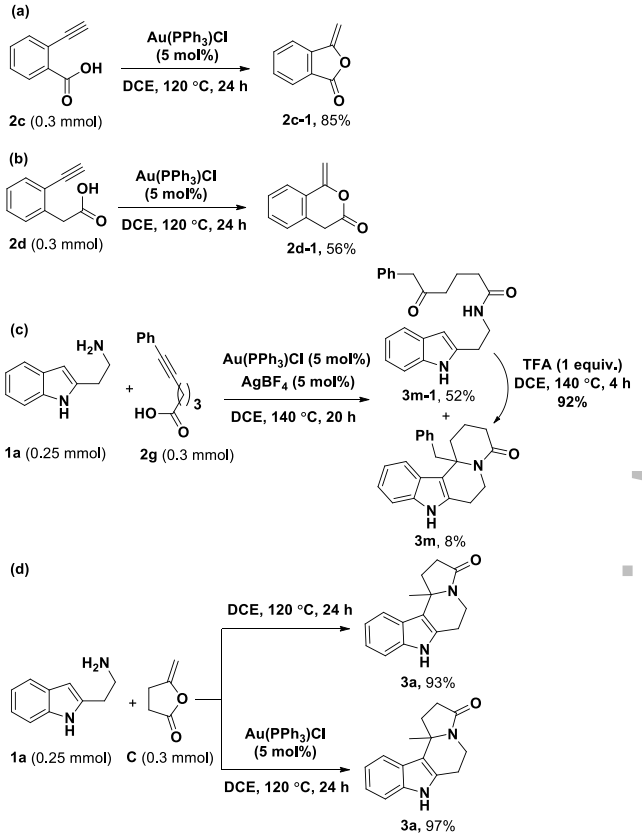
of heterocycles is evidently appealing and promising in diversity oriented synthesis because it provides a platform to assemble thousands of NCHCs with scaffold diversity in an efficient manner.

To further illustrate the practicality of this methodology, the cascade reaction between **1a** and **2a** was carried out on a gram scale under optimal conditions. Impressively, the desired product **3a** was obtained in 90% yield (Scheme 7a). In addition, the reported potent α_{1A}-adrenoceptor antagonists[7g] **5ag-1**, **5ah-1**, **5ai-1** were prepared easily *via* a simple reduction of the corresponding precursors in our library (Scheme 7b). Besides, a pharmacological screening of these NCHCs in this library to evaluate their inhibitory activities against human cancer cell lines A549 and HL60 resulted in the identification of two potent compounds **3g** and **9k**, which exhibited moderate to good inhibition activities as compared with the positive control Adriamycin (Table 2). These aspects further highlight the advantages and potential applications of our approach.

Table 2. Antiproliferative activities of **3g** and **9k** against human cancer cell lines A549 and HL60.

Compound	Concentration (μM)	Inhibition rate (%)	
		A549	HL60
3g	10	67.8	72.7
9k	10	62.6	-
Adriamycin	10	92.1	87.2

Furthermore, mechanistic studies were performed to probe the reaction mechanism. When 2-ethynylbenzoic acid (**2c**) or 2-(2-ethynylphenyl)acetic acid (**2d**) was subjected to the standard conditions without ANs, the corresponding enol lactone **2c-1** or **2d-1**, whose structure was confirmed by ^{1}HNMR, ^{13}CNMR and HRMS, was isolated as the product (Scheme 8a and 8b). In addition, the aminolysis product **3m-1** of the enol lactone derived from 6-phenylhex-5-ynoic acid **2g** in the reaction of 2-(1*H*-indol-2-yl)ethanamine **1a** and 6-phenylhex-5-ynoic



Scheme 8. Mechanistic study experiments.

acid **2g** was isolated in 52% yield, and the treatment of **3m-1** with TFA in DCE at 140 °C for 4 h provided the target product **3m** in a high yield (Scheme 8c). These results suggest that the enol lactone species is likely to be involved in this cascade reaction. Besides, the reaction of **1a** with the commercially available enol lactone **C** could afford the desired product **3a** with or without $Au(PPh_3)Cl$, and a higher yield was obtained in the presence of $Au(PPh_3)Cl$ as compared with catalyst-free conditions (Scheme 8d). This indicates that the gold catalyst may not only catalyze the formation of enol lactone intermediate, but also promote the iminium ion formation.

Based on the above mechanistic study results, we proposed a plausible catalytic cycle (Scheme 9). The complexation of the Au catalyst to the alkyne moiety of AAs gives intermediate **D1**, which undergoes intramolecular *exo* cyclization to afford the vinylgold intermediate **D2**. Then the protodemetalation of **D2** occurs to provide the key enol lactone intermediate **D3** with the release of the Au catalyst. The subsequent aminolysis of **D3** by ANs produces intermediate **D4**. Then the coordination of the Au catalyst to the carbonyl of **D4** takes place to generate intermediate **D5**, which undergoes a sequential nucleophilic addition and iminium ion formation to yield intermediate **D7**. The final nucleophilic cyclization of **D7** provides the products and regenerates the Au catalyst. In brief, two catalytic cycles were involved in the proposed reaction mechanism. The Au catalyst could catalyze the

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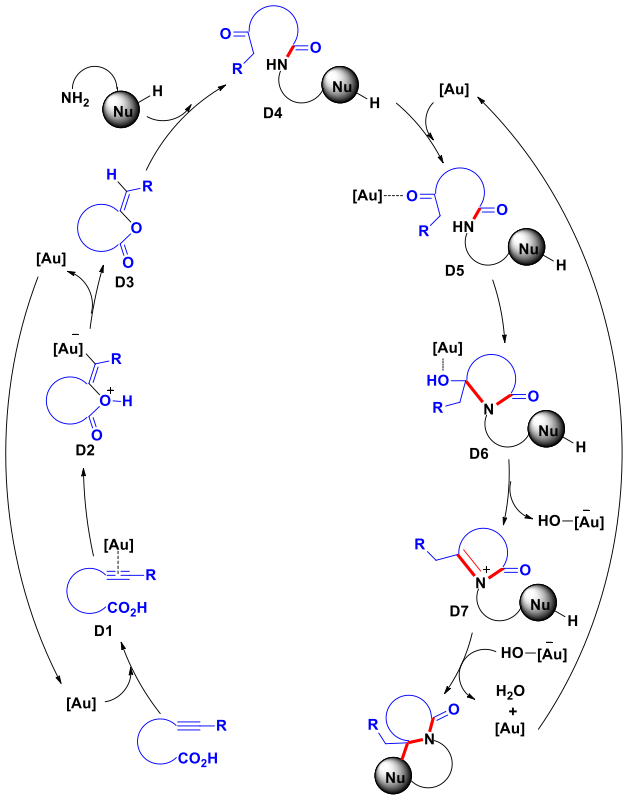

Scheme 9. Proposed catalytic cycle.

formation of enol lactone intermediate as well as the iminium ion intermediate. Besides, CF_3CO_2H could accelerate the formation of iminium ion intermediate to promote this cascade reaction.

Conclusion

In summary, we empolyed 1,3-unsubstituted 2-(1*H*-indol-2-yl)ethanamines for the first time to react with AAs to achieve gold-catalyzed highly selective cascade reaction to furnish novel indole-fused skeletons. More importantly, this gold catalytic system has been successfully used for the rapid construction of an indole/pyrrole/thiophene/benzene/naphthalene/pyridine-based NCHCs library with scaffold diversity and molecular complexity by employing various ANs and diverse AAs as the scaffold-building reagents. This synthetic protocol exhibits valuable features of readily available inputs, operational simplicity, extraordinarily broad substrate scope, good to high yields, excellent selectivity, high bond-forming efficiency, and step economy. In addition, two potent compounds with good antiproliferative activities were identified from this library, highlighting the potential and value of this strategy. Considering the large presence of NCHCs in natural and pharmaceutical products, the approach presented here is very promising as it could provide a rapid and powerful tool to construct a library of thousands of NCHCs with a large diverse scaffolds. Further bioactivity studies of this library are currently in progress in our laboratory, and we expect these valuable nitrogen-containing heterocycles embedded with privileged structures may find more pharmaceutical applications.

Experimental Section

General information

Unless noted, the reagents were purchased from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on HSGF 254 (0.15-0.2 mm thickness), visualized by irradiation with UV light (254 nm). Column chromatography was performed using silica gel FCP 200-300. Melting points were measured with a micro melting point apparatus. Nuclear magnetic resonance spectra were recorded on a Brucker instrument. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were measured on a spectrometer.

Preparation procedure of $Au(PPh_3)OTf$

$Au(PPh_3)OTf$ was prepared *in situ* by the reaction of $Au(PPh_3)Cl$ and AgOTf according to the literature process.[20] A mixture of $Au(PPh_3)Cl$ (24.7 mg, 0.05 mmol) and AgOTf (12.8 mg, 0.05 mmol) in dry toluene (2.0 ml) was stirred at room temperature for 16 h. Then $Au(PPh_3)OTf$ was obtained quantitatively in toluene (0.025 mol/L), while AgCl was deposited at the bottom as white solids.

Preparation and characterization data of the terminally substituted alkynoic acids 2f-2k

5-phenylpent-4-ynoic acid (2f): $SOCl_2$ (5.8 ml, 80.0 mmol) was added dropwise to a solution of 4-pentynoic acid (981.0 mg, 10.0 mmol) in methanol (20.0 ml) at 0 °C, and the mixture was heated to reflux for 4 h. Then the reaction mixture was concentrated, and the residue obtained was dissolved in ethyl acetate (30.0 ml), the resulting mixture was washed with saturated $NaHCO_3$ aqueous solution, water and brine, dried over Na_2SO_4, and concentrated to give crude methyl pent-4-ynoate (1.0 g, 89%). To a solution of pent-4-ynoate (1.0 g, 8.92 mmol) in DMF (5.0 ml) and Et_3N (5.0 ml) was added $PdCl_2(PPh_3)_2$ (313.0 mg, 445.92 μmol), CuI (169.85 mg, 891.85 μmol), and iodobenzene (999.7 μl, 8.92 mmol), and the resulting mixture was stirred under nitrogen atmosphere at room temperature for 8 hours. Then water (100.0 ml) was added and the reaction mixture was extracted with ethyl acetate (30.0 ml x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue obtained was purified to give methyl 5-phenylpent-4-ynoate (1.43 g, 85%). To a solution of methyl 5-phenylpent-4-ynoate (1.43 g, 7.6 mmol) in MeOH (5.0 ml) was added 1 mol/L NaOH aqueous solution (15.2 ml) at room temperature. Two hours later, the reaction mixture was acidified with 1 mol/L HCl aqueous solution (25.0 ml), and the resulting mixture was extracted with ethyl acetate (20.0 ml x 3). The combined organic extracts were washed with saturated $NaHCO_3$ aqueous solution, water and brine, dried over Na_2SO_4, and concentrated. The residue obtained was purified to give 5-phenylpent-4-ynoic acid as a white solid (1.25 g, 94%). Mp 95-96 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 7.51-7.20 (m, 5H), 2.67-2.60 (m, 2H), 2.57-2.51 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.96, 131.27, 128.60, 128.07, 123.03, 89.56, 80.53, 33.07, 14.77; LRMS (ESI) *m/z*: 173 $[M-H]^-$; HRMS (ESI) *m/z* calculated for $C_{11}H_9O_2$ $[M-H]^-$ 173.0608, found: 173.0604.

6-phenylhex-5-ynoic acid (2g): 6-phenylhex-5-ynoic acid was prepared following the similar procedure carried out for 5-phenylpent-4-ynoic acid. Yellow oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 7.53-7.18 (m, 5H), 2.46 (t, J = 7.1 Hz, 2H), 2.38 (t, J = 7.3 Hz, 2H), 1.81-1.72 (m, J = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.06, 131.28, 128.58, 127.99, 123.15, 89.86, 80.98, 32.61, 23.70, 18.12; LRMS (ESI) *m/z*: 189 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{12}H_{12}O_2+H^+$ 189.0910, found: 189.0909.

2-(phenylethynyl)benzoic acid (2h): $SOCl_2$ (2.9 ml, 40.0 mmol) was added dropwise to a solution of 2-iodobenzoic acid (1.24 g, 5.0 mmol) in methanol (20.0 ml) at 0 °C, and the mixture was heated to reflux for 4 h. Then the reaction mixture was concentrated, and the residue obtained was dissolved in ethyl acetate (30 ml), the resulting mixture was washed with saturated $NaHCO_3$ aqueous solution, water and brine, dried over Na_2SO_4, and concentrated. The residue obtained was purified to give methyl 2-iodobenzoate (1.18 g, 90%). To a solution of methyl 2-iodobenzoate (1.18 g, 4.5 mmol) in DMF (5.0 ml) and Et_3N (5.0 ml) was added $PdCl_2(PPh_3)_2$ (158.03 mg, 225.15 μmol), CuI (85.76 mg, 450.31 μmol), and ethynylbenzene (494.53 μl, 4.5 mmol), and the resulting mixture was stirred under nitrogen atmosphere at room temperature for 8 hours. Then water (100.0 ml) was added and the reaction mixture was extracted with ethyl acetate (30.0 ml x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue obtained was purified to give methyl 2-(phenylethynyl)benzoate (870.2 mg, 82%). To a solution of methyl 2-(phenylethynyl)benzoate (870.2 mg, 3.68 mmol) in MeOH (5.0 ml) was added 1 mol/L NaOH aqueous solution (7.36 ml) at room temperature. Two hours later, the reaction mixture was acidified with 1 mol/L HCl aqueous solution (15.0 ml), and the resulting mixture was extracted with ethyl acetate (20.0 ml x 3). The combined organic extracts were washed with saturated $NaHCO_3$ aqueous solution, water and brine, dried over Na_2SO_4, and concentrated. The residue obtained was purified to give 2-(phenylethynyl)benzoic acid as a pale yellow solid (778.8 mg, 95%). Mp 119-120 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 7.92 (dd, J = 7.8, 1.0 Hz, 1H), 7.71-7.65 (m, 1H), 7.63-7.58 (m, 1H), 7.57-7.48 (m, 3H), 7.48-7.40 (m, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.18, 133.58, 133.22, 131.77, 131.34, 130.13, 128.92, 128.79, 128.60, 122.68, 122.20, 93.56, 88.62; LRMS (ESI) *m/z*: 223 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{10}O_2+H^+$ 223.0754, found: 223.0751.

2-(2-(phenylethynyl)phenyl)acetic acid (2i): 2-(2-(phenylethynyl)phenyl)acetic acid was prepared following the similar procedure carried out for 2-(phenylethynyl)benzoic acid. White solid, mp 117-118 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 7.62-7.51 (m, 3H), 7.49-7.37 (m, 5H), 7.36-7.30 (m, 1H), 3.83 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.11, 137.41, 131.45, 131.28, 130.51, 128.85, 128.76, 127.10, 122.71, 122.38, 93.45, 87.67, 39.76; LRMS (ESI) *m/z*: 237 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{12}O_2+H^+$ 237.0910, found: 237.0912.

2-(hex-1-yn-1-yl)benzoic acid (2j): 2-(hex-1-yn-1-yl)benzoic acid was prepared following the similar procedure carried out for 2-(phenylethynyl)benzoic acid. Pale yellow oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.58-7.44 (m, 2H), 7.44-7.34 (m, 1H), 2.44 (t, J = 6.5 Hz, 2H), 1.58-1.40 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.47, 133.61, 133.42, 131.35, 129.61, 127.58, 123.08, 95.33, 79.42, 30.17, 21.32, 18.71, 13.55; LRMS (ESI) *m/z*: 203 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{13}H_{14}O_2+H^+$ 203.1067, found: 203.1065.

2-(2-(hex-1-yn-1-yl)phenyl)acetic acid (2k): 2-(2-(hex-1-yn-1-yl)phenyl)acetic acid was prepared following the similar procedure carried out for 2-(phenylethynyl)benzoic acid. Pale yellow oil, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.31-7.26 (m, 2H), 7.26-7.20 (m, 1H), 3.70 (s, 2H), 2.43 (t, J = 6.8 Hz, 2H), 1.57-1.49 (m, 2H), 1.48-1.38 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.10, 136.93, 131.37, 130.21, 127.74, 126.85, 123.72, 94.81, 78.79, 39.37, 30.27, 21.40, 18.46, 13.50; LRMS (ESI) *m/z*: 217 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{14}H_{16}O_2+H^+$ 217.1223, found: 217.1223.

General procedure for the synthesis of compounds 3a-3c, 5aa, 5ac

A 25 mL Schlenk tube equipped with a magnetic stir bar was charged with amine nucleophiles (0.25 mmol), alkynoic acids (0.3 mmol), $Au(PPh_3)Cl$ (0.0125 mmol), DCE (2.0 ml), and then capped with a septa. After that, the tube was kept in the preheated oil bath at 120 °C for 24 h. Then the reaction was cooled to ambient temperature, and saturated Na_2CO_3 solution (25 ml) was added. The mixture obtained was extracted with ethyl acetate (3 × 15 ml). The combined organic phase was washed brine, dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel to give the desired products.

General procedure for the synthesis of compounds 3d-3k, 5ab, 5ad-5bd, 7a-7j, 9a-9v

A 25 mL Schlenk tube equipped with a magnetic stir bar was charged with amine nucleophiles (0.25 mmol), alkynoic acids (0.3 mmol), $Au(PPh_3)Cl$ (0.0125 mmol), DCE (2.0 ml), and then capped with a septa. After that, the tube was kept in the preheated oil bath at the temperature indicated for 20 h. After the reaction was cooled, CF_3CO_2H (0.25 mmol) was added into the reaction mixture, and the resulting mixture was stirred at the temperature indicated for another 4 h. Then the reaction was cooled to ambient temperature, and saturated Na_2CO_3 solution (25 ml) was added. The mixture obtained was extracted with ethyl acetate (3 × 15 ml). The combined organic phase was washed brine, dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel to give the desired products.

General procedure for the synthesis of compounds 3l-3q

A 25 mL Schlenk tube equipped with a magnetic stir bar was charged with amine nucleophiles (0.25 mmol), alkynoic acids (0.3 mmol), $Au(PPh_3)Cl$ (0.0125 mmol), $AgBF_4$ (0.0125 mmol), DCE (2.0 ml), and then capped with a septa. After that, the tube was kept in the preheated oil bath at 140 °C for 20 h. After the reaction was cooled, CF_3CO_2H (0.25 mmol) was added into the reaction mixture, and the resulting mixture was stirred at 140 °C for another 4 h. Then the reaction was cooled to ambient temperature, and saturated Na_2CO_3 solution (25 ml) was added. The mixture obtained was extracted with ethyl acetate (3 × 15 ml). The combined organic phase was washed brine, dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel to give the desired products.

11c-methyl-5,6,7,11c-tetrahydro-1*H*-indolizino[7,8-*b*]indol-3(2*H*)-one (3a): yellow solid (57.6 mg, yield 96%), mp 96-97 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.90 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.08-7.00 (m, 1H), 7.00-6.92 (m, 1H), 4.27-4.18 (m, 1H), 3.16-3.04 (m, 1H), 2.81-2.67 (m, 2H), 2.65-2.54 (m, 1H), 2.54-2.47 (m, 1H), 2.27-2.17 (m, 1H), 2.02-1.92 (m, 1H), 1.54 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.54, 135.89, 130.53, 123.91, 120.53, 118.64, 117.92, 115.29, 111.11, 59.20, 33.23, 33.21, 30.15, 25.02, 22.77; LRMS (ESI) *m/z*: 241 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{16}N_2O+H^+$ 241.1335, found: 241.1332.

10-methoxy-11c-methyl-5,6,7,11c-tetrahydro-1*H*-indolizino[7,8-*b*]indol-3(2*H*)-one (3b): pale yellow solid

(61.9 mg, yield 92%), mp 193-194 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.72 (s, 1H), 7.19 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H), 6.69 (dd, J = 8.7, 2.4 Hz, 1H), 4.25-4.15 (m, 1H), 3.77 (s, 3H), 3.14-3.03 (m, 1H), 2.79-2.65 (m, 2H), 2.64-2.52 (m, 2H), 2.27-2.18 (m, 1H), 2.01-1.91 (m, 1H), 1.54 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.54, 153.06, 131.26, 131.00, 124.22, 115.11, 111.66, 109.84, 100.59, 59.17, 55.47, 33.19, 33.01, 30.11, 24.76, 22.86; LRMS (ESI) *m/z*: 271 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{18}N_2O_2+H^+$ 271.1441, found: 271.1437.

10,11c-dimethyl-5,6,7,11c-tetrahydro-1*H*-indolizino[7,8-*b*]indol-3(2*H*)-one (3c): pale yellow oil (57.8 mg, yield 91%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.75 (s, 1H), 7.25 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 6.86 (dd, J = 8.2, 1.0 Hz, 1H), 4.26-4.15 (m, 1H), 3.15-3.03 (m, 1H), 2.80-2.65 (m, 2H), 2.64-2.54 (m, 1H), 2.50-2.46 (m, 1H), 2.38 (s, 3H), 2.29-2.17 (m, 1H), 2.02-1.91 (m, 1H), 1.53 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.54, 134.24, 130.53, 127.05, 124.15, 122.04, 117.65, 114.84, 110.83, 59.24, 33.27, 33.24, 30.17, 25.00, 22.82, 21.31; LRMS (ESI) *m/z*: 255 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{18}N_2O+H^+$ 255.1492, found: 255.1489.

10-fluoro-11c-methyl-5,6,7,11c-tetrahydro-1*H*-indolizino[7,8-*b*]indol-3(2*H*)-one (3d): pale yellow solid (53.8 mg, yield 83%), mp 104-105 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.34-7.21 (m, 2H), 6.93-6.82 (m, 1H), 4.28-4.15 (m, 1H), 3.16-3.01 (m, 1H), 2.83-2.67 (m, 2H), 2.64-2.51 (m, 2H), 2.28-2.16 (m, 1H), 1.99-1.87 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.54, 156.70 (d, J_{C-F} = 231.1 Hz), 132.88, 132.51, 124.00 (d, J_{C-F} = 10.1 Hz), 115.69 (d, J_{C-F} = 4.5 Hz), 111.91 (d, J_{C-F} = 9.9 Hz), 108.33 (d, J_{C-F} = 25.8 Hz), 102.88 (d, J_{C-F} = 23.4 Hz), 59.03, 33.09, 32.93, 30.11, 24.76, 22.85; LRMS (ESI) *m/z*: 259 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{15}FN_2O+H^+$ 259.1241, found: 259.1238.

12c-methyl-1,2,3,6,7,12c-hexahydroindolo[3,2-*a*]quinolizin-4(8*H*)-one (3e): white solid (47.9 mg, yield 75%), mp 132-133 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.07-6.99 (m, 1H), 6.99-6.90 (m, 1H), 4.92-4.80 (m, 1H), 3.01-2.89 (m, 1H), 2.78-2.60 (m, 3H), 2.43-2.32 (m, 1H), 2.32-2.19 (m, 1H), 2.01-1.85 (m, 1H), 1.77-1.65 (m, 2H), 1.63 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.08, 136.10, 131.92, 123.96, 120.25, 118.63, 118.49, 115.68, 111.09, 57.04, 35.59, 34.68, 31.94, 25.11, 23.26, 16.53; LRMS (ESI) *m/z*: 255 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{18}N_2O+H^+$ 255.1492, found: 255.1488.

13b-methyl-6,7-dihydro-5*H*-benzo[1,2]indolizino[7,8-*b*]indol-9(13b*H*)-one (3f): pale yellow solid (64.8 mg, yield 90%), mp 235-236 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.10 (s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.12-8.03 (m, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.69-7.64 (m, 1H), 7.52-7.44 (m, 1H), 7.34-7.26 (m, 1H), 7.12-7.03 (m, 2H), 4.56-4.46 (m, 1H), 3.45-3.37 (m, 1H), 2.91-2.80 (m, 1H), 2.80-2.70 (m, 1H), 1.90 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.33, 151.36, 135.88, 132.31, 131.99, 130.21, 128.08, 124.33, 123.19, 123.06, 120.71, 119.04, 119.01, 111.64, 111.26, 63.56, 34.65, 25.75, 23.42; LRMS (ESI) *m/z*: 289 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{16}N_2O+H^+$ 289.1335, found: 289.1330.

14c-methyl-8,9,10,14c-tetrahydroindolo[3',2':3,4]pyrido[2,1-*a*]isoquinolin-6(5*H*)-one (3g): yellow solid (70.1 mg, yield 93%), mp 250-251 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.26 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.44-7.38 (m, 2H), 7.30-7.19 (m, 2H), 7.15-7.04 (m, 3H), 4.95-4.86 (m, 1H), 4.10 (d, J = 19.2 Hz, 1H), 3.62 (d, J = 19.4 Hz, 1H), 3.02-2.89 (m, 1H), 2.84-2.73 (m, 1H), 2.72-2.60 (m, 1H), 1.89 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.32, 141.44, 136.03, 134.55, 132.37, 127.67, 127.15, 126.20, 126.05, 124.74, 120.52, 120.23, 119.18, 111.52, 111.24, 61.51, 38.20, 36.86, 25.69, 23.26; LRMS (ESI) *m/z*: 303 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{18}N_2O+H^+$ 303.1492, found: 303.1486.

2-hexyl-11c-methyl-5,6,7,11c-tetrahydro-1*H*-indolizino[7,8-*b*]indol-3(2*H*)-one (3h): pale yellow oil [74.7 mg, yield 92% (dr = 5:1)], and the two diastereomers were separable by chromatography. The major diastereomer: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.52-7.44 (m, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.08-6.91 (m, 2H), 4.28-4.14 (m, 1H), 3.22-3.01 (m, 1H), 2.88-2.53 (m, 4H), 1.82-1.66 (m, 1H), 1.58-1.48 (m, 3H), 1.39-1.08 (m, 10H), 0.90-0.75 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.75, 135.90, 130.33, 123.92, 120.54, 118.62, 117.99, 115.59, 111.10, 57.22, 40.71, 40.51, 33.18, 31.20, 30.60, 28.73, 26.60, 24.68, 22.93, 22.06, 13.96; LRMS (ESI) *m/z*: 325 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{21}H_{28}N_2O+H^+$ 325.2274, found: 325.2268.

2-hexyl-10-methoxy-11c-methyl-5,6,7,11c-tetrahydro-1*H*-indolizino[7,8-*b*]indol-3(2*H*)-one (3i): pale yellow oil [84.8 mg, yield 96% (dr = 3.3:1)], and the two diastereomers were inseparable by chromatography. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.22-7.14 (m, 1H), 6.99-6.91 (m, 1H), 6.72-6.65 (m, 1H), 4.27-4.12 (m, 1H), 3.77 (s, 3H), 3.24-3.02 (m, 1H), 2.87-2.53 (m, 4H), 1.81-1.67 (m, 1H), 1.57-1.48 (m, 3H), 1.43-1.10 (m, 10H), 0.91-0.79 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.77, 153.09, 131.07, 131.03, 124.26, 115.44, 111.65, 109.85, 100.68, 57.22, 55.51, 40.52, 40.50, 33.18, 31.20, 30.60, 28.76, 26.61, 24.36, 23.04, 22.08, 13.95; LRMS (ESI) *m/z*: 355 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{22}H_{30}N_2O_2+H^+$ 355.2380, found: 355.2378.

2-hexyl-10,11c-dimethyl-5,6,7,11c-tetrahydro-1*H*-indolizino[7,8-*b*]indol-3(2*H*)-one (3j): pale yellow oil [69.1 mg, yield 82% (dr = 3:1)], and the two diastereomers were inseparable by chromatography. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 7.26 (s, 1H), 7.20-7.14 (m, 1H), 6.85 (d, J = 8.2 Hz, 1H), 4.27-4.12 (m, 1H), 3.24-3.03 (m, 1H), 2.86-2.54 (m, 4H), 2.37 (s, 3H), 1.83-1.67 (m, 1H), 1.58-1.48 (m, 3H), 1.42-1.08 (m, 10H), 0.90-0.78 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.73, 134.25, 130.30, 127.03, 124.15, 122.03, 117.68, 115.15, 110.80, 57.23, 40.76, 40.51, 33.19, 31.21, 30.60, 28.75, 26.60, 24.61, 22.96, 22.07, 21.29, 13.95; LRMS (ESI) *m/z*: 339 $[M+H]^+$, HRMS (ESI) *m/z* calculated for $C_{22}H_{30}N_2O+H^+$ 339.2431, found: 339.2428.

10-fluoro-2-hexyl-11c-methyl-5,6,7,11c-tetrahydro-1*H*-indolizino[7,8-*b*]indol-3(2*H*)-one (3k): yellow oil [60.1 mg, yield 70% (dr = 2.6:1)], and the two diastereomers were inseparable by chromatography. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.34-7.21 (m, 2H), 6.92-6.80 (m, 1H), 4.28-4.11 (m, 1H), 3.24-3.03 (m, 1H), 2.89-2.51 (m, 4H), 1.82-1.67 (m, 1H), 1.55-1.45 (m, 3H), 1.44-1.03 (m, 10H), 0.91-0.76 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.77, 156.70 (d, J_{C-F} = 231.0 Hz), 132.66, 132.50, 124.00 (d, J_{C-F} = 10.0 Hz), 115.98 (d, J_{C-F} = 4.6 Hz), 111.88 (d, J_{C-F} = 9.8 Hz), 108.33 (d, J_{C-F} = 25.8 Hz), 102.95 (d, J_{C-F} = 23.5 Hz), 57.05, 40.48, 40.38, 33.05, 31.19, 30.57, 28.71, 26.58, 24.41, 22.98, 22.04, 13.94; LRMS (ESI) *m/z*: 343 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{21}H_{27}FN_2O+H^+$ 343.2180, found: 343.2178.

11c-benzyl-5,6,7,11c-tetrahydro-1*H*-indolizino[7,8-*b*]indol-3(2*H*)-one (3l): pale yellow oil (52.8 mg, yield 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.26-7.23 (m, 3H), 7.22-7.13 (m, 2H), 7.12-7.06 (m, 2H), 4.50 (dd, J = 12.9, 6.4 Hz, 1H), 3.30 (d, J = 13.9 Hz, 1H), 3.21 (d, J = 13.9 Hz, 1H), 3.08-2.98 (m, 1H), 2.97-2.85 (m, 1H), 2.72-2.60 (m, 2H), 2.22-2.09 (m, 2H), 1.78-1.65 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.27, 136.70, 136.20, 130.55, 130.24, 128.51, 127.05, 124.36, 121.82, 119.90, 118.48, 115.89, 111.33, 63.79, 44.61, 34.29, 31.64, 30.97, 23.13; LRMS (ESI) *m/z*: 317 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{21}H_{20}N_2O+H^+$ 317.1648, found: 317.1651.

12c-benzyl-1,2,3,6,7,12c-hexahydroindolo[3,2-*a*]quinolizin-4(8*H*)-one (3m): pale yellow oil (42.1 mg, yield 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.23-7.14 (m, 3H), 7.06-6.96 (m, 3H), 6.94-6.86 (m, 1H), 4.85-4.74 (m, 1H), 3.41 (d, *J* = 13.5 Hz, 1H), 3.24 (d, *J* = 13.6 Hz, 1H), 2.81-2.64 (m, 3H), 2.61-2.53 (m, 1H), 2.24-2.05 (m, 2H), 1.90-1.78 (m, 1H), 1.68-1.54 (m, 1H), 1.52-1.41 (m, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.23, 137.82, 136.01, 132.97, 130.35, 127.91, 126.43, 124.32, 120.25, 118.98, 118.50, 114.22, 111.10, 60.85, 44.27, 35.01, 33.86, 31.69, 22.95, 16.34; LRMS (ESI) *m/z*: 331 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{22}H_{22}N_2O$ $+H^+$ 331.1805, found: 331.1812.

13b-benzyl-6,7-dihydro-5*H*-benzo[1,2]indolizino[7,8-*b*]indol-9(13b*H*)-one (3n): white solid (64.8 mg, yield 71%), mp 281-282 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.14 (s, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 7.66-7.58 (m, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.39-7.30 (m, 2H), 7.20-7.08 (m, 2H), 7.08-6.98 (m, 3H), 6.95-6.87 (m, 2H), 4.53 (dd, *J* = 13.0, 5.6 Hz, 1H), 3.85 (d, *J* = 13.9 Hz, 1H), 3.57 (d, *J* = 13.8 Hz, 1H), 3.49-3.38 (m, 1H), 2.91-2.72 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.69, 148.85, 135.93, 135.74, 132.77, 131.36, 130.99, 129.98, 127.83, 127.25, 126.17, 124.40, 123.87, 122.58, 120.74, 119.39, 119.12, 111.31, 111.13, 67.12, 42.72, 34.78, 23.45; LRMS (ESI) *m/z*: 365 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{25}H_{20}N_2O+H^+$ 365.1648, found: 365.1649.

14c-benzyl-8,9,10,14c-tetrahydroindolo[3',2':3,4]pyrido[2,1-*a*]isoquinolin-6(5*H*)-one (3o): pale yellow oil (45.2 mg, yield 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.96-7.88 (m, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.50-7.42 (m, 1H), 7.33-7.28 (m, 2H), 7.28-7.20 (m, 2H), 7.16-7.08 (m, 2H), 7.08-7.00 (m, 2H), 6.80-6.71 (m, 2H), 4.79 (dd, *J* = 12.7, 4.3 Hz, 1H), 3.96-3.76 (m, 3H), 3.40 (d, *J* = 13.8 Hz, 1H), 2.67-2.56 (m, 1H), 2.48-2.38 (m, 1H), 1.84-1.73 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.65, 140.98, 136.36, 136.08, 135.68, 132.27, 130.37, 128.23, 128.00, 127.71, 127.31, 126.87, 126.75, 125.97, 121.64, 121.40, 120.53, 111.66, 109.94, 66.48, 44.96, 39.14, 38.75, 23.34; LRMS (ESI) *m/z*: 379 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{26}H_{22}N_2O+H^+$ 379.1805, found: 379.1815.

13b-pentyl-6,7-dihydro-5*H*-benzo[1,2]indolizino[7,8-*b*]indol-9(13b*H*)-one (3p): pale yellow oil (44.6 mg, yield 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.62-7.54 (m, 1H), 7.45-7.38 (m, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.23-7.12 (m, 2H), 4.77 (dd, *J* = 13.1, 6.1 Hz, 1H), 3.38-3.24 (m, 1H), 3.13-2.98 (m, 1H), 2.76-2.58 (m, 2H), 2.24-2.10 (m, 1H), 1.20-1.02 (m, 5H), 0.89-0.83 (m, 1H), 0.77 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.42, 149.58, 136.09, 132.02, 131.85, 131.81, 128.13, 124.85, 123.91, 122.90, 121.75, 119.99, 119.43, 113.53, 111.43, 67.44, 38.22, 35.27, 31.80, 24.14, 23.15, 22.52, 14.09; LRMS (ESI) *m/z*: 345 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{23}H_{24}N_2O+H^+$ 345.1961, found: 345.1966.

11b-methyl-5,6,11,11b-tetrahydro-1*H*-indolizino[8,7-*b*]indol-3(2*H*)-one (5aa): white solid (53.8 mg, yield 90%), mp 260-261 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.06 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.10-7.02 (m, 1H), 7.01-6.94 (m, 1H), 4.25-4.16 (m, 1H), 3.11-3.00 (m, 1H), 2.75-2.67 (m, 1H), 2.66-2.55 (m, 2H), 2.32-2.20 (m, 2H), 2.07-1.99 (m, 1H), 1.54 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.88, 138.95, 135.93, 126.27, 120.99, 118.58, 117.98, 111.13, 104.66, 58.88, 34.26, 32.58, 30.08, 24.95, 20.90; LRMS (ESI) *m/z*: 241 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{16}N_2O+H^+$ 241.1335, found: 241.1331.

2-hexyl-11b-methyl-5,6,11,11b-tetrahydro-1*H*-indolizino[8,7-*b*]indol-3(2*H*)-one (5ab): white solid [70.9 mg, yield 87% (dr = 1.1:1)], and the two diastereomers were separable by chromatography. Diastereomer 1: white solid, mp 207-209 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.39-7.25 (m, 2H), 7.10-7.00 (m, 1H), 7.00-6.90 (m, 1H), 4.21-4.09 (m, 1H), 3.24-3.11 (m, 1H), 2.74-2.54 (m, 3H), 2.30-2.17 (m, 1H), 1.91-1.81 (m, 1H), 1.79-1.68 (m, 1H), 1.59 (s, 3H), 1.44-1.19 (m, 9H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.32, 138.66, 135.84, 126.41, 121.01, 118.56, 117.85, 111.13, 105.33, 58.18, 41.11, 37.53, 35.21, 31.59, 31.20, 28.57, 28.52, 26.86, 22.06, 20.13, 13.97; LRMS (ESI) *m/z*: 325 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{21}H_{28}N_2O+H^+$ 325.2274, found: 325.2271. Diastereomer 2: white solid, mp 250-252 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.09-7.02 (m, 1H), 7.00-6.93 (m, 1H), 4.24-4.17 (m, 1H), 3.09-3.01 (m, 1H), 2.78-2.61 (m, 2H), 2.61-2.50 (m, 2H), 1.76-1.68 (m, 1H), 1.65-1.56 (m, 1H), 1.53 (s, 3H), 1.35-1.08 (m, 9H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.06, 139.19, 135.93, 126.26, 121.01, 118.60, 118.01, 111.12, 104.38, 56.94, 40.41, 39.84, 34.21, 31.19, 30.40, 28.65, 26.52, 24.53, 22.03, 21.06, 13.96; LRMS (ESI) *m/z*: 325 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{21}H_{28}N_2O+H^+$ 325.2274, found: 325.2272.

8-methoxy-11b-methyl-5,6,11,11b-tetrahydro-1*H*-indolizino[8,7-*b*]indol-3(2*H*)-one (5ac): yellow oil (63.7 mg, yield 94%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.88 (s, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 2.3 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.24-4.15 (m, 1H), 3.74 (s, 3H), 3.10-2.98 (m, 1H), 2.73-2.64 (m, 1H), 2.64-2.52 (m, 2H), 2.31-2.20 (m, 2H), 2.07-1.97 (m, 1H), 1.53 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.86, 153.20, 139.67, 130.94, 126.60, 111.75, 110.78, 104.55, 100.18, 58.93, 55.38, 34.30, 32.63, 30.09, 24.99, 21.01; LRMS (ESI) *m/z*: 271 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{18}N_2O_2+H^+$ 271.1441, found: 271.1437.

2-hexyl-8-methoxy-11b-methyl-5,6,11,11b-tetrahydro-1*H*-indolizino[8,7-*b*]indol-3(2*H*)-one (5ad): white solid [53.8 mg, yield 61% (dr = 1.2:1)], and the two diastereomers were separable by chromatography. Diastereomer 1: white solid, mp 200-202 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.69 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.22-4.07 (m, 1H), 3.73 (s, 3H), 3.24-3.10 (m, 1H), 2.71-2.53 (m, 3H), 2.29-2.16 (m, 1H), 1.90-1.79 (m, 1H), 1.78-1.67 (m, 1H), 1.59 (s, 3H), 1.47-1.17 (m, 9H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.29, 153.20, 139.37, 130.87, 126.74, 111.73, 110.80, 105.21, 100.06, 58.21, 55.38, 41.10, 37.56, 35.23, 31.58, 31.20, 28.57, 28.55, 26.86, 22.06, 20.21, 13.96; LRMS (ESI) *m/z*: 355 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{22}H_{30}N_2O_2+H^+$ 355.2380, found: 355.2377. Diastereomer 2: white solid, mp 184-185 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.26-4.14 (m, 1H), 3.74 (s, 3H), 3.10-2.97 (m, 1H), 2.75-2.60 (m, 2H), 2.61-2.53 (m, 1H), 2.50-2.45 (m, 1H), 1.79-1.67 (m, 1H), 1.65-1.56 (m, 1H), 1.52 (s, 3H), 1.33-1.11 (m, 9H), 0.84 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.05, 153.22, 139.91, 130.95, 126.60, 111.71, 110.76, 104.28, 100.22, 56.97, 55.39, 40.40, 39.88, 34.23, 31.17, 30.40, 28.64, 26.50, 24.56, 22.01, 21.14, 13.94; LRMS (ESI) *m/z*: 355 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{22}H_{30}N_2O_2+H^+$ 355.2380, found: 355.2379.

12b-methyl-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (5ae): white solid (45.4 mg, yield 71%), mp 255-256 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.10-7.02 (m, 1H), 7.00-6.93 (m, 1H), 4.90-4.81 (m, 1H), 2.99-2.87 (m, 1H), 2.69-2.62 (m, 1H), 2.61-2.53 (m, 1H), 2.45-2.32 (m, 2H), 2.32-2.21 (m, 1H), 1.97-1.86 (m, 1H), 1.80-1.68 (m, 2H), 1.60 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.92, 139.68, 135.95, 126.19, 120.94, 118.53, 117.86, 111.05, 105.79, 56.37, 35.55, 34.77, 31.78, 25.32, 21.02, 16.30; LRMS (ESI) *m/z*: 255

$[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{18}N_2O+H^+$ 255.1492, found: 255.1488.

9-methoxy-12b-methyl-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (5af): pale yellow solid (55.9 mg, yield 79%), mp 190-191 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.90-4.79 (m, 1H), 3.74 (s, 3H), 2.99-2.86 (m, 1H), 2.66-2.51 (m, 2H), 2.42-2.21 (m, 3H), 1.97-1.84 (m, 1H), 1.79-1.66 (m, 2H), 1.59 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.90, 153.18, 140.39, 130.97, 126.50, 111.67, 110.73, 105.69, 100.05, 56.41, 55.38, 35.59, 34.79, 31.77, 25.39, 21.10, 16.33; LRMS (ESI) *m/z*: 285 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{20}N_2O_2+H^+$ 285.1598, found: 285.1593.

13b-methyl-7,8,13,13b-tetrahydro-5*H*-benzo[1,2]indolizino[8,7-*b*]indol-5-one (5ag): white solid (63.6 mg, yield 88%), mp 283-284 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (s, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 7.79-7.68 (m, 2H), 7.58-7.49 (m, 1H), 7.44-7.34 (m, 2H), 7.15-7.05 (m, 1H), 7.03-6.93 (m, 1H), 4.59-4.47 (m, 1H), 3.47-3.36 (m, 1H), 2.85-2.75 (m, 1H), 2.75-2.63 (m, 1H), 1.86 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.19, 149.33, 136.17, 135.17, 132.22, 130.25, 128.61, 125.97, 123.17, 122.77, 121.60, 118.88, 118.32, 111.21, 106.34, 62.01, 35.42, 25.89, 21.45; LRMS (ESI) *m/z*: 289 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{16}N_2O+H^+$ 289.1335, found: 289.1330.

10-methoxy-13b-methyl-7,8,13,13b-tetrahydro-5*H*-benzo[1,2]indolizino[8,7-*b*]indol-5-one (5ah): white solid (70.2 mg, yield 88%), mp 164-165 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.29 (d, *J* = 7.9 Hz, 1H), 7.77-7.67 (m, 2H), 7.58-7.47 (m, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 2.1 Hz, 1H), 6.73 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.57-4.45 (m, 1H), 3.73 (s, 3H), 3.45-3.35 (m, 1H), 2.81-2.73 (m, 1H), 2.72-2.60 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.15, 153.34, 149.37, 135.78, 132.21, 131.18, 130.24, 128.59, 126.32, 123.15, 122.76, 111.89, 111.54, 106.18, 100.29, 62.04, 55.36, 35.45, 25.96, 21.55; LRMS (ESI) *m/z*: 319 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{18}N_2O_2+H^+$ 319.1441, found: 319.1435.

14b-methyl-8,9,14,14b-tetrahydroindolo[2',3':3,4]pyrido[2,1-*a*]isoquinolin-6(5*H*)-one (5ai): pale yellow solid (65.0 mg, yield 86%), mp 137-138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H), 7.52-7.43 (m, 3H), 7.31-7.24 (m, 2H), 7.24-7.18 (m, 1H), 7.18-7.12 (m, 1H), 7.08-6.98 (m, 1H), 4.96-4.85 (m, 1H), 4.08 (d, *J* = 19.2 Hz, 1H), 3.63 (d, *J* = 19.4 Hz, 1H), 2.96-2.86 (m, 1H), 2.86-2.75 (m, 1H), 2.50-2.41 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.96, 139.88, 136.11, 135.07, 132.26, 127.79, 127.45, 126.35, 125.97, 124.13, 121.43, 118.81, 118.18, 111.30, 109.24, 60.89, 37.99, 37.89, 26.20, 21.05; LRMS (ESI) *m/z*: 303 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{18}N_2O+H^+$ 303.1492, found: 303.1487.

12b-methyl-1,5,6,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[1,2-*a*]indol-3(2*H*)-one (5aj): white solid (55.3 mg, yield 92%), mp 121-122 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.15-7.09 (m, 1H), 7.08-7.01 (m, 1H), 6.34 (s, 1H), 4.34-4.22 (m, 2H), 3.81-3.68 (m, 1H), 3.49-3.38 (m, 1H), 2.65-2.53 (m, 1H), 2.47-2.36 (m, 1H), 2.33-2.17 (m, 2H), 1.59 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.10, 142.15, 135.22, 127.61, 120.73, 119.90, 119.78, 109.62, 95.46, 58.63, 40.85, 34.33, 33.57, 29.65, 27.25; LRMS (ESI) *m/z*: 241 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{16}N_2O+H^+$ 241.1335, found: 241.1330.

8,12b-dimethyl-1,5,6,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[1,2-*a*]indol-3(2*H*)-one (5ak): yellow solid (57.7 mg, yield 91%), mp 159-161 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31 (d, *J* = 7.7 Hz, 1H), 6.91-6.85 (m, 1H), 6.80 (d, *J* = 7.1 Hz, 1H), 6.32 (s, 1H), 4.78-4.68 (m, 1H), 4.25-4.17 (m, 1H), 4.16-4.06 (m, 1H), 3.44-3.36 (m, 1H), 2.68 (s, 3H), 2.62-2.53 (m, 1H), 2.44-2.35 (m, 1H), 2.29-2.15 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.94, 142.25, 134.40, 128.28, 123.66, 121.20, 119.69, 118.03, 96.39, 58.53, 43.98, 34.71, 34.01, 29.63, 27.27, 19.81; LRMS (ESI) *m/z*: 255 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{18}N_2O+H^+$ 255.1492, found: 255.1487.

8-ethyl-12b-methyl-1,5,6,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[1,2-*a*]indol-3(2*H*)-one (5al): colorless oil (56.4 mg, yield 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.09-7.02 (m, 1H), 7.01-6.95 (m, 1H), 6.32 (s, 1H), 4.65-4.55 (m, 1H), 4.51-4.40 (m, 1H), 4.25-4.10 (m, 1H), 3.49-3.34 (m, 1H), 3.16-2.98 (m, 2H), 2.71-2.55 (m, 1H), 2.52-2.31 (m, 3H), 1.65 (s, 3H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.01, 142.05, 134.38, 129.05, 127.83, 122.98, 120.56, 118.51, 97.62, 59.34, 44.39, 35.16, 34.77, 30.25, 27.78, 26.06, 16.51; LRMS (ESI) *m/z*: 269 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{20}N_2O+H^+$ 269.1648, found: 269.1644.

10-methoxy-12b-methyl-1,5,6,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[1,2-*a*]indol-3(2*H*)-one (5am): pale yellow oil (62.4 mg, yield 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.8 Hz, 1H), 7.06-7.01 (m, 1H), 6.85 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.20 (s, 1H), 4.50 (dd, *J* = 13.6, 4.9 Hz, 1H), 4.15 (dd, *J* = 11.6, 4.6 Hz, 1H), 3.90-3.82 (m, 4H), 3.43-3.31 (m, 1H), 2.69-2.56 (m, 1H), 2.51-2.32 (m, 3H), 1.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.31, 154.75, 142.22, 130.98, 128.47, 111.61, 109.85, 102.43, 95.87, 59.49, 55.99, 41.23, 34.77, 34.20, 30.26, 27.65; LRMS (ESI) *m/z*: 271 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{18}N_2O_2+H^+$ 271.1441, found: 271.1436.

12b-methyl-3-oxo-1,2,3,5,6,12b-hexahydropyrrolo[2',1':3,4]pyrazino[1,2-*a*]indole-10-carbonitrile (5an): yellow solid (54.3 mg, yield 82%), mp 182-183 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 6.54 (s, 1H), 4.45-4.36 (m, 1H), 4.33-4.24 (m, 1H), 3.89-3.77 (m, 1H), 3.50-3.39 (m, 1H), 2.66-2.54 (m, 1H), 2.48-2.40 (m, 1H), 2.32-2.17 (m, 2H), 1.60 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.10, 144.85, 136.80, 127.37, 125.40, 123.57, 120.62, 111.12, 101.83, 96.60, 58.59, 41.28, 34.21, 33.33, 29.57, 27.06; LRMS (ESI) *m/z*: 266 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{15}N_3O+H^+$ 266.1288, found: 266.1285.

12b-methyl-10-nitro-1,5,6,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[1,2-*a*]indol-3(2*H*)-one (5ao): yellow oil (32.9 mg, yield 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 2.2 Hz, 1H), 8.07 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.28 (d, *J* = 9.1 Hz, 1H), 6.46 (s, 1H), 4.57 (dd, *J* = 13.8, 4.5 Hz, 1H), 4.27 (dd, *J* = 12.0, 3.9 Hz, 1H), 4.02-3.90 (m, 1H), 3.48-3.36 (m, 1H), 2.69-2.58 (m, 1H), 2.53-2.35 (m, 3H), 1.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.04, 145.02, 142.25, 138.45, 127.30, 117.54, 117.23, 109.10, 98.66, 59.28, 41.72, 34.78, 33.82, 30.11, 27.63; LRMS (ESI) *m/z*: 286 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{15}N_3O_3+H^+$ 286.1186, found: 286.1182.

10-fluoro-12b-methyl-1,5,6,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[1,2-*a*]indol-3(2*H*)-one (5ap): colorless oil (95.1 mg, yield 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.12 (m, 2H), 6.99-6.88 (m, 1H), 6.25 (s, 1H), 4.57-4.46 (m, 1H), 4.22-4.12 (m, 1H), 3.94-3.80 (m, 1H), 3.46-3.31 (m, 1H), 2.68-2.54 (m, 1H), 2.51-2.31 (m, 3H), 1.63 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.10, 158.34 (d, J_{C-F} = 235.0 Hz), 143.30, 132.31, 128.33 (d, J_{C-F} = 10.3 Hz), 109.86 (d, J_{C-F} = 17.5 Hz), 109.68, 105.36 (d, J_{C-F} = 23.6 Hz), 96.28 (d, J_{C-F} = 4.5 Hz), 59.35, 41.32, 34.75, 34.05, 30.22, 27.62; LRMS (ESI) *m/z*: 259 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{15}FN_2O+H^+$ 259.1241, found: 259.1239.

10-bromo-12b-methyl-1,5,6,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[1,2-*a*]indol-3(2*H*)-one (5aq): pale yellow solid (67.6 mg, yield 85%), mp 119-120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, *J* = 1.8 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.30 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.42 (s, 1H), 4.41-4.30 (m, 2H), 3.89-3.76 (m, 1H), 3.56-3.44 (m, 1H), 2.72-2.60 (m, 1H), 2.52-2.43 (m, 1H), 2.37-2.23 (m, 2H), 1.64 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.06, 143.69, 133.97, 129.41, 123.17, 122.09, 112.30, 111.72, 95.27, 58.55, 41.03, 34.23, 33.41, 29.60, 27.10; LRMS (ESI) *m/z*: 321 ([M+H]$^+$, Br^{81}), 319 ([M+H]$^+$, Br^{79}); HRMS (ESI) *m/z* calculated for $C_{15}H_{15}BrN_2O+H^+$ 319.0441, found: 319.0439.

2-hexyl-12b-methyl-1,5,6,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[1,2-*a*]indol-3(2*H*)-one (5ar): pale yellow oil [46.1 mg, yield 57% (dr = 1.7:1)], and the two diastereomers were inseparable by chromatography. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60-7.56 (m, 0.88H), 7.30-7.24 (m, 1.14H), 7.23-7.18 (m, 0.91H), 7.16-7.11 (m, 0.87H), 6.30 (s, 0.52H), 6.29 (s, 0.31H), 4.58-4.46 (m, 0.89H), 4.29-4.20 (m, 0.33H), 4.17-4.07 (m, 0.54H), 3.98-3.91 (m, 0.53H), 3.90-3.83 (m, 0.34H), 3.56-3.45 (m, 0.53H), 3.42-3.32 (m, 0.30H), 2.81-2.74 (m, 0.53H), 2.70-2.62 (m, 0.68H), 2.47-2.37 (m, 0.58H), 2.09-2.00 (m, 0.60H), 2.01-1.90 (m, 1.35H), 1.69 (s, 1.71H), 1.62 (s, 1.04H), 1.55-1.14 (m, 9.70H), 0.93-0.82 (m, 3.12H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.20, 174.63, 142.18, 141.52, 136.21, 135.51, 128.18, 127.90, 121.62, 121.55, 120.48, 120.46, 109.19, 109.15, 96.36, 96.11, 58.44, 57.51, 42.32, 41.85, 41.53, 41.11, 40.53, 40.47, 34.55, 34.17, 31.96, 31.82, 31.77, 30.86, 30.59, 29.25, 27.52, 27.30, 27.25, 22.72, 22.68, 14.20; LRMS (ESI) *m/z*: 325[M+H]$^+$; HRMS (ESI) *m/z* calculated for $C_{21}H_{28}N_2O+H^+$ 325.2274, found: 325.2273.

13b-methyl-2,3,6,7-tetrahydro-1*H*-pyrido[2',1':3,4]pyrazino[1,2-*a*]indol-4(13b*H*)-one (5as): white solid (42.2 mg, yield 66%), mp 113-114 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.50 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.14-7.07 (m, 1H), 7.06-7.01 (m, 1H), 6.34 (s, 1H), 4.95-4.85 (m, 1H), 4.33-4.24 (m, 1H), 3.81-3.70 (m, 1H), 3.40-3.25 (m, 1H), 2.42-2.26 (m, 3H), 2.07-1.99 (m, 1H), 1.98-1.88 (m, 1H), 1.78-1.69 (m, 1H), 1.67 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.11, 142.39, 135.06, 127.66, 120.55, 119.85, 119.70, 109.41, 95.16, 56.72, 41.23, 36.60, 34.53, 31.66, 28.24, 16.87; LRMS (ESI) *m/z*: 255 [M+H]$^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{18}N_2O+H^+$ 255.1492, found: 255.1488.

11-methoxy-13b-methyl-2,3,6,7-tetrahydro-1*H*-pyrido[2',1':3,4]pyrazino[1,2-*a*]indol-4(13b*H*)-one (5at): pale yellow oil (56.7 mg, yield 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.17 (s, 1H), 5.15 (dd, *J* = 13.7, 3.6 Hz, 1H), 4.13 (dd, *J* = 11.7, 3.2 Hz, 1H), 3.97-3.78 (m, 4H), 3.39-3.22 (m, 1H), 2.63-2.28 (m, 3H), 2.21-1.83 (m, 3H), 1.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.49, 154.73, 142.60, 130.91, 128.50, 111.50, 109.74, 102.38, 95.41, 57.36, 56.06, 41.67, 37.37, 35.30, 32.18, 28.77, 17.38; LRMS (ESI) *m/z*: 285 [M+H]$^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{20}N_2O_2+H^+$ 285.1598, found: 285.1594.

9-ethyl-13b-methyl-2,3,6,7-tetrahydro-1*H*-pyrido[2',1':3,4]pyrazino[1,2-*a*]indol-4(13b*H*)-one (5au): pale yellow oil (51.1 mg, yield 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.37 (m, 1H), 7.09-7.01 (m, 1H), 7.00-6.93 (m, 1H), 6.28 (s, 1H), 5.13-5.01 (m, 1H), 4.62-4.50 (m, 1H), 4.33-4.18 (m, 1H), 3.39-3.21 (m, 1H), 3.14-3.00 (m, 2H), 2.65-2.22 (m, 3H), 2.19-1.83 (m, 3H), 1.74 (s, 3H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.23, 142.35, 134.20, 129.06, 127.79, 122.62, 120.42, 118.38, 97.12, 57.49, 44.90, 37.67, 35.99, 31.89, 28.63, 25.79, 17.37, 16.59; LRMS (ESI) *m/z*: 283 [M+H]$^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{22}N_2O+H^+$ 283.1805, found: 283.1801.

10-fluoro-13b-methyl-2,3,6,7-tetrahydro-1*H*-pyrido[2',1':3,4]pyrazino[1,2-*a*]indol-4(13b*H*)-one (5av): pale yellow oil (39.7 mg, yield 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.6, 5.3 Hz, 1H), 6.98-6.83 (m, 2H), 6.22 (s, 1H), 5.15 (ddd, *J* = 13.8, 4.6, 1.2 Hz, 1H), 4.08 (ddd, *J* = 11.6, 4.3, 1.3 Hz, 1H), 3.94-3.82 (m, 1H), 3.38-3.24 (m, 1H), 2.61-2.49 (m, 1H), 2.48-2.38 (m, 1H), 2.36-2.29 (m, 1H), 2.21-2.09 (m, 1H), 2.03-1.93 (m, 1H), 1.93-1.83 (m, 1H), 1.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.46, 159.51 (d, J_{C-F} = 237.8 Hz), 142.49 (d, J_{C-F} = 3.6 Hz), 135.55 (d, J_{C-F} = 11.9 Hz), 124.46, 121.10 (d, J_{C-F} = 9.9 Hz), 108.93 (d, J_{C-F} = 24.4 Hz), 95.75, 95.58 (d, J_{C-F} = 26.4 Hz), 57.35, 41.72, 37.37, 35.16, 32.15, 28.85, 17.35; LRMS (ESI) *m/z*: 273 [M+H]$^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{17}FN_2O+H^+$ 273.1398, found: 273.1393.

13b-methyl-6,7-dihydroisoindolo[1',2':3,4]pyrazino[1,2-*a*]indol-9(13b*H*)-one (5aw): pale yellow solid (52.5 mg, yield 73%), mp 149-150 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, *J* = 7.6 Hz, 1H), 7.80-7.69 (m, 2H), 7.59-7.48 (m, 2H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.17-7.09 (m, 1H), 7.08-7.00 (m, 1H), 6.84 (s, 1H), 4.68-4.57 (m, 1H), 4.45-4.31 (m, 1H), 3.90-3.75 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.58, 150.30, 137.82, 135.25, 132.70, 129.85, 128.71, 127.29, 123.08, 121.17, 120.01, 119.95, 109.91, 97.80, 61.38, 41.06, 34.25, 28.19; LRMS (ESI) *m/z*: 289 [M+H]$^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{16}N_2O+H^+$ 289.1335, found: 289.1332.

15b-methyl-8,9-dihydro-5*H*-indolo[2',1':3,4]pyrazino[2,1-*a*]isoquinolin-6(15b*H*)-one (5ax): yellow solid (41.3 mg, yield 55%), mp 235-236 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.44-7.38 (m, 2H), 7.33-7.25 (m, 2H), 7.23-7.15 (m, 2H), 7.15-7.08 (m, 1H), 6.83 (s, 1H), 4.99-4.90 (m, 1H), 4.40-4.31 (m, 1H), 4.10 (d, *J* = 19.4 Hz, 1H), 3.81-3.72 (m, 1H), 3.68 (d, *J* = 19.5 Hz, 1H), 3.20-3.08 (m, 1H), 1.89 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.25, 138.64, 136.90, 136.55, 132.07, 128.00, 127.65, 127.20, 126.45, 124.22, 121.37, 120.31, 119.92, 109.74, 101.43, 61.84, 42.84, 37.73, 37.40, 28.57; LRMS (ESI) *m/z*: 303 [M+H]$^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{18}N_2O+H^+$ 303.1492, found: 303.1487.

13b-methyl-5,6,7,13b-tetrahydro-1*H*-pyrrolo[2',1':3,4][1,4]diazepino[1,2-*a*]indol-3(2*H*)-one (5ay): colorless oil (46.2 mg, yield 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.24-7.19 (m, 1H), 7.13-7.06 (m, 1H), 6.45 (s, 1H), 4.56-4.33 (m, 2H), 4.20 (ddd, *J* = 14.8, 9.1, 2.5 Hz, 1H), 3.17-3.04 (m, 1H), 2.80-2.70 (m, 1H), 2.53-2.42 (m, 2H), 2.14-1.88 (m, 3H), 1.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.15, 142.53, 137.66, 126.93, 122.01, 120.69, 119.87, 109.04, 99.59, 62.41, 43.37, 38.51, 34.96, 30.47, 28.05, 26.37; LRMS (ESI) *m/z*: 255 [M+H]$^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{18}N_2O+H^+$ 255.1492, found: 255.1489.

9-ethyl-13b-methyl-5,6,7,13b-tetrahydro-1*H*-pyrrolo[2',1':3,4][1,4]diazepino[1,2-*a*]indol-3(2*H*)-one (5az): pale yellow oil (54.7 mg, yield 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.06-6.96 (m, 2H), 6.48 (s, 1H), 4.68-4.58 (m, 1H), 4.49 (ddd, *J* = 15.1, 7.0, 2.9 Hz, 1H), 4.29 (ddd, *J* = 14.1, 5.8, 2.8 Hz, 1H), 3.16-2.96 (m, 3H), 2.73-2.61 (m, 1H), 2.56-2.43 (m, 2H), 2.15-1.93 (m, 3H), 1.73 (s, 3H), 1.37 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.15, 142.62, 135.62, 128.17, 127.02, 124.35, 120.09, 118.96, 101.49, 62.71, 44.41, 37.80, 35.57, 30.42, 28.09, 27.20, 26.23, 15.89; LRMS (ESI) *m/z*: 283 [M+H]$^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{22}N_2O+H^+$ 283.1805, found: 283.1802.

10-fluoro-13b-methyl-5,6,7,13b-tetrahydro-1*H*-pyrrolo[2',1':3,4][1,4]diazepino[1,2-*a*]indol-3(2*H*)-one (5ba): pale yellow oil (42.9 mg, yield 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.6, 5.5 Hz, 1H), 6.96 (dd, *J* = 10.3, 2.0 Hz, 1H), 6.89-6.80 (m, 1H), 6.40 (s, 1H), 4.43-4.27 (m, 2H), 4.20-4.06 (m, 1H), 3.16-3.02 (m, 1H), 2.78-

2.64 (m, 1H), 2.51-2.40 (m, 2H), 2.12-1.87 (m, 3H), 1.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.02, 159.98 (d, J_{C-F} = 237.7 Hz), 142.96 (d, J_{C-F} = 3.6 Hz), 137.75 (d, J_{C-F} = 11.8 Hz), 123.15, 121.36 (d, J_{C-F} = 10.1 Hz), 108.48 (d, J_{C-F} = 24.4 Hz), 99.51, 95.70 (d, J_{C-F} = 26.8 Hz), 62.20, 43.81, 38.45, 34.74, 30.40, 28.00, 26.29; LRMS (ESI) *m/z*: 273 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{17}FN_2O+H^+$ 273.1398, found: 273.1392.

14b-methyl-1,14b-dihydroindolo[1,2-*a*]pyrrolo[2,1-*c*]quinoxalin-3(2*H*)-one (5bb): pale yellow solid (64.3 mg, yield 89%), mp 179-180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, *J* = 8.1 Hz, 1H), 8.13-8.04 (m, 2H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.46-7.39 (m, 1H), 7.35-7.26 (m, 2H), 7.25-7.17 (m, 1H), 6.64 (s, 1H), 2.95-2.81 (m, 1H), 2.69-2.55 (m, 2H), 2.55-2.45 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.18, 142.66, 133.14, 129.30, 128.79, 125.81, 125.74, 124.08, 122.97, 122.70, 121.39, 121.16, 117.24, 111.80, 97.57, 59.35, 31.19, 30.04, 25.92; LRMS (ESI) *m/z*: 289 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{16}N_2O+H^+$ 289.1335, found: 289.1331.

15b-methyl-2,3-dihydro-1*H*-indolo[1,2-*a*]pyrido[2,1-*c*]quinoxalin-4(15b*H*)-one (5bc): pale yellow oil (50.3 mg, yield 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08-8.01 (m, 2H), 7.71-7.64 (m, 2H), 7.47-7.40 (m, 1H), 7.33-7.24 (m, 2H), 7.23-7.17 (m, 1H), 6.60 (s, 1H), 2.71-2.56 (m, 2H), 2.42-2.28 (m, 2H), 1.97-1.75 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.17, 142.52, 133.20, 130.55, 129.10, 128.41, 127.78, 126.59, 123.42, 122.80, 121.25, 121.18, 116.89, 111.53, 96.76, 57.29, 33.27, 32.89, 27.70, 17.12; LRMS (ESI) *m/z*: 303 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{18}N_2O+H^+$ 303.1492, found: 303.1486.

15b-methylindolo[1,2-*a*]isoindolo[1,2-*c*]quinoxalin-11(15b*H*)-one (5bd): white solid (52.3 mg, yield 62%), mp 149-150 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, *J* = 7.6 Hz, 1H), 8.31-8.26 (m, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.04 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.96-7.87 (m, 2H), 7.76-7.68 (m, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.57-7.51 (m, 1H), 7.47-7.40 (m, 1H), 7.35-7.29 (m, 1H), 7.24-7.18 (m, 1H), 6.77 (s, 1H), 1.65 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.12, 146.45, 137.13, 133.86, 133.53, 129.71, 129.49, 129.32, 128.95, 126.54, 124.60, 124.42, 124.03, 123.85, 123.67, 123.46, 121.63, 121.33, 117.52, 111.94, 99.28, 61.21, 26.30; LRMS (ESI) *m/z*: 337 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{23}H_{16}N_2O+H^+$ 337.1335, found: 337.1329.

11b-methyl-4,5-dihydro-3*H*-pyrrolo[3',2':3,4]pyrido[2,1-*a*]isoindol-7(11b*H*)-one (7a): pale yellow solid (41.1 mg, yield 69%), mp 237-238 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.68-7.60 (m, 2H), 7.49-7.42 (m, 1H), 6.62-6.55 (m, 1H), 6.31-6.26 (m, 1H), 4.48-4.37 (m, 1H), 3.41-3.27 (m, 1H), 2.66-2.54 (m, 2H), 1.66 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.84, 152.18, 131.93, 129.95, 127.76, 122.75, 122.73, 122.34, 119.86, 116.84, 103.97, 62.26, 34.48, 27.71, 22.62; LRMS (ESI) *m/z*: 239 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{14}N_2O+H^+$ 239.1179, found: 239.1175.

12b-methyl-5,6-dihydropyrrolo[2',1':3,4]pyrazino[2,1-*a*]isoindol-8(12b*H*)-one (7b): pale yellow solid (50.6 mg, yield 85%), mp 156-157 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06 (d, *J* = 7.9 Hz, 1H), 7.75-7.65 (m, 2H), 7.55-7.47 (m, 1H), 6.67-6.60 (m, 1H), 6.39-6.31 (m, 1H), 6.06-5.98 (m, 1H), 4.45 (dd, *J* = 13.3, 4.2 Hz, 1H), 4.08 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.78-3.70 (m, 1H), 3.69-3.60 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.82, 151.09, 132.61, 129.96, 129.64, 128.35, 122.95, 122.78, 119.44, 107.82, 104.20, 61.35, 43.80, 34.87, 28.51; LRMS (ESI) *m/z*: 239 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{14}N_2O+H^+$ 239.1179, found: 239.1175.

9a-methyl-4,5,9,9a-tetrahydrothieno[3,2-*g*]indolizin-7(8*H*)-one (7c): colorless oil (47.5 mg, yield 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40 (d, *J* = 5.0 Hz, 1H), 6.80 (d, *J* = 5.1 Hz, 1H), 4.11 (dd, *J* = 13.3, 6.2 Hz, 1H), 3.07-2.96 (m, 1H), 2.72-2.63 (m, 1H), 2.61-2.51 (m, 2H), 2.32-2.19 (m, 2H), 2.03-1.92 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.66, 141.84, 132.28, 127.06, 123.48, 60.38, 35.08, 33.58, 30.20, 27.88, 25.10; LRMS (ESI) *m/z*: 208 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{11}H_{13}NOS+H^+$ 208.0791, found: 208.0788.

11b-methyl-4,5-dihydrothieno[2',3':3,4]pyrido[2,1-*a*]isoindol-7(11b*H*)-one (7d): pale yellow solid (59.2 mg, yield 93%), mp 137-138 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97-7.90 (m, 1H), 7.76-7.67 (m, 2H), 7.57-7.49 (m, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 6.82 (d, *J* = 5.1 Hz, 1H), 4.43 (dd, *J* = 13.5, 6.2 Hz, 1H), 3.40 (ddd, *J* = 13.4, 12.0, 4.7 Hz, 1H), 2.76 (dd, *J* = 16.2, 4.5 Hz, 1H), 2.62 (ddd, *J* = 16.2, 11.7, 6.5 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.55, 150.20, 137.99, 133.42, 132.47, 130.02, 128.68, 127.07, 124.45, 123.13, 122.41, 63.14, 34.35, 28.78, 25.59; LRMS (ESI) *m/z*: 256 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{13}NOS+H^+$ 256.0791, found: 256.0789.

12b-methyl-8,12b-dihydro-4*H*-thieno[2',3':3,4]pyrido[2,1-*a*]isoquinolin-7(5*H*)-one (7e): pale yellow solid (38.6 mg, yield 57%), mp 155-156 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.77-7.71 (m, 1H), 7.55 (d, *J* = 5.1 Hz, 1H), 7.32-7.22 (m, 3H), 6.91 (d, *J* = 5.1 Hz, 1H), 4.90-4.79 (m, 1H), 3.97 (d, *J* = 20.2 Hz, 1H), 3.64 (d, *J* = 20.3 Hz, 1H), 3.10-2.99 (m, 1H), 2.76-2.68 (m, 1H), 2.50-2.44 (m, 1H), 1.87 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.85, 139.01, 138.79, 136.38, 131.27, 127.97, 127.59, 127.45, 126.50, 124.84, 124.55, 62.60, 37.03, 36.71, 31.74, 25.20; LRMS (ESI) *m/z*: 270 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{15}NOS+H^+$ 270.0947, found: 270.0942.

9a-methyl-4,5,9,9a-tetrahydrothieno[2,3-*g*]indolizin-7(8*H*)-one (7f): pale yellow solid (39.5 mg, yield 76%). mp 128-129 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (d, *J* = 5.1 Hz, 1H), 6.99 (d, *J* = 5.2 Hz, 1H), 4.15 (dd, *J* = 13.2, 5.6 Hz, 1H), 3.09-2.98 (m, 1H), 2.85-2.76 (m, 1H) 2.74-2.62 (m, 1H), 2.61-2.52 (m, 1H), 2.31-2.15 (m, 2H), 1.90-1.79 (m, 1H), 1.42 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.57, 141.76, 131.34, 124.18, 124.06, 60.37, 33.69, 33.40, 30.06, 25.75, 24.31; LRMS (ESI) *m/z*: 208 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{11}H_{13}NOS+H^+$ 208.0791, found: 208.0788.

11b-methyl-4,5-dihydrothieno[3',2':3,4]pyrido[2,1-*a*]isoindol-7(11b*H*)-one (7g): yellow solid (58.6 mg, yield 92%), mp 199-200 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, *J* = 7.6 Hz, 1H), 7.74-7.63 (m, 2H), 7.56-7.48 (m, 2H), 7.39 (d, *J* = 5.3 Hz, 1H), 4.47 (dd, *J* = 13.4, 5.7 Hz, 1H), 3.46-3.38 (m, 1H), 2.93-2.84 (m, 1H), 2.82-2.71 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.78, 150.24, 137.84, 132.75, 132.30, 130.06, 128.41, 125.25, 124.03, 122.99, 122.98, 63.45, 34.70, 27.02, 24.81; LRMS (ESI) *m/z*: 256 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{13}NOS+H^+$ 256.0791, found: 256.0785.

8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (7h): white solid (55.5 mg, yield 85%), mp 53-54 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.78 (s, 1H), 6.66 (s, 1H), 4.08-4.00 (m, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.05-2.96 (m, 1H), 2.70-2.62 (m, 2H), 2.59-2.47 (m, 1H), 2.45-2.37 (m, 1H), 2.25-2.15 (m, 1H), 1.93-1.82 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.27, 147.74, 147.38, 134.89, 124.06, 111.90, 108.70, 60.31, 55.76, 55.47, 34.28, 33.43, 30.20, 27.72, 26.81; LRMS (ESI) *m/z*: 262 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{15}H_{19}NO_3+H^+$ 262.1438, found: 262.1434.

9,10-dimethoxy-11b-methyl-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one (7i): white solid (45.1 mg, yield 66%), mp 75-76 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (s, 1H), 6.65 (s, 1H), 4.75-4.63 (m, 1H),

3.74 (s, 3H), 3.71 (s, 3H), 2.87-2.75 (m, 1H), 2.68-2.53 (m, 2H), 2.49-2.41 (m, 1H), 2.37-2.16 (m, 2H), 1.96-1.81 (m, 1H), 1.75-1.64 (m, 1H), 1.64-1.57 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.68, 147.44, 147.17, 135.24, 125.45, 111.74, 109.31, 58.21, 55.84, 55.41, 36.66, 34.85, 31.54, 28.47, 27.26, 16.55; LRMS (ESI) *m/z*: 276 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{21}NO_3+H^+$ 276.1594, found: 276.1589.

2,3-dimethoxy-12b-methyl-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (7j): white solid (66.7 mg, yield 86%), mp 187-188 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (d, *J* = 7.7 Hz, 1H), 7.72-7.65 (m, 2H), 7.53-7.47 (m, 1H), 7.39 (s, 1H), 6.69 (s, 1H), 4.39-4.31 (m, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.42-3.34 (m, 1H), 2.83-2.67 (m, 2H), 1.82 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.48, 151.09, 147.75, 147.50, 132.16, 130.82, 130.34, 128.27, 125.26, 123.38, 122.80, 112.22, 110.23, 63.38, 56.07, 55.45, 34.63, 28.75, 28.19; LRMS (ESI) *m/z*: 310 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{19}NO_3+H^+$ 310.1438, found: 310.1432.

3a-methyl-3,3a-dihydro-1*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione (9a): white solid (47.1 mg, yield 87%), mp 114-115 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08-7.92 (m, 2H), 7.83-7.76 (m, 1H), 7.44-7.36 (m, 1H), 2.82-2.71 (m, 1H), 2.68-2.59 (m, 1H), 2.48-2.41 (m, 2H), 1.63 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.74, 161.12, 136.08, 135.65, 129.86, 125.51, 120.47, 115.69, 95.42, 31.72, 29.06, 24.01; LRMS (ESI) *m/z*: 218 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{12}H_{11}NO_3+H^+$ 218.0812, found: 218.0809.

4a-methyl-2,3,4,4a-tetrahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-1,6-dione (9b): colorless oil (37.6 mg, yield 65%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98-7.93 (m, 1H), 7.77-7.70 (m, 2H), 7.46-7.39 (m, 1H), 2.68-2.58 (m, 1H), 2.55-2.48 (m, 1H), 2.31-2.21 (m, 2H), 1.95-1.86 (m, 1H), 1.86-1.77 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.04, 161.83, 138.55, 134.13, 128.65, 126.10, 119.86, 92.69, 34.88, 32.91, 25.85, 16.12; LRMS (ESI) *m/z*: 232 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{13}H_{13}NO_3+H^+$ 232.0968, found: 232.0965.

6a-methyl-5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-dione (9c): pale yellow solid (31.2 mg, yield 47%), mp 138-139 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.06-8.00 (m, 2H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.93-7.85 (m, 2H), 7.79-7.73 (m, 1H), 7.51-7.45 (m, 1H), 1.94 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.06, 161.32, 143.85, 135.98, 135.68, 134.35, 131.28, 130.15, 129.42, 125.73, 124.22, 123.16, 121.19, 115.32, 92.53, 23.39; LRMS (ESI) *m/z*: 266 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{11}NO_3+H^+$ 266.0812, found: 266.0807.

3a-methyl-3,3a-dihydro-1*H*-naphtho[2,3-*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione (9d): yellow solid (62.7 mg, yield 94%), mp 228-230 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.44 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.67-7.62 (m, 1H), 7.56-7.51 (m, 1H), 2.84-2.77 (m, 1H), 2.76-2.68 (m, 1H), 2.68-2.61 (m, 1H), 2.50-2.42 (m, 1H), 1.72 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.72, 162.30, 136.68, 133.20, 131.07, 130.48, 129.89, 129.74, 128.02, 126.89, 119.44, 115.70, 95.71, 32.32, 29.62, 25.66; LRMS (ESI) *m/z*: 268 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{13}NO_3+H^+$ 268.0968, found: 268.0962.

4a-methyl-2,3,4,4a-tetrahydronaphtho[2,3-*d*]pyrido[2,1-*b*][1,3]oxazine-1,6-dione (9e): pale yellow oil (56.7 mg, yield 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.22 (s, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.66-7.61 (m, 1H), 7.57-7.53 (m, 1H), 2.74-2.61 (m, 2H), 2.52-2.46 (m, 1H), 2.22-2.12 (m, 2H), 1.94-1.87 (m, 1H), 1.64 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.30, 163.29, 135.95, 133.05, 131.84, 130.78, 129.56, 129.49, 128.24, 127.11, 124.86, 119.21, 92.53, 36.27, 33.68, 27.68, 16.73; LRMS (ESI) *m/z*: 282 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{15}NO_3+H^+$ 282.1125, found: 282.1117.

4b-methyl-4b*H*-naphtho[2',3':4,5][1,3]oxazino[2,3-*a*]isoindole-6,14-dione (9f): white solid (71.1 mg, yield 90%), mp 210-212 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.49 (s, 1H), 8.02-7.95 (m, 3H), 7.81-7.79 (m, 1H), 7.78-7.74 (m, 1H), 7.69-7.64 (m, 2H), 7.58-7.54 (m, 1H), 1.98 (s, 3H); ^{13}C NMR (151 MHz,) δ 164.68, 162.41, 144.04, 136.93, 133.93, 133.54, 131.07, 130.87, 130.41, 130.30, 130.03, 129.85, 128.00, 126.82, 124.78, 122.63, 119.39, 115.03, 92.73, 25.00; LRMS (ESI) *m/z*: 316 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{13}NO_3+H^+$ 316.0968, found: 316.0959.

6a-methyl-7,8-dihydro-5*H*-pyrido[2,3-*d*]pyrrolo[2,1-*b*][1,3]oxazine-5,9(6a*H*)-dione (9g): colorless oil (19.0 mg, yield 35%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 4.9, 1.9 Hz, 1H), 8.42 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.36 (dd, *J* = 7.7, 4.9 Hz, 1H), 2.86-2.69 (m, 2H), 2.68-2.60 (m, 1H), 2.52-2.41 (m, 1H), 1.72 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.58, 161.32, 155.13, 149.05, 139.45, 121.98, 112.97, 96.08, 32.25, 29.76, 25.38; LRMS (ESI) *m/z*: 219 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{11}H_{10}N_2O_3+H^+$ 219.0764, found: 219.0763.

3a-methyl-2,3,3a,5-tetrahydro-1*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazin-1-one (9h): pale yellow oil (18.3 mg, yield 36%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20 (d, *J* = 8.1 Hz, 1H), 7.32-7.25 (m, 1H), 7.21-7.16 (m, 1H), 7.16-7.10 (m, 1H), 4.99 (d, *J* = 16.0 Hz, 1H), 4.88 (d, *J* = 16.0 Hz, 1H), 2.76-2.65 (m, 1H), 2.43 (ddd, *J* = 17.1, 10.0, 2.1 Hz, 1H), 2.29-2.19 (m, 1H), 2.07-1.97 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.92, 132.65, 127.14, 124.69, 123.67, 123.17, 119.21, 89.63, 61.98, 32.53, 29.65, 20.73; LRMS (ESI) *m/z*: 204 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{12}H_{13}NO_2+H^+$ 204.1019, found: 204.1017.

6a-methyl-5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindol-11(6a*H*)-one (9i): colorless oil (18.5 mg, yield 29%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.68-7.60 (m, 2H), 7.59-7.54 (m, 1H), 7.40-7.35 (m, 1H), 7.19-7.15 (m, 1H), 7.14-7.10 (m, 1H), 5.20 (d, *J* = 15.3 Hz, 1H), 4.98 (d, *J* = 15.3 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.22, 146.07, 133.09, 132.63, 131.24, 130.17, 127.86, 124.33, 124.32, 124.22, 122.96, 121.81, 121.50, 88.12, 63.26, 20.80; LRMS (ESI) *m/z*: 252 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{13}NO_2+H^+$ 252.1019, found: 252.1018.

3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (9j): white solid (43.0 mg, yield 80%), mp 177-178 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.65-7.57 (m, 1H), 7.32-7.25 (m, 1H), 2.78-2.68 (m, 1H), 2.56-2.49 (m, 1H), 2.30-2.19 (m, 2H), 1.42 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.88, 161.24, 135.69, 133.19, 127.72, 124.51, 119.89, 119.75, 74.00, 32.43, 29.62, 26.36; LRMS (ESI) *m/z*: 217 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{12}H_{12}N_2O_2+H^+$ 217.0972, found: 217.0969.

2-hexyl-3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (9k): white solid [60.7 mg, yield 81% (dr = 5:1)], mp 100-101 °C, and the two diastereomers were separable by chromatography. The major diastereomer: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.12 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.91 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.2, 7.5, 1.6 Hz, 1H), 7.32-7.23 (m, 1H), 2.86-2.73 (m, 1H), 2.48-2.37 (m, 1H), 1.95-1.76 (m, 2H), 1.42 (s, 3H), 1.39-1.19 (m, 9H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.29, 161.12, 135.62, 133.22, 127.76, 124.36, 119.52, 119.50, 72.13, 40.04, 39.45, 31.19, 29.84, 28.62, 26.35, 26.06, 22.07, 13.97; LRMS (ESI) *m/z*: 301 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{24}N_2O_2+H^+$ 301.1911, found: 301.1909.

4a-methyl-3,4,4a,5-tetrahydro-1*H*-pyrido[1,2-*a*]quinazoline-1,6(2*H*)-dione (9l): white solid (36.8 mg, yield 64%), mp 198-199 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.86 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.60-7.52 (m, 1H), 7.36-7.28 (m, 1H), 2.62-2.54 (m, 1H), 2.48-2.39 (m, 1H), 2.17-2.09 (m, 1H), 2.09-2.02 (m, 1H), 1.90-1.74 (m, 2H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.77, 162.31, 138.08, 131.76, 126.54, 126.22, 125.25, 123.70, 71.07, 34.68, 33.08, 28.29, 16.61; LRMS (ESI) *m/z*: 231 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{13}H_{14}N_2O_2+H^+$ 231.1128, found: 231.1126.

6a-methyl-6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione (9m): white solid (51.5 mg, yield 78%), mp 219-220 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.04-7.98 (m, 2H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.85-7.78 (m, 1H), 7.77-7.71 (m, 1H), 7.70-7.64 (m, 1H), 7.42-7.36 (m, 1H), 1.72 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.44, 162.54, 145.97, 135.17, 133.68, 133.62, 130.09, 129.40, 127.96, 125.12, 124.00, 122.89, 121.24, 119.80, 74.17, 27.26; LRMS (ESI) *m/z*: 265 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{12}N_2O_2+H^+$ 265.0972, found: 265.0966.

4b-methyl-4b*H*-isoquinolino[2,1-*a*]quinazoline-6,12(5*H*,13*H*)-dione (9n): yellow solid (57.6 mg, yield 83%), mp 225-226 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, 1H), 7.93 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.79-7.71 (m, 1H), 7.68-7.61 (m, 1H), 7.45-7.36 (m, 3H), 7.30-7.23 (m, 1H), 4.16 (d, *J* = 21.1 Hz, 1H), 3.84 (d, *J* = 21.2 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.54, 161.90, 137.55, 133.11, 132.15, 128.77, 128.64, 127.47, 127.22, 126.63, 126.18, 126.15, 125.66, 123.33, 73.91, 35.25, 30.55; LRMS (ESI) *m/z*: 279 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{14}N_2O_2+H^+$ 279.1128, found: 279.1122.

3a,4-dimethyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (9o): white solid (52.4 mg, yield 91%), mp 105-107 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 8.2, 0.8 Hz, 1H), 8.08 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.56-7.51 (m, 1H), 7.27-7.24 (m, 1H), 3.07 (s, 3H), 2.70-2.63 (m, 2H), 2.48-2.39 (m, 1H), 2.30 (ddd, *J* = 12.0, 6.1, 4.0 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.26, 162.10, 135.25, 133.40, 128.64, 124.98, 119.72, 119.39, 78.55, 32.43, 30.30, 27.78, 21.79; LRMS (ESI) *m/z*: 231 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{13}H_{14}N_2O_2+H^+$ 231.1128, found: 231.1127.

4a,5-dimethyl-3,4,4a,5-tetrahydro-1*H*-pyrido[1,2-*a*]quinazoline-1,6(2*H*)-dione (9p): white solid (45.3 mg, yield 74%), mp 138-139 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.62 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.54-7.49 (m, 1H), 7.32-7.28 (m, 1H), 3.12 (s, 3H), 2.74-2.65 (m, 1H), 2.63-2.55 (m, 1H), 2.44-2.36 (m, 1H), 2.17-2.10 (m, 1H), 1.98-1.86 (m, 2H), 1.39 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.34, 163.59, 137.36, 131.96, 127.79, 126.21, 125.97, 123.93, 75.47, 34.45, 33.72, 27.51, 24.59, 16.94; LRMS (ESI) *m/z*: 245 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{14}H_{16}N_2O_2+H^+$ 245.1285, found: 245.1284.

6,6a-dimethyl-6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione (9q): white solid (43.3 mg, yield 62%), mp 182-184 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 8.1, 1.0 Hz, 1H), 8.05-7.99 (m, 2H), 7.76-7.70 (m, 2H), 7.67-7.63 (m, 2H), 7.37-7.32 (m, 1H), 3.25 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.02, 162.95, 143.29, 134.80, 133.51, 132.79, 131.39, 130.45, 128.90, 125.50, 125.18, 124.65, 121.82, 120.65, 78.09, 29.59, 23.25; LRMS (ESI) *m/z*: 279 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{17}H_{14}N_2O_2+H^+$ 279.1128, found: 279.1127.

4b,5-dimethyl-4b*H*-isoquinolino[2,1-*a*]quinazoline-6,12(5*H*,13*H*)-dione (9r): yellow oil (27.7 mg, yield 38%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.92 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.67-7.62 (m, 1H), 7.53-7.47 (m, 2H), 7.47-7.43 (m, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 4.08 (d, *J* = 20.8 Hz, 1H), 3.90 (d, *J* = 21.0 Hz, 1H), 2.66 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.18, 162.15, 138.58, 131.88, 131.83, 130.62, 129.89, 128.94, 128.02, 127.66, 127.01, 126.93, 126.70, 125.24, 76.73, 36.24, 29.91, 25.70; LRMS (ESI) *m/z*: 293 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{18}H_{16}N_2O_2+H^+$ 293.1285, found: 293.1284.

3a-methyl-2,3,3a,4-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-one (9s): colorless oil (26.2 mg, yield 56%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.98-6.93 (m, 1H), 6.84-6.79 (m, 1H), 6.68 (dd, *J* = 7.7, 0.7 Hz, 1H), 2.78 (ddd, *J* = 16.8, 11.7, 8.5 Hz, 1H), 2.54 (ddd, *J* = 16.8, 8.5, 1.6 Hz, 1H), 2.44-2.33 (m, 2H), 1.51 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.85, 142.81, 128.68, 125.36, 120.29, 115.54, 110.71, 85.71, 37.79, 33.74, 26.33; LRMS (ESI) *m/z*: 189 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{11}H_{12}N_2O+H^+$ 189.1022, found: 189.1023.

12a-methyl-12,12a-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one (9t): colorless oil (24.4 mg, yield 39%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02-7.98 (m, 1H), 7.41 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.37-7.33 (m, 1H), 7.33-7.30 (m, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.02-6.97 (m, 1H), 6.93-6.89 (m, 1H), 6.85 (dd, *J* = 7.6, 0.5 Hz, 1H), 4.48 (s, 1H), 3.88 (d, *J* = 19.0 Hz, 1H), 3.71 (d, *J* = 19.0 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.54, 139.35, 139.12, 131.28, 129.84, 128.44, 127.95, 127.65, 125.02, 123.17, 121.58, 116.63, 111.97, 82.31, 38.67, 29.46; LRMS (ESI) *m/z*: 251 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{14}N_2O+H^+$ 251.1179, found: 251.1178.

3a-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazolin-1(9*H*)-one (9u): white solid (42.8 mg, yield 85%), mp 141-143 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.02-6.93 (m, 2H), 6.64-6.57 (m, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 6.09 (s, 1H), 4.76 (d, *J* = 16.7 Hz, 1H), 4.09 (d, *J* = 16.7 Hz, 1H), 2.38-2.27 (m, 2H), 2.08-1.93 (m, 2H), 1.41 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.89, 143.01, 127.26, 126.60, 117.23, 116.24, 115.56, 71.08, 37.99, 31.78, 29.17, 25.00; LRMS (ESI) *m/z*: 203 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{12}H_{14}N_2O+H^+$ 203.1179, found: 203.1178.

4b-methyl-4b,5-dihydroisoindolo[1,2-*b*]quinazolin-12(10*H*)-one (9v): pale yellow solid (26.8 mg, yield 43%), mp 222-223 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.87-7.81 (m, 1H), 7.74-7.68 (m, 2H), 7.59-7.52 (m, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.05-6.98 (m, 1H), 6.76 (s, 1H), 6.71-6.65 (m, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.07 (d, *J* = 17.0 Hz, 1H), 4.40 (d, *J* = 17.0 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.94, 148.44, 141.59, 132.19, 130.25, 129.12, 127.56, 126.83, 123.12, 121.92, 117.69, 116.15, 115.56, 70.66, 37.33, 23.43; LRMS (ESI) *m/z*: 251 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{16}H_{14}N_2O+H^+$ 251.1179, found: 251.1178.

General procedure of the preparation of 5ag-1, **5ah-1**, **5ai-1**

To a suspension of $LiAlH_4$ (0.4 mmol) and $AlCl_3$ (0.4 mmol) in anhydrous THF was added a THF solution of **5ag/5ah/5ai** (0.2 mmol) dropwise at 0 °C. After addition, the mixture was heated to reflux for 4 h. After the reaction was cooled, dichloromethane (100 ml) was added to dilute the reaction mixture, and water was added dropwise at 0 °C to quench the reaction. Then, the solid which precipitated out was removed by filtration, and the organic phase obtained was dried with Na_2SO_4 and concentrated. The residue was purified to give **5ag-1**/**5ah-1**/**5ai-1**.

13b-methyl-7,8,13,13b-tetrahydro-5*H*-benzo[1,2]indolizino[8,7-*b*]indole (5ag-1): pale yellow solid (43.8 mg, yield 80%), mp 204-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.85-7.74 (m, 2H), 7.31-7.22 (m, 2H), 7.21-7.13 (m, 2H), 7.13-7.03 (m, 2H), 4.27-4.18 (m, 2H), 3.54-3.38 (m, 2H), 3.28-3.13 (m, 1H), 2.62-2.53 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ

135.53, 131.75, 126.46, 126.38, 124.88, 122.76, 122.44, 120.16, 118.98, 118.29, 110.81, 52.72, 41.00, 26.19, 17.09; LRMS (ESI) *m/z*: 275 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{19}H_{18}N_2+H^+$ 275.1543, found: 275.1541.

10-methoxy-13b-methyl-7,8,13,13b-tetrahydro-5*H*-benzo[1,2]indolizino[8,7-*b*]indole (5ah-1): pale yellow oil (47.6 mg, yield 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.33-7.27 (m, 1H), 7.25-7.18 (m, 2H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.26-4.15 (m, 2H), 3.84 (s, 3H), 3.54-3.43 (m, 2H), 3.13 (ddd, *J* = 16.2, 11.1, 6.4 Hz, 1H), 2.60 (ddd, *J* = 15.8, 4.3, 1.4 Hz, 1H), 1.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.22, 144.86, 138.98, 137.76, 131.33, 127.74, 127.67, 127.38, 123.38, 121.14, 111.73, 111.66, 106.87, 100.87, 64.95, 56.13, 53.25, 41.68, 25.98, 16.43; LRMS (ESI) *m/z*: 305 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{20}N_2O+H^+$ 305.1648, found: 305.1645.

14b-methyl-5,6,8,9,14,14b-hexahydroindolo[2',3':3,4]pyrido[2,1-*a*]isoquinoline (5ai-1): pale yellow oil (47.1 mg, yield 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.37-7.31 (m, 1H), 7.31-7.27 (m, 1H), 7.25-7.20 (m, 1H), 7.19-7.05 (m, 3H), 3.76 (ddd, *J* = 13.9, 10.0, 5.8 Hz, 1H), 3.26 (ddd, *J* = 13.8, 6.1, 2.6 Hz, 1H), 3.19-3.15 (m, 1H), 3.14-3.07 (m, 1H), 3.07-2.91 (m, 2H), 2.85-2.66 (m, 2H), 1.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.97, 137.45, 135.79, 134.53, 130.12, 127.71, 126.80, 126.55, 125.95, 121.81, 119.60, 118.46, 110.98, 105.93, 58.34, 46.83, 45.45, 30.39, 28.80, 17.87; LRMS (ESI) *m/z*: 289 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{20}H_{20}N_2+H^+$ 289.1699, found: 289.1695.

3-methyleneisobenzofuran-1(3*H*)-one (2c-1): colorless oil (37.1 mg, yield 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.91-7.85 (m, 1H), 7.79-7.63 (m, 1H), 5.63 (d, *J* = 3.0 Hz, 1H), 5.33 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.02, 151.94, 139.12, 134.61, 130.60, 125.42, 125.22, 120.73, 91.44; LRMS (ESI) *m/z*: 147 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_9H_6O_2+H^+$ 147.0441, found: 147.0438.

1-methyleneisochroman-3-one (2d-1): pale yellow oil (26.8 mg, yield 56%).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 1H), 7.39-7.35 (m, 1H), 7.35-7.31 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 5.13 (d, *J* = 2.4 Hz, 1H), 5.03 (d, *J* = 2.5 Hz, 1H), 3.84 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.29, 153.76, 130.08, 128.62, 127.95, 127.44, 127.24, 124.81, 95.09, 34.94; LRMS (ESI) *m/z*: 161 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{10}H_8O_2+H^+$ 161.0597, found: 161.0593.

***N*-(2-(1*H*-indol-2-yl)ethyl)-5-oxo-6-phenylhexanamide (3m-1)**: pale yellow oil (45.6 mg, yield 52%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.93-7.86 (m, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.33-7.25 (m, 3H), 7.25-7.20 (m, 1H), 7.18-7.12 (m, 2H), 7.01-6.96 (m, 1H), 6.94-6.89 (m, 1H), 6.16 (s, 1H), 3.68 (s, 2H), 3.42-3.35 (m, 2H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.03 (t, *J* = 7.3 Hz, 2H), 1.70-1.62 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 207.66, 171.61, 137.50, 135.99, 134.87, 129.54, 128.28, 128.23, 126.44, 120.08, 119.11, 118.55, 110.62, 98.75, 48.71, 40.78, 38.24, 34.34, 28.02, 19.36; LRMS (ESI) *m/z*: 349 $[M+H]^+$; HRMS (ESI) *m/z* calculated for $C_{22}H_{24}N_2O_2+H^+$ 349.1911, found: 349.1910.

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Gold-catalyzed Rapid Construction of Nitrogen-containing Heterocyclic Compound Library with Scaffold Diversity and Molecular Complexity

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