A Sequential One-Pot Protocol for the Synthesis of Dihydrobenzo[6,7]indolo-[3′,4′:3,4,5]azepino[2,1-*a*]isoquinolines Using a Gold–Silver Combined Catalyst[1]

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Abstract: A sequential one-pot protocol for the synthesis of indole-based peri-annulated polyheterocycles using trifluoroacetic acid and a gold–silver combined catalyst system is described. The reaction is thought to proceed via an imine formation–cationic π-cyclization–alkyne activation–intramolecular hydroamination sequence to yield novel dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinolines in good yields.

Key words: polyheterocycles, alkyne, indole, annulation, Lewis acid, regioselective

The search for one-pot reactions that facilitate the formation of multiple bonds, either in one step, or in tandem,[2] to access natural product inspired polyheterocycles with architectural complexity, remains a major challenge for organic chemists. In continuation of our studies on the design and development of one-pot procedures for the syntheses[3] of polyheterocycles by employing internal alkyne-based reactants, we focused our attention on peri-annulated indole-based polyheterocycles.[4] This framework is present in many natural products,[5] and is associated with a broad range of activities.[6] A detailed survey of the literature failed to reveal any reports on the one-pot synthesis of natural product inspired peri-annulated indole-based polyheterocycles. Thus, the development of methods for the rapid, one-pot synthesis of these types of compounds under mild conditions remains an area of significant interest.

To synthesize the peri-annulated indole-based polyheterocycles, we proposed to carry out a one-pot condensation of two bifunctional reactants derived from an indole and an internal alkyne. We envisaged that such a strategy would trigger two sequential cyclizations in a single operation, thereby enhancing the structural complexity of the final product. Accordingly, we commenced our studies by condensing indole-based substrate **1a**[7] with 2-alkynyl benzaldehyde **2a**, in an effort to facilitate cationic π-cyclization between C-3 of the indole and an iminium ion, followed by an in situ intramolecular hydroamination[8] or carbocyclization[9] reaction between the alkyne moiety and either the benzazepine N–H or C-2 of the indole. Since both these cyclizations require the presence of a Brønsted acid[10] and a coinage metal (Au, Ag, Cu) derived Lewis acid[11] (for activating the imine and the alkyne respectively), the challenge remained to combine both sets of conditions in a one-pot format.

Initially, substrate **1a** was treated with aldehyde **2a** in the presence of trifluoroacetic acid (2%) and the combined catalyst, chloro(triphenylphosphine)gold(I)–silver hexafluoroantimonate ($AuClPPh_3$–$AgSbF_6$) in acetonitrile, and the progress of the reaction was monitored by TLC and HPLC. The reaction was complete in 20 minutes affording, after column chromatography, a new product in 45% yield. The structure of this product was elucidated by a combination of homo- and heteronuclear two-dimensional NMR experiments. Of the four possible structures, the product was characterized as the peri-annulated indole-based polyheterocycle, 9-(*p*-tolyl)-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (**3a**),[12] arising from sequential cationic π-cyclization and regioselective intramolecular hydroamination (Scheme 1).

It is interesting to note that, as envisaged, our strategy comprising the one-pot condensation of two bifunctional reactants led to product **3a** with a complex novel architecture comprising a benzazepine ring annulated to an isoquinoline moiety on one side, and an indole moiety on the other.

Benzazepines and isoquinolines are important classes of compounds present in many natural products and in numerous pharmaceutically active compounds.[13] Figure 1 highlights selected HMBC, COSY and NOE correlations, which helped establish the structure of **3a**. This was further supported by performing restrained molecular dynamics calculations using Discover 3.0 software. Distance restraints were derived on the basis of NOE intensities.

Having developed a one-pot method for the synthesis of peri-annulated indole-based polyheterocycles, we next optimized the reaction conditions in order to improve the yield of **3a**; the results are summarized in Table 1. Since the combination of the Brønsted acid and the gold–silver complex furnished the final product via two consecutive cyclizations in a poor yield (45%), we decided to add the

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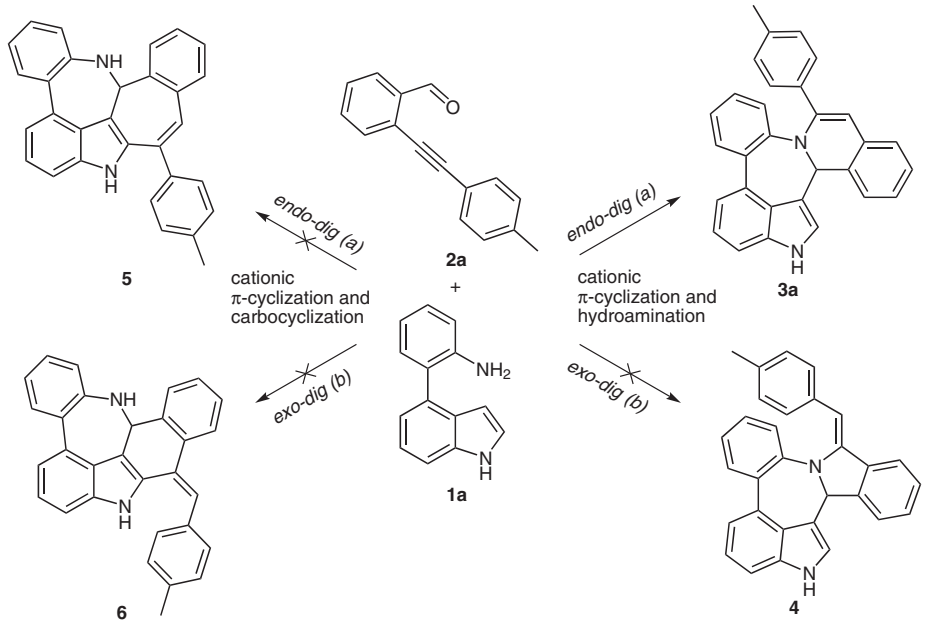


Scheme 1 Structures of the four regioisomeric products (**3a**, **4**–**6**) that can potentially be obtained from the reaction of **1a** and **2a**

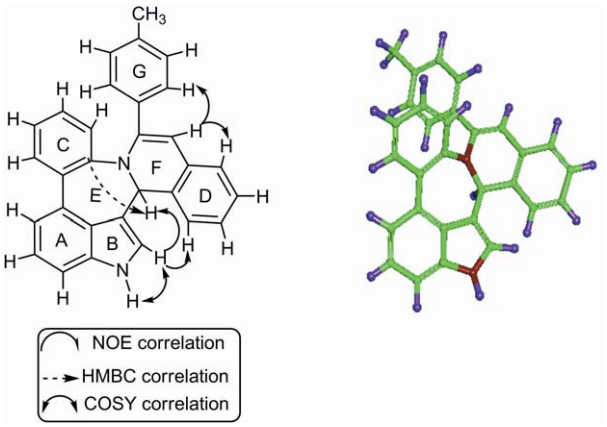
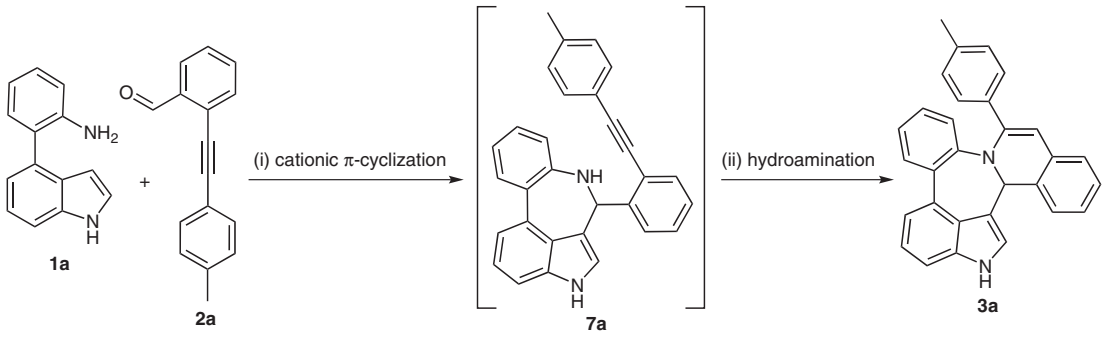


Figure 1 Important HMBC, COSY and NOE correlations present in **3a** and the energy minimized structure (1 ns restrained MD run)

two reagents sequentially. Accordingly, substrate **1a** was initially condensed with **2a** in the presence of trifluoroacetic acid (2%) in dichloromethane at room temperature, which was followed by the addition of the chloro(triphenylphosphine)gold(I)–silver hexafluoroantimonate (15 mol%) catalytic system. The progress of the reaction, in both steps, was monitored by HPLC and, pleasingly, the two cyclizations were both found to be complete within 10 minutes giving the desired polyheterocycle **3a** in 79% isolated yield (Table 1, entry 1). Increasing or decreasing the loading of the gold–silver bimetallic complex either had no effect, or led to a reduction in the isolated yield of **3a** (Table 1, entries 2–5). Similarly, increasing the concentration of the Brønsted acid, trifluoroacetic acid, from 2% to 5% and 10% had a detrimental effect on the yield (Table 1, entries 5–7). Switching the solvent from dichloromethane to water, acetonitrile, 1,2-dichloroethane, toluene or *N*,*N*-dimethylformamide either failed to give the desired product or produced polyheterocycle **3a** in reduced yield (Table 1, entries 10–14). Performing the reaction in the presence of either trifluoroacetic acid or the gold–silver mixture alone failed to furnish the desired product (Table 1, entries 8 and 9). Replacing silver hexafluoroantimonate with silver triflate (AgOTf), and chloro(triphenylphosphine)gold(I) with other gold salts, resulted in the formation of **3a** in significantly lower yields (Table 1, entries 15–20). Similarly, running the reactions in the presence of only a gold or silver salt furnished **3a** in poor yields or not at all (Table 1, entries 21–25).

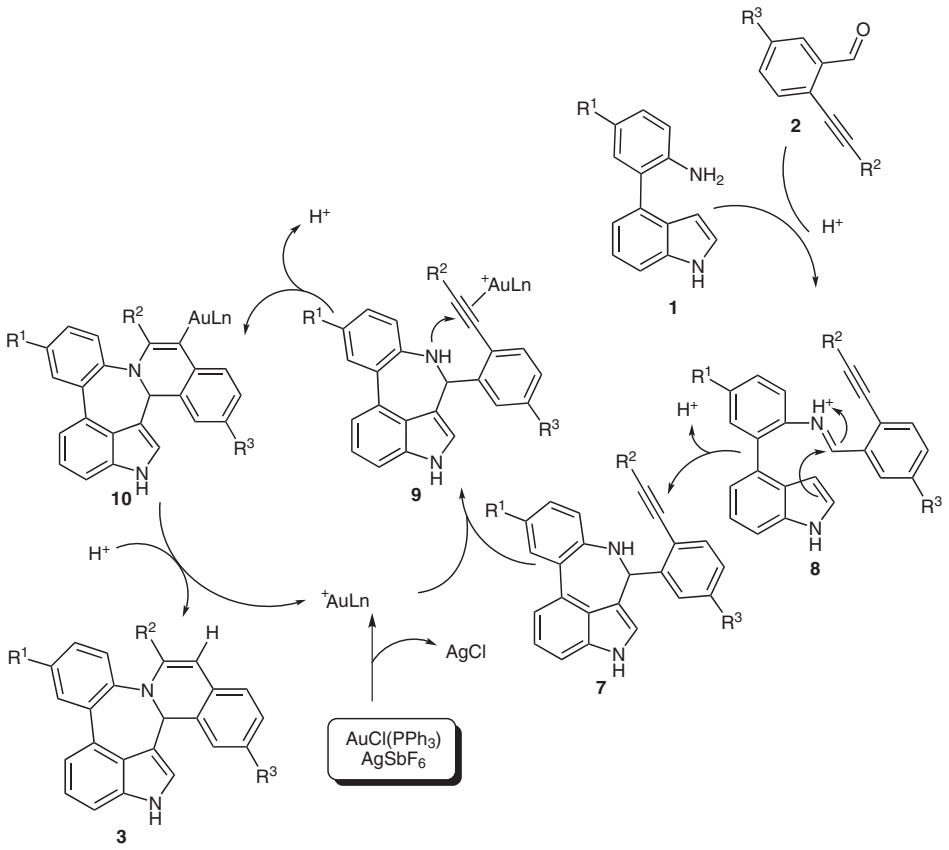
A plausible mechanism for the synthesis of dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline **3** *via* a sequential one-pot method is shown in Scheme 2. The first step involves the condensation of amine **1** with aldehyde **2** to furnish an imine, followed by its activation under acidic conditions to form iminium ion **8**. The latter triggers the formation of a C–C bond via a cationic π-(7-*endo-trig*) cyclization followed by deprotonation leading to benzazepine intermediate **7**. Next, the alkyne moiety in **7** is activated by the gold complex to give intermediate **9**, the alkyne moiety of which undergoes regioselective attack by the azepine nitrogen (instead of C-2) to form **10** via hydroamination. Finally, intermediate **10** undergoes protodeauration to afford dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline **3**. Hence, this two-component sequential reaction proceeds via a sequence involving iminium ion formation–cationic π-cyclization–alkyne activation–intramolecular hydroamination–protodeauration in a one-pot fashion.

Table 1 Optimization of the Reaction Conditions for the One-Pot Synthesis of **3a** in Sequential Format[a]



Entry	Sequential reaction conditions in one pot		Yield of **3a** (%)[d]
	(i) Cationic π-cyclization[b]	(ii) Hydroamination[c]	
1	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 15 mol% $AuClPPh_3$–$AgSbF_6$	79
2	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 20 mol% $AuClPPh_3$–$AgSbF_6$	75
3	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 5 mol% $AuClPPh_3$–$AgSbF_6$	51
4	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 10 mol% $AuClPPh_3$–$AgSbF_6$	57
5	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 2 mol% $AuClPPh_3$–$AgSbF_6$	43
6	(i) 5% TFA, CH_2Cl_2, r.t.	(ii) 15 mol% $AuClPPh_3$–$AgSbF_6$	73
7	(i) 10% TFA, CH_2Cl_2, r.t.	(ii) 15 mol% $AuClPPh_3$–$AgSbF_6$	61
8	2% TFA, CH_2Cl_2, r.t.		NR[e]
9	15 mol% $AuClPPh_3$–$AgSbF_6$, CH_2Cl_2, r.t.		NR[e]
10	(i) 2% TFA, H_2O, r.t.	(ii) 15 mol% $AuClPPh_3$–$AgSbF_6$	NR[e]
11	(i) 2% TFA, MeCN, r.t.	(ii) 15 mol% $AuClPPh_3$–$AgSbF_6$	53
12	(i) 2% TFA, DCE, r.t.	(ii) 15 mol% $AuClPPh_3$–$AgSbF_6$	65
13	(i) 2% TFA, toluene, r.t.	(ii) 15 mol% $AuClPPh_3$–$AgSbF_6$	37
14	(i) 2% TFA, DMF, r.t.	(ii) 15 mol% $AuClPPh_3$–$AgSbF_6$	15
15	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 15 mol% $AuClPPh_3$–AgOTf	56
16	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 15 mol% $AuCl_3$–$AgSbF_6$	trace
17	(i) 15 mol% $Yb(OTf)_3$, MeCN, r.t.	(ii) 15 mol% $AuCl_3$–$AgSbF_6$	10
18	(i) 15 mol% $Yb(OTf)_3$, MeCN, r.t.	(ii) 15 mol% $AuCl_3$–$AgSbF_6$	15
19	(i) 15 mol% PTSA, MeCN, r.t.	(ii) 15 mol% $AuCl_3$–$AgSbF_6$	45
20	(i) 15 mol% PTSA, CH_2Cl_2, r.t.	(ii) 15 mol% $AuCl_3$–$AgSbF_6$	59
21	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 15 mol% $AuCl_3$	25
22	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 15 mol% $AuClPPh_3$	10
23	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 15 mol% $AgSbF_6$	15
24	(i) 2% TFA, CH_2Cl_2, r.t.	(ii) 15 mol% AgOTf	NR[e]
25	(i) 2% TFA, MeCN, r.t.	(ii) 15 mol% $AuCl_3$	20

[a] All reactions were carried out on 1 mmol scale with amine/alkynyl aldehyde = 1:1.1, solvent (2.0 mL).
[b] Stirred for 10 min.
[c] Stirred for 10 min.
[d] Yield of isolated product.
[e] NR = no reaction.



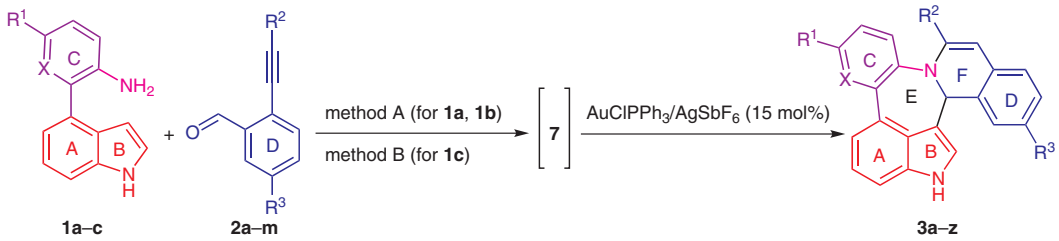
Scheme 2 A plausible mechanistic pathway for the synthesis of polyheterocycle **3**

Next, we examined the efficacy of substrates **1b** and **1c** to undergo this cationic π-cyclization and hydroamination under the optimized conditions. Although substrate **1b** bearing a 4-methyl group on ring C (Table 2) reacted efficiently to give the cyclized product, indole **1c** possessing a pyridine instead of an aryl ring (Table 2), failed to give the desired cyclized product. A careful analysis of the reaction with substrate **1c** revealed that the failure to obtain the desired product **3** was due to incomplete trifluoroacetic acid catalyzed cationic π-cyclization. This prompted us to replace trifluoroacetic acid with other Brønsted acids for the cationic π-cyclization step, and of the different reagents employed, *p*-toluenesulfonic acid (15 mol%) in dichloromethane furnished the cationic π-cyclized intermediate (equivalent to **7** in Scheme 2) in 83% isolated yield. Encouraged by this finding, we evaluated the efficacy of *p*-toluenesulfonic acid in combination with the gold–silver catalyst for the conversion of substrate **1c** into polyheterocycle **3z**. Accordingly, substrate **1c** was treated with **2b** in the presence of *p*-toluenesulfonic acid (15 mol%) in dichloromethane at room temperature for 10 minutes, which was followed by the addition of the gold–silver (15 mol%) catalytic system. Pleasingly, the desired product **3z** was obtained in 71% isolated yield.

After successfully optimizing the reaction conditions for substrates **1a**–**c**, we examined the scope and limitations of this strategy by studying the effect of different substituents on the 2-alkynyl aldehydes **2**, which were formed by reactions of six alkynes with three different bromobenzaldehydes, via Sonogashira coupling using a reported procedure.[12] In all cases, the substrates underwent efficiently the sequential cationic π-cyclization and hydroamination to furnish the corresponding products (26 in total), as single regioisomers in 61–79% isolated yields (Table 2). The electronic effects of the various substituents present on the aromatic substrates **2a**–**m** (R^2 and R^3) proved negligible as both electron-donating and electron-withdrawing groups were tolerated. The use of aliphatic alkynes failed to furnish the desired dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinolines.

In conclusion, we have developed a sequential, one-pot, atom-economic method for the construction of the highly substituted peri-annulated polyheterocycles dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinolines in good yields, via the trifluoroacetic acid–gold–silver catalyzed sequential cationic π-cyclization and subsequent hydroamination reaction. The salient feature of this strategy involves the regioselective electrophilic 7-*endo*-*trig* cationic π-cyclization followed by 6-*endo*-*dig* hydroamination reactions.

Table 2 Synthesis of Dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinolines[a]



Entry	Indole	R^1	X	Aldehyde	R^2	R^3	Product	Yield (%)
1	**1a**	H	C	**2a**	4-MeC_6H_4	H	**3a**	79
2	**1a**	H	C	**2b**	Ph	H	**3b**	76
3	**1a**	H	C	**2c**	4-*t*-BuC_6H_4	H	**3c**	75
4	**1a**	H	C	**2d**	4-$MeOC_6H_4$	H	**3d**	70
5	**1a**	H	C	**2e**	2-$O_2NC_6H_4$	H	**3e**	71
6	**1a**	H	C	**2f**	cyclohexen-1-yl	H	**3f**	78
7	**1a**	H	C	**2g**	Ph	F	**3g**	69
8	**1a**	H	C	**2h**	4-MeC_6H_4	F	**3h**	71
9	**1a**	H	C	**2i**	4-*t*-BuC_6H_4	F	**3i**	73
10	**1a**	H	C	**2j**	cyclohexen-1-yl	F	**3j**	75
11	**1a**	H	C	**2k**	Ph	OMe	**3k**	67
12	**1a**	H	C	**2l**	cyclohexen-1-yl	OMe	**3l**	68
13	**1b**	4-Me	C	**2b**	Ph	H	**3m**	65
14	**1b**	4-Me	C	**2a**	4-MeC_6H_4	H	**3n**	63
15	**1b**	4-Me	C	**2c**	4-*t*-BuC_6H_4	H	**3o**	66
16	**1b**	4-Me	C	**2f**	cyclohexen-1-yl	H	**3p**	69
17	**1b**	4-Me	C	**2d**	4-$MeOC_6H_4$	H	**3q**	70
18	**1b**	4-Me	C	**2g**	Ph	F	**3r**	71
19	**1b**	4-Me	C	**2i**	4-*t*-BuC_6H_4	F	**3s**	72
20	**1b**	4-Me	C	**2j**	cyclohexen-1-yl	F	**3t**	75
21	**1b**	4-Me	C	**2l**	cyclohexen-1-yl	OMe	**3u**	66
22	**1c**	H	N	**2h**	4-MeC_6H_4	F	**3v**	64
23	**1c**	H	N	**2j**	cyclohexen-1-yl	F	**3w**	65
24	**1c**	H	N	**2m**	4-*t*-BuC_6H_4	OMe	**3x**	61
25	**1c**	H	N	**2l**	cyclohexen-1-yl	OMe	**3y**	63
26	**1c**	H	N	**2b**	Ph	H	**3z**	71

[a] Method A: TFA (2%), CH_2Cl_2. Method B: TsOH (15 mol%), CH_2Cl_2.

All reagents and solvents were purchased from commercial sources and were used without purification. Column chromatography was performed using silica gel 60 (Thomas Baker, 100–200 mesh) as the stationary phase. All reactions were monitored by thin-layer chromatography (TLC) using Merck KGaA aluminium-backed TLC silica gel 60 F_{254} plates. Melting points were determined on a Büchi B-545 apparatus and are uncorrected. IR spectra were obtained using a Perkin-Elmer RX I FTIR spectrophotometer. ^{1}H NMR (200 MHz, 300 MHz or 400 MHz) and ^{13}C NMR (50 MHz, 75 MHz or 100 MHz) spectra were recorded using a Bruker Avance DRX-300 spectrometer. Chemical shifts (δ) are given in ppm relative to the residual signals of tetramethylsilane in $CDCl_3$, or those of the deuterated solvents ($CDCl_3$ or DMSO-d_6). Multiplicities are reported as

follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m). High-resolution mass spectrometry was accomplished with a 3000 mass spectrometer, using a Waters Agilent 6520-Q-TofMS/MS system and JEOL-AccuTOF JMS-T100LC.

Aldehydes 2a–m; Typical Procedure

To a soln of 2-bromobenzaldehyde (10.8 mmol) and ethynylbenzene (13.0 mmol) in Et_3N (20 mL) was added CuI (0.10 mmol) under an N_2 atm. The reaction mixture was degassed with N_2 for 15 min, followed by the addition of $PdCl_2(PPh_3)_2$ (0.21 mmol) at r.t. The resulting mixture was stirred at 80 °C for 2 h. After completion of the reaction, the mixture was diluted with aq NH_4Cl soln (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the desired product **2b** (1.91 g, 85%).

The characterization data for aldehydes **2a**–**m** can be found in the Supporting Information.

3-[2-(*p*-Tolylethynyl)phenyl]-3,4-dihydro-1*H*-benzo[6,7]azepino[3,4,5-*cd*]indole (7a); Typical Procedure

A soln of **1a** (1 equiv) and aldehyde **2a** (1.1 equiv) was treated with a soln of TFA (2%) in $>CH_2Cl_2$ (5 mL). The mixture was stirred at r.t. for 10 min. After completion of the reaction, aq $NaHCO_3$ soln (10 mL) was added to the mixture and the aq layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhyd Na_2SO_4 and the solvent removed in vacuo. The crude residue was purified by trituration with 5% Et_2O in hexane to afford pure compound **7a**.

Yield: 0.179 g (91%); white solid; mp 145–147 °C, R_f = 0.51 (EtOAc–hexane, 1:4).

IR (KBr): 3475, 3020, 2401, 1606 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.00 (d, J = 1.8 Hz, 1 H), 7.88 (d, J = 7.0 Hz, 1 H), 7.63–7.60 (m, 1 H), 7.46 (d, J = 7.4 Hz, 1 H), 7.40–7.36 (m, 3 H), 7.31–7.26 (m, 3 H), 7.22 (d, J = 8.0 Hz, 2 H), 7.10–7.00 (m, 4 H), 6.75 (d, J = 1.9 Hz, 1 H), 6.00 (s, 1 H), 5.57 (d, J = 2.1 Hz, 1 H), 2.34 (s, 3 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 148.0, 145.2, 138.6, 136.6, 131.7, 131.1, 130.5, 129.3, 128.6, 128.4, 127.7, 127.4, 127.1, 125.6, 123.2, 121.8, 121.3, 120.8, 119.1, 118.4, 117.2, 110.0, 93.7, 87.3, 58.0, 20.9.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{30}H_{23}N_2$: 411.1861; found: 411.1855.

Polyheterocycles 3a–u; General Procedure

To a stirred soln of substrate **1a**,**b** (1 mmol) in CH_2Cl_2 (5 mL) was added 2-alkynyl aldehyde **2a**–**k** (1.2 mmol) and TFA (2%). The mixture was allowed to stir under an N_2 atm at r.t. for 10 min, followed by the addition of the $AuClPPh_3$–$AgSbF_6$ (15 mol%) catalyst system. The mixture was then stirred at r.t. for a further 10 min. The progress of the reaction was monitored by TLC. After completion, the mixture was quenched with aq $NaHCO_3$ soln and the aq layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over anhyd Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (EtOAc–hexane) to afford products **3a**–**u**.

Polyheterocycles 3v–z; General Procedure

To a stirred soln of substrate **1c** (1 mmol) in CH_2Cl_2 (5 mL) was added 2-alkynyl aldehyde **2b**,**h**,**j**,**l**,**m** (1.2 mmol) and PTSA (15 mol%). The mixture was allowed to stir under an N_2 atm at r.t. for 10 min, followed by the addition of the $AuClPPh_3$–$AgSbF_6$ (15 mol%) catalyst system. The mixture was then stirred at r.t. for a further 10 min. The progress of the reaction was monitored by TLC. After completion, the mixture was quenched with aq $NaHCO_3$ soln and the aq layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over anhyd Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (EtOAc–hexane) to afford products **3v**–**z**.

9-(*p*-Tolyl)-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3a)

Yield: 0.155 g (79%); yellow solid; mp 195–198 °C; R_f = 0.63 (EtOAc–hexane, 1:4).

IR (KBr): 3465, 3019, 2401, 1605 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.93 (d, J = 2.0 Hz, 1 H), 7.96 (dd, J_1 = 8.0, J_2 = 1.0 Hz, 1 H), 7.48 (d, J = 7.4 Hz, 1 H), 7.41 (d, J = 7.8 Hz, 1 H), 7.32 (t, J = 7.7 Hz, 1 H), 7.25–7.17 (m, 3 H), 7.12–7.08 (m, 2 H), 7.01 (td, J_1 = 7.8, J_2 = 1.3 Hz 1 H), 6.81–6.77 (m, 1 H), 6.78 (d, J = 8.2 Hz, 2 H), 6.70 (d, J = 8.1 Hz, 2 H), 6.40–6.39 (m, 1 H), 6.09 (s, 1 H), 5.44 (s, 1 H), 2.09 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.5, 143.2, 138.2, 137.1, 136.7, 134.9, 133.4, 130.2, 129.1, 128.5, 128.2, 127.7, 127.5, 127.1, 126.7, 126.3, 126.0, 125.1, 124.3, 123.1, 122.5, 122.4, 121.1, 118.7, 110.9, 99.6, 60.6, 20.5.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{30}H_{23}N_2$: 411.1861; found: 411.1855.

9-Phenyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3b)

Yield: 0.144 g (76%); yellow solid; mp 175–178 °C; R_f = 0.64 (EtOAc–hexane, 1:4).

IR (KBr): 3433, 2963, 2054, 1615 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 10.99 (s, 1 H), 8.01 (d, J = 7.8 Hz, 1 H), 7.54 (d, J = 7.4 Hz, 1 H), 7.46 (d, J = 7.8 Hz, 1 H), 7.38 (d, J = 7.6 Hz, 1 H), 7.28–7.22 (m, 3 H), 7.18–7.13 (m, 2 H), 7.07–6.99 (m, 4 H), 6.87–6.84 (m, 3 H), 6.45 (s, 1 H), 6.15 (s, 1 H), 5.52 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 145.3, 143.2, 138.2, 137.8, 137.1, 133.3, 130.2, 129.1, 128.5, 127.8, 127.6, 127.4, 127.1, 126.8, 126.4, 126.0, 125.1, 124.5, 123.3, 122.5, 122.4, 121.2, 118.8, 111.0, 100.1, 60.6.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{29}H_{21}N_2$: 397.1705; found: 397.1705.

9-[4-(*tert*-Butyl)phenyl]-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3c)

Yield: 0.162 g (75%); yellow solid; mp 178–183 °C; R_f = 0.61 (EtOAc–hexane, 1:4).

IR (KBr): 3439, 2993, 2021, 1655 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.0 Hz, 1 H), 7.86 (s, 1 H), 7.51 (d, J = 7.5 Hz, 1 H), 7.33 (t, J = 7.9 Hz, 1 H), 7.23–7.21 (m, 2 H), 7.16–7.13 (m, 1 H), 7.11–7.07 (m, 3 H), 6.97–6.94 (m, 3 H), 6.89–6.86 (m, 1 H), 6.81 (d, J = 8.3 Hz, 2 H), 6.36 (s, 1 H), 6.11 (s, 1 H), 5.52 (s, 1 H), 1.12 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.4, 146.1, 144.0, 138.4, 137.3, 135.2, 134.3, 131.4, 129.7, 128.8, 128.1, 127.9, 127.3, 127.1, 126.2, 125.9, 124.6, 124.4, 123.5, 123.2, 121.0, 119.9, 110.4, 100.1, 61.3, 34.5, 31.3.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{33}H_{29}N_2$: 453.2331; found: 453.2324.

9-(4-Methoxyphenyl)-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3d)

Yield: 0.143 g (70%); yellow solid; mp 157–162 °C; R_f = 0.61 (EtOAc–hexane, 1:4).

IR (KBr): 3478, 3021, 2062, 1596 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 10.97 (d, J = 1.9 Hz, 1 H), 8.01 (d, J = 7.1 Hz, 1 H), 7.53 (d, J = 7.2 Hz, 1 H), 7.44 (d, J = 7.7 Hz, 1 H), 7.38–7.33 (m, 1 H), 7.29–7.20 (m, 3 H), 7.15–7.07 (m, 2 H), 7.04 (d, J = 1.1 Hz, 1 H), 6.84 (dd, J_1 = 7.8, J_2 = 1.0 Hz, 1 H), 6.78

(d, J = 8.7 Hz, 2 H), 6.58 (d, J = 8.7 Hz, 2 H), 6.43 (s, 1 H), 6.12 (s, 1 H), 5.45 (s, 1 H), 3.62 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.5, 145.5, 142.9, 138.2, 137.1, 133.6, 130.1, 130.0, 129.2, 129.1, 128.5, 127.5, 127.0, 126.7, 126.3, 126.0, 125.1, 124.1, 123.0, 122.5, 122.4, 121.1, 118.8, 113.0, 110.9, 99.2, 60.6, 54.8.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{30}H_{23}N_2O$: 427.1810; found: 427.1803.

9-(2-Nitrophenyl)-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3e)
Yield: 0.150 g (71%); yellow solid; mp 190–192 °C; R_f = 0.63 (EtOAc–hexane, 1:4).

IR (KBr): 3500, 3012, 2054, 1610 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.04 (s, 1 H), 7.99 (d, J = 7.7 Hz, 1 H), 7.77 (d, J = 7.5 Hz, 1 H), 7.66–7.63 (m, 1 H), 7.53–7.46 (m, 3 H), 7.42–7.37 (m, 1 H), 7.34–7.22 (m, 5 H), 7.19–7.06 (m, 2 H), 7.03 (d, J = 7.2 Hz, 1 H), 6.37 (s, 1 H), 6.12 (s, 1 H), 5.22 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 144.2, 138.8, 138.3, 137.1, 133.9, 132.8, 131.2, 131.0, 130.4, 129.7, 129.0, 128.7, 127.6, 127.5, 127.3, 125.9, 124.9, 123.6, 123.2, 122.5, 122.2, 121.5, 118.8, 111.2, 99.5, 60.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{29}H_{20}N_3O_2$: 442.1556; found: 442.1542.

9-(Cyclohex-1-en-1-yl)-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3f)
Yield: 0.150 g (78%); yellow solid; mp 145–148 °C; R_f = 0.63 (EtOAc–hexane, 1:4).

IR (KBr): 3438, 2992, 2042, 1696 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.89 (d, J = 1.8 Hz, 1 H), 8.03 (d, J = 6.9 Hz, 1 H), 7.45 (d, J = 7.4 Hz, 1 H), 7.41–7.35 (m, 2 H), 7.31–7.26 (m, 2 H), 7.24–7.21 (m, 1 H), 7.19–7.16 (m, 1 H), 7.13–7.11 (m, 1 H), 7.09–7.07 (m, 1 H), 7.05–7.01 (m, 1 H), 6.34 (s, 1 H), 5.98 (s, 1 H), 5.67 (s, 1 H), 5.31 (s, 1 H), 1.29–1.23 (m, 2 H), 1.16–1.11 (m, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 146.1, 145.2, 137.8, 137.0, 135.3, 133.5, 130.2, 129.1, 128.3, 127.7, 127.4, 126.7, 126.6, 126.5, 125.8, 125.2, 123.8, 122.8, 122.3, 122.2, 121.0, 118.5, 110.6, 96.9, 60.2, 26.4, 24.7, 21.8, 21.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{29}H_{25}N_2$: 401.2018; found: 401.2006.

13-Fluoro-9-phenyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3g)
Yield: 0.137 g (69%); yellow solid; mp 165–166 °C; R_f = 0.62 (EtOAc–hexane, 1:4).

IR (KBr): 3480, 3033, 2454, 1609 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.03 (d, J = 1.9 Hz, 1 H), 8.00 (d, J = 7.2 Hz, 1 H), 7.53 (d, J = 7.5 Hz, 1 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.37 (d, J = 7.7 Hz, 1 H), 7.28–7.22 (m, 1 H), 7.18–7.11 (m, 4 H), 7.05–7.01 (m, 3 H), 6.86–6.82 (m, 3 H), 6.54 (s, 1 H), 6.20–6.18 (m, 1 H), 5.54 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.5, 158.3, 145.2, 144.1, 142.6, 139.1, 138.2, 137.6, 137.1, 130.1, 130.0, 129.9, 129.2, 128.7, 128.6, 128.5, 127.7, 127.6, 127.5, 127.1, 126.4, 125.1, 124.8, 124.7, 124.6, 122.5, 121.8, 121.1, 118.8, 114.4, 114.1, 113.1, 112.8, 111.0, 99.2, 60.2 (extra peaks are present due to ^{13}C–^{19}F couplings).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{29}H_{20}FN_2$: 415.1611; found: 415.1590.

13-Fluoro-9-(*p*-tolyl)-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3h)
Yield: 0.146 g (71%); yellow solid; mp 172–174 °C; R_f = 0.59 (EtOAc–hexane, 1:4).

IR (KBr): 3472, 2998, 2058, 1598 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.02 (d, J = 1.90 Hz, 1 H), 8.00 (d, J = 7.3 Hz, 1 H), 7.52 (d, J = 7.3 Hz, 1 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.38–7.33 (m, 1 H), 7.28–7.23 (m, 1 H), 7.19–7.08 (m, 3 H), 7.05–7.03 (m, 1 H), 6.85–6.81 (m, 3 H), 6.73 (d, J = 8.1 Hz, 2 H), 6.53 (s, 1 H), 6.16 (s, 1 H), 5.50 (s, 1 H), 2.12 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.4, 158.2, 145.3, 142.6, 138.2, 137.1, 136.7, 134.8, 130.2, 130.1, 129.2, 128.6, 128.5, 128.2, 127.7, 127.1, 126.4, 125.1, 124.6, 124.5, 122.5, 121.8, 121.0, 118.8, 114.4, 113.0, 112.7, 111.0, 98.8, 60.2, 20.5 (extra peaks are present due to ^{13}C–^{19}F couplings).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{30}H_{22}FN_2$: 429.1767; found: 429.1758.

9-[4-(*tert*-Butyl)phenyl]-13-fluoro-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3i)
Yield: 0.164 g (73%); yellow solid; mp 139–142 °C; R_f = 0.60 (EtOAc–hexane, 1:4).

IR (KBr): 3454, 3025, 2148, 1602 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.01 (s, 1 H), 8.02 (d, J = 7.6 Hz, 1 H), 7.60–7.53 (m, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 7.39–7.34 (m, 1 H), 7.26 (t, J = 7.1 Hz, 1 H), 7.13–7.11 (m, 3 H), 7.07–7.01 (m, 3 H), 6.87 (d, J = 7.7 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 2 H), 6.53 (s, 1 H), 6.16 (s, 1 H), 5.53 (s, 1 H), 1.13 (s, 9 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.4, 158.3, 149.9, 145.4, 142.3, 138.1, 137.1, 134.7, 130.2, 130.1, 129.1, 128.6, 128.5, 127.4, 127.1, 126.4, 125.1, 124.6, 124.5, 124.4, 122.5, 121.8, 121.0, 118.9, 114.4, 114.1, 113.0, 112.7, 110.9, 99.2, 60.3, 34.0, 30.8 (extra peaks are present due to ^{13}C–^{19}F couplings).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{33}H_{28}FN_2$: 471.2237; found: 471.2228.

9-(Cyclohex-1-en-1-yl)-13-fluoro-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3j)
Yield: 0.150 g (75%); yellow solid; mp 135–137 °C; R_f = 0.55 (EtOAc–hexane, 1:4).

IR (KBr): 3434, 2963, 2132, 1686 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.93 (s, 1 H), 8.03 (d, J = 7.5 Hz, 1 H), 7.44 (d, J = 7.4 Hz, 1 H), 7.41–7.35 (m, 2 H), 7.30–7.24 (m, 2 H), 7.11–7.04 (m, 4 H), 6.43 (s, 1 H), 6.02 (s, 1 H), 5.65 (s, 1 H), 5.33 (s, 1 H), 1.81 (s, 2 H), 1.26–1.11 (m, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.1, 157.9, 145.52, 145.50, 145.1, 137.8, 137.0, 135.2, 130.2, 129.1, 128.5, 128.4, 128.3, 127.7, 126.8, 126.5, 125.1, 124.2, 124.1, 122.3, 121.7, 120.9, 118.6, 114.2, 113.9, 112.9, 112.6, 110.7, 96.1, 59.9, 26.4, 24.6, 21.8, 21.3 (extra peaks are present due to ^{13}C–^{19}F couplings).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{29}H_{24}FN_2$: 419.1924; found: 419.1916.

13-Methoxy-9-phenyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3k)
Yield: 0.137 g (67%); yellow solid; mp 141–145 °C; R_f = 0.50 (EtOAc–hexane, 1:4).

IR (KBr): 3502, 3012, 2111, 1625 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.90 (m, 2 H), 7.49 (d, J = 7.2 Hz, 1 H), 7.36–7.34 (m, 1 H), 7.30 (d, J = 9.6 Hz, 1 H), 7.24 (d, J = 9.0 Hz, 1 H), 7.17–7.12 (m, 1 H), 7.05 (d, J = 8.3 Hz, 1 H), 6.97–6.91 (m, 4 H), 6.88–6.87 (m, 2 H), 6.85–6.84 (m, 1 H), 6.73 (d, J = 2.3 Hz, 1 H), 6.49 (s, 1 H), 6.14 (s, 1 H), 5.53 (s, 1 H), 3.79 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 146.2, 142.2, 138.3, 137.4, 131.6, 131.5, 129.7, 128.9, 128.8, 128.6, 128.4, 127.6, 127.3, 127.2, 126.1, 126.0, 124.8, 123.9, 123.2, 120.7, 119.9, 116.3, 113.4, 112.2, 110.4, 100.2, 61.3, 55.6.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{23}N_2O$: 427.1810; found: 427.1794.

9-(Cyclohex-1-en-1-yl)-13-methoxy-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3l)
Yield: 0.140 g (68%); yellow solid; mp 130–135 °C; R_f = 0.52 (EtOAc–hexane, 1:4).

IR (KBr): 3460, 3021, 2102, 1593 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.87 (s, 1 H), 8.02 (d, *J* = 7.6 Hz, 1 H), 7.61 (m, 1 H), 7.42 (d, *J* = 7.4 Hz, 1 H), 7.37–7.34 (m, 2 H), 7.28–7.25 (m, 2 H), 7.06 (d, *J* = 7.6 Hz, 1 H), 6.97 (d, *J* = 8.7 Hz, 1 H), 6.81 (s, 1 H), 6.42 (s, 1 H), 5.98 (s, 1 H), 5.63 (s, 1 H), 5.31 (s, 1 H), 3.76 (s, 3 H), 1.81 (s, 2 H), 1.26–1.23 (m, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.6, 145.7, 143.9, 137.6, 137.0, 135.4, 130.3, 129.0, 128.3, 128.2, 127.1, 126.7, 126.4, 126.2, 125.3, 123.9, 122.2, 120.7, 118.5, 113.0, 111.7, 110.6, 97.0, 60.3, 55.1, 26.4, 24.7, 21.9, 21.4.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{27}N_2O$: 431.2123; found: 431.2118.

5-Methyl-9-phenyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3m)
Yield: 0.120 g (65%); yellow solid; mp 185–190 °C; R_f = 0.55 (EtOAc–hexane, 1:4).

IR (KBr): 3509, 3025, 2132, 1609 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.97 (d, *J* = 1.6 Hz, 1 H), 7.81 (s, 1 H), 7.54 (d, *J* = 7.3 Hz, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 7.38–7.33 (m, 1 H), 7.29–7.20 (m, 2 H), 7.17–7.09 (m, 2 H), 7.07–6.99 (m, 3 H), 6.86–6.84 (m, 3 H), 6.74 (d, *J* = 7.9 Hz, 1 H), 6.43 (s, 1 H), 6.10 (s, 1 H), 5.48 (s, 1 H), 2.33 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 143.3, 142.9, 137.9, 137.8, 137.1, 135.4, 133.4, 130.2, 128.9, 128.8, 127.8, 127.6, 127.5, 127.4, 126.7, 126.0, 125.1, 124.3, 123.2, 122.5, 122.4, 121.1, 118.7, 110.9, 99.7, 60.7, 20.6.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{23}N_2$: 411.1861; found: 411.1851.

5-Methyl-9-(*p*-tolyl)-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3n)
Yield: 0.120 g (63%); reddish oil; R_f = 0.56 (EtOAc–hexane, 1:4).

IR (neat): 3468, 2952, 2121, 1646 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.96 (d, *J* = 1.8 Hz, 1 H), 7.80 (s, 1 H), 7.52 (d, *J* = 7.1 Hz, 1 H), 7.44–7.37 (m, 2 H), 7.35–7.32 (m, 1 H), 7.30–7.29 (m, 1 H), 7.20–7.16 (m, 2 H), 7.14–7.11 (m, 2 H), 6.84 (d, *J* = 8.1 Hz, 2 H), 6.73 (d, *J* = 8.2 Hz, 2 H), 6.41 (s, 1 H), 6.08 (s, 1 H), 5.43 (s, 1 H), 2.34 (s, 3 H), 2.14 (s, 3 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 143.3, 143.0, 137.9, 137.1, 136.7, 135.3, 133.5, 131.7, 130.3, 128.9, 128.2, 127.7, 126.7, 125.9, 125.1, 124.1, 123.0, 122.5, 121.1, 118.6, 110.8, 99.2, 60.7, 20.6, 20.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{31}H_{25}N_2$: 425.2018; found: 425.2007.

9-[4-(*tert*-Butyl)phenyl]-5-methyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3o)
Yield: 0.138 g (66%); reddish oil; R_f = 0.57 (EtOAc–hexane, 1:4).

IR (neat): 3452, 3028, 2502, 1582 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.64 (s, 1 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.24 (t, *J* = 7.8 Hz, 1 H), 7.14 (d, *J* = 7.3 Hz, 2 H), 6.99–6.98 (m, 2 H), 6.88 (d, *J* = 8.1 Hz, 2 H), 6.73 (d, *J* = 8.2 Hz, 2 H), 6.69 (s, 2 H), 6.28 (s, 1 H), 6.00 (s, 1 H), 5.41 (s, 1 H), 2.23 (s, 3 H), 1.04 (s, 9 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 150.3, 144.2, 143.7, 138.1, 137.3, 135.6, 135.3, 134.4, 131.6, 129.4, 129.3, 128.2, 128.1, 127.8, 127.1, 126.2, 124.6, 124.2, 124.1, 123.4, 123.1, 121.0, 119.7, 110.3, 99.8, 61.4, 34.5, 31.3, 21.3.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{34}H_{31}N_2$: 467.2487; found: 467.2472.

9-(Cyclohex-1-en-1-yl)-5-methyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3p)
Yield: 0.128 g (69%); yellow solid; mp 180–183 °C; R_f = 0.60 (EtOAc–hexane, 1:4).

IR (KBr): 3434, 2863, 2132, 1696 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.87 (s, 1 H), 7.84 (s, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 7.8 Hz, 1 H), 7.27 (d, *J* = 7.7 Hz, 1 H), 7.23–7.19 (m, 1 H), 7.15–7.08 (m, 3 H), 7.05–7.03 (m, 1 H), 6.99 (d, *J* = 8.0 Hz, 1 H), 6.31 (s, 1 H), 5.93 (s, 1 H), 5.68 (s, 1 H), 5.27 (s, 1 H), 2.44 (s, 3 H), 1.85 (s, 2 H), 1.28–1.27 (m, 6 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 146.3, 142.9, 137.5, 137.0, 135.5, 133.6, 130.3, 128.8, 127.5, 127.4, 126.6, 125.8, 125.2, 123.6, 122.7, 122.4, 122.2, 120.9, 118.4, 110.5, 96.5, 60.3, 26.4, 24.7, 21.9, 21.4, 20.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{27}N_2$: 415.2174; found: 415.2163.

9-(4-Methoxyphenyl)-5-methyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3q)
Yield: 0.138 g (70%); reddish oil; R_f = 0.52 (EtOAc–hexane, 1:4).

IR (neat): 3472, 3015, 2401, 1605 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (s, 1 H), 7.83 (d, *J* = 8.7 Hz, 2 H), 7.51 (d, *J* = 8.3 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 6.0 Hz, 3 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.81 (s, 1 H), 6.79–6.77 (m, 2 H), 6.50 (s, 1 H), 6.10 (d, *J* = 1.2 Hz, 1 H), 5.45 (s, 1 H), 3.85 (s, 3 H), 2.04 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.9, 144.1, 143.6, 139.4, 137.7, 136.3, 136.0, 133.6, 132.8, 132.3, 131.8, 129.8, 129.5, 128.2, 127.8, 127.1, 126.7, 126.2, 123.6, 123.3, 123.1, 121.0, 119.7, 113.1, 110.4, 98.9, 61.3, 55.5, 20.9.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{31}H_{25}N_2O$: 441.1967; found: 441.1954.

13-Fluoro-5-methyl-9-phenyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3r)
Yield: 0.136 g (71%); yellow solid; mp 177–180 °C; R_f = 0.52 (EtOAc–hexane, 1:4).

IR (KBr): 3473, 2998, 2512, 1512 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.01 (s, 1 H), 7.80 (s, 1 H), 7.53 (d, *J* = 7.3 Hz, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.19–7.11 (m, 3 H), 7.08–6.99 (m, 3 H), 6.87–6.82 (m, 3 H), 6.74 (d, *J* = 7.9 Hz, 1 H), 6.52 (s, 1 H), 6.13 (s, 1 H), 5.50 (s, 1 H), 2.33 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.5, 158.3, 142.8, 142.7, 137.9, 137.7, 137.1, 135.5, 130.2, 130.1, 130.0, 128.9, 128.6, 128.5, 127.8, 127.6, 127.4, 125.0, 124.6, 124.5, 122.5, 121.8, 121.0, 118.7, 114.4, 114.1, 113.0, 112.7, 110.9, 98.9, 60.3, 20.6 (extra peaks are present due to ^{13}C–^{19}F couplings).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{22}FN_2$: 429.1767; found: 429.1750.

9-[4-(*tert*-Butyl)phenyl]-13-fluoro-5-methyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3s)
Yield: 0.156 g (72%); white solid; mp 195–198 °C; R_f = 0.59 (EtOAc–hexane, 1:4).

IR (KBr): 3509, 3120, 2509, 1612 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.72 (s, 1 H), 7.52 (d, *J* = 7.5 Hz, 1 H), 7.35 (t, *J* = 7.9 Hz, 1 H), 7.27–7.23 (m, 1 H), 7.05–7.00 (m, 1 H), 6.98–6.93 (m, 3 H), 6.87–6.78 (m, 5 H), 6.43 (s, 1 H), 6.07 (s, 1 H), 5.47 (s, 1 H), 2.32 (s, 3 H), 1.03 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 158.9, 150.4, 143.6, 143.5, 138.0, 137.4, 135.7, 135.1, 131.6, 130.7, 129.4, 128.7, 128.6, 128.3, 128.0, 125.9, 124.6, 124.5, 123.5, 123.3, 120.7, 119.9, 114.8, 114.5, 113.1, 112.8, 110.4, 99.0, 61.3, 34.5, 31.3, 21.3 (extra peaks are present due to ^{13}C–^{19}F couplings).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{30}FN_2$: 485.2393; found: 485.2380.

9-(Cyclohex-1-en-1-yl)-13-fluoro-5-methyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3t)
Yield: 0.145 g (75%); reddish oil; R_f = 0.59 (EtOAc–hexane, 1:4).

IR (neat): 3502, 2902, 2502, 1580 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.86 (s, 1 H), 7.80 (s, 1 H), 7.41 (d, *J* = 7.4 Hz, 1 H), 7.31 (d, *J* = 7.9 Hz, 1 H), 7.23 (d, *J* = 7.6 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 3 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 6.36 (s, 1 H), 5.92 (s, 1 H), 5.62 (s, 1 H), 5.25 (s, 1 H), 2.40 (s, 3 H), 2.40 (s, 2 H), 1.98 (s, 3 H), 1.79 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.9, 158.7, 146.8, 143.3, 139.4, 137.9, 137.3, 136.0, 135.9, 131.5, 129.4, 129.3, 128.6, 127.9, 125.8, 124.3, 124.2, 123.4, 123.1, 120.6, 119.6, 114.6, 114.3, 114.2, 113.0, 112.7, 110.1, 95.7, 60.5, 27.0, 25.4, 22.8, 22.5, 21.4 (extra peaks are present due to ^{13}C–^{19}F couplings).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{26}FN_2$: 433.2080; found: 433.2072.

9-(Cyclohex-1-en-1-yl)-13-methoxy-5-methyl-14b,16-dihydrobenzo[6,7]indolo[3′,4′:3,4,5]azepino[2,1-*a*]isoquinoline (3u)
Yield: 0.132 g (66%); reddish oil; R_f = 0.63 (EtOAc–hexane, 1:4).

IR (neat): 3433, 2969, 2135, 1656 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.74 (s, 1 H), 7.42 (d, *J* = 6.9 Hz, 1 H), 7.28 (s, 1 H), 7.22 (d, *J* = 5.4 Hz, 1 H), 7.00 (s, 2 H), 6.96 (d, *J* = 8.6 Hz, 1 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 6.66 (s, 1 H), 6.41 (s, 1 H), 5.95 (s, 1 H), 5.68 (s, 1 H), 5.33 (s, 1 H), 3.77 (s, 3 H), 2.42 (s, 3 H), 2.03–2.00 (m, 5 H), 1.83 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.9, 145.5, 143.8, 139.4, 137.3, 136.1, 129.4, 129.2, 128.5, 128.0, 127.8, 126.0, 124.2, 123.8, 123.6, 122.9, 120.6, 119.5, 114.2, 113.3, 112.0, 110.0, 96.3, 61.1, 55.6, 27.0, 25.5, 22.6, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{29}N_2O$: 445.2280; found: 445.2267.

13-Fluoro-9-(*p*-tolyl)-14b,16-dihydroindolo[3′,4′:3,4,5]pyrido[2′,3′:6,7]azepino[2,1-*a*]isoquinoline (3v)
Yield: 0.131 g (64%); yellow solid; mp 130–133 °C; R_f = 0.49 (EtOAc–hexane, 1:4).

IR (KBr): 3424, 2763, 2522, 1626 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 3.1 Hz, 1 H), 8.33 (s, 1 H), 8.17 (d, *J* = 7.1 Hz, 1 H), 7.69 (d, *J* = 8.1 Hz, 1 H), 7.53 (s, 4 H), 7.49 (s, 6 H), 6.22 (s, 1 H), 6.01 (s, 1 H), 5.56 (s, 1 H), 2.39 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.3, 159.1, 155.4, 152.6, 147.6, 147.5, 146.6, 141.3, 140.5, 138.6, 138.1, 137.8, 133.9, 133.7, 132.3, 132.2, 130.9, 129.7, 129.6, 129.2, 128.6, 128.4, 124.8, 122.4, 122.3, 122.1, 120.3, 119.7, 112.7, 112.2, 100.3, 59.5, 20.9 (extra peaks are present due to ^{13}C–^{19}F couplings).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{21}FN_3$: 430.1720; found: 430.1714.

9-(Cyclohex-1-en-1-yl)-13-fluoro-14b,16-dihydroindolo[3′,4′:3,4,5]pyrido[2′,3′:6,7]azepino[2,1-*a*]isoquinoline (3w)
Yield: 0.130 g (65%); yellow solid; mp 135–137 °C; R_f = 0.52 (EtOAc–hexane, 1:4).

IR (KBr): 3534, 2963, 2532, 1526 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.06–11.01 (m, 1 H), 8.66–8.61 (m, 1 H), 8.17–8.07 (m, 1 H), 7.92–7.90 (m, 1 H), 7.48–7.46 (m, 1 H), 7.33–7.30 (m, 2 H), 7.18–7.15 (m, 1 H), 7.10–7.08 (m, 2 H), 6.51–6.48 (m, 1 H), 6.08–6.04 (m, 2 H), 5.67–5.64 (m, 1 H), 1.82 (s, 2 H), 1.26–1.14 (m, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.3, 158.2, 146.7, 145.2, 140.9, 137.0, 136.6, 134.7, 133.8, 133.7, 132.2, 129.8, 129.7, 129.5, 128.5, 127.4, 121.9, 121.3, 121.2, 120.0, 114.1, 113.0, 111.9, 97.6, 59.7, 36.5, 24.7, 21.7, 21.2 (extra peaks are present due to ^{13}C–^{19}F couplings).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{23}FN_3$: 420.1876; found: 420.1868.

9-[4-(*tert*-Butyl)phenyl]-13-methoxy-14b,16-dihydroindolo[3′,4′:3,4,5]pyrido[2′,3′:6,7]azepino[2,1-*a*]isoquinoline (3x)
Yield: 0.140 g (61%); yellow solid; mp 129–133 °C; R_f = 0.48 (EtOAc–hexane, 1:4).

IR (KBr): 3502, 3012, 2205, 1598 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.02 (s, 1 H), 8.46 (s, 1 H), 8.11 (d, *J* = 6.7 Hz, 1 H), 7.51–7.48 (m, 2 H), 7.40 (s, 1 H), 7.18–7.10 (m, 2 H), 7.03–7.01 (m, 3 H), 6.90 (s, 2 H), 6.74–6.72 (m, 1 H), 6.56 (s, 1 H), 6.13 (s, 1 H), 5.62 (s, 1 H), 3.79 (s, 3 H), 1.12 (s, 9 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 157.2, 149.7, 146.2, 141.8, 140.4, 137.1, 136.4, 134.5, 133.8, 133.6, 132.2, 129.9, 129.7, 129.5, 128.5, 127.3, 124.5, 122.0, 121.8, 121.5, 121.2, 120.2, 113.3, 111.9, 101.8, 60.0, 55.1, 34.0, 30.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{30}N_3O$: 484.2389; found: 484.2384.

9-(Cyclohex-1-en-1-yl)-13-methoxy-14b,16-dihydroindolo[3′,4′:3,4,5]pyrido[2′,3′:6,7]azepino[2,1-*a*]isoquinoline (3y)
Yield: 0.129 g (63%); reddish oil; R_f = 0.50 (EtOAc–hexane, 1:4).

IR (neat): 3472, 2993, 2522, 1626 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.95 (d, *J* = 1.9 Hz, 1 H), 8.60–8.58 (m, 1 H), 8.07 (d, *J* = 7.4 Hz, 1 H), 7.46–7.41 (m, 2 H), 7.32–7.26 (m, 2 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.88–6.85 (m, 2 H), 6.47 (s, 1 H), 6.00 (s, 1 H), 5.65 (s, 1 H), 5.42 (s, 1 H), 3.77 (s, 3 H), 1.83 (s, 2 H), 1.27 (s, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.9, 146.3, 143.5, 141.4, 140.2, 139.0, 134.9, 134.1, 129.9, 128.6, 127.9, 126.1, 124.1, 123.1, 122.6, 121.2, 115.6, 113.2, 111.9, 111.8, 98.6, 59.7, 55.1, 26.5, 24.7, 21.8, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{26}N_3O$: 432.2076; found: 432.2066.

9-Phenyl-14b,16-dihydroindolo[3′,4′:3,4,5]pyrido[2′,3′:6,7]azepino[2,1-*a*]isoquinoline (3z)
Yield: 0.134 g (71%); yellow solid; mp 185–188 °C; R_f = 0.51 (EtOAc–hexane, 1:4).

IR (KBr): 3473, 3020, 2401, 1605 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.05 (s, 1 H), 8.45 (d, *J* = 3.7 Hz, 1 H), 8.12 (d, *J* = 7.4 Hz, 1 H), 7.66–7.61 (m, 2 H), 7.51 (d, *J* = 7.9 Hz, 1 H), 7.41–7.36 (m, 1 H), 7.28–7.25 (m, 1 H), 7.21–7.19 (m, 3 H), 7.06–7.03 (m, 3 H), 6.79 (d, *J* = 6.9 Hz, 2 H), 6.48 (s, 1 H), 6.16 (s, 1 H), 5.62 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.6, 146.5, 142.9, 141.3, 137.3, 137.1, 136.7, 133.8, 133.7, 133.0, 129.8, 129.7, 129.5, 127.8, 127.0, 126.1, 125.5, 123.5, 122.1, 121.9, 121.6, 120.3, 112.2, 101.6, 59.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{20}N_3$: 398.1657; found: 398.1667.

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(12) See the Supporting Information for details.

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