Post Ugi Gold(I)- and Platinum(II)-Catalyzed Alkyne Activation: Synthesis of Diversely Substituted Fused Azepinones and Pyridinones

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Abstract: A post-Ugi late-transition-metal-catalyzed intramolecular hydroarylation approach opens a new gateway for the synthesis of diversely substituted pyrrolopyridinones, pyrroloazepinones thiophenoazepinones, azepinoindoles, and azepinobenzothiophenes applying mild reaction conditions. A detailed investigation of the scope of this strategy is discussed.

Key words: gold, platinum, alkyne, Ugi, azepinone, pyridinone

Azepines fused with an aryl or heteroaryl subunit represent a widely studied class of biologically interesting medium-sized ring systems.[1] A plethora of literature is available for the construction of these heterocyclic systems employing various multistep synthetic sequences.[2] Although these approaches are useful for the construction of specific molecules, a general highly chemo-, regio-, and stereoselective methodology is desirable. Recent developments in transition-metal-catalyzed alkyne activation have opened the way for the synthesis of various carbocycles and heterocycles.[3] Compared to other transition metals, the selectivity of gold and platinum catalysts towards alkyne activation, is remarkable.[4,5] Although successful, most strategies lack the aspect of diversity. One of the best ways to address this is the application of multicomponent[6–8] reactions allowing the introduction of various functional groups in one step.

Our group, which is dedicated to the development of new diversity-oriented methodologies based on transition-metal catalysis and multicomponent reactions, has reported various approaches for the synthesis of biologically interesting heterocycles.[9] Inspired by our latest findings on the post-Ugi gold-catalyzed synthesis of pyrrolopyridinones and on the platinum-catalyzed synthesis of pyrroloazepinones,[10] we performed a detailed study of the scope of these protocols employing different heterocycles such as pyrrole, thiophene, benzothiophene, and indole (Scheme 1).

Ugi-4CR of 2-formylpyrrole **1**[10] with amine **2**, alkynoic acid **3**, and isonitrile **4** in methanol at 50 °C gives Ugi adducts **5a–d** in good to excellent yields. These compounds were subjected to our previously developed conditions for intramolecular hydroarylation. Upon reaction with $Au(PPh_3)OTf$ in chloroform at 50 °C for three hours, the corresponding pyrrolopyridinones **6a–d** were obtained in good yields (Table 1) via *exo-dig* cyclization of the pyrrole on the internal alkyne followed by rearrangement. Remarkably even in the presence of an indole substituent, the intramolecular hydroarylation takes place on the pyrrole ring, clearly showing the higher nucleophilicity of the latter[11] (Table 1, entry 3, **6c**).

Reaction of Ugi adducts **5a–d** with $PtCl_2$ in chloroform at 50 °C for 14 hours resulted in the formation of the pyrroloazepinones **7** as the major product (Table 1). This 7-membered fused ring system is formed via an *endo-dig* cyclization of the pyrrole on the internal alkyne, followed by rearrangement.[10] The cationic nature of the gold in $Au(PPh_3)OTf$, activates the alkyne to a larger extent compared to $PtCl_2$ allowing the pyrrole ring to attack quickly. This is why the reaction time, in the case of $Au(PPh_3)OTf$, is shorter compared to $PtCl_2$. The presence of an indole substituent seems to inhibit the cyclization (Table 1, entry 3).

After these interesting observations on pyrrole we were keen to extend this methodology to the readily available 2-formylthiophene, 2-formylindole, and 2-formylbenzothiophene. The Ugi-4CR of 2-formylthiophene (**8a**) with *p*-methoxybenzylamine (**2d**), but-2-ynoic acid (**3a**), and *tert*-butyl isonitrile (**4b**) in methanol at 50 °C delivers the Ugi adduct **9a** in 86% yield. This compound when treated with $Au(PPh_3)OTf$ (5 mol%) in chloroform, did not react even after 24 hours, and only starting material was recovered (Scheme 2).

In contrast, when the same Ugi adduct **9a** was subjected to $PtCl_2$ (5 mol%) in chloroform, the expected thiophenoazepinone was formed in 58% yield (Scheme 2).

The proposed mechanism for the formation of the thiophenoazepinone is depicted in Scheme 3. The nucleophilic C2-position of the thiophene[5h] attacks on the platinum(II)-activated alkyne in an *endo-dig* fashion giving rise to the spiro intermediate **B**. This intermediate undergoes a 1,2-shift followed by deprotonation and

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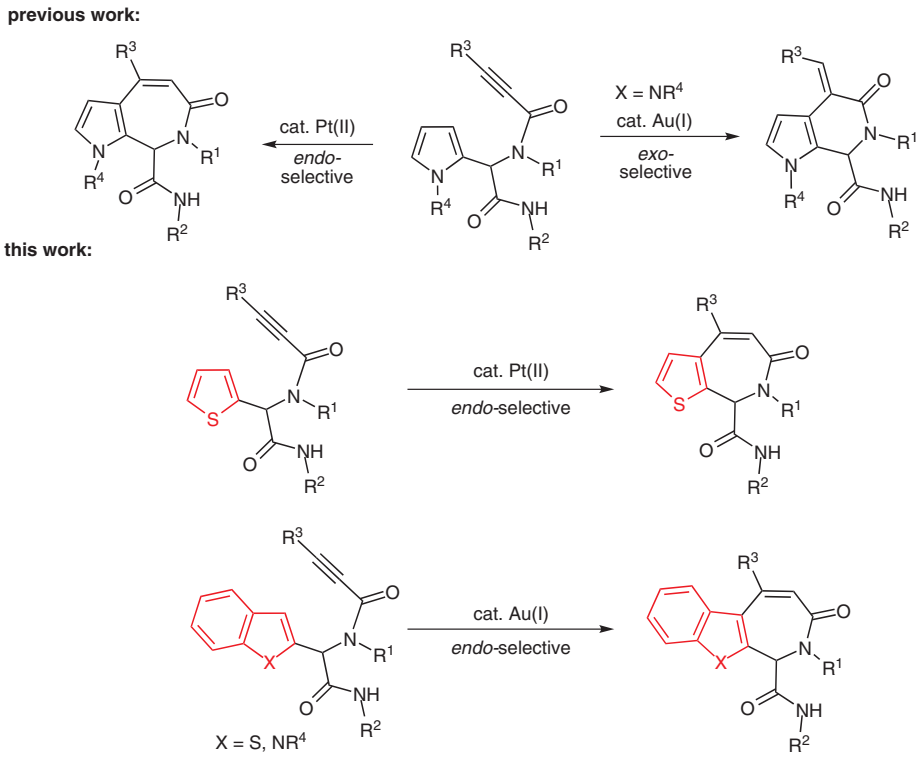
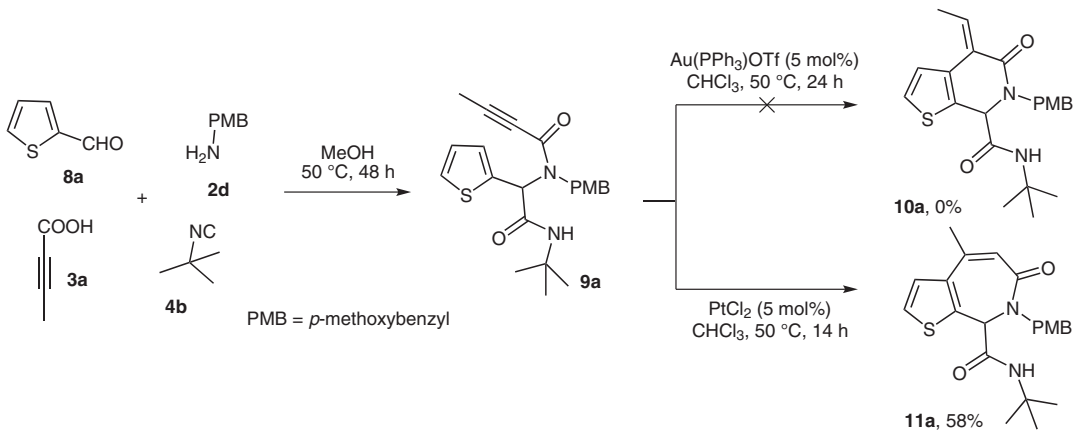


Scheme 1 Comparison of this work with our previous report

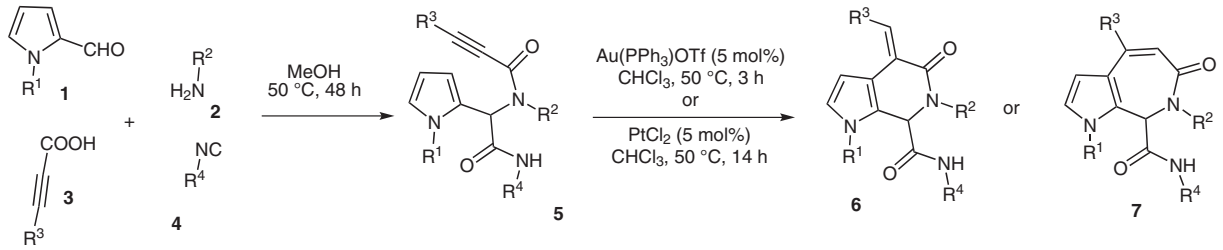
protodeplatination to form the thiophenoazepinone **11a** (Scheme 3).

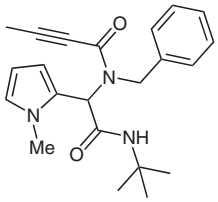
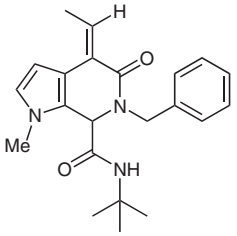
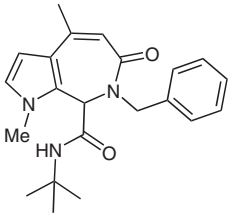
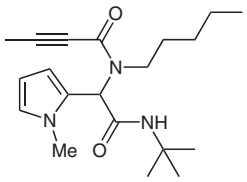
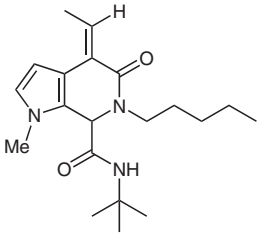
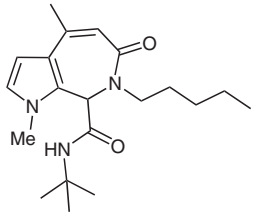
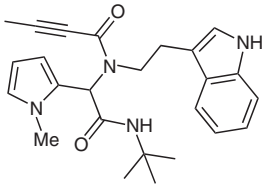
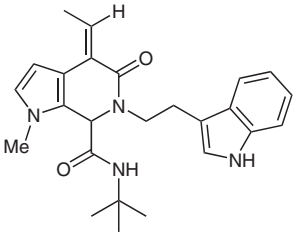
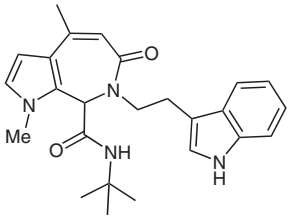
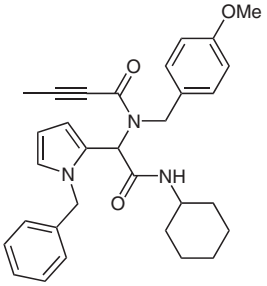
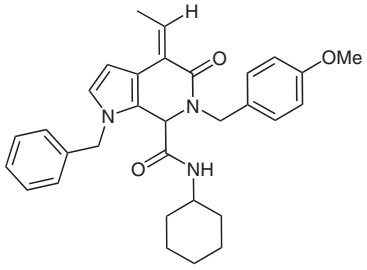
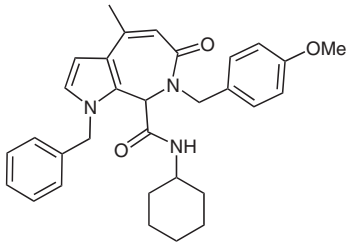
The Ugi-4CR of 2-formylindole (**12a**) and 2-formylbenzothiophene (**13a**) with amine **2**, alkynoic acid **3**, and isonitrile **4** in methanol at 50 °C gives the corresponding Ugi adducts **14a**–**g** and **15a**,**b** in good to excellent yields. As the nucleophilicity of indole and benzothiophene is lower compared to that of pyrrole and thiophene, we were keen to know the effect of gold(I) and platinum(II) catalysis on the obtained Ugi adducts **14** and **15**. Upon treatment of these compounds with $Au(PPh_3)OTf$ (5 mol%) in chloroform, only 7-membered ring formation was observed via *endo-dig* attack of the aromatic ring on the activated alkyne resulting in the formation of azepinoindoles **16a**–**g** and azepinobenzothiophenes **17a**,**b**, respectively (Table 2). As is evident from the examples in Table 2 various substituents are compatible with this protocol. A bulky substituent like a phenyl group is well tolerated on the alkyne and delivers the corresponding azepinones in excellent yields (Table 2, entries 3, 4, 6, and 9). These examples also discard the possibility of nucleophilic attack from 2nd position because the spiro intermediate formation in the presence of a phenyl substituent would be sterically unfavored in such a mild reaction condition. Ugi adducts **14** and **15** did not give any cyclized product upon treatment with $PtCl_2$, and only starting material was recovered. This observation clearly shows that $PtCl_2$ is not effective for the less nucleophilic indole and benzothiophene ring systems.



Scheme 2 Post-Ugi $PtCl_2$-catalyzed synthesis of thiophenoazepinones

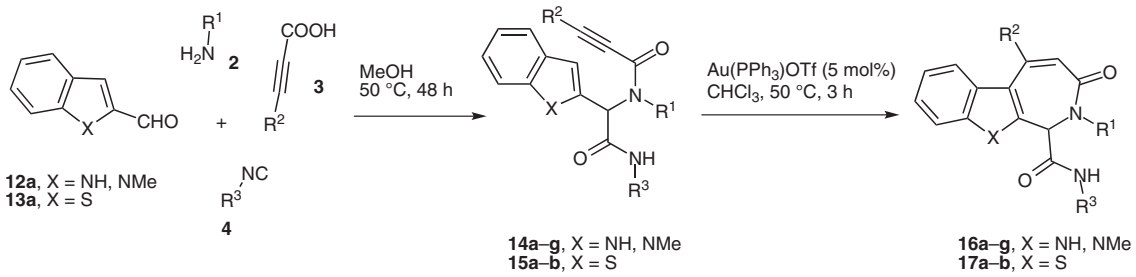
Table 1 Regioselective Synthesis of Pyrrolopyridinones and Pyrroloazepinones



Entry	Ugi adduct **5**[a]	Pyrrolopyridinones **6**[a] (conditions A)[b]	Pyrroloazepinone **7**[a] (conditions B)[c]
1	 **5a** (73%)	 **6a** (62%)	 **7a** (79%)
2	 **5b** (86%)	 **6b** (76%)	 **7b** (82%)
3	 **5c** (56%)	 **6c** (60%)	 **7c** (0%)[d]
4	 **5d** (73%)	 **6d** (84%)	 **7d** (60%)[e]

[a] Yields are isolated yields.
[b] Conditions A: reactions were run on a 0.25 mmol scale of **5** with $AuPPh_3Cl$ (5 mol%), AgOTf (5 mol%), and $CHCl_3$ (2 mL) in a screw capped vial at 50 °C for 3 h.
[c] Conditions B: reactions were carried on a 0.25 mmol scale of **5** with $PtCl_2$ (5 mol%) and $CHCl_3$ (2 mL) in a screw capped vial at 50 °C for 14 h.
[d] No product was formed even after 24 h; only starting **5c** was recovered.
[e] Also 25% of **6d** was formed as a minor product, employing conditions B.

Table 2 Synthesis of Azepinoindoles and Azepinobenzothiophenes via Post-Ugi Au(I)-Catalyzed Intramolecular Hydroarylation



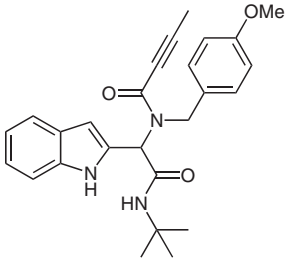
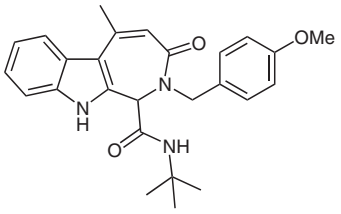
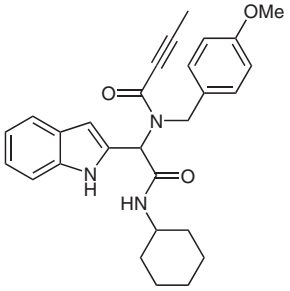
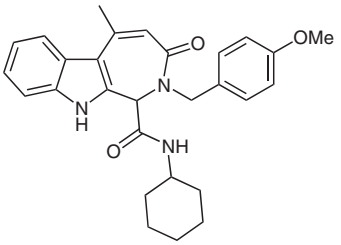
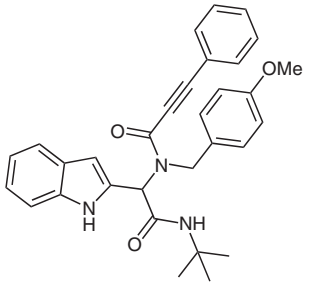
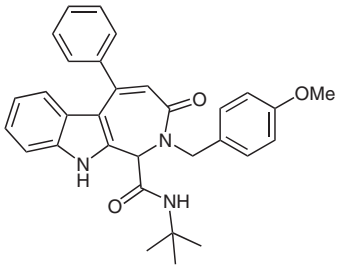
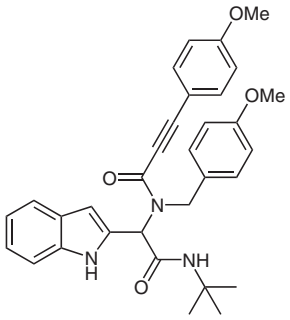
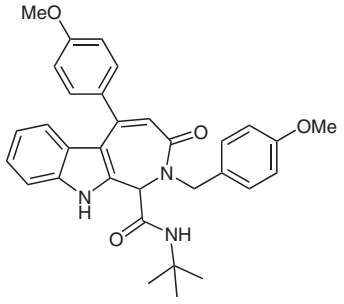
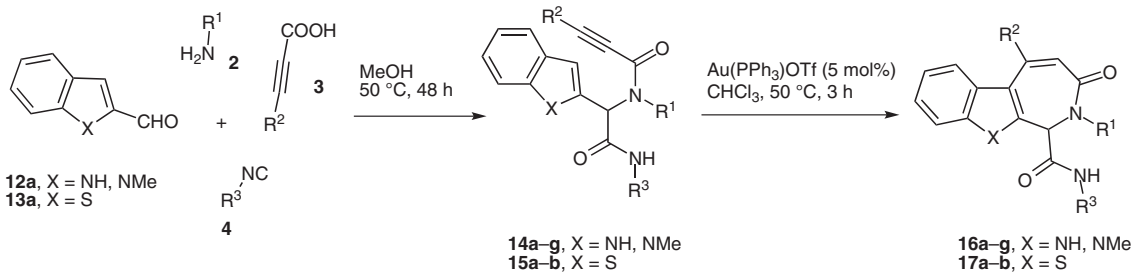
Entry	Ugi adducts **14** and **15**[a]	Compounds **16** and **17**[a,b]
1	 **14a** (75%)	 **16a** (81%)
2	 **14b** (48%)	 **16b** (90%)
3	 **14c** (88%)	 **16c** (88%)
4	 **14d** (69%)	 **16d** (85%)

Table 2 Synthesis of Azepinoindoles and Azepinobenzothiophenes via Post-Ugi Au(I)-Catalyzed Intramolecular Hydroarylation (continued)



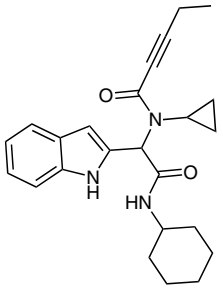
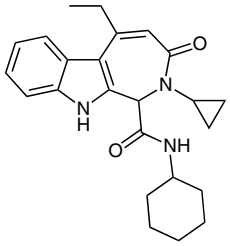
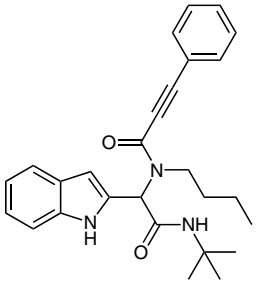
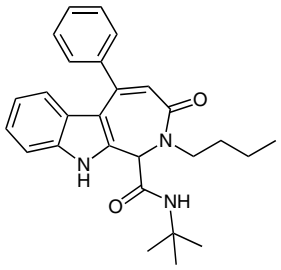
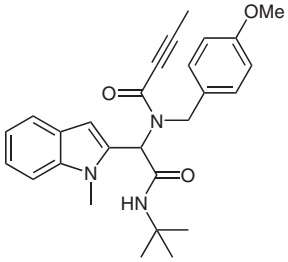
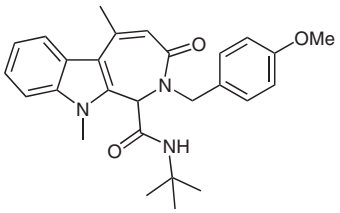
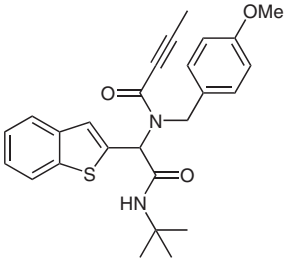
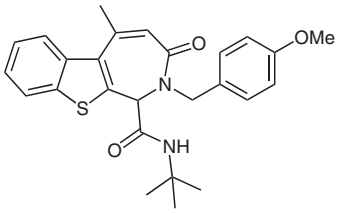
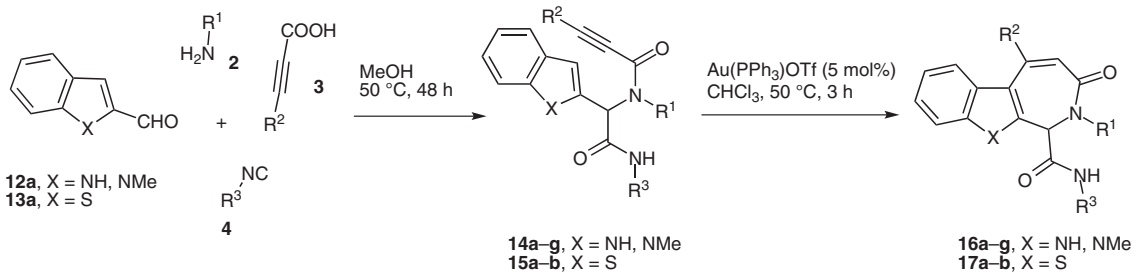
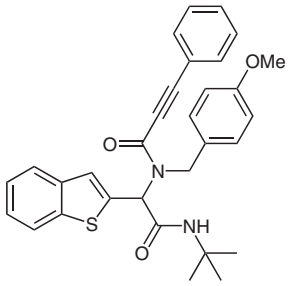
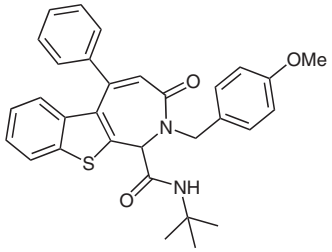
Entry	Ugi adducts **14** and **15**[a]	Compounds **16** and **17**[a,b]
5	 **14e** (77%)	 **16e** (92%)
6	 **14f** (53%)	 **16f** (79%)
7	 **14g** (76%)	 **16g** (83%)
8	 **15a** (70%)	 **17a** (80%)

Table 2 Synthesis of Azepinoindoles and Azepinobenzothiophenes via Post-Ugi Au(I)-Catalyzed Intramolecular Hydroarylation (continued)



Entry	Ugi adducts **14** and **15**[a]	Compounds **16** and **17**[a,b]
9	 **15b** (95%)	 **17b** (91%)

[a] Yields are isolated yields.
[b] All the reactions were run on a 0.25 mmol scale of **14** or **15** with $AuPPh_3Cl$ (5 mol%), AgOTf (5 mol%), and $CHCl_3$ (2 mL) in a screw capped vial at 50 °C for 3 h.

The proposed mechanism for the formation of azepinoindoles and azepinobenzothiophenes is shown in the Scheme 4. Direct attack of the nucleophilic C3-position of the heterocyclic ring[5h] on the activated alkyne occurs in an *endo-dig* fashion resulting in the formation of intermediate **B**. Subsequent deprotonation and protodeauration results in the formation of the corresponding azepinones **16** and **17** (Scheme 4).

Although we have no hard proof regarding the mechanisms to explain the different outcome of the reactions, the results might be interpreted as follows. According to the literature, pyrrole[5a,10] and thiophene[5h,x,y,12] perform nucleophilic attack preferably via the second position and thus 5- or 6- membered spiro intermediates are obvious in our case. Apart from the nucleophilicity of the substrate, the steric bulk of the catalyst might be playing a crucial role. In comparison, $Au(PPh_3)OTf$ is bulkier than $PtCl_2$, thus it prefers an *exo-dig* attack to avoid steric hindrance in the spiro intermediate stage. This hypothesis is supported by the fact that AuCl or $AuCl_3$ gives only *endo-dig* cyclization.[10] So in the case of five- or six-membered spiro intermediate pathways $Au(PPh_3)OTf$ forms the *exo-dig* product while $PtCl_2$ forms the *endo-dig* compound. On the contrary, indole[9b,c] and benzothiophene prefer attack via its third position and will not form a spiro intermediate, thus allowing the $Au(PPh_3)OTf$ to produce the *endo-dig* product.

In conclusion, we have elaborated post-Ugi gold(I)- and platinum(II)-catalyzed intramolecular hydroarylation approaches for the synthesis of diversely substituted fused pyridinones and azepinones. The diversity introduced via Ugi reaction, the regioselectivity assured by the gold(I) or platinum(II) catalysis during ring closure, and the mild reaction conditions are the merits of these protocols.

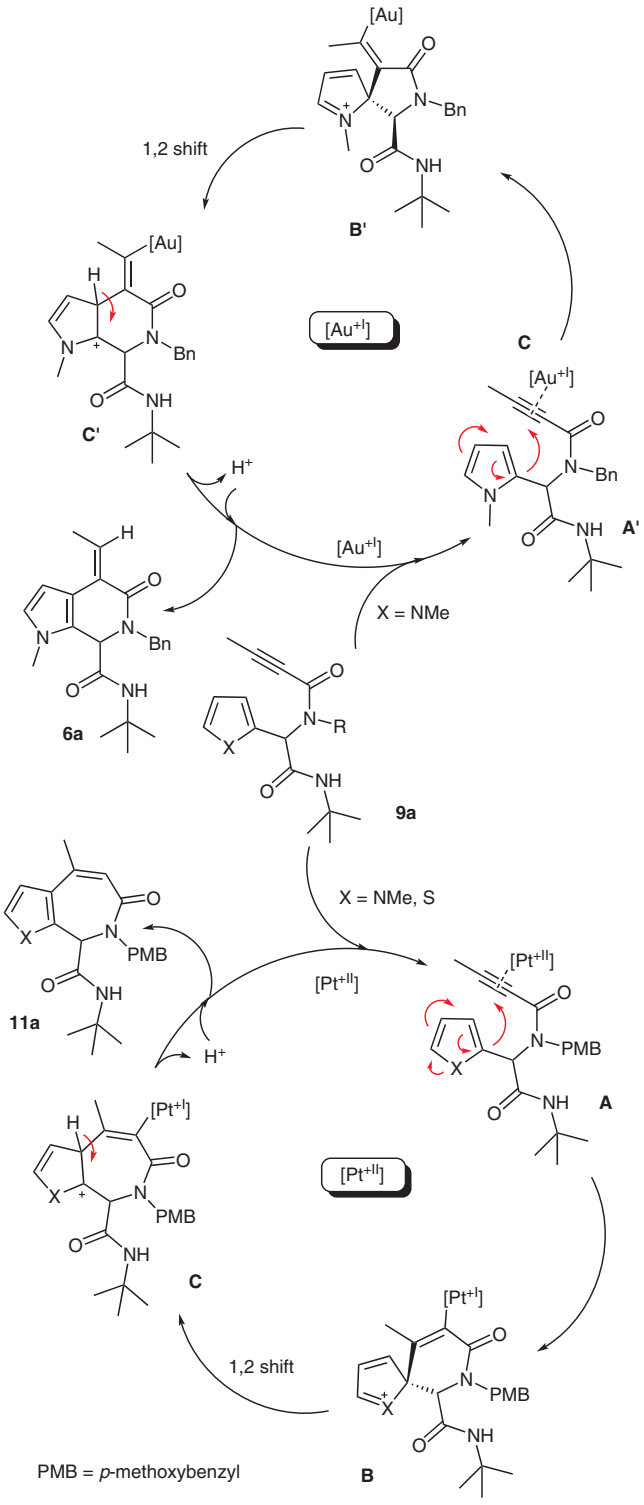
The ^1H (300 or 400 MHz) and ^{13}C (75 or 100 MHz) chemical shifts are reported in parts per million relative to TMS using the residual solvent signal as the internal reference. Standard abbreviations were used to designate chemical shift multiplicities. The ^{13}C NMR spectra are proton decoupled. The melting points were determined on a digital apparatus and are uncorrected. High-resolution mass spectra were recorded by using double-focusing magnetic sector and at an ion source temperature of 150–250 °C, as required. High-resolution EI-mass spectra were performed with a resolution of 10 000. Aldehyde **1b** was synthesized according to a known literature procedure.[13] The reagents and catalysts were purchased from commercial sources and used as such. Reactions were typically run in oven-dried screw-cap vial under inert atmosphere.

Ugi Products 5a–d; General Procedure

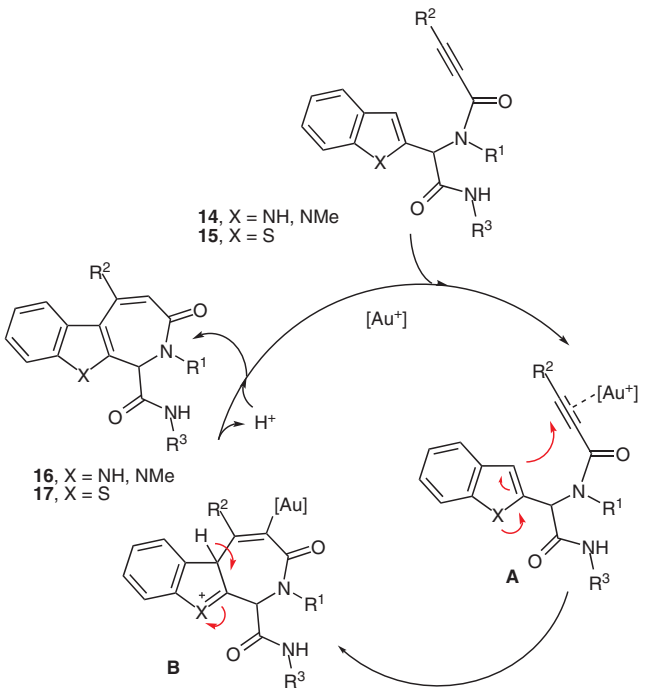
To a solution of pyrrole-2-carbaldehyde **1a**,**b** (2 mmol) in MeOH (3 mL) were added successively Na_2SO_4 (0.3 g), the appropriate amine **2a**–**d** (1.2 equiv), acid **3a** (1.2 equiv), and isonitrile **4a**,**b** (1.2 equiv) in a screw capped vial equipped with a magnetic stir bar. The reaction mixture was stirred at 50 °C for 24–48 h in a closed vial. After completion of the reaction (as indicated on TLC), the mixture was diluted with EtOAc (100 mL) and extracted with H_2O (50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to obtain a residue, which was subjected to silica gel column chromatography (50% EtOAc in heptane) to afford the desired products **5a**–**d** (Table 1).

***N*-Benzyl-*N*-[2-(*tert*-butylamino)-1-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl]but-2-ynamide (5a)**

Yield: 534 mg (73%); white solid, mp 167–169 °C; rotameric ratio ~1:3.



Scheme 3 Proposed mechanism for the formation of pyrrolopyridinone, pyrroloazepinone and thiophenoazepinone



Scheme 4 Proposed mechanism for the formation of azepinoindoles and azepinobezothiophenes

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12 (m, 3 H), 6.87 (m, 1.81 H), 6.66 (m, 0.22 H), 6.26 (m, 1.78 H), 6.10 (m, 0.24 H), 5.98 (m, 1.74 H), 5.90 (0.22 H), 5.60 (br s, 0.72 H), 5.48 (br s, 0.19 H), 5.11 (d, J = 15.91 Hz, 0.73 H), 4.51 (d, J = 15.91 Hz, 1.26 H), 4.33 (d, J = 14.91 Hz, 1.26 H), 3.12 (s, 0.71 H), 3.00 (s, 2.27 H), 2.02–1.98 (m, 3 H), 1.33–1.27 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 167.3, 156.1, 137.8, 137.5, 129.2, 128.5, 128.0, 127.8, 127.6, 127.2, 126.8, 126.4, 124.9, 123.7, 123.3, 111.6, 111.4, 107.5 (2), 91.2, 90.4, 74.1, 73.3, 60.1, 53.7, 51.7, 50.5, 46.3, 33.2, 33.1, 28.6, 28.5, 28.4, 4.1.

HRMS: m/z calcd for $C_{22}H_{27}N_3O_2$: 365.2103; found: 365.2121.

***N*-[2-(*tert*-Butylamino)-1-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl]-*N*-pentylbut-2-ynamide (5b)**
Yield: 594 mg (86%); yellow solid; mp 169–171 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.64 (br s, 1 H), 6.32 (br s, 1 H), 6.15 (s, 1 H), 6.09 (br s, 1 H), 5.71 (br s, 1 H), 3.57–3.32 (m, 5 H), 1.99 (s, 3 H), 1.38–1.34 (m, 10 H), 1.19–1.03 (m, 4 H), 0.78 (t, J = 7.07 Hz, 3 H), 0.54–0.50 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 155.4, 125.5, 123.3, 111.3, 107.7, 89.1, 73.6, 52.7, 51.7, 47.0, 33.7, 28.9, 28.7, 28.6, 28.4, 21.8, 13.8, 4.0.

HRMS: m/z calcd for $C_{20}H_{31}N_3O_2$: 345.2416; found: 345.2388.

***N*-[2-(1*H*-Indol-3-yl)ethyl]-*N*-[2-(*tert*-butylamino)-1-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl]but-2-ynamide (5c)**
Yield: 469 mg (56%); off-white solid; mp 177–179 °C; rotameric ratio ~1:9.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (br s, 1 H), 7.47 (d, J = 7.75 Hz, 1 H), 7.31 (d, J = 8.15 Hz, 1 H), 7.14 (t, J = 7.56 Hz, 1 H), 7.05 (t, J = 7.26 Hz, 1 H), 6.88 (br s, 0.11 H), 6.81 (d, J = 1.98 Hz, 0.87 H), 6.72 (br s, 1 H), 6.44 (d, J = 3.47 Hz, 0.90 H), 6.29 (br s, 0.11 H), 6.21–6.19 (m, 1.82 H), 5.69 (br s, 1 H), 3.86–3.76 (m, 1 H), 3.71–3.60 (m, 1.44 H), 3.56 (s, 2.59 H), 2.88–2.79 (m, 0.98 H), 2.05 (s, 0.29 H), 2.02–1.96 (m, 3.71 H), 1.35 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 155.5, 136.2, 127.2, 125.6, 123.7, 122.1, 121.7, 118.9, 118.5, 112.6, 111.5, 111.2, 107.9, 89.3, 73.6, 53.1, 51.7, 47.9, 33.7, 28.6 (2), 25.0, 3.9.

HRMS: m/z calcd for $C_{25}H_{30}N_4O_2$: 418.2369; found: 418.2335.

***N*-[1-(1-Benzyl-1*H*-pyrrol-2-yl)-2-(cyclohexylamino)-2-oxoethyl]-*N*-(4-methoxybenzyl)but-2-ynamide (5d)**
Yield: 726 mg (73%), white solid; mp 130–131 °C; rotameric ratio ~1:2.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 3 H), 6.98–6.82 (m, 4 H), 6.73–6.70 (m, 2.36 H), 6.64 (br s, 0.40 H), 6.49 (br s, 0.62 H), 6.37 (br s, 0.63 H), 6.28 (br s, 0.44 H), 6.21 (t, *J* = 3.24 Hz, 0.36 H), 6.09 (t, *J* = 3.24 Hz, 0.61 H), 5.87 (s, 0.63 H), 5.79 (s, 0.32 H), 5.24–5.14 (m, 1 H), 4.86 (d, *J* = 16.05 Hz, 0.66 H), 4.70–4.66 (m, 1.34 H), 4.52–4.23 (m, 2 H), 3.76–3.75 (m, 3 H), 3.70–3.63 (m, 1 H), 1.95 (s, 2 H), 1.86–1.70 (m, 3 H), 1.61–1.51 (m, 4 H), 1.32–1.23 (m, 2 H), 1.00–0.81 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 167.1, 158.7, 158.5, 155.9, 155.5, 137.5, 137.3, 130.4, 130.3, 129.9, 128.9 (2), 128.8 (2), 128.7, 127.7 (2), 126.8, 126.6 (2), 124.8, 124.7, 123.9, 123.2, 113.5, 113.4, 112.5, 112.4, 108.0, 107.9, 90.9, 90.2, 74.1, 73.0, 59.5, 55.2 (2), 53.6, 50.5, 50.2, 49.8, 48.4, 48.3, 45.6, 32.6, 32.5, 32.4, 25.4 (2), 24.6 (2), 4.1, 3.9.

HRMS: *m*/*z* calcd for $C_{31}H_{35}N_3O_3$: 497.2678; found: 497.2657.

Au(PPh$_3$)OTf-Catalyzed Cyclization of 5a–d to 6a–d; General Procedure

To a glass vial were loaded Au(PPh$_3$)Cl (5 mol%) and AgOTf (5 mol%) along with $CHCl_3$ (2 mL). The respective Ugi product **5a–d** (0.25 mmol) was added and the reaction mixture was stirred at 50 °C in a screw capped vial until completion (3 h). After completion, the mixture was partitioned between EtOAc (100 mL) and H_2O (50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (10% Et_2O in CH_2Cl_2) to afford compound **6a–d** (Table 1).

(*E*)-6-Benzyl-*N*-*tert*-butyl-4-ethylidene-1-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamide (6a)

Yield: 57 mg (62%); yellow solid; mp 190–192 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 5 H), 6.95 (q, *J* = 7.59 Hz, 1 H), 6.63 (d, *J* = 2.85 Hz, 1 H), 6.39 (d, *J* = 2.85 Hz, 1 H), 5.60 (d, *J* = 14.79 Hz, 1 H), 5.34 (br s, 1 H), 4.84 (s, 1 H), 3.99 (d, *J* = 14.75 Hz, 1 H), 3.57 (s, 3 H), 2.10 (d, *J* = 7.55 Hz, 1 H), 1.21 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 164.8, 136.3, 129.4, 128.7, 128.5, 127.6, 124.6, 123.8, 121.8, 116.1, 105.3, 61.6, 51.6, 49.3, 34.2, 28.4, 14.8.

HRMS: *m*/*z* calcd for $C_{22}H_{27}N_3O_2$: 365.2103; found: 365.2119.

(*E*)-*N*-*tert*-Butyl-4-ethylidene-1-methyl-5-oxo-6-pentyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamide (6b)

Yield: 66 mg (76%); green solid; mp 119–121 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86 (q, *J* = 7.50 Hz, 1 H), 6.66 (d, *J* = 2.78 Hz, 1 H), 6.38 (d, *J* = 2.89 Hz, 1 H), 5.34 (br s, 1 H), 4.94 (s, 1 H), 4.09–4.02 (m, 1 H), 3.69 (s, 3 H), 2.99–2.89 (m, 1 H), 2.07 (d, *J* = 7.67 Hz, 3 H), 1.63–1.58 (m, 2 H), 1.32–1.31 (m, 4 H), 1.23 (s, 9 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4, 164.5, 128.6, 124.6, 124.0, 121.9, 116.1, 105.3, 62.7, 51.6, 47.4, 34.4, 29.1, 28.4, 26.8, 22.4, 14.8, 13.9.

HRMS: *m*/*z* calcd for $C_{20}H_{31}N_3O_2$: 345.2416; found: 345.2419.

(*E*)-6-[2-(1*H*-Indol-3-yl)ethyl]-*N*-(*tert*-butyl)-4-ethylidene-1-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamide (6c)

Yield: 63 mg (60%); green solid; mp 181–183 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (br s, 1 H), 7.68 (d, *J* = 8.08 Hz, 1 H), 7.33 (d, *J* = 8.24 Hz, 1 H), 7.16 (t, *J* = 7.45 Hz, 1 H), 7.08–7.01 (m, 2 H), 6.91 (q, *J* = 7.56 Hz, 1 H), 6.60 (d, *J* = 2.84 Hz, 1 H), 6.37 (d, *J* = 2.84 Hz, 1 H), 5.36 (br s, 1 H), 4.73 (s, 1 H), 4.44–4.36 (m, 1 H), 3.44 (s, 3 H), 3.25–3.08 (m, 3 H), 2.10 (d, *J* = 7.50 Hz, 3 H), 1.19 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 164.9, 136.2, 128.4, 127.3, 124.4, 124.3, 122.2, 122.1, 122.0, 119.4, 119.0, 116.0, 113.0, 110.9, 105.2, 62.9, 51.6, 48.6, 34.1, 28.4, 23.3, 14.8.

HRMS: *m*/*z* calcd for $C_{25}H_{30}N_4O_2$: 418.2369; found: 418.2362.

(*E*)-1-Benzyl-*N*-cyclohexyl-4-ethylidene-6-(4-methoxybenzyl)-5-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamide (6d)

Yield: 105 mg (84%); white solid; mp 134–135 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18–7.16 (m, 3 H), 7.04 (d, *J* = 8.46 Hz, 2 H), 6.97–6.87 (m, 3 H), 6.71–6.68 (m, 3 H), 6.40 (d, *J* = 2.88 Hz, 1 H), 5.58 (d, *J* = 8.01 Hz, 1 H), 5.52–5.43 (m, 2 H), 5.00 (d, *J* = 15.84 Hz, 1 H), 4.83 (s, 1 H), 3.76–3.69 (m, 4 H), 3.63–3.54 (m, 1 H), 2.10 (d, *J* = 7.51 Hz, 3 H), 1.83–1.78 (m, 1 H), 1.66–1.58 (m, 3 H), 1.33–1.25 (m, 3 H), 1.04–1.00 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.0, 165.2, 159.0, 136.9, 129.6 (2), 128.6, 128.0, 127.5, 126.7, 124.3, 121.8, 116.7, 114.0, 105.6, 59.7, 55.2, 51.0, 49.0, 48.6, 32.7, 32.4, 25.3, 24.5 (2), 14.9.

HRMS: *m*/*z* calcd for $C_{31}H_{35}N_3O_3$: 497.2678; found: 497.2678.

PtCl$_2$-Catalyzed Cyclization of 5a–d to 7a–d; General Procedure

To a glass vial was loaded $PtCl_2$ (5 mol%) along with $CHCl_3$ (2 mL). The respective Ugi product **5a–d** (0.25 mmol) was added and the reaction mixture was stirred at 50 °C in a screw capped vial until completion (14 h). After completion, the mixture was partitioned between EtOAc (100 mL) and H_2O (50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (20% Et_2O in CH_2Cl_2) to afford compound **7a–d** (Table 1).

7-Benzyl-*N*-*tert*-butyl-1,4-dimethyl-6-oxo-1,6,7,8-tetrahydropyrrolo[2,3-*c*]azepine-8-carboxamide (7a)

Yield: 72 mg (79%), white solid; mp 142–144 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.21 (m, 5 H), 6.48 (d, *J* = 2.85 Hz, 1 H), 6.17 (d, *J* = 2.85 Hz, 1 H), 5.96 (s, 1 H), 5.37–5.32 (m, 2 H), 4.74 (s 1 H), 4.48 (d, *J* = 14.98 Hz, 1 H), 3.04 (s, 3 H), 2.14 (s, 3 H), 1.15 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 167.2, 141.4, 137.3, 128.9, 128.6, 127.9, 127.8, 123.1, 121.4, 118.8, 105.9, 55.9, 52.6, 51.6, 33.1, 28.3, 22.8.

HRMS: *m*/*z* calcd for $C_{22}H_{27}N_3O_2$: 365.2103; found: 365.2107.

N-*tert*-Butyl-1,4-dimethyl-6-oxo-7-pentyl-1,6,7,8-tetrahydropyrrolo[2,3-*c*]azepine-8-carboxamide (7b)

Yield: 71 mg (82%), white solid; mp 147–149 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.61 (d, *J* = 2.87 Hz, 1 H), 6.19 (d, *J* = 2.87 Hz, 1 H), 5.87 (s, 1 H), 5.63 (br s, 1 H), 4.81 (s, 1 H), 3.90–3.80 (m, 1 H), 3.71 (s, 3 H), 3.46–3.36 (m, 1 H), 2.11 (s, 3 H), 1.62–1.55 (m, 2 H), 1.29–1.24 (m, 13 H), 0.85 (t, *J* = 7.08 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 167.2, 141.0, 128.1, 123.2, 121.4, 118.8, 106.0, 58.0, 51.8, 50.6, 33.9, 28.9, 28.6, 28.4, 22.8, 22.4, 13.9.

HRMS: *m*/*z* calcd for $C_{20}H_{31}N_3O_2$: 345.2416; found: 345.2391.

1-Benzyl-*N*-cyclohexyl-7-(4-methoxybenzyl)-4-methyl-6-oxo-1,6,7,8-tetrahydropyrrolo[2,3-*c*]azepine-8-carboxamide (7d)

Yield: 75 mg (60%); off-white solid; mp 204–206 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 3 H), 7.08 (d, *J* = 8.57 Hz, 2 H), 7.02 (d, *J* = 7.59 Hz, 2 H), 6.84 (d, *J* = 8.57 Hz, 2 H), 6.70 (d, *J* = 2.89 Hz, 1 H), 6.26 (d, *J* = 2.89 Hz, 1 H), 5.92 (s, 1 H), 4.93–4.85 (m, 2 H), 4.71 (s, 1 H), 4.65 (d, *J* = 14.45 Hz, 1 H), 4.41 (d, *J* = 15.61 Hz, 1 H), 4.04 (d, *J* = 14.45 Hz, 1 H), 3.78 (s, 3 H), 3.45–3.39 (m, 1 H), 2.12 (s, 3 H), 1.49–1.46 (m, 5 H), 1.19–1.15 (m, 2 H), 1.02 (m, 1 H), 0.69–0.59 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 166.7, 159.5, 140.9, 137.4, 130.3, 129.6, 129.3, 128.3, 127.5, 126.5, 123.1, 122.5, 119.4, 114.4, 106.2, 55.3, 51.7, 50.6, 48.3, 32.4, 32.2, 25.3, 24.5, 22.9.

HRMS: *m*/*z* calcd for $C_{31}H_{35}N_3O_3$: 497.2678; found: 497.2671.

***N*-[2-(Cyclohexylamino)-2-oxo-1-(thiophen-2-yl)ethyl]-*N*-(4-methoxybenzyl)but-2-ynamide (9a)**
The Ugi adduct **9a** was synthesized following the same procedure used for the Ugi adducts **5a**–**d**; yield: 730 mg (86%); white solid; mp 140–142 °C; rotameric ratio ~1:5.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 5.25 Hz, 0.18 H), 7.25 (d, *J* = 5.25 Hz, 0.82 H), 7.10 (d, *J* = 8.66 Hz, 2 H), 7.04–6.99 (m, 1.20 H), 6.90–6.87 (m, 0.80 H), 6.77 (d, *J* = 8.66 Hz, 2 H), 6.21 (s, 0.17 H), 5.93 (d, *J* = 8.05 Hz, 0.76 H), 5.79 (s, 0.79 H), 5.47 (d, *J* = 8.27 Hz, 0.16 H), 4.82–4.71 (m, 1.60 H), 4.64 (d, *J* = 15.06 Hz, 0.20 H), 4.33 (d, *J* = 15.06 Hz, 0.20 H), 3.77 (s, 3 H), 3.67–3.63 (m, 1 H), 2.01 (s, 0.52 H), 1.96 (s, 2.47 H), 1.88–1.83 (m, 0.93 H), 1.73–1.51 (m, 5.10 H), 1.32–1.23 (m, 2 H), 1.14–0.98 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 166.7, 159.0, 158.9, 155.5 (2), 136.6, 136.0, 129.9, 129.7, 129.4, 128.8, 128.7, 128.4, 127.5, 127.3, 126.6, 126.3, 113.9, 113.6, 91.8, 90.6, 73.5, 73.2, 61.9, 57.5, 55.2 (2), 51.2, 48.6, 48.5, 46.5, 32.5, 32.4, 32.3, 25.4 (2), 24.6 (2), 24.5, 4.2, 4.1.

HRMS: *m*/*z* calcd for $C_{24}H_{28}N_2O_3S$: 424.1821; found: 424.1835.

***N*-Cyclohexyl-7-(4-methoxybenzyl)-4-methyl-6-oxo-7,8-dihydro-6*H*-thieno[2,3-*c*]azepine-8-carboxamide (11a)**
The product **11a** was synthesized following the same procedure used for cyclized products **7a**–**d**; yield: 62 mg (58%); off-white solid; mp 208–210 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (m, 3 H), 7.09 (d, *J* = 5.27 Hz, 1 H), 6.86 (d, *J* = 8.66 Hz, 2 H), 6.14 (s, 1 H), 5.16 (d, *J* = 8.50 Hz, 1 H), 5.18–5.15 (m, 2 H), 4.63 (d, *J* = 14.61 Hz, 1 H), 3.80 (s, 3 H), 3.58 (m, 1 H), 2.17 (s, 3 H), 1.70–1.64 (m, 5 H), 1.25 (m, 2 H), 1.07 (m, 1 H), 0.88 (m, 1 H), 0.74 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 166.1, 159.5, 139.4, 138.2, 135.4, 130.2, 128.8, 126.4, 124.8, 124.1, 114.3, 57.9, 55.3, 51.6, 48.6, 32.7, 32.5, 25.3, 24.5, 23.4.

HRMS: *m*/*z* calcd for $C_{24}H_{28}N_2O_3S$: 424.1821; found: 424.1824.

Ugi Products 14a–g and 15a,b
The Ugi adducts **14a**–**g** and **15a**,**b** were synthesized following the same procedure used for Ugi adducts **5a**–**d** (Table 2).

***N*-[2-(*tert*-Butylamino)-1-(1*H*-indol-2-yl)-2-oxoethyl]-*N*-(4-methoxybenzyl)but-2-ynamide (14a)**
Yield: 647 mg (75%); off-white solid; mp 166–168 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.69 (br s, 1 H), 7.52 (d, *J* = 8.26 Hz, 1 H), 7.34 (d, *J* = 8.26 Hz, 1 H), 7.21–7.08 (m, 4 H), 6.78 (d, *J* = 8.44 Hz, 2 H), 6.24 (s, 1 H), 5.76 (br s, 1 H), 5.25 (s, 1 H), 4.86 (d, *J* = 15.77 Hz, 1 H), 4.67 (d, *J* = 15.77 Hz, 1 H), 3.76 (s, 3 H), 2.00 (s, 3 H), 1.22 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 159.2, 156.2, 136.4, 132.0, 129.1, 127.8, 127.2, 122.5, 120.5, 119.8, 113.9, 111.6, 104.9, 91.2, 73.3, 57.7, 55.2, 53.1, 51.6, 28.5, 4.1.

HRMS: *m*/*z* calcd for $C_{26}H_{29}N_3O_3$: 431.2209; found: 431.2207.

***N*-[2-(Cyclohexylamino)-1-(1*H*-indol-2-yl)-2-oxoethyl]-*N*-(4-methoxybenzyl)but-2-ynamide (14b)**
Yield: 439 mg (48%); off-white solid; mp 165–167 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.67 (br s, 1 H), 7.53 (d, *J* = 7.46 Hz, 1 H), 7.34 (d, *J* = 7.46 Hz, 1 H), 7.20–7.09 (m, 4 H), 6.80 (d, *J* = 7.46 Hz, 2 H), 6.27 (s, 1 H), 5.67 (br s, 1 H), 5.18 (s, 1 H), 4.79 (s, 2 H), 3.76–3.65 (m, 4 H), 1.99 (s, 3 H), 1.88–1.51 (m, 5 H), 1.31–1.19 (m, 2 H), 1.08–0.90 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 159.3, 156.3, 136.5, 131.9, 129.2, 127.6, 127.1, 122.6, 120.5, 119.9, 113.9, 111.6, 105.0, 91.1, 73.2, 57.6, 55.3, 55.2, 53.3, 48.7, 32.7, 32.4, 25.4, 24.7, 24.6, 4.1.

HRMS: *m*/*z* calcd for $C_{28}H_{31}N_3O_3$: 457.2365; found: 457.2376.

***N*-[2-(*tert*-Butylamino)-1-(1*H*-indol-2-yl)-2-oxoethyl]-*N*-(4-methoxybenzyl)-3-phenylpropiolamide (14c)**
Yield: 869 mg (88%); orange solid; mp 135–137 °C; rotameric ratio ~1:5.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.72 (br s, 1 H), 7.55–7.47 (m, 3 H), 7.41–7.33 (m, 4 H), 7.22–7.18 (m, 3 H), 7.09 (t, *J* = 7.33 Hz, 1 H), 6.80–6.69 (m, 2 H), 6.29 (s, 0.84 H), 5.79 (s, 0.80 H), 5.62–5.60 (m, 0.36 H), 5.33 (s, 0.80 H), 5.29 (s, 0.22 H), 5.05 (d, *J* = 15.86 Hz, 0.16 H), 4.95 (d, *J* = 15.82 Hz, 0.82 H), 4.78 (d, *J* = 15.86 Hz, 0.82 H), 4.64 (d, *J* = 15.86 Hz, 0.19 H), 3.76–3.74 (m, 3 H), 1.30 (s, 1.50 H), 1.25 (s, 7.50 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 159.2, 156.2, 136.4, 132.6, 132.5, 132.4, 131.8, 131.0, 130.3, 129.1, 128.5, 128.4 (3), 127.8, 127.2, 122.6, 120.5, 119.9, 119.8, 114.0, 113.9, 113.6, 111.6, 105.0, 92.0, 81.5, 57.9, 55.2, 53.1, 51.7, 28.5 (2).

HRMS: *m*/*z* calcd for $C_{31}H_{31}N_3O_3$: 493.2365; found: 493.2372.

***N*-[2-(*tert*-Butylamino)-1-(1*H*-indol-2-yl)-2-oxoethyl]-*N*-(4-methoxybenzyl)-3-(4-methoxyphenyl)propiolamide (14d)**
Yield: 723 mg (69%); off-white solid; mp 96–98 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (br s, 1 H), 7.53 (d, *J* = 8.15 Hz, 1 H), 7.42–7.34 (m, 3 H), 7.20–7.18 (m, 3 H), 7.08 (t, *J* = 7.46 Hz, 1 H), 6.84–6.76 (m, 4 H), 6.30 (s, 1 H), 5.84 (br s, 1 H), 5.39 (s, 1 H), 4.94 (d, *J* = 15.80 Hz, 1 H), 4.77 (d, *J* = 15.80 Hz, 1 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 1.24 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 161.3, 159.2, 156.5, 136.4, 134.5, 134.4 132.0, 130.4, 129.1, 128.0, 127.2, 122.5, 120.5, 119.8, 114.3, 114.2 (2), 113.9, 111.8, 111.6, 104.9, 92.8, 81.0, 57.7, 55.3 (2), 55.2, 53.0, 51.6, 28.5.

HRMS: *m*/*z* calcd for $C_{32}H_{33}N_3O_4$: 523.2471; found: 523.2464.

***N*-[2-(Cyclohexylamino)-1-(1*H*-indol-2-yl)-2-oxoethyl]-*N*-cyclopropylpent-2-ynamide (14e)**
Yield: 603 mg (77%); off-white solid; mp 205–207 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.80 (br s, 1 H), 7.59 (d, *J* = 8.05 Hz, 1 H), 7.36 (d, *J* = 8.05 Hz, 1 H), 7.23–7.09 (m, 2 H), 6.51 (s, 1 H), 5.58 (d, *J* = 8.04 Hz, 1 H), 5.26 (s, 1 H), 3.80–3.70 (m, 1 H), 3.05–2.98 (m, 1 H), 2.40 (q, *J* = 7.46 Hz, 2 H), 1.90–1.75 (m, 2 H), 1.61–1.51 (m, 2 H), 1.36–1.18 (m, 6 H), 1.07–0.81 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 158.8, 136.5, 133.1, 127.2, 122.7, 120.5, 119.9, 111.7, 104.4, 97.2, 74.4, 62.5, 48.9, 33.5, 32.8, 32.5, 25.3, 24.7 (2), 12.8, 10.7, 8.0.

HRMS: *m*/*z* calcd for $C_{24}H_{29}N_3O_2$: 391.2260; found: 391.2266.

***N*-Butyl-*N*-[2-(*tert*-butylamino)-1-(1*H*-indol-2-yl)-2-oxoethyl]-3-phenylpropiolamide (14f)**
Yield: 455 mg (53%); brown solid; mp 150–152 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.98 (br s, 1 H), 7.60 (d, *J* = 7.89 Hz, 1 H), 7.53–7.51 (m, 2 H), 7.42–7.34 (m, 4 H), 7.22 (t, *J* = 7.40 Hz, 1 H), 7.12 (t, *J* = 7.34 Hz, 1 H), 6.53 (s, 1 H), 6.06 (br s, 1 H), 5.55 (s, 1 H), 3.81–3.71 (m, 1 H), 3.59–3.49 (m, 1 H), 1.71–1.50 (m, 4 H), 1.32 (s, 9 H), 0.84 (t, *J* = 7.38 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 155.9, 136.4, 132.4, 132.1, 130.3, 128.6, 127.3, 122.6, 120.6, 120.2, 120.0, 111.7, 104.7, 91.4, 81.4, 57.7, 51.8, 49.8, 31.2, 28.5, 19.9, 13.6.

HRMS: *m*/*z* calcd for $C_{27}H_{31}N_3O_2$: 429.2416; found: 429.2425.

***N*-[2-(*tert*-Butylamino)-1-(1-methyl-1*H*-indol-2-yl)-2-oxoethyl]-*N*-(4-methoxybenzyl)but-2-ynamide (14g)**
Yield: 676 mg (76%); white solid; mp 186–188 °C; rotameric ratio ~1:1.2.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (s, 0.43 H), 7.85 (s, 0.55 H), 7.59 (d, *J* = 7.84 Hz, 0.45 H), 7.52 (d, *J* = 7.84 Hz, 0.56 H), 7.15–6.99 (m, 3 H), 6.52–6.50 (m, 1.54 H), 6.44 (s, 0.59 H), 6.31–6.25 (m, 3 H), 6.17 (s, 1 H), 5.01 (d, *J* = 15.97 Hz, 0.55 H), 4.90 (d, *J* = 15.00 Hz, 0.44 H), 4.48 (d, *J* = 15.97 Hz, 0.52 H), 4.03 (d,

J = 15.00 Hz, 0.45 H), 3.54–3.51 (m, 3 H), 3.08–3.05 (m, 3 H), 2.08–2.02 (m, 3 H), 1.31–1.27 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.7, 167.4, 157.7, 154.7, 136.9, 136.7, 134.1, 134.0, 129.7, 129.2, 129.1, 128.1, 127.4, 126.6, 126.4, 121.7, 121.4, 120.4, 120.1, 119.3, 119.0, 112.5 (2), 109.4, 109.2, 102.7, 102.6, 91.1, 90.4, 74.0, 72.9, 57.4, 54.8, 54.7, 52.7, 50.4 (2), 49.5, 46.2, 28.8, 28.2, 3.6, 3.3.

HRMS: m/z calcd for $C_{27}H_{31}N_3O_3$: 445.2365; found: 445.2364.

***N*-[1-(Benzo[*b*]thiophen-2-yl)-2-(*tert*-butylamino)-2-oxoethyl]-*N*-(4-methoxybenzyl)but-2-ynamide (15a)**
Yield: 586 mg (70%); white solid; mp 126–128 °C; rotameric ratio ~1:3.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.64 (m, 2 H), 7.36–7.29 (m, 2 H), 7.23–7.11 (m, 3 H), 6.78–6.69 (m, 2 H), 6.10 (s, 0.19 H), 6.00 (br s, 0.73 H), 5.74 (s, 0.78 H), 5.48 (br s, 0.17 H), 4.82 (s, 1.52 H), 4.66–4.48 (m, 0.39 H), 3.75 (s, 0.65 H), 3.71 (s, 2.36 H), 1.99 (s, 3 H), 1.25 (s, 7 H), 1.14 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 159.0, 155.6, 140.7, 138.7, 137.4, 130.1, 128.9, 128.7, 126.1, 124.6, 124.2, 123.6, 122.1, 114.2, 113.7, 90.9, 73.5, 58.9, 55.2, 51.7, 28.4, 28.1, 4.1.

HRMS: m/z calcd for $C_{26}H_{28}N_2O_3S$: 448.1821; found: 448.1806.

***N*-[1-(Benzo[*b*]thiophen-2-yl)-2-(*tert*-butylamino)-2-oxoethyl]-*N*-(4-methoxybenzyl)-3-phenylpropiolamide (15b)**
Yield: 970 mg (95%); yellow solid; mp 66–68 °C; rotameric ratio ~1:3.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.66 (m, 2 H), 7.5–7.52 (m, 0.44 H), 7.47–7.44 (m, 1.54 H), 7.40–7.28 (m, 6.62 H), 7.18 (d, J = 8.74 Hz, 1.60 H), 6.80 (d, J = 8.75 Hz, 0.50 H), 6.71 (d, J = 8.75 Hz, 1.51 H), 6.07 (s, 0.23 H), 6.01 (br s, 0.68 H), 5.83 (s, 0.74 H), 5.52 (br s, 0.15 H), 4.93 (s, 1.42 H), 4.77–4.59 (m, 0.46 H), 3.76 (s, 0.76 H), 3.70 (s, 2.28 H), 1.28 (s, 7.25 H), 1.12 (s, 1.72 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 166.4, 159.4, 159.0, 155.7, 140.7, 138.7, 137.4, 132.8, 132.5, 130.5, 130.3 (2), 129.5, 128.9, 128.7, 128.5, 126.3, 124.9, 124.7, 124.4, 124.3, 123.8, 123.7, 120.1, 114.3, 113.8, 92.9, 91.7, 81.8, 81.5, 63.1, 58.9, 55.3, 55.2, 51.8, 51.7, 28.5, 28.2.

HRMS: m/z calcd for $C_{31}H_{30}N_2O_3S$: 510.1977; found: 510.1984.

Compounds 16a–g and 17a,b
The products **16a–f** and **17a**,**b** were synthesized following the same procedure used for the cyclized products **6a–d** (Table 2).

***N*-(*tert*-Butyl)-2-(4-methoxybenzyl)-5-methyl-3-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]indole-1-carboxamide (16a)**
Yield: 87 mg (77%); off-white solid; mp 95–97 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.11 (br s, 1 H), 7.75 (t, J = 3.51 Hz, 1 H), 7.20–7.11 (m, 5 H), 6.77 (d, J = 7.92 Hz, 2 H), 6.05 (s, 1 H), 5.71 (br s, 1 H), 4.98 (d, J = 14.52 Hz, 1 H), 4.92 (s, 1 H), 4.49 (d, J = 13.56 Hz, 1 H), 3.75 (s, 3 H), 2.48 (s, 3 H), 1.11 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 159.3, 142.8, 135.8, 135.1, 129.9, 129.1, 125.4, 122.6, 120.8, 120.2, 119.1, 114.2, 112.9, 111.8, 55.3, 51.8, 28.2, 23.9, 14.1.

HRMS: m/z calcd for $C_{26}H_{29}N_3O_3$: 431.2209; found: 431.2224.

***N*-Cyclohexyl-2-(4-methoxybenzyl)-5-methyl-3-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]indole-1-carboxamide (16b)**

Yield: 103 mg (90%); off-white solid; mp 226–228 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.58 (br s, 1 H), 7.73 (d, J = 7.75 Hz, 1 H), 7.25–7.02 (m, 5 H), 6.74 (d, J = 7.66 Hz, 2 H), 6.02 (s, 1 H), 5.70 (br s, 1 H), 5.04 (s, 1 H), 4.90 (d, J = 14.34 Hz, 1 H), 4.50 (d, J = 14.34 Hz, 1 H), 3.73 (s, 3 H), 3.59 (m, 1 H), 2.48 (s, 3 H), 1.58 (m, 3 H), 1.25 (m, 4 H), 1.06 (m, 1 H), 0.86 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 166.7, 159.3, 142.8, 135.9, 134.8, 129.9, 129.0, 125.4, 122.6, 120.8, 120.1, 119.0, 114.3, 112.8, 111.9, 55.2, 48.9, 32.6, 32.3, 29.6, 25.2, 24.6, 24.5, 24.0.

HRMS: m/z calcd for $C_{28}H_{31}N_3O_3$: 457.2365; found: 457.2366.

***N*-*tert*-Butyl-2-(4-methoxybenzyl)-3-oxo-5-phenyl-1,2,3,10-tetrahydroazepino[3,4-*b*]indole-1-carboxamide (16c)**
Yield: 109 mg (88%); white solid; mp 286–288 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.11 (br s, 1 H), 7.49–7.39 (m, 5 H), 7.19–7.10 (m, 3 H), 7.02 (t, J = 7.76 Hz, 1 H), 6.85 (t, J = 7.45 Hz, 1 H), 6.75 (d, J = 7.85 Hz, 2 H), 6.56 (d, J = 8.05 Hz, 1 H), 6.34 (s, 1 H), 5.69 (br s, 1 H), 5.09 (s, 1 H), 4.83 (br s, 2 H), 3.73 (s, 3 H), 1.10 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 159.3, 144.3, 139.8, 135.8, 135.7, 129.9, 128.9, 128.5, 128.4, 125.6, 122.7, 120.6, 120.3, 114.2, 111.6, 111.5, 58.8, 55.3, 52.6, 52.0, 28.2.

HRMS: m/z calcd for $C_{31}H_{31}N_3O_3$: 493.2365; found: 493.2354.

***N*-*tert*-Butyl-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)-3-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]indole-1-carboxamide (16d)**
Yield: 111 mg (85%); off-white solid; mp 299–302 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.50 (br s, 1 H), 7.46 (d, J = 8.40 Hz, 1 H), 7.31 (d, J = 8.40 Hz, 2 H), 7.20 (d, J = 8.05 Hz, 2 H), 7.08 (t, J = 7.56 Hz, 1 H), 6.98 (d, J = 8.66 Hz, 2 H), 6.85–6.82 (m, 3 H), 6.48 (d, J = 8.02 Hz, 1 H), 6.11 (br s, 1 H), 5.64 (s, 1 H), 5.31 (s, 1 H), 4.72 (d, J = 14.99 Hz, 1 H), 4.62 (d, J = 14.74 Hz, 1 H), 3.80 (m, 3 H), 3.69 (3 H), 1.10 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.8, 165.8, 159.7, 158.5, 141.6, 137.1, 135.7, 132.0, 129.5, 129.3, 125.4, 121.5, 119.7, 119.5, 113.8, 113.7, 112.3, 109.7, 66.9, 55.1, 55.0, 50.8, 27.9, 25.0.

HRMS: m/z calcd for $C_{32}H_{33}N_3O_4$: 523.2471; found: 523.2460.

***N*-Cyclohexyl-2-cyclopropyl-5-ethyl-3-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]indole-1-carboxamide (16e)**
Yield: 90 mg (92%); yellow solid; mp 136–138 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.78 (br s, 1 H), 7.69 (d, J = 7.88 Hz, 1 H), 7.47 (d, J = 7.88 Hz, 1 H), 7.17 (t, J = 7.69 Hz, 1 H), 7.09 (t, J = 7.36 Hz, 1 H), 6.93 (d, J = 8.15 Hz, 1 H), 5.68 (s, 1 H), 5.16 (s, 1 H), 3.55 (m, 1 H), 2.94–2.87 (m, 2 H), 2.63–2.53 (m, 1 H), 1.60–1.47 (m, 4 H), 1.24–1.12 (m, 5 H), 1.03 (t, J = 7.41 Hz, 3 H), 0.85–0.67 (m, 3 H), 0.61–0.54 (m, 1 H), 0.43–0.38 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.0, 166.6, 146.1, 136.8, 136.1, 125.3, 122.2, 120.8, 120.3, 119.2, 112.8, 110.5, 60.0, 55.2, 49.1, 33.3, 32.4, 32.3, 29.7, 25.4, 25.3, 13.4, 9.8, 6.4.

HRMS: m/z calcd for $C_{24}H_{29}N_3O_2$: 391.2260; found: 391.2267.

***N*-*tert*-Butyl-2-butyl-3-oxo-5-phenyl-1,2,3,10-tetrahydroazepino[3,4-*b*]indole-1-carboxamide (16f)**
Yield: 85 mg (79%); yellow solid; mp 264–267 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.69 (br s, 1 H), 7.50 (d, J = 8.27 Hz, 1 H), 7.44–7.38 (m, 5 H), 7.09 (t, J = 7.66 Hz, 1 H), 6.82 (t, J = 7.48 Hz, 1 H), 6.49–6.40 (m, 2 H), 5.96 (s, 1 H), 5.27 (s, 1 H), 3.83 (m, 1 H), 3.27 (m, 1 H), 1.48–11.45 (m, 2 H), 1.09 (m, 11 H), 0.79 (t, J = 7.34 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.5, 166.0, 141.1, 139.8, 137.3, 135.8, 128.6, 128.3, 128.0, 125.3, 121.6, 121.3, 119.6, 119.4, 112.3, 109.6, 58.3, 54.8, 51.0, 29.6, 28.0, 19.3, 13.6.

HRMS: m/z calcd for $C_{27}H_{31}N_3O_2$: 429.2416; found: 429.2403.

***N*-(*tert*-Butyl)-2-(4-methoxybenzyl)-5,10-dimethyl-3-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]indole-1-carboxamide (16g)**
Yield: 92 mg (83%); white solid; mp 237–239 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, J = 7.93 Hz, 1 H), 7.46 (d, J = 8.10 Hz, 1 H), 7.20 (t, J = 7.17 Hz, 1 H), 7.13–7.10 (m, 3 H), 6.76 (d, J = 8.32 Hz, 2 H), 6.11 (s, 1 H), 5.84 (s, 1 H), 5.41 (s, 1 H),

5.08 (d, J = 14.33 Hz, 1 H), 4.35 (d, J = 14.33 Hz, 1 H), 3.67 (s, 3 H), 3.38 (s, 3 H), 2.35 (s, 3 H), 1.12 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 167.1, 159.4, 140.5, 138.5, 137.8, 130.8, 130.3, 125.2, 122.7, 121.2, 121.0, 120.9, 114.7, 112.2, 111.6, 57.0, 55.9, 52.0, 51.9, 30.2, 29.0, 24.1.

HRMS: m/z calcd for $C_{27}H_{31}N_3O_3$: 445.2365; found: 445.2361.

***N*-(*tert*-Butyl)-2-(4-methoxybenzyl)-5-methyl-3-oxo-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]azepine-1-carboxamide (17a)**
Yield: 90 mg (80%); white solid; mp 235–237 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.02 Hz, 1 H), 7.79 (d, J = 8.21 Hz, 1 H), 7.41–7.36 (m, 2 H), 7.28 (d, J = 8.47 Hz, 2 H), 6.86 (d, J = 8.49 Hz, 2 H), 6.26 (s, 1 H), 5.27 (br s, 1 H), 4.91 (d, J = 14.53 Hz, 1 H), 4.83 (s, 1 H), 4.49 (d, J = 14.45 Hz, 1 H), 3.80 (m, 3 H), 2.42 (3 H), 1.13 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 165.9, 159.6, 140.0, 139.1, 138.0, 137.3, 132.5, 130.3, 128.7, 125.9, 124.9, 124.8, 123.6, 122.8, 114.5, 59.2, 55.3, 51.8, 51.4, 28.2, 23.0.

HRMS: m/z calcd for $C_{26}H_{28}N_2O_3S$: 448.1821; found: 448.1829.

***N*-(*tert*-Butyl)-2-(4-methoxybenzyl)-3-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[4,5]thieno[2,3-*c*]azepine-1-carboxamide (17b)**
Yield: 116 mg (91%); white solid; mp 248–250 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.17 Hz, 1 H), 7.36–7.23 (m, 8 H), 7.06 (t, J = 7.55 Hz, 1 H), 6.88 (d, J = 8.59 Hz, 2 H), 6.74 (d, J = 8.35 Hz, 1 H), 6.51 (s, 1 H), 5.39 (s, 1 H), 4.96–4.90 (m, 2 H), 4.62 (d, J = 14.50 Hz, 1 H), 3.80 (s, 3 H), 1.10 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 165.7, 159.6, 142.7, 139.5, 139.1, 139.0, 137.5, 131.0, 130.4, 129.0, 128.5 (2), 128.1, 126.0, 124.7, 124.4, 124.3, 122.4, 114.5, 59.3, 55.3, 51.9, 51.8, 28.1.

HRMS: m/z calcd for $C_{31}H_{30}N_2O_3S$: 510.1977; found: 510.1976.

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