Chapter 2

Development of Synthetic Protocols to Generate Diversely Substituted Fused Indole Derivatives
INTRODUCTION

The indole ring system represents one of the most abundant and important heterocycles in nature. Found in a hugely diverse array of biologically significant natural compounds, from simple derivatives such as the neurotransmitter serotonin (1) to complex alkaloids such as the clinically used anticancer agent mitomycin C (2) and vinblastine (3), and the antihypertensive alkaloid reserpine (4) (Figure 1), the importance of indoles to biological chemistry cannot be overstated.\(^1\) Additionally, a number of important synthetic drugs contain an indole motif, including sumatriptan (5), tadalafil (6), rizatriptan (7) and fluvastatin (8) (Figure 2), accounting for a total of $3.2bn in sales in 2010.\(^2\)

![Figure 1. Some naturally occurring indole-based molecules.](image1)

![Figure 2. Four clinically used indole-based drugs.](image2)
Indole moiety in drugs

The indole moiety is present in a number of drugs currently in the market. Most of them belong to triptans (9-14) which are used mainly for the treatment of migraine headaches (Figure 3).

![Figure 3. Currently available drugs from the triptan group.]

All members of this group are agonists of migraine associated 5HT1B and 5HT1D serotonin receptors. Sumatriptan (5, Imitrex) was developed by Glaxo for the treatment of migraines and introduced into the market as the first member of the triptan family. Relative to the second generation triptans, sumatriptan (5) has a lower oral bioavailability and a shorter half-life. Frovatriptan (14, FROVA) was developed by Vernalis for the treatment of menstruation associated headaches. Frovatriptan’s (14) affinity for migraine specific serotonin receptors 5HT1B is believed to be the highest among all triptans. In addition, frovatriptan binds to 5HT1D and 5HT7 receptor subtypes. Zolmitriptan (10) marketed by AstraZeneca is used to treat acute migraine attacks and cluster headaches. GlaxoSmithKline’s naratriptan (9, Amerge) is also used in the treatment of migraines and some of its side effects include dizziness, tiredness, tingling of the hands and feet, and dry mouth. All available triptans are well tolerated and effective. The highest incidence of central nervous system (CNS) related side effects (dizziness, drowsiness) was reported for zolmitriptan 10 (5 mg), rizatriptan 11 (10 mg), and eletriptan 12 (40 mg, 80 mg). The differences in side-effect profiles for triptans are not likely caused by their different affinity toward
serotonin receptors or other neurological receptors in the CNS. There is a positive correlation between the lipophilicity coefficient and CNS side effects; these undesired effects are also dose-dependent.

**In the pipeline: novel indole-derived structures**

One of the new molecules reported in the past few years sharing structure similarities with indole alkaloids is the Wyeth compound, WAY-161503 (15, Figure 4), a selective 5HT2C receptor agonist. According to a recent report, research conducted on the action of WAY-161503 (15) confirms that 5HT2C receptors may play an inhibitory role in the regulation of reward-related behavior. WAY-161503 is covered by several patents and is claimed to be useful for the treatment or prevention of urinary incontinence, as well as for depressive disorders. Another compound, WAY-163909 (16, Figure 4), a selective 5HT2C receptor agonist, was found to be of potential utility in obesity treatment. The same compound exhibited antidepressant and antipsychotic activity in preclinical animal models. A melatonin receptor agonist that has recently completed phase II clinical trials for sleep disorders in blind individuals, PD-6735 (17, Figure 4), also contains an indole moiety. The drug was not only effective in re-establishing the right day/night cycle but also displayed an excellent safety profile.

![Figure 4. Indole derived drugs.](image)

The continued development of routes towards indoles has been a central theme in organic synthesis over the last century, in keeping with their importance. However, there are still limitations on the chemical space which is easily accessible; this can be readily observed by comparison of the naturally occurring indole drugs with their synthetic counterparts. In particular, the substitution pattern around the six-membered
ring is notably less complex in synthetic indoles than in naturally occurring ones. To our knowledge, there are no synthetic indoles bearing substituents at more than one of the benzenoid ring positions currently in clinical use. We attribute this observation not to any perceived pharmacological disadvantages of highly substituted indoles, but rather to their relative synthetic intractability. Hence, there is still room for improvement in the field of indole synthesis.

In the last two or three decades the emphasis on and applications of green chemical principles, introduced some significant advances in organic synthesis, such as combinatorial chemistry, multicomponent processes (MCPs), organofluorine chemistry, organocatalysis, microwave synthesis and sonochemistry, etc. Among these new developments, MCP techniques (including multicomponent reactions (MCRs) and one-pot multicomponent reactions) played a leading role and the field experienced tremendous expansion.\(^\text{12}\) MCR is defined as a process in which three or more different starting materials react together and/or sequentially to yield ideally a major product. Another variation of MCPs involves the sequential addition of three or more different compounds in two or more steps to the same reaction vessel, entitled one-pot multicomponent reactions.

**Synthesis of indole bearing natural products via MCPs**

Indole alkaloids usually have complex structures and chemists normally prefer to synthesize them by means of multistep processes. However, MCRs methodology offers an alternative method with a reduced number of steps.\(^\text{13}\) For example, the one-pot synthesis of the precursors of (±)-allo-yohimban (18) and (±)-nitraraine (19) (Scheme 1).\(^\text{14}\) In this method the C=N bond of the cyclic imines, acryloyl chloride, and 2,4-pentadienyltin are coupled together, followed by the spontaneous intramolecular Diels–Alder cycloaddition reaction.

Ishikura *et al.*\(^\text{15}\) employed a palladium catalyst for the one-pot carbonylation and cross-coupling reaction of indolyborates with vinyl triflates in the presence of carbon monoxide to prepare 2-acylindole 20. Compound 20 is converted to 21 by acid catalysis and then used as precursor for the synthesis of Yuehchukene (YCH) (Scheme 2).\(^\text{16}\)
Scheme 1. MCRs in the synthesis of (+)-allo-yohimban and (+)-nitraraine.

Scheme 2. Palladium Cross-Coupling in the Synthesis of YCHs.

A typical natural product such as sperrillamide 23 and its analogues were synthesized with MCRs (Scheme 3). Dömling and co-workers reported a solution phase Ugi 4-CR method to get access to these compounds. The antibiotic and cytotoxic activities of these compounds were evaluated. Several of the synthetic analogues are more potent than the original natural product.
Recently, Takiguchi et al. reported the asymmetric total synthesis of two anticancer natural products 25 and 26 employing a common tricyclic imine precursor 24 and an Ugi reaction (Scheme 4). Thus N-acetylardeemin 25 was accessed by the Ugi-3CR of 24 with anthranilic acid, isocyanide, and N-protected D-Ala in toluene followed by deprotection and polycondensation, whereas fructigenine 26 was synthesized by the Ugi-3CR of 24 with p-methoxybenzyl isocyanide and Boc-Phe with subsequent deprotection and diketopiperazine ring closure under basic conditions. In both cases, the Ugi reaction was highly stereoselective and the isocyanide attack takes place preferentially from the side opposite the bulky reverse-prenyl group of imine 24.
Chataigner and Piettre have described the feasibility of a multicomponent domino [4 + 2]/[3 + 2] cycloaddition reaction with electron-poor nitroheteroaromatics.\textsuperscript{19} 3-Nitroindole is used for the rapid and efficient generation of tetracyclic dearomatized diamines \textsuperscript{28} featuring a quaternary center at one of the ring junctions (Scheme 4). It is clear that it would be quite difficult to prepare these novel structures with alternative synthetic methods. The reduction products of \textsuperscript{27} are considered to be potential candidates for the design and preparation of novel catalysts in the context of asymmetric synthesis. Activation of 3-nitroindole at high pressure allows it to behave as electron-poor heterodienes for a [4 + 2] cyclization with vinyl ethers to form \textsuperscript{27}. The latter participates in a [3 + 2] cycloaddition process with acrylate to give \textsuperscript{29} in good yield. Already similar sequence cycloaddition has been reported for $\beta$-nitrostyrenyl compounds.\textsuperscript{20}

Advances in technology have brought an explosion in the number of possible drug targets and at least one-third of these possible drug targets contain hetero-aromatic fragments.\textsuperscript{21} To tackle this challenge, organic chemists have to strive for more selective, rapid and diversity oriented processes. As a result, the use of transition-metal-catalyzed reactions has increased tremendously. Due to the vast possibilities of making the reactions selective, by playing with the properties of metal, transition-metal-catalysis has been the area of focus in the last three decades. Recent advances in transition-metal-catalysis have increased the mechanistic understanding of many
transformations in heterocyclic chemistry. Furthermore the development of new ligands has increased the fine tunability of the metal properties. Metal-catalyzed cyclizations of aromatic and heteroaromatic compounds with alkynes have attracted much attention in the last decade. In particular, intramolecular gold-, platinum- and indium-catalyzed hydroarylations, cycloisomerizations, and cycloadditions offer new ways for the efficient construction of biologically interesting carbo- and heterocycles. Recent elegant examples also include the use of N-heterocycles; for example, Echavarren et al. and England and Padwa reported intramolecular cyclizations of indole derivatives in the presence of gold catalysts.

Taking lead from above mentioned pioneering work, we explored the versatility of the metals (gold, platinum and indium), that catalyse a highly regioselective intramolecular hydroarylation reaction exclusively on the C3-position of indole ring.

In Section-A, we have explored a fascile and environmentally benign post-Ugi gold-catalyzed regio- and diastereoselective intramolecular domino cyclization strategy for the synthesis of a diversely substituted spiroindoline derivatives. The first step in this process involved Ugi-four component reaction (Ugi-4CR) to generate Ugi-adduct. The resulting Ugi-adduct was further subjected to intramolecular cyclization reaction. This post-Ugi intramolecular domino strategy involved the formation of a new C-C and a new C-N bonds thereby leading to the formation of fused spirocycle merely in two-steps. This observation was remarkable as the attack on the α-position of an alkyne conjugated with amide is rare and trapping of the spiro-intermediate by a sterically hindered amide is rather unexpected, not to mention the observed diastereoselectivity. Further, the mechanistic cycle during the course of the intramolecular domino cyclization reaction was further confirmed by X-ray crystallography of spiroindoline.

In Section-B, we have explored a regioselective cyclization for the synthesis of novel tricyclic benzo[c,d]indole cores. This protocol involves switching the regioselectivity via post-Ugi intramolecular hydroarylation to azepino- and azocino-[c,d]indolones. In this intramolecular cyclization reaction, indium(III) and gold(I) catalysts were used to achieve the switch in regioselectivity of the product.
REFERENCES


Section A

Diversity Oriented Approach to Spiroindolines: Post-Ugi Gold-Catalyzed Diastereoselective Domino Cyclization
INTRODUCTION

There is no better way to appreciate the limitations of the available tools of organic synthesis than to contemplate how one would prepare, in a practical fashion, natural products having novel structures. Spirocycles, structures which have two or more rings joined at a single carbon, remain a challenging motif for synthetic chemists. Some of the most important spirocycles are spirooxindole and spiroindoline alkaloids that are isolated from natural sources. These natural products have been the focus of total syntheses from several groups, in part because of their challenging structures, but also because several of these alkaloids possess interesting biological activity e.g. the anticancer drug vinblastine. The various methods used in the formation of the asymmetric quaternary spirocenter in the 3-position of both spirooxindoles and spiroindoline alkaloids. Besides the interesting ring system common to this class of molecules, these indole alkaloids also possess a spiro quaternary carbon. Total synthesis of these alkaloids not only pose a challenge to synthetic chemists due to the complex and very compact structure, but provide another route to these important compounds since only small amounts of some of these alkaloids can be isolated from natural sources. In addition to the cis-pyrrolidino[2,3-b]indoline unit linking pattern, the quaternary carbon center stereogenicity and aminal connectivity are other potential sources of structural diversity in these tryptamine-derived natural products. Five constitutional isomers differing in their aminal connectivity can be formed from the hypothetical precursor, tetraaminodialdehyde1 (Figure 1). Natural products are presently known that contain four of these skeletons.3

Biological importance

Spiroindole alkaloids are an important class of natural products; several of its members exhibit an interesting array of biological activities such as antitumor, adrenergic blocking,4 and glycine antagonist5 activities. The Strychnos alkaloid class of molecules includes compounds such as strychnine (7), tubifoline (8), and aspidospermine (9), as well as vinblastine and vindoline, which are important anticancer drug agents.
Perophoramidine (10) is the first reported metabolite from the genus *Perophora*. In addition, perophoramidine (10) exhibits cytotoxicity toward the HCT116 colon carcinoma cell line with an IC\textsubscript{50} value of 60 μM and induce apoptosis via PARP cleavage within 24 h. Perophoramidine (10)\(^7\) and communesins (12-19)\(^8\) are structurally related indole alkaloid, have architectures that are unique among known indole alkaloids. They possess a complex multiring system, bisamidine or bisaminal functionality, and two vicinal quaternary carbon centers between the two ethylene groups. The two ethylene groups are *trans* to each other in perophoramidine (10) and *cis* in communesins (12-19) (Figure 2).\(^9\) Preliminary biological evaluation has revealed that these alkaloids possess significant cytotoxicity against P-388 lymphocytic leukemia cells and insecticidal activity.\(^10\) Previously in the laboratories of Pfizer UK, structurally related compounds were discovered in an antihelminthic screen exhibiting activity against the free-living nematode *Caenorhabditis elegans*.\(^11\)

Figure 1. Isomeric bisaminals formed by the dehydration of the hypothetical precursor tetraaminodialdehyde\(^1\).
Microbial metabolites such as avermectin are attracting increasing attention as potential pesticides, and they are expected to overcome the resistance and pollution that have become associated with the use of synthetic pesticides.\textsuperscript{12} In a study, it was found that the acetone extract of okara (the insoluble residue of soyabean) fermented with this strain was found to exhibit the insecticidal activity against silkworms. Later on these structures were determined as three new communesin congeners communesins C, D, E (\textsuperscript{14}, \textsuperscript{15}, \textsuperscript{16}).\textsuperscript{13} In another report antiproliferative activity was examined using several human leukemia cell lines. Since the known communesins A (\textsuperscript{13}) and B (\textsuperscript{12}) were described to inhibit proliferation of mouse leukemic cells P-388,\textsuperscript{14} it was further investigated whether the isolated communesins B, C, D (\textsuperscript{12}, \textsuperscript{14}, \textsuperscript{15}) would also be growth inhibitory to other tumor cell lines. They were tested on a series of human leukemia cell lines by the MTT assay and through radioactive thymidine incorporation. All three compounds exhibited a moderate antiproliferative activity.\textsuperscript{15}
Literature reports for the synthesis of functionalized polycyclic spiroindolines

Thenovel architecture together with their biological activities made indoline skeleton an appealing target for synthetic chemists. Over the last decade, enormous efforts have been devoted to the development of novel and practical synthetic strategies for the construction of this molecular motif. Although successful, most of the reports contain either multistep sequences or lack the aspects of diversity and mild reaction conditions.

In 2000, Kobayashi et al. reported the synthesis of vindoline (24) which involved a [4+2] cycloaddition as the key step. The [4+2] precursor possessed an existing stereogenic center [that ultimately came from readily available (R)-glyceraldehyde acetonide], and the resulting product was obtained as a single enantiomer. The precursor of the [4+2] reaction is shown in Scheme 1. The total synthesis of (−)-vindoline was accomplished in seven steps from 23. This synthesis was partially based on the synthesis of (−)-vindorosine by Kuehne et al. several years prior, which utilized the [4+2] cycloaddition approach.

![Scheme 1. Synthesis of (−)-vindoline.](image)
Recently, a novel tandem Mannich/intramolecular aminal formation between tryptamines and salicylaldehydes\(^{25}\) was reported (Scheme 2).\(^{18}\) This tandem reaction started from easily available materials to afford highly functionalized spiro-fused six-membered indolines\(^{26}\) in good to excellent yields with the generation of up to three new stereogenic centers (a highly congested continuous spiro quaternary center, and two tertiary stereocenters in a highly economical and effective fashion) in excellent regio and diastereoselectivities.

![Scheme 2. Tandem Mannich/intramolecular aminal reaction between tryptamines and salicylaldehydes.](image)

A new copper-catalyzed spirocyclization has been reported by El Kaïm et al.\(^{19}\) This reaction probably involves radicals generated from enolates by a copper(II)-triggered oxidation. This simple procedure produces remarkably complex final structures. In these one-pot reactions, the four-component nature of the first Ugi step contributes to the formation of complex alkaloid-like structures with high diversity. The programmed combination of this multi-component reaction with sequential secondary transformations provides a powerful approach to reach high molecular complexity. This new synthesis of complex indolines (28) in one step underscores the potential of such synthetic approaches (Scheme 3).

![Scheme 3. Post-Ugi copper-catalyzed spirocyclization.](image)

The reaction mechanism probably involves the oxidative generation of a peptidyl radical\(^{30}\) triggered by copper(II) salts. A 5-exo-dig cyclization, followed by a further
oxidation of the \(\alpha\)-aminoalkyl radical\(^{31}\) forms an iminium\(^{32}\) trapped by the vicinal amide moiety (Scheme 4).

![Scheme 4. Proposed radical mechanism for spirocyclization.](image)

Recently, a novel catalyst-free multicomponent reaction for the construction of polycyclic spiroindolines (34) by using a 2-isocyanopropylindole with different types of aromatic aldehydes (33) and malononitrile was reported (Scheme 5).\(^{20}\) The reaction proceeded under mild conditions and yielded the products in good to excellent yields with high diastereoselectivities.

![Scheme 5. Catalyst-free construction of polycyclic spiroindolines.](image)

A plausible mechanism for this multicomponent reaction was proposed.\(^{21}\) Firstly, the reaction is initiated by Knoevenagel condensation of malononitrile and the aldehyde to perform the benzylidenemalononitrile (35). Then, the isocyanide undergoes nucleophilic addition to intermediate 36 followed by nucleophilic attack by the C-3 of indole to afford spiro intermediate 37. Subsequently, this intermediate undergoes intramolecular nucleophilic addition to afford polycyclic spiroindoline derivatives 34 (Scheme 6).

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An efficient protocol was developed for assembling a polycyclic spiroindolinescaffold, which involves an intramolecular oxidative coupling of dianions derived from indole-embodied β-ketoamides using iodine as the oxidant, and subsequent attack of oxygen anion to the resultant imine moiety (Scheme 7).

An unprecedented atom/step economic synthesis of fused tetracyclic N(H)-free pyranyl indolines, via gold-catalyzed cascade intramolecular cyclization was documented by Bandini et al. In this reaction high level of chemo-, regio- and diastereoselectivity were obtained for a range of densely functionalized compounds (Scheme 8).
Mechanistically, although detailed experimental evidences are still elusive, a tentative hypothesis is depicted in Scheme 9. Here, the initial Au(I)-assisted electrophilic activation of the triple bond can trigger a Friedel–Crafts-type alkylation of the indole ring, with the formation of spirovinyl-gold intermediates 45 and 46. Then, the regioselective functionalization of the C-3 position of the indole nucleus could provide an avenue toward the trapping of the incipient iminium group by the hydroxyl group. Finally, the protodeauration step would result into the desired tetracyclic compounds 42/44.

**Scheme 9.** Tentative mechanistic sketch for intramolecular cascade cyclization.

Further studies into the development of an enantioselective cascade reaction for the preparation of tetracyclic fused indolines was developed using chiral gold catalyst (Scheme 10).

**Scheme 10.** Enantioselective intramolecular cascade cyclization.
OBJECTIVE AND WORK STRATEGY

The pursuit of synthetic efficiency continues to stimulate the design and development of new concepts and innovative synthetic strategies in both academic research and industrial applications. One of the most effective ways to improve synthetic efficiency is to implement reaction cascades, which have emerged as powerful tools to give a rapid increase in molecular complexity from simple and readily available starting materials. It is obvious that such transformations require fewer solvents and adsorbents and less energy, hence minimizing waste management in comparison to a series of individual stepwise reactions. In recent years, considerable efforts have been devoted to the development of tandem or domino reactions.26

The proven pharmacological activity of indole alkaloids,27 combined with their challenging molecular skeletons, concurs to define this class of polycyclic fused molecular architectures featuring quaternary stereocenters, and represent stimulating/nontrivial synthetic exercises for organic chemists.28 Although cascade/tandem methodologies are rising to prominence,29 elaborate multi-step synthetic sequences are still normally required for the preparation of stereochemically defined indoline alkaloids.30 As a consequence, it is not surprising to record a growing need for selective and sustainable procedures for the preparation of densely functionalized polycyclic indolines.Gold-catalyzed carbocyclization strategies have attracted much attention recently due to their selective and efficient activation of C-C triple bond towards a wide range of nucleophiles.Domino approaches, involving gold-catalysis, lead to complex heterocyclic compounds under exceedingly mild reaction conditions. We considered that synthesis of spiroindolines might be readily accessible through a serendipitous discovered post-Ugi gold-catalyzed intramolecular domino cyclization sequence producing spiroindolines.
A post-Ugi intramolecular domino cyclization reaction of Ugi-adduct 51 using combination of Au(PPh$_3$)Cl and AgSbF$_6$ as a catalyst in chloroform in order to achieve exo-dig cyclized spiroindolines 52. Thus, we have reported four-component two-step procedure to provide a new, rapid, and environmentally benign catalytic diastereoselective synthesis of spiroindoline derivatives through a post-Ugi gold catalyzed intramolecular domino cyclization (Scheme 11). This post-Ugi intramolecular domino strategy involved the formation of a new C-C bond and a new C-N bond, thereby leading to the formation of fused spirocycle. So, we began to investigate the possibility and scope of this reaction.

Scheme 11. Diastereoselective intramolecular cyclization to spiroindolines.

In continuation of this work and our continuous effort, we applied the developed protocol for a similar post-Ugi gold-catalyzed intramolecular domino cyclization sequence for the synthesis of spiroindolines using propargyl amines as alkyne source (Scheme 12).

RESULTS AND DISCUSSION

Establishment of reaction condition: Ugi 4-CR\textsuperscript{33} of indole-3-carbaldehyde \textit{47a} with \textit{p}-methoxybenzyl amine \textit{48a}, \textit{tert}-butyl isonitrile \textit{49a} and 2-butyric acid \textit{50a} in methanol at 50 °C gave Ugi adduct \textit{51a} in 71% yield. This Ugi adduct \textit{51a} when treated with 5 mole\% of Au(PPh\textsubscript{3})OTf in chloroform, the expected outcome was the \textit{endo}-dig cyclization product indoloazepinone \textit{52a}′; but surprisingly only \textit{exo}-dig cyclization occurred with full selectivity, followed by intramolecular trapping of this spirointermediate to generate tetracyclic spiroindoline \textit{52a} in 61% yield (Scheme 13). This intriguing observation was rather unexpected as the attack on \textit{α}-position of conjugated alkyne is rare and trapping of the spirointermediate by amidic N in presence of bulky \textit{tert}-butyl group is sterically hindered, not to mention the diastereoselectivity. Since the 61% yield of \textit{52a} was not satisfactory we optimized the catalysis conditions (Table 1). While gold(X-Phos) with different counter ions did not improve the yield, normal gold chlorides and Au(PPh\textsubscript{3})Cl did not yield any conversion (Table 1, entries 2-7), reaction with Au(PPh\textsubscript{3})SbF\textsubscript{6} afforded an improved yield of 75% in merely 2 h (Table 1, entry 8). Even replacing -SbF\textsubscript{6} with other counter ions or using ACN[JohnPhos]Au(I)SbF\textsubscript{6} did not yield better results (Table 1, entries 9-11).

Scheme 13. Unexpected gold-catalyzed domino cyclization.
Table 1. Optimization of the domino cyclization.\textsuperscript{a}

\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & Catalyst(mole%) & Solvent  & Time(h) & \%Conversion\textsuperscript{b}(\%Yield) \\
\hline
1 & Au(PPh\textsubscript{3})OTf \textsubscript{(5)} & CDCl\textsubscript{3} & 3 & 100 (61) \\
2 & Au(PPh\textsubscript{3})SbF\textsubscript{6} \textsubscript{(5)} & CDCl\textsubscript{3} & 3 & 100 (59) \\
3 & Au(PPh\textsubscript{3})BF\textsubscript{4} \textsubscript{(5)} & CDCl\textsubscript{3} & 20 & 40 \\
4 & Au(PPh\textsubscript{3})NTf\textsubscript{2} \textsubscript{(5)} & CDCl\textsubscript{3} & 20 & 100 (67) \\
5 & AuCl \textsubscript{(5)} & CDCl\textsubscript{3} & 20 & 0 \\
6 & AuCl\textsubscript{3} \textsubscript{(5)} & CDCl\textsubscript{3} & 20 & Traces \\
7 & Au(PPh\textsubscript{3})Cl \textsubscript{(5)} & CDCl\textsubscript{3} & 20 & 0 \\
8 & Au(PPh\textsubscript{3})SbF\textsubscript{6} \textsubscript{(5)} & CDCl\textsubscript{3} & 2 & 100 (75) \\
9 & Au(PPh\textsubscript{3})BF\textsubscript{4} \textsubscript{(5)} & CDCl\textsubscript{3} & 20 & 20 \\
10 & Au(PPh\textsubscript{3})NTf\textsubscript{2} \textsubscript{(5)} & CDCl\textsubscript{3} & 20 & 100 (64) \\
11 & ACN[JohnPhos]Au(I) \textsubscript{SbF\textsubscript{6} (5)} & CDCl\textsubscript{3} & 20 & 100 (62) \\
12 & AgOTf \textsubscript{(5)} & CDCl\textsubscript{3} & 20 & 35 \\
13 & AgSbF\textsubscript{6} \textsubscript{(5)} & CDCl\textsubscript{3} & 20 & 50 \\
14 & Au(PPh\textsubscript{3})SbF\textsubscript{6} \textsubscript{(5)} & CDCl\textsubscript{3} & 0.5 & 100 (72) \\
15 & Au(PPh\textsubscript{3})SbF\textsubscript{6} \textsubscript{(5)} & CDCl\textsubscript{3} & 0.25 & 100 (58)\textsuperscript{a} \\
16 & Au(PPh\textsubscript{3})SbF\textsubscript{6} \textsubscript{(2)} & CDCl\textsubscript{3} & 20 & 50 \\
17 & Au(PPh\textsubscript{3})SbF\textsubscript{6} \textsubscript{(5)} & DCM-\textsubscript{d\textsubscript{2}} & 3 & 100 (70) \\
18 & Au(PPh\textsubscript{3})SbF\textsubscript{6} \textsubscript{(5)} & ACN-\textsubscript{d\textsubscript{3}} & 20 & 80 \\
19 & Au(PPh\textsubscript{3})SbF\textsubscript{6} \textsubscript{(5)} & THF-\textsubscript{d\textsubscript{6}} & 20 & Traces \\
20 & Au(PPh\textsubscript{3})SbF\textsubscript{6} \textsubscript{(5)} & MeOH & 2 & 100 (46)\textsuperscript{a} \\
\hline
\end{tabular}

\textsuperscript{a}Unless otherwise noted, all reactions were run with 51a (0.1 mmol) and a catalyst loading of 5 mole\% in a screw-cap vial at RT. \textsuperscript{b}Conversion based on \textsuperscript{1}H NMR analysis; yields given in parentheses are yields of isolated products. \textsuperscript{c}Reaction at 50°C. \textsuperscript{d}Reaction at 100°C. \textsuperscript{e}Unidentified by-products were formed. \textsuperscript{f}Catalyst loading of 2 mole\%.

Control experiments with AgOTf and AgSbF\textsubscript{6} gave only moderate yields (Table 1, entries 12-13). Reaction with best catalyst system Au(PPh\textsubscript{3})SbF\textsubscript{6} at 50 °C reduced the time but with little less yield, while increasing the temperature to 100 °C decreased the yield to 58% (Table 1, entries 14-15). While decreasing the catalyst loading to 2 mole\% gave only 50% conversion after 20 h, changing the solvent did not yield better results (Table 1, entries 16-20).
Table 2. Optimization for the intramolecular domino hydroarylation.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mole%)</th>
<th>Acid(1equiv)</th>
<th>Time(h)</th>
<th>%Yield\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Au(P(<em>{3})H(</em>{3}))SbF(_{6}) (5)</td>
<td>-</td>
<td>2</td>
<td>55\textsuperscript{c}</td>
</tr>
<tr>
<td>2</td>
<td>Au(P(<em>{3})H(</em>{3}))SbF(_{6}) (5)</td>
<td>TFA</td>
<td>2</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>PtCl(_{2}) (5)</td>
<td>-</td>
<td>10</td>
<td>\textdagger</td>
</tr>
<tr>
<td>4</td>
<td>PtCl(_{2}) (5)</td>
<td>TFA</td>
<td>10</td>
<td>\textdagger</td>
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<tr>
<td>5</td>
<td>-</td>
<td>TFA</td>
<td>10</td>
<td>\textdagger</td>
</tr>
<tr>
<td>6</td>
<td>Au(P(<em>{3})H(</em>{3}))SbF(_{6}) (5)</td>
<td>PTSA</td>
<td>2</td>
<td>70</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All the reactions were run on 0.1 mmol scale of 53a using chloroform (2 mL) as solvent at rt. \textsuperscript{b}Isolated yields. \textsuperscript{c}Unidentified by-products were formed. \textsuperscript{d}No conversion.

Further extending the substrate scope, we switched to phenyl acetic acid as an acid component and propargyl amine as an amine component in the Ugi-4CR. Thus Ugi-4CR of indole-3-carbaldehyde 47a, propargyl amine 48h, phenyl acetic acid 49e and tert-butyl isonitrile 50a in methanol at 50 °C gave the Ugi-adduct 53a with an excellent yield of 94%. Having this compound 53a in hand we were keen to use the previously developed conditions for intramolecular hydroarylation. Reaction of 53a with 5 mole\% of Au(P\(_{3}\)H\(_{3}\))SbF\(_{6}\) in chloroform at room temperature produced the desired spiroindoline 54a in a moderate yield of 55% along with some unidentified by-products (Table 2, entry 1). The purpose of a protic acid with a gold catalyst is known in the literature.\textsuperscript{34} To our delight, when the above reaction was carried out with 1 equivalent of trifluoroacetic acid (TFA) the yield was improved to 81% (Table 2, entry 2). Aside from being a good proton source TFA might be working as a co-ligand. Experiments with PtCl\(_{2}\) as catalyst did not show any conversion and the starting material was recovered quantitatively (Table 2, entries 3 and 4). In the absence of the gold catalyst no product could be observed (Table 2, entry 5). The application of \(p\)-tolyl sulfonic acid (PTSA) instead of TFA did not give a better result (Table 2, entry 6).
The title compound was synthesized by Ugi four component reaction from indole-3-carbaldehyde 47a with p-methoxybenzyl amine 48a, tert-butyl isonitrile 49a and 2-butylnoic acid 50a in methanol at 50 °C. The title compound 51a was obtained in 71% yield as a white solid having melting point 73-75 °C. The 1H NMR spectrum, suggested that compound appears in the form of rotameric mixture in the ratio of ~1:3 (Figure 3). The peak in the range of δ 1.19-1.26, integrating for nine protons was observed for tertiary butyl group (H-2′′′) (Figure 3). Further the alkynoic methyl group (H-4) was observed as two sets of peaks at δ 1.93 and 2.07, while methoxy group appeared at δ 3.67-3.69 (Figure 3). The presence of two sets of broad singlets at δ 8.42 and 8.26 corresponds to indole –NH group. In the 1H NMR, two sets of singlet at δ 6.19 and 6.35 indicated the appearance of chiral proton H-1′′ due to formation of Ugi-aaduct 51a(Figure 3). The 13C NMR spectrum showed characteristic peaks at δ 168.4 and 158.3 for the two carbonyl groups and peak at δ 29.0 further confirms the presence of the tertiary butyl group (Figure 3). The peaks for remaining protons and carbons were also observed in the1H and 13C NMR spectrum (Figure 3). The structure of compound was also confirmed from its HRMS which showed the peak at 431.2200 for [M]+ which was in accordance with the calculated values of 431.2209.

On the basis of above spectral studies, the compound 51a was assigned the structure: \( N-(2-(\text{tert-} \text{butylamino})-1-(1H-\text{indol-3-yl})-2-\text{oxoethyl})-N-(4-\text{methoxybenzyl})\text{but-2-ynamide.} \)
Figure 3. $^1$H and $^{13}$C NMR spectrum of N-(2-(tert-butlamino)-1-(1H-indol-3-yl)-2-oxoethyl)-N-(4-methoxybenzyl)but-2-ynamide (51a) in CDCl$_3$. 
(E)-5-(tert-Butyl)-1-ethylidene-3-(4-methoxybenzyl)-3,3a,5a,6-tetrahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52a)

The title compound was synthesized by the post-Ugi intramolecular domino cyclization of \( N\)-(2-(tert-butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-\( N\)-(4-methoxybenzyl)but-2-ynamide (51a), \( \text{Au(PPh}_3\text{)}\text{Cl} \) and \( \text{AgSbF}_6 \) in chloroform at room temperature. It was obtained in 75% of yield as a white solid having melting point 197-199 °C. In the \( ^1\text{H} \) NMR spectrum, the disappearance of the rotameric peaks and shift of indole –NH from \( \delta 8.42 \) (in the precursor 51a) to \( \delta 4.44-4.48 \) clearly indicated the formation of the title compound (Figure 4). C-5a proton of indoline moiety appears as a doublet at \( \delta 5.59 \) due to coupling with indole –NH, which in turn appear as doublet at \( \delta 4.44-4.48 \) and thus confirming the formation of tetracyclic compound (Figure 4). Further, appearance of the methyl group (H-2′) and tertiary butyl group (H-2′′′) as a doublet and singlet in the range of \( \delta 1.40-1.46 \) and the observance of H-1′ as a quartet in the range of \( \delta 6.82-6.85 \) confirms the formation of exocyclic spiro compound (Figure 4). The \( ^{13}\text{C} \) NMR spectrum showed the characteristic peak at \( \delta 170.6 \) and 166.4 for two carbonyl groups and a peak at \( \delta 28.1 \) confirms the presence of the tertiary butyl group (Figure 4). The peaks for remaining protons and carbons were also observed in its \( ^1\text{H} \) and \( ^{13}\text{C} \) NMR spectrum (Figure 4). The structure of compound was also confirmed from its HRMS which showed the peak at 431.2194 for [M]\(^+\) and was in accordance with the calculated values of 431.2209. Further, the geometry of the compound was confirmed by single X-ray crystallography (Figure 5).

On the basis of above spectral studies, the compound 52a was assigned the structure: (E)-5-(tert-butyl)-1-ethylidene-3-(4-methoxybenzyl)-3,3a,5a,6-tetrahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione.
Figure 4. $^1$H and $^{13}$C NMR spectrum of (E)-5-(tert-butyl)-1-ethylidene-3-(4-methoxybenzyl)-3,3a,5a,6-tetrahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52a) in CDCl$_3$. 
X-ray crystallographic analysis: The structure of compound 52a was unambiguously assigned by X-ray crystallography (Figure 5).

[Diagram of compound 52a]

Figure 5. Crystal structure of compound 52a. Thermal ellipsoids are drawn at the 50% probability level.

Single crystals of 52a, suitable for X-ray diffraction were obtained by slow evaporation from methanol at room temperature. X-ray intensity data were collected at 100K on an Agilent Supernova diffractometer, equipped with an Atlas CCD detector, using Mo Kα radiation (λ = 0.7107 Å). The images were interpreted and integrated with the CrysAlisPro software from Agilent Technologies. Using Olex2, the structure was solved by the ShelxS structure solution program using Direct Methods and refined with the ShelxL refinement package using full-matrix least squares minimization on $F^2$. Non hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode with isotropic temperature factors were fixed at 1.2 times Ueq of the parent atoms (1.5 for methyl groups).

Crystallographic data: C$_{26}$H$_{29}$N$_3$O$_3$, $M$ = 431.52 g mol$^{-1}$, triclinic, $P$-1 (no. 2), $a$ = 10.4127(4) Å, $b$ = 13.8739(6) Å, $c$ = 16.7454(7) Å, $\alpha$ = 80.534(3), $\beta$ = 86.021(3), $\gamma$ = 75.153(4), $V$ = 2305.56(16) Å$^3$, $T$ = 100.00(10) K, $Z$ = 4, $\rho$$_{calcd}$ = 1.243 g cm$^{-3}$, $\mu$(Mo Kα) = 0.082 mm$^{-1}$, $F$(000) = 920.0, crystal size 0.3 x 0.3 x 0.2 mm$^3$, 17088 reflections measured, 9398 unique ($R$$_{int}$ = 0.0172) which were used in all calculations. The final $wR_2$ was 0.1160 (all data) and the $R_1$ was 0.0469 (>2sigma(I)).
The title compound was synthesized by Ugi four component reaction from indole-3-carbaldehyde 47a, propargyl amine 48h, phenyl acetic acid 49e and tert-butyl isonitrile 50a in methanol at 50 °C. The title compound 53a was obtained with an excellent isolated yield of 94% as a white solid having melting point 62-64 °C. In the 1H NMR spectrum, the peak at δ 1.35, integrating for nine protons indicate the presence of the tertiary butyl group (H-2‴‴), while the peak at δ 1.91 corresponds to the propargylic proton (Figure 6). The peak δ 6.45 further confirms the presence of a chiral C-2 proton due to the formation of Ugi adduct (Figure 6). A broad singlet at δ 8.25, integrating for one proton was assigned for indole –NH. The 13C NMR spectrum showed the characteristic peak at δ 172.2 and 168.8 for two carbonyl carbons and further a peak at δ 28.6 confirms the presence of the tertiary butyl group in the compound (Figure 6). The peaks for remaining protons and carbons were also observed in its 1H and 13C NMR spectrum (Figure 6). The structure of compound was further confirmed from its HRMS which showed the peak at 401.2100 for [M]+ and was in accordance with the calculated value of 401.2103.

On the basis of above spectral studies, the compound 53a was assigned the structure: N-(tert-butyl)-2-(1H-indol-3-yl)-2-(2-phenyl-N-(prop-2-yn-1-yl)acetamido)acetamide.
Figure 6. $^1$H NMR and $^{13}$C NMR spectrum of $N$-(tert-butyl)-2-(1H-indol-3-yl)-2-(2-phenyl- $N$-(prop-2-yn-1-yl)acetamido)acetamide (53a) in CDCl$_3$. 

Section A: Diversity Oriented Approach to Spiroindolines.....
5-(tert-Butyl)-1-methylene-3-(2-phenylacetyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54a)

The title compound (8a) was synthesized by the post-Ugi intramolecular domino cyclization of \( N-(\text{tert-butyl})-2-(1H-\text{indol}-3-\text{yl})-2-(\text{2-phenyl}-N-(\text{prop-2-yn-1-yl})\text{acetamido})\text{acetamide} \) (53a) using \( \text{Au(PPh}_3\text{)Cl, AgSbF}_6 \), and trifluoroacetic acid (TFA) in chloroform at room temperature. The compound 54a was obtained in 81% of yield as a white solid having melting point 72-74 °C. In the \(^1\text{H NMR peak at } \delta 1.50 \) was observed integrating for nine protons (H-2′′′) that accounts for the tertiary butyl group (Figure 7). Two doublets at \( \delta 5.48 \) and 4.38 were assigned for the H-5a and -NH protons respectively and this suggest that indole is being transferred into indoline moiety (Figure 7). The peaks at \( \delta 5.33 \) and 4.94 confirms the presence of an exocyclic methylene group (H-1′) in the title compound. The \(^{13}\text{C NMR spectrum showed the characteristic peaks at } \delta 171.0 \) and 170.8 for two carbonyl groups, furthermore a peak at \( \delta 28.0 \) in \(^{13}\text{C NMR} \) confirms the presence of the tertiary butyl group. The peak at \( \delta 110.1 \) is due to the presence of exocyclic methylene group. The peaks for remaining protons and carbons were also observed in its \(^1\text{H and } ^{13}\text{C NMR spectrum} \) (Figure 7). The structure of compound was further confirmed from its HRMS which showed the peak at 401.2111 for \([M]^+\) that is in accordance with the calculated value of 401.2103.

On the basis of above spectral studies, the compound 54a was assigned the structure: 5-(tert-butyl)-1-methylene-3-(2-phenylacetyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one.
Figure 7. $^1$H NMR and $^{13}$C NMR spectrum of 5-(tert-butyl)-1-methylene-3-(2-phenylacetyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indol-4(5H)-one (54a) in CDCl$_3$. 

Section A: Diversity Oriented Approach to Spiroindolines......
Scope of the reaction: To evaluate the scope and limitations of our optimized protocol (Table 1, entry 8) different Ugi-adducts were synthesized from indole-3-carbaldehyde in good to excellent yields, and subjected to the domino cyclization (Table 3). Various substituents on the alkyne, isonitrile, indole and amine residue are tolerated (Table 3, 52a-e,j-i). In case of bulky substituents on the alkyne part, like p-methoxyphenyl and iso-propyl, the yields decreased to 50% and 57% respectively (Table 3, 52f,g). Methyl substitution at the 2-position of the indole core totally inhibited the cyclization and starting material was recovered quantitatively (Table 3, 52k).

The application of D-(+)-1-phenylethylamine in the Ugi-reaction resulted in an inseparable mixture of diastereoisomers in a 1:1 ratio. When subjected to the domino cyclization, two diastereoisomeric spiroindolines 52la (35%) and 52lb (25%) were formed in a combined yield of 79%. A tosyl group on the indole nitrogen strongly diminished the nucleophilicity of this core and hence no cyclized product could be observed (Table 3, 52m).

Table 3. Scope and limitations of domino cyclization to spiroindolines.a

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<tr>
<th>Entry</th>
<th>Ugi-adduct51</th>
<th>Yieldb(%)</th>
<th>Spiroindolines52</th>
<th>Yieldb(%)</th>
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84
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<th>Spiroindolines&lt;sub&gt;52&lt;/sub&gt;</th>
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Having the optimized conditions in hand (Table 2, entry 2), various Ugi-adducts 53a-q were synthesized and subjected to this hydroarylation domino cyclization sequence (Table 4). Different substituents are well tolerated and the spiroindolines were obtained in good to excellent yields. A methyl substituent on the indole nitrogen did not hamper the domino cyclization (Table 4, 54e,g,l,m,o,p). Substituents like tert-butyl, cyclohexyl and n-butyl on the isonitrile are well tolerated for the domino cyclization on the second position of the indole (Table 4, 54a-q). Regarding the substituents imanating from the acid part, tert-butyl gave a decreased yield probably due to steric hindrance (Table 4, 54f). It is noteworthy that the gold-catalyzed intramolecular hydroarylation exclusively gives the exo-dig product in all cases and this together with complete diastereoselectivity.
Table 4. Scope and limitations of intramolecular domino cyclization.\textsuperscript{a}

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<tr>
<th>Entry</th>
<th>Ugi-adduct\textsuperscript{53}</th>
<th>Yield\textsuperscript{a}(%)</th>
<th>Spiroindolines\textsuperscript{54}</th>
<th>Yield\textsuperscript{a}(%)</th>
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Mechanistic studies: The diastereoselectivity can be easily explained by the mechanism\textsuperscript{37} (Scheme 14). After the activation of the triple bond of the Ugi-adduct (R)-51a (R-enantiomer) by cationic gold, nucleophilic attack of the 3-position of the indole can occur from two sides.

**Scheme 14.** Plausible mechanism for the diastereoselective domino cyclization to spiroindolines.
If the attack occurs from the back side of the indole core, intermediate 56 is formed. However, trapping of the intermediate iminium ion in 56 by the secondary amide, is sterically impossible. As a result the newly formed spiro-ring reopens to the intermediate 55. On the contrary, when the attack occurs from the front side of the indole core, resulting in the spiro intermediate 57, trapping of the iminium ion is perfectly possible. Spiroindoline 52a is formed, with the two newly formed chiral centres being S, S.

It was observed that the chiral centre already present in the Ugi-adduct, directs the domino cyclization diastereoselectively. According to our knowledge this was the first report of the synthesis of spiroindolines via a domino cyclization involving a “branched-handed” pre-cyclization architecture (Figure 8).

![Previous approaches](image1.png) ![Our "branched-handed" approach](image2.png)

**Figure 8.** “Branched-handed” pre-cyclization architecture.

**CONCLUSIONS**

In conclusion, we have developed a diversity-oriented approach towards the synthesis of complex spiroindolines from readily available starting materials. The Ugi-4CR, being the first step, generates diversity, while an efficient gold(I)-catalyzed diastereoselective domino cyclization employing mild reaction conditions, results in the formation of these spiroindolines. The unprecedented application of a branched-handed pre-cyclization architecture, the unexpected selective exo-attack of the indole on the propargylic amide, and the unique diastereoselectivity (control of three chiral centres) are the merits of this protocol.
EXPERIMENTAL SECTION

Table 5. Starting materials.

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**General procedure for synthesis of Ugi products 51a-m.**

To a solution of 3-formylindole 47a-e (200mg, 1 equiv) in methanol (3 mL) were added successively Na₂SO₄ (0.3g), amine 48a-g (1.2 equiv), alkynoic acid 49a-d (1.2 equiv) and isonitrile 50a-d (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 closed vial. After completion of the reaction, the mixture was diluted with EtOAc (100 mL) and was extracted with water (50 mL). Organic layer was washed with brine (50 mL), dried over magnesium sulfate and evaporated under reduced pressure to obtain
residue which was subjected to silica gel column chromatography (80% EtOAc in heptane) affording the desired product **51a-m** as solid.

Ugi products appear as mixture of two rotamers (~ 1:3), so $^1$H and $^{13}$C NMR spectra are not very characteristic.

$\textit{N-}(2-(\textit{tert-Butylamino})-1-(1H-indol-3-yl)-2-oxoethyl)$-$\textit{N-}(4-methoxybenzyl)$but-2-ynamide (51a)

![Diagram of 51a](image)

White solid; Yield 71%; Melting point: 73-75 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.42 (bs, 0.25H, -NH), 8.26 (bs, 0.75H, -NH), 7.53 (d, $J$= 2.34Hz, 0.70H, H-4""), 7.47 (d, $J$= 7.94Hz, 0.26H, H-4""), 7.41-7.03 (m, 4H, H-2""", H-5""", H-6"" & H-7""), 6.93 (d, $J$= 9.21Hz, 0.44H, H-2' & H-6'), 6.87 (d, $J$= 8.88Hz, 1.33H, H-2' & H-6'), 6.60 (d, $J$= 9.20Hz, 0.43H, H-3' & H-5'), 6.54 (d, $J$= 8.88Hz, 1.40H, H-3' & H-5'), 6.35 (s, 0.20H, H-1""), 6.19 (s, 0.71H, H-1""), 5.98 (bs, 0.73H, -CONH), 5.55 (bs, 0.24H, -CONH), 4.71-4.66 (m, 1.86H, H$_a$& H$_b$), 3.69-3.67 (m, 3H, -OMe), 2.07 (s, 0.72H, H-4), 1.93 (s, 2.15H, H-4), 1.26-1.19 (m, 9H, H-2"""").

$^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 168.4, 158.6, 158.3, 156.0(2), 136.1, 135.6, 129.9, 129.6, 128.3, 127.0, 126.1, 122.4, 120.4, 120.0, 118.6, 113.6, 113.3, 111.5, 111.1, 108.8, 91.6, 90.2, 73.9, 73.5, 60.7, 55.2 (2), 54.3, 51.3(2), 50.2, 45.3, 35.4, 31.8, 29.0, 28.5, 28.3, 26.4, 26.3, 22.6, 14.1, 4.2, 4.1.

**HRMS:** Calculated for C$_{26}$H$_{29}$N$_3$O$_3$ 445. 431.2209, found 431.2200.
N-(2-(tert-Butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-N-pentylbut-2-ynamide (51b)

White solid; Yield 50%; Melting point: 96-98 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.39-8.33 (m, 1H, -NH), 7.75 (d, $J$=2.29Hz,0.85H, H-4''), 7.56 (d, $J$= 7.72Hz, 0.16H, H-4''), 7.49-7.38 (m, 2H, H-2'' & H-7''), 7.24-7.10 (m, 2H, H-5'' & H-6''), 6.29-6.27 (m, 1H, H-1''), 6.19 (bs, 0.82H, -CONH), 5.72 (bs, 0.18H, -CONH), 3.57-3.47 (m, 1H, H$_2$), 3.37-3.27 (m, 1H, H$_3$), 2.08 (s, 0.45H, H-4), 2.00 (s, 2.55H, H-4), 1.55-1.34 (m, 10H, H-2' & H-2''), 1.12-0.98 (m, 5H, H-2', H-3' & H-4'), 0.71 (t, $J$= 7.04Hz, 2.48H, H-5''), 0.63 (t, $J$= 7.04Hz, 0.52H, H-5'').

$^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 168.9, 155.7, 135.7, 127.0, 126.0, 125.2, 122.7, 122.5, 120.1, 118.6, 118.5, 111.6, 111.3, 109.3, 108.8, 90.0, 89.4, 73.7, 53.8, 51.7, 51.3, 47.0, 29.1, 28.9, 28.6, 28.5, 27.3, 21.9, 21.8, 13.8, 13.7, 4.2, 4.0.

HRMS: Calculated for C$_{25}$H$_{31}$N$_3$O$_2$ 381.2416 found 381.2424.

N-(2-(tert-Butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-N-cyclohexylbut-2-ynamide (51c)

Light yellow solid; Yield 45%; Melting point: 198-200 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.31 (bs, 1H, -NH), 7.64-7.51 (m, 2H, H-2'' & H-4''), 7.40 (d, $J$= 8.03Hz,1H, H-7''), 7.23-7.14 (m, 2H, H-5'' & H-6'''), 6.18 (s, 0.18H, H-1''),
Section A: Diversity Oriented Approach to Spiroindolines.....

6.00 (s, 0.82H, H-1’’’), 5.82 (bs, 0.18H, -CONH), 5.36 (bs, 0.82H, -CONH), 4.20-4.08 (m, 0.84H, CyH), 3.51-3.46 (m, 0.17H, CyH), 2.05-2.02 (m, 3H, H-4), 1.89-1.82 (m, 2H, CyH), 1.64-1.59 (m, 2H, CyH), 1.37-1.18 (m, 15H, CyH & H-2’’’’’).

$^{13}$C NMR (75.5 MHz, CDCl$_3$):δ 168.6, 154.8, 135.7, 126.3, 125.2, 122.4, 122.2, 120.1, 120.0, 118.7, 118.2, 111.6, 110.9, 89.6, 74.1, 59.2, 55.0, 51.5, 51.2, 35.4, 32.7, 31.9, 31.8, 31.7, 31.6, 28.6, 28.5, 26.4, 26.3, 25.9(2), 25.2, 22.9, 22.6, 14.1, 4.1.

HRMS: Calculated for C$_{24}$H$_{31}$N$_3$O$_2$ 393.2416 found 393.2416.

$^N$-(2-(tert-Butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-$^N$-(4-methoxybenzyl)pent-2-ynamide(51d)

White solid; Yield 85%; Melting point: 63-65 °C.

$^1$H NMR (300 MHz, CDCl$_3$):δ 8.30 (bs, 0.23H, -NH), 8.18 (bs, 0.77H, -NH), 7.55 (d, $J$= 2.42Hz,0.71H, H-4’’’), 7.48 (d, $J$= 7.53Hz,0.29H, H-4’’’), 7.42-7.27 (m, 2H, H-2’’’’ & H-7’’’), 7.22-7.04 (m, 2H, H-5’’’ & H-6’’’), 6.95-6.86 (m, 2H, H-2’ & H-6’), 6.62-6.53 (m, 2H, H-3’ & H-5’), 6.36 (s, 0.26H, H-1’’’), 6.22 (s, 0.74H, H-1’’’), 5.97 (bs, 0.74H, -CONH), 5.53 (bs, 0.24H, -CONH), 4.72-4.62 (m, 1.72H, H$_a$/H$_b$), 4.13 (d, $J$= 15.06Hz,0.29H, H$_b$), 3.69-3.67 (m, 3H, -OMe), 2.43 (q, $J$= 763Hz,0.50H, H-4), 2.29 (q, $J$= 7.51Hz,1.50H, H-4), 1.26-1.19 (m, 9.50H, H-5 & H-2’’’’’), 1.09(t, $J$= 7.29Hz,2.50H, H-5).

$^{13}$C NMR (75.5 MHz, CDCl$_3$):δ 168.5, 158.6, 158.3, 156.1, 156.0, 136.1, 135.6, 130.3, 129.9, 129.7, 128.3, 127.0(2), 126.1, 125.4, 122.7, 122.3, 120.3, 120.0, 118.6(2), 113.6, 113.2, 111.5, 111.2, 109.1, 108.9, 96.7, 95.4, 74.0, 73.5, 60.7(2), 55.2(2), 54.3, 51.4, 51.3, 50.2, 45.3, 35.4, 31.8, 28.5, 28.3, 12.8, 12.7, 12.6.

HRMS: Calculated for C$_{27}$H$_{31}$N$_3$O$_3$ 445.2365 found 445.2361
**N-(2-(Cyclohexylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-N-(4-methoxybenzyl)but-2-ynamide (51e)**

White solid; Yield 69%; Melting point: 81-83 °C.

**H NMR (300 MHz, CDCl₃):** δ 8.33 (bs, 0.25H, -NH), 8.21 (bs, 0.75H, -NH), 7.56 (d, J= 2.26Hz, 0.73H, H-4""""), 7.47 (d, J= 8.17Hz, 0.25H, H-4""""), 7.41-7.36 (m, 0.89H, H-7""""), 7.31-7.26 (m, 1.16H, H-2"""" & H-7""""), 7.23-7.05 (m, 2H, H-5"""" & H-6""""), 6.96-6.90 (m, 2H, H-2' & H-6'), 6.64-6.57 (m, 2H, H-3' & H-5'), 6.46 (s, 0.25H, H-1""""), 6.20 (s, 0.68H, H-1'""""), 6.01 (d, J= 8.48Hz, 0.67H, -CONH), 5.56 (d, J= 8.08Hz, 0.24H, -CONH), 4.75-4.70 (m, 1.39H, H₃& H₆), 4.15-4.07 (m, 0.63H, H₆), 3.82-3.69 (m, 4H, CyH & -OMe), 2.07 (s, 1.26H, H-4), 2.04 (s, 1.74H, H-4), 1.87-1.62 (m, 5H, CyH), 1.32-1.23 (m, 2.60H, CyH), 1.15-0.98 (2.55H, CyH).

**C NMR (75.5 MHz, CDCl₃):** δ 168.5, 168.2, 158.7, 158.5, 156.0, 136.2, 135.7, 130.3, 129.8, 129.4, 128.5, 127.0, 126.2, 125.4, 122.7, 122.3, 120.4, 120.0, 118.5, 113.7, 113.3, 111.6, 111.2, 108.8, 108.6, 90.3, 73.8, 60.4, 55.2, 54.2, 50.4, 48.4, 32.6, 32.5, 25.4(2), 24.7, 24.6, 21.0, 14.1, 4.2, 4.1.

**HRMS:** Calculated for C₂₈H₃₃N₅O₃ 457.2365 found 457.2363.

**N-Butyl-N-(2-(tert-butyramino)-1-(1H-indol-3-yl)-2-oxoethyl)-3-(4-methoxyphenyl)propiolamide (51f)**

White solid; Yield 53%; Melting point: 166-168 °C.
Section A: Diversity Oriented Approach to Spiroindolines.....

$^1$H NMR (300 MHz, CDCl$_3$):$\delta$ 8.34-8.29 (m, 1H, -NH), 7.84 (d, $J$= 2.96Hz, 0.20H, H-4""""), 7.78 (d, $J$= 2.16Hz, 0.82H, H-4""""), 7.54-7.39 (m, 4H, H-2', H-6', H-2"" & H-7""), 7.23-7.11 (m, 2H, H-5"" & H-6""), 6.90-6.85 (m, 2H, H-3' & H-5'), 6.37-6.34 (m, 1H, H-Benzyl-ynamide (51g)

51.4, 46.9, 31.6, 28.6(2), 20.1, 13.5.

122.6, 120.5, 120.2, 118.6, 114.3, 114.2, 112., 111.3, 108.9, 91.0, 81.3, 55.3, 53.9(2), 51.4, 46.9, 31.6, 28.6(2), 20.1, 13.5.

HRMS: Calculated for C$_{28}$H$_{33}$N$_3$O$_3$ 459.2522 found 459.2527.

$N$-Benzy|$N$-(2-(tert-butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-4-methylpent-2-ynamide (51g)

Light yellow solid; Yield 48%; Melting point: 138-140 °C.

$^1$H NMR (300 MHz, CDCl$_3$):$\delta$ 8.32 (bs, 0.22H, -NH), 8.19 (bs, 0.80H, -NH), 7.52-7.45 (m, 1.70H, H-2"" & H-7""), 7.35 (d, $J$= 8.04Hz, 0.30H, H-4""), 7.32-7.26 (m, 1H, H-7""), 7.21-6.93 (m, 7H, H-2', H-3', H-4', H-5', H-6', H-5"" & H-6""), 6.39 (s, 0.22H, H-1""), 6.30 (s, 0.79H, H-1""), 5.95 (bs, 0.80H, -CONH), 5.53 (bs, 0.22H, -CONH), 4.85-4.71 (m, 1.76H, H$_a$& H$_b$), 4.26 (d, $J$= 15.08Hz, 0.24H, H$_b$), 2.84-2.75 (m, 0.25, H-4), 2.62-2.53 (m, 0.75H, H-4), 1.28 (s, 7H, H-2""""), 1.19 (s, 2H, H-2""""), 1.07-1.04 (m, 5H, H-5), 0.87-0.84 (m, 1H, H-5).

$^{13}$C NMR (75.5 MHz, CDCl$_3$):$\delta$ 168.4, 156.4, 137.7, 135.6, 128.4, 128.1, 127.7, 127.0, 126.8, 126.5, 126.1, 122.4, 120.1, 118.7, 111.5, 111.1, 108.9, 98.9, 73.8, 54.1, 51.4, 50.6, 45.9, 28.5, 28.3, 22.0(2), 21.6, 20.6.

HRMS: Calculated for C$_{27}$H$_{31}$N$_3$O$_2$ 429.2416 found 429.2406.
Section A: Diversity Oriented Approach to Spiroindolines.....

\[ N-(2-(tert-Butylamino)-1-(1-methyl-1H-indol-3-yl)-2-oxoethyl)-N-(4-methoxybenzyl)but-2-ynamide \ (51h) \]

Offwhite solid; Yield 87%; Melting point: 60-62 °C.

\[ ^1H \text{NMR (300 MHz, CDCl}_3)\delta 7.46 \text{(d, } J=8.27\text{Hz, 0.20H, H-4'''), 7.39-7.37 (m, 1.80H, H-2'' & H-4'''), 7.28-7.15 (m, 2H, H-6'' & H-7'''), 7.08-7.03 (m, 1H, H-5'''), 6.94-6.84 (m, 2H, H-2' & H-6'), 6.61-6.53 (m, 2H, H-3' & H-5'), 6.34 (s, 0.22H, H-1'), 6.18 (s, 0.78H, H-1''), 6.01 (bs, 0.21H, -CONH), 5.56 (bs, 0.21H, -CONH), 4.76-4.61 (m, 1.75H, H_4& H_b), 4.18 (d, \ J=14.94\text{Hz, 0.24H, H_b}, 3.77-3.75 (m, 1H, -OMe), 3.70-3.68 (m, 5H, -NMe & -OMe), 2.07 (s, 0.64H, H-4), 1.94 (s, 2.37H, H-4), 1.26 (s, 7H, H-2''''), 1.19 (s, 2H, H-2'''''). \]

\[ ^13C \text{NMR (75.5 MHz, CDCl}_3)\delta 168.4, 158.3, 155.9, 136.4, 130.7, 130.3, 129.8, 129.6, 128.3, 127.6, 121.9, 119.6, 118.7, 113.5, 113.1, 109.1, 107.1, 90.1, 73.9, 55.2(2), 54.1, 51.3, 50.1, 32.9, 32.8, 28.5, 28.3, 4.1. \]

\[ \text{HRMS: Calculated for } C_{27}H_{31}N_3O_3 445.2365 \text{ found } 445.2364. \]

\[ N-(4-Methoxybenzyl)-N-(1-(7-methyl-1H-indol-3-yl)-2-oxo-2-(2,4,4-trimethylpentan-2-yl amino)ethyl)but-2-ynamide \ (51i) \]

Red semi-solid; Yield 48%.
**Section A: Diversity Oriented Approach to Spiroindolines**

**1H NMR (300 MHz, CDCl₃):** δ 8.06-8.02 (m, 1H, -NH), 7.60 (d, J= 2.31Hz, 0.78H, H-4"'), 7.37 (d, J= 2.07Hz, 0.22H, H-4''), 7.25-7.22 (m, 1H, H-6'''), 7.04-6.87 (m, 4H, H-2', H-6', H-2'' & H-5'''), 6.60-6.52 (m, 2H, H-3' & H-5'), 6.41 (s, 0.25H, H-1''), 6.15 (s, 0.75H, H-1''), 6.02 (bs, 0.71H, -CONH), 5.58 (bs, 0.30H, -CONH), 4.71-4.57 (m, 1.68H, Hₜ/Hₜ), 4.25 (d, J= 14.60Hz, 0.34H, Hₜ), 3.68-3.67 (m, 3H, -OMe), 2.48 (s, 0.82H, -Me), 2.43 (s, 2.20H, -Me), 2.07 (s, 0.84H, H-4), 1.93 (s, 2.15H, H-4), 1.39 (s, 2H, H-3'''), 1.33-1.21 (m, 6H, H-1'''), 0.92-0.91 (m, 9H, H-5'''').

**13C NMR (75.5 MHz, CDCl₃):** δ 168.0, 162.6, 160.4, 158.3, 155.9, 135.1, 129.8, 129.5, 128.4, 126.7, 125.9, 123.2, 122.9, 120.2(2), 116.3, 113.4, 113.1, 109.3, 90.1, 73.9, 56.0, 55.4, 55.3, 55.1, 54.5, 54.0, 52.0, 51.9, 50.2, 31.7, 31.6, 31.5, 31.4, 31.3, 30.9, 29.2, 28.8, 28.5, 16.4, 4.1.

HRMS: Calculated for C₃₁H₃₉N₃O₅ 501.2991 found 501.3013.

N-(2-(Cyclohexylamino)-1-(7-methyl-1H-indol-3-yl)-2-oxoethyl)-N-cyclopropylbut-2-yname (51j)

![Chemical Structure](image)

Light yellow solid; Yield 61%; Melting point: 90-92 °C.

**1H NMR (300 MHz, CDCl₃):** δ 8.06-8.02 (m, 1H, -NH), 7.66 (d, J= 2.17Hz, 1H, H-2'''), 7.35 (d, J= 7.52Hz, 1H, H-4''), 7.10-7.02 (m, 2H, H-5'' & H-6'''), 6.16 (d, J= 7.86Hz, 1H, -CONH), 6.05 (s, 1H, H-1''), 3.82-3.72 (m, 1H, CyH), 2.51 (s, 3H, -Me), 2.44-2.37 (m, 1H, H-1'), 2.01 (s, 3H, H-4), 1.91-1.80 (m, 2H, CyH), 1.66-1.55 (m, 3H, CyH), 1.37-1.28 (m, 2H, CyH), 1.16-1.04 (m, 4H, H-2', CyH), 0.85-0.74 (m, 2H, H-2'), 0.58-0.51 (m, 1H, H-2').

**13C NMR (75.5 MHz, CDCl₃):** δ 168.9, 157.9, 135.1, 126.6, 125.8, 122.9, 120.6, 120.4, 116.0, 109.7, 90.9, 74.5, 56.9, 48.4, 32.7, 32.6, 30.9, 30.0, 25.5, 24.7, 16.5, 10.3, 7.8, 4.1.

HRMS: Calculated for C₂₄H₂₉N₃O₂ 391.2260 found 391.2261.
N-(2-(Butylamino)-1-(2-methyl-1H-indol-3-yl)-2-oxoethyl)-N-cyclopropylbut-2-ynamide (51k)

Brown solid; Yield 71%; Melting point: 178-180 °C.

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.24 (bs, 1H, -NH), 7.52 (d, J= 7.98Hz, 1H, H-4′′′), 7.31 (d, J= 7.97Hz, 1H, H-7′′′), 7.17-7.05 (m, 2H, H-5′′′ & H-6′′′), 6.37 (s, 1H, H-1′), 5.69 (bs, 1H, -CONH), 3.30-3.23 (m, 2H, H-1′′′′), 2.40-2.33 (m, 4H, H-1′ & -Me), 2.00 (s, 3H, H-4), 1.45-1.37 (m, 2H, H-2′′′′), 1.28-1.18 (m, 3H, H-2′ & H-3′′′′), 0.85 (m, 3H, H-4′′′′), 0.75-0.67 (m, 1H, H-2′), 0.62-0.55 (m, 1H, H-2′), 0.51-0.44 (m, 1H, H-2′).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 169.7, 157.8, 135.8, 135.1, 127.9, 121.4, 119.9, 119.1, 110.5, 105.0, 90.7(2), 74.8, 55.6, 39.7, 31.4, 30.9, 28.8, 20.0, 13.6, 12.3, 9.8, 8.4, 4.1.

HRMS: Calculated for C$_{22}$H$_{27}$N$_3$O$_2$ 365.2103 found 365.2110.

N-(2-(Cyclohexylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-N-((R)-1-phenylethyl)but-2-ynamide (51l).

dr 1:1 (used further as a mixture of two distereoisomers)

Purple solid; Yield 47%; Melting point: 80-82 °C.
\(^1\text{H NMR (300 MHz, CDCl} _3\)): \(\delta\) 8.36 (bs, 0.72H, -NH), 8.15 (bs, 0.28H, -NH), 7.66 (d, \(J=\) 2.00Hz, 0.72H, H-4’’’’), 7.56 (d, \(J=\) 7.68Hz, 1H, H-2’’’’), 7.45-7.29 (m, 4.24H, H-2’’’’ & H-6’’’’), 7.23-7.05 (m, 3H, H-3’’, H-5’’ & H-5’’’’), 6.98-6.96 (m, 1H, H-4’’’’), 6.87-6.81 (m, 1H, H-1’’’’), 6.15 (d, \(J=\) 8.58Hz, 0.30H, -CONH), 5.84-5.74 (m, 1H, 1.75H, CyH & -CONH), 3.76-3.62 (m, 1H, H-2’’’’), 1.94-1.87 (m, 6H, H-4 & H-1’), 1.71-1.59 (m, 2H, CyH), 1.54-1.46 (m, 2H, CyH), 1.26-1.20 (m, 2H, CyH), 1.07-0.89 (m, 4H, CyH).

\(^13\text{C NMR (75.5 MHz, CDCl} _3\)): \(\delta\) 168.8, 167.7, 155.1, 155.0, 139.4, 139.2, 135.5, 135.0, 128.3, 128.0, 127.8, 127.7, 127.6, 127.3, 126.6(2), 126.1, 125.6, 122.3, 121.8, 120.0, 119.6, 118.1, 118.0, 111.6, 110.9, 110.3, 90.2, 90.0, 74.0, 56.9, 54.6, 53.5, 48.6, 48.3, 35.4, 32.7(2), 32.5, 31.8, 30.9, 26.4, 25.4, 24.7, 24.6, 22.6, 18.3, 17.5, 14.1, 4.1, 4.0.

HRMS: Calculated for C\(_{28}\)H\(_{31}\)N\(_3\)O\(_2\) found 441.2416.

\(N\)-(2-(tert-Butylamino)-2-oxo-1-(1-tosyl-1H-indol-3-yl)ethyl)-\(N\)-(4-methoxybenzyl)but-2-ynamide (51m)

White solid; Yield 61%; Melting point: 73-75 °C.

\(^1\text{H NMR (300 MHz, CDCl} _3\)): \(\delta\) 8.00-7.93 (m, 1H, H-4’’’’), 7.86-7.76 (m, 3H, H-7’’’’, H-2’’’’ & H-6’’’’), 7.32-7.07 (m, 5H, H-2’’’’, H-5’’’’, H-6’’’’ & H-3’’’’& H-5’’’’), 6.85 (d, \(J=\) 8.73Hz, 0.44H, H-2’ & H-6’), 6.77 (d, \(J=\) 8.58Hz, 1.56H, H-2’ & H-6’), 6.49 (d, \(J=\) 8.58Hz, 0.48H, H-3’ & H-5’), 6.40 (d, \(J=\) 8.73Hz, 1.54H, H-3’ & H-5’), 6.20 (s, 0.24H, H-1’), 6.14 (s, 0.76H, H-1’’), 5.91 (bs, 0.80H, -CONH), 5.49 (bs, 0.22H, -
diethyl ether in dichloromethane) to afford compound 51a. The residue obtained was purified by silica gel column chromatography (20% EtOAc) to obtained compound 51a.

HRMS: Calculated for C_{33}H_{35}N_{3}O_{2}S: 585.2297 found 585.2303.

General procedure for Au(PPh_{3})SbF_{6} catalyzed domino cyclization.

To a glass vial Au(PPh_{3})Cl (5 mole%) and AgSbF_{6} (5 mole%) were loaded along with chloroform (2 mL). Ugi product 51a-m (0.2 mmol) was added and reaction mixture was stirred at rt in a screw capped vial until completion of reaction. After completion, reaction mixture was partitioned between EtOAc (100 mL) and water (50 mL). Organic layer was washed with brine (50 mL), dried over magnesium sulfate and evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (20% diethyl ether in dichloromethane) to afford compound 52a-j.

(\textit{E})-5-(\textit{tert}-Butyl)-1-ethylidene-3-(4-methoxybenzyl)-3,3a,5a,6-tetrahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indole-2,4(H,5H)-dione (52a)

White Solid; Yield 75%; Melting point: 197-199 °C.

\textbf{1H NMR (400 MHz, CDCl_{3})}: δ 7.33 (d, J= 8.56Hz, 2H, H-2” & H-6”), 7.11-7.03 (m, 1H, H-8), 6.86-6.80 (m, 3H, H-1’, H-3” & H-5”), 6.73-6.71 (m, 2H, H-9 & H-10), 6.61 (d, J= 7.80Hz, 1H, H-7), 5.59 (d, J=4.20 Hz, 1H, H-5a), 5.23 (d, J=14.32 Hz, 1H, H_{a}), 4.48-4.44 (m, 2H, H_{b} & -NH), 3.80 (s, 1H, H-3a), 3.77 (s, 3H, -OMe), 1.48-1.46 (m, 12H, H-2’ & H-2”’).

\textbf{13C NMR (100.5 MHz, CDCl_{3})}: δ 170.6, 166.4, 159.1, 148.3, 137.1, 134.2, 130.2, 130.1, 129.2, 128.2, 123.4, 120.7, 114.0, 110.0, 82.5, 65.7, 55.2, 55.0, 51.8, 44.4, 28.1, 13.7.
HRMS: Calculated for C_{29}H_{39}N_{3}O_{3} 431.2209, found 431.2194.

(E)-5-(tert-Butyl)-1-ethylidene-3-pentyl-3,3a,5a,6-tetrahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52b)

White Solid; Yield 80%; Melting point: 138-140 °C.

{\textit{H} NMR (300 MHz, CDCl}_3): \delta 7.14 (t, J = 8.19Hz, 1H, H-8), 6.93 (d, J =7.35Hz, 1H, H-10), 6.83-6.75 (m, 2H, H-9 & H-1'), 6.67 (d, J = 7.89Hz, 1H, H-7), 5.59 (d, J = 4.14Hz, 1H, H-5a), 4.50 (d, J = 3.96Hz, 1H, -NH), 4.00 (s, 1H, H-3a), 3.90-3.78 (m, 1H, H_a), 3.54-3.50 (m, 1H, H_b), 1.78-1.62 (m, 2H, H-2'), 1.47-1.45 (m, 12H, H-2' & H-2'''), 1.38-1.23 (m, 4H, H-3'' & H-4''), 0.88 (t, J = 7.03Hz, 3H, H-5 '').

C NMR (75.5 MHz, CDCl}_3): \delta 170.5, 166.5, 148.4, 137.0, 133.4, 130.3, 129.3, 123.4, 120.7, 110.2, 82.6, 67.1, 55.0, 52.0, 41.7, 28.9, 28.0, 26.4, 22.3, 14.0, 13.6.

HRMS: Calculated for C_{33}H_{31}N_{3}O_{2} 381.2416, found 381.2415.

(E)-5-(tert-Butyl)-3-cyclohexyl-1-ethylidene-3,3a,5a,6-tetrahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52c)

White Solid; Yield 79%; Melting point: 193-195 °C.

{\textit{H} NMR (300 MHz, CDCl}_3): \delta 7.13 (t, J = 7.47Hz, 1H, H-8), 6.93 (d, J =7.35Hz, 1H, H-10), 6.82-6.70 (m, 2H, H-9 & H-1'), 6.66 (d, J = 7.92Hz, 1H, H-7), 5.58 (d, J = 3.6Hz,
1H, H-5a), 4.47 (d, J = 3.39Hz, 1H, -NH), 4.07 (s, 1H, H-3a), 4.00-3.89 (m, 1H, CyH), 1.94-1.65 (m, 6H, CyH), 1.47-1.43 (m, 12H, H-2′ & H-2′′), 1.38-1.22 (m, 4H, CyH).

\[^{13}\text{C NMR} (75.5 \text{ MHz, CDCl}_3): \delta \] 170.8, 166.6, 148.4, 137.4, 132.9, 130.4, 129.2, 123.5, 120.7, 110.1, 82.1, 67.4, 54.9, 54.8, 52.2, 30.3, 29.1, 27.9, 25.9, 25.8, 25.2, 13.5.

HRMS: Calculated for C\textsubscript{24}H\textsubscript{31}N\textsubscript{3}O\textsubscript{2} 393.2416, found 393.2414.

\((E)-5-5-(\text{tert}-\text{Butyl})-3-(4\text{-methoxybenzyl})-1\text{-propylidene}-3,3a,5a,6\text{-tetrahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]}\text{indole-2,4(1H,5H)-dione(52d)}

![Structure of compound 52d](image)

White Solid; Yield 77%; Melting point: 189-191 °C.

\[^{1}\text{H NMR} (300 \text{ MHz, CDCl}_3): \delta \] 7.33 (d, J= 8.46Hz, 2H, H-2′′ & H-6′′), 7.10-7.03 (m, 1H, H-8), 6.83 (d, J= 8.64Hz, 2H, H-3′ & H-5′′), 6.75-6.69 (m, 3H, H-9, H-10 & H-1′), 6.61 (d, J= 7.89Hz, 1H, H-7), 5.55 (d, J= 4.14Hz, 1H, H-5a), 5.24 (d, J= 14.31Hz, 1H, H\textsubscript{a}), 4.49-4.44 (m, 2H, H\textsubscript{b} & -NH), 3.79 (s, 1H, H-3a), 3.77 (s, 3H, -OMe), 1.92-1.67 (m, 2H, H-2′), 1.47(s, 9H, H-2′′), 0.80 (t, 3H, H-3′).

\[^{13}\text{C NMR} (75.5 \text{ MHz, CDCl}_3): \delta \] 170.6, 166.5, 159.0, 148.2, 140.8, 135.6, 130.6, 130.1, 129.2, 128.1, 123.4, 120.6,114.0, 110.1, 83.0, 65.7, 55.2, 55.0, 51.8, 44.4, 28.1, 21.6, 12.7.

HRMS: Calculated for C\textsubscript{27}H\textsubscript{31}N\textsubscript{3}O\textsubscript{3} 445.2365, found 445.2365.

\((E)-5-5-(\text{Cyclohexyl})-1\text{-ethylidene}-3-(4\text{-methoxybenzyl})-3,3a,5a,6\text{-tetrahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]}\text{indole-2,4(1H,5H)-dione (52e)}

![Structure of compound 52e](image)

Offwhite solid; Yield 70%; Melting point: 80-82 °C.
1H NMR (300 MHz, CDCl3): δ 7.34 (d, J = 8.67 Hz, 2H, H-2′′ & H-6″), 7.11-7.05 (m, 1H, H-8), 6.86-6.80 (m, 3H, H-1′, H-3′ & H-5″), 6.73-6.72 (m, 2H, H-9 & H-10), 6.61 (d, J = 7.92 Hz, 1H, H-7), 5.44 (d, J = 2.21 Hz, 1H, H-5a), 5.25 (d, J = 14.13 Hz, 1H, Hb), 4.54 (bs, 1H, -NH), 4.45 (d, J = 14.10 Hz, 1H, Hb), 3.88 (s, 1H, H-3a), 3.81-3.74 (m, 4H, CyH & -OMe), 1.90-1.68 (m, 4H, CyH), 1.63-1.49 (m, 2H, CyH), 1.45 (d, J = 7.35 Hz, 3H, H-2′), 1.41-1.12 (m, 4H, CyH).

13C NMR (75.5 MHz, CDCl3): δ 169.4, 166.3, 159.1, 148.3, 136.8, 134.4, 130.2, 130.0, 129.3, 128.0, 123.5, 120.6, 114.0, 110.0, 81.1, 64.9, 55.2, 52.8 (2), 44.4, 31.9, 30.1, 25.8, 25.6, 25.4, 13.5.

HRMS: Calculated for C28H31N3O3 457.2365, found 457.2372.

(E)-5-(tert-butyl)-3-butyl-1-(4-methoxybenzylidene)-3,3a,5a,6-tetrahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52f)

White Solid; Yield 50%; Melting point: 245-247 °C.

1H NMR (300 MHz, CDCl3): δ 7.22 (t, J =7.53 Hz, 1H, H-8), 7.13 (d, J =7.35 Hz, 1H, H-10), 6.95 (d, J = 8.85 Hz, 2H, H-2′′ & H-6″), 6.85 (t, J =7.68 Hz, 1H, H-9), 6.79-6.73 (m, 3H, H-7, H-3′ & H-5″), 6.33 (s, 1H, H-1′), 5.45 (d, J = 4. 35 Hz, 1H, H-5a), 4.45 (d, J = 3.93 Hz, 1H, -NH), 4.25-4.15 (m, 2H, H-3a & Hb), 3.77 (s, 3H, -OMe), 3.10-3.01 (m, 1H, Hb), 1.42-1.19 (m, 13H, H-2″′, H-3″′ & H-2″′′), 0.82 (t, J = 7.17 Hz, 3H, H-4″′″).

13C NMR (75.5 MHz, CDCl3): δ 171.7, 161.9, 160.1, 148.3, 146.3, 129.8, 129.2, 129.1, 128.9, 125.2, 123.4, 120.5, 114.2, 110.6, 79.7, 65.7, 55.2, 54.7, 54.4, 45.9, 29.3, 28.1, 19.9, 13.7.

HRMS: Calculated for C28H33N3O3 459.2522, found 459.2520.
(E)-3-Benzyl-5-(tert-butyl)-1-(2-methylpropylidene)-3,3a,5a,6-tetrahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52g)

White Solid; Yield 73%; Melting point: 183-185 °C.

\(^1^\text{H NMR (300 MHz, CDCl}_3\): \(\delta\) 7.39-7.37 (m, 2H, H-2'' & H-6''), 7.33-7.28 (m, 2H, H-9 & H-10), 7.26-7.21 (m, 1H, H-8), 7.07 (t, \(J = 7.45\text{Hz}\), 1H, H-4''), 6.77-6.68 (m, 2H, H-3'' & H-5''), 6.61 (d, \(J = 7.71\text{Hz}\), 1H, H-7), 6.56 (d, \(J = 11.28\text{Hz}\), 1H, H-1'), 5.55 (d, \(J = 4.14\text{Hz}\), 1H, H-5a), 5.30 (d, \(J = 14.49\text{Hz}\), 1H, Hb), 4.55 (d, \(J = 14.49\text{Hz}\), 1H, Hb), 4.47 (d, \(J = 3.96\text{Hz}\), 1H, -NH), 3.80 (s, 1H, H-3a), 2.16-2.03 (m, 1H, H-2'), 1.47 (s, 9H, H-2''), 0.97 (d, \(J = 6.57\text{Hz}\), 3H, H-3'), 0.61 (d, \(J = 6.42\text{Hz}\), 3H, H-3').

\(^1^\text{C NMR (75.5 MHz, CDCl}_3\): \(\delta\) 170.6, 166.9, 148.1, 145.9, 136.09, 133.6, 130.9, 129.2, 128.6(2), 127.6, 123.4, 120.6, 110.1, 83.4, 65.8, 55.0, 51.9, 45.0, 28.1, 22.1, 21.1.

HRMS: Calculated for \(C_{27}H_{31}N_{3}O_4\) 429.2416, found 429.2418.

(\(E\))-5-(tert-Butyl)-1-ethylidene-3-(4-methoxybenzyl)-6-methyl-3,3a,5a,6-tetrahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52h)

White Solid; Yield 73%; Melting point: 183-185 °C.

\(^1^\text{H NMR (300 MHz, CDCl}_3\): \(\delta\) 7.31 (d, \(J = 8.49\text{Hz}\), 2H, H-2'' & H-6''), 7.17-7.12 (m, 1H, H-8), 6.88-6.80 (m, 3H, H-1', H-3'' & H-5''), 6.73-6.71 (m, 2H, H-9 & H-10), 6.57 (d, \(J = 7.92\text{Hz}\), 1H, H-7), 5.21-5.16 (m, 2H, H-5a & Hb), 4.41 (d, \(J = 14.31\text{Hz}\), 1H, Hb), 3.76 (s, 3H, -OMe), 3.71 (s, 1H, H-3a), 3.05 (s, 3H, -NMe), 1.49 (s, 9H, H-2''), 1.45 (d, \(J = 7.35\text{Hz}\), 3H, H-2').
13C NMR (75.5 MHz, CDCl3): δ 171.4, 166.5, 159.0, 151.9, 135.6, 133.9, 130.4, 130.1, 129.3, 128.1, 122.7, 120.5, 113.9, 110.1, 90.9, 65.7, 55.2(2), 51.9, 44.4, 38.7, 28.4, 14.0.

HRMS: Calculated for C_{27}H_{31}N_{3}O_{3} 445.2365, found 445.2361.

(E)-1-Ethylidene-3-(4-methoxybenzyl)-7-methyl-5-(2,4,4-trimethylpentan-2-yl)-3,3a,5a,6-tetrahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52i)

White Solid; Yield 67%; Melting point: 88-90 °C.

1H NMR (300 MHz, CDCl3): δ 7.32 (d, J =8.67Hz, 2H, H-2'' & H-6''), 6.91 (d, J =7.35Hz, 1H, H-8), 6.86-6.78 (m, 3H, H-1', H-3'' & H-5''), 6.67 (t, J = 7.53Hz, 1H, H-9), 6.56 (d, J = 7.35Hz, 1H, H-10), 5.67 (d, J = 4.58Hz, 1H, H-5a), 5.24 (d, J = 14.31Hz, 1H, H_6), 4.45 (d, J = 14.31Hz, 1H, H_6), 4.16 (d, J = 4.32Hz, 1H, -NH), 3.76 (m, 4H, H-3a & -OCH_3), 2.13 (s, 3H, -Me), 1.57-1.46 (m, 9H, H-2' & H-1''), 1.31-1.22 (m, 2H, H-3''), 0.93 (s, 9H, H-5'').

13C NMR (75.5 MHz, CDCl3): δ 170.6, 166.4, 159.0, 146.8, 137.0, 134.0, 130.1, 129.9(2), 128.1, 121.0, 120.6, 119.7, 114.0, 83.2, 65.8, 59.2, 55.2, 52.0, 49.6, 44.2, 31.7, 31.4, 29.8, 27.9, 16.7, 13.8.

HRMS: Calculated for C_{31}H_{39}N_{3}O_{3} 501.2991, found 501.3010.

(E)-5-Cyclohexyl-3-cyclopropyl-1-ethylidene-7-methyl-3,3a,5a,6-tetrahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52j)

White Solid; Yield 65%; Melting point: 287-289 °C.
$^1$H NMR (300 MHz, CDCl$_3$): δ 6.97 (t, $J = 4.20$Hz, 1H, H-9), 6.79-6.72 (m, 3H, H-8, H-10 & H-1′′′′), 5.47(d, $J = 4.14$Hz, 1H, H-5a), 4.28(d, $J = 4.17$Hz, 1H, -NH), 3.95 (s, 1H, H-3a), 3.88-3.78 (m, 1H, CyH), 2.97-2.90 (m, 1H, H-1′′), 2.17 (s, 3H, -Me), 2.05-1.96 (m, 1H, CyH), 1.88-1.65 (m, 4H, CyH), 1.63-1.50 (m, 2H, CyH), 1.45 (d, $J = 7.35$Hz, 3H, H-2′), 1.38-1.32 (m, 2H, CyH), 1.28-1.11 (m, 3H, H-2′′ & CyH), 1.08-0.80 (m, 1H, H-2′′′′), 0.68-0.59 (m, 1H, H-2′′″).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 169.4, 167.4, 147.1, 136.9, 133.9, 130.1, 129.6, 120.9, 120.6, 119.7, 80.7, 68.1, 53.2, 52.7, 32.0, 30.2, 25.8, 25.6(2), 25.5, 16.7, 13.7, 7.7, 5.7.

HRMS: Calculated for C$_{24}$H$_{29}$N$_3$O$_2$ 391.2260, found 391.2261.

Synthesis of compounds 52la & 52lb:

The Ugi adduct 51l (mixture of two diastereoisomers) was used for the domino cyclization using the same method as described previously. After completion of the reaction two diastereoisomers of cyclized product were observed on TLC, which were separated by column chromatography (20% diethyl ether in DCM). Combined isolated yield was 79%. The exact configuration of the newly formed diastereomeric spiroindolines could not be analyzed, as the compounds did not give good crystals for X-ray analysis. So, one of them is RRSS and another is RSRR, where the first chiral centre is introduced via a chiral amine, second is generated by Ugi reaction and the last two are generated by domino cyclization.

(E)-5-Cyclohexyl-1-ethylidene-3-((R)-1-phenylethyl)-3,3a,5a,6-tetrahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52la)

White Solid; Yield 35% (upper spot on TLC); Melting point: 95-97 °C.

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.44 (d, $J = 7.35$Hz, 2H, H-3′′′ & H-5′′′′), 7.33-7.22 (m, 3H, H-2′′′′, H-4′′ & H-6′′′′), 7.12 (t, $J = 7.24$Hz, 1H, H-8), 6.87(d, $J = 7.17$Hz, 1H, H-10), 6.80-6.70 (m, 2H, H-9 & H-1′), 6.64 (d, $J = 7.92$Hz, 1H, H-7), 5.43-5.36 (m, 2H, H-
5a&H-2′′), 4.53 (d, J = 3.18Hz, 1H, -NH), 4.14 (s, 1H, H-3a), 3.69-3.59 (m, 1H, CyH), 1.93 (d, J = 7.14Hz, 3H, H-2′′), 1.85-1.62 (m, 4H, CyH), 1.53-1.48 (m, 2H, CyH), 1.42 (d, J = 7.53Hz, 3H, H-1′′), 1.37-1.29 (m, 2H, CyH), 1.28-1.11 (m, 2H, CyH).

13C NMR (75.5 MHz, CDCl3): δ 169.2, 167.0, 148.2, 141.6, 136.8, 133.7, 129.9, 129.4, 128.2, 127.1, 126.9, 123.7, 120.7, 110.1, 80.9, 66.8, 54.1, 53.4, 53.0, 31.6, 30.0, 25.7, 25.6, 25.4, 17.6, 13.3.

HRMS: Calculated for C28H31N3O2 441.2416, found 441.2416.

(E)-5-Cyclohexyl-1-ethylidene-3-((R)-1-phenylethyl)-3,3a,5a,6-tetrahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indole-2,4(1H,5H)-dione (52lb)

White Solid; Yield 25% (lower spot on TLC); Melting point: 94-96 °C.

1H NMR (300 MHz, CDCl3): δ 7.50 (d, J = 7.32Hz, 2H, H-3′′ & H-5′′), 7.32 (t, J = 7.55Hz, 2H, H-8 & H-4′′), 7.26-7.21 (m, 1H, H-10), 7.09-7.03 (m, 1H, H-9), 6.84-6.76 (m, 1H, H-1′′), 6.70-6.69 (m, 2H, H-2′′ & H-6′′), 6.58 (d, J = 7.92Hz, 1H, H-7), 5.67 (q, J = 7.17Hz, 1H, H-2′′), 5.44 (d, J = 3.96Hz, 1H, H-5a), 4.48 (d, J = 3.57Hz, 1H, -NH), 3.81-3.71 (m, 2H, H-3a & CyH), 1.96-1.86 (m, 2H, CyH), 1.80 (d, J = 7.14Hz, 3H, H-2′′), 1.74-1.66 (m, 2H, CyH), 1.54-1.48 (m, 2H, CyH), 1.46 (d, J = 7.53Hz, 3H, H-1′′), 1.41-1.28 (m, 2H, CyH), 1.22-1.11 (m, 2H, CyH).

13C NMR (75.5 MHz, CDCl3): δ 169.7, 166.9, 148.2, 139.0, 136.8, 134.1, 134.0, 130.2, 129.2, 128.4, 127.7, 123.3, 120.6, 109.9, 80.3, 65.8, 53.1, 53.0, 52.8, 31.8, 30.1, 25.7, 25.6, 25.4, 17.6, 13.6.

HRMS: Calculated for C28H31N3O2 441.2416, found 441.2403.

General procedure for the synthesis of Ugi products 53a-q.

To a solution of substituted indole-3-carbaldehyde 47 (1.5 mmol) in methanol (5 mL) were added successively Na2SO4 (0.3g), propargylamine 48h (1.1 equiv), acid 49e-
h (1.1 equiv) and isonitrile 50 (1.1 equiv) in a 25 mL round-bottom flask equipped with a magnetic stir bar. The reaction mixture was stirred at 50 °C for 24 h. After completion of the reaction, the mixture was diluted with EtOAc (100 mL) and was extracted with water (50 mL). Organic layer was washed with brine (50 mL), dried over magnesium sulfate and evaporated under reduced pressure to obtain residue which was subjected to silica gel column chromatography (80% EtOAc in heptane) to afford the desired product 53a-q as solid.

**N-(tert-Butyl)-2-(1H-indol-3-yl)-2-(2-phenyl-N-(prop-2-yn-1-yl)acetamido)acetamide (53a)**

White solid; Yield 94%; Melting point: 62-64 °C.

**¹H NMR (300 MHz, CDCl₃):** δ 8.25 (bs, 1H, -NH), 7.62 (d, J= 2.41Hz, 1H, H-5′′′′), 7.44-7.31 (m, 7H, H-2′′′, H-3′′, H-5′′, H-6′′, H-4′′′′, H-5′′′′ & H-7′′′′), 7.20 (t, J= 8.05Hz, 1H, H-4′′), 7.07 (t, J= 7.50Hz, 1H, H-6′′′′), 6.45 (s, 1H, H-2), 5.98 (bs, 1H, -CONH), 4.05 (bs, 2H, H-1′′′′), 3.96 (s, 2H, H-2′′), 1.91 (s, 1H, H-3′′′′), 1.35 (s, 9H, H-2′′′′′′).

**¹³C NMR (75.5 MHz, CDCl₃):** δ 172.1, 168.8, 135.8, 134.5, 129.0, 128.6, 127.0, 126.9, 125.9(2), 122.6, 120.1, 119.0, 111.1, 79.5, 71.7, 53.8, 51.5, 41.1, 34.2, 28.6.

**HRMS:** Calculated for C₂₅H₂₇N₃O₂ 401.2103, found 401.2100.

**N-Cyclohexyl-2-(1H-indol-3-y1)-2-(2-phenyl-N-(prop-2-yn-1-yl)acetamido)acetamide (53b)**

Orange solid; Yield 87%; Melting point: 69-71 °C.


Section A: Diversity Oriented Approach to Spiroindolines

1H NMR (300 MHz, CDCl3): δ 8.41 (bs, 1H, -NH), 7.59 (s, 1H, H-2′′′), 7.43-7.31 (m, 7H, H-2″, H-3″, H-5″, H-6″, H-4″′, H-5″′ & H-7″′), 7.19 (t, J = 7.52Hz, 1H, H-4″′), 7.06 (t, J = 7.33Hz, 1H, H-6″′), 6.53 (s, 1H, H-2), 6.05 (d, J = 8.16Hz, 1H, -CONH), 4.03 (s, 2H, H-1″″), 3.95 (s, 2H, H-2″), 3.82-3.79 (m, 1H, CyH), 1.95-1.87 (m, 3H, H-3″″), 1.66-1.56 (m, 2H, CyH), 1.40-1.25 (m, 3H, CyH), 1.15-1.09 (m, 3H, CyH).

13C NMR (75.5 MHz, CDCl3): δ 172.2, 168.6, 135.9, 134.5, 129.0, 128.7, 127.0, 126.9, 126.1, 122.6, 120.1, 118.9, 111.3, 109.0, 79.4, 71.9, 53.7, 48.4, 41.1, 34.3, 32.8, 32.7, 25.4, 24.7.

HRMS: Calculated for C27H29N3O2 427.2260, found 427.2251.

N-(tert-Butyl)-2-(7-methyl-1H-indol-3-yl)-2-(2-phenyl-N-(prop-2-yn-1-yl)acetamido)acetamide (53c)

![Chemical Structure]

Offwhite solid; Yield 86%; Melting point: 68-70 °C.

1H NMR (300 MHz, CDCl3): δ 8.32 (bs, 1H, -NH), 7.60 (d, J = 2.29Hz, 1H, H-2″′), 7.36-7.27 (m, 6H, H-2″, H-3″, H-4″, H-5″, H-6″ & H-4″′), 6.99-6.98 (m, 2H, H-5″′ & H-6″′), 6.42 (s, 1H, H-2), 6.00 (bs, 1H, -CONH), 4.04 (d, J = 2.17Hz, 2H, H-1″″), 3.96 (s, 2H, H-2″), 2.47 (s, 3H, -Me), 1.96 (t, J = 2.37Hz, 1H, H-3″′), 1.35 (s, 9H, H-2″″′).

13C NMR (75.5 MHz, CDCl3): δ 172.1, 168.9, 135.5, 134.5, 129.0, 128.6, 126.9, 126.5, 125.8, 123.0, 120.5, 120.2, 116.5, 109.4, 79.6, 71.9, 54.4, 51.4, 41.1, 34.3, 28.5, 16.5.

HRMS: Calculated for C26H29N3O2 415.2260, found 415.2250.
**N-Cyclohexyl-2-(2-(4-methoxyphenyl)-N-(prop-2-yn-1-yl)acetamido)-2-(7-methyl-1H-indol-3-yl)acetamide (53d)**

White solid; Yield 69%; Melting point: 78-80 °C.

\[^1^H\text{NMR (300 MHz, CDCl}_3\text{):} \delta 8.28 (bs, 1H, -NH), 7.62 (d, J= 2.15Hz, 1H, H-2'''''), 7.24-7.21 (m, 3H, H-2'', H-6'' & H-5'''''), 7.00-6.98 (m, 2H, H-4'''' & H-6'''''), 6.85 (d, J= 8.50Hz, 2H, H-3'' & H-5''), 6.49 (s, 1H, H-2), 6.04 (d, J= 8.35Hz, 1H, -CONH), 4.02 (d, J= 1.98Hz, 2H, H-1'''), 3.89 (s, 2H, H-2'), 3.78-3.80 (m, 4H, CyH & -OME), 2.48 (s, 3H, -Me), 1.99 (bs, 1H, H-3'''), 1.91-1.87 (m, 2H, CyH), 1.69-1.64 (m, 3H, CyH), 1.36-1.28 (m, 2H, CyH), 1.15-1.12 (m, 3H, CyH).

\[^1^C\text{NMR (75.5 MHz, CDCl}_3\text{):} \delta 172.5, 168.7, 158.6, 135.6, 130.1, 130.0, 126.5, 125.9, 123.0, 120.5, 120.2, 116.5, 114.1, 109.3, 79.6, 71.9, 55.2, 54.1, 48.4, 40.3, 34.3, 32.8, 32.6, 25.5, 24.8, 16.6.

**HRMS:** Calculated for C_{29}H_{33}N_3O_3 471.2522, found 471.2533.

**N-(tert-Butyl)-2-(2-(4-methoxyphenyl)-N-(prop-2-yn-1-yl)acetamido)-2-(1-methyl-1H-indol-3-yl)acetamide (53e)**

Off-white solid; Yield 72%; Melting point: 178-180 °C.
HRMS: Calculated for C_{43}H_{41}N_{3}O_{3} 393.2416, found 393.2402.

$^{13}$C NMR (300 MHz, CDCl$_3$): $\delta$ 172.4, 168.9, 158.6, 136.7, 130.6, 127.5, 126.5, 122.1, 119.5, 119.1, 114.1, 109.2, 107.4, 79.6, 71.7, 55.2, 53.9, 51.4, 40.3, 34.0, 32.9, 28.6.

HRMS: Calculated for C_{29}H_{31}N_{3}O_{3} 445.2365, found 445.2361.

$N$-(2-(Cyclohexylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-$N$-(prop-2-yn-1-yl)pivalamide (53f)

Orange solid; Yield 68%; Melting point: 73-75 °C.

$^{1}$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.46 (bs, 1H, -NH), 7.61 (s, 1H, H-2′′′), 7.45-7.37 (m, 2H, H-4′′′ & H-7′′′), 7.20 (t, $J$= 7.68Hz, 1H, H-6′′′), 7.11 (t, $J$= 7.50Hz, 1H, H-5′′′), 6.34-6.29 (m, 2H, H-1′ & -CONH), 4.27 (d, $J$= 18.38Hz, 1H, H-1′′′), 4.02 (d, $J$= 18.38Hz, 1H, H-1′′′), 3.89-3.79 (m, 1H, CyH), 1.96-1.88 (m, 3H, H-3′ &CyH), 1.69-1.63 (m, 3H, CyH), 1.38-1.32 (m, 11H, H-3&CyH), 1.21-1.13 (m, 3H, CyH).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 178.5, 169.3, 136.0, 126.3, 123.9, 122.3, 120.0, 118.4, 111.5, 108.7, 80.2, 72.1, 48.4, 39.6, 35.7, 32.8, 32.7, 30.9, 28.6, 25.4, 24.7, 24.6.

HRMS: Calculated for C_{24}H_{31}N_{3}O_{2} 393.2416, found 393.2402.
\(N\)-(tert-Butyl)-2-(1-methyl-1H-indol-3-yl)-2-(2-phenyl-N-(prop-2-yn-1-yl)acetamido)acetamide (53g)

White solid; Yield 77%; Melting point: 134-136 °C.

\(^1\)H NMR (300 MHz, CDCl\(_3\)):\(\delta\) 7.51 (s, 1H, H-2‴″), 7.38 (d, \(J=7.92\)Hz, 1H, H-4‴″), 7.32-7.24 (m, 6H, H-2″, H-3″, H-4″, H-5″, H-6″ & H-6‴″), 7.20 (d, \(J=7.68\)Hz, 1H, H-7‴″), 7.05 (t, \(J=7.53\)Hz, 1H, H-5‴″), 6.43 (s, 1H, H-2), 6.04 (bs, 1H, -CONH), 4.02 (d, \(J=2.17\)Hz, 2H, H-1″″), 3.95 (s, 2H, H-2″), 3.78 (s, 3H, -NMe), 1.95 (bs, 1H, H-3″″), 1.35 (s, 9H, H-2‴″″).

\(^1\)C NMR (75.5 MHz, CDCl\(_3\)):\(\delta\) 172.1, 168.8, 136.7, 134.3, 130.6, 129.0, 128.6, 127.5, 126.9, 122.1, 119.6, 119.1, 109.2, 107.4, 79.5, 71.8, 53.9, 51.4, 41.2, 34.1, 32.9, 28.6.

HRMS: Calculated for C\(_{26}\)H\(_{30}\)N\(_3\)O\(_2\) 415.2260, found 415.2263.

\(N\)-(2-(tert-Butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-3-phenyl-N-(prop-2-yn-1-yl)propanamide (53h)

White solid; Yield 79%; Melting point: 172-174 °C.

\(^1\)H NMR (300 MHz, CDCl\(_3\)):\(\delta\) 8.33 (bs, 1H, -NH), 7.56 (d, \(J=2.09\)Hz, 1H, H-2‴″), 7.41-7.35(m, 2H, H-3′ & H-5′), 7.28-7.21 (m, 6H, H-2′, H-4′, H-6′, H-4‴″, H-6‴″ & H-7‴″), 7.08 (t, \(J=7.41\)Hz, 1H, H-5‴″), 6.46 (s, 1H, H-1″″), 5.91 (bs, 1H, -CONH), 4.03 (d, \(J=2.19\)Hz, 2H, H-1″″), 3.09 (t, \(J=7.94\) Hz, 2H, H-2″), 2.87 (t, \(J=7.94\)Hz, 2H, H-3″), 1.83 (bs, 1H, H-3‴″), 1.35 (s, 9H, H-2‴″″).
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$^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 173.2, 169.2, 141.0, 136.0, 128.4, 126.9, 126.0, 125.9, 122.5, 120.0, 118.8, 111.4, 109.1, 79.5, 71.7, 54.1, 51.5, 35.3, 34.2, 31.0, 28.5.

HRMS: Calculated for C$_{26}$H$_{28}$N$_5$O$_2$ 415.2260, found 415.2250.

$N$-(tert-Butyl)-2-((1H-indol-3-yl)-2-(2-(4-methoxyphenyl)-N-(prop-2-yn-1-yl)acetamido)acetamide (53i)

![Chemical Structure]

Offwhite solid; Yield 67%; Melting point: 148-150 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.40 (bs, 1H, -NH), 7.59 (s, 1H, H-2''), 7.41 (d, $J=7.93$Hz, 1H, H-4''), 7.35 (d, $J=8.16$Hz, 1H, H-7''), 7.24-7.16 (m, 3H, H-2'', H-6'' & H-6''''), 7.06 (t, $J=7.48$Hz, 1H, H-5'''), 6.85 (d, $J=8.57$Hz, 2H, H-3'' & H-5''), 6.44 (s, 1H, H-2), 6.00 (bs, 1H, -CONH), 4.05 (bs, 2H, H-1''), 3.89 (s, 2H, H-2'), 3.79 (s, 3H, -OMe), 1.92 (bs, 1H, H-3''), 1.35 (s, 9H, H-2'''').

$^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 172.4, 168.9, 158.6, 135.9, 130.0, 127.0, 126.5, 125.9, 122.6, 120.0, 119.0, 114.1, 111.2, 109.3, 79.6, 71.7, 55.2, 54.0, 51.5, 40.2, 34.2, 28.6.

HRMS: Calculated for C$_{26}$H$_{28}$N$_5$O$_3$ 431.2209, found 431.2209.

$N$-Cyclohexyl-2-((1H-indol-3-yl)-2-(2-(4-methoxyphenyl)-N-(prop-2-yn-1-yl)acetamido)acetamide (53j)

![Chemical Structure]

Orange solid; Yield 89%; Melting point: 153-155 °C.
**Section A: Diversity Oriented Approach to Spiroindolines**

1H NMR (300 MHz, CDCl₃): δ 8.42 (bs, 1H, -NH), 7.59 (s, 1H, H-2‴′″), 7.41 (d, J= 7.96Hz, 1H, H-4‴′″), 7.35 (d, J= 8.12Hz, 1H, H-7‴′″), 7.24-7.16 (m, 3H, H-2″, H-6″ & H-6‴′″), 7.06 (t, J= 7.47Hz, 1H, H-5‴′″), 6.85 (d, J= 8.55Hz, 2H, H-3″ & H-5″″), 6.52 (s, 1H, H-2), 6.06 (d, J= 7.89Hz, 1H, -CONH), 4.03 (bs, 2H, H-1‴″), 3.88 (s, 2H, H-2′), 3.79 (m, 4H, CyH & -OMe), 1.95-1.87 (m, 3H, H-3″ & H-5″), 6.52 (s, 1H, H), 1.66-1.56 (m, 2H, H), 1.35-1.26 (m, 3H, CyH), 1.15-1.12 (m, 3H, CyH).

13C NMR (75.5 MHz, CDCl₃): δ 172.5, 168.8, 158.6, 136.0, 130.1, 126.9, 126.5, 126.1, 122.5, 119.9, 118.8, 114.1, 111.4, 108.8, 79.5, 71.8, 55.2, 53.9, 48.4, 40.2, 34.3, 32.7, 32.6, 25.4, 24.7.

HRMS: Calculated for C₂₈H₂₋N₃O₃ 457.2365, found 457.2394.

**N-Butyl-2-(1H-indol-3-yl)-2-(2-phenyl-N-(prop-2-yn-1-yl)acetamido)acetamide (53k)**

![Chemical Structure]

Offwhite solid; Yield 63%; Melting point: 90-92 °C.

1H NMR (300 MHz, CDCl₃): δ 8.37 (bs, 1H, -NH), 7.62 (s, 1H, H-2‴′″), 7.42-7.19 (m, 8H, H-2″, H-3″, H-4″, H-5″, H-6″, H-4‴″, H-6‴″ & H-7‴″), 7.06 (t, J= 7.34Hz, 1H, H-5‴″), 6.53 (s, 1H, H-2), 6.18 (bs, 1H, -CONH), 4.05 (s, 2H, H-1‴″), 3.95 (s, 2H, H-2′), 3.28-3.26 (m, 2H, H-1‴″), 1.95 (s, 1H, H-3‴″), 1.47-1.44 (m, 2H, H-2‴″), 1.32-1.29 (m, 2H, H-3‴″), 0.89 (t, J= 6.93Hz, 3H, H-4‴″).

13C NMR (75.5 MHz, CDCl₃): δ 172.2, 169.5, 135.9, 134.4, 129.1, 128.6, 127.0, 126.9, 126.1, 122.6, 120.1, 118.9, 111.2, 108.9, 79.3, 71.8, 53.5, 41.1, 39.3, 34.3, 31.4, 20.0, 13.7.

HRMS: Calculated for C₂₅H₂₋N₃O₂ 401.2103, found 401.2101.
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*N-Cyclohexyl-2-(1-methyl-1H-indol-3-yl)-2-(2-phenyl-N-(prop-2-yn-1-yl)acetamido)acetamide (53l)*

White solid; Yield 77%; Melting point: 183-185 °C.

**¹H NMR (300 MHz, CDCl₃):**
δ 7.50 (s, 1H, H-2‴‴), 7.40-7.19 (m, 8H, H-2″, H-3‴, H-4‴, H-5‴, H-6‴, H-4‴‴, H-6‴‴ & H-7‴‴), 7.05 (t, J = 7.46Hz, 1H, H-5‴‴), 6.50 (s, 1H, H-2), 6.08 (d, J = 8.11Hz, 1H, -CONH), 4.02 (s, 2H, H-1‴‴), 3.95 (s, 2H, H-2′), 3.85-3.78 (m, 3H, CyH&-NMe), 1.98-1.88 (m, 3H, H-3‴‴ & CyH), 1.64-1.57 (m, 2H, CyH), 1.41-1.25 (m, 3H, CyH), 1.16-1.14 (m, 3H, CyH).

**¹³C NMR (75.5 MHz, CDCl₃):**
δ 172.1, 168.6, 136.7, 134.5, 130.6, 129.0, 128.6, 127.5, 126.9, 122.1, 119.6, 119.0, 109.2, 107.3, 79.5, 71.8, 53.5, 48.3, 41.2, 34.2, 32.9, 32.8, 32.7, 25.5, 24.7.

**HRMS:** Calculated for C₂₉H₃₁N₃O₂ 441.2416, found 441.2411.

*N-Cyclohexyl-2-(2-(4-methoxyphenyl)-N-(prop-2-yn-1-yl)acetamido)-2-(1-methyl-1H-indol-3-yl)acetamide (53m)*

White solid; Yield 74%; Melting point: 119-121 °C.

**¹H NMR (300 MHz, CDCl₃):**
δ 7.50 (s, 1H, H-2‴‴), 7.38 (d, J = 7.96Hz, 1H, H-4‴‴), 7.29 (d, J = 8.20Hz, 1H, H-7‴‴), 7.24-7.21 (m, 3H, H-2″, H-6″ & H-6‴‴), 7.05 (t, J = 7.33Hz,
1H, H-5‴‴), 6.86 (d, J= 8.51Hz, 2H, H-3″ & H-5‴), 6.49 (s, 1H, H-2), 6.08 (d, J= 7.98Hz, 1H, -CONH), 4.01 (bs, 2H, H-1‴‴), 3.88 (s, 2H, H-2′), 3.79-3.78 (m, 7H, CyH, -NMe & -OMe), 1.98 (bs, 1H, H-3‴‴), 1.92-1.88 (m, 2H, CyH), 1.70-1.66 (m, 3H, CyH), 1.37-1.29 (m, 2H, CyH), 1.16-1.14 (m, 3H, CyH).

$^{13}$C NMR (75.5 MHz, CDCl$_3$):δ 172.4, 168.6, 158.6, 136.7, 130.6, 130.0, 127.5, 126.1, 122.1, 119.6, 119.1, 114.1, 109.2, 107.3, 79.5, 71.8, 55.2, 53.5, 48.3, 40.3, 34.1, 32.9, 32.8, 32.7, 25.5, 24.7.

HRMS: Calculated for C$_{20}$H$_{33}$N$_3$O$_3$ 471.2522, found 471.2517.

N-(2-(Cyclohexylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-3-phenyl-N-(prop-2-yn-1-yl)propanamide (53n)

Offwhite solid; Yield 65%; Melting point: 62-64 °C.

$^1$H NMR (300 MHz, CDCl$_3$):δ 8.32 (bs, 1H, -NH), 7.59 (d, J= 1.90Hz, 1H, H-2‴‴), 7.40-7.36 (m, 2H, H-4‴‴ & H-7‴‴), 7.28-7.18 (m, 6H, H-2′, H-3′, H-4′, H-5′, H-6′ & H-6‴‴), 7.08 (t, J= 7.44Hz, 1H, H-5‴‴), 6.53 (s, 1H, H-1″″), 6.00 (d, J= 7.93Hz, 1H, -CONH), 4.02 (d, J= 1.98Hz, 2H, H-1‴‴), 3.82-3.79 (m, 1H, CyH), 3.09 (t, J= 7.60Hz, 2H, H-2), 2.86 (t, J= 7.46Hz, 2H, H-3), 1.92-1.88 (m, 3H, H-3‴‴ &CyH), 1.70-1.65 (m, 3H, CyH), 1.37-1.33 (m, 3H, CyH), 1.16-1.12 (m, 2H, CyH).

$^{13}$C NMR (75.5 MHz, CDCl$_3$):δ 173.3, 168.8, 141.1, 135.9, 128.5, 128.4, 126.9, 126.1, 125.9, 122.6, 120.1, 118.9, 111.2, 109.2, 79.4, 77.2, 71.6, 53.4, 48.4, 35.4, 34.1, 32.8, 32.6, 31.1, 25.4, 24.7.

HRMS: Calculated for C$_{28}$H$_{31}$N$_3$O$_2$ 441.2416, found 441.2415.
**N-(2-(tert-Butylamino)-1-(1-methyl-1H-indol-3-yl)-2-oxoethyl)-3-phenyl-N-(prop-2-yne-1-yl)propanamide (53o)**

White solid; Yield 68%; Melting point: 112-114 °C.

**1H NMR (300 MHz, CDCl3):**
\[\delta 7.47 (s, 1H, H-2'''), 7.35 (d, J= 7.88Hz, 1H, H-4'''), 7.31-7.20 (m, 7H, H-2', H-3', H-4', H-5', H-6', H-6''' & H-7'''), 7.07 (t, J= 7.40Hz, 1H, H-5'''), 6.43 (s, 1H, H-1''), 5.98 (bs 1H, -CONH), 4.01 (bs, 2H, H-1'''), 3.79 (s, 3H, -NMe), 3.12-3.07 (m, 2H, H-2), 2.89-2.86 (m, 2H, H-3), 1.88 (s, 1H, H-3'''), 1.35 (s, 9H, H-2''''').

**13C NMR (75.5 MHz, CDCl3):**
\[\delta 173.1, 169.0, 141.1, 136.7, 130.4, 128.4(2), 127.5, 126.0, 122.1, 119.7, 119.0, 109.2, 107.6, 79.5, 71.5, 53.6, 51.4, 35.3, 34.0, 32.9, 31.1, 28.6.\]

**HRMS:** Calculated for C_{27}H_{31}N_{3}O_{2}: 429.2416, found 429.2426.

**N-(2-(Cyclohexylamino)-1-(1-methyl-1H-indol-3-yl)-2-oxoethyl)-3-phenyl-N-(prop-2-yne-1-yl)propanamide (53p)**

Offwhite solid; Yield 58%; Melting point: 157-159 °C.

**1H NMR (300 MHz, CDCl3):**
\[\delta 7.47 (s, 1H, H-2'''), 7.36 (d, J= 8.01Hz, 1H, H-4'''), 7.31-7.21 (m, 7H, H-2', H-3', H-4', H-5', H-6', H-6''' & H-7'''), 7.07 (t, J= 7.26Hz, 1H, H-5'''), 6.49 (s, 1H, H-1''), 6.03 (d, J= 7.79Hz, 1H, -CONH), 4.00 (bs, 2H, H-1'''), 3.78 (m, 4H, CyH& -NMe), 3.11-3.06 (m, 2H, H-2), 2.89-2.87 (m, 2H, H-3), 1.92-1.89 (m, 3H, H-3''' &CyH), 1.70-1.66 (m, 3H, CyH), 1.37-1.29 (m, 2H, CyH), 1.16-1.10 (m, 3H, CyH).
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\[ ^{13}C\text{ NMR (75.5 MHz, CDCl}_3\text{):} \delta 173.2, 168.7, 141.1, 136.8, 130.5, 128.4, 127.5, 126.1, 122.1, 119.7, 119.0, 109.3, 107.5, 79.5, 71.6, 53.3, 48.4, 35.4, 34.1, 32.9, 32.8, 32.7, 31.1, 25.5, 24.7.\]

**HRMS:** Calculated for C_{29}H_{33}N_{3}O_{2} 455.2573, found 455.2568.

\[ \text{N-Butyl-2-}(1H\text{-indol-3-yl})\text{-}2\text{-}(2\text{-}(4\text{methoxyphenyl})\text{-}N\text{(prop-2-yn-1-yl)}\text{acetamido)acetamide (53q)} \]

Yellow solid; Yield 59%; Melting point: 105-107 °C.

\[ ^1H\text{ NMR (300 MHz, CDCl}_3\text{):} \delta 8.46 \text{ (bs, 1H, -NH), 7.60 (s, 1H, H-2''''), 7.41-7.34 (m, 2H, H-4''' & H-7''''), 7.25-7.16 (m, 3H, H-2'', H-6'' & H-6''''), 7.06 (t, J= 7.40Hz, 1H, H-5''''), 6.85 (d, J= 8.18Hz, 2H, H-3'' & H-5''), 6.52 (s, 1H, H-2), 6.20 (bs, 1H, -NH), 4.04 (s, 2H, H-1'''), 3.88 (s, 2H, H-2'), 3.79 (s, 3H, -OMe), 3.28-3.26 (m, 2H, H-1'''''), 1.96 (s, 1H, H-3''''), 1.46-1.44 (m, 2H, H-2'''''), 1.31-1.26 (m, 2H, H-3''''''), 0.89 (t, J= 7.06Hz, 3H, H-4'''''). \]

\[ ^{13}C\text{ NMR (75.5 MHz, CDCl}_3\text{):} \delta 172.5, 169.6, 158.6, 135.9, 130.1, 126.9, 126.4, 126.2, 122.5, 120.0, 118.8, 114.1, 111.3, 108.8, 79.4, 71.8, 55.2, 53.7, 40.2, 39.3, 34.3, 31.3, 20.0, 13.7.\]

**HRMS:** Calculated for C_{26}H_{20}N_{3}O_{3} 431.2209, found 431.2202.

**General procedure for the synthesis of spiroindolines 54a-q**

To a screw capped vial Au(PPh_3)Cl (5 mole%) and AgSbF_6 (5 mole%) were loaded along with chloroform (2 mL). Ugi product 53 (0.2 mmol) was added followed by TFA (1 equiv.) and reaction mixture was stirred at room temperature until completion of reaction. After completion, reaction mixture was partitioned between EtOAc (100 mL) and 2N K_2CO_3 solution (2x50 mL). Organic layer was washed with brine (50 mL), dried over magnesium sulfate and evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (10% diethyl ether in dichloromethane) to afford compound 54a-q.
**5-(tert-Butyl)-1-methylene-3-(2-phenylacetyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54a)**

White Solid; Yield 81%; Melting point: 72–74 °C.

**¹H NMR (300 MHz, CDCl₃):** δ 7.26-7.16 (m, 5H, H-9, H-10, H-3′′, H-4′′ & H-5′′), 7.10 (t, J = 7.50 Hz, 1H, H-8), 6.75-6.63 (m, 3H, H-7, H-2′′ & H-6′′), 5.48 (d, J = 4.5Hz, 1H, H-5a), 5.33 (bs, 1H, H-1′), 4.94 (bs, 1H, H-1′), 4.80 (d, J = 16.56 Hz, 1H, H-2), 4.55 (s, 1H, H-3a), 4.38 (d, J = 4.35 Hz, 1H, -NH), 4.06-4.00 (m, 3H, H-2 & H-2′′), 1.50 (s, 9H, H-2″″).

**¹³C NMR (75.5 MHz, CDCl₃):** δ 171.0, 170.8, 149.3, 148.9, 135.0, 130.4, 129.2, 129.0, 128.5, 126.6, 123.8, 120.6, 111.6, 110.1, 83.6, 69.5, 60.1, 55.3, 50.5, 40.8, 28.0

**HRMS:** Calculated for C₂₅H₂₇N₅O₂ 401.2103, found 401.2111.

**5-Cyclohexyl-1-methylene-3-(2-phenylacetyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54b)**

White Solid; Yield 70%; Melting point: 91–93 °C.

**¹H NMR (300 MHz, CDCl₃):** δ 7.32-7.16 (m, 5H, H-8, H-10, H-3′′, H-4′′ & H-5′′), 7.11 (t, J = 7.43Hz, 1H, H-9), 6.75-6.69 (m, 3H, H-7, H-2′′ & H-6′′), 6.64 (d, J = 7.92Hz, 1H, H-7), 5.36 (d, J = 4.14Hz, 1H, H-5a), 5.28 (bs, 1H, H-1′), 4.86-4.76 (m, 2H, H-2 &H-1′),
4.61 (s, 1H, H-3a), 4.45 (d, J = 3.39Hz, 1H, -NH), 4.05-3.99 (m, 3H, H-2 & H-2")
3.93-3.79 (m, 1H, CyH), 2.02-1.68 (m, 4H, CyH), 1.57-1.46 (m, 2H, CyH), 1.38-1.25 (m, 2H, CyH),
1.21-1.08 (m, 2H, CyH).

**$^{13}$C NMR (75.5 MHz, CDCl$_3$):**
δ 170.8, 170.1, 148.9, 148.7, 135.0, 130.0, 129.4, 129.1, 128.5, 126.6, 123.9, 120.7, 111.5, 110.3, 81.8, 68.7, 61.3, 52.8, 50.7, 40.8, 32.0, 30.3, 25.7, 25.5, 25.4.

**HRMS:** Calculated for C$_{25}$H$_{29}$N$_{3}$O$_2$ 427.2260, found 427.2264.

5-(tert-Butyl)-7-methyl-1-methylene-3-(2-phenylacetyl)-1,2,3,3a,5a,6-hexahydro-
pyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54c)

Yellow Solid; Yield 60%; Melting point: 79-81 °C.

**$^1$H NMR (300 MHz, CDCl$_3$):**
δ 7.35-7.17 (m, 5H, H-2″, H-3″, H-4″, H-5″ & H-6″),
6.94 (d, J = 7.35Hz, 1H, H-8), 6.68 (t, J = 7.43Hz, 1H, H-9), 6.55 (d, J = 7.44Hz, 1H, H-10), 5.49(d, J = 4.53Hz, 1H, H-5a), 5.31(bs, 1H, H-1′), 4.92-4.77(m, 2H, H-2 & H-1′),
4.54 (s, 1H, H-3a), 4.14-4.06 (m, 2H, H-2 & -NH), 4.00-3.99 (m, 2H, H-2″), 2.15 (s, 3H, -Me), 1.51 (s, 9H, H-2″″)

**$^{13}$C NMR (75.5 MHz, CDCl$_3$):**
δ 171.1, 170.8, 149.4, 147.4, 135.0, 130.0, 129.9, 129.1, 128.4, 126.6, 121.2, 120.9, 119.8, 111.5, 83.5, 69.6, 60.5, 55.3, 50.5, 40.8, 28.1, 16.7.

**HRMS:** Calculated for C$_{26}$H$_{29}$N$_{3}$O$_2$ 415.2260, found 415.2251.
5-Cyclohexyl-3-(2-(4-methoxyphenyl)acetyl)-7-methyl-1-methylene-1,2,3,3a,5a,6-hexahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indol-4(5H)-one (54d)

Yellow solid; Yield 76%; Melting point: 77-79 °C.

\[ ^1H \text{NMR (300 MHz, CDCl}_3\]: \delta 7.18 (d, J = 8.45 Hz, 2H, H-2″ & H-6″), 6.95 (d, J = 7.51 Hz, 1H, H-8), 6.80 (d, J = 8.62 Hz, 2H, H-3″ & H-5″), 6.70 (t, J = 7.40 Hz, 1H, H-9), 6.57 (d, J = 7.46 Hz, 1H, H-10), 5.36 (s, 1H, H-5a), 5.27 (bs, 1H, H-1′), 4.85-4.75 (m, 2H, H-2 & H-1′), 4.61 (s, 1H, H-3a), 4.16 (bs, 1H, -NH), 4.04-3.90 (m, 4H, H-2, H-2″&CyH), 3.76 (s, 3H, -OMe), 2.15 (s, 3H, -Me), 1.75-1.34 (m, 10H, CyH).

\[ ^13C \text{NMR (75.5 MHz, CDCl}_3\]: \delta 171.2, 170.1, 158.4, 148.8, 147.5, 130.2, 130.1, 129.6, 127.1, 121.3, 120.9, 120.0, 114.0, 111.3, 81.7, 68.8, 61.7, 55.2, 52.9, 50.7, 39.9, 32.0, 30.3, 25.7, 25.5, 25.4, 16.7.

HRMS: Calculated for C_{20}H_{33}N_5O_3 471.2522, found 471.2525.

5-(tert-Butyl)-3-(2-(4-methoxyphenyl)acetyl)-6-methyl-1-methylene-1,2,3,3a,5a,6-hexahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indol-4(5H)-one (54e)

Brown solid; Yield 66%; Melting point: 50-52 °C.
HRMS: Calculated for C27H31N3O3 445.2365, found 445.2379.

Orange solid; Yield 40%; Melting point: 105-107 °C.

1H NMR (300 MHz, CDCl3): δ 7.12 (t, J = 7.43Hz, 1H, H-8), 6.89 (d, J = 7.29Hz, 1H, H-10), 6.77 (t, J = 7.51Hz, 1H, H-9), 6.66 (d, J = 7.85Hz, 1H, H-7), 5.39-5.34 (m, 2H, H-5a & H-1’), 5.16 (bs, 1H, H-1’), 5.02 (s, 1H, H-3a), 4.86 (d, J = 16.23Hz, 1H, H-2), 3.96-3.91 (m, 2H, H-2 & -NH), 2.70 (bs, 1H, CyH), 1.83-1.68 (m, 4H, CyH), 1.40-1.28 (m, 15H, H-3”, CyH).

13C NMR (75.5 MHz, CDCl3): δ 181.6, 170.4, 154.6, 149.4, 130.4, 129.2, 123.8, 120.4, 111.3, 110.0, 81.9, 69.1, 52.3, 51.8, 39.4, 32.1, 30.4, 28.5, 25.9, 25.7, 25.4(2).

HRMS: Calculated for C24H31N3O2 393.2416, found 393.2417.
5-(tert-Butyl)-6-methyl-1-methylene-3-(2-phenylacetyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indol-4(5H)-one (54g)

White solid; Yield 71%; Melting point: 181-183 °C.

$^1$H NMR (300 MHz, CDCl$_3$):$\delta$ 7.20-7.14 (m, 6H, H-10, H-2'''', H-3''', H-4''', H-5''' & H-6''''), 6.74-6.73 (m, 2H, H-7 & H-8), 6.55 (d, $J = 7.95$Hz, 1H, H-9), 5.37 (bs, 1H, H-5a), 5.07-5.04 (m, 2H, H-1'), 4.77 (d, $J = 16.85$Hz, 1H, H-2), 4.50 (s, 1H, H-3a), 4.08-3.95 (m, 3H, -NMe), 2.97 (s, 3H, H-2 & H-2''), 1.52 (s, 9H, H-2''''').

$^{13}$C NMR (75.5 MHz, CDCl$_3$):$\delta$ 172.4, 171.0, 151.2, 147.4, 135.0, 130.3, 129.2, 129.1, 128.4, 126.5, 123.0, 120.0, 111.6, 108.9, 90.3, 69.6, 60.8, 55.5, 51.0, 40.7, 36.3, 28.4.

HRMS: Calculated for C$_{26}$H$_{29}$N$_5$O$_2$ 415.2260, found 415.2228.

5-(tert-Butyl)-1-methylene-3-(3-phenylpropanoyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indol-4(5H)-one (54h)

White solid; Yield 83%; Melting point: 179-181 °C.

$^1$H NMR (300 MHz, CDCl$_3$):$\delta$ 7.20-7.10 (m, 6H, H-10, H-2'''', H-3''', H-4''', H-5''' & H-6'''''), 6.83-6.75 (m, 2H, H-8 & H-9), 6.65 (d, $J = 7.81$Hz, 1H, H-7), 5.48 (d, $J = 4.28$Hz, 1H, H-5a), 5.34 (bs, 1H, H-1'), 4.98 (bs, 1H, H-1'), 4.78 (d, $J = 16.71$Hz, 1H, H-2), 4.44 (s, 1H, H-3a), 4.38 (d, $J = 3.86$Hz, 1H, -NH), 4.03 (d, $J = 16.71$Hz, 1H, H-2), 3.13-2.97 (m, 4H, H-2'' & H-3''), 1.47 (s, 9H, H-2'''').
13C NMR (75.5 MHz, CDCl3): δ 172.1, 171.0, 149.2, 149.0, 141.3, 130.6, 129.3, 128.4, 128.3, 125.9, 123.8, 120.6, 111.6, 110.1, 83.5, 69.6, 60.2, 55.2, 50.5, 35.6, 31.1, 28.0.

HRMS: Calculated for C26H38N2O2 415.2260, found 415.2246.

5-(tert-Butyl)-3-(2-(4-methoxyphenyl)acetyl)-1-methylene-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54i)

Off white solid; Yield 69%; Melting point: 168-170 °C.

1H NMR (300 MHz, CDCl3): δ 7.17-7.08 (m, 3H, H-10, H-2′′ & H-6’’’), 6.79-6.63 (m, 5H, H-7, H-8, H-9, H-3′′ & H-5’’’), 5.48 (d, J = 4.08Hz, 1H, H-5a), 5.32 (bs, 1H, H-1′), 4.94 (bs, 1H, H-1′), 4.79 (d, J = 16.61Hz, 1H, H-2), 4.56 (s, 1H, H-3a), 4.40 (d, J = 4.14Hz, 1H, -NH), 4.01 (d, J = 16.61Hz, 1H, H-2), 3.92 (s, 2H, H-2′′) 3.75 (s, 3H, -OMe) 1.49 (s, 9H, H-2’’’).

13C NMR (75.5 MHz, CDCl3): δ 171.1(2), 158.3, 149.3, 148.9, 130.4, 130.1, 129.2, 127.0, 123.8, 120.6, 113.9, 111.6, 110.1, 83.6, 69.5, 60.1, 55.3, 55.2, 50.5, 40.0, 28.0.

HRMS: Calculated for C26H38N2O3 431.2209, found 431.2211.

5-Cyclohexyl-3-(2-(4-methoxyphenyl)acetyl)-1-methylene-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54j)

White solid; Yield 75%; Melting point: 153-155 °C.
1H NMR (300 MHz, CDCl3): δ 7.20-7.09 (m, 3H, H-10, H-2′′ & H-6′′), 6.81-6.63 (m, 5H, H-7, H-8, H-9, H-3′′ & H-5′′), 5.36 (d, J = 4.36Hz, 1H, H-5a), 5.28 (bs, 1H, H-1′), 4.86-4.76 (m, 2H, H-2 & H-1′), 4.62 (s, 1H, H-3a) 4.42 (d, J = 3.59Hz, 1H, -NH), 4.03-3.97 (m, 3H, H-2 & H-2′′), 3.92-3.85 (m, 1H, CyH), 3.76 (s, 3H, -OMe), 2.03-1.99 (m, 1H, CyH), 1.86-1.69 (m, 4H, CyH), 1.52-1.25 (m, 5H, CyH).

13C NMR (75.5 MHz, CDCl3): δ 170.1, 170.1, 158.4, 148.9, 148.8, 130.1, 130.0, 129.3, 127.0, 123.9, 120.6, 114.0, 111.4, 110.3, 81.8, 68.7, 61.3, 55.2, 52.8, 50.7, 39.9, 32.0, 30.3, 25.7, 25.5, 25.4.

HRMS: Calculated for C29H31N5O3 457.2365, found 457.2359.

5-Butyl-1-methylene-3-(2-phenylacetyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54k)

Yellow solid; Yield 80%; Melting point: 42-44 °C.

1H NMR (300 MHz, CDCl3): δ 7.29-7.28 (m, 5H, H-2′′, H-3′′, H-4′′, H-5′′ & H-6′′), 7.13 (t, J = 7.59Hz, 1H, H-8), 6.79-6.65 (m, 3H, H-7, H-9 & H-10), 5.24-5.20 (m, 2H, H-5a & H-1′), 4.83 (d, J = 16.34Hz, 1H, H-2), 4.72 (bs, 1H, H-1′), 4.58-4.47 (m, 2H, H-3a & -NH), 4.21 (d, J = 15.52Hz, 1H, H-2), 4.08-3.99 (m, 2H, H-2′′), 3.61-3.53 (m, 1H, H-1′′′), 3.23-3.14 (m, 1H, H-1′′′′), 1.58-1.56 (m, 2H, H-2′′′′), 1.37-1.30 (m, 2H, H-3′′′′), 0.95 (t, J = 7.44Hz, 3H, H-4′′′′).

13C NMR (75.5 MHz, CDCl3): δ 170.9, 169.9, 148.9, 148.2, 135.0, 129.7, 129.5, 129.1, 128.5, 126.7, 124.4, 121.1, 111.2, 111.0, 82.3, 68.1, 61.6, 50.7, 41.0, 40.9, 29.1, 20.2, 13.7.

HRMS: Calculated for C25H27N3O2 401.2103, found 401.2101.
5-Cyclohexyl-6-methyl-1-methylene-3-(2-phenylacetyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54l)

White solid; Yield 74%; Melting point: 70-72 °C.

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.25-7.18 (m, 6H, H-10, H-2′′′, H-3′′′, H-4′′′, H-5′′′ & H-6′′′), 6.72-6.55 (m, 3H, H-7, H-8 & H-9), 5.28 (s, 1H, H-5a), 4.81-4.76 (m, 3H, H-1′ & H-1’′ & H-2), 4.54 (s, 1H, H-3a), 4.06-4.03 (m, 3H, H-2 & H-2′′), 3.57 (m, 1H, CyH), 3.04 (s, 3H, -NMe), 2.00-1.71 (m, 6H, CyH), 1.25-1.18 (m, 4H, CyH).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 170.9, 170.7, 151.6, 148.6, 135.0, 130.1, 129.5, 129.1, 128.5, 126.6, 123.5, 120.1, 111.5, 109.2, 91.1, 68.8, 60.8, 55.6, 50.8, 40.8, 37.8, 30.3, 29.5, 26.0, 25.9, 25.3.

HRMS: Calculated for C$_{28}$H$_{31}$N$_3$O$_2$ 441.2416, found 441.2400.

5-Cyclohexyl-3-(2-(4-methoxyphenyl)acetyl)-6-methyl-1-methylene-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54m)

White solid; Yield 68%; Melting point: 146-148 °C.
$^1$H NMR (300 MHz, CDCl$_3$): δ 7.20-7.16 (m, 3H, H-10, H-2′′ & H-6′′), 6.80 (d, $J = 8.6$ Hz, 2H, H-3′′ & H-5′′), 6.75-6.65 (m, 2H, H-8 & H-9), 6.56 (d, $J = 8.07$ Hz, 1H, H-7), 5.28 (s, 1H, H-5a), 4.83-4.75 (m, 3H, H-2 & H-1′), 4.55 (s, 1H, H-3a), 4.05-3.96 (m, 3H, H-2 & H-2′′), 3.76 (s, 3H, -OMe), 3.61-3.53 (m, 1H, CyH), 3.03 (s, 3H, -NMe), 1.89-1.81 (m, 5H, CyH), 1.31-1.22 (m, 5H, CyH).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 171.2, 170.7, 158.4, 151.6, 148.7, 130.1, 129.4, 127.0, 123.5, 120.0, 113.9, 111.5, 109.2, 91.1, 68.8, 60.8, 55.6, 55.2, 50.8, 39.9, 37.8, 30.3, 29.5, 26.0, 25.9, 25.3.

HRMS: Calculated for C$_{29}$H$_{33}$N$_3$O$_3$ 471.2522, found 471.2541.

5-Cyclohexyl-1-methylene-3-(3-phenylpropanoyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(SH)-one (54n)

White solid; Yield 72%; Melting point: 73-75 °C.

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.22-7.14 (m, 6H, H-10, H-2′′, H-3′′, H-4′′, H-5′′ & H-6′′), 6.83-6.65 (m, 3H, H-7, H-8 & H-9), 5.37-5.30 (m, 2H, H-5a & H-1′), 4.90 (bs, 1H, H-1′), 4.77 (d, $J = 16.88$ Hz, 1H, H-2), 4.50 (s, 1H, -NH), 4.40 (s, 1H, H-3a), 4.02 (d, $J = 16.94$ Hz, 1H, H-2), 3.86 (m, 1H, CyH), 3.18 (m, 1H, H-3′′), 3.03 (m, 2H, H-2′′), 2.73 (m, 1H, H-3′′), 1.83-1.73 (m, 4H, CyH), 1.57-1.16 (m, 6H, CyH).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 172.2, 170.1, 149.0, 148.7, 141.3, 130.1, 129.4, 128.4, 128.3, 125.9, 124.0, 120.6, 111.4, 110.3, 81.7, 68.9, 61.4, 52.7, 50.7, 35.6, 32.0, 31.2, 30.3, 25.7, 25.5, 25.4.

HRMS: Calculated for C$_{28}$H$_{31}$N$_3$O$_2$ 441.2416, found 441.2414.
5-(tert-Butyl)-6-methyl-1-methylene-3-(3-phenylpropanoyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54o)

White solid; Yield 60%; Melting point: 54-56 °C.

$^1$H NMR (300 MHz, CDCl$_3$):$\delta$ 7.25-7.19 (m, 6H, H-10, H-2‴, H-3‴, H-4‴, H-5‴ & H-6‴), 6.82-6.78 (m, 2H, H-8 & H-9), 6.55 (bs, 1H, H-7), 5.39 (bs, 1H, H-5a), 5.07 (bs, 2H, H-1′), 4.75 (d, $J = 16.63$Hz, 1H, H-2), 4.38 (s, 1H, H-3a), 4.04 (d, $J = 16.69$Hz, 1H, H-2), 2.95(m, 6H, H-2‴, H-3‴ & -NMe), 2.65 (m, 1H, H-3″), 1.49 (s, 9H, H-2‴).

$^{13}$C NMR (75.5 MHz, CDCl$_3$):$\delta$ 172.5, 172.3, 151.1, 147.2, 141.3, 130.4, 128.4, 128.3, 125.9, 123.0, 119.9, 111.6, 108.6, 90.1, 69.7, 60.8, 55.4, 50.9, 35.8, 35.6, 31.1, 28.4.

HRMS: Calculated for C$_{27}$H$_{31}$N$_{3}$O$_{2}$ 429.2416, found 429.2395.

5-Cyclohexyl-6-methyl-1-methylene-3-(3-phenylpropanoyl)-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-b]indol-4(5H)-one (54p)

White solid; Yield 84%; Melting point: 125-127 °C.

$^1$H NMR (300 MHz, CDCl$_3$):$\delta$ 7.22-7.17 (m, 6H, H-10, H-2‴, H-3‴, H-4‴, H-5‴ & H-6‴), 6.81-6.75 (m, 2H, H-8 & H-9), 6.56 (d, $J = 8.01$Hz, 1H, H-7), 5.30 (s, 1H, H-5a), 4.86-4.73 (m, 3H, H-2 & H-1′), 4.43 (s, 1H, H-3a), 4.04 (d, $J = 16.67$Hz, 1H, H-2), 3.57-
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3.49 (m, 1H, CyH), 3.18-3.12 (m, 1H, H-3‴), 3.10-2.98 (m, 5H, H-2‴ & -NMe), 2.77-2.67 (m, 1H, H-3‴), 1.90-1.70 (m, 6H, 5-Butyl-3-(2-(4-methoxyphenyl)acetyl)-1-methylene-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-C]indol-4(5H)-one (54q)

**$^{13}$C NMR (75.5 MHz, CDCl$_3$):** δ 172.2, 170.7, 151.7, 148.5, 141.3, 130.3, 129.5, 128.4, 128.3, 125.9, 123.5, 120.0, 119.1, 91.1, 69.0, 60.9, 55.6, 50.7, 37.6, 35.6, 31.2, 30.3, 29.4, 26.0, 25.9, 25.2.

**HRMS:** Calculated for C$_{20}$H$_{33}$N$_3$O$_2$ 455.2573, found 455.2599.

5-Butyl-3-(2-(4-methoxyphenyl)acetyl)-1-methylene-1,2,3,3a,5a,6-hexahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-C]indol-4(5H)-one (54q)

![Chemical Structure](image)

Offwhite solid; Yield 69%; Melting point: 49-51 °C.

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.21 (d, $J = 8.53$Hz, 2H, H-2‴ & H-6‴), 7.21 (t, $J = 7.52$Hz, 1H, H-8), 6.84-6.75 (m, 3H, H-9, H-3‴ & H-5‴), 6.70-6.67 (m, 2H, H-7 & H-10), 5.24-5.20 (m, 2H, H-5a & H-1′), 4.81 (d, $J = 16.19$Hz, 1H, H-2), 4.72 (bs, 1H, H-1′), 4.59 (s, 1H, H-3a), 4.50 (d, $J = 4.40$Hz, 1H, -NH), 4.13-3.97 (3H, H-2 & H-2‴), 3.78 (s, 3H, -OMe), 3.63-3.53 (m, 1H, H-1‴), 3.23-3.14 (m, 1H, H-1‴‴), 1.37-1.25 (m, 4H, H-2‴‴ & H-3‴‴), 0.95 (t, $J = 7.35$Hz, 1H, H-4‴‴).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 171.2, 169.9, 158.4, 148.9, 148.2, 130.1, 129.8, 129.5, 127.0, 124.4, 121.0, 114.0, 111.2, 111.0, 82.3, 68.1, 61.6, 55.2, 50.7, 41.0, 40.0, 29.1, 20.1, 13.7.

**HRMS:** Calculated for C$_{26}$H$_{29}$N$_3$O$_3$ 431.2209, found 431.2203.
REFERENCES


Section A: Diversity Oriented Approach to Spiroindolines…..


Section A: Diversity Oriented Approach to Spiroindolines.....


35. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html.


Section B

Switching the Regioselectivity via Indium(III) and Gold(I) Catalysis: a Post-Ugi Intramolecular Hydroarylation to Azepino- and Azocino-[c,d]indolones
INTRODUCTION

The tricyclic benzo[c,d]indole alkaloids are a diverse class of natural products and possess a range of chemical structures and a wealth of biological activities.\(^1\) These have attracted substantial interest in recent years (Figure 1),\(^3\) such compounds are isolated from both terrestrial and marine fungi. In addition to the diverse biological activities exhibited by these natural products, their structural diversity is also notable. Some of the representative indole-based natural products that contain tricyclic benzo[c,d]indole cores like lysergic acid (1),\(^4\) clavicipitic acid (2),\(^5\) aurantionclavine (3), communesin F (4),\(^6\) and welwitindolinones (5-9)\(^7\) etc. have been shown in the Figure 1. The welwitindolinones (5-9) are a small group of oxindole alkaloids, these were first isolated by Moore and coworkers from the extracts of the blue-green cyanobacteria *Hapalosiphon wetwitschii* and *Westiella intracta* in 1994.\(^8\) These compounds, possess a unique bicyclo-[4.3.1]decane ring system, were isolated together with the related fisherindoles and hapalindoles, and have a putative biogenetic relationship among these alkaloids. The related alkaloids 3-hydroxy-N-methylwelwitindolinone C isothiocyanate (7), 3-hydroxy-N-methylwelwitindolinone C isonitrile (8), and N-methylwelwitindolinone D isonitrile (9) with the same skeletal framework were later isolated from the cyanophytes *Fischerella muscicola* and *Fischerella major*.\(^9\) Among the welwitindolinones reported, one compound, N-methylwelwitindolinone C isothiocyanate (5), was found interesting, due to its fascinating molecular architecture and its apparent ability to reverse multi-drug resistance (MDR).\(^10\) Despite widespread interest in the development of routes towards welwitindolinones, no total synthesis has emerged to date.\(^11\) Further, Decursivine (12), a tricyclic benzo[c,d]indole natural alkaloid was isolated in 2002 from *Rhaphidophora decursiva*, a plant found in the Cuc Phuong National Park in Vietnam.\(^12\) Spectroscopic analysis of decursivine (12) showed a remarkable resemblance with serotobenine, a natural product isolated from safflower seeds (*Carthamus tinctorius* L.) by Sato and co-workers in 1985.\(^13\) Both decursivine (12) and serotobenine (13) supposedly\(^14\) share a common biosynthesis from serotonin and an appropriately substituted cinnamic acid.\(^15\) The unique heterocyclic structure of tricyclic indole alkaloids, which includes an indole moiety is a significant structural moiety in medicinal chemistry, and has prompted the scientific community to explore the new synthetic routes in order to synthesize their analogues.
Biological importance

Indole-based fused heterocycles belong to the most widely distributed naturally occurring compounds, isolated from plants, fungi and marine organisms. The range of applications for these therapeutically relevant compounds includes protein kinase C inhibitors, 5-HT agonists, melatonin agonists and glucocorticoid receptor modulators, displaying cytotoxic, antiviral, antimicrobial, antiparasitic, antiinflammatory, antiserotonin, Ca²⁺, calmodulin antagonistic and antitopoisomerase-I activities. These polyheterocycles frequently feature structurally diverse novel frameworks and remain a source of new natural product-inspired chemical entities for chemical biology research. Decursivine (12) is an optically active natural indole alkaloid that exhibits antimalarial activity against D6 and W2 clones of *Plasmodium falciparum*. However, the natural structurally related (±)-

Figure 1. Naturally occurring tricyclic indole alkaloids.
serotobenine (13) is not active against *Plasmodium falciparum*.\(^{19}\) Ergot alkaloids are a pharmacologically highly important class of natural products, since they possess a wide spectrum of biological activities.\(^{20}\) Currently, a variety of synthetic analogues have been clinically used as vasodilator, prolactin inhibitor, an anti-Parkinsonian, and other therapeutics. These compounds have been attractive targets for synthetic chemists because of the unique tetracyclic ergoline skeleton containing a tetrahydropyridine and a \([c,d]\)-fused indole.\(^{21}\) Among ergot alkaloids, lysergic acid (1) is pivotal for the synthesis of a variety of its congeners.

Multiple-drug-resistance (MDR) is known to operate via several pathways to diminish the effectiveness of anticancer medicines used in chemotherapy.\(^{22}\) Drug efflux via upregulated production of P-glycoprotein, a membrane transport protein for lipophilic molecules, is the most commonly observed MDR mechanism.\(^{23}\) Agents that inhibit P-glycoprotein and/or are active against MDR cells have significant value in cancer treatment due to their potential applications as single and combination therapies in the treatment of MDR tumors.\(^{24}\) In the study directed towards the family of the welwitindolinone alkaloids (5-9), it was found that *N*-methylwelwitindolinone C isothiocyanate (5) was responsible for the antifungal activity, P-glycoprotein-mediated MDR-reversing and larvacidal activities associated with the algae extracts.\(^{25}\) However, it was later shown that welwitindolinone (5-9) is a cytotoxin itself and inhibits the proliferation of SK-OV-3 and A-10 cells (IC\(_{50}\), 72 and 900 nM, respectively), and more importantly, arrests P-glycoprotein-overexpressing MCF-7/AdR cells (IC\(_{50}\), 130 nM) in the G2 mitotic phase. Moreover, immunofluorescence studies of tubulin organization revealed that *N*-methylwelwitindolinone C isothiocyanate (5) causes dose-dependent disruption of microtubules in intact cells. Additional experimentation suggested that welwitindolinone does not bind to either the colchicine or taxol sites. Thus, this compound represents a new antimicrotubule agent that may be useful for the treatment of drug-resistant tumors.\(^{26}\) Recently Canan Koch *et al.*\(^{27}\) evaluated the potential of novel tricyclic indole derivatives, as potent PARP-1 (PolyADP-ribose polymerase-1, an enzyme responsible for cellular repair and survival)\(^{28}\) inhibitors for the treatment of cancer in combination with selected cytotoxic agents.
Literature reports for the synthesis of tricyclic benzo[c,d]indole derivatives

The remarkable biological properties and fascinating structures of tricyclic benzo[c,d]indole derivatives have stimulated considerable interest in the synthetic community. Many indole-based natural products exhibited a wide variety of important biological activities that made them attractive synthetic targets over the years. The total synthesis of such naturally occurring alkaloids are widely mentioned in literature. Apart from the multistep syntheses, many elegant methods and strategies have been devised and used for the synthesis of their analogues.

The venerable Fischer indole synthesis, which was reported over 100 years ago, still remains of considerable value for its operational simplicity, despite the limited availability of the starting aryl hydrazines. As depicted in Scheme 1, aryl hydrazide (15) having the carbonyl group attached to the meta-position may cyclize into tricyclic benzo[c,d]indole (17) after the hydrazone intermediate (16) is formed.

![Scheme 1](image-url)

Based on above reports, Cho and co-workers have also utilized the above strategy of intramolecular Fischer indolization. It was found that aryl hydrazides (18) that contain a latent carbonyl group tethered to the para-position of the aromatic ring undergoes the Fischer indolization reaction in an intramolecular fashion. Strategic insertion of a C-C double bond in the tether enabled the indole product to form tricyclic benzo-[c,d]indoles (19) in good overall yield by an aromatic [3,3] sigmatropic rearrangement reaction (Scheme 2).

![Scheme 2](image-url)
Recently, Kundu et al.\textsuperscript{33} reported an interesting mild and efficient method for the synthesis of indole-based perifused polycycles through water-accelerated cationic $\pi$-(7-endo-trig) cyclization in water. The strategy involves condensation of arylamine moieties linked to C-4 in indole/azaindole systems with arylaldehydes in water, a catalytic amount of Brønsted acid facilitate cationic $\pi$-cyclisation of the resulting aldimines to furnish indole-annulated sevenmembered rings through the involvement of the nucleophilic indole C-3, which is in the “meta” position relative to C-4 (Scheme 3).

Later, Cuny and co-workers\textsuperscript{34} elaborated a concise two step approach that exploits a Suzuki–Miyaura coupling to introduce ortho-ketoaryls, ketoheteroaryls, or ketocycloalkenes at the C-3 position of indoles, followed by intramolecular $\alpha$-arylation of the ketones to form tetracyclic indole derivatives\textsuperscript{25} (Scheme 4).

![Scheme 3. Water-Assisted Synthesis of Indole-Fused Heterocycles.](image)

![Scheme 4. The intramolecular ketone $\alpha$-arylation.](image)
Nevertheless, the Pd-catalyzed intramolecular α-arylation of ketones has not often been used in indole chemistry, although it may allow the construction of tetracyclic structures in only a few steps.

In recent years, a number of catalytic asymmetric Pictet-Spengler reactions have been developed for the synthesis of optically active six-membered nitrogen-containing heterocycles with high enantioselectivity. A catalytic asymmetric Pictet-Spengler strategy was reported to construct nitrogen-containing heterocycles by replacing the aldehyde with an imine. It was observed that 4-(2-aminoaryl)indoles smoothly undergo the asymmetric Pictet-Spengler-type reaction with imines in the presence of a chiral phosphoric acid to give structurally diverse indolo[3,4-c,d][1]benzazepines in a highly enantioselective manner (Scheme 5).

Scheme 5. Catalytic asymmetric synthesis of indolo[3,4-c,d][1]-benzazepines (27).

An efficient protocol for the synthesis of tricyclic azocino[c,d]indoles (29) was reported by Van der Eycken and co-workers (Scheme 6). The key step in this process was the construction of the eight-membered ring by applying a Pd-catalyzed intramolecular acetylene hydroarylation reaction, which occurs regio- and stereoselectively.

OBJECTIVE AND WORK STRATEGY

Intrigued by its structural complexity and promising biological activity, much attention has been paid to the construction of indole-fused ring systems due to their broad range of interesting biological properties. Catalytic modification of the pyrrole ring of indole has recently emerged as a powerful approach to the construction of indole-fused ring systems. However, they are limited to 1,2- and 2,3-fused indole derivatives.\(^{(42)}\)

![Figure 2](image)

**Figure 2.** Indole-fused ring systems based on the catalytic modification of the pyrrole ring of indole.

Such a structurally complex and diverse alkaloids require a particular protocol, having multistep sequences and having harsh reaction conditions, which is efficient for that particular type while less so for another structurally different class of analogues. Because of interesting targets for their intriguing biological activities and molecular architectures of tricyclic benzo[c,d]indole cores, development of milder, efficient, environmentally benign, diversity oriented and atom economical routes for rapid access to such functionalized indole derivatives under mild conditions are of high demand in organic synthesis. In spite of recent advances, the synthesis of such natural products is often complicated by the lack of adequate synthetic methods for producing the tricyclic azepino- or azocino-[c,d]indolone core. Transition-metal-catalyzed intramolecular cyclizations of aromatic and heteroaromatic compounds with alkynes, is carried out that offer new pathways for the efficient construction of tricyclic benzo[c,d]indole core.\(^{(43)}\) Moreover, gold and indium catalyzed intramolecular reactions under very mild conditions are attaining substantial attention which is attributed to their higher efficiency and straightforward synthetic protocol.\(^{(44)}\) Contrary to other transition-metal-catalysts, gold is an environment friendly, non-hazardous and robust in nature, which often has an remarkable effect on the regio- and chemoselectivity of organic reactions. Inspired by the advancement of intramolecular hydroarylation reactions, biological profile of fused tricyclic benzo[c,d]indole core and our efforts in diversity oriented synthesis of
heterocycles, it would be highly desirable to develop a more versatile and milder route for these compounds. Over the years, multicomponent reactions (MCRs) have received increasing attention due to their simplicity, efficiency, atom economy, shortened reaction times, and the possibility for diversity-oriented synthesis. The combination of MCRs with transition metal-catalysis provides a unique alternative to diversely substituted heterocycles in few steps as compared to traditional multistep processes. Motivated by these findings and as a result of our interest in exploring the synthetic utility of both transition metal catalysis and multicomponent reactions, we envisaged that a post-Ugi regioselective intramolecular hydroarylation reaction could provide an expedient access to azepino- and azocino-[c,d]indolone systems.

We considered that tricyclic azepino/azocino indolones (benzo[c,d]indolones) might be easily accessible by switching the regioselectivity using gold(I) and indium(III) catalysts. A post-Ugi intramolecular hydroarylation reaction of Ugi-adduct 34 using In(OTf)$_3$ as a catalyst in DCE was used for _exo_-dig product 35 and combination of Au(IPr)Cl and AgNTf$_2$ was used as a catalyst in DCE in order to achieve _endo_-dig cyclized product 36. Thus, we have reported a four-component two-step procedure to provide a new, rapid, and environmentally benign catalytic regioselective synthesis of 3,4-fused indole derivatives, benzo[c,d]indoles, through a post-Ugi gold catalyzed intramolecular hydroarylation (Scheme 7). This post-Ugi intramolecular hydroarylation strategy involved the formation of new C-C bonds thereby leading to the formation of fused benzo[c,d]indolones. Thus, we started to investigate the possibility and scope of this reaction.

![Scheme 7](image-url)

_Scheme 7_. Regioselective synthesis of azepino- and azocino-[c,d]indolone systems.
RESULTS AND DISCUSSION

Establishment of reaction condition: As a result of our recent interest in the chemistry of the indole core, the Ugi four-component reaction (4-CR) of indole-4-carbaldehyde (30a) with \( p \)-methoxybenzyl amine (31a), 2-butynoic acid (32a) and tert-butylisonitrile (33a) in methanol at 50 °C gave Ugi-adduct 34a in 98% yield. This was further used for investigating the intramolecular hydroarylation. The application of cationic (Ipr)AuNTf\(_2\) (10 mole%) at 80 °C furnished 40% of azocinoindolone 36a, while heating at 100 °C gave 100% conversion, with an isolated yield of 78% (Table 1, entries 1 and 2). However, employing (Ipr)AuSbF\(_6\), (Ipr)AuOTf, (Ipr)AuBF\(_4\), Au(PPh\(_3\))NTf\(_2\) or Au(Phos)NTf\(_2\) did not improve the yield but led to a mixture of azepinoindolone 35a and azocinoindolone 36a (Table 1, entries 3-7). The application of AuCl\(_3\), AuCl, (Ipr)AuCl, and AgNTf\(_2\) gave almost no conversion (Table 1, entries 8-11). However, these observations encouraged us to further optimize the conditions for the switch of selectivity for the formation of 35a or 36a selectively.

Interestingly, experiments with In(OTf)\(_3\) (10 mole%) at 80 °C for 24 h gave 85% conversion into azepinoindolone 35a, while upon heating at 100 °C, 100% conversion was obtained in 3 h with 35a being the major product in 80% isolated yield (Table 1, entries 12 and 13). Negligible or a very small conversion was observed in case of Bi(OTf)\(_3\), Ln(OTf)\(_3\), Eu(OTf)\(_3\) and PtCl\(_2\) (Table 1, entries 14-17). A change of the solvent when cationic gold was used, decreased the yield and selectivity (Table 1, entries 18 and 19), while for the indium catalyst decomposition of the product was observed (Table 1, entries 20 and 21). Diminishing the catalyst loading to 5 mole% resulted in a decreased conversion in both the cases (Table 1, entries 22 and 23).
### Table 1 Optimization of the intramolecular hydroarylation.\(^a\)

![Diagram](image.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mole %)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Conversion (%) ((35a/36a)^b)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>(Ipr)AuNTf(_2)(10)</td>
<td>DCE</td>
<td>24</td>
<td>80</td>
<td>40 (0/40)</td>
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<tr>
<td>2</td>
<td>(Ipr)AuNTf(_2)(10)</td>
<td>DCE</td>
<td>8</td>
<td>100</td>
<td>100 (0/78)(^c)</td>
</tr>
<tr>
<td>3</td>
<td>(Ipr)AuSbF(_5)(10)</td>
<td>DCE</td>
<td>24</td>
<td>100</td>
<td>100 (15/64)(^c)</td>
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<tr>
<td>4</td>
<td>(Ipr)AuOTf(10)</td>
<td>DCE</td>
<td>24</td>
<td>100</td>
<td>80 (20/60)</td>
</tr>
<tr>
<td>5</td>
<td>(Ipr)AuBF(_3)(10)</td>
<td>DCE</td>
<td>24</td>
<td>100</td>
<td>90 (25/65)</td>
</tr>
<tr>
<td>6</td>
<td>Au(PPh(_3))NTf(_2)(10)</td>
<td>DCE</td>
<td>24</td>
<td>100</td>
<td>50 (20/30)</td>
</tr>
<tr>
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<td>100</td>
<td>80 (50/30)</td>
</tr>
<tr>
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<td>AuCl(_3)(10)</td>
<td>DCE</td>
<td>24</td>
<td>100</td>
<td>0 (0/0)</td>
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<td>100</td>
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<td>100</td>
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<td>11</td>
<td>AgNTf(_2)(10)</td>
<td>DCE</td>
<td>24</td>
<td>100</td>
<td>10 (0/10)</td>
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<td>80</td>
<td>85 (85/0)</td>
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<td>DCE</td>
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<td>100</td>
<td>100 (80/0)(^c)</td>
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<td>60 (10/50)</td>
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<td>100 (58/0)(^c,d)</td>
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<tr>
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<td>100</td>
<td>100 (60/0)(^c,d)</td>
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<td>DCE</td>
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<td>100</td>
<td>50 (0/50)</td>
</tr>
<tr>
<td>23</td>
<td>In(OTf(_3))(5)</td>
<td>DCE</td>
<td>24</td>
<td>100</td>
<td>20 (20/0)</td>
</tr>
</tbody>
</table>

\(^a\)All reactions were run on a 0.1 mmol scale of 34a.\(^b\)Conversion and ratio based on 1H NMR analysis.\(^c\)Isolated yields.\(^d\)Decomposition of the product takes place.
N-(2-(tert-Butylamino)-1-(1H-indol-4-yl)-2-oxoethyl)-N-(4-methoxybenzyl)but-2-ynamide (34a)

The title compound was synthesized by performing Ugi four component reaction from indole-4-carbaldehyde (30a), p-methoxybenzyl amine (31a), 2-butyanoic acid (32a) and tert-butylenonitrile (33a) in methanol at 50 °C. The Ugi-adduct 34a was obtained in 98% of isolated yield as an off-white solid having melting point 105-107 °C. The 1H NMR spectrum suggest the compound appear in the form of rotameric mixture in the ratio of ~1:2. The peak in the range of δ 1.19-1.29, integrating for nine protons (in ratio 1:2) was observed for tert-butyl group (H-2”). The alkynoic methyl group (H-4) was observed as a set of peaks at δ 1.90 and 2.06, while methoxy group appear at δ 3.65-3.70. The presence of two sets of broad singlets at δ 8.39 and 4.22 corresponds to indole –NH group. In the 1H NMR, the peak at δ 5.48 as a broad singlet for one proton was further assigned for amodic –NH group in the compound34a. The 13C NMR spectrum showed characteristic peaks at δ 168.9 and 158.7 for the two carbonyl groups and a set of peaks at δ 28.3 and 28.5, further confirms the presence of tert-butyl group. The peaks for the remaining protons and carbons were also observed in its 1H and 13C NMR spectrum. The compound was further confirmed from its HRMS which showed the peak at 431.2208 for [M⁺] and was in accordance with the calculated value of 431.2209.

On the basis of above spectral studies, the compound 34a was assigned the structure: N-(2-(tert-butylamino)-1-(1H-indol-4-yl)-2-oxoethyl)-N-(4-methoxybenzyl)but-2-ynamide.
**Figure 3.** $^1$H and $^{13}$C NMR spectrum of $N$-(2-(tert-butylamino)-1-(1H-indol-4-yl)-2-oxoethyl)-$N$-(4-methoxybenzyl)but-2-ynamide (34a) in CDCl$_3$. 
Section B: Switching the Regioselectivity via Indium(III) and Gold (I)....

(E)-N-tert-Butyl-3-ethylidene-5-(4-methoxybenzyl)-4-oxo-3,4,5,6-tetrahydro-1H-azepino[5,4,3-\textit{c,d}]indole-6-carboxamide (35a)

The title compound was synthesized by the post-Ugi intramolecular hydroarylation reaction of \( N-(2-(\text{tert}-\text{butylamino})-1-(1H-\text{indol-4-yl})-2-\text{oxoethyl})-N-(4-\text{methoxybenzyl})\text{but-2-ynamide (34a)} \) using catalyst In(OTf)\(_3\) in DCE at 100 °C. The title compound 35a was obtained in 80% of isolated yield as a yellow solid having melting point 103-105 °C. In the \(^1\text{H} \text{NMR} \) spectrum, the disappearance of the rotameric peaks and shift of indole –NH from δ 8.39-8.22 to δ 11.28 clearly indicated the formation of the title compound. Furthermore, appearance of methyl group (H-2‴‴) as doublet at δ 2.11 and corresponding proton H-1‴‴ as a quartet in the aromatic region at δ 6.89-6.72 confirms the presence of exocyclic ring at indole. The \(^{13}\text{C} \text{NMR} \) spectrum showed the characteristic peaks at δ 167.5 and 166.1 for two carbonyl groups. The peak at δ 28.2 confirms the presence of tert-butyl group. In the \(^{13}\text{C} \text{NMR} \) spectrum, the shift of peak from δ 100.0-100.5 (in the precursor 34a) to δ 99.8 was observed, which suggests the cyclization occurs at C-3 position of indole. The peaks for the remaining protons and carbons were also observed in its \(^1\text{H} \text{and}^{13}\text{C} \text{NMR} \) spectrum. The compound was further confirmed from its HRMS which showed the peak at 431.2179 for \([\text{M}^+\) and was in accordance with the calculated value of 431.2209.

On the basis of above spectral studies, the compound 35a was assigned the structure:

\((E)-N-\text{tert-butyl-3-ethylidene-5-(4-methoxybenzyl)-4-oxo-3,4,5,6-tetrahydro-1H-azepino[5,4,3-\textit{c,d}]indole-6-carboxamide.} \)
**Figure 4.** $^1$H and $^{13}$C NMR spectrum of \((E)-N\text{-}\text{tert}-\text{butyl}-3\text{-}\text{ethyldiene}-5\text{-}(4\text{-}\text{methoxybenzyl})\text{-}4\text{-}\text{oxo}-3,4,5,6\text{-}\text{tetrahydro}-1\text{H}\text{-}\text{azepino}[5,4,3\text{-}c,d]\text{indole}-6\text{-}\text{carboxamide (35a)}\) in DMSO-$d_6$. 
Section B: Switching the Regioselectivity via Indium(III) and Gold (I)....

(Z)-N-tert-Butyl-6-(4-methoxybenzyl)-3-methyl-5-oxo-1,5,6,7-tetrahydroazocino[5,4,3-c,d]indole-7-carboxamide (36a)

The title compound was synthesized by the post-Ugi intramolecular hydroarylation reaction of \( N-(2-(tert-butylamino)-1-(1\text{H-indol-4-yl})-2-oxoethyl)-N-(4-methoxybenzyl)\)but-2-ynamide (34a) using catalyst (IPr)AuCl and AgNTf₂, in DCE at 100 °C. The title compound 36a was obtained in 78% of isolated yield as a grey solid having melting point 247-249 °C. In the \(^1\text{H}\) NMR spectrum, the disappearance of the rotameric peaks and shift of indole –NH from \( \delta \) 8.39-8.22 (in the precursor 34a) to \( \delta \) 8.55 clearly indicated the formation of the title compound. Further appearance of methyl group (C-3-CH₃) as a singlet at \( \delta \) 2.28 and adjacent proton (H-4) as a singlet at \( \delta \) 6.21 confirms the presence of endocyclic ring at indole. The chiral proton (H-7) was observed as a singlet at \( \delta \) 5.24. The \(^{13}\text{C}\) NMR spectrum showed the characteristic peaks at \( \delta \) 167.9 and 167.2 for two carbonyl carbons, further a peak at \( \delta \) 28.2 confirms the presence of the tert-butyl group. In the \(^{13}\text{C}\) NMR spectrum, the shift of peak from \( \delta \) 100.0-100.5 (in the precursor 34a) to \( \delta \) 111.3 was observed, which indicates the cyclization takes place at C-3 position of indole moiety. The peaks for the remaining protons and carbons were also observed in its \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectrum. The compound was further confirmed from its HRMS which showed the peak at 431.2319 for [M⁺] and was in accordance with the calculated value of 431.2209.

On the basis of above spectral studies, the compound 36a was assigned the structure: (Z)-N-tert-butyl-6-(4-methoxybenzyl)-3-methyl-5-oxo-1,5,6,7-tetrahydroazocino[5,4,3-c,d]indole-7-carboxamide.
Figure 5. $^1$H and $^{13}$C NMR spectrum of (Z)-N-tert-butyl-6-(4-methoxybenzyl)-3-methyl-5-oxo-1,5,6,7-tetrahydroazocino[5,4,3-c,d]indole-7-carboxamide (36a) in CDCl$_3$. 
Scope of the reaction: Having established the optimized conditions for this regioselective intramolecular hydroarylation, diversely substituted Ugi-adducts 34a-j were synthesized and the substrate scope of the reaction was investigated (Table 2). Mostly the exo-dig cyclization proceeds smoothly when indium was used, giving azepinoindolones 35a-j in good yields. Various substituents on the starting isonitrile, amine, alkyne and indole are well tolerated (Table 2).

Table 2 Substrate scope for regioselective hydroarylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ugi-adduct 34 Yield (%)</th>
<th>Azepinoindolone* Yield (%)</th>
<th>Azocinoindolone* Yield (%)</th>
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<tr>
<td>a</td>
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<td>b</td>
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<td><img src="image" alt="Azepinoindolone 35" /></td>
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<td>e</td>
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<td>g</td>
<td><img src="image" alt="Ugi-adduct 34" /></td>
<td><img src="image" alt="Azepinoindolone 35" /></td>
<td><img src="image" alt="Azocinoindolone 36" /></td>
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</tbody>
</table>
A bulky alkynesubstituent like phenyl is also well tolerated, delivering 35h. Surprisingly the application of a tosyl protected indole did not affect the nucleophilicity of the ring and 35i was obtained in 73% yield.

The same Ugi-adducts 34a-j were subjected to endo-dig cyclization by reaction with cationic gold. Pleasingly, most of the reactions proceeded well and the corresponding azocinoidolones 36 were isolated in good yields (Table 2). Upon using an aliphatic amine or a phenyl substituted alkyneonly 40% and 44% respectively, of the endo-dig cyclized product was observed (Table 2, 36f and 36h). Also with terminal acetylene only a moderate yield of 40% was obtained (Table 2, 36g). Intriguingly, in contrast to the exo-dig cyclization (35i), a tosyl protected indole did not undergo endo-dig cyclization.

To demonstrate the synthetic utility of the developed methodology, propargyl amine was used as the alkyne source for the synthesis of Ugi-adduct 34k. When it was subjected to the intramolecular hydroarylation employing In(OTf)3 in the presence of TFA as co-catalyst and IPr(Au)NTf2, exclusive formation of the exo-dig cycloisomerized product 35k was observed in 62% and 70% yield respectively (Scheme 8).
Mechanistic studies: A plausible mechanism based on literature report is depicted in Scheme 9.

Coordination of the metal with the alkyne in 34a generates intermediate 37. In the case of indium the nucleophilic attack of the indole C-3‴ position on the activated alkyne occurs in an exo-dig fashion generating intermediate 38, which upon deprotonation gives 39 and
this in turn on protodemettalation forms azepinoindolone $35a$. When cationic gold is used, the nucleophilic attack of the indole C-3‴ position on the activated alkyne occurs in an \textit{endo}-dig fashion generating intermediate $40$, which upon deprotonation gives $41$ and this in turn on protodeauration forms azocinoindolone $36$.

**CONCLUSIONS**

In conclusion, we have developed an efficient post-Ugi regioselective intramolecular hydroarylation approach for the synthesis of azepinoindolones and azocinoindolones. Employing indium(III)- and gold(I)-catalysis, the ring closure can be directed towards an \textit{exo}-dig or \textit{endo}-dig cyclization, respectively. Moreover, our efficient synthetic route opens new avenues for regioslective formation of 7 and 8 membered indole fused tricyclic ring having a wide range of functional groups during the Ugi-reaction. We believe that this will provide a better and more practical alternative to the existing methodologies for the synthesis of benzo[cd]indole cores and may find their pharmaceutical applications after further investigations.

**EXPERIMENTAL SECTION**

**Table 3.** Starting materials.

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Amine</th>
<th>2-Alkyne acid</th>
<th>Isonitrile</th>
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</table>
Synthesis of 1-Tosyl-1H-indole-4-carbaldehyde (30c)

To a stirred mixture of sodium hydroxide (416 mg, 3 equiv), tetra-n-butylammonium bisulfate (35 mg), and methylene chloride (10 ml) was added 4-formylindole (500 mg, 3.446 mmol), followed at once by a solution of p-toluenesulfonyl chloride (821 mg, 1.25 equiv) in 5 ml of methylene chloride. During addition, the internal temperature was maintained at 5-10°C. The reaction mixture was stirred at this temperature for 30 minutes and completion of reaction was checked using TLC (15% ethyl acetate in heptane). On completion of the reaction, the mixture was diluted with dichloromethane (100 mL) and was extracted with water (50 mL). Organic layer was washed with brine (50 mL), dried over magnesium sulfate and evaporated under reduced pressure to obtain residue which was subjected to silica gel column chromatography (15% ethylacetate in heptane) to afford the desired product 30c as solid.

White solid; Yield 73%; Melting point: 143-145°C.

$^1$H NMR (300 MHz, CDCl$_3$): δ 10.17 (s, 1H, -CHO), 8.27 (d, J= 8.28Hz, 1H, H-7), 7.78-7.71 (m, 4H, H-2, H-5, H-2′ & H-6′), 7.50-7.48 (m, 2H, H-3 & H-6), 7.24 (d, J= 8.26Hz, 2H, H-3′ & H-5′), 2.34 (s, 3H, -CH$_3$).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 192.2, 145.4, 135.3, 134.9, 130.0, 129.4(2), 128.9, 128.8, 126.8, 124.2, 119.2, 108.4, 21.5.

HRMS: Calculated for C$_{16}$H$_{13}$NO$_3$S 299.0616, found 299.0603.

General procedure for synthesis of Ugi products34a-k.

To a solution of carbaldehyde 30a-d (200mg, 1 equiv) in methanol (3 mL) were added successively Na$_2$SO$_4$ (0.3g), amine 31a-e (1.2 equiv), acid 32a-e (1.2 equiv) and isonitrile 33a-b (1.2 equiv) in a screw capped vial equipped with a magnetic stir bar.
The reaction mixture was stirred at 50 °C temperature for 12-24 hr in closed vial. After completion of the reaction, the mixture was diluted with EtOAc (100 mL) and was extracted with water (50 mL). Organic layer was washed with brine (50 mL), dried over magnesium sulfate and evaporated under reduced pressure to obtain residue which was subjected to silica gel column chromatography (80% EtOAc in Heptane) to afford the desired product **34a-k** as solid.

Ugi products appear as mixture of two rotamers, so $^1$H and $^{13}$C NMR spectra are not very characteristic.

**N-(2-(tert-Butylamino)-1-(1H-indol-4-yl)-2-oxoethyl)-N-(4-methoxybenzyl)but-2-ynamide (34a)**

![Chemical structure](image)

Off-white solid; Yield 98% (mixture of rotamers ~ 1:2); Melting point: 105-107°C.

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.39 (bs, 0.35H, -NH), 8.22 (bs, 0.64H, -NH), 7.40 (d, $J$= 8.03Hz, 0.34H, H-7’’’’), 7.26-7.06 (m, 4H, H-2’, H-6’, H-2''’’, H-5’’’ & H-7’’’’), 6.90 (d, $J$= 8.16Hz, 0.66H, H-2’’’’), 6.69-6.60 (m, 2H, H-3’ & H-5’), 6.46-6.43 (m, 2.39H, H-1’’’, H-3’’’ & H-6’’’’), 6.35 (s, 0.63H, H-1’”), 5.48 (bs, 1H, -CONH), 4.94 (d, $J$= 16.28Hz, 0.65H, H$_a$/H$_b$), 4.68-4.56 (m, 1H, H$_a$/H$_b$), 3.88 (d, $J$= 15.03Hz, 0.35H, H$_a$/H$_b$), 3.70-3.65 (m, 3H, -OMe), 2.06 (s, 1H, H-4), 1.90 (m, 2H, H-4), 1.29 (s, 6H, H-2’’’’’), 1.19 (s, 3H, H-2’’’’’’).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 168.9, 168.5, 158.7, 158.1, 156.4, 156.2, 136.0, 135.7, 130.2, 130.1, 129.7, 128.2(2), 125.8, 125.6, 125.4, 125.0, 121.6, 120.5(2), 113.6, 113.0, 112.3, 111.9, 100.5, 100.0, 91.7, 90.2, 74.1, 73.4, 66.2, 60.1, 55.2, 55.1, 51.5, 51.4, 50.6, 45.3, 28.5, 28.3, 4.1, 4.0.

HRMS: Calculated for C$_{28}$H$_{29}$N$_3$O$_3$ 431.2209, found 431.2208.
N-(2-(Cyclohexylamino)-1-(1H-indol-4-yl)-2-oxoethyl)-N-(4-methoxybenzyl)but-2-ynamide (34b)

Offwhite solid; Yield 87% (mixture of rotamers ~ 1:1); Melting point: 84-86 °C.

^1^H NMR (300 MHz, DMSO-d_6): δ 11.13-11.08 (m, 1H, -NH), 8.19 (d, J= 7.28Hz, 0.47H, -CONH), 8.08 (d, J= 7.28Hz, 0.51H, -CONH), 7.35-7.25 (m, 2H, H-2'''' & H-7''''), 7.08-6.85 (m, 2H, H-2' & H-6'), 6.62-6.59 (m, 1H, H-5''''), 6.47-6.28 (m, 5H, H-3', H-5', H-1'', H-3'''' & H-6''), 4.74 (d, J= 16.26Hz, 0.48H, H_a/H_b), 4.61-4.53 (m, 1H, H_a/H_b), 4.22 (d, J= 15.39Hz, 0.47H, H_a/H_b), 3.68-3.59 (m, 4H, CyH& -OMe), 2.04 (s, 1.49H, H-4), 1.86 (s, 1.50H, H-4), 1.63 (m, 6H, CyH), 1.14-1.06 (m, 4H, CyH).

^13^C NMR (75.5 MHz, DMSO-d_6): δ 168.2, 167.9, 157.4, 157.2, 155.0, 154.6, 135.8, 135.7, 130.3, 130.1, 128.4, 127.7, 127.0, 126.9, 125.5, 125.3, 120.6(2), 118.7, 118.6, 112.5, 112.3, 111.7, 111.4, 99.4, 99.3, 89.9, 89.7, 74.3, 73.4, 63.2, 58.4, 54.8, 54.7, 49.5, 47.7, 47.6, 46.7, 34.8, 32.1, 31.9, 25.8, 25.7, 25.1, 24.5, 24.4, 3.5, 3.2.

HRMS: Calculated for C_{28}H_{31}N_{3}O_{5} 457.2365, found 332.1527 (M-125).

N-(2-(tert-Butylamino)-1-(1H-indol-4-yl)-2-oxoethyl)-N-(4-methoxybenzyl)pent-2-ynamide (34c)

Offwhite solid; Yield 80% (mixture of rotamers ~ 1:1); Melting point: 69-71°C.
Section B: Switching the Regioselectivity via Indium(III) and Gold (I)...

¹H NMR (300 MHz, DMSO-d₆): δ 11.09-11.06 (m, 1H, -NH), 7.96 (s, 0.48H, -CONH), 7.85 (s, 0.51H, -CONH), 7.34-7.25 (m, 2H, H-2' & H-6'), 7.10-6.89 (m, 2H, H-2'' & H-7''), 6.72 (d, J= 8.74Hz, 0.35H, H-5''), 6.59 (d, J= 8.58Hz, 1H, H-5'' & H-3''), 6.48-6.30 (m, 4.65H, H-3', H-5', H-1'', H-3'''&H-6'''), 4.76 (d, J= 16.63Hz, 0.39H, H₆/H₇), 4.62-4.52 (m, 1H, H₈/H₉), 4.15 (d, J= 15.35Hz, 0.39H, H₈/H₉), 3.58-3.55 (m, 3H, -OMe), 2.46-2.39 (m, 1H, H-4), 2.24-2.17 (m, 1H, H-4), 1.26-1.21 (m, 9H, H-2''''), 0.93-0.83 (m, 3H, H-5).

¹³C NMR (75.5 MHz, DMSO-d₆): δ 168.9, 168.6, 157.3, 157.2, 155.1, 154.7, 135.8, 135.7, 130.5, 130.1, 128.3, 127.9, 127.8, 127.5, 127.2, 125.4, 125.2, 120.6, 120.5, 118.7(2), 112.5, 112.2, 111.6, 111.3, 99.6, 99.5, 94.5, 94.2, 74.6, 73.5, 63.4, 58.5, 54.8, 54.7, 50.4, 50.3, 49.5, 46.9, 28.3(2), 12.6, 12.4, 11.9, 11.6.

HRMS: Calculated for C₂₇H₃₁N₃O₃ 445.2365, found 445.2344.

N-(2-(tert-Butylamino)-1-(1-methyl-1H-indol-4-yl)-2-oxoethyl)-N-(4-methoxybenzyl)but-2-ynamide (34d)

Yellow solid; Yield 93% (mixture of rotamers ~ 1:1); Melting point: 59-61°C.

¹H NMR (300 MHz, DMSO-d₆): δ 7.96 (s, 0.45H, -NH), 7.84 (s, 0.53H, -NH), 7.37 (d, J= 8.29Hz, 0.52H, H-7''), 7.30-7.24 (m, 1.44H, H-2'' & H-7''), 7.14-6.91 (m, 2H, H-2' & H-6'), 6.82-6.56 (m, 2H, H-5'' & H-6''), 6.45-6.38 (m, 3H, H-3'H-5'& H-3''''), 6.29-6.25 (m 1H, H-1''), 4.79 (d, J= 16.57Hz, 0.51H, H₆/H₇), 4.63-4.50 (m, 1H, H₈/H₉), 4.14 (d, J= 15.50Hz, 0.48H, H₈/H₉), 3.73-3.71 (m, 3H, -OMe), 3.59-3.57 (m, 3H, -NMe), 2.05 (s, 1.51H, H-4), 1.87 (s, 1.50H, H-4), 1.25-1.20 (m, 9H, H-2'''').

¹³C NMR (75.5 MHz, DMSO-d₆): δ 168.8, 168.5, 157.3, 157.2, 155.0, 154.8, 136.4, 130.6, 130.2, 130.1, 129.6, 129.4, 128.3, 128.2, 127.5, 127.4, 120.7, 120.6, 118.9, 118.7, 112.4, 112.2, 109.9, 109.6, 98.9, 98.8, 90.0, 89.6, 74.4, 73.4, 63.2, 58.4, 54.8, 54.7, 50.4, 50.3, 49.6, 46.8, 32.4(2), 28.3(2), 3.6, 3.2.

HRMS: Calculated for C₂₇H₃₁N₃O₃ 445.2365, found 445.2369.
N-(2-(tert-butylamino)-1-(1H-indol-4-yl)-2-oxoethyl)-N-(3,4-dimethoxybenzyl)but-2-ynamide (34e)

Offwhite solid; Yield 92% (mixture of rotamers ~ 1:1); Melting point: 129-131°C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.16-11.10 (m, 1H, -NH), 7.93 (s, 0.48H, -CONH), 7.80 (s, 0.51H, -CONH), 7.36-7.27 (m, 2H, H-5‴& H-7‴), 7.11-6.92 (m, 2H, H-2‴ & H-6‴), 6.54-6.26 (m, 4H, H-2′, H-5′, H-6′ & H-3‴), 5.92 (s, 0.50H, H-1″), 5.74 (s, 0.49H, H-1″), 7.74 (d, $J = 16.50$Hz, 0.49H, H$_d$/H$_b$), 4.63-4.56 (m, 1H, H$_a$/H$_b$), 4.21 (d, $J = 15.51$Hz, 0.43H, H$_d$/H$_b$), 3.57-3.55 (m, 3H, -OMe), 3.25-3.22 (m, 3H, -OMe), 2.08 (s, 2H, H-4), 1.84 (s, 1H, H-4), 1.27 (s, 4H, H-2‴″), 1.22 (s, 5H, H-2‴″).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 169.1, 168.7, 155.1, 154.6, 147.7, 147.5, 146.8, 146.7, 135.8, 135.7, 131.2, 130.8, 128.0, 127.9, 127.4, 127.2, 125.5, 125.3, 120.7, 119.8, 119.0, 118.9, 118.8, 111.7, 111.4, 110.8, 110.5, 109.9, 99.7, 99.6, 89.8, 89.7, 74.5, 73.4, 63.2, 58.2, 55.3, 54.4, 50.3(2), 49.9, 47.4, 30.6, 28.3(2), 3.5, 3.2.

HRMS: Calculated for C$_{27}$H$_{31}$N$_3$O$_4$ 461.2315, found 461.2319.

N-Butyl-N-(2-(cyclohexylamino)-1-(1H-indol-4-yl)-2-oxoethyl)but-2-ynamide (34f)

Yellow solid; Yield 62% (mixture of rotamers ~ 2:3); Melting point: 206-208 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.23-11.19 (m, 1H, -NH), 8.18 (d, $J = 7.04$Hz, 0.40H, -CONH), 8.08 (d, $J = 7.04$Hz, 0.59H, -CONH), 7.40-7.37 (m, 2H, H-5‴″ & H-
7′′′), 7.09-7.07 (m, 1H, H-2′′′′), 6.90 (bs, 1H, H-6′′′′), 6.39-6.38 (m, 1.39H, H-1′′ & H-3′′′′), 6.25 (s, 0.60H, H-1′″), 3.61 (m, 1H, CyH), 3.21-3.07 (m, 2H, H-1′), 2.08-1.99 (m, 3H, H-4), 1.65-1.52 (m, 6H, H-2′&CyH), 1.23-1.06 (m, 6H, H-3′ &CyH), 0.82-0.75 (m, 2H, CyH), 0.47-0.40 (m, 3H, H-4′).

\[^{13}\text{C} \text{ NMR (75.5 MHz, DMSO-d}_6\text{):}\] δ 168.2, 168.0, 154.1, 153.9, 135.7, 135.6, 127.8, 127.5, 127.3, 126.9, 125.7, 125.5, 120.7, 118.6, 111.7, 111.5, 99.2, 89.3, 88.4, 73.9, 73.5, 62.9, 57.6, 47.7, 47.6, 46.3, 43.8, 32.2, 32.0, 31.3, 29.1, 25.1, 24.6, 24.4, 19.4, 19.3, 13.2, 13.1, 3.50, 3.20.

HRMS: Calculated for C\(_{24}\)H\(_{31}\)N\(_3\)O\(_2\) 393.2416, found 393.2429.

\(N\)-(2-(tert-Butylamino)-1-(1H-indol-4-yl)-2-oxoethyl)-N-(3,4-dimethoxybenzyl)propiolamide(34g)

\[
\begin{align*}
\text{Offwhite solid; Yield 91% (mixture of rotamers ~ 1:1); Melting point: 135-137 °C.}
\end{align*}
\]

\[^{1}\text{H} \text{ NMR (300 MHz, DMSO-d}_6\text{):}\] δ 11.18-11.08 (m, 1H, -NH), 7.99 (s, 0.48H, -CONH), 7.85 (s, 0.51H, -CONH), 7.37-7.24 (m, 2H, H-5′′′ & H-7′′′′), 7.80 (t, \(J=8.29\)Hz, 0.51H, H-6′′′′), 7.02-6.90 (m, 1.51H, H-6′′′′ & H-2′′′′), 6.51-6.45 (m, 2.50H, H-2′, H-5′, &H-6′′), 6.35-6.27 (m, 1.50H, H-5′ & H-3′′′'), 6.01 (s, 0.51H, H-1′′′′), 5.69 (s, 0.49H, H-1′′′′), 4.81 (d, \(J=16.81\)Hz, 0.50H, H\(_a\)/H\(_b\)), 4.69-4.60 (m, 1H, H\(_a\)/H\(_b\)), 4.39 (s, 0.46H, H\(_a\)/H\(_b\)), 4.25 (d, \(J=15.87\)Hz, 0.50H, H\(_a\)/H\(_b\)), 3.57-3.55 (m, 3.41H, -OMe), 3.31 (s, 2H, H-3 & -OMe), 3.20 (s, 1.51H, H-3 & -OMe), 1.26-1.21 (m, 9H, H-2′′′′).

\[^{13}\text{C} \text{ NMR (75.5 MHz, DMSO-d}_6\text{):}\] δ 168.6, 168.4, 154.3, 153.7, 147.6(2), 146.8(2), 135.9, 135.7, 130.5, 130.4, 128.0, 127.9, 127.1, 126.9, 125.7, 125.3, 120.7, 120.6, 119.9, 118.9(2), 118.7, 111.9, 111.5, 110.8, 110.7, 110.4, 109.8, 99.6(2), 82.6, 82.4, 76.9, 76.0, 63.3, 58.3, 55.3, 54.8, 54.6, 54.5, 50.5, 50.4, 49.8, 47.6, 28.3(2).

HRMS: Calculated for C\(_{26}\)H\(_{29}\)N\(_3\)O\(_4\) 447.2158, found 447.2180.
N-(2-(tert-Butylamino)-1-(1H-indol-4-yl)-2-oxoethyl)-N-(4-methoxybenzyl)-3-phenylpropiolamide (34h)

Offwhite solid; Yield 76% (mixture of rotamers ~ 1:1); Melting point: 85-87 °C.

**^1H NMR (300 MHz, DMSO-\(d_6\)):** \(\delta\) 11.11 (bs, 1H, -NH), 8.14 (s, 0.53H, -CONH), 7.94 (s, 0.47H, -CONH), 7.72 (d, \(J = 7.09\)Hz, 1H, H-7’’’), 7.53-7.28 (m, 6H, H-2’, H-3’, H-5’, H-6’, H-2” & H-6”), 7.12-6.94 (m, 2H, H-4’ & H-6’’’), 6.69 (d, \(J = 8.56\)Hz, 1H, H-5’’’), 6.58-6.55 (m, 1H, H-2’’’), 6.48-6.37 (m, 4H, H-3”, H-5”, H-1’” & H-3’’’), 4.88 (d, \(J = 16.61\)Hz, 0.39H, H\(_d/H_b\)), 4.72-4.62 (m, 1H, H\(_d/H_b\)), 4.22 (d, \(J = 15.31\)Hz, 0.52H, H\(_d/H_b\)), 3.57 (s, 3H, -OMe), 1.24-1.23 (m, 9H, H-2’’’).

**^13C NMR (75.5 MHz, DMSO-\(d_6\)):** \(\delta\) 168.8, 168.5, 157.4, 157.3, 155.0, 154.6, 135.8, 135.7, 132.7, 132.0, 130.6, 130.5, 130.4, 129.9, 128.7, 128.4, 127.9, 127.4, 127.1, 125.5, 125.4, 120.6, 119.7, 118.9, 112.7, 111.7, 111.5, 99.6, 99.4, 89.7, 89.5, 82.9, 81.9, 63.7, 58.7, 54.8, 54.7, 50.4, 28.3, 28.2.

**HRMS:** Calculated for C\(_{31}\)H\(_{31}\)N\(_3\)O\(_5\) 493.2365, found 493.2360.

N-(2-(tert-Butylamino)-2-oxo-1-(1-tosyl-1H-indol-4-yl)ethyl)-N-(4-methoxybenzyl)but-2-ynamide (34i)

White solid; Yield 68% (mixture of rotamers ~ 1:1); Melting point: 91-93 °C.
Section B: Switching the Regioselectivity via Indium(III) and Gold (I)…. 

\[ \text{H NMR (300 MHz, DMSO-}d_6\text{):} \delta 7.97 \text{ (s, 0.45H, -CONH), 7.88-7.83 (m, 3H, -CONH, H-7'''', H-2''' & H-6'''), 7.75-7.72 (m, 1.55H, H-7''' & H-2'''), 7.40-7.30 (m, 2.54H, H-2', H-6' & H-6'''), 7.23 (t, J = 8.18Hz, 0.47H, H-6'''), 7.16 (d, J = 7.59Hz, 0.47H, H-5''''), 7.09 (d, J = 7.59Hz, 0.55H, H-5'''), 6.55-6.51 (m, 1H, H-3''''), 6.37-6.36 (m, 2H, H-3'''' & H-5'''''), 6.28-6.19 (m, 3H, H-3', H-5' & H-1'''), 4.87 (d, J = 16.63Hz, 0.53H, H_\alpha/H_\beta), 4.72 (d, J = 15.20Hz, 0.45H, H_\alpha/H_\beta), 4.48 (d, J = 16.63Hz, 0.54H, H_\alpha/H_\beta), 4.01 (d, J = 15.20Hz, 0.48H, H_\alpha/H_\beta), 3.59-3.57 (m, 3H, -OMe), 2.32 (s, 3H, -CH_3), 2.03 (s, 1.40H, H-4), 1.88 (s, 1.61H, H-4), 1.23-1.18 (m, 9H, H-2'''''). 

\[ \text{C NMR (75.5 MHz, DMSO-}d_6\text{):} \delta 168.2, 167.9, 157.4, 157.3, 154.9, 154.6, 145.5, 134.3, 134.2, 133.8, 133.6, 130.7, 130.6, 130.2, 129.8, 129.7, 129.1, 128.8, 128.0, 127.2, 126.9, 126.7(2), 124.5, 124.3, 122.9, 122.8, 113.1, 112.8, 112.5, 112.3, 107.1(2), 90.5, 90.0, 74.0, 73.0, 62.0, 57.1, 54.8, 54.7, 50.4(2), 28.2(2), 20.9, 3.5, 3.2. 

HRMS: Calculated for C_{33}H_{33}N_{5}O_{5}S_{5}85.2297, found 485.1051 (M-100).

\[ \text{N-}((1H-Indol-4-yl)methyl)-\text{N-}(2-\text{(}tert\text{-butylamino)}\text{-2-oxo-1-phenylethyl))but-2-yramid (34j) } \]

White solid; Yield 84% (mixture of rotamers – 2:3); Melting point: 83-85 °C.

\[ \text{H NMR (300 MHz, DMSO-}d_6\text{):} \delta 11.02-10.97 (m, 1H, -NH), 7.88 (s, 0.43H, -CONH), 7.65 (s, 0.58H, -CONH), 7.24-7.12 (m, 7H, H-2'', H-3'', H-4'', H-5'', H-6'', H-5''' & H-7'''''), 6.90 (t, J = 7.61Hz, 0.55H, H-6'''''), 6.82 (t, J = 7.61Hz, 0.44H, H-6''''), 6.61 (d, J = 7.08Hz, 0.55H, H-2''''), 6.46 (d, J = 7.08Hz, 0.39H, H-2'''''), 6.35 (bs, 0.57H, H-3''''), 6.26 (bs, 0.42H, H-3'''''), 6.12 (s, 0.40H, H-1''), 5.89 (s, 0.54H, H-1''), 5.26 (d, J = 17.24Hz, 0.50H, H_\alpha/H_\beta), 4.96-4.86 (m, 1H, H_\alpha/H_\beta), 4.59 (d, J = 16.43Hz, 0.37H, H_\alpha/H_\beta), 2.03 (s, 1.30H, H-4), 1.71 (s, 1.70H, H-4), 1.19 (s, 4H, H-2'''), 1.10 (s, 5H, H-2'''). \]
13C NMR (75.5 MHz, DMSO-d6): δ 168.2, 167.9, 155.3, 154.8, 135.8(2), 135.4, 135.3, 129.4, 128.9, 128.8(2), 128.0, 127.9, 127.7, 127.5, 125.0, 124.9, 124.7, 124.5, 120.5, 120.3, 116.0, 115.7, 109.8, 109.4, 98.8, 98.7, 90.2, 89.1, 74.1, 73.6, 64.8, 61.3, 50.4, 50.2, 48.4, 45.3, 28.1(2), 3.6, 3.2.

HRMS: Calculated for C_{23}H_{27}N_{5}O_{2} 401.2103, found 401.2117.

N-tert-Butyl-2-(1H-indol-4-yl)-2-(2-phenyl-N-(prop-2-ynyl)acetamido)acetamide (34k)

Offwhite solid; Yield 64% (mixture of rotamers ~ 1:3); Melting point: 80-82 °C.

1H NMR (300 MHz, DMSO-d6): δ 11.12 (bs, 1H, -NH), 8.02 (s, 0.25H, -CONH), 7.88 (s, 0.73H, -CONH), 7.38-7.24 (m, 7H, H-2′′′, H-3′′′, H-4′′′, H-5′′′, H-6′′′, H-5′′′′ & H-7′′′′), 7.07 (t, J = 7.75Hz, 1H, H-6′′′′), 6.90 (d, J = 7.17Hz, 1H, H-2′′′′), 6.51 (s, 0.69H, H-2), 6.28-6.22 (m, 1H, H-3′′′′), 6.06 (s, 0.22H, H-2), 4.14-3.77 (m, 4H, H-2′ & H-1′′′), 2.71 (s, 0.62H, H-3′′′′), 2.46 (s, 0.40H, H-3′′′′), 1.29-1.27 (m, 9H, H-2′′′′).

13C NMR (75.5 MHz, DMSO-d6): δ 170.8, 170.6, 169.2, 168.5, 135.9, 135.8, 135.6, 129.4, 128.1, 127.8, 126.3, 125.1, 120.6, 118.3, 118.2, 111.7, 111.5, 99.9, 99.7, 73.3, 71.5, 62.4, 58.0, 54.8, 50.6, 50.4, 34.6, 33.8, 28.4, 28.3.

HRMS: Calculated for C_{23}H_{27}N_{5}O_{2} 401.2103, found 401.2098.

Method A: General procedure for In(OTf)_3 catalyzed cyclization.

To a glass vial In(OTf)_3 (10 mole%) was loaded along with dry dichloroethane (2 mL). Ugi product 34a-j (0.25 mmol) was added. The reaction vial was evacuated-backfilled with argon (4 cycles) and was stirred at 100 °C until completion of reaction. After completion, reaction mixture was partitioned between EtOAc (100 mL) and water (50 mL). Organic layer was washed with brine (50 mL), dried over magnesium sulfate and
evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (3% methanol in dichloromethane) to afford compound 35a-j.

(E)-N-tert-Butyl-3-ethylidene-5-(4-methoxybenzyl)-4-oxo-3,4,5,6-tetrahydro-1H-azepino[5,4,3-c,d]indole-6-carboxamide (35a)

Yellow solid; Yield 80%; Melting point: 103-105 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.28 (s, 1H, -NH), 8.08 (s, 1H, -CONH), 7.42-7.39 (m, 2H, H-2 & H-7), 7.29 (d, $J$ = 8.63Hz, 1H, H-9), 7.19 (d, $J$ = 8.54Hz, 2H, H-2″ & H-6″), 6.89-6.72 (m, 4H, H-8, H-3″, H-5″ & H-1″″), 5.38 (s, 1H, H-6), 4.93 (d, $J$ = 15.23Hz, 1H, H$_b$), 4.19 (d, $J$ = 15.23Hz, 1H, H$_b$), 3.67 (s, 3H, -OMe), 2.11 (d, $J$ = 7.65Hz, 3H, H-2″″), 1.10 (s, 9H, H-2″″).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): δ 167.5, 166.1, 158.3, 134.6, 130.5, 129.7, 128.6, 128.2, 126.0, 124.4, 123.2, 122.2, 120.4, 113.6, 110.8, 99.8, 62.9, 54.9, 50.5, 48.3, 28.2, 15.5.

HRMS: Calculated for C$_{26}$H$_{29}$N$_3$O$_3$ 431.2209, found 431.2179.

(E)-N-Cyclohexyl-3-ethylidene-5-(4-methoxybenzyl)-4-oxo-3,4,5,6-tetrahydro-1H-azepino[5,4,3-c,d]indole-6-carboxamide (35b)

Offwhite solid; Yield 70%; Melting point: 108-110 °C.
\textbf{1H NMR (300 MHz, DMSO-\textit{d}_6):} δ11.28 (s, 1H, -NH), 8.25 (d, J = 8.00Hz, 1H, -CONH), 7.41-7.38 (m, 2H, H-2 & H-7), 7.27 (d, J = 8.62Hz, 1H, H-9), 7.17 (d, J = 8.52Hz, 2H, H-2'' & H-6''), 6.84-6.71 (m, 4H, H-8, H-3'', H-5'' & H-1'''), 5.31 (s, 1H, H-1), 2.09 (d, J = 15.03Hz, 1H, H_a), 4.16 (d, J = 15.03Hz, 1H, H_b), 3.68 (s, 3H, -OMe), 3.33 (m, 1H, H-1'), 2.09 (d, J = 7.57Hz, 3H, H-2''), 1.62-1.42 (m, 5H, C\textit{CyH}), 1.12-1.09 (m, 5H, C\textit{CyH}).

\textbf{13C NMR (75.5 MHz, DMSO-\textit{d}_6):} δ 167.2, 166.4, 158.3, 134.6, 130.6, 129.4, 128.7, 128.4, 126.0, 124.4, 123.0, 122.3, 120.4, 113.6, 110.8, 99.8, 62.3, 54.9, 48.4, 47.9, 32.2, 32.0, 25.1, 24.2, 24.1, 15.4.

\textbf{HRMS:} Calculated for C_{28}H_{31}N_{5}O_{3} 457.2365, found 457.2349.

\textit{(E)-N-tert-Butyl-5-(4-methoxybenzyl)-4-oxo-3-propylidene-3,4,5,6-tetrahydro-1H-azepino[5,4,3-c,d]indole-6-carboxamide (35c)}

Brown solid; Yield 69%; Melting point: 77-79 °C.

\textbf{1H NMR (300 MHz, DMSO-\textit{d}_6):} δ11.29 (bs, 1H, -NH), 8.06 (s, 1H, -CONH), 7.41-7.39 (m, 2H, H-2 & H-7), 7.24-7.18 (m, 3H, H-9, H-2'' & H-6''), 6.84-6.81 (m, 3H, H-3'', H-5'' & H-1'''), 6.60 (t, J = 7.55Hz, 1H, H-8), 5.38 (s, 1H, H-6), 4.95 (d, J = 15.06Hz, 1H, H_a), 4.17 (d, J = 15.06Hz, 1H, H_b), 3.67 (s, 3H, -OMe), 2.68-2.58 (m, 1H, H-2''), 1.64-1.58 (m, 1H, H-2''), 1.24 (t, J = 7.10Hz, 3H, H-3''), 1.11 (s, 9H, H-2').

\textbf{13C NMR (75.5 MHz, DMSO-\textit{d}_6):} δ 167.5, 166.2, 158.3, 135.6, 134.7, 129.7, 129.0, 128.6, 126.0, 124.4, 123.2, 122.4, 120.2, 113.6, 110.9, 99.9, 63.0, 55.0, 50.5, 48.4, 28.2, 22.4, 14.2.

\textbf{HRMS:} Calculated for C_{27}H_{31}N_{5}O_{3} 445.2365, found 445.2398.
(E)-N-tert-Butyl-3-ethyldiene-5-(4-methoxybenzyl)-1-methyl-4-oxo-3,4,5,6-tetrahydro-1H-azepino[5,4,c,d]indole-6-carboxamide (35d)

Yellow solid; Yield 80%; Melting point: 75-77 °C.

\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 8.06 (s, 1H, -CONH), 7.46-7.33 (m, 3H, H-2, H-7 & H-9), 7.17 (d, \(J = 7.69\) Hz, 2H, H-2'' & H-6''), 6.82-6.76 (m, 4H, H-8, H-3'', H-5'' & H-1'''), 5.38 (s, 1H, H-6), 4.93 (d, \(J = 15.24\) Hz, 1H, H_a), 4.19 (d, \(J = 15.24\) Hz, 1H, H_b), 3.79 (s, 3H, -OMe), 3.67 (s, 3H, -NCH_3), 2.11 (d, \(J = 7.11\) Hz, 3H, H-2''), 1.10 (s, 9H, H-2'').

\(^{13}\)C NMR (75.5 MHz, DMSO-\(d_6\)): \(\delta\) 167.5, 166.2, 158.3, 135.1, 130.4, 130.3, 129.7, 128.6, 124.7, 123.5, 122.4, 120.4, 113.6, 109.2, 99.1, 62.8, 55.0, 50.5, 48.4, 32.6, 28.2, 15.5.

HRMS: Calculated for C_{27}H_{31}N_3O_3 445.2365, found 445.2393.

(E)-N-tert-Butyl-5-(3,4-dimethoxybenzyl)-3-ethyldiene-4-oxo-3,4,5,6-tetrahydro-1H-azepino[5,4,c,d]indole-6-carboxamide (35e)

White solid; Yield 89%; Melting point: 219-221 °C.

\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 11.28 (bs, 1H, -NH), 8.00 (s, 1H, -CONH), 7.42-7.39 (m, 2H, H-2 & H-7), 7.29 (d, \(J = 8.54\) Hz, 1H, H-9), 6.89 (s, 1H, H-2''), 6.83-6.81 (m, 2H, H-8, H-6''), 6.74-6.71 (m, 2H, H-5'' & H-1'''), 5.38 (s, 1H, H-6), 4.91 (d, \(J = 15.40\) Hz, 1H, H_a), 4.24 (d, \(J = 15.40\) Hz, 1H, H_b), 3.66-3.64 (m, 6H, -OMe), 2.11 (d, \(J = 7.65\) Hz, 3H, H-2''), 1.09 (s, 9H, H-2'').
**Section B: Switching the Regioselectivity via Indium(III) and Gold (I)....**

\(^{13}\text{C\ NMR (75.5 MHz, DMSO-}d_6\):} \delta 167.5, 166.3, 148.5, 147.9, 134.6, 130.6, 130.1, 128.3, 126.0, 124.4, 123.3, 122.3, 120.4, 119.1, 111.7, 111.6, 110.8, 99.8, 63.0, 55.5, 55.3, 50.5, 48.7, 28.2, 15.5.

**HRMS:** Calculated for \( \text{C}_{27}\text{H}_{31}\text{N}_5\text{O}_4 \) 461.2315, found 461.2323.

\((E)-5\text{-Butyl-}\text{N-cyclohexyl-3-ethylidene-4-oxo-3,4,5,6-tetrahydro-1H-azepino[5,4,3-}
\text{c,d} \text{]indole-6-carboxamide (35f)}\)

Brown solid; Yield 86%; Melting point: 95-97 °C.

\(^1\text{H\ NMR (300 MHz, DMSO-}d_6\):} \delta 1.28 (bs, 1H, -NH), 8.36 (d, \( J = 7.57\text{Hz} \), 1H, H-2), 7.41-7.38 (m, 2H, H-7 & H-8), 7.25 (d, \( J = 8.41\text{Hz} \), 1H, H-9), 6.88 (s, 1H, H-2), 6.67 (q, \( J = 7.48\text{Hz} \), 1H, H-1”), 5.33 (s, 1H, H-6), 3.60-3.58 (m, 1H, CyH), 3.33 (m, 1H, H-1”), 3.22 (m, 1H, H-1”), 2.06 (d, \( J = 7.30\text{Hz} \), 3H, H-2”), 1.78-1.48 (m, 7H, H-2” & CyH), 1.23-1.15 (m, 7H, H-3” & CyH), 0.87 (t, \( J = 6.75\text{Hz} \), 3H, H-4”).

\(^{13}\text{C\ NMR (75.5 MHz, DMSO-}d_6\):} \delta 167.8, 166.0, 134.6, 130.7, 127.8, 126.0, 124.4, 123.1, 122.4, 120.3, 110.7, 99.7, 62.3, 47.8, 45.8, 32.2, 32.0, 29.4, 25.1, 24.2, 24.1, 19.7, 15.4, 13.7.

**HRMS:** Calculated for \( \text{C}_{25}\text{H}_{33}\text{N}_5\text{O}_4 \) 393.2416, found 393.2411.

\(N\text{-\textit{tert-}Butyl-5-(3,4-dimethoxybenzyl)-3-methylene-4-oxo-3,4,5,6-tetrahydro-1H-}
\text{azepino[5,4,3-}
\text{c,d} \text{]indole-6-carboxamide (35g)}\)

Yellow solid; Yield 86%; Melting point: 99-101 °C.
Section B: Switching the Regioselectivity via Indium(III) and Gold (I)...

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 11.31 (bs, 1H, -NH), 8.18 (s, 1H, -CONH), 7.48-7.39 (m, 3H, H-2, H-7 & H-2’’’), 6.93-6.77 (m, 4H, H-8, H-9, H-5’’’ & H-6’’’), 6.13 (s, 1H, H$_d$), 5.97 (s, 1H, H$_e$), 5.46 (s, 1H, H-6), 5.04 (d, $J$= 15.38Hz, 1H, H$_a$), 4.16 (d, $J$= 15.38Hz, 1H, H$_b$), 3.69 (s, 6H, -OMe), 1.09 (s, 9H, H-2’’).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta$ 167.3, 164.1, 148.6, 147.9, 136.2, 135.3, 129.8, 125.8, 123.8, 122.6, 122.0, 119.1, 117.4, 115.0, 112.0, 111.8, 111.7, 100.3, 63.1, 55.5, 55.4, 50.6, 48.4, 28.2.

HRMS: Calculated for C$_{26}$H$_{29}$N$_3$O$_4$ 447.2158, found 447.2145.

(3E)-3-Benzylidene-$N$-$tert$-butyl-5-(4-methoxybenzyl)-4-oxo-3,4,5,6-tetrahydro-1H-azepino[5,4,3-c,d]indole-6-carboxamide (35h)

Yellow solid; Yield 60%; Melting point: 108-110 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 11.28 (s, 1H, -NH), 8.08 (s, 1H, -CONH), 7.49 (s, 1H, H-2), 7.36 (m, 3H, H-1’’’, H-2’’’’ & H-6’’’’), 7.29-7.21 (m, 5H, H-2’’, H-6’’, H-3’’’’, H-4’’’’ & H-5’’’’), 7.08 (d, $J$= 8.66Hz, 1H, H-7), 6.92-6.83 (m, 4H, H-8, H-9, H-3'' & H-5’’’’), 5.46 (s, 1H, H-6), 4.95 (d, $J$= 15.12Hz, 1H, H$_a$), 4.30 (d, $J$= 15.12Hz, 1H, H$_b$), 3.68 (s, 3H, -OMe), 1.14 (s, 9H, H-2’’’).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta$ 167.5, 166.0, 158.4, 136.8, 134.8, 130.7, 129.5, 129.2, 128.9, 128.7, 128.2, 127.6, 126.0, 124.4, 121.6, 120.9, 113.7, 110.6, 100.0, 63.0, 55.0, 50.6, 48.6, 28.2.

HRMS: Calculated for C$_{31}$H$_{31}$N$_3$O$_3$ 493.2365, found 496.2379.
(E)-N-tert-Butyl-3-ethylidene-5-(4-methoxybenzyl)-4-oxo-1-tosyl-3,4,5,6-tetrahydro-1H-azepino[5,4,3-c,d]indole-6-carboxamide (35i)

Offwhite solid; Yield 73%; Melting point: 199-201 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.09 (s, 1H, -CONH), 7.92 (m, 4H, H-2, H-9, H-2‴‴ & H-6‴‴), 7.54 (d, $J$= 8.54Hz, 1H, H-7), 7.39 (d, $J$= 7.81Hz, 2H, H-3‴‴ & H-5‴‴), 7.24 (bs, 1H, H-8), 7.18 (d, $J$= 7.81Hz, 2H, H-2″ & H-6″), 6.89-6.81 (m, 3H, H-3″, H-5″ & H-1″″), 5.34 (s, 1H, H-6), 4.77 (d, $J$= 14.76Hz, 1H, H$_a$), 4.29 (d, $J$= 14.76Hz, 1H, H$_b$), 3.67 (s, 3H, -OMe), 2.31 (s, 3H, -CH$_3$), 2.11 (d, $J$= 7.43Hz, 3H, H-2″″), 1.03 (s, 9H, H-2″).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta$ 166.9, 165.6, 158.4, 145.7, 134.0, 132.5, 131.3, 130.3, 129.4, 129.3, 128.8, 127.6, 127.1, 126.8, 124.6, 123.7, 113.6, 112.2, 107.0, 62.3, 55.0, 50.6, 48.7, 28.1, 21.0, 15.5.

HRMS: Calculated for C$_{33}$H$_{35}$N$_3$O$_5$S585.2297, found 585.2273.

(Ε)-N-tert-Butyl-2-(3-ethylidene-4-oxo-3,4-dihydro-1H-azepino[5,4,3-c,d]indol-5(6H)-yl)-2-phenylacetamide (35j)

White solid; Yield 77%; Melting point: 267-269 °C.
$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 11.27 (bs, 1H, -NH), 8.03 (s, 1H, -CONH), 7.39-7.23 (m, 8H, H-7, H-8, H-9, H-2‴”, H-3‴”, H-4‴”, H-5‴” & H-6‴”), 6.76 (q, $J= 7.52$Hz, 1H, H-1‴”), 6.37 (s, 1H, H-2”), 6.05 (s, 1H, H-2”), 4.88 (d, $J= 16.03$Hz, 1H, H-6), 4.09 (d, $J= 16.03$Hz, 1H, H-6), 2.08 (d, $J= 7.41$Hz, 3H, H-2‴”), 1.28 (s, 9H, H-2”).

$^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta$ 168.9, 167.1, 136.6, 134.5, 131.0, 129.8, 128.6, 128.5, 127.7, 126.0, 124.4, 124.0, 121.4, 120.2, 110.2, 98.4, 59.3, 50.4, 44.1, 28.4, 15.2.

HRMS: Calculated for C$_{25}$H$_{27}$N$_3$O$_2$ 401.2103, found 401.2112.

Method B: General procedure for (IPr)AuNTf$_2$ catalyzed cyclization.

To a glass vial (IPr)AuCl (10 mole%) and AgNTf$_2$ (10 mole%) were loaded along with anhydrous dichloroethane (2 mL). Ugi product 34a-j (0.25 mmol) was added and the reaction vial was evacuated-backfilled with argon (4 cycles) and was stirred at 100 °C until completion of reaction. After completion, reaction mixture was partitioned between EtOAc (100 mL) and water (50 mL). Organic layer was washed with brine (50 mL), dried over magnesium sulfate and evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (5% methanol in dichloromethane) to afford the desired compound (36a-j).

(Z)-N-tert-Butyl-6-(4-methoxybenzyl)-3-methyl-5-oxo-1,5,6,7-tetrahydroazocino[5,4,3-c,d]indole-7-carboxamide (36a)

Grey solid; Yield 78%; Melting point: 247-249 °C.
**Section B: Switching the Regioselectivity via Indium(III) and Gold (I)...**

\[^1\text{H} \text{NMR} (300 \text{ MHz}, \text{CDCl}_3)\]: δ8.55 (bs, 1H, -NH), 7.37-7.30 (m, 4H, H-2, H-8, H-2'' & H-6''), 7.16 (bs, 1H, H-10), 6.84 (d, J= 7.22Hz, 2H, H-3'' & H-5''), 6.32 (s, 1H, -CONH), 6.21 (s, 1H, H-9), 5.24 (s, 1H, H-4), 5.16-5.09 (m, 2H, H-7 & H_8), 4.32 (d, J= 14.34Hz, 1H, H_9), 3.80 (s, 3H, -OMe), 2.28 (s, 3H, -CH_3), 1.10 (s, 9H, H-2'').

\[^{13}\text{C} \text{NMR} (75.5 \text{ MHz}, \text{CDCl}_3)\]: δ 167.9, 167.2, 159.3, 145.0, 136.1, 130.3, 129.0, 128.1, 127.9, 127.3, 125.6, 123.2, 121.0, 114.4, 111.3, 100.0, 60.7, 55.3, 51.4, 51.3, 28.2, 24.4.

**HRMS:** Calculated for C_{28}H_{30}N_3O_3 431.2209, found 461.2319.

(Z)-N-Cyclohexyl-6-(4-methoxybenzyl)-3-methyl-5-oxo-1,5,6,7-tetrahydrazocino[5,4,3-c,d]indole-7-carboxamide (36b)

Brown solid; Yield 68%; Melting point: 204-206 °C.

\[^1\text{H} \text{NMR} (300 \text{ MHz}, \text{DMSO-d}_6)\]: δ11.26 (bs, 1H, -NH), 7.41-7.34 (m, 2H, H-8 & H-10), 7.26-7.18 (m, 3H, H-9, H-2'' & H-6''), 6.71 (d, J= 7.66Hz, 2H, H-3'' & H-5''), 6.57 (s, 1H, H-2), 6.14 (d, J= 7.49Hz, 1H, -CONH), 5.95 (s, 1H, H-4), 5.47 (s, 1H, H-7), 4.61 (s, 2H, H_8 & H_9), 3.65 (s, 3H, -OMe), 3.47 (m, 1H, CyH), 2.18 (s, 3H, -CH_3), 1.61-1.49 (m, 5H, CyH), 1.18-0.96 (m, 5H, CyH).

\[^{13}\text{C} \text{NMR} (75.5 \text{ MHz}, \text{DMSO-d}_6)\]: δ 167.4, 166.1, 158.3, 155.5, 143.2, 136.0, 129.7, 128.4, 127.4, 126.9, 126.1, 123.1, 120.1, 113.5, 111.1, 100.0, 61.1, 54.9, 51.5, 47.9, 34.8, 31.9, 31.7, 25.0, 24.6, 23.9.

**HRMS:** Calculated for C_{28}H_{31}N_3O_3 457.2365, found 457.2360.
(Z)-N-tert-Butyl-3-ethyl-6-(4-methoxybenzyl)-5-oxo-1,5,6,7-tetrahydroazocino[5,4,3-c,d]indole-7-carboxamide (36c)

Offwhite solid; Yield 76%; Melting point: 95-97 °C.

^1^H NMR (300 MHz, DMSO-d_6): δ 11.30 (bs, 1H, -NH), 7.43-7.25 (m, 6H, H-2, H-8, H-9, H-10, H-2'' & H-6''), 6.81 (d, J= 8.42Hz, 2H, H-3'' & H-5''), 5.95 (s, 1H, -CONH), 5.44 (s, 1H, H-4), 5.34 (s, 1H, H-7), 4.83 (d, J= 14.18Hz, 1H, H_a), 4.31 (d, J= 14.18Hz, 1H, H_b), 3.69 (s, 3H, -OMe), 2.72-2.56 (m, 2H, H-1'''), 1.03-0.96 (m, 12H, H-2'' & H-2''').

^13^C NMR (75.5 MHz, DMSO-d_6): δ 167.4, 166.1, 158.6, 149.0, 135.8, 130.0, 129.7, 129.1, 127.7, 126.2, 125.8, 121.1, 119.8, 113.9, 111.1, 100.0, 61.7, 55.0, 51.4, 50.5, 29.5, 28.0, 12.4.

HRMS: Calculated for C_{27}H_{31}N_{3}O_{3} 445.2365, found 445.2387.

(Z)-N-tert-Butyl-6-(4-methoxybenzyl)-1,3-dimethyl-5-oxo-1,5,6,7-tetrahydroazocino[5,4,3-c,d]indole-7-carboxamide (36d)

Yellow solid; Yield 75%; Melting point: 66-68 °C.
Section B: Switching the Regioselectivity via Indium(III) and Gold (I)....

1H NMR (300 MHz, DMSO-d6): δ 7.47 (d, J = 8.26 Hz, 1H, H-10), 7.36-7.26 (m, 4H, H-2, H-9, H-2'' & H-6''), 6.76 (d, J = 7.84 Hz, 2H, H-3''' & H-5'''), 6.68 (bs, 1H, H-8), 6.00 (s, 1H, -CONH), 5.46 (s, 1H, H-4), 5.23 (s, 1H, H-7), 4.69 (d, J = 14.33 Hz, 1H, Hδ), 4.49 (d, J = 14.33 Hz, 1H, Hδ), 3.80 (s, 3H, -OMe), 3.67 (s, 3H, -NMe), 2.21 (s, 3H, -CH3), 1.04 (s, 9H, H-2'').

13C NMR (75.5 MHz, DMSO-d6): δ 172.8, 171.2, 163.7, 148.6, 141.6, 135.9, 135.0 (2), 133.9, 132.8, 132.3, 128.5, 125.4, 119.0, 114.8, 104.5, 66.6, 60.2, 56.8, 55.8, 37.9, 33.1, 29.2.

HRMS: Calculated for C27H31N3O4 461.2315, found 461.2313.

(Z)-N-tert-Butyl-6-(3,4-dimethoxybenzyl)-3-methyl-5-oxo-1,5,6,7-tetrahydroazocino[5,4,3-c,d]indole-7-carboxamide (36e)

[Diagram of the molecule]

Offwhite solid; Yield 76%; Melting point: 263-265 °C.

1H NMR (300 MHz, DMSO-d6): δ 10.96 (bs, 1H, -NH), 7.91 (s, 1H, H-2), 7.37 (d, J = 7.65 Hz, 1H, H-8), 7.17-6.96 (m, 6H, H-9, H-10, H-2'', H-5'', H-6'' & -CONH), 6.37 (s, 1H, H-4), 6.19 (s, 1H, H-7), 4.13 (dd, J = 15.37 Hz, 2H, Hδ), 3.74-3.64 (m, 6H, -Ome), 2.20 (s, 3H, -CH3), 1.30 (s, 9H, H-2'').

13C NMR (75.5 MHz, DMSO-d6): δ 174.6, 170.6, 153.6, 153.1, 152.3, 148.1, 140.7, 135.5, 134.9, 134.2, 130.1, 128.4, 125.5, 123.6, 116.6, 114.7, 104.6, 97.8, 63.2, 60.8, 59.6, 55.6, 33.7, 29.0.

HRMS: Calculated for C27H31N3O4 461.2315, found 461.2313.
(Z)-6-Butyl-N-cyclohexyl-3-methyl-5-oxo-1,5,6,7-tetrahydroazocino[5,4,3-c,d]indole-7-carboxamide (36f)

\[
\begin{align*}
\text{Brown solid; Yield 40\%; Melting point: 88-90 °C.}
\end{align*}
\]

\(^1\text{H NMR (300 MHz, DMSO-}d_6)\text{:} \delta\ 11.30\ (bs, 1H, -NH), 7.43\ (m, 2H, H-8 & H-9), 7.25\ (d, J= 8.80Hz, 1H, H-10), 6.94\ (s, 1H, H-2), 6.42\ (d, J= 8.22Hz, 1H, -CONH), 5.88\ (s, 1H, H-4), 5.52\ (s, 1H, H-7), 3.73\ (m, 1H,CyH), 3.53\ (m, 1H, H-1”), 3.28\ (m, 1H, H-1”) 2.16\ (s, 3H, -CH₃), 1.54\ (m, 5H, CyH), 1.32-1.11\ (m, 9H, H-2”, H-3” &CyH), 0.65\ (t, J= 6.83Hz, 3H, H-4”).
\]

\(^1\text{C NMR (75.5 MHz, DMSO-}d_6)\text{:} \delta\ 167.6, 165.7, 142.4, 136.8, 136.0, 128.9, 127.2, 127.0, 126.2, 123.6, 120.1, 111.1, 100.4, 61.1, 48.0, 32.0, 31.8, 29.8, 25.0, 24.8, 23.8, 19.2, 13.5.
\]

HRMS: Calculated for C₂₄H₃₁N₅O₂ 393.2416, found 393.2424.

(Z)-N-tert-butyl-6-(3,4-dimethoxybenzyl)-5-oxo-1,5,6,7-tetrahydroazocino[5,4,3-c,d]indole-7-carboxamide (36g)

\[
\begin{align*}
\text{Brown solid; Yield 40%; Melting point: 97-99 °C.}
\end{align*}
\]

\(^1\text{H NMR (300 MHz, DMSO-}d_6)\text{:} \delta\ 11.22\ (bs, 1H, -NH), 8.06\ (s, 1H, H-2), 7.41\ (d, J= 8.21Hz, 1H, H-8), 7.30\ (bs, 1H, H-6”), 7.18-7.12\ (m, 2H, H-9 & H-10), 7.00\ (d, J= 7.20Hz, 1H, H-5”), 6.79\ (s, 1H, H-3), 6.56\ (s, 1H, H-2”), 6.23-6.20\ (m, 2H, H-4 & -}
CONH), 6.10 (s, 1H, H-7), 4.85 (d, J= 17.52Hz, 1H, H_a), 3.78 (s, 3H, -OMe), 3.63 (s, 3H, -OMe), 3.57 (d, J= 17.52Hz, 1H, H_b), 1.30 (s, 9H, H-2”).

\textbf{\textsuperscript{13}C NMR (75.5 MHz, DMSO-\textit{d}_6):} \delta 169.2, 162.4, 149.4, 148.3, 135.7, 134.1, 127.4, 127.2, 125.6, 123.3, 122.0, 120.8, 118.7, 116.4, 111.6, 108.3, 106.1, 99.2, 57.8, 55.6, 55.4, 50.4, 46.5, 28.4.

\textbf{HRMS:} Calculated for C_{26}H_{20}N_{5}O_{4} 447.2158, found 447.2161.

(Z)-\textit{N-}tert-Butyl-6-(4-methoxybenzyl)-5-oxo-3-phenyl-1,5,6,7-tetrahydroazocino[5,4,3-\textit{c,d}]indole-7-carboxamide (36h)

Brown solid; Yield 44%; Melting point: 130-132 °C.

\textbf{\textsuperscript{1}H NMR (300 MHz, DMSO-\textit{d}_6):} \delta 11.34 (bs, 1H, -NH), 7.38-7.30 (m, 10H, H-2, H-8, H-10, H-2”, H-6”, H-2”’, H-3”’, H-4”’, H-5”’ & H-6”’), 6.77-6.74 (m, 3H, H-9, H-3”’ & H-5””), 6.14 (s, 1H, -CONH), 5.67-5.61 (m, 2H, H-4 & H-7), 4.78 (d, J= 14.66Hz, 1H, H_a), 4.54 (d, J= 14.66Hz, 1H, H_b), 3.67 (s, 3H, -OMe), 0.94 (s, 9H, H-2”).

\textbf{\textsuperscript{13}C NMR (75.5 MHz, DMSO-\textit{d}_6):} \delta 167.5, 166.2, 147.7, 141.9, 136.1, 129.9, 129.8, 129.5, 128.6, 128.3, 128.1, 127.4, 126.3, 126.2, 123.1(2), 113.7, 110.9, 100.2, 61.9, 55.0, 51.8, 50.7, 27.8.

\textbf{HRMS:} Calculated for C_{31}H_{31}N_{5}O_{3} 493.2365, found 493.2369.
(Z)-N-tert-Butyl-2-(3-methyl-5-oxazocino[5,4,3-c,d]indol-6(1H,5H,7H)-yl)-2-phenylacetamide (36j)

White solid; Yield 81%; Melting point: 253-255 °C.

1H NMR (300 MHz, DMSO-d6): δ 11.10 (bs, 1H, -NH), 7.32-7.12 (m, 10H, -H-2, -H-8, -H-9, -H-10, -H-2″, -H-3″, -H-4″, -H-5″, -H-6″ & -CONH), 6.24 (s, 1H, -H-4), 6.01 (s, 1H, -H-1′), 4.51-4.28 (m, 2H, -H-7), 2.32 (s, 3H, -CH3), 1.21 (s, 9H, -H-2″).

13C NMR (75.5 MHz, DMSO-d6): δ 167.2, 144.9, 136.4, 135.8, 129.1, 128.9, 128.6, 128.2, 127.7, 125.6, 125.3, 122.3, 120.0, 110.7, 99.8, 61.2, 50.2, 43.7, 28.2, 24.8.

HRMS: Calculated for C23H27N3O2 401.2103, found 401.2104.

N-tert-Butyl-3-methyl-5-(2-phenylacetyl)-5,6-dihydro-1H-azepino[5,4,3-c,d]indole-6-carboxamide (35k)

Grey solid; Yield 62% (Method A); 70% (Method B); Melting point: 85-87 °C.

1H NMR (300 MHz, DMSO-d6): δ 11.42 (bs, 1H), 7.48 (s, 1H, -CONH), 7.34 (d, J= 8.13Hz, 1H, -H-7), 7.17-7.09 (m, 6H, -H-2, -H-2″, -H-3″, -H-4″, -H-5″, -H-6″ & -H-6″′), 6.95 (d, J= 7.12Hz, 1H, -H-9), 6.35 (m, 3H, -H-4, -H-6 & -H-8), 3.79 (d, J= 15.58Hz, 1H, -H-2″′), 3.65 (d, J= 15.58Hz, 1H, -H-2″′), 2.08 (s, 3H, -CH3), 1.10 (s, 9H, -H-2″).

13C NMR (75.5 MHz, DMSO-d6): δ 169.7, 167.4, 136.3, 135.4, 130.8, 129.3, 127.9, 126.2, 125.4, 123.7, 123.5, 121.4, 120.1, 119.2, 114.4, 111.2, 61.5, 50.3, 40.8, 28.2, 18.1.

HRMS: Calculated for C25H27N3O2 401.2103, found 401.2124.
REFERENCES


