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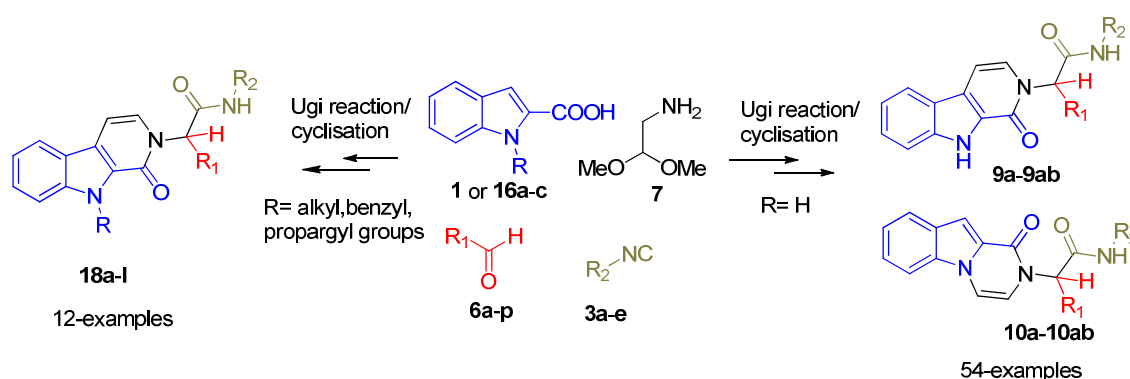
Diversity oriented synthesis of β -carbolinone and indolo-pyrazinone analogues based on an Ugi four component reaction and subsequent cyclisation of the resulting indole intermediate

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Graphical Abstract:



Abstract: One pot domino multicomponent reaction for a rapid, integrated and versatile synthesis of highly functionalized β -carbolinones (**9a-9ab**) and indolo-pyrazinones (**10a-10ab**) has been established. The reaction involves an Ugi-four component reaction of indole 2-carboxylic acid (**1** or **16a-c**), aryl or alkyl aldehyde (**6a-p**), isocyanide (**3a-e**), and aminoacetaldehyde dimethyl acetal (**7**) followed by *in situ* acid-mediated deprotection/activation/electrophilic cyclisation/and aromatisation. The products were obtained from Ugi adducts in good to excellent yield within short periods of 20-30 min at room temperature (35 °C). The potential of the methodology is proved by development of a

diverse library of heterocyclic compounds with point and skeletal diversity. Moreover, the synthesis has also been accomplished using N-substituted derivatives of indole 2-carboxylic acid that delivers highly diverse N-substituted β -carbolinones (**18a-l**) heterocycles of medicinal importance.

Keywords: Indole, Ugi reaction, β -carbolinone, pyrazinone, cyclisation

Introduction: Much attention has been drawn in the recent years towards the isocyanide based multi component reactions (IMCRs), especially the Ugi-four component reaction (Ugi-4CR),¹ the Ugi-three component reaction (Ugi-3CR),² and the Passerni reaction³ due to their ability to generate diverse heterocycles for medicinal chemistry. Aside from the vast array of more traditional methods, the Ugi-4CR offers a powerful and atom-economical way to construct functionalized molecular architecture from readily available starting materials such as aldehydes, amines, isocyanides, and carboxylic acids.⁴ These MCRs are of particular interest due to their mild reaction conditions, operational simplicity, atom economy, wide functional group tolerance, and are ideal for achieving environmentally friendly reactions.⁵ The combination of multicomponent reactions (MCRs) with post-condensation modifications *via* various ring-forming reactions has proven to be a powerful tool for accessing novel heterocyclic scaffolds. However the post modifications of Ugi products are generally restricted to a single chemical reaction which limits its scope in diversity oriented synthesis of complex molecules.⁶ Thus, the new domino Ugi/cyclisation reactions, which allowed the rapid construction of elaborate or highly functionalized heterocyclics in one single operation, has always been welcomed by the scientific community.^{7,8}

In recent decades, indole precursors have found extensive applications as a key component in multi component processes as they provide additional diversity and functionalization to product library.⁹ Indole nucleus containing natural product such as β -carboline, β -

carbolinone, spirooxindoles etc., are not limited to privileged structures that have the ability to bind with several receptors else the attractive scaffolds for drug discovery.¹⁰ Indole heterocyclic, β -carboline core containing natural products and related synthetic derivatives have found extensive application in medicinal chemistry as antitumour, antimalarial, antileishmanial, anticancer, and other life style related diseases.¹¹ It occurs in numerous natural products from fungi, bacteria, and plant isolates. Some of the examples have been shown (**Fig. 1**) like tetrahydro- β -carboline derivatives (**I**) having antitumour activity through inhibition of transforming growth factor beta (TGF- β).¹² Likewise, Evodiamine (**II**), a quinazolinocarboline alkaloid from chinese herb¹² and levendamycin (**III**), isolated from the fermentation broths of *Streptomyces lavendulae*, shows excellent antitumour activity.¹² 6-Methoxy-1,2,3,4-tetrahydro- β -carboline (pinoline) (**IV**) is believed to have a major role as an europrotective and in the regulation of adrenal gland.¹² Racemic spirotetrahydro β -carboline-based spiroazepine indole (**V**) has also been recently shown to exhibit antiplasmodial activity.¹²

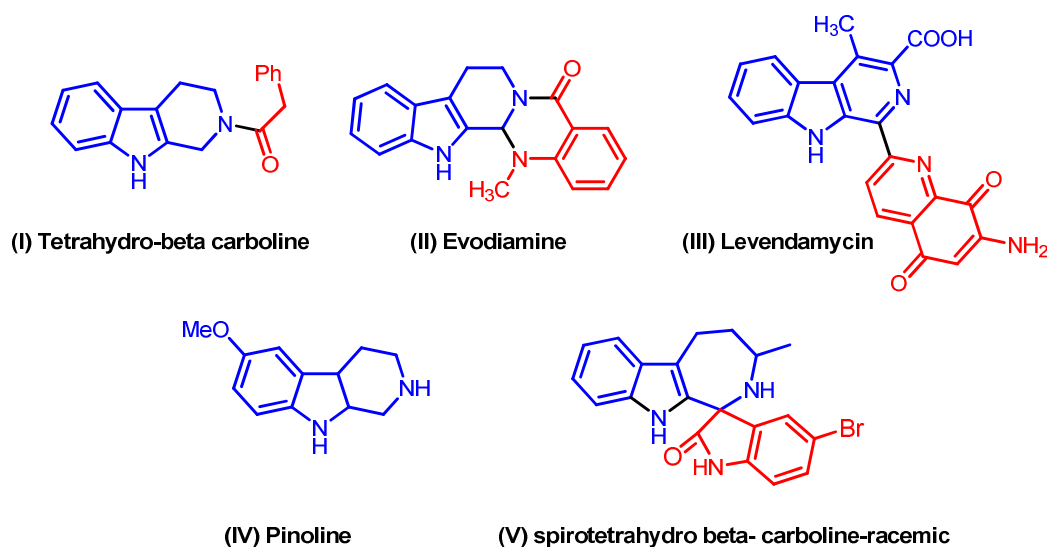


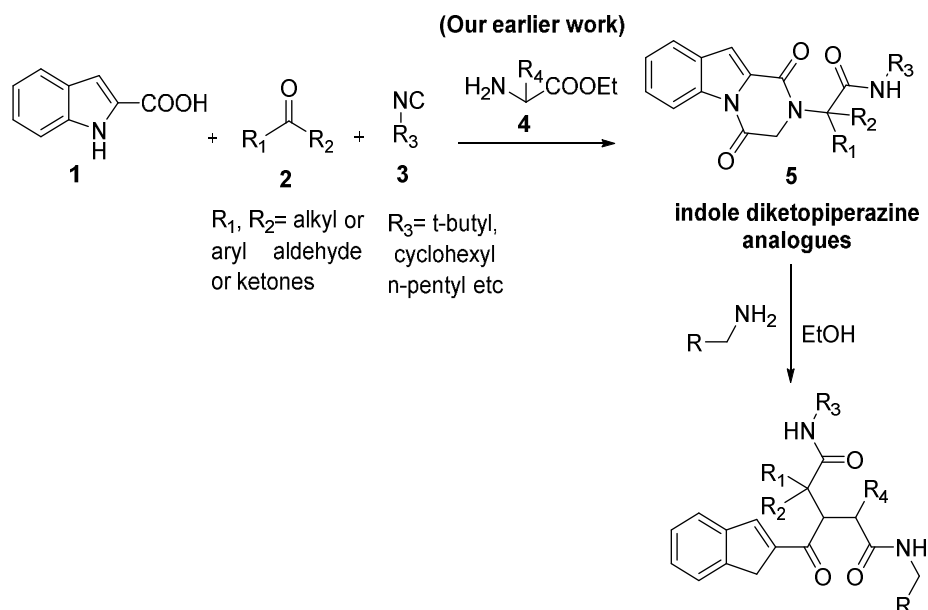
Figure 1: Biologically active natural and synthetic therapeutic agents containing β -carboline core.

A pyrido-1-one annulated indole derivative, the β -carbolinone ring systems is a common motif plays a prominent role in organic and medicinal chemistry, such as affinity for the benzodiazepine receptor, antileukemic, and central nervous system depressing properties.¹³ Further, the β -carbolinone ring containing natural product strychnocarpine is a well-known muscle relaxant and a 5-hydroxytryptamine receptor stimulant.¹⁴ Beside having significant medicinal values, β -carbolinone heterocyclics have been less explored and, only a few methods for their syntheses have been reported in the literature. Among these are the first solid phase and liquid phase syntheses of β -carbolinones with the generation of four points diversity for various hydrophobic and hydrophilic groups by Wen-Ren Li *et al.*¹⁵ Later in 2008, Padwa *et al.*, reported the preparation of a series of β -carbolinones in single step starting from *N*-propargyl indole-2-carboxamides.^{12c}

Moreover, Pyrazinones derivatives are found alone and/or embedded with several privilege heterocyclics which displays prominent biological activity and are featured in several naturally occurring molecules and synthetic derivatives.¹⁶ We have also been interested in the synthesis of indole fused pyrazinone heterocycles due to their significance in chemical biology.¹⁵ In pursuit of a protocol for preparing functionalized β -carbolinones (**9**) and indolopyrazinones (**10**) with diverse pharmacological properties, we envisioned the four component Ugi-MCR/post cyclisation approach using preorganised substrates. The scaffolds **9** and **10** illustrate the flexibility and complexity which is achieved in single operation and at the same time results in the combination of two the most bioactive rings indole and pyrido-2-one.

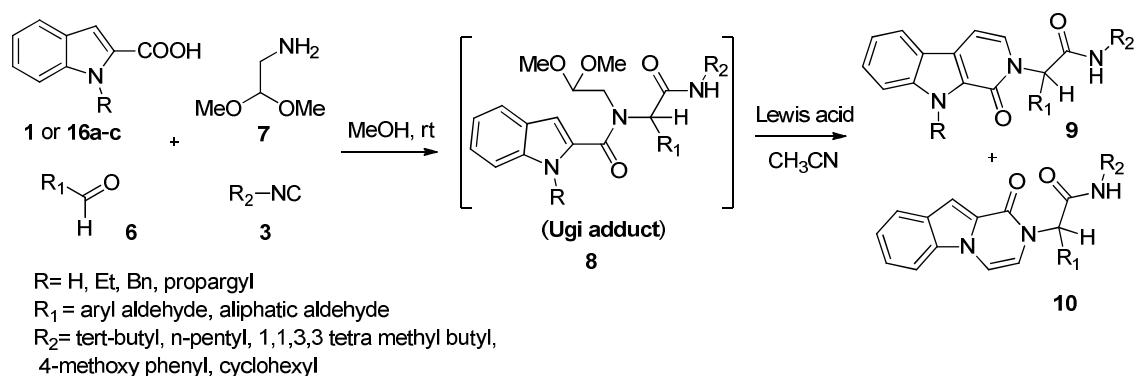
Indeed, our group has long had an interest in discovering new synthetic strategies utilising the Ugi MCR/post modification approaches for accessing biologically important heterocycles.¹⁷ Very recently, we reported the synthesis of biologically important indole diketopiperazine (**5**) analogues *via* four component Ugi reaction and

Scheme 1: Synthesis of indole fused diketopiperazines (5**)**



subsequent ring opening leading to a library of dipeptides (**Scheme 1**).¹⁷ In this continuation, we next directed our efforts towards the reaction of the Ugi precursors indole-2-carboxylic acid (**1**) or N-substituted indole-2-carboxylic acid (**16a-c**), aryl or alkyl aldehyde (**6a-p**), and isocyanide (**3**), aminoacetaldehyde dimethyl acetal (**7**), and their subsequent deprotection/activation/electrophilic cyclisation/aromatisation at room temperature (35 °C) to afford diverse set of β -carbolinones (**9**) in good to excellent yield along with small amount of indolo-pyrazinones (**10**) (**Scheme 2**). It is noteworthy that, the new protocol avoids the use of any transition metal catalyst, thereby excluding their contamination during synthesis, favourable for biological screening.¹⁸

Scheme 2: Synthesis of β -carbolinones and indolo-pyrazinones derivative from Ugi precursors

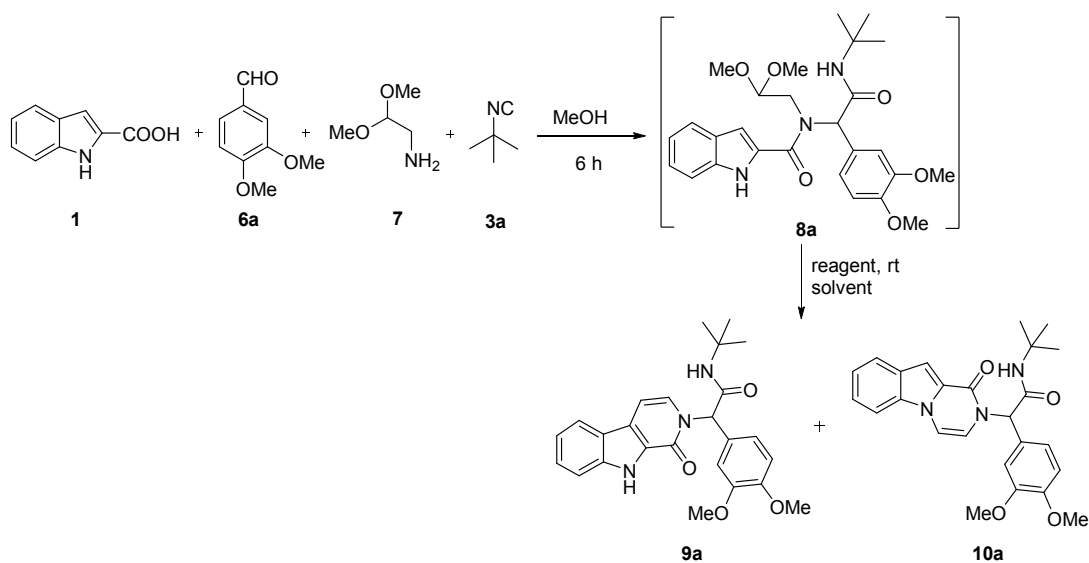


To the best of our knowledge, this is first report for such Ugi-4CR of indole 2-carboxylic acid, aminoacetaldehyde dimethyl acetal, aryl aldehyde, and isocyanide and/or subsequent cyclisation under acidic medium.

Result and Discussion: As part of our on-going research on Ugi MCRs, we studied the reaction of indole-2-carboxylic acid (**1**), 3,4-dimethoxy benzaldehyde (**6a**), aminoacetaldehyde dimethyl acetal (**7**), and tertiary butyl isocyanides (**3a**) in methanol for 6h at rt (35 °C), that resulted in the formation of Ugi adduct **8a** as the major product. The methanol was removed *in vacuo* and further reaction was performed directly by stirring of Ugi adduct **8a** in CH₃CN under BF₃·OEt₂ (2.0 equiv.) for 60 min. at rt (35 °C), which furnished the cyclised product **9a** and **10a**, albeit in lower yields (entry 1, **Table1**).

The products **9a** and **10a** were isolated from column chromatography and characterised by IR, HRMS, ¹H NMR and ¹³C NMR spectra (see **supporting information**).²⁰ To identify the optimal reaction conditions for the domino reaction, we checked different catalysts, solvents and temperatures and the results of this study are depicted in **Table 1**.

Table1:Optimisation of reaction condition for synthesis of β -carbolinone and indolopyrazinone derivatives.^a



Entry	Reagents (equiv)	Solvents	Time (min)	Yield ^b	
				9a	10a
1	BF ₃ .OEt ₂ (1.0)	MeOH	60	22	10
2	BF ₃ .OEt ₂ (1.0)	CH ₃ CN	60	45	11
3	AlCl ₃ (1.0)	Toluene	60	24	Traces
4	TFA (0.2)	Toluene	120	52	8
5	TFA (0.2)	CH ₃ CN	120	66	8
6	TFA (0.5)	CH ₃ CN	45	72	8
7	TFA (1.0)	CH₃CN	20	79	11
8	TFA (1.0)	THF	20	73	8
9	TFA (1.0)	DCM	45	47	7
10	TFA (1.0)	Chloroform	45	46	7

11	TFA (2.0)	CH ₃ CN	20	78	10
12	PTSA (0.2)	CH ₃ CN	120	52	8
13	PTSA (1.0)	CH₃CN	20	72	9
14	MSA(1.0)	CH ₃ CN	30	69	8
15	TFMSA (1.0)	CH ₃ CN	30	57	7
16	HClO ₄ (1.0)	CH ₃ CN	60	UN ^c	-
17	Acetic acid	-	60	UN ^d	-
18	Acetic acid (5.0)	Toluene	60	UN ^d	-
19	-	CH ₃ CN	>120	NR ^e	-
20	TFA (1.0)	CH ₃ CN	60	65 ^f	7
21	TFA (1.0)	CH ₃ CN	15	45 ^g	7

^a Reaction conditions: step 1: indole 2-carboxylic acid (**1**) (1 mmol), 3, 4-dimethoxy benzaldehyde (**6a**) (1 mmol), aminoacetaldehyde dimethyl acetal (**7**) (1.1 mmol), tertiary butyl isocyanide (**3a**) (1.1 mmol) in 3 mL solvent, reaction time 6h, rt (35 °C). Step 2: substrate Ugi adducts **8a** (1 mmol), TFA (1.0 equiv.), solvent (2 mL), rt (35 °C), reaction time (20 min.), ^b Isolated yield. ^c unidentified mixture. ^d reaction temperature (rt (35 °C) and/or 90 °C). ^e no reaction. ^f reaction temperature (0 °C). ^g reaction temperature (75 °C).

The one step one pot reaction of Ugi/cyclisation reaction using MeOH was unsuccessful since the reaction generates additional impurities in the reaction mixture, restricting the use of MeOH as solvent for promoting cyclisation (entry 1, **Table 1**). To obtain the desired product (**9a** and **10a**), we tested the reaction using different Brønsted and Lewis acids which is depicted in **Table 1**. In our initial efforts, using BF₃·OEt₂ with CH₃CN solvent does not leads any significant change in yield of desired products (entry 2, **Table 1**). Performing the cyclisation with AlCl₃ in toluene generates inseparable reaction mixture (entry 3, **Table 1**). Next, we examine a set of Brønsted acids in different solvents (entries 4–19, **Table 1**) where,

trifluoro acetic acid (TFA) (entry 7, **Table 1**), *p*-toluene sulphonic acid (PTSA) (entry 13, **Table 1**), and/or methanesulphonic acid (MSA) (entry 14, **Table 1**) seemed promising for cyclisation of Ugi product. It may be due to the acidic strength of TFA (pKa $\sim$ -0.25), PTSA (pKa $\sim$ -2.58) and, MSA (pKa $\sim$ -2.60) are good enough to enhance the electrophilicity of the oxo-group for intramolecular cyclisation *via* C-3 or N-1 position of indole ring consequently good yield of cyclisation. However, in case of trifluoromethanesulphonic acid (TFMSA, pKa $\sim$ -14.0) (entry 15, **Table 1**) and/or perchloric acid (HClO₄, pKa $\sim$ -10.0) (entry 16, **Table 1**), being highly acidic in nature may protonate the N-1 of indole ring and thus reduce the nucleophilicity of C-3 carbon of indole ring thus the lower yield of cyclisation. In other hand, the acid (like CH₃COOH, pKa $\sim$ +4.76) having high pKa value i.e. weak acidic strength is not enough to enhance the electrophilicity of oxo-group therefore low feasibility of cyclisation (entry 17 and 18, **Table 1**).

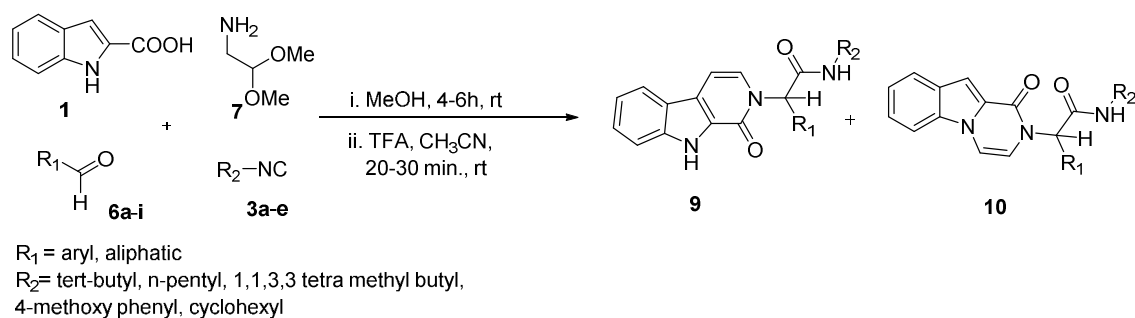
Due to the volatile nature of TFA (72 °C) and easily removed by evaporation without neutralization or extraction in organic solvents, is the reagent of choice which prompted us to further optimize the reaction condition using TFA. Therefore, further refinement was limited to varying the solvent and temperature. We also investigated the amount of TFA required for this reaction and it was observed that with decreasing the amount of catalyst, the yields also decreased (entries 5-7, **Table 1**). It is observed that further increase of the catalyst loading to 2.0 equiv. has no obvious influence on the reaction (entry 11, **Table 1**). Subsequently, the effect of solvent was examined where DCM, and/or CHCl₃ showed no superiority to toluene as solvents but in THF and/or CH₃CN a good yield of product was observed with reduction in reaction time (compare entries 4, 7, 8, 9, 10, **Table 1**). When the reaction was carried out using 1.0 equivalent of TFA in CH₃CN, a complete disappearance of starting materials was observed while attaining the highest yield of **9a** and **10a** (79% and 11% yield respectively, entry 7, **Table 1**). As predicted, the reaction did not work at all without cyclizing reagent

(entry 19, **Table 1**). We have also done the Ugi post cyclisation reaction at lower temperature (0 °C) which delivered the low yield of regioisomers in longer time (entry 20, **Table 1**). It is noteworthy that, at a reaction temperature of 75 °C, the yield of the desired product was decreased significantly (entry 21, **Table 1**).

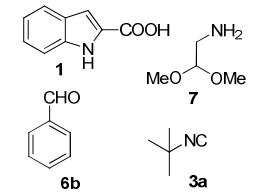
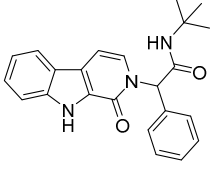
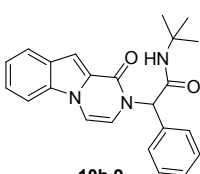
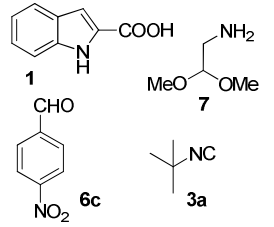
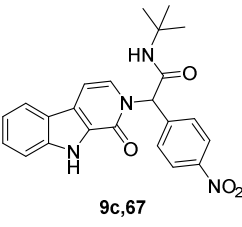
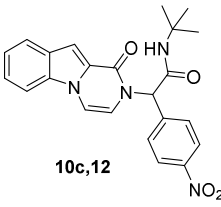
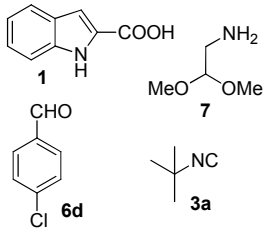
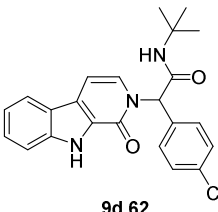
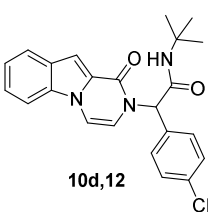
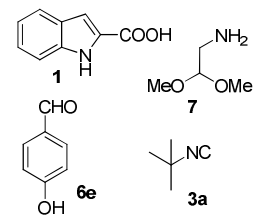
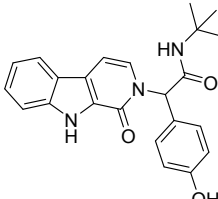
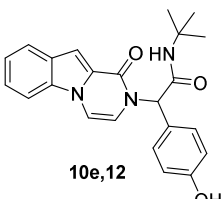
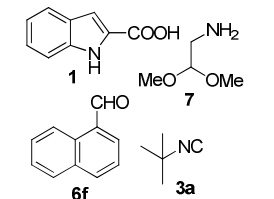
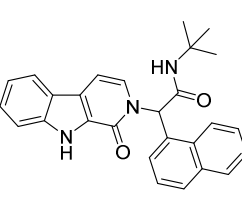
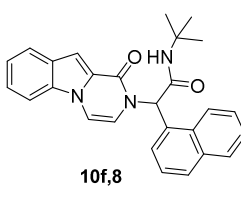
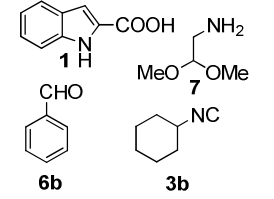
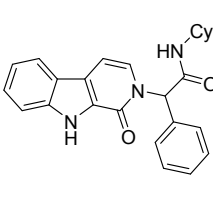
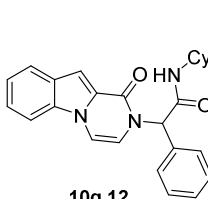
The scope and limitations of this one pot domino Ugi/cyclisation process (entry 7, **Table 1**), were next examined by employing diverse aromatic/heteroaromatic (HetAr)/aliphatic aldehydes appended with various substituents (**6a-i**, **Table 2**). The complete list of the synthesized compounds (**9a-9ab** and **10a-10ab**) with corresponding starting materials is given in the supporting information (**S-Table 1**). It is interesting to note that in all cases whether aromatic aldehydes with electron-withdrawing and/or electron-donating groups were used, products were obtained with minimal variation in isolated yields (**Table 2**; 58–79%). The presented protocol shows extensive evaluation of the transformation that not only reveals novel reactivity facets and expanded scope of the method but also provides β -carbolinone and indolo-pyrazinone chemotypes featuring unexplored functional, skeletal, and fusion patterns of indole heterocycles. We have synthesized several β -carbolinone and indolo-pyrazinone derivatives containing halogens such as fluoro, chloro, bromo based on their role in introducing lipophilicity in molecules in medicinal chemistry (entry 4, **Table 2** and see supporting information; **Table 1**). The 4-nitro benzaldehyde (**6c**) with a strong electron withdrawing substituent also provides the cyclized product in good yield (entry 3, **Table 2**). Sterically hindered 1-naphthaldehyde (**6f**) with tertiary butyl isocyanide (**3a**) provides the cyclized products in 74% yield (entry 6, **Table 2**). Further, 4-Hydroxy benzaldehyde (**6e**) and n-pentyl carbon aldehyde (**6g**) were also used as aldehyde sources for extensively evaluating the chemoselectivity profile of the transformation. The 1, 4-terephthalaldehyde has also demonstrated usefulness for domino Ugi/cyclisation reactions, leading to the bis analogue of β -carbolinone as the major product in good yield (entries 12, **Table 2**).²¹ Inspired by the

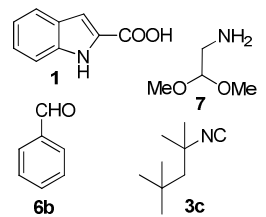
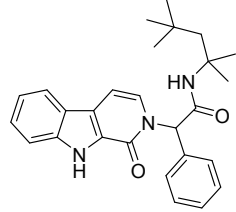
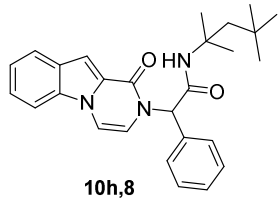
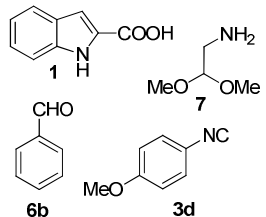
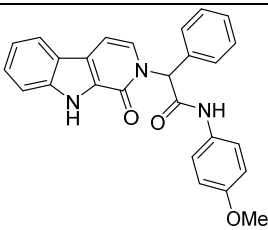
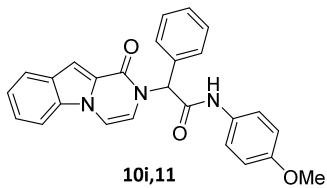
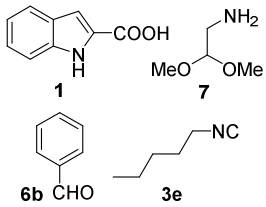
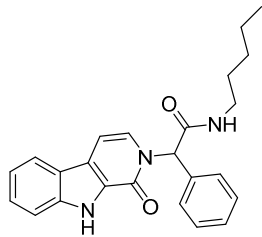
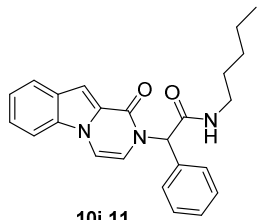
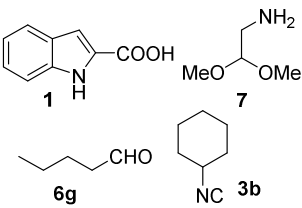
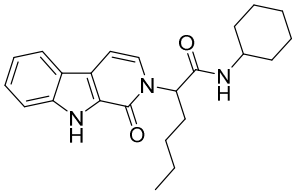
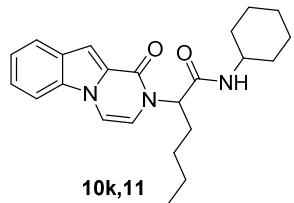
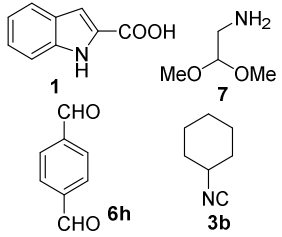
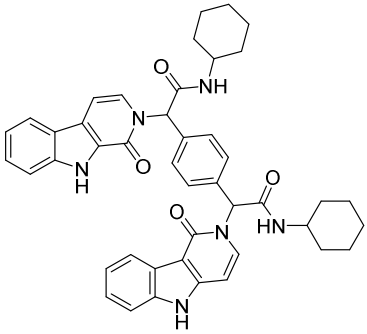
biological activity of marinocarboline A-D²² containing the β -carboline nucleus, we have utilised a indole 3-carboxaldehyde precursor, which delivered β -carboline (inseparable from reaction mixture) and indolo-pyrazinone polyheterocycles in relatively lower yield (entry13, **Table 2**). However, we were unable to obtain any product from ketones under the optimized conditions which limits this methodology for such substrates. Cyclohexyl isocyanide (**3b**), 1,1,3,3-tetramethyl butyl isocyanide (**3c**), 4-methoxyphenyl isocyanide (**3d**), and n-pentyl isocyanide (**3e**) were also used as isocyanides for diversification in the products library.

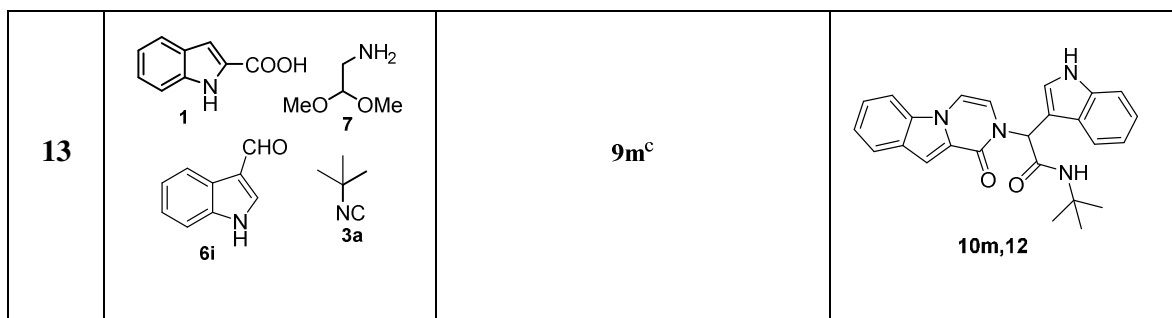
Table 2: One pot, Two Step Synthesis of β -carbolinones (9a-m) and indolo-pyrazinones (10a-m) derivative^a.



entry	Starting material	Cyclised product	
		Yield % ^b	
		9	10
1		 9a,79	 10a,11

2			
3			
4			
5			
6			
7			

8	 1 6b 7 3c	 9h,69	 10h,8
9	 1 6b 7 3d	 9i,46	 10i,11
10	 1 6b 7 3e	 9j,72	 10j,11
11	 1 6g 7 3b	 9k,73	 10k,11
12	 1 6h 7 3b	 9l,58	



^a Reaction conditions: step 1: indole 2-carboxylic acid (**1**) (1 mmol), aryl or alkyl aldehyde (**6a-i**) (1 mmol), aminoacetaldehyde dimethyl acetal (**7**) (1.1 mmol), alkyl or aryl isocyanide (**3a-e**) (1.1 mmol) in 3 mL solvent at rt (35 °C). Step 2: substrate Ugi adducts **8a-m** (1 mmol), TFA (1.0 equiv.), CH₃CN (2 mL), reaction time (20-30 min.), rt (35 °C), ^b Isolated yield. ^c Inseparable from reaction mixture.

A proposed mechanism of the TFA-mediated domino reaction for both of the cyclised product **9a** and **10a** is depicted in **Figure 2**. The first step is the general Ugi reaction which includes continuous stirring of Ugi precursors for 4-6h at rt (35 °C). The second step includes a domino deprotection, activation, and electrophilic cyclisation followed by aromatisation for product formation. Based on a literature survey, we envisaged that such a transformation can only occur under acid medium.²³ The Ugi precursor, subjected to TFA for protonation involves the conversion of acetal to aldehyde first, which then forms an oxonium ion **11**. This oxonium ion **11** has two nucleophilic centres indole N-1 and indole C-3 which can attack to the positive carbon. Out of the two possibilities, the most nucleophilic site is indole C-3, which attacks first and provides the cyclised intermediate **12**. This intermediate **12** afforded the desired product **9a** in good yield with removal of methanol, presumably because of the acidic conditions employed. The product **10a** is found as a minor side product *via* intermediate **13**, and results from the involvement of indole N-1 site in cyclisation.

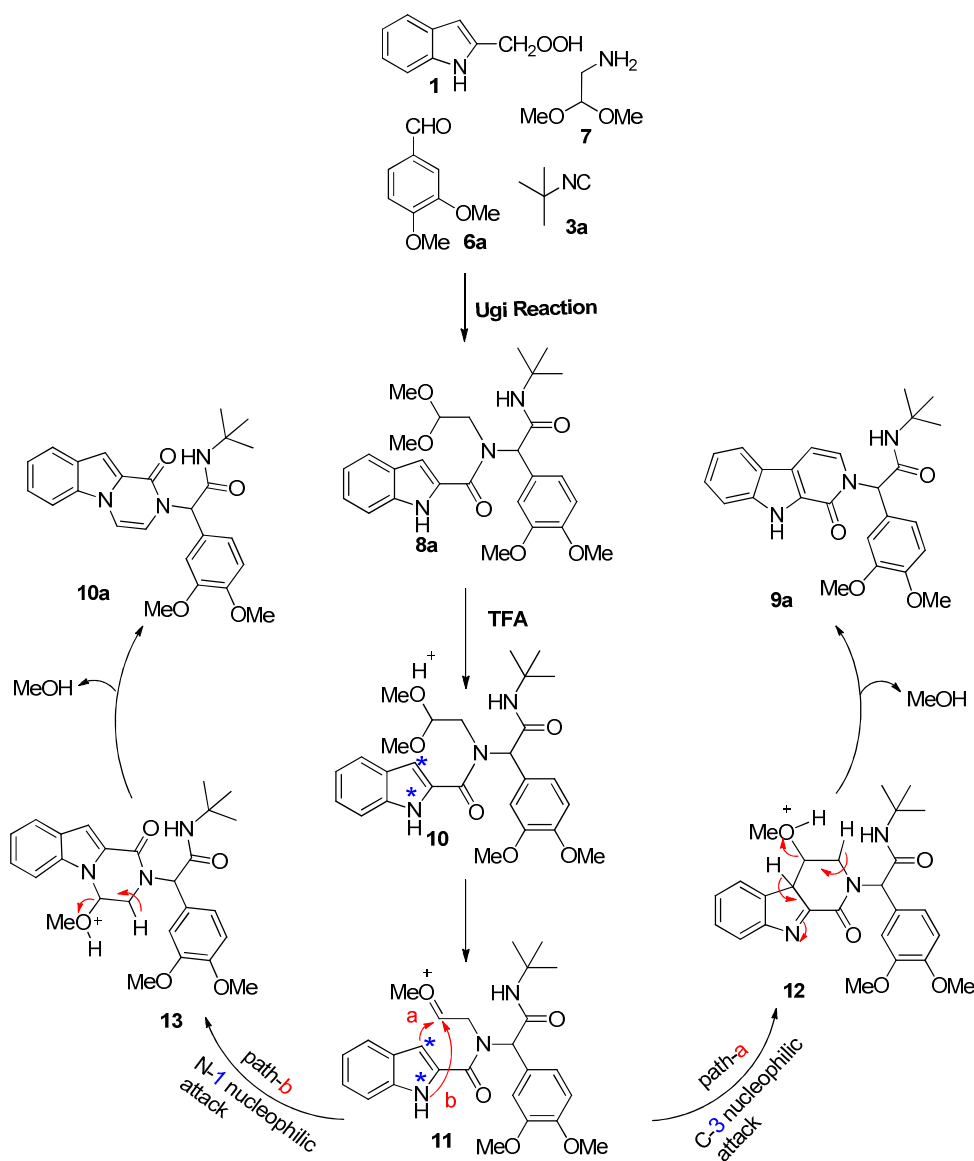


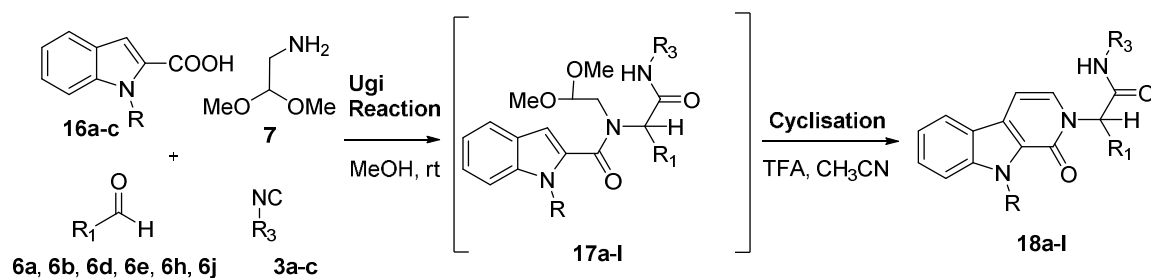
Figure 2: Plausible mechanism for product formation

Further, we have extended the substrate scope of this domino reaction by introducing N-substituted indole-3-carboxylic acids as a carboxylic acid component. The desired N-substituted indole-2-carboxylic acids (**16a-c**) were achieved in good yield only in three steps starting from indole-2-carboxylic acid. Prior to N-functionalization, the substrate **1** was protected through ester formation with thionyl chloride/ethanol leading to indole-2-carboxylic ethyl ester **14**. This intermediate **14** is reacted with corresponding alkyl or benzyl

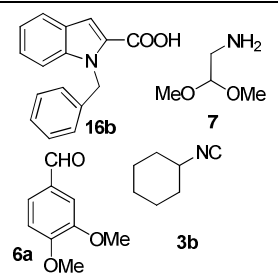
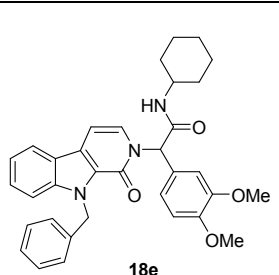
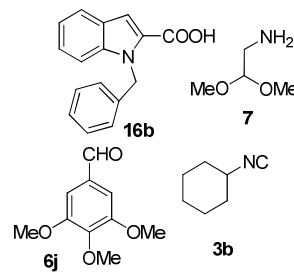
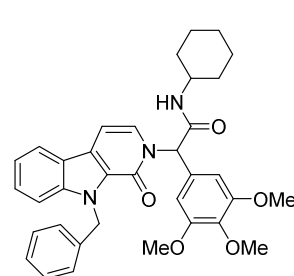
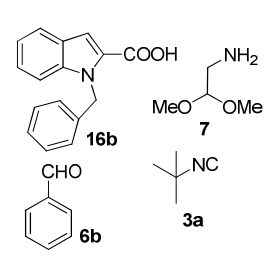
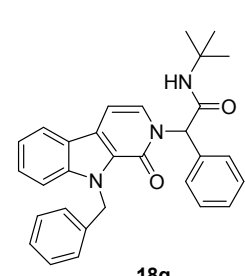
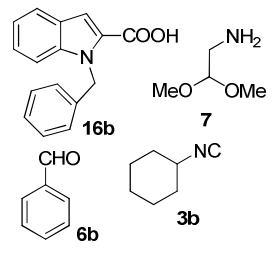
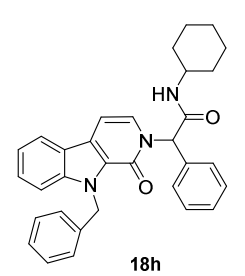
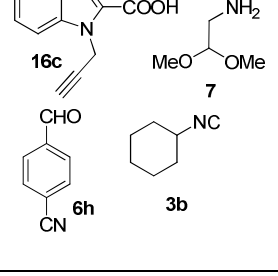
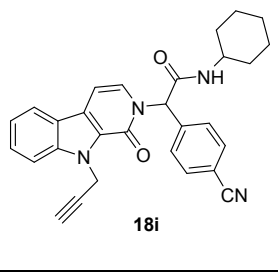
or propargyl halide in presence of NaH in DMF providing N-substituted indole-2-carboxylic ethyl ester **15a-c**. This is followed by hydrolysis with KOH in equimolar ratios of THF:MeOH:H₂O solvent providing the salt of the carboxylic acid which upon neutralisation with dilute hydrochloric acid (pH=2) provided the desired Ugi precursor N-substituted indole-2-carboxylic acid (**16a-c**) in moderate to good yield (see supporting information, **Scheme 1**).

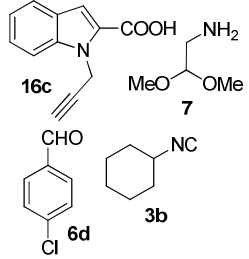
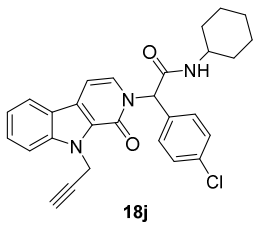
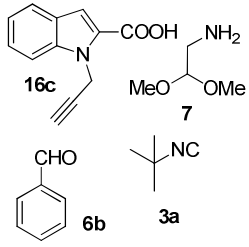
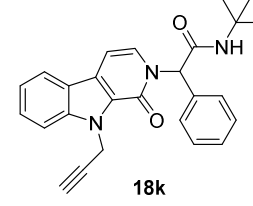
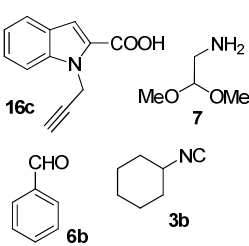
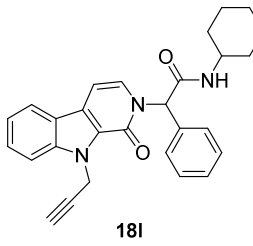
Once these N-substituted indole-2-carboxylic acids (**16a-c**) were in hand, they were subjected to domino Ugi 4CR/cyclisation reaction together with an aryl aldehyde (**6a** or **6b** or **6d** or **6e** or **6h** or **6j**), aminoacetaldehyde dimethyl acetal (**7**), and isocyanides (**3a-c**) under our optimised reaction conditions. Interestingly, all the N-substituted indole-2-carboxylic acids were successfully transformed into the desired N-substituted β -carbolinone analogues (**18a-l**) in excellent yield. Moreover, we found that in all cases products were obtained with minimal variation in isolated yield. We have also notice that cyclisation reaction of Ugi adduct of N-substituted precursors were achieved in lesser time (15-20 min) compared to that of the Ugi product derived from 1H-indole-2-carboxylic acid (20-30 min), which may be due to indole ring activation from the substituents (alkyl, benzyl and propargyl groups). The input of propargyl group over the N-1 position of indole allows a further diversification point on carbolinone heterocycle (entry 9-12, **Table 3**), which could be highly desirable for structural and biological activity assessments. These propargyl linked carbolinones can be further elaborated using various reactions for eg. [3+2]-click reactions,²⁴ aldehyde/alkyne/secondary amine coupling reactions,²⁵ Sonogashira reactions²⁶ and many other cyclisation reactions²⁷.

Table 3: Synthesis of N-substituted β -carbolinone analogues (18a-l) from Ugi/post cyclisation approach.^a



Entry	Starting material	Cyclised product (18a-l)	Yield % ^b
1.			79
2.			81
3.			77
4.			68

5.			72
6			77
7			69
8.			68
9.			71

10.			74
a11.			69
12.			64

^a Reaction conditions: step 1: N-substituted indole 2-carboxylic acid (**16a-c**) (1 mmol), aryl aldehyde (**6a**, **6b**, **6d**, **6e**, **6h**, **6j**) (1 mmol), aminoacetaldehyde dimethyl acetal (**7**) (1.1 mmol), alkyl isocyanide (**3a-c**) (1.1 mmol) in 3 mL solvent, 4-6h, rt (35 °C). Step 2: substrate Ugi adducts **17a-l** (1 mmol), TFA (1.0 equiv.), CH₃CN (2 mL), reaction time (15-20 min.), rt (35 °C), ^b Isolated yield.

Conclusion: In Summary, we have constructed a library of biologically valuable heterocyclic compounds using domino Ugi/post cyclisation approach in a one pot procedure. Our methodology is straightforward to execute and useful in the preparation of wide variety of β -carbolinones and indolo-pyrazinones analogues. In addition, we also applied our protocol to N-substituted indole 2-carboxylic acid precursors which delivered indole C-3 cyclised β -carbolinones in excellent yield. The salient feature of our protocol is atom economy, operational simplicity, high yield and easily available precursors in a very short period of time. By further elaboration and diversification of the various functionally substituted

scaffolds, a wide range of structurally and spatially diverse compounds can be produced. We anticipated that this protocol will open the door for the medicinal chemist to synthesise such frameworks and test for biological activity.

Experimental Section:

General: Melting points are uncorrected and were determined in capillary tubes on a precision melting point apparatus containing silicon oil. IR spectra were recorded on an FTIR spectrophotometer and are reported in terms of frequency of absorption (cm^{-1}). ^1H NMR spectra were recorded on a 400 MHz and 500 MHz spectrometer in CDCl_3 or $\text{DMSO}-d_6$ (all signals are reported in *ppm* with the internal chloroform signal at 7.26-7.28 *ppm*, or the internal DMSO signal at 2.50 *ppm* as standard). ^{13}C NMR spectra were recorded on 100 MHz and 125 MHz spectrometers in CDCl_3 or $\text{DMSO}-d_6$ (all signals are reported in *ppm* with the internal chloroform signal at 77.21 *ppm*, or the internal DMSO signal at 39.51 *ppm* as standard). Chemical shifts δ are given in *ppm* relative to the residual signals of tetramethylsilane in CDCl_3 or deuterated solvent $\text{CDCl}_3/\text{DMSO}-d_6$ for ^1H and ^{13}C NMR spectrometers. Coupling constants *J* are reported in hertz (Hz). Multiplicities are reported as follows: singlet (s), broad (br), doublet (d), triplet (t), quartet (q), and multiplet (m). The HRMS spectra were recorded as ESI-HRMS on Q-TOF, LC-MS/MS mass spectrometer. Reaction progress was routinely monitored by thin-layer chromatography (TLC) on precoated silica gel plates. Column chromatography was performed over silica gel. All the solvents and chemicals were used as procured from the suppliers.

Experimental procedure:

General Procedure 1.

The Two Step One-Pot Synthesis of β -carbolinone (9a-9ab) and indolo-pyrazinone (10a-10ab) analogues: To a mixture of the corresponding aldehyde (**6a-p**) (1.0 mmol) in MeOH, aminoacetaldehyde dimethyl acetal (**7**) (1.1 mmol) was added followed by the addition of

indole 2-carboxylic acid (**1**) (1.0 mmol), the isocyanide (**3a-e**) (1.1 mmol). The reaction was allowed to run for 4-6 h at room temperature (35 °C). The progress of reaction was monitored by TLC. Once starting material was consumed, the MeOH was (*in vacuo*) at low temperature followed by the addition of CH₃CN. The sticky mass was stirred at rt (35 °C) for 5 min. To homogenize the reaction mixture, at which point TFA (1.0 equiv.) was added and the mixture was stirred for 20-30 min. at rt (35 °C). When the reaction was completed (as determined by TLC) the reaction solvents was (*in vacuo*) and directly proceeded for column chromatography (hexane/AcOEt) using 100-200 mesh silica gel to afford the desired product **9a-9ab** and **10a-10ab**.

N-(tert-Butyl)-2-(3,4-dimethoxyphenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-

yl)acetamide (9a). Isolated as a green solid; 79 % yield (342 mg); mp 150-153 °C; IR (KBr) ν_{max} : 3398, 3019, 1647, 1215, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 11.00 (s, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8 Hz, 1H), 6.98 (s, 1H), 6.96 (d, *J* = 4.9 Hz, 1H), 6.94 (s, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.27 (s, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 1.40 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ : 167.6, 156.0, 149.4, 140.1, 128.0, 127.1, 127.0, 126.6, 125.3, 122.2, 121.7, 121.3, 120.0, 112.6, 112.0, 111.3, 101.4, 61.1, 55.8, 52.0, 28.6 ppm; HRMS (ESI) calcd for [C₂₅H₂₈N₃O₄]⁺ 434.2080; found 434.2065.

N-(tert-Butyl)-2-(3,4-dimethoxyphenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-

yl)acetamide (10a). Isolated as a yellow solid; 11 % yield (47 mg); mp 90-93 °C; IR (KBr) ν_{max} : 3393, 2926, 1627, 1068, 762 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.84 (d, *J* = 8 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.44 (s, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 6.2 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 1.9 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.63 (s, 1H), 6.55 (d, *J* = 6.2 Hz, 1H), 5.98 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 1.41 (s,

9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.6, 157.4, 149.4, 132.1, 127.7, 127.4, 127.2, 124.1, 122.6, 122.4, 121.6, 113.3, 111.9, 111.3, 110.5, 105.7, 103.3, 59.2, 55.9, 52.1, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_4]^+$ 434.2080; found 434.2065.

N-(tert-Butyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-phenylacetamide(9b). Isolated as a white solid; 64 % yield (238 mg); mp 123-126 °C; IR (KBr) ν_{max} : 3310, 3019, 1648, 1216, 759 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.58 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 7.3 Hz, 1H), 7.47-7.43 (m, 5H), 7.27 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.03 (d, J = 7 Hz, 1H), 6.96 (s, 1H), 6.07 (bs, 1H), 1.41 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.4, 155.6, 140.3, 135.6, 129.2, 129.1, 129.0, 127.5, 126.8, 126.7, 126.1, 121.9, 121.3, 120.3, 112.7, 102.3, 61.9, 52.2, 28.5 *ppm*; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_2]^+$ 374.1869; found 374.1859.

N-(tert-Butyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)-2-phenylacetamide (10b). Isolated as an orange solid; 9 % yield (33 mg); mp 151-155 °C; IR (KBr) ν_{max} : 3422, 3019, 1630, 1215, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.84 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.47-7.41 (m, 4H), 7.39 (d, J = 6.7 Hz, 2H), 7.33 (s, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 6 Hz, 1H), 6.74 (s, 1H), 6.56 (d, J = 6.1 Hz, 1H), 6.03 (s, 1H), 1.42 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.4, 157.4, 135.5, 132.1, 129.1, 128.9, 128.8, 127.7, 127.2, 124.1, 122.6, 122.4, 113.4, 110.4, 105.7, 103.4, 59.2, 52.1, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_2]^+$ 374.1869; found 374.1865.

N-(tert-Butyl)-2-(4-nitrophenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide (9c). Isolated as a yellow solid; 67 % yield (280 mg); mp 120-123 °C; IR (KBr) ν_{max} : 3398, 3019, 1648, 1215, 769 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.11 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.24 (s, 1H), 8.22 (s, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.57 (s, 2H), 7.55 (s, 1H), 7.22 (d, J = 7.2 Hz, 1H), 7.05 (s, 1H), 7.03 (d, J = 7.1 Hz, 1H), 6.99 (s, 1H), 6.41 (s, 1H), 1.41 (s, 9H)

ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 168.8, 166.4, 155.7, 143.2, 141.4, 139.8, 129.8, 129.4, 127.5, 126.1, 125.6, 124.2, 124.0, 121.4, 120.6, 112.4, 102.2, 60.3, 52.4, 28.5 *ppm*. HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{23}\text{N}_4\text{O}_4]^+$ 419.1719; found 419.1701.

N-(tert-Butyl)-2-(4-nitrophenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide (10c).

Isolated as a pale yellow solid; 12 % yield (50 mg); mp 130-133 °C; IR (KBr) ν_{max} : 3399, 3019, 1648, 1215, 770 cm^{-1} ; ^1H NMR(400 MHz, CDCl_3) δ : 8.26 (d, J = 8.9 Hz, 2H), 7.83 (d, J = 8 Hz, 1H), 7.62 (d, J = 8.5 Hz, 3H), 7.43 (t, J = 6.8 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 7.31 (s, 1H), 6.88 (s, 1H), 6.64 (d, J = 6.2 Hz, 1H), 6.60 (s, 1H), 1.43 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 166.3, 157.3, 147.9, 142.6, 132.3, 129.5, 127.6, 126.5, 124.7, 124.1, 122.8, 122.7, 112.5, 110.5, 106.7, 104.3, 58.3, 52.5, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{23}\text{N}_4\text{O}_4]^+$ 419.1719; found 419.1713.

N-(tert-Butyl)-2-(4-chlorophenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(9d). Isolated as a white solid; 62 % yield (252 mg); mp 113-116 °C; IR (KBr) ν_{max} : 3400, 3019, 1622, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 11.16 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.5 Hz, 2H), 7.17 (d, J = 7.4 Hz, 2H), 7.13 (s, 2H), 6.97 (d, J = 7.4 Hz, 1H), 6.49 (s, 1H), 1.40 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.2, 156.0, 140.1, 134.7, 130.2, 129.2, 127.0, 126.4, 125.3, 122.1, 121.3, 120.2, 112.6, 101.8, 60.4, 52.1, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{23}\text{ClN}_3\text{O}_2]^+$ 408.1479; found 408.1465.

N-(tert-Butyl)-2-(4-chlorophenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(10d). Isolated as a white solid; 11 % yield (44 mg); mp 135-137 °C; IR (KBr) ν_{max} : 3400, 3019, 1628, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.85 (d, J = 8 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.45 (s, 1H), 7.43 (t, J = 8 Hz, 1H), 7.39 (t, J = 1.1 Hz, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 7.26 (d, J = 6.1 Hz, 1H), 6.68 (s, 1H), 6.55 (d, J = 6.1 Hz, 1H), 6.01 (s, 1H), 1.41 (s,

9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.1, 157.3, 134.8, 134.0, 132.2, 130.2, 129.3, 127.6, 126.9, 124.3, 122.6, 113.1, 110.5, 106.0, 103.6, 58.4, 52.2, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{23}\text{ClN}_3\text{O}_2]^+$ 408.1479; found 408.1473.

N-(tert-Butyl)-2-(4-hydroxyphenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide (9e). Isolated as a white solid; 72 % yield (280 mg); mp 160-163 °C; IR (KBr) ν_{max} : 3400, 3019, 1647, 1215, 758 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9.63 (s, 1H), 8.20 (s, 1H), 7.98 (d, J = 8 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.45-7.39 (m, 2H), 7.27 (d, J = 8.6 Hz, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 7 Hz, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 6.80 (s, 1H), 6.78 (s, 1H), 1.29 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3 + $\text{DMSO}-d_6$) δ : 168.0, 157.3, 155.8, 139.7, 130.4, 127.1, 126.6, 126.2, 125.4, 122.0, 121.2, 120.0, 115.9, 112.2, 101.1, 61.0, 51.6, 28.2 *ppm*; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_3]^+$ 390.1818; found 390.1804.

N-(tert-Butyl)-2-(4-hydroxyphenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide (10e). Isolated as a white solid; 12 % yield (47 mg); mp 150-153 °C; IR (KBr) ν_{max} : 3400, 3019, 1625, 1216, 769 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.82 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.43 (s, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 6 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 6.56 (s, 1H), 6.51 (d, J = 6.1 Hz, 1H), 6.00 (s, 1H), 1.39 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 168.0, 157.9, 156.5, 132.1, 130.6, 127.6, 127.4, 126.7, 124.2, 122.8, 122.5, 116.1, 114.6, 112.0, 105.7, 102.3, 58.8, 51.1, 28.8 *ppm*; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_3]^+$ 390.1818; found 390.1822.

N-(tert-Butyl)-2-(naphthalen-1-yl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide (9f). Isolated as a white solid; 74 % yield (313 mg); mp 220-223 °C; IR (KBr) ν_{max} : 3399, 3019, 1647, 1215, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.43 (s, 1H), 8.01-7.96 (m, 2H), 7.91-7.86 (m, 3H), 7.66 (d, J = 2.8 Hz, 1H), 7.63 (d, J = 5.4 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H),

7.50-7.45 (m, 1H), 7.44-7.41 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 6.83 (d, J = 7.3 Hz, 1H), 5.96 (s, 1H), 1.44 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.9, 155.7, 139.9, 134.1, 131.7, 130.2, 128.9, 127.7, 127.6, 127.2, 126.9, 126.4, 126.3, 125.2, 123.1, 122.3, 121.3, 120.0, 112.6, 101.0, 58.4, 52.2, 28.6s *ppm*; HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{26}\text{N}_3\text{O}_2]^+$ 424.2025; found 424.2023.

N-(tert-Butyl)-2-(naphthalen-1-yl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(**10f**). Isolated as a white solid; 8 % yield (34 mg); mp 140-143 °C; IR (KBr) ν_{max} : 3419, 3019, 1618, 1215, 756 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 8.00-7.95 (m, 2H), 7.92-7.89 (m, 1H), 7.84 (d, J = 7.8 Hz, 2H), 7.60 (d, J = 7.7 Hz, 1H), 7.56 (s, 1H), 7.54 (d, J = 2.4 Hz, 1H), 7.53 (t, J = 4 Hz, 2H), 7.38 (t, J = 7 Hz, 1H), 7.32 (d, J = 5.9 Hz, 2H), 7.12 (d, J = 6.2 Hz, 1H), 6.41 (d, J = 6 Hz, 1H), 5.81 (s, 1H), 1.44 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.9, 157.0, 134.0, 132.0, 131.6, 131.0, 130.2, 128.9, 127.7, 127.1, 126.5, 125.1, 124.1, 123.0, 122.5, 122.4, 113.0, 110.4, 105.6, 103.4, 56.7, 52.2, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{26}\text{N}_3\text{O}_2]^+$ 424.2025, found 424.2022.

N-Cyclohexyl-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-phenylacetamide (9g). Isolated as a white solid; 72 % yield (287 mg); mp 171-174 °C; IR (KBr) ν_{max} : 3400, 3019, 2933 1650, 1215, 759 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.80 (s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 2.5 Hz, 1H), 7.44 (m, 2H), 7.42 (t, J = 1.4 Hz, 2H), 7.406-7.400 (t, J = 1.6 Hz, 1H), 7.21 (d, J = 7.3 Hz, 2H), 7.10 (s, 1H), 6.96 (d, J = 7 Hz, 1H), 6.31 (d, J = 8 Hz, 1H), 3.94-3.86 (m, 1H), 2.01 (d, J = 12.5 Hz, 1H), 1.93 (d, J = 9.6 Hz, 2H), 1.71-1.65 (m, 2H), 1.62-1.57 (m, 1H), 1.39-1.32 (m, 2H), 1.19-1.13 (m, 2H) *ppm*; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 167.3, 155.5, 139.9, 137.6, 129.3, 128.9, 128.6, 127.7, 127.3, 126.8, 123.6, 122.2, 121.6, 120.0, 113.0, 99.7, 59.6, 48.5, 32.6, 32.6, 25.6, 24.9 *ppm*; HRMS (ESI) calcd for $[\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_2]^+$ 400.2025; found 400.2021.

N-Cyclohexyl-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)-2-phenylacetamide (10g). Isolated as a white solid; 12 % yield (48 mg); mp 170-173 °C; IR (KBr) $\nu_{\max}$: 3400, 3019, 2929, 1629, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.83 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.46-7.38 (m, 7H), 7.33 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 6 Hz, 1H), 6.80 (s, 1H), 6.62 (d, J = 5.8 Hz, 1H), 6.26 (d, J = 8 Hz, 1H), 3.90-3.87 (m, 1H), 2.03 (d, J = 12.5 Hz, 1H), 1.96 (d, J = 12.4 Hz, 1H), 1.75-1.68 (m, 2H), 1.64-1.59 (m, 1H), 1.44-1.34 (m, 2H), 1.25-1.14 (m, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.2, 157.4, 135.3, 132.1, 129.1, 128.8, 127.7, 127.1, 124.1, 122.6, 122.4, 113.4, 110.5, 105.8, 103.5, 59.0, 48.9, 32.8, 32.7, 25.4, 24.7 *ppm*; HRMS (ESI) calcd for $[\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_2]^+$ 400.2025; found 400.2022.

2-(1-Oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-phenyl-N-(2,4,4-trimethylpentan-2-yl)acetamide (9h). Isolated as a green solid; 69 % yield (296 mg); mp 110-113 °C; IR (KBr) $\nu_{\max}$: 3418, 3019, 1648, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.85 (s, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.48-7.42 (m, 3H), 7.41 (t, J = 7.4 Hz, 3H), 7.25-7.21 (m, 1H), 7.04 (s, 1H), 6.98 (d, J = 7.2 Hz, 1H), 6.17 (s, 1H), 1.85 (d, J = 14.5 Hz, 1H), 1.66 (d, J = 14.8 Hz, 1H), 1.49 (s, 3H), 1.46 (s, 3H), 0.90 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.0, 156.0, 140.1, 135.9, 129.1, 128.9, 128.7, 127.2, 127.0, 126.4, 125.1, 122.2, 121.2, 120.1, 112.7, 101.6, 61.6, 56.1, 52.2, 31.3, 28.9, 28.5 *ppm*; HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{32}\text{N}_3\text{O}_2]^+$ 430.2495; found 430.2483.

2-(1-Oxopyrazino[1,2-a]indol-2(1H)-yl)-2-phenyl-N-(2,4,4-trimethylpentan-2-yl)acetamide (10h). Isolated as a white solid; 8 % yield (34 mg); mp 160-163 °C; IR (KBr) $\nu_{\max}$: 3323, 3019, 1617, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.85 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.48 (t, J = 8 Hz, 3H), 7.43 (t, J = 3 Hz, 1H), 7.41 (t, J = 2.4 Hz, 2H), 7.40 (d, J = 3.2 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.25 (d, J = 6.2 Hz, 1H), 6.68 (s, 1H), 6.58 (d, J = 6.1 Hz, 1H), 5.94 (s, 1H), 1.91 (d, J = 14.8 Hz, 1H), 1.63 (d, J = 14.7 Hz, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 0.95 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.0, 157.3, 135.2,

132.1, 129.1, 128.9, 128.8, 127.7, 127.1, 124.1, 122.6, 122.4, 113.3, 110.5, 105.8, 103.5, 59.5, 56.2, 52.1, 31.4, 29.0, 28.6 *ppm*; HRMS (ESI) calcd for $[C_{27}H_{32}N_3O_2]^+$ 430.2495; found 430.2493.

N-(4-Methoxyphenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-phenylacetamide (9i).

Isolated as a yellow solid; 46 % yield (194 mg); mp 180-183 °C; IR (KBr) $\nu_{\max}$: 3401, 3019, 1644, 1215, 758 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d^6) δ : 10.60 (s, 1H), 8.00 (d, J = 8 Hz, 1H), 7.57-7.54 (m, 3H), 7.50-7.38 (m, 7H), 7.20 (t, J = 8 Hz, 1H), 7.07 (s, 1H), 6.98 (s, 2H), 6.93-6.89 (m, 2H), 3.72 (s, 3H) *ppm*; ^{13}C NMR (100 MHz, DMSO- d^6) δ : 166.8, 156.0, 155.6, 139.9, 136.6, 132.2, 129.6, 129.4, 129.4, 127.39, 127.32, 126.95, 123.8, 122.1, 121.7, 121.2, 120.1, 114.4, 113.0, 100.0, 60.9, 55.6 *ppm*; HRMS (ESI) calcd for $[C_{26}H_{22}N_3O_3]^+$ 424.1661; found 424.1656.

N-(4-Methoxyphenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)-2-phenylacetamide (10i).

Isolated as a pink solid; 11 % yield (46 mg); mp 160-163 °C; IR (KBr) $\nu_{\max}$: 3392, 1623, 1403, 1215, 765 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 8.54 (s, 1H), 7.82 (d, J = 8 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.53 (d, J = 9 Hz, 4H), 7.43 (t, J = 4.0 Hz, 5H), 7.33 (d, J = 7.5 Hz, 1H), 7.30 (ds, J = 4.5 Hz, 2H), 7.06 (s, 1H), 6.85 (d, J = 8.9 Hz, 1H), 6.67 (d, J = 6.1 Hz, 1H), 3.78 (s, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 166.4, 157.6, 156.6, 134.7, 132.1, 130.7, 129.2, 128.9, 127.7, 126.9, 124.3, 122.6, 122.5, 121.7, 114.1, 113.2, 110.5, 106.2, 103.6, 59.8, 55.4 *ppm*; HRMS (ESI) calcd for $[C_{26}H_{22}N_3O_3]^+$ 424.1661; found 424.1663.

2-(1-Oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-N-pentyl-2-phenylacetamide (9j). Isolated as a yellow solid; 72 % yield (279 mg); mp 110-113 °C; IR (KBr) $\nu_{\max}$: 3399, 3019, 1646, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 9.91 (s, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 7 Hz, 1H), 7.45-7.40 (m, 5H), 7.27 (t, J = 7.3 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.00 (s, 1H), 6.95 (d, J = 7.4 Hz, 1H), 6.32 (s, 1H), 3.40-3.30 (m, 2H), 1.55 (t, J = 8.0 Hz, 2H), 1.30-1.27 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H) *ppm*; ^{13}C NMR (100 MHz, DMSO- d_6) δ :

168.2, 155.5, 139.9, 137.3, 129.4, 129.1, 128.8, 127.5, 127.3, 126.8, 123.6, 122.1, 121.7, 120.1, 112.9, 99.8, 59.9, 39.2, 28.98, 28.92, 22.2, 14.3 ppm; HRMS (ESI) calcd for $[C_{24}H_{26}N_3O_2]^+$ 388.2025, found 388.2026.

2-(1-Oxopyrazino[1,2-a]indol-2(1H)-yl)-N-pentyl-2-phenylacetamide (10j). Isolated as a yellow solid; 11 % yield (42 mg); mp 125-127 °C; IR (KBr) $\nu_{\max}$: 3398, 3018, 1619, 1215, 757 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ : 7.85 (d, J = 8 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.45 (s, 2H), 7.43 (d, J = 7.6 Hz, 4H), 7.39 (d, J = 4.6 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.26 (d, J = 6 Hz, 1H), 6.77 (s, 1H), 6.59 (d, J = 6 Hz, 1H), 6.17 (bs, 1H), 3.43-3.30 (m, 2H), 1.58 (t, J = 8.0 Hz, 2H), 1.34-1.29 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ : 168.0, 157.4, 135.0, 132.1, 129.1, 128.8, 127.7, 127.3, 127.1, 124.2, 122.6, 122.5, 113.2, 110.5, 106.0, 103.5, 59.1, 39.9, 29.0, 29.0, 22.2, 13.9 ppm; HRMS (ESI) calcd for $[C_{24}H_{26}N_3O_2]^+$ 388.2025; found 388.2018.

N-Cyclohexyl-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)hexanamide (9k). Isolated as a white solid; 13 % yield (49 mg); mp 220-223 °C; IR (KBr) $\nu_{\max}$: 3400, 3019, 1649, 1215, 770 cm^{-1} ; 1H NMR (400 MHz, $DMSO-d_6$) δ : 11.91 (s, 1H), 8.22 (d, J = 8 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.43 (t, J = 7.1 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 5.69-5.65 (m, 1H), 3.55-3.52 (m, 1H), 2.05-2.00 (m, 1H), 1.91-1.86 (m, 1H), 1.76 (d, J = 9.3 Hz, 1H), 1.66 (bs, 3H), 1.55 (d, J = 12.1 Hz, 1H), 1.33-1.26 (m, 2H), 1.24-1.15 (m, 4H), 1.13-1.08 (m, 3H), 0.83 (t, J = 8 Hz, 3H) ppm; poor solubility so carbon is not clear; HRMS (ESI) calcd for $[C_{23}H_{30}N_3O_2]^+$ 380.2338; found 380.2334.

N-Cyclohexyl-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)hexanamide (10k). Isolated as a yellow solid; 11 % yield (42 mg); mp 150-153 °C; IR (KBr) $\nu_{\max}$: 3413, 3018, 2931, 1627, 1215, 757 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ : 7.85 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 8.4 Hz,

1H), 7.45 (t, J = 8 Hz, 2H), 7.37 (t, J = 6.1 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 5.9 Hz, 1H), 6.20 (d, J = 8.2 Hz, 1H), 5.44 (t, J = 7.8 Hz, 1H), 3.78-3.69(m, 1H), 2.20-2.11 (m, 1H), 1.96-1.86 (m, 2H), 1.80 (t, J = 12.0 Hz, 2H), 1.66 (t, J = 20.0 Hz, 3H), 1.41-1.31 (m, 3H), 1.27-1.23 (m, 2H), 1.21-1.06 (m, 3H), 0.92 (t, J = 6.8 Hz, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 168.5, 157.4, 132.1, 127.7, 127.1, 124.3, 122.6, 111.1, 110.5, 106.7, 103.5, 55.5, 48.5, 32.8, 32.7, 27.8, 25.4, 24.7, 24.6, 22.3, 13.8 *ppm*; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{30}\text{N}_3\text{O}_2]^+$ 380.2338; found 380.2335.

N-Cyclohexyl-2-(4-(2-(cyclohexylamino)-2-oxo-1-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)ethyl)phenyl)-2-(1-oxo-1H-pyrido[4,3-b]indol-2(5H)-yl)acetamide (9l). Isolated as a white solid; 58 % yield (418 mg); mp 200-203 °C; IR (KBr) ν_{max} : 3389, 3019, 1649, 1215, 757 cm^{-1} ; ^1H NMR (500 MHz, DMSO-d_6) δ : 11.99 (s, 2H), 8.61-8.58 (m, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.84-7.80 (m, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.43 (t, J = 7.7 Hz, 3H), 7.38 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 9.4 Hz, 2H), 7.32(t, J = 3.9 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 7.10 (t, J = 7.4 Hz, 2H), 6.97 (s, 1H), 6.96 (d, J = 3.7 Hz, 2H), 3.67-3.59 (m, 2H), 1.82 (d, J = 10.9 Hz, 2H), 1.75 (d, J = 10.3 Hz, 2H), 1.63-1.52 (m, 6H), 1.29-1.19 (m, 4H), 1.16-1.09 (m, 6H) *ppm*; ^{13}C NMR (100 MHz, DMSO-d_6) δ : 167.0, 155.5, 139.9, 129.9, 129.2, 127.4, 127.2, 126.6, 123.6, 122.4, 122.1, 121.5, 119.9, 112.9, 106.2, 99.8, 59.0, 48.6, 32.6, 25.6, 24.9s *ppm*; HRMS (ESI) calcd for $[\text{C}_{44}\text{H}_{45}\text{N}_6\text{O}_4]^+$ 721.3502; found 721.3475.

N-(tert-Butyl)-2-(1H-indol-3-yl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide (10m). Isolated as a brown solid; 12 % yield (49 mg); mp 160-163 °C; IR (KBr) ν_{max} : 3398, 3019, 1650, 1215, 769 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 8.92 (s, 1H), 8.21 (s, 1H), 7.96 (d, J = 8 Hz, 1H), 7.55 (d, J = 3.7 Hz, 2H), 7.54 (d, J = 2.8 Hz, 1H), 7.41 (s, 1H), 7.35 (d, J = 6.8 Hz, 2H), 7.20 (t, J = 5.8 Hz, 1H), 7.16 (t, J = 8.0 Hz, 2H), 7.02 (t, J = 7.7 Hz, 1H), 6.69 (s, 1H), 6.50 (s, 1H), 6.33 (t, J = 5.5 Hz, 1H), 1.33 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 172.0, 159.7, 136.2, 131.6, 126.9, 126.7, 124.3, 124.0, 123.0, 122.7, 122.1, 121.9, 119.4, 119.1,

117.2, 113.6, 111.3, 110.5, 110.4, 106.1, 51.3, 41.9, 28.6 *ppm*; HRMS (ESI) calcd for $[C_{25}H_{25}N_4O_2]^+$ 413.1978; found 413.1974.

N-(tert-Butyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-(3,4,5-

trimethoxyphenyl)acetamide (9n). Isolated as a gray solid; 68 % yield (314 mg); mp 170-173 °C; IR (KBr) $\nu_{\max}$: 3400, 3019, 1647, 1215, 757 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ : 10.72 (s, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 7.4 Hz, 1H), 7.25 (t, J = 7.2 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 7 Hz, 2H), 6.69 (s, 2H), 6.14 (bs, 1H), 3.88 (s, 3H), 3.80 (s, 6H), 1.41 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.5, 153.6, 140.1, 138.2, 131.2, 127.1, 126.9, 126.6, 125.2, 122.2, 121.3, 120.0, 112.6, 106.2, 101.3, 61.2, 60.8, 56.0, 52.0, 28.5 *ppm*; HRMS (ESI) calcd for $[C_{26}H_{30}N_3O_5]^+$ 464.2185; found: 464.2207.

N-(tert-Butyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)-2-(3,4,5-

trimethoxyphenyl)acetamide (10n). Isolated as a yellow solid; 12 % yield (55 mg); mp 150-154 °C; IR (KBr) $\nu_{\max}$: 3343, 3015, 2927, 1628, 1218, 759 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.85 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.34-7.30 (m, 1H), 7.27 (d, J = 6.4 Hz, 1H), 6.69 (s, 2H), 6.60 (bs, 1H), 6.58 (d, J =6.4 Hz, 1H), 5.85 (s, 1H), 3.88 (s, 3H), 3.85 (s, 6H), 1.43 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.4, 157.4, 153.7, 138.3, 132.1, 130.5, 127.7, 127.1, 124.2, 122.6, 122.5, 113.3, 110.5, 106.1, 105.7, 103.4, 60.8, 59.3, 56.2, 52.1, 28.5 *ppm*; HRMS (ESI) calcd for $[C_{26}H_{30}N_3O_5]^+$ 464.2185; found 464.2217.

N-(tert-Butyl)-2-(4-methoxyphenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(9o). Isolated as a green solid; 71 % yield (286 mg); mp 160-164 °C; IR (KBr) $\nu_{\max}$: 3421, 3019, 1647, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.26 (s, 1H) 7.93 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 6.9 Hz, 1H), 7.40 (d, J = 9 Hz, 2H), 7.25 (t, J = 7.4

Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 6.96 (d, J = 8.1 Hz, 3H), 6.92 (d, J = 7.2 Hz, 1H), 6.06 (s, 1H), 3.84 (s, 3H), 1.40 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.7, 159.8, 156.0, 139.9, 130.4, 127.9, 127.2, 126.9, 126.5, 125.0, 122.3, 121.2, 120.0, 114.5, 112.6, 101.1, 60.7, 55.3, 52.0, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_3]^+$ 404.1974; found 404.1971.

N-(tert-Butyl)-2-(4-methoxyphenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(**10o**). Isolated as a pink solid; 13 % yield (52 mg); mp 167-170 °C; IR (KBr) ν_{max} : 3421, 3019, 1629, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.84 (d, J = 8 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.44 (s, 1H), 7.40-7.37 (m, 3H), 7.32 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 6.6 Hz, 1H), 6.96 (d, J = 9.1 Hz, 2H), 6.65 (s, 1H), 6.54 (d, J = 6.3 Hz, 1H), 5.92 (s, 1H), 3.84 (s, 3H), 1.41 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.7, 159.9, 157.3, 132.1, 130.3, 127.7, 127.2, 124.0, 122.5, 122.4, 114.5, 113.4, 110.4, 105.6, 103.2, 58.9, 55.3, 52.0, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_3]^+$ 404.1974; found 404.1972.

N-(tert-Butyl)-2-(4-fluorophenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(**9p**). Isolated as a yellow solid; 64 % yield (250 mg); mp 150-155 °C; IR (KBr) ν_{max} : 3420, 3019, 1647, 1215, 769 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.67 (s, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.46-7.41 (m, 3H), 7.25 (t, J = 7.4 Hz, 1H), 7.16 (d, J = 7.1 Hz, 1H), 7.12 (t, J = 8.5 Hz, 2H), 7.02 (s, 1H), 6.97 (d, J = 7.3 Hz, 1H), 6.26 (s, 1H), 1.39 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.3, 155.9, 139.9, 131.8, 130.8, 130.7, 127.1, 126.3, 125.2, 122.2, 121.3, 120.2, 116.2, 116.0, 112.5, 101.6, 60.3, 52.1, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{23}\text{FN}_3\text{O}_2]^+$ 392.1774; found 392.1769.

N-(tert-Butyl)-2-(4-fluorophenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(**10p**). Isolated as an orange solid; 12 % yield (47 mg); mp 178-180 °C; IR (KBr) ν_{max} : 3418, 3018, 1629, 1217, 759 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.85 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.46-7.43 (m, 3H), 7.41 (t, J = 1.3 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.26 (d,

$J = 6.2$ Hz, 1H), 7.14 (t, $J = 8.6$ Hz, 2H), 6.67 (s, 1H), 6.54 (d, $J = 6.3$ Hz, 1H), 5.94 (bs, 1H), 1.41 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.3, 157.3, 132.2, 131.2, 130.8, 130.7, 127.7, 127.0, 124.3, 122.6, 122.5, 116.2, 116.0, 113.0, 110.4, 105.9, 103.6, 58.4, 52.2, 28.6 ppm; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{23}\text{FN}_3\text{O}_2]^+$ 392.1774; found 392.1769.

2-(4-Bromophenyl)-N-(tert-butyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(9q). Isolated as a yellow solid; 62 % yield (280 mg); mp 98-101 °C; IR (KBr) ν_{max} : 3400, 3019, 1625, 1215, 760 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.77 (s, 1H), 7.94 (d, $J = 8$ Hz, 1H), 7.58-7.52 (m, 3H), 7.46 (t, $J = 7.6$ Hz, 1H), 7.32 (s, 2H), 7.25 (t, $J = 7.6$ Hz, 1H), 7.16 (d, $J = 7.2$ Hz, 1H), 7.04 (s, 1H), 6.97 (d, $J = 7.2$ Hz, 1H), 6.33 (s, 1H), 1.39 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.1, 156.0, 140.1, 135.2, 132.2, 130.5, 127.1, 127.0, 126.4, 125.3, 122.9, 122.2, 121.3, 120.2, 112.6, 101.8, 60.5, 52.1, 28.6 ppm; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{23}\text{BrN}_3\text{O}_2]^+$ 452.0974; found 452.0961.

2-(4-Bromophenyl)-N-(tert-butyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(10q). Isolated as a white solid; 8 % yield (36 mg); mp 135-138 °C; IR (KBr) ν_{max} : 3400, 3019, 1629, 1215, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.85 (d, $J = 8.2$ Hz, 1H), 7.64 (d, $J = 8.4$ Hz, 1H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.46 (s, 1H), 7.43 (t, $J = 7.5$ Hz, 1H), 7.34 (d, $J = 8.5$ Hz, 3H), 7.26 (d, $J = 6.2$ Hz, 1H), 6.65 (s, 1H), 6.54 (d, $J = 6.1$ Hz, 1H), 5.99 (s, 1H), 1.41 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.0, 157.3, 134.5, 132.3, 132.2, 130.5, 127.6, 126.9, 124.3, 123.0, 122.6, 122.5, 113.0, 110.5, 106.0, 103.6, 58.4, 52.2, 28.6 ppm; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{23}\text{BrN}_3\text{O}_2]^+$ 452.0974; found 452.0970.

N-(tert-Butyl)-2-(4-cyanophenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(9r). Isolated as a white solid; 69 % yield (275 mg); mp 150-152 °C; IR (KBr) ν_{max} : 3356, 3019, 1651, 1215, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.01 (s, 1H), 7.97 (d, $J = 7.8$ Hz, 1H), 7.70 (d, $J = 7.8$ Hz, 2H), 7.57 (d, $J = 8.5$ Hz, 1H), 7.52 (t, $J = 7.1$ Hz, 3H), 7.30 (d, $J = 15$

Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 6.98 (bs, 1H), 6.28 (s, 1H), 1.40 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, DMSO- d_6) δ : 166.9, 155.4, 143.4, 139.9, 133.2, 129.7, 127.4, 127.2, 126.9, 123.7, 122.2, 121.7, 120.1, 118.9, 113.0, 111.4, 100.1, 59.5, 51.4, 28.7 *ppm*; HRMS (ESI) calcd for $[\text{C}_{24}\text{H}_{23}\text{N}_4\text{O}_2]^+$ 399.1821; found 399.1806.

N-(tert-Butyl)-2-(4-cyanophenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(**10r**). Isolated as an orange solid; 11 % yield (44 mg); mp 170-173 °C; IR (KBr) ν_{max} : 3358, 3019, 1629, 1215, 760 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.84 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.44 (s, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 5.3 Hz, 1H), 6.79 (s, 1H), 6.59 (d, J = 6.2 Hz, 1H), 6.38 (s, 1H), 1.42 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 166.5, 157.3, 140.9, 132.6, 132.3, 129.2, 127.6, 126.6, 124.6, 122.7, 122.6, 118.2, 112.7, 110.5, 106.5, 104.0, 58.5, 52.3, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{24}\text{H}_{23}\text{N}_4\text{O}_2]^+$ 399.1821; found 399.1808.

N-(tert-Butyl)-2-(2-chlorophenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(**9s**). Isolated as a white solid; 68 % yield (277 mg); mp 150-153 °C; IR (KBr) ν_{max} : 3400, 3019, 1650, 1330, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 11.09 (s, 1H), 7.92 (d, J = 8 Hz, 1H), 7.64-7.59 (m, 2H), 7.46-7.42 (m, 2H), 7.40-7.36 (m, 3H), 7.25 (d, J = 12.1 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.96 (d, J = 7.3 Hz, 1H), 6.24 (s, 1H), 1.41 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.0, 155.8, 140.0, 135.3, 133.7, 130.4, 130.2, 127.3, 126.9, 125.6, 124.9, 122.2, 121.1, 120.0, 112.8, 101.5, 60.0, 52.1, 28.5 *ppm*; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{23}\text{ClN}_3\text{O}_2]^+$ 408.1479; found 408.1460.

N-(tert-Butyl)-2-(2-chlorophenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(**10s**). Isolated as a pink solid; 9 % yield (37 mg); mp 170-173 °C; IR (KBr) ν_{max} : 3019, 2926, 1632, 1215, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.84(d, J = 8.0 Hz, 1H), 7.69 (d, J = 3.9 Hz, 1H), 7.67 (d, J = 4.0 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.48 (t, J = 3.5 Hz, 2H), 7.45 (s,

1H), 7.42-7.36 (m, 3H), 7.33 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 6.3 Hz, 1H), 6.79 (s, 1H), 6.38 (d, J = 8.0 Hz, 1H), 6.00 (s, 1H), 1.41 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.0, 157.0, 135.3, 132.9, 132.1, 130.5, 130.4, 130.3, 127.7, 127.2, 127.1, 124.1, 122.6, 122.4, 112.8, 110.4, 105.9, 103.5, 58.1, 52.2, 28.5 ppm; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{23}\text{ClN}_3\text{O}_2]^+$ 408.1479; found 408.1460.

N-(tert-Butyl)-2-(2,4-dichlorophenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-

yl)acetamide (9t). Isolated as a white solid; 69 % yield (304 mg); mp 170-173 °C; IR (KBr) ν_{max} : 3398, 1642, 1405, 1215, 762 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 9.84 (s, 1H), 7.95 (d, J = 8 Hz, 1H), 7.57 (d, J = 3.8 Hz, 1H), 7.55 (d, J = 4 Hz, 1H), 7.50 (t, J = 7.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.00-6.94 (m, 3H), 6.06 (s, 1H), 1.40 (s, 9H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 166.7, 155.6, 139.7, 135.7, 135.6, 132.3, 130.9, 130.1, 127.5, 127.3, 125.7, 125.3, 122.0, 121.2, 120.2, 112.3, 101.8, 59.1, 51.9, 28.2 ppm; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{22}\text{Cl}_2\text{N}_3\text{O}_2]^+$ 442.1089; found 442.1080.

N-(tert-Butyl)-2-(2,4-dichlorophenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(10t). Isolated as an oily compound; 12 % yield (53 mg); IR (KBr) ν_{max} : 3399, 1645, 1405, 1215, 770 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.83 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 1.9 Hz, 1H), 7.43 (s, 1H), 7.41 (m, 3H), 7.33 (t, J = 6.9 Hz, 2H), 7.26 (d, J = 6 Hz, 1H), 6.75 (bs, 1H), 6.39 (d, J = 6.2 Hz, 1H), 6.18 (bs, 1H), 1.40 (s, 9H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 166.8, 156.2, 135.6, 134.7, 133.5, 132.3, 131.9, 130.0, 128.4, 127.4, 127.3, 124.5, 122.9, 122.6, 113.8, 112.1, 106.5, 102.8, 57.8, 51.8, 28.7 ppm; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{22}\text{Cl}_2\text{N}_3\text{O}_2]^+$ 442.1089; found 442.1087.

2-(4-Chlorophenyl)-N-cyclohexyl-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(9u). Isolated as a white solid, 74 % yield (320 mg); mp 170-173 °C; IR (KBr) ν_{max} : 3400, 3019, 1647, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.33 (s, 1H), 7.94 (d, J = 8 Hz,

1H), 7.56 (d, J = 8.5 Hz, 1H), 7.47-7.43 (t, J = 8 Hz, 2H), 7.37 (bs, 3H), 7.26 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.01 (s, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.33 (d, J = 6.0 Hz, 1H), 3.91-3.82 (m, 1H), 2.00 (d, J = 12.6 Hz, 1H), 1.91 (d, J = 12.2 Hz, 1H), 1.72-1.60 (m, 3H), 1.59-1.32 (m, 2H), 1.18- 1.12 (m, 3H) *ppm*; ^{13}C NMR (125 MHz, CDCl_3) δ : 166.8, 155.8, 134.3, 130.2, 129.2, 127.2, 126.4, 125.0, 121.4, 120.4, 112.4, 101.6, 60.1, 49.0, 32.8, 32.7, 25.3, 24.7, 14.2 *ppm*; HRMS (ESI) calcd for $[\text{C}_{25}\text{H}_{25}\text{ClN}_3\text{O}_2]^+$ 434.1635, found 434.1622.

2-(4-Chlorophenyl)-N-cyclohexyl-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(**10u**). Isolated as a white solid; 11 % yield (48 mg); mp 180-183 °C; IR (KBr) ν_{max} : 3400, 3019, 2929, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.84 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.44 (d, J = 12.1 Hz, 2H), 7.39 (bs, 4H), 7.34 (t, J = 7.3 Hz, 1H), 7.27 (d, J = 6.3 Hz, 1H), 6.74 (s, 1H), 6.60 (d, J = 6.2 Hz, 1H), 6.23 (d, J = 7.9 Hz, 1H), 3.91-3.82 (m, 1H), 2.01 (d, J = 12.0 Hz, 1H), 1.95 (d, J = 12.3 Hz, 1H), 1.72s-1.68 (m, 3H), 1.64-1.59 (m, 2H), 1.41-1.34 (m, 2H), 1.23-1.14 (m, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 166.8, 157.3, 134.8, 133.8, 132.2, 130.1, 129.2, 127.6, 126.9, 124.3, 122.6, 122.6, 113.0, 110.5, 106.1, 103.7, 58.2, 49.0, 32.8, 32.7, 25.4, 24.7 *ppm*; HRMS (ESI) calcd for $[\text{C}_{25}\text{H}_{25}\text{ClN}_3\text{O}_2]^+$ 434.1635; found 434.1629.

N-Cyclohexyl-2-(4-fluorophenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(**9v**). Isolated as a white solid; 69 % yield (288 mg); mp 160-163 °C; IR (KBr) ν_{max} : 3417, 3019, 1647, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.14 (s, 1H), 7.95 (d, J = 8 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.45-7.42 (m, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.12 (t, J = 8.7 Hz, 2H), 7.00 (s, 1H), 6.97 (d, J = 7.1 Hz, 1H), 6.23 (d, J = 8.2 Hz, 1H), 3.90-3.85 (m, 1H), 2.00 (d, J = 12.1 Hz, 1H), 1.93 (d, J = 12.7 Hz, 1H), 1.72-1.65 (m, 2H), 1.63-1.58 (m, 1H), 1.40-1.32 (m, 2H), 1.20-1.12 (m, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.1, 155.9, 139.8, 131.6, 130.8, 130.7, 127.1, 127.0, 126.3,

125.1, 122.2, 121.3, 120.3, 116.2, 116.0, 112.5, 101.6, 60.1, 48.9, 32.8, 32.7, 25.3, 24.7ppm;
HRMS (ESI) calcd for $[C_{25}H_{25}FN_3O_2]^+$ 418.1931; found 418.1913.

N-Cyclohexyl-2-(4-fluorophenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(**10v**). Isolated as a white solid; 10 % yield (42 mg); mp 130-133 °C; IR (KBr) $\nu_{\max}$: 3400, 3019, 2927, 1636, 1215, 758 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ : 7.85 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.47 (t, J = 6.2 Hz, 3H), 7.41 (d, J = 8.3 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 6.3 Hz, 1H), 7.13 (t, J = 8.6 Hz, 2H), 6.72 (s, 1H), 6.59 (d, J = 6.2 Hz, 1H), 6.08 (d, J = 7.8 Hz, 1H), 3.92-3.82 (m, 1H), 2.01 (t, J = 12.4 Hz, 2H), 1.73-1.68 (m, 2H), 1.64-1.60 (m, 2H), 1.39 (t, J = 4 Hz, 2H), 1.22-1.17 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ : 167.0, 157.3, 132.2, 131.0, 130.7, 130.6, 127.7, 127.0, 124.3, 122.6, 122.5, 116.1, 116.0, 112.9, 110.4, 106.1, 103.7, 58.2, 48.9, 32.7, 30.3, 25.4, 24.7ppm; HRMS (ESI) calcd for $[C_{25}H_{25}FN_3O_2]^+$ 418.1931; found 418.1911.

2-(4-Bromophenyl)-N-cyclohexyl-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(**9w**). Isolated as a yellow solid; 68 % yield (324 mg); mp 188-191 °C; IR (KBr) $\nu_{\max}$: 3399, 3019, 2933, 1652, 1215, 770 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ : 9.99 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.56-7.53 (m, 3H), 7.49 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.27 (t, J = 7.7 Hz, 1H), 7.19 (d, J = 7.3 Hz, 1H), 6.96 (d, J = 7.4 Hz, 1H), 6.22 (d, J = 7.4 Hz, 1H), 3.91-3.84 (m, 1H), 1.99 (d, J = 13.8 Hz, 1H), 1.92 (d, J = 13 Hz, 1H), 1.73 (t, J = 10.0 Hz, 1H), 1.69-1.59 (m, 2H), 1.39-1.31 (m, 2H), 1.21-1.11 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ : 166.8, 155.8, 152.7, 139.6, 132.2, 130.5, 127.2, 126.4, 122.9, 122.4, 121.4, 120.4, 112.3, 101.5, 60.1, 49.0, 32.8, 32.7, 25.3, 24.6ppm; HRMS (ESI) calcd for $[C_{25}H_{25}BrN_3O_2]^+$ 478.1130; found 478.1127.

2-(4-Bromophenyl)-N-cyclohexyl-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(**10w**). Isolated as a yellow solid; 11 % yield (52 mg); mp 155-158 °C; IR (KBr) $\nu_{\max}$: 3400,

3019, 2928, 1629, 1215, 769 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 7.85 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 7.43-7.34 (m, 1H), 7.33 (s, 1H), 7.27 (d, J = 2.7 Hz, 2H), 7.02 (s, 1H), 6.69 (s, 1H), 6.59 (d, J = 6.2 Hz, 1H), 6.11 (d, J = 7.4 Hz, 1H), 3.90-3.83 (m, 1H), 2.00 (d, J = 11.4 Hz, 2H), 1.94 (d, J = 11.9 Hz, 2H), 1.63 (d, J = 11.9 Hz, 2H), 1.40 (t, J = 10.0 Hz, 3H), 1.22 (t, J = 10.0 Hz, 2H) *ppm*; poor solubility of the compound so carbon nmr is not produced; HRMS (ESI) calcd for $[\text{C}_{25}\text{H}_{25}\text{BrN}_3\text{O}_2]^+$ 478.1130; found 478.1123.

2-(4-Cyanophenyl)-N-cyclohexyl-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(**9x**). Isolated as a white solid; 69 % yield (292 mg); mp 165-167 °C; IR (KBr) ν_{max} : 3313, 3019, 1644, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 9.94 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.54-7.46 (m, 4H), 7.30 (d, J = 14.6 Hz, 1H), 7.22 (d, J = 7 Hz, 1H), 7.04 (s, 1H), 7.02 (d, J = 7 Hz, 1H), 6.41 (d, J = 7 Hz, 1H), 3.92-3.82 (m, 1H), 2.01 (d, J = 12.3 Hz, 1H), 1.91 (d, J = 11.6 Hz, 1H), 1.70-1.58 (m, 2H), 1.41-1.32 (m, 2H), 1.24-1.13 (m, 4H) *ppm*; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 166.5, 155.4, 143.1, 139.9, 133.3, 129.7, 127.3, 127.2, 126.9, 123.7, 122.1, 121.7, 120.2, 118.9, 113.0, 111.4, 100.4, 59.3, 48.6, 32.5, 25.5, 24.8 *ppm*; HRMS (ESI) calcd for $[\text{C}_{26}\text{H}_{25}\text{N}_4\text{O}_2]^+$ 425.1978; found 425.1965.

2-(4-Cyanophenyl)-N-cyclohexyl-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide (10x).

Isolated as a white solid; 11 % yield (47 mg); mp 170-173 °C; IR (KBr) ν_{max} : 3398, 3274, 2926, 1637, 1216, 759 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.86 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8 Hz, 2H), 7.46-7.42 (m, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 6 Hz, 1H), 6.79 (s, 1H), 6.61 (d, J = 6.1 Hz, 1H), 6.31 (d, J = 7.8 Hz, 1H), 3.91-3.83 (m, 1H), 2.03 (d, J = 13.1 Hz, 1H), 1.94 (d, J = 13 Hz, 1H), 1.76-1.68 (m, 2H), 1.45-1.28 (m, 2H), 1.25-1.11 (m, 4H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 166.1, 157.3, 140.6, 132.6, 132.3, 129.2, 127.6, 126.6, 124.7, 122.8, 122.7, 118.1, 112.5, 110.5, 106.7,

104.2, 58.2, 49.1, 32.8, 32.7, 25.3, 24.7 ppm; HRMS (ESI) calcd for $[C_{26}H_{25}N_4O_2]^+$ 425.1978; found 425.1967.

N-Cyclohexyl-2-(4-hydroxyphenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(**9y**). Isolated as a white solid; 66 % yield (274 mg); mp 160-163 °C; IR (KBr) $\nu_{\max}$: 3399, 3019, 1644, 1215, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 9.78 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 7.4 Hz, 1H), 7.24 (t, J = 6.8 Hz, 4H), 7.17 (d, J = 7.2 Hz, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.83 (bs, 2H), 6.81 (s, 1H), 3.89-3.81 (m, 1H), 1.96-1.92 (m, 1H), 1.89-1.87 (m, 1H), 1.60-1.55 (m, 2H), 1.36-1.32 (m, 2H), 1.17-1.12 (m, 4H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 167.7, 157.9, 155.5, 139.8, 130.5, 127.6, 127.4, 126.7, 123.6, 122.1, 121.7, 120.0, 116.1, 112.9, 99.4, 59.6, 48.4, 32.6, 25.6, 24.9, 24.9 ppm; HRMS (ESI) calcd for $[C_{25}H_{26}N_3O_3]^+$ 416.1974; found 416.1961.

N-Cyclohexyl-2-(4-hydroxyphenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide

(**10y**). Isolated as a white solid; 9 % yield (37 mg); mp 191-193 °C; IR (KBr) $\nu_{\max}$: 3745, 3399, 3019, 2931, 1628, 1216, 771 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9.66 (s, 1H), 8.43 (d, J = 7.6 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 5.9 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.31 (d, J = 14.8 Hz, 1H), 7.15 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 6.54 (s, 1H), 6.42 (d, J = 6.2 Hz, 1H), 3.66-3.60 (m, 1H), 1.81-1.76 (m, 2H), 1.70-1.64 (m, 2H), 1.56 (d, J = 12.3 Hz, 1H), 1.28-1.22 (m, 3H), 1.15-1.11 (m, 2H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 167.6, 158.0, 156.5, 132.2, 130.8, 130.6, 127.5, 127.4, 126.4, 124.3, 122.8, 122.5, 116.2, 116.0, 114.5, 112.0, 105.9, 102.4, 58.7, 48.4, 32.67, 32.61, 25.6, 24.97, 24.90 ppm; HRMS (ESI) calcd for $[C_{25}H_{26}N_3O_3]^+$ 416.1974; found 416.1964.

N-Cyclohexyl-2-(4-nitrophenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide

(**9z**). Isolated as a yellow solid; 61 % yield (271 mg); mp 150-153 °C; IR (KBr) $\nu_{\max}$: 3391, 1647, 1402, 1068, 768 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 9.96 (s, 1H), 8.24 (d, J = 8.5 Hz,

2H), 7.97 (d, J = 8.1 Hz, 1H), 7.57 (s, 1H), 7.55 (s, 1H), 7.53 (s, 1H), 7.50 (t, J = 6.9 Hz, 1H), 7.30 (d, J = 14.8 Hz, 1H), 7.25 (d, J = 7.3 Hz, 1H), 7.08 (s, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.50 (bs, 1H), 3.89-3.83 (m, 1H), 2.02 (d, J = 12.6 Hz, 1H), 1.91 (d, J = 12.3 Hz, 1H), 1.72-1.69 (m, 1H), 1.66-1.62 (m, 1H), 1.60-1.59 (m, 1H), 1.41-1.33 (m, 2H), 1.22 (t, J = 4.0 Hz, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 166.2, 155.7, 147.7, 143.0, 139.8, 129.8, 129.3, 127.5, 126.7, 126.1, 125.4, 124.2, 124.0, 122.2, 121.4, 120.7, 112.4, 102.4, 59.9, 49.2, 32.8, 25.3, 24.7 *ppm*; HRMS (ESI) calcd for $[\text{C}_{25}\text{H}_{25}\text{N}_4\text{O}_4]^+$ 445.1876; found 445.1868.

N-Cyclohexyl-2-(4-nitrophenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)acetamide (10z).

Isolated as a yellow solid; 8 % yield (36 mg); mp 215-218°C; IR (KBr) ν_{max} : 3413, 3019, 1649, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 8.27 (d, J = 12 Hz, 2H), 7.86 (d, J = 8 Hz, 1H), 7.66 (t, J = 12 Hz, 3H), 7.48 (s, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 6.1 Hz, 1H), 6.83 (s, 1H), 6.63 (d, J = 6.0 Hz, 1H), 6.32 (d, J = 7.7 Hz, 1H), 3.93-3.84 (m, 1H), 2.04 (d, J = 13.2 Hz, 1H), 1.95 (d, J = 11.4 Hz, 1H), 1.78-1.70 (m, 2H), 1.67-1.64 (m, 1H), 1.42-1.35 (m, 2H), 1.23-1.15 (m, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 166.1, 157.3, 147.9, 142.5, 132.3, 129.4, 127.6, 126.5, 124.7, 124.0, 122.8, 122.7, 112.5, 110.5, 106.8, 104.3, 58.0, 49.1, 32.8, 32.7, 25.3, 24.7 *ppm*; HRMS (ESI) calcd for $[\text{C}_{25}\text{H}_{25}\text{N}_4\text{O}_4]^+$ 445.1876; found 445.1875.

N-Cyclohexyl-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-(3,4,5-

trimethoxyphenyl)acetamide (9aa). Isolated as a green solid; 76 % yield (372 mg); mp 160-163°C; IR (KBr) ν_{max} : 3400, 3019, 1647, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 10.10 (s, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.27-7.21 (m, 2H), 6.97 (d, J = 7.2 Hz, 1H), 6.92 (s, 1H), 6.70 (s, 2H), 6.10 (d, J = 7.9 Hz, 1H), 3.88 (s, 3H), 3.87-3.85 (m, 1H), 3.82 (s, 6H), 2.03 (d, J = 15.8 Hz, 1H), 1.95 (d, J = 12.4 Hz, 1H), 1.64-1.59 (m, 2H), 1.41-1.34 (m, 2H), 1.24-1.15 (m, 4H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.1, 155.9, 153.6, 139.9, 138.3, 130.9, 127.0, 126.4, 125.1, 122.3, 121.3, 120.2,

112.5, 106.2, 101.4, 60.9, 60.8, 56.2, 48.9, 32.8, 32.6, 25.4, 24.7ppm; HRMS (ESI) calcd for $[\text{C}_{28}\text{H}_{32}\text{N}_3\text{O}_5]^+$ 490.2342; found 490.2328.

N-Cyclohexyl-2-(1-oxopyrazino[1,2-a]indol-2(1H)-yl)-2-(3,4,5-

trimethoxyphenyl)acetamide (10aa). Isolated as a white solid; 8 % yield (39 mg); mp 202-205 °C; IR (KBr) ν_{max} : 3400, 3019, 2933, 1635, 1215, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.85 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.46 (s, 1H), 7.43 (t, J = 6.7 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 6 Hz, 1H), 6.71 (s, 2H), 6.64 (s, 1H), 6.62 (d, J = 6.2 Hz, 1H), 5.93 (d, J = 8.1 Hz, 1H), 3.93-3.89 (m, 1H), 3.88 (s, 3H), 3.85 (s, 6H), 2.02-1.99 (m, 2H), 1.97 (d, J = 12.4 Hz, 2H), 1.74 (d, J = 12.0 Hz, 1H), 1.66-1.61 (m, 2H), 1.42-1.18 (m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.0, 157.3, 153.6, 138.4, 132.1, 130.3, 127.7, 127.1, 124.2, 122.6, 122.5, 113.2, 110.5, 106.1, 105.8, 103.5, 60.8, 59.1, 56.2, 48.9, 32.9, 32.6, 25.4, 24.7ppm; HRMS (ESI) calcd for $[\text{C}_{28}\text{H}_{32}\text{N}_3\text{O}_5]^+$ 490.2342; found 490.2329.

N-Cyclohexyl-2-(3,4-dimethoxyphenyl)-2-(1-oxo-1H-pyrido[3,4-b]indol-2(9H)-

yl)acetamide (9ab). Isolated as a green solid; 78 % yield (358 mg); mp 165-168 °C; IR (KBr) ν_{max} : 3392, 3019, 2934, 1650, 1215, 759 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 9.96 (s, 1H), 7.95 (d, J = 8 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.27 (t, J = 7.8 Hz, 2H), 7.20 (d, J = 7.1 Hz, 1H), 7.06 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 5.8 Hz, 1H), 6.92 (t, J = 6.6 Hz, 2H), 6.08 (d, J = 7.4 Hz, 1H), 3.91 (s, 3H), 3.89-3.86 (m, 1H), 3.83 (s, 3H), 2.01 (d, J = 10.6 Hz, 1H), 1.95 (d, J = 13.4 Hz, 1H), 1.63 (d, J = 12.0 Hz, 2H), 1.39 (t, J = 8.0 Hz, 2H), 1.22-1.14 (m, 4H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.3, 155.8, 149.4, 139.8, 127.8, 127.1, 126.5, 125.1, 122.2, 121.7, 121.3, 120.2, 112.5, 112.0, 111.3, 101.3, 60.8, 55.9, 48.9, 32.8, 32.6, 25.4, 24.7ppm; HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{30}\text{N}_3\text{O}_4]^+$ 460.2236; found 460.2232.

N-Cyclohexyl-2-(3,4-dimethoxyphenyl)-2-(1-oxopyrazino[1,2-a]indol-2(1H)-

yl)acetamide (10ab). Isolated as a yellow solid; 12 % yield (55 mg); mp 175-177 °C; IR

(KBr) $\nu_{\max}$: 3391, 3019, 2934, 1637, 1215, 757 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 7.84 (d, J = 6.3 Hz, 1H), 7.64 (d, J = 6.8 Hz, 1H), 7.45 (s, 1H), 7.42 (t, J = 5.8 Hz, 1H), 7.33 (t, J = 6 Hz, 1H), 7.25 (d, J = 4.7 Hz, 1H), 7.07 (d, J = 6.7 Hz, 1H), 6.95 (d, J = 1.6 Hz, 1H), 6.91 (d, J = 6.4 Hz, 1H), 6.66 (s, 1H), 6.58 (d, J = 5 Hz, 1H), 5.95 (d, J = 6.5 Hz, 1H), 3.91 (s, 3H), 3.90-3.88 (m, 1H), 3.86 (s, 3H), 1.99-1.94 (m, 2H), 1.74-1.69 (m, 2H), 1.62-1.60 (m, 1H), 1.40-1.35 (m, 2H), 1.23-1.16 (m, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.2, 157.3, 149.5, 149.4, 132.1, 127.7, 127.27, 127.22, 124.1, 122.6, 122.4, 121.6, 113.2, 111.9, 111.3, 110.5, 105.8, 103.3, 58.9, 56.0, 55.9, 48.9, 32.9, 32.7, 25.4, 24.7 *ppm*; HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{30}\text{N}_3\text{O}_4]^+$ 460.2236; found 460.2232.

General Procedure 2.

Synthesis of intermediate 15a-c. To a stirred solution of ethyl 1H-indole-2-carboxylate (**14**) (1.0 equiv.) in DMF, sodium hydride (2.0 equiv.) was added and the mixture was then stirred for 5 min. followed by the addition of desired alkyl or benzyl or propargyl halide (1.0-2.0 equiv.) for 1.5-3.0 h at rt (35 °C). After completion (as monitored by TLC), the reaction mixture was poured into water and extracted with ethyl acetate (20 mL x3), the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to provide the solid mass. Which was purified by column chromatography (hexane/AcOEt) mixtures using 100-200 mesh silica gel to afford the desired product **15a-c**.

General Procedure 3.

Synthesis of intermediate 16a-c: Ethyl N-substituted-1H-indole-2-carboxylate (**15a-c**) (1.0 equiv.) was dissolved in a 1:1:1 solution of THF:MeOH:H₂O followed by addition of potassium hydroxide (3.0 equiv.) at 90 °C. This reaction mixture was allowed to reflux for 1.5 h. After the completion of the reaction, the solvent was removed *in vacuo* and neutralized with dilute HCl to pH 2.0. This aqueous layer was then extracted with ethyl acetate (20 mL x 3) and the combined organics were dried over Na_2SO_4 and evaporated under reduced pressure

to provide a solid mass. Which was purified by column chromatography (hexane/AcOEt) mixtures using 100-200 mesh silica gel to afford the desired product **16a-c**.

General Procedure 4:

The Two Step One-Pot Synthesis of N-alkylated β -carbolinone (18a-l) analogues: To a mixture of the corresponding aldehyde (**6a**, **6b**, **6d**, **6e**, **6h**, **6j**) (1.0 mmol) in MeOH, aminoacetaldehyde dimethyl acetal (**7**) (1.1 mmol) was added followed by the addition of the N-substituted indole 2-carboxylic acid (**16a-c**) (1.0 mmol), the isocyanide (**3a-c**) (1.1 mmol) and the mixture was stirred 4-6 h at 35 °C. The progress of reaction was monitored by TLC. Once starting materials were consumed, the MeOH was evaporated *in vacuo* at low temperature followed by addition of CH₃CN. The sticky mass was stirred at 35 °C for 5 min. to homogenize the reaction mixture at which point TFA (1.0 equiv.) was added and the mixture was stirred for 20-25 min. at 35 °C. When the reaction was completed (as determined by TLC) the reaction solvents was (*in vacuo*) and directly proceeded for column chromatography (hexane/AcOEt) mixtures using 100-200 mesh silica gel to afford the desired product **18a-l**.

N-(tert-Butyl)-2-(3,4-dimethoxyphenyl)-2-(9-ethyl-1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)acetamide (18a). Isolated as a yellow solid; 79 % yield (364 mg); mp 152-155 °C; IR (KBr) ν_{max} : 3338, 3017, 1646, 1217, 759 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.94 (d, *J*= 7.9 Hz, 1H), 7.51 (d, *J*= 4 Hz, 2H), 7.25-7.22 (m, 1H), 7.10 (d, *J*=7.2 Hz, 1H), 7.07 (d, *J*= 8.2 Hz, 1H), 6.96 (d, *J*= 1.9 Hz, 1H), 6.92 (d, *J*= 8.3 Hz, 1H), 6.87 (d, *J*= 7.2 Hz, 1H), 6.79 (s, 1H), 5.92(s,1H), 4.96-4.85 (m, 2H), 3.92 (s, 3H), 3.86 (s, 3H), 1.51 (t, *J*= 7 Hz, 3H), 1.41 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ : 167.8, 156.1, 149.4, 140.0, 128.2, 126.7, 126.7, 125.8, 125.0, 121.8, 121.5, 121.4, 119.8, 112.1, 111.3, 110.0, 100.1, 60.6, 55.9, 52.0, 39.5, 28.6, 16.0 ppm; HRMS (ESI) calcd for [C₂₇H₃₂N₃O₄]⁺ 462.2393; found 462.2390.

N-Cyclohexyl-2-(9-ethyl-1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-phenylacetamide

(**18b**). Isolated as a yellow solid; 84 % yield (346 mg); mp 212-215 °C; IR (KBr) ν_{max} : 3400, 3019, 1646, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.95 (d, J = 8 Hz, 1H), 7.52 (d, J = 1.1 Hz, 1H), 7.50 (d, J = 0.8 Hz, 1H), 7.44 (t, J = 4.0 Hz, 2H), 7.42 (d, J = 2.3 Hz, 1H), 7.40 (t, J = 4.0 Hz, 1H), 7.26-7.22 (m, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.96 (s, 1H), 6.89 (d, J = 7 Hz, 1H), 6.11 (d, J = 8.1 Hz, 1H), 4.92-4.86 (m, 2H), 3.93-3.84 (m, 1H), 2.03 (d, J = 12 Hz, 1H), 1.96 (d, J = 11.7 Hz, 1H), 1.73-1.68 (m, 2H), 1.62-1.58 (m, 1H), 1.49 (t, J = 7.2 Hz, 3H), 1.41-1.33 (m, 2H), 1.22-1.14 (m, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.5, 156.1, 140.0, 136.1, 129.05, 129.00, 128.6, 126.88, 126.82, 125.7, 124.9, 121.5, 121.4, 119.9, 110.0, 100.4, 60.5, 48.9, 39.5, 32.8, 32.6, 25.4, 24.7, 16.0 *ppm*; HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{30}\text{N}_3\text{O}_2]^+$ 428.2338; found 428.2324.

2-(4-Cyanophenyl)-2-(9-ethyl-1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-N-(2,4,4-trimethylpentan-2-yl)acetamide (18c)

(**18c**). Isolated as a white solid; 77 % yield (371 mg); mp 167-170 °C; IR (KBr) ν_{max} : 3400, 3020, 1647, 1215, 760 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.98 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 6.2 Hz, 3H), 7.51 (s, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 6.97 (d, J = 7.2 Hz, 1H), 6.89 (s, 1H), 6.29 (s, 1H), 4.97-4.89 (m, 1H), 4.88-4.80 (m, 1H), 1.85 (d, J = 14.9 Hz, 1H), 1.67 (d, J = 15 Hz, 1H), 1.47 (s, 3H), 1.46 (s, 3H), 1.30 (t, J = 6.7 Hz, 3H), 0.88 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 166.3, 155.9, 141.4, 140.1, 132.5, 129.3, 127.2, 126.0, 125.6, 125.0, 121.4, 120.2, 118.3, 112.2, 110.1, 101.4, 60.3, 56.2, 51.6, 39.6, 31.5, 31.2, 28.8, 16.0 *ppm*; HRMS (ESI) calcd for $[\text{C}_{30}\text{H}_{35}\text{N}_4\text{O}_2]^+$ 483.2760; found 483.2746.

N-Cyclohexyl-2-(9-ethyl-1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-(4-hydroxyphenyl)acetamide (18d)

(**18d**). Isolated as a white solid; 68 % yield (301 mg); mp 200-203 °C; IR (KBr) ν_{max} : 3399, 1641, 1404, 764 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9.65 (s, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.51 (t, J = 7.8

Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.13 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 6.75 (s, 1H), 4.87-4.81 (m, 2H), 3.66-3.57 (m, 1H), 1.82 (d, J = 11.3 Hz, 1H), 1.76 (t, J = 9.9 Hz, 1H), 1.70 (t, J = 10.6 Hz, 2H), 1.56 (d, J = 13.4 Hz, 1H), 1.36 (t, J = 6.7 Hz, 3H), 1.28-1.20 (m, 3H), 1.17-1.16 (t, J = 3.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ : 167.7, 157.9, 155.7, 139.9, 130.6, 128.1, 127.4, 127.1, 125.5, 124.4, 121.8, 121.3, 120.2, 116.1, 110.9, 99.1, 59.6, 48.5, 32.7, 32.5, 25.6, 24.9, 24.9, 16.4 ppm; HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{30}\text{N}_3\text{O}_3]^+$ 444.2287; found 444.2284.

2-(9-Benzyl-1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-N-cyclohexyl-2-(3,4-

dimethoxyphenyl)acetamide (18e). Isolated as a white solid; 72 % yield (395 mg); mp 102-105 °C; IR (KBr) ν_{max} : 3400, 1645, 1404, 1216, 762 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.96 (d, J = 8 Hz, 1H), 7.44 (d, J = 6.2 Hz, 2H), 7.26 (t, J = 8.0 Hz, 4H), 7.21 (d, J = 1.6 Hz, 3H), 7.17 (s, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 1.8 Hz, 2H), 6.92-6.89 (m, 1H), 6.83 (s, 1H), 6.14 (s, 2H), 6.06 (d, J = 7.5 Hz, 1H), 3.91 (s, 3H), 3.90-3.86 (m, 1H), 3.85 (s, 3H), 1.98 (d, J = 12.9 Hz, 1H), 1.93 (d, J = 13.6 Hz, 1H), 1.71 (t, J = 4.0 Hz, 2H), 1.61-1.57 (m, 1H), 1.38-1.31 (m, 2H), 1.18-1.10 (m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 165.0, 153.7, 146.8, 138.2, 135.9, 126.0, 125.4, 124.5, 124.4, 124.1, 123.5, 122.8, 119.4, 119.3, 119.2, 118.8, 117.7, 109.6, 108.7, 108.3, 97.7, 57.8, 53.46, 53.40, 46.3, 45.4, 30.2, 30.0, 29.0, 22.8, 22.1 ppm; HRMS (ESI) calcd for $[\text{C}_{34}\text{H}_{36}\text{N}_3\text{O}_4]^+$ 550.2706; found 550.2704.

2-(9-Benzyl-1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-N-cyclohexyl-2-(3,4,5-

trimethoxyphenyl)acetamide (18f). Isolated as a white solid; 71 % yield (446 mg); mp 95-98 °C; IR (KBr) ν_{max} : 3398, 3019, 1647, 1215, 759 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.97(d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.27 (t, J = 2.6 Hz, 1H), 7.26-7.24 (m, 2H), 7.23-7.22 (m, 3H), 7.21 (d, J = 2.2 Hz, 1H), 7.19 (t, J = 1.6 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 6.82 (s, 1H), 6.70 (s, 2H), 6.15 (d, J = 5.4 Hz, 2H), 6.06 (d, J = 7.2 Hz, 1H), 3.88 (s, 3H), 3.86-3.84 (m, 1H), 3.83 (s, 6H), 2.00 (d, J = 12.9 Hz, 1H), 1.89 (d, J = 12.9 Hz, 1H), 1.71-1.67 (m, 2H),

1.60-1.58 (m, 1H), 1.39-1.33 (m, 2H), 1.21-1.14 (m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.3, 156.2, 153.6, 140.8, 138.4, 138.3, 131.1, 128.5, 127.1, 127.0, 126.7, 126.6, 126.0, 125.4, 121.7, 121.4, 120.3, 110.9, 106.7, 106.3, 100.4, 60.8, 60.5, 56.3, 56.2, 48.8, 47.9, 32.7, 32.5, 25.4, 24.7 ppm; HRMS (ESI) calcd for $[\text{C}_{35}\text{H}_{38}\text{N}_3\text{O}_5]^+$ 580.2811; found 580.2811.

2-(9-Benzyl-1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-N-(tert-butyl)-2-phenylacetamide

(**18g**). Isolated as a white solid; 69 % yield (319 mg); mp 230-233 °C; IR (KBr) ν_{max} : 3400, 3019, 1649, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.95 (d, J = 8 Hz, 1H), 7.47 (t, J = 4.0 Hz, 3H), 7.43 (d, J = 2.3 Hz, 3H), 7.40 (t, J = 4.0 Hz, 2H), 7.27 (t, J = 1.5 Hz, 1H), 7.25 (s, 1H), 7.24-7.20 (m, 4H), 7.16 (d, J = 7 Hz, 1H), 6.89 (d, J = 7.2 Hz, 1H), 6.14 (s, 2H), 6.00 (bs, 1H), 1.39 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.6, 156.3, 140.7, 138.4, 136.1, 129.1, 129.0, 128.6, 128.5, 127.3, 127.09, 127.04, 126.7, 126.0, 125.3, 121.8, 121.3, 120.2, 110.9, 100.2, 60.7, 52.0, 47.9, 28.6 ppm; HRMS (ESI) calcd for $[\text{C}_{30}\text{H}_{30}\text{N}_3\text{O}_2]^+$ 464.2338; found 464.2335.

2-(9-Benzyl-1-oxo-1H-pyrido[3,4-b]indol-2(9H)-yl)-N-cyclohexyl-2-phenylacetamide

(**18h**). Isolated as a white solid; 68 % yield (332 mg); mp 191-194 °C; IR (KBr) ν_{max} : 3400, 3019, 1647, 1215, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.96 (d, J = 7.9 Hz, 1H), 7.46-7.44 (m, 3H), 7.43 (d, J = 5.3 Hz, 3H), 7.40 (t, J = 2.4 Hz, 2H), 7.38 (d, J = 7.0 Hz, 4H), 7.27-7.23 (m, 2H), 7.20 (d, J = 7.2 Hz, 1H), 6.93 (s, 1H), 6.91 (s, 1H), 6.14 (d, J = 9.2 Hz, 2H), 3.90-3.81 (m, 1H), 1.99 (d, J = 12.2 Hz, 1H), 1.91 (d, J = 12 Hz, 1H), 1.73-1.68 (m, 2H), 1.62-1.57 (m, 1H), 1.38 (t, J = 12.0 Hz, 2H), 1.18-1.09 (m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.4, 156.3, 140.7, 138.4, 136.0, 129.04, 129.01, 128.6, 128.5, 128.2, 127.3, 127.0, 126.7, 126.0, 125.3, 121.7, 121.3, 120.3, 110.9, 100.4, 60.5, 48.9, 47.9, 32.7, 32.5, 25.4, 24.7 ppm; HRMS (ESI) calcd for $[\text{C}_{32}\text{H}_{32}\text{N}_3\text{O}_2]^+$ 490.2495; found 490.2489.

2-(4-Cyanophenyl)-N-cyclohexyl-2-(1-oxo-9-(prop-2-yn-1-yl)-1H-pyrido[3,4-b]indol-

2(9H)-yl)acetamide (18i). Isolated as a white solid; 71 % yield (329 mg); mp 170-173 °C; IR (KBr) $\nu_{\max}$: 3405, 3019, 1648, 1216, 760 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 7.97 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 7.8 Hz, 2H), 7.66 (d, J = 8.3 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 7.53 (d, J = 7.8 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.21 (d, J = 7 Hz, 1H), 6.99 (s, 1H), 6.97 (d, J = 7 Hz, 1H), 6.41 (d, J = 7.6 Hz, 1H), 5.76-5.74 (m, 2H), 3.89-3.82 (m, 1H), 2.32 (s, 1H), 2.01 (d, J = 11.9 Hz, 1H), 1.91 (d, J = 12.1 Hz, 1H), 1.75-1.70 (m, 2H), 1.63-1.59 (m, 1H), 1.40-1.33 (m, 2H), 1.23-1.16 (m, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 166.4, 156.1, 141.4, 140.3, 132.6, 129.3, 127.6, 127.0, 125.9, 125.0, 121.8, 121.5, 121.0, 118.3, 112.4, 110.8, 101.3, 78.6, 72.7, 59.6, 49.1, 33.8, 32.7, 32.5, 25.3, 24.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{29}\text{H}_{29}\text{N}_4\text{O}_2]^+$ 463.2134; found 463.2132.

2-(4-Chlorophenyl)-N-cyclohexyl-2-(1-oxo-9-(prop-2-yn-1-yl)-1H-pyrido[3,4-b]indol-

2(9H)-yl)acetamide (18j). Isolated as a white solid; 74 % yield (350 mg); mp 190-193 °C; IR (KBr) $\nu_{\max}$: 3418, 3019, 1648, 1215, 757 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 7.96 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.58 (t, J = 6.9 Hz, 1H), 7.45-7.40 (m, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.18 (d, J = 7.4 Hz, 1H), 6.92 (s, 1H), 6.91 (d, J = 7.2 Hz, 1H), 6.21 (d, J = 7.5 Hz, 1H), 5.84 (d, J = 17.9 Hz, 2H), 5.74 (d, J = 17.7 Hz, 1H), 3.87-3.85 (m, 1H), 2.31 (s, 1H), 2.01 (d, J = 12.6 Hz, 1H), 1.93 (d, J = 13.5 Hz, 1H), 1.73-1.70 (m, 2H), 1.63-1.59 (m, 1H), 1.40-1.33 (m, 2H), 1.21-1.14 (m, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.0, 156.1, 140.3, 134.7, 134.4, 130.3, 129.2, 127.3, 127.2, 125.7, 125.1, 121.9, 121.5, 120.8, 110.7, 100.7, 78.7, 72.6, 59.5, 49.0, 33.8, 32.8, 32.5, 25.4, 24.7 *ppm*; HRMS (ESI) calcd for $[\text{C}_{28}\text{H}_{29}\text{ClN}_3\text{O}_2]^+$ 472.1792; found 472.1790.

N-(tert-Butyl)-2-(1-oxo-9-(prop-2-yn-1-yl)-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-

phenylacetamide (18k). Isolated as a white solid; 69 % yield (283 mg); mp 210-213 °C; IR (KBr) $\nu_{\max}$: 3405, 1643, 1398, 1216, 762 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.94 (d, J = 9.2

Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.57 (t, J = 7 Hz, 1H), 7.47-7.45 (m, 3H), 7.43 (s, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 7.3 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.91 (s, 1H), 6.88 (d, J = 7.1 Hz, 1H), 6.01 (s, 1H), 5.90 (d, J = 17.8 Hz, 1H), 5.74 (d, J = 17.8 Hz, 1H), 2.32 (t, J = 2.3 Hz, 1H), 1.42 (s, 9H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.5, 156.2, 140.3, 136.1, 129.1, 129.0, 128.7, 127.6, 127.2, 125.7, 125.2, 121.9, 121.4, 120.6, 110.7, 100.2, 78.9, 72.5, 60.5, 52.1, 33.7, 28.6 *ppm*; HRMS (ESI) calcd for $[\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_2]^+$ 412.2025; found 412.2014.

N-Cyclohexyl-2-(1-oxo-9-(prop-2-yn-1-yl)-1H-pyrido[3,4-b]indol-2(9H)-yl)-2-

phenylacetamide (18l). Isolated as a white solid; 64 % yield (280 mg); mp 218-221 °C; IR (KBr) ν_{max} : 3303, 2930, 1646, 1218, 759 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.95 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 6.9 Hz, 1H), 7.46 (bs, 1H), 7.44 (bs, 2H), 7.42 (bs, 1H), 7.40 (d, J = 6.8 Hz, 1H), 7.31 (s, 1H), 7.19 (d, J = 7.1 Hz, 1H), 6.95 (s, 1H), 6.89 (d, J = 7.3 Hz, 1H), 6.12 (d, J = 7.7 Hz, 1H), 5.88 (d, J = 17.6 Hz, 1H), 5.75 (d, J = 17.6 Hz, 1H), 3.92-3.85 (m, 1H), 2.32 (t, J = 1.9 Hz, 1H), 2.03 (d, J = 12.7 Hz, 1H), 1.96 (d, J = 12.2 Hz, 1H), 1.74-1.69 (m, 2H), 1.64-1.58 (m, 1H), 1.41-1.33 (m, 2H), 1.23-1.14 (m, 3H) *ppm*; ^{13}C NMR (100 MHz, CDCl_3) δ : 167.3, 156.2, 140.2, 135.9, 129.0, 129.0, 128.7, 127.6, 127.2, 125.6, 125.2, 121.9, 121.4, 120.7, 110.7, 100.3, 78.8, 72.5, 60.4, 48.9, 33.8, 32.8, 32.6, 25.4, 24.7 *ppm*; HRMS (ESI) calcd for $[\text{C}_{28}\text{H}_{28}\text{N}_3\text{O}_2]^+$ 438.2182; found 438.2177.

Acknowledgements: P. Purohit and A. K. Pandey gratefully acknowledge financial support by the CSIR, New Delhi for Senior Research Fellowships (SRF). We also thank SAIF division, CSIR-CDRI for providing analytical facilities. CDRI Communication no. is.....

Supporting Information: Copies of ^1H and ^{13}C NMR spectra of synthesized compounds are available as supplementary data.

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