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ARTICLE

$In(OTf)_3$ Assisted Synthesis of β-Carboline C-3 Tethered Imidazo[1,2-*a*]azine Derivatives

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Synthesis of β-carboline based natural products and synthetic derivatives is one of the frontier areas of research owing to their medicinal properties. It is envisaged that 3-formyl-9*H*-β-carboline is a potential precursor and offers new vistas for construction of variety of heterocyclic architectures at C-3 position of β-carboline skeleton. In this context, an efficient protocol has been developed to serve the synthesis of β-carbolines C-3 tethered imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine, and imidazo[1,2-*a*]pyrazine derivatives via exploration of Groebke-Blackburn-Bienayme (GBB) reaction. The present protocol offers several advantages like operational simplicity, high atom economy, appreciable structural diversity and easy purification procedure.

Introduction

β-Carboline, also known as norharmane, is a prototype compound belonging to a class of nitrogen containing heterocycles which is chemically pyrido[3,4-*b*]indole framework.[1] β-Carboline containing alkaloids are wide spread in animal and plant kingdom, and it is estimated that this framework is represented by more than one third of total natural products extracted from different sources (Figure 1).[2] Nature uses L-tryptophan as the key precursor for the biosynthesis of β-carboline skeleton which is considered to be the reason behind their colossal abundance.[3] This privileged scaffold is gifted with broad spectrum of pharmacological properties including anticancer, antimalarial, anxiolytic, antibacterial, antifungal, antiviral, anti-HIV, anti-alzheimer, antihypnotic, anticonvulsant etc.[4] It has been revealed that bulk of these alkaloids display potent anticancer properties by intercalating into DNA strands, inhibiting topoisomerases, CDK, MK-2, Ikk, kinesin-like protein Eg5 and PLK1 etc.[5] Interestingly, some of β-carboline containing drugs have also been commercialized successfully such as tadalafil and abecarnil are used clinically for the treatment of erectile dysfunction and CNS disorders.[6] Due to their enormous medicinal importance, synthesis of β-carboline containing derivatives have been an exciting area of research and accordingly several elegant approaches have been devised.[7]

In organic synthesis, generation of complexity from simple and readily available starting materials in minimal number of steps is always desired and multicomponent reactions (MCR) offer an efficient tool to fulfil this purpose.[8] In this aspect, Groebke-Blackburn-Bienayme (GBB) reaction, a variant of Ugi reaction results in formation of a densely substituted N-fused imidazole framework which is represented by several commercial drugs like Zolpidem, Olprinone, Soraprazan, Zolmidine and many others under pre-clinical trials.[9] GBB reaction is one of the most newly discovered (1998) methodology which has been applauded by the scientific community as indicated by increasing number of publications in this field including more than 2000 patent applications since 1998.[10]

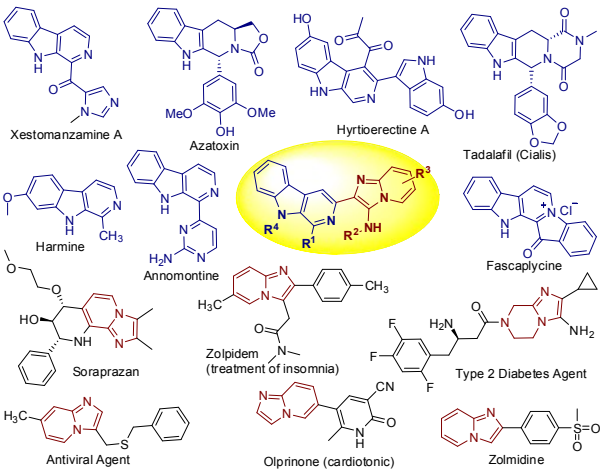

Figure 1. Examples of β-carboline and imidazo[1,2-*a*]azine containing bioactive natural products and commercial drugs

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[e] † *Electronic supplementary information (ESI) available: General procedure and NMR Spectra of compounds. See DOI: 10.1039/x0xx00000x*

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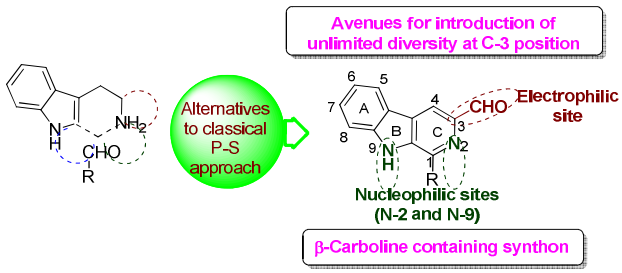


Figure 2. Pictorial representation of versatility of 3-formyl-9*H*-β-carboline

Recently, our research group reviewed the potential of this methodology (GBB) and updated the pharmacology of imidazo[1,2-*a*]pyridine frameworks[11] which revealed that these drug-like molecules display wide range of biological properties like anticancer,[12] antimicrobial, antiviral, anticonvulsant and many more.[13] Fascinated by the medicinal profile of these two pharmacophores, we developed β-carboline C-1 imidazopyridine hybrids via the application of this 3-component approach.[14a] The preliminary biological screening provided us intriguing results which inspired us to further expand the domain of library. Recently, Kamal and co-workers discovered that β-carboline C-3 tethered benzimidazole derivatives act as potent anticancer agents.[15] The findings of Kamal *et al*. further guided us to introduce imidazopyridine framework (which is isostere/mimic of benzimidazole) at C-3 position in β–carboline and supported the designed prototype for our current anticancer project. Accordingly, we explored 3-formyl-9*H*-β-carbolines for the synthesis of designed prototype as this precursor has a lot of potential and offer several avenues to introduce variety of bioactive heterocyclic scaffolds at C-3 position of β–carboline which is not possible through classical methods like Pictet-Spengler (P-S) or Bischler Napieralski cyclisation. It is projected that presence of two nucleophilic sites (N-2 and N-9) in close proximity of electrophilic site (formyl group at C-3) with several sites for diversification at C-1, C-4, C-5, C-6, C-7 and C-8 makes this precursor a useful template in this prospect (Figure 2). A detailed review of literature database revealed that only limited approaches were documented toward exploration of this precursor for installation of diversity at β–Carboline skeleton but not adequate to demonstrate its significance as depicted in Figure 3.[15-16] Therefore, we herein wish to report the synthesis of β-carboline C-3 tethered imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines, and imidazo[1,2-*a*]pyrazine derivatives via exploration of Groebke-Blackburn-Bienayme multicomponent reaction of 3-formyl-9*H*-pyrido[3,4-*b*]indoles, 2-aminoazines and isonitriles.

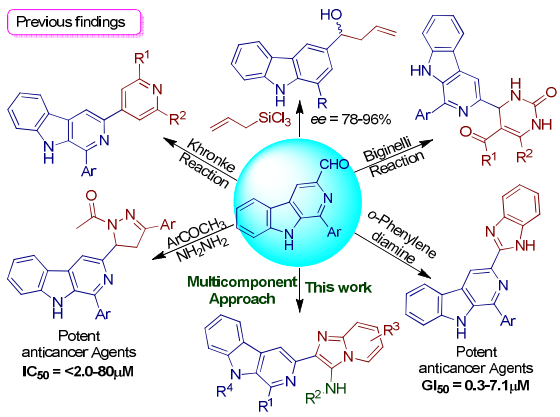
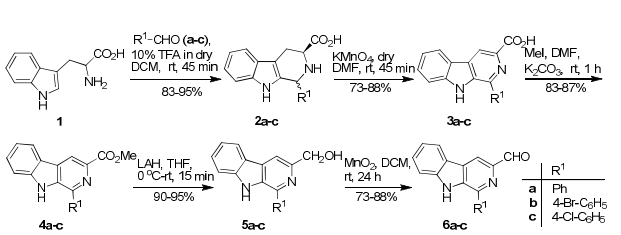


Figure 3. A summary of previous reports[15-16] toward exploration of 3-formyl-9*H*-β-carbolines

Results and Discussion

The present study commenced with the synthesis of substituted 3-formyl-9*H*-β-carbolines (**6a-c**) which was achieved via modification in the previously reported procedure as described in Scheme 1.[15, 17] L-tryptophan (**1**) was used as the precursor and subjected to Pictet-Spengler (P-S) condensation with various aldehydes (**a-c**) in dry DCM at room temperature for the chemical synthesis of tetrahydro-β-carboline derivatives (**2a-c**). It was pleasing to see that P-S condensation with L-tryptophan (**1**) was very fast as compared to tryptophan ester and the reaction was completed in 45 min only.[15] Next, the oxidation of C-ring of tetrahydro-β-carbolines (**2a-c**) was achieved via reaction with $KMnO_4$ in anhydrous DMF (45 min) to produce the β-carboline derivatives (**3a-c**). It was interesting to see that oxidation with $KMnO_4$ was selective and no decarboxylation was observed.[17] Further treatment of **3a-c** with methyl iodide in presence of K_2CO_3 yielded the corresponding methyl ester (**4a-c**) in high yield (83-87%) and reduction of ester functionality with $LiAlH_4$ in dry THF furnished the alcohols (**5a-c**) in excellent yield (90-95%) within 15 min. The oxidation of alcohol derivatives (**5a-c**) with MnO_2 in dry DCM yielded the desired 3-formyl-9*H*-β-carbolines (**6a-c**) in 73-88% yield. This method has advantages including application to gram scale synthesis and convenience of avoiding column chromatography purification.

Having synthesized starting substrates, next we intended at achieving the synthesis of our targeted prototype i.e. β-carboline tethered imidazoazines. Accordingly, the optimization studies were performed by using 1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carbaldehyde (**6b**), 2-aminopyridine (**A**) and ethylisocyanoacetate (**X**) as model substrates. After an extensive review of literature, it was concluded that H_2O, EtOH, MeOH and toluene were the best solvents for various multicomponent transformations.[18] As water shows unique reactivity profile, we initiated our studies in water as a solvent under catalyst-free condition at 100 °C but the formation of desired product was not observed (Table 1, entry 1).[19]



Scheme 1. Synthesis of 3-formyl-9*H*-pyrido[3,4-*b*]indole derivatives

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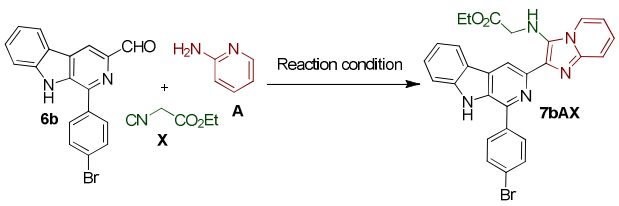
Table 1. Optimization of reaction conditions[a]

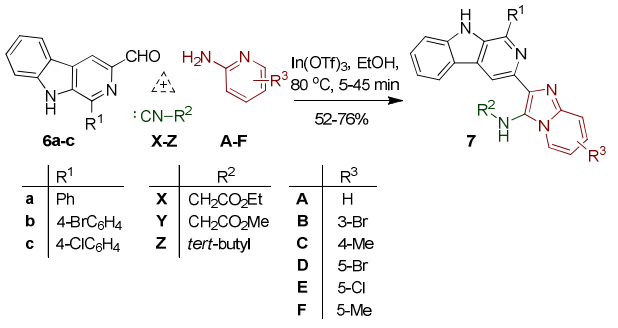


Entry	Catalyst (mol%)	Solvent[b]	Temp. (°C)[c]	Time	Yield (%)[d]
1[e]	-	H_2O	100	48 h	**6b**
2[e]	-	EtOH	80	48 h	29 + **6b**
3	$In(OTf)_3$ (10)	H_2O	100	48 h	**6b**
4	$In(OTf)_3$ (10)	EtOH	80	35 min	62
5	$In(OTf)_3$ (5)	EtOH	80	1.5 h	48 + **6b**
6	**$In(OTf)_3$ (15)**	**EtOH**	**80**	**15 min**	**73**
7	$In(OTf)_3$ (20)	EtOH	80	5 min	69
8	$In(OTf)_3$ (10)	EtOH	rt	48 h	20 + **6b**
9	$In(OTf)_3$ (15)	MeOH	80	25 min	69
10	$In(OTf)_3$ (15)	Toluene	rt	48 h	24 + **6b**
11	$In(OTf)_3$ (15)	Toluene	120	50 min	65
12	*p*-TSA (15)	Toluene	120	6.5 h	55
13	TFA (15)	CH_2Cl_2	60	7 h	45
14	$La(OTf)_3$ (15)	EtOH	80	1 h	59
15	$Yb(OTf)_3$ (15)	EtOH	80	4 h	50
16	$Zn(OTf)_2$ (15)	EtOH	80	45 min	53
17	AgOTf (15)	EtOH	80	3.5 h	47
18	$InCl_3$ (15)	EtOH	80	5 h	26
19	$LaCl_3$ (15)	EtOH	80	3 h	42
20	$ZnCl_2$ (15)	EtOH	80	2.5 h	34

[a]All the reaction were carried out with 0.25 mmol of **6b**, 0.26 mmol of 2-amino pyridine (**A**), 0.28 mmol of isonitrile (**X**) in 3 mL of solvent. [b]Anhydrous solvent was used for entries 9-13. [c]The temperature of oil bath. [d]Isolated yields of the purified product (The yield for entries 2, 5, 8 and 10 are on actual basis). [d]No catalyst was used for entries 1-2.

However, when the reaction was executed in EtOH as the solvent, formation of product was observed but starting materials were not consumed completely even after 48 h (Table 1, entry 2). A short silica gel column chromatographic purification of the reaction mixture yielded the pure product in 29% yield and the spectroscopic analysis confirmed the structure of product as **7bAX**. Thereafter, we next focused on improving the efficacy of the methodology for the synthesis of β-carboline substituted imidazo[1,2-*a*]pyridines. Our recent studies revealed that $In(OTf)_3$ was a superior catalyst for GBB transformation and therefore, we envisaged to explore $In(OTf)_3$ to increase the yield of product.[14] However, reaction failed to deliver the desired product in water in presence of $In(OTf)_3$ which indicates that solubility of reactants was a limiting factor (Table 1, entry 3). Interestingly, when the reactants were assembled in EtOH at 80 °C in presence of $In(OTf)_3$ (10 mol%), reaction was completed within 35 min and product was afforded in 62% yield (Table 1, entry 4). Further, it was observed that yield of the desired product dropped dramatically upon decreasing the catalyst loading which resulted in incomplete conversion of substrates as well (Table 1, entry 5). Interestingly, an increase in catalyst loading to 15 mol% resulted in increased yield (73%) and shorter duration (Table 1, entry 6). However, when catalyst loading was further increased to 20 mol%, the reaction time was reduced considerably (5 min), but yield was dropped slightly from 73% to 69% (Table 1, entry 7). On the other hand, reaction at room temperature yielded the product in poor yield and the reaction was not completed even after 48 h (Table 1, entry 8). In comparison to EtOH, the desired product was obtained even in lower yield when MeOH and toluene were used as solvent (Table 1, entries 9-11). Similarly, *p*-TSA and TFA catalysed reactions in toluene and dichloromethane offered the product in 55% and 45% yields respectively. After a careful optimization of reaction parameters such as solvent and catalyst loading, we screened the efficiency of other Lewis acids for similar transformation (Table 1, entries 14-20). All the Lewis acids yielded the desired product albeit in moderate yield (Table 1, entries 14-20). The results of standardization studies are presented in Table-1 which led us to conclude that the reaction of model substrates in the presence of 15 mol% of $In(OTf)_3$ as catalyst in EtOH as solvent under refluxing conditions refers to be the best reaction conditions for the synthesis of β-carboline C-3 substituted imidazo[1,2-*a*]pyridine (Table 1, entry 6) (**7bAX**).

Having optimized conditions in hand, we investigated the scope of reaction by reacting 3-formyl-9*H*-β-carbolines (**6a-c**), 2-aminopyridines (**A-F**) and isocyanides (**X-Z**) as depicted in Scheme 2. It was satisfying to note that all the substrates responded positively to yield the desired β-carboline C-3 substituted imidazo[1,2-*a*]pyridine derivatives in moderate to good yields (52-76%). It was observed that reaction was relatively faster with *tert*-butylisonitrile (**Z**) as compared to methyl or ethyl isocyanoacetate (**X-Y**). Similarly, it was analysed that this multicomponent transformation was more facile with **6b** (3-formyl-9*H*-β-carboline derivative accommodating 4-bromophenyl substituent at C-1 position) as compared to other precursors (**6a** and **6c**). Overall, the reaction was found to be general and competent to afford the desired library of compounds (**7**) (Figure 4).



Scheme 2. $In(OTf)_3$ assisted synthesis of β-carboline C-3 substituted imidazo[1,2-*a*]pyridine derivatives (**7**)

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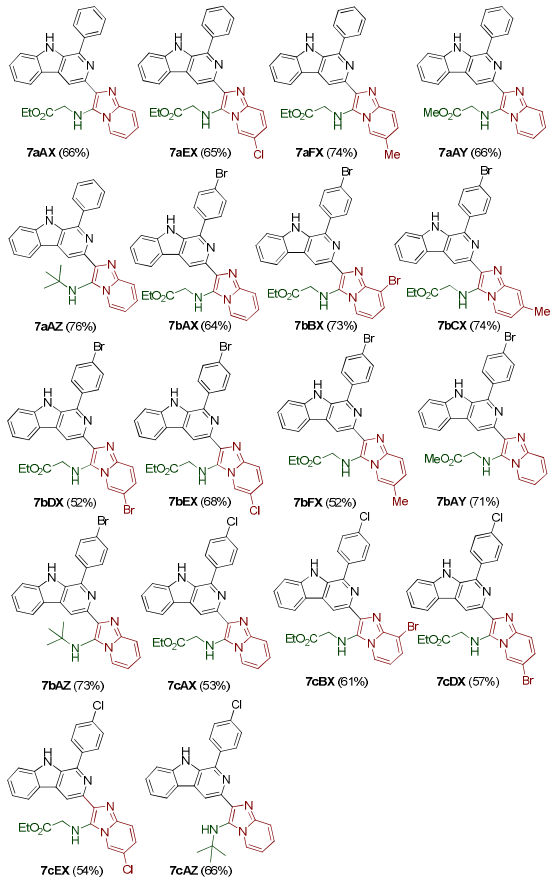
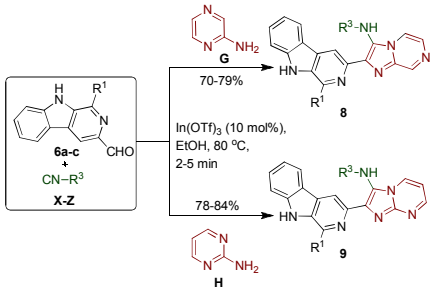


Figure 4. Library of various β-carboline C-3 tethered imidazo[1,2-*a*]pyridine derivatives (**7**)

The applicability of this multicomponent approach was further examined by varying the amine component with 2-aminopyrazine (**G**) and 2-aminopyrimidine (**H**) as illustrated in Scheme 3. Surprisingly, reaction of 2-aminopyrazine (**G**) and 2-aminopyrimidine (**H**) was even faster and more facile as compared to 2-aminopyridines (**A-F**). The reaction was completed within 2-5 min in presence of 10 mol% of $In(OTf)_3$ (lower catalyst loading relative to synthesis of **7**) in EtOH and the desired β-carboline C-3 tethered imidazo[1,2-*a*]pyrazine (**8**) and imidazo[1,2-*a*]pyrimidine (**9**) derivatives (Figure 5) were produced smoothly in 70-84% yield (Scheme 3). More importantly, the reaction was regioselective with 2-aminopyrimidine to afford 3-aminoimidazopyrimidines (**9**).[20]



Scheme 3. Synthesis of β-carboline C-3 substituted imidazo[1,2-*a*]pyrazine and imidazo[1,2-*a*]pyrimidine derivatives (**8-9**)

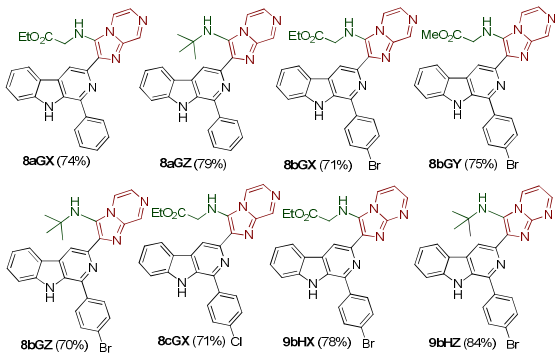
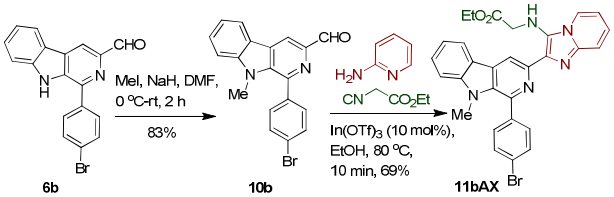


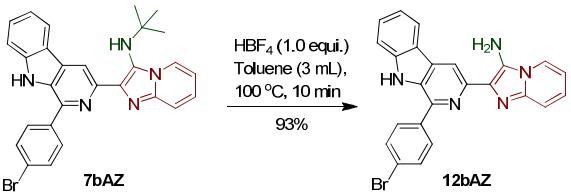
Figure 5. Structure of β-carboline C-3 substituted imidazo[1,2-*a*]pyrazine and imidazo[1,2-*a*]pyrimidine derivatives (**8-9**)



Scheme 4. Synthesis of β-carboline C-3 substituted imidazo[1,2-*a*]pyridine (**11bAX**) from 3-formyl, 9-methylpyrido[3,4-*b*]indole (**10b**)

To examine the effect of substituent at N-9 on the course of reaction, the study was further extended with *N*-methyl derivative of **6b**. Interestingly **10b** showed more affinity toward 2-aminopyridine (**A**) and ethylisocyanoacetate (**X**) in presence of $In(OTf)_3$ (10 mol%) in EtOH to afford **11bAX** (Scheme 4). It was observed that GBB reaction with **10b** was faster as compared to **6b** and was completed in 10 min to produce the desired product in 69% yield. To further expand the scope of methodology, it was decided to remove the *tert*-butyl substituent so that the resulting primary amine group can be further functionalised. Treatment of **7bAZ** with 40% aqueous HBF_4 in toluene (Scheme 5) successfully afforded 2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-amine (**12bAZ**) in excellent yield.

Based on the observation of studies, a plausible mechanism for the formation of β-carboline C-3 tethered imidazo[1,2-*a*]azine



Scheme 5. HBF_4 assisted synthesis of 3-aminoimidazo[1,2-*a*]pyridine via dealkylation of **7bAZ**

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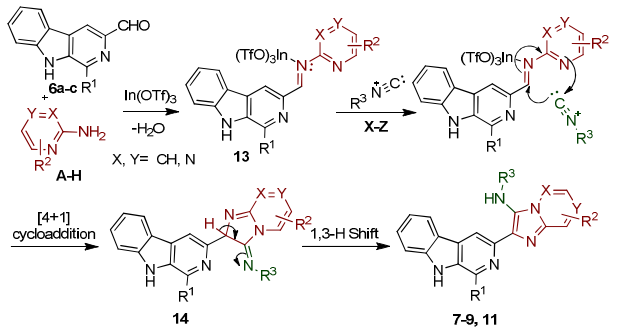

Figure 6. Proposed mechanism for the formation of β-carboline C-3 tethered imidazo[1,2-*a*]azine conjugates (**7-9** and **11**).

derivatives (**7-9** and **11**) is depicted in Figure 6. It is anticipated that reaction proceeds with the initial formation of Schiff base (**13**) via the condensation of 3-fomyl β-carbolines (**6a-c**) and 2-aminoazine (**A-H**) followed by a nonconcerted [4+1] cycloaddition between the Schiff base (**13**) and isonitrile (**X-Z**) to generate the intermediate **14**. Further, 1,3-prototropic shift may yield the β-carboline C-3 linked imidazo[1,2-*a*]azines (**7-9** and **11**).

Conclusions

In summary, we have successfully demonstrated the applicability of 3-formyl 1-aryl-9*H*-pyrido[3,4-*b*]indole for the synthesis of β-carboline C-3 tethered imidazo-azine derivatives via exploration of $In(OTf)_3$ assisted Groebke-Blackburn-Bienayme multicomponent approach. The reaction was found to be more facile with 1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carbaldehyde, 2-aminopyrazine/2-aminopyrimidine and *tert*-butylisocyanide in comparison to other substrates. Scope of the reaction was further extended by carrying out the HBF_4 mediated dealkylation of one of the derivatives afforded from *tert*-butylisocyanide. The anticancer evaluation studies are underway and will be reported in due course of time. Further, it is envisaged that 3-formyl 9*H*-pyrido[3,4-*b*]indole is a potent precursor and offer unlimited opportunities for installation of bioactive heterocyclic frameworks to generate molecular hybrids which may display unique properties and deliver drugs, ligands and other materials.

Experimental

General Section

The chemicals and reagents were purchased from Sigma Aldrich, Acros, Avera Synthesis, Spectrochem Pvt. Ltd. and used without further purification. Anhydrous solvents (CH_2Cl_2) utilised in the reactions were dried and freshly distilled before use. However, commercial anhydrous DMF, MeOH and Toluene (Spectrochem make) were used as such without further distillation. Absolute EtOH was used during this study. Thin layer chromatography (TLC) was performed using pre-coated aluminium plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Column chromatography was performed using Spectrochem make silica gel (60–120 mesh). Melting points were determined in open head capillary tubes on a Precision Digital melting point apparatus (LABCO make) containing silicon oil and are uncorrected. IR spectra were recorded using Agilent FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on Avance III Bruker spectrometer at operating frequencies of 400MHz (^{1}H) or 100 MHz (^{13}C) as indicated in the individual spectrum, using TMS as an internal standard. The MS spectra were recorded on Xevo G2-SQ TOF (Water, USA) or Thermo Finnigan LCQ Advantage, Ion Trap Mass Spectrometer. Elemental analyses were performed on a Carlo–Erba's 108 or an Elementar's Vario EL III microanalyzer. The room temperature varied between 25 °C and 35 °C. The multiplicity in ^{1}H-NMR spectra is presented as s for singlet; d for doublet; dd for doublet of doublet; t for triplet and m for multiplet.

Experimental Section

General procedure for the synthesis of compounds 7 and 11 as exemplified for ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7bAX). To a stirred solution of 2-aminopyridine **A** (0.10 g, 1.06 mmol) and (1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carbaldehyde, **6b** (0.35 g, 1.01 mmol) in EtOH (3 mL), $In(OTf)_3$ (0.09 g, 0.16 mmol) was added. Thereafter, ethyl isocyanoacetate, **X** (127 µL, 1.17 mmol) was added to the reaction mixture and the content was refluxed at 80 °C for 15 minutes. After the completion of reaction, as monitored by TLC, the reaction content was cooled to room temperature and 5 mL of ice cold water was added to the reaction content which resulted in the formation of a yellow solid. The solid product was filtered under vacuum, air dried, triturated and washed with hexane: ethylacetate (70:30, v/v) (4 x 5 mL) to obtain the analytically pure product **7bAX** (0.37 g from 0.10 g, 64%) as a yellow solid.

Ethyl 2-((2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7aAX). Yield: 66% (0.32 g from 0.10 g) as a light yellow solid; m.p. 82-83 °C; R_f = 0.79 (hexane/EtOAc, 30/70, v/v); IR (neat): ν_{max}(cm^{-1}) = 1732 (CO_2Et), 3249(NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.60 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 3.91 (s, 2 H, $NHCH_2$), 4.08 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 6.82 (t, *J* = 6.7 Hz, 1 H, $NHCH_2$), 7.14-7.18 (m, 1 H, ArH), 7.31 (t, *J* = 7.4 Hz, 1 H, ArH), 7.51 (t, *J* = 8.4 Hz, 2 H, ArH), 7.56 (d, *J* = 8.0 Hz, 1 H, ArH), 7.59-7.64 (m, 3 H, ArH), 8.03 (d, *J* = 7.6 Hz, 2 H, ArH), 8.14 (d, *J* = 6.6 Hz, 1 H, ArH), 8.22 (d, *J* = 7.9 Hz, 1 H, ArH), 8.56 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.87 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 49.1, 61.1, 111.1, 111.6, 112.0, 117.5, 120.5, 122.4, 122.5, 122.7, 123.8, 128.2, 128.6, 128.7, 128.8, 129.2, 131.2, 132.4, 132.8, 138.9, 140.9, 141.1, 145.0, 171.0 ppm; MS (ES):*m/z* (%) = 462.2 $[M+1]^+$; $C_{28}H_{23}N_5O_2$ (461.1852): calcd. for C, 72.87; H, 5.02; N, 15.17; found C, 73.05; H, 5.08; N, 15.26.

Ethyl 2-((6-chloro-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7aEX). Yield: 65% (0.18 g from 0.07 g) as a light yellow solid; m.p. 160-161 °C; R_f = 0.64 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1724 (CO_2Et), 3314(NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.13 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 3.92 (s, 2 H, $NHCH_2$), 4.10 (q, *J* = 7.1 Hz, 2 H,

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$CO_2CH_2CH_3$), 6.33 (s, 1 H, N*H*CH_2), 7.12 (d, *J* = 9.5 Hz 1 H, ArH), 7.33 (t, *J* = 7.1 Hz, 1 H, ArH), 7.50-7.59 (m, 4 H, ArH), 7.63 (t, *J* = 7.5 Hz, 2 H, ArH), 8.03 (d, *J* = 7.5 Hz, 2 H, ArH), 8.20 (s, 1 H, ArH), 8.23 (s, 1 H, ArH), 8.51 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.86 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 49.1, 61.4, 111.3, 111.8, 118.0, 118.8, 120.6, 120.7, 120.8, 122.5, 122.6, 125.3, 128.3, 128.9, 129.1, 129.4, 131.3, 132.7, 134.3, 138.7, 139.5, 141.0, 141.8, 144.5, 171.0 ppm; MS (ES):*m*/*z* (%) = 496.1 $[M+1]^+$, 498.1 $[M+3]^+$; $C_{28}H_{22}ClN_5O_2$ (495.1462): calcd. for C, 67.81; H, 4.47; N, 14.12; found C, 67.96; H, 4.49; N, 14.19.

Ethyl 2-((6-methyl-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7aFX). Yield: 74% (0.16 g from 0.05 g) as a dark brown solid; m.p. 110-111 °C; R_f = 0.63 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1732 (CO_2Et), 3320(NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ= 1.10 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.40 (s, 3 H, $ArCH_3$), 3.91 (s, 2 H, NHCH_2) 4,08 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.23 (s, 1 H, N*H*CH_2), 6.58 (d, *J* = 8.4 Hz, 1 H, ArH), 7.13 (d, *J* = 9.2 Hz, 1 H, ArH), 7.38 (d, *J* = 8.9 Hz, 1 H, ArH), 7.47-7.65 (m, 5 H, ArH), 8.00 (t, *J* = 7.4 Hz, 3 H, ArH), 8.21 (d, *J* = 8.0 Hz, 1 H, ArH), 8.65 (s, 1 H, ArH), 8.81 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 16.7, 21.1, 29.0, 60.4, 110.6, 112.5, 113.0, 115.3, 119.7, 120.7, 121.4, 121.9, 122.3, 128.6, 128.7, 128.9, 135.1, 137.3, 139.8, 140.7, 141.6, 142.2, 155.0, 172.0 ppm; MS (ES):*m*/*z* (%) = 476.2 $[M+1]^+$, 478.2 $[M+3]^+$; $C_{29}H_{25}N_5O_2$ (475.2008): calcd. for C, 73.25; H, 5.30; N, 14.73; found C, 73.41; H, 5.31; N, 14.77.

Methyl 2-((2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7aAY). Yield: 66% (0.16 g from 0.05 g) as a dark yellow solid; m.p. 149-150 °C; R_f = 0.56 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1740 (CO_2Et), 3294(NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.60 (s, 3 H, $COOCH_3$), 3.92 (s, 2 H, NHCH_2), 6.37 (s, 1 H, N*H*CH_2), 6.85 (t, *J* = 6.7 Hz, 1 H, ArH), 7.18 (t, *J* = 7.8 Hz, 1 H, ArH), 7.28 (t, *J* = 7.2 Hz, 2 H, ArH), 7.48-7.56 (m, 2 H, ArH), 7.58-7.65 (m, 3 H, ArH), 8.01 (d, *J* = 7.2 Hz, 2 H, ArH), 8.15 (d, *J* = 6.8 Hz, 1 H, ArH), 8.20 (d, *J* = 7.8 Hz, 1 H, ArH), 8.63 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.86 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.4, 29.8, 49.0, 52.1, 111.2, 111.7, 112.3, 112.4, 117.2, 120.6, 122.4, 122.8, 128.2, 128.4, 128.8, 128.9, 129.3, 129.5, 138.6, 141.0, 171.3, 175.6 ppm; MS (ES):*m*/*z* (%) = 448.1 $[M+1]^+$, 450.1 $[M+3]^+$; $C_{27}H_{21}N_5O_2$ (447.1695): calcd. for C, 72.47; H, 4.73; N, 15.65; found C, 72.64; H, 4.79; N, 15.77.

***N*-(*tert*-butyl)-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-amine (7aAZ)** Yield: 76% (0.35 g from 0.10 g) as a yellow solid; m.p. 134-135 °C; R_f = 0.64 (hexane/EtOAc, 30/70, v/v); IR (neat): ν_{max}(cm^{-1}) = 3294 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.07 (s, 9 H, $C(CH_3)_3$), 6.84 (t, *J* = 6.7 Hz, 1 H, NH), 7.21 (t, *J* = 7.8 Hz, 1 H, ArH), 7.29 (d, *J* = 7.8 Hz, 1 H, ArH), 7.46 (d, *J* = 7.4 Hz, 1 H, ArH), 7.52 (t, *J* = 5.7 Hz, 2 H, ArH), 7.58 (t, *J* = 7.5 Hz, 2 H, ArH), 7.67 (d, *J* = 9.1 Hz, 1 H, ArH), 8.02 (t, *J* = 8.9 Hz, 3 H, ArH), 8.18 (d, *J* = 7.8 Hz, 1 H, ArH), 8.35 (d, *J* = 6.8 Hz, 1 H, ArH), 8.64 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.86 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.1, 57.3, 111.1, 111.6, 111.7, 117.3, 120.5, 122.3, 122.6, 123.7, 124.2, 127.9, 128.1, 128.6, 128.9, 129.2, 131.2, 132.4, 136.1, 138.9, 140.9, 141.1, 141.8, 145.6 ppm; MS (ES):*m*/*z* (%) = 432.2 $[M+1]^+$; $C_{28}H_{25}N_5$ (431.2110): calcd. for C, 77.93; H, 5.84; N, 16.23; found C, 78.12; H, 5.89; N, 16.31.

Ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7bAX). Yield: 64% (0.37 g from 0.10 g) as a yellow solid; m.p. 106-107 °C, R_f = 0.53 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) =1739 (CO_2Et), 3304 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.12 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 3.86 (s, 2 H, NHCH_2), 4.07 (q, *J* = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 5.94 (s, 1 H, N*H*CH_2), 7.05 (t, *J* = 6.6 Hz, 1 H, ArH), 7.13 (t, *J* = 7.2 Hz, 1 H, ArH), 7.42 (t, *J* = 7.4 Hz, 2 H, ArH), 7.51 (d, *J* = 8.1 Hz, 1 H, ArH), 7.58 (d, *J* = 8.1 Hz, 2 H, ArH), 7.82 (d, *J* = 8.2 Hz, 3 H, ArH), 8.05 (d, *J* = 7.7 Hz, 1 H, ArH), 8.30 (d, *J* = 6.4 Hz, 1 H, ArH), 8.63 (s, 1 H, ArH), 8.92 (s, 1 H, $NH_{\beta\text{-carboline}}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 48.8, 61.3, 111.5, 111.8, 113.2, 116.4, 120.6, 122.0, 122.1, 123.1, 123.2, 126.0, 128.1, 128.8, 129.7, 130.9, 131.2, 132.2, 137.0, 139.9, 140.3, 141.0, 142.2, 171.0 ppm; MS (ES):*m*/*z*(%) = 540.1 $[M+1]^+$, 542.1 $[M+3]^+$; $C_{28}H_{22}BrN_5O_2$ (539.0957): calcd. for C, 62.23; H, 4.10; N, 12.96; found C, 62.41; H, 4.13; N, 12.99.

Ethyl 2-((8-bromo-2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7bBX). Yield: 73% (0.19 g from 0.08 g) as a light yellow solid; m.p. 138-139 °C; R_f = 0.50 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1744 (CO_2Et), 3261 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.06 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 3.92-3.98 (m, 4 H, NHCH_2 and $CO_2CH_2CH_3$), 6.79 (t, *J* = 6.8 Hz, 1 H, ArH), 7.29 (t, *J* = 7.7 Hz, 3 H, ArH), 7.39 (s, 1 H, ArH), 7.51 (t, *J* = 7.1 Hz, 2 H, ArH), 7.67 (d, *J* = 8.2 Hz, 2 H, ArH), 7.79 (d, *J* = 7.0 Hz, 2 H, ArH), 8.14 (d, *J* = 6.6 Hz, 2 H, ArH), 8.71 (s, 1 H, $NH_{\beta\text{-carboline}}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.0, 48.3, 61.5, 111.9, 112.1, 112.2, 112.7, 121.2, 121.3, 122.3, 122.5, 127.2, 128.8, 129.7, 129.9, 131.5, 132.6, 139.3, 142.2, 171.5 ppm; MS (ES):*m*/*z*(%) = 618.0 $[M+1]^+$, 620.0 $[M+3]^+$; $C_{28}H_{21}Br_2N_5O_2$ (617.0062): calcd. for C, 54.30; H, 3.42; N, 11.31; found C, 54.42; H, 3.44; N, 11.36.

Ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7bCX). Yield: 74% (0.38 g from 0.10 g) as a yellow solid; m.p. 178-179 °C; R_f = 0.67 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1739 (CO_2Et), 3256 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.13 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 2.42 (s, 3 H, $ArCH_3$), 3.87 (s, 2 H, NHCH_2), 4.10 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.67 (d, *J* = 6.9 Hz, 1 H, N*H*CH_2), 7.29 (t, *J* = 7.4 Hz, 1 H, ArH), 7.36 (s, 1 H, ArH), 7.50-7.55 (m, 3 H, ArH), 7.71 (d, *J* = 7.6 Hz, 2 H, ArH), 7.91 (d, *J* = 8.0 Hz, 2 H, ArH), 8.02 (d, *J* = 6.9 Hz, 1 H, ArH), 8.15 (d, *J* = 7.1 Hz, 1 H, ArH), 8.55 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.81 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 21.6, 49.2, 61.2, 111.2, 111.7, 114.9, 115.7, 120.6, 121.7, 122.0, 122.3, 122.4, 123.0, 128.2, 128.7, 19.8, 131.4, 132.2, 132.3, 136.0, 137.7, 137.8, 140.3, 141.0, 171.0 ppm; MS (ES):*m*/*z*(%) = 554.1 $[M+1]^+$, 556.1 $[M+3]^+$; $C_{29}H_{24}BrN_5O_2$ (553.1113): calcd. for C, 62.82; H, 4.36; N, 12.63; found C, 63.03; H, 4.40; N, 12.70.

Ethyl 2-((6-bromo-2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7bDX). Yield: 52% (0.14 g from 0.08 g) as a light yellow solid; m.p. 128-129 °C; R_f = 0.72 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1739 (CO_2Et), 3326 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.14 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 3.88 (s, 2 H, NHCH_2), 4.09 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.05 (s, 1 H, N*H*CH_2), 7.23 (t, *J* = 7.3 Hz, 2 H, ArH), 7.32 (d, *J* = 9.4 Hz, 1 H, ArH), 7.48-7.53 (m, 2 H, ArH), 7.59 (d, *J* = 9.4 Hz, 1 H, ArH), 7.66 (d, *J* = 8.2 Hz, 2 H, ArH), 7.84 (d, *J* = 8.2 Hz, 2 H, ArH), 8.12 (d, *J* = 7.8 Hz, 1 H, ArH), 8.33 (s, 1 H, ArH), 8.72 (s, 1 H, $NH_{\beta\text{-carboline}}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 48.9, 61.4, 107.2, 111.5, 111.8, 118.0, 120.8, 122.3, 122.9, 123.2, 127.5, 128.7, 129.0, 129.8, 131.4, 132.4, 133.5, 137.4, 139.3, 140.5, 141.0, 144.2, 170.8 ppm; MS (ES):*m*/*z*(%) = 618.0 $[M+1]^+$, 620.0 $[M+3]^+$; $C_{28}H_{21}Br_2N_5O_2$

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(617.0062): calcd. for C, 54.30; H, 3.42; N, 11.31; found C, 54.48; H, 3.45; N, 11.39.

Ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-6-chloroimidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7bEX). Yield: 68 % (0.23 g from 0.08 g) as a yellow solid; m.p. 159-160 ^{o}C; R_f = 0.70 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1742 (CO_2Et), 3308 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.14 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 3.88 (s, 2 H, $NHCH_2$), 4.08 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.00 (s, 1 H, $NHCH_2$), 7.2 (t, *J* = 7.3 Hz, 1 H, ArH), 7.27 (d, *J* = 11.0 Hz, 1 H, ArH), 7.46-7.52 (m, 2 H, ArH), 7.64-7.69 (m, 3 H, ArH), 7.84 (d, *J* = 8.0 Hz, 2 H, ArH), 8.10 (d, *J* = 7.6 Hz, 1 H, ArH), 8.27 (s, 1 H, ArH), 8.69 (s, 1 H, ArH), 8.83 (s, 1 H, $NH_{\beta\text{-carboline}}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 48.8, 61.4, 111.5, 111.8, 117.5, 120.8, 120.8, 121.0, 122.2, 122.3, 123.3, 126.0, 129.0, 129.8, 131.4, 132.4, 137.2, 139.0, 140.4, 141.0, 141.0 ppm; MS (ES):*m*/*z*(%) = 574.0 [M+1]$^+$, 576.0 [M+3]$^+$; $C_{28}H_{21}BrClN_5O_2$ (573.0567): calcd. for C, 58.50; H, 3.68; N, 12.18; found C, 58.69; H, 3.71; N, 12.26.

Ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7bFX). Yield: 52% (0.13 g from 0.05 g) as a light yellow solid; m.p. 218-219 ^{o}C; R_f = 0.70 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1740 (CO_2Et), 3274 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.14 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.37 (s, 3 H, $ArCH_3$), 3.90 (d, *J* = 6.4 Hz, 2 H, $NHCH_2$), 4.12 (q, *J* = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 6.30 (t, *J* = 7.5 Hz, 1 H, $NHCH_2$), 7.01 (dd, J_1 = 1.6 Hz, J_2 = 9.5 Hz, 1 H, ArH), 7.33 (d, *J* = 7.4 Hz, 1 H, ArH), 7.49-7.58 (m, 3 H, ArH), 7.74 (d, *J* = 8.4 Hz, 2 H, ArH), 7.89 (s, 1 H, ArH), 7.93 (d, *J* = 8.4 Hz, 2 H, ArH), 8.22 (d, *J* = 7.9 Hz, 1 H, ArH), 8.40 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.87 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 18.6, 49.0, 61.2, 111.2, 111.6, 117.0, 120.2, 120.7, 121.7, 122.4, 122.5, 123.1, 127.1, 128.4, 128.8, 129.8, 130.0, 131.5, 132.2, 132.5, 132.6, 137.8, 140.4, 141.0, 145.5, 171.0 ppm; MS (ES):*m*/*z*(%) = 554.1 [M+1]$^+$, 556.1 [M+3]$^+$; $C_{29}H_{24}BrN_5O_2$ (553.1113): calcd. for C, 62.82; H, 4.36; N, 12.63; found C, 62.98; H, 4.38; N, 12.69.

Methyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7bAY). Yield: 71% (0.20 g from 0.05 g) as a yellow solid; m.p. 132-133 ^{o}C; R_f = 0.85 (hexane/EtOAc, 30/70, v/v); IR (neat): ν_{max}(cm^{-1}) = 1749 (CO_2Et), 3264 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.64 (s, 3 H, $COOCH_3$), 3.91 (s, 2 H, $NHCH_2$), 6.32 (s, 1 H, $NHCH_2$), 6.83 (t, *J* = 6.7 Hz, 1 H, ArH), 7.17 (t, *J* = 7.8 Hz, 1 H, ArH), 7.32 (t, *J* = 7.4 Hz, 1 H, ArH), 7.51 (d, *J* = 8.1 Hz, 1 H, ArH), 7.56 (t, *J* = 7.5 Hz, 1 H, ArH), 7.62 (d, *J* = 9.1 Hz, 1 H, ArH), 7.73 (d, *J* = 8.2 Hz, 2 H, ArH), 7.92 (d, *J* = 8.2 Hz, 2 H, ArH), 8.13 (d, *J* = 6.9 Hz, 1 H, ArH), 8.21 (d, *J* = 7.8 Hz, 1 H, ArH), 8.50 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.88 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 49.0, 52.1, 111.4, 111.7, 112.1, 117.6, 120.8, 122.4, 122.5, 122.7, 123.1, 124.0, 128.6, 128.9, 129.8, 131.6, 132.3, 132.4, 132.8, 137.8, 140.5, 141.0, 141.2, 141.7, 145.2, 171.3 ppm; MS (ES):*m*/*z*(%) = 526.1 [M+1]$^+$, 528.1 [M+3]$^+$; $C_{27}H_{20}BrN_5O_2$ (525.0800): calcd. for C, 61.61; H, 3.83; N, 13.30; found C, 61.82; H, 3.89; N, 13.41.

2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-N-(*tert*-butyl)imidazo[1,2-*a*]pyridin-3-amine (7bAZ). Yield: 73% (0.19 g from 0.05 g) as a yellow solid; m.p. 214-215 ^{o}C; R_f = 0.80 (hexane/EtOAc, 30/70, v/v); IR (neat): ν_{max}(cm^{-1}) = 1731 (CO_2Et), 3328 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.08 (s, 9 H, $C((CH_3)_3)$, 5.85 (s, 1 H, NH), 6.73-6.78 (m, 1 H, ArH), 7.12 (t, *J* = 7.7 Hz, 1 H, ArH), 7.31 (t, *J* = 7.3 Hz, 1 H, ArH), 7.51-7.53 (m, 2 H, ArH), 7.56 (d, *J* = 9.5 Hz, 1 H, ArH), 7.60 (d, *J* = 7.7 Hz, 1 H, ArH), 7.72 (d, *J* = 8.2 Hz, 1 H, ArH), 7.92 (d, *J* = 8.3 Hz, 1 H, ArH), 8.04 (d, *J* = 7.5 Hz, 1 H, ArH), 8.20-8.23 (m, 1 H, ArH), 8.31 (d, *J* = 6.9 Hz, 1 H, ArH), 8.51 (d, *J* = 11.0 Hz, 1 H, ArH), 8.86 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.9, 57.3, 111.1, 111.2, 111.6, 111.7, 112.0, 117.3, 120.5, 122.4, 123.7, 124.2, 128.1, 128.6, 128.8, 128.9, 129.2, 129.6, 132.3, 132.4, 135.9, 136.1, 137.8, 138.9, 140.9, 141.1, 141.8 ppm; MS (ES):*m*/*z* (%) = 510.1 [M+1]$^+$, 512.1 [M+3]$^+$; $C_{28}H_{24}BrN_5$ (509.1215): calcd. for C, 65.89; H, 4.74; N, 13.72; found C, 66.12; H, 4.78; N, 13.79.

Ethyl 2-((2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7cAX). Yield: 53% (0.07 g from 0.03 g) as a light yellow solid; m.p. 126-127 ^{o}C; R_f = 0.53 (hexane/EtOAc, 50/50, v/v; IR (neat): ν_{max}(cm^{-1}) = 1732 (CO_2Et), 3314 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.01 (t, *J* = 6.9 Hz, 3 H, $CO_2CH_2CH_3$), 3.79 (s, 2 H, $NHCH_2$), 3.97 (q, *J* = 6.8 Hz, 2 H, $CO_2CH_2CH_3$), 6.19 (s, 1 H, $NHCH_2$), 6.96 (t, *J* = 6.8 Hz, 1 H, ArH), 7.18 (t, *J* = 6.5 Hz, 1 H, ArH), 7.28 (d, *J* = 7.3 Hz, 2 H, ArH), 7.41 (t, *J* = 7.4 Hz, 1 H, ArH), 7.56 (t, *J* = 11.6 Hz, 2 H, ArH), 7.71 (d, *J* = 6.1 Hz, 2 H, ArH), 7.98 (d, *J* = 7.1 Hz, 3 H, ArH), 8.35 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.57 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 49.0, 61.2, 109.6, 111.2, 111.7, 112.1, 113.6, 117.4, 120.5, 122.2, 122.3, 122.7, 123.9, 128.6, 128.7, 128.9, 129.3, 129.5, 131.3, 134.7, 137.2, 138.7, 141.1, 144.9, 146.0, 171.0 ppm; MS (ES):*m*/*z*(%) = 496.1 [M+1]$^+$, 498.1 [M+3]$^+$; $C_{28}H_{22}ClN_5O_2$ (495.1462): calcd. for C, 67.81; H, 4.47; N, 14.12; found C, 68.00; H, 4.50; N, 14.19.

Ethyl 2-((8-bromo-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7cBX). Yield: 61% (0.10 g from 0.05 g) as a yellow solid; m.p. 123-124 ^{o}C; R_f = 0.74 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1739 (CO_2Et), 3297 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.11 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 3.87 (s, 2 H, $NHCH_2$), 4.09 (q, *J* = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 6.71 (t, *J* = 7.0 Hz, 1 H, $NHCH_2$), 7.31 (t, *J* = 6.9 Hz, 1 H, ArH), 7.42 (d, *J* = 7.1 Hz, 1 H, ArH), 7.52-7.58 (m, 5 H, ArH), 7.95 (d, *J* = 8.4 Hz, 2 H, ArH), 8.13 (t, *J* = 8.1 Hz, 2 H, ArH), 8.62 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.90 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 49.0, 61.3, 111.7, 112.0, 112.0, 120.6, 122.1, 122.4, 122.6, 126.1, 128.8, 129.3, 129.4, 130.0, 131.3, 132.5, 133.7, 134.7, 137.2, 138.7, 140.3, 141.0, 144.4, 170.8 ppm; MS (ES):*m*/*z*(%) = 574.1 [M+1]$^+$, 576.1 [M+3]$^+$; $C_{28}H_{21}BrClN_5O_2$ (573.0567): calcd. for C, 58.50; H, 3.68; N, 12.18; found C, 58.62; H, 3.71; N, 12.26.

Ethyl 2-((6-bromo-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7cDX). Yield: 57% (0.09 g from 0.05 g) as a yellow solid; m.p. 156-157 ^{o}C; R_f = 0.72 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1745 (CO_2Et), 3073 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.15 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 3.98 (s, 2 H, $NHCH_2$), 4.12 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 6.23 (s, 1 H, ArH), 7.22 (d, *J* = 9.4 Hz, 1 H, ArH), 7.32 (t, *J* = 7.3 Hz, 1 H, ArH), 7.52 (t, *J* = 10.1 Hz, 3 H, ArH), 7.58 (d, *J* = 8.2 Hz, 2 H, ArH), 7.97 (d, *J* = 8.0 Hz, 2 H, ArH), 8.21 (d, *J* = 7.6 Hz, 1 H, ArH), 8.27 (s, 1 H, ArH), 8.48 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.85 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 48.9, 61.3, 107.0, 111.3, 111.7, 118.0, 120.6, 122.3, 122.8, 127.2, 128.7, 128.8, 129.3, 129.5, 131.3, 132.4, 133.8, 134.8, 137.0, 139.4, 140.4, 141.0, 144.4, 170.8 ppm; MS (ES):*m*/*z*(%) = 574.0 [M+1]$^+$, 576.0 [M+3]$^+$; $C_{28}H_{21}BrClN_5O_2$ (573.0567): calcd. for C, 58.50; H, 3.68; N, 12.18; found C, 58.67; H, 3.72; N, 12.23.

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Ethyl 2-((6-chloro-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (7cEX). Yield: 54% (0.11 g from 0.05 g) as a dark brown solid; m.p. 102-103 ^{o}C; R_f = 0.72 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 1743 (CO_2Et), 3308 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.15 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 3.88 (s, 2 H, $NHCH_2$), 4.13 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.21 (s, 1 H, $NHCH_2$), 7.10 (dd, J_1 = 1.8 Hz, J_2 = 9.6 Hz, 1 H, ArH), 7.30 (t, *J* = 7.3 Hz, 1 H, ArH), 7.49-7.58 (m, 5 H, ArH), 7.93 (d, *J* = 8.4 Hz, 2 H, ArH), 8.15 (d, *J* = 7.7 Hz, 2 H, ArH), 8.62 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.81 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 48.8, 61.3, 111.5, 111.7, 117.6, 120.6, 120.8, 122.3, 125.5, 128.9, 129.4, 129.5, 131.4, 132.4, 133.6, 134.9, 137.0, 139.2, 140.4, 150.0, 144.0, 170.8 ppm; MS (ES):*m/z*(%) = 530.1 [M+1]$^+$, 532.1 [M+3]$^+$; $C_{28}H_{21}Cl_2N_5O_2$ (529.1072): calcd. for C, 63.40; H, 3.99; N, 13.20; found C, 63.56; H, 4.01; N,13.26.

N-(*tert*-butyl)-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl) imidazo[1,2-*a*]pyridin-3-amine (7cAZ). Yield: 66% (0.16 g from 0.05 g) as a light orange solid; m.p. 224-225 ^{o}C; R_f = 0.53 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) = 3303 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.08 (s, 9 H,$(C(CH_3)_3)$, 5.74 (s, 1 H, NH), 6.76 (t, *J* = 6.7 Hz, 1 H, ArH), 7.14 (t, *J* = 7.5 Hz, 1 H, ArH), 7.32 (t, *J* = 7.3 Hz, 1 H, ArH), 7.52 (t, *J* = 8.1, 1 H, ArH), 7.56-7.60 (m, 4 H, ArH), 7.99 (d, *J* = 8.4 Hz, 2 H, ArH), 8.21 (d, *J* = 7.8 Hz, 1 H, ArH), 8.31 (d, *J* = 7.0 Hz, 1 H, ArH), 8.47 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.86 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.1, 57.3, 111.3, 111.7, 112.0, 117.1, 120.7, 122.3, 122.5, 124.0, 124.2, 127.8, 128.8, 129.3, 129.4, 131.5, 132.3, 134.8, 135.8, 137.3, 139.8, 141.0, 141.8, 145.5 ppm; MS (ES):*m/z* (%) = 466.17 [M+1]$^+$, 468.17 [M+3]$^+$; $C_{28}H_{24}ClN_5$ (465.1720): calcd. for C, 72.17; H, 5.19; N, 15.03; found C, 72.36; H, 5.22; N, 15.09.

General procedure for the synthesis of compounds 8 and 9 as exemplified for ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (8bGX). To a stirred solution of 2-aminopyrazine **G** (0.08 g, 0.79 mmol) and (1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carbaldehyde **6b** (0.26 g, 0.75 mmol) in EtOH (3 mL), was added $In(OTf)_3$ (0.04 g, 0.08 mmol) followed by the addition of ethyl isocyanoacetate **X** (95 µl, 87 mmol). The reaction mixture was refluxed at 80 ^{o}C for 5 minutes. After the completion of reaction which was monitored by TLC, the reaction content was cooled to room temperature followed by addition of 5 mL of ice cold water to it which resulted in the formation of a yellow solid. Solid compound was filtered under vacuum and was further washed with hexane:ethylacetate (70:30, v/v) (10 mL X 4) solution to obtain the analytically pure product **8bGX** (0.30 g from 0.08 g, 71%) as a yellow solid.

Ethyl 2-((2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*] pyrazin-3-yl)amino)acetate (8aGX). Yield: 74% (0.18 g from 0.05 g) as an orange solid; m.p. 227-228 ^{o}C; R_f = 0.62 (hexane/EtOAc, 30/70, v/v); IR (neat): ν_{max}(cm^{-1}) = 1738 (CO_2Et), 3302 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.10 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 3.99 (d, *J* = 5.3 Hz, 2 H, $NHCH_2$), 4.06-4.13 (m, 2 H, $CO_2CH_2CH_3$), 6.99 (s, 1 H, $NHCH_2$), 7.35 (t, *J* = 7.5 Hz, 1 H, ArH), 7.52-7.67 (m, 5 H, ArH), 7.85 (d, *J* = 4.1 Hz, 1 H, ArH), 7.99-8.05 (m, 3 H, ArH), 8.27 (d, *J* = 8.4 Hz, 1 H, ArH), 8.54 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.94 (s, 1 H, ArH), 9.04 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 13.8, 47.3, 60.4, 111.0, 112.5, 116.6, 119.8, 121.1, 122.0, 128.3, 128.4, 128.6, 128.8, 129.0, 130.2, 130.4, 132.1, 132.7, 135.0, 138.0, 141.1, 141.7, 142.5, 143.3, 170.8 ppm; MS (ES):*m/z* (%) = 463.1 [M+1]$^+$; $C_{27}H_{22}N_6O_2$ (462.1804): calcd. for C, 70.12; H, 4.79; N, 18.17; found C, 70.31; H, 4.82; N, 18.23.

***N*-(*tert*-butyl)-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-amine (8aGZ).** Yield: 79% (0.18 from 0.05 g) as an orange solid; m.p. 163-164 ^{o}C; R_f = 0.70 (hexane/EtOAc, 30/70, v/v); IR (neat): ν_{max}(cm^{-1}) = 1732 (CO_2Et), 3204 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.11 (s, 9 H, $C(CH_3)_3$), 6.01 (s, 1 H, NH), 7.34 (t, *J* = 7.4 Hz, 1 H, ArH), 7.51-7.59 (m, 2 H, ArH), 7.63 (t, *J* = 7.6 Hz, 2 H, ArH), 7.81 (d, *J* = 4.6 Hz, 1 H, ArH), 7.99 (s, 1 H, ArH), 8.03 (d, *J* = 7.5 Hz, 2 H, ArH), 8.20 (d, *J* = 4.5 Hz, 1 H, ArH), 8.25 (d, *J* = 7.9 Hz, 1 H, ArH), 8.60 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.91 (s, 1 H, ArH), 9.03 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.2, 57.9, 111.8, 112.1, 117.1, 120.9, 122.4, 128.0, 128.6, 129.1, 129.3, 129.4, 132.7, 137.1, 141.2, 143.3 ppm; MS (ES):*m/z* (%) = 433.2 [M+1]$^+$; $C_{27}H_{24}N_6$ (432.2062): calcd. for C, 74.98; H, 5.59; N, 19.43; found C, 75.16; H, 5.65; N, 19.54.

Ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo [1,2-*a*]pyrazin-3-yl)amino)acetate (8bGX). Yield: 71% (0.30 g from 0.08) as a dark yellow solid; m.p. 209-210 ^{o}C; R_f = 0.82 (hexane/EtOAc, 30/70, v/v); IR (neat): ν_{max}(cm^{-1}) = 1747 (CO_2Et), 3346(NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.13 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 3.97 (d, *J* = 6.4 Hz, 2 H, $NHCH_2$), 4.11 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.89 (t, *J* = 6.6 Hz, 1 H, $NHCH_2$), 7.35 (t, *J* = 7.3 Hz, 1 H, ArH), 7.52 (d, *J* = 8.1 Hz, 1 H, ArH), 7.58 (t, *J* = 7.6 Hz, 1 H, ArH), 7.76 (d, *J* = 8.4 Hz, 2 H, ArH), 7.84 (d, *J* = 4.6 Hz, 1 H, ArH), 7.93 (d, *J* = 8.4 Hz, 2 H, ArH), 7.99-8.01 (dd, J_1 = 1.3 Hz, J_2 = 4.8 Hz, 1 H, ArH), 8.24 (d, *J* = 7.8 Hz, 1 H, ArH), 8.49 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.92 (s, 1 H, ArH), 9.03 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 48.2, 61.5, 111.8, 111.8, 115.5, 121.0 122.4, 122.4, 123.4, 129.1, 129.8, 130.4, 131.5, 132.6, 134.4, 136.1, 137.4, 140.5, 140.5, 143.5, 144.4, 170.5 ppm; MS (ES):*m/z*(%) = 541.0 [M+1]$^+$, 543.0 [M+3]$^+$; $C_{27}H_{21}BrN_6O_2$ (540.0909): calcd. for C, 59.90; H, 3.91; N, 15.52; found C, 60.06; H, 3.94; N, 15.59.

Methyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl) imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (8bGY). Yield: 75% (0.21 g from 0.05) as an orange solid; m.p. 149-150 ^{o}C; R_f = 0.70 (hexane/EtOAc, 30/70, v/v); IR (neat): ν_{max}(cm^{-1}) = 1744 (CO_2Et), 3240 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.65 (s, 3 H, $COOCH_3$), 3.99 (s, 2 H, $NHCH_2$), 6.86 (s, 1 H, $NHCH_2$), 7.36 (t, *J* = 7.5 Hz, 1 H, ArH), 7.53 (d, *J* = 8.2 Hz, 1 H, ArH), 7.59 (t, *J* = 7.6 Hz, 1 H, ArH), 7.77 (d, *J* = 8.1 Hz, 2 H, ArH), 7.85 (d, *J* = 4.7 Hz, 1 H, ArH), 7.94 (d, *J* = 8.3 Hz, 2 H, ArH), 7.98-8.01 (m, 1 H, ArH), 8.25 (d, *J* = 7.8 Hz, 1 H, ArH), 8.50 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.93 (s, 1 H, ArH), 9.04 (s, 1 H, ArH), ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 47.1, 51.7, 111.4, 112.5, 116.7, 119.9, 121.1, 122.1, 122.2, 128.3, 128.7, 130.2, 130.6, 131.6, 131.8, 132.1, 132.4, 132.6, 135.1, 137.2, 139.9, 141.8, 142.6, 143.4, 171.4 ppm; MS (ES):*m/z*(%) = 527.1 [M+1]$^+$, 529.1 [M+3]$^+$; $C_{26}H_{19}BrN_6O_2$ (526.0753): calcd. for C, 59.21; H, 3.63; N, 15.94; found C, 59.39; H, 3.67; N, 16.01.

2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-N-(*tert*-butyl) imidazo[1,2-*a*]pyrimidin-3-amine (8bGZ). Yield: 70% (0.21 g from 0.05 g) as a yellow solid; m.p. 192-193 ^{o}C; R_f = 0.72 (hexane/EtOAc, 50/50, v/v); IR (neat): ν_{max}(cm^{-1}) =1725 (CO_2Et), 3301 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.03 (s, 9 H, $C(CH_3)_3$), 7.36 (t, *J* = 7.6 Hz, 1 H, ArH), 7.43-7.53 (m, 5 H, ArH), 7.92 (t, *J* = 7.9 Hz, 3 H, ArH), 8.17 (t, *J* = 4.9 Hz, 1 H, ArH), 8.22 (d, *J* = 4.6 Hz, 1 H, ArH), 8.64 (s, 1 H, $NH_{\beta\text{-carboline}}$), 9.04 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.2, 60.0, 111.8, 111.9, 112.0, 112.1, 112.2, 117.2, 121.2, 122.4, 128.0,

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128.8, 128.9, 129.0, 129.7, 130.0, 134.5, 137.3, 143.4 ppm; MS (ES):*m*/*z*(%) = 511.1 $[M+1]^+$, 513.1 $[M+3]^+$; $C_{27}H_{23}BrN_6$ (510.1168): calcd. for C, 63.41; H, 4.53; N, 16.43; found C, 63.58; H, 4.55; N, 16.49.

Ethyl 2-((2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo [1,2-*a*]pyrazin-3-yl)amino)acetate (8cGX). Yield: 71% (0.08 g from 0.03 g) as a yellow solid; m.p. 180-181 °C; R_f = 0.67 (hexane/EtOAc, 30/70, v/v); IR (neat): $\nu_{max}(cm^{-1})$ = 1745 (CO_2Et), 3085 (NH); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.13 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 3.98 (d, *J* = 6.5 Hz, 2 H, $NHCH_2$), 4.11 (q, *J* = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 6.91 (t, *J* = 6.7 Hz, 1 H, $NHCH_2$), 7.36 (t, *J* = 7.5 Hz, 1 H, ArH), 7.52-7.62 (m, 4 H, ArH), 7.85 (d, *J* = 4.6 Hz, 1 H, ArH), 8.00-8.02 (m, 3 H, ArH), 8.25 (d, *J* = 7.8 Hz, 1 H, ArH), 8.48 (s, 1 H, $NH_{\beta\text{-carboline}}$), 8.93 (s, 1 H, ArH), 9.04 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 48.2, 61.5, 111.8, 115.5, 120.9, 122.3, 122.4, 129.1, 129.5, 129.6, 130.4, 131.5, 132.7, 134.4, 135.1, 136.1, 137.0, 140.5, 141.0, 143.5, 144.3, 170.1 ppm; MS (ES):*m*/*z* (%) = 497.1 $[M+1]^+$, 499.1 $[M+3]^+$; $C_{27}H_{21}ClN_6O_2$ (496.1415): calcd. for C, 65.26; H, 4.26; N, 16.91; found C, 65.44; H, 4.28; N, 16.96.

Ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo [1,2-*a*]pyrimidin-3-yl)amino)acetate (9bHX). Yield: 78% (0.23 g from 0.05 g) as a yellow solid; m.p. 171-172 °C; R_f = 0.61 (hexane/EtOAc, 30/70, v/v); IR (neat): $\nu_{max}(cm^{-1})$ = 1732 (CO_2Et), 3264 (NH); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.01 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.89 (s, 2 H, $NHCH_2$), 3.98 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.46 (t, *J* = 6.4 Hz, 1 H, $NHCH_2$), 7.02-7.09 (m, 1 H, ArH), 7.26-7.35 (m, 1 H, ArH), 7.57-7.68 (m, 2 H, ArH), 7.84 (t, *J* = 7.5 Hz, 2 H, ArH), 7.95 (s, 1 H, ArH), 8.09 (d, *J* = 8.2 Hz, 2 H, ArH), 8.41 (t, *J* = 6.7 Hz, 1 H, ArH), 8.46-8.49 (m, 1 H, ArH), 8.84 (d, *J* = 5.2 Hz, 1 H, ArH), 8.92 (m, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.8, 48.0, 60.4, 108.0, 110.1, 111.5, 112.4, 119.9, 121.2, 122.1, 130.5, 130.6, 131.8, 131.9, 137.4, 141.6, 141.7, 141.8, 142.9, 143.7, 145.8, 148.6, 152.1, 171.1 ppm; MS (ES):*m*/*z* (%) = 541.1 $[M+1]^+$, 543.1 $[M+3]^+$; $C_{27}H_{21}BrN_6O_2$ (540.0909): calcd. for C, 59.90; H, 3.91; N, 15.52; found C, 60.10; H, 3.95; N, 15.59.

2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-N-(*tert*-butyl) imidazo[1,2-*a*]pyrimidin-3-amine (9bHZ). Yield: 84% (0.23 g from 0.05 g) as a yellow solid; m.p. 89-90 °C; R_f = 0.46 (hexane/EtOAc, 30/70, v/v); IR (neat): $\nu_{max}(cm^{-1})$ = 3286 (NH); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.10 (s, 9 H, $C(CH_3)_3$), 5.29 (s, 1 H, NH), 6.80-6.84 (m, 1 H, ArH), 7.29-7.33 (m, 1 H, ArH), 7.49-7.56 (m, 2 H, ArH), 7.61 (t, *J* = 7.5 Hz, 2 H, ArH), 7.71 (d, *J* = 8.3 Hz, 1 H, ArH), 7.90 (d, *J* = 8.2 Hz, 1 H, ArH), 8.02 (d, *J* = 7.5 Hz, 1 H, ArH), 8.20 (d, *J* = 8.0 Hz, 1 H, ArH), 8.47-8.48 (m, 1 H, ArH), 8.60 (d, *J* = 5.6 Hz, 1 H, ArH), 8.98 (d, *J* = 11.1 Hz, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 30.1, 57.5, 107.7, 107.8, 111.7, 112.7, 120.7, 122.3, 128.1, 128.8, 128.9, 129.2, 129.6, 131.5, 132.6, 141.0, 144.7, 148.9, 158.3 ppm; MS (ES):*m*/*z* (%) = 511.1 $[M+1]^+$, 513.1 $[M+3]^+$; $C_{27}H_{23}BrN_6$ (510.1168): calcd. for C, 63.41; H, 4.53; N, 16.43; found C, 63.59; H, 4.57; N, 16.52.

Ethyl 2-((2-(1-(4-bromophenyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (11bAX). Yield: 69% (0.41 g from 0.10 g) as a yellow solid; m.p. 148-149 °C; R_f = 0.68 (hexane/EtOAc, 50/50, v/v); IR (neat): $\nu_{max}(cm^{-1})$ = 1731 (CO_2Et), 3328 (NH); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.15 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 3.53 (s, 3 H, NCH_3), 3.84 (s, 2 H, $NHCH_2$), 4.07 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.15 (s, 1 H, $NHCH_2$), 6.80 (t, *J* = 6.4 Hz, 1 H, ArH), 7.15 (t, *J* = 7.7 Hz, 1 H, ArH), 7.25 (d, *J* = 4.9 Hz, 1 H, ArH), 7.33 (t, *J* = 7.4 Hz, 1 H, ArH), 7.60-7.63 (m, 4 H, ArH), 7.69 (d, *J* = 8.3 Hz, 2 H, ArH), 8.12 (d, *J* = 6.7 Hz, 1 H, ArH), 8.27 (d, *J* = 7.8 Hz, 1 H, ArH), 8.88 (d, *J* = 4.8 Hz, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 33.5, 49.1, 61.2, 109.9, 110.9, 112.0, 117.6, 120.4, 121.9, 122.2, 122.7, 123.8, 128.7, 128.8, 131.4, 131.5, 131.8, 132.9, 134.1, 139.2, 141.2, 141.5, 143.6, 144.2, 170.9 ppm; MS (ES):*m*/*z* (%) = 554.1 $[M+1]^+$, 556.1 $[M+3]^+$; $C_{29}H_{24}BrN_5O_2$ (553.1113): calcd. for C, 62.82; H, 4.36; N, 12.63; found C, 63.05; H, 4.41; N, 12.71.

General procedure for the synthesis of 2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-amine (12bAZ). To a stirred solution of **7bAZ** (0.15 g, 0.29 mmol) in toluene (2 mL), HBF_4 (19 µL, 0.30 mmol) was added and refluxed the reaction mixture at 120 °C for 15 minutes. After the completion of reaction which was monitored by TLC, the reaction content was cooled to room temperature and toluene was decanted. Crude compound was washed with ethyl acetate (4 x 5 mL) to obtain the analytically pure product, **12bAZ** (0.14 g from 0.15 g, 93%) as a yellow solid.

2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*] pyridin-3-amine (12bAZ). Yield: 93% (0.13 g from 0.15 g) as a bright yellow solid; m.p. 168-169 °C; R_f = 0.44 (hexane/EtOAc, 10/90, v/v); IR (neat): $\nu_{max}(cm^{-1})$ = 3383 and 3390 (NH_2); ^1H NMR (400 MHz, DMSO-d_6) δ = 4.82 (s, 2 H, NH_2), 7.36 (t, *J* = 7.5 Hz, 1 H, ArH), 7.52 (t, *J* = 6.8 Hz, 1 H, ArH), 7.61-7.65 (m, 2 H, ArH), 7.68-7.73 (m, 2 H, ArH), 7.84 (t, *J* = 7.9 Hz, 1 H, ArH), 7.88-7.91 (m, 2 H, ArH), 8.08 (d, *J* = 8.4 Hz, 1 H, ArH), 8.13 (d, *J* = 7.4 Hz, 1 H, ArH), 8.28 (d, *J* = 7.9 Hz, 1 H, ArH), 8.70 (t, *J* = 6.3 Hz, 1 H, ArH), 8.74 (d, *J* = 4.7 Hz, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 110.3, 111.8, 112.9, 113.7, 116.2, 120.2, 120.7, 121.6, 124.3, 129.0, 129.1, 129.3, 129.6, 130.2, 130.6, 131.2, 131.9, 132.0, 134.8, 137.0, 137.6, 141.9, 142.3 ppm; MS (ES):*m*/*z* (%) = 454.1 $[M+1]^+$, 456.1 $[M+3]^+$; $C_{24}H_{16}BrN_5$ (453.0589): calcd. for C, 63.45; H, 3.55; N, 15.41; found C, 63.68; H, 3.60; N, 15.49.

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Notes and references

1 R. Cao, W. Peng, Z. Wang and A. Xung, *Curr. Med. Chem*., 2007, **14**, 479–500.

2 (a) K.-B. Wang, Y.-T. Di, Y. Bao, C.-M. Yuan, G. Chen, D.-H. Li, J. Bai, H.-P. He, X.-J. Hao, Y.-H. Pei, Y.-K. Jing, Z.-L. Li and H.-M. Hua, *Org. Lett.*, 2014, **16**, 4028–4031; (b) K.-B. Wang, C.-M. Yuan, C.-M. Xue, D.-H. Li, Y.-K. Jing, H.-P. He, X.-J. Hao, Y.-T. Di, Z.-L. Li and H.-M. Hua, *RSC Adv.*, 2014, **4**, 53725–53729; (c) T. D. Tran, N. B. Pham, M. Ekins, J. N. A. Hooper and R. J. Quinn, *Mar. Drugs*, 2015, **13**, 4556–4575; (d) R. J. R.

View Article Online
DOI: 10.1039/C6NJ03210A

Jaeger, M. Lamshoft, S. Gottfried, M. Spiteller and P. Spiteller, *J. Nat. Prod*., 2013, **76**, 127−134; (e) S. L. Wong, H. S. Chang, G. J. Wang, M. Y. Chiang, H. Y. Huang, C. H. Chen, S. C. Tsai, C. H. Lin and I. S. Chen, *J. Nat. Prod.,* 2011, **74**, 2489−2496; (f) S. T. S. Chan, A. N. Pearce, M. J. Page, M. Kaiser and B. R. Copp, *J. Nat. Prod.,* 2011, **74**, 1972−1979; (g) W. H. Jiao, H. Gao, C. Y. Li, F. Zhao, R. W. Jiang, Y. Wang, G. X. Zhou and X. S. Yao, *J. Nat. Prod.*, 2010, **73**, 167−171; (h) Y. F. Chen, P. C. Kuo, H. H. Chan, I. J. Kuo, F. W. Lin, C. R. Su, M. L. Yang, D. T. Li and T. S. Wu, *J. Nat. Prod*., 2010, **73**, 1993−1998; (i) L. He, S. Y. Liao, C. P. Tan, Y. Y. Lu, C. X. Xu, L. N. Ji and Z. W. Mao, *Chem. Commun*., 2014, **50**, 5611−5614; (j) N. S. Rajapaksa, M. A. McGowan, M. Rienzo and E. N. Jacobsen, *Org. Lett*., 2013, **15**, 706−709; (k) C. Rannoux, F. Roussi, P. Retailleau and F. Gueritte, *Org. Lett*., 2010, **12**, 1240−1243; (l) Q. Yin, S. G. Wang and S. L. You, *Org. Lett*., 2013, **15**, 2688−2691; (m) K.-B. Wang, Y.-T. Di, Y. Bao, C.-M. Yuan, G. Chen, D.-H. Li, J. Bai, H.-P. He, X.-J. Hao, Y.-H. Pei, Y.-K. Jing, Z.-L. Li and H.-M. Hua, *Org. Lett*., 2014, **16**, 4028−4031; (n) J. Lee, T. W. M. J. Cho, J. K. Kim, S. Joo, J. H. Yang, G. S. Chae, K. Choi, J. H. Kwon and D. H. Choi, *Chem. Commun.*, 2013, **49**, 6788−6790; (o) C. W. Lee, Y. Im, J. A. Seo and J. Y. Lee, *Chem. Commun*., 2013, **49**, 9860−9862; (p) Q. Cai, X. W. Liang, S. G. Wang, J. W. Zhang, X. Zhang and S. L. You, *Org. Lett*., 2012, **14**, 5022−5025; (q) L. Wang, X. Xie and Y. H. Liu, *Org. Lett.*, 2012, **14**, 5848−5851; (r) E. Ascic, C. L. Hansen, S. T. L. Quement and T. E. Nielsen, *Chem. Commun*., 2012, **48**, 3345−3347; (s) K. C. Nicolaou, J. L. Kiappes, W. W. Tian, V. B. Gondi and J. Becker, *Org. Lett*., 2011, **13**, 3924−3927.

3 H. Rommelspacher, C. Wernicke, J. Lehmann, β-Carbolines: Occurrence, Biosynthesis, and Biodegradation, 2011, **1**, 105-113. DOI:10.1007/978-1-4614-1542-8_6.

4 (a) N. Goel, N. Singh and R. Saini, *Nat. Sci*., 2009, **7**, 129−134; (b) T. P. Hamsa and G. Kuttan, *Eur. J. Pharmacol.*, 2010, **649**, 64−73; (c) F. Lamchouri, H. Toufik, S. M. Bouzzine, M. Hamidi and M. Bouachrine, *J. Mater. Environ. Sci*., 2010, **1**, 343−352; (d) L. Farouk, A. Laroubi, R. Aboufatima, A. Benharref and A. Chait, *J. Ethnopharmacology*, 2008, **115**, 449−454; (e) F. A. Khan, A. Maalik, Z. Iqbal and I. Malik, *Eur. J. Pharmacol*., 2013, **721**, 391−394; (f) A. Daugan, P. Grondin, C. Ruault, A.-C. L. M. de Gouville, H. Coste, J. Kirilovsky, F. Hyafil and R. Labaudiniere, *J. Med. Chem*., 2003, **46**, 4525–4532; (g) H. Chen, P. Gao, M. Zhang, W. Liao and J. Zhang, *New J. Chem*., 2014, **38**, 4155–4166; (h) S. Wang, K. Fang, G. Dong, S. Chen, N. Liu, Z. Miao, J. Yao, J. Li, W. Zhang and C. Sheng, *J. Med. Chem*., 2015, **58**, 6678–6696; (i) H. Du, H. Gu, N. Li and J. Wang, *Med. Chem. Commun.*, 2016, **7**, 636–645; (J) A. S. Gothelf, K. V. Gothelf, R. G. Hazell and K. A. Jorgensen, *Angew. Chem. Int. Ed.,* 2002, **41**, 4236–4238.

5 (a) H. Guan, H. Chen, W. Peng, Y. Ma, R. Cao, X. Liu and A. Xu, *Eur. J. Med. Chem*., 2006, **41**, 1167−1179; (b) Y. Funayama, K. Nishio, K. Wakabayashi, M. Nagao, K. Shimoi, T. Ohira, S. Hasegawa and N. Saijo, *Mutat. Res*., 1996, **349**, 183−191; (c) A. C. Castro, L. C. Dang, F. Soucy, L. Grenier, H. Mazdiyasni, M. Hottelet, L. Parent, C. Pien, V. Palombella and J. Adams, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2419−2422; (d) Y. Song, D. Kesuma, J. Wang, Y. Deng, J. Duan, J. H. Wang and R. Z. Qi, *Biochem. Biophys. Res. Commun*., 2004, **317**, 128−132;

6 (a) L. A. Sorbera, L. Martin, P. A. Leeson and J. Castaner, *Drugs Future*, 2001, **26**, 15–19; (b) A. Daugan, P. Grondin, C. Ruault, A.-C. L. M. de Gouville, H. Coste, J. Kirilovsky, F. Hyafil and R. Labaudiniere, *J. Med. Chem*., 2003, **46**, 4525–4532; (c) L. Turski, D. N. Stephens, L. H. Jensen, E. N. Peterson, B. S. Meldrum, S. Patel, J. B. Hansen, W. Loscher, H. H. Schneider and R. Schmiechen, *J. Pharmacol. Exp. Ther.,* 1990, **253**, 344–352; (d) G. N. Maw, C. M. Allerton, E. Gbekor and W. A. Million, *Bioorg. Med. Chem. Lett*., 2003, **13**, 1425–1428.

7 (a) E. D. Cox and J. Cook, *Chem. Rev.,* 1995, **95**, 1797–1842; (b) J. Royer, M. Bonin and L. Micouin, *Chem. Rev*., 2004, **104**, 2311–2352; (c) D. Chandrasekhar, S. Borra, J. B. Nanubolu and R. A. Maurya, *Org. Lett*., 2016, **18**, 2974–297; (d) Y.-P. Zhu, M.-C. Liu, Q. Cai, F.-C. Jia and A.-X. Wu, *Chem. Eur. J*., 2013, **19**, 10132–10137; (e) A. L. Pumphrey, H. Dong and T. G. Driver, *Angew. Chem. Int. Ed*., 2012, **51**, 5920–5923; (f) S. T. Ding, Z. Z. Shi and N. Jiao, *Org. Lett*., 2010, **12**, 1540–1543; (g) D. B. England and A. Padwa, *Org. Lett*., 2008, **10**, 3631-3634.

8 (a) C. de Graaff, E. Ruijter and R. V. A. Orru, *Chem. Soc. Rev*., 2012, **41**, 3969–4009; (b) D. M. D'Souza and T. J. J. Muller, *Chem. Soc. Rev*., 2007, **36**, 1095–1108; (c) A. K. Bagdi, S. Santra, K. Monir and A. Hajra, *Chem. Commun*., 2015, **51**, 1555–1575; (d) R. P. Gore and A. P. Rajput, *Drug Invent. Today*, 2013, **5**, 148–152; (e) J. E. Biggs-Houck, A. Younai and J. T Shaw, *Curr. Opin. Chem. Biom*., 2010, **14**, 371–382; (f) H. Bienayme and K. Bouzid, *Angew. Chem., Int. Ed*., 1998, **37**, 2234–2237; (g) S. Vidyacharan, A. H. Shinde, B. Satpathi and D. S. Sharada, *Green Chem*., 2014, **16**, 1168–1175; (h) S. Swami, N. Devi, A. Agarwala, V. Singh and R. Shrivastava, *Tetrahedron Lett*., 2016, **57**, 1346–1350; (i) N. Devi, D. Singh, R. K. Sunkaria, C. C. Malakar, S. Mehra, R. K. Rawal and V. Singh, *ChemistrySelect,* 2016, **1**, 4696–4703; (j) F. Hu and M. Szostak, *Adv. Synth. Catal*., 2015, **357**, 2583–2614; (k) A. B. Atar, J. S. Kim, K. T. Lima and Y. T. Jeong, *New J. Chem*., 2015, **39**, 396–402; (l) B.-L. Li, M. Zhang, H.-C. Hu, X. Dub and Z.-H. Zhang, *New J. Chem*., 2014, **38**, 2435-2442; (m) H. P. Kalmode, K. S. Vadagaonkar, K. Murugan and A. C. Chaskar, *New J. Chem*., 2015, **39**, 4631–4639; (n) S. Banerjee and A. Sahaa, *New J. Chem*., 2013, **37**, 4170–4175; (o) A. Ghorbani-Choghamarani and B. Tahmasbia, *New J. Chem*., 2016, **40**, 1205–1212.

9 (a) K. Gudmundsson and S. D. Boggs, (EN) Chemical Compounds. PCT Int. Appl., WO 2006026703, 2006; (b) C. Hamdouchi, J. d. Blas, M. d. Prado, J. Gruber, B. A. Heinz, and L. Vance, *J. Med. Chem*., 1999, **42**, 50–59; (c) J. J. Kaminsky and A. M. Doweyko, *J. Med. Chem*., 1999, **40**, 427–436; (d) M. Lhassani, O. Chavignon, J. M. Chezal, J. C. Teulade, J. P. Chapat, R. Snoeck, G. Andrei, J. Balzarini, E. D. Clerc and A. Gueiffier, *Eur. J. Med. Chem*., 1999, **34**, 271–274; (e) C. Maul, B. Sundermann, H.-H. Hennies, J. Schneider and M. Gerlach, Patent WO01027109, 2001; (f) D. Elleder, J. A. T. Young, T. J. Baiga and J. P. Noel, Patent WO2009061856, 2009.

10 (a) C. Enguehard-Gueiffier and A. Gueiffier, *Mini-Rev. Med. Chem.*, 2007, **7**, 888–899; (b) G. C. Moraski, P. A. Miller, M. A. Bailey, J. Ollinger, T. Parish, H. I. Boshoff, S. Cho, J. R. Anderson, S. Mulugeta, S. G. Franzblau and M. J. Miller, *ACS Infect. Dis*., 2015, **1**, 85–90; (c) M. Yamanaka, K. Miyake, S. Suda, H. Ohhara and T. Ogawa, *Chem. Pharm. Bull*., 1991, **39**, 1556–1567; (d) M. L. Bode, A. L. Rousseau, D. Gravestock, S. S. Moleele and D. W. C. W. Van, WO 2010032195, 2010; (e) G. Naresh, R. Kant, and T. Narender, *Org. Lett*., 2014, **16**, 4528–4531; (f) K. V. Sashidhara, L. R. Singh, D. Choudhary, A. Arun, S. Gupta, S. Adhikary, G. R. Palnati, R. Konwar and R. Trivedi, *RSC Adv*., 2016, **6**, 80037–80048; (g) P. Wadhwa, T. Kaur and A. Sharma, *RSC Adv*., 2015, **5**, 44353–44360; (h) D. Dheer, K. R. Reddy, S. K. Rath, P. L. Sangwan, P. Das and R. Shankar, *RSC Adv*., 2016, **6**, 38033–38036; (i) S. K. Guchhait and C. Madaan, *Org. Biomol. Chem*., 2010, **8**, 3631–3634; (i) S. K. Guchhait, V. Chaudhary and C. Madaan, *Org. Biomol. Chem*., 2012, **10**, 9271–9277; (j) A. Modi, W. Ali and B. K. Patel, *Adv. Synth. Catal*., 2016, **358**, 2100–2107; (k) J. Ren, M. Yang, H. Liu, D. Cao, D. Chen, J. Li, L. Tang, J. He, Y.-L. Chen, M. Geng, B. Xiong and J. Shen,

View Article Online
DOI: 10.1039/C6NJ03210A

Org. Biomol. Chem., 2015, **13**, 1531–1535; (l) P. R. Adiyala, G. S. Mani, J. B. Nanubolu, K. C. Shekar and R. A. Maurya, *Org. Lett.*, 2015, **17**, 4308–4311.

11 (a) N. Devi, R. K. Rawal and V. Singh, *Tetrahedron*, 2015, **71**, 183–232; (b) N. Devi, D. Singh, R. K. Rawal, J. Bariwal and V. Singh, *Curr. Top. Med. Chem*., 2016, **16**, 2963–2994.

12 (a) A. T. Baviskar, C. Madaan, R. Preet, P. Mohapatra, V. Jain, A. Agarwal, S. K. Guchhait, C. N. Kundu and U. C. Banerjee, *J. Med. Chem.*, 2011, **54**, 5013–5030; (b) A. T. Baviskar, S. M. Amrutkar, N. Trivedi, V. Chaudhary, A. Nayak, S. K. Guchhait, U. C. Banerjee, P.V. Bharatam and C. N. Kundu, *ACS Med. Chem. Lett*., 2015, **6**, 481−485; (c) M. Hayakawa, H. Kaizawa, H. K.-I. Kawaguchi, N. Ishikawa, T. Koizumi, T. Ohishi, M. Yamano, M. Okada, M. Ohta, S. Tsukamoto, F. I. Raynaud, M. D. Waterfield, P. Parkerd and P. Workma, *Bioorg. Med. Chem*., 2007, **15**, 403–412.

13 (a) A. Deep, R. K. Bhatia, R. Kaur, S. Kumar, U. K. Jain, H. Singh, S. Batra, D. Kaushik and P. K. Deb, *Curr. Top. Med. Chem*., 2016, **16**, DOI: 10.2174/ 1568026616666160530153233; (b) R. Goel, V. Luxami and K. Paul, *Curr. Top. Med. Chem*., 2016, **16**, DOI: 10.2174/ 1568026616666160414122644; (c) T. L. S. Kishbaugh, *Curr. Top. Med. Chem*., 2016, **16**, 3274–3302.

14 (a) N. Devi, D. Singh, Honey, S. Mor, S. Chaudhary, R. K Rawal, V. Kumar, A. K Chowdhury and V. Singh, *RSC Adv*., 2016, **6**, 43881–43891; (b) D. Singh, N. Devi, V. kumar, C. C. Malakar, S. Mehra, S. Rattan, R. K. Rawal and V. Singh, *Org. Biomol. Chem*., 2016, **14**, 8154–8166; (c) D. Singh, N. Devi, V. Kumar, C. C. Malakar, S. Mehra, R. K Rawal, B. S. Kaith and V. Singh, *RSC Adv*., 2016, **6**, 88066-88076; (d) V. Singh, S. Hutait and S. Batra, *Eur. J. Org. Chem*., 2010, 3684–3691; (e) V. Singh and S. Batra, *Curr. Org. Synth*., 2012, **9**, 513–528; (f) S. Hutait, V. Singh and S. Batra, *Eur. J. Org. Chem*., 2010, 6269–6276; (g) V. Singh, S. Hutait, S. Biswas and S. Batra, *Eur. J. Org. Chem*., 2010, 531–539; (h) V. Singh, S. Hutait and S. Batra, *Eur. J. Org. Chem*., 2009, 6211–6216.

15 A. Kamal, M. P. N. Rao, P. Swapna, V. Srinivasulu, C. Bagul, A. B. Shaik, K. Mullagiri, J. Kovvuri, V. S. Reddy, K. Vidyasagar and N. Nagesh, *Org. Biomol. Chem*., 2014, **12**, 2370–2387.

16 (a) A. Kamal, V. Srinivasulu, V. L. Nayak, M. Sathish, N. Shankaraiah, C. Bagul, N. V. S. Reddy, N. Rangaraj and N. Nagesh, *ChemMedChem,* 2014, **9**, 2084–2098 (b) P. Abranyi-Balogh, A. Dancso, D. Frigyes, B. Volk, G. Keglevich and M. Milen, *Tetrahedron*, 2014, **70**, 5711–5719; (c) L. Liu, Q. Yang, H. Yua, J.-L. Li, Y.-N. Pei, H.-J. Zhu, Z.-Q. Li and X.-K. Wang, *Tetrahedron*, 2015, **71,** 3296–3302; (d) Y. Ling, C. Xu, L. Luo, J. Cao, J. Feng, Y. Xue, Q. Zhu, C. Ju, F. Li, Y. Zhang, Y. Zhang and X. Ling, *J. Med. Chem.*, 2015, **58,** 9214–9227; (e) N. Shankaraiah, P. Sharma, S. Pedapati, S. Nekkanti, V. Srinivasulu, N. P. Kumar and A. Kamal, *Lett. Drug Des. Discov*., 2016, **13**, 335–342; (f) M. Zhang and D. Sun, *Anticancer Agents Med. Chem*., 2015, **15**, 537–547.

17 (a) S. Hati and S. Sen, *Tetrahedron Lett*., 2016, **57**, 1040–1043; (b) A. Kamal, M. Sathish, A. V. G. Prasanthi, J. Chetna, Y. Tangella, V. Srinivasulu, N. Shankaraiahb and A. Alarific, *RSC Adv*., 2015, **5**, 90121–90126; (c) A. Kamal, Y. Tangella, K. L. Manasa, M. Sathish, V. Srinivasulu, J. Chetna and A. Alarifi, *Org Biomol Chem*., 2015, **13**, 8652–8662; (d) Q. Wu, R. Cao, M. Feng, X. Guan, C. Ma, J. Liu, H. Song and W. Peng, *Eur. J. Med. Chem*., 2009, **44**, 533–540; (e) N. Shankaraiah, K. P. Siraj, S. Nekkanti, V. Srinivasulu, P. Sharma, K. R. Senwar, M. Sathish, M. V. P. S. Vishnuvardhan, S. Ramakrishna, C. Jadala, N. Nagesh and A. Kamal, *Bioorg. Chem.,* 2015, **59**, 130–139; (f) Z. Li, S. Chen, S. Zhu, J. Luo, Y. Zhang and Q, Weng, *Molecules* 2015, **20**, 13941-13957.

18 (a) R. Goel, V. Luxami and K. Paul, *Org. Biomol. Chem*., 2015, **13**, 3525–3555; (b) S. Shaaban and B. F. Abdel-Wahab, *Mol. Divers*., 2016, **20**, 233–254; (c) J. E. Biggs-Houck, A. Younai and J. T. Shaw, *Curr. Opin. Chem. Biol*., 2010, **14**, 371–382; (d) A. Domling, *Chem., Rev*., 2006, **106**, 17–89; (e) R. C. Cioc, E. Ruijter and R. V. A. Orru, *Green Chem*., 2014, **16**, 2958–2975; (f) P. Slobbe, E. Ruijter and R. V. A. Orru, *Med. Chem. Commun*., 2012, **3**, 1189–1218; (g) R. Goel, V. Luxami and K. Paul, *RSC Adv*., 2015, **5**, 81608–81637; (h) S. Sadjadi, M. M. Heravi and N. Nazari, *RSC Adv*., 2016, **6**, 53203–53272; (i) T. Kaur, P. Wadhwa, S. Bagchi and A. Sharma, *Chem. Commun*., 2016, **52**, 6958–6976.

19 M. Adib, M. Mahdavi, M. A. Noghania and P. Mirzaei, *Tetrahedron Lett*., 2007, **48**, 7263–7265.

20 G. S. Mandair, M. Light, A. Russell, M. Hursthouse and M. Bradley, *Tetrahedron Lett.,* 2002, **43**, 4267–4268.

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$In(OTf)_3$ Assisted Synthesis of β-Carboline C-3 Tethered Imidazo[1,2-*a*]azine Derivatives

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Graphical Abstract