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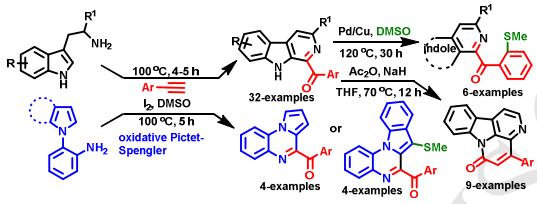

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Iodine-mediated oxidative Pictet-Spengler reaction using terminal alkyne as the 2-oxoaldehyde surrogate for the synthesis of 1-aroyl-β-carbolines and fused-nitrogen heterocycles§

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ABSTRACT

An efficient iodine-mediated oxidative Pictet-Spengler reaction in dimethyl sulphoxide (DMSO) using terminal alkynes as the 2-oxoaldehyde surrogate for the synthesis of aryl (9*H*-pyrido[3,4-*b*]indol-1-yl)methanones is described. The scope of the protocol includes the total synthesis of Fascaplysin, Eudistomins Y_1 and Y_2. The methodology is extended for preparing pyrrolo[1,2-*a*]-quinoxaline and indolo[1,5-*a*]quinoxaline derivatives. The utility of 1-aroyl-β-carbolines was demonstrated by performing palladium-catalyzed β-carboline directed *ortho*-C(sp2)-H functionalization of the phenyl ring with thiomethyl (SMe) group using DMSO as source and for accessing 4-aryl-canthin-6-ones.

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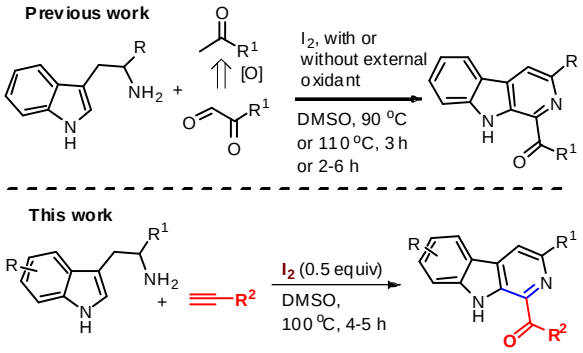
1. Introduction

β-Carboline represents a privileged structural motif that is found in many natural products with important biological activities.[1-2] Amongst them, several β-carboline derivatives with aroyl substitution at the C-1 position were reported to display potent antiinflammatory, anti-malarial, anti-cancer, anti-phospholipase A2, P-glycoprotein-inducer and anti-microbial activities.[3] Traditionally, the Pictet–Spengler reaction of tryptamine or tryptophan methyl ester derivatives with 2-oxoaldehydes is performed under strong acidic condition to obtain 1-acyl (or aroyl)-β-carbolines.[3a,b,4] Nonetheless, with continuous development in applications of oxidative coupling reaction, Wu et al. pioneered to disclose iodine-mediated oxidative domino reaction between acetophenones and tryptamine in the presence of an external oxidant under DMSO as medium for the synthesis of 1-aroyl-β-carbolines (Scheme 1).[5] The reaction was suggested to proceed via oxidation of acetophenone to 2-oxoaldehyde in situ, under the influence of iodine (0.8 equiv) and an external oxidant (1.5 equiv). Later, Ahmed et al. too demonstrated synthesis of analogous compounds via iodine-mediated two-step one-pot reaction between tryptamine and acetophenones.[6] Notably they performed



Scheme 1. Oxidative Pictet-Spengler reaction for the synthesis of 1-aroyl-β-carbolines.

the reaction employing 1.0 equiv of iodine but did not use any external oxidant. They extended the scope of the protocol to terminal alkenes which in the presence of iodine (1.0 equiv) and IBX (1.0 equiv) in DMSO as medium furnished 1-aroyl-β-carbolines albeit in moderate yields. We have been interested in accessing 1-aroyl-β-carbolines for probing the β-carboline-directed C(sp2)-H functionalization of the aromatic ring as

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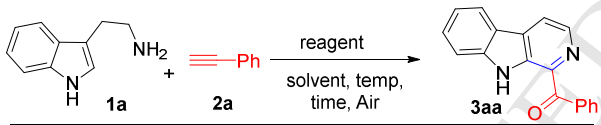
prelude to preparing more complex structures.[7] Like acetophenones, terminal alkynes undergo iodine-mediated transformation to 2-oxoaldehydes under oxidative conditions.[8] As there is lack of report for use of terminal alkynes in the oxidative Pictet-Spengler reaction, we sought to explore their utility towards synthesizing 1-aroyl-β-carbolines and extending it to pyrrole and indole-based fused heterocycles. The envisaged approach is expected to offer a complementary route to these heterocycles. Herein we present the details of our study in this direction. The developed protocol was extended to preparing a few simple β-carboline-based natural compounds. In context of our interest in palladium-catalyzed β-carboline-directed *ortho*-C(sp2)-H functionalization of the phenyl ring, the title compounds were successfully thiomethylated in the presence of DMSO. Additionally, treating them with acetic anhydride resulted into easy access to 4-aryl-canthin-6-ones.

2. Results and Discussion

We commenced our investigations by reacting tryptamine **(1a)** with phenylacetylene (**2a**) (1.2 equiv) in the presence of iodine (30 mol %) in DMSO as the medium under air atmosphere at room temperature. Unfortunately, the reaction failed and therefore it was repeated under heating at 80 °C. Gratifyingly, the reaction was completed in 8 h resulting in a mixture of products from which the major compound was only in 46% isolated yield and was identified to be the expected phenyl(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3aa)** (Table 1 entry 2). The yield of **3aa** (65%) improved when the same reaction was performed at 100 °C for 6 h (Table 1, entry 3). Towards obtaining superior yield of **3aa** other reagents including *N*-iodosuccinimide (NIS), *N*-bromosuccinimide (NBS), KI, and tetrabutylammonium iodide

Table 1. Optimization of the Reaction Conditions for oxidative Pictet-Spengler reaction using terminal alkyne[a]



1a 2a 3aa

entry	reagent (equiv)	solvent	temp	time (h)	yield (%)[b]
1	I_2 (0.3)	DMSO	25	12.0	-
2	I_2 (0.3)	DMSO	80	8.0	46
3	I_2 (0.3)	DMSO	100	6.0	65
4	NIS (0.3)	DMSO	100	6.0	22
5	NBS (0.3)	DMSO	100	6.0	18
6	KI (0.3)	DMSO	100	6.0	ND
7	TBAI (0.3)	DMSO	100	6.0	ND
8	**I_2 (0.5)**	**DMSO**	**100**	**4.0**	**84**
9[c]	I_2 (0.5)	DMSO	100	4.0	43
10[d]	I_2 (0.5)	DMSO	100	4.0	68
11	I_2 (0.8)	DMSO	100	4.0	80
12	I_2 (1.0)	DMSO	100	4.0	77
13	I_2 (0.5)	DMA	100	4.0	ND
14	I_2 (0.5)	H_2O	100	4.0	ND
15	I_2 (0.5)	DMF	100	4.0	ND

[a]Reaction conditions: All reactions were carried out using **1a** (0.2 g, 1.25 mmol), **2a** (165 µL, 1.49 mmol), DMSO (5 mL). [b]Isolated yields [c]Reactions were performed under inert atmosphere. [d] Oxidant H_2O_2 (2.0 equiv).

(TBAI) were screened (entries 4-7), but with no success. Subsequently titrating the loading of iodine, it was pleasing to discover that with 50 mol % of iodine the reaction was completed in 4 h to give **3aa** in 84% yield (Table 1, entry 8). Performing the reaction under inert atmosphere or adding an external oxidant (H_2O_2), however had detrimental effect on the reaction. Finally, screening of the solvents revealed that reaction failed in DMA, H_2O or DMF as medium (entries 13-15). Thus the optimized reaction conditions that produced best yield of **3aa** was heating tryptamine **1a** (1.0 mmol), phenylacetylene **2a** (1.2 mmol), and iodine (50 mol %) at 100 °C in DMSO for 4 h.

With optimized conditions for the protocol in hand, we investigated the scope with respect to both reactants. In first set of reactions tryptamine **(1a)** was treated with different terminal alkynes under the optimized conditions (Scheme 2). It was observed that all alkynes **(2b-s)** reacted with **1a** to give the respective 1-benzoyl-β-carbolines **(3aa-as)** in 74-95% yields. Notably the reactions of alkynes with phenyl ring bearing electron withdrawing groups were completed in 5 h as compared to 4 h for the ones with electron donating groups. The terminal alkynes **2t-v** bearing the heteroaryl group were also compatible to the protocol to produce substituted 1-aroyl-β-carbolines **(3at-3av)** in good yields. However, the reaction of aliphatic alkyne i.e. 1-hexyne was unsuccessful. Next the tryptamine was replaced by tryptophan alkyl esters **(1b** and **1c)** and it was found they reacted smoothly with all terminal alkynes to afford the corresponding β-carboline derivatives. Likewise, 5-chlorotryptamine **1d** was compatible with the protocol resulting in formation of the expected product **3da** in 75% yield.

A plausible mechanism for the reaction is outlined in Scheme 3. Initially the primary alkyne **2a** in the presence of iodine-DMSO is transformed to 2-iodo-1-phenylethan-1-one **(A)** which is oxidized in situ to afford the 2-oxoaldehyde **(B)** followed by its usual Pictet-Spengler reaction with tryptamine **(1a)** to afford the product **3aa**. In order to provide support for the mechanism, we treated 2-iodo-1-phenylethan-1-one **(4)** with **1a** independently that resulted in formation of **3aa** (Scheme 4). Further to ascertain that the 2-oxocarbaldehyde **(5)** was the species involved for the Pictet-Spengler reaction, it was treated with tryptamine in DMSO at 100 °C to produce **3aa** in 92% yield in 1 h.

In order to assess the usefulness of the methodology for synthesizing natural products, **3ah** was used for preparing Eudistomin Y_1 **(6)** and Y_2 **(7)** whereas **3am** was transformed into fascaplysin **(8)** (Scheme 5). Based on the results of the study, we reasoned that reaction of diethynylbenzene would offer a dimeric β-carboline. Accordingly, 1,3-diethynylbenzene **(2x)** was prepared and reacted with 2.0 equiv of **1a** but we found that only one alkyne group participated in the reaction to afford **3ax** (Scheme 6). Increasing the amount of iodine or varying reaction conditions did not influence the outcome and **3ax** was obtained exclusively. Assuming that the steric constraint could be a contributing factor towards this observation, next we reacted 1,4-diethynylbenzene **(2y)** with **1a** following the optimized procedure. It was pleasing to discover that the reaction was successful to furnish **9** in 75% yield.

Aiming to examine scope of the protocol for the synthesis of isoquinolines, in a representative reaction 3,4-dimethoxy-phenylethylamine **(10)** was treated with 3,5-dimethoxyphenylacetylene **(2z)** under the optimized condition. The reaction offered (*E*)-1,4-bis(3,4-dimethoxyphenyl)but-2-ene-1,4-dione **(11)** in 78% yield instead of the expected isoquinoline, suggesting self-condensation of the two alkyne units (Scheme 7). This was ascertained by treating **2z** exclusively with I_2 in DMSO as medium to obtain **11**. Though it is reported that terminal as

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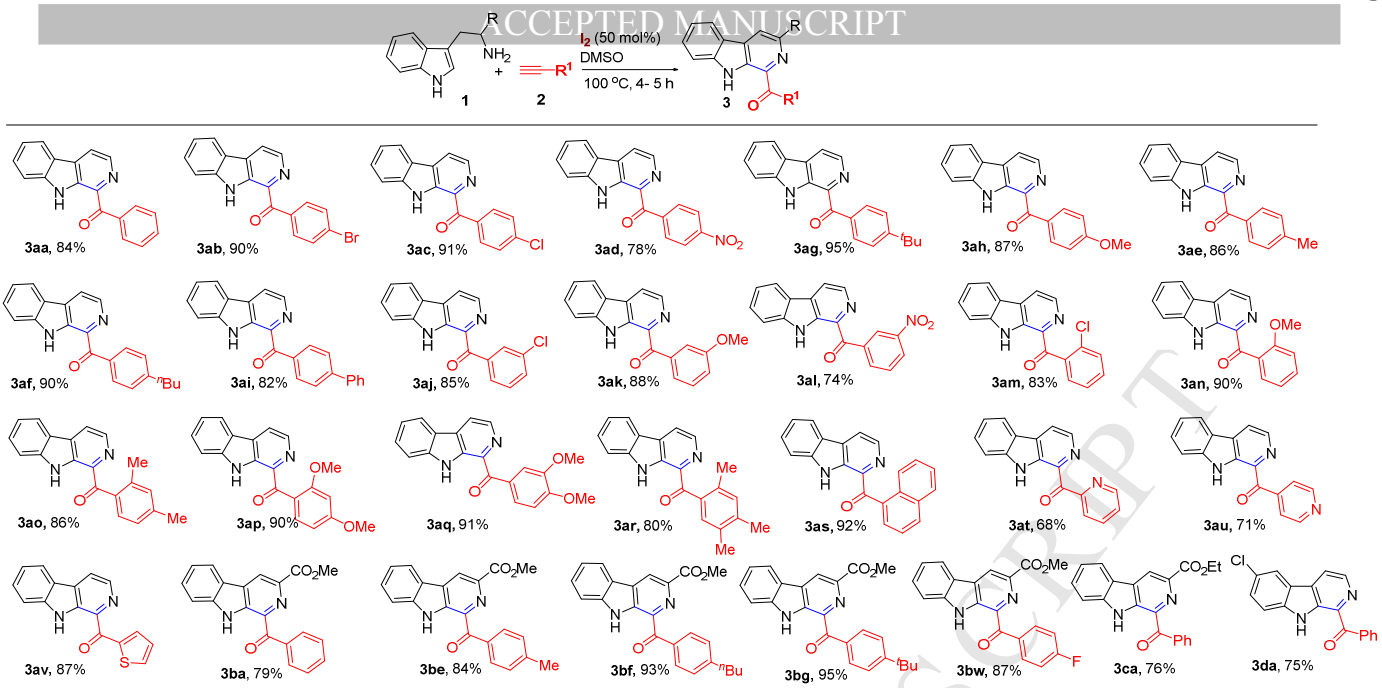
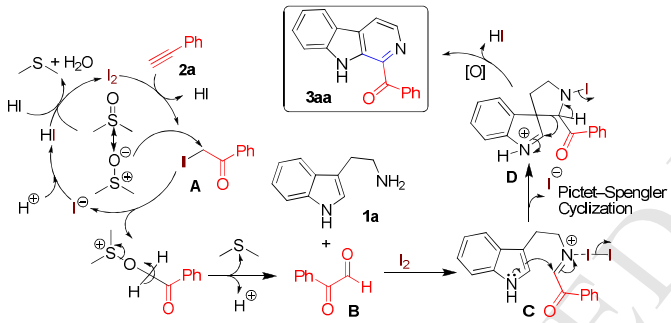
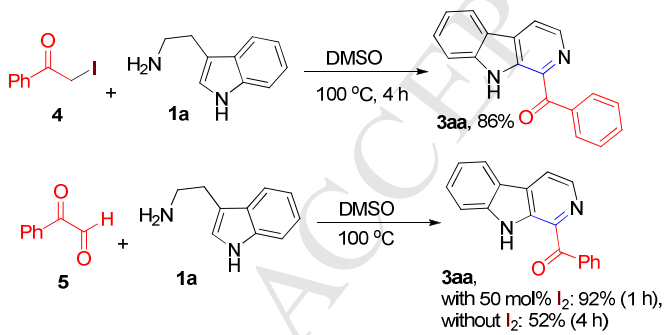


Scheme 2. Scope of the protocol for the synthesis of 1-aroyl-β-carbolines

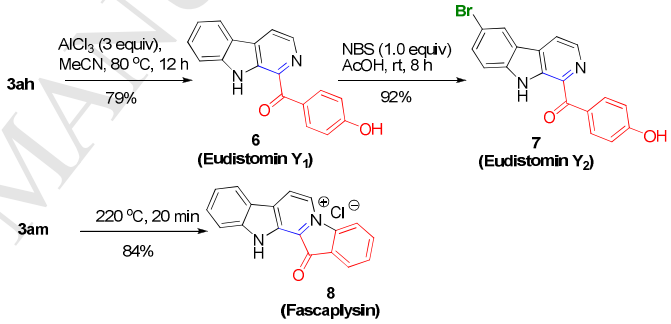


Scheme 3. Plausible mechanism for the reaction

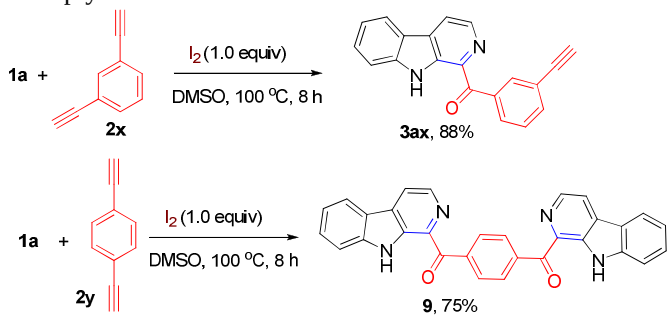


Scheme 4. Control experiments.

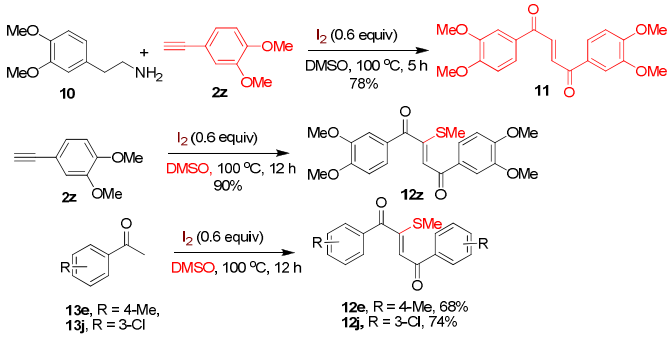
well as internal alkynes undergo iron(III) perchlorate-mediated oxidative dimerization to produce such conjugated diketones,[9] there is lack of report of similar transformation in the presence of iodine. Conversely, acetophenones and terminal alkynes are known to afford 2-thio-1,4-enediones via CuI/ DMSO or I_2/Lewis acid/DMSO, respectively under heating.[10] This prompted us to probe the outcome of the self- condensation reaction of alkyne **2z** beyond 5 h, and we found that in 12 h



Scheme 5. Synthesis of Eudistomin Y1 and Y2 and Fascaplysin.



Scheme 6. Scope of the protocol with diethynylbenzenes.



Scheme 7. Self-condensation of alkynes under different conditions.

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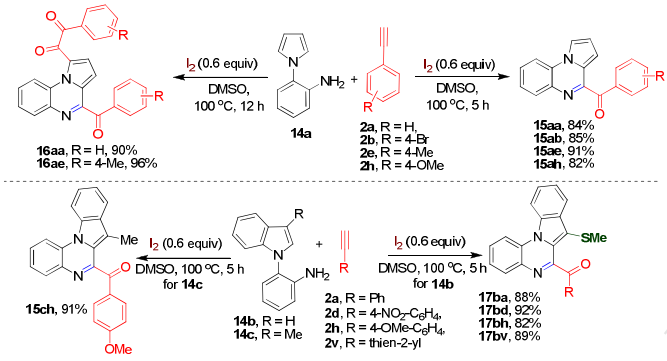
the expected 2-thio-1,4-enedione **(12z)** was isolated in 90% yield. Alternatively, treating acetophenones **(13e,13j)** with I_2 in DMSO as a medium for 12 h under heating afforded the corresponding 2-thio-1,4-enediones **(12e,12j)** in good yields. This result suggests that contrary to the previous reports, such transformation can be accomplished under metal-free condition.

In the next stage, pyrrole- and indole-based substrates **14a** and **14b,c** were evaluated for their compatibility to the protocol. Treating **14a** with different alkynes **2a**, **2b**, **2e** and **2h** smoothly afforded corresponding products **15aa, 15ab, 15ae** and **15ah** in 82-91% yields (Scheme 8). Very recently, Wu et al. disclosed the para-selective coupling of phenols with aryl methyl ketones by overcoming the challenge of self-condensation of arylmethyl ketones.[11] Based on this report we hypothesized that use of higher amount of terminal alkyne would offer more glyoxal which may induce concomitant oxidative Pictet-Spengler reaction and electrophilic substitution of the 2-position (electron-rich) of the pyrrole subunit. Accordingly, we probed the reaction of **14a** with 2.5 equiv of **2a** and **2e** in the presence of I_2 in DMSO as medium for 12 h. We were delighted to note the formation of **16aa** and **16ae**, respectively in excellent yields (Scheme 8).

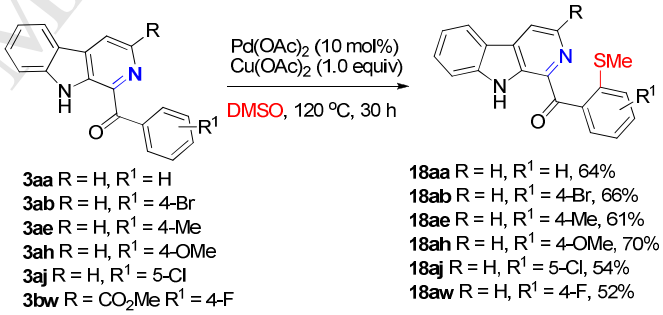


Scheme 8. Reaction of 1,2-dihydroisoquinoline-fused quinazolinone with iodine.

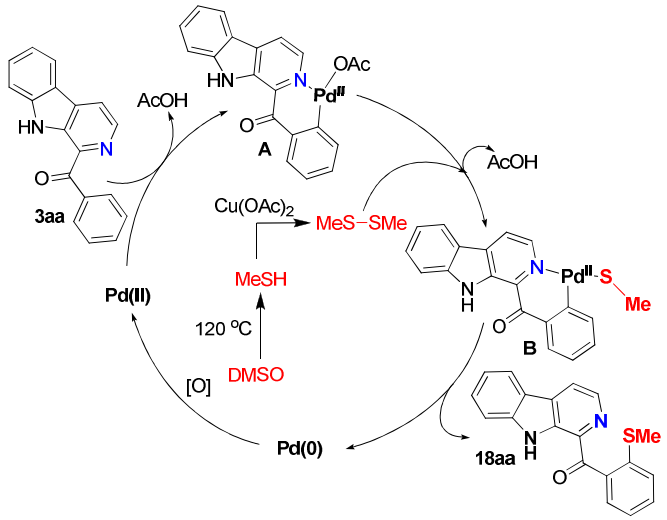
Interestingly however, treating the *N*-substituted indole **14b** with alkyne **2a** gave the 3-thiomethylated indolo[1,2-*a*]quinoxaline **17ba** in 84% yield. The formation of **17ba** is attributed to initial oxidative Pictet Spengler reaction of alkyne with **14b** followed by nucleophilic attack of thiomethyl group onto the unsubstituted 3-position of the indole. The thiomethyl group in turn originates from the dimethylsulphide which is liberated from DMSO in the presence of HI during the reaction. Similar thiomethylation was not observed when acetophenone was employed as the source of glyoxal for oxidative Pictet-Spengler reaction of indoles in the presence of iodine and DMSO.[12] We discovered that the developed protocol was general in nature as reactions of **14b** with other alkynes **2d, 2h** and **2v** gave the respective products **17bd**, **17bh**, **17bv** in 82-92% yields. Perhaps higher loading of iodine and longer reaction time as compared to previous report may be attributed to such difference in results. Conversely, when the 3-position of the indole was blocked by placing a methyl group as in **14c**, its reaction with **2d** resulted in the formation of the expected product **15ch** in 91% yields.

Encouraged by the above results and in our interest to study the β-carboline-directed C(sp2)-H functionalization of the aromatic ring of the benzoyl moiety, we probed installing the thiomethyl group using DMSO at he ortho-position.[13] Most often copper salts have been used in stoichiometric amount in reports describing DMSO-mediated thiomethylation of phenyl ring via oxidative C(sp2)-H activation.[14] As a consequence, initially we probed the reaction of **3aa** with $Cu(OAc)_2$ under different conditions, but failed. Subsequently we performed the reaction of **3aa** with $Pd(OAc)_2$ (10 mol%) in the presence of $Cu(OAc)_2$ (1.0 equiv) in DMSO as medium under heating. Fortunately, at 120 ^oC, the reaction was successful to afford the required (2-(methylthio)phenyl)(9*H*-pyrido[3,4-*b*]indol-1- yl)methanone **(18aa)** in 64% yield (Scheme 9). The success of this reaction prompted us to study the generality of β-carboline-directed thiomethylation of the phenyl ring. As a result, **3ab,3ae,3ah,3aj,3bw** were subjected to the Pd-catalyzed oxidative reaction under the optimized conditions. Although all substrates afforded the thiomethylated products **18ab,18ae,18ah,18aj**, it was noticed that **3bw** invariably underwent decarboxylative removal of the ester moiety to furnish **18aw** exclusively. Mechanistically, the reaction is suggested to proceed via Pd(II)-intermediate as shown in Scheme 10.

Finally, we sought to study the utility of the 1-aroyl-β-carbolines for generating substituted canthin-6-ones. It may be noted that though several substituted canthin-6-ones are known, there is lack of report describing the synthesis of 4-aryl substituted canthin-6-one. In one of the approaches with limited scope, 1-formyl-β-carboline was treated with acetyl chloride or acetic anhydride in the presence of a base to offer canthin-6-one.[15] Therefore, we considered probing the reported protocol for preparing substituted canthin-6-ones and after a short screening discovered that reaction of substituted 1-aroyl-β-carbolines **(3aa-ac, 3ae, 3ah, 3aj, 3am, 3av)** with acetic anhydride in the presence of sodium hydride as the base in THF as medium under heating afforded the corresponding 4-aryl substituted canthin-6-ones **(19aa-ac, 19ae, 19ah, 19aj, 19am, 19av)** in good yields (Scheme 11).



Scheme 9. β-Carboline-directed thiomethylation under oxidative conditions



Scheme 10. Plausible mechanism for oxidative thiomethylation.

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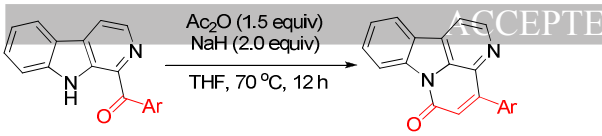

3aa Ar = Ph
3ab Ar = 4-Br-C_6H_4
3ac Ar = 4-Cl-C_6H_4
3ae Ar = 4-Me-C_6H_4
3ah Ar = 4-OMe-C_6H_4
3aj Ar = 3-Cl-C_6H_4
3ak Ar = 3-OMe-C_6H_4
3am Ar = 2-Cl-C_6H_4
3av Ar = thiophen-2-yl

19aa Ar = Ph, 83%
19ab Ar = 4-Br-C_6H_4, 76%
19ac Ar = 4-Cl-C_6H_4, 78%
19ae Ar = 4-Me-C_6H_4, 85%
19ah Ar = 4-OMe-C_6H_4, 84%
19aj Ar = 3-Cl-C_6H_4, 79%
19ak Ar = 3-OMe-C_6H_4, 77%
19am Ar = 2-Cl-C_6H_4, 75%
19av Ar = thiophen-2-yl, 72%

Scheme 11. Synthesis of 4-aryl substituted canthin-6-ones.

3. Conclusion

In summary, we have developed an alternative route to the synthesis of 1-aroyl-β-carbolines via iodine-mediated oxidative Pictet-Spengler reaction using terminal alkynes as the 2-oxoaldehyde surrogate. Lower loading of iodine and better yields of products as compared to the reported methodologies where acetophenones have been used as the 2-oxoaldehyde source are attractive attributes of this protocol. The protocol is amenable to aryl terminal alkynes whereas alkyl-based terminal alkynes failed to react. The generality of the methodology is further demonstrated via oxidative Pictet-Spengler reaction of pyrrole and indole-based substrates. Moreover, it was shown that based on the amount of alkyne used, divergent products can be accessed for the pyrrole-based substrates. However, the protocol is not suited to produce isoquinolines since terminal alkyne during the reaction underwent oxidative dimerization to produce enedione derivative. Interestingly longer duration of the reaction afforded 2-methylthio-1,4-ene-diones in good yields. Further, the methodology accommodates acetophenones to afford the 2-methylthio-1,4-ene-diones under metal-free conditions. This work also revealed palladium-catalyzed β-carboline-directed oxidative thiomethylation of the phenyl ring in 1-aroyl-β-carbolines which are also versatile precursor to 4-aryl-canthin-6-ones.

4. Experimental

4.1. *General*

Unless otherwise stated all reactions were performed in non-dry glassware under an air atmosphere and were monitored by analytical thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining with $KMnO_4$ and charring on a hot plate. The melting points were recorded on a hot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 and 500 MHz spectrometers and are reported in ppm using solvent residue ($CDCl_3$: ^{1}H; δ = 7.26 ppm, ^{13}C δ = 77.16 ppm; DMSO-d_6: ^{1}H; δ = 2.50 ppm; ^{13}C δ = 39.5 ppm; CD_3OD: ^{13}C δ = 49.2 ppm) as an internal reference relative to TMS (chemical shifts in δ). Peak multiplicities of ^{1}H-NMR signals were designated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet) etc. Coupling constants (J) are in Hz. The LC-ESI-MS were recorded on triple quadrupole Mass spectrometer. Column chromatography was performed using silica gel (particle size 100-200 mesh). Analytical grade solvents for the column chromatography were used as received. Commercial grade reagents and solvents were purchased from different commercial sources and used without further purification.

4.2. *General Procedure for transformation of **1** to **3** as exemplified for **3aa** .*

To a stirred solution of phenylacetylene **2a** (165 µL, 1.49 mmol) in DMSO (5 mL) were added molecular iodine (0.157 g, 0.62 mmol) and **1a** (0.2 g, 1.25 mmol) at room temperature and the reaction was allowed to continue for 4 h at 100 °C. Thereafter, the reaction was quenched by adding aqueous $Na_2S_2O_3$ (10% w/v, 10 mL) and the resulting mixture was extracted with EtOAc (3 x 20 mL). The organic fractions were pooled, dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude product thus obtained was purified by chromatography over a column of silica gel using hexanes/ EtOAc (8.0:2.0, v/v) as eluent to afford the desired product **3aa** (0.285 g, 84%) as a yellow solid.

4.2.1. Phenyl(9*H*-pyrido[3,4-b]indol-1-yl)methanone **(3aa).**[5] Mp 132-134 °C [Lit 130-131 °C]; R_f = 0.42 (hexane: EtOAc, 6:4, v/v); IR (KBr) ν_{max}: 669, 759, 1115, 1705, 2401 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.26-7.29 (m, 1H, ArH), 7.44-7.48 (m, 2H, ArH), 7.52-7.56 (m, 3H, ArH), 8.08-8.11 (m, 2H, ArH), 8.24-8.26 (m, 2H, ArH), 8.54 (d, J = 4.9Hz, 1H, ArH), 7.67 (s, 1H, ArH) 10.38 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.0, 118.5, 120.8, 120.9, 121.8, 128.0, 129.3, 131.2, 131.7, 132.4, 137.4, 137.6, 138.1, 141.1, 195.5. MS (ESI+): m/z = 273.1. ESI-HR-MS calculated for $C_{18}H_{12}N_2O$ (M^++H): 273.1028, found: 273.1025.

4.2.2. (4-Bromophenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3ab).**[5]. Yield: 90% (0.394 g from 0.2 g); a yellow solid, mp 176-178 oC [Lit 180-181 oC]; R_f = 0.70 (hexane: EtOAc, 8:2, v/v); IR (KBr) νmax: 778, 1089, 1248, 1702, 2348 cm-1. 1H NMR (400 MHz, CDCl3): δ (ppm) 6.34 (bs, 1H, ArH), 7.42 (d, J = 8.3 Hz, 1H, ArH), 7.65-7.71 (m, 3H, ArH), 7.89 (dd, J_1 = 1.6 Hz, J_2 = 8.5 Hz, 1H, ArH), 8.13 (d, J = 4.9 Hz, 1H, ArH), 8.27 (d, J = 8.5 Hz, 2H, ArH), 8.51-8.52 (m, 1H, ArH), 8.63 (d, J = 4.9 Hz, 1H, ArH), 10.46 (m, 1H, NH); 13C NMR (100 MHz, CDCl3): δ (ppm) = 113.9, 118.8, 123.3, 127.8, 130.4, 130.8, 131.4, 132.8, 136.0, 136.2, 137.1, 137.7, 138.0, 138.5, 140.0, 194.0. MS (ESI+): m/z = 351.0. ESI-HR-MS calculated for C18H11BrN2O (M++H): 351.0133, found: 351.0138.

4.2.3. (4-Chlorophenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3ac).**[5]. Yield: 91% (0.345 g from 0.2 g); a yellow solid, mp 160-162 °C [Lit 162-163 °C]; R_f = 0.71 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 689, 989, 1145, 1568, 1698, 3256 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.26-7.31 (m, 1H, ArH), 7.44 (d, J = 8.6 Hz, 2H, ArH), 7.53-7.57 (m, 2H, ArH), 8.09-8.12 (m, 2H, ArH), 8.26 (d, J = 8.4 Hz, 2H, ArH), 8.52 (d, J = 4.8 Hz, 1H, ArH), 10.36 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.3, 119.0, 121.1, 121.2, 122.2, 128.6, 129.8, 132.1, 133.1, 136.1, 136.4, 137.7, 138.4, 139.3, 141.4, 194.3. MS (ESI+): m/z = 307.1. ESI-HR-MS calculated for $C_{18}H_{11}ClN_2O$ (M^++H): 307.0638, found: 307.0642.

4.2.4. (4-Nitrophenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3ad).**[5] Yield: 78% (0.308 g from 0.2 g); a yellow solid, mp 240-242 °C [Lit 243-244 °C]; R_f = 0.62 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 689, 1256, 1708, 2356, 3006 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.35 (dt, J_1 = 0.6 Hz, J_2 = 7.8 Hz, 1H, ArH), 7.64 (dt, J_1 = 1.1 Hz, J_2

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= 8.2 Hz, 1H, ArH), 7.85 (d, *J* = 8.2 Hz, 1H, ArH), 8.34-8.36 (m, 3H, ArH), 8.39-8.42 (m, 2H, ArH), 8.49-8.54 (m, 2H, ArH), 12.18 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 113.6, 120.0, 120.5, 120.9, 122.4, 123.4, 129.6, 131.8, 132.3, 135.8, 136.4, 137.9, 142.3, 143.7, 149.6, 193.5. MS (ESI+): m/z = 318.1. ESI-HR-MS calculated for $C_{18}H_{11}N_3O_3$ (M^++H): 318.0879, found: 318.0883.

4.2.5. (9*H*-Pyrido[3,4-*b*]indol-1-yl)(*p*-tolyl)methanone **(3ae).**[5]. Yield: 86% (0.307 g from 0.2 g); a yellow solid, mp 153-155 °C [Lit 155-156 °C]; R_f = 0.72 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 789, 1025, 1489, 1701, 2896 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.48 (s, 3H, CH_3), 7.34-7.38 (m, 3H, ArH), 7.62-7.64 (m, 2H, ArH), 8.16-8.21 (m, 2H, ArH), 8.28 (d, *J* = 8.4 Hz, 2H, ArH), 8.63 (d, *J* = 4.9 Hz, 1H, ArH), 10.49 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 21.7, 112.0, 118.3, 120.7, 120.9, 121.8, 128.8, 129.2, 131.4, 131.6, 134.9, 136.6, 137.3, 137.9, 141.0, 143.2, 195.1. MS (ESI+): m/z = 287.1. ESI-HR-MS calculated for $C_{19}H_{14}N_2O$ (M^++H): 287.1184, found: 287.1185.

4.2.6. (4-Butylphenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3af)**. Yield: 90% (0.368 g from 0.2 g); a yellow solid, mp 189-191 °C; R_f = 0.70 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 789, 1256, 1700, 3256 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.99 (t, *J* = 7.4 Hz, 3H, CH_3), 1.43 (q, *J* = 7.4 Hz, 2H, CH_2), 1.65-1.76 (m, 2H, CH_2), 2.74 (t, *J* = 7.6 Hz, 2H, ArH), 7.33-7.38 (m, 3H, ArH), 7.57-7.63 (m, 2H, ArH), 8.14-8.18 (m, 2H, ArH), 8.32 (d, *J* = 8.1 Hz, 2H, ArH), 8.63 (d, *J* = 4.8 Hz, 1H, ArH), 10.52 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 13.9, 22.4, 33.3, 35.8, 112.0, 118.3, 120.7, 120.8, 121.8, 128.2, 129.2, 131.5, 131.6, 135.1, 136.6, 137.3, 137.9, 141.0, 148.1, 195.0. MS (ESI+): m/z = 329.1. ESI-HR-MS calculated for $C_{22}H_{20}N_2O$ (M^++H): 329.1654, found: 329.1656.

4.2.7. (4-*tert*-Butylphenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3ag)**. Yield: 95% (0.389 g from 0.2 g); a yellow solid, mp 193-195 °C; R_f = 0.71 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1710, 2356 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.38 (s, 9H, CH_3), 7.32-7.38 (m, 1H, ArH), 7.55-7.64 (m, 4H, ArH), 8.07-8.18 (m, 2H, ArH), 8.29 (d, *J* = 8.4 Hz, 2H, ArH), 8.61-8.63 (m, 1H, ArH), 10.47 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 31.2, 35.1, 112.0, 118.4, 120.7, 121.8, 125.1, 129.2, 131.2, 134.8, 137.5, 138.0, 138.4, 141.0, 156.0, 195.1. MS (ESI+): m/z = 329.2. ESI-HR-MS calculated for $C_{22}H_{20}N_2O$ (M^++H): 329.1654, found: 329.1656.

4.2.8. (4-Methoxyphenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3ah).**[5]. Yield: 87% (0.339 g from 0.2 g); a yellow solid, mp 168-170 °C [Lit 169-170 °C]; R_f = 0.66 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1547, 1623, 1697, 2389 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.88 (s, 3H, OMe), 7.12 (dd, J_1 = 1.9 Hz, J_2 = 6.8 Hz, 2H, ArH), 7.29-7.33 (m, 1H, ArH), 7.58-7.62 (m, 1H, ArH), 7.79 (d, *J* = 8.3 Hz, 1H, ArH), 8.30-8.34 (m, 3H, ArH), 8.42 (d, *J* = 4.9 Hz, 1H, ArH), 8.53 (d, *J* = 4.9 Hz, 1H, ArH), 11.98 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 56.0, 113.4, 113.9, 118.9, 120.6, 122.3, 129.3, 130.2, 131.3, 133.8, 136.2, 137.4, 137.5, 142.0, 163.3, 192.1. MS (ESI+): m/z = 303.1. ESI-HR-MS calculated for $C_{19}H_{14}N_2O_2$ (M^++H): 303.1134, found: 303.1138.

4.2.9. Biphenyl-4-yl(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3ai).**[5]. Yield: 82% (0.356 g from 0.2 g); a yellow solid, mp 182-184 °C [Lit 182-183 °C]; R_f = 0.65 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1652, 1708, 3456 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24-7.27 (m, 1H, ArH), 7.31 (t, *J* = 7.4 Hz, 1H, ArH), 7.39 (t, *J* = 7.1 Hz, 2H, ArH), 7.51-7.52 (m, 2H, ArH), 7.57-7.59 (m, 2H, ArH), 7.66 (d, *J* = 8.5 Hz, 2H, ArH), 8.06-8.09 (m, 2H, ArH), 8.34 (d, *J* = 8.6 Hz, 2H, ArH), 8.54 (d, *J* = 4.9 Hz, 1H, ArH), 10.40 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.0, 118.5, 120.8, 120.9, 121.8, 126.8, 127.4, 128.0, 128.9, 129.3, 131.7, 131.8, 136.3, 136.5, 137.3, 138.0, 140.4, 141.0, 145.1, 194.9. MS (ESI+): m/z = 349.1. ESI-HR-MS calculated for $C_{24}H_{16}N_2O$ (M^++H): 349.1341, found: 349.1345.

4.2.10. (3-Chlorophenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3aj)**. Yield: 85% (0.324 g from 0.2 g); a yellow solid, mp 206-208°C; R_f = 0.69 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 648, 985, 1145, 1623, 1702, 2689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35-7.39 (m, 1H, ArH), 7.48 (t, *J* = 7.8 Hz, 1H, ArH), 7.57-7.66 (m, 3H, ArH), 8.17-8.19 (m, 2H, ArH), 8.24-8.27 (m, 1H, ArH), 8.36 (t, *J* = 1.7 Hz, 1H, ArH), 8.62 (d, *J* = 4.9 Hz, 1H, ArH), 10.45 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.0, 118.8, 120.8, 120.9, 121.8, 129.3, 129.4, 131.2, 131.8, 132.2, 134.1, 135.8, 137.4, 138.1, 139.0, 141.1, 193.8. MS (ESI+): m/z = 307.1. ESI-HR-MS calculated for $C_{18}H_{11}ClN_2O$ (M^++H): 307.0638, found: 307.0643.

4.2.11. (3-Methoxyphenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3ak)**. Yield: 88% (0.331 g from 0.2 g); a yellow solid, mp 184-186 °C; R_f = 0.66 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1614, 1699, 3214 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.79 (s, 3H, OCH_3), 7.05-7.07 (m, 1H, ArH), 7.22-7.26 (m, 1H, ArH), 7.35 (t, *J* = 8.1 Hz, 1H, ArH), 7.46-7.51 (m, 2H, ArH), 7.78 (s, 1H, ArH), 7.78 (d, *J* = 7.7 Hz, 1H, ArH), 8.03-8.07 (m, 2H, ArH), 8.51 (d, *J* = 4.8 Hz, 1H, ArH), 10.36 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 55.5, 112.0, 115.8, 118.5, 118.7, 120.7, 120.8, 121.8, 124.0, 129.0, 129.3, 131.7, 136.3, 137.3, 138.0, 138.8, 141.0, 159.3, 195.2. MS (ESI+): m/z = 303.1. ESI-HR-MS calculated for $C_{19}H_{14}N_2O_2$ (M^++H): 303.1134, found: 303.1132.

4.2.12. (3-Nitrophenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3al)**. Yield: 74% (0.292 g from 0.2 g); a yellow solid, mp 212-214 °C; R_f = 0.63 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1256, 1625, 1696, 2986 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.27-7.31 (m, 1H, ArH), 7.52-7.64 (m, 3H, ArH), 8.08-8.12 (m, 2H, ArH), 8.35 (dd, J_1 = 1.1 Hz, J_2 = 8.2 Hz, 1H, ArH), 8.52 (d, *J* = 4.8 Hz, 1H, ArH), 8.61 (d, *J* = 7.7 Hz, 1H, ArH), 9.17 (s, 1H, ArH), 10.34 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.1, 119.2, 120.8, 121.1, 121.9, 126.5, 129.0, 129.6, 132.0, 135.3, 136.9, 137.5, 138.3, 138.8, 141.0, 147.9, 192.6. MS (ESI+): m/z = 318.0. ESI-HR-MS calculated for $C_{18}H_{11}N_3O_3$ (M^++H): 318.0879, found: 318.0881.

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4.2.13. (2-Chlorophenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (**3am**).[3a] Yield: 83% (0.317 g from 0.2 g); a yellow solid, mp 202-204 ^{o}C [Lit 203-205 ^{o}C]; R_f = 0.70 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 789, 1148, 1620, 1701, 3025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33-7.51 (m, 4H, ArH), 7.58-7.62 (m, 3H, ArH), 8.14-8.17 (m, 2H, ArH), 8.54 (d, *J* = 4.8 Hz, 1H, ArH), 10.48 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.1, 119.2, 120.7, 121.0, 121.9, 126.3, 129.5, 129.9, 130.0, 131.2, 131.8, 135.5, 136.8, 138.4, 138.8, 141.3, 197.6. MS (ESI+): m/z = 307.0. ESI-HR-MS calculated for $C_{18}H_{11}ClN_2O$ (M^++H): 307.0638, found: 307.0635.

4.2.14. (2-Methoxyphenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3an).**[5] .Yield: 90% (0.339 g from 0.2 g); a yellow solid, mp 220-222 ^{o}C [Lit 219-220 ^{o}C]; R_f = 0.68 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1608, 1703, 2789, 3123 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.69 (s, 3H, OCH_3), 6.97-7.04 (m, 2H, ArH), 7.25-7.29 (m, 1H, ArH), 7.41-7.45 (m, 1H, ArH), 7.49 (dd, J_1 = 1.6 Hz, J_2 = 7.5 Hz, 1H, ArH), 7.53-7.55 (m, 2H, ArH), 8.05 (d, J = 4.8 Hz, 1H, ArH), 8.09 (d, *J* = 7.6 Hz, 1H, ArH), 8.46 (d, *J* = 4.9 Hz, 1H, ArH), 10.36 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 55.9, 111.9, 112.1, 118.7, 120.3, 120.8, 121.9, 128.7, 129.3, 130.2, 131.6, 132.1, 136.6, 138.6, 141.3, 157.9, 198.8. MS (ESI+): m/z = 303.1. ESI-HR-MS calculated for $C_{19}H_{14}N_2O_2$ (M^++H): 303.1134, found: 303.1138.

4.2.15. (2,4-Dimethylphenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3ao).** Yield: 86% (0.322 g from 0.2 g); a yellow solid, mp 228-230 ^{o}C; R*f* = 0.73 (hexane: EtOAc, 8:2, v/v); IR (KBr) *v*max: 778, 1125, 1614, 2896 cm-1. ^{1}H NMR (400 MHz, CDCl3): δ (ppm) 2.31 (s, 6H, CH_3), 7.03-7.06 (m, 2H, ArH), 7.24-7.28 (m, 1H, ArH), 7.47-7.53 (m, 3H, ArH), 8.04 (d, *J* = 4.9 Hz, 1H, ArH), 8.08 (d, *J* = 7.6 Hz, 1H, ArH), 8.48 (d, *J* = 4.9 Hz, 1H, ArH), 10.43 (, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 20.3, 21.5, 112.0, 118.6, 120.8, 121.8, 125.8, 129.3, 130.3, 131.7, 131.8, 135.3, 136.6, 136.9, 137.8, 138.5, 140.8, 141.1, 200.1. MS (ESI+): m/z = 301.1. ESI-HR-MS calculated for $C_{20}H_{16}N_2O$ (M^++H): 301.1341, found: 301.1344.

4.2.16. (2,4-Dimethoxyphenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3ap).** Yield: 90% (0.373 g from 0.2 g); a yellow solid, mp 185-187 ^{o}C; R*f* = 0.61 (hexane: EtOAc, 8:2, v/v); IR (KBr) *v*max: 778, 1204, 1706, 2456, 2963 cm-1. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.70 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.51-6.55 (m, 2H, ArH), 7.24-7.28 (m, 1H, ArH), 7.52-7.53 (m, 2H, ArH), 7.61 (d, *J* = 8.4 Hz, 1H, ArH), 8.04 (d, *J* = 4.9 Hz, 1H, ArH), 8.09 (d, *J* = 7.8 Hz, 1H, ArH), 8.47 (d, *J* = 4.9 Hz, 1H, ArH), 10.35 (bs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 55.6, 55.9, 99.3, 104.5, 112.1, 118.4, 120.7, 120.9, 121.1, 121.9, 129.3, 131.6, 133.1, 136.8, 137.1, 138.3, 141.3, 160.4, 163.5, 196.9. MS (ESI+): m/z = 333.1. ESI-HR-MS calculated for $C_{20}H_{16}N_2O_3$ (M^++H): 333.1239, found: 333.1243.

4.2.17. (3,4-Dimethoxyphenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3aq).**[3a] Yield: 91% (0.377 g from 0.2 g); a yellow solid, mp 233-235 ^{o}C; IR (KBr) νmax: 668, 778, 1699, 2896 cm-1. R*f* = 0.63 (hexane: EtOAc, 8:2, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.01 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 7.03 (d, *J* = 8.6 Hz, 1H, ArH), 7.34-7.38 (m, 1H, ArH), 7.60-7.65 (m, 2H, ArH), 8.01 (d, *J* = 1.4 Hz, 1H, ArH), 8.17-8.21 (m, 2H, ArH), 8.29 (d, J_1 = 1.4 Hz, J_2 = 8.3 Hz, 1H, ArH), 8.62 (d, *J* = 4.9 Hz, 1H, ArH), 10.47 (bs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 56.0, 56.1, 110.0, 111.9, 113.6, 118.2, 120.6, 120.9, 121.7, 126.9, 129.2, 130.2, 131.6, 136.9, 137.3, 137.8, 140.9, 148.6, 153.0, 193.1. MS (ESI+): m/z = 333.1. ESI-HR-MS calculated for $C_{20}H_{16}N_2O_3$ (M^++H): 333.1239, found: 333.1240.

4.2.18. (9*H*-Pyrido[3,4-*b*]indol-1-yl)(2,4,5-trimethylphenyl)methanone **(3ar)**. Yield: 80% (0.313 g from 0.2 g); a yellow solid, mp 191-193 ^{o}C; R_f = 0.70 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1624, 1702, 2356, 3025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.07 (s, 6H, CH_3), 2.32 (s, 3H, CH_3), 6.80 (s, 1H, ArH), 6.86 (s, 2H, ArH), 7.54-7.55 (m, 2H, ArH), 8.06 (d, *J* = 4.9 Hz, ^{1}H, ArH), 8.11 (d, *J* = 7.8 Hz, 1H, ArH), 8.47 (d, *J* = 4.9 Hz, 1H, ArH), 10.53 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 19.8, 20.3, 21.4, 112.2, 119.2, 121.0, 122.0, 128.5, 128.8, 129.5, 131.9, 134.5, 135.9, 136.3, 136.5, 137.2, 138.9, 139.2, 139.8, 141.4, 204.6. MS (ESI+): m/z = 315.2. ESI-HR-MS calculated for $C_{21}H_{18}N_2O$ (M^++H): 315.1497, found: 315.1494.

4.2.19. Naphthalen-1-yl(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3as).**[5]. Yield: 92% (0.369 g from 0.2 g); a yellow solid, mp 122-124 ^{o}C [Lit 123-124 ^{o}C]; R_f = 0.62(hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1625, 1710, 1752, 2356 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35-7.39 (m, 1H, ArH), 7.48-7.52 (m, 2H, ArH), 7.58-7.64 (m, 3H, ArH), 7.92-7.94 (m, 2H, ArH), 8.03 (d, *J* = 8.2 Hz, 1H, ArH), 8.15-8.21 (m, 3H, ArH), 8.53 (d, *J* = 4.9 Hz, 1H, ArH), 10.61 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.1, 118.8, 120.8, 120.9, 121.9, 124.4, 125.6, 126.1, 127.0, 128.5, 129.4, 129.5, 131.3, 131.4, 131.8, 133.9, 135.5, 136.7, 137.3, 138.6, 141.2, 199.4. MS (ESI+): m/z = 323.2. ESI-HR-MS calculated for $C_{22}H_{14}N_2O$ (M^++H): 323.1184, found: 323.1188.

4.2.20. Pyridin-2-yl(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3at)**. Yield: 68% (0.231 g from 0.2 g); a brown solid, mp 237-239 ^{o}C; R_f = 0.58 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 669, 789, 1254, 1620, 1697, 2378 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23-7.27 (m, 1H, ArH), 7.39 (dd, J_1 = 5.1 Hz, J_2 = 7.3 Hz, 1H, ArH), 7.50-7.53 (m, 2H, ArH), 7.78-7.82 (m, 1H, ArH), 8.05-8.07 (m, 2H, ArH), 8.14 (d, *J* = 7.7 Hz, 1H, ArH), 8.51 (d, *J* = 4.9 Hz, 1H, ArH), 8.77 (d, *J* = 4.5 Hz, 1H, ArH), 10.40 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.3, 119.0, 120.8, 120.9, 121.9, 125.8, 126.4, 129.5, 131.8, 135.6, 136.3, 137.5, 138.6, 141.2, 149.8, 155.1, 194.5. MS (ESI+): m/z = 274.1. ESI-HR-MS calculated for $C_{17}H_{11}N_3O$ (M^++H): 274.0980, found: 274.0984.

4.2.21. Pyridin-4-yl(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(3au)**. Yield: 71% (0.241 g from 0.2 g); a yellow solid, mp 213-215 ^{o}C; R_f = 0.60 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 745, 1123, 1658, 1711, 1752, 2569, 3254 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29-7.32 (m, 1H, ArH), 7.56-7.57 (m, 2H, ArH), 8.04 (dd, J_1 = 1.4 Hz, J_2 = 4.5 Hz, 2H, ArH), 8.11-8.15 (m, 2H,

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ArH), 8.53 (d, *J* = 4.9 Hz, 1H, ArH), 8.78 (d, *J* = 5.7 Hz, 2H, ArH), 10.36 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.2, 119.5, 120.9, 121.3, 122.0, 124.4, 129.8, 132.2, 135.4, 137.5, 138.5, 141.2, 144.2, 150.2, 194.5. MS (ESI+): m/z = 274.1. ESI-HR-MS calculated for $C_{17}H_{11}N_3O$ (M^++H): 274.0980, found: 274.0983.

4.2.22. (9*H*-Pyrido[3,4-*b*]indol-1-yl)(thiophen-2-yl)methanone **(3av).**[5]. Yield: 87% (0.301 g from 0.2 g); a yellow solid, mp 211-212 ^{o}C [Lit 208-210 ^{o}C]; R_f = 0.65 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 668, 1145, 1623, 1702, 2354, 3012 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.16-71.18 (m, 1H, ArH), 7.25-7.29 (m, 1H, ArH), 7.51-7.57 (m, 2H, ArH), 7.73 (dd, J_1 = 4.8 Hz, J_2 = 0.97 Hz, 1H, ArH), 8.09-8.12 (m, 2H, ArH), 8.53-8.56 (m, 2H, ArH), 10.42 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 112.0, 118.8, 120.8, 121.8, 127.4, 129.3, 131.7, 135.7, 136.4, 136.8, 137.7, 139.8, 141.1, 185.3. MS (ESI+): m/z = 279.0. ESI-HR-MS calculated for $C_{16}H_{10}N_2OS$ (M^++H): 279.0592, found: 279.0595.

4.2.23. Methyl 1-benzoyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(3ba).**[6]. Yield: 79% (0.239 g from 0.2 g); a grey solid, mp 234-236 ^{o}C [Lit 237-238 ^{o}C]; R_f = 0.68 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1623, 1708, 1746, 2354, 3247 cm^{-1}. ^{1}H NMR (400 MHz $CDCl_3$): δ (ppm) 3.99 (s, 3H, CO_2CH_3), 7.32-7.36 (m, 1H, ArH), 7.47-7.58 (m, 5H, ArH), 8.17 (d, *J* = 7.9 Hz, 1H, ArH), 8.55 (d, *J* = 7.9 Hz, 2H, ArH), 8.98 (s, 1H, ArH), 10.62 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 52.9, 112.5, 120.8, 121.4, 121.8, 122.2, 128.3, 129.9, 132.1, 133.1, 136.6, 136.9, 138.4, 141.4, 166.3, 193.9. MS (ESI+): m/z = 331.1. ESI-HR-MS calculated for $C_{20}H_{14}N_2O_3$ (M^++H): 331.1083, found: 331.1080.

4.2.24. Methyl 1-(4-methylbenzoyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3be**).[6] Yield: 84% (0.265 g from 0.2 g); a yellow solid, mp 211-213 ^{o}C [Lit 214-215 ^{o}C]; R_f = 0.68 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 667, 1247, 1548, 1634, 1706, 1738, 2896, 3254 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.49 (s, 3H, CH_3), 4.09 (s, 3H, CO_2CH_3), 7.37-7.44 (m, 3H, ArH), 7.66-7.69 (m, 2H, ArH), 8.25 (d, *J* = 7.8 Hz, 1H, ArH), 8.57 (d, *J* = 7.9 Hz, 2H, ArH), 9.06 (s, 1H, ArH), 10.72 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 21.9, 52.8, 112.5, 120.6, 121.3, 121.7, 122.1, 129.0, 129.8, 132.1, 132.2, 134.3, 136.0, 136.4, 138.3, 141.4, 143.9, 166.4, 193.3. MS (ESI+): m/z = 345.1. ESI-HR-MS calculated for $C_{21}H_{16}N_2O_3$ (M^++H): 345.1239, found: 345.1243.

4.2.25. Methyl 1-(4-butylbenzoyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(3bf)**. Yield: 93% (0.329 g from 0.2 g); a yellow solid, mp 178-180 ^{o}C; R_f = 0.69 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1708, 1745, 3263 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.88 (t, *J* = 7.4 Hz, 3H, CH_3), 1.33 (q, *J* = 7.6 Hz, 2H, CH_2), 1.56-1.62 (m, 2H, CH_2), 2.65 (t, *J* = 7.6 Hz, 2H, CH_2), 4.01 (s, 3H, CO_2CH_3), 7.28-7.35 (m, 3H, ArH), 7.54-7.58 (m, 2H, ArH), 8.15 (d, *J* = 7.8 Hz, 1H, ArH), 8.51 (d, *J* = 8.3 Hz, 2H, ArH), 8.96 (s, 1H, ArH), 10.64 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 14.1, 22.5, 33.4, 35.9, 52.9, 112.5, 120.6, 121.3, 121.7, 122.1, 128.4, 129.8, 132.1, 132.3, 134.5, 136.0, 136.5, 138.4, 141.4, 148.9, 166.4, 193.3. MS (ESI+): m/z = 387.0. ESI-HR-MS calculated for $C_{24}H_{22}N_2O_3$ (M^++H): 387.1709, found: 387.1711.

4.2.26. Methyl 1-(4-*tert*-butylbenzoyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3bg**). Yield: 95% (0.336 g from 0.2 g); a yellow solid, mp 230-232 ^{o}C; R_f = 0.67 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 778, 1254, 1645, 1710, 1752, 3457 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.33 (s, 9H, CH_3), 4.01 (s, 3H, CO_2CH_3), 7.31-7.35 (m, 1H, ArH), 7.51-7.61 (m, 4H, ArH), 8.16 (d, *J* = 7.9 Hz, 1H, ArH), 8.54 (d, *J* = 8.4 Hz, 2H, ArH), 8.97 (s, 1H, ArH), 10.65 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 31.1, 35.2, 52.8, 112.4, 120.5, 121.2, 121.6, 122.0, 125.2, 129.7, 131.9, 134.1, 135.9, 136.3, 138.3, 141.3, 156.7, 166.2, 193.2. MS (ESI+): m/z = 387.1. ESI-HR-MS calculated for $C_{24}H_{22}N_2O_3$ (M^++H): 387.1709, found: 387.1712.

4.2.27. Methyl 1-(4-fluorobenzoyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(3bw)**. Yield: 87% (0.277 g from 0.2 g); a yellow solid, mp 185-187 ^{o}C; R_f = 0.65 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1708, 1740, 2945 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.99 (s, 3H, CH_3), 7.12-7.17 (m, 2H, ArH), 7.31-7.35 (m, 1H, ArH), 7.55-7.60 (m, 2H, ArH), 8.15 (d, *J* = 7.9 Hz, 1H, ArH), 8.64-8.67 (m, ArH), 8.95 (s, 1H, ArH), 10.58 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 52.8, 112.4, 115.3 (d, *J* = 21.9 Hz), 120.6, 121.8, (d, *J* = 32.6 Hz), 129.8, 132.1, 133.0, 134.7(d, J = 8.9 Hz), 135.5, 136.3, 138.2, 141.3, 165.8 (d, J = 255.4 Hz), 166.1, 191.7. MS (ESI+): m/z = 349.1. ESI-HR-MS calculated for $C_{20}H_{13}FN_2O_3$ (M^++H): 349.0988, found: 349.0991.

4.2.28. Ethyl 1-benzoyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(3ca)**. Yield: 76% (0.225 g from 0.2 g); a yellow solid, mp 202-204 ^{o}C; R_f = 0.68 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1245, 1547, 1623, 1697, 1735, 3256 cm^{-1} ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.41 (t, *J* = 7.2 Hz, 3H, CH_3), 4.41 (q, *J* = 6.9 Hz, 2H, CH_2), 7.38 (t, *J* = 7.8 Hz, 1H, ArH), 7.60 (t, *J* = 7.8 Hz, 2H, ArH), 7.66-7.72 (m, 2H, ArH), 8.86 (d, *J* = 8.2 Hz, 1H, ArH), 8.49 (t, *J* = 8.0 Hz, 3H, ArH), 9.17 (s, 1H, ArH), 12.47 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 14.1, 60.6, 113.2, 120.0, 120.7, 121.7, 127.7, 129.0, 131.3, 132.4, 132.5, 135.2, 135.5, 136.6, 136.7, 142.0, 164.7, 191.8. MS (ESI+): m/z = 345.1. ESI-HR-MS calculated for $C_{21}H_{16}N_2O_3$ (M^++H): 345.1239, found: 345.1242.

4.2.29. 6-Chloro-9*H*-pyrido[3,4-*b*]indol-1-yl)(phenyl)methanone **(3da)**. Yield: 75% (0.236 g from 0.2 g); a yellow solid, mp 196-198 ^{o}C; R_f = 0.68 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1625, 1706, 1723, 2319 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58-7.65 (m, 5H, ArH), 8.17 (bs, 2H, ArH), 8.35 (d, *J* = 6.9 Hz, 2H, ArH), 8.65 (s, 1H, ArH), 10.52 (bs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 113.1, 118.6, 121.5, 122.0, 126.4, 128.1, 129.5, 130.7, 132.6, 137.4, 137.6, 138.3, 139.3, 142.1, 196.8. MS (ESI+): m/z = 307.1. ESI-HR-MS calculated for $C_{18}H_{11}ClN_2O$ (M^++H): 307.0638, found: 307.0641.

4.2.30. (3-Ethynylphenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (**3ax**). Yield: 88% (0.325 g from

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0.2 g); a yellow solid, mp 168-170 °C; R_f = 0.62 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 978, 1025, 1235, 1456, 1589, 1604, 1699, 1735, 3258 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.05 (s, 1H, H-C≡C), 7.25-7.28 (m, 1H, ArH), 7.42 (t, J = 7.7 Hz, 1H, ArH), 7.52-7.55 (m, 2H, ArH), 7.63 (d, J = 7.7 Hz, 1H, ArH), 8.07-8.09 (m, 2H, ArH), 8.23 (d, J = 7.5 Hz, 1H, ArH), 8.38 (s, 1H, ArH), 8.53 (d, J = 4.8 Hz, 1H, ArH), 10.35 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 77.9, 83.4, 112.2, 111.8, 120.9, 121.0, 121.9, 122.3, 128.2, 129.5, 131.6, 131.8, 135.0, 135.7, 136.1, 137.5, 137.8, 138.3, 141.2, 194.5. MS (ESI+): m/z = 297.1. ESI-HR-MS calculated for $C_{20}H_{12}N_2O$ (M^++H): 297.1028, found: 297.1031.

4.3. *Experimental procedure for the formation of Eudistomin Y1 **(6)**.*

To a stirred solution of **3ah** (0.15 g, 0.49 mmol) in MeCN (10 mL) was added $AlCl_3$ (0.198 g, 1.49 mmol) and the resulting reaction mixture was reflux for 18 h. After completion of the reaction (as monitored by TLC), the reaction mixture was quenched by adding H_2O (5 mL) extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by chromatography over a column of silica gel using hexanes/ EtOAc (6.0:4.0, v/v) as eluent to afford the desired product **6** (0.124 g, 79%) as a yellow solid

4.3.1. (4-Hydroxyphenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone **(6).**[5]. Mp 215-217 °C [Lit 217-218 °C]; R_f = 0.56 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 659, 758, 1056, 1458, 1589, 1710, 2569, 3296 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.94 (d, J = 8.7 Hz, 2H, ArH), 7.31 (t, J = 7.8 Hz, 1H, ArH) 7.60 (t, J = 7.4 Hz, 1H, ArH), 7.79 (d, J = 8.1 Hz, 1H, ArH), 8.27 (d, J = 8.4 Hz, 2H, ArH), 8.32 (d, J = 7.8 Hz, 1H, ArH), 8.41 (d, J = 4.9 Hz, 1H, ArH), 8.52 (d, J = 4.9 Hz, 1H, ArH), 10.39 (s, 1H, NH), 11.94 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d^6): δ (ppm) = 112.8, 114.8, 118.2, 119.9, 120.0, 121.7, 128.3, 128.8, 130.7, 133.7, 135.6, 136.8, 137.4, 141.5, 161.8, 191.4. MS (ESI+): m/z = 289.1. ESI-HR-MS calculated for $C_{18}H_{12}N_2O_2$ (M^++H): 289.0977, found: 289.0980.

4.4. *Experimental procedure for formation of Eudistomin Y2 (**7**).*

To a stirred solution of **6** (0.1 g, 0.34 mmol) in AcOH (5 mL) was added NBS (0.062 g, 0.34 mmol) at room temperature and the reaction was allowed to continue for 8 h. After completion (as monitored by TLC), the reaction mixture was neutralised with aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc (3 × 15 mL) and water (25 mL). The organic layers were pooled, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish a residue that was purified by silica gel column chromatography using hexanes/ EtOAc (6.0:4.0, v/v) as eluent to afford **7** (0.072 g, 91%) as a yellow solid.

4.4.1. 6-Bromo-9*H*-pyrido[3,4-*b*]indol-1-yl)(4-hydroxyphenyl)methanone **(7)**[5]. Mp 270-272 °C [Lit 273-274°C]; R_f = 0.55 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 633, 869, 1204, 1563, 1608, 1712, 2354, 3025, 3248 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.60 (d, J = 7.4 Hz, 2H, ArH), 8.32 (t, J = 6.9 Hz, 1H, ArH) 8.40 (d, J = 4.6 Hz, 1H, ArH), 8.47 (d, J = 4.4 Hz, 1H, ArH), 8.51-8.57 (m, 4H, ArH), 10.38 (s, 1H, NH), 11.93 (s, 1H, OH); ^{13}C NMR (100 MHz DMSO- d_6): δ (ppm) = 110.9, 112.8, 114.8, 118.2, 119.0, 120.0, 121.7, 128.3, 128.8, 130.7, 133.7, 135.4, 135.6, 136.8, 137.4, 141.5, 161.8, 191.3. MS (ESI+): m/z = 367.2. ESI-HR-MS calculated for $C_{18}H_{11}BrN_2O_2$ (M^++H): 367.0082, found: 367.0085.

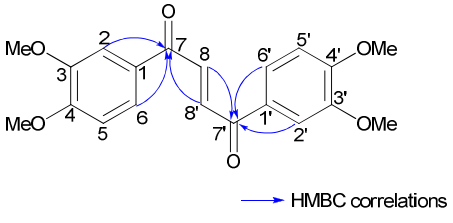
4.5. *Experimental procedure for Fascaplysin **8**.*

A round bottom flask charged with **3am** (0.1 g) was heated at 220 °C for 20 minutes. The content was cooled and the residue was recrystallized from CH_2Cl_2/diethyl ether producing corresponding quaternary fascaplysin analogs **8** (0.084 g, 84%) as dark red solid.

4.5.1. Fascaplysin (**8**)[6]. Mp 233-235 °C [Lit 230-232 °C]; R_f = 0.11 (hexane: EtOAc, 6:4, v/v); IR (KBr) ν_{max}: 769, 896, 1269, 1523, 1647, 1711, 2389, 3214 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.32 (t, J = 7.4 Hz, 1H, ArH), 7.46-7.62 (m, 5H, ArH), 7.88 (d, J = 8.3 Hz, 1H, ArH), 8.31 (d, J = 8.1 Hz, 1H, ArH), 8.41-8.45 (m, 2H, ArH), 12.25 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 113.6, 120.1, 120.4, 120.9, 122.3, 127.2, 129.6, 129.8, 130.0, 130.7, 131.5, 131.8, 135.7, 135.8, 138.3, 139.8, 142.4, 196.6. MS (ESI+): m/z = 271.1. ESI-HR-MS calculated for $C_{18}H_{11}N_2O$ $(M)^+$: 271.0866, found: 271.0869.

4.5.2. 1,4-Phenylenebis((9*H*-pyrido[3,4-*b*]indol-1-yl)methanone) **(9)**. Yield: 75% (0.277 g from 0.2 g); a yellow solid, mp <250 °C; R_f = 0.48 (hexane: EtOAc, 6:4, v/v); IR (KBr) ν_{max}: 698, 768, 965, 1253, 1524, 1635, 1706, 2354, 2589 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.35 (bs, 2H, ArH), 7.63 (bs, 2H, ArH), 7.84 (d, J = 7.1 Hz, 2H, ArH), 8.13 (d, J = 7.7 Hz, 2H, ArH), 8.24-8.36 (m, 5H, ArH), 8.50-8.58 (m, 3H, ArH), 12.13 (bs, 1H, NH), 12.17 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 113.5, 119.7, 120.5, 120.8, 122.3, 129.2, 129.5, 130.5, 131.2, 131.7, 134.0, 136.3, 136.4, 137.8, 141.7, 142.2, 167.4, 194.2. MS (ESI+): m/z = 467.1. ESI-HR-MS calculated for $C_{30}H_{18}N_4O_2$ (M^++H): 467.1508, found: 467.1511.

4.5.3. (*E*)-1,4-bis(3,4-dimethoxyphenyl)but-2-ene-1,4-dione **(11).** Yield: 90% (0.351 g from 0.2 g); a yellow solid, mp 198-200 °C; R_f = 0.54 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 675, 778, 925, 1026, 1536, 1645, 1713, 2458 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.91 (s, 12H, OCH_3), 6.87 (d, J = 8.2 Hz, 2H, ArH), 7.55 (s, 2H, H-C=C-H), 7.67 (d, J = 7.9 Hz, 1H, ArH), 7.96 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 56.2, 56.3, 110.3, 110.7, 124.2, 130.4, 134.5, 149.6, 154.3, 188.1. MS (ESI+): m/z = 357.1. ESI-HR-MS calculated for $C_{20}H_{20}O_6$ (M^++H): 357.1338, found: 357.1341. Three bond HMBC correlations of 2, 6-H and 8'-H to C-7 and 2', 6'-H and H-8 to C-7' confirmed the formation of the compound. Although compound is symmetrical in nature even then it showed an important three bond HMBC correlations of 8'-H to C-7 and H-8 to C-7', which strengthened the formation of a symmetrical dimer



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4.5.4. 1,4-Bis(3,4-dimethoxyphenyl)-2-(methylthio)but-2-ene-1,4-dione (**12z**). Yield: 78% (0.193 g from 0.2 g); a yellow solid, mp 140-142 ^{o}C; R_f = 0.56 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1602, 1694, 2348, 3214 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.16 (s, 3H, SCH_3), 3.93 (s, 3H, OCH_3), 3.94 (s. 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.86 (d, J = 8.3 Hz, 1H, ArH), 6.92 (d, J = 8.4 Hz, 1H, ArH), 7.07 (s, 1H, ArH), 7.52 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, ArH), 7.61 (d, J = 1.9 Hz, 2H, ArH), 7.67 (dd, J_1 = 8.4 Hz, J_2 = 1.7 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 15.5, 55.9, 56.0, 56.1, 56.3, 110.0, 110.3, 110.4, 110.5, 115.7, 122.3, 126.3, 128.1, 131.1, 149.2, 149.5, 153.0, 154.8, 159.9, 186.8, 190.6. MS (ESI+): m/z = 403.1. ESI-HR-MS calculated for $C_{21}H_{22}O_6S$ (M^++H): 403.1215, found: 403.1213.

4.5.5. 2-(Methylthio)-1,4-dip-tolylbut-2-ene-1,4-dione **(12e).** Yield: 68% (0.181 g from 0.2 g); a yellow solid, mp 95-97 ^{o}C; R_f = 0.62 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 789, 1258, 1635, 1702, 2789 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.14 (s, 3H, SCH_3), 2.39 (s, 3H, CH_3), 2.45 (s. 3H, CH_3), 7.06 (s, 1H, H-C=C), 7.23 (d, J = 8.1 Hz, 2H, ArH), 7.32 (d, J = 8.1 Hz, 2H, ArH), 7.84 (d, J = 8.2 Hz, 2H, ArH), 7.95 (dd, J = 8.2 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 15.4, 21.6, 21.8, 115.9, 128.2, 129.3, 129.8, 130.2, 143.5, 146.0, 160.3, 187.9, 191.6. MS (ESI+): m/z = 311.1. ESI-HR-MS calculated for $C_{19}H_{18}O_2S$ (M^++H): 311.1106, found: 311.1109.

4.5.6. 1,4-Bis(3-chlorophenyl)-2-(methylthio)but-2-ene-1,4-dione **(12j).** Yield: 74% (0.190 g from 0.2 g); a yellow solid, mp 178-180 ^{o}C; R_f = 0.60 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1298, 1547, 1658, 1714, 2589 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.17 (s, 3H, SCH_3), 7.01 (s, 1H, H-C=C), 7.39 (t, J = 7.8 Hz, 1H, ArH), 7.46-7.53 (m, 2H, ArH), 7.63-7.66 (m, 1H, ArH), 7.79-7.81 (m, 1H, ArH), 7.90-7.94 (m, 2H, ArH), 8.03 (t, J = 1.7 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 15.5, 115.7, 126.1, 128.1, 128.2, 129.6, 130.0, 130.5, 132.7, 134.8, 135.0, 135.6, 136.4, 139.4, 160.9, 186.7, 190.4. MS (ESI+): m/z = 351.1. ESI-HR-MS calculated for $C_{17}H_{12}Cl_2O_2S$ (M^++H): 351.0013, found: 351.0019.

4.5.7. Phenyl(pyrrolo[1,2-*a*]quinoxalin-4-yl)methanone **(15aa).**[12] **.** Yield: 84% (0.289 g from 0.2 g); a yellow solid, mp 148-150 ^{o}C; R_f = 0.68 (hexane: EtOAc, 9:1, v/v); IR (KBr) ν_{max}: 668, 963, 1249, 1624, 1704, 2349 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.96-6.97 (m, 1H, ArH), 7.21-7.25 (m, 1H, ArH), 7.46-7.52 (m, 3H, ArH), 7.62-7.65 (m, 2H, ArH), 7.92-7.93 (m, 1H, ArH), 8.02-8.03 (m, 2H, ArH), 8.16-8.18 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 108.9, 113.9, 114.8, 114.9, 124.4, 125.5, 127.9, 128.4, 129.4, 131.0, 131.1, 133.6, 134.8, 135.9, 149.9, 192.4. MS (ESI+): m/z = 273.0. ESI-HR-MS calculated for $C_{18}H_{12}N_2O$ (M^++H): 273.1028, found: 273.1033.

4.5.8. (4-Bromophenyl)(pyrrolo[1,2-*a*]quinoxalin-4-yl)methanone (**15ab**). Yield: 85% (0.376 g from 0.2 g); a yellow solid, mp 161-163 ^{o}C; R_f = 0.65 (hexane: EtOAc, 9:1, v/v); IR (KBr) ν_{max}: 1247, 1647, 1689, 1712, 3289 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.91 (dd, J_1 = 3.9 Hz, J_2 = 2.8 Hz, 1H, ArH), 7.20 (dd, J_1 = 4.2 Hz, J_2 = 0.8 Hz, 1H, ArH), 7.40-7.44 (m, 1H, ArH), 7.44-7.61 (m, 3H, ArH), 7.86 (d, J = 8.1 Hz, 1H, ArH), 7.93-8.09 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 109.1, 113.9, 114.8, 115.0, 124.3, 125.5, 128.8, 129.7, 131.2, 131.6, 132.6, 134.6, 134.8, 149.2, 191.3. MS (ESI+): m/z = 351.2. ESI-HR-MS calculated for $C_{18}H_{11}BrN_2O$ (M^++H): 351.0133, found: 351.0138.

4.5.9. Pyrrolo[1,2-*a*]quinoxalin-4-yl(*p*-tolyl)methanone **(15ae).** Yield: 91% (0.329 g from 0.2 g); a yellow solid, mp 164-166 ^{o}C; R_f = 0.66 (hexane: EtOAc, 9:1, v/v); IR (KBr) ν_{max}: 758, 936, 1298, 1536, 1637, 1714, 2389, 3014 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44 (s, 3H, CH_3), 6.94 (dd, J_1 = 3.9 Hz, J_2 = 2.7 Hz, 1H, ArH), 7.16 (dd, J_1 = 4.0 Hz, J_2 = 1.1 Hz, 1H, ArH), 7.29 (d, J = 8.2 Hz, 2H, ArH), 7.45-7.48 (m, 1H, ArH), 7.57-7.62 (m, 1H, ArH), 7.91 (d, J = 8.2 Hz, 1H, ArH), 8.01-8.03 (m, 2H, ArH), 8.06 (d, J = 8.2 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 21.8, 108.8, 113.9, 114.7, 114.8, 124.4, 125.4, 127.9, 129.1, 129.3, 131.0, 131.2, 133.3, 134.8, 144.7, 150.4, 192.0. MS (ESI+): m/z = 287.1. ESI-HR-MS calculated for $C_{19}H_{14}N_2O$ (M^++H): 287.1184, found: 287.1184.

4.5.10. (4-Methoxyphenyl)(pyrrolo[1,2-*a*]quinoxalin-4-yl)methanone (**15ah**). Yield: 82% (0.313 g from 0.2 g); a yellow solid, mp 184-186 ^{o}C; R_f = 0.63 (hexane: EtOAc, 9:1, v/v); IR (KBr) ν_{max}: 889, 1298, 1547, 1612, 1704, 2596 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.89 (s, 3H, OCH_3), 6.93-6.98 (m, 3H, ArH), 7.15 (dd, J_1 = 4.1 Hz, J_2 = 1.1 Hz, 1H, ArH), 7.46-7.50 (m, 1H, ArH), 7.59-7.63 (m, 1H, ArH), 7.91-7.93 (m, 1H, ArH), 8.02-8.05 (m, 2H, ArH), 8.18 (d, J = 8.9 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 55.6, 108.8, 113.7, 113.9, 114.7, 114.8, 124.5, 125.4, 127.9, 128.6, 129.2, 130.9, 133.4, 134.8, 150.7, 164.2, 190.8. MS (ESI+): m/z = 303.1. ESI-HR-MS calculated for $C_{19}H_{14}N_2O_2$ (M^++H): 303.1134, found: 303.1138.

4.5.11. 1-(4-Benzoylpyrrolo[1,2-*a*]quinoxalin-1-yl)-2-phenylethane-1,2-dione (**16aa**). Yield: 90% (0.460 g from 0.2 g); a yellow solid, mp 202-204 ^{o}C; R_f = 0.55 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1589, 1612, 1657, 1714, 2689, 3145 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 (d, J = 4.7 Hz, 1H, ArH), 7.54-7.58 (m, 5H, ArH), 7.67-7.12 (m, 3H, ArH), 7.81-7.83 (m, 1H, ArH), 8.05-8.07 (m, 2H, ArH), 8.17-8.19 (m, 3H, ArH), 9.26 (dd, J_1 = 8.6 Hz, J_2 = 0.9 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 109.8, 120.3, 127.5, 127.8, 128.5, 128.7, 129.0, 130.2, 130.3, 130.4, 131.2, 131.9, 133.0, 133.9, 134.8, 135.4, 136.6, 149.1, 182.7, 191.4, 193.1. MS (ESI+): m/z = 405.2. ESI-HR-MS calculated for $C_{26}H_{16}N_2O_3$ (M^++H): 405.1239, found: 405.1243.

4.5.12. 1-(4-(4-Methylbenzoyl)pyrrolo[1,2-*a*]quinoxalin-1-yl)-2-*p*-tolylethane-1,2-dione (**16ae**). Yield: 92% (0.524 g from 0.2 g); a yellow solid, mp 210-212 ^{o}C; R_f = 0.53 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 1247, 1607, 1669, 1712, 3289 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.29 (d, J = 4.7 Hz, 1H, ArH), 7.31 (d, J = 3.5 Hz, 2H, ArH), 7.33 (d, J = 3.5 Hz, 2H, ArH), 7.49 (d, J = 4.6 Hz, 1H, ArH), 7.64-7.68 (m, 1H, ArH), 7.75-7.79 (m,

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1H, ArH), 7.93 (d, *J* = 8.3 Hz, 2H, ArH), 8.05 (d, *J* = 8.3 Hz, 2H, ArH), 8.14 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H, ArH), 9.23 (dd, J_1 = 8.6 Hz, J_2 = 0.9 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 21.8, 21.9, 109.7, 120.3, 127.4, 127.9, 128.7, 129.3, 129.8, 130.0, 130.2, 130.4, 130.5, 131.2, 131.9, 132.8, 136.6, 145.2, 146.2, 149.5, 182.9, 191.1, 192.9. MS (ESI+): m/z = 433.2. ESI-HR-MS calculated for $C_{28}H_{20}N_2O_3$ (M^++H): 433.1552, found: 433.1555.

4.5.13. (7-(Methylthio)indolo[1,2-*a*]quinoxalin-6-yl)(phenyl)methanone (**17ba**). Yield: 88% (0.311 g from 0.2 g); a yellow solid, mp 222-224 °C; R_f = 0.60 (hexane: EtOAc, 9:1, v/v); IR (KBr) ν_{max}: 774, 1247, 1685, 1702, 2496, 3247 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.09 (s, 3H, SCH_3), 7.48-7.75 (m, 7H, ArH), 8.05 (d, J = 7.5 Hz, 2H, ArH), 8.09 (d, *J* = 7.9 Hz, 1H, ArH), 8.16 (d, *J* = 7.9 Hz, 1H, ArH), 8.55 (d, *J* = 8.6 Hz, 1H, ArH), 8.59 (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 20.1, 106.2, 114.8, 114.9, 121.4, 123.6, 124.8, 125.6, 128.7, 129.1, 129.7, 130.0, 130.4, 130.9, 121.3, 133.0, 133.8, 135.4, 136.1, 154.8, 192.5. MS (ESI+): m/z = 369.0. ESI-HR-MS calculated for $C_{23}H_{16}N_2OS$ (M^++H): 369.1062, found: 369.1059.

4.5.14. (7-(Methylthio)indolo[1,2-*a*]quinoxalin-6-yl)(4-nitrophenyl)methanone (**17bd**). Yield: 82% (0.325 g from 0.2 g); a yellow solid, mp 188-190 °C; R_f = 0.58 (hexane: EtOAc, 9:1, v/v); IR (KBr) ν_{max}: 875, 967, 1238, 1526, 1645, 1702, 2549, 3145 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.05 (s, 3H, SCH_3), 7.44-7.51 (m, 2H, ArH), 7.59-7.67 (m, 2H, ArH), 7.97 (d, *J* = 7.9 Hz, 1H, ArH), 8.04-8.13 (m, 3H, ArH), 8.24-8.26 (m, 3H, ArH), 8.45-8.51 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 20.3, 105.9, 114.9, 115.0, 121.4, 123.9, 125.0, 125.9, 130.2, 130.5, 130.8, 131.0, 131.1, 131.4, 132.0, 133.2, 134.6, 135.3, 140.6, 150.6, 153.5, 190.5. MS (ESI+): m/z = 414.1. ESI-HR-MS calculated for $C_{23}H_{15}N_3O_3S$ (M^++H): 414.0912, found: 414.0915.

4.5.15. (4-Methoxyphenyl)(7-(methylthio)indolo[1,2-*a*]quinoxalin-6-yl)methanone (**17bh**). Yield: 92% (0.352 g from 0.2 g); a yellow solid, mp 152-154 °C; R_f = 0.62 (hexane: EtOAc, 9:1, v/v); IR (KBr) ν_{max}: 1247, 1675, 1712, 3289 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.03 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 6.87 (d, *J* = 8.8 Hz, 2H, ArH), 7.38-7.48 (m, 2H, ArH), 7.54-7.63 (m, 2H, ArH), 7.91 (d, *J* = 8.7 Hz, 2H, ArH), 7.98 (d, *J* = 7.8 Hz, 1H, ArH), 8.06 (d, *J* = 8.0 Hz, 1H, ArH), 8.43 (d, *J* = 8.6 Hz, 1H, ArH), 8.47 (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 20.3, 55.6, 106.3, 114.1, 114.8, 114.9, 121.4, 123.6, 124.8, 125.5, 129.3, 129.6, 130.4, 130.8, 132.4, 135.4, 155.0, 164.2, 191.2. MS (ESI+): m/z = 399.2. ESI-HR-MS calculated for $C_{24}H_{18}N_2O_2S$ (M^++H): 399.1167, found: 399.1164.

4.5.16. (7-(Methylthio)indolo[1,2-*a*]quinoxalin-6-yl)(thiophen-2-yl)methanone (**17bv**). Yield: 89% (0.320 g from 0.2 g); a yellow solid, mp 214-216 °C; R_f = 0.59 (hexane: EtOAc, 9:1, v/v); IR (KBr) ν_{max}: 1478, 1621, 1697, 2746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.16 (s, 3H, CH_3), 7.10 (s, 1H, ArH), 7.46 (t, *J* = 7.3 Hz, 1H, ArH), 7.52 (t, *J* = 7.4 Hz, 1H, ArH), 7.59-7.69 (m, 3H, ArH), 7.79 (d, *J* = 4.0 Hz, 1H, ArH), 8.04 (d, *J* = 7.8 Hz, 1H, ArH), 8.13 (d, *J* = 7.8 Hz, 1H, ArH), 8.47 (d, *J* = 8.6 Hz, 1H, ArH), 8.51 (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 20.2, 106.5, 114.8, 114.9, 121.4, 123.6, 124.8, 125.6, 128.3, 128.6, 129.9, 130.5, 130.9, 131.4, 132.9, 135.2, 135.6, 143.3, 153.7, 184.8. MS (ESI+): m/z = 375.1. ESI-HR-MS calculated for $C_{21}H_{14}N_2OS_2$ (M^++H): 375.0626, found: 375.0628.

4.5.17. (4-Methoxyphenyl)(7-methylindolo[1,2-*a*]quinoxalin-6-yl)methanone (**15ch**). Yield: 91% (0.3 g from 0.2 g); a yellow solid, mp 156-158 °C [Lit 162-163 °C]; R_f = 0.66 (hexane: EtOAc, 9:1, v/v); IR (KBr) ν_{max}: 689, 1249, 1628, 1696, 2378 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H, CH_3), 4.06 (s, 3H, OCH_3), 7.15 (d, *J* = 8.9 Hz, 2H, ArH), 7.66 (t, *J* = 7.4 Hz, 1H, ArH), 7.72 (t, *J* = 7.6 Hz, 1H, ArH), 7.79-7.89 (m, 2H, ArH), 8.19 (d, *J* = 8.7 Hz, 2H, ArH), 8.24 (dd, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H, ArH), 8.32 (d, *J* = 7.9 Hz, 1H, ArH), 8.68 (d, *J* = 8.8 Hz, 1H, ArH), 8.71 (d, *J* = 8.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 10.7, 55.6, 110.9, 114.2, 114.9, 121.5, 123.7, 134.9, 125.6, 129.7, 130.5, 130.9, 131.5, 132.5, 133.1, 135.5, 155.1, 164.3, 191.3. MS (ESI+): m/z = 367.1. ESI-HR-MS calculated for $C_{24}H_{18}N_2O_2$ (M^++H): 367.1447, found: 367.1449.

4.6. *General Procedure for thiomethylation as exemplified for **18aa**.*

To a solution of **3aa** (0.1 g, 0.36 mmol) in DMSO (5 mL) were added $Pd(OAc)_2$ (0.082 g, 0.036 mmol) and $Cu(OAc)_2$ (0.065 g, 0.36 mmol) and the mixture was stirred under heating at 120 °C for 30 h. On completion as monitored by the TLC, the mixture was quenched with water and extracted with EtOAc (3 x 20 mL). The organic layers were pooled, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnsih a residue. This residue was purified by silica gel column chromatography using hexanes/ EtOAc (8.0:2.0, v/v) as eluent to afford **18aa** (0.074 g, 64%) as a yellow solid.

4.6.1. (2-(Methylthio)phenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (**18aa**). Mp 168-170 °C; R_f = 0.69 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 665, 856, 1246, 1623, 1702, 2563, 3266 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.43 (s, 3H, SCH_3), 6.97-7.04 (m, 2H, ArH), 7.25-7.29 (m, 1H, ArH), 7.41-7.45 (m, 1H, ArH), 7.48-7.49 (m, 1H, ArH), 7.52-7.55 (m, 2H, ArH), 8.05 (d, *J* = 4.9 Hz, 1H, ArH), 8.10 (d, *J* = 7.6 Hz, 1H, ArH), 8.46 (d, *J* = 4.9 Hz, 1H, ArH), 10.36 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 16.4, 111.9, 112.1, 118.7, 120.4, 120.8, 121.8, 128.7, 129.3, 130.2, 131.6, 132.1, 136.6, 138.6, 140.1, 141.3, 198.8. MS (ESI+): m/z = 319.1. ESI-HR-MS calculated for $C_{19}H_{14}N_2OS$ (M^++H): 319.0905, found: 319.0911.

4.6.2. (4-Bromo-2-(methylthio)phenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (**18ab**). Yield: 66% (0.074 g from 0.1 g); a yellow solid, mp 202-204 °C; R_f = 0.67 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 887, 1145, 1656, 1697, 2459, 3045 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.58 (m, 3H SCH_3), 7.15 (dd, J_1 = 2.5 Hz, J_2 = 8.5 Hz, 1H, ArH), 7.32-7.39 (m, 3H, ArH), 7.55-7.58 (m, 1H, ArH), 7.63-7.64 (m, 1H, ArH), 8.21 (d, *J* = 7.5 Hz, 1H, ArH), 8.37 (d, *J* = 8.4 Hz, 1H, ArH), 8.63 (s, 1H, ArH), 10.48 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 16.2, 112.0, 119.1, 120.7,

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120.9, 121.8, 123.9, 124.5, 124.7, 128.0, 129.3, 131.8, 133.7, 138.5, 138.6, 141.0, 145.2, 147.1, 194.2. MS (ESI+): m/z = 397.0. ESI-HR-MS calculated for $C_{19}H_{13}BrN_2OS$ (M^++H): 397.0010, found: 397.0009.

4.6.3. (4-Methyl-2-(methylthio)phenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (**18ae**). Yield: 61% (0.071 g from 0.2 g); a yellow solid, mp 177-178 °C; R_f = 0.70 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 986, 1292, 1546, 1647, 1703, 2569, 2756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H SCH_3), 2.47 (s, 3H, ArH), 6.79 (s, 1H, ArH), 6.83 (d, *J* = 7.8 Hz, 1H, ArH), 7.25-7.28 (m, 1H, ArH), 7.43 (d, *J* = 7.8 Hz, 1H, ArH), 7.52-7.54 (m, 2H, ArH), 8.04 (d, *J* = 5.1 Hz, 1H, ArH), 8.09 (d, *J* = 7.9 Hz, 1H, ArH), 8.46 (d, *J* = 4.9 Hz, 1H, ArH), 10.45 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 16.4, 22.0, 112.1, 112.6, 118.5, 120.6, 120.8, 121.0, 121.8, 125.7, 129.1, 130.5, 131.5, 136.6, 136.8, 138.5, 139.7, 141.2, 142.9, 198.4. MS (ESI+): m/z = 333.1. ESI-HR-MS calculated for $C_{20}H_{16}N_2OS$ (M^++H): 333.1062, found: 333.1066.

4.6.4. (4-Methoxy-2-(methylthio)phenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (**18ah**). Yield: 70% (0.08 g from 0.1 g); a yellow solid, mp 145-147 °C; R_f = 0.64 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 668, 956, 1146, 1536, 1643, 1710, 2563, 3056 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H SCH_3), 3.81 (s, 3H, OCH_3), 6.50 (d, *J* = 2.1 Hz, 1H, ArH), 6.52-6.55 (m, 1H, ArH), 7.24-7.28 (m, 1H, ArH), 7.51-7.53 (m, 2H, ArH), 7.60 (d, *J* = 8.5 Hz, 1H, ArH), 8.04 (d, *J* = 4.9 Hz, 1H, ArH), 8.09 (d, *J* = 7.8 Hz, 1H, ArH), 8.47 (d, *J* = 4.9 Hz, 1H, ArH), 10.35 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 15.9, 55.9, 99.3, 104.5, 112.1, 118.4, 120.7, 120.9, 121.1, 121.8, 129.3, 131.6, 133.0, 136.8, 137.1, 138.3, 139.8, 141.3, 163.6, 196.9. MS (ESI+): m/z = 349.1. ESI-HR-MS calculated for $C_{20}H_{16}N_2O_2S$ (M^++H): 349.1011, found: 349.1013.

4.6.5. (5-Chloro-2-(methylthio)phenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (**18aj**). Yield: 54% (0.062 g from 0.1 g); a grey solid, mp 180-182 °C; R_f = 0.66 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 779, 936, 1238, 1543, 1659, 1702, 2614, 3214 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.47 (s, 3H SCH_3), 7.01 (d, *J* = 8.8 Hz, 1H, ArH), 7.37-7.41 (m, 1H, ArH), 7.46-7.49 (m, 1H, ArH), 7.55 (d, *J* = 2.3 Hz, 1H, ArH), 7.65 (bs, 2H, ArH), 8.17-8.22 (m, 2H, ArH), 8.57 (d, *J* = 4.8 Hz, 1H, ArH), 10.41 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 16.4, 112.2, 113.2, 119.0, 120.8, 121.0, 121.9, 125.6, 129.5, 129.8, 130.2, 121.6, 121.8, 136.1, 136.7, 138.8, 140.0, 141.3, 197.3. MS (ESI+): m/z = 353.1. ESI-HR-MS calculated for $C_{19}H_{13}ClN_2OS$ (M^++H): 353.0515, found: 353.0518.

4.6.6. (4-Fluoro-2-(methylthio)phenyl)(9*H*-pyrido[3,4-*b*]indol-1-yl)methanone (**18aw**). Yield: 52% (0.050 g from 0.1 g); a yellow solid, mp 196-198 °C; R_f = 0.68 (hexane: EtOAc, 8:2, v/v); IR (KBr) ν_{max}: 856, 965, 1247, 1563, 1632, 1711, 2549, 2789 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)2.40 (s, 3H, SCH_3), 7.02 (d, *J* = 8.9 Hz, 1H, ArH), 7.49 (d, *J* = 4.1 Hz, 1H, ArH), 7.73 (s, 2H, ArH), 8.28 (d, *J* = 7.0 Hz, 2H, ArH), 9.11-9.15 (m, 1H, ArH), 10.75 (d, *J* = 10.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 16.7, 112.5, 115.4 (d, *J* = 21.9 Hz), 120.7, 121.3, 121.9 (d, *J* = 32.1 Hz), 129.4, 132.2, 134.8 (d, *J* = 9.2 Hz), 136.4, 138.4, 139.8, 141.4, 143.0, 165.9 (d, *J* = 255.2 Hz), 191.8. MS (ESI+): m/z = 337.1. ESI-HR-MS calculated for $C_{19}H_{13}FN_2OS$ (M^++H): 337.0811, found: 337.0809.

4.7. *General Procedure for the synthesis of Canthin-6-ones **19** as exemplified for **19aa**.*

To a stirred solution of **3aa** (0.1 g, 0.36 mmol) in THF (5 mL) was added NaH (60% dispersion in mineral oil) (2.0 equiv) at 0 °C. After 15 min. acetic anhydride (0.052 µL, 0.54 mmol) was added to the above solution. After 15 min the reaction mixture was transferred to oil bath and heated at 70 °C. After completion of reaction (as monitored by TLC), the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layers were collected, dried over anhydrous Na_2SO_4 and evaporated to get the crude product. The crude product was purified by column chromatography over a column of silica gel using hexanes/EtOAc (8.0:2.0, v/v) as eluent to get **19aa** (0.089 g, 83%) as a pale yellow solid.

4.7.1. 4-Phenyl-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one **(19aa)**. Yield: 83% (0.089 g from 0.1 g); a pale yellow solid, mp 146-148 °C; R_f = 0.62 (Hexanes: EtOAc, 8:2, v/v). IR (KBr) ν_{max}: 669, 759, 1215, 1668, 2401, 3020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.94 (s, 1H, H-C=C), 7.41-7.49 (m, 4H, ArH), 7.59-7.63 (m, 1H, ArH), 7.79-7.82 (m, 2H, ArH), 7.87 (d, *J* = 4.9 Hz, 1H, ArH), 8.00 (d, *J* = 7.7 Hz, 1H, ArH), 8.59 (d, *J* = 8.2 Hz, 1H, ArH), 8.78 (d, *J* = 4.9 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 116.4, 117.4, 122.7, 124.7, 125.7, 126.5, 128.7, 129.9, 130.1, 130.8, 130.9, 132.6, 134.5, 135.9, 139.2, 145.6, 151.3, 159.7. MS (ESI+) m/z = 297.1. ESI-HRMS calculated for $C_{20}H_{12}N_2O$ $[MH]^+$: 297.1028, found: 297.1032.

4.7.2. 4-(4-Bromophenyl)-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one **(19ab)**. Yield: 76% (0.081 g from 0.1 g); a white solid, mp 196-198 °C; R_f = 0.64 (Hexanes: EtOAc, 8:2, v/v). IR (KBr) ν_{max}: 756, 1215, 1667, 2400, 3020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.95 (s, 1H, H-C=C), 7.47 (t, *J* = 7.7 Hz, 1H, ArH), 7.61-7.66 (m, 3H, ArH), 7.67-7.72 (m, 2H, ArH), 7.93 (d, *J* = 4.9 Hz, 1H, ArH), 8.1 (d, *J* = 7.8 Hz, 1H, ArH), 8.63 (d, *J* = 8.2 Hz, 1H, ArH), 8.79 (d, *J* = 4.9 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 116.5, 117.4, 122.7, 124.6, 124.7, 125.8, 126.4, 130.9, 131.1, 131.6, 131.9, 132.5, 133.2, 135.5, 139.2, 145.6, 149.9, 159.5. MS (ESI+) m/z = 375.0. ESI-HRMS calculated for $C_{20}H_{11}BrN_2O$ $[M^+$+H]: 375.0133, found: 375.0130.

4.7.3. 4-(4-Chlorophenyl)-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one **(19ac)**. Yield: 78% (0.084 g from 0.1 g); a white solid, mp 182-184 °C; R_f = 0.66 (Hexanes: EtOAc, 8:2, v/v). IR (KBr) ν_{max}: 759, 1215, 1669, 2402, 3020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.91 (s, 1H, H-C=C) 7.43 (t, *J* = 8.4, 3H, ArH), 7.59-7.63 (m, 1H, ArH), 7.76 (d, *J* = 8.5 Hz, 2H, ArH), 7.87 (d, *J* = 4.9 Hz, 1H, ArH), 8.00 (d, *J* = 7.7 Hz, 1H, ArH), 8.57 (d, *J* = 8.2 Hz, 1H, ArH), 8.76 (d, *J* = 4.9 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 116.5, 117.4, 122.7, 124.7, 125.8, 126.4, 128.9, 130.9, 131.0, 131.4, 132.5, 132.8, 135.5, 136.3, 139.2, 145.6, 149.9, 159.5. MS (ESI+) m/z = 331.1. ESI-

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HRMS calculated for $C_{20}H_{11}ClN_2O$ [M^++H]: 331.0638, found: 331.0637.

4.7.4. 4-(*p*-Tolyl)-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one **(19ae)**. Yield: 85% (0.093 g from 0.1 g); a pale yellow solid, mp 176-178 °C; R_f = 0.64 (Hexanes: EtOAc, 8:2, v/v). IR (KBr) ν_{max}: 669, 758, 1215, 1667, 2401, 3020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = .2.38 (s, 3H, CH_3), 6.94 (s, 1H, H-C=C), 7.29 (d, J = 8.0 Hz, 2H, ArH), 7.44 (t, *J* = 7.6 Hz, 1H, ArH), 7.63 (t, *J* = 7.6 Hz, 1H, ArH), 7.72 (d, *J* = 8.1 Hz, 2H, ArH), 7.89 (d, *J* = 4.9 Hz, 1H, ArH), 8.03 (d, *J* = 7.8 Hz, 1H, ArH), 8.62 (d, *J* = 8.2 Hz, 1H, ArH), 8.79 (d, *J* = 4.9 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 21.5, 116.3, 117.4, 122.6, 124.7, 125.6, 125.9, 129.4, 130.0, 130.7, 130.9, 131.6, 132.5, 136.0, 139.2, 140.1, 145.6, 151.2, 159.8. MS (ESI+) m/z = 311.1. ESI-HRMS calculated for $C_{21}H_{14}N_2O$ [M^++H]: 311.1184, found: 311.1186.

4.7.5. 4-(4-Methoxyphenyl)-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one **(19ah)**. Yield: 84% (0.091 g from 0.1 g); a pale yellow solid, mp 132-134 °C; R_f = 0.58 (Hexanes: EtOAc, 8:2, v/v). IR (KBr) ν_{max}: 670, 758, 1215, 1665, 2400, 3020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.82 (s, 3H, OCH_3), 6.90 (s, 1H, H-C=C), 6.98-7.01 (m, 2H, ArH), 7.40-7.44 (m, 1H, ArH), 7.59-7.63 (m, 1H, ArH), 7.80-7.87 (m, 3H, ArH), 8.00 (d, *J* = 7.8 Hz, 1H, ArH), 8.59 (d, *J* = 8.2 Hz, 1H, ArH), 8.78 (d, *J* = 4.9 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 55.5, 114.2, 116.2, 117.4, 122.6, 124.7, 125.2, 125.5, 126.8, 130.8, 130.9, 131.6, 132.6, 136.1, 139.2, 145.4, 150.6, 159.9, 161.2. MS (ESI+) m/z = 327.1. ESI-HRMS calculated for $C_{21}H_{14}N_2O_2$ [M^++H]: 327.1134, found: 327.1134.

4.7.6. 4-(3-Chlorophenyl)-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one **(19aj)**. Yield: 79% (0.086 g from 0.1 g); a pale yellow solid, mp 168-170 °C; R_f = 0.66 (Hexanes: EtOAc, 8:2, v/v). IR (KBr) ν_{max}: 757, 1216, 1668, 2400, 3020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.03 (s, 1H, H-C=C), 7.47-7.56 (m, 3H, ArH), 7.70-7.91 (m, 2H, ArH), 7.91 (d, *J* = 1.4 Hz, 1H, ArH), 8.00 (d, *J* = 4.9 Hz, 1H, ArH), 8.13 (d, *J* = 7.7 Hz, 1H, ArH), 8.69 (d, *J* = 8.2 Hz, 1H, ArH), 8.88 (d, *J* = 4.9 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 116.5, 117.3, 122.6, 124.6, 125.7, 126.8, 128.1, 129.8, 129.8, 130.0, 130.8, 130.9, 132.4, 134.5, 135.3, 135.9, 139.1, 145.6, 149.6, 159.3. MS (ESI+) m/z = 331.1. ESI-HRMS calculated for $C_{20}H_{11}ClN_2O$ [M^++H]: 331.0638, found: 331.0635.

4.7.7. 4-(3-Methoxyphenyl)-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one **(19ak)**. Yield: 77% (0.084 g from 0.1 g); a pale yellow solid, mp 124-126 °C; R_f = 0.58 (Hexanes: EtOAc, 8:2, v/v). IR (KBr) ν_{max}: 669, 757, 1215, 1668, 3020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.82 (s, 3H, OCH_3), 6.95 (s, 1H, H-C=C), 6.97-7.00 (m, 1H, ArH), 7.36-7.39 (m, 3H, ArH), 7.42-7.46 (m, 1H, ArH), 7.59-7.64 (m, 1H, ArH), 7.88 (d, *J* = 4.9 Hz, 1H, ArH), 8.02 (d, *J* = 7.8 Hz, 1H, ArH), 8.60 (d, *J* = 8.2 Hz, 1H, ArH), 8.79 (d, *J* = 4.9 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 55.4, 115.4, 115.6, 116.3, 117.3, 122.3, 122.5, 124.6, 125.5, 126.4, 129.6, 130.7, 130.8, 132.4, 135.6, 135.7, 139.1, 145.5, 151.0, 159.6, 159.6. MS (ESI+) m/z = 327.1. ESI-HRMS calculated for $C_{21}H_{14}N_2O_2$ [M^++H]: 327.1134, found: 327.1132.

4.7.8. 4-(2-Chlorophenyl)-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one **(19am)**. Yield: 75% (0.081 g from 0.1 g); a brown solid, mp 172-174 °C; R_f = 0.66 (Hexanes: EtOAc, 8:2, v/v). IR (KBr) ν_{max}: 758, 1215, 1668, 2401, 3020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.89 (s, 1H, H-C=C), 7.35-7.51 (m, 5H, ArH), 7.61-7.65 (m, 1H, ArH), 7.87 (d, *J* = 4.9 Hz, 1H, ArH), 8.03 (d, *J* = 7.8 Hz, 1H, ArH), 8.62 (d, *J* = 8.2 Hz, 1H, ArH), 8.74 (d, *J* = 4.9 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 116.6, 117.5, 122.8, 124.8, 125.8, 126.9, 128.7, 130.2, 130.6, 130.8, 131.0, 131.3, 132.2, 133.4, 133.9, 135.9, 139.4, 145.9, 150.1, 159.4. MS (ESI+) m/z = 331.1. ESI-HRMS calculated for $C_{20}H_{11}ClN_2O$ [M^++H]: 331.0638, found: 331.0636.

4.7.9. 4-(Thiophen-2-yl)-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one **(19av)**. Yield: 72% (0.079 g from 0.1 g); a yellow solid, mp 150-152 °C; R_f = 0.60 (Hexanes: EtOAc, 8:2, v/v). IR (KBr) ν_{max}: 667, 758, 1214, 1667, 2402, 3020 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.31 (t, *J* = 4.0 Hz, 1H, ArH), 7.38 (s, 1H, H-C=C), 7.59 (t, *J* = 7.6 Hz, 1H, ArH), 7.78 (t, *J* = 7.6 Hz, 1H, ArH), 7.97 (d, *J* = 5.0 Hz, 1H, ArH), 8.35-8.41 (m, 3H, ArH), 8.52 (d, *J* = 8.1 Hz, 1H, ArH), 8.92 (d, *J* = 4.9 Hz, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 116.7, 118.1, 121.5, 124.1, 124.8, 126.0, 130.5, 131.1, 131.4, 133.6, 134.5, 138.9, 142.5, 145.3, 159.3. MS (ESI+) m/z = 303.0. ESI-HRMS calculated for $C_{18}H_{10}N_2OS$ [M^++H]: 303.0592, found: 303.0595.

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References and notes

1. a) Yang, H.; Luo, Y.; Zhao, H.; Wu, J.; Chen, Y. *Nat. Prod. Res.* **2016**, *30*, 42–45. b) Lood, C. S.; Koskinen, A. M. P. *Chemistry of Heterocyclic Compounds* (New York, NY, United States) **2015**, 50, 1367–1387. c) Anouhe, J.-B. S.; Adima, A. A.; Niamke, F. B.; Stien, D.; Amian, B K.; Blandinieres, P-A.; Virieux, D.; Pirat, J.-L.; Kati-Coulibaly, S.; Amusant, N. *Phytochem. Lett.* **2015**, *12*, 158–163. d) Zhang, Y.; Wang, G.; Lv, H.; Luo, J.; Kong, L. *Nat. Prod. Res.* **2015**, *29*, 1207–1211. e) Jiao, W.-H.; Chen, G.-D.; Gao, H.; Li, J.; Gu, B.-B.; Xu, T.-T.; Yu, H.-B.; Shi, G.-H.; Yang, F.; Yao, X.-S.; Lin, H.-W. *J. Nat. Prod.* **2015**, *78*, 125–130. f) Wang, K.-B.; Yuan, C.-M.; Xue, C.-M.; Li, D.-H.; Jing, Y.-K. He, H.-P.; Hao, X.-J.; Di, Y.-T.; Li, Z.-L.; Hua, H.-M. *RSC Adv.* **2014**, *4*, 53725–53729. g) Wang, K.-B.; Di, Y.-T.; Bao, Y.; Yuan, C.-M.; Chen, G.; Li, D.-H.; Bai, J.; He, H.-P.; Hao, X.-J.; Pei, Y.-H.; Jing, Y.-K.; Li, Z.-L.; Hua, H.-M. *Org. Lett.* **2014**, *16*, 4028–4031.
2. a) Zhang, M.; Sun, D. *Anti-Cancer Agents Med. Chem.* **2015**, *15*, 537–547. b) Ohishi, K.; Toume, K.; Arai, M. A.; Koyano, T.; Kowithayakorn, T.; Mizoguchi, T.; Itoh, M.; Ishibashi, M. *J. Nat. Prod.* **2015**, *78*, 1139–1146. c) Dighe, S. U.; Khan, S.; Soni, I.; Jain, P.; Shukla, S.; Yadav, R.; Sen, P.; Meeran, S. M.; Batra, S. *J. Med. Chem.* **2015**, *58*, 3485−3499 and references cited therein. d) Sasaki, T.; Li, W.; Higai, K.; Koike, K. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1979–1981. e) Stroedke, B.; Gehring, A. P.; Bracher, F.

ACCEPTED MANUSCRIPT

Arch. der Pharm. **2015**, *348*, 125–131. f) Ashok, P.; Ganguly, S.; Murugesan, S. *Mini-Rev. Med. Chem*. **2013**, *13*, 1778–1791. g) Moloudizargari, M.; Mikaili, P.; Aghajanshakeri, S.; Asghari, M. H.; Shayegh, J. *Pharmacogn. Rev*. **2013**, *7*, 199–212. h) Bharate, S. B.; Manda, S.; Mupparapu, N.; Battini, N.; Vishwakarma, R. A. *Mini Rev. Med. Chem*. **2012**, *12*, 650–664.

3. a) Manda, S.; Sharma, S.; Wani, A.; Joshi, P.; Kumar, V.; Guru, S. K.; Bharate, S. S.; Bhushan, S.; Vishwakarma, R. A.; Kumar, A.; Bharate, S. B. *Eur. J. Med. Chem.* **2016**, *107*, 1-11. b) Jin, H.; Zhang, P.; Bijian, K.; Ren, S.; Wan, S.; Jamali, M. A. A.; Jiang, T. *Mar. Drugs* **2013**, *11*, 1427–1439. c) Won, T. H.; Jeon, J.-e.; Lee, S. H.; Rho, B. J.; Oh, K. B.; Shin, J. *Bioorg. Med. Chem*. **2012**, *20*, 4082–4087. d) Huang, H.; Yao, Y.; He, Z.; Yang, T.; Ma, J.; Tian, X.; Li, Y.; Huang, C.; Chen, X.; Li, W.; Zhang, S.; Zhang, C.; Ju, J. *J. Nat. Prod*. **2011**, *74*, 2122–2127. e) Yang, M. L.; Kuo, P. C.; Hwang, T. L.; Chiou, W. F.; Qian, K.; Lai, C. Y.; Lee, K. H.; Wu, T. S. *Bioorg. Med. Chem*. **2011**, *19*, 1674–1682. f) Inman, W. D.; Bray, W. M.; Gassner, N. C.; Lokey, R. S.; Tenney, K.; Shen, Y. Y.; TenDyke, K.; Suh, T.; Crews, P. *J. Nat. Prod*. **2010**, *73*, 255–257. g) Wang, W.; Nam, S. J.; Lee, B. C.; Kang, H. *J. Nat. Prod*. **2008**, *71*, 163–166. h) Sauleau, P.; Martin, M. T.; Dau, M. E. T. H.; Youssef, D. T. A.; Kondracki, M. L. B. *J. Nat. Prod*. **2006**, *69*, 1676–1679.
4. a) Liew, L. P. P.; Fleming, J. M.; Longeon, A.; Mouray, E.; Florent, I.; Bourguet-Kondracki, M. L.; Copp, B. R. *Tetrahedron*. **2014**, *70*, 4910-4920. b) Bharate, S. B.; Manda, S.; Joshi, P.; Singh, B.; Vishwakarma, R.A. *Med. Chem. Commun*. **2012**, *3*, 1098–1103. c) Yang, M. L.; Kuo, P. C.; Hwang, T.-L.; Chiou, W.-F.; Qian, K.; Lai, C.-Y.; Lee, K.-H.; Wu, T.-S. *Bioorg. Med. Chem*. **2011**, *19* 1674–1682. d) Kulkarni, A.; Abid, M.; Török, B.; Huang, X. *Tetrahedron Lett*. **2009**, *50*, 1791-1794. e) Yang, M. L.; Kuo, P. C.; Damu, A. G.; Chang, R.-J.; Chiou, W.-F.; Wu, T.-S. *Tetrahedron* **2006**, *62*, 10900–10906.
5. Zhu, Y.-P.; Liu, M.-C.; Cai, Q.; Jia, F.-C.; Wu, A.-X. *Chem. Eur. J*. **2013**, *19*, 10132–10137.
6. Battini, N.; Padala, A. K.; Mupparapu, N.; Vishwakarma, R. A.; Ahmed, Q. N. *RSC Adv*. **2014**, *4*, 26258–26263.
7. a) Kolle, S.; Batra, S. *Org. Biomol. Chem*. **2015**, *13*, 10376–10385. b) Kolle, S.; Batra, S. *RSC Adv*. **2016**, *6*, 50658–50665.
8. a) Raju, R.; Reddy, R. V.; Rao, V. M.; Naresh, V. V.; Rao, A. V. *Tetrahedron Lett*. **2016**, 57, 2838–2841. b) Tang, D.; Wang, J.; Wu, P.; Guo, X.; Li, J.-H.; Yang, S.; Chen, B.-H. *RSC Adv*. **2016**, *6*, 12514-12518. c) Satish, G.; Polu, A.; Ramar, T.; Ilangovan, A. *J. Org. Chem*. **2015**, *80*, 5167–5175. d) Vadagaonkar, K. S.; Kalmode, H. P.; Murugan, K.; Chaskar, A. C. *RSC Adv*. **2015**, *5*, 5580–5590. e) Kalmode, H. P.; Vadagaonkar, K. S.; Chaskar, A. C. *Synthesis*. **2015**, *47*, 429–438. f) Devari, S.; Kumar, A.; Deshidi, R.; Shah, B. A. *Chem. Commun*. **2015**, *51*, 5013–5016. g) Deshidi, R.; Kumar, M.; Devari, S.; Shah, B. A. *Chem. Commun*. **2014**, *50*, 9533–9535. h) Viswanadham, K. K. D. R.; Reddy, M. P.; Sathyanarayana, P.; Ravi, O.; Kant, R.; Bathula, S. R. *Chem. Commun*. **2014**, *50*, 13517–13520. i) Kalmode, H. P.; Vadagaonkar, K. S.; Chaskar, A.C. *RSC Adv*. **2014,** *4*, 60316–60326. j) Xue, W.-J.; Zhang, W.; Zheng, K.-L.; Dai, Y.; Guo, Y.-Q.; Li, H.-Z.; Gao, F.-F.; Wu, A.-X. *Asian J. Org. Chem*. **2013,** *2*, 638–641. k) Zhu, Y.-P.; Jia, F.-C.; Liu, M.-C.; Wu, A.-X. *Org. Lett*. **2012**, *14*, 4414–4417.
9. a) Rana, K.; Kaur, B.; Kumar, B.; Kumar, H.; Anand, R. D. *Ind. J. Chem*. **2001**, *40B*, 1170-1171; b) Parmar, A.; Kumar. H. *Synth. Commun*. **2007**, *31*, 2301-2308.
10. a) from alkyne- Devari, S.; Kumar, A.; Deshidi, R.; Shah, B. A. *Chem. Commun*. **2015**, *51*, 5013-5016; from acetophenone- b) Yin, G.; Wang, Z.; Chen, A.; Gao, M.; Wu, A.; Pan, Y. *J. Org. Chem*. **2008**, *73*, 3377-3383. c) Yin, G.; Zhou, B.; Meng, X.; Wu, A.; Pan, Y. *Org. Lett*. **2006**, *8*, 2245-2248.
11. Xiang, J. -C.; Cheng, Y.; Wang, M.; Wu, Y.-D.; Wu, A. -X. *Org. Lett*. **2016**, *18*, 4360-4363.
12. Zhang, Z.; Xie, C.; Tan, X.; Song, G.; Wen, L.; Gao, H.; Ma, C. *Org. Chem. Front*. **2015**, *2*, 942–946.
13. For recent review on applications of DMSO as reagent, see (a) Wu, X.-F.; Natte, K. *Adv. Synth. Catal*. **2016**, *358*, 336–352. (b) Jones-Mansah, E.; Karki, M.; Magolan, J. *Synthesis* **2016**, *48*, 1421–1436.
14. a) Sharma, P.; Rohilla, S.; Jain, N. *J. Org. Chem*. **2015**, *80*, 4116–4122. b) Dai, C.; Xu, Z.; Huang, F.; Yu, Z.; Gao, Y. F. *J. Org. Chem*. **2012**, *77*, 4414–4419. c) Chu, L.; Yue, X.; Qing, F. L. *Org. Lett*. **2010**, *12*, 1644–1647.
15. a) Brahmbhatt, K. G.; Ahmed, N.; Sabde, S.; Mitra, D.; Singh, I. P.; Bhutani, K. K. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 4416-4419. b) Takasu, K.; Shimogama, T.; Saiin, C.; Kim, H-S.; Wataya, Y.; Brun, R.; Ihara M. *Chem. Pharm. Bull*. **2005**, *53*, 653-661. c) Giudice, M. R. D.; Gatta, F.; Settimj, G. *J. Heterocyclic Chem*. **1990**, *27*, 967-973.

Supplementary Material- Copies of ^{1}H, ^{13}C-NMR, 2D-NMR (**11**) are provided.

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