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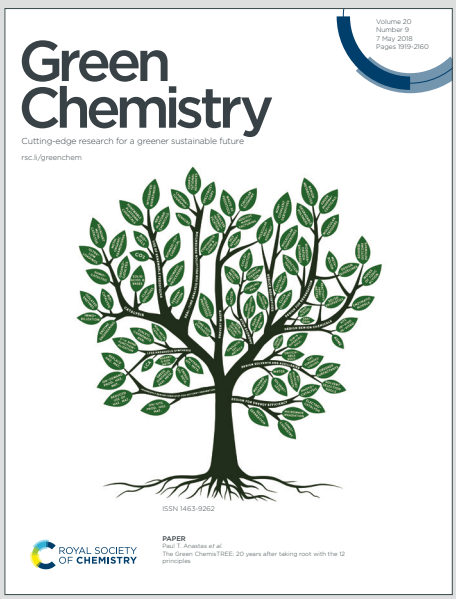

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ARTICLE

Reusable, Homogeneous Water Soluble Photoredox Catalyzed Oxidative Dehydrogenation of N-heterocycles in Biphasic System: Applications to Synthesis of Biologically Active Natural Products

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Herein, a simple and efficient method for the oxidative dehydrogenation (ODH) of tetrahydro-β-carbolines, indolines and (iso)quinolines is described using reusable, homogeneous cobalt-phthalocyanine photoredox catalyst in a biphasic medium. Biphasic system offers an advantage of easy separation of product and an efficient reusability of the homogeneous photoredox catalyst. Also, the current system significantly helps to overcome the solubility issue of substrate and catalyst at room temperature. The potential applications to organic transformations are demonstrated by the synthesis of various biologically active N-heterocycles such as indoles, (iso)quinolines and β-carbolines and natural products such as eudistomin U, norharmane, harmane and precursor to perlolyrine and flazin. Without isolation and purification, the catalyst solution can be reused up to 5 times with almost comparable reactivity. Further, efficiency of the reaction was demonstrated in gram scale. To the best of our knowledge, this is the first report on ODH reactions using a non noble, reusable and homogeneous cobalt photoredox catalyst under environmetally friendly conditions.

Introduction

Catalytic oxidative dehydrogenation of N-heterocycles is one of the important reactions in manufacturing of intermediates for the biologically active molecules.[1] Molecules containing N-heterocycles such as β-carbolines, (iso)quinolines and indoles form an important class of molecules that are present in several natural products, synthetic drugs, building blocks, etc. Given their significance, the development of efficient and environmentally benign methodologies for the synthesis of aromatic N-heterocycles is increasingly becoming indispensable for synthetic chemists. Importantly, the key step for the synthesis of these molecules is aromatization from their corresponding partially saturated N-heterocycles. Yet, oxidative dehydrogenation of nitrogen heterocycles is carried out by the well-known oxidant mediated reactions[2-10], but these methods either require expensive reagents, generation of stoichiometric waste, poor yields or lack of general application. Another way to access heteroaromatic moieties is from their heterocyclic precursors using bio-inspired aerobic dehydrogenation. In this respect, quinine based catalysts are reported to access the ODH of amines.[11] Notably, transition metal catalyzed dehydrogenation is found to be attractive among the industrial community for the manufacturing of essential synthetic intermediates.[12–16] However, these reactions utilize the heterogeneous catalysts which are precious, expensive, require high temperature and less tolerance of various functional groups. Non-noble transition metal catalysts have also been explored for the oxidative dehydrogenation of heterocycles using air as oxidant[17]. Nevertheless, shortcomings are apparent, including high temperature and the use of additives. Furthermore, we have recently reported a metal free dehydrogenation of tetrahydro-β-carbolines into β-carbolines in N-methyl pyrrolidone using oxygen as oxidant.[18] But, reaction requires high temperature and scope of the methodology was restricted to β-carbolines and related substrates.

To overcome these drawbacks, visible light based reactions are increasingly becoming significant in recent times due to their cheap and environmentally benign reaction conditions.[19-20] Though catalytic dehydrogenation of diverse N-heterocycles was reported using a visible-light photoredox catalyst,[21] but they involve the use of noble metals, environment polluting organic solvents, additives and tedious work up. It is important to note that use of water alone as a solvent may attract the water soluble substrates as good starting materials. Against this background, we herein demonstrate a simple and convenient route for the synthesis of various N-heterocycles *via* visible light driven reusable homogeneous water soluble cobalt catalyzed oxidative dehydrogenation in biphasic medium. Furthermore, we have extended the scope of this methodology for the synthesis of biologically active natural

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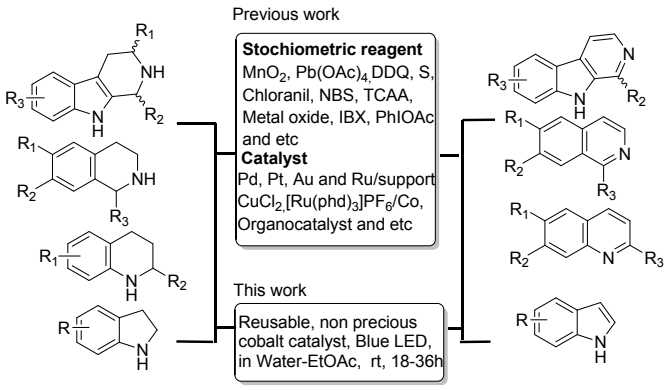
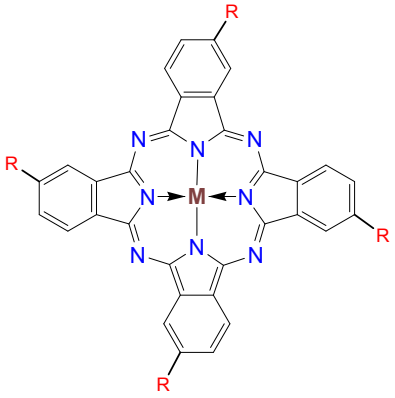
products such as eudistomin U, norharmane, harmane and precursor to perlolyrine and flazin.



Scheme 1 Oxidative dehydrogenation of partially saturated N-heterocycles to N-heterocycles

Results and discussion

Initially, we investigated the catalytic ODH of tetrahydro-β-carboline **1a** as the model substrate (Table 1). The reaction of **1a** was carried out using commercially available non-precious cobalt phthalocyanine, (CoPc, **3a**, Figure 1) photoredox catalyst (1mol %) in acetonitrile (ACN) in presence of visible light under ambient air as oxidant at room temperature for 12h. Gratifyingly, product **2a** was obtained in 89 % isolated yield in our first attempt. Notably, phthalocyanine based metal complexes are known[22] to show very good visible light-absorbing properties (See SI, Figure 3). Further, our attempt to carry out the reaction in water did not yield the desired result due to insoluble nature of **3a**. This result prompted us to look for water soluble catalyst. Interestingly, there are reports on metal phthalocyanines bearing different functional groups which are proved to be water soluble, particularly sodium salt of cobalt phthalocyanine tetrasulfonic acid $[CoPc(SO_3Na)_4]$.[23] As a significance, $[CoPc(SO_3Na)_4]$ (**3b**) was synthesized in two steps. In first step, $CoPc(SO_3H)_4$ (**3b'**) was prepared from the procedure reported in the literature,[23a] and in the second step, treatment of **3b'** with NaOH (50% w/w) led to the formation of catalyst **3b** (See SI). Reaction of **1a** with **3b** (1 mol%) was carried out in the presence of visible-light irradiation in water under an ambient air atmosphere, but we noticed that the reaction led to the moderate conversion with 65% isolated yield (Table 1, entry 2). The lower yield may be due to the partial solubility of starting material in aqueous medium. To overcome the solubility issue, the reaction was employed in a binary solvent system, such as a mixture of water and ACN in a 2:1 ratio. To our delight, the reaction gave rise to **2a** in 90 % isolated yield (Table 1, entry 3). Notably, an excellent isolated yield (92%) was achieved under the same reaction conditions (Table 1, entry 4) when switching the solvent mixture from water/ ACN to water/ethanol in the same ratio (2:1). In line with our effort to go green, the use of ethanol is found to be an environmentally preferable solvent. But, separation of product from the reaction mixture was found to be tedious due to the presence of ethanol. To mitigate this



R = H; M = Co (**3a**)
R = -SO_3Na; M = Co (**3b**)
R = -SO_3Na; M = Fe (**3c**)
R = -SO_3Na; M = Ni (**3d**)
R = -SO_3Na; M = Cu (**3e**)

Fig. 1 Different catalysts employed for optimization studies on dehydrogenation of N-heterocycles

drawback, we envisioned to employ the biphasic solvent system. Initially, reaction was carried out in water/toluene (1:1) system while keeping the other parameters constant. Reaction led to the desired product with lower yield (34%, Table 1, entry 5). Other biphasic systems such as water:EtOAc, water:$CHCl_3$ and water:DCM were also investigated (Table 1, entries 6-8). Gratifyingly, water:EtOAc system gave rise to a complete conversion with 92% isolated yield in 18 h. Simple separation of organic layer from aqueous layer led to the pure product while catalyst was retained in aqueous layer. DCM and $CHCl_3$ systems gave the products in moderate yields with 60 and 63 % respectively (Table 1, entries 7-8). The result obtained with water:EtOAc system has encouraged us to explore the other water-soluble non-precious phthalocyanine based metal catalysts such as $FePc(SO_3Na)_4$ (**3c**), $NiPc(SO_3Na)_4$ (**3d**) and $CuPc(SO_3Na)_4$ (**3e**) for the ODH reaction of **1a** under same reaction conditions. However, the catalysts investigated have resulted in low yields ranging from 21 % to 28 % (Table 1, entry 9-11). Hence, catalyst **3b** was chosen for further studies based on the results obtained. The reaction was carried out without catalyst in the presence of visible light (Table 1, entry 12), no reaction was observed. Moreover, the reaction did not proceed under dark conditions (Table 1, entry 13). The reaction was carried out under the strict exclusion of oxygen while maintaining the argon atmosphere (Table 1, entry 14) but no progress was seen. These results prove that visible light, oxygen, and photoredox catalyst are essential to accomplish the reaction. A biphasic solvent system of water and ethyl acetate was found to be the suitable solvent system for the current ODH. Under the standard reaction conditions, a low catalyst loading from 0.1 mol% and 0.5 mol% of **3b** gave **2a** in 55% and 72 % respectively (Table 1, entries 15 and 16). To the best of our knowledge, this is the first report on a visible light catalytic ODH of partially saturated N-heterocycles using single, non-precious photoredox cobalt catalyst in biphasic medium.

Table 1 Optimization of the reaction conditions[a]

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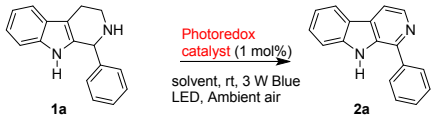
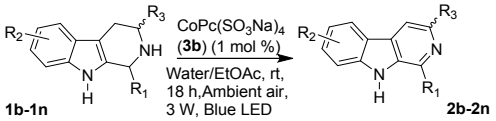


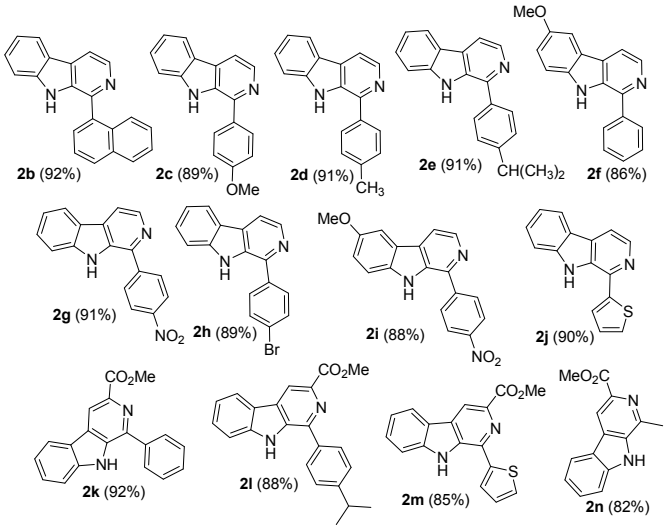
S. No	Catalyst	Solvent	Yield (%)[b] 2a
1	(1 mol% **3a**)	ACN	89
2	(1 mol% **3b**)	H_2O	65
3	(1 mol% **3b**)	H_2O/ ACN	90
4	(1 mol% **3b**)	H_2O/EtOH	92
5	(1 mol% **3b**)	H_2O/Toluene	34
6	(1 mol% **3b**)	H_2O/EtOAc	92
7	(1 mol% **3b**)	H_2O/$CHCl_3$	63
8	(1 mol% **3b**)	H_2O/DCM	60
9	(1 mol% **3c**)	H_2O/ EtOAc	28
10	(1mol% **3d**)	H_2O/ EtOAc	21
11	(1mol% **3e**)	H_2O/ EtOAc	23
12	No catalyst	H_2O/ EtOAc	NR
13	Under dark	H_2O/ EtOAc	NR
14	Without air	H_2O/ EtOAc	NR
15	(0.1mol%)(**3b**)	H_2O/ EtOAc	55
16	(0.5mol%)(**3b**)	H_2O/ EtOAc	72

[a]Reaction conditions: 0.5 mmol of **1a**, under air atmosphere under blue LED irradiation at room temperature for 12-18 h, H_2O/ EtOAc (1:1; 3 ml); [b]Isolated yield. NR = No reaction

With the establishment of optimal reaction conditions, we investigated the general applicability of the methodology. The present water soluble cobalt-photoredox catalyst **3b** was then employed in the ODH of diverse tetrahydro-β-carbolines. As shown in Table 2, the current ODH process is compatible with various substituted tetrahydro-β-carbolines containing electron-rich or electron-deficient groups, giving rise to the anticipated ODH products with good to excellent yields. The presence of an electron-donating group at the C1 position of the tetrahydro-β-carbolines showed a more or less similar reactivity compared to that of substrates with electron-deficient groups. Thus, tetrahydro-β-carbolines with an electron-donating naphthyl (**1b**), 4-methoxyphenyl (**1c**), 4-methylphenyl (**1d**), 4-isopropyl phenyl (**1e**) groups at C1 position underwent efficiently to afford the corresponding ODH products and the yields ranged from 89 to 92%. Even substrate (**1f**) bearing electron-donating methoxy group at 5th position gave rise to 86 % yield. Under optimal conditions, electron-deficient groups such as 4-NO_2 phenyl (**1g**) and 4-Br phenyl (**1h**) groups at C1 position reacted well to afford the ODH products in 91 % and 89 % yields, respectively. Substrate (**1i**) bearing electron-withdrawing 4-NO_2 phenyl at C1 position and electron-donating methoxy group at 5th position was also found to give the product **2i** in 88 % isolated yield. The presence of thiophene (**1j**) at C1 position was also found to be suitable for the ODH under optimized catalytic conditions to obtain the product **2j** in 90 % isolated yield. Furthermore, we extended the scope of the reaction to tetrahydro-β-carboline methyl esters (**1k** - **1n**) and the reaction underwent smoothly to afford the corresponding ODH products **2k** - **2n**. Substituents were found to show a marginal influence on the activity of this catalytic system. Substrate **1k** bearing phenyl substitution at C1 position gave 92% isolated yield while 88 % yield was obtained for substrate **1l** bearing electron-donating isopropyl group. Besides, heteroaryl (**1m**) and alkyl (**1n**) groups present at C1 position on tetrahydro-β-carboline methyl esters led to the desired products **2m** and **2n** with 85% and 82% yields respectively under optimized conditions.

Table 2 Cobalt photoredox catalyzed oxidative dehydrogenaration of tetrahydro-β-carbolines (THβC's)[a]



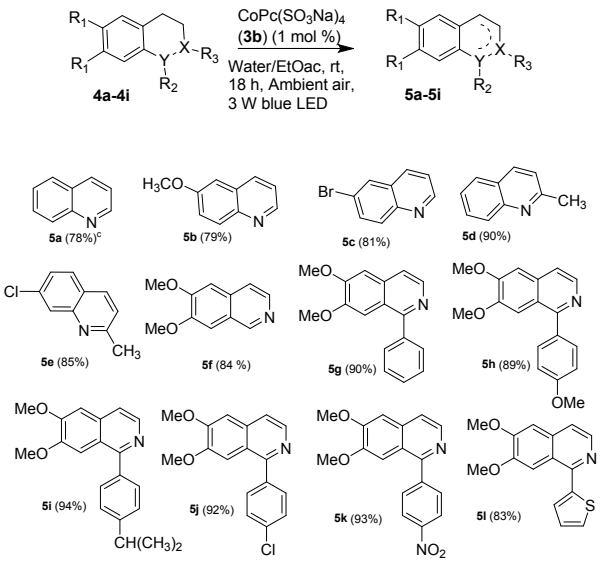


[a]Reaction conditions: Tetrahydro-β-carbolines (**1b**-**1n**) (0.5 mmol), $CoPc(SO_3Na)_4$ (**3b**) (1.0 mol%), H_2O:EtOAc (1:1; 3 mL), under air atmosphere, visible-light irradiation, room temperature, 18 h. [b]Isolated yields in parentheses.

Encouraged by the results obtained above, we attempted to apply this water soluble cobalt catalyzed ODH route to other important partially saturated N-heterocycles. Quinolines and isoquinolines are another essential class of N-heteroarenes with potential biological activities and their skeletons are present in various pharmaceuticals and natural products. Nevertheless, the preparation of quinolines and isoquinolines is well documented,[24] photo redox catalyzed oxidative dehydrogenation would offer a direct synthetic route to biologically active quinolines and isoquinolines under environmentally friendly reaction conditions. As shown in Table 3, the present catalytic system exhibited an excellent activity in the ODH of various tetrahydroquinolines (**4a**-**4e**) and tetrahydroisoquinolines (**4f**-**4l**) to the corresponding quinolines (**5a**-**5e**) and isoquinolines (**5f**-**5l**) respectively. The readily accessible substrate, tetrahydroquinoline (**4a**) was

employed under regular reaction conditions. The reaction proceeded well to afford the product **5a** in 51 % isolated yield after 24 h. But, our sustained effort towards the improvement of yield by increasing the catalyst loading from 1 mol % to 2 mol % helped significantly to obtain 78 % isolated yield. Further, the substrate (**4b**) bearing the 6-methoxy group gave rise to 79 % isolated yield while 81 % was obtained for substrate (**4c**) bearing 5-bromo group under **5a** conditions. On the contrary, tetrahydroquinoline (**4d**) bearing methyl substitution at the C2 position proceeded smoothly to afford the desired ODH product in 90% yield. Similarly, the substrate bearing the electron-withdrawing functional group was also active. Thus, 7-chloroquinoline (**5e**) was obtained in 85% yield. Since our present single, homogeneous water-soluble cobalt photoredox catalyst **3b** displayed a good activity for the synthesis of different substituted quinolines, it was further extended to study the synthesis of isoquinolines under the optimized conditions. As shown in Table 3, a variety of unsubstituted and substituted 6, 7-dimethoxy-isoquinolines (**4f**-**4l**) were subjected to the present photoredox catalyzed ODH under optimized conditions. Substrate (**4f**) with

Table 3 Cobalt photoredox catalyzed oxidative dehydrogenation of tetrahydroquinolines and tetrahydroisoquinolines[a]

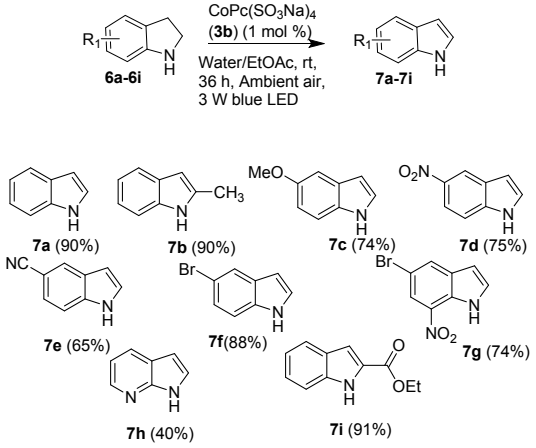


[a]Reaction conditions: Substrates (**4a**-**4l**) (0.5 mmol), $CoPc(SO_3Na)_4$ (1.0 mol%), H_2O:EtOAc (1:1; 3.0 mL), Under air atmosphere under visible-light irradiation at room temperature for 18 h. [b]Isolated yields in parentheses. [c]$CoPc(SO_3Na)_4$ (2 mol%)

no substitution at C1 position resulted in very good yield (84 %). Substrates with aryl and heteroaryl substituents at the C1 position had no significant effect on the activity of this catalytic system. Notably, phenyl (**4g**), 4-methoxyphenyl (**4h**), 4-isopropylphenyl (**4i**), 4-chlorophenyl (**4j**) and 4-nitrophenyl (**4k**) groups at C1 position were well tolerated and yielded the desired products in very good to excellent yields (89 to 94%). Presence of thiophene (**4l**) at C1 position led to the desired ODH product **5l** in 83% isolated yield. These results prove the efficiency of the catalyst for the ODH reaction of different substrates.

Furthermore, the current methodology was applied successfully for the synthesis of other important indole compounds under optimized reaction conditions. Particularly, indole skeletons are prevalent in several biologically active molecules.[25] Notably, there are several reports on the synthesis of indoles.[26] Beller group[26c] had demonstrated the ODH of indoline to the corresponding indole using nanostructured iron oxides surrounded by nitrogen-doped-graphene shells immobilized on carbon support. Another heterogeneous catalyst, Intermetallic Pd_3Pb supported on Al_2O_3[26d] was also employed to obtain the indole through the ODH of indoline. Similarly, organo photo redox catalystyzed[21e] ODH of various indolines to indoles were also achieved. Despite the methods mentioned above produced good to very good yields, but the present methodology offers an easy separation and an environmentally friendly approachfor the synthesis of indoles. As shown in Table 4, the ODH of indolines (**6a**-**6i**) proceeded smoothly to the corresponding indoles (**7a**-**7i**) in excellent yields (Table 4). The reaction of unsubstituted indoline (**6a**) gave rise to complete conversion in 36 h under optimized conditions. Isolated yield was found to be excellent with 90%. An increase in catalyst loading from 1 mol % to 2 mol % brought down the reaction time to 30h with 90 % isolated yield. Hence, the current methodology offered a complete conversion with excellent yield in a biphasic water and ethyl acetate medium. Overall, the reaction was tolerant of functional groups present on the indole ring and yields were found to be moderate to excellent (40 % to 91 %; Table 4). These results highlight the importance of the present cobalt photoredox catalytic system when compared to Pd/C catalysts for oxidative dehydrogenations since the latter can promote undesired reactions with aryl halides.[27]

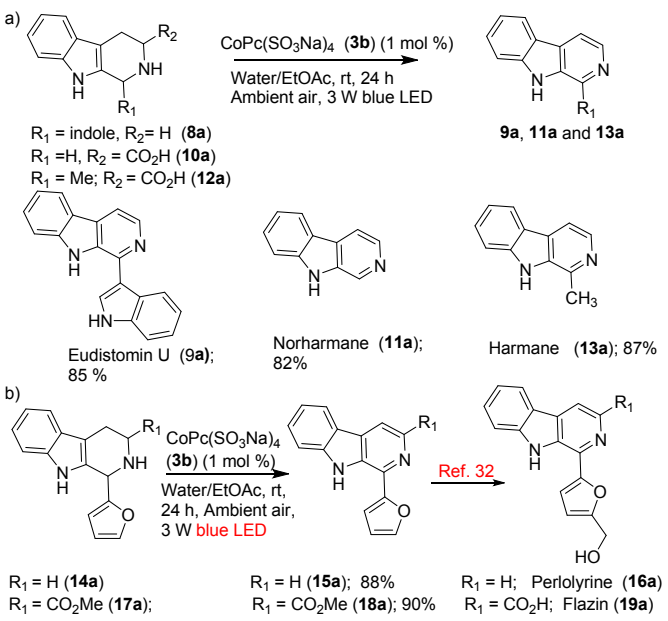
Table 4 Cobalt photoredox catalyzed oxidative dehydrogenation of indolines.[a]



[a]Reaction conditions: Substrates **6a**-**6i** (0.5 mmol), $CoPc(SO_3Na)_4$ (**3b**) (1.0 mol%), H_2O:EtOAc (1:1; 3.0 mL), air atmosphere under visible-light irradiation at room temperature for 36 h. [b]Isolated yields in parentheses.

Applications to total synthesis of natural products

β-carboline natural products bearing different functional groups such as eudistomin U, norharmane, harmane, perlolyrine and flazin show a wide range of biological activities[28]. Though there are reports on the synthesis of these natural products, the key step is found to be the aromatization.[29] To our delight, dehydrogenation of **8a** selectively yielded eudistomin U (**9a**) in 85% isolated yield under the optimized conditions (Scheme 2). Eudistomin U (**9a**) is obtained in just two stages without any protection and deprotection strategy using our current methodology. The work hitherto published by Panarese et al.[30] had demonstrated the synthesis of **9a** via aromatization using IBX. Nevertheless aromatization was found to be efficient, but the target natural product, **9a** requires multi-steps, harsh reaction conditions, and the overall yield is rather low. Another interesting biologically active natural product, norharmane (**11a**) with no substitution at the C1 position, was achieved *via* decarboxylative ODH by treating the compound (**10a**) containing the carboxylic group at C3 position under optimized conditions. The desired product **11a** was achieved in 82% isolated yield after 24 h. It is pertinent to mention that reaction was found to be slow when there is no substituent at C3 position on **10a**. Similarly, another biologically important natural product, harmane (**13a**) was obtained in excellent yields (87%) from starting material (**12a**) (Scheme 2).



* Water:EtOAc:ethanol (1:1:0.1) system was used for substrates **10a** and **12a**

Scheme 2 Synthesis of biologically active natural products

Furthermore, we attempted to synthesize the highly fluorescent β-carboline alkaloids containing furan moiety at C1 position such as perlolyrine (**16a**) and flazin (**19a**). Particularly, these two alkaloids are widely found in nature and are obtained from plants, bacteria, Japanese sake and soy sauce.[31] Though there are few reports from the literature on the total syntheses of **16a** and **19a**[32] but they have their disadvantages such as the requirement of expensive reagents, harsh reaction conditions, and poor yields. We herein report a highly practical synthesis using our ODH strategy. Compound **14a** underwent a smooth reaction to afford the precursor to **16a**[33] in 88 % yield under optimized reaction conditions. Similarly, compound **18a** precursor to **19a**[33] was also obtained from starting material **17a** in 90 % isolated yield. Importantly, photoredox catalyst remained in the aqueous phase has prompted us to test the reusability. Reaction of **17a** was carried out in 1.0 mmol under the optimized conditions. Reaction led to the product **18a** in 90 % yield. Once the reaction completed, organic layer was separated and the aqueous portion was extracted with ethyl acetate twice to ensure the complete recovery of soluble organic compounds. Futhermore, our effort on scaling up the reaction of **17a** in 5.0 mmol using the current catalytic system worked efficiently to afford the compound **18a** in 81 % yield. Reaction was carried out using 30 W blue LED and time of the reaction was 32h.

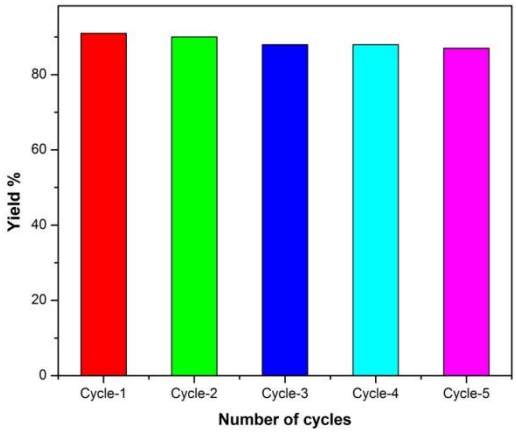


Fig. 2 Reusability of the catalyst under optimized conditions

This strategy was envisioned to accomplish the comprehensive circulation of aqueous phase containing photocatalyst. Thus, we carried out the recovery of the aqueous phase. It's worth mentioning that the aqueous phase with catalyst could be reused up to 5 times with almost comparable reactivity and only a slight decrease of yield (Fig. 2). Hence, homogeneous catalyst **3b** in aqueous phase is proved to be an efficient catalytic system for the dehydrogenation of nitrogen heterocycles.

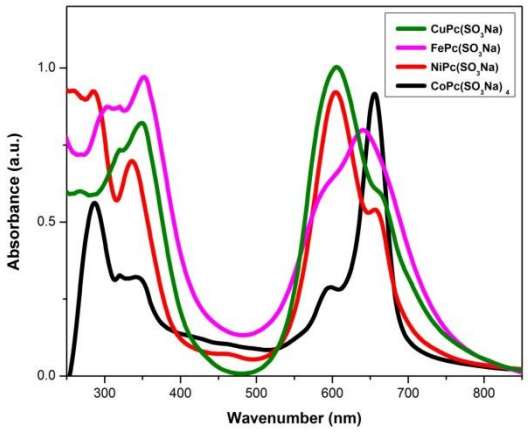


Fig. 3 Comparison of UV-Visible spectral absorbance of different water soluble $MPc(SO_3Na)_4$ [M = Co (**3b**), Fe(**3c**), Ni (**3d**) and Cu (**3e**)] photoredox catalysts measured in ethanol.

To understand the mechanism of the water-soluble $CoPc(SO_3Na)_4$ (**3b**) catalyzed ODH of partially saturated N-heterocycles, a few control experiments were carried out. The photoredox catalyst **3b** absorbs visible light to initiate the single electron transfer (SET) process and is responsible for the success of the reaction. (Fig. 3) The cyclic voltammetry experiment was carried out to ascertain the ground-state redox properties of $CoPc(SO_3Na)_4$. The obtained values were used to calculate the reduction potentials of redox couples as +1.09 V for $[CoPc(SO_3Na)_4]/[CoPc(SO_3Na)_4]^{\cdot+}$ and -1.01 V for $[CoPc(SO_3Na)_4]/[CoPc(SO_3Na)_4]^{\cdot-}$ vs SCE (see SI, Fig 5). Hence, the excited state reduction potential for $[CoPc(SO_3Na)_4]^*/[CoPc(SO_3Na)_4]^{\cdot-}$ was evaluated as +1.17 V using the Rehm–Weller formalism (see SI).[34] The oxidation potential of **1a** was found to be + 0.83 V vs. SCE (see SI, Fig 6). Electrochemical outcomes suggests that the tetrahydro-β-carboline (**1a**) could reduce excited state of $CoPc(SO_3Na)_4$ *via* single electron transfer (SET). Furthermore, luminescence quenching experiment was investigated and a gradual reduction in the emission maxima of $CoPc(SO_3Na)_4$ was observed when tetrahydro-β-carboline (**1a**) was used as the quencher (Fig. 4). Thus, a reductive quenching mechanism is operative.

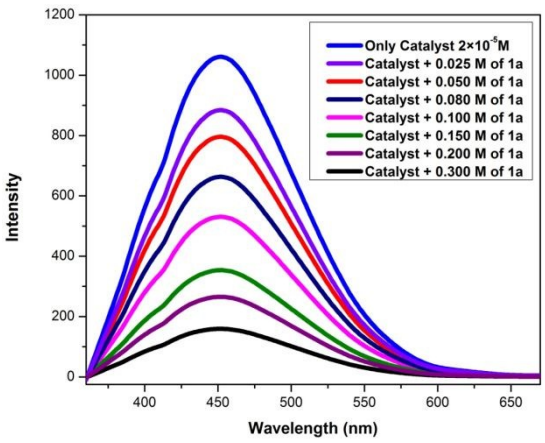
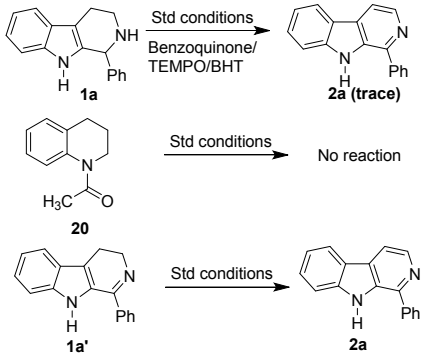


Figure 4. Fluorescence emission spectra of the $CoPc(SO_3Na)_4$ in presence of substrate **1a**.



Scheme 3 Study on control experiments

To check the formation of superoxide anion radical, the oxidation of tetrahydro-β-carboline (**1a**) in the presence of different radical suppressing agents such as benzoquinone/TEMPO/BHT was investigated under standard conditions. Particularly, the formation of β-carboline was not obtained in the presence of these radical scavengers.

It indicates that the reaction proceeded by radical species, e.g. the superoxide radical anion ($O_2^{\cdot-}$). Our findings are also in good agreement with the previously reported work on the suppression of the formation of $O_2^{\cdot-}$ by BHT.[26c] Furthermore, presence of $O_2^{\cdot-}$ species was confirmed by the reaction of nitro blue tetrazolium (NBT) which is a selective $O_2^{\cdot-}$ radical scavenger. At different time intervals, absorbance of NBT between 256 to 259 nm was measured using UV-Vis spectrometer under standard ODH reaction conditions (Fig. 5). A gradual decrease in the absorbance of NBT has clearly supported the visible light catalysed generation of $O_2^{\cdot-}$ radicals wherein reduction of NBT takes place by $O_2^{\cdot-}$ radicals. Subsequently, the abstraction of two H atoms by $O_2^{\cdot-}$ via oxidation of amine radical cation [**A**] to form a dihydro-β-carboline [**C**] and H_2O_2.[35] Furthermore, a titration reaction with

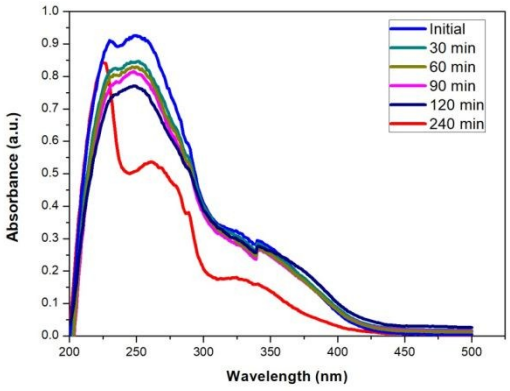
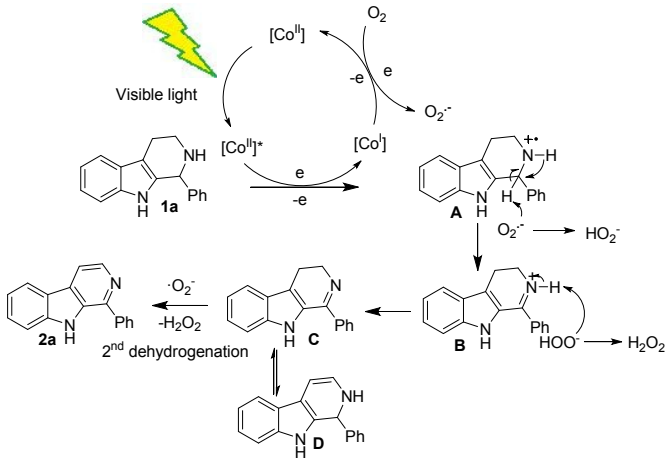


Figure 5. Determination of reduction of NBT by superoxide radical anion ($O_2^{\cdot-}$) using UV- Visible spectrophotometer.



Scheme 4 A plausible mechanism for dehydrogenation of THβC.

KI (See SI, Fig. 7) confirmed the presence of H_2O_2 in the reaction mixture.[36] Tautomerization of the dihydro-β-carboline intermediate **C** into **D** helps to achieve the target β-carboline product **2a** through a second dehydrogenation step. Remarkably, no dehydrogenation product was obtained when 1-(3,4-dihydroquinolin-1(2H)-yl)ethanone (**20**) used as a substrate. This result indicates that the presence of the N-H functional group in the cycloalkane is vital for the dehydrogenation. Also, it is difficult for the formation of a direct C=C bond. Interestingly, 1-phenyl-4,9-dihydro-3*H*-pyrido[3,4-b]indole (**1a'**) was investigated for the oxidative dehydrogenation and observed that **1a'** completely got dehydrogenated and resulted in **2a** in excellent yield (91 %). The above results confirm that the isomerization process between **C** and **D** is very fast and directly led to product **2a**. Therefore, we propose the plausible mechanism for the ODH reaction of **1a** (Scheme 4). Initially, irradiation of $Co^{II}Pc(SO_3Na)_4$ (**3b**) using visible light affords the excited state complex $*Co^{II}Pc(SO_3Na)_4$ (**3b**) species followed by formation of reduced complex $Co^{I}Pc(SO_3Na)_4$ (**3b**) by the single-electron transfer from substrate **1a** and then formation of superoxide anion radical ($O_2^{\cdot-}$) as shown in scheme 4.

Conclusions

In summary, a reusable and homogeneous water soluble catalytic system towards a visible light driven oxidative dehydrogenation of partially saturated N-heterocycles to N-heterocycles was established under environmentally friendly reaction conditions. Biphasic system significantly overcomes substrate solubility issue in the reaction medium. Also, biphasic system demonstrates for an efficient isolation of product, catalytic reusability and gram scale viability. The reaction was found to be suitable for the synthesis of a wide range of products such as β-carbolines, β-carboline esters, quinolines, isoquinolines, and indoles. Furthermore, the scope of the methodology was extended to the synthesis of some of the biologically important β-carboline natural products such as norharmane, harmane, eudistomin U and precursor to perlolyrine and flazin.

Experimental general methods

All chemicals used in the reactions (aromatic aldehydes, aliphatic aldehydes and hetero aldehydes were purchased from either Aldrich or Acros Organics and used without further purification. $CDCl_3$ and DMSO-d_6 for NMR sample preparation were purchased from Aldrich, India. Dry solvents such as ACN, EtOH, EtOAc, DCE, $CHCl_3$ and toluene used in synthesis with minimum purity of 99.9 % were purchased from Aldrich and Finar, India. All catalytic experiments were carried out using standard techniques. Thin-layer chromatography (TLC) was performed using 60 mesh silica gel plates visualized with short-wavelength UV light (254 nm). Silica gel 60 (230 - 400 mesh) was used for flash column chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 500 instrument (500 MHz for ^{1}H and 126 MHz for ^{13}C). Chemical shifts (δ) were measured in ppm relative to $CDCl_3$ and DMSO-d_6 δ = 77.0 and 39.51, respectively for ^{13}C as internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, *J*, are reported in hertz. UV-Visible spectra were recorded using Lab man - 1900S UV-Visible spectrophotometer. 3 W blue LED bulb (0.5 and 1 mmol scale reactions) and 30 W blue LED bulb (5 mmol scale reaction) were used for the present reaction.

Synthesis and characterization of substrates:

Synthesis of Tetrahydro-β-carboline (1a-1n), Tetrahydroisoqunolines (4f-4l) and phenyl-4,9-dihydro-3H-pyrido[3,4-b]indole (1a')

Synthesis of starting materials **1** (**a-n**) was achieved by following the procedure reported in the literature [37] and the synthesized compounds were in agreement with the reported data. Synthesis of starting materials **4** (**f-l**) was achieved by following the procedure reported in the literature [38] and the synthesized compounds were in agreement with the reported data. Starting materials **4**(**a-e**) and **6** (**a-i**) were purchased from Aldrich Co., TCI, Alfa Aesar and used as received. Compound **1a'** was prepared according to the general procedure.[39] Photoredox catalyst, CoPc (**3a**) was purchased from Sigma Aldrich, India.

Synthesis of water soluble sodium salt of cobalt phthalocyanine tetrasulfonic acid $CoPc(SO_3Na)_4$ (3b)

A mixture of monosodium salt of 4-sulfophthalic acid (4.32 g, 16.2 mmol), ammonium chloride (0.47 g, 9 mmol), ammonium molybdate (68 mg, 0.06 mmol), urea (5.8 g, 97 mmol), and $CoCl_2.6H_2O$ (1.15 g, 4.3 mmol) in nitrobenzene (15 mL) was heated at 180-190 °C under vigorous stirring for 8 h. The solid cake thus obtained was separated by filtration, washed with methanol, and dried. The purification of prepared $CoPc(SO_3H)_4$ (**3b'**) was performed according to the published method. The blue colored $CoPc(SO_3H)_4$ (**3b'**) was obtained in 74% yield (2.95 g). The above compound ($CoPc(SO_3H)_4$) was dissolved in a minimum amount of methanol and aqueous NaOH (50%, w/w) was added dropwise to the reaction mixture and allowed to boil gently for about 1hr. The resulting solution was allowed to cool under ice bath. The sodium salt of the compound was slowly precipitated out from the solution. The formed precipitate was filtered and dried under vacuum to obtain the cobalt catalyst **3b** in 85 % yield. IR ν_{max} cm^{-1}, 3489 (–NH), 3140 (C–H), 1631 (C=C), 1401 (C=N), 1194 (S=O), 1033 (C-N) (SI, Fig. 2,); UV λ_{max} nm: 655.53, 595.22, 342.75, 286.03. Elemental analysis for $C_{32}H_{12}CoN_8Na_4O_{12}S_4$: Calculated C, 39.23; H, 1.23; N, 11.44; Found C, 39.10; H, 1.21; N, 11.57. MALDI-TOF MS: Calculated 978.838; Found 979.318.

Same procedure was adapted to obtain the photoredox catalysts **3c**, **3d** and **3e**.

3c: IR ν_{max} cm^{-1}, 3480 (–NH), 3149 (C–H), 1622 (C=C), 1400 (C=N), 1195 (S=O), 1030 (C-N); UV λ_{max} nm: 639.69, 588.33, 350.17, 300.34.

3d: IR ν_{max} cm^{-1}, 3481 (–NH), 3152 (C–H), 1632(C=C), 1404 (C=N), 1194 (S=O), 1031 (C-N); UV λ_{max} nm: 655.53, 602.89, 335.86, 285.77.

3e: IR ν_{max} cm^{-1}, 3480 (–NH), 3148 (C–H), 1631(C=C), 1402 (C=N), 1196 (S=O), 1032 (C-N); UV λ_{max} nm: 663.45, 605.45, 347.61, 267.37.

The UV-Visible spectra of photoredox catalysts **3b**, **3c**, **3d** and **3e** were recorded in ethanol (Figure 3)

General procedure on oxidative dehydrogenation of partially saturated N-heterocycles:

In a clean 15 mL reaction tube with a magnetic stirring bar was added partially saturated N-heterocycles (0.5 mmol), Cobalt catalyst (1.0 mol %), and 3 mL of water/ethylacetate (1:1). The reaction mixture was purged with oxygen for five minutes. Then the reaction tube was placed on a magnetic stirrer with two 3 W white LED light kept about 5 cm away from it and irradiated at room temperature with constant stirring for 18-36 h. Temperature was maintained using cooling fan. After the reaction was complete, the reaction mixture was extracted with EtOAc (3 x 10 mL). Organic fractions were combined, washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography on silica gel using an eluent of EtOAc and hexanes to obtain the desired N–heterocycles.

1-Phenyl-9H-pyrido[3,4-b]indole (2a)[18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 92 % yield (112 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42 (d, *J* = 5.2 Hz, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 8.08 (d, *J* = 5.2 Hz, 1H), 7.98 (d, *J* = 7.7 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.25 (t, *J* = 7.3 Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 142.7, 141.6, 138.9, 138.8, 133.5, 129.6, 129.2, 129.0, 128.9, 128.6, 122.0, 121.3, 120.0, 114.3, 112.9 ppm.

1-(Naphthalen-1-yl)-9H-pyrido[3,4-b]indole (2b)[18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield : 92 % yield (135 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (d, *J* = 5.2 Hz, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 8.19 (d, *J* = 5.2 Hz, 1H), 8.08 (d, *J* = 7.4 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.71 (t, *J* = 7.2 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.59 – 7.45 (m, 3H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.1 Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 143.0, 141.2, 138.4, 135.6, 134.9, 134.0, 131.5, 129.2, 129.0, 128.8, 127.9, 126.8, 126.5, 126.1, 125.7, 122.2, 121.1, 120.0, 114.5, 112.6 ppm.

1-(4-Methoxyphenyl)-9H-pyrido[3,4-b]indole (2c)[18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield : 89 % yield (122 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (d, *J* = 5.2 Hz, 1H), 8.20 (s, 1H), 8.04 (d, *J* = 5.2 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 3.84(s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.0, 142.5, 141.3, 138.6, 133.0, 130.9, 130.0, 129.5, 128.7, 122.0, 121.1, 120.1, 114.6, 113.8, 112.7, 55.7 ppm.

1-(*p*-tolyl)-9H-pyrido[3,4-b]indole (2d)[18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 91 % yield (118 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.50 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.25 (d, *J* = 7.8 Hz, 1H), 8.09 (d, *J* = 5.1 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 2.43 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 142.7, 141.6, 138.7, 138.5, 136.0, 133.4, 129.8, 129.6, 128.7, 128.6, 122.1, 121.3, 119.9, 114.1, 112.9, 21.4 ppm.

1-(4-Isopropylphenyl)-9H-pyrido[3,4-b]indole (2e)[18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield : 91 % yield (130 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.40 (d, *J* = 5.2 Hz, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 8.06 (d, *J* = 5.2 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 3.09 – 2.79 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 6H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.4, 142.6, 141.3, 138.6, 136.0, 133.2, 129.6, 128.7, 128.7, 127.2, 122.0, 121.1, 120.1, 114.1, 112.8, 33.7, 24.2 ppm.

6-Methoxy-1-phenyl-9H-pyrido[3,4-b]indole (2f)[18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield : 86 % yield (118 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (d, *J* = 5.2 Hz, 1H), 8.08 (d, *J* = 5.2 Hz, 1H), 7.98 (d, *J* = 7.3 Hz, 2H), 7.77 (d, *J* = 2.3 Hz, 1H), 7.58 (dd, *J* = 15.9, 8.2 Hz, 3H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.19 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.85 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.9, 142.6, 138.4, 138.1, 136.2, 133.7, 129.5, 129.3, 129.1, 128.6, 121.4, 118.8, 114.4, 113.7, 103.6, 56.0 ppm.

1-(4-Nitrophenyl)-9H-pyrido[3,4-b]indole (2g)[18]:

The title compound was prepared according to the general procedure above to give the compound as a pale yellow solid. Yield: 91 % yield (132 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (d, *J* = 3.6 Hz, 1H), 8.41 (d, *J* = 7.8 Hz, 2H), 8.33 – 8.04 (m, 4H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.29 (t, *J* = 7.1 Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 147.5, 144.7, 141.5, 139.0, 133.6, 130.3, 129.9, 129.2, 124.3, 122.2, 120.9, 120.4, 115.6, 112.5 ppm.

1-(4-Bromophenyl)-9H-pyrido[3,4-b]indole (2h)[18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 89 % yield (143 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (d, *J* = 5.2 Hz, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 8.10 (d, *J* = 5.2 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (t, *J* = 7.1 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 141.4, 141.2, 138.8, 137.6, 133.2, 132.2, 130.8, 129.9, 128.9, 122.5, 122.1, 121.0, 120.2, 114.7, 112.7 ppm.

6-Methoxy-1-(4-nitrophenyl)-9H-pyrido[3,4-b]indole (2i)[18]:

The title compound was prepared according to the general procedure above to give the compound as a pale yellow solid. Yield: 88% yield (140mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.43 (dd, *J* = 17.2, 6.5 Hz, 1H), 8.22 (dd, *J* = 23.1, 6.5 Hz, 1H), 7.81 (s, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 3.67 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.2, 147.5, 144.7, 139.8,

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138.5, 136.3, 134.1, 130.2, 129.8, 124.3, 121.3, 119.2, 115.7, 113.7, 103.8, 56.0 ppm.

1-(Thiophen-2-yl)-9H-pyrido[3,4-b]indole (2j) [18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 90 % yield (113 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (d, *J* = 5.0 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 9.4 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 4.8 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.27 (t, *J* = 7.4 Hz, 1H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 143.7, 141.4, 138.5, 136.8, 131.1, 130.2, 129.0, 129.0, 128.4, 126.1, 122.0, 121.0, 120.5, 114.4, 112.9 ppm.

Methyl 1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate (2k) [18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 92 % yield (139 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.35 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.69 (d, J = 8.2 Hz, 1H), 7.61 (ddd, J = 8.3, 6.4, 4.1 Hz, 3H), 7.55 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 3.91 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.6, 142.6, 141.6, 137.7, 137.0, 134.8, 129.5, 129.33, 129.2, 128.9, 122.3, 121.4, 121.0, 117.0, 113.1, 52.6 ppm.

Methyl 1-(4-isopropylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate (2l) [18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 88 % yield (151 mg); ^{1}H NMR (500 MHz, DMSO) δ 8.81 (s, 1H), 8.32 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 3.90 (s, 3H), 3.11 – 2.82 (m, 1H), 1.23 (d, *J* = 6.7 Hz, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 150.6, 143.3, 142.3, 137.6, 136.0, 135.4, 129.8, 129.6, 127.8, 122.9, 122.0, 121.6, 117.5, 113.8, 53.2, 34.4, 24.8 ppm.

Methyl 1-(thiophen-2-yl)-9H-pyrido[3,4-b]indole-3-carboxylate (2m) [18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 85 % yield (131mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.42 (d, *J* = 7.9 Hz, 1H), 8.16 (d, *J* = 3.2 Hz, 1H), 7.83 (t, *J* = 7.0 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 2H), 3.99 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.2, 142.5, 141.7, 136.7, 136.7, 132.7, 130.1, 129.5, 129.3, 129.0, 127.0, 122.3, 121.3, 116.8, 113.32, 52.7 ppm.

Methyl 1-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (2n) [18]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 82 % yield (99 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.52 (m, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 2.78 (s, 3H), 13C NMR (126 MHz, DMSO-d_6) δ 167.2, 143.3, 141.5, 137.0, 136.7, 129.5, 127.7, 122.9, 122.1, 121.3, 116.9, 113.3, 53.0, 21.0 ppm.

Quinoline (5a)[21f]:

The title compound was prepared according to the general procedure above to give the compound as a pale yellow liquid. Yield: 78 % yield (50 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (d, *J* = 4.2 Hz, 1H), 8.10 (dd, *J* = 22.1, 8.4 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.39 – 7.29 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 148.2, 135.9, 129.40, 129.3, 128.2, 127.7, 126.4, 121.0.

6-Methoxyquinoline (5b)[21f]

The title compound was prepared according to the general procedure above to give the compound as a pale yellow liquid. Yield: 79 % yield (63 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 4.2, 1.5 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 9.2 Hz, 1H), 6.91 – 6.81 (m, 2H), 6.57 (d, *J* = 2.8 Hz, 1H), 3.44 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 147.9, 144.4, 134.8, 130.8, 129.3, 122.2, 121.3, 105.1, 55.5 ppm.

6-Bromoquinoline (5c)[21f]:

The title compound was prepared according to the general procedure above to give the compound as a pale yellow liquid. Yield: 82 % yield (85 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.11 – 8.00 (m, 1H), 7.96 (d, *J* = 6.3 Hz, 1H), 7.95 (s, 1H), 7.76 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, CDCl3) δ 150.71, 146.78, 135.10, 132.97, 131.18, 129.81, 129.34, 121.90, 120.48 ppm.

2-Methylquinoline (5d) [21f]:

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 90 % yield (64 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 1H), 2.75 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 147.8, 136.1, 129.4, 128.6, 127.5, 126.4, 125.6, 122.0, 25.3 ppm.

7-Chloro-2-methylquinoline (5e):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 85 % yield (75 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.45 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 2.75 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 148.2, 135.9, 135.2, 128.7, 127.7, 126.7, 124.9, 122.3, 25.4 ppm. HRMS (ESI) m/z calculated for $C_{10}H_9ClN$ $[M + H]^+$ 178.0424; found 178.0428.

6,7-dimethoxyisoquinoline (5f)

The title compound was prepared according to the general procedure above to give the compound as a liquid. Yield: 84 % yield (79 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.29 (d, *J* = 5.6 Hz, 1H), 7.41 (d, *J* = 5.6 Hz, 1H), 7.09 (s, 1H), 6.96 (s, 1H), 3.93 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 150.3, 149.9, 141.8, 132.5, 124.7, 119.3, 105.3, 104.5, 77.4, 77.1, 76.9, 56.1, 56.0 ppm. HRMS (ESI) m/z calculated for $C_{11}H_{12}NO_2$ $[M + H]^+$ 190.0868; found 190.0865.

6,7-Dimethoxy-1-phenylisoquinoline (5g):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 90 % yield (121 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.36 (d, *J* = 5.2 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.36 (d, *J* = 5.5 Hz, 2H), 7.24 (s, 1H), 6.97 (s, 1H), 3.89 (s, 3H), 3.72 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.1, 151.6, 148.9, 140.1, 138.9, 132.7, 128.5, 127.4, 127.4, 121.4, 117.7, 104.4, 103.9, 54.9, 54.7

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ppm. HRMS (ESI) m/z calculated for $C_{17}H_{16}NO_2$ [M + H]$^+$ 266.1181; found 266.1185.

6,7-Dimethoxy-1-(4-methoxyphenyl)isoquinoline (5h):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 89 % yield (131 mg); Yield : 84 % yield(64mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.38 (d, *J* = 5.6 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.34 (m, 2H), 7.40 (d, *J* = 5.5 Hz, 1H), 7.34 (s, 1H), 7.19 (s, 1H), 7.04 (s, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 3.97 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 158.0, 152.6, 149.9, 141.3, 133.8, 132.5, 130.9, 122.5, 118.4, 113.8, 105.7, 105.0, 56.1, 55.9, 55.4 ppm. HRMS (ESI) m/z calculated for $C_{18}H_{18}NO_3$ [M + H]$^+$ 296.1287; found 296.1285.

1-(4-Isopropylphenyl)-6,7-dimethoxyisoquinoline (5i):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 94 % yield (144 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.34 (d, *J* = 5.4 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.34 (m, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.98 (s, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 2.90 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 152.6, 149.9, 149.2, 141.3, 137.5, 133.8, 129.6, 126.5, 122.4, 118.5, 105.7, 105.0, 56.0, 55.9, 34.0, 24.0 ppm. HRMS (ESI) m/z calculated for $C_{20}H_{22}NO_2$ [M + H]$^+$ 308.1651; found 308.1654.

1-(4-Chlorophenyl)-6,7-dimethoxyisoquinoline (5j):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 92 % yield (138 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.30 (d, *J* = 5.5 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.33 (m, 3H), 7.12 (s, 1H), 6.92 (s, 1H), 3.85 (s, 3H), 3.70 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ: 156.7, 152.6, 150.1, 141.2, 138.5, 134.4, 133.7, 130.9, 128.6, 122.3, 118.9, 105.0, 104.9, 55.9, 55.8. HRMS (ESI) m/z calculated for $C_{17}H_{15}ClNO_2$ [M + H]$^+$ 300.0791; found 300.0794.

6,7-Dimethoxy-1-(4-nitrophenyl)isoquinoline (5k):

The title compound was prepared according to the general procedure above to give the compound as a pale yellow solid. Yield: 93 % yield (144 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.43 (d, *J* = 5.5 Hz, 1H), 8.32 (d, *J* = 8.7 Hz, 2H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 5.6 Hz, 1H), 7.14 (s, 1H), 7.09 (s, 1H), 3.99 (s, 3H), 3.80 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 153.0, 150.6, 147.8, 146.5, 141.5, 133.9, 130.6, 123.7, 122.3, 119.8, 105.2, 104.3, 56.2, 55.9 ppm. HRMS (ESI) m/z calculated for $C_{17}H_{15}N_2O_4$ [M + H]$^+$ 311.1032; found 311.1034.

6,7-Dimethoxy-1-(thiophen-2-yl)isoquinoline (5l):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 83 % yield (113 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 5.5 Hz, 1H), 7.72 (s, 1H), 7.52 (d, *J* = 2.6 Hz, 1H), 7.44 (d, *J* = 5.0 Hz, 1H), 7.36 (s, 1H), 7.12 (s, 1H), 7.01 (d, *J* = 3.5 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 151.1, 150.5, 143.4, 141.2, 134.0, 127.6, 127.5, 127.4, 122.0, 118.8, 105.1, 105.0, 56.0, 56.0 ppm. HRMS (ESI) m/z calculated for $C_{15}H_{14}NO_2S$ [M + H]+ 272.0745; found 272.0743.

Indole (7a) [21e]**:**

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield : 90 % yield (53 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (bs, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.28 (t, *J* = 8.6 Hz, 1H), 7.24 (s, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.74 – 6.37 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8, 127.9, 124.5, 122.1, 120.9, 119.9, 111.3, 102.5 ppm.

2-Methylindole (7b) [6]**:**

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 90 % yield (60 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 17.4 Hz, 2H), 6.27 (s, 1H), 2.46 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0, 135.1, 129.0, 120.9, 119.6, 110.2, 100.4, 13.7 ppm.

5-Methoxyindole (7c) [21e]**:**

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 74 % yield (54mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.18 (t, *J* = 2.8 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.50 (t, *J* = 3.0 Hz, 1H), 3.87 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 131.0, 128.3, 125.0, 112.3, 111.9, 102.4, 102.3, 55.9 ppm.

5-Nitroindole (7d) [21e]**:**

The title compound was prepared according to the general procedure above to give the compound as a yellow solid. Yield: 75% yield (61 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.62 (d, *J* = 2.1 Hz, 1H), 8.12 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.42 – 7.36 (m, 1H), 6.77 – 6.68 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.9, 138.8, 127.4, 127.2, 118.0, 117.7, 111.0, 105.1 ppm

5-Cyanoindole (7e):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 65 % yield (46 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.99 (d, *J* = 0.6 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.38 – 7.32 (m, 1H), 6.65 – 6.57 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 127.7, 126.6, 126.4, 124.8, 121.0, 112.1, 103.3, 102.6 ppm; HRMS (ESI) m/z calculated for $C_9H_7N_2$ [M + H]+ 143.0609; found 143.0611.

5- Bromoindole (7f) [21e]**:**

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 88 % yield (89 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.78 (s, 1H), 7.27 (s, 2H), 7.23 – 7.20 (m, 1H), 6.71 – 6.15 (m, 1H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.3, 129.5, 125.3, 124.74, 123.1, 112.9, 112.4, 102.2.

5-Bromo-7-nitro indole (7g):

The title compound was prepared according to the general procedure above to give the compound as a yellow solid. Yield : 74 % yield (89 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 8.11 – 7.89 (m, 1H), 7.70 – 7.27 (m, 1H), 6.81 – 6.49 (m, 1H).). ^{13}C NMR (126 MHz, $CDCl_3$) 133.2,

131.1, 128.1, 127.9, 121.6, 111.4, 103.6 ppm. HRMS (ESI) m/z calculated for $C_8H_6BrN_2O_2$ $[M + H]^+$ 240.9613; found: 240.9615.

7-Azaindole (7h):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 40 % yield (24 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.49 (s, 1H), 8.36 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.99 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.41 (d, *J* = 3.5 Hz, 1H), 7.11 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.52 (d, *J* = 3.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 142.3, 129.1, 125.4, 120.6, 115.7, 100.7 ppm. HRMS (ESI) m/z calculated for $C_7H_7N_2$ $[M+H]^+$ 119.0609; found: 119.0611.

Ethyl indole-2-carboxylate (7i) [21e]**:**

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield : 91 % yield (86 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.27 (s, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 136.9, 127.5, 125.4, 122.6, 120.8, 111.9, 108.7, 61.1, 14.4 ppm.

Eudistomin U (9a)

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 85 % yield (120 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.75 (s, 1H), 11.34 (s, 1H), 8.59 (d, *J* = 7.9 Hz, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 8.34 (d, *J* = 2.4 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 5.1 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.56 (dd, *J* = 21.7, 14.1 Hz, 2H), 7.24 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 141.3, 140.3, 137.6, 136.8, 132.4, 128.7, 128.2, 126.6, 126.4, 122.4, 122.4, 121.7, 121.4, 120.2, 119.8, 112.8, 112.8, 111.9, 111.9 ppm. HRMS (ESI) m/z calculated for $C_{19}H_{13}N_3$ $[M + H]^+$ 284.1188; found 284.1182.

9H-pyrido[3,4-b]indole (11a):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 82 % yield (69 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.31 (s, 1H), 8.20 (d, *J* = 7.2 Hz, 1H), 8.09 (s, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 6.6 Hz, 1H), 7.22 (d, *J* = 6.9 Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 140.9, 138.3, 136.2, 134.0, 128.8, 128.1, 122.2, 120.8, 119.9, 115.3, 112.3 ppm.

1-Methyl-9H-pyrido[3,4-b]indole (13a):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 87 % yield (79 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 – 8.03 (m, 1H), 7.94 (d, *J* = 5.3 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 2.74 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 142.3, 140.7, 137.5, 134.7, 128.6, 127.6, 122.2, 121.3, 119.9, 113.3, 112.4 ppm.

1-(Furan-2-yl)-9H-pyrido[3,4-b]indole (15a):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 88 % yield (103 mg); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (d, *J* = 5.1 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 8.03 (d, *J* = 5.1 Hz, 1H), 7.95 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.17 (m, 2H), 6.75 (s, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.2, 144.3, 141.4, 138.4, 133.3, 130.8, 130.0, 129.0, 122.0, 120.7, 120.3, 114.3, 112.9, 112.7, 109.4 ppm. HRMS (ESI) m/z calculated for $C_{15}H_{11}N_2O$ $[M+H]^+$ 235.0871; found 235.0875.

Methyl 1-(furan-2-yl)-9H-pyrido[3,4-b]indole-3-carboxylate (18a):

The title compound was prepared according to the general procedure above to give the compound as a white solid. Yield: 90% yield (131 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.24 (d, *J* = 7.9 Hz, 1H), 7.95 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.56 (t, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 4.1 Hz, 1H), 7.26 (t, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 5.2 Hz, 1H), 3.89 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO) δ 166.8, 153.0, 145.2, 142.2, 137.1, 133.7, 132.8, 130.3, 129.8, 122.6, 121.62, 121.6, 117.2, 113.8, 113.3, 111.0, 53.1 ppm. HRMS (ESI) m/z calculated for $C_{17}H_{13}N_2O_3$ $[M+H]^+$: 293.0926; found 293.0929.

1-(3,4-dihydroquinolin-1(2H)-yl)ethanone (20)

The starting material **20** was prepared in 1 mmol scale by following the procedure reported in the literature [40]. Yield: 80% yield (140 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 – 7.02 (m, 4H), 3.70 (d, *J* = 5.7 Hz, 2H), 2.64 (t, *J* = 6.0 Hz, 2H), 2.15 (s, 3H), 1.88 (m *J* = 6.5 Hz, 2H) ppm.^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 128.4, 126.1, 125.2, 124.6, 26.9, 24.1, 23.1 ppm.

Conflicts of interest

"There are no conflicts to declare".

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