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A FACILE ULTRASOUND ASSISTED FOR AN EFFICIENT SYNTHESIS OF IMIDAZO[1,2-*a*]PYRAZINE-FUSED *β*-CARBOLINES

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Abstract – An efficient tandem process for the synthesis of imidazo[1,2-*a*]-pyrazine-fused *β*-carbolines is described. The construction of these compounds was achieved by three component reaction of 1*H*-indole-3-carbaldehyde, 2-aminopyrazine and trimethylsilyl cyanide *via* Groebke-Blackburn-Bienaymé reaction, followed by cyclization through the Pictet-Spengler reaction of the resulting 3-aminoimidazo[1,2-*a*]pyrazine which allowed access to the title heterocycles under ultrasound irradiation.

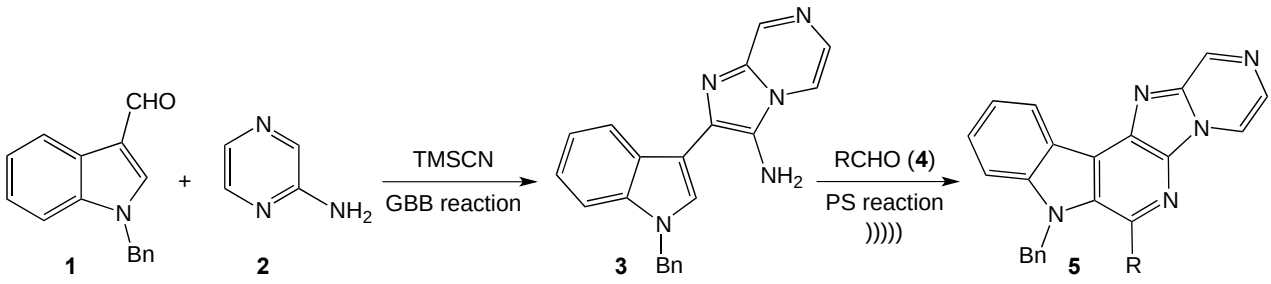
Pyridine-fused indoles, commonly known as carbolines, are one of the most important and abundant heterocycles. In particular, the privileged pyrido[3,4-*b*]indole (*β*-carboline) scaffold is a significant substructure prevalent in a variety of bioactive natural products and druglike molecules.[1] Molecules containing a *β*-carboline core unit exhibit numerous biological activities such as antitumor, antileishmanial, antihypertensive, anti-HIV, anti-inflammatory and many others.[2] Consequently, many protocols have been developed for the synthesis of *β*-carboline derivatives. Among them, approaches based on the Pictet-Spengler (PS) and Bischler-Napieralski (BN) reactions are the most widely used.[3]

3-Aminoimidazo[1,2-*a*]pyrazines are important building blocks for the pharmaceutical and agrochemical industries. These compounds are accessible through the three component Groebke-Blackburn-Bienaymé cyclization (GBB reaction) involving an aldehyde, an amine and an isonitrile.[4-6] Recently, it became attractive to the scientific community, especially to pharmaceutical research groups, because a broad variety of target compounds can be made by varying the three compounds, leading to combinatorial libraries.[7]

In recent years, the application of ultrasound as a powerful technique in synthetic organic chemistry became extremely efficient and attractive. Ultrasonic irradiation is widely used today in organic synthesis and has an intense impact on the way chemists approach organic and parallel synthesis, and a large

number of organic reactions have been done by using ultrasonic irradiation.[8]

In order to build such a multi-heterocyclic compound, our group recently focused on developing new heterocyclic system *via* the PS reaction,[9] we report herein, the synthesis of novel imidazo[1,2-*a*]-pyrazine-fused *β*-carbolines by the application of GBB and PS reaction under ultrasonic irradiation (Scheme 1).



Scheme 1. Syntheses of imidazo[1,2-*a*]pyrazine-fused *β*-carbolines

The synthetic route for the title compounds **5** was illustrated in Scheme 1. The key intermediate amine **3**, 2-(1-benzyl-1*H*-indol-3-yl)imidazo[1,2-*a*]pyrazin-3-amine, was prepared in good yields by the reaction of 1-benzyl-1*H*-indole-3-carbaldehyde (**1**), 2-aminopyrazine (**2**) and trimethylsilyl cyanide (TMSCN) in [bmim]Br without any catalyst *via* GBB reaction (Scheme 1). Elemental analysis and spectral data supported its structure. Its IR spectrum contains absorbance at 3416 and 3347 cm^{-1}, demonstrating the presence of the amino group. Its ^{1}H-NMR spectrum shows the presence of a D_2O exchangeable broad singlet at *δ* 5.85 (2H) which can be attributed to the NH_2 protons, and the singlet peak at δ 5.42 corresponding to *N*-benzyl (CH_2) of indole nucleus. The multiplet between 7.21-8.32 ppm (13H) corresponding to the aromatic protons of benzene, indole, and pyrazine nucleus.

In order to investigate the effects of ultrasonic irradiation and to evaluate and compare conventional heating with ultrasound assisted method, we selected benzaldehyde **4a** as model aromatic aldehyde to react with equimolar amounts of intermediate amine **3** for the preparation of imidazo[1,2-*a*]pyrazine-fused *β*-carboline **5a** using *p*-toluenesulfonic acid (*p*-TsOH) as catalyst in different solvents, such as EtOH, MeCN, HOAc, DMF, and ionic liquids ([bmim]Br), respectively. The results are summarized in Table 1.

As can be seen from Table 1, the best result was obtained when the reaction was carried out in [bmim]Br at 80 °C (Table 1, entry 6). Indeed, the reaction using [bmim]Br proceeded in higher yield and shorter reaction time than that using another solvents as reaction medium (Table 1, entries 1-4). The optimum amount of *p*-TsOH was observed to be 10 mol%. A lower amount of catalyst affected the yield of the product, while a higher concentration had no effect on the isolated yield (Table 1, entries 8, 9).

In addition, different acid catalysts such as sulfamic acid (SA), methanesulfonic acid (MSA), and trifluoroacetic acid (TFA) were screened for the optimal reaction conditions (Table 1, entries 10-12). As shown in Table 1, *p*-TsOH was the best catalyst for this reaction. In all reactions it was found that use of ultrasound irradiation lead to faster reaction and higher yields. So it shows use of ultrasound radiations improves the rate of reaction and also yields of products formed.

Table 1. Optimization of reaction conditions on the synthesis of **5a**[a]

Entry	Catalyst (mol%)	Solvent	Temp (°C)	With sonication[b]		Without sonication	
				Time (h)	Yield (%)[c]	Time (h)	Yield (%)[c]
1	*p*-TsOH (10)	EtOH	80	3	64	15	36
2	*p*-TsOH (10)	MeCN	80	3	68	14	42
3	*p*-TsOH (10)	HOAc	80	2	75	12	45
4	*p*-TsOH (10)	DMF	80	2	70	12	53
5	*p*-TsOH (10)	[bmim]Br	80	1	84	10	71
6	*p*-TsOH (10)	[bmim]Br	60	2	83	12	73
7	*p*-TsOH (10)	[bmim]Br	100	1	80	10	78
8	*p*-TsOH (5)	[bmim]Br	80	2	76	12	64
9	*p*-TsOH (15)	[bmim]Br	80	1	81	8	72
10	SA (10)	[bmim]Br	80	1.5	72	9	60
11	MSA (10)	[bmim]Br	80	2	63	12	65
12	TFA (10)	[bmim]Br	80	1	75	8	70

[a] Reaction conditions: **3** (1.0 mmol), benzaldehyde (**4a**, 1.0 mmol), solvent (5 mL). [b] Constant frequency: 300 W. [c] Isolated yields.

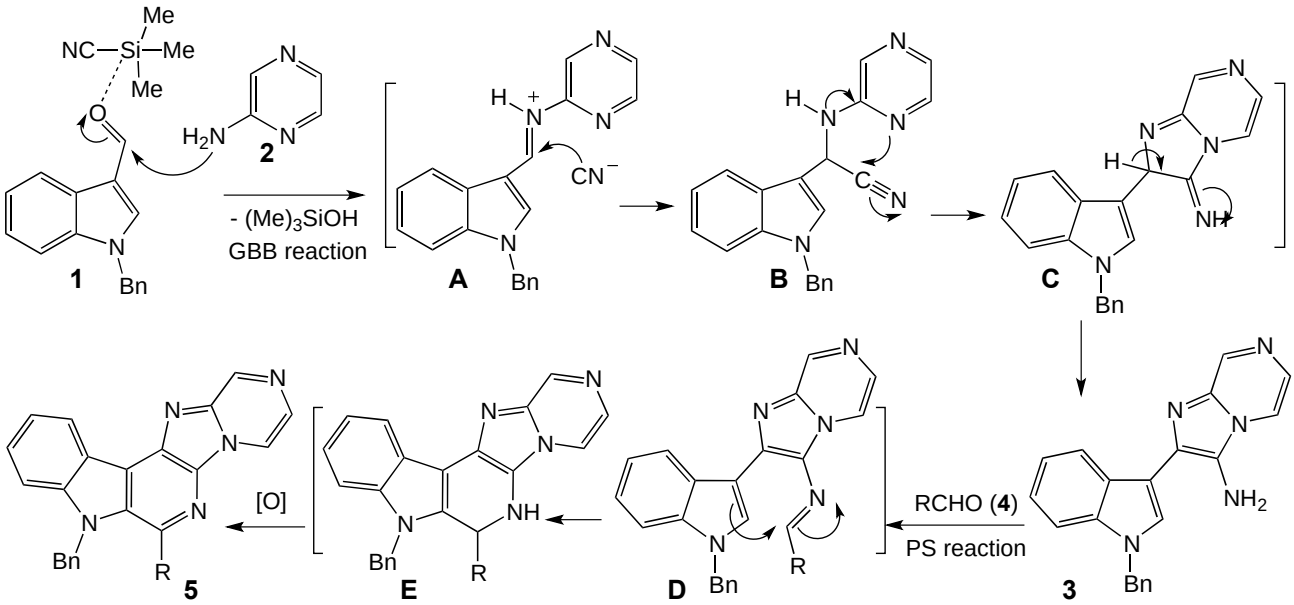
When optimizing the model reaction, pyrazino[2',1':2,3]imidazo[4,5-*c*]-*β*-carboline derivatives were synthesized *via* the Pictet-Spengler reaction. The results are summarized in Table 2. The reaction of intermediate amine (**3**) and a variety of arylaldehydes (**4**) was carried out under ultrasonic irradiation in [bmim]Br and *p*-TsOH as catalyst at 80 °C in good yields. It can be observed that the process tolerates both electron-donating and electron-withdrawing substituents in benzaldehydes.

All the products were characterized by ^{1}H- and ^{13}C-NMR, IR spectroscopy and elemental analyses.

Table 2. Synthesis of pyrazino[2',1':2,3]imidazo[4,5-*c*]-*β*-carbolines **5**

Entry	**4** / R		Time / h	Product	Yield / %
1	**4a**	C_6H_5	1	**5a**	84
2	**4b**	4-MeC_6H_4	1	**5b**	85
3	**4c**	2-$MeOC_6H_4$	1.5	**5c**	76
4	**4d**	3-$MeOC_6H_4$	1	**5d**	88
5	**4e**	4-$MeOC_6H_4$	1	**5e**	85
6	**4f**	4-HOC_6H_4	1	**5f**	82
7	**4g**	4-ClC_6H_4	1	**5g**	75
8	**4h**	4-$NO_2C_6H_4$	1.5	**5h**	74
9	**4i**	2-furyl	1	**5i**	79

The proposed mechanism of the process is summarized in Scheme 2. It is conceivable that the initial event is the formation of iminium ion **A** from 1-benzyl-1*H*-indole-3-carbaldehyde **1** and 2-aminopyrazine **2**. On the basis of the well established chemistry of the reactions of TMSCN with imines, intermediate **B** was obtained by nucleophilic attack of cyanide on **A**. The pyrazine nitrogen of **B** is in a favorable position for cyclization to produce intermediate **3**. Next, the amine **3** underwent a cationic *π*-cyclization with aldehyde (**4**) under Pictet-Spengler cyclization to form **D**, which effects aromatization of the resulting pentacyclic intermediate E, *via* air-oxidation, yielded the final products **5**.



Scheme 2. Proposed reaction mechanism for the formation of compound **5**

In summary, we have demonstrated for the efficient method for the synthesis of imidazo[1,2-*a*]-pyrazine-fused *β*-carbolines, by applying a Groebke-Blackburn-Bienaymé and Pictet-Spengler reactions under ultrasound irradiation. This approach offers an effective route for the construction of new fused *β*-carboline frameworks in a two-step process from commercially available starting materials. The products were obtained in good yields and short reaction times.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. Elemental analysis were performed by a HP-MOD 1106 microanalyzer. Ultrasound assisted reactions were carried out using a KQ-250E medical ultrasound cleaner with a frequency of 40 kHz and an output power of 300 W.

Preparation of 2-(1-benzyl-1*H*-indol-3-yl)imidazo[1,2-*a*]pyrazin-3-amine (3): To a solution of 1-benzyl-1*H*-indole-3-carbaldehyde **1** (2.35 g, 10.0 mmol), 2-aminopyrazine **2** (0.95 g, 10.0 mmol) in [bmim]Br (15 g) was added TMSCN (1.18 g, 12.0 mmol). The mixture was heated at 80 °C for 8 h. After completion of the reaction, as indicated by TLC, to the mixture was added water (50 mL) and stirred for 30 min. The solid was filtered and recrystallized from HOAc to give **3**. Yield: 80%, Yellow crystals. mp 230-232 °C; IR (KBr): *ν* 3415, 3357 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): *δ* 5.42 (s, 2H), 5.85 (s, 2H), 7.21-7.32 (m, 7H), 7.48 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.73 (s, 1H), 7.72 (d, *J* = 4.2 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 8.32 (d, *J* = 4.2 Hz, 1H). Anal. Calcd for $C_{21}H_{17}N_5$: C 74.32, H 5.05, N 20.63. Found: C 74.41, H 5.08, N 20.69.

Typical Procedure for the Preparation of 7-Arylpyrazino[2",1":2',3']imidazo[4',5':2,3]pyrido-[4,5-*b*]indoles. A mixture of 2-(1-benzyl-1*H*-indol-3-yl)imidazo[1,2-*a*]pyrazin-3-amine (**3**) (338 mg, 1.0 mmol), aldehyde (1.0 mmol), and *p*-TsOH (10 mg, 0.1 mmol) in [bmim]Br (5 g) was sonicated at 80 °C. After completion of the reaction as indicated by TLC, the reaction mixture was filtered and the precipitate washed with water. The crude product was purified by recrystallization from HOAc to afford the pure products **5a-i**.

8-Benzyl-7-phenylpyrazino[2",1":2',3']imidazo[4',5':2,3]pyrido[4,5-*b*]indole (5a): Yellow crystals. mp >300 °C; IR (KBr): *ν* 3035, 2983, 2931, 1643, 1626 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): *δ* 5.46 (s, 2H), 7.31-7.33 (m, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.45-7.49 (m, 6H), 7.79 (d, *J* = 4.4 Hz, 1H), 7.94-7.97 (m, 2H), 8.12 (d, *J* = 4.4 Hz, 1H), 8.28 (s, 1H), 8.84 (d, *J* = 4.4 Hz, 1H), 9.16-9.18 (m, 1H), 9.24-9.27 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): *δ* 48.8, 107.2, 111.3, 117.7, 119.5, 121.5, 123.5, 126.6, 127.4, 128.2, 128.7, 129.0, 129.9, 130.1, 130.2, 134.6, 135.7, 136.9, 138.0, 138.5, 142.6, 142.8, 158.7, 158.9. Anal. Calcd for $C_{28}H_{19}N_5$: C 79.04, H 4.50, N 16.46. Found: C 79.16, H 4.54, N 16.50.

8-Benzyl-7-(4-methylphenyl)pyrazino[2",1":2',3']imidazo[4',5':2,3]pyrido[4,5-*b*]indole (5b): Yellow crystals. mp >300 °C; IR (KBr): *v* 3063, 2985, 2930, 1656, 1627 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.54 (s, 3H), 5.67 (s, 2H), 7.27-7.29 (m, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.46-7.50 (m, 5H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 4.4 Hz, 1H), 8.25 (s, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 8.82 (d, *J* = 4.4 Hz, 1H), 9.14-9.16 (m, 1H), 9.20-9.21 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 49.6, 56.5, 108.5, 111.0, 117.3, 120.5, 121.9, 122.5, 126.6 127.8, 128.0, 128.9, 129.1, 129.9, 130.0, 130.2, 134.2, 135.3, 136.6, 138.1, 138.2, 142.2, 142.6, 158.4, 158.5. Anal. Calcd for $C_{29}H_{21}N_5$: C 79.25, H 4.82, N 15.93. Found: C 79.32, H 4.86, N 15.98.

8-Benzyl-7-(2-methoxyphenyl)pyrazino[2",1":2',3']imidazo[4',5':2,3]pyrido[4,5-*b*]indole (5c): Yellow crystals. mp >300 °C; IR (KBr): *v* 3046, 2987, 2943, 1648, 1621 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.98 (s, 3H), 5.41 (s, 2H), 7.19-7.22 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.47-7.51 (m, 6H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.92-7.96 (m, 2H), 8.15 (d, *J* = 4.4 Hz, 1H), 8.22 (s, 1H), 8.74 (d, *J* = 4.4 Hz, 1H), 9.01-9.02 (m, 1H), 9.20-9.23 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 48.2, 57.4, 109.2, 111.6, 117.3, 119.2, 121.1, 123.3, 126.0, 127.1, 128.1, 128.5, 129.1, 129.7, 130.0, 130.2, 134.0, 135.2, 136.6, 138.1, 138.3, 142.0, 142.8, 158.0, 158.4. Anal. Calcd for $C_{29}H_{21}N_5O$: C 76.47, H 4.65, N 15.37. Found: C 76.56, H 4.71, N 15.43.

8-Benzyl-7-(3-methoxyphenyl)pyrazino[2",1":2',3']imidazo[4',5':2,3]pyrido[4,5-*b*]indole (5d): Yellow crystals. mp >300 °C; IR (KBr): *v* 3053, 2982, 2946, 1642, 1637 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.94 (s, 3H), 5.43 (s, 2H), 7.31-7.37 (m, 3H), 7.42-7.47 (m, 5H), 7.82 (d, *J* = 8.4 Hz, 1H), 8.01-8.05 (m, 2H), 8.14 (d, *J* = 4.4 Hz, 1H), 8.35 (s, 1H), 8.76 (d, *J* = 4.4 Hz, 1H), 9.02-9.04 (m, 1H), 9.16-9.17 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 48.4, 55.4, 107.8, 111.3, 117.2, 119.6, 121.5, 123.3, 126.8, 127.8, 128.3, 128.9, 129.1, 129.9, 130.0, 130.2, 134.5, 135.8, 136.7, 138.1, 138.6, 142.8, 142.9, 157.6, 158.7. Anal. Calcd for $C_{29}H_{21}N_5O$: C 76.47, H 4.65, N 15.37. Found: C 76.55, H 4.72, N 15.44.

8-Benzyl-7-(4-methoxyphenyl)pyrazino[2",1":2',3']imidazo[4',5':2,3]pyrido[4,5-*b*]indole (5e): Yellow crystals. mp >300 °C; IR (KBr): *v* 3054, 2989, 2935, 1640, 1636 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H), 5.51 (s, 2H), 7.06-7.14 (m, 3H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.31-7.34 (m, 3H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 4.2 Hz, 1H), 8.08 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.63-8.64 (m, 1H), 8.95-8.97 (m, 1H), 9.04-9.05 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 49.6, 55.9, 108.6, 110.9, 114.8, 117.2, 120.5, 121.9, 122.5, 126.6, 127.8, 128.0, 128.4, 129.1, 129.5, 129.8, 130.1, 130.8, 134.7, 136.5, 137.9, 138.2, 142.5, 158.5, 162.6. Anal. Calcd for $C_{29}H_{21}N_5O$: C 76.47, H 4.65, N 15.37. Found: C 76.53, H 4.69, N 15.40.

8-Benzyl-7-(4-hydroxyphenyl)pyrazino[2",1":2',3']imidazo[4',5':2,3]pyrido[4,5-*b*]indole (5f): Yellow crystals. mp >300 °C; IR (KBr): *v* 3033, 2972, 1654, 1615 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6):

δ 5.40 (s, 2H), 7.29-7.32 (m, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.47-7.50 (m, 6H), 7.89 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 4.4 Hz, 1H), 8.28 (s, 1H), 8.84 (d, J = 4.4 Hz, 1H), 9.03-9.07 (m, 1H), 9.14-9.16 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 49.6, 107.0, 111.5, 117.9, 119.5, 121.7, 123.7, 126.6, 127.5, 1280, 128.6, 129.2, 129.9, 130.5, 130.8, 134.3, 135.9, 136.7, 138.0, 138.5, 142.2, 142.8, 158.7, 158.6. Anal. Calcd for $C_{28}H_{19}N_5O$: C 76.17, H 4.34, N 15.86. Found: C 76.23, H 4.38, N 15.90.

8-Benzyl-7-(4-Chlorophenyl)pyrazino[2",1":2',3']imidazo[4',5':2,3]pyrido[4,5-*b*]indole (5g): Yellow crystals. mp >300 °C; IR (KBr): v 3026, 2967, 1643, 1613 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.45 (s, 2H), 7.11-7.15 (m, 2H), 7.41 (t, J = 8.4 Hz, 1H), 7.59-7.63 (m, 6H), 8.03 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 4.4 Hz, 1H), 8.28 (s, 1H), 8.68 (d, J = 4.4 Hz, 1H), 9.01-9.03 (m, 1H), 9.13-9.16 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 49.8, 110.2, 111.5, 117.1, 119.2, 121.5, 123.4, 126.0, 127.6, 128.2, 128.4, 129.4, 129.7, 130.0, 130.4, 134.0, 135.5, 136.6, 138.0, 138.9, 142.5, 143.6, 158.9, 160.2. Anal. Calcd for $C_{28}H_{18}ClN_5$: C 73.12, H 3.94, N 15.23. Found: C 73.19, H 3.97, N 15.26.

8-Benzyl-7-(4-nitrophenyl)pyrazino[2",1":2',3']imidazo[4',5':2,3]pyrido[4,5-*b*]indole (5h): Yellow crystals. mp >300 °C; IR (KBr): v 3034, 2973, 1654, 1621 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.53 (s, 2H), 7.16-7.19 (m, 2H), 7.46 (t, J = 8.4 Hz, 1H), 7.61-7.65 (m, 6H), 8.17 (d, J = 4.4 Hz, 1H), 8.25 (s, 1H), 8.60 (d, J = 4.4 Hz, 1H), 8.89 (d, J = 9.0 Hz, 2H), 9.07-9.09 (m, 1H), 9.17-9.18 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 49.5, 111.2, 111.9, 117.3, 119.1, 121.2, 123.5, 126.2, 127.3, 128.0, 128.3, 129.4, 129.7, 130.1, 130.2, 134.5, 135.3, 136.1, 138.3, 138.6, 143.2, 144.6, 158.7, 161.8. Anal. Calcd for $C_{28}H_{18}N_6O_2$: C 71.48, H 3.86, N 17.86. Found: C 71.53, H 3.91, N 17.90.

8-Benzyl-7-furylpyrazino[2",1":2',3']imidazo[4',5':2,3]pyrido[4,5-*b*]indole (5i): Yellow crystals. mp >300 °C; IR (KBr): v 3016, 2981, 1643, 1614 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.41 (s, 2H), 7.16-7.19 (m, 3H), 7.24-7.27 (m, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.42-7.47 (m, 3H), 7.73 (d, J = 8.4 Hz, 1H), 7.90-7.94 (m, 2H), 8.15 (d, J = 4.4 Hz, 1H), 8.26 (s, 1H), 8.80 (d, J = 4.4 Hz, 1H), 9.09-9.10 (m, 1H), 9.24-9.27 (m, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 48.3, 102.3, 110.1, 117.3, 119.1, 121.0, 122.5, 126.3, 127.4, 128.0, 128.1, 129.0, 129.2, 130.1, 130.7, 134.6, 135.1, 136.2, 138.0, 138.4, 142.0, 142.5, 157.7, 158.1. Anal. Calcd for $C_{26}H_{17}N_5O$: C 75.17, H 4.12, N 16.86. Found: C 75.24, H 4.17, N 16.90.

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