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Note

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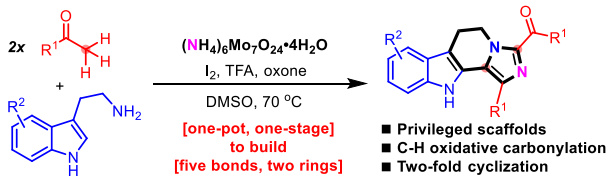
Supporting Information Placeholder

TOC Graphic:



ABSTRACT: An expeditious one-step synthesis of the imidazopyridoindole scaffold was achieved through the C–H oxidation/two-fold cyclization reaction of methyl ketone and tryptamine derivatives. Mild oxidizing conditions were employed to realize the efficient oxidative of C(sp^3)–H bonds, while suppressing overoxidation of the intermediate and ensuring the cross-trapping of two in situ generated acylimine intermediates.

Imidazopyridoindole, which comprises a *β*-carboline system attached to an imidazole ring (Figure 1-a, **i**), is a privileged scaffold present in a variety of bioactive lead compounds.[1–5] For example, compound **ii** has been used as a hypnotic and sedative,[1] while compound **iii** has shown anticonvulsive activity in the maximal electroshock seizure test.[2] Notably, compound **iv**, which was prepared via a four-step synthesis from resin-bound dipeptides,[3a] is a bioavailable anti-Alzheimer agent that inhibits Ab25–35 neurotoxicity toward the rat pheochromocytoma PC-12 cell line.[3b] Furthermore, Peganumine A (**v**), which contains an imidaz-opyridoindole scaffold, has been shown to be an anticancer drug candidate exhibiting significant cytotoxic effects.[4] However, synthetic endeavors towards imidazopyridoindoles have been limited. A classic literature approach requires multi operation steps from commercially available materials tryptamine[1,6] (Figure 1-b). Based on the leading strategy of BIOS,[7] we focused on the bond construction of imidazopyridoindole in an attempt to develop an expeditious protocol for the synthesis of analogues of this value-added scaffold.

In our reaction design, methyl ketone and tryptamine were employed to produce the target using a cascade coupling reaction[8] driven by C–H oxidation,[9] followed by two-fold cyclization[10] sequences. The cross-trapping of two in situ generated acylimine intermediates 2*H*-*β*-carboline-acylimine (**T1**) and 1-imino-2-one derivative (**T2**) are considered as a key approach. However, **T1** is unable to be trapped by additional nitrogen donor, but could be rapidly transformed into fully aromatic *β*-carboline in high temperature and high oxidizing conditions.[11] As a result, the most challenging aspect of this synthesis was the modulation of the reaction pathway through versatile reactive intermediates.[12] We assumed that to

regulate the oxidative environment and strike a balance between ensuring that C–H oxidation runs smoothly and avoiding overoxidation of **T1**. Furthermore, the in situ trapping of **T1** is rarely reported but a significant way to develop new method for the synthesis of indole alkaloid-like skeletons. Herein, a successful execution of our logic design is reported, providing an unprecedented one-pot one-stage synthesis of imidazopyridoindoles (Figure 1-c).

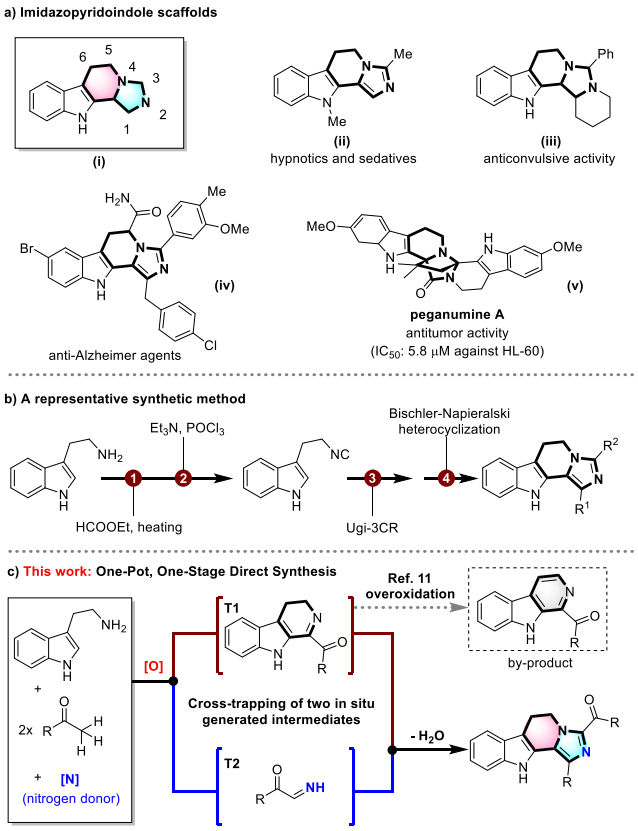
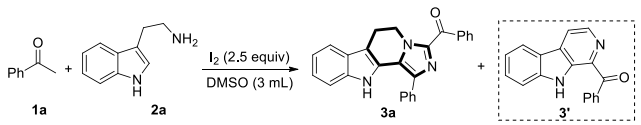


Figure 1. Representative Imidazopyridoindole Compounds and Related Synthetic Methods.

Our study commenced with the model reaction of acetophenone (**1a**) and tryptamine (**2a**) with 2.0 equiv of NH_4Cl at 110 ^oC. To realize C–H oxidation, 2.5 equiv of I_2 and solvent DMSO, were used. TFA (1.0 equiv) was also added to promote C–H oxidation and the Pictet–Spengler reaction.[13] The major product was the single cyclization product, *β*-carboline **3'**. To our delight, a small amount (<10% yield) of imidazopyridoindole **3a** was obtained (Table 1, entry 1). However, the high temperature had led to the strong oxidation environment generating **3'**. A lower temperature (70 ^oC) was attempted in the presence of additional oxidant oxone (0.2 equiv) to ensure C(sp^3)–H oxidation of acetophenone (**1a**). This resulted in a significant improvement, with a 31% yield of **3a** and supression of **3'** generation (entry 2). Next, different nitrogen donors were investigated, of which ammonium molybdate gave the best result (85% of **3a** and <10% of **3'**) (entries 3–7). Yields were not further improved when switching TFA with other acids, such as TFAA, TfOH, HI, or Lewis acid $Cu(NO_3)_2•3H_2O$ (entries 8–11). Furthermore, a variety of oxidants were screened, but failed to improve the yields (entries 12–15). Finally, we optimized the nitrogen donor dosage with the results showing that 1/3 equiv of ammonium molybdate gave the best yield (entry 7).

Table 1. Reaction Optimization[(a)].

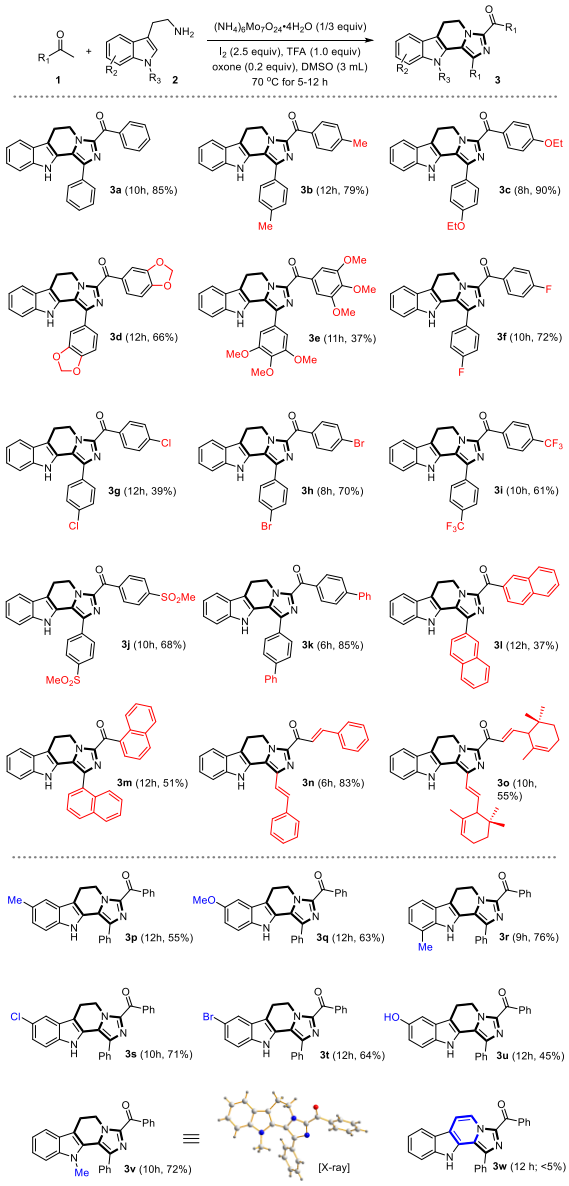


entry	[N] (2.0)	acid (1.0)	oxidant (0.2)	temp. (℃)	**3a (3')** (%)[b]
1	NH_4Cl	TFA	-	110	<10 (77)
2	NH_4Cl	TFA	oxone	70	31 (43)
3	NH_4OAc	TFA	oxone	70	trace
4	$NH_3.H_2O$	TFA	oxone	70	trace
5	NH_4PF_6	TFA	oxone	70	54 (27)
6	$NH_4Al(SO_4)_2$	TFA	oxone	70	trace
7	**ammonium molybdate (1/3)**	**TFA**	**oxone**	**70**	**85 (<10)**
8	AM[c] (1/3)	TFAA	oxone	70	trace
9	AM (1/3)	TfOH	oxone	70	67
10	AM (1/3)	HI[d]	oxone	70	trace
11	AM (1/3)	$Cu(NO_3)_2$ $3H_2O$	oxone	70	trace
12	AM (1/3)	TFA	H_2O_2	70	trace
13	AM (1/3)	TFA	$Na_2S_2O_4$	70	49
14	AM (1/3)	TFA	$K_2S_2O_4$	70	66
15	AM (1/3)	TFA	TBHP	70	21

[a] Reaction conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), acid, oxidant and I_2 (2.5 mmol) were added in DMSO (3.0 mL) and stirred for 10 h. Reactions were carried out in a pressure vessel. [b]Isolated yields. [c]AM = ammonium molybdate ($(NH_4)_6Mo_7O_{24}•4H_2O$). [d]Using hydriodic acid, 57 wt.% solution in H_2O. TFA = trifluoroacetic acid. Oxone = potassium peroxomonosulfate. TFAA = trifluoroacetic anhydride. TBHP = t-butyl hydroperoxide.

With optimal conditions in hand, we tested the reaction scope using various substituted methyl ketones and tryptamine derivatives (Scheme 1). Aryl methyl ketones bearing electron-donating groups (4-Me, 4-OEt) gave good yields (**3b**, 79%; **3c**, 90%). However, when bearing more than one electron-donating substituents (3,4-OCH_2O, 3,4,5-OCH_3), desired imidazopyridoindoles **3d** and **3e** were furnished in relative low yields (66% and 37%, respectively). Aromatic ketones bearing halogen substituents, such as 4–F, 4–Cl, and 4–Br, afforded the corresponding products in moderate yields (**3f**, 72%; **3g**, 39%; **3h**, 70%), allowing further modifications. When electron-withdrawing substituents were employed, desired products bearing 4-CF_3, 4-SO_2Me, and 4-Ph groups were readily prepared (**3i**, 61%; **3j**, 68%; **3k**, 85%). Sterically hindered substituents 2-naphthyl methyl ketone and 1-naphthyl methyl ketone were also transformed into products with moderate yields (**3l**, 37%; **3m**, 51%) under these conditions. We investigated using unsaturated methyl ketones to further expand the scope. (E)-4-phenylbut-3-en-2-one afforded imidazopyridoindole **3n** smoothly

in 83% yield. Fatty chain substrate α-ionone was also applicable, producing **3o** in 55% yield. These results determined that sensitive groups were tolerated under these mild conditions. However, this reaction still has limitations in substrate scope. For example, simple ketone such as propan-2-one could not transform into desired product. Ethyl acetate, N-phenylacetamide and 4-phenylbut-3-yn-2-one are also failed to afford the corresponding imidazopyridoindole derivatives. Next, we investigated tryptamine substrate scope. Tryptamines bearing electron-donating groups (5-Me, 5-OMe, and 7-Me) afforded **3p**–**3r** in moderate yields (55–76%). Sensitive halogens groups were also tolerated (**3s**, 71%; **3t**, 64%). Therefore, the electronic nature of the tryptamine substrates had little influence on the reactivity. To our delight, serotonin,[14] which is a privileged scaffold in bioactivity studies, afforded **3u** in 45% yield. Furthermore, N-Me tryptamine congeners were well tolerated, furnishing desired product **3v** in reasonable yield (72%), for which the structure was unambiguously confirmed by X-ray crystallography (please see Supporting information Fig. S2 and Table S1). Natural tryptophan could not be converted to imidazopyridoindole targets. Instead, a little trace of β-carboline-imidazo was obtained through decarboxylative oxidation (**3w**, <5%).

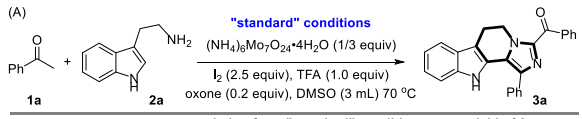


Scheme 1. Scope of Imidazopyridoindole Synthesis.

Next, we investigated the mechanism experimentally. The reaction of **1a** under standard conditions without

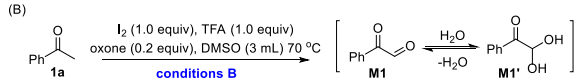
adding TFA or oxone, the yield of **3a** decreased sharply (Scheme 2-A, entries 2 and 3). When react at room temperature or replace DMSO to DMF, the transformation did not occur (Scheme 2-A, entries 4 and 5). These results determined that, acid, oxidant, proper heating temperature and DMSO are all necessary. Next, we conducted **1a** in a similar condition without adding tryptamine and nitrogen donor, oxidation product **M1** and its hydrate isomer **M1'** could be isolated with or without TFA and oxone. However, when reacted at room temperature, **M1** and **M1'** could only be detected with the addition of TFA and oxone which determined that TFA and oxone could promote C(sp^3)-H oxidation approach in low temperature (Scheme 2-B). Using commercially available **M1'** or prepared 2-iodo-1-phenylethanone (**1aa**) with tryptamine (2:1 mole ratio) under standard conditions with 0.5 equiv of I_2, **3a** could be afforded in 87% and 82% yield, respectively (Scheme 2-C) which determined **M1** and **1aa** are key intermediates. To the same reaction without adding nitrogen donor, 2*H*-*β*-carboline-acylimine **T1** could be isolated in 32% yield (Scheme 2-D). Conducted **M1'** and ammonium molybdate (6: 1 mole ratio) in DMSO-d_6 for 20 min afford 2-imino-1-phenylethanone **T2** (Scheme 2-E, please see Supporting information Fig. S1). According to these results, we suggested that **T1** and **T2** are both key intermediates. Reaction of **T1**, ammonium molybdate and phenylglyoxal hydrated species (**M1'**) or 1-(4-ethoxyphenyl)-2,2-dihydroxyethanone (**M2'**) gave desired products **3a** or asymmetric product **3x** in 84% and 61% yield, respectively (Scheme 2-F), the by-product is also **3'**. These results proved our hypothesis that the reaction pathway involving a cross-trapping of two in situ generated acylimine intermediates **T1** and **T2**.

(A)



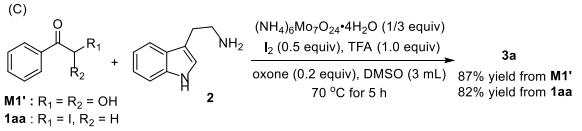
entry	variation from "standard" conditions	yield of 3a
1	none	85%
2	without adding of TFA	trace
3	without adding of oxone	16%
4	react at room temperature	trace
5	DMF instead of DMSO	trace

(B)

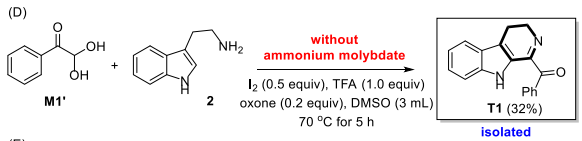


entry	variation from conditions B	yield of [M1+M1']
1	none	46%
2	without TFA and oxone	41%
3	react at room temperature	14%
4	react at room temperature without TFA and oxone	trace

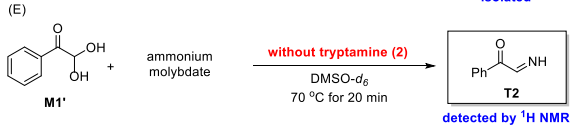
(C)



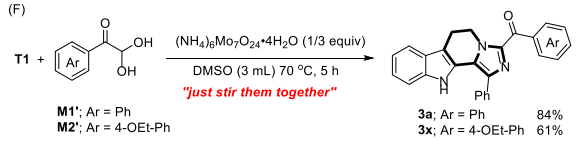
(D)



(E)

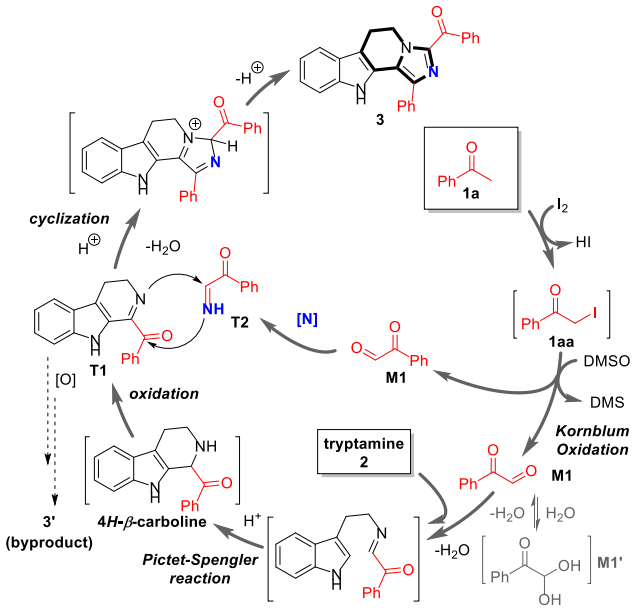


(F)



Scheme 2. Control Experiments.

Based on the above results and related reports,[15] a mechanism is proposed in Scheme 3. Initially, the combination of I_2, DMSO, TFA and oxone enabled oxidation of C (sp^3)–H in methyl ketones in a relative low temperature gave phenylglyoxal **M1**. The Pictet–Spengler reaction of **M1** and tryptamine then afforded the 4H-*β*-carboline intermediate which is unstable. It could transform into 2*H*-*β*-carboline-acylimine **T1** quickly. As a minor pathway, **T1** could undergo overoxidation to generate *β*-carboline **3'** as a byproduct. However, under our mild oxidizing conditions, **T1** could be trapped by acylimine intermediates **T2** which generated in situ through the condensation of a nitrogen donor with another **M1**. Cyclization and proton transformation realize imidazole formation, affording the desired product, imidazopyridoindole **3**.



Scheme 3. Possible Reaction Mechanism.

In conclusion, we report the straightforward synthesis of value-added imidazopyridoindole scaffolds from simple materials. Mild oxidizing reaction conditions were chosen to generate 2*H*-β-carboline-acylimine, which could be trapped by subsequent cross-trapping without overoxidation. Using this approach, a wide library of imidazopyridoindoles with diverse substitution diversity can be readily prepared. The trapping strategy of 2*H*-β-carboline-acylimine intermediate will also give inspirations to prepare other indole alkaloid-like targets.

Experimental Section

General

All substrates and reagents were commercially available and used without further purification. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using alkaline aluminum oxide (200–300 mesh). IR spectra were recorded on a Perkin-Elmer PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}.^{1}H spectra were recorded in $CDCl_3$ or DMSO-d_6 on 600 MHz NMR spectrometers and resonances (δ) are given in parts per million relative to tetramethylsilane. Data are

reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet q = quadruple), coupling constants (Hz) and integration. ^{13}C spectra were recorded in $CDCl_3$ or DMSO-d_6 on 150 MHz. NMR spectrometers and resonances (δ) are given in ppm. HRMS were obtained on a Bruker 7-tesla FT-ICR MS equipped with an electrospray source. The X-ray crystal structure determinations were obtained on a Bruker SMART APEX CCD system. Melting points were determined using XT-4 apparatus.

General procedure for the synthesis

A mixture of acetophenone **1a** (2.0 mmol), tryptamine **2a** (1.0 mmol), $(NH_4)_6Mo_7O_{24}$•$4H_2O$ (ammonium molybdate) (0.33 mmol), trifluoroacetic acid (1.0 mmol), I_2 (2.5 mmol), potassium peroxomonosulfate (0.2 mmol) and DMSO (3.0 mL) were added in a pressure vessel, then stirred at 70 ^oC for 10 h. Then added 50 mL water and 30 mL saturated brine solution to the mixture and extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: petroleum ether /EtOAc=7/1) to afford the product **3a** as yellow crystalline solid (330 mg, 85%).

Analytical Data for Compounds 3

phenyl(1-phenyl-6,11-dihydro-5H-imidazo [1',5':1,2]pyrido[3,4-b]indol-3-yl)methanone: (3a)

Yellow crystalline solid; 330 mg, 85% yield. mp = 214-215 ℃; IR (KBr) νmax: 1630, 1426, 1259, 1002, 907, 771, 676, cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.44 – 8.29 (m, 3H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.56 – 7.50 (m, 2H), 7.49 – 7.43 (m, 4H), 7.41 – 7.36 (m, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.20 – 7.16 (m, 1H), 7.15 – 7.10 (m, 1H), 4.83 (t, *J* = 7.2 Hz, 2H), 3.20 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.5, 142.4, 137.3, 136.7, 136.6, 134.4, 132.6, 131.0, 129.0, 128.13, 128.0, 127.7, 125.8, 124.8, 123.3, 120.4, 118.6, 111.4, 110.4, 103.7, 44.3, 20.7. HRMS (ESI) m/z calcd for $C_{26}H_{20}N_3O^+$ $(M+H)^+$ 390.1601, found 390.1605.

p-tolyl(1-(p-tolyl)-6,11-dihydro-5H-imidazo [1',5':1,2]pyrido[3,4-b]indol-3-yl)methanone: (3b)

Yellow crystalline solid; 327 mg, 79% yield. mp = 152-154 ℃; IR (KBr) νmax: 1623, 1603, 1438, 1328, 1261, 1177, 961, 906, 742 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.29 (d, *J* = 7.8 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.23 (m, 5H), 7.20 – 7.17 (m, 1H), 7.16 – 7.12 (m, 1H), 4.83 (t, *J* = 7.2 Hz, 2H), 3.22 (t, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.3, 143.5, 142.6, 138.0, 136.8, 136.6, 134.8, 131.6, 131.2, 129.8, 128.7, 127.6, 125.9, 125.0, 124.4, 123.1, 120.4, 118.6, 111.4, 110.1, 44.3, 21.7, 21.3, 20.8. HRMS (ESI) m/z calcd for $C_{28}H_{24}N_3O^+$ $(M+H)^+$ 418.1914, found 418.1910.

(4-ethoxyphenyl)(1-(4-ethoxyphenyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)methanone: (3c)

Yellow crystalline solid; 429 mg, 90% yield. mp = 217-218 ℃; IR (KBr) νmax: 1618, 1598, 1444, , 1333, 1253, 1169, 1044 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.36 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.16-7.10 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.77 (t, *J* = 7.2 Hz, 2H), 4.03-3.97 (m, 4H), 3.17 (t, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.9, 162.7,

158.8, 142.5, 136.6, 136.3, 133.3, 129.9, 129.0, 126.6, 125.8, 125.2, 123.9, 122.9, 120.2, 118.4, 114.8, 113.6, 111.4, 109.7, 63.5, 63.4, 44.2, 20.7, 14.7. HRMS (ESI) m/z calcd for $C_{30}H_{28}N_3O_3^+$ $(M+H)^+$ 478.2125, found 478.2137.

benzo[d][1,3]dioxol-5-yl(1-(benzo[d][1,3]dioxol-5-yl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)methanone: (3d)

Yellow crystalline solid; 315 mg, 66% yield. mp = 242-243 ℃; IR (KBr) νmax: 1620, 1479, 1256, 1027, 1005 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.29 (s, 1H), 7.27 (d, *J* = 6.6 Hz, 2H), 7.24 – 7.21 (m, 1H), 7.19 – 7.14 (m, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.08-6.05 (m, 4H), 4.86 (t, *J* = 7.2 Hz, 2H), 3.25 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 180.5, 151.4, 147.7, 147.2, 147.1, 141.9, 137.6, 135.6, 131.3, 127.9, 127.6, 125.5, 124.7, 124.2, 122.5, 121.2, 119.7, 118.5, 112.5, 110.3, 110.0, 108.9, 107.9, 102.0, 101.2, 79.2, 44.2, 20.2. HRMS (ESI) m/z calcd for $C_{28}H_{20}N_3O_5^+$ $(M+H)^+$ 478.1397, found 478.1399.

(3,4,5-trimethoxyphenyl)(1-(3,4,5-trimethoxyphenyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)methanone: (3e)

Yellow crystalline solid; 209 mg, 37% yield. mp = 261-264 ℃; IR (KBr) νmax: 1631, 1576, 1465, 1451, 1336, 1326, 1127, 1003, 767 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.90 (s, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.20 – 7.10 (m, 3H), 7.10 – 7.04 (m, 1H), 4.78 (t, *J* = 6.0 Hz, 2H), 3.89 (s, 6H), 3.81-3.79 (m, 9H), 3.75 (s, 3H), 3.21 (t, *J* = 6.0 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 180.7, 153.3, 152.3, 141.8, 137.7, 137.1, 135.7, 132.0, 129.1, 125.4, 124.7, 122.8, 119.8, 118.6, 112.4, 110.9, 108.5, 104.0, 603, 60.1, 55.9, 55.5, 44.4, 20.2. HRMS (ESI) m/z calcd for $C_{32}H_{32}N_3O_7^+$ $(M+H)^+$ 570.2235, found 570.2233.

(4-fluorophenyl)(1-(4-fluorophenyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)methanone:(3f)

Yellow crystalline solid; 307 mg, 72% yield. mp = 243-245 ℃; IR (KBr) νmax: 1666, 1632, 1598, 1437, 1223, 1154, 907cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.51 – 8.39 (m, 2H), 8.20 (s, 1H), 7.81 – 7.72 (m, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.25-7.13 (m, 6H), 4.87 (t, *J* = 7.2 Hz, 2H), 3.26 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.9, 166.5, 161.9, 142.3, 136.7, 135.8, 133.7, 133.7, 133.6, 133.6, 130.5, 129.6, 129.5, 125.8, 124.8, 124.6, 123.6, 120.6, 118.8, 116.3, 116.1, 115.3, 115.1, 111.5, 110.8, 44.5, 20.8. HRMS (ESI) m/z calcd for $C_{26}H_{18}F_2N_3O^+$ $(M+H)^+$ 426.1412, found 426.1415.

(4-chlorophenyl)(1-(4-chlorophenyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)methanone: (3g)

Orange crystalline solid; 187 mg, 39% yield. mp = 286-287 ℃; IR (KBr) νmax: 1635, 1586, 1438, 1284, 1089, 960, 741 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.95 (s, 1H), 8.30 (d, *J* = 7.8 Hz, 2H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.66 – 7.50 (m, 5H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.19 – 7.12 (m, 1H), 7.10 – 7.04

(m, 1H), 4.74 (t, *J* = 7.2 Hz, 2H), 3.20 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 181.4, 141.9, 137.8, 135.9, 134.8, 132.6, 132.5, 132.4, 129.1, 129.0, 128.3, 125.5, 125.4, 124.3, 122.8, 119.8, 118.7, 112.5, 111.1, 44.2, 20.3. HRMS (ESI) m/z calcd for $C_{26}H_{17}Cl_2N_3ONa^+$ $(M+Na)^+$ 480.0641, found 480.0636.

(4-bromophenyl)(1-(4-bromophenyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)metha

none: (3h)

Orange powder solid; 381 mg, 70% yield. mp = 277-278 ℃; IR (KBr) νmax: 1636, 1440, 1259, 903, 831, 740 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.8 Hz, 2H), 8.20 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.24 (s, 1H), 7.20 – 7.16 (m, 1H), 4.89 (t, *J* = 6.6 Hz, 2H), 3.27 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.3, 142.4, 136.8, 136.1, 135.7, 133.3, 132.6, 132.4, 131.4, 129.3, 128.1, 125.8, 125.2, 124.4, 123.8, 122.4, 120.7, 118.9, 111.6, 111.2, 44.5, 20.8. HRMS (ESI) m/z calcd for $C_{26}H_{18}Br_2N_3O^+$ $(M+H)^+$ 545.98111, found 545.98114.

(4-(trifluoromethyl)phenyl)(1-(4-(trifluoromethyl)phenyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,

4-b]indol-3-yl)methanone: (3i)

Yellow crystalline solid; 322 mg, 61% yield. mp = 228-230 ℃; IR (KBr) νmax: 1643, 1620, 1326, 1119, 1108, 1066, cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.8 Hz, 2H), 8.20 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.28-7.25 (m, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 4.91 (t, *J* = 7.2 Hz, 2H), 3.29 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.4, 142.4, 140.2, 137.9, 136.9, 135.5, 134.0, 133.7, 131.2, 130.3, 130.0, 129.9, 127.8, 126.2, 126.0, 125.7, 125.0, 124.8, 124.6, 124.0, 123.1, 122.8, 120.9, 119.0, 111.8, 111.6, 103.9, 44.5, 20.8 HRMS (ESI) m/z calcd for $C_{28}H_{18}F_6N_3O^+$ $(M+H)^+$ 526.1349, found 526.1347.

(4-(methylsulfonyl)phenyl)(1-(4-(methylsulfonyl)phenyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4

-b]indol-3-yl)methanone: (3j)

Orange crystalline solid; 386 mg, 68% yield. mp = 237-240 ℃; IR (KBr) νmax: 1637, 1441, 1330, 1295, 1151, 780 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.12 (s, 1H), 8.43 (d, *J* = 7.8 Hz, 2H), 8.17 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 2H), 8.04 (s, 3H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.12 – 7.05 (m, 1H), 4.79 (t, *J* = 6.6 Hz, 2H), 3.32 (s, 3H), 3.28 (s, 3H), 3.24 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 181.9, 143.7, 142.1, 141.4, 139.6, 138.6, 138.0, 134.6, 131.4, 130.2, 128.0, 127.8, 127.4, 126.7, 126.6, 125.5, 124.0, 123.2, 120.0, 118.9, 112.6, 111.9, 44.2, 43.7, 43.3, 20.2. HRMS (ESI) m/z calcd for $C_{28}H_{23}N_3O_5S_2Na^+$ $(M+H)^+$ 568.0971, found 568.1000.

[1,1'-biphenyl]-4-yl(1-([1,1'-biphenyl]-4-yl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)

methanone: (3k)

Yellow crystalline solid; 461 mg, 85% yield. mp = 185-186 ℃; IR (KBr) νmax: 1631, 1600, 1440, 1264, 909, 747, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.38 (d, *J* = 7.8 Hz, 2H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 7H), 7.42 – 7.38 (m, 2H), 7.35 (t, *J* = 7.2 Hz, 3H), 7.31 – 7.27 (m, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.14 – 7.10 (m, 1H), 4.68 (t, *J* = 6.6 Hz, 2H), 3.08 (t, *J* = 6.6 Hz, 2H).^{13}C NMR (150 MHz, $CDCl_3$) δ 182.9, 145.2, 142.7, 140.7, 140.3, 140.1, 136.8, 136.4, 136.1, 133.3, 131.6, 128.8, 128.1, 127.7, 127.5, 127.3, 126.9, 126.6, 125.8, 124.9, 123.3, 120.4, 118.7, 111.6, 110.6, 44.3, 20.7. HRMS (ESI) m/z calcd for $C_{38}H_{28}N_3O^+$ $(M+H)^+$ 542.2227, found 542.2214.

naphthalen-2-yl(1-(naphthalen-2-yl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)metha

none: (3l)

Yellow crystalline solid; 181 mg, 37% yield. mp = 198-200 ℃; IR (KBr) νmax: 1688, 1629, 1441, 1021, 783cm^{-1}; ^1H NMR (600 MHz,$CDCl_3$) δ 8.45 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 6.6 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.92 (dd, *J* = 16.4, 8.2 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.57 (d, *J* = 7.2 Hz, 3H), 7.54 – 7.49 (m, 3H), 7.44 – 7.40 (m, 1H), 7.16 – 7.11 (m, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 5.15 (d, *J* = 6.6 Hz, 2H), 3.38 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.73, 143.46, 136.70, 135.54, 135.51, 135.27, 134.11, 133.85, 132.19, 131.88, 131.29, 130.61, 129.29, 128.43, 128.38, 127.71, 127.17, 126.90, 126.66, 126.35, 126.07, 125.88, 125.77, 125.58, 125.40, 124.56, 124.33, 123.33, 120.44, 118.78, 111.39, 110.27, 77.21, 77.00, 76.79, 44.57, 20.93. HRMS (ESI) m/z calcd for $C_{34}H_{24}N_3O^+$ $(M+H)^+$ 490.19139, found 490.19138.

naphthalen-1-yl(1-(naphthalen-1-yl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)metha

none: (3m)

Yellow crystalline solid; 250 mg, 51% yield. mp = 111-112 ℃; IR (KBr) νmax: 1629, 1590, 1463, 1331, 1251, 903, 783, 775, 727 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.01-7.96 (m, 4H), 7.64-7.56 (m, 6H), 7.51 – 7.47 (m, 1H), 7.36 – 7.32 (m, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.12 – 7.08 (m, 1H), 7.08 – 7.04 (m, 1H), 5.06 (t, *J* = 6.6 Hz, 2H), 3.35 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 186.4, 142.8, 137.7, 136.2, 135.3, 133.8, 133.1, 131.6, 131.2, 130.7, 130.5, 129.1, 128.6, 128.4, 128.1, 127.6, 127.1, 127.1, 126.2, 126.1, 125.9, 125.9, 125.5, 124.6, 124.3, 122.6, 119.6, 118.6, 112.4, 110.2, 44.2, 20.3. HRMS (ESI) m/z calcd for $C_{34}H_{24}N_3O^+$ $(M+H)^+$ 490. 19139, found 490.1938.

(E)-3-phenyl-1-(1-((E)-styryl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)prop-2-en-1-o

ne: (3n)

Yellow powder; 366 mg, 83% yield. mp = 234-247 ℃; IR (KBr) νmax: 1644, 1633, 1599, 1574, 1447, 1260, 1040, 802 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.16 (d, *J* = 16.2 Hz, 1H), 7.84 (d, *J* = 16.2 Hz, 1H), 7.71-7.70 (m, 2H), 7.61 (s, 1H), 7.60 – 7.57 (m, 2H), 7.46 (s, 1H), 7.42-7.40 (m, 3H), 7.38 (s, 1H), 7.32 – 7.27 (m, 2H), 7.25 (t, *J* = 6.6 Hz, 2H), 7.21-7.18 (m, 2H), 4.87 (t, *J* = 7.2 Hz, 2H),

3.18 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.1, 143.4, 143.3, 137.7, 137.0, 135.0, 134.7, 130.7, 130.4, 128.8, 128.7, 127.9, 126.7, 126.5, 126.1, 125.1, 123.6, 123.2, 120.8, 119.0, 118.5, 111.6, 111.3, 44.0, 20.8. HRMS (ESI) m/z calcd for $C_{30}H_{24}N_3O^+$ $(M+H)^+$ 442.1914, found 442.1915.

(E)-3-(2,6,6-trimethylcyclohex-2-en-1-yl)-1-(1-((E)-2-(2,6,6-trimethylcyclohex-2-en-1-yl)vinyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)prop-2-en-1-one: (3o)

Yellow oil; 293 mg, 55% yield. IR (KBr) νmax: 1632.43, cm^{-1}; IR (KBr) νmax: 1653, 1447, 1420, 1283, 1095, 1025, 801 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 15.0 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.97 (dd, *J* = 15.6, 10.2 Hz, 1H), 6.57 (d, *J* = 15.0 Hz, 1H), 6.41 (dd, *J* = 15.6, 10.2 Hz, 1H), 5.56 (s, 1H), 5.46 (s, 1H), 4.91 (s, 1H), 4.83 (d, *J* = 4.2 Hz, 1H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.43 (d, *J* = 10.2 Hz, 1H), 2.32 (d, *J* = 9.6 Hz, 1H), 2.08 (s, 2H), 2.04 (s, 2H), 1.72 (s, 3H), 1.58 (s, 3H), 1.24-1.22 (m, 2H), 0.96 (s, 3H), 0.93 (s, 6H), 0.87 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.1, 149.4, 142.8, 137.3, 135.0, 134.3, 133.5, 132.1, 127.5, 125.9, 125.4, 125.1, 123.2, 122.2, 121.5, 120.4, 118.7, 111.4, 110.3, 55.1, 54.3, 43.9, 32.5, 32.1, 31.2, 31.1, 28.0, 27.7, 26.8, 26.6, 23.0, 22.8, 22.8, 20.8. HRMS (ESI) m/z calcd for $C_{36}H_{44}N_3O^+$ $(M+H)^+$ 534.3479, found 534.3478.

(8-methyl-1-phenyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)(phenyl)methanone: (3p)

Yellow crystalline solid; 221 mg, 55% yield. mp = 236-238 ℃; IR (KBr) νmax: 1727, 1627, 1449, 1276, 1025, 798 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 7.8 Hz, 2H), 8.31 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.55 – 7.47 (m, 4H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.39 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 4.87 (t, *J* = 7.2 Hz, 2H), 3.23 (t, *J* = 7.2 Hz, 2H), 2.50 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 183.7, 142.5, 137.5, 135.0, 134.6, 132.7, 131.1, 129.9, 129.2, 128.2, 128.1, 1280, 128.0, 127.8, 126.1, 125.1, 124.9, 118.4, 111.1, 110.1, 44.5, 21.5, 20.8. HRMS (ESI) m/z calcd for $C_{27}H_{22}N_3O^+$ $(M+H)^+$ 404.1757, found 404.1758.

(8-methoxy-1-phenyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)(phenyl)methanone: (3q)

Yellow crystalline solid; 264 mg, 63% yield. mp = 171-174 ℃; IR (KBr) νmax: 1627, 1450, 1428, 1414, 1325, 1288, 1176, 924, 697 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6.6 Hz, 2H), 8.19 (s, 1H), 7.81 (d, *J* = 6.6 Hz, 2H), 7.56 (s, 1H), 7.49-7.41 (m, 4H), 7.43 (d, *J* = 6.6 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.98 (s, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 4.95 – 4.82 (m, 2H), 3.87 (s, 3H), 3.29 – 3.16 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.5, 154.5, 142.4, 137.4, 136.7, 134.4, 132.6, 131.7, 131.0, 129.0, 128.1, 127.9, 127.7, 126.2, 125.4 124.9, 113.6, 112.2, 110.1, 100.0, 55.7, 44.3, 20.7. HRMS (ESI) m/z calcd for $C_{27}H_{22}N_3O_2^+$ $(M+H)^+$420.1707, found 420.1709.

(10-methyl-1-phenyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)(phenyl)methanone: (3r)

Yellow powder; 306 mg, 76% yield. mp = 126-127 ℃; IR (KBr) νmax:1634, 1451, 1433, 1261, 1022, 802, 680, cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.8 Hz, 2H), 8.19 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 2H), 7.53 – 7.36 (m, 7H), 7.04 (t, *J* = 6.6 Hz, 1H), 6.98 (d, *J* = 6.6 Hz, 1H), 4.81 (t, *J* = 6.6 Hz, 2H), 3.16 (t, *J* = 6.6 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.4, 142.4, 137.3, 136.6, 136.1 134.5, 132.6, 130.9, 128.9, 128.2, 127.9, 127.6, 125.3, 124.9, 124.4, 123.8, 120.6, 120.3, 116.4, 110.9, 44.3, 20.8, 16.3. HRMS (ESI) m/z calcd for $C_{27}H_{22}N_3O^+$ $(M+H)^+$ 404.1757, found 404.1759.

(8-chloro-1-phenyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)(phenyl)methanone: (3s)

Yellow crystalline solid; 300 mg, 71% yield. mp = 232-233 ℃; IR (KBr) νmax: 1637, 1277, 1049, 1025, 1005, 674 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.28 (d, *J* = 6.6 Hz, 2H), 7.80 (d, *J* = 6.6 Hz, 2H), 7.66 (s, 2H), 7.58 – 7.49 (m, 4H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 4.74-4.72 (m, 2H), 3.20-3.19 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.45, 142.49, 137.15, 137.02, 134.99, 134.13, 132.66, 130.89, 129.02, 128.12, 127.89, 127.62, 126.77, 126.11, 125.90, 124.20, 123.22, 117.94, 112.51, 109.62, 44.18, 20.52. HRMS (ESI) m/z calcd for $C_{26}H_{19}ClN_3O^+$ $(M+H)^+$ 424.12112, found 424.12112.

(8-bromo-1-phenyl-6,11-dihydro-5H-imidazo[1',5':1,2] pyrido[3,4-b]indol-3-yl)(phenyl)methanone: (3t)

Yellow crystalline solid; 298 mg, 64% yield. mp = 214-217 ℃; IR (KBr) νmax: 1626, 1449, 1431, 1275, 962, 789, 687 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.67 (s, 1H), 7.57 – 7.54 (m, 1H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.43 – 7.40 (m, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 4.85 (t, *J* = 7.2 Hz, 2H), 3.18 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.7, 142.7, 137.2, 135.2, 134.3, 132.8, 131. 0, 129.2, 128.3, 128.0, 127.8, 127.6, 126.0, 124.2, 121.3, 113.6, 112.8, 109.6, 44.3, 20.6. HRMS (ESI) m/z calcd for $C_{26}H_{19}BrN_3O^+$ $(M+H)^+$ 468.0706, found 468.0707.

(8-hydroxy-1-phenyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)(phenyl)methanone: (3u)

Yellow crystalline solid; 182 mg, 45% yield. mp = 243-245 ℃; IR (KBr) νmax: 1634, 1451, 1432, 1293, 1046, 976, 695 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.91 (s, 1H), 9.42 (s, 1H), 8.28 (d, *J* = 7.2 Hz, 2H), 7.78 (d, *J* = 7.2 Hz, 2H), 7.65 (d, *J* = 6.6 Hz, 1H), 7.62 – 7.46 (m, 4H), 7.43 (d, *J* = 6.6 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.76-4.74 (m, 2H), 3.50-3.48 (m, 2H). ^{13}C NMR (150MHz, DMSO-d_6) δ 182.9, 146.9, 142.0, 137.3, 136.2, 133.8, 132.8, 130.7, 129.0, 128.1, 127.8, 127.4, 125.9, 124.5, 123.6, 113.6, 111.8, 109.6, 108.9, 44.2, 21.5. HRMS (ESI) m/z calcd for $C_{26}H_{20}N_3O_2$+ $(M+H)^+$ 406.15500, found 406.15503.

(11-methyl-1-phenyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)(phenyl)methanone:

(3v)

Yellow crystalline solid; 290 mg, 72% yield. mp = 161-164 ℃; IR (KBr) νmax: 1631, 1453, 1434, 1267, 902, 742, 731, 695, cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 8.31 (d, J = 7.8 Hz, 2H), 7.67 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.2 Hz, 2H), 7.51 (t, J = 7.2 Hz, 2H), 7.45 (d, J = 7.8 Hz, 2H), 7.25 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 4.71 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 6.0 Hz, 2H), 3.18 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.8, 142.4, 139.5, 137.2, 136.6, 134.9, 132.9, 130.7, 128.7, 128.4, 128.2, 128.1, 125.7, 124.3, 122.8, 120.2, 119.0, 111.8, 110.7, 44.1, 33.5, 20.9. HRMS (ESI) m/z calcd for $C_{27}H_{22}N_3O^+$ $(M+H)^+$ 404.1757, found 404.1759.

(4-ethoxyphenyl)(1-phenyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-3-yl)methanone: (3x)

Yellow crystalline solid; 262 mg, 61% yield. mp = 190-192 ℃; ^1H NMR (600 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.35 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 7.2 Hz, 2H), 7.58 – 7.47 (m, 3H), 7.46-7.42 (m, 2H), 7.14 (t, J = 7.2 Hz, 1H), 7.05 (t, J = 10.2 Hz, 3H), 4.69 (s, 2H), 4.10 (d, J = 6.6 Hz, 2H), 3.17 (s, 2H), 1.35 (t, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 181.2, 162.5, 142.4, 137.7, 135.6, 134.0, 133.2, 129.6, 129.0, 127.7, 127.3, 125.6, 124.8, 124.4, 122.6, 119.7, 118.5, 113.9, 112.6, 110.5, 63.6, 44.1, 20.3, 14.6. HRMS (ESI) m/z calcd for $C_{28}H_{24}N_3O_2^+$ $(M+H)^+$ 434.18630, found 434.18631.

ASSOCIATED CONTENT

Supporting Information

Crystallographic data and copies of the ^1H and ^{13}C NMR spectra are involved. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

1 J. B. Fourtillan, M. Fourtillan, O. Karam, F. Zunino, J. C. Jacquesy, J. P. Tafani, Dihydroimidazo[5,1-a]-β-carboline derivatives, method for preparing same and use thereof as medicine US20060089372 A1.

2 M. Stanislaw, D. Malgorzata, E. Chojnacka-Wojcik, E. Tatar-czynska, A. Lewandowska, *Pol. J. Pharmacol. Pharm.* **1986**, *38*, 403-405.

3 (a) R. A. Houghten, *Proc. Natl. Acad. Sci.* **1985**, *82*, 5131-5135. (b) N. Reixach, E. Crooks, J. M. Ostresh, R. A. Houghten, S. E. Blondelle, *J. Struct. Biol.* **2000**, *130*, 247-258. (c) J. M. Ostresh, R. A. Houghten, US Patent 5856107, **1999**. (d) Nefzi, A. Ostresh, J. M. Yu, J. P. Houghten, R. A. *J. Org. Chem.* **2004**, *69*, 3603-3609.

4 (a) K. B. Wang, Y. T. Di, Y. Bao, C. M. Yuan, G. Chen, D. H. Li, J. Bai, H. P. He, X. J. Hao, Y. H. Pei, Y. K. Jing, Z. L. Li, H. M. Hua, *Org. Lett.* **2014**, *16*, 4028-4031. (b) C. Piemontesi, Q. Wang, J. P. Zhu, *J. Am. Chem. Soc.* **2016**, *138*, 11148-11151.

5 (a) R. A. Glennon, B. Grella, R. J. Tyacke, A. Lau, J. Westa-way, A. L. Hudson, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 527-529. (b) B. Juskowiak, E. Galezowsk, N. Koczorowska. T. W. Hermann, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3627-3630. (c) J. M. Ostresh, Preparation and biological activity of imidaz-opyridoindole and imidazopyridobenzothiophene combinatorial libraries. WO 9834112, A1 (d) C. Brochu, C. Grand-Maitre, M. Joly, C. Kuhn, M. Bertrand-Laperle, M. Pesant, Preparation of tetrahydro-azafluorene analogs as hepatitis C inhibitors. WO 2013026162, A1.

6 (a) A. Silvani, G. Lesma, S. Crippa, V. Vece, *Tetrahedron*, **2014**, *70*, 3994-4001. (b) J. M. Saya, B. Oppelaar, R. C. Cioc, G. Heijden, C. M. L. V. Velde, R. V. A. Orru, E. Ruijter, *Chem. Commun.* **2016**, *52*, 12482-12485. (c) I. W. Elliott, *J. Org. Chem.*, **1962**, *27*, 3302-3305. (d) Y. Kanaoka, E. Sato, O. Yonemitsu, *Tetrahedron*, **1968**, *24*, 2591-2594.

7 (a) A. Noren-Muller, J. I. Reis-Corrêa, H. Prinz, C. Rosenbaum, K. Saxena, H. J. Schwalbe, D. Vestweber, G. Cagna, S. Schunk, O. Schwarz, H. Schiewe, H. Waldmann, *Proc. Natl. Acad. Sci.* USA **2006**, *103*, 10606-10611. (b) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234-6246.

8 (a) C. L. Sun, B. J. Li, Z. J. Shi, *Chem. Rev.* **2011**, *111*, 1293-1314; (b) C. J. Li, *Acc. Chem. Res.* **2009**, *42*, 335-344. (c) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115.

9 (a) E. J. Horn, B. R. Rosen, Y Chen, J. Z. Tang, K. Chen, M. D. Eastgate, P. S. Baran, *Nature* **2016**, *533*, 77-81. (b) Y. Ka-wamata, M. Yan, Z. Q. Liu, D. H. Bao, J. S. Chen, J. T. Starr, P. S. Baran, *J. Am. Chem. Soc*. **2017**, *139*, 7448-7451. (c) Y. F. Liang, X. Y. Li, X. Y. Wang, M. C. Zou, C. H. Tang, Y. J. Liang, S. Song, N. Jiao, *J. Am. Chem. Soc.* **2016**, *138*, 12271-12277. (d) W. Zhou, W. Y. Fan, Q. J. Jiang, Y. F. Liang, N. Jiao, *Org. Lett.* **2015**, *17*, 2542-2545. (e) K. Moriyama, M. Takemura, H. Togo, *Org. Lett.* **2012**, *14*, 2414-2417. (f) H. Peng, A. J. Lin, Y. Zhang, H. L. Jiang, J. C. Zhou, Y. X. Cheng, C. J. Zhu, H. W. Hu, *ACS Catal.* **2012**, *2*, 163-167.

10 (a) S. Z. Jiang, X. Y. Zeng, X. Liang, T. Lei, K. Wei, Y. R. Yang, *Angew. Chem. Int. Ed.* **2016**, *55*, 4044-4048. (b) K. Mori, K. Kurihara, S. Yabe, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2014**, *136*, 3744-3747. (c) L. N. Guo, X. H. Duan, X. Y. Liu, J. Hu, H. P. Bi, Y. M. Liang, *Org. Lett.* **2007**, *9*, 5425-5428. (d) Z. H. Ren, H. Guan, Z. Y. M. Liang, *J. Org. Chem.* **2009**, *74*, 3145-3147. (e) W. H. Chiou, Y. H. Lin, G. T. Chen, Y. K. Gao, Y. C. Tseng, C. L. Kao, J. C. Tsai, *Chem. Commun.*, **2011**, *47*, 3562-3564. (f) T. J. Li, Z. Q. Liu, H. M. Yin, C. S. Yao, B. Jiang, X. S. Wang, S. J. Tu, X. L. Li, G. G. Li, *J. Org. Chem.* **2013**, *78*, 11414-11420. (g) J. M. Tang, B. Q. Xu, X. Mao, H. Y. Yang, X. X. Wang, X. Lv, *J. Org. Chem.* **2015**, *80*, 11108-11114. (h) H. Y. Zhao, Y. C. Wang, X. L. Cao, Q. F. Pang, H. S. Wang, Y. M. Pan, *RSC Adv.* **2017**, *7*, 24011-24014.

11 (a) M. D. Garcı á, A. J. Wilson, D. P. G. Emmerson, P. R. Jenkins, *Chem. Commun.* **2006**, 2586–2588. (b) A. Kulkarni, M. Abid, B. Torok, X. D. Huang, *Tetrahedron Lett.* **2009**, *50*, 1791-1794. (c)

T. H. Trieu, J. Dong, Q. Zhang, B. Zheng, T. Z. Meng, X. Lu, X. X. Shi, *Eur. J. Org. Chem.* **2013**, 3271–3277. (d) Zhu, Y. P.; Liu, M. C.; Cai, Q.; Jia, F. C.; Wu, A. X. *Chem. Eur. J.* **2013**, *19*, 10132-10137.

12 S. Y. Liu, W. F. Yao, Y. Liu, Q. H. Wei, J. H. Chen, X. Wu, F. Xia, W. H. Hu, *Sci. Adv.* **2017**, *3*, e1602467.

13 J. Stöckigt, A. P. Antonchick, F. R. Wu, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8538-8564 and references cited therein.

14 (a) M. Dukat, P. D. Mosier, R. Kolanos, B. L. Roth, R. A. Glen-non, *J. Med. Chem.* **2008**, *51*, 603-611. (b) S. G. Yuan, Q. Peng, K. Palczewski, H. Vogel, S. Filipek, *Angew. Chem. Int. Ed.* **2016**, *55*, 8661-8665.

15 (a) C. Zhang, C. K. De, R. Mal, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 416-417. (b) C. Zhang, D. Das, D. Seidel, *Chem. Sci.*, **2011**, *2*, 233-236. (c) R. Salame, E. Gravel, K. Leblanc, E. Poupon, *Org. Lett.* **2009**, *11*, 1891-1894. (d) H. H. Fang, X. Y. Wu, L. L. Nie, X. Y. Dai, J. Chen, W. G. Cao, G. Zhao, *Org. Lett.* **2010**, *12*, 5366-5369. (e) C. A. Holloway, M. E. Muratore, R. L. Storer, D. J. Dixon, *Org. Lett.* **2010**, *12*, 4720-4723. (f) D. Chandrasekhar, S. Borra, J. S. Kapure, G. S. Shivaji, G. Srinivasulu, R. A. Maurya, *Org. Chem. Front.*, **2015**, *2*, 1308-1312. (g) D. Zhu, J. Sun, C. G. Yan, *RSC Adv*., **2014**, *4*, 62817-62826.