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Selective Synthesis of Polyfunctionalized Pyrido[2,3-*b*]indoles by Multicomponent Domino Reactions

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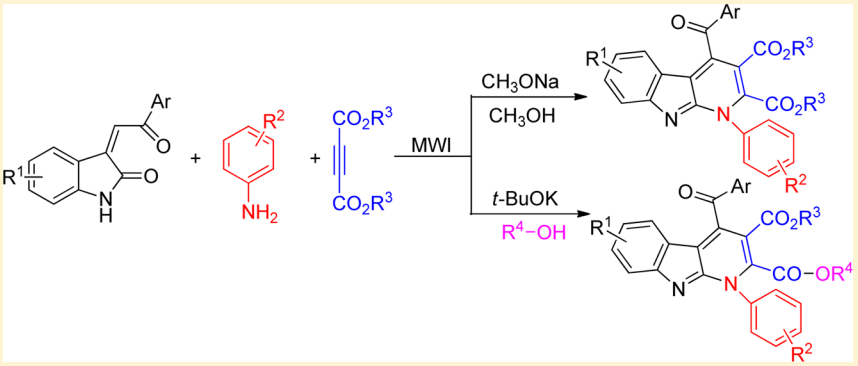
Supporting Information



ABSTRACT: A series of novel polyfunctionalized pyrido[2,3-*b*]indoles were synthesized by three- or four-component domino reactions under microwave irradiation. This protocol has the advantages of readily available starting materials, short reaction times, high yields, easy workup, and high chemo- and regioselectivities.

INTRODUCTION

The efficient construction of polyheterocyclic skeletons bearing several different functionalities is a challenging theme in modern synthetic organic synthesis.[1] Among these polyheterocyclic skeletons, the structurally diverse pyrido[2,3-*b*]indoles (α-carbolines) have received renewed interest, because of their biological activities such as anti-inflammatory, antiviral, anxiolytic, antitumor, antileukemic, and central-nervous-system-stimulating activities.[2] Some natural products such as grossularine-1 and -2, mescengricin, and GABA modulator contain this tricyclic core (Figure 1). Because of the unique chemical and biological properties of these compounds, many methodologies for the synthesis of pyrido[2,3-*b*]indole derivatives have been developed, namely, modified Graebe–Ullmann reactions of triazoles,[3] intramolecular Diels–Alder reactions,[4] cyclization of azaindoles,[5] and other methods.[6] However, most of these methods give low yields and require several steps from unavailable starting materials. The development of an efficient protocol for direct construction of the polyfunctionalized pyrido[2,3-*b*]indole skeleton from readily available starting materials is therefore desirable.

In recent years, efficient synthetic strategies for the selective construction of diverse and complex heterocyclic molecules have been developed. Multicomponent domino reactions (MDRs), in which more than two components are combined in a single synthetic operation, have been extensively used as a powerful strategy in the total synthesis of natural products and some important building blocks.[7] In these MDRs, multiple stereocenters are generated with step economy, and the purification of precursors and tedious protection and deprotection of functional groups are avoided.[8] These features make MDRs suitable for the construction of diverse and

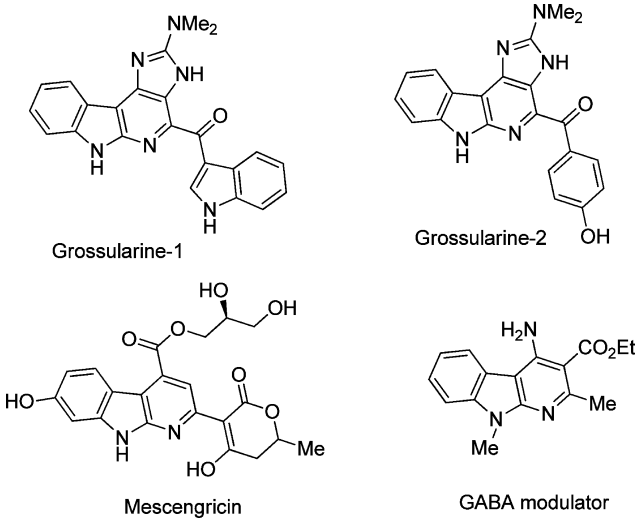


Figure 1. Structures of naturally occurring and bioactive pyrido[2,3-*b*]indoles.

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Scheme 1. New Multicomponent Domino Reactions

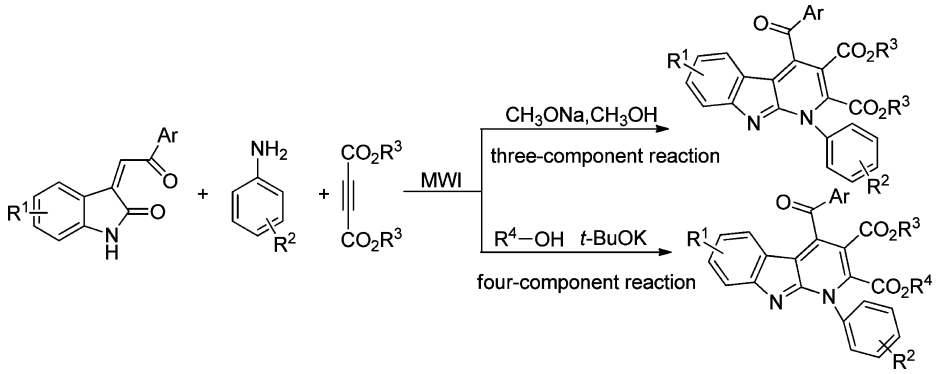
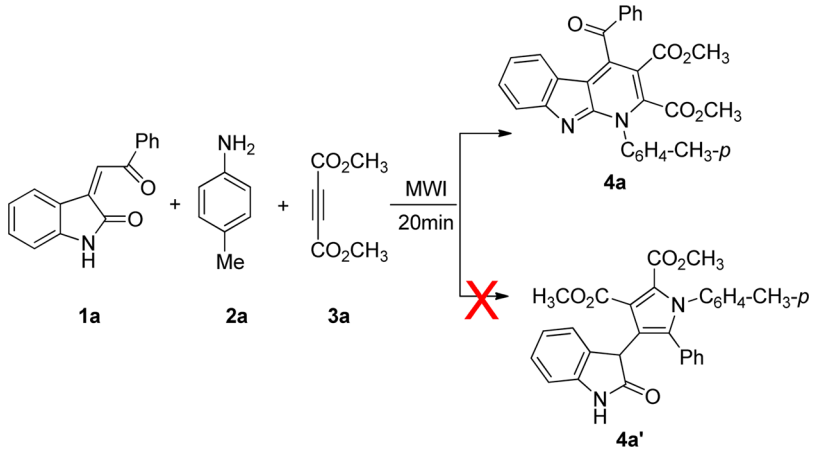


Table 1. Optimization of Reaction Conditions for Synthesis of 4a under Microwave Irradiation



entry	solvent	catalyst (mol %)	T (°C)	yield[a] (%)
1	CH_3OH	none	90	trace
2	CH_3OH	NaOH (10)	90	67
3	CH_2Cl_2	NaOH (10)	55	25
4	toluene	NaOH (10)	110	31
5	C_2H_5OH	NaOH (10)	100	trace (57[b])
6	DMF	NaOH (10)	110	57
7	CH_3OH	C_2H_5ONa (10)	90	74
8	CH_3OH	CH_3ONa (10)	90	86
9	CH_3OH	Cs_2CO_3 (10)	90	53
10	CH_3OH	*t*-BuOK (10)	90	80
11	CH_3OH	piperidine (10)	90	71
12	CH_3OH	pyridine (10)	90	69
13	CH_3OH	CH_3ONa (5)	90	75
14	CH_3OH	CH_3ONa (15)	90	62
15	CH_3OH	CH_3ONa (10)	50	48
16	CH_3OH	CH_3ONa (10)	60	49
17	CH_3OH	CH_3ONa (10)	70	69
18	CH_3OH	CH_3ONa (10)	80	74

[a]Yields determined by high-performance liquid chromatography combined with mass spectrometry (HPLC-MS). [b]Yield of transesterification product.

complex heterocyclic molecules from readily available starting materials.[9] Recently, we developed a series of MDRs for the construction of some multiple functionalized heterocyclic molecules of chemical and pharmaceutical importance.[10] As a part of our work on this project, we studied the efficient construction of novel polyfunctionalized pyrido[2,3-*b*]indoles by three- or four-component domino reactions of 3-aroylmethylidene-2-oxindoles, anilines, and acetylenedicarboxylates or alcohols under microwave irradiation (Scheme 1).

RESULTS AND DISCUSSION

First, we evaluated the three-component domino reaction of 3-benzoylmethylidene-2-oxindole (**1a**), which was derived from the reaction of indoline-2,3-dione with acetophenone, *p*-toluidine (**2a**), and dimethyl but-2-ynedioate (**3a**). The

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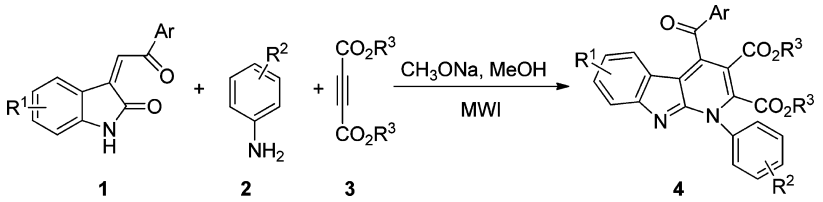
Table 2. Synthesis of Compounds 4 under Microwave Irradiation



1 2 3 4

entry	product	R^1	Ar	R^2	R^3	isolated yield (%)
1	**4a**	H	C_6H_5	4-CH_3	CH_3	82
2	**4b**	H	C_6H_5	4-CH_3O	CH_3	84
3	**4c**	H	C_6H_5	4-C_2H_5O	CH_3	88
4	**4d**	H	C_6H_5	4-$(CH_3)_2CH$	CH_3	82
5	**4e**	H	C_6H_5	4-$(CH_3)_3C$	CH_3	76
6	**4f**	H	4-$CH_3C_6H_4$	4-CH_3	CH_3	86
7	**4g**	H	4-$CH_3C_6H_4$	4-CH_3O	CH_3	85
8	**4h**	H	4-$CH_3C_6H_4$	4-C_2H_5O	CH_3	88
9	**4i**	H	4-$CH_3C_6H_4$	4-Br	CH_3	76
10	**4j**	H	4-$CH_3C_6H_4$	4-$(CH_3)_2CH$	CH_3	83
11	**4k**	H	4-$MeOC_6H_4$	4-CH_3O	CH_3	87
12	**4l**	H	4-BrC_6H_4	4-CH_3	CH_3	78
13	**4m**	H	4-$MeOC_6H_4$	4-CH_3	CH_3	89
14	**4n**	H	4-$MeOC_6H_4$	4-Br	CH_3	80
15	**4o**	H	C_6H_5	3-Cl-4-CH_3	CH_3	56
16	**4p**	H	2-$CH_3C_6H_4$	4-CH_3	CH_3	84
17	**4q**	H	furan-2-yl	4-CH_3	CH_3	85
18	**4r**	5-F	4-$CH_3C_6H_4$	4-CH_3	CH_3	78
19	**4s**	5-Me	4-$CH_3C_6H_4$	4-CH_3	CH_3	76
20	**4t**	H	C_6H_5	4-CH_3	C_2H_5	90
21	**4u**	H	C_6H_5	4-CH_3O	C_2H_5	85
22	**4v**	H	C_6H_5	4-$(CH_3)_2CH$	C_2H_5	86
23	**4w**	H	C_6H_5	4-C_2H_5O	C_2H_5	83
24	**4x**	H	4-$CH_3C_6H_4$	4-CH_3	C_2H_5	87
25	**4y**	H	4-$CH_3C_6H_4$	4-CH_3O	C_2H_5	79
26	**4z**	H	4-$CH_3C_6H_4$	4-Br	C_2H_5	76

reaction mixture, which consisted of a 1:1:1 mixture of **1a**, **2a**, and **3a**, was tested under different conditions. The results are summarized in Table 1. The optimization process indicated that the reaction did not proceed in methanol under catalyst-free conditions (Table 1, entry 1). When the reaction was carried out in the presence of NaOH (10 mol %) in methanol, the novel product **4a**, which was formed by decarbonylation of the oxindole lactam, was obtained in 67% yield. However, the normal product, namely, pentasubstituted pyrrole (**4a′**),[11] was not obtained. This shows that the reaction proceeded in a different direction when the reaction medium was changed from acidic to basic conditions. We then attempted to improve the yield by using different solvents. We found that methanol gave much better results than dichloromethane, toluene, ethanol, and dimethylformamide (DMF) (Table 1, entries 2−6). In addition, the catalytic efficiencies of several other bases were evaluated. In all cases, 10 mol % of the catalyst was used, and the reaction was carried out in methanol at 90 °C for 20 min under microwave irradiation. The results showed that CH_3ONa was a better catalyst than NaOH, EtONa, Cs_2CO_3, *t*-BuOK, piperidine, and pyridine (Table 1, entries 2 and 7−12).

After having identified CH_3ONa as the best catalyst for the transformation, we evaluated the amount of CH_3ONa required. The results showed that 10 mol % CH_3ONa was effective in promoting this reaction; the addition of larger amounts of the catalyst did not improve the yields (Table 1, entries 8, 13, and 14). The optimum reaction temperature was determined by performing the reaction with 10 mol % CH_3ONa at 50, 60, 70, 80, and 90 °C; the desired product **4a** was obtained in yields of 48%, 49%, 69%, 74%, and 86%, respectively (Table 1, entries 8 and 15−18). The best reaction temperature was therefore 90 °C, so the optimum conditions were determined to be 10 mol % CH_3ONa in methanol at 90 °C under microwave irradiation.

We investigated the substrate scope of the transformation, using the optimum conditions (Table 2). As shown in Table 2, phenyl, 4-methylphenyl, 4-methoxyphenyl, 4-bromophenyl, or furan-2-yl on the 3-aroylmethylidene-2-oxindole ring and phenyl groups bearing either electron-donating groups (such as methyl, methoxy, ethoxy, isopropyl, and *tert*-butyl groups) or electron-withdrawing groups (such as bromo and chloro groups) on the aniline ring were well tolerated under the reaction conditions and afforded the desired products in satisfactory yields.

Interestingly, when the model reaction was performed in ethanol using 10 mol % NaOH as the catalyst, the desired product was not obtained (Table 1, entry 5). Thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC) indicated that the starting materials had disappeared, and the product was identified as **6a**. Compound **6a** is the transesterification product of compound **4a** with ethanol. This transesterification occurred regioselectively at C-2, so **6a′** was not obtained (Scheme 2). We then optimized the

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Scheme 2. New Four-Component Domino Reaction

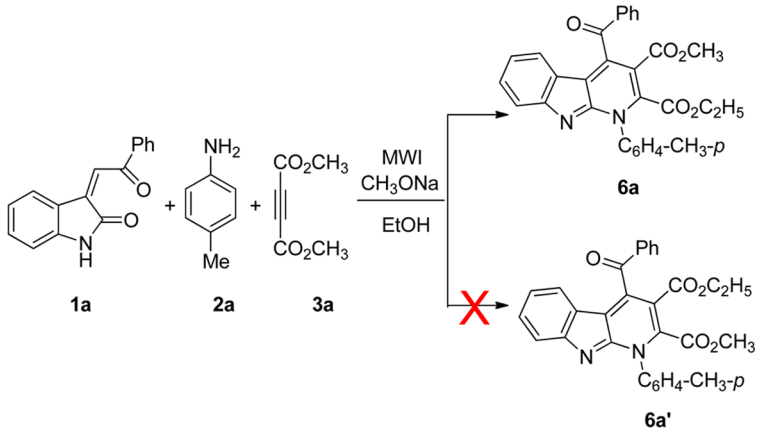
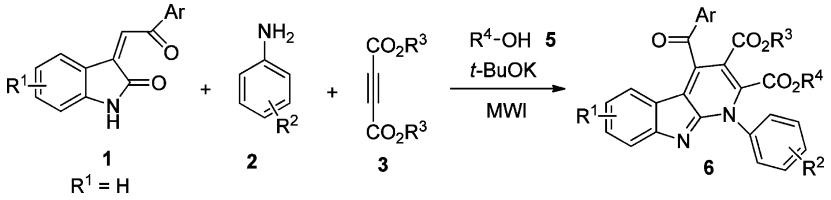


Table 3. Synthesis of Compounds 6 under Microwave Irradiation



entry	product	Ar	R^2	R^3	R^4	isolated yield (%)
1	**6a**	C_6H_5	4-CH_3	CH_3	C_2H_5	82
2	**6b**	4-$CH_3C_6H_4$	4-C_2H_5O	CH_3	C_2H_5	88
3	**6c**	4-$CH_3C_6H_4$	4-CH_3	CH_3	C_2H_5	89
4	**6d**	4-$CH_3C_6H_4$	4-CH_3O	CH_3	C_2H_5	93
5	**6e**	furan-2-yl	4-CH_3	CH_3	C_2H_5	63
6	**6f**	C_6H_5	4-CH_3	C_2H_5	CH_3	86
7	**6g**	C_6H_5	4-C_2H_5O	C_2H_5	CH_3	87
8	**6h**	C_6H_5	4-CH_3O	C_2H_5	CH_3	87
9	**6i**	C_6H_5	4-*i*-Pr	C_2H_5	CH_3	89
10	**6j**	4-$CH_3C_6H_4$	4-C_2H_5O	C_2H_5	CH_3	85
11	**6k**	4-ClC_6H_4	4-CH_3	C_2H_5	CH_3	71
12	**6l**	C_6H_5	4-CH_3	CH_3	*n*-C_3H_7	70
13	**6m**	C_6H_5	4-C_2H_5O	CH_3	*n*-C_3H_7	72
14	**6n**	C_6H_5	4-CH_3	CH_3	*n*-C_4H_9	16[a]
15	**6o**	C_6H_5	4-CH_3	CH_3	*i*-C_3H_7	8[a]
16	**6p**	C_6H_5	4-CH_3	CH_3	$C_6H_5CH_2$	trace[a]

[a]Yields determined by HPLC-MS.

reaction conditions. The best reaction conditions were 10 mol % *t*-BuOK as the catalyst at 90 °C for 20 min under microwave irradiation. Under the optimum reaction conditions, the series of pyrido[2,3-*b*]indoles **6** were synthesized in good yields (Table 3). The data in Table 3 show that methanol, ethanol, and *n*-propanol were suitable for this reaction. However, when other alcohols such as butanol, 2-propanol, and phenylmethanol were used, the product yields were low (Table 3, entries 14−16), or no products were obtained.

The structures of products **4** and **6** were determined based on their IR, ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS) spectra. The structures of compounds **4a** and **6a** were further confirmed by X-ray diffraction analysis (see Supporting Information).

Based on literature reports,[12] we propose a mechanism for the current MDRs (Scheme 3). The first reaction is the formation of an active *β*-enamino ester (**A**) by amine addition to the acetylenedicarboxylate. Then, Michael addition of **A** to the exocyclic carbon atom of the 3-aroylmethylidene-2-oxindole gives the intermediate **B**. Intermediate **B** undergoes intramolecular nucleophilic addition of an amino group to the carbonyl group of the oxindole lactam to give intermediate **C**. Dehydration of intermediate **C**, followed by aromatization, gives **4**. Other products **6** could also be obtained by base-catalyzed transesterification of **4** with the alcohol; this was confirmed experimentally. When the reaction of **4a**, 10 mol % *t*-BuOK, and ethanol was performed under the above conditions for 20 min, the desired product **6a** was obtained in 84% yield.

CONCLUSIONS

In summary, we have developed a procedure for the facile synthesis of various potentially biologically active polyfunctionalized pyrido[2,3-*b*]indoles, using novel three- or four-component domino reactions. This protocol has the advantages of mild reaction conditions, convenient one-pot operation,

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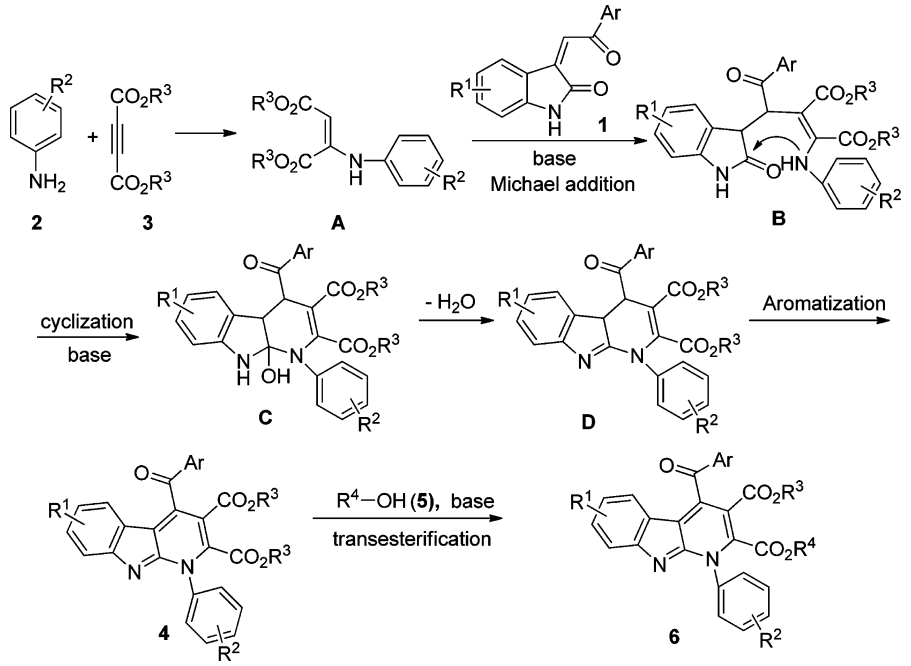
Scheme 3. Proposed Mechanism of Multicomponent Domino Reactions



short reaction times, excellent chemo- and regioselectivities, and atom economy.

EXPERIMENTAL SECTION

General Methods. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. The reaction temperatures were measured by infrared detector during microwave heating.

Representative Synthesis of 4. *Dimethyl 4-Benzoyl-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4a**).* Typically, 3-benzoylmethylidene-2-oxindole (**1a**, 1.0 mmol), *p*-toluidine (**2a**, 1 mmol) and dimethyl but-2-ynedioate (**3a**, 1.0 mmol) were introduced into a 5 mL initiator reaction vial, after which 10 mol % CH_3ONa and methanol (2 mL) were successively added. Subsequently, the reaction vial was closed, and the reaction mixture was prestirred for 10 s. The mixture was irradiated at 90 °C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The precipitate was collected and washed with 95% EtOH to give the pure product **4a** as a yellow solid, 0.392 g, yield 82%, purity 99.9%; mp 264−266 °C; IR (KBr, ν, cm^{-1}) 2960, 1742, 1714, 1671, 1600, 1515, 1435, 1404, 1385, 1325, 1295, 1253, 1175, 1083, 1024, 797; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.00 (d, J = 7.6 Hz, 2H), 7.75−7.71 (m, 1H), 7.60−7.53 (m, 5H), 7.47−7.43 (m, 3H), 7.30 (d, J = 8.0 Hz, 1H), 7.06−7.03 (m, 1H), 3.60 (s, 3H), 3.58 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.7, 164.1, 162.2, 155.7, 154.1, 141.5, 141.1, 140.5, 135.9, 135.4, 135.0, 130.1, 129.8, 129.7, 129.3, 128.4, 123.8, 122.6, 122.1, 121.3, 119.3, 106.5, 53.9, 53.3, 21.4; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{22}N_2O_5$ 478.1529 $[M]^+$, found 478.1516.

*Dimethyl 4-Benzoyl-1-(4-methoxyphenyl)-1H-pyrido[2,3-b]-indole-2,3-dicarboxylate (**4b**).* Yellow solid, 0.415 g, yield 84%, purity 98.7%; mp 224−226 °C; IR (KBr, ν, cm^{-1}) 2955, 2841, 1739, 1715, 1670, 1603, 1523, 1508, 1433, 1399, 1323, 1293, 1255, 1236, 1219, 1112, 1081, 1029, 1002, 926, 841, 767; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.99 (d, J = 7.2 Hz, 2H), 7.75−7.71 (m, 1H), 7.60−7.57 (m, 5H), 7.47−7.43 (m, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.06−7.03 (m, 1H), 3.90 (s, 3H), 3.62 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.7, 164.1, 162.3, 160.7, 155.7, 154.3, 141.9, 141.1, 135.9, 135.0, 130.5, 129.9, 129.8, 129.7, 129.3, 123.7, 122.6, 122.2, 121.3, 119.3, 114.7, 106.4, 56.1, 53.9, 53.3; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{22}N_2O_6$ 494.1478 $[M]^+$, found 494.1483.

*Dimethyl 4-Benzoyl-1-(4-ethoxyphenyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4c**).* Yellow solid, 0.447 g, yield 88%, purity 99.5%; mp 229−231 °C; IR (KBr, ν, cm^{-1}) 2951, 1740, 1716, 1677, 1599, 1511, 1434, 1404, 1383, 1323, 1295, 1255, 1219, 1177, 1114, 1082, 1045, 926, 841, 794, 764; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.00 (d, J = 7.2 Hz, 2H), 7.75−7.71 (m, 1H), 7.60−7.56 (m, 5H), 7.47−7.43 (m, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.06−7.02 (m, 1H), 4.16 (q, J = 6.8 Hz, 2H), 3.62 (s, 3H), 3.58 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.7, 164.1, 162.3, 160.0, 155.7, 154.3, 141.9, 141.1, 135.9, 135.0, 130.3, 129.9, 129.7, 129.3, 123.7, 122.6, 122.2, 121.3, 119.3, 115.1, 106.4, 64.0, 53.9, 53.2, 15.1; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{24}N_2O_6$ 508.1634 $[M]^+$, found 508.1639.

*Dimethyl 4-Benzoyl-1-(4-isopropylphenyl)-1H-pyrido[2,3-b]-indole-2,3-dicarboxylate (**4d**).* Yellow solid, 0.415 g, yield 82%, purity 99.8%; mp 234−236 °C; IR (KBr, ν, cm^{-1}) 2958, 1744, 1713, 1673, 1598, 1521, 1434, 1403, 1325, 1279, 1237, 1175, 1080, 951, 927, 866, 794, 739; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.01 (d, J = 7.6 Hz, 2H), 7.75−7.71 (m, 1H), 7.61−7.57 (m, 5H), 7.53 (d, J = 8.4 Hz, 2H), 7.47−7.43 (m, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.07−7.03 (m, 1H), 3.57 (s, 3H), 3.55 (s, 3H), 3.10−3.03 (m, 1H), 1.31 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.7, 164.1, 162.3, 155.7, 154.1, 151.0, 141.6, 141.1, 135.9, 135.6, 135.0, 129.8, 129.7, 129.3, 128.5, 127.5, 123.8, 122.6, 122.1, 121.3, 119.3, 106.5, 53.7, 53.3, 33.7, 24.2; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{26}N_2O_5$ 506.1842 $[M]^+$, found 506.1849.

*Dimethyl 4-Benzoyl-1-[4-(tert-butyl)phenyl]-1H-pyrido[2,3-b]-indole-2,3-dicarboxylate (**4e**).* Yellow solid, 0.396 g, yield 76%, purity 99.1%; mp 184−186 °C; IR (KBr, ν, cm^{-1}) 2960, 1754, 1728, 1682, 1601, 1511, 1459, 1340, 1238, 1215, 1084, 1020, 823, 775, 720; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.00 (d, J = 7.2 Hz, 2H), 7.75−7.72 (m, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.61−7.57 (m, 5H), 7.47−7.43 (m, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.07−7.03 (m, 1H), 3.57 (s, 3H), 3.54 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 192.8, 163.2, 161.2, 155.0, 150.8, 142.1, 135.7, 135.3, 133.8, 131.3, 130.0, 129.8, 129.5, 127.3, 126.9, 123.3, 123.0, 122.5, 122.4, 116.2, 54.3, 54.0, 35.4, 34.8, 31.5, 31.5; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{29}N_2O_5$ 521.2076 $[M + H]^+$, found 521.2073.

*Dimethyl 4-(4-Methylbenzoyl)-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4f**).* Yellow solid, 0.424 g, yield 86%, purity 98.6%;

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mp 262−264 °C; IR (KBr, ν, cm^{-1}) 2949, 1742, 1716, 1669, 1604, 1515, 1436, 1404, 1385, 1324, 1297, 1237, 1175, 1113, 1082, 953, 929, 759, 721; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.89 (d, J = 8.0 Hz, 2H), 7.58−7.54 (m, 3H), 7.46−7.42 (m, 3H), 7.38 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.06−7.02 (m, 1H), 3.60 (s, 3H), 3.58 (s, 3H), 2.47 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.2, 164.1, 162.3, 155.7, 154.1, 145.7, 141.5, 141.3, 140.5, 135.4, 133.5, 130.3, 130.1, 129.7, 129.5, 128.4, 123.7, 122.6, 122.2, 121.2, 119.3, 106.6, 53.8, 53.3, 21.8, 21.4; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{24}N_2O_5$ 492.1685 [M]$^+$, found 492.1694.

*Dimethyl 1-(4-Methoxyphenyl)-4-(4-methylbenzoyl)-1H-pyrido-[2,3-b]indole-2,3-dicarboxylate (**4g**).* Yellow solid, 0.432 g, yield 85%, purity 99.0%; mp 252−254 °C; IR (KBr, ν, cm^{-1}) 2954, 1741, 1716, 1659, 1603, 1508, 1434, 1399, 1323, 1294, 1254, 1221, 1176, 1114, 1082, 1028, 926, 863, 781, 764; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.88 (d, J = 8.0 Hz, 2H), 7.57 (m, 3H), 7.46−7.42 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.06−7.02 (m, 1H), 3.89 (s, 3H), 3.61 (s, 3H), 3.58 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.2, 164.1, 162.3, 160.6, 155.6, 154.3, 145.7, 141.8, 141.3, 133.5, 130.5, 130.3, 130.0, 129.7, 129.5, 123.6, 122.6, 122.2, 121.2, 119.2, 114.7, 106.5, 56.0, 53.9, 53.2, 21.8; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{24}N_2O_6$ 508.1634 [M]$^+$, found 508.1646.

*Dimethyl 1-(4-Ethoxyphenyl)-4-(4-methylbenzoyl)-1H-pyrido-[2,3-b]indole-2,3-dicarboxylate (**4h**).* Yellow solid, 0.460 g, yield 88%, purity 98.4%; mp 242−244 °C; IR (KBr, ν, cm^{-1}) 2953, 1739, 1716, 1674, 1638, 1617, 1511, 1436, 1402, 1384, 1323, 1296, 1256, 1222, 1175, 1114, 1082, 1046, 926, 783, 739; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.88 (d, J = 8.0 Hz, 2H), 7.60−7.56 (m, 3H), 7.46−7.42 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.06−7.02 (m, 1H), 4.16 (q, J = 6.8 Hz, 2H), 3.61 (s, 3H), 3.58 (s, 3H), 2.40 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.2, 164.1, 162.3, 160.0, 155.6, 154.3, 145.7, 141.9, 141.3, 133.6, 130.3, 129.9, 129.7, 129.5, 123.6, 122.6, 122.2, 121.2, 119.2, 115.1, 106.5, 64.0, 53.8, 53.2, 21.8, 15.1; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{26}N_2O_6$ 522.1791 [M]$^+$, found 522.1800. Anal. Calcd for $C_{31}H_{26}N_2O_6$: C, 71.25; H, 5.02; N, 5.36. Found: C, 71.59; H, 4.98; N, 5.36.

*Dimethyl 1-(4-Bromophenyl)-4-(4-methylbenzoyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4i**).* Yellow solid, 0.424 g, yield 76%, purity 99.7%; mp 218−221 °C; IR (KBr, ν, cm^{-1}) 2952, 1740, 1717, 1670, 1604, 1518, 1488, 1437, 1400, 1385, 1325, 1296, 1255, 1224, 1175, 1145, 1080, 1013, 926, 799, 725; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.89 (d, J = 6.8 Hz, 3H), 7.68 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 7.2 Hz, 2H), 7.47−7.43 (m, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.07−7.03 (m, 1H), 3.63 (s, 3H), 3.58 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.1, 164.1, 162.3, 155.7, 154.0, 145.6, 141.3, 141.0, 137.3, 133.6, 132.8, 130.3, 129.5, 124.2, 124.0, 122.7, 122.2, 121.4, 119.3, 114.7, 107.0, 100.0, 54.0, 53.3, 31.16, 21.8; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{21}BrN_2O_5$ 556.0634 [M]$^+$, found 556.0640.

*Dimethyl 1-(4-Isopropylphenyl)-4-(4-methylbenzoyl)-1H-pyrido-[2,3-b]indole-2,3-dicarboxylate (**4j**).* Yellow solid, 0.432 g, yield 83%, purity 99.5%; mp 256−258 °C; IR (KBr, ν, cm^{-1}) 2955, 1743, 1720, 1669, 1604, 1521, 1436, 1400, 1384, 1369, 1296, 1237, 1222, 1177, 1145, 1114, 1080, 926, 894, 759; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.89 (d, J = 8.0 Hz, 2H), 7.59−7.52 (m, 5H), 7.46−7.42 (m, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.06−7.03 (m, 1H), 3.57 (s, 3H), 3.55 (s, 3H), 3.08−3.05 (m, 1H), 2.40 (s, 3H), 1.31 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.2, 164.1, 162.3, 155.7, 154.1, 151.0, 145.7, 141.6, 141.3, 135.7, 133.5, 130.3, 130.1, 129.7, 129.5, 128.5, 127.5, 123.7, 122.7, 122.2, 121.3, 119.2, 106.6, 53.7, 53.2, 33.7, 24.2, 21.8; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{28}N_2O_5$ 520.1998 [M]$^+$, found 520.1998. Anal. Calcd for $C_{32}H_{28}N_2O_5$: C, 73.83; H, 5.42; N, 5.38. Found: C, 73.51; H, 5.76; N, 5.06.

*Dimethyl 4-(4-Methoxybenzoyl)-1-(4-methoxyphenyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4k**).* Yellow solid, 0.456 g, yield 87%, purity 98.3%; mp 254−256 °C; IR (KBr, ν, cm^{-1}) 2954, 2842, 1743, 1715, 1659, 1597, 1509, 1432, 1398, 1255, 1223, 1168, 1018, 930, 841, 818, 766; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.96 (d, J = 8.0 Hz, 2H), 7.60−7.57 (m, 3H), 7.46−7.43 (m, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.20−7.17 (m, 2H), 7.10−7.03 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.62 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 192.0, 164.5, 164.2, 162.4, 160.6, 155.6, 154.3, 141.8, 141.5, 131.9, 130.5, 130.0, 129.9, 129.6, 129.0, 123.6, 122.7, 122.3, 121.2, 119.2, 115.0, 114.8, 114.7, 106.6, 56.1, 56.0, 53.9, 53.2; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{24}N_2O_7$ 524.1584 [M]$^+$, found 524.1581. Anal. Calcd for $C_{30}H_{24}N_2O_7$: C, 68.70; H, 4.61; N, 5.34. Found: C, 68.76; H, 4.92; N, 5.06.

*Dimethyl 4-(4-Bromobenzoyl)-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4l**).* Yellow solid, 0.435 g, yield 78%, purity 98.9%; mp 258−260 °C; IR (KBr, ν, cm^{-1}) 2954, 1740, 1713, 1674, 1620, 1586, 1515, 1436, 1405, 1384, 1323, 1297, 1233, 1172, 1144, 1113, 1082, 928, 860, 794, 723; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.94 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.51−7.48 (m, 3H), 7.32 (d, J = 8.0 Hz, 1H), 7.12−7.09 (m, 1H), 3.64 (s, 3H), 3.63 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 192.9, 164.0, 162.2, 155.7, 154.1, 141.6, 140.5, 140.4, 135.4, 135.0, 132.9, 131.2, 130.1, 129.9, 129.3, 128.4, 123.8, 122.5, 122.0, 121.4, 119.4, 106.3, 53.9, 53.4, 21.4; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{21}BrN_2O_5$ 556.0634 [M]$^+$, found 556.0644.

*Dimethyl 4-(4-Methoxybenzoyl)-1-(p-tolyl)-1H-pyrido[2,3-b]-indole-2,3-dicarboxylate (**4m**).* Yellow solid, 0.453 g, yield 89%, purity 99.1%; mp 248−250 °C; IR (KBr, ν, cm^{-1}) 2953, 1741, 1718, 1663, 1598, 1512, 1436, 1403, 1323, 1296, 1251, 1165, 1082, 1028, 956, 802, 759; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.96 (d, J = 8.4 Hz, 2H), 7.58−7.51 (m, 3H), 7.46−7.42 (m, 3H), 7.31 (d, J = 7.6 Hz, 1H), 7.10−7.03 (m, 3H), 3.86 (s, 3H), 3.60 (s, 3H), 3.59(s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 192.0, 164.5, 164.2, 162.3, 155.7, 154.1, 141.5, 141.4, 140.5, 135.5, 131.9, 130.1, 129.7, 129.0, 128.5, 128.3, 123.6, 122.7, 122.2, 121.2, 119.2, 115.0, 106.8, 56.1, 53.8, 53.2, 21.4; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{24}N_2O_6$ 508.1634 [M]$^+$, found 508,1636.

*Dimethyl 1-(4-Bromophenyl)-4-(4-methoxybenzoyl)-1H-pyrido-[2,3-b]indole-2,3-dicarboxylate (**4n**).* Yellow solid, 0.459 g, yield 80%, purity 99.0%; mp 238−240 °C; IR (KBr, ν, cm^{-1}) 2924, 2853, 1738, 1719, 1664, 1600, 1573, 1514, 1487, 1426, 1402, 1323, 1299, 1250, 1167, 1109, 1015, 997, 925, 861, 735; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.96 (d, J = 8.0 Hz, 2H), 7.90 (s, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.47−7.43 (m, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.10−7.04 (m, 3H), 3.86 (s, 3H), 3.64 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 191.9, 164.5, 164.2, 162.3, 155.7, 154.0, 141.4, 140.9, 137.3, 132.8, 131.9, 131.0, 130.8, 129.8, 129.0, 124.2, 123.9, 122.8, 122.2, 121.3, 119.2, 115.0, 107.2, 56.1, 54.0, 53.3; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{21}BrNaN_2O_6$ 595.0481 [M + Na]$^+$, found 595.0466. Anal. Calcd for $C_{29}H_{21}BrN_2O_6$: C, 60.75; H, 3.69; N, 4.89. Found: C, 60.52; H, 3.76; N, 4.81.

*Dimethyl 4-Benzoyl-1-(3-chloro-4-methylphenyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4o**).* Yellow solid, 0.287 g, yield 56%, purity 99.9%; mp 262−264 °C; IR (KBr, ν, cm^{-1}) 2925, 2853, 1741, 1718, 1660, 1603, 1582, 1529, 1485, 1431, 1408, 1323, 1300, 1250, 1171, 1109, 1015, 998, 924, 862, 735; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.99 (d, J = 7.6 Hz, 2H), 7.89 (s, 1H), 7.75−7.71 (m, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.60−7.57 (m, 4H), 7.48−7.43 (m, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.07−7.03 (m, 1H), 3.64 (s, 3H), 3.59 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.6, 164.1, 162.2, 155.7, 141.1, 141.0, 138.6, 136.7, 135.9, 135.0, 133.7, 132.1, 129.9, 129.7, 129.4, 129.2, 127.4, 124.1, 122.7, 122.2, 121.4, 119.3, 106.8, 54.0, 53.3, 21.2, 20.0; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{21}ClN_2O_5$ 512.1139 [M]$^+$, found 512.1129. Anal. Calcd for $C_{29}H_{21}ClN_2O_5$: C, 67.90; H, 4.13; N, 5.46. Found: C, 67.98; H, 4.43; N, 5.78.

*Dimethyl 4-(2-Methylbenzoyl)-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4p**).* Yellow solid, 0.414 g, yield 84%, purity 99.6%; mp 216−218 °C; IR (KBr, ν, cm^{-1}) 2950, 2923, 1744, 1714, 1669, 1504, 1436, 1402, 1322, 1296, 1234, 1183, 1080, 1023, 954, 805, 737, 721; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.59−7.52 (m, 6H), 7.47−7.44 (m, 3H), 7.33 (d, J = 8.0 Hz, 1H), 7.23−7.19 (m, 1H),

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7.09−7.05 (m, 1H), 3.58 (s, 6H), 2.85 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 195.1, 164.3, 162.3, 155.7, 154.3, 142.1, 141.5, 140.5, 135.5, 134.1, 134.0, 133.0, 132.9, 130.1, 129.8, 128.4, 126.8, 123.8, 122.7, 122.4, 121.3, 119.3, 106.6, 53.9, 53.4, 22.3, 21.4; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{24}N_2O_5$ 492.1685 $[M]^+$, found 492.1694.

*Dimethyl 4-(2-Furoyl)-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4q**).* Yellow solid, 0.398 g, yield 85%, purity 99.6%; mp 246−248 °C; IR (KBr, ν, cm^{-1}) 2948, 1745, 1728, 1663, 1618, 1535, 1493, 1440, 1407, 1379, 1329, 1296, 1247, 1223, 1176, 1089, 1011, 927, 804, 727; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.15 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.54−7.50 (m, 4H), 7.46 (d, J = 7.6 Hz, 3H), 7.16−7.13 (m, 1H), 6.80 (s, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 180.4, 164.2, 162.2, 155.8, 154.2, 151.8, 150.1, 141.3, 140.6, 139.4, 135.4, 130.2, 130.0, 128.4, 128.3, 124.4, 122.8, 122.1, 121.9, 121.5, 119.4, 113.8, 106.7, 53.9, 53.5, 21.4; HRMS (ESI-TOF) m/z calcd for $C_{27}H_{21}N_2O_6$ 469.1400 $[M + H]^+$, found 469.1371.

*Dimethyl 6-Fluoro-4-(4-methylbenzoyl)-1-(p-tolyl)-1H-pyrido-[2,3-b]indole-2,3-dicarboxylate (**4r**).* Yellow solid, 0.397 g, yield 78%, purity 98.9%; mp 230−232 °C; IR (KBr, ν, cm^{-1}) 2976, 2369, 1738, 1720, 1669, 1601, 1526, 1509, 1405, 1200, 1171, 1081, 1009, 970, 863, 778, 742; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.89 (d, J = 8.0 Hz, 2H), 7.63−7.59 (m, 1H), 7.54 (s, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 10.0 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 3.60 (s, 3H), 3.58 (s, 3H), 2.46 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 189.7, 176.8, 169.1, 164.1, 162.3, 155.6, 154.1, 146.0, 145.7, 141.5, 141.3, 140.5, 135.5, 135.2, 133.6, 130.4, 130.1, 129.6, 129.5, 128.4, 119.3, 106.6, 53.9, 53.3, 21.8, 21.4; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{24}FN_2O_5$ 511.1669 $[M + H]^+$, found: 511.1665. Anal. Calcd for $C_{30}H_{23}FN_2O_5$: C, 70.58; H, 4.54; N, 5.49. Found: C, 70.39; H, 4.78; N, 5.50.

*Dimethyl 6-Methyl-4-(4-methylbenzoyl)-1-(p-tolyl)-1H-pyrido-[2,3-b]indole-2,3-dicarboxylate (**4s**).* Yellow solid, 0.385 g, yield 76%, purity 99.7%; mp 225−227 °C; IR (KBr, ν, cm^{-1}) 2923, 2854, 1740, 1718, 1687, 1603, 1507, 1434, 1383, 1313, 1291, 1276, 1240, 1206, 1176, 1079, 1023, 969, 813, 737, 718; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.87 (d, J = 7.6 Hz, 2H), 7.52 (s, 2H), 7.47−7.43 (m, 3H), 7.38 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.10 (s, 1H), 3.58 (s, 3H), 3.56 (s, 3H), 2.46 (s, 3H), 2.41 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.2, 164.1, 162.3, 153.8, 153.7, 145.6, 141.3, 141.0, 140.4, 135.4, 133.6, 131.1, 130.3, 130.1, 130.0, 129.4, 128.4, 123.6, 122.4, 122.3, 119.0, 106.3, 53.8, 53.2, 21.8, 21.6, 21.3; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{27}N_2O_5$ 507.1920 $[M + H]^+$, found 507.1918.

*Diethyl 4-Benzoyl-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4t**).* Yellow solid, 0.456 g, yield 90%, purity 99.9%; mp 244−246 °C; IR (KBr, ν, cm^{-1}) 2928, 1738, 1700, 1677, 1597, 1524, 1509, 1443, 1402, 1321, 1292, 1278, 1240, 1202, 1173, 1113, 1083, 1008, 862, 832, 740, 709, 696; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.02 (d, J = 7.6 Hz, 2H), 7.76−7.72 (m, 1H), 7.61−7.54 (m, 5H), 7.47−7.42 (m, 3H), 7.29 (d, J = 8.0 Hz, 1H), 7.05−7.02 (m, 1H), 4.05 (q, J = 7.2 Hz, 4H), 2.48 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.6, 163.6, 161.6, 155.7, 154.1, 141.7, 141.2, 140.5, 135.9, 135.4, 135.0, 130.0, 129.7, 129.5, 128.6, 123.6, 122.6, 122.1, 121.2, 119.3, 106.5, 63.1, 62.5, 21.3, 13.7, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{26}N_2O_5$: 506.1846 $[M]^+$, found: 506.1854. Anal. Calcd for $C_{31}H_{26}N_2O_5$: C, 73.50; H, 5.17; N, 5.53. Found: C, 73.19; H, 5.48; N, 5.24.

*Diethyl 4-Benzoyl-1-(4-methoxyphenyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4u**).* Yellow solid, 0.444 g, yield 85%, purity 99.8%; mp 216−218 °C; IR (KBr, ν, cm^{-1}) 2979, 1739, 1720, 1673, 1596, 1511, 1427, 1405, 1292, 1249, 1207, 1114, 1082, 1004, 970, 816, 760, 697; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.02 (d, J = 7.6 Hz, 2H), 7.76−7.72 (m, 1H), 7.61−7.57 (m, 5H), 7.46−7.42(m, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.05−7.02 (m, 1H), 4.09−4.03 (m, 4H), 3.89 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.7, 163.6, 161.7, 160.8, 155.7, 154.3, 142.0, 141.2, 136.0, 135.0, 130.4, 130.2, 129.7, 129.6, 129.5, 123.5, 122.6, 122.2, 121.2, 119.3, 114.7, 106.4, 63.1, 62.5, 56.1, 13.7, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{26}N_2O_6$ 522.1791 $[M]^+$, found 522.1794.

*Diethyl 4-Benzoyl-1-(4-isopropylphenyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4v**).* Yellow solid, 0.460 g, yield 86%, purity 99.6%; mp 198−200 °C; IR (KBr, ν, cm^{-1}) 2960, 1737, 1720, 1696, 1600, 1532, 1426, 1400, 1292, 1230, 1201, 1114, 1052, 1028, 960, 830, 735; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.03 (d, J = 7.6 Hz, 2H), 7.77−7.72 (m, 1H), 7.61−7.58 (m, 5H), 7.53 (d, J = 8.0 Hz, 2H), 7.46−7.43 (m, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.06−7.02 (m, 1H), 4.09−3.98 (m, 4H), 3.03−3.08 (m, 1H), 1.30 (d, J = 6.8 Hz, 6H), 0.91 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.6, 163.6, 161.6, 155.7, 154.1, 151.2, 141.8, 141.2, 135.9, 135.6, 135.0, 129.8, 129.7, 129.5, 128.8, 127.4, 123.6, 122.6, 122.1, 121.2, 119.3, 106.5, 63.0, 62.5, 33.8, 24.2, 13.6, 13.5; HRMS (ESI-TOF) m/z calcd for $C_{33}H_{30}N_2O_5$ 534.2155 $[M]^+$, found 534.2164.

*Diethyl 4-Benzoyl-1-(4-ethoxyphenyl)-1H-pyrido-[2,3-b]indole-2,3-dicarboxylate (**4w**).* Yellow solid, 0.445 g, yield 83%, purity 99.3%; mp 196−198 °C; IR (KBr, ν, cm^{-1}) 2976, 1739, 1700, 1673, 1596, 1511, 1427, 1406, 1367, 1249, 1201, 1145, 1114, 1082, 1004, 970, 861, 789, 739; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.02 (d, J = 7.6 Hz, 2H), 7.75−7.72 (m, 1H), 7.61−7.57 (m, 5H), 7.46−7.42 (m, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.05−7.01 (m, 1H), 4.16 (q, J = 6.8 Hz, 2H), 4.05 (q, J = 6.8 Hz, 4H), 1.40 (t, J = 6.8 Hz, 3H), 0.99 (t, J = 6.8 Hz), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.7, 163.6, 161.7, 160.0, 155.7, 154.3, 142.1, 141.2, 136.0, 135.0, 130.3, 130.2, 129.7, 129.5, 123.5, 122.6, 122.2, 121.2, 119.3, 115.1, 106.4, 64.1, 63.1, 62.5, 15.0, 13.7, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{28}N_2O_6$ 536.1947 $[M]^+$, found 536.1946. Anal. Calcd for $C_{32}H_{28}N_2O_6$: C, 71.63; H, 5.26; N, 5.22. Found: C, 71.82; H, 5.09; N, 5.39.

*Diethyl 4-(4-Methylbenzoyl)-1-(p-tolyl)-1H-pyrido-[2,3-b]indole-2,3-dicarboxylate (**4x**).* Yellow solid, 0.453 g, yield 87%, purity 99.7%; mp 214−216 °C; IR (KBr, ν, cm^{-1}) 2976, 1738, 1721, 1668, 1601, 1526, 1508, 1440, 1403, 1320, 1293, 1239, 1202, 1171, 1112, 1081, 1009, 970, 863, 778, 742; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.91 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 8.0 Hz, 3H), 7.47−7.43 (m, 3H), 7.39 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.05−7.02 (m, 1H), 3.99−4.10 (m, 4H), 2.46 (s, 3H), 2.41 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.2, 163.6, 161.7, 155.7, 154.1, 145.7, 141.6, 141.4, 140.5, 135.4, 133.6, 130.3, 130.0, 129.6, 128.6, 123.5, 122.7, 122.2, 121.2, 119.2, 106.6, 63.1, 62.4, 21.8, 21.3, 13.7, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{28}N_2O_5$ 520.1998 $[M]^+$, found 520.2006.

*Diethyl 1-(4-Methoxyphenyl)-4-(4-methylbenzoyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4y**).* Yellow solid, 0.424 g, yield 79%, purity 99.5%; mp 200−202 °C; IR (KBr, ν, cm^{-1}) 2977, 2836, 1738, 1720, 1666, 1603, 1510, 1469, 1438, 1407, 1319, 1294, 1255, 1201, 1112, 1081, 1020, 971, 862, 838, 741; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.90 (d, J = 7.2 Hz, 2H), 7.57 (d, J = 8.0 Hz, 3H), 7.45−7.38 (m, 3H), 7.28 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 7.2 Hz, 2H), 7.05−7.01 (m, 1H), 4.12−4.01 (m, 4H), 3.89 (s, 3H), 2.40 (s, 3H), 0.99 (t, J = 6.8 Hz, 3H), 0.93 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.2, 163.6, 161.7, 160.8, 155.6, 154.3, 145.7, 142.0, 141.4, 133.6, 130.4, 130.3, 130.2, 129.6, 123.4, 122.6, 122.2, 121.1, 119.2, 114.7, 106.5, 63.1, 62.4, 56.1, 21.8, 13.7, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{28}N_2O_6$ 536.1947 $[M]^+$, found 536.1950. Anal. Calcd for $C_{32}H_{28}N_2O_6$: C, 71.63; H, 5.26; N, 5.22. Found: C, 71.55; H, 5.24; N, 5.25.

*Diethyl 1-(4-Bromophenyl)-4-(4-methylbenzoyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**4z**).* Yellow solid, 0.445 g, yield 76%, purity 99.3%; mp 206−208 °C; IR (KBr, ν, cm^{-1}) 2977, 1736, 1721, 1667, 1602, 1528, 1511, 1486, 1411, 1396, 1293, 1251, 1202, 1172, 1144, 1079, 1070, 971, 861, 777, 762; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.90 (d, J = 7.2 Hz, 4H), 7.67 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 6.8 Hz, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 7.06−7.02 (m, 1H), 4.11−4.06 (m, 4H), 2.41 (s, 3H), 0.99 (t, J = 6.8 Hz, 3H), 0.93 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.1, 163.6, 161.6, 155.6, 154.0, 145.8,

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141.4, 141.1, 137.2, 133.6, 132.7, 131.1, 130.3, 129.8, 129.6, 124.2, 123.8, 122.7, 122.2, 121.3, 119.2, 107.0, 63.3, 62.5, 21.8, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{25}BrN_2O_5$ 584.0947 $[M]^+$, found 584.0954.

Representative Synthesis of 6. *2-Ethyl 3-Methyl 4-Benzoyl-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6a**).* Typically, 3-benzoylmethylidene-2-oxindole (**1a**, 1.0 mmol), *p*-toluidine (**2a**, 1 mmol), dimethyl but-2-ynedioate (**3a**, 1.0 mmol), and ethanol (**5a**, 2 mL) were introduced into a 5 mL initiator reaction vial, and 10 mol % *t*-BuOK was then added. Subsequently, the reaction vial was closed, and the reaction mixture was prestirred for 10 s. The mixture was irradiated at 90 °C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The precipitate was collected and purified by column chromatography (petroleum ether/acetone = 8:1) to give the pure product **6a** as a yellow solid, 0.404 g, yield 82%, purity 99.6%; mp 192−194 °C; IR (KBr, ν, cm^{-1}) 2954, 1739, 1720, 1673, 1620, 1598, 1512, 1405, 1323, 1295, 1200, 1082, 792, 866, 696; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.00 (d, J = 8.0 Hz, 2H, Ar), 7.75−7.71 (m, 1H), 7.60−7.54 (m, 5H), 7.47−7.42 (m, 3H), 7.29 (d, J = 8.0 Hz, 1H), 7.06−7.02 (m, 1H), 4.06 (q, J = 7.2 Hz, 2H), 3.57 (s, 3H), 2.46 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.7, 164.1, 161.7, 155.8, 154.1, 141.7, 141.2, 140.6, 135.9, 135.4, 135.0, 130.0, 129.8, 129.4, 128.6, 123.7, 122.6, 122.2, 121.3, 119.3, 106.5, 63.2, 53.2, 21.4, 13.8; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{25}N_2O_5$ 493.1763 $[M + H]^+$, found 493.1758.

*2-Ethyl 3-Methyl 1-(4-Ethoxyphenyl)-4-(4-methylbenzoyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6b**).* Yellow solid, 0.472 g, yield 88%, purity 99.9%; mp 220−222 °C; IR (KBr, ν, cm^{-1}) 2954, 1722, 1675, 1603, 1509, 1438, 1295, 1254, 1174, 1114, 1017, 959, 866, 737; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.89 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 8.0 Hz, 3H), 7.46−7.42 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.05−7.02 (m, 1H), 4.16 (q, J = 6.8 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 3.57 (s, 3H), 2.41 (s, 3H), 1.40 (t, J = 6.8 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.3, 191.6, 187.9, 179.2, 164.2, 161.5, 160.1, 155.6, 150.6, 145.6, 141.4, 136.6, 133.6, 132.1, 130.3, 130.2, 129.5, 122.7, 115.2, 105.9, 99.3, 64.1, 63.2, 53.1, 21.8, 15.0, 13.8; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{29}N_2O_6$ 537.2026 $[M + H]^+$, found 537.2042. Anal. Calcd for $C_{32}H_{28}N_2O_6$: C, 71.63; H, 5.26; N, 5.22. Found: C, 71.88; H, 5.39; N, 5.20.

*2-Ethyl 3-Methyl 4-(4-Methylbenzoyl)-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6c**).* Yellow solid, 0.451 g, yield 89%, purity 99.5%; mp 250−252 °C; IR (KBr, ν, cm^{-1}) 2978, 1740, 1725, 1672, 1601, 1526, 1429, 1280, 1200, 1144, 1083, 1024, 866, 779, 739; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.89 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 8.0 Hz, 3H), 7.47−7.42 (m, 3H), 7.38 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.06−7.02 (m, 1H), 4.06 (q, J = 6.8 Hz, 2H), 3.58 (s, 3H), 2.46 (s, 3H), 2.40 (s, 3H), 1.00 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.2, 164.2, 161.7, 155.7, 154.1, 145.7, 141.6, 141.4, 140.5, 135.4, 133.6, 130.3, 130.0, 129.7, 129.5, 128.6, 123.6, 122.7, 122.2, 121.2, 119.3, 106.6, 63.2, 53.1, 21.8, 21.4, 13.8; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{27}N_2O_5$ 507.1920 $[M + H]^+$, found 507.1915.

*2-Ethyl 3-Methyl 1-(4-Methoxyphenyl)-4-(4-methylbenzoyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6d**).* Yellow solid, 0.486 g, yield 93%, purity 99.6%; mp 212−214 °C; IR (KBr, ν, cm^{-1}) 2928, 1735, 1720, 1663, 1603, 1508, 1439, 1321, 1293, 1199, 1025, 973, 780, 764; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.89 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 3H), 7.46−7.37 (m, 3H), 7.29 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.05−7.02 (m, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.89 (s, 3H), 3.58 (s, 3H), 2.40 (s, 3H), 1.02 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.3, 164.2, 161.7, 160.8, 155.7, 154.3, 145.7, 142.0, 141.4, 133.6, 130.5, 130.4, 130.2, 129.7, 129.5, 123.6, 122.7, 122.3, 121.2, 119.3, 114.7, 106.5, 63.2, 56.1, 53.1, 21.8, 13.8; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{27}N_2O_6$ 523.1869 $[M + H]^+$, found 523.1860.

*2-Ethyl 3-Methyl 4-(2-Furoyl)-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6e**).* Yellow solid, 0.304 g, yield 63%, purity 98.7%; mp 234−236 °C; IR (KBr, ν, cm^{-1}) 2954, 1741, 1721, 1673, 1600, 1526, 1492, 1436, 1405, 1375, 1324, 1291, 1259, 1179, 1141, 1086, 1011, 926, 798, 723; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.16 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 6.8 Hz, 1H), 7.51−7.49 (m, 3H), 7.46−7.42 (m, 3H), 7.15−7.11 (m, 1H), 6.80−6.79 (m, 1H), 4.06 (q, J = 7.2 Hz, 2H), 3.66 (s, 3H), 2.46 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 180.4, 164.2, 161.6, 155.8, 154.2, 151.8, 150.1, 141.4, 140.6, 139.5, 135.4, 130.1, 130.0, 128.6, 128.5, 124.2, 122.8, 122.1, 121.4, 119.4, 113.8, 106.6, 63.3, 53.4, 21.3, 13.8; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{23}N_2O_6$ 483.1556 $[M + H]^+$, found 483.1553.

*3-Ethyl 2-Methyl 4-Benzoyl-1-(p-tolyl)-1H-pyrido-[2,3-b]indole-2,3-dicarboxylate (**6f**).* Yellow solid, 0.424 g, yield 86%, purity 99.2%; mp 235−237 °C; IR (KBr, ν, cm^{-1}) 2954, 1742, 1702, 1674, 1599, 1509, 1432, 1420, 1294, 1234, 1215, 1082, 928, 819, 794, 708; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.03 (d, J = 7.6 Hz, 2H), 7.76−7.72 (m, 1H), 7.61−7.54 (m, 5H), 7.47−7.42 (m, 3H), 7.31 (d, J = 8.0 Hz, 1H), 7.06−7.02 (m, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.58 (s, 3H), 2.47 (s, 3H), 0.90 (t, J = 7.2 Hz, 3H) ; ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.6, 163.6, 162.3, 155.7, 154.1, 141.6, 141.2, 140.6, 136.0, 135.4, 135.1, 130.1, 129.8, 129.7, 129.5, 128.4, 123.7, 122.6, 122.2, 121.3, 119.3, 106.6, 62.6, 53.7, 21.4, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{25}N_2O_5$ 493.1763 $[M + H]^+$, found 493.1764.

*3-Ethyl 2-Methyl 4-Benzoyl-1-(4-ethoxyphenyl)-1H-pyrido-[2,3-b]indole-2,3-dicarboxylate (**6g**).* Yellow solid, 0.455 g, yield 87%, purity 98.9%; mp 194−196 °C; IR (KBr, ν, cm^{-1}) 2985, 1746, 1715, 1679, 1599, 1510, 1470, 1386, 1292, 1256, 1208, 1116, 1045, 927, 840, 794, 736; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.03 (d, J = 7.6 Hz, 2H), 7.75−7.72 (m, 1H), 7.60−7.57 (m, 5H), 7.47−7.43 (m, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.06−7.03 (m, 1H), 4.14 (q, J = 6.8 Hz, 2H), 4.06 (q, J = 7.2 Hz, 2H), 3.60 (s, 3H), 1.40 (t, J = 6.8 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.6, 163.6, 162.3, 160.1, 142.0, 141.3, 136.0, 135.1, 130.2, 130.0, 129.9, 129.8, 129.7, 129.5, 123.6, 122.7, 122.1, 121.4, 119.1, 115.2, 64.1, 62.6, 53.8, 15.1, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{27}N_2O_6$ 523.1869 $[M + H]^+$, found 523.1860. Anal. Calcd for $C_{31}H_{26}N_2O_6$: C, 71.25; H, 5.02; N, 5.36. Found: C, 71.27; H, 5.17; N, 5.27.

*3-Ethyl 2-Methyl 4-Benzoyl-1-(4-methoxyphenyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6h**).* Yellow solid, 0.442 g, yield 87%, purity 99.9%; mp 236−238 °C; IR (KBr, ν, cm^{-1}) 2951, 1759, 1741, 1675, 1601, 1509, 1407, 1295, 1217, 1182, 1082, 1021, 928, 838, 737, 698; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.03 (d, J = 7.6 Hz, 2H), 7.75−7.72 (m, 1H), 7.61−7.58 (m, 5H), 7.46−7.43 (m, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.06−7.02 (m, 1H), 4.06 (q, J = 6.8 Hz, 2H), 3.89 (s, 3H), 3.60 (s, 3H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.7, 163.6, 162.3, 160.7, 155.7, 154.4, 142.0, 141.2, 136.0, 135.0, 130.5, 130.0, 129.7, 129.5, 123.7, 122.6, 122.2, 121.3, 119.3, 114.7, 106.5, 62.6, 56.1, 53.7, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{24}NaN_2O_6$ 531.1532 $[M + Na]^+$, found 531.1538. Anal. Calcd for $C_{30}H_{24}N_2O_6$: C, 70.86; H, 4.76; N, 5.51. Found: C, 70.82; 4.79; N, 5.36.

*3-Ethyl 2-Methyl 4-Benzoyl-1-(4-isopropylphenyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6i**).* Yellow solid, 0.463 g, yield 89%, purity 99.8%; mp 176−178 °C; IR (KBr, ν, cm^{-1}) 2960, 1744, 1709, 1674, 1598, 1501, 1468, 1434, 1405, 1294, 1175, 1080, 1008, 928, 794, 737; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.02 (d, J = 8.0 Hz, 2H), 7.76−7.72 (m, 1H), 7.61−7.58 (m, 5H), 7.53 (d, J = 8.0 Hz, 2H), 7.46−7.43 (m, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.06−7.03 (m, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.53 (s, 3H), 3.10−3.03 (m, 1H), 1.32 (s, 3H), 1.30 (s, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm) 193.6, 163.6, 162.3, 155.7, 154.1, 151.1, 141.7, 141.2, 136.0, 135.6, 135.1, 129.8, 129.5, 128.6, 127.5, 123.8, 122.6, 122.2, 121.3, 119.3, 106.6, 62.6, 53.6, 33.8, 24.2, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{29}N_2O_5$ 521.2076 $[M + H]^+$, found 521.2081.

*3-Ethyl 2-Methyl 1-(4-Ethoxyphenyl)-4-(4-methylbenzoyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6j**).* Yellow solid, 0.456 g, yield 85%, purity 99.3%; mp 230−232 °C; IR (KBr, ν, cm^{-1}) 2982, 1740, 1717, 1674, 1602, 1524, 1509, 1385, 1238, 1207, 1144, 1115,

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1082, 1046, 856, 764; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 7.91 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 8.0 Hz, 3H), 7.46−7.42 (m, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.06−7.02 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 4.07−4.04 (m, 2H), 3.62−3.58 (m, 3H), 2.40 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.2, 163.6, 162.3, 160.0, 155.7, 154.3, 145.7, 141.9, 141.4, 133.7, 130.3, 130.0, 129.6, 123.6, 122.7, 122.3, 121.2, 119.3, 115.1, 106.5, 64.1, 62.5, 53.7, 21.8, 15.1, 13.6; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{29}N_2O_6$ 537.2026 $[M + H]^+$, found 537.2036. Anal. Calcd for $C_{32}H_{28}N_2O_6$: C, 71.63; H, 5.26; N, 5.22. Found: C, 71.33; H, 5.42; N, 5.08.

*3-Ethyl 2-Methyl 4-(4-Chlorobenzoyl)-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6k**).* Yellow solid, 0.374 g, yield 71%, purity 99.5%; mp 240−242 °C; IR (KBr, ν, cm^{-1}) 2956, 1745, 1724, 1673, 1610, 1519, 1490, 1443, 1400, 1382, 1320, 1292, 1235, 1169, 1140, 1078, 1010, 927, 798, 724; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.04 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.47−7.44 (m, 3H), 7.29 (d, J = 8.0 Hz), 7.08−7.04 (m, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.58 (s, 3H), 2.47 (s, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 192.7, 164.1, 163.6, 162.2, 155.8, 154.2, 141.7, 140.6, 140.0, 135.4, 134.8, 131.4, 131.2, 130.1, 130.0, 129.9, 128.4, 123.8, 122.6, 122.1, 121.4, 119.4, 106.4, 62.7, 53.8, 53.4, 21.4, 13.7; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{24}ClN_2O_5$ 527.1374 $[M + H]^+$, found 527.1373.

*3-Methyl 2-Propyl 4-Benzoyl-1-(p-tolyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6l**).* Yellow solid, 0.355 g, yield 70%, purity 98.7%; mp 248−250 °C; IR IR (KBr, ν, cm^{-1}) 2964, 1738, 1711, 1668, 1623, 1606, 1538, 1520, 1408, 1200, 1176, 1087, 1011, 976, 859, 792; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.00 (d, J = 7.2 Hz, 2H), 7.75−7.71 (m, 1H), 7.61−7.53 (m, 5H), 7.47−7.42 (m, 3H), 7.28 (d, J = 8.0 Hz, 1H), 7.06−7.02 (m, 1H), 3.95−3.92 (m, 2H), 3.57 (s, 3H), 2.46 (s, 3H), 1.43 (q, J = 6.8 Hz, 2H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.3, 164.1, 161.7, 155.7, 154.1, 145.7, 141.7, 141.4, 140.6, 135.4, 133.6, 130.4, 130.0, 129.8, 129.5, 128.6, 123.6, 122.7, 122.2, 121.3, 119.3, 106.6, 63.2, 53.1, 21.3, 13.8, 10.7; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{27}N_2O_5$ 507.1920 $[M + H]^+$, found 507.1927.

*3-Methyl 2-Propyl 4-Benzoyl-1-(4-ethoxyphenyl)-1H-pyrido[2,3-b]indole-2,3-dicarboxylate (**6m**).* Yellow solid, 0.386 g, yield 72%, purity 99.6%; mp 168−170 °C; (KBr, ν, cm^{-1}) 2927, 1738, 1719, 1673, 1638, 1523, 1428, 1385, 1295, 1200, 1114, 1081, 769, 693; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm) 8.00 (d, J = 7.6 Hz, 2H), 7.75−7.71 (m, 1H), 7.61−7.57 (m, 5H), 7.46−7.42 (m, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.06−7.02 (m, 1H), 4.16 (q, J = 6.8 Hz, 2H), 4.01−3.91 (m, 2H), 3.57 (s, 3H), 1.50−1.42 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm) 193.8, 164.1, 161.9, 160.0, 155.7, 154.3, 142.1, 141.2, 135.9, 135.0, 130.3, 130.1, 129.8, 129.4, 123.6, 122.6, 122.2, 121.2, 119.3, 115.1, 106.4, 68.7, 64.1, 53.2, 31.5, 21.4, 15.0, 10.7; HRMS (ESI-TOF) m/z calcd for $C_{32}H_{29}N_2O_6$ 537.2026 $[M + H]^+$, found 537.2037.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data, ^{1}H and ^{13}C NMR spectra, and crystallographic data for products **4a** and **6a**. 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) (a) Ruggieri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 5745. (b) Ruggeri, B. R.; McClure, K. F.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 1530. (c) Wanner, M. J.; Koomen, G.-J. *J. Org. Chem.* **1995**, *60*, 5634. (d) Gravel, E.; Poupon, E.; Hocquemiller, R. *Org. Lett.* **2005**, *7*, 2497. (e) Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 6241.

(2) (a) Paolini, L. *Sci. Rep. Ist. Super. Sanita* **1961**, *1*, 86. (b) Okamoto, T.; Akase, T.; Izumi, S.; Inaba, S.; Yamamoto, H. Japanese Patent 7220196, 1972; *Chem. Abstr.* **1972**, *77*, 152142. (c) Winters, J.; Di Mola, N. West German Patent 2442513, 1975; *Chem. Abstr.* **1975**, *82*, 156255. (d) Kim, J. S.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 3431. (e) Pogodaeva, N. N.; Shagum, V. A.; Semenov, A. A. *Khim.-Fram. Zh.* **1985**, *19*, 1054. (f) Peczyska-Czoch, W.; Pognan, F.; Kaczmarek, L.; Boratynski, J. *J. Med. Chem.* **1994**, *37*, 3503. (g) Tsai, J. Y.; Lin, Y. C.; Hsu, M. H.; Kuo, S. C.; Huang, L. J. *Kaohsiung J. Med. Sci.* **2010**, *26*, 593.

(3) (a) Rivalle, C.; Ducrocq, C.; Lhoster, J. M.; Wendling, F.; Bisagni, E.; Chermann, J. C. *Tetrahedron* **1981**, *37*, 2097. (b) Kaczmarek, L.; Balicki, R.; Nantka-Namirski, P.; Peczynska-Czoch, W.; Mordarski, M. *Arch. Pharm.* **1988**, *321*, 463. (c) Mehta, L. K.; Parrick, J.; Payne, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1261. (d) Vera-Luque, P.; Alajarin, R.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2006**, *8*, 415. (e) Schneider, C.; Gueyrard, D.; Popowycz, F.; Joseph, B.; Goekjian, P. G. *Synlett* **2007**, 2237. (f) Sako, K.; Aoyama, H.; Sato, S.; Hashimoto, Y.; Baba, M. *Bioorg. Med. Chem.* **2008**, *16*, 3780.

(4) (a) Tahri, A.; Buysens, K. J.; Van der Eycken, E. V.; Vandenberghe, D. M.; Hoonaert, G. J. *Tetrahedron* **1998**, *54*, 13211. (b) Molina, P.; Alajarin, M.; Vidal, A.; Sanchez-Andranda, P. *J. Org. Chem.* **1992**, *57*, 929. (c) Forbes, I. T.; Johnson, C. N.; Thompson, M. *Synth. Commun.* **1993**, *23*, 715.

(5) Liger, F.; Popowycz, F.; Besson, T.; Picot, L.; Galmarini, C. M.; Joseph, B. *Bioorg. Med. Chem.* **2007**, *15*, 5615.

(6) (a) Yamazaki, T.; Matoba, K.; Imoto, S.; Terashima, M. *Chem. Pharm. Bull.* **1976**, *24*, 3011. (b) Molina, P.; Fresneda, P. M. *Synthesis* **1989**, 878. (c) Forbes, I. T.; Johnson, C. N.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 275. (d) Laha, J. K.; Barolo, S. M.; Rossi, R. A.; Cuny, G. D. *J. Org. Chem.* **2011**, *76*, 6421. (e) Markey, S. J.; Lewis, W.; Moody, C. J. *Org. Lett.* **2013**, *15*, 6306. (f) Erba, E.; Gelmi, M. L.; Pocar, D. *Tetrahedron* **2000**, *56*, 9991. (g) Becalli, E. M.; Clerici, F.; Marchesini, A. *Tetrahedron* **2001**, *57*, 4787. (h) Portela-Cubillo, F.; Surgenor, B. A.; Aitken, R. A.; Walton, J. C. *J. Org. Chem.* **2008**, *73*, 8124.

(7) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Zhu, J., Bienayme, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005. (c) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (d) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463. (e) Ivanov, A. S. *Chem. Soc. Rev.* **2008**, *37*, 789. (f) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413.

(8) (a) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2304. (b) Lu, M.; Zhu, D.; Lu, Y.; Hou, B.; Tan, B.; Zhong, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 10187. (c) Huang, Y.; Waljji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (d) Enders, D.; Huttl, M. R. M.; Grondal, C.; Raab,

G. *Nature* **2006**, *441*, 861. (e) Yang, J. W.; Fonseca, H. M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036.
(9) (a) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427. (b) Shestopalov, A. M.; Emeliyanova, Y. M.; Shestiopolov, A. A.; Rodinovskaya, L. A.; Niazimbetova, Z. I.; Evans, D. H. *Org. Lett.* **2002**, *4*, 423. (c) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147. (d) Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309. (e) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205. (f) Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848. (g) Li, M.; Cao, H.; Wang, Y.; Lv, X. L.; Wen, L. R. *Org. Lett.* **2012**, *14*, 3470. (h) Hao, W. J.; Xu, X. P.; Bai, H. W.; Wang, S. Y.; Ji, S. J. *Org. Lett.* **2012**, *14*, 4894. (i) Wen, L. R.; Shi, Y. J.; Liu, G. Y.; Li, M. *J. Org. Chem.* **2012**, *77*, 4252. (j) Jiang, B.; Li, Q. Y.; Zhang, H.; Tu, S. J.; Pindi, S.; Li, G. *Org. Lett.* **2012**, *14*, 700.
(10) (a) Shi, C.; Wang, J.; Chen, H.; Shi, D. *J. Comb. Chem.* **2010**, *12*, 430. (b) Chen, H.; Shi, D. *J. Comb. Chem.* **2010**, *12*, 571. (c) Li, Y.; Chen, H.; Shi, C.; Shi, D.; Ji, S. *J. Comb. Chem.* **2010**, *12*, 231. (d) Huang, Z.; Hu, Y.; Zhou, Y.; Shi, D. *ACS Comb. Sci.* **2011**, *13*, 45. (e) Chen, H.; Shi, D. *Tetrahedron* **2011**, *67*, 5686. (f) Lin, W.; Dou, G. L.; Hu, M. H.; Cao, C. P.; Huang, Z. B.; Shi, D. Q. *Org. Lett.* **2013**, *15*, 1238. (g) Cao, C.; Lin, W.; Hu, M.; Huang, Z.; Shi, D. *Chem. Commun.* **2013**, *49*, 6983. (h) Feng, X.; Wang, Q.; Lin, W.; Dou, G.; Huang, Z.; Shi, D. *Org. Lett.* **2013**, *15*, 2542. (i) Wang, H.; Liu, X.; Feng, X.; Huang, Z.; Shi, D. *Green Chem.* **2013**, *15*, 3307.
(11) Han, Y.; Sun, J.; Yan, C. G. *Tetrahedron* **2012**, *68*, 8256.
(12) (a) Devi, I.; Kumarb, B. S. D.; Bhuyana, P. J. *Tetrahedron Lett.* **2003**, *44*, 8307. (b) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienok, A. *Org. Lett.* **2006**, *8*, 899. (c) Li, M. Y.; Xu, H. W.; Fan, W.; Ye, Q.; Wang, X.; Jiang, B.; Wang, S. L.; Tu, S. J. *Tetrahedron* **2014**, *70*, 1004.