Three-Component One-Pot Synthesis of 3-(2-Furanyl)indoles from Acetylenedicarboxylate, Isocyanide, and 3-Formylindole

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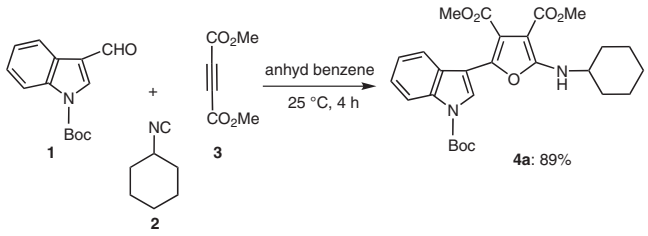
Abstract: The zwitterions derived from isocyanide and dimethyl acetylenedicarboxylate undergo smooth condensation with 3-formylindoles in benzene at room temperature to give the corresponding 3-(2-furanyl)indoles in good yields. This method provides a simple and convenient route to produce a wide range of 3-heteroarylindoles in a one-pot operation.

Key words: 3-formylindoles, isocyanides, DMAD, zwitterions, 3-furanylindoles

The multi-component reactions (MCRs) are highly important because of their wide range of applications in pharmaceutical chemistry for production of the diverse structural scaffolds and combinatorial libraries for drug discovery.[1] They are extremely convergent, producing a remarkably high increase of molecular complexity in just one step.[2] The cycloaddition of 1,4-dipoles with various electrophiles such as aldehydes, imines, quinones, activated alkenes, and aza-aromatic systems is one of the most versatile methods to generate a wide range of heterocycles including aminofurans, pyrroles, and novel spirolactones.[3,4] Furthermore, the cycloaddition of zwitterions derived from isocyanide and dimethyl acetylenedicarboxylate (DMAD) with phenyl isocyanate, diethyl mesoxalate, and dimethyl azodicarboxylate has also been reported to produce six-membered heterocycles.[5,6] Besides isocyanides, other nucleophiles such as triphenylphosphine, tertiary amines, and N-heterocyclic carbenes have also been utilized to generate zwitterions from dimethyl acetylenedicarboxylate (DMAD). Subsequently, these highly reactive zwitterions have been trapped with different electrophiles.

Indole nucleus is frequently found in medicinal chemistry and is considered as a 'privileged scaffold'.[7] Substituted indoles are capable of binding to many receptors with high affinity. Therefore, there is a continuing interest in the development of improved methods for the synthesis of 3-substituted indoles.[8] Given this proven utility, it seems likely that the synthesis of a novel series of 3-furanylindoles would provide additional lead molecules for use in drug discovery. It is known that the introduction of two or more different heterocyclic moieties in a single molecule often enhances the biological activity significantly. Until now, only two approaches have been reported for the synthesis of 3-furanylindoles.[9] However, the synthesis of pyrrolyl- and furanylindoles could not be achieved by the well-known Fischer indole synthesis.[10] Furthermore, there have been no reports on the synthesis of 3-(2-furanyl)indoles via zwitterionic intermediates.

Recently, we have reported the coupling of indoles with zwitterions derived from quinolines/isoquinolines and dimethyl acetylenedicarboxylate to furnish indol-3-ylquinolines/isoquinolines.[11] In addition to this, the condensation of alkynes with activated quinolines and isoquinolines has also been reported using gold(III) chloride to generate alkynylated aza-aromatic systems.[12] This result provided an inspiration to study the annulation of zwitterions, derived from DMAD and isocyanides with 3-formylindoles. Thus, treatment of 3-formylindole with cyclohexyl isocyanide and dimethyl acetylenedicarboxylate in benzene at room temperature gave the corresponding dimethyl 2-(1-*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-5-(cyclohexylamino)furan-3,4-dicarboxylate (**4a**) in 89% yield (Scheme 1).



Scheme 1 Reaction of cyclohexyl isocyanide, DMAD, and 3-formylindole

Encouraged by the results obtained with 3-formylindole, we turned our attention to other substituted 3-formylindoles. Interestingly, various 3-formylindoles such as 5-bromo-, and 5-methoxy derivatives underwent smooth condensation with in situ formed zwitterions from isocyanide and DMAD (Table 1). Simple indole-3-carboxaldehyde failed to give the desired product under similar conditions. It is noteworthy to mention that reaction was successful only with *N*-Boc-3-formylindoles. Other isocyanides such as *tert*-butyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide also participated well in this reaction (Table 1).

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Table 1 Three-Component One-Pot Synthesis of 3-Furanylindoles

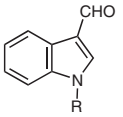
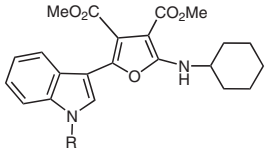
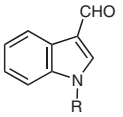
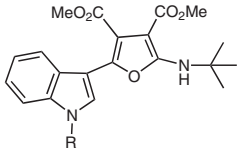
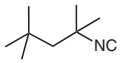
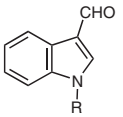
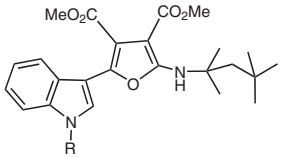
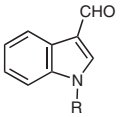
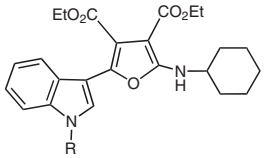
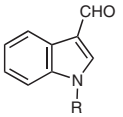
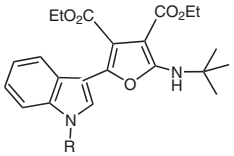
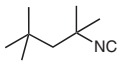
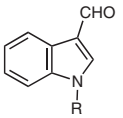
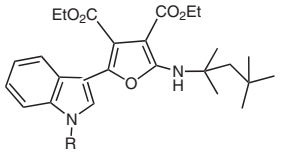
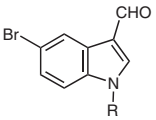
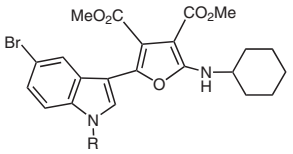
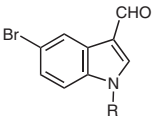
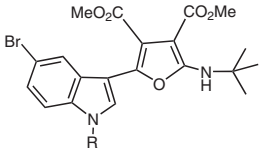
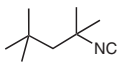
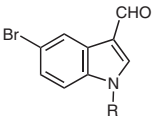
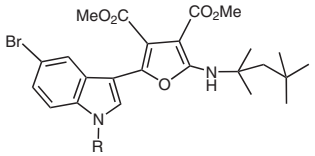
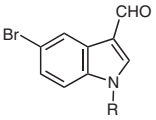
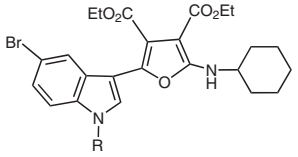
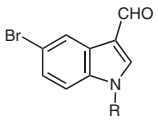
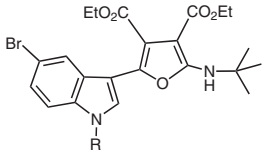
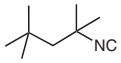
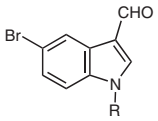
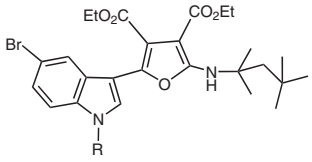
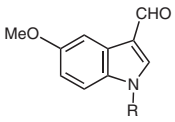
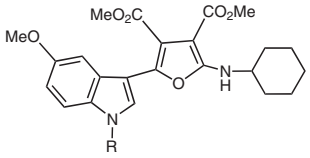
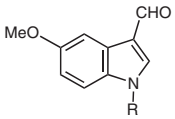
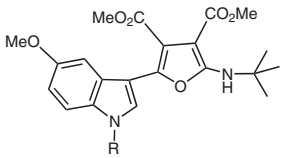
Entry	Isocyanide	Enal/DMAD/DEAD[a]	Product **4**[b]	Time (h)	Yield (%)[c]
a				4.0	89
b				4.0	87
c				4.0	90
d				4.0	92
e				4.0	94
f				4.0	91
g				4.0	92
h				4.0	89
i				4.0	85
j				4.0	88

Table 1 Three-Component One-Pot Synthesis of 3-Furanylindoles (continued)

Entry	Isocyanide	Enal/DMAD/DEAD[a]	Product **4**[b]	Time (h)	Yield (%)[c]
k				4.0	87
l				4.0	89
m				6.0	75
n				6.0	76

[a] DMAD was used for the preparation of **4a–c**,**g–i**,**m**,**n** and DEAD was used for the preparation of **4d–f**,**j–l**.
[b] All the products were characterized by NMR, IR, and mass spectrometry; R = Boc.
[c] Yield refers to pure products after chromatography.

Diethyl acetylenedicarboxylate (DEAD) was also equally effective for this conversion (Table 1, entries **d–f** and **j–l**). The structure of **4a–n** was established using ^{1}H, ^{13}C NMR, IR, and HRMS. The scope and generality of this process is illustrated with respect to various 3-formylindoles and isocyanides and the results are presented in Table 1. This method offers several advantages such as high yields of products, mild reaction conditions, greater regioselectivity, cleaner reaction profiles, and operational simplicity. The effect of various solvents such as water, THF, acetonitrile, and benzene was studied for this conversion. As solvent, benzene appeared to give the best results. No desired product was formed in water. The proposed structure of **4h** was established by X-ray crystallography (Figure 1).

Mechanistically, isocyanide may initially react with dimethyl acetylenedicarboxylate to generate the 1,4-dipole. The highly reactive zwitterion undergoes subsequent annulation with 3-formylindole to give the desired furanylindole (Scheme 2).

In conclusion, we have developed a novel three-component reaction to accomplish the synthesis of 3-furanylindoles in a single step operation. The zwitterion generated by the addition of isocyanide to dimethyl acetylenedicarboxylate has been trapped by *N*-Boc-3-formylindoles to produce *N*-Boc-3-furanylindoles in good yields. We believe that this method may be useful in generating a wide range of 3-furanylindoles for drug discovery program.

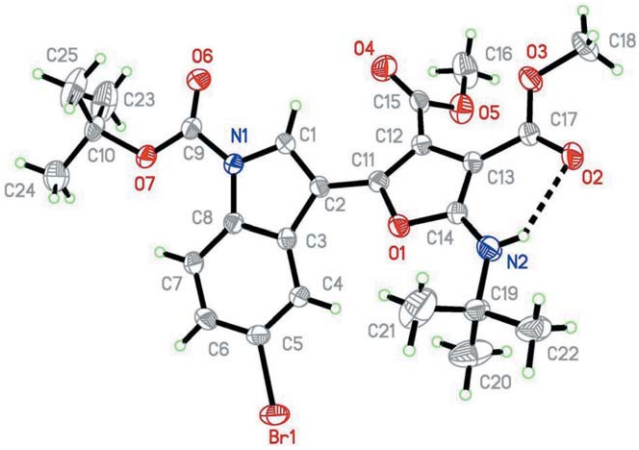
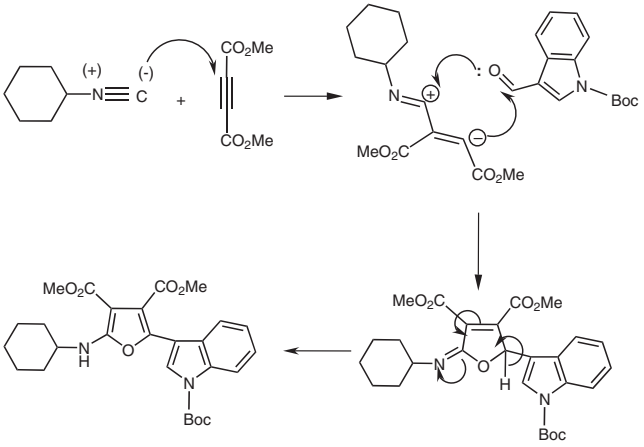


Figure 1 X-ray crystal structure of **4h**

Melting points were recorded on Büchi R-535 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FT-IR spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C spectra were recorded on Varian Gemini 200 and Bruker 300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

Dimethyl 2-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-5-(cyclohexylamino)furan-3,4-dicarboxylate (4a); Typical Procedure

A mixture of cyclohexyl isocyanide (0.044 g, 0.4 mmol) and dimethyl acetylenedicarboxylate (0.048 g, 0.4 mmol) in anhyd benzene (5 mL) was purged with N_2 at r.t. After 5 min, *N*-Boc-3-formylindole (0.100 g, 0.4 mmol) was added and then the resulting



Scheme 2 A plausible reaction mechanism

mixture was allowed to stir at r.t. in benzene for 4 h. After completion of the reaction as monitored by TLC, the solvent was evaporated in vacuo and the crude product was purified by column chromatography on silica gel using EtOAc and hexane as eluent to give the pure 3-furanylindole **4a**; yellow solid; mp 126–128 °C.

IR (KBr): 3358, 2925, 2853, 1737, 1676, 1614, 1457, 1370, 1234, 1154, 1106, 1073 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.1 Hz, 1 H), 7.99 (s, 1 H), 7.82 (d, *J* = 7.3 Hz, 1 H), 7.38–7.26 (m, 2 H), 6.66 (d, *J* = 8.1 Hz, 1 H), 3.86 (s, 3 H), 3.79 (s, 4 H), 2.08–1.79 (m, 6 H), 1.68 (s, 9 H), 1.44–1.33 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 164.6, 161.4, 149.4, 138.5, 135.1, 128, 124.8, 124.2, 123.1, 120.7, 115.3, 113.6, 110.0, 86.7, 84.1, 61.0, 59.5, 51.5, 33.6, 28.1, 25.4, 24.4.

ESIMS: *m*/*z* = 497 (M + H).

HRMS-ESI: *m*/*z* calcd for $C_{27}H_{33}N_2O_7$: 497.2287; found: 497.2295.

Dimethyl 2-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-5-(*tert*-butylamino)furan-3,4-dicarboxylate (4b)
Yellow solid; mp 117–120 °C.

IR (KBr): 3500, 2922, 2852, 1714, 1512, 1461, 1376, 1258, 1140, 1036 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.1 Hz, 1 H), 7.96 (s, 1 H), 7.82 (d, *J* = 7.3 Hz, 1 H), 7.39–7.26 (m, 2 H), 6.94 (s, 1 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 1.68 (s, 9 H), 1.49 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 164.7, 161.9, 149.2, 138.3, 135.1, 127.9, 124.8, 124.6, 123.1, 120.4, 115.3, 113.6, 110.0, 87.8, 84.1, 61.2, 59.5, 52.6, 30.0, 28.0.

ESIMS: *m*/*z* = 471 (M + H), 493 (M + Na).

HRMS-ESI: *m*/*z* calcd for $C_{25}H_{31}N_2O_7$: 471.2131; found: 471.2135.

Dimethyl 2-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-5-(2,4,4-trimethylpentan-2-ylamino)furan-3,4-dicarboxylate (4c)
Pale yellow liquid.

IR (film): 3337, 2952, 1738, 1675, 1608, 1455, 1371, 1216, 1154, 1087 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.3 Hz, 1 H), 7.95 (s, 1 H), 7.83 (d, *J* = 7.7 Hz, 1 H), 7.39–7.26 (m, 2 H), 7.05 (s, 1 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 1.81 (s, 2 H), 1.68 (s, 9 H), 1.54 (s, 6 H), 1.04 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 165.1, 161.8, 149.2, 138.6, 135.1, 127.8, 124.8, 123.0, 120.4, 115.3, 113.3, 109.9, 87.2, 84.1, 56.3, 53.4, 52.1, 51.0, 31.4, 30.3, 29.6, 28.0.

ESIMS: *m*/*z* = 527 (M + H).

HRMS-ESI: *m*/*z* calcd for $C_{29}H_{39}N_2O_7$: 527.2757; found: 527.240.

Diethyl 2-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-5-(cyclohexylamino)furan-3,4-dicarboxylate (4d)
Pale yellow liquid.

IR (film): 3347, 2979, 2932, 2856, 1733, 1673, 1614, 1545, 1472, 1374, 1340, 1250, 1215, 1155, 1104, 1070, 1037 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 7.9 Hz, 1 H), 7.97 (s, 1 H), 7.80 (d, *J* = 7.3 Hz, 1 H), 7.34–7.22 (m, 2 H), 6.69 (d, *J* = 8.1 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 4.24 (q, *J* = 6.9 Hz, 2 H), 3.73 (s, 1 H), 2.08–1.80 (m, 3 H), 1.68 (s, 9 H), 1.55–1.43 (m, 5 H), 1.36–1.33 (m, 6 H), 0.88–0.83 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 164.6, 161.4, 149.2, 138.5, 135.1, 128, 124.2, 123.1, 120.7, 115.3, 113.6, 110.0, 86.7, 84.1, 61.2, 59.5, 51.5, 33.6, 28.1, 25.5, 24.4, 14.4, 14.1.

ESIMS: *m*/*z* = 525 (M + H), 547 (M + Na).

HRMS-ESI: *m*/*z* calcd for $C_{29}H_{37}N_2O_7$: 525.2600; found: 525.2592.

Diethyl 2-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-5-(*tert*-butylamino)furan-3,4-dicarboxylate (4e)
Pale yellow liquid.

IR (film): 3332, 2979, 2934, 1737, 1673, 1607, 1547, 1453, 1371, 1297, 1267, 1209, 1155, 1088, 1051 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.1 Hz, 1 H), 7.95 (s, 1 H), 7.82 (d, *J* = 7.3 Hz, 1 H), 7.36–7.24 (m, 2 H), 6.95 (s, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 4.24 (q, *J* = 6.9 Hz, 2 H), 1.68 (s, 9 H), 1.50 (s, 9 H), 1.33–1.36 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 164.7, 161.9, 149.2, 138.3, 135.1, 127.9, 124.8, 124.6, 123.1, 120.4, 115.3, 113.6, 110.0, 87.8, 84.1, 61.2, 59.5, 52.6, 30.0, 28.0, 14.3, 14.1.

ESIMS: *m*/*z* = 499 (M + H).

HRMS-ESI: *m*/*z* calcd for $C_{27}H_{35}N_2O_7$: 499.2444; found: 499.2450.

Diethyl 2-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-5-(2,4,4-trimethylpentan-2-ylamino)furan-3,4-dicarboxylate (4f)
Pale yellow liquid.

IR (film): 3332, 2974, 1737, 1671, 1607, 1547, 1454, 1371, 1213, 1154, 1086, 1051 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.3 Hz, 1 H), 7.94 (s, 1 H), 7.84 (d, *J* = 7.5 Hz, 1 H), 7.36–7.23 (m, 2 H), 7.07 (s, 1 H), 4.35–4.20 (m, 4 H), 1.82 (s, 2 H), 1.68 (s, 9 H), 1.54 (s, 6 H), 1.36–1.33 (m, 6 H), 1.05 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 164.7, 161.7, 149.2, 138, 135.1, 127.9, 124.7, 124.5, 123.0, 120.5, 115.3, 113.7, 110.0, 87.5, 84.0, 61.2, 59.5, 56.32, 53.4, 31.6, 31.4, 30.3, 28.0, 14.3, 14.1.

ESIMS: *m*/*z* = 555 (M + H), 577 (M + Na).

HRMS-ESI: *m*/*z* calcd for $C_{31}H_{43}N_2O_7$: 555.3070; found: 555.3056.

Dimethyl 2-[5-Bromo-1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-5-cyclohexylamino)furan-3,4-dicarboxylate (4g)
Pale orange solid; mp 185–187 °C.

IR (KBr): 3356, 2931, 2854, 1738, 1675, 1616, 1541, 1451, 1368, 1268, 1231, 1153, 1107, 1073 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.06–8.01 (m, 3 H), 7.42–7.39 (d, *J* = 1.9 Hz, 1 H), 6.66 (d, *J* = 7.9 Hz, 1 H), 3.84 (s, 3 H), 3.78 (s, 4 H), 2.17–2.14 (m, 2 H), 1.87–1.83 (m, 2 H), 1.68 (s, 9 H), 1.54–1.41 (m, 5 H), 1.33–1.28 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 164.7, 161.3, 148.8, 138.6, 133.7, 129.4, 127.5, 124.9, 123.8, 116.6, 116.5, 113.1, 109.2, 86.3, 84.6, 52.1, 51.9, 51.0, 33.7, 28.0, 25.3, 24.7.

ESIMS: *m*/*z* = 575 (M + H).

HRMS-ESI: *m*/*z* calcd for $C_{27}H_{32}BrN_2O_7$: 575.1392; found: 575.1400.

Dimethyl 2-[5-Bromo-1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-5-(*tert*-butylamino)furan-3,4-dicarboxylate (4h)
White crystalline solid; mp 183–185 °C.

IR (KBr): 3327, 3148, 2974, 1747, 1669, 1617, 1541, 1450, 1369, 1272, 1216, 1154, 1084, 1051 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–7.99 (m, 3 H), 7.44 (d, *J* = 1.8 Hz, 1 H), 6.96 (s, 1 H), 3.88 (s, 3 H), 3.80 (s, 3 H), 1.68 (s, 9 H), 1.52 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 164.8, 161.8, 148.8, 138.2, 133.7, 129.4, 127.6, 125.5, 123.4, 116.6, 116.4, 113.4, 109.2, 87.6, 84.6, 52.7, 52.1, 51.0, 29.9, 28.0.

ESIMS: *m*/*z* = 549 (M + H).

HRMS-ESI: *m*/*z* calcd for $C_{25}H_{30}BrN_2O_7$: 549.1236; found: 549.1228.

Dimethyl 2-[5-Bromo-1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-5-(2,4,4-trimethylpentan-2-ylamino)furan-3,4-dicarboxylate (4i)
Yellow liquid.

IR (film): 3418, 2952, 1740, 1674, 1608, 1540, 1451, 1367, 1268, 1220, 1153, 1087, 1052 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.6 Hz, 1 H), 8.01 (d, *J* = 2.0 Hz, 1 H), 7.96 (s, 1 H), 7.42 (d, *J* = 2.0 Hz, 1 H), 7.09 (s, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 1.83 (s, 2 H), 1.68 (s, 9 H), 1.56 (s, 6 H), 1.06 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 165, 161.7, 148.9, 137.9, 133.8, 129.4, 127.6, 125.5, 123.3, 116.7, 116.5, 113.6, 109.3, 87.2, 84.6, 56.4, 53.5, 52.2, 51.0, 31.4, 30.3, 29.6, 28.0.

ESIMS: *m*/*z* = 605 (M + H).

HRMS-ESI: *m*/*z* calcd for $C_{29}H_{38}BrN_2O_7$: 605.1862; found: 605.1855.

Diethyl 2-[5-Bromo-1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-5-(cyclohexylamino)furan-3,4-dicarboxylate (4j)
Yellow solid; mp 118–120 °C.

IR (KBr): 3459, 3160, 2978, 2930, 2855, 1748, 1669, 1623, 1541, 1452, 1370, 1270, 1230, 1102, 1069 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.9 Hz, 1 H), 8.01 (d, *J* = 1.6 Hz, 1 H), 7.99 (s, 1 H), 7.41 (d, *J* = 2.4 Hz, 1 H), 6.67 (d, *J* = 7.3 Hz, 1 H), 4.32 (q, *J* = 6.5 Hz, 2 H), 4.24 (q, *J* = 7.3 Hz, 2 H), 2.15 (s, 2 H), 1.87–1.79 (m, 2 H), 1.68 (s, 9 H), 1.60–1.41 (m, 5 H), 1.36 (t, *J* = 6.5 Hz, 3 H), 1.32 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 164.5, 161.3, 148.9, 138.0, 133.8, 129.5, 127.6, 124.7, 123.8, 116.7, 116.5, 113.7, 109.4, 86.6, 84.6, 61.3, 59.6, 51.8, 33.7, 28.0, 25.4, 24.7, 14.4, 14.1.

ESIMS: *m*/*z* = 603 (M + H).

HRMS-ESI: *m*/*z* calcd for $C_{27}H_{37}BrN_2O_7$ + Na: 603.1681; found: 603.1659.

Diethyl 2-[5-Bromo-1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-5-(*tert*-butylamino)furan-3,4-dicarboxylate (4k)
Orange solid; mp 166–168 °C.

IR (KBr): 3351, 3160, 2979, 2933, 1739, 1672, 1608, 1542, 1451, 1369, 1270, 1209, 1155, 1088, 1052 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07–8.02 (m, 2 H), 7.90 (s, 1 H), 7.42 (d, *J* = 1.8 Hz, 1 H), 6.96 (s, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 1.67 (s, 9 H), 1.52 (s, 9 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.32 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 164.6, 161.8, 148.9, 137.7, 133.8, 129.5, 127.6, 125.2, 123.4, 116.7, 116.5, 113.9, 109.4, 87.8, 84.6, 61.3, 59.6, 52.7, 30.0, 28.0, 14.3, 14.1.

ESIMS: *m*/*z* = 577 (M + H).

HRMS-ESI: *m*/*z* calcd for $C_{27}H_{34}BrN_2O_7$: 577.1549; found: 577.1553.

Dethyl 2-[5-Bromo-1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl]-5-(2,4,4-trimethylpentan-2-ylamino)furan-3,4-dicarboxylate (4l)
Yellow liquid.

IR (film): 3332, 2975, 1739, 1671, 1607, 1542, 1451, 1368, 1267, 1214, 1154, 1086, 1052 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.4 Hz, 1 H), 8.01 (s, 1 H), 7.93 (s, 1 H), 7.43 (d, *J* = 8.4 Hz, 1 H), 7.08 (s, 1 H), 4.31 (q, *J* = 6.7 Hz, 2 H), 4.24 (q, *J* = 6.7 Hz, 2 H), 1.83 (s, 2 H), 1.67 (s, 9 H), 1.56 (s, 6 H), 1.35 (t, *J* = 6.7, 7.5 Hz, 3 H), 1.32 (t, *J* = 6.7 Hz, 3 H), 1.06 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 164.7, 161.7, 148.9, 137.3, 133.9, 129.5, 127.6, 125.2, 123.3, 116.7, 116.5, 114.1, 109.4, 87.5, 84.6, 61.4, 59.6, 56.4, 53.5, 31.5, 30.3, 29.6, 28.0, 14.3, 14.1.

ESIMS: *m*/*z* = 633 (M + H).

HRMS-ESI: *m*/*z* calcd for $C_{31}H_{42}BrN_2O_7$: 633.2175; found: 633.2177.

Dimethyl 2-[1-(*tert*-Butoxycarbonyl)-5-methoxy-1*H*-indol-3-yl]-5-(cyclohexylamino)furan-3,4-dicarboxylate (4m)
Brown liquid.

IR (film): 3348, 2928, 2854, 1734, 1675, 1617, 1471, 1372, 1248, 1155, 1105, 1072, 1034 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (br d, *J* = 9.0 Hz, 1 H), 7.94 (s, 1 H), 7.24 (d, *J* = 2.2 Hz, 1 H), 6.91 (d, *J* = 2.1 Hz, 1 H), 6.70 (d, *J* = 7.5 Hz, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.78 (s, 4 H), 2.15–2.04 (m, 2 H), 1.84–1.71 (m, 2 H), 1.69 (s, 9 H), 1.43–1.22 (m, 3 H), 1.21–1.11 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 164.6, 161.4, 156.0, 149.2, 138.6, 129.8, 128.7, 124.7, 115.9, 113.9, 113.5, 109.8, 103.0, 86.6, 83.9, 61.2, 59.5, 55.4, 51.4, 33.6, 25.3, 24.5.

ESIMS: *m*/*z* = 527 (M + H), 549 (M + Na).

HRMS-ESI: *m*/*z* calcd for $C_{28}H_{35}N_2O_8$: 527.2393; found: 527.2412.

Dimethyl 2-[1-(*tert*-Butoxycarbonyl)-5-methoxy-1*H*-indol-3-yl]-5-(*tert*-butylamino)furan-3,4-dicarboxylate (4n)
Brown liquid.

IR (film): 3450, 2929, 1735, 1675, 1609, 1545, 1471, 1373, 1251, 1211, 1156, 1091, 1054 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.8 Hz, 1 H), 7.92 (s, 1 H), 7.25 (s,1 H), 6.95–6.90 (m, 2 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 1.68 (s, 9 H), 1.52 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 165.0, 161.9, 156.1, 149.2, 138.9, 129.7, 128.6, 125.3, 116.1, 114.3, 113.0, 109.7, 102.4, 87.7, 84.0, 55.5, 52.7, 52.2, 51.0, 30.0, 28.0.

ESIMS: *m*/*z* = 501 (M + H), 523 (M + Na).

HRMS-ESI: *m*/*z* calcd for $C_{26}H_{33}N_2O_8$: 501.2236; found: 501.2239.

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