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AN APPROACH TO THE SYNTHESIS OF NOVEL DIHYDROINDOLES BEARING ELECTRON-WITHDRAWING GROUPS AT C-2 POSITION

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Abstract – The synthesis of novel dihydroindoles **8a–d** and **9a–d** bearing electron-withdrawing groups at C-2 position is presented. The key step of this approach is an efficient intramolecular Diels-Alder reaction of *N*-alkenylated 2-amino-3-furancarbonitriles **4a–d** and **5a–d**.

Nitrogen-containing heterocyclic ring systems such as indoles[1] and dihydroindoles,[2] namely indolines, have shown a great potential in pharmaceutical research and serve as versatile scaffolds in experimental drug design. As a consequence, the synthesis and functionalization of indoles[3] and indolines[4] has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of them have been developed.

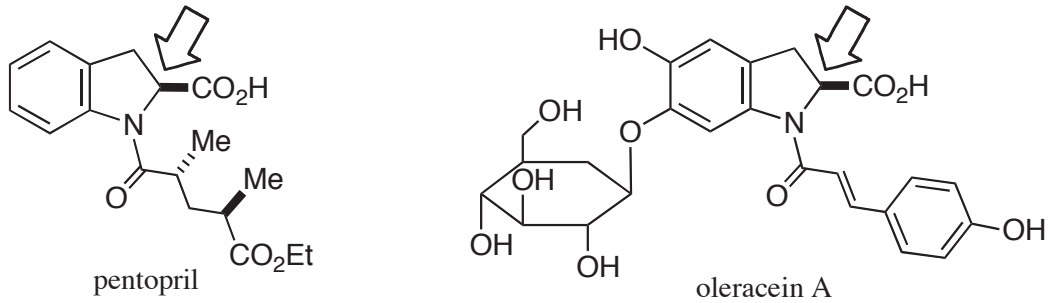
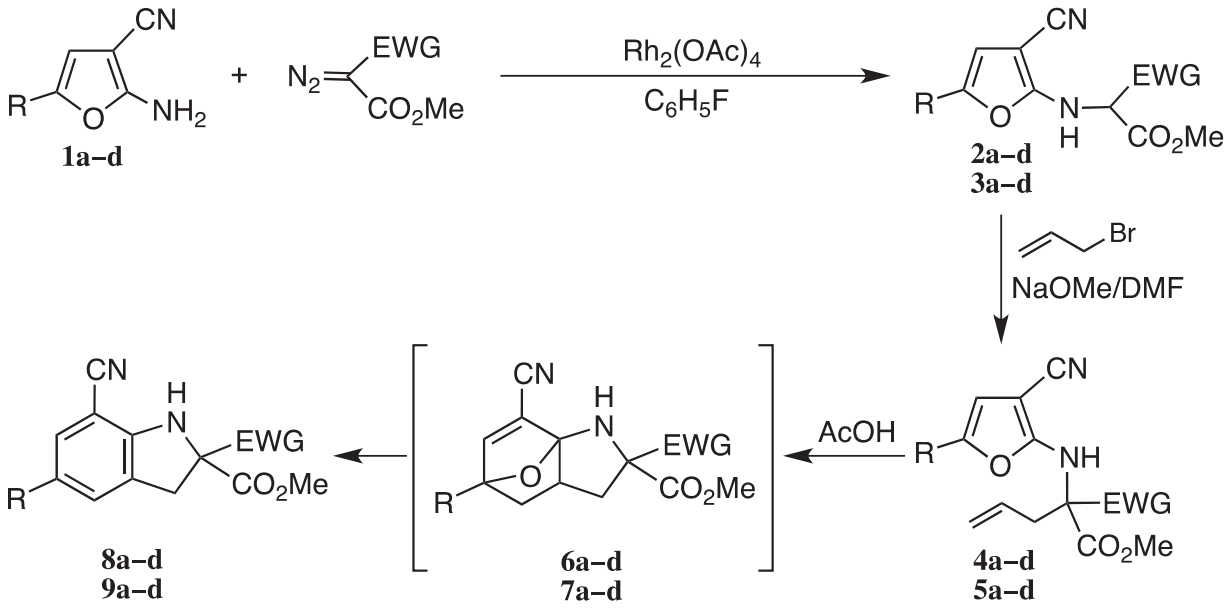


Figure 1. Representative bioactive indoline derivatives

Indoline derivatives, such as pentopril[2b] and oleracein A,[2f] are the structural components of several important pharmaceutically active compounds (Figure 1). In their ring system, it is worth noting that a proton is replaced with an electron-withdrawing group in the C-2 position of indoline skeleton. Our general point of interest goes to the synthesis of novel indolines having electron-withdrawing groups at C-2 position. In connection with our current research interests in this area, the construction of the

functionalized indoline ring system through an intramolecular Diels-Alder reaction has been shown to be a simple and versatile tool for a rapid assembly of indoline derivatives.[5] As 2-amino-3-furancarbonitriles **1a–d** are easily available by established synthetic procedures,[6] we focused our attention on the development of a new method for the preparation of indoline derivatives using them as starting materials. In this paper, we wish to report the synthesis of novel indoline derivatives.

Initially, we examined the N-H insertion reaction[7] of 2-amino-3-furancarbonitriles **1a–d** with α-diazocarbonyl compounds such as dimethyl diazomalonate and methyl diazoacetoacetate (Scheme 1). The reaction of **1a** with dimethyl diazomalonate was chosen as a model. After different conditions were screened, we were delighted to find that the N-H insertion product **2a** was obtained from this reaction with rhodium(II) acetate dimer [$Rh_2(OAc)_4$] as catalyst in a suitable solvent at 70 °C for 1 h. After screening solvents, we found fluorobenzene was the best solvent. With the optimized reaction conditions in hand, **1a–d** were subjected to react with dimethyl diazomalonate and methyl diazoacetoacetate, and the representative results are summarized in Table 1.



a: R = C_6H_5, **b**: R = 4-Cl-C_6H_4, **c**: R = 4-Me-C_6H_4, **d**: R = 4-MeO-C_6H_4

2,**4**,**6**,**8**: EWG = CO_2Me, **3**,**5**,**7**,**9**: EWG = COMe

Scheme 1

Table 1. Synthesis of **2a–d** and **3a–d** according to Scheme 1

Entry	Substrate	R	EWG	Product	Yield (%)
1	**1a**	C_6H_5	CO_2Me	**2a**	90
2	**1b**	4-Cl-C_6H_4	CO_2Me	**2b**	81
3	**1c**	4-Me-C_6H_4	CO_2Me	**2c**	74
4	**1d**	4-MeO-C_6H_4	CO_2Me	**2d**	85
5	**1a**	C_6H_5	COMe	**3a**	72
6	**1b**	4-Cl-C_6H_4	COMe	**3b**	74
7	**1c**	4-Me-C_6H_4	COMe	**3c**	67
8	**1d**	4-MeO-C_6H_4	COMe	**3d**	67

We next tried the *C*-propenylation reaction of the N-H insertion products **2a–d** and **3a–d** with 3-bromopropene (Scheme 1). Thus, compounds **2a–d** and **3a–d** were reacted with 3-bromopropene in the presence of sodium methoxide in DMF at room temperature to provide the corresponding compounds **4a–d** and **5a–d** in moderate yields (Table 2). In this reaction, although we examined several reaction conditions, for example, substrate/base molar ratio and solvent, our attempts were unacceptable with respect to yield. It seemed that *C*-propenylation reaction of **2a–d** and **3a–d** did not proceed readily because of the influence of steric hindrance of the tertiary carbanion with three bulky substituents.

Table 2. Synthesis of **4a–d** and **5a–d** according to Scheme 1

Entry	Substrate	R	EWG	Product	Yield (%)
1	**2a**	C_6H_5	CO_2Me	**4a**	32
2	**2b**	4-Cl-C_6H_4	CO_2Me	**4b**	46
3	**2c**	4-Me-C_6H_4	CO_2Me	**4c**	34
4	**2d**	4-MeO-C_6H_4	CO_2Me	**4d**	47
5	**3a**	C_6H_5	COMe	**5a**	21
6	**3b**	4-Cl-C_6H_4	COMe	**5b**	41
7	**3c**	4-Me-C_6H_4	COMe	**5c**	42
8	**3d**	4-MeO-C_6H_4	COMe	**5d**	36

By comparison of the IR spectra, NMR spectra, mass spectra, and elemental analyses of **4a–d** and **5a–d**, it seems that the structural assignments given to these compounds are correct (see experimental section). For example, the ^{1}H NMR spectrum of **4a** in $CDCl_3$ exhibits a two-proton doublet at δ 3.14 assignable to the methylene protons of 2-propene, a two-proton multiplet in the range of δ 5.09–5.18 assignable to the

3-H proton of 2-propene, and a one-proton multiplet in the range of δ 5.60–5.69 assignable to the 2-H proton of 2-propene. The ^{13}C NMR spectrum of **4a** in $CDCl_3$ shows a signal at δ 38.2 because of the methylene carbon of 2-propene, a signal at δ 68.0 because of the quaternary C-2 carbon, a signal at δ 120.8 because of the C-3 carbon of 2-propene, and a signal at δ 130.2 because of the C-2 carbon of 2-propene.

Finally, we attempted the intramolecular Diels-Alder reaction of **4a–d** and **5a–d** (Scheme 1). As a consequence, treatment of **4a–d** and **5a–d** in boiling acetic acid for 3 h caused an intramolecular Diels-Alder reaction to furnish the desired indolines **8a–d** and **9a–d** in moderate to good yields (Table 3). In this reaction, the key intermediates **6a–d** and **7a–d** were not detected at all. These products **8a–d** and **9a–d** gave satisfactory elemental analyses and spectroscopic data (IR, ^1H NMR, ^{13}C NMR, mass) consistent with their assigned structures (see experimental section). For example, the ^1H NMR spectrum of **8a** in $CDCl_3$ exhibits a two-proton singlet at δ 3.78 assignable to the methylene protons. The ^{13}C NMR spectrum of **8a** in $CDCl_3$ shows a signal at δ 36.8 because of the methylene C-3 carbon and a signal at δ 72.8 because of the quaternary C-2 carbon.

Table 3. Synthesis of **8a–d** and **9a–d** according to Scheme 1

Entry	Substrate	R	EWG	Product	Yield (%)
1	**4a**	C_6H_5	CO_2Me	**8a**	83
2	**4b**	4-Cl-C_6H_4	CO_2Me	**8b**	76
3	**4c**	4-Me-C_6H_4	CO_2Me	**8c**	60
4	**4d**	4-MeO-C_6H_4	CO_2Me	**8d**	52
5	**5a**	C_6H_5	COMe	**9a**	38
6	**5b**	4-Cl-C_6H_4	COMe	**9b**	65
7	**5c**	4-Me-C_6H_4	COMe	**9c**	93
8	**5d**	4-MeO-C_6H_4	COMe	**9d**	43

Fortunately, we found the reaction condition under which the key intermediate **6a** could be isolated (Scheme 1). Indeed, when a solution of **4a** in 1,2-dichlorobenzene was refluxed for 24 h, the oxabridged cycloadduct **6a** was obtained in 60% yield. Interestingly, in this reaction, the indoline **8a** was not detected at all. Thermal treatment of **6a** with acetic acid for 1.5 h caused a ring-opening/dehydration to give the desired **8a** (77% yield), which was shown to be identical with the sample prepared from **4a** with acetic acid on the basis of a mixed melting point determination and a comparison of the IR spectrum.

On the basis of the above experimental results, the formation of **8a–d** and **9a–d** could be explained by possible mechanism presented in Scheme 1. Thus, these intramolecular Diels-Alder reactions of **4a–d** and

5a–d are assumed to proceed through the formation of the oxabridged cycloadducts **6a–d** and **7a–d**. Subsequently, a ring-opening/dehydration reaction of cycloadducts **6a–d** and **7a–d** easily occurs in the presence of acetic acid and then indolines **8a–d** and **9a–d** would be produced.

In conclusion, we have demonstrated the synthesis of novel dihydroindoles bearing electron-withdrawing groups at C-2 position. The key intramolecular Diels-Alder reaction of *N*-alkenylated 2-amino-3-furancarbonitriles proceeds smoothly to furnish the corresponding dihydroindoles. Functionalized dihydroindole derivatives are important synthons in organic synthesis and for the preparation of biologically active compounds with interest in medicinal chemistry.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-A500 spectrometer at 500 and 125 MHz, respectively. The ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to TMS as internal standard. Positive FAB MS spectra were obtained on a JEOL JMS-700T spectrometer. Elemental analyses were performed on YANACO MT-6 CHN analyzer. The starting compounds, 2-amino-3-furancarbonitriles **1a–d**, were prepared in this laboratory according to the procedure reported in literature.[6]

General procedure for the preparation of 2a–d and 3a–d from 1a–d and α-diazocarbonyl compounds.

A solution of **1a–d** (20 mmol), dimethy diazomalonate (3.79 g, 24 mmol) and/or methyl diazoacetoacetate (3.41 g, 24 mmol) and $Rh_2(OAc)_4$ (0.10 g, 0.23 mmol) in C_6H_5F (80 mL) was stirred at 70 ℃ for 1 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel with CH_2Cl_2 as eluent to afford **2a–d** and **3a–d**.

2-[(3-Cyano-5-phenyl-2-furanyl)amino]propanedioic acid 1,3-dimethyl ester (2a): Colorless columns (5.65 g, 90%), mp 134–135 ℃ (acetone); IR (KBr): ν 3309 (NH), 2212 (CN), 1750, 1736 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 6H, $2CO_2CH_3$), 5.18 (d, *J* = 7.9 Hz, 1H, 2-H), 5.88 (d, *J* = 7.9 Hz, 1H, NH), 6.55 (s, 1H, furan 4-H), 7.22–7.26 (m, 1H, aryl H), 7.34–7.37 (m, 2H, aryl H), 7.42–7.45 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 53.8 ($2CO_2\mathit{C}H_3$), 58.9 (C-2), 71.4 (furan C-3), 105.8 (furan C-4), 114.6 (CN), 122.9, 127.6, 128.76, 128.81, 129.0 (C aryl), 145.3 (furan C-5), 159.2 (furan C-2), 166.2 (2CO); MS: *m/z* 315 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.09; H, 4.49; N 8.79.

2-{[5-(4-Chlorophenyl)-3-cyano-2-furanyl]amino}propanedioic acid 1,3-dimethyl ester (2b): Colorless columns (5.67 g, 81%), mp 133–135 ℃ (acetone); IR (KBr): ν 3328 (NH), 2210 (CN), 1749, 1734 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 6H, $2CO_2CH_3$), 5.17 (d, *J* = 7.9 Hz, 1H, 2-H), 5.94 (d, *J* = 7.9 Hz, 1H, NH), 6.55 (s, 1H, furan 4-H), 7.31–7.33 (m, 2H, aryl H), 7.35–7.38 (m, 2H, aryl H); ^{13}C

NMR ($CDCl_3$): δ 53.8 ($2CO_2\mathit{C}H_3$), 58.9 (C-2), 71.5 (furan C-3), 106.4 (furan C-4), 114.2 (CN), 124.1, 127.4, 129.1, 133.2 (C aryl), 144.4 (furan C-5), 159.3 (furan C-2), 166.1 (2CO); MS: *m/z* 349 $[M+H]^+$. Anal. Calcd for $C_{16}H_{13}ClN_2O_5$: C, 55.10; H, 3.76; N, 8.03. Found: C, 54.89; H, 3.80; N, 7.99.

2-{[3-Cyano-5-(4-methylphenyl)-2-furanyl]amino}propanedioic acid 1,3-dimethyl ester (2c): Colorless columns (4.85 g, 74%), mp 137–138 ℃ (acetone); IR (KBr): ν 3304 (NH), 2207 (CN), 1758, 1737 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 3.88 (s, 6H, $2CO_2CH_3$), 5.17 (d, *J* = 8.1 Hz, 1H, 2-H), 5.86 (d, *J* = 8.1 Hz, 1H, NH), 6.48 (s, 1H, furan 4-H), 7.14–7.16 (m, 2H, aryl H), 7.32–7.34 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 21.2 (CH_3) 53.8 ($2CO_2\mathit{C}H_3$), 58.9 (C-2), 71.2 (furan C-3), 104.9 (furan C-4), 114.6 (CN), 122.9, 126.3, 129.5, 137.5 (C aryl), 145.7 (furan C-5), 159.0 (furan C-2), 166.2 (2CO); MS: *m/z* 329 $[M+H]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 61.98; H, 4.96; N 8.48.

2-{[3-Cyano-5-(4-methoxyphenyl)-2-furanyl]amino}propanedioic acid 1,3-dimethyl ester (2d): Colorless needles (5.85 g, 85%), mp 116–117 ℃ (acetone); IR (KBr): ν 3328 (NH), 2210 (CN), 1749, 1734 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 3.82 (s, 3H, OCH_3), 3.88 (s, 6H, $2CO_2CH_3$), 5.16 (d, *J* = 8.2 Hz, 1H, 2-H), 5.84 (d, *J* = 8.2 Hz, 1H, NH), 6.39 (s, 1H, furan 4-H), 6.88–6.90 (m, 2H, aryl H), 7.36–7.38 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 53.8 ($2CO_2\mathit{C}H_3$), 55.3 (OCH_3), 59.0 (C-2), 71.2 (furan C-3), 103.9 (furan C-4), 114.3 (C aryl), 114.6 (CN), 121.9, 124.5 (C aryl), 145.6 (furan C-5), 158.9 (furan C-2), 159.3 (C aryl), 166.3 (2CO); MS: *m/z* 345 $[M+H]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.10; H, 4.84; N 8.12.

2-[(3-Cyano-5-phenyl-2-furanyl)amino]-3-oxobutanoic acid methyl ester (3a): Colorless columns (4.30 g, 72%), mp 107–108 ℃ (acetone); IR (KBr) : ν 3329 (NH), 2204 (CN), 1755, 1726 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.49 (s, 3H, $COCH_3$), 3.89 (s, 3H, CO_2CH_3), 5.29 (d, *J* = 7.0 Hz, 1H, 2-H), 6.14 (d, *J* = 7.0 Hz, 1H, NH), 6.54 (s, 1H, furan 4-H), 7.22–7.26 (m, 1H, aryl H), 7.33–7.37 (m, 2H, aryl H), 7.42–7.44 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 27.3 ($CO\mathit{C}H_3$), 53.9 ($CO_2\mathit{C}H_3$), 65.7 (C-2), 70.4 (furan C-3), 105.8 (furan C-4), 114.9 (CN), 122.8, 127.5, 128.8 (C aryl), 128.9 (furan C-5), 145.1 (C aryl), 159.5 (furan C-2), 166.2, 196.9 (CO); MS: *m/z* 299 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N 9.39. Found: C, 64.29; H, 4.71; N 9.29.

2-{[5-(4-Chlorophenyl)-3-cyano-2-furanyl]amino}-3-oxobutanoic acid methyl ester (3b): Colorless columns (4.89 g, 74%), mp 134–135 ℃ (acetone); IR (KBr): ν 3310 (NH), 2205 (CN), 1751, 1728 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.48 (s, 3H, $COCH_3$), 3.89 (s, 3H, CO_2CH_3), 5.28 (d, *J* = 7.0 Hz, 1H, 2-H), 6.15 (d, *J* = 7.0 Hz, 1H, NH), 6.53 (s, 1H, furan 4-H), 7.30–7.37 (m, 4H, aryl H); ^{13}C NMR ($CDCl_3$): δ 27.3 ($CO\mathit{C}H_3$), 53.9 ($CO_2\mathit{C}H_3$), 65.7 (C-2), 70.7 (furan C-3), 106.4 (furan C-4), 114.6 (CN), 124.1, 127.5, 129.0, 133.2 (C aryl), 144.1 (furan C-5), 159.7 (furan C-2), 166.1, 196.8 (CO); MS: *m/z* 333 $[M+H]^+$. Anal. Calcd for $C_{16}H_{13}ClN_2O_4$ $0.15H_2O$: C, 57.29; H, 4.00; N, 8.35. Found: C, 57.27; H, 4.05; N,

8.36.

2-{[3-Cyano-5-(4-methylphenyl)-2-furanyl]amino}-3-oxobutanoic acid methyl ester (3c): Colorless columns (4.18 g, 67%), mp 136–137 ℃ (acetone); IR (KBr): ν 3322 (NH), 2208 (CN), 1750, 1726 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 2.47 (s, 3H, $COCH_3$), 3.88 (s, 3H, CO_2CH_3), 5.27 (d, J = 7.3 Hz, 1H, 2-H), 6.07 (d, J = 7.3 Hz, 1H, NH), 6.46 (s, 1H, furan 4-H), 7.15–7.17 (m, 2H, aryl H), 7.31–7.34 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 21.2 (CH_3), 27.3 ($COCH_3$), 53.8 (CO_2CH_3), 65.8 (C-2), 70.5 (furan C-3), 104.9 (furan C-4), 114.9 (CN), 122.9, 126.3, 129.5, 137.5 (C aryl), 145.5 (furan C-5), 159.4 (furan C-2), 166.2, 197.0 (CO); MS: *m/z* 313 $[M+H]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.28; H, 5.21; N 8.96.

2-{[3-Cyano-5-(4-methoxyphenyl)-2-furanyl]amino}-3-oxobutanoic acid methyl ester (3d): Colorless needles (4.38 g, 67%), mp 119–120 ℃ (acetone); IR (KBr): ν 3245 (NH), 2209 (CN), 1728, 1667 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H, $COCH_3$), 3.80 (s, 1H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 5.70 (s, 1H, 2-H), 6.39 (s, 1H, furan 4-H), 6.88–6.90 (m, 2H, aryl H), 7.38–7.40 (m, 2H, aryl H), 12.37 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 18.0 ($CO\mathit{C}H_3$), 52.2 (OCH_3), 55.3 ($CO_2\mathit{C}H_3$), 70.3 (furan C-3), 101.3 (C-2), 104.1 (furan C-4), 114.3 (C aryl), 114.9 (CN), 122.2, 124.4 (C aryl), 145.2 (furan C-5), 159.2 (CO), 161.3 (furan C-2), 170.7 (C aryl), 177.0 (CO); MS: *m/z* 329 $[M+H]^+$. Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 61.98; H, 4.97; N 8.57.

General procedure for the preparation of 4a–d and 5a–d from 2a–d and/or 3a–d and 3-bromopropene.

To an ice-cooled and stirred mixture of **2a–d** and/or **3a–d** (2.5 mmol) and sodium methoxide (0.18 g, 3.25 mmol) in DMF (10 mL), 3-bromopropene (0.61 g, 5 mmol) was added. The mixture was stirred at rt for 3 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel with CH_2Cl_2 as the eluent to give **4a–d** and **5a–d**.

2-[(3-Cyano-5-phenyl-2-furanyl)amino]-2-(2-propen-1-yl)propanedioic acid 1,3-dimethyl ester (4a): Colorless columns (0.28 g, 32%), mp 121–123 ℃ (Et_2O); IR (KBr): ν 3346 (NH), 2218 (CN), 1761, 1741 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 3.14 (d, J = 7.3 Hz, 2H, 2-propene 1-H), 3.82 (s, 6H, CO_2CH_3), 5.09–5.18 (m, 2H, 2-propene 3-H), 5.60–5.69 (m, 1H, 2-propene 2-H), 6.17 (s, 1H, NH), 6.57 (s, 1H, furan 4-H), 7.22–7.26 (s, 1H, aryl H), 7.34–7.42 (s, 4H, aryl H); ^{13}C NMR ($CDCl_3$): δ 38.2 (2-propene C-1), 53.8 ($2CO_2\mathit{C}H_3$), 68.0 (C-2), 72.3 (furan C-3), 105.5 (furan C-4), 114.4 (CN), 120.8 (2-propene C-3), 122.7, 127.4, 128.9, 129.0 (C aryl), 130.2 (2-propene C-2), 145.5 (furan C-5), 158.9 (furan C-2), 167.8 (CO); MS: *m/z* 355 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.43; H, 5.17; N, 7.93.

2-{[5-(4-Chlorophenyl)-3-cyano-2-furanyl]amino}-2-(2-propen-1-yl)propanedioic acid 1,3-dimethyl ester (4b): Colorless columns (0.45 g, 46%), mp 120–121 ℃ (Et_2O); IR (KBr): 3287 (NH), 2215 (CN),

1749 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 3.13 (d, *J* = 7.3 Hz, 2H, 2-propene 1-H), 3.82 (s, 6H, $2CO_2CH_3$), 5.09–5.20 (m, 2H, 2-propene 3-H), 5.59–5.69 (m, 1H, 2-propene 2-H), 6.21 (s, 1H, NH), 6.57 (s, 1H, furan 4-H), 7.33 (s, 4H, aryl H); ^{13}C NMR ($CDCl_3$): δ 38.2 (2-propene C-1), 53.9 ($2CO_2\mathit{C}H_3$), 68.0 (C-2), 72.4 (furan C-3), 106.0 (furan C-4), 114.2 (CN), 120.9 (2-propene C-3), 123.9, 127.5, 129.2 (C aryl), 130.0 (2-propene C-2), 133.1 (C aryl), 144.4 (furan C-5), 158.9 (furan C-2), 167.8 (CO); MS: *m*/*z* 389 $[M+H]^+$. Anal. Calcd for $C_{19}H_{17}ClN_2O_5$: C, 58.69; H, 4.41; N, 7.21. Found: C, 58.72; H, 4.51; N, 7.28.

2-{[3-Cyano-5-(4-methylphenyl)-2-furanyl]amino}-2-(2-propen-1-yl)propanedioic acid 1,3-dimethyl ester (4c): Yellow oil (0.31 g, 34%); IR (neat): ν 3377 (NH), 2216 (CN), 1747 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 3.13 (d, *J* = 7.3 Hz, 2H, 2-propene 1-H), 3.82 (s, 6H, $2CO_2CH_3$), 5.09–5.18 (m, 2H, 2-propene 3-H), 5.60–5.69 (m, 1H, 2-propene 2-H), 6.13 (s, 1H, NH), 6.50 (s, 1H, furan 4-H), 7.16–7.18 (m, 2H, aryl H), 7.26–7.31 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 21.2 (CH_3), 38.3 (2-propene C-1), 53.8 ($2CO_2\mathit{C}H_3$), 68.1 (C-2), 72.3 (furan C-3), 104.5 (furan C-4), 114.5 (CN), 120.8 (2-propene C-3), 122.7, 126.3, 129.6 (C aryl), 130.2 (2-propene C-2), 137.4 (C aryl), 145.9 (furan C-5), 158.6 (furan C-2), 167.9 (CO); MS: *m*/*z* 368 $[M+H]^+$. Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.34; H, 5.78; N, 7.44.

2-{[3-cyano-5-(4-methoxyphenyl)-2-furanyl]amino}-2-(2-propen-1-yl)propanedioic acid 1,3-dimethyl ester (4d): Colorless columns (0.45 g, 47%), mp 105–106 ℃ (Et_2O); IR (KBr): ν 3269 (NH), 2217 (CN), 1749 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 3.12 (d, *J* = 7.3 Hz, 2H, 2-propene 1-H), 3.82 (s, 9H, OCH_3 and $2CO_2CH_3$), 5.09–5.18 (m, 2H, 2-propene 3-H), 5.61–5.69 (m, 1H, 2-propene 2-H), 6.10 (s, 1H, NH), 6.41 (s, 1H, furan 4-H), 6.88–6.92 (m, 2H, aryl H), 7.32–7.35 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 38.2 (2-propene C-1), 53.8 ($2CO_2\mathit{C}H_3$), 55.3 (OCH_3), 68.1 (C-2), 72.4 (furan C-3), 103.5 (furan C-4), 114.5 (C aryl), 114.6 (CN), 120.8 (2-propene C-3), 122.0, 124.3 (C aryl), 130.2 (2-propene C-2), 145.8 (furan C-5), 158.5 (furan C-2), 159.2 (C aryl), 167.9 (CO); MS: *m*/*z* 385 $[M+H]^+$. Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.49; H, 5.33; N, 7.18.

2-Acetyl-2-[(3-cyano-5-phenyl-2-furanyl)amino]-4-pentenoic acid methyl ester (5a): Colorless columns (0.18 g, 21%), mp 91–92 ℃ (Et_2O); IR (KBr): ν 3434 (NH), 2212 (CN), 1651, 1613 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H, $COCH_3$), 3.81 (s, 3H, CO_2CH_3), 4.00–4.05 (m, 1H, 4-pentene 3-H), 4.34–4.39 (m, 1H, 4-pentene 3-H), 5.25–5.34 (m, 2H, 4-pentene 5-H), 5.29–6.00 (m, 1H, 4-pentene 4-H), 6.57 (s, 1H, furan 4-H), 7.21–7.26 (m, 1H, aryl H), 7.34–7.38 (m, 2H, aryl H), 7.46–7.48 (m, 2H, aryl H), 12.49 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 18.3 ($CO\mathit{C}H_3$), 52.2 ($CO_2\mathit{C}H_3$), 54.8 (4-pentene C-3), 70.0 (furan C-3), 106.2 (C-2), 107.1 (furan C-4), 115.4 (CN), 119.7 (4-pentene C-5), 122.6, 127.2, 128.8, 129.3 (C aryl), 132.2 (4-pentene C-4), 144.4 (furan C-5), 161.6 (furan C-2), 170.7, 177.9 (CO); MS: *m*/*z* 339 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.23; H, 5.39; N, 8.20.

2-Acetyl-2-{[5-(4-chlorophenyl)-3-cyano-2-furanyl]amino}-4-pentenoic acid methyl ester (5b):

Colorless columns (0.38 g, 41%), mp 131–132 ℃ (Et_2O); IR (KBr): ν 3343 (NH), 2213 (CN), 1750, 1728 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.27 (s, 3H, $COCH_3$), 3.02–3.07 (m, 1H, 4-pentene 3-H), 3.15–3.20 (m, 1H, 4-pentene 3-H), 3.82 (s, 3H, CO_2CH_3), 5.07–5.17 (m, 2H, 4-pentene 5-H), 5.51–5.59 (m, 1H, 4-pentene 4-H), 6.41 (s, 1H, NH), 6.57 (s, 1H, furan 4-H), 7.26–7.35 (m, 4H, aryl H); ^{13}C NMR ($CDCl_3$): δ 24.4 ($COCH_3$), 37.1 (4-pentene C-3), 53.9 (CO_2CH_3), 72.3 (furan C-3), 73.3 (C-2), 106.0 (furan C-4), 114.2 (CN), 120.8 (4-pentene C-5), 123.9, 127.4, 129.2 (C aryl), 129.8 (4-pentene C-4), 133.2 (C aryl) 144.4 (furan C-5), 159.0 (furan C-2), 168.4, 198.3 (CO); MS: *m/z* 373 $[M+H]^+$. Anal. Calcd for $C_{19}H_{17}ClN_2O_4$: C, 61.21; H, 4.60; N, 7.51. Found: C, 61.19; H, 4.62; N, 7.54.

2-Acetyl-2-{[3-cyano-5-(4-methylphenyl)-2-furanyl]amino}-4-pentenoic acid methyl ester (5c): Yellow oil (0.37 g, 42%); IR (neat): ν 3360 (NH), 2214 (CN), 1748, 1730 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.27 (s, 3H, $COCH_3$), 2.34 (s, 3H, CH_3), 3.02–3.07 (m, 1H, 4-pentene 3-H), 3.15–3.21 (m, 1H, 4-pentene 3-H), 3.81 (s, 3H, CO_2CH_3), 5.06–5.16 (m, 2H, 4-pentene 5-H), 5.51–5.60 (m, 1H, 4-pentene 3-H), 6.35 (s, 1H, NH), 6.49 (s, 1H, furan 4-H), 7.15–7.17 (m, 2H, aryl H), 7.23–7.27 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 21.2 (CH_3), 24.4 ($COCH_3$), 37.1 (4-pentene C-3), 53.9 (CO_2CH_3), 72.1 (furan C-3), 73.4 (C-2), 104.5 (furan C-4), 114.5 (CN), 120.7 (4-pentene C-5), 122.7, 124.1, 126.2, 129.6, 129.7 (C aryl), 130.0 (4-pentene C-4), 137.5 (C aryl), 145.8 (furan C-5), 158.7 (furan C-2), 168.5, 198.5 (CO); MS: *m/z* 353 $[M+H]^+$. Anal. Calcd for $C_{20}H_{20}N_2O_4$ $0.25H_2O$: C, 67.31; H, 5.79; N, 7.85. Found: C, 67.39; H, 5.73; N, 7.92.

2-Acetyl-2-{[3-cyano-5-(4-methoxyphenyl)-2-furanyl]amino}-4-pentenoic acid methyl ester (5d): Colorless columns (0.33 g, 36%), mp 112–113 ℃ (Et_2O); IR (KBr): ν 3309 (NH), 2213 (CN), 1752, 1727 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.26 (s, 3H, $COCH_3$), 3.01–3.05 (m, 1H, 4-pentene 3-H), 3.15–3.19 (m, 1H, 4-pentene 3-H), 3.81 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 5.07–5.17 (m, 2H, 4-pentene 5-H), 5.53–5.57 (m, 1H, 4-pentene 4-H), 6.31 (s, 1H, NH), 6.41 (s, 1H, furan 4-H), 6.89–6.92 (m, 2H, aryl H), 7.29–7.32 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 24.5 ($COCH_3$), 37.1 (4-pentene C-3), 53.9 (CO_2CH_3), 55.3 (OCH_3), 72.2 (furan C-3), 73.3 (C-2), 103.4 (furan C-4), 114.5 (C aryl), 114.6 (CN), 120.7 (4-pentene C-5), 121.9, 124.3 (C aryl), 130.0 (4-pentene C-4), 145.7 (furan C-5), 158.6 (furan C-2), 159.2 (C aryl), 168.5, 198.6 (CO); MS: *m/z* 369 $[M+H]^+$. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.14; H, 5.51; N, 7.61.

General procedure for preparation of 8a–d and 9a–d from 4a–d and 5a–d.

A solution of **4a–d** and/or **5a–d** (1.0 mmol) in AcOH (10 mL) was refluxed for 3 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel with CH_2Cl_2 as eluent to yield **8a–d** and **9a–d**.

7-Cyano-1,3-dihydro-5-phenyl-2*H*-indole-2,2-dicarboxylic acid 2,2-dimethyl ester (8a): Colorless columns (0.28 g, 83%), mp 132–133 ℃ (Et_2O); IR (KBr): ν 3309 (NH), 2224 (CN), 1744 cm^{-1} (CO); ^1H

NMR ($CDCl_3$): δ 3.78 (s, 2H, 3-H), 3.85 (s, 6H, $2CO_2CH_3$), 5.61 (br s, 1H, NH), 7.30–7.33 (m, 1H, aryl H), 7.38–7.46 (m, 6H, aryl H); ^{13}C NMR ($CDCl_3$): δ 36.8 (C-3), 53.7 ($2CO_2CH_3$), 72.8 (C-2), 92.3 (C aryl), 116.9 (CN), 126.5, 127.3, 127.6, 127.8, 128.8, 128.9, 133.6, 139.3, 150.6 (C aryl), 169.5 (2CO); MS: *m/z* 337 $[M+H]^+$. Anal. Calcd for $C_{19}H_{16}N_2O_4$ $0.3H_2O$: C, 66.78; H, 4.90; N, 8.20. Found: C, 66.76; H, 4.85; N, 8.13.

5-(4-Chlorophenyl)-7-cyano-1,3-dihydro-2*H*-indole-2,2-dicarboxylic acid 2,2-dimethyl ester (8b): Colorless columns (0.28 g, 76%), mp 175–176 ℃ (Et_2O); IR (KBr): ν 3312 (NH), 2228 (CN), 1740 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 3.77 (s, 2H, 3-H), 3.85 (s, 6H, $2CO_2CH_3$), 5.62 (br s, 1H, NH), 7.36 (s, 4H, aryl H), 7.39–7.41 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 36.8 (C-3), 53.7 ($2CO_2CH_3$), 72.8 (C-2), 92.3 (C aryl), 116.7 (CN), 127.5, 127.7, 127.8, 128.7, 129.1, 132.3, 133.4, 137.8, 150.8 (C aryl), 169.4 (2CO); MS: *m/z* 371 $[M+H]^+$. Anal. Calcd for $C_{19}H_{15}ClN_2O_4$: C, 61.55; H, 4.08; N, 7.56. Found: C, 61.58; H, 4.20; N, 7.62.

7-Cyano-1,3-dihydro-5-(4-methylphenyl)-2*H*-indole-2,2-dicarboxylic acid 2,2-dimethyl ester (8c): Colorless columns (0.21 g, 60%), mp 170–171 ℃ (Et_2O); IR (KBr): 3304 (NH), 2226 (CN), 1742 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 3.77 (s, 2H, 3-H), 3.84 (s, 6H, $2CO_2CH_3$), 5.57 (br s, 1H, NH), 7.19–7.21 (m, 2H, aryl H), 7.31–7.34 (m, 2H, aryl H), 7.41–7.43 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 21.0 (CH_3), 36.9 (C-3), 53.6 ($2CO_2CH_3$), 72.8 (C-2), 92.3 (C aryl), 114.4 (C aryl), 116.9 (CN), 126.3, 127.5, 127.6, 128.5, 129.6, 133.7, 136.5, 137.1, 150.4 (C aryl), 169.5 (2CO); MS: *m/z* 351 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.55; H, 5.27; N, 7.90.

7-Cyano-1,3-dihydro-5-(4-methoxyphenyl)-2*H*-indole-2,2-dicarboxylic acid 2,2-dimethyl ester (8d): Colorless columns (0.19 g, 52%), mp 188–189 ℃ (Et_2O); IR (KBr): ν 3307 (NH), 2226 (CN), 1741 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ 3.76 (s, 2H, 3-H), 3.83 (s, 3H, OCH_3), 3.84 (s, 6H, $2CO_2CH_3$), 5.55 (br s, 1H, NH), 6.92–6.94 (m, 2H, aryl H), 7.34–7.40 (m, 4H, aryl H); ^{13}C NMR ($CDCl_3$): δ 36.9 (C-3), 53.6 ($2CO_2CH_3$), 55.3 (OCH_3), 72.8 (C-2), 92.4, 114.4 (C aryl), 116.9 (CN), 127.46, 127.55, 127.57, 128.3, 132.0, 133.5, 150.2, 159.2 (C aryl), 169.6 (2CO); MS: *m/z* 367 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.45; H, 5.07; N, 7.53.

2-Acetyl-7-cyano-2,3-dihydro-5-phenyl-1*H*-indole-2-carboxylic acid methyl ester (9a): Colorless columns (0.12 g, 38%), mp 160–161 ℃ (Et_2O); IR (KBr): ν 3307 (NH), 2221 (CN), 1749, 1735 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H, $COCH_3$), 3.54 (d, J = 17.5 Hz, 1H, 3-H), 3.66 (d, J = 17.5 Hz, 1H, 3-H), 3.76 (s, 3H, CO_2CH_3), 7.28–7.32 (m, 1H, aryl H), 7.39–7.43 (m, 2H, aryl H), 7.57–7.63 (m, 4H, aryl H), 8.22 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 25.3 ($COCH_3$), 35.1 (C-3), 53.0 (CO_2CH_3), 77.3 (C-2), 89.5 (C aryl), 117.3 (CN), 125.9, 126.8, 127.4, 128.3, 128.5, 128.8, 130.7, 138.6 151.3 (C aryl), 170.5, 201.9 (CO); MS: *m/z* 321 $[M+H]^+$. Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.31; H, 5.11; N, 8.76.

2-Acetyl-5-(4-chlorophenyl)-7-cyano-2,3-dihydro-1*H*-indole-2-carboxylic acid methyl ester (9b): Colorless columns (0.23 g, 65%), mp 211–213 ℃ (Et_2O); IR (KBr): ν 3305 (NH), 2223 (CN), 1742, 1715 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H, $COCH_3$), 3.53 (d, *J* = 17.5 Hz, 1H, 3-H), 3.65 (d, *J* = 17.5 Hz, 1H, 3-H), 3.76 (s, 3H, CO_2CH_3), 7.43–7.46 (m, 2H, aryl H), 7.60–7.63 (m, 4H, aryl H), 8.29 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 25.3 ($COCH_3$), 35.1 (C-3), 53.0 (CO_2CH_3), 77.4 (C-2), 89.4 (C aryl), 117.2 (CN), 127.2, 127.6, 128.4, 128.6, 128.7, 129.2, 131.6, 137.5, 151.6 (C aryl), 170.4, 201.9 (CO); MS: *m/z* 355 $[M+H]^+$. Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.19; H, 4.28; N, 7.87.

2-Acetyl-7-cyano-2,3-dihydro-5-(4-methylphenyl)-1*H*-indole-2-carboxylic acid methyl ester (9c): Colorless columns (0.31 g, 93%), mp 161–163 ℃ (Et_2O); IR (KBr): ν 3309 (NH), 2220 (CN), 1748, 1715 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 2.31 (s, 6H, $COCH_3$, CH_3), 3.53 (d, *J* = 17.7 Hz, 1H, 3-H), 3.65 (d, *J* = 17.7 Hz, 1H, 3-H), 3.76 (s, 3H, CO_2CH_3), 7.21 (d, *J* = 8.2 Hz, 2H, aryl H), 7.47 (d, *J* = 8.2 Hz, 2H, aryl H), 7.55–7.56 (m, 1H, aryl H), 7.60 (s, 1H, aryl H), 8.17 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) : δ 20.5 (CH_3), 25.3 ($COCH_3$), 35.2 (C-3), 53.0 (CO_2CH_3), 77.3 (C-2), 89.5 (C aryl), 117.3 (CN), 125.7, 127.2, 127.8, 128.4, 129.4, 130.7, 135.8, 136.1, 151.1 (C aryl), 170.5, 201.9 (CO); MS: *m/z* 335 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.88; H, 5.47; N, 8.39.

2-Acetyl-7-cyano-2,3-dihydro-5-(4-methoxyphenyl)-1*H*-indole-2-carboxylic acid methyl ester (9d): Colorless columns (0.15 g, 43%), mp 150–151 ℃ (Et_2O); IR (KBr): ν 3327 (NH), 2219 (CN), 1749, 1726 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H, $COCH_3$), 3.52 (d, *J* = 17.5 Hz, 1H, 3-H), 3.64 (d, *J* = 17.5 Hz, 1H, 3-H), 3.76 (s, 3H, CO_2CH_3), 3.78 (s, 3H, $COCH_3$), 6.96–6.98 (m, 2H, aryl H), 7.51–7.52 (m, 3H, aryl H), 7.57 (s, 1H, aryl H), 8.12 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 25.3 ($COCH_3$), 35.2 (C-3), 53.0 (CO_2CH_3), 55.1 (OCH_3), 77.3 (C-2), 89.5, 114.2 (C aryl), 117.4 (CN), 126.99, 127.04, 127.5, 128.4, 130.6, 131.1, 150.8, 158.5 (C aryl), 170.5, 202.0 (CO); MS: *m/z* 351 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.56; H, 5.22; N, 7.98.

The preparation of 6a from 4a.

A solution of **4a** (0.35 g, 1 mmol) in 1,2-dichlorobenzene (10 mL) was refluxed for 24 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel with CH_2Cl_2:acetone (8:1) as eluent to provide 7-cyano-1,3,3a,4,5,7a-hexahydro-5-phenyl-5,7a-epoxy-2*H*-indole-2,2-dicarboxylic acid dimethyl ether (**6a**): This compound was obtained as colorless columns (0.21 g, 60%), mp 180–182 ℃ (Et_2O); IR (KBr): ν 3462 (NH), 2237 (CN), 1739 cm^{-1}(CO); ^1H NMR ($CDCl_3$): δ 1.87 (t, *J* = 13.1 Hz, 1H, 4-H), 2.08 (dd, *J* = 10.7, 13.1 Hz, 1H, 3-H), 2.17–2.20 (m, 1H, 4-H), 2.72 (dd, *J* = 7.9, 13.1 Hz, 1H, 3-H), 3.49–3.52 (m, 1H, 3a-H), 3.73 (s, 3H, CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 6.33 (s, 1H, NH), 7.28–7.44 (m, 6H, 6-H and aryl H); ^{13}C NMR ($CDCl_3$): δ 36.7 (C-3), 42.1 (C-3a), 42.7 (C-4) 52.8, 53.1 (CO_2CH_3), 71.1 (C-5), 84.8 (C-2), 109.8 (C-7), 114.6 (CN), 124.8, 127.4, 128.2, 145.6 (C aryl),

158.9 (C-6), 168.4, 169.1 (CO), 173.4 (C-7a); MS: *m/z* 355 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.15; H, 5.16; N, 7.88.

The preparation of 8a from 6a.

A solution of **6a** (0.35 g, 1 mmol) in AcOH (10 mL) was refluxed for 1.5 h. After removal the solvent *in vacuo*, the residue was purified by column chromatography on silica gel with CH_2Cl_2 as eluent to give **8a** (0.26 g, 77%), which was shown to be identical with the sample prepared from **4a** with AcOH on the basis of a mixed melting point determination and a comparison of the IR spectrum.

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