Supporting Information

One-Pot Chemoselective Domino Condensation to Form Fused Pyrrolo-Pyrazino-Indolizines Framework: Discovery of Novel AIE Molecules

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1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254}. Visualization on TLC was achieved by the use of UV light (254 nm). Solvents mixtures were understood as volume/volume. Purifications of reaction products were carried out by chromatography using silica gel (200–300 mesh). Melting points were determined with a SGW X-4 digital melting point apparatus, and the thermometer was uncorrected. NMR spectra were mostly recorded for $^1$H NMR at 500 MHz and for $^{13}$C NMR at 125 MHz. For $^1$H NMR, tetramethylsilane (TMS) served as internal standard ($\delta$). The spectra data presented here are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (s) in Hertz. For $^{13}$C NMR TMS ($\delta = 0$), CDCl$_3$ ($\delta = 77.05$) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS were obtained using ESI ionization. UV-Visible absorption spectra were measured using Shimadzu UV-1800 spectrophotometer. Fluorescence spectra were measured on a Shimadzu RF-5301PC spectrometer with a slit width 5 nm for emission. The water/DMSO mixtures with different water fractions were prepared by slowly adding distilled water into the DMSO solution of samples under ultrasound at room temperature. Fluorescence quantum yields of compounds in solution and in powders were measured on Absolutely Photoluminescence Quantum Yield Measurement System (HAMAMARSU, C11347-11Quantaurus-QY). The transmission electron microscopy (TEM) images were measured on JEOL JEM-1230, Japan.
2. Optimization of reaction conditions

Table S1. Optimization of intermolecular aldol cyclization conditions\(^a\)

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<th>yield (%) (^b)</th>
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<td>72</td>
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\(^a\) Reaction Conditions: 1a-1 (0.2 mmol, 1.0 equiv.), 1b-1 (0.2 mmol, 1.0 equiv.), base (0.24 mmol, 1.2 equiv.), 4.0 ml of solvent, 12 h. \(^b\) Isolated yield. \(^c\) Further changes in the ratios cannot improve the reaction yield.

3. General procedure for the synthesis

3.1. General procedure for the synthesis of 1a

\[ R^1-C=O + Br_2, \text{Et}_2O, \text{rt, 12h} \rightarrow R^1-C=O-Br \]

\[ R^1-C=O-Br + K_2CO_3, \text{CHO, CH}_3\text{CN, rt, 12h} \rightarrow \text{R}^1-\text{C}=\text{O} + \text{N-CHO} \]

Bromine (20.0 mmol, 1.0 eq) was added dropwise to a solution of ketone (20.0 mmol, 1.0 equiv.) in Et\(_2\)O (30 mL). The reaction mixture was stirred at room temperature for 12 h. A saturated sodium thiosulfate solution (70 mL) was added and stirred for 30 min. The organic layer was washed by saturated NaHCO\(_3\) solution (30 mL × 3) and dried over anhydrous Na\(_2\)SO\(_4\). After evaporation, the resulting residue was subjected to column chromatography (hexane:EtOAc = 15:1) to get the substituted methyl bromide.\(^1\)
A mixture of 1H-pyrrole-2-carboxaldehyde (5.0 mmol, 1.0 equiv.), substituted methyl bromide (5.5 mmol, 1.1 equiv.) and K$_2$CO$_3$ (6.0 mmol, 1.2 equiv.) was stirred in CH$_3$CN (40 mL) at room temperature. After being stirred for 12 h, the reaction mixture was concentrated under reduced pressure, diluted with EtOAc (30 mL), and washed with H$_2$O (30 mL). The aqueous phase was extracted with ethyl acetate (30 mL) one more time. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane:EtOAc = 10:1) to afford 1a as white solid. These compounds have been described in the literature earlier,$^{2-4}$ except for 1a-11. 1-(2-(4-(Dimethylamino)phenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (1a-11): $^1$H NMR (500 MHz, CDCl$_3$): δ 9.51 (1H, d, J = 1.0 Hz), 7.90 (2H, dt, J = 9.5, 2.0 Hz), 7.00 (1H, dd, J = 4.0, 1.5 Hz), 7.48 (1H, tt, J = 7.5, 1.0 Hz), 6.88 (2H, d, J = 9.0 Hz), 6.33 (1H, dd, J = 4.0, 2.5 Hz), 5.67 (2H, s), 3.07 (6H, s); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 190.5, 179.8, 153.8, 132.8, 131.7, 130.3, 124.7, 122.7, 110.9, 110.1, 53.8, 40.1; HRMS Calcd. for C$_{15}$H$_{16}$N$_2$O$_2$ + H$^+$: 257.1294, found: 257.1290.

3.2. General procedure for the synthesis of 1b

To a cold solution of hydroxylamine hydrochloride (0.38g, 5.5 mmol, 1.1 equiv.) in anhydrous acetonitrile (50 mL), triethylamine (0.77 mL, 5.5 mmol, 1.1 equiv.) and 1H-pyrrole-2-carboxaldehyde (5.0 mmol, 1.0 equiv.) were added and stirred for around 30 mins. Then phthalic anhydride (0.75g, 5.05 mmol, 1.01 equiv.) was slowly added under nitrogen protection. The resulting mixture was stirred at 80 °C for about 8 h. After concentration, the resulting residue was added cold CH$_2$Cl$_2$ (30 mL × 3) and stirred. The combined filtrates were washed with 5% ammonia water to remove phthalic acid completely. The separated organic layer was dried over anhydrous Na$_2$SO$_4$, and then concentrated under reduced pressure. Finally the residue was purified by passing it through a short silica gel column using CHCl$_3$ as eluent to give pure 1H-pyrrole-2-carbonitrile as
yellow oil (80%).\textsuperscript{5} A mixture of 1H-pyrrole-2-carbonitrile (3.0 mmol, 1.0 equiv.), substituted methyl bromide (3.3 mmol, 1.1 equiv.) and K$_2$CO$_3$ (3.6 mmol, 1.2 equiv.) was stirred in CH$_3$CN (20 mL) at room temperature. After being stirred for 12 h, the reaction mixture was concentrated under reduced pressure, diluted with EtOAc (30 mL), and washed with H$_2$O (30 mL). The water layer was extracted with EtOAc (30 mL) one more time. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane:EtOAc = 10:1) to afford 1b as white solid. These compounds have been described in the literature earlier,\textsuperscript{6} except for 1b-13. 1-(2-oxo-2-(4-(Trifluoromethyl)phenyl)ethyl)-1H-pyrrole-2-carbonitrile (1b-13): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.09 (2H, d, $J$ = 8.0 Hz), 7.81 (2H, d, $J$ = 8.5 Hz), 6.90 (1H, dd, $J$ = 4.0, 1.5 Hz), 6.88 (1H, dd, $J$ = 2.5, 1.5 Hz), 6.30 (1H, dd, $J$ = 4.0, 2.5 Hz), 5.50 (2H, s); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 190.8, 136.7, 135.6 ($^1$J$_{C,F}$=38.8 Hz), 128.5, 128.0, 126.2 ($^1$J$_{C,F}$=3.8Hz), 123.3 ($^1$J$_{C,F}$=271.3 Hz), 120.7, 113.4, 110.4, 105.0, 54.3; HRMS Calcd. for C$_{14}$H$_9$F$_3$N$_2$O + H$: 279.0745$, found: 279.0749.

3.3. Experimental section and characterization data of 2

General procedure for products 3: A mixture of N-substituted pyrrole-2-carbaldehyde 1a (0.2 mmol, 1.0 equiv.), N-substituted pyrrole-2-carbonitrile 1b (0.2 mmol, 1.0 equiv.) and t-BuOK (0.24 mmol, 1.2 equiv.) were stirred in mixed solvent (DMF:toluene = 1:1, 4.0 mL) at 120 °C under N$_2$. After being stirred for 12 h, the reaction was quenched by 8.0 mL water and the mixture was extracted with EtOAc (3 × 8.0 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 15:1) to provide the desired product 2.

Phenyl[5-phenylpyrrolo[1′,2′:1,6]pyrazino[2,3-g]indolizin-6-yl]methanone (2a): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-1 (21.3 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbonitrile 1b-1 (21.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2a as yellow
solid (27.7 mg, 72% yield). Mp: 116–118 °C. 1H NMR (500 MHz, CDCl3): δ 7.70 (2H, dt, J = 7.0, 1.0 Hz), 7.67 (1H, s), 7.46 (1H, tt, J = 7.5, 1.5 Hz), 7.30 (2H, tt, J = 7.5, 1.0 Hz), 7.24 (1H, m), 7.00 (5H, m), 6.90 (1H, dd, J = 4.0, 3.0 Hz), 6.76 (1H, dd, J = 4.0, 1.0 Hz), 6.74 (1H, dd, J = 4.0, 1.5 Hz), 6.61 (1H, dd, J = 3.0, 1.5 Hz), 6.03 (1H, dd, J = 4.0, 3.0 Hz); 13C NMR (125 MHz, CDCl3): δ 191.6, 135.4, 132.3, 132.0, 131.3, 130.0, 129.4, 128.9, 128.8, 128.1, 128.0, 127.1, 122.1, 120.6, 119.0, 119.0, 113.9, 113.8, 109.0, 106.1, 103.1; HRMS Calcd. for C20H15N3O + H+: 388.1450, found: 388.1453.

(5-Phenylpyrrolo[1’,2’:1,6]pyrazino[2,3-g]indolizin-6-yl)(m-tolyl)methanone (2b): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-1 (21.3 mg, 0.1 mmol) and 1-(2-oxo-2-(p-tolyl)ethy)-1H-pyrrole-2-carbonitrile 1b-2 (22.4 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2b as yellow solid (20.9 mg, 52% yield). Mp: 124–125 °C. 1H NMR (500 MHz, CDCl3): δ 7.70 (2H, dt, J = 7.0, 1.5 Hz), 7.65 (1H, s), 7.48 (1H, tt, J = 7.5, 1.0 Hz), 7.31 (2H, tt, J = 7.5, 1.0 Hz), 7.20 (1H, d, J = 7.5, 2.5 Hz), 6.88 (1H, dd, J = 4.0, 2.5 Hz), 6.87 (2H, d, J = 7.5 Hz), 6.81 (2H, d, J = 7.5 Hz), 6.74 (2H, m), 6.62 (1H, dd, J = 2.5, 1.5 Hz), 6.04 (1H, dd, J = 4.0, 3.0 Hz), 2.13 (3H, s); 13C NMR (125 MHz, CDCl3): δ 191.7, 137.9, 135.6, 134.3, 132.0, 131.2, 129.8, 129.4, 129.2, 128.9, 128.8, 128.7, 127.3, 122.1, 120.6, 118.9, 116.2, 113.8, 113.7, 109.9, 106.1, 102.9, 21.1; HRMS Calcd. for C27H18N3O + H+: 402.1606, found: 402.1602.

(4-Methoxyphenyl)(5-phenylpyrrolo[1’,2’:1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2c): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-1 (21.3 mg, 0.1 mmol) and 1-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carbonitrile 1b-3 (24.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2c as yellow solid (23.4 mg, 56% yield). Mp: 143–145 °C. 1H NMR (500 MHz, CDCl3): δ 7.70 (2H, dt, J = 8.0, 1.0 Hz), 7.64 (1H, s), 7.48 (1H, dt, J = 7.0, 1.5 Hz), 7.31 (2H, t, J = 7.5 Hz), 7.22 (1H, d, J = 8.0 Hz), 6.89 (3H, m), 6.75 (1H, dd, J = 4.0, 1.5 Hz), 6.74 (1H, dd, J = 4.0, 1.5 Hz), 6.63 (1H, dd, J = 2.5, 1.5 Hz), 6.53 (2H, d, J = 9.0 Hz), 6.05 (1H, dd, J = 4.0, 2.5 Hz), 3.64 (3H, s); 13C NMR (125 MHz, CDCl3): δ 191.8, 165.8, 159.2, 135.6, 134.4, 131.9, 131.2, 129.4, 128.8, 127.3, 124.4, 121.8, 120.6, 118.9, 116.1, 113.8, 113.7, 113.5, 109.9, 110.0, 110.3, 113.5; HRMS Calcd. for C27H19O16N3O + H+: 418.1556, found: 418.1562.

(4-Fluorophenyl)(5-phenylpyrrolo[1’,2’:1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2d): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-1 (21.3 mg, 0.1 mmol) and 1-(2-(4-fluorophenyl)-2-oxoethyl)-1H-pyrrole-2-carbonitrile 1b-4 (22.8 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2d as yellow solid (25.9 mg, 64% yield). Mp: 125–127 °C. 1H NMR (500 MHz, CDCl3): δ 7.69 (2H, dd, J = 8.0, 1.0 Hz), 7.66 (1H, s), 7.50 (1H, t, J = 7.5 Hz), 7.33 (2H, t, J = 8.0 Hz), 7.23 (1H, d, J = 1.5 Hz), 6.98 (2H, m), 6.91 (1H, dd, J = 4.0, 2.0 Hz), 6.76 (1H, dd, J = 4.0, 1.0 Hz), 6.73 (1H, dd, J = 4.0, 1.5 Hz), 6.71 (2H, t, J = 8.5 Hz), 6.64 (1H, dd, J = 2.5, 1.5 Hz), 6.06 (1H, dd, J = 4.0, 3.0 Hz); 13C NMR (125 MHz, CDCl3): δ 191.5, 162.3 (d, J = 309.0 Hz), 135.5, 134.6, 132.1, 131.8 (d, J = 10.5 Hz), 131.2, 129.4, 129.0, 128.8, 128.3, 127.0, 121.1, 120.7, 119.1, 116.4, 115.2 (d, J = 27.1 Hz), 114.0, 113.7, 110.1, 106.2, 103.3; HRMS Calcd. for C26H16FNO + H+: 406.1356, found: 406.1352.
Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-1 (21.3 mg, 0.1 mmol) and 1-(2-(4-chlorophenyl)-2-oxoethyl)-1H-pyrrole-2-carbonitrile 1b-5 (24.4 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2e as yellow solid (24.0 mg, 57% yield). Mp: 115–117 °C. 1H NMR (500 MHz, CDCl3): δ7.70 (2H, dt, J = 7.5, 1.5 Hz), 7.66 (1H, s), 7.52 (1H, tt, J = 7.0, 1.5 Hz), 7.35 (2H, tt, J = 7.5, 1.5 Hz), 7.20 (1H, m), 7.00 (2H, d, J = 8.5 Hz), 6.93 (2H, d, J = 8.5 Hz), 6.91 (1H, dd, J = 3.5, 3.0 Hz), 6.76 (1H, dd, J = 4.0, 0.5 Hz), 6.74 (1H, dd, J = 4.0, 1.5 Hz), 6.65 (1H, J = 3.5, 2.0 Hz), 6.07 (1H, dd, J = 4.0, 2.5 Hz); 13C NMR (125 MHz, CDCl3): δ 191.3, 135.4, 134.7, 134.4, 132.2, 131.3, 131.2, 130.8, 129.4, 129.0, 128.7, 128.3, 126.8, 120.9, 120.8, 119.1, 116.5, 114.0, 113.6, 110.2, 106.2, 103.3; HRMS Calcd. for C26H16ClN3O + H+: 422.1060, found: 422.1063.

(4-Bromophenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2f): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-1 (21.3 mg, 0.1 mmol) and 1-(2-(4-bromophenyl)-2-oxoethyl)-1H-pyrrole-2-carbonitrile 1b-6 (28.8 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2f as yellow solid (27.9 mg, 60% yield). Mp: 132–134 °C. 1H NMR (500 MHz, CDCl3): δ 7.70 (2H, dt, J = 8.0, 1.5 Hz), 7.66 (1H, s), 7.53 (1H, tt, J = 7.5, 1.5 Hz), 7.35 (2H, tt, J = 8.0, 1.5 Hz), 7.20 (1H, m), 7.15 (2H, d, J = 7.5 Hz), 6.91 (1H, dd, J = 4.0, 3.0 Hz), 6.87 (2H, d, J = 8.5 Hz), 6.76 (1H, dd, J = 4.0, 1.0 Hz), 6.75 (1H, dd, J = 4.0, 1.5 Hz), 6.65 (1H, dd, J = 3.0, 1.5 Hz), 6.08 (1H, J = 4.0, 2.5 Hz); 13C NMR (125 MHz, CDCl3): δ 191.2, 135.4, 134.7, 132.1, 131.6, 131.3, 131.2, 131.1, 129.4, 129.0, 128.7, 127.7, 122.7, 120.9, 120.8, 119.2, 116.5, 114.0, 113.7, 110.2, 106.2, 103.3; HRMS Calcd. for C26H16BrN3O + H+: 466.0555, found: 466.0552.

(3-Methoxyphenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2g): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-1 (21.3 mg, 0.1 mmol) and 1-(2-(3-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carbonitrile 1b-7 (24.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2g as yellow solid (22.2 mg, 51% yield). Mp: 138–140 °C. 1H NMR (500 MHz, CDCl3): δ 7.71 (2H, d, J = 8.0 Hz), 7.66 (1H, s), 7.49 (1H, tt, J = 7.5, 1.0 Hz), 7.32 (2H, t, J = 7.5 Hz), 7.24 (1H, d, J = 2.5 Hz), 6.91 (2H, m), 6.76 (2H, m), 6.63 (1H, dd, J = 3.0, 2.0 Hz), 6.58 (2H, m), 6.50 (1H, t, J = 1.5 Hz), 6.05 (1H, dd, J = 4.0, 2.5 Hz), 3.55 (3H, s); 13C NMR (125 MHz, CDCl3): δ 191.6, 159.0, 135.6, 134.4, 133.5, 131.9, 131.2, 129.4, 129.1, 128.9, 128.8, 127.0, 122.6, 121.9, 120.6, 119.0, 116.3, 114.8, 114.7, 113.9, 113.8, 110.0, 106.1, 103.1, 55.1; HRMS Calcd. for C27H18N3O2 + H+: 418.1556, found: 418.1551.

(2-Methoxyphenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2h): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-1 (21.3 mg, 0.1 mmol) and 1-(2-(2-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carbonitrile 1b-8 (24.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2h as yellow solid (17.9 mg, 43% yield). Mp: 142–144 °C. 1H NMR (500 MHz, CDCl3): δ 7.72 (2H, dt, J = 8.5, 1.5 Hz), 7.61 (1H, s), 7.43 (1H, tt, J = 7.5, 1.5 Hz), 7.30 (1H, m), 7.24 (2H, tt, J = 7.5, 2.0 Hz), 7.12 (1H, dd, J = 7.5, 1.5 Hz), 7.01 (1H, dd, J = 8.0, 3.5, 1.5 Hz), 6.88 (1H, dd, J = 4.0, 2.5 Hz), 6.73 (3H, m), 6.48 (1H, s), 6.35 (1H, d, J = 8.0 Hz), 5.93 (1H, dd, J = 4.0, 2.5 Hz), 3.49 (3H, s); 13C NMR (125 MHz, CDCl3): δ 191.8, 156.7, 135.9, 134.0, 132.6, 132.1, 131.5, 130.4, 129.2, 128.8, 128.3, 128.2, 121.4, 120.1, 120.0, 119.5, 118.30, 115.8, 113.9, 113.7, 109.6, 108.9, 105.8, 102.8, 54.5; HRMS Calcd. for C27H19N3O2 + H+: 418.1556, found: 418.1553.
1-(5-Phenylpyrrolo[1′,2′:1,6]pyrazino[2,3-g]indolizin-6-yl)ethane (2i): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-I (21.3 mg, 0.1 mmol) and 1-(2-oxopropyl)-1H-pyrrole-2-carbonitride 1b-9 (14.8 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2i as yellow solid (18.5 mg, 57% yield). Mp: 138–140 °C. 1H NMR (500 MHz, CDCl3): δ 7.94 (2H, dt, J = 8.5, 1.5 Hz), 7.66 (1H, tt, J = 7.5, 1.5 Hz), 7.52 (1H, s), 7.52 (2H, t, J = 7.5 Hz), 7.08 (1H, d, J = 2.5 Hz), 6.96 (1H, dd J = 3.5, 1.5 Hz), 6.95 (1H, dd, J = 2.5, 1.5 Hz), 6.80 (1H, dd, J = 4.0, 3.0 Hz), 6.65 (1H, dd, J = 4.0, 1.0 Hz), 6.36 (1H, dd, J = 4.0, 3.0 Hz), 1.80 (3H, s). 13C NMR (125 MHz, CDCl3): δ 191.9, 135.2, 135.1, 131.1, 131.0, 129.7, 129.6, 128.4, 120.8, 119.1, 115.9, 115.6, 113.5, 110.4, 106.2, 102.6, 13.0; HRMS Calcd. for C29H15N3O + H+: 326.1295, found: 326.1295.

Cyclopropyl(5-phenylpyrrolo[1′,2′:1,6]pyrazino[2,3-g]indolizin-6-yl)methane (2j): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-I (21.3 mg, 0.1 mmol) and 1-(2-cyclopropyl-2-oxoethyl)-1H-pyrrole-2-carbonitride 1b-10 (17.4 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2j as yellow solid (18.2 mg, 52% yield). Mp: 127–129 °C. 1H NMR (500 MHz, CDCl3): δ 8.03 (2H, d, J = 7.0 Hz), 7.65 (1H, tt, J = 7.0, 1.0 Hz), 7.52 (2H, t, J = 7.0 Hz), 7.53 (1H, s), 7.28 (1H, d, J = 2.5 Hz), 6.97 (2H, m), 6.85 (1H, dd, J = 4.0, 3.0 Hz), 6.66 (1H, dd, J = 4.0, 1.0 Hz), 6.34 (1H, dd, J = 4.0, 3.0 Hz), 1.51 (1H, m), 0.25 (4H, m). 13C NMR (125 MHz, CDCl3): δ 13C NMR (126 MHz, CDCl3) δ = 192.25, 136.5, 134.6, 132.9, 131.2, 129.6, 129.4, 129.3, 128.6, 120.7, 118.8, 115.8, 114.1, 113.4, 110.1, 106.4, 102.7, 10.7, 6.6; HRMS Calcd. for C29H17N3O + H+: 352.1450, found: 352.1446.

Furan-2-yl(5-phenylpyrrolo[1′,2′:1,6]pyrazino[2,3-g]indolizin-6-yl)methane (2k): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-I (21.3 mg, 0.1 mmol) and 1-(2-(furan-2-yl)-2-oxoethyl)-1H-pyrrole-2-carbonitride 1b-11 (20.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2k as yellow solid (18.1 mg, 48% yield). Mp: 124–126 °C. 1H NMR (500 MHz, CDCl3): δ 7.81 (2H, dt, J = 8.0, 1.5 Hz), 7.46 (1H, s), 7.52 (1H, tt, J = 7.5, 1.0 Hz), 7.38 (2H, t, J = 8.0 Hz), 7.34 (1H, m), 7.03 (1H, d, J = 1.0 Hz), 6.91 (1H, dd, J = 4.0, 3.0 Hz), 6.89 (1H, dd, J = 4.0, 2.0 Hz), 6.80 (1H, dd, J = 2.5, 1.0 Hz), 6.74 (1H, dd, J = 4.0, 1.0 Hz), 6.22 (1H, dd, J = 4.0, 3.0 Hz), 6.04 (1H, J = 3.0, 1.5 Hz), 5.76 (1H, J = 3.5, 0.5 Hz); 13C NMR (125 MHz, CDCl3): δ 191.2, 144.8, 143.3, 135.3, 134.4, 131.9, 131.1, 129.2, 128.9, 128.4, 125.6, 120.7, 119.6, 116.7, 114.4, 113.4, 112.6, 112.0, 111.3, 110.2, 106.3, 103.7; HRMS Calcd. for C29H15N3O2 + H+: 378.1243, found: 378.1238.

(5-Phenylpyrrolo[1′,2′:1,6]pyrazino[2,3-g]indolizin-6-yl)(thiophen-2-yl)methane (2l): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-I (21.3 mg, 0.1 mmol) and 1-(2-oxo-2-(thiophen-2-yl)ethyl)-1H-pyrrole-2-carbonitride 1b-12 (21.6 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2l as yellow solid (20.4 mg, 52% yield). Mp: 148–150 °C. 1H NMR (500 MHz, CDCl3): δ 7.75 (2H, dt, J = 7.0, 1.0 Hz), 7.65 (1H, s), 7.51 (1H, tt, J = 7.5, 1.5 Hz), 7.35 (2H, t, J = 7.5 Hz), 7.26 (1H, m), 7.06 (1H, dd, J = 5.0, 1.0 Hz), 6.90 (1H, dd, J = 4.0, 2.5 Hz), 6.81 (2H, m), 6.75 (1H, dd, J = 3.5, 0.5 Hz), 6.72 (1H, dd, J = 3.0, 1.0 Hz), 6.68 (1H, dd, J = 5.0, 3.5 Hz), 6.14 (1H, J = 3.5, 2.5 Hz); 13C NMR (125 MHz, CDCl3): δ 191.4, 135.2, 134.5, 132.8, 132.7, 131.2, 130.8, 129.4, 128.9, 128.6, 126.9, 126.7, 120.8, 119.0, 116.6, 115.1, 114.1, 113.6, 110.2, 106.5, 103.5; HRMS
Phenyl(5-(p-tolyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methane (2m): Following the general procedure, 1-(2-oxo-2-(p-tolyl)ethyl)-1H-pyrrole-2-carboxaldehyde 1a-2 (22.7 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbonitrile 1b-1 (21.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2m as yellow solid (22.5 mg, 56% yield). Mp: 130–132 °C. 1H NMR (500 MHz, CDCl3): δ 7.65 (1H, s), 7.62 (2H, d, J = 8.0 Hz), 7.18 (1H, d, J = 2.5 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.02 (5H, m), 6.88 (1H, dd, J = 4.0, 2.5 Hz), 6.74 (2H, m), 6.61 (1H, dd, J = 2.5, 1.5 Hz), 6.02 (1H, dd, J = 4.0, 3.0 Hz), 2.33 (3H, s); 13C NMR (125 MHz, CDCl3): δ 191.0, 145.8, 132.9, 132.4, 132.3, 131.2, 130.0, 129.7, 129.7, 128.9, 128.0, 127.2, 121.6, 120.6, 118.7, 116.2, 113.8, 113.8, 109.9, 106.1, 102.9, 21.9; HRMS Calcd. for C27H18N3O + H+: 402.1606, found: 402.1610.

(5-(4-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methane (2n): Following the general procedure, 1-(2-(4-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxaldehyde 1a-3 (24.3 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbonitrile 1b-1 (21.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2n as yellow solid (24.2 mg, 58% yield). Mp: 137–139 °C. 1H NMR (500 MHz, CDCl3): δ 7.70 (2H, d, J = 9.0 Hz), 7.64 (1H, s), 7.18 (1H, d, J = 2.5 Hz), 7.03 (5H, m), 6.88 (1H, dd, J = 4.0, 2.5 Hz), 6.79 (2H, d, J = 9.0 Hz), 6.73 (2H, m), 6.60 (1H, dd, J = 3.0, 1.5 Hz), 6.02 (1H, dd, J = 4.0, 3.0 Hz), 3.80 (3H, s); 13C NMR (125 MHz, CDCl3): δ 189.7, 164.7, 132.5, 132.4, 131.2, 130.0, 128.9, 128.3, 128.0, 127.2, 121.3, 120.6, 118.6, 116.2, 114.2, 113.9, 113.7, 109.9, 106.0, 102.8, 55.6; HRMS Calcd. for C27H19N3O2 + H+: 418.1556, found: 418.1558.

(5-(4-Chlorophenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methane (2o): Following the general procedure, 1-(2-(4-chlorophenyl)-2-oxoethyl)-1H-pyrrole-2-carboxaldehyde 1a-4 (24.7 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbonitrile 1b-1 (21.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2o as yellow solid (18.9 mg, 45% yield). Mp: 139–141 °C. 1H NMR (500 MHz, CDCl3): δ 7.67 (1H, s), 7.61 (2H, dt, J = 8.5, 1.5 Hz), 7.27 (2H, dt, J = 7.0, 2.0 Hz), 7.24 (1H, d, J = 2.5 Hz), 7.07 (1H, tt, J = 7.5, 1.0 Hz), 7.03 (2H, tt, J = 8.0, 1.5 Hz), 6.97 (2H, d, J = 7.0 Hz), 6.92 (1H, dd, J = 4.0, 3.0 Hz), 6.76 (1H, dd, J = 4.0, 0.5 Hz), 6.74 (1H, dd, J = 4.0, 1.5 Hz), 6.60 (1H, dd, J = 2.5, 1.5 Hz), 6.03 (1H, J = 4.0, 3.0 Hz); 13C NMR (125 MHz, CDCl3): δ 190.5, 140.9, 134.0, 132.2, 131.4, 131.3, 130.7, 130.0, 129.2, 128.8, 128.3, 128.2, 126.9, 120.6, 119.3, 116.4, 113.8, 113.7, 109.9, 106.1, 103.3; HRMS Calcd. for C26H16ClN3O + H+: 422.1060, found: 422.1067.

(5-(4-Bromophenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methane (2p): Following the general procedure, 1-(2-(4-bromophenyl)-2-oxoethyl)-1H-pyrrole-2-carboxaldehyde 1a-5 (29.1 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbonitrile 1b-1 (21.0 mg, 0.1 mmol) were purified. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2p as yellow solid (26.5 mg, 57% yield). Mp: 142–144 °C. 1H NMR (500 MHz, CDCl3): δ 7.67 (1H, s), 7.53 (2H, dt, J = 9.0, 2.0 Hz), 7.43 (2H, dt, J = 8.5, 2.0 Hz), 7.24 (1H, m), 7.05 (1H, tt, J = 8.5, 1.5 Hz), 7.03 (2H, td, J = 7.5, 1.5 Hz), 6.96 (2H, dt, J = 7.0, 1.5 Hz), 6.92 (1H, dd, J = 4.0, 3.0 Hz), 6.76 (1H, dd, J = 4.0, 0.5 Hz), 6.74 (1H, dd, J = 4.0, 1.5), 6.60 (1H, dd, J = 2.5, 1.5 Hz), 6.03 (1H, J = 4.0, 3.0 Hz); 13C NMR (125 MHz, CDCl3): δ 190.7, 134.4, 132.2, 131.3, 131.2, 130.7, 130.0, 129.8, 128.8, 128.3, 128.2, 126.9, 122.4, 120.7, 119.3, 116.4, 113.8, 113.7, 110.0,
(5-(3-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2q):
Following the general procedure, 1-(2-(3-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde 1a-6 (24.3 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbonitrile 1b-1 (21.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2q as yellow solid (22.1 mg, 53% yield). Mp: 126–128 °C. 1H NMR (500 MHz, CDCl3): δ 7.66 (1H, s), 7.26 (1H, dt, J = 7.5, 1.5 Hz), 7.20 (2H, m), 7.03 (6H, m), 6.90 (1H, dd, J = 4.0, 2.5 Hz), 6.75 (1H, dd, J = 4.0, 1.0 Hz), 6.72 (1H, dd, J = 4.0, 1.5 Hz), 6.61 (1H, dd, J = 3.0, 1.5 Hz), 6.03 (1H, dd, J = 4.0, 3.0 Hz), 3.76 (3H, s); 13C NMR (125 MHz, CDCl3): δ 191.4, 159.8, 136.8, 132.3, 132.0, 131.2, 130.0, 129.9, 128.8, 128.1, 128.1, 127.1, 122.6, 122.1, 121.5, 120.6, 119.0, 116.3, 113.9, 113.8, 112.6, 109.9, 106.2, 103.1, 55.5; HRMS Calcd. for C26H18BrN3O + H+: 466.0555, found: 466.0557.

(5-(2-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2r):
Following the general procedure, 1-(2-(2-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde 1a-7 (24.3 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbonitrile 1b-1 (21.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2r as yellow solid (19.6 mg, 47% yield). Mp: 123–125 °C. 1H NMR (500 MHz, CDCl3): δ 7.59 (1H, s), 7.43 (1H, dd, J = 8.0, 2.0 Hz), 7.38 (1H, d, J = 2.5 Hz), 7.33 (1H, ddd, J = 7.0, 2.0, 1.0 Hz), 7.02 (1H, tt, J = 7.0, 1.5 Hz), 6.97 (2H, t, J = 8.0 Hz), 6.93 (2H, d, J = 7.0 Hz), 6.91 (1H, dd, J = 4.0, 2.5 Hz), 6.79 (1H, td, J = 8.0, 0.5 Hz), 6.71 (3H, m), 6.56 (1H, dd, J = 2.5, 1.5 Hz), 5.98 (1H, dd, J = 4.0, 3.0 Hz), 3.51 (3H, s); 13C NMR (125 MHz, CDCl3): δ 190.5, 159.3, 135.0, 134.9, 132.8, 131.2, 129.8, 128.9, 127.7, 127.3, 126.8, 120.9, 120.7, 120.3, 118.4, 115.8, 113.9, 113.6, 111.5, 109.7, 106.2, 102.6, 55.9; HRMS Calcd. for C27H16N3O2 + H+: 418.1556, found: 418.1548.

(5-(Furan-2-yl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2s):
Following the general procedure, 1-(2-(furan-2-yl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde 1a-8 (20.3 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbonitrile 1b-1 (21.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2s as yellow solid (20.0 mg, 53% yield). Mp: 153–155 °C. 1H NMR (500 MHz, CDCl3): δ 7.81 (2H, dd, J = 7.0, 1.5 Hz), 7.64 (1H, s), 7.53 (1H, tt, J = 7.5, 1.5 Hz), 7.38 (2H, t, J = 8.0 Hz), 7.34 (1H, m), 7.03 (1H, dd, J = 2.0, 1.0 Hz), 6.91 (1H, dd, J = 4.0, 3.0 Hz), 6.90 (1H, dd, J = 4.0, 1.5 Hz), 6.80 (1H, dd, J = 3.0, 1.5 Hz), 6.74 (1H, dd, J = 4.0, 1.0 Hz), 6.22 (1H, dd, J = 4.0, 2.5 Hz), 6.04 (1H, dd, J = 3.5, 2.0 Hz), 5.76 (1H, dd, J = 3.0, 1.0 Hz); 13C NMR (125 MHz, CDCl3): δ 191.2, 144.8, 143.3, 135.5, 134.4, 131.9, 131.1, 129.2, 128.9, 128.4, 125.6, 120.7, 119.6, 116.7, 114.4, 113.4, 112.6, 112.0, 111.3, 110.2, 106.3, 103.7; HRMS Calcd. for C24H15N3O2 + H+: 378.1243, found: 378.1247.

Phenyl(5-(thiophen-2-yl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2t):
Following the general procedure, 1-(2-oxo-2-(thiophen-2-yl)ethyl)-1H-pyrrole-2-carbaldehyde 1a-9 (21.9 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbonitrile 1b-1 (21.0 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2t as yellow solid (18.1 mg, 46% yield). Mp: 148–150 °C. 1H NMR (500 MHz, CDCl3): δ 7.63 (1H, s), 7.62 (1H, dd, J = 4.0, 1.0 Hz), 7.41 (1H, dd, J = 4.0, 1.0 Hz), 7.33 (1H, m), 7.07 (5H, m), 6.92 (2H, m), 6.75 (2H, m), 6.58 (1H, dd, J = 2.0, 1.5 Hz), 6.03 (1H, dd, J = 3.5, 2.0 Hz); 13C
NMR (125 MHz, CDCl$_3$): $\delta$ 183.3, 142.6, 136.7, 135.9, 132.5, 131.8, 131.2, 129.9, 128.9, 128.4, 128.2, 128.1, 127.0, 121.7, 120.6, 119.2, 116.3, 113.9, 113.8, 109.9, 106.1, 103.2; HRMS Calcd. for C$_{24}$H$_{18}$N$_3$OS $+ \text{H}^+$: 393.0936, found: 393.0942.

(5-(4-(dimethylamino)phenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(4-(trifluoromethyl)phenyl)methanone (2u): Following the general procedure, 1-(2-oxo-2-(thiophen-2-yl)ethyl)-1$H$-pyrrole-2-carbaldehyde 1a-10 (25.6 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1$H$-pyrrole-2-carbonitrile 1b-13 (27.8 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2u as yellow solid (28.4 mg, 57% yield). Mp: 158−160 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.62 (3H, m), 7.31 (2H, d, $J = 8.5$ Hz), 7.20 (3H, m), 6.88 (1H, dd, $J = 4.0$, 3.0 Hz), 6.73 (2H, m), 6.63 (1H, m), 6.53 (2H, d, $J = 9.5$ Hz), 6.05 (1H, dd, $J = 4.0$, 3.0 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): 187.7, 154.5, 136.8, 133.8, 132.2, 131.1, 130.3, 129.7 (q, $^2$J$_{C,F} = 32.1$ HZ), 126.8, 124.8 (q, $^3$J$_{C,F} = 3.8$ HZ), 123.8 (q, $^1$J$_{C,F} = 270.8$ HZ), 122.7, 120.8, 119.3, 118.2, 116.3, 114.1, 113.7, 111.1, 110.1, 106.1, 102.8, 40.0; HRMS Calcd. for C$_{29}$H$_{21}$F$_3$N$_4$O $+ \text{H}^+$: 499.1746, found: 499.1751.
4. Mechanistic investigations

A mixture of N-substituted pyrrole-2-carbaldehyde 1a (0.1 mmol, 1.0 equiv.) and t-BuOK (0.12 mmol, 1.2 equiv.) were stirred in mixed solvent (DMF:toluene = 1:1, 2.0 mL) at 120 °C under N₂. After being stirred for 12 h, the reaction was quenched by 4.0 mL water and the mixture was extracted with EtOAc (3 × 4.0 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. By using 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde (1a-1), 1-(2-(4-chlorophenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (1a-4) and 1-(2-oxo-2-(p-tolyl)ethyl)-1H-pyrrole-2-carbaldehyde (1a-2) as starting materials, small amount of desired product 3a (1.0 mg), 3b (3.3 mg) and 3c (1.7 mg) was obtained from the residue after column chromatography (hexane:EtOAc = 15:1). The structures of 3a, 3b and 3c were confirmed by TLC and NMR, which was consistent with our previous report (Tetrahedron 2018, 74, 6088–6094).

5. References

6. Photophysical properties of compounds 2

**Figure S1.** Emission spectra (left) of 2a ($\lambda_{ex} = 378$ nm) and fluorescence photographs (right) of 2a (under 365 nm) in different solvents. (concentration: 30 µM)

**Figure S2.** Emission spectra (left) of 2a ($\lambda_{ex} = 378$ nm) and fluorescence photographs (right) of 2a (under normal light and 365 nm) in different water fraction. (concentration: 10 µM)

**Figure S3.** UV absorption (left, DMSO, 10 µM) and emission spectra (right) of 2a in DMSO (blue line, 10 µM) and in 95% water/DMSO mixture (red line, 10 µM).
Figure S4. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2b in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

Figure S5. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2c in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

Figure S6. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2d in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).
Figure S7. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2e in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

Figure S8. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2f in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

Figure S9. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2g in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).
**Figure S10.** UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2h in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

**Figure S11.** UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2i in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

**Figure S12.** UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2j in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).
**Figure S13.** UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2k in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

**Figure S14.** UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2l in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

**Figure S15.** UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2m in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).
Figure S16. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2n in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

Figure S17. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2o in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

Figure S18. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2p in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).
Figure S19. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2q in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

Figure S20. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2r in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

Figure S21. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2s in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).
**Figure S22.** UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2t in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

**Figure S23.** UV absorption (left, DMSO, 10 μM) and emission spectra (right) of 2u in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).
7. Cell culture and cytotoxicity

7.1 Cell culture and cytotoxicity

CT26 cells were cultured in RPMI-1640 medium (Sigma) while HUVEC cells in DMEM medium (Sigma) containing 10% fetal bovine serum (FBS) and a mixture of 0.1 mg/mL streptomycin and 100 units/mL penicillin at 37 °C in a humidified 5% CO₂ atmosphere. The cytotoxicity of 2a was determined by MTT assay. Firstly, cells were seeded in 96-well plate at a density of $1 \times 10^4$ cells per well and allowed to attach overnight. Then the cells were exposed to 2a at a series of concentrations for 24 hours. Subsequently, MTT solution (5 mg·mL⁻¹) was added to each well for an additional 4 hours incubation at 37 °C. After that, the medium was replaced with 100μL of DMSO to dissolve the insoluble and purple formazan crystals in the bottom of the well. The plate was shaken for 30 min, and the absorbance of the solution in each well was measured by microplate reader at 570 nm. Cell viability was calculated in reference to negative cells without exposure to test agents. All of experiments were repeated thrice.

Figure S24. MTT assay of CT26 cells and HUVECs incubation (24h) with 2a at different concentrations

7.2 Cellular uptake

CT26 cells were seeded in 24-well plate at a density of $5 \times 10^4$ cells per well and allowed to attach overnight. Subsequently, the cells were treated with 2a at a final concentration of 30 μg·mL⁻¹ for 2, 6 and 10 hours. After washing trice with PBS and fixed, the cells were observed using confocal laser scanning microscope (Olympus BX61, Japan, FITC channel).
8. NMR spectroscopic data

1-(2-(4-(Dimethylamino)phenyl)-2-oxoethyl)-1H-pyrrole-2-carbaldehyde (1a-11)
1-(2-oxo-2-(4-(Trifluoromethyl)phenyl)ethyl)-1H-pyrrole-2-carbonitrile (1b-13)
Phenyl(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2a)
(5-Phenylpyrrolo[1,2'-1,6]pyrazino[2,3-g]indolizin-6-yl)(m-tolyl)methanone (2b)
(4-Methoxyphenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2c)
(4-Fluorophenyl)(5-phenylypyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2d)
(4-Chlorophenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2e)
(4-Bromophenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2f)
(3-Methoxyphenyl)(5-phenylpyrrolo[1’,2’:1,6]pyrazino[2,3-g]indolin-6-yl)methanone (2g)
(2-Methoxyphenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2h)
1-(5-Phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)ethanone (2i)
Cyclopropyl(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2j)
Furan-2-yl(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2k)
(5-Phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(thiophen-2-yl)methanone (2I)
Phenyl(5-(p-tolyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2m)
(5-(4-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2n)
(5-(4-Chlorophenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2o)
(5-(4-Bromophenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2p)
5-(3-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2q)

(5-(2-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2r)
(5-(Furan-2-yl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2s)
Phenyl(5-(thiophen-2-yl)pyrrolo[1’,2’:1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2t)
(5-(4-(dimethylamino)phenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(4-(trifluoromethyl)phenyl)methanone (2u)
9. Characterization data for 2b

(5-Phenylpyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(m-tolyl)methanone (2b): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1H-pyrrole-2-carbaldehyde 1a-1 (21.3 mg, 0.1 mmol) and 1-(2-oxo-2-(p-tolyl)ethyl)-1H-pyrrole-2-carbonitrile 1b-2 (22.4 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded 2b as yellow solid (20.9 mg, 52% yield). Mp: 124-125 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.70 (2H, dt, $J = 7.0, 1.5$ Hz), 7.65 (1H, s), 7.48 (1H, tt, $J = 7.5, 1.0$ Hz), 7.31 (2H, tt, $J = 7.5, 1.0$ Hz), 7.20 (1H, d, $J = 7.5, 2.5$ Hz), 6.88 (1H, dd, $J = 4.0, 2.5$ Hz), 6.87 (2H, d, $J = 7.5$ Hz), 6.81 (2H, d, $J = 7.5$ Hz), 6.74 (2H, m), 6.62 (1H, dd, $J = 2.5, 1.5$ Hz), 6.04 (1H, dd, $J = 4.0, 3.0$ Hz), 2.13 (3H, s); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 191.7, 137.9, 135.6, 134.3, 132.0, 131.2, 129.8, 129.4, 129.2, 128.9, 128.8, 128.7, 127.3, 122.1, 120.6, 118.9, 116.2, 113.8, 113.7, 109.9, 106.1, 102.9, 21.1; HRMS Calcd. for C$_{27}$H$_{19}$N$_3$O + H$: 402.1606, found: 402.1602.

$^1$H NMR of 2b
$^{13}$C NMR of 2b

HSQC of 2b
All carbon and hydrogen atoms can be confirmed by the NMR data, and the correlation from HMBC showed the structure of 2b. C-1 (δ 113.8) and H-17 (δ 6.86), C-4 (δ 132.0) and H-12 (δ 7.65) of 2b were determined by ¹H NMR, ¹³C NMR, HSQC and HMBC. The correlation of C-1 and H-17 from HMBC showed the first step of aldol condensation. The second step of aldol condensation and further aldimine condensation can be showed by the correlation of C-4 and H-12 from HMBC.