Synthesis of Fused Indolines by Interrupted Fischer Indolization in a Microfluidic Reactor

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Materials and Methods

A. General Reagent Information

All chemicals used for synthesis were used as received from commercial sources. Phenylhydrazine, 4-bromophenylhydrazine hydrochloride, 2-bromophenylhydrazine hydrochloride hydrate, and 2-fluorophenylhydrazine hydrochloride were obtained from TCI. All other chemicals were synthesized as previously reported17 from the Garg lab.
B. General Information for Flow Reactor Setup

The experiments were conducted using the commercially available Asia continuous-flow system from Syrris. The system configuration consisted of an Asia Pressurized Input Store, Syringe Pump, Reagent Injector, Chip Climate Controller, and Pressure Controller, all connected via PTFE tubing (1.6 mm OD x 0.5 mm ID) purchased from Syrris. The Pressurized Input Store allowed storage of our mobile solvent phase under an inert nitrogen atmosphere. From the Store, solvent would flow to two separate Syringe pumps, then to the Reagent Injector, Chip Climate Controller, and Backpressure Regulator. The system’s modular design allowed for independent modification to each reaction parameter. Individual flow rates could be independently changed at each Syringe Pump, which determined residence and reaction time through the reactor. This time derived from the reactor chip volume, divided by the combined flow rate through it. Reaction temperatures could be controlled through the Chip Climate Controller, which houses the microfluidic chip reactor, and reaction pressure could be changed (as in Table 1) through the Backpressure Regulator.

![Asia Flow Reactor Scheme](image_url)

**Figure S-1.** Asia Flow Reactor Scheme
C. General Procedure for Flow Reactor Syntheses and Purification

Unless stated otherwise, reactions were performed in a Syrris 1000 μL glass microfluidic chip reactor (part number 2100146). Prepared stock solutions of the phenylhydrazine and lactol were charged into separate 1 mL syringes and injected into the Reagent Injector Inputs A and B. In cases when reagents did not readily dissolve, sonication and heating were used until the reagents were fully dissolved. Reagents were then introduced into the microfluidic chip reactor by Pumps A and B. The mixture was pumped through the reactor at a predetermined flow rate to achieve desired residence times. Crude product was then purified via flash chromatography using a CombiFlash Rf200 instrument and prepacked silica gel (300–400 mesh) cartridges (Hexanes, 5 minutes; 100% Hexanes → 5:95 (EtOAc:Hexanes), 10 minutes; 5:95 (EtOAc:Hexanes),
5 minutes; 5:95 (EtOAc:Hexanes) -> 1:4 (EtOAc:Hexanes), 10 minutes; 1:4 (EtOAc:Hexanes) -> 7:3 (EtOAc:Hexanes), 5 minutes). Fractions corresponding to the product were combined and isolated under vacuum.

D. General Analytical Information

Analytical thin–layer chromatographic separations were carried out on silica gel (60 Å particle size, 250 µm thickness, F-254, Silicycle) coated glass plates; spots were visualized with UV light. HPLC data was gathered using an Agilent 1260 Infinity instrument and an Agilent Poroshell-120 column (2.7 um particle size, 4.6 mm diameter x 50 mm length) using a gradient method of 60:40 (Acetonitrile:H2O) to 98:2 (Acetonitrile:H2O) over 5 minutes. \( ^1 \)H NMR spectra were recorded using a 400 MHz Bruker spectrometer and reported in parts per million (ppm, \( \delta \)) relative to chemical residual \( ^1 \)H resonance of the solvent CDCl\(_3\) at 7.26 ppm. Data for \( ^1 \)H NMR spectra are reported as follows: chemical shift (ppm, \( \delta \)), multiplicity, coupling constant (Hz), and integration. \( ^{13} \)C NMR spectra are reported in terms of chemical shift (ppm, \( \delta \)), relative to the central line of CDCl\(_3\) at 77.16 ppm.
Experimental Procedures.

E. Optimization of Flow Parameters

Entries 1-6. Phenylhydrazine 4 (0.2 M in AcOH/H$_2$O (1:1 v/v), 50 μL, .01 mmol, 1 equiv) was injected into Pump A. Lactol 5 (0.22 M in AcOH/H$_2$O (1:1 v/v), 50 μL, .011 mmol, 1.1 equiv) was injected into Pump B. Temperature, pressure, and flow rates were changed to achieve designated reaction conditions. The chip was flushed with AcOH/H$_2$O (1:1 v/v) to elute the product. Crude product was collected in a flask. Product yields were determined by HPLC. Yield was obtained by percent ratio of the product peak to that for the starting materials.

Entry 7. Phenylhydrazine 4 (0.5 M in AcOH/H$_2$O (1:1 v/v), 50 μL, .025 mmol, 1 equiv) was injected into Pump A. Lactol 5 (0.55 M in AcOH/H$_2$O (1:1 v/v), 50 μL, .028 mmol, 1.1 equiv) was injected into Pump B. Chip reactor was preheated to 120 °C and pressure was set to 3 bar. Pumps A and B were both set to 50 μL/min flow rates to achieve a 10 minute residence time. The chip was flushed with AcOH/H$_2$O (1:1 v/v) to elute the product. Crude product was collected in a flask. Product yield was determined by HPLC to be 97%

Entry 8. Scale-up reaction. Phenylhydrazine 4 (0.5 M in AcOH/H$_2$O (1:1 v/v), 5 mL, 2.5 mmol, 1 equiv) was injected into Pump A. Lactol 5 (0.55 M in AcOH/H$_2$O (1:1 v/v), 5 mL, 2.75 mmol, 1.1 equiv) was injected into Pump B. Chip reactor was preheated to 120 °C and pressure was set to 3 bar. Pumps A and B were both set to 100 μL/min flow rates to achieve a final 200 μL/min flow rate and 5 minute residence time in the reactor.
Crude product was collected in a flask, and crude yield was determined by HPLC. The crude product was quenched with a solution of sat. aq. NaHCO₃ (2x30 mL) and extracted with EtOAc (2x 60 mL). Combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography afforded furoindoline 6 ((3aS,8aS)-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole) as a brown oil (285 mg, 65% yield). Rf 0.3 (3:1 Hexanes:EtOAc); ¹H NMR (400 MHz, Chloroform-d) δ 7.12 – 7.03 (m, 2H), 6.77 (t, J= 7.4Hz, 1H), 6.59 (d, J = 7.8 Hz, 1H), 5.29 (s, 1H), 3.97 (ddd, J = 8.7, 7.2, 1.6 Hz, 1H), 3.58 (ddd, J= 11.1, 8.6, 5.2 Hz 1H), 2.21-2.06 (m, 2H), 1.48 (s, 3H).

Spectral data match those previously reported.¹

F. Synthesis of Indolines with Phenylhydrazine Variants

Representative Procedure. Synthesis of Indoline 14 (Table 2, entry 1) is used as an example.

Phenylhydrazine 7 (0.5 M in AcOH/H₂O (1:1 v/v), 500 uL, 0.25 mmol, 1 equiv) was injected into Pump A. Lactol 5 (0.55 M in AcOH/H₂O (1:1 v/v), 500 uL, 0.28 mmol, 1.1 equiv) was injected into Pump B. Chip reactor was preheated to 120 ℃ and pressure was set to 3 bar. Pumps A and B were both set to 100 μL/min flow rates to achieve a 5 minute residence time. The crude product was quenched with a solution of sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (3 x 20 mL). Combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography afforded furoindoline 14 ((3aS,8aS)-3a,7-dimethyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole) as a brown solid (78% yield, average of two experiments). Rₚ 0.4 (3:1 Hexanes:EtOAc); ¹H NMR (400 MHz, Chloroform-d) δ 6.95 (d, J = 7.9 Hz, 1H), 6.91 (d, J = 6.4 Hz, 1H), 6.72 (t, J = 7.4 Hz, 1H), 5.32 (s, 1H), 3.95 (ddd, J = 8.8, 7.2, 1.7 Hz, 1H), 3.68 – 3.45 (m, 1H), 2.21 – 2.17 (m, 1H), 2.15 (s, 3H), 2.13 – 2.04 (m, 1H), 1.48 (s, 3H). Spectral data match those previously reported.¹

Any modifications of the conditions shown in this representative procedure are specified in the following schemes, which depict all of the reactions in Table 2.
**Indoline 15 (Table 2, entry 2).** Purification by flash chromatography afforded furoindoline 15 ((3aS,8aS)-7-chloro-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole) as a yellow solid (57% yield, average of two experiments). Rf 0.4 (3:1 Hexanes:EtOAc); \(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 7.05 (d, \(J = 9.1\) Hz, 1H), 6.96 (d, \(J = 8.4\) Hz, 1H), 6.71 – 6.65 (m, 1H), 5.33 (s, 1H), 3.97 (ddd, \(J = 8.8, 7.1, 1.7\) Hz, 1H), 3.57 (ddd, \(J = 11.1, 8.7, 5.2\) Hz, 1H), 2.16 (ddd, \(J = 11.7, 5.2, 1.4\) Hz, 1H), 2.13 – 2.04 (m, 1H), 1.48 (s, 3H). Spectral data match those previously reported.\(^1\)
**Indoline 16 (Table 2, entry 3).** Purification by flash chromatography afforded furoindoline 16 ((3a$\delta$,8a$\delta$)-3a,8-dimethyl-3,3a,8,8a-tetrahydro-2$H$-furo[2,3-b]indole) as a colorless oil (68% yield, average of two experiments). $R_f$ 0.5 (3:1 Hexanes:EtOAc); $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.14 – 7.08 (m, 1H), 7.05 (d, $J = 6.4$ Hz, 1H), 6.68 (t, $J = 7.8$ Hz, 1H), 6.37 (d, $J = 7.8$ Hz, 1H), 5.07 (s, 1H), 3.95 (ddd, $J = 8.7$, 7.2, 1.6 Hz, 1H), 3.46 (ddd, $J = 11.0$, 8.6, 5.3 Hz, 1H), 2.93 (s, 3H), 2.29 – 1.91 (m, 2H), 1.46 (s, 3H). Spectral data match those previously reported."
Indoline 17 (Table 2, entry 4). Purification by flash chromatography afforded furoindoline 17 ((3aS,8aS)-7-fluoro-3a-methyl-3,3a,8,8a-tetrahydro- 1H-furo[2,3-b]indole) as a brown amorphous solid (34% yield, average of two experiments). Rf 0.4 (3:1 Hexanes:EtOAc); 1H NMR (400 MHz, Chloroform-d) δ 6.88 – 6.81 (m, 2H), 6.69 (ddd, J = 8.2, 7.3, 4.6 Hz, 1H), 5.33 (s, 1H), 3.97 (ddd, J = 8.8, 7.2, 1.7 Hz, 1H), 3.57 (ddd, J = 11.1, 8.7, 5.2 Hz, 1H), 2.18 (ddd, J = 12.0, 5.2, 1.7 Hz, 1H), 2.09 (ddd, J = 12.0, 11.1, 7.2 Hz, 1H), 1.48 (s, 3H); 13C NMR (101 MHz, Chloroform-d) δ 147.73 (J_{C,F} = 2.39), 137.69 (J_{C,F} = 0.05), 136.16 (J_{C,F} = 0.13), 119.54 (J_{C,F} = 0.06), 118.55 (J_{C,F} = 0.03), 114.63 (J_{C,F} = 0.17), 100.23, 67.77, 54.83, 41.55, 24.69; 19F NMR (376 MHz, Chloroform-d) δ -136.09 (two minor peaks seen in 19F NMR spectrum could be inseparable isomers likely from impurities in the starting hydrazine). HRMS-ESI (m/z) [M + H]^+ calcd for C11H13FNO+, 194.09757; found, 194.09755.
Indoline 18 (Table 2, entry 5). Phenylhydrazine 11 (0.25 M in AcOH/H\textsubscript{2}O (1:1 v/v), 500 uL, 1 equiv) was injected into Pump A. Lactol 5 (0.275 M in AcOH/H\textsubscript{2}O (1:1 v/v), 500 uL, 1.1 equiv) was injected into Pump B. Chip reactor was preheated to 120 °C and pressure was set to 3 bar. Pumps A and B were both set to 100 μL/min flow rates to achieve a 5 minute residence time. The crude product was quenched with a solution of sat. aq. NaHCO\textsubscript{3} (20 mL) and extracted with EtOAc (3 x 20 mL). Combined organic phases were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. Purification by flash chromatography afforded furoindoline 18 ((3aS,8aS)-5-bromo-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole) as a yellow oil (55% yield, average of two experiments). \textit{Rf} 0.3 (3:1 Hexanes:EtOAc); \textit{\textsuperscript{1}H NMR} (400 MHz, Chloroform-\textit{d}) \textit{δ} 7.16 (d, \textit{J} = 1.7 Hz, 1H), 7.13 (dd, \textit{J} = 8.2, 2.0 Hz, 1H), 6.45 (d, \textit{J} = 8.4 Hz, 1H), 5.26 (s, 1H), 3.96 (ddd, \textit{J} = 8.8, 7.1, 1.7 Hz, 1H), 3.61 – 3.48 (m, 1H), 2.19 – 2.12 (m, 1H), 2.11 – 2.03 (m, 1H), 1.46 (s, 3H); \textit{\textsuperscript{13}C NMR} (101 MHz, Chloroform-\textit{d}) \textit{δ} 148.08, 136.58, 130.78, 126.31, 110.52, 109.72, 99.92, 67.57, 54.19, 41.56, 24.74; HRMS-ESI (m/z) [M + H]\textsuperscript{+} calcd for C\textsubscript{11}H\textsubscript{13}BrNO\textsuperscript{+}, 254.01750; found, 254.01751.
Indoline 19 (Table 2, entry 6). Purification by flash chromatography afforded furoindoline 19 
((3aS,8aS)-7-bromo-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole) as a yellow solid 
(56% yield, average of two experiments). Melting point 39-43 °C; Rf 0.4 (3:1 Hexanes:EtOAc); 
$^1$H NMR (400 MHz, Chloroform-\textit{d}) $\delta$ 7.19 (d, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 8.3$ Hz, 1H), 6.67 – 
6.59 (m, 1H), 5.32 (s, 1H), 3.97 (ddd, $J = 8.7, 7.1, 1.7$ Hz, 1H), 3.62 – 3.53 (m, 1H), 2.20 – 2.13 
(m, 1H), 2.12 – 2.04 (m, 1H), 1.48 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-\textit{d}) $\delta$ 147.55, 
135.38, 130.59, 121.92, 120.08, 101.79, 98.91, 67.62, 55.48, 41.73, 24.85; HRMS-ESI (m/z) [M + H]$^+$ calcd for C$_{11}$H$_{13}$BrNO$^+$, 254.01750; found, 254.01755.
Indoline 20 (Table 2, entry 7). Purification by flash chromatography afforded furoindoline 20 ((3aS,8aS)-5-methoxy-3a-methyl-3,3a,8,8a-tetrahydro-2H-furo[3’,2’:4,5]pyrrolo[3,2-b]pyridine) as a yellow solid (40% yield, average of two experiments). R\textsubscript{f} 0.3 (3:1 Hexanes:EtOAc); \textsuperscript{1}H NMR (500 MHz, Chloroform-\textit{d}) $\delta$ 6.88 (d, $J = 8.4$ Hz, 1H), 6.43 (d, $J = 8.4$ Hz, 1H), 5.27 (s, 1H), 3.97 (ddd, $J = 9.0$, 7.5, 1.7 Hz, 1H), 3.87 (s, 3H), 3.53 (ddd, $J = 11.1$, 8.7, 5.3 Hz, 1H), 2.40 (ddd, $J = 12.1$, 5.3, 1.5 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.47 (s, 3H). Spectral data match those previously reported.\textsuperscript{2}

G. Synthesis of Indolines with Lactol Variants

Representative Procedure. Synthesis of Indoline 24 (Table 3, entry 1) is used as an example.

Due to insolubility issues with the lactol a more dilute solution of the starting materials were used (Table 3, entry 1-3). Phenylhydrazine 4 (0.4 M in AcOH/H₂O (1:1 v/v), 500 μL, 1 equiv) was injected into Pump A. Lactol 21 (0.44 M in AcOH/H₂O (1:1 v/v), 500 μL, 1.1 equiv) into Pump B. Chip reactor was preheated to 120 °C and pressure was set to 3 bar. Pumps A and B were both set to 100 μL/min flow rates to achieve a 5 minute residence time. The crude product eluted and quenched with a solution of sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (3 x 20 mL). Combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography afforded furoindoline 24 ((3αR,8αS)-3α-phenyl-3,3α,8,8α-tetrahydro-2H-furo[2,3-b]indole) as a colorless oil (49% yield, average of two experiments). Rf 0.4 (3:1 Hexanes:EtOAc); ¹H NMR (400 MHz, Chloroform-d) δ 7.37 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 7.12 – 7.07 (m, 1H), 7.05 – 7.01 (m, 1H), 6.76 (td, J = 7.4, 1.0 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 5.62 (s, 1H), 4.19 – 4.13 (m, 1H), 3.75 – 3.62 (m, 1H), 2.83 – 2.68 (m, 1H), 2.52 (dd, J = 11.9, 4.4 Hz, 1H). Spectral data match those previously reported.¹

Any modifications of the conditions shown in this representative procedure are specified in the following schemes, which depict all of the reactions in Table 3.
**Indoline 25 (Table 3, entry 2).** Phenylhydrazine 4 (0.1 M in AcOH/H₂O (1:1 v/v), 500 uL, 1 equiv) was injected into Pump A. Hemiaminal 22 (0.11 M in AcOH/H₂O (1:1 v/v), 500 uL, 1.1 equiv) was injected into Pump B. Chip reactor was preheated to 120 °C and pressure was set to 3 bar. Pumps A and B were both set to 100 μL/min flow rates to achieve a 5 minute residence time. The crude product was quenched with a solution of sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (3 x 20 mL). Combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography afforded pyrrolidinoindoline 25 ((3aS, 8aS)-3a-methyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole) as a yellow solid (42% yield, average of two experiments). Rf 0.4 (3:1 Hexanes:EtOAc); ¹H NMR (400 MHz, Chloroform-d) δ 7.74 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.07 (td, J = 7.7, 1.3 Hz, 1H), 7.02 – 6.98 (m, 1H), 6.76 (td, J = 7.4, 0.9 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 5.03 (s, 1H), 3.41 (ddd, J = 10.4, 7.9, 2.6 Hz, 1H), 3.13 (td, J = 10.2, 6.1 Hz, 1H), 2.44 (s, 3H), 2.19 – 2.12 (m, 1H), 1.78 (ddd, J = 12.5, 10.1, 7.9 Hz, 1H), 1.27 (s, 3H). Spectral data match those previously reported.¹
**Indoline 26 (Table 3, entry 3).** Phenylhydrazine 4 (0.4 M in AcOH, 500 μL, 1 equiv) was injected into Pump A. Hemiaminal 23 (0.44 M in AcOH, 500 μL, 1.1 equiv) was injected into Pump B. Chip reactor was preheated to 120 °C and pressure was set to 3 bar. Pumps A and B were both set to 100 μL/min flow rates to achieve a 5 minute residence time. The crude product was quenched with a solution of sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (3 x 20). Combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography afforded pyrrolidinoindoline 26 ((4aS,9aS)-4a-methyl-1-tosyl-2,3,4,4a,9,9a-hexahydro-1H-pyrido[2,3-b]indole) as a yellow amorphous solid (21% yield, average of two experiments). Rf 0.5 (3:1 Hexanes:EtOAc); ¹H NMR (400 MHz, Chloroform-d) δ 7.75 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.06 – 7.00 (m, 1H), 6.96 (d, J = 7.3 Hz, 1H), 6.75 (t, J = 7.9 Hz, 1H), 6.59 (d, J = 7.7 Hz, 1H), 5.18 (s, 1H), 3.75 – 3.61 (m, 1H), 3.27 – 3.12 (m, 1H), 2.45 (s, 3H), 1.72 – 1.41 (m, 4H), 1.26 (s, 3H). Spectral data match those previously reported.¹
NMR Spectra

Ordered by compound number

$^1$H NMR data provided for all compounds

$^{13}$C NMR data provided for new compounds 17, 18, 19

$^{19}$F NMR data provided for new compound 17
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The image contains a chemical structure and a 1H NMR spectrum. The spectrum shows peaks at various ppm values, with corresponding chemical shifts indicated in the figure.
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![Chemical Structure](image)

### Spectral Data

- **Me and N**: 2.11, 3.00, 1.02, 1.04, 0.98, 0.97, 1.06, 0.98, 1.00
- **I**: 1.46, 2.02, 2.03, 2.05, 2.06, 2.07, 2.09, 2.12, 2.13, 2.14, 2.16, 2.93, 3.43, 3.44, 3.45, 3.46, 3.46, 3.47, 3.48, 3.49, 3.93, 3.95, 3.97, 5.07, 6.36, 6.38, 6.66, 6.68, 6.70, 7.04, 7.05, 7.08, 7.11, 7.12

### NMR Spectrum

-/ppm:
  - 0.97 to 1.00
  - 1.46 to 2.16
  - 2.93 to 3.49
  - 5.07 to 7.12