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Synthesis of Bio-Derived Cinnolines and their Flow-Based Conversion to 1,4-Dihydrocinnoline Derivatives

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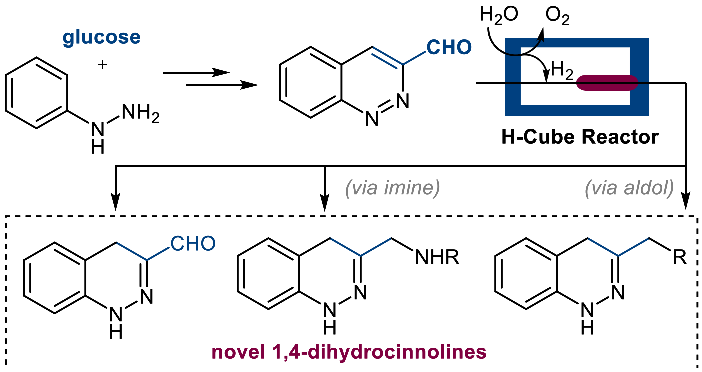

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Abstract Starting from phenyl hydrazine and glucose, the versatile cinnoline scaffold is obtained on multi-gram scale and further derivatized. A simple continuous flow hydrogenation process enables the conversion of selected cinnolines into their 1,4-dihydrocinnoline counterparts. These products are generated in high yield and purity with residence times of less than 1 minute and along with their cinnoline precursors are expected to serve as valuable heterocyclic building blocks for future medicinal chemistry programs.

Key words flow synthesis, cinnoline, dihydrocinnoline, hydrogenation, H-cube

Cinnolines (**1**) are valuable aromatic bicycles that contain two adjacent nitrogen atoms in the same six-membered ring thus making them derivatives of the monocyclic pyridazine scaffold. Together with their isomeric quinazoline (**2**) and quinoxaline (**3**) counterparts, cinnolines are frequently encountered heterocycles in drug discovery programs[1] (Figure 1).

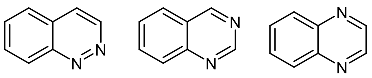
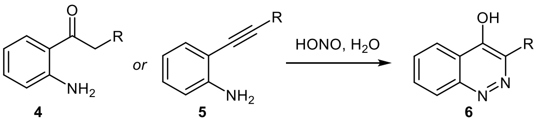

1, cinnoline **2**, quinazoline **3**, quinoxaline

Figure 1: Structures of cinnoline, quinazoline and quinoxaline.

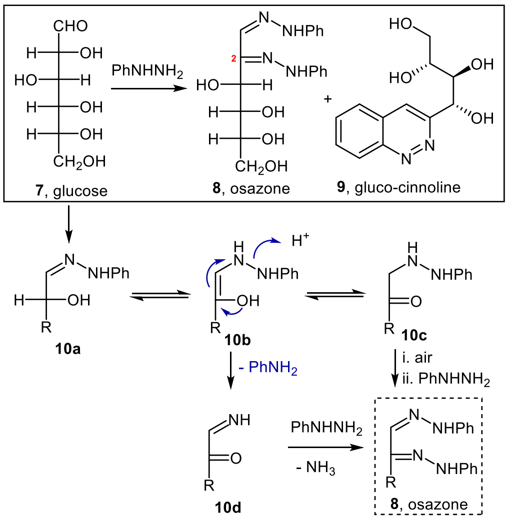
Despite a persistent need for valuable synthetic procedures generating such structures most cinnolines are prepared by a limited number of reactions.[2] Oftentimes these involve hazardous diazonium intermediates that are prepared via standard diazotization processes (Scheme 1).



Scheme 1: Exemplar routes generating the cinnoline scaffold.

To investigate the suitability of an alternative cinnoline synthesis that would provide the desired heterocyclic structure in a single step from readily available substrates we set out to study the reaction between phenyl hydrazine and glucose. This approach is appealing as it not only utilizes biorenewable carbohydrate feedstocks,[3] but moreover facilitates the further derivatization of the cinnoline structure due to the brevity of the synthesis.

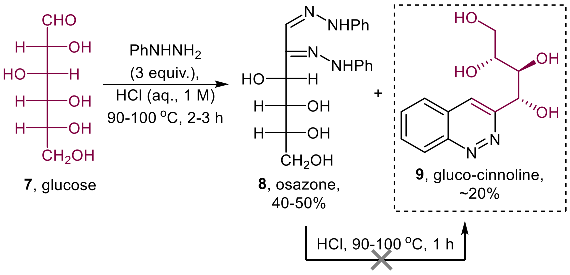
Interestingly, the acid-mediated condensation reaction between reducing sugars and excess phenyl hydrazine is a well-documented process in carbohydrate chemistry and the formation of a yellow precipitate, known as osazone (**8**), was first reported by Fischer over a century ago.[4] Subsequently, the structure of this osazone species was established to contain two adjacent phenyl hydrazone moieties.[5]



Scheme 2: Formation of osazone **8** and cinnoline derivative **9**.

Further studies indicated that the formal oxidation at C2 of the carbohydrate results from an Amadori rearrangement (**10a** to **10c**) that either forms β-keto-hydrazone **10c** which then oxidizes by air or undergoes a reduction of the N-N single bond in its enaminol form (**10b**) to liberate aniline and ammonia prior to condensation with further phenyl hydrazine.[6] As a consequence of this mechanism, glucose can be replaced by related carbohydrates such as fructose furnishing the identical osazone species **8**.[7] Importantly, in this process a significant amount of a cinnoline species bearing a polyol side chain (**9**) is formed when employing glucose as starting material (Scheme 2).

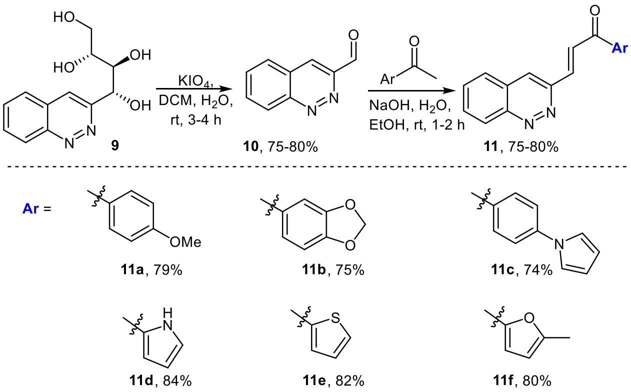
We commenced our studies by reacting excess phenyl hydrazine (3 equiv.) with α-D-glucose (1 equiv.) in aqueous hydrochloric acid (1 M). As expected, a yellow precipitate formed within 1 h upon heating at 90-100 °C. After cooling this mixture and filtering the yellow osazone adduct (**8**), the filtrate was basified and extracted with DCM to remove organic by-products such as aniline. Gratifyingly, the desired cinnoline product (**9**) precipitated from the remaining aqueous phase and was isolated as a pale brown solid that did not need any further purification. This process can be scaled to rapidly give 5 g of the desired cinnoline product (**9**, ~20% yield) along with a larger quantity of the osazone species (**8**, typically 40-50% yield). Unfortunately, several attempts to increase the yield of **9** by varying the acid type and stoichiometry as well as reaction time and temperature were ultimately unsuccessful. Additionally, subjecting osazone **8** to the reaction conditions did not furnish cinnoline **9** indicating that contrary to expectation the cinnoline does not form through a simple Friedel-Crafts type acylation process from its osazone precursor (Scheme 3).



Scheme 3: Synthesis of gluco-cinnoline **9**.

Having multi-gram quantities of cinnoline species **9** in hand we decided to convert its polyol side chain into an aldehyde functionality. This was accomplished by reacting **9** in a biphasic mixture (DCM/water, 1:1) with KIO_4 (4 equiv.) rendering the desired aldehyde **10** in high yield and purity (Scheme 4). We next derivatized this aldehyde moiety in crossed aldol condensation reactions with different acetophenones to yield a small selection of novel enone products for further evaluations.

Next, we turned our attention at studying the hydrogenation of these aldol adducts (**11**). Specifically, we were interested in evaluating the feasibility of chemoselectively reducing the enone alkene. To this end we wished to use a continuous flow protocol that would facilitate performing these hydrogenations in a safe and convenient manner, whilst being able to rapidly study standard catalysts under varying conditions (temperature, pressure, concentration).[8] This was best accomplished by using an H-Cube flow reactor, that produces hydrogen gas *in situ* by means of electrolysis of water, before directing the substrate solution (saturated with hydrogen) over a pre-packed catalyst bed.[9]



Scheme 4: Synthesis and derivatization of cinnoline species.

We thus prepared stock solutions of our substrates (**11**, EtOH/EtOAc 1:1, 0.25 M) and pumped these via an HPLC pump operating at a flow rate of 1 mL/min over a catalyst cartridge containing Pd/C (10%, cartridge length 50 mm, rt) prior to passing an in-built back-pressure regulator and collection of the resulting product solution.

Pleasingly, a quick set of reactions identified these conditions as suitable to cleanly reduce the embedded enone to the corresponding ketone, within the short contact time of less than 1 min of the substrate within the catalyst cartridge. Additionally, the partial reduction of the cinnoline ring structure was observed in all cases. This was indicated by ^{1}H-NMR spectroscopy showing the presence of a new benzylic methylene group as well as a N-H signal, both of which were confirmed by HSQC experiments. To unambiguously confirm the structure of these new products we exploited single crystal X-ray diffraction experiments confirming the presence of both an ethyl fragment and a 1,4-dihydrocinnoline moiety (Figure 2).[10]

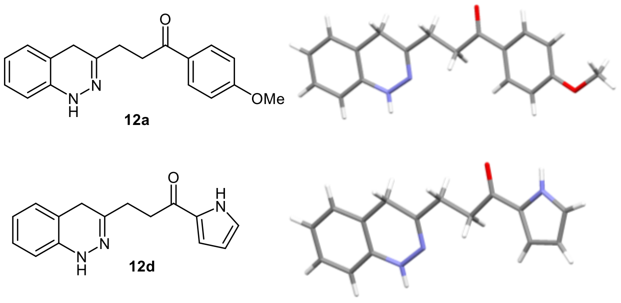
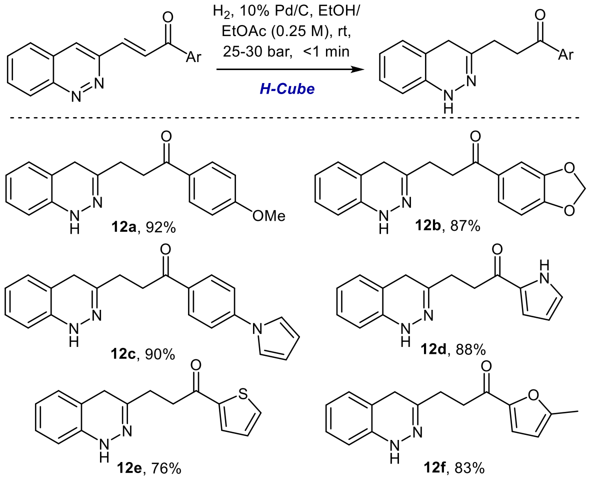


Figure 2: X-ray structures of products **12a** and **12d**.

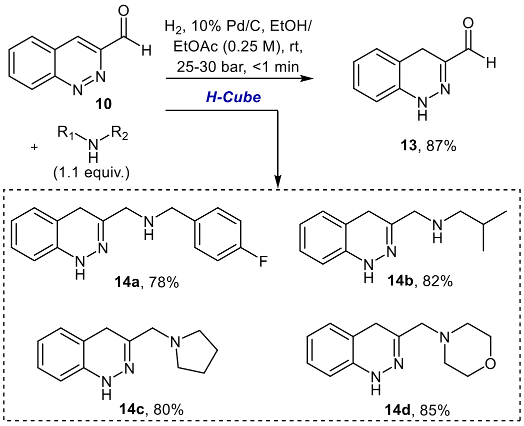
The prevalence for the 1,4-isomer of the dihydrocinnoline structure likely results from an initial hydrogenation of the N=N double bond following tautomerization to yield the benzylic methylene group along with a fully substituted hydrazone fragment. We next subjected the remaining enone precursors to the described flow hydrogenation conditions and were able to obtain the analogous hydrogenation products in high yields as shown in Scheme 5. Pleasingly, this confirm the preferred reduction mode to encompass both the exocyclic alkene and the cinnoline moiety. All products **12a-f** were successfully converted into their 1,4-dihydrocinnoline counterparts in high chemical yield. This allowed to incorporate different aryl and heteroaryl appendages including pyrroles, furans and thiophenes.

To the best of our knowledge, the generation of 1,4-dihydrocinnolines via hydrogenation of cinnolines is unknown in literature, although being the most direct and facile approach to yield these under-explored entities.[11]



Scheme 5: 1,4-Dihydrocinnolines prepared in flow mode.

To further expand on this new entry into the 1,4-dihydrocinnoline scaffold, we opted to evaluate the flow-based hydrogenation of related cinnoline structures that are readily accessible from aldehyde building block **10**. To this end we targeted the hydrogenation of aldehyde **10** as well as several imine derivatives that would yield the corresponding reductive amination products (**14a**-**14d**). Pleasingly, it was established that aldehyde **10** smoothly underwent the desired partial hydrogenation to render the desired 1,4-dihydrocinnoline derivative bearing the unaffected aldehyde functionality. Furthermore, the related hydrogenation process of *in situ* generated imines delivered a small selection of amines bearing the 1,4-dihydrocinnoline moiety as a substituent. All these products were generated in high yields and good purity with residence times of <1 minute in the H-Cube flow reactor (10% Pd/C cartridge, 1 mL/min, rt, 40 bar) thus demonstrating the simplicity with which these entities can be created on demand (Scheme 6).



Scheme 6: Further 1,4-dihydrocinnoline products.

In conclusion, we report the effective generation of a cinnoline-3-carbaldehyde building block that is prepared on multi-gram scale from readily available glucose and phenyl hydrazine. The value of this material is demonstrated by exploiting the aldehyde functionality by means of aldol condensation and imine formation reactions. In addition, we describe the facile flow-based hydrogenation of these materials that selectively furnish novel 1,4-dihydrocinnoline systems. As these are under-explored drug-like structures, we anticipate that they may serve as valuable building blocks in future medicinal chemistry programmes.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(12) **Synthesis of gluco-cinnoline 9**: A mixture of glucose (12.0 g, 66 mmol) and phenyl hydrazine (39.9 g, 369 mmol) was heated in aqueous hydrochloric acid (1 M, 180 mL) at 95-100 °C for 2-3 h. After cooling to room temperature, the yellow precipitate of osazone **8** was separated by suction filtration and washed with cold acetonitrile (yield range 40-50%). The aqueous filtrate was basified to pH 11 (8 M NaOH, aq.) and extracted with CH_2Cl_2 (3 x 50 mL). The aqueous layer was neutralized with aq. HCl leading to the slow crystallization of the desired product **9** (yield ~20%) in a process that can be accelerated by directing a stream of nitrogen over this solution.

(1*R*,2*S*,3*R*)-1-(Cinnolin-3-yl)butane-1,2,3,4-tetraol, 9 (gluco-cinnoline): Beige solid. ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 8.42 (d, *J* = 8.6 Hz, 1H), 8.16 (s, 1H), 8.06 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.87 (ddd, *J* = 8.5, 6.6, 1.6 Hz, 1H), 7.84 – 7.79 (m, 1H), 5.48 (br s, 2H), 4.73 (br s, 1H), 4.40 (br s, 2H), 3.81 (d, *J* = 8.5 Hz, 1H), 3.73 – 3.61 (m, 2H), 3.46 (dd, J = 11.3, 6.1 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 160.5 (C), 149.8 (C), 131.5 (CH), 130.7 (CH), 129.2 (CH), 127.7 (CH), 126.3 (C), 120.9 (CH), 74.7 (CH), 71.9 (CH), 71.8 (CH), 64.1 (CH_2). IR: ν = 3178 (s), 2935 (w), 2832 (w), 1434 (w), 1411 (w), 1090 (s), 1046 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{12}H_{15}N_2O_4$ 251.1032; found: 251.1030.

(13) **Synthesis of cinnoline-3-carbaldehyde 10**: To a suspension of KIO_4 (3.5 equiv.) in water (0.7 M), was added a mixture of glucocinnoline (**9**, 1.0 equiv in CH_2Cl_2, 0.5 M). The resulting biphasic mixture was stirred vigorously at room temperature until full consumption of starting material was observed by tlc (2-3 h). Upon filtration of the organic phase over a plug of silica and evaporation the desired aldehyde product **10** was isolated as a light brown solid.

Cinnoline-3-carbaldehyde 10: Light-brown solid. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 10.69 (s, 1H), 8.65 (d, *J* = 9.0 Hz, 1H), 8.49 (d, *J* = 1.0 Hz, 1H), 8.05 – 7.98 (m, 2H), 7.86 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H). ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 192.6 (CH), 151.8 (C), 149.5 (C), 133.3 (CH), 132.2 (CH), 130.1 (CH), 128.4 (CH), 125.4 (C), 122.2 (CH). IR: ν = 3047 (w), 2846 (w), 1711 (s), 1479 (m), 1362 (m), 1154 (m), 766 (s), 752 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_9H_7N_2O$ 159.0558; found: 159.0552.

Synthesis of cinnoline enone adducts 11a-11f: To a mixture of cinnoline-3-carbaldehyde (1 equiv.) and the corresponding acetophenone (1 equiv.) in MeCN (0.5 M) is added a solution of NaOH (1 equiv.) dissolved in a 50:50 mixture ethanol/water (0.5 M). The resulting mixture is stirred at room temperature leading to precipitation of the desired product within 1 h, which is isolated by suction filtration.

(*E*)-3-(Cinnolin-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one, 11a: Yellow solid; melting range: 164 °C (decomposition). Yield 240 mg, 79%. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 8.62 (d, *J* = 15.3 Hz, 1H), 8.59 – 8.56 (m, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 8.01 (d, *J* = 15.3 Hz, 1H), 7.90 (d, *J* = 0.8 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.80 – 7.74 (m, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H). ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 188.3 (C), 163.8 (C), 150.3 (C), 149.7 (C), 139.2 (CH), 131.7 (CH), 131.2 (2CH), 131.1 (CH), 130.7 (C), 130.2 (CH), 127.1 (CH), 126.3 (CH), 125.9 (C), 123.4 (CH), 114.0 (2CH), 55.5 (CH_3). IR: ν = 2988 (m), 1660 (m), 1596 (s), 1305 (m), 1261 (s), 1163 (s), 1021 (s), 825 (s), 740 (s), 597 (m). HRMS (ES-TOF)$^+$: m/z calcd for $C_{18}H_{14}N_2O_2Na$ 313.0953; found: 313.0951.

(*E*)-1-(Benzo[d][1,3]dioxol-5-yl)-3-(cinnolin-3-yl)prop-2-en-1-one, 11b: Beige solid. Yield 227 mg, 75%. ^{1}H-NMR (500 MHz, CDCl$_3$): δ = 8.62 (d, *J* = 8.3 Hz, 1H), 8.60 (d, *J* = 15.1 Hz, 1H), 8.04 (d, *J* = 15.1 Hz, 1H), 7.94 (s, 1H), 7.93 – 7.88 (m, 2H), 7.86 – 7.79 (m, 2H), 7.65 (d, *J* = 1.8 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.10 (s, 2H). ^{13}C-NMR (125 MHz, CDCl$_3$): δ = 188.0 (C), 152.2 (C), 150.3 (C), 149.6 (C), 148.5 (C), 139.5 (CH), 132.7 (C), 131.8 (CH), 131.2 (CH), 130.2 (CH), 127.1 (CH), 126.2 (CH), 125.9 (C), 125.4 (CH), 123.5 (CH), 108.5 (CH), 108.1 (CH), 102.0 (CH_2). IR: ν = 3058 (w), 1664 (m), 1622 (m), 1598 (m), 1579 (m), 1506 (s), 1441 (s), 1358 (s), 1269 (s), 1094 (s), 1033 (s), 734 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{18}H_{13}N_2O_3$ 305.0926; found: 305.0925.

(*E*)-1-(4-(1*H*-Pyrrol-1-yl)phenyl)-3-(cinnolin-3-yl)prop-2-en-1-one, 11c: Beige solid. Yield 242 mg, 74%. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 8.65 (d, *J* = 15.3 Hz, 1H), 8.62 – 8.58 (m, 1H), 8.27 – 8.22 (m, 2H), 8.06 (d, *J* = 15.3 Hz, 1H), 7.93 (s, 1H), 7.91 – 7.86 (m, 2H), 7.82 – 7.77 (m, 1H), 7.56 – 7.51 (m, 2H), 7.22 – 7.19 (m, 2H), 6.41 – 6.38 (m, 2H). ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 188.5 (C), 150.3 (C), 149.5 (C), 144.2 (C), 139.9 (CH), 134.5 (C), 131.8 (CH), 131.3 (CH), 130.7 (2CH), 130.2 (CH), 127.1 (CH), 125.9 (CH), 125.8 (C), 123.7 (CH), 119.5 (2CH), 119.0 (2CH), 111.7 (2CH). IR: ν = 3047 (w), 2922 (w), 1661 (m), 1599 (s), 1578 (m), 1520 (m), 1476 (m), 1378 (s), 1326 (m), 1189 (s), 843 (m), 722 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{21}H_{16}N_3O$ 326.1293; found: 326.1280.

(*E*)-3-(Cinnolin-3-yl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one, 11d: Beige solid. Yield 208 mg, 84%. ^{1}H-NMR (400 MHz, d$_6$-DMSO): δ = 12.09 (s, 1H), 8.66 (s, 1H), 8.49 (d, *J* = 8.3 Hz, 1H), 8.23 (d, *J* = 15.6 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 15.6 Hz, 1H), 7.99 – 7.94 (m, 1H), 7.93 – 7.86 (m, 1H), 7.35 (d, *J* = 3.9 Hz, 1H), 7.23 – 7.18 (m, 1H), 6.29 (dd, *J* = 3.9, 2.4 Hz, 1H). ^{13}C-NMR (100 MHz, d$_6$-DMSO): δ = 177.6 (C), 150.5 (C), 150.1 (C), 138.1 (CH), 133.4 (C), 132.5 (CH), 132.2 (CH), 129.6 (CH), 128.1 (CH), 127.7 (CH), 127.4 (CH), 126.0 (C), 123.2 (CH), 118.4 (CH), 111.0 (CH). IR: ν = 3274 (m), 3012 (w), 1651 (m), 1618 (m), 1593 (m), 1444 (m), 1427 (s), 1188 (m), 728 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{15}H_{12}N_3O$ 250.0980; found: 250.0971.

(*E*)-3-(Cinnolin-3-yl)-1-(thiophen-2-yl)prop-2-en-1-one, 11e: Off-white solid. Yield 216 mg, 82%. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 8.62 – 8.57 (m, 1H), 8.49 (d, *J* = 15.2 Hz, 1H), 8.04 (d, *J* = 15.2 Hz, 1H), 8.02 – 7.98 (m, 1H), 7.92 (s, 1H), 7.91 – 7.85 (m, 2H), 7.82 – 7.76 (m, 1H), 7.73 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.22 (dd, *J* = 5.0, 3.8 Hz, 1H). ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 182.0 (C), 150.3 (C), 149.3 (C), 145.5 (C), 139.3 (CH), 134.7 (CH), 132.8 (CH), 131.8 (CH), 131.3 (CH), 130.2 (CH), 128.5 (CH), 127.1 (CH), 126.1 (CH), 125.8 (C), 123.8 (CH). IR: ν = 3105 (w), 1655 (s), 1603 (s), 1579 (m), 1518 (m), 1417 (s), 1281 (m), 1270 (m), 975 (m), 729 (s), 717 (s).

HRMS (ES-TOF)$^+$: m/z calcd for $C_{15}H_{11}N_2OS$ 267.0592; found: 267.0588.

(*E*)-3-(Cinnolin-3-yl)-1-(5-methylfuran-2-yl)prop-2-en-1-one, 11f: Yellow solid. Yield 212 mg, 80%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 8.9 Hz, 1H), 8.36 (d, *J* = 15.3 Hz, 1H), 8.03 (d, *J* = 15.3 Hz, 1H), 7.88 (s, 1H), 7.82 – 7.87 (m, 2H), 7.79 – 7.72 (m, 1H), 7.37 (d, *J* = 3.5 Hz, 1H), 6.23 (d, *J* = 3.5 Hz, 1H), 2.43 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.7 (C), 159.0 (C), 152.4 (C), 150.2 (C), 149.4 (C), 138.6 (CH), 131.7 (CH), 131.2 (CH), 130.2 (CH), 127.1 (CH), 126.0 (CH), 125.8 (C), 123.5 (CH), 120.8 (CH), 109.6 (CH), 14.2 (CH_3). IR: ν = 3116 (w), 1658 (m), 1607 (m), 1511 (s), 1330 (m), 1292 (m), 1207 (m), 1063 (m), 756 (m), 734 (m). HRMS (ES-TOF)$^+$: m/z calcd for $C_{16}H_{13}N_2O_2$ 265.0977; found: 265.0975.

(14) **Synthesis of 1,4-dihydrocinnolines 12a-12f**: A stock solution of substrates **11a-11f** (0.25 M, EtOH/EtOAc 1:1) was prepared and passed through a H-Cube Mini™ flow reactor equipped with a suitable catalyst cartridge (10% Pd/C, 50 mm, rt) at a flow rate of 1 mL/min. After evaporation of the resulting solutions the solvent was evaporated in vacuo prior to ^{1}H-NMR analysis.

3-(1,4-Dihydrocinnolin-3-yl)-1-(4-methoxyphenyl)propan-1-one, 12a: Beige solid. Yield 135 mg, 92%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 9.0 Hz, 2H), 7.21 (s, 1H), 7.10 (td, *J* = 7.7, 1.5 Hz, 1H), 7.03 – 7.00 (m, 1H), 6.94 – 6.88 (m, 3H), 6.65 (dd, *J* = 7.8, 1.1 Hz, 1H), 3.85 (s, 3H), 3.31 (s, 2H), 3.28 – 3.23 (m, 2H), 2.73 (dd, *J* = 7.9, 6.5 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 197.7 (C), 163.4 (C), 145.7 (C), 140.2 (C), 130.3 (2CH), 130.0 (C), 127.6 (CH), 127.0 (CH), 122.1 (CH), 116.2 (C), 113.7 (2CH), 111.7 (CH), 55.4 (CH_3), 34.1 (CH_2), 30.5 (CH_2), 30.2 (CH_2). IR: ν = 3303 (m), 2922 (m), 1673 (s), 1596 (s), 1487 (s), 1306 (m), 1261 (s), 1210 (s), 1164 (s), 1023 (m), 984 (m), 836 (s), 749 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{18}H_{19}N_2O_2$ 295.1447; found: 295.1438. X-ray data for $C_{18}H_{18}N_2O_2$; space group P21/c; a 15.4438(2), b = 4.67192 (6), c = 21.2967(3), α = 90, β = 106.399(2), γ = 90; CCDC-1959846.

1-(Benzo[d][1,3]dioxol-5-yl)-3-(1,4-dihydrocinnolin-3-yl)propan-1-one, 12b: Beige solid. Yield 132 mg, 87%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.46 (d, *J* = 1.8 Hz, 1H), 7.18 (s, 1H), 7.10 (td, *J* = 7.6, 1.5 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.91 (td, *J* = 7.4, 1.2 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.65 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.02 (s, 2H), 3.31 (s, 2H), 3.25 – 3.20 (m, 2H), 2.72 (t, *J* = 7.1 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 197.2 (C), 151.6 (C), 148.1 (C), 145.5 (C), 140.2 (C), 131.8 (C), 127.6 (CH), 127.0 (CH), 124.3 (CH), 122.2 (CH), 116.2 (CH), 111.7 (CH), 107.9 (CH), 107.8 (CH), 101.8 (CH_2), 34.2 (CH_2), 30.5 (CH_2), 30.2 (CH_2). IR: ν = 3365 (m), 2903 (m), 1673 (m), 1600 (m), 1503 (m), 1485 (m), 1442 (s), 1250 (s), 1037 (m), 933 (m), 753 (m). HRMS (ES-TOF)$^+$: m/z calcd for $C_{18}H_{17}N_2O_3$ 309.1234; found: 309.1239.

1-(4-(1*H*-Pyrrol-1-yl)phenyl)-3-(1,4-dihydrocinnolin-3-yl)propan-1-one, 12c: Beige solid. Yield 148 mg, 90%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.19 (s, 1H), 7.17 – 7.14 (m, 2H), 7.10 (td, *J* = 7.6, 1.5 Hz, 1H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.38 (t, *J* = 2.2 Hz, 2H), 3.33 (s, 2H), 3.29 (t, *J* = 7.0 Hz, 2H), 2.76 (t, *J* = 7.0 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 197.9 (C), 145.4 (C), 143.9 (C), 140.2 (C), 133.8 (C), 129.9 (2CH), 127.6 (CH), 127.1 (CH), 122.2 (CH), 119.4 (2CH), 119.0 (2CH), 116.1 (C), 111.7 (CH), 111.5 (2CH), 34.2 (CH_2), 30.4 (CH_2), 30.3 (CH_2). IR: ν = 3358 (m), 2923 (m), 1677 (s), 1602 (s), 1520 (m), 1475 (s), 1334 (s), 1186 (m), 1066 (m), 729 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{21}H_{20}N_3O$ 330.1606; found: 330.1599.

3-(1,4-Dihydrocinnolin-3-yl)-1-(1*H*-pyrrol-2-yl)propan-1-one, 12d: Beige solid. Yield 110 mg, 88%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.42 (s, 1H), 7.25 (s, 1H), 7.10 (td, *J* = 7.6, 1.5 Hz, 1H), 7.03 – 6.98 (m, 2H), 6.96 – 6.93 (m, 1H), 6.91 (t, *J* = 7.1 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.25 (dd, *J* = 4.2, 2.1 Hz, 1H), 3.30 (s, 2H), 3.11 (dd, *J* = 8.3, 6.6 Hz, 2H), 2.72 (dd, *J* = 8.3, 6.5 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 189.5 (C), 145.5 (C), 140.2 (C), 131.8 (C), 127.5 (CH), 127.0 (CH), 124.3 (CH), 122.2 (CH), 116.1 (C), 116.1 (CH), 111.8 (CH), 110.6 (CH), 33.8 (CH_2), 30.8 (CH_2), 30.1 (CH_2). IR: ν = 3296 (br), 2917 (w), 1635 (s), 1478 (m), 1403 (s), 1107 (m), 750 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{15}H_{16}N_3O$ 254.1293; found: 254.1297. X-ray data for $C_{15}H_{15}N_3O$; space group P21/n; a 13.7977(5), b = 4.6368(2), c = 19.8961(8), α = 90, β = 91.707(4), γ = 90; CCDC-1959847.

3-(1,4-Dihydrocinnolin-3-yl)-1-(thiophen-2-yl)propan-1-one, 12e: Yellow solid. Yield 101 mg, 76%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.78 (dd, *J* = 3.9, 1.3 Hz, 1H), 7.64 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.22 (s, 1H), 7.15 – 7.11 (m, 2H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.94 (td, *J* = 7.3, 1.3 Hz, 1H), 6.68 (dd, *J* = 7.8, 1.0 Hz, 1H), 3.34 (s, 2H), 3.28 (dd, *J* = 7.8, 6.4 Hz, 2H), 2.80 – 2.75 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 192.2 (C), 145.2 (C), 144.2 (C), 140.2 (C), 133.4 (CH), 131.9 (CH), 128.1 (CH), 127.6 (CH), 127.1 (CH), 122.2 (CH), 116.1 (C), 111.8 (CH), 35.2 (CH_2), 30.5 (CH_2), 30.2 (CH_2). IR: ν = 3359 (m), 3089 (w), 2903 (w), 1659 (s), 1596 (m), 1475 (s), 1415 (s), 1252 (m), 854 (m), 752 (s), 724 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{15}H_{15}N_2OS$ 271.0905; found: 271.0898.

3-(1,4-Dihydrocinnolin-3-yl)-1-(5-methylfuran-2-yl)propan-1-one, 12f: Off-white solid. Yield 112 mg, 83%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.19 (s, 1H), 7.11 (d, *J* = 3.3 Hz, 1H), 7.09 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.94 – 6.88 (m, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.12 (d, *J* = 3.5 Hz, 1H), 3.29 (s, 2H), 3.12 – 3.06 (m, 2H), 2.71 (dd, *J* = 8.2, 6.6 Hz, 2H), 2.37 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 187.6 (C), 157.7 (C), 151.3 (C), 145.4 (C), 140.2 (C), 127.6 (CH), 127.0 (CH), 122.2 (CH), 119.0 (CH), 116.2 (C), 111.7 (CH), 108.8 (CH), 34.0 (CH_2), 30.3 (CH_2), 30.1 (CH_2), 14.0 (CH_3). IR: ν = 3350 (m), 2922 (w), 1663 (s), 1596 (m), 1515 (s), 1478 (m), 1207 (m), 1072 (m), 1027 (m), 799 (m), 752 (m). HRMS (ES-TOF)$^+$: m/z calcd for $C_{16}H_{16}N_2O_2Na$ 291.1109; found: 291.1120.

(15) **Synthesis of 1,4-dihydrocinnolines 13 and 14a-14d**: A stock solution of substrate **10** (0.25 M, EtOH/EtOAc 1:1) was prepared and passed through a H-Cube Mini™ flow reactor equipped with a suitable catalyst cartridge (10% Pd/C, 50 mm, rt) at a flow rate of 1 mL/min. After evaporation of the resulting solutions the solvent was evaporated in vacuo prior to ^{1}H-NMR analysis. In case of the reductive amination products **14**, the desired amine component (1.1 equiv.) was added to the stock solution of aldehyde **10** and stirred at 50 °C for 30 min before passing the resulting imine solution through the H-Cube reactor under analogous conditions.

1,4-Dihydrocinnoline-3-carbaldehyde, 13: Yellow solid. Yield 140 mg, 87%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.46 (s, 1H), 8.27 (s, 1H), 7.14 (td, *J* = 7.5, 1.6 Hz, 1H), 7.06 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.04 – 6.98 (m, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 3.62 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 190.6 (CH), 141.4 (C), 136.5 (C), 129.0 (CH), 127.7 (CH), 124.8 (CH), 116.8 (C), 112.7 (CH), 21.9 (CH_2). IR: ν = 3266 (m), 3016 (w), 2818 (w), 1649 (s), 1579 (m), 1481 (m), 1349 (m), 1254 (m), 1178 (s), 722 (m). HRMS (ES-TOF)$^+$: m/z calcd for $C_9H_9N_2O$ 161.0715; found: 161.0714.

1-(1,4-Dihydrocinnolin-3-yl)-*N*-(4-fluorobenzyl)methanamine, 14a: Yellow oil. Yield 104 mg, 78%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.32 – 7.28 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 8.4 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 3.78 (s, 2H), 3.45 (s, 2H), 3.32 (s, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 162.0 (CF, d, *J* = 245 Hz), 144.8 (C), 140.2 (C), 135.7 (C), 129.8 (2CH, d, *J* = 8 Hz), 127.7 (CH), 127.1 (CH), 122.4 (CH), 116.1 (C), 115.2 (2CH, d, *J* = 21 Hz), 111.8 (CH), 53.4 (CH_2), 52.6 (CH_2), 28.2 (CH_2). ^{19}F-NMR (471 MHz, $CDCl_3$): δ = -116.0. IR: ν = 3291 (m), 2839 (m), 1597 (m), 1507 (s), 1475 (s), 1344 (m), 1253 (s), 1155 (m), 1092 (m), 823 (s), 751 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{16}H_{17}N_3F$ 270.1407; found: 270.1395.

***N*-((1,4-Dihydrocinnolin-3-yl)methyl)-2-methylpropan-1-amine, 14b:** Brown oil. Yield 90 mg, 82%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (s, 1H), 7.10 (td, *J* = 7.6, 1.6 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.92 (td, *J* = 7.4, 1.2 Hz, 1H), 6.68 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.48 (s, 2H), 3.32 (s, 2H), 2.48 (d, *J* = 6.7 Hz, 2H), 1.81 (dp, *J* = 13.3, 6.6 Hz, 1H), 0.91 (d, J = 6.8 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 140.0 (C), 127.7 (CH), 127.1 (CH), 122.4 (CH), 115.9

(C), 111.8 (CH), 110.0 (C), 57.2 (CH_2), 53.7 (CH_2), 28.1 (CH_2), 27.9 (CH), 20.6 ($2CH_3$). IR: ν = 3282 (m), 2954 (m), 2870 (m), 1672 (m), 1596 (m), 1474 (s), 1302 (m), 1252 (m), 1172 (m), 750 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{13}H_{20}N_3$ 218.1657; found: 218.1659.

3-(Pyrrolidin-1-ylmethyl)-1,4-dihydrocinnoline, **14c:** Yellow oil. Yield 85 mg, 80%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36 (br s, 1H), 7.09 (td, *J* = 7.6, 1.6 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.92 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.68 – 6.64 (m, 1H), 3.38 (s, 2H), 3.26 (s, 2H), 2.51 (ddd, *J* = 6.7, 4.2, 1.7 Hz, 4H), 1.80 – 1.74 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.4 (C), 140.2 (C), 127.7 (CH), 127.0 (CH), 122.2 (CH), 116.5 (C), 111.7 (CH), 61.2 (CH_2), 54.3 (CH_2), 28.1 ($2CH_2$), 23.6 ($2CH_2$). IR: ν = 3288 (m), 3020 (m), 2800 (m), 1596 (m), 1475 (s), 1301 (m), 1253 (m), 1069 (m), 744 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{13}H_{18}N_3$ 216.1501; found: 216.1496.

4-((1,4-Dihydrocinnolin-3-yl)methyl)morpholine, **14d:** Brown oil. Yield 98 mg, 85%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (br s, 1H), 7.11 (td, *J* = 7.6, 1.5 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.93 (t, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 3.73 – 3.67 (m, 4H), 3.37 (s, 2H), 3.13 (s, 2H), 2.48 – 2.42 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 144.0 (C), 140.0 (C), 127.7 (CH), 127.1 (CH), 122.5 (CH), 116.3 (C), 111.8 (CH), 66.9 ($2CH_2$), 63.8 (CH_2), 53.7 (CH_2), 28.0 ($2CH_2$). IR: ν = 3320 (m), 2961 (w), 2858 (m), 2813 (m), 1678 (w), 1597 (m), 1476 (s), 1353 (m), 1301 (m), 1116 (s), 1005 (m), 864 (m), 752 (s). HRMS (ES-TOF)$^+$: m/z calcd for $C_{13}H_{18}N_3O$ 232.1450; found: 232.1448.