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Note

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Redox condensations of *o*-nitrobenzaldehydes with amines under mild conditions – total synthesis of the Vasicinone family

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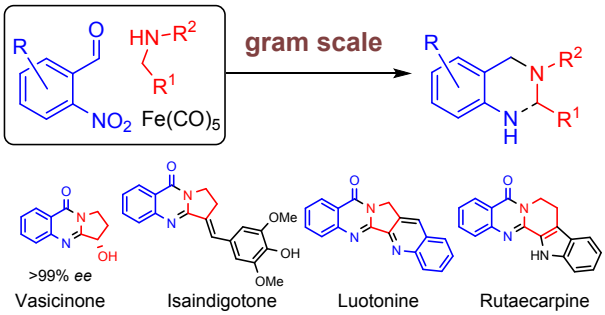
Supporting Information Placeholder



ABSTRACT: A total synthesis of the Vasicinone family of natural products from bulk chemicals was developed. Reductive condensation of *o*-nitrobenzaldehydes with amines utilizing iron pentacarbonyl as a reducing agent followed by subsequent oxidation leads to a great variety of polycyclic nitrogen-containing heterocycles under mild conditions. Enantiomerically pure Vasicinone, Rutaecarpine, Isaindigotone, and Luotonine were synthesized from readily available starting materials like hydroxyproline, nitrobenzaldehyde, pyrrolidine, and piperidine in two-four operational steps without chromatography. The anti-fungal activity of all products was tested.

Vasicinone is a natural compound (quinazoline alkaloid family) with bronchodilatory activity, which was initially isolated from *Adhatoda Vasica* Nees.[1] A substantial number of structurally related quinazolinones were isolated from natural sources or prepared synthetically.[2] These compounds possess a broad range of bioactivity, e.g. anti-tumor, anti-endotoxic, anti-fungal, etc. Some state-of-the-art approaches toward quinazolinones include transformations of complex molecules using aza-Wittig or aza-Nazarov reactions, photoredox cyclizations, reductive cyclizations of different anthranilic acid derivatives, and so on.[3] In most cases, these approaches involve multistep synthesis from complex molecules. Therefore, a direct approach that allows the synthesis of quinazolines or quinazolinones directly from readily available and inexpensive starting materials would represent a development of high synthetic value.

The initial idea of this project was to develop a total syntheses of Luotonine A and Rutaecarpine. The structure of Luotonine (Figure 1) inspired retrosynthetic breakdown into two molecules of *o*-nitrobenzaldehyde and one molecule of hydroxyproline as bulk and cheap precursors. We started with the development of reductive condensation procedures for the coupling of these molecules. The same transformation would be useful for the preparation of other members of Vasicinone family, e.g. Rutaecarpine and Isaindigotone.

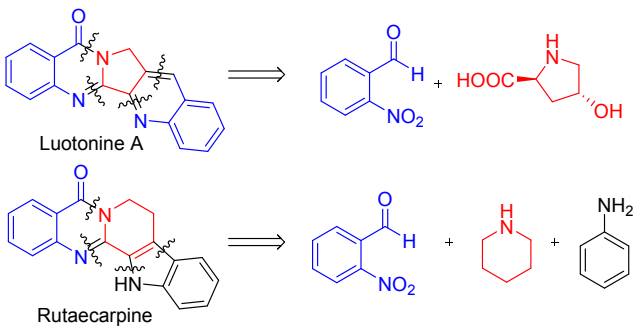
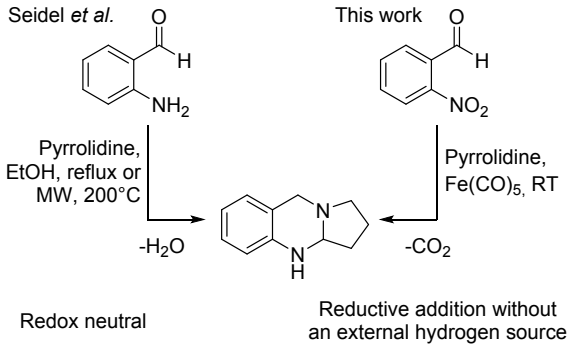


Figure 1. Retrosynthetic analysis of Luotonine A and Rutaecarpine

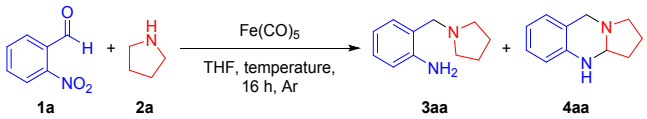
Analysis of the literature has shown that a great contribution to this field was made by Seidel et al.[4] They reported the synthesis of quinazolinones via oxidation of the corresponding quinazolines, which can be prepared from *o*-aminobenzaldehydes and pyrrolidines. However, the need to use *o*-aminobenzaldehydes as starting molecules decreased the synthetic merit of this approach. *o*-Aminobenzaldehydes are unstable compounds with very limited commercial availability (especially in bulk quantities), and Seidel's group prepared them from the corresponding *o*-aminobenzonitriles by reduction with DIBAL-H. We, therefore, designed the synthetic sequence towards quinazolines and quinazolinones to start with *o*-nitrobenzaldehyde, which is an inexpensive, stable, and readily available reagent. (Scheme 1).

Scheme 1. Approaches to quinazoline synthesis.



Metal carbonyls are selective and powerful agents for reductive organic transformations.[5] We have previously shown that iron pentacarbonyl can be used in direct reductive amination[6] and reductive condensation between CH-acids and aldehydes.[7a] Moreover, iron pentacarbonyl is inexpensive and widely available, and besides that, it is a useful compound for cancer treatment.[7b] At the same time, iron compounds are known as catalysts for CH-amination reactions, for example, conversion of *o*-substituted aryl azides to indoles.[8]

Table 1 Initial optimization experiments



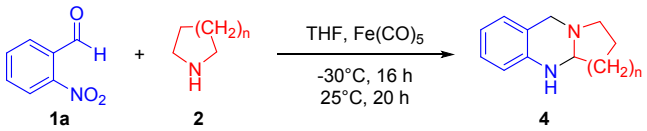
Entry	Temperature	**3aa**[a]	**4aa**[a]
1[b]	4°C	17%	75%
2[c]	25°C	25%	69%
3[c,d]	25°C	10%	34%
4[e]	40°C	27%	67%
5[e]	60°C	39%	60%
6[e]	90°C	59%	22%
7[e]	120°C	81%	traces

[a] NMR yield. [b] The reaction was carried out overnight. 1.3 mmol of **1a,** 3.9 mmol of **2a**, and 2.6 mmol of $Fe(CO)_5$ were used. See the general procedure. [c] 3.9 mmol of $Fe(CO)_5$ were used. [d] Under air. [e] 3.9 mmol of $Fe(CO)_5$ were used. 3 hours heating at indicated temperature, then overnight at room temperature.

We found that *o*-nitrobenzaldehyde can react with pyrrolidine and iron pentacarbonyl, resulting in a mixture of quinazoline product **4aa** and fully reduced aniline **3aa.** Quinazolines **4** can serve as convenient precursors to various alkaloids, so we focused our research on their synthesis. Table 1 summarizes the influence of different parameters on the reaction outcome (detailed data on the reaction optimization, side products, and possible mechanisms are provided in SI). Temperature demonstrated the strongest effect on the reaction outcome. Lower reaction temperatures led to increased amounts of quinazoline **4aa** in the reaction mixture, whereas higher temperatures favored the formation of aniline **3aa**. The inert atmosphere was also an important factor as the presence of air led to substantially inferior yields.

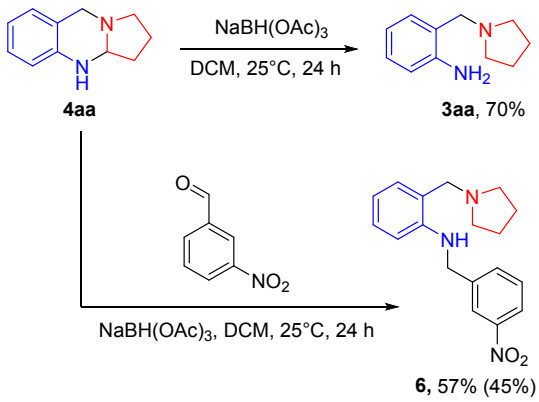
With the optimized conditions in hand, we proceeded to investigation of the substrate scope and started with the synthesis of the two products of tricyclic family **4** (**4aa** and **4ad**, scheme 2). Notably, quinazolines **4** appeared to be very sensitive to reduction: as mild of a reductant as triacetoxyborohydride[9] easily converts them into anilines **3** (scheme 3). We carried out reductive amination between quinazoline **4aa** and *m*-nitrobenzaldehyde and no other products besides compound **6** were detected.

Scheme 2. Formation of quinazoline products 4



4aa: n = 1, 73% (70%) (scaled up to 3 g)
4ad: n = 2, 70% (62%) isolated yields are in parentheses

Scheme 3 Reductive amination of quinazoline 4aa

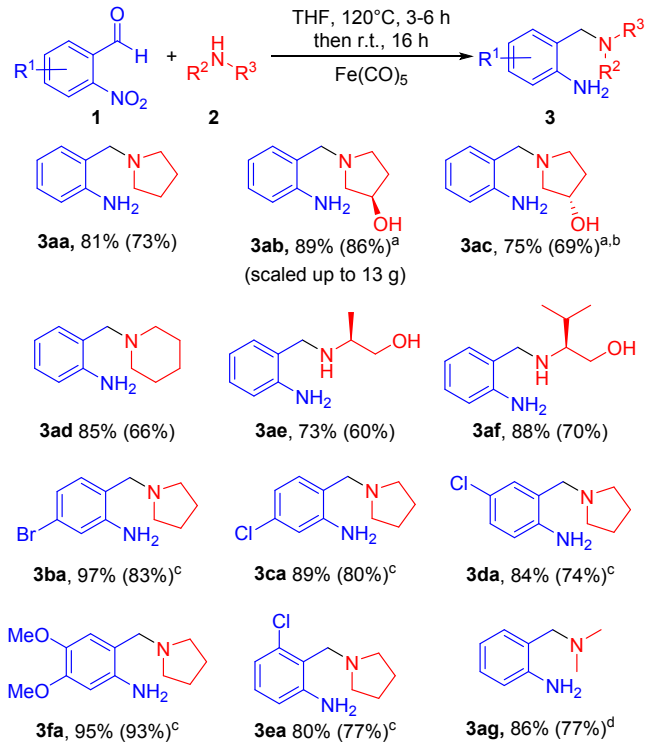


One can see from the data shown above that a greater reducing potential of the system leads to higher yields of anilines **3.** The preparation of anilines **3** was then investigated in greater detail. Various combinations of primary and secondary amines with *o*-nitrobenzaldehydes were tested and good reaction outcomes were observed regardless of the electronic properties of the substituent in the aromatic ring (Scheme 4).

Since the goal of this project was to develop a concise total synthesis of natural compounds, e.g. Luotonine A, a quinazolinone core was of greater synthetic interest versus a quinazoline one. Thus, we developed an *in situ* modification that allows obtaining molecules containing scaffold **5**. Various approaches to oxidation of quinazolines have been reported by Seidel et al.[4b,4c] Potassium permanganate appeared to be a convenient reagent to convert quinazolines into quinazolinones (stable and easy-to-handle alkaloids). We used this approach to

work up the reaction mixtures containing quinazolines **4**. As a result, different alkaloids were prepared in a single operational step from commercially available and stable *o*-nitrobenzaldehydes and secondary amines with convenient isolation of target products. This protocol is easily scalable since it does not require any rare reagents or special conditions (Scheme 5). Moreover, chromatography can be avoided in most cases since the purity of the crude products exceeded 90% even without purification. The reaction outcome was not strongly dependent on the electronic properties of substituents in the aromatic ring. Notably, the protocol tolerates bromo-substituted aromatics, which is interesting in the context of high inhibitory activities of certain bromo-substituted quinazolinone alkaloids against topoisomerases I and II.[10] Moreover, the ability to use bromo-substituted aromatics in this method opens the pathway for further modifications of the products via cross-coupling reactions. Unfortunately, oxidation with potassium permanganate could not be applied to the synthesis of quinazolinones **5** from amines **3**. In such cases, tert-butyl hydroperoxide could be used as an oxidant, which was demonstrated by preparation of compound **5ag**.

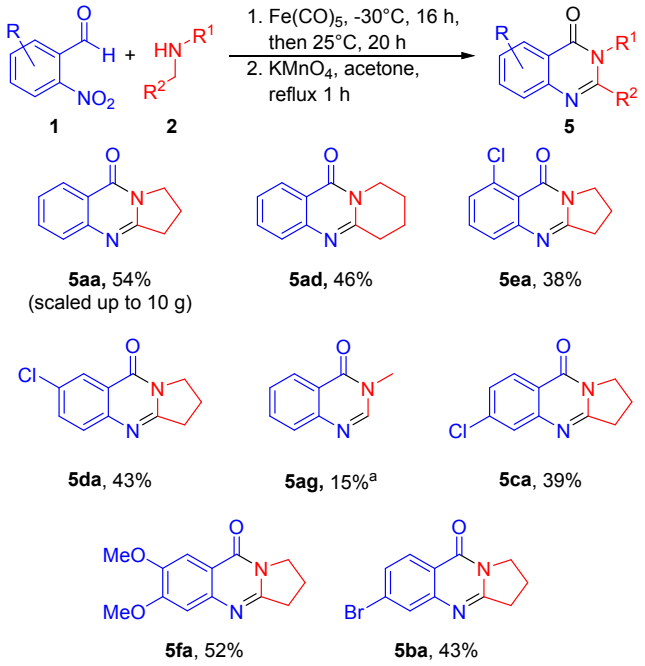
Scheme 4. Substrate scope for the synthesis of anilines 3.



3 hours heating at 120°C, then overnight at room temperature. 1.3 mmol of **1,** 3.9 mmol of **2**, and 3.9 mmol of $Fe(CO)_5$ were used. NMR yields. Isolated yields are in parentheses. [a] DMF was used as a solvent. [b] An amine was generated from corresponding hydrochloride in the reaction mixture. [c] 1.3 mmol of **1,** 6.5 mmol of **2**, and 3.9 mmol of $Fe(CO)_5$ were used. 6 hours at 120°C. [d] Initial mixing of starting molecules at -70°C, then gradual warming up to r.t. and stirring overnight at r.t. 1.3 mmol of **1,** 6.5 mmol of **2**, and 3.9 mmol of $Fe(CO)_5$ were used.

The developed protocol was applied to the preparation of some natural alkaloids and their analogs. First, natural Vasicinone and its isomers were prepared. We started from *R*-3-hydroxypyrrolidines and prepared Vasicinone and related molecules using the developed protocol with iron pentacarbonyl. The particular reaction between hydroxypyrrolidine and nitrobenzaldehyde cannot be set up in tetrahydrofuran due to the low solubility of the amine. Thus, we were unable to obtain the reaction mixture enriched with quinazoline for the oxidative treatment with potassium permanganate. We, therefore, prepared anilines **3ab** and **3ac** in high yields using DMF as a solvent and oxidized them using tert-butyl hydroperoxide. Hydroxypyrrolidine (required for the synthesis of **3ab**) can be prepared from natural *L*-hydroxyproline via one-step decarboxylation (Scheme 6).[11] Organic byproducts of the reductive condensation between *o*-nitrobenzaldehyde and hydroxypyrrolidine do not interfere with the oxidation of **3ab** to *R*-Vasicinone. The resulting *R*-Vasicinone was crystallized from the reaction mixture and therefore no chromatography was required for the entire synthetic sequence starting from *o*-nitrobenzaldehyde and *L*-hydroxyproline. Together with very low costs associated with starting materials and reagents, this fact can compensate for the low yield on the last step. All isomers of Vasicinone were prepared and isolated likewise (**5ab**, **5ac**, **5ab'**, **5ac'**). Detailed procedures and characterization are described in the experimental section.

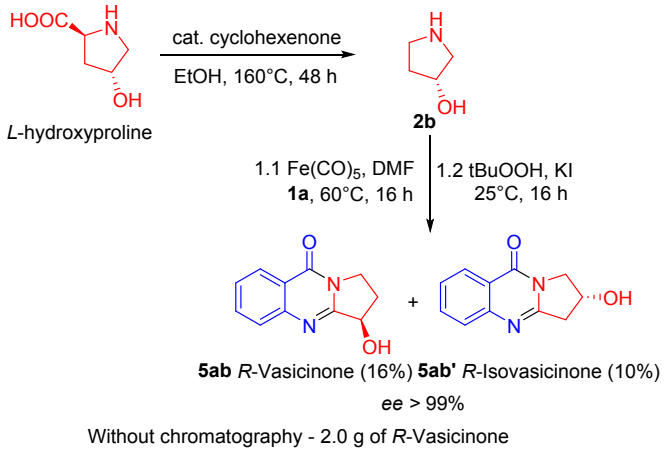
Scheme 5. Substrate scope for the one-pot synthesis of quinazolinones 5.



1.3 mmol of **1,** 3.9 mmol of **2**, and 3.9 mmol of $Fe(CO)_5$ were used. Isolated yields. [a] Prepared from **3ag** using oxidation by tBuOOH, see experimental section.

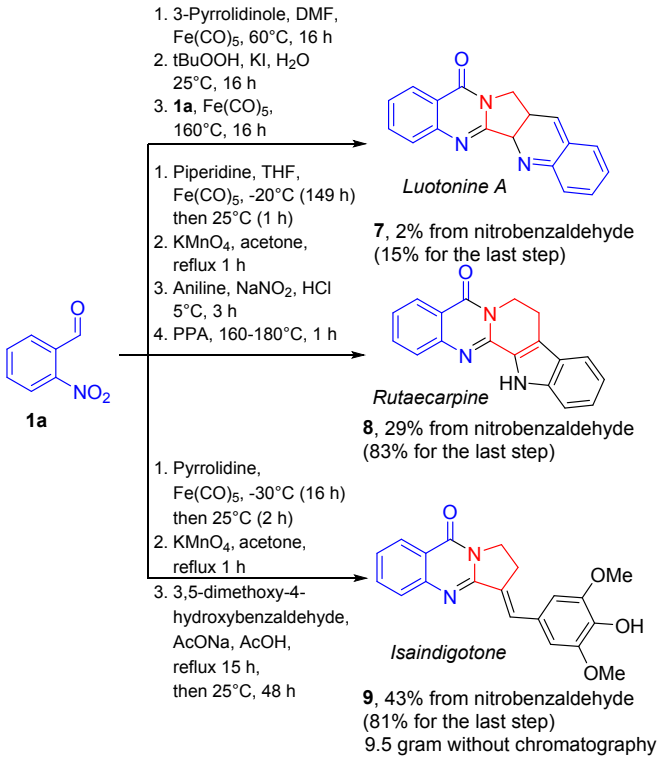
Quinazolinones **5** open a simple synthetic pathway to other alkaloids via one or two-step protocols. This was demonstrated by the preparation of Luotonine A **7**, Rutaecarpine **8**, and Isaindigotone **9**.

Scheme 6. Preparation of Vasicinone and its isomers



We developed a novel synthetic route towards Luotonine A starting from *o*-nitrobenzaldehyde and Vasicinone by using iron pentacarbonyl as a reducing agent. To the best of our knowledge, no direct condensations of this type were disclosed earlier. Thus, Luotonine was prepared from 2 molecules of *o*-nitrobenzaldehyde and one molecule of hydroxyproline in 3 operational steps (Scheme 7). Even though yields in Luotonine synthesis were lower than we expected, two new reactions were found during this work.

Scheme 7. Preparation of Luotonine A, Rutaecarpine, Bromorutaecarpine and Isaindigotone



Quinazolinones **5aa** and **5ad** were used as starting molecules for the preparation of Isaindigotone and Rutaecarpine respectively. Isaindigotone was prepared on a gram scale (9.5 g) from *o*-nitrobenzaldehyde without the need for chromatography.

Anti-fungal activity of all compounds, prepared during this work, was tested: the effect against some widespread agriculturally-relevant fungi was investigated (10 species). Compounds **6, 5ag, 3da**, Rutaecarpine **8**, and Isaindigotone **9** showed inhibitory activity, comparable to or even higher than commercially available fungicide Triadimefon. All details are provided in SI.

In conclusion, the unique reducing ability of iron pentacarbonyl allows tandem reduction of the aromatic nitro group with CH-activation of aliphatic CH-bond, leading to the formation of quinazolines or *o*-substituted anilines. Quinazolines can be oxidized *in situ* to the corresponding Vasicinone analogs thus opening a convenient and scalable way to different molecules of interesting biomedical potential. This was demonstrated by the preparation of 15 natural or synthetic alkaloids.

EXPERIMENTAL SECTION

General information

Unless otherwise stated, all reagents were purchased from commercial suppliers and were used without further purification, THF was distilled over sodium/benzophenone. DMF was distilled over CaH_2. ^1H and ^{13}C NMR spectra were recorded on Bruker AV-300, AV-400, AV-600, and Varian Inova-400 spectrometers at ambient temperature. Chemical shifts δ are reported in ppm using the solvent resonance signal as an internal standard. NMR yields were calculated with mesitylene, p-dinitrobenzene, or DMF as internal standards (unless otherwise noted). The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, p = pentet (quintet); coupling constants are given in Hertz (Hz). Chemical shifts are reported in parts per million relative to $CHCl_3$ (7.26 and 77.16 ppm for ^1H and ^{13}C respectively), DMSO (2.50 ppm for ^1H, 39.52 for ^{13}C). All ^{13}C NMR spectra were recorded with proton decoupling.

High-resolution mass spectra (HRMS) were registered on a Bruker Daltonics microTOF-Q II hybrid quadrupole time-of-flight mass spectrometer using electrospray ionization (ESI); measurements were done in positive ion mode. The voltage on the capillary was 4500 V; range of scanned masses, *m/z* 50-3000; external calibration (Electrospray Calibrant Solution; Fluka, Germany); nebulizer pressure: 0.4 bar; flow rate: 3 µl/min; nitrogen as dry gas (6 l/min); interface temperature: 180 °C.

Enantiomeric excesses were measured using Shimadzu HPLC equipped with Daicel Chiralpak IA-3 column (4.6 × 150 mm) and diode array detector. Hexane/isopropanol mixtures were used as eluent with a flow rate 1 mL/min.

Analytical gas chromatography (GC) was performed using a Chromatec Crystal 5000.2 Gas Chromatograph fitted with a flame ionization detector (He was used as the carrier gas, 37 mL/min) and MS detector. Injections were made on a Chromatec CR-5 and Chromatec CR-5MS (30 meters) capillary column. The injector temperature was 250 °C, the FID temperature was 250 °C, with a split ratio of 50:1. Column compartment temperature program: 60°C for 4 min, 60°C → 250°C at 30°C/min, 250°C for 10 min. MSD parameters: ion source temperature 200°C, transfer line temperature 230°C. Retention times (t_R) and integrated ratios were obtained using Chromatec Analytic Software.

In most cases, chromatographic isolation was done using flash chromatograph InterChim PuriFlash in DCM – MeOH binary system with UV detection. Details about particular gradient parameters for chromatography are provided for each substance.

$[\alpha]_D^{20}$ was measured using PerkinElmer polarimeter Model341 in 10 cm cell (5 mL) at 589 nm.

Unless otherwise stated, all procedures were carried out under argon atmosphere using the standard Schleck technique. When freezing of reaction mixtures below -30 ° C was needed, an acetone-liquid nitrogen bath was used. Reactions at -30°C were carried out inside a freezer. Heating was carried out using an oil bath with a controlled temperature.

A detailed description of biotests is provided in SI.

*General procedure A: Preparation of anilines **3***

Appropriate screw-cap Schlenk tube was prepared according to the standard Schlenk technique and charged with the indicated amounts of *o*-nitrobenzaldehyde, amine, and a solvent. The reaction mixture was frozen in liquid nitrogen to the solid state. After that, the indicated amount of iron pentacarbonyl was added. It is also possible to combine the reactants at -70°C or even at higher temperatures (up to -10°C), but in this case temperature control should be applied to avoid rapid warming up of the reaction. At -10°C slow addition of iron carbonyl to the reaction mixture with accurate temperature control is required. Schlenk tube was disconnected from the Schlenk line and put into an acetone-liquid nitrogen bath. The bath with the Schlenk tube was allowed to warm up to room temperature slowly. The reaction usually initiates at approx. 0°C. It is also possible to add iron pentacarbonyl to a solution of aldehyde, then freeze the solution and add amine to the frozen reaction mixture.

After warming up to room temperature, the reaction vessel was transferred to a preheated oil bath and kept at elevated temperature for the indicated time (in most cases 120°C for 3 hours). The reaction time at elevated temperatures is important. Usually, 120°C for 3-6 hours is enough. If the reaction mixture is left at this temperature overnight, products start to degrade. After cooling the reaction mixture to room temperature it was allowed to stir overnight. However, this step is not necessary, and it is possible to work up the reaction right after cooling it down. After that, the reaction mixture was quenched with a 10% HCl solution to achieve pH≈1 in the water phase. Then the resulting mixture was extracted with DCM three times (or until the organic layer became colorless). The water phase was basified with NaOH solution to pH 12 and extracted with DCM three times. In case of reactions for more than 1 mmol scale intermediate filtration from iron hydroxides may be required. The combined organic phase after the second extraction (extraction of basified solution) was dried over anhydrous sodium sulfate and concentrated under reduced pressure.

*General procedure B: Preparation of quinazolinones **5***

Appropriate screw-cap Schlenk tube was prepared according to the standard Schlenk technique and charged with the indicated amounts of *o*-nitrobenzaldehyde, amine, and a solvent. The reaction mixture was frozen in liquid nitrogen to the solid state, and the indicated amount of iron pentacarbonyl was added. It is also possible to combine the reactants at -70°C or even at higher temperatures (up to -10°C), but in this case temperature control should be applied to avoid rapid warming up of the reaction. At -10°C very slow addition of iron carbonyl to the reaction mixture with accurate temperature control is required. Schlenk tube was disconnected from the Schlenk line and put into an acetone-liquid nitrogen bath. The bath with a Schlenk tube was allowed to warm up to -30°C. After that, it was allowed to stir at this temperature overnight. It is very important to warm up the reaction mixture gradually. If the reaction mixture is warmed up to about 0°C in 30 minutes after the addition of iron pentacarbonyl, a very vigorous exothermic reaction initiates, which leads to self-heating of the reaction mixture. Concentrated reaction mixture solution (approx. 5 mmol/mL), being allowed to warm up too fast, emits as much heat as it is needed to boil the DMF, used as a solvent. This leads to the preferential formation of anilines **3** with only traces of quinazolines **4.** Products **4** are unstable at elevated temperatures in the presence of iron pentacarbonyl and transforms into products **3** under these conditions. After stirring at -30°C overnight the reaction vessel was allowed to warm up to room temperature and then stirring was continued for 20 hrs.

After that, the reaction mixture was quenched with 10% HCl solution to achieve pH≈1 in the water phase. Then the resulting mixture was extracted with DCM three times (or until the organic layer became colorless). The water phase was basified with NaOH solution to pH 12 and extracted with DCM three times. In case of reactions for more than 1 mmol scale intermediate filtration from iron hydroxides may be required. The combined organic phase after the second extraction (extraction of basified solution) was dried over sodium sulfate and concentrated under reduced pressure. GC and NMR analyses of the resulting mixture show that it contains mostly quinazoline **4** with 20-50% of aniline **3** and 10-15% of deoxyvasicine.

Then the organic residue was dissolved in acetone and 10 equivalents of $KMnO_4$, which was grinded to a thin powder beforehand, were added. The reaction mixture was refluxed for the indicated time under air. GCMS analysis was used to check the completeness of reaction. Usually, 1 hour is enough to achieve complete oxidation to quinazolinone **5**. Three hours of reflux was enough in all cases. It is not recommended to leave this reaction mixture overnight as deoxyvasicine, deoxyvasicione and other amines present in this reaction mixture are more or less strong bases. For example, deoxyvasicine **4'** is structurally similar to DBU. They can catalyze acetone self-aldol reaction, leading to 4-hydroxy-4-methylpentan-2-one formation, which was detected in all reactions of this type. After the reaction was complete, $KMnO_4$ and MnO_2 residues were filtered off, and acetone was removed under reduced pressure.

In some cases, the solution has a violet color after filtration as it contains small amounts of dissolved $KMnO_4$. In this case, isopropyl alcohol can be added to reduce the soluble $KMnO_4$ to insoluble MnO_2. After that, removal of the solvents in a vacuum, dissolving of the organic residue in DCM and the second filtration of the resulting solution is needed.

4-hydroxy-4-methylpentan-2-one can be removed under a high vacuum with heating (its boiling point is 166°C at normal pressure) or separated chromatographically. Quinazolinones **5** can be purified by standard laboratory techniques or used as-is for further modifications since their purity after described workup is about 80-90%.

Synthesis of quinazolines 4

*1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline (**4aa**)*

25 mL Schlenk tube was prepared according to the standard Schlenk technique and charged with *o*-nitrobenzaldehyde (128.6 mg, 100 mol%, 0.85 mmol), pyrrolidine (349 µL, 300 mol%, 4.25 mmol) and 5 mL of THF. The reaction mixture was frozen in liquid nitrogen to the solid state, and iron pentacarbonyl (344 µL, 300 mol%, 2.6 mmol) was added. Schlenk tube was disconnected from the Shlenk line and put into an acetone-liquid nitrogen bath. The bath with a Schlenk tube was allowed to warm up to -30°C and the mixture was stirred at this temperature overnight. After overnight stirring at -30°C reaction vessel was allowed to warm to room temperature and stirring was continued for an additional 20 hrs. Some additional experimental details and considerations are provided in General procedure B.

The reaction mixture was quenched with 10% HCl solution to achieve pH of water phase around 1, resulting mixture was extracted with DCM three times (or until colorless organic layer), water phase was basified with NaOH solution to pH 12 and extracted with DCM three times. Combined organic phase after the second extraction (extraction of basified solution) was dried over anhydrous sodium sulfate and concentrated under reduced pressure. 74% yield by NMR. 15% of **3aa** was also detected in the reaction mixture. Pure product was isolated by column chromatography to yield 94 mg (63%) of **4aa** as a yellowish solid (eluent: hexane:ethyl acetate:triethylamine = 1:2:0.3, Rf 0.4). Melting point 63-64°C. (lit. melting point 63-64°C) [12]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.02 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.70 (t, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 7.9 Hz, 1H), 4.18 – 4.11 (m, 1H), 4.04 (d, *J* = 15.6 Hz, 1H), 3.90 (d, *J* = 15.6 Hz, 1H), 3.85 – 3.67 (br s, 1H), 3.03 (td, *J* = 8.8, 5.5 Hz, 1H), 2.68 (dt, *J* = 8.8, 5.5 Hz, 1H), 2.19 – 2.07 (m, 1H), 2.05 – 1.84 (m, 2H), 1.66 (ddt, *J* = 12.2, 10.2, 4.4 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 143.1, 127.4, 127.2, 119.6, 118.2, 115.1, 71.4, 50.7, 50.4, 32.0, 21.3.

NMR spectra are in accordance with literature data. [4a]

*Gram scale synthesis of **4aa***

250 mL Schlenk tube was prepared according to the standard Schlenk technique and charged with *o*-nitrobenzaldehyde (3 g, 100 mol%, 19.85 mmol), pyrrolidine (4.89 mL, 300 mol%, 59.55 mmol) and 50 mL of THF. The reaction mixture was frozen in liquid nitrogen to the solid state, and iron pentacarbonyl (8.05 mL, 300 mol%, 59.55 mmol) was added. Schlenk tube was disconnected from the Shlenk line and put into an acetone-liquid nitrogen bath. The bath with a Schlenk tube was allowed to warm up to -30°C and the mixture was stirred at this temperature overnight. After overnight stirring at -30°C reaction vessel was allowed to warm to room temperature and stirring was continued for an additional 20 hrs. Some additional experimental details and considerations are provided in General procedure B.

The reaction mixture was quenched with 10% HCl solution to achieve pH of water phase around 1, resulting mixture was extracted with DCM three times (or until colorless organic layer), the water phase was basified with NaOH solution to pH 12 and extracted with DCM three times. The combined organic phase after the second extraction (extraction of basified solution) was dried over anhydrous sodium sulfate and concentrated under reduced pressure. 73% yield by NMR. 14% of **3aa** was also detected in the reaction mixture. The pure product was isolated by column chromatography to yield 2.42 g (70%) of **4aa** as a yellowish solid (eluent: hexane:ethyl acetate:triethylamine = 1:2:0.3, Rf 0.4). Characterization is provided above with the milligram scale synthesis.

*5a,6,7,8,9,11-hexahydro-5H-pyrido[2,1-b]quinazoline (**4ad**)*

Schlenk tube was prepared according to the standard Schlenk technique and charged with *o*-nitrobenzaldehyde (2.0 g, 100 mol%, 13.23 mmol), piperidine (3.92 mL, 300 mol%, 39.70 mmol) and 50 mL of THF. The reaction mixture was frozen in acetone-liquid nitrogen bath to the solid state, and iron pentacarbonyl (5.33 mL, 300 mol%, 39.70 mmol) was added. Reaction mixture was slowly warmed up (-110°C → -20°C for 8 h) and stirred (149 h (-20°C) → 2h (0°C) → 1h (r.t)) until dark brown color developed.

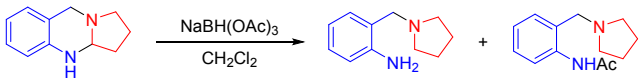
The reaction mixture was quenched with 10% HCl solution to achieve pH of water phase around 1, resulting mixture was extracted with DCM three times (or until colorless organic layer), the water phase was basified with NaOH solution to pH 12 and extracted with DCM three times. The combined organic phase after the second extraction (extraction of basified solution) was dried over anhydrous sodium sulfate and concentrated under reduced pressure. 70% yield by NMR. 20% of **4aa** was also detected in the reaction mixture. The obtained dark yellow oil was purified by column chromatography (eluent: hexane:ethyl acetate:triethylamine = 1:2:0.1 Rf 0.3) to afford 1.52 g (62%) of the product as a slightly yellow solid. Melting point 71-73°C (lit. melting point 71-72°C).[13]

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.01 (t, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 7.3 Hz, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 1H), 3.84 – 3.79 (br s, 1H), 3.79 – 3.70 (m, 3H), 3.10 – 3.03 (m, 1H), 2.29 – 2.22 (m, 1H), 1.97 – 1.90 (m, 1H), 1.83 – 1.76 (m, 1H), 1.76 – 1.71 (m, 2H), 1.62 – 1.54 (m, 1H), 1.52 – 1.43 (m, 1H).

^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ 141.9, 127.6, 126.9, 119.3, 118.3, 114.7, 70.4, 56.1, 52.1, 31.8, 25.3, 21.6.

NMR spectra are in accordance with literature data.[13]

Reduction of 1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline with sodium triacetoxyborohydride



4aa **3aa** **Ac-3aa**

A 10 mL vial was charged with sodium triacetoxyborohydride (182.5 mg, 300 mol%, 0.861 mmol) and a solution of 1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline **4aa** (50 mg, 100 mol%, 0.287 mmol) in DCM (1 mL) under air. The reaction mixture was stirred at room temperature for 24 h, then quenched by adding an aqueous saturated solution of $NaHCO_3$ (3 mL) and the product was extracted with EtOAc (3x5 mL), dried with anhydrous Na_2SO_4, and the solvent was evaporated to give an yellow oil. 70% NMR yield of aniline **3aa** and 15% of acylated byproduct **Ac-3aa**.

NMR spectra (full characterization is provided in corresponding section):

3aa: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.13 – 7.04 (m, 1H), 7.03 – 6.97 (m, 1H), 6.70 – 6.58 (m, 2H), 4.94 – 4.52 (br s, 2H), 3.62 (s, 2H), 2.50 – 2.43 (m, 4H), 1.80 – 1.72 (m, 4H).

Ac-3aa: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.13 – 10.90 (br s, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 7.33 – 7.24 (m, 1H), 7.13 – 7.04 (m, 1H), 7.02 – 6.94 (m, 1H), 3.70 (s, 2H), 2.57 – 2.51 (m, 4H), 2.13 (s, 3H), 1.88 – 1.80 (m, 4H).

*N-(3-nitrobenzyl)-2-(pyrrolidin-1-ylmethyl)aniline (**6**)*

A 10 mL vial was charged with sodium triacetoxyborohydride (182.5 mg, 300 mol%, 0.861 mmol), a solution of 1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazoline **4aa** (50 mg, 100 mol%, 0.287 mmol) and 3-nitrobenzaldedhyde (52 mg, 150 mol%, 0.344 mmol) in DCM (1 mL). The reaction mixture was stirred at the room temperature for 24h, then quenched by adding an aqueous saturated solution of $NaHCO_3$ (3 mL) and the product was extracted with EtOAc (3x5mL), dried with anhydrous Na_2SO_4, and the solvent was evaporated to give an orange oil. 57% yield by NMR. Product was purified by column chromatography (eluent: hexane:ethyl acetate:triethylamine = 3:1:0.01, Rf 0.3) to afford 40 mg (45%) of the product as yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.49 (dd appears as t, *J* = 7.9 Hz, 1H), 7.20 – 7.08 (br s, 1H), 7.08 (dd appears as t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.63 (dd appears as t, *J* = 7.3 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 4.49 (s, 2H), 3.69 (s, 2H), 2.57 – 2.43 (m, 4H), 1.84 – 1.73 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 148.7, 147.4, 142.9, 133.2, 129.6, 129.5, 128.4, 123.9, 122.1, 121.8, 116.8, 110.1, 60.0, 53.8, 46.7, 23.8.

HRMS: Calculated for $C_{18}H_{22}N_3O_2^+$ ([M+H]$^+$): 312.1707; Found: 312.1703

Synthesis of anilines 3

*2-(pyrrolidin-1-ylmethyl)aniline (**3aa**)*

Some important general details are described in general procedure A. A dry 25 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 2-Nitrobenzaldehyde (200 mg, 100 mol%, 1.32 mmol) and pyrrolidine (326 µL, 300 mol%, 3.97 mmol) in 4 mL of THF were added. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (536 µL, 300 mol%, 3.97 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 120 °C. After 4 h of heating, the reaction mixture was cooled to room temperature and stirred during 16 h (overnight). The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (2 mL) and distilled water (30 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×30 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (4×30 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. 81% yield by NMR. The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.6 in 10:1 DCM:MeOH) to afford 172 mg (73%) of the product **3aa** as a slightly yellow solid. Melting point 32-34°C (lit. melting point 31-32°C).[14] Alternatively this product can be purified by preparative thin-layer chromatography (eluent = ethyl acetate:hexane:triethylamine = 13.3:6.6:1; Rf 0.52).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 (t, *J* = 7.71 Hz, 1H), 7.01 (d, *J* = 7.33, 1H), 6.68-6.63 (m, 2H), 4.80-4.62 (br s, 2H), 3.62 (s, 2H), 2.49-2.46 (m, 4H), 1.78-1.73 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 147.0, 129.8, 128.2, 123.9, 117.6, 115.4, 59.4, 53.8, 23.7.

NMR spectra are in accordance with literature data. [15]

*(R)-1-(2-aminobenzyl)pyrrolidin-3-ol (**3ab**)*

Some important general details are described in general procedure A. A dry 100 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 2-Nitrobenzaldehyde (1.0 g, 100 mol%, 6.62 mmol), *(R)*-pyrrolidinol (1.73 g, 300 mol%, 19.85 mmol, >99% enantiomeric purity) (may be prepared by decarboxylation of chiral hydroxyproline or pursued; procedure for decarboxylation is provided in the section about Vasicinone preparation) and 40 mL of DMF were added. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (2.68 mL, 300 mol%, 19.85 mmol) was added under argon atmosphere to a frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 60°C and stirred at this temperature overnight. The reaction mixture was quenched with conc. HCl (10 mL) and distilled water (100 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×50 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (4×50 mL). Filtration from iron hydroxides may be required. The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 89%. The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.4 in 10:1 DCM:MeOH) to afford 1.030 g (86%) as a white solid. Melting point 72-73°C. ($[\alpha]^D_{20}$ = +6.5°, 10.3 mg/mL in $CHCl_3$).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 6.71 – 6.60 (m, 2H), 4.35 (s, 1H), 4.14 – 3.76 (br s, 2H), 3.66 (d, *J* = 12.9 Hz, 1H), 3.61 (d, *J* = 12.9 Hz, 1H), 2.83 (q, *J* = 7.5, 6.7 Hz, 1H), 2.66 – 2.52 (m, 2H), 2.34 (q, *J* = 8.1 Hz, 1H), 2.23 – 2.10 (m, 1H), 1.73 (dt, *J* = 14.1, 7.2 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 146.7, 129.9, 128.4, 123.5, 117.8, 115.6, 71.5, 62.8, 59.2, 52.4, 35.1.

Chiral HPLC: Cellucoat 3 column; 1 mL/min heptane/isopropanol: 95/5; detection at 240 nm. t_R (R) = 17.8 min, t_R (S) = 20.9 min, ee > 99%.

NMR spectra are in accordance with the literature data.[16]

*(S)-1-(2-aminobenzyl)pyrrolidin-3-ol (**3ac**)*

Some important general details are described in general procedure A. A dry 100 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. *(S)*-pyrrolidinol hydrochloride (4.91 g, 300 mol%, 39.70 mmol, >99% enantiomeric purity), potassium tert-butoxide (4.46 g, 300 mol%, 39.70 mmol) and 50 mL of DMF were added. Resulting suspension was stirred for 30 min. 2-Nitrobenzaldehyde (2.0 g, 100 mol%, 13.23 mmol) was added. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (5.36 mL, 300 mol%, 39.70 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 60°C and stirred at this temperature overnight. The reaction mixture was quenched with conc. HCl (10 mL) and distilled water (100 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×50 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (4×50 mL). Filtration from iron

hydroxides may be required. The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 75%. The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.4 in 10:1 DCM:MeOH) to afford 1.75 g (69%) as a white solid. Melting point 73-74°C. ($[\alpha]^D_{20}$ = -3.7°, 4.3 mg/mL in $CHCl_3$).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.08 (td, *J* = 7.4, 1.6 Hz, 1H), 7.00 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.71 – 6.60 (m, 2H), 4.31 (ddt, *J* = 7.7, 5.3, 2.7 Hz, 1H), 4.90 – 3.01 (br s, 2H), 3.62 (d, *J* = 12.9 Hz, 1H), 3.57 (d, *J* = 12.9 Hz, 1H), 2.82 – 2.73 (m, 1H), 2.60 – 2.44 (m, 2H), 2.28 (td, *J* = 8.8, 6.4 Hz, 1H), 2.20 – 2.07 (m, 1H), 1.74 – 1.61 (m, 1H).

^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 146.5, 129.8, 128.4, 123.5, 117.9, 115.6, 71.2, 62.7, 59.1, 52.4, 34.9.

Chiral HPLC: Cellucoat 3 column; 1 mL/min heptane/isopropanol: 95/5; detection at 240 nm. t_R (R) = 17.8 min, t_R (S) = 20.9 min, ee > 99%

NMR spectra are in accordance with literature data. [17]

*2-(piperidin-1-ylmethyl)aniline (**3ad**)*

Some important general details are described in general procedure A. A dry 25 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 2-Nitrobenzaldehyde (150 mg, 100 mol%, 1 mmol), iron pentacarbonyl (400 µL, 300 mol%, 3 mmol) and THF (2 mL) were added. The reaction mixture was frozen with liquid nitrogen up to solid state. Piperidine (293 µl, 300 mol%, 3 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 120 °C. After 3 h of heating, the reaction mixture was cooled up to room temperature and stirred during 16 h. The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (2 mL) and distilled water (10 mL) (pH 1-2). This mixture was extracted with dichloromethane (2×5 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (4×10 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 85%. The residue was purified by preparative gradient column chromatography (eluent = EtOAc:hexane (1/100) → (100/1), Rf 0.5) to afford 124 mg (66%) of the product as a slightly yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 1H), 6.68-6.63 (m, 2H), 5.02 – 4.93 (br s, 2H), 3.50 (s, 2H), 2.44-2.34 (m, 4H), 1.59-1.53 (m, 4H), 1.48-1.42 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 147.2, 130.6, 128.4, 122.4, 117.5, 115.6, 62.6, 54.1, 26.1, 24.5.

NMR spectra are in accordance with literature data. [18]

*2-((2-aminobenzyl)amino)propan-1-ol (**3ae**)*

Some important general details are described in general procedure A. A dry 25 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 2-Nitrobenzaldehyde (150 mg, 100 mol%, 1 mmol), iron pentacarbonyl (400 µL, 300 mol%, 3 mmol) and THF (2 mL) were added. The reaction mixture was frozen with liquid nitrogen up to solid state. *(S)*-(+)-2-amino-1-propanol (232 µl, 300 mol%, 3 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 120 °C. After 3 h of heating, the reaction mixture was cooled up to room temperature and stirred during 16 h. The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (1 mL) and distilled water (10 mL) (pH 1-2). This mixture was extracted with dichloromethane (2×5 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (4×10 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 73% (with mesitylene as internal standard). The residue was purified by preparative thin-layer chromatography (eluent = ethyl acetate:hexane:triethylamine = 33.3:6.6:1, R_f = 0.48) to afford 108 mg (60%) of the product as a white solid. ($[\alpha]^D_{20}$ = +4.9°, 4.5 mg/mL in $CHCl_3$). Melting point 81-82°C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.72-6.66 (m, 2H), 3.91 (d, *J* = 12.5 Hz, 1H), 3.74 (d, *J* = 12.5 Hz, 1H), 3.61 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.35 (dd, *J* = 10.7, 7.1 Hz, 1H), 3.45 – 3.02 (br s, 3H), 2.87-2.79 (m, 1H), 1.11 (d, *J* = 6.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 146.3, 130.1, 128.7, 124.0, 118.2, 116.1, 66.2, 54.3, 49.9, 16.9.

NMR spectra are in accordance with literature data. [19]

*2-((2-aminobenzyl)amino)-3-methylbutan-1-ol (**3af**)*

Some important general details are described in general procedure A. A dry 25 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 2-Nitrobenzaldehyde (150 mg, 100 mol%, 1 mmol), iron pentacarbonyl (400 µL, 300 mol%, 3 mmol) and THF (2 mL) were added. The reaction mixture was frozen with liquid nitrogen up to solid state. *(S)*-(+)-2-Amino-3-methyl-1-butanol (328 µl, 300 mol%, 3 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 120°C. After 3 h of heating, the reaction mixture was cooled up to room temperature and stirred during 16 h. The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (1 mL) and distilled water (10 mL) (pH 1-2). This mixture was extracted with dichloromethane (2×5 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (4×10 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 88%. (with mesitylene as internal standard, average of two experiments). The residue was purified by preparative thin-layer chromatography (eluent = ethyl acetate:hexane:triethylamine = 13.3:6.6:1, R_f = 0.5) to afford 143 mg (70%) of the product as a beige solid. ($[\alpha]^D_{20}$ = +19°, 4.8 mg/mL in $CHCl_3$). Melting point 54-56°C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.10 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.72-6.76 (m, 2H), 3.84 (d, *J* = 12.5 Hz, 1H), 3.78 (d, *J* = 12.5 Hz, 1H), 3.65 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.46 (dd, *J* = 10.9, 6.8 Hz, 1H), 3.52 – 3.14 (br s, 3H), 2.46-2.42 (m, 1H), 1.90 (dq, *J* = 13.2, 6.7 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 146.3, 130.1, 128.6, 124.3, 118.2, 116.1, 64.1, 61.3, 50.5, 28.7, 19.3, 18.7.

HRMS: Calculated for $C_{12}H_{21}N_2O^+$ ([M+H]$^+$): 209.1648; Found: 209.1648.

*5-bromo-2-(pyrrolidin-1-ylmethyl)aniline (**3ba**)*

Some important general details are described in general procedure A. A dry 25 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 4-bromo-2-nitrobenzaldehyde (150 mg, 100 mol%, 0.65 mmol), iron pentacarbonyl (263 µL, 300 mol%, 1.97 mmol) and THF (2 mL) were added. The reaction mixture was frozen with liquid nitrogen up to solid state. Pyrrolidine (268 µl, 500 mol%, 3.26 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 120 °C. After 6 h of heating, the reaction mixture was cooled up to room temperature and stirred overnight. The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (3 mL) and distilled water (20 mL) (pH 1-2). This mixture was extracted with dichloromethane (2×20 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (3×20 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 97% (with 1,4-dinitrobenzene as internal standard). The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.3 in 10:1 DCM:MeOH). Isolation using preparative TLC is also possible (for TLC: R_f = 0.58 in hexane:ethyl acetate:triethylamine = 5:1:0.3) to afford 138 mg (83%) as a beige solid. Melting point 38-39°C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.85 (d, *J* = 7.6 Hz, 1H), 6.76-6.74 (m, 2H), 4.99-4.80 (br s, 2H), 3.55 (s, 2H), 2.44 (m, 4H), 1.75 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 148.5, 130.9, 122.9, 121.6, 120.2, 117.8, 59.1, 53.7, 23.8.

HRMS: Calculated for $C_{11}H_{16}BrN_2^+$ ([M+H]$^+$): 255.0491; Found: 255.0494

*5-chloro-2-(pyrrolidin-1-ylmethyl)aniline (**3ca**)*

Some important general details are described in general procedure A. A dry 25 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 4-chloro-2-nitrobenzaldehyde (150 mg, 100 mol%, 0.81 mmol), iron pentacarbonyl (326 µL, 300 mol%, 2.43 mmol) and THF (2 mL) were added. The reaction mixture was frozen with liquid nitrogen up to solid state. Pyrrolidine (332 µl, 500 mol%, 4.04 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 120 °C. After 6 h of heating, the reaction mixture was cooled up to room temperature and stirred overnight. The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (3 mL) and distilled water (20 mL) (pH 1-2). This mixture was extracted with dichloromethane (2×20 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (3×20 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 89% (with 1,4-dinitrobenzene as internal standard). The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.3 in 10:1 DCM:MeOH) to afford 136 mg (80%) as a beige solid. Melting point 41-43°C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.92 (d, *J* = 8.4 Hz, 1H), 6.63-6.62 (m, 2H), 5.06-4.74 (br s, 2H), 3.59 (s, 2H), 2.46 (m, 4H), 1.77 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 148.3, 133.5, 130.6, 122.5, 117.3, 115.0, 59.1, 53.8, 23.8.

HRMS: Calculated for $C_{11}H_{16}ClN_2^+$ ([M+H]$^+$): 211.0997; Found: 211.0997.

*4-chloro-2-(pyrrolidin-1-ylmethyl)aniline (**3da**)*

Some important general details are described in general procedure A. A dry 25 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 5-chloro-2-nitrobenzaldehyde (150 mg, 100 mol%, 0.81 mmol), iron pentacarbonyl (326 µL, 300 mol%, 2.43 mmol) and THF (2 mL) were added. The reaction mixture was frozen with liquid nitrogen up to solid state. Pyrrolidine (332 µl, 500 mol%, 4.04 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 120°C. After 6 h of heating, the reaction mixture was cooled up to room temperature and stirred overnight. The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (3 mL) and distilled water (20 mL) (pH 1-2). This mixture was extracted with dichloromethane (2×20 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (3×20 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 84% (with 1,4-dinitrobenzene as internal standard). The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.6 in 10:1 DCM:MeOH) to afford 125 mg (74%) as a beige solid. Melting point 65-66°C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03-6.98 (m, 2H), 6.54 (d, *J* = 9.8 Hz, 1H), 4.99-4.56 (br s, 2H), 3.55 (s, 2H), 2.45 (m, 4H), 1.76 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 145.6, 129.3, 127.8, 125.6, 121.9, 116.3, 59.1, 53.8, 23.8.

HRMS: Calculated for $C_{11}H_{16}ClN_2^+$ ([M+H]$^+$): 211.0997; Found: 211.0994

*4,5-dimethoxy-2-(pyrrolidin-1-ylmethyl)aniline (**3fa**)*

Some important general details are described in general procedure A. A dry 25 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 4,5-dimethoxy-2-nitrobenzaldehyde (150 mg, 100 mol%, 0.71 mmol), iron pentacarbonyl (287 µL, 300 mol%, 2.13 mmol) and THF (2 mL) were added. The reaction mixture was frozen with liquid nitrogen up to solid state. Pyrrolidine (175 µl, 300 mol%, 2.13 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 120 °C. After 6 h of heating, the reaction mixture was cooled up to room temperature and stirred overnight. The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (3 mL) and distilled water (20 mL) (pH 1-2). This mixture was extracted with dichloromethane (2×20 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with

dichloromethane (3×20 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 95% (with 1,4-dinitrobenzene as internal standard). The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.6 in 10:1 DCM:MeOH) to afford 164 mg (93%) as a beige solid. Melting point 81-82°C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.58 (s, 1H), 6.25 (s, 1H), 4.81-4.03 (br s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.53 (s, 2H), 2.45 (m, 4H), 1.74 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 149.1, 141.0, 140.8, 115.4, 114.9, 100.8, 59.0, 57.0, 55.9, 53.8, 23.7.

HRMS: Calculated for $C_{13}H_{21}N_2O_2^+$ ([M+H]$^+$): 237.1598; Found: 237.1597

*3-chloro-2-(pyrrolidin-1-ylmethyl)aniline (**3ea**)*

Some important general details are described in general procedure A. A dry 25 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 2-chloro-6-nitrobenzaldehyde (150 mg, 100 mol%, 0.81 mmol), iron pentacarbonyl (326 µL, 300 mol%, 2.43 mmol) and THF (2 mL) were added. The reaction mixture was frozen with liquid nitrogen up to solid state. Pyrrolidine (332 µl, 500 mol%, 4.04 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 120 °C. After 6 h of heating, the reaction mixture was cooled up to room temperature and stirred overnight. The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (3 mL) and distilled water (20 mL) (pH 1-2). This mixture was extracted with dichloromethane (2×20 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (3×20 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 80% (with 1,4-dinitrobenzene as internal standard). The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.7 in 10:1 DCM:MeOH) to afford 130 mg (77%) as a beige oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.96 (t, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 7.9 Hz, 1H), 5.13-4.85 (br s, 2H), 3.85 (s, 2H), 2.52 (m, 4H), 1.76 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 149.0, 134.3, 128.4, 121.1, 118.7, 114.0, 53.9, 53.5, 23.8.

HRMS: Calculated for $C_{11}H_{16}ClN_2^+$ ([M+H]$^+$): 211.0997; Found: 211.0997

*2-((dimethylamino)methyl)aniline (**3ag**)*

Some important general details are described in general procedures A and B. A dry 25 mL screw-cap Schlenk tube with a magnetic stirring bar was flushed with argon three times. 200 mg (1.32 mmol) of 2-nitrobenzaldehyde and dimethylamine solution in THF (3.68 mL of 1.8 M solution, 6.62 mmol, 500 mol%) were added. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (536 µL, 300 mol%, 3.97 mmol) were added under argon atmosphere to the frozen mixture. Schlenk tube was disconnected from the Shlenk line, and put into the acetone-liquid nitrogen bath. The bath with a Schlenk tube was allowed to warm up to -30°C and stirred at this temperature overnight. It is very important to warm up reaction mixture gradually. Details are provided in general procedure B. After overnight stirring at -30°C reaction vessel was allowed to warm to room temperature and stirring was continued for 20 hrs. The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (2 mL) and distilled water (30 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×30 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (4×30 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. 86% yield by NMR The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.7 in 10:1 DCM:MeOH) to afford 153 mg (77%) of the product **3ag** as a slightly yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 (td, *J* = 7.6, 1.6 Hz, 1H), 6.98 (dd, *J* = 7.3, 1.5 Hz, 1H), 6.69 – 6.62 (m, 2H), 4.82 – 4.61 (br s, 2H), 3.41 (s, 2H), 2.19 (s, 6H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 147.2, 130.3, 128.4, 123.4, 117.6, 115.5, 63.5, 45.1.

NMR spectra are in accordance with the literature data. [20]

Synthesis of quinazolinones 5

*2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (**5aa**)*

6 mmol (0.5 g) scale synthesis is provided here. 10 g scale synthesis is provided in the section about Isaindigotone preparation. 50 mL Schlenk tube with a magnetic stirring bar was prepared according to the standard Schlenk technique and charged with *o*-nitrobenzaldehyde (900 mg, 100 mol%, 6 mmol), pyrrolidine (1.48 mL, 300 mol%, 18 mmol) and 12 mL of THF. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (2.42 mL, 300 mol%, 18 mmol) was added under argon atmosphere to a frozen mixture. Schlenk tube was disconnected from the Schlenk line, and put into the acetone-liquid nitrogen bath. The bath with a Schlenk tube was allowed to warm up to -30°C and stirred at this temperature overnight. It is very important to warm up reaction mixture gradually. Details are provided in general procedure B. After overnight stirring at -30°C reaction vessel was allowed to warm to room temperature and stirring was continued for 20 hrs.

The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (4.5 mL) and distilled water (20 mL) (to pH 1-2). This mixture was extracted with dichloromethane (2×10 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (4×20 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. The mixture of **3aa** and **4aa** was obtained in the ratio 1/5 (m = 853 mg, 82%) as a yellowish solid. It was used in the next step without additional purification.

This organic residue was dissolved in 50 mL of acetone, put into a round-bottom flask (100 mL), and $KMnO_4$ (9.5 g, 1000 mol%, 60 mmol), grinded to thin powder, was added. The reaction mixture was refluxed for 1 hour. Some additional details are provided in general procedure B. After the reaction was complete, $KMnO_4$ and MnO_2 residues were filtered off, and acetone was removed at reduced pressure. The crude product has a purity around 90%. It was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30

min, Rf 0.6 in 10:1 DCM:MeOH) to get 598 mg (54% from nitrobenzaldehyde) as a white solid. Melting point 110-115°C (lit. melting point 105-107°C).[4a]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 4.21 (t, *J* = 7.3 Hz, 2H), 3.18 (t, *J* = 8.0 Hz, 2H), 2.29 (p, *J* = 7.8 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 161.1, 159.5, 149.2, 134.2, 126.8, 126.4, 126.3, 120.5, 46.6, 32.6, 19.6.

NMR spectra are in accordance with literature data.[4a]

*6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one (**5ad**)*

A round-bottom flask (250 mL) was charged with **4ad** (1.2 g, 100 mol%, 63.74 mmol) and 100 mL of acetone. $KMnO_4$ (15.11 g, 500 mol%, 95.61 mmol) was grinded to powder and added to the reaction mixture. It was refluxed for 4 h (the reaction was monitored by TLC). Then the reaction mixture was filtered to separate from MnO_2. The dark purple solution was evaporated under reduced pressure. DCM was added to the rest of reaction mixture and insoluble MnO_2 was filtered off through a pad of silica gel. The orange solution was evaporated under reduced pressure. The product was obtained as slightly yellow solid (592 mg) in 46% yield. TLC (eluent: hexane:ethyl acetate:triethylamine = 1:2:0.1, Rf 0.43). Melting point 79-82°C (lit. melting point 81-83°C).[21]

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.11 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.58 (td, *J* = 7.6, 1.5 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 3.94 (t, *J* = 6.3 Hz, 2H), 2.87 (t, *J* = 6.7 Hz, 2H), 1.86 (dq, *J* = 32.1, 6.3 Hz, 4H).

^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ 161.9, 154.8, 147.1, 134.0, 126.4, 126.1, 125.9, 120.2, 42.2, 31.7, 21.9, 19.2.

NMR spectra are in accordance with literature data.[21]

*8-chloro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (**5ea**)*

25 mL Schlenk tube with a magnetic stirring bar was prepared according to the standard Schlenk technique and charged with 2-chloro-6-nitrobenzaldehyde (200 mg, 100 mol%, 1.08 mmol), pyrrolidine (266 µL, 300 mol%, 3.24 mmol) and 5 mL of THF. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (436 µL, 300 mol%, 3.24 mmol) was added under argon atmosphere to a frozen mixture. Schlenk tube was disconnected from the Shlenk line, and put into the acetone-liquid nitrogen bath. The bath with a Schlenk tube was allowed to warm up to -30°C and stirred at this temperature overnight. It is very important to warm up reaction mixture gradually. Details are provided in general procedure B. After overnight stirring at -30°C reaction vessel was allowed to warm to room temperature and stirring was continued for 20 hrs.

The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (1.5 mL) and distilled water (20 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×30 mL). The water layer was separated. NaOH solution was added to the water layer up to pH 12. It was extracted with dichloromethane (4×30 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated.

This organic residue was dissolved in 50 mL of acetone, put into a round-bottom flask (100 mL), and $KMnO_4$ (1.7 g, 1000 mol%, 10.8 mmol), grinded to thin powder, was added. The reaction mixture was refluxed for 1 hour. Some additional details are provided in general procedure B. After completeness of reaction $KMnO_4$ and MnO_2 residues were filtered off, and acetone was removed under reduced pressure. The crude product has a purity around 90%. It was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.5 in 10:1 DCM:MeOH) to get 90 mg (38% from nitrobenzaldehyde) as an off-white solid. Melting point 152-153°C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.48 (m, 2H), 7.40 (dd, *J* = 7.4, 1.6 Hz, 1H), 4.19 – 4.15 (m, 2H), 3.15 (t, *J* = 8.0 Hz, 2H), 2.27 (p, *J* = 7.8 Hz, 2H).

^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ 158.2, 157.2, 149.9, 132.2, 131.6, 127.1, 124.3, 115.9, 45.0, 30.7, 17.4.

HRMS: Calculated for $C_{11}H_{10}ClN_2O^+$ ([M+H]$^+$): 221.0476; Found: 221.0475

Calculated for $C_{11}H_9ClN_2ONa^+$ ([M+Na]$^+$): 243.0296; Found: 243.0297

*7-chloro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (**5da**)*

25 mL Schlenk tube with a magnetic stirring bar was prepared according to the standard Schlenk technique and charged with 5-chloro-2-nitrobenzaldehyde (200 mg, 100 mol%, 1.08 mmol), pyrrolidine (266 µL, 300 mol%, 3.24 mmol) and 5 mL of THF. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (436 µL, 300 mol%, 3.24 mmol) was added under argon atmosphere to a frozen mixture. Schlenk tube was disconnected from the Shlenk line, and put into the acetone-liquid nitrogen bath. The bath with a Schlenk tube was allowed to warm up to -30°C and stirred at this temperature overnight. It is very important to warm up reaction mixture gradually. Details are provided in general procedure B. After overnight stirring at -30°C reaction vessel was allowed to warm to room temperature and stirring was continued for 20 hrs.

The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (1.5 mL) and distilled water (20 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×30 mL). The water layer was separated. NaOH solution was added to the water layer up to pH 12. It was extracted with dichloromethane (4×30 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated.

This organic residue was dissolved in 50 mL of acetone, put into a round-bottom flask (100 mL), and $KMnO_4$ (1.7 g, 1000 mol%, 10.8 mmol), grinded to thin powder, was added. The reaction mixture was refluxed for 1 hour. Some additional details are provided in general procedure B. After completeness of reaction $KMnO_4$ and MnO_2 residues were filtered off, and acetone was removed at reduced pressure. The crude product has a purity around 90%. It was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.7 in 10:1 DCM:MeOH) to get 102.3 mg (43% from nitrobenzaldehyde) as an off-white solid. Melting point 176-177°C. (lit. melting point 177°C). [22]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.62 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 4.18 (t, *J* = 7.3 Hz, 2H), 3.15 (t, *J* = 7.9 Hz, 2H), 2.28 (p, *J* = 7.7 Hz, 2H).

^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 160.0, 159.9, 147.7, 134.6, 132.0, 128.5, 125.8, 121.6, 46.7, 32.6, 19.6.

NMR spectra are in accordance to the literature data [23]

*3-methylquinazolin-4(3H)-one (**5ag**)*

100 mL round bottom flask with magnetic stirring bar was charged with 2-((dimethylamino)methyl)aniline (**3ag**) (198 mg, 100 mol%, 1.32 mmol), potassium iodide (65.6 mg, 30 mol%, 0.4 mmol), 70% water solution of *tert*-butyl hydroperoxide was added (1.8 mL, 1000 mol%, 13.18 mmol) and 1.8 mL of distilled water. Stirring was continued overnight.

The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (1.5 mL) and distilled water (20 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×30 mL). The water layer was separated. NaOH solution was added to the water layer up to pH 12. It was extracted with dichloromethane (4×30 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated.

The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.6 in 10:1 DCM:MeOH) to get 32 mg (15%) as a white solid. Melting point 110-111°C. (lit. melting point 110-112°C).[24]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 8.0 Hz, 1H), 8.05 (s, 1H), 7.79 – 7.67 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 3.60 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 161.7, 148.4, 146.9, 134.3, 127.6, 127.4, 126.7, 122.1, 34.2.

NMR spectra are in accordance to the literature data.[24]

*6-chloro-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (**5ca**)*

25 mL Schlenk tube with a magnetic stirring bar was prepared according to the standard Schlenk technique and charged with 4-chloro-2-nitrobenzaldehyde (200 mg, 100 mol%, 1.08 mmol), pyrrolidine (266 µL, 300 mol%, 3.24 mmol) and 5 mL of THF. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (436 µL, 300 mol%, 3.24 mmol) was added under argon atmosphere to a frozen mixture. Schlenk tube was disconnected from the Shlenk line, and put into the acetone-liquid nitrogen bath. The bath with a Schlenk tube was allowed to warm up to -30°C and stirred at this temperature overnight. It is very important to warm up reaction mixture gradually. Details are provided in general procedure B. After overnight stirring at -30°C reaction vessel was allowed to warm to room temperature and stirring was continued for 20 hrs.

The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (1.5 mL) and distilled water (20 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×30 mL). The water layer was separated. NaOH solution was added to the water layer up to pH 12. It was extracted with dichloromethane (4×30 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated.

This organic residue was dissolved in 50 mL of acetone, put into a round-bottom flask (100 mL), and $KMnO_4$ (1.7 g, 1000 mol%, 10.8 mmol), grinded to thin powder, was added. The reaction mixture was refluxed for 1 hour. Some additional details are provided in general procedure B. After completeness of reaction $KMnO_4$ and MnO_2 residues were filtered off, and acetone was removed at reduced pressure. The crude product has a purity around 90%. It was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.7 in 10:1 DCM:MeOH) to get 93 mg (39% from nitrobenzaldehyde) as an off-white solid. Melting point 187-188°C. (lit. melting point 186-188°C).[25]

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.59 (s, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 4.17 (t, *J* = 7.3 Hz, 2H), 3.15 (t, *J* = 8.0 Hz, 2H), 2.28 (p, *J* = 7.7 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 160.9, 160.4, 150.2, 140.4, 127.9, 126.9, 126.5, 119.1, 46.7, 32.7, 19.6.

HRMS: Calculated for $C_{11}H_{10}ClN_2O^+$ ([M+H]$^+$): 221.0476; Found: 221.0476

^{1}H NMR spectrum is in accordance with literature data. [25]

*6,7-dimethoxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (**5fa**)*

25 mL Schlenk tube with a magnetic stirring bar was prepared according to the standard Schlenk technique and charged with 4,5-dimethoxy-2-nitrobenzaldehyde (200 mg, 100 mol%, 0.947 mmol), pyrrolidine (233 µL, 300 mol%, 2.84 mmol) and 5 mL of THF. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (384 µL, 300 mol%, 2.84 mmol) was added under argon atmosphere to a frozen mixture. Schlenk tube was disconnected from the Schlenk line, and put into the acetone-liquid nitrogen bath. The bath with a Schlenk tube was allowed to warm up to -30°C and stirred at this temperature overnight. It is very important to warm up reaction mixture gradually. Details are provided in general procedure B. After overnight stirring at -30°C reaction vessel was allowed to warm to room temperature and stirring was continued for 20 hrs.

The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (1.5 mL) and distilled water (20 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×30 mL). The water layer was separated. NaOH solution was added to the water layer up to pH 12. It was extracted with dichloromethane (4×30 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated.

This organic residue was dissolved in 50 mL of acetone, put into a round-bottom flask (100 mL), and $KMnO_4$ (1.5 g, 1000 mol%, 9,47 mmol), grinded to thin powder, was added. The reaction mixture was refluxed for 1 hour. Some additional details are provided in general procedure B. After completeness of reaction $KMnO_4$ and MnO_2 residues were filtered off, and acetone was removed at reduced pressure. The crude product has a purity around 80%. It was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.5 in 10:1 DCM:MeOH) to get 121 mg (52% from nitrobenzaldehyde) as a yellow solid. Melting point 205-206°C. (lit. melting point 205-207°C).[26]

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.50 (s, 1H), 6.96 (s, 1H), 4.13 (dd, *J* = 8.0, 6.5 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.08 (t, *J* = 7.9 Hz, 2H), 2.22 (p, *J* = 7.8 Hz, 2H).

^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ 160.4, 158.1, 154.7, 148.5, 145.4, 113.7, 107.3, 105.4, 56.3, 56.2, 46.5, 32.4, 19.6.

*6-bromo-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one (**5ba**)*

25 mL Schlenk tube with a magnetic stirring bar was prepared according to the standard Schlenk technique and charged with 4-bromo-2-nitrobenzaldehyde (200 mg, 100 mol%, 0.870

mmol), pyrrolidine (214 µL, 300 mol%, 2.61 mmol) and 5 mL of THF. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (352 µL, 300 mol%, 2.61 mmol) was added under argon atmosphere to a frozen mixture. Schlenk tube was disconnected from the Shlenk line, and put into the acetone-liquid nitrogen bath. The bath with a Schlenk tube was allowed to warm up to -30°C and stirred at this temperature overnight. It is very important to warm up the reaction mixture gradually. Details are provided in general procedure B. After overnight stirring at -30°C reaction vessel was allowed to warm to room temperature and stirring was continued for 20 hrs.

The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (1.5 mL) and distilled water (20 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×30 mL). The water layer was separated. NaOH solution was added to the water layer up to pH 12. It was extracted with dichloromethane (4×30 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated.

This organic residue was dissolved in 50 mL of acetone, put into a round-bottom flask (100 mL), and $KMnO_4$ (686 mg, 500 mol%, 4.35 mmol), grinded to thin powder, was added. The reaction mixture was refluxed for 1 hour. Some additional details are provided in general procedure B. After completeness of reaction $KMnO_4$ and MnO_2 residues were filtered off, and acetone was removed at reduced pressure. The crude product has a purity around 80%. It was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.3 in 50:1 DCM:MeOH) to get 100 mg (43% from nitrobenzaldehyde) as a white solid. Melting point 223-225°C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 8.5 Hz, 1H), 7.78 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 4.17 (t, *J* = 7.3 Hz, 2H), 3.16 (t, *J* = 7.8 Hz, 2H), 2.28 (p, *J* = 7.6 Hz, 2H).

^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 160.9, 160.6, 150.3, 129.7, 129.7, 128.9, 127.9, 119.5, 46.7, 32.7, 19.6.

HRMS: Calculated for $C_{11}H_{10}BrN_2O^+$ ([M+H]$^+$): 264.9971; Found: 264.9966.

Vasicinone and its isomers

This section describes preparation of natural *S*-vasicinone and its enantio- and regioisomers.

*(R)-pyrrolidin-3-ol preparation (**2b**)*

Reaction was carried out by modified procedure of Martens et al.[11] A 100 mL stainless steel autoclave with magnetic stirring bar was charged with *(L)*-hydroxyproline (48.5 g, 100 mol%, 0.37 mmol), cyclohexanone (3.58 mL, 10 mol%, 37 mmol) and 30 mL of ethanol. Autoclave was sealed, flushed 3 times with nitrogen and kept at 160°C for 48 hours. Autoclave was cooled to the room temperature, opened, and the content was transferred to the 100 mL round bottom flask. Methanol was used as a rinsing solvent. Solvents were evaporated and the product was distilled off in vacuum to get 13 g (40%) as a colorless viscous liquid. Boiling point 80-82°C at 1 mbar.

^{1}H NMR (400 MHz, d_6-DMSO) δ 4.17 – 4.11 (m, 1H), 2.91 – 2.82 (m, 1H), 2.76 – 2.63 (m, 2H), 2.61 – 2.56 (m, 1H), 2.51 – 2.48 (m, 1H), 1.75 – 1.65 (m, 1H), 1.55 – 1.46 (m, 1H).

^{13}C{^{1}H} NMR (101 MHz, d_6-DMSO) δ 71.0, 55.3, 44.8, 35.6.

NMR spectra are in accordance with literature data. [11]

The enantiomeric excess was determined by GC using a Chromatec Crystal 5000.2 Gas Chromatograph fitted with a flame ionization detector, on Astec Chiraldex G-TA capillary column (30m x 250 µm), column temperature = 125 °C (isothermal), injector temperature = 250°C, detector temperature = 250°C, flow rate (He) = 34.26 cm/s, split ratio = 100:1: t_R (*R*) = 24.1 min, t_R *(S)* = 27.1 min, ee > 99%.

*(R)-1-(2-aminobenzyl)pyrrolidin-3-ol (**3ab**)* scaled-up experiment

Some important general details are described in general procedure A. A small scale procedure is described above. A dry 250 mL Schlenk tube with a magnetic stirring bar was flushed with argon three times. 2-Nitrobenzaldehyde (10 g, 100 mol%, 66.17 mmol), *(R)*-pyrrolidinol (17.3 g, 300 mol%, 198.52 mmol) and 100 mL of DMF were added. The reaction mixture was frozen with liquid nitrogen up to solid state. Iron pentacarbonyl (26.82 mL, 300 mol%, 198.52 mmol) was added under argon atmosphere to the frozen mixture. It was slowly warmed up to room temperature. Schlenk tube with the reaction mixture was placed into an oil bath preheated to 60°C and stirred at this temperature overnight. The reaction mixture was quenched with conc. HCl (20 mL) and distilled water (400 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×100 mL). The water layer was separated. NaOH was added to the water layer up to pH 12. It was extracted with dichloromethane (4×100 mL). Filtration from iron hydroxides may be required. The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated. NMR yield 86%. DMF residues were removed in high vacuum, and the residue was dissolved in 50 mL of DCM. The product was purified by flash chromatography on silica gel (the cake of silica gel had 6 cm in diameter and 4 cm in height): DCM solution was applied to silica gel, the cake was washed with 50 mL of DCM, than washed with 200 mL of DCM and MeOH mixture (10:1 v/v) (collected separately). Resulting solution was evaporated on the rotary evaporator to get 13.7 g of the crude oil with 93% purity (by NMR), used in the next step without additional purification.

*(R)-3-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one ((R)-Vasicione, **5ab**) and (R)-2-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one ((R)-Isovasicinone, **5ab'**)*

200 mL round bottom flask with magnetic stirring bar was charged with crude *(R)*-1-(2-aminobenzyl)pyrrolidin-3-ol (**3ab**) from the previous step and potassium iodide (3.3 g, 30 mol%, 19.85 mmol) under air atmosphere. Then 70% water solution of tert-butyl hydroperoxide (90.6 mL, 1000 mol%, 661.72 mmol) and 90 mL of distilled water were added. Self-heating to approx. 50°C was noted. Stirring was continued overnight.

The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (15 mL) and distilled water (200 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×100 mL). The water layer was separated. NaOH solution was added to the water layer up to pH 12. It was extracted with dichloromethane (4×100 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated to get 4 g of brown oil.

The residue was dissolved in 5 mL of DCM with 2% MeOH and left at -30°C overnight. 2.0 g (15%) of *(R)*-Vasicinone **5ab** was obtained as a white precipitate. The mother liquid was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (isocratic elution 3% MeOH for 20 min, then gradient to 10% MeOH for 20 min), Rf

of **5ab** is 0.50 in 10:1 DCM:MeOH and Rf of **5ab'** 0.45 in 10:1 DCM:MeOH) to get 95 mg of **5ab** and 1.3 g (10%) of **5ab'** as a white solid.

***(R)*-Vasicinone 5ab:** Melting point 210-211°C. (lit. melting point 200-201°C).[25] ($[\alpha]^{D}_{20}$ = +54°, 3.5 mg/mL in $CHCl_3$).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.79 – 7.70 (m, 2H), 7.49 (ddd, J = 8.3, 6.0, 2.1 Hz, 1H), 5.76 – 5.69 (br s, 1H), 5.26 (t, *J* = 7.6 Hz, 1H), 4.38 (ddd, *J* = 12.4, 8.7, 3.7 Hz, 1H), 4.01 (dt, *J* = 12.3, 7.8 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.37 – 2.25 (m, 1H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 160.7, 160.6, 148.6, 134.6, 127.1, 126.7, 126.7, 121.0, 71.9, 43.5, 29.5.

NMR spectra are in accordance with literature data. [25]

Chiral HPLC: Daicel Chiralpak IA-3 column (4.6 × 150 mm); 1 mL/min heptane/isopropanol: 90/10; detection at 254 nm. t_R (R) = 19.2 min, t_R (S) = 21.1 min, ee > 99%

***(R)*-Isovasicinone 5ab':** Melting point 167-168 °C. (lit. melting point 168-171°C).[4b] ($[\alpha]^{D}_{20}$ = -16°, 4.8 mg/mL in $CHCl_3$). Enantiomeric purity >99% (chiral HPLC).

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 4.83 – 4.75 (m, 1H), 4.33 (d, *J* = 13.3 Hz, 1H), 4.17 (dd, *J* = 13.3, 4.7 Hz, 1H), 3.82 – 3.68 (br s, 1H), 3.38 (dd, *J* = 17.8, 5.6 Hz, 1H), 3.18 (d, *J* = 18.1 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 161.0, 158.0, 148.7, 134.5, 126.6, 126.5, 126.4, 120.3, 65.7, 55.5, 42.4.

NMR spectra are in accordance with literature data. [4b]

Chiral HPLC: Cellucoat 3 column; 1 mL/min heptane/isopropanol: 80/20; detection at 227 nm. t_R (R) = 7.0 min, t_R (S) = 5.6 min, ee > 99%.

*(S)-3-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one ((S)-Vasicinone, **5ac**) and (S)-2-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one ((S)-Isovasicinone, **5ac'**)*

50 mL round bottom flask with magnetic stirring bar was charged with *(S)*-1-(2-aminobenzyl)pyrrolidin-3-ol (**3ac**) (preparation is described above) (740 mg, 100 mol%, 3.85 mmol), then potassium iodide (191 mg, 30 mol%, 1.15 mmol), 70% water solution of tert-butyl hydroperoxide (5.27 mL, 1000 mol%, 38.5 mmol) and 5 mL of distilled water were added under air atmosphere. Stirring was continued overnight.

The reaction mixture was transferred to a round-bottom flask and quenched with conc. HCl (1 mL) and distilled water (50 mL) (to pH 1-2). This mixture was extracted with dichloromethane (3×50 mL). The water layer was separated. NaOH solution was added to the water layer up to pH 12. It was extracted with dichloromethane (4×50 mL). The organic layer was dried using anhydrous Na_2SO_4, and solvent was evaporated.

The resulting mixture was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (isocratic elution 3% MeOH for 20 min, then gradient to 10% MeOH for 20 min), Rf of **5ac** is 0.50 in 10:1 DCM:MeOH and Rf of **5ac'** 0.45 in 10:1 DCM:MeOH) to get 109 mg of **5ac** (14%) as a white solid and 86 mg of **5ac'** (11%) as an off-white solid.

***(S)*-Vasicinone 5ac:** Melting point 200-201°C. (lit. melting point 200-201°C).[15] ($[\alpha]^{D}_{20}$ = -32°, 3.1 mg/mL in $CHCl_3$).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 8.3 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.48 (ddd, *J* = 8.2, 6.4, 2.0 Hz, 1H), 6.36 – 6.27 (br s, 1H), 5.24 (t, *J* = 7.5 Hz, 1H), 4.36 (ddd, *J* = 12.4, 8.8, 3.9 Hz, 1H), 4.00 (dt, *J* = 12.2, 7.7 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.37 – 2.25 (m, 1H).

^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ 160.7, 160.5, 148.7, 134.6, 127.1, 126.8, 126.8, 121.1, 72.0, 43.5, 29.6.

NMR spectra are in accordance with literature data. [25]

Chiral HPLC: Daicel Chiralpak IA-3 column (4.6 × 150 mm); 1 mL/min heptane/isopropanol: 90/10; detection at 254 nm. t_R (R) = 19.2 min, t_R (S) = 21.1 min, ee 99%.

***(S)*-Isovasicinone 5ac':** Melting point 159-160°C. ($[\alpha]^{D}_{20}$ = +8°, 3.1 mg/mL in $CHCl_3$).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 4.78 (t, *J* = 4.9 Hz, 1H), 4.32 (d, *J* = 13.1 Hz, 1H), 4.16 (dd, *J* = 13.1, 4.8 Hz, 1H), 4.02 – 3.71 (br s, 1H), 3.37 (dd, *J* = 17.6, 5.7 Hz, 1H), 3.18 (d, *J* = 17.6 Hz, 1H).

^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ 161.0, 157.9, 148.8, 134.5, 126.7, 126.6, 126.5, 120.5, 65.9, 55.5, 42.4.

Chiral HPLC: Cellucoat 3 column; 1 mL/min heptane/isopropanol: 80/20; detection at 227 nm. t_R (R) = 7.0 min, t_R (S) = 5.6 min, ee = 96%.

Luotonine A (7)

1 mL high pressure vial with a magnetic stirring bar was flushed with argon two times. *(R)*-Vasicinone (**5ab**) (30 mg, 0.149 mmol, 100 mol%) and 2-nitrobenzaldehyde **1a** with 100 µL of THF were added. Both organic precursors were grinded to a thin powder and thoroughly mixed before addition. Iron pentacarbonyl (60 µL, 0.447 mmol, 300 mol%) was added, the vial was sealed and kept at 160°C with stirring overnight. Then the reaction vial was cooled, opened, and its content was suspended in 20 mL of DCM using ultrasonic bath. Resulting suspension was filtered through a layer of silica gel (3 cm in diameter, 2 cm in height). The silica gel cake was washed with 50 mL of ethyl acetate. Combined solution (DCM and ethyl acetate) was evaporated, and the residue was purified using preparative flash chromatograph InterChim PuriFlash in hexane – ethyl acetate binary system (isocratic elution 30% ethyl acetate for 10 min, then gradient to 100% of ethyl acetate for 20 min) to afford 6.4 mg (15%) as a white solid, Rf of **6** is 0.3 in 1:1 hexane:ethyl acetate mixture. mp: 267-268 °C (lit. mp: 265-270 °C). [27]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 – 8.39 (m, 3H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.89 – 7.79 (m, 2H), 7.72 – 7.63 (m, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 5.33 (s, 2H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 160.8, 152.7, 151.3, 149.6, 149.5, 134.7, 131.7, 130.8 (2C), 129.6, 128.9 (2C), 128.7, 128.1, 127.6, 126.6, 121.4, 47.5.

NMR spectra are in accordance with literature data. [27]

Rutaecarpine (8)

The synthesis was done according to procedures, described by Fang and Zhou.[28] For the preparation of phenyldiazonium chloride, to a cooled solution of aniline hydrochloride (120 mg, 0.94 mmol, 110 mol%) in 20% hydrochloric acid (2 mL) a solution of sodium nitrite (65 mg, 0.94 mmol, 110 mol%) in water (2 mL) was added dropwise at 0°C. The reaction mixture was stirred for 15 min and diluted with acetic acid (4 mL) and then was adjusted to pH=4 using sodium acetate (0.8g). After

that a solution of the quinazolinone (170 mg, 0.85 mmol, 110 mol%) in 50% acetic acid (5 mL) was added to this solution of phenyldiazonium chloride dropwise at 0°C over a period of 15 min. The reaction mixture was stirred for 3 h at 5 °C. The mixture was then allowed to stay overnight in a refrigerator. The precipitated crystals were collected and washed with water, dried in vacuum to obtain crude product (*E*)-6-(2-phenylhydrazono)-8,9-dihydro-6Hpyrido[2,1-b]quinazolin-11(7H)-one 245 mg, 95% yield, it was used directly without further purification.

The obtained hydrazone (200 mg, 0.65 mmol) was added to polyphosphoric acid (1 g) at 160-180°, and the reaction mixture was stirred for 60 minutes. pH of the cooled, diluted (with 20 mL of water) reaction mixture was adjusted to 5 with 25% aqueous ammonia solution and extracted by ethyl acetate (20 mL x 3), the organic phase was dried by anhydrous Na_2SO_4. Solvent was removed and the residue was purified by column cromatofraphy on silica gel using hexane and ethyl acetate (4:1) to obtain Rutaecarpine: yellow solid, mp: 255 - 258 °C (lit. mp: 257 - 259 °C), 167 mg, 83% yield.[29]

^{1}H NMR (600 MHz, d_6-DMSO) δ 11.60 (s, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.03 (t, J = 7.4 Hz, 1H), 4.35 (t, J = 6.9 Hz, 2H), 3.08 (t, J = 6.9 Hz, 2H).

^{13}C{^{1}H} NMR (151 MHz, d_6-DMSO) δ 161.72, 147.86, 145.70, 139.25, 135.34, 127.46, 127.21, 127.18, 126.91, 125.73, 125.55, 121.01, 120.70, 120.68, 118.82, 113.21, 41.62, 19.46.

NMR spectra are in accordance with literature data. [28]

Isaindigotone (9)

*Step 1.1. Synthesis of a mixture of **3aa** and **4aa***

Some additional general details are provided in general procedure B. A dry Schlenk tube (250 mL) with a magnetic stirring bar was flushed with argon 3 times. 2-Nitrobenzaldehyde (9.97 g, 100 mol%, 66 mmol), iron pentacarbonyl (27 mL, 300 mol%, 198 mmol) and THF (132 mL) were added. The reaction mixture was frozen with liquid nitrogen up to a solid state. Pyrrolidine (27 mL, 500 mol%, 330 mmol) was added under argon atmosphere to the frozen mixture. Then it was slowly warmed up to -20°C and stirred at this temperature overnight. Slow warming up is highly important, see general procedure B. After that the mixture was warmed up to room temperature and stirred for 2 hours. Then it was transferred into a beaker (500 mL), 200 mL of distilled water and 60 mL conc. HCl were added. Reaction mixture was transferred into a separating funnel (1 L). Acidic water layer was extracted with CH_2Cl_2 (2*300 mL). Then organic layer was washed with acidic water (1*200 mL). NaOH was added to the water layer up to pH 12. The mixture was cooled to room temperature and CH_2Cl_2 (400 mL) was added. Mixture was stirred for 1 hour and then filtered via Schott's filter with cotton to separate the solution from insoluble iron hydroxides. Organic layer was separated; water layer was extracted with CH_2Cl_2 (3*200 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. NMR analysis with 1,4-dinitrobenzene as an internal standard showed that organic residue contains **4aa** (71%), and **3aa** (14%). This mixture (12.6 g) was used in the next stage without purification.

*Step 1.2. Synthesis of deoxyvasicinone **5aa***

A round-bottom flask (2 L) was charged with the mixture of **4aa** and **3aa** (12.6 g, 46.8 mmol of **4aa**, 9.2 mmol of **3aa**) at a ratio of 5/1 (**4aa**/**3aa**). Acetone (800 mL) was added. $KMnO_4$ (100 g, 650 mmol) was grinded into powder and added to the reaction mixture. It was refluxed for 1 h under air atmosphere. Then the reaction mixture was filtered to remove MnO_2. The orange solution was evaporated under reduced pressure. The reaction mixture (14.5 g) contained the target compound (**5aa**) and the product of condensation between two molecules of acetone according to ^{1}H NMR spectra in the ratio (1/1 molar ratio). The side product was evaporated under reduced pressure in high vacuum. Absence of the product of condensation between two molecules of acetone was confirmed by GCMS analysis. The yield of target compound **5aa** (53% normalized by the starting o-nitrobenzaldehide) was determined by ^{1}H NMR with DMF as an internal standard. The product was used in the next stage without purification. Some additional considerations are provided in general procedure B.

*Step 2. Synthesis of Isaindigotone (**9**)*

The synthetic procedure was similar to described by Jahng.[30] A round-bottom flask (250 mL) was charged with deoxyvasicinone from the previous step (6.5 g, 35 mmol, 100 mol%), 4-hydroxy-3,5-dimethoxybenzaldehyde (12.7 g, 70 mmol, 200 mol%), AcONa (573 mg, 7 mmol, 20 mol%) and AcOH (70 mL) under air atmosphere. The reaction mixture was refluxed for 15 h and then stirred for 48 h to get easy to handle precipitate. The precipitate was filtered, washed with cool EtOH and dried under reduced pressure. The product was obtained as a yellow solid (9.5 g) in 81% yield with 99% purity, thus it does not require any additional purification. Melting point 264-270°C (lit. data 248-249°C).[31]

Total yield of Isaindigatone (normalized to the starting *o*-nitrobenzaldehyde) = 43%.

^{1}H (400 MHz, d_6-DMSO) δ: 9.17-8.77 (br s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.79 (t, J = 7.9 Hz, 1H), 7.68-7.66 (m, 2H), 7.45 (t, 7.5 Hz, 1H), 6.95 (s, 2H), 4.18 (t, J = 6.9 Hz, 2H), 3.84 (s, 6H), 3.38-3.30 (m, 2H).

^{13}C{^{1}H} NMR (151 MHz, d_6-DMSO) δ: 160.2, 156.1, 149.5, 148.0, 137.1, 134.2, 130.0, 129.3, 126.8, 125.8, 125.7, 125.6, 120.4, 107.7, 56.0, 44.1, 24.9.

NMR spectra are in accordance with literature data. [32]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, compounds characterization, copies of all relevant spectra (PDF)

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