SCOPE AND LIMITATIONS OF THE T-REACTION EMPLOYING SOME FUNCTIONALIZED C-H-ACIDS AND NATURALLY OCCURRING SECONDARY AMINES

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  e-mail: vkartsev@ibscreen.chg.ru

Abstract - Scope and limitations of the T-reaction with emphasis on using chiral, natural products as starting materials to prepare novel chiral heterocycles is studied and the diastereoselective introduction of newly formed stereocenters is explained via proposed mechanisms.

INTRODUCTION

The T-reaction is currently being used with increased frequency for the creation of new C-C bonds in [1,2-α]-fused quinoline-type heterocycles. The key feature of the T-reaction encompasses a thermal isomerization leading to cyclization, a sequence governed by the tert-amino-effect, i.e. interaction of a tertiary aromatic amine substituted with its unsaturated ortho-substituent having electron-withdrawing substituents Y, Y’ in a conjugated arrangement (Scheme 1). The transformation was explained by virtue of a chiral, helical [1,5]-dipolar intermediate, generated upon a suprafacial [1,5]-hydrideshift from an α-amino-carbon to the benzylic position as the rate-determining step taking place upon heating. The transfer being accompanied by charge separation in the molecule, subsequent intramolecular addition of the carb-anion to the iminium-doublebond is brought about, accomplishing C-C-bond formation from a practically nonactivated NCH-moiety.
Scheme 1: The tert-amino-effect operative in the T-reaction.

As is to be described in this paper, we investigated this protocol for the economical and yield-efficient preparation of structurally diverse heterocycles, ultimately allowing for the straightforward generation and isolation of orthogonally functionalized products bearing stereoselectively introduced centers of chirality.

RESULTS AND DISCUSSION
The two-step-procedure towards 1,2,3,4-tetrahydroquinolines consisted first of aryl amination (see Schemes 2, 3) of secondary amines with ortho-halo-substituted aromatic aldehydes, either via nucleophilic aromatic substitution or Pd-catalyzed Buchwald-Hartwig crosscoupling followed by the tandem T-reaction in protic solvents (see schemes). We examined variations on the C-H-acid moiety, namely employing mono- (X = NO2, Y = H), disubstituted (X, Y = COR, COOR, CONHR, NCOR or CN) and heterocyclic active methylene compounds 2,2-dimethyl-[1,3]-dioxane-4,6-dione (Meldrum’s acid, see Scheme 4) and 1,3-dimethylpyrimidine-2,4,6-trione (N,N-dimethylbarbituric acid). When X ≠ Y, new stereogenic centers are formed. With X = Y, follow-up transformations still lead to stereochemically defined products.

Scheme 2: Synthesis of 1,2,3-substituted tetrahydroquinolines in the T-reaction.

Preferably the condensation and cyclization is performed as a one pot procedure and with 11 and 12, isolation and characterisation of the benzylidenic intermediates was unsuccessful in all but one case. Thus, the description of the corresponding reaction rates as “anomalously” high in comparison to open-chain active methylene compounds with similar electron-withdrawing properties is validated.
The introduction of a variety of nucleophilic secondary amines 5-8 into aromatic cores I-IV is summarized in Scheme 3. The reaction was carried out either via nucleophilic aromatic substitution of ortho-fluoro or ortho-chloro substituted aldehydes or Buchwald-Hartwig Pd-catalyzed aryl amination employing ortho-bromo aromatic aldehydes as starting materials towards the coupling of sensitive or sterically hindered nucleophiles. The latter was found to be advantageous for achieving C-N bond formation, giving access to substituted products in generally better yield and shorter reaction times compared to SN₂₅-type reactions. Beyond that, the Pd-mediated coupling presented no significant advantage over the conventional base-catalyzed reaction in the case of unsubstituted or otherwise insensitive nucleophiles (5a-d). Both methods allowed for the preparation of non-racemic arylated tert-anilines (HNR₃R₄= 6, 8). The inferior yield of the reaction employing 8 in respect to its closely related open-chain analog 7 may illustrate the points made above.
Table 1: Reaction conditions and yields for N-Arylation, as depicted in Scheme 2

<table>
<thead>
<tr>
<th>Product</th>
<th>Scaffold</th>
<th>Method</th>
<th>R₁, R₂</th>
<th>HNR₃R₄</th>
<th>Temp [°C], Time [h], isolated yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>I</td>
<td>I</td>
<td>H, H</td>
<td></td>
<td>6  95, 20, 79</td>
</tr>
<tr>
<td>9b</td>
<td>I</td>
<td>I</td>
<td>H, H</td>
<td></td>
<td>7  90, 60, 67</td>
</tr>
<tr>
<td>9c</td>
<td>I</td>
<td>I</td>
<td>H, H</td>
<td></td>
<td>8  90, 110, 36</td>
</tr>
<tr>
<td>9d</td>
<td>I</td>
<td>II</td>
<td>H, H</td>
<td></td>
<td>5a 150, 16, 87</td>
</tr>
<tr>
<td>9e</td>
<td>I</td>
<td>II</td>
<td>H, H</td>
<td></td>
<td>5b 150, 16, 93</td>
</tr>
<tr>
<td>9f</td>
<td>I</td>
<td>II</td>
<td>F, H</td>
<td></td>
<td>5a 60, 200, 63</td>
</tr>
<tr>
<td>9g</td>
<td>I</td>
<td>II</td>
<td>H, F</td>
<td></td>
<td>5a 100, 20, 76</td>
</tr>
<tr>
<td>9h</td>
<td>I</td>
<td>II</td>
<td>F, H</td>
<td></td>
<td>5b 120, 52, 79</td>
</tr>
<tr>
<td>9i</td>
<td>I</td>
<td>II</td>
<td>H, F</td>
<td></td>
<td>5c 100, 20, 57</td>
</tr>
<tr>
<td>9j</td>
<td>I</td>
<td>II</td>
<td>F, H</td>
<td></td>
<td>5c 120, 52, 56</td>
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<tr>
<td>9k</td>
<td>II</td>
<td>II</td>
<td>H, H</td>
<td></td>
<td>5a  60, 14, 63</td>
</tr>
<tr>
<td>9l</td>
<td>II</td>
<td>II</td>
<td>H, H</td>
<td></td>
<td>5c  80, 20, 56</td>
</tr>
<tr>
<td>9m</td>
<td>II</td>
<td>II</td>
<td>OCH₃, H</td>
<td></td>
<td>5c  80, 20, 54</td>
</tr>
<tr>
<td>9n</td>
<td>II</td>
<td>II</td>
<td>OCH₃, H</td>
<td></td>
<td>5d  80, 40, 93</td>
</tr>
<tr>
<td>9o</td>
<td>II</td>
<td>II</td>
<td>-O-CH₂-O-</td>
<td></td>
<td>5a  70, 20, 60</td>
</tr>
<tr>
<td>9p</td>
<td>II</td>
<td>II</td>
<td>-O-CH₂-O-</td>
<td></td>
<td>5b  80, 40, 75</td>
</tr>
<tr>
<td>9q</td>
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<td>II</td>
<td>-O-CH₂-O-</td>
<td></td>
<td>5c  80, 20, 66</td>
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<tr>
<td>9r</td>
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<td>II</td>
<td>-O-CH₂-O-</td>
<td></td>
<td>5d  80, 50, 88</td>
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<tr>
<td>9s</td>
<td>III</td>
<td>II</td>
<td>-</td>
<td></td>
<td>5a  100, 20, 76</td>
</tr>
<tr>
<td>9t</td>
<td>III</td>
<td>II</td>
<td>-</td>
<td></td>
<td>5c  100, 2, quant.</td>
</tr>
<tr>
<td>9u</td>
<td>IV</td>
<td>II</td>
<td>-</td>
<td></td>
<td>5c  100, 20, 51</td>
</tr>
<tr>
<td>9v</td>
<td>IV</td>
<td>II</td>
<td>-</td>
<td></td>
<td>5d  100, 16, 75</td>
</tr>
</tbody>
</table>

a Reaction performed in DCE.

Table 2: Reaction conditions and yields for T-reactions, as depicted in Scheme 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scaffold</th>
<th>R₁, R₂</th>
<th>Z</th>
<th>Y-Y'-Y</th>
<th>Temp. [°C], Time [h], isolated yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>I</td>
<td>H, H</td>
<td>-</td>
<td>A</td>
<td>75, 2, 97</td>
</tr>
<tr>
<td>13b</td>
<td>I</td>
<td>H, H</td>
<td>CH₂</td>
<td>A</td>
<td>75, 1, 96</td>
</tr>
<tr>
<td>13c</td>
<td>I</td>
<td>H, F</td>
<td>CH₂</td>
<td>B</td>
<td>75, 6, 93</td>
</tr>
<tr>
<td>13d</td>
<td>I</td>
<td>H, F</td>
<td>O</td>
<td>B</td>
<td>100, 6, quant.</td>
</tr>
<tr>
<td>13e</td>
<td>II</td>
<td>H, H</td>
<td>-</td>
<td>B</td>
<td>75, 30, quant.</td>
</tr>
<tr>
<td>13f</td>
<td>II</td>
<td>-O-CH₂-O-</td>
<td>-</td>
<td>A</td>
<td>75, 20, 99</td>
</tr>
<tr>
<td>13g</td>
<td>II</td>
<td>-O-CH₂-O-</td>
<td>O</td>
<td>A</td>
<td>75, 20, 51</td>
</tr>
<tr>
<td>13h</td>
<td>II</td>
<td>-O-CH₂-O-</td>
<td>O</td>
<td>B</td>
<td>75, 45, 88</td>
</tr>
<tr>
<td>13i</td>
<td>II</td>
<td>-O-CH₂-O-</td>
<td>CH₂</td>
<td>A</td>
<td>75, 4, 99</td>
</tr>
<tr>
<td>13j</td>
<td>II</td>
<td>-O-CH₂-O-</td>
<td>CH₂</td>
<td>B</td>
<td>100, 6, 92</td>
</tr>
<tr>
<td>13k</td>
<td>II</td>
<td>-O-CH₂-O-</td>
<td>NCH₃</td>
<td>B</td>
<td>75, 30, quant.</td>
</tr>
<tr>
<td>13l</td>
<td>III</td>
<td>-</td>
<td>O</td>
<td>A</td>
<td>75, 100, 95</td>
</tr>
<tr>
<td>13m</td>
<td>IV</td>
<td>-</td>
<td>CH₂</td>
<td>B</td>
<td>100, 24, 88</td>
</tr>
<tr>
<td>13n</td>
<td>IV</td>
<td>-</td>
<td>O</td>
<td>A</td>
<td>100, 100, 75</td>
</tr>
<tr>
<td>13o</td>
<td>IV</td>
<td>-</td>
<td>O</td>
<td>B</td>
<td>100, 90, 60</td>
</tr>
</tbody>
</table>

Employing cyclic C-H acids 11 and 12 (Scheme 4) furnished corresponding racemic spiro-substituted fused heterocycles 13 in good to excellent yields, providing derivatives of novel heterocycles [1,3]thiazolo[5¹,4²:5,6]pyrido[2,1-c][1,4]oxazinone (13l), 1,3-benzodioxolo[5,6-g]pyrido[1,2-a]-1,8-naphthyridine (13i,j), 1,3-benzodioxolo[5,6-g][1,4]oxazino[4,3-a]-1,8-naphthyridine (13g,h), 1,3-benzodioxolo[5,6-g]pyrazino[1,2-a]-1,8-naphthyridine (13k) and derivatives of known heterocycles pyrazolo-
Scheme 4: Tandem-cyclizations of *ortho*-cycloalkylamino substituted aromatic aldehydes via *tert*-amino-effect using Meldrum’s or *N,N*-dimethylbarbituric acid

[4',3':5,6]pyrido[2,1-c][1,4]oxazine (13n,o), pyrazolo[4,3-c]quinolizine (13m) and 1,3-benzodioxolo[5,6-g]pyrrolo[1,2-a]-1,8-naphthyridine (13f). In the case of condensation-cyclization using 11, prolonged heating often led to decomposition of the *spiro*-heterocycle *in situ*, furnishing the corresponding free carboxylic acid (see also Scheme 7).

Scheme 5: Stereo- and regioselective T-reactions on *N*-(2-formyl)phen-1-yl] arylated derivatives of natural products

Derivatives of naturally occurring 2-phenylethlamines from *Lophophora williamsii* were subjected to the T-reaction using 1 eq. of *N,N*-dimethylbarbituric acid. With the derivative 9b of (-)-anhalonine, the only isolated product was characterized as 14 where ring closure had taken place regio- and stereoselectively on the more substituted *α*-amino carbon.8,17 The *N*-methylmescaline derivative 9c cyclizes regioselectively to yield 15.
Spirofused 1,3-dioxane-4,6-diones 13a,b, easily accessible by a T-reaction with Meldrum’s acid, were converted into corresponding carboxylic acids in excellent yields, either by hydrolysis and decarboxylation under acidic conditions, or upon prolonged heating. In compliance with earlier results,\textsuperscript{18} the preferred diastereomer 16 is that in which the vicinal protons at the two stereocenters are related \textit{trans} to each other, furnishing the \((\mu)\) diastereomer.\textsuperscript{19} This was deduced from the value of the vicinal coupling constants \(^3J\) of protons in \(^{1}\text{H}-\text{NMR}\) at the stereogenic phenylethylenic and bridgehead \(\alpha\)-amino carbon, observed to be 9.8-10 (16a) and 9.4-9.6 (16b) Hz, respectively, and assigned using 400 MHz HC- and HH-COSY of 16 and 17. Moreover, formation of novel carboxylic acids occurred upon prolonged heating of the reaction mixture. Thus, [1,3]dioxolo[6,7]isoquinoline-13-carboxylic acids 19, 20 and hexahydrobenzo[g]pyrrolo[1,2-\(a\)]-1,8-naphthyridine-4-carboxylic acid 21 are available in acceptable yields (Scheme 7).

As it was known that the T-reaction is capable of inducing stereocenters in high selectivity,\textsuperscript{2,3,7,8} we decided to further investigate this reaction using unsymmetrical active methylene compounds. The reaction of 2-piperidine-1-yl-benzaldehyde 9e with 3-oxo-3-phenylpropionitrile 23 proceeds in favor of the \((4a,5-\mu)\) isomer 24 with the cyano moiety located \textit{trans} to the bridgehead hydrogen (Scheme 8) as determined by single crystal XRD (Figure 2). Two conformers of the pure \((4a,5-\mu)\)-isomer co-crystallized from MeOH in a 1:1 ratio (together with their respective mirror images). The unit cell thus contains four distinguishable structures in this racemic compound.
Scheme 7: T-reactions using Meldrum’s acid. \(^c\) Configuration of major isomer unassigned. \(^d\) Ratio assessed via \(^1\)H-NMR.

Scheme 8: Stereochemical outcome of T-reactions employing unsymmetrical active methylene compounds
A similar outcome was observed for the reaction of 9e with 26, the structure of the major diastereomer determined by single crystal XRD and shown to be the (4a,5-l) isomer 28 (Scheme 8 and Figure 1).

**Figure 1:** XRD of compound 28. (50% probability thermal ellipsoids crystallographic numbering, non-stereogenic hydrogens omitted for clarity, dashed lines on right model indicate H-bonding between N1-N2 and S1-O1.)

**Figure 2:** XRD of two conformers of compound 24 (ORTEP drawing, 50 % probability, crystallographic numbering, non-stereogenic hydrogens omitted for clarity). In below: Asymmetric unit cell, hydrogens omitted.
We explain the formation of the major \( (4a,5-u) \)-isomer of 24 as follows: There is good evidence that the T-reaction proceeds via a suprafacial \([1,5]\)-hydride transfer\(^3\) of the two possible Knoevenagel intermediates 29 (Scheme 9). Assuming that there is no equilibration in the zwitterionic intermediate\(^2\) generated after hydride migration, 8 possible cyclization products have to be considered. It is further known that the vinyl double bond preferably points out of the steric congestion with the amine substituent.\(^2\) As \( \text{Ha} \) and \( \text{Hb} \) are indistinguishable, the stereochemical outcome is determined by the \( E \) to \( Z \) ratio of intermediates 29. These considerations also explain the preferred formation of 28 from 9e and 26.

**Scheme 9**: Overall scheme of supposedly viated pathways of cyclization via tert-amino-effect, compounds 23 and 24

Scheme 10 depicts the product ratios arising from the T-reactions of optically pure 9a. Here, the diastereomer distribution was principally concluded from NOESY experiments (Figure 3) and supported by 400 MHz HH-COSY, HSQC and HMBC experiments.

Unexpectedly, we failed to locate any NOE interactions between H1 and H3a or between H3a and CO\(_2\)-CH\(_3\) in isomers 30-33. Proceeding from the known configuration of H1 onward along the pyrrolidine ring
resulted in the determination of the configuration of the stereogenic protons at C3a. Elucidating signal enhancements between H1 and H2u, further H3a and H3d were observed whereas H3a showed no NOE with H3u in the main isomer. In contrast, H3a interacted with H5u in the minor isomer.

Scheme 10: Diastereoselective T-reactions of L-proline substituted benzaldehydes

Figure 3: Selected NOE correlations for 30, 31, 32, 33 generate analogous signals.

In Scheme 11, a possible mechanism accounting for this stereopreference is hypothesized. Assuming a transient destabilizing interaction \(^2\) occurs in the unsaturated intermediate between the chiral \(\alpha\)-amino proton and H9 in the phenyl ring in 34, such an interaction would disfavor the placement of \(Hb\) in a coplanar orientation for subsequent hydride-migration. Conversely, the migration of \(Ha\) does not suffer from a comparable sterical hindrance.
Further, we studied the T-reaction using nitromethane. Using 9d (Table 1), a mixture of separable nitro compounds 35-38 (Scheme 12) was obtained. 9e did not give rise to any cyclized compounds. Comparable relative rates of cyclization for pyrrolidine vs. piperidine as the tert-amino substituent were reported earlier. Lewis acid catalysis using AlCl₃ only slightly improves the yield and does not considerably shorten the time required to reach the thermodynamic equilibrium of the four main compounds present in the reaction mixture at that stage. This underscores the surprising inertness of T-substrates towards catalysis probably owing to the concerted nature of hydride transfer and fast subsequent C-C bond formation. The relative configuration at the stereogenic centers in the major isomer isolated upon cyclization (35) was assigned to be (3a,4-α) from 3J = 9.6 Hz at these positions and confirmed by 400-MHz HC- and HH-COSY-experiments.

A side product from the preparation of the ortho-piperidinyl-nitrostyrene 37 was isolated, and its structure was assigned to be 39 via single crystal XRD (Figure 4). It may be worthy of note that a 2,4-disubstituted 1,3,5-trinitropentane fragment in an open chain arrangement has not yet been reported to date in the literature.

Scheme 11: Explanation of the diastereomeric preference in T-reactions using prolines
**Scheme 12**: Nitro-functionalized [1,2-a]fused hexahydroquinolines via tert-amino-effect. i) MeNO₂, 0.2 eq. KF, 2 eq. HNMe₂.HCl; C₆H₅Me, Δ, 110 °C, 2-3 h, Dean-Stark trap. ii) n-BuOH, Δ, 118 °C; 80 h (n=0) or 220 h (n=1). iii) n-BuOH, Δ, 118 °C, 90 h, AlCl₃ cat./ stoich. iv) 1 eq. NH₄OAc, 1.1 eq. MeNO₂, Δ, 118 °C, 120 h. v) 1 eq. NH₄OAc, 1.1 eq. MeNO₂, Δ, 118 °C, 60 h, AlCl₃ cat.

**Figure 4**: XRD of compound 39 (20 % thermal ellipsoids, hydrogens omitted for clarity, crystallographic numbering, view from two opposite sides)

**Table 3**: Yields of 35-38, as depicted in scheme 11

<table>
<thead>
<tr>
<th>n</th>
<th>Path</th>
<th>Isolated yield of 35 and 36 (%)</th>
<th>Isolated yield of 37 and 38 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>ii), iii)</td>
<td>39: (3a,4-u): (3a,4-l) ≥ 12:1.</td>
<td>37a: &lt;1; 38a: 11.</td>
</tr>
<tr>
<td>0</td>
<td>iv)</td>
<td>25; (3a,4-u): (3a,4-l) ≥ 23:2</td>
<td>37a: 16; 38a: 20.</td>
</tr>
<tr>
<td>0</td>
<td>v)</td>
<td>27; (3a,4-u): (3a,4-l) ≥ 25:2</td>
<td>37a: 8; 38a: 19.</td>
</tr>
<tr>
<td>1</td>
<td>ii), iii)</td>
<td>traces²</td>
<td>37b: 40; 38b: not determined.</td>
</tr>
</tbody>
</table>

Attempts to utilize methyl nitroacetate, N-methylhydantoin or ethyl acetoacetate as C-H acids gave the T-products only in low yield (Scheme 13, Table 4).

² detectable by TLC-staining in molybdatophosphate, compound stains characteristically cherry-red to purple, as was found to be a general phenomenon with all [1,2-a]-quinolines covered in this paper.
**Scheme 13:** Further T-reactions employing unsymmetrically substituted C-H-acids

**Table 4:** Reaction conditions and yields for T-reactions, as depicted in Scheme 12. \(^\dagger\)Nature of major diastereomer unassessed.

<table>
<thead>
<tr>
<th>n</th>
<th>X</th>
<th>Y</th>
<th>Reaction time [h]</th>
<th>Yield of V (%)</th>
<th>Yield of VI (%)</th>
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</thead>
<tbody>
<tr>
<td>40</td>
<td>NO₂</td>
<td>CO₂Me</td>
<td>60</td>
<td>15 (ratio ≥ 10:1)(^\dagger)</td>
<td>59 (E/Z-mixture)</td>
</tr>
<tr>
<td>41</td>
<td>MeCO</td>
<td>CO₂Me</td>
<td>220</td>
<td>7 (ratio ≥ 7:1)(^\dagger)</td>
<td>60 (E/Z-mixture)</td>
</tr>
<tr>
<td>42</td>
<td>MeCO</td>
<td>CO₂Me</td>
<td>250</td>
<td>3 (ratio ≥ 4:1)(^\dagger)</td>
<td>49 (E/Z-mixture)</td>
</tr>
<tr>
<td>43</td>
<td>N-N</td>
<td>X-Y</td>
<td>290</td>
<td>traces(^\ddagger)</td>
<td>59 (E:Z = 2:3)</td>
</tr>
</tbody>
</table>

**CONCLUSION**

We have successfully employed the T-reaction in the synthesis of derivatives of natural products. In introducing a Pd-catalyzed cross-coupling, an extension in scope regarding secondary amine nucleophiles has been realized. Efficient domino processes using the tert-amino-effect allowed for the selective formation of functionalized stereogenic centers. Thus, novel valuable quinolines as promising building blocks have become readily available.

**EXPERIMENTAL**

Melting points (°C) were determined in a BUCHI B-545 and are uncorrected. \(^1\)H-NMR spectra were recorded on 200-MHz-spectra Bruker AVANCE 200 and 400-MHz-spectra on a Bruker AVANCE 400, respectively, with tetramethylsilane as internal standard. \(^13\)C-NMR were recorded on the AVANCE 200 at 50 MHz. Chemical shifts are given in ppm and coupling constants in Hz. \(^1\)H-\(^1\)H-spin decoupling and DEPT \(\Theta 45^\circ\) were used. In case of \(^13\)C-NMR, additional indication from J-modulated measurements is given after the chemical shift and is either (J), (2J) or (-) meaning \(\nu_{\text{res}} \sim J\) (CH/CH₃), \(\nu_{\text{res}} \sim J/2\) (CH₂) or no signal for \(C_{\text{quar}}\) in the DEPT experiment. Mass spectra were obtained by electron impact via GC-MS with an FID-detector (240 °C) on a ThermoQuest Trace GC 2000 using a DB5 capillary column (30 m x 0.32 mm i.d.).MALDI-MS/MS was performed on a MALDI IV Benchtop TOF mass spectrometer equipped with ESI trap, ion source 337 nm N₂-Laser (3 ns pulse duration) and curved field reflectron, in low energy CID. Optical rotations were obtained using a Perkin-Elmer 241 polarimeter (1dm cell); specific optical
rotation was calculated using the equation: \( \alpha = \frac{\alpha_{589\,nm} \cdot 100}{(L\,\text{dm}) \cdot c\,[\text{g/100mL}]} \).

Single crystal X-ray data were collected on a Bruker Smart APEX CCD area detector diffractometer using graphite-monochromated Mo K\(_\alpha\) radiation (\(\lambda = 0.71073\,\text{Å}\), sealed X-ray tube) and 0.3° \(\omega\)-scan frames covering complete spheres of the reciprocal space, detector distance: 50 mm, 512x512 pixels. Corrections for absorption (multi-scan (SADABS; Bruker, 2003) \(T_{\min} = 0.92, T_{\max} = 0.99\), \(\lambda/2\) effects, and crystal decay were applied. The structures were solved by direct methods using the program SHELXS97. Structure refinement on \(F^2\) was carried out with the program SHELXL97, as well. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted in idealized positions and were refined riding with the atoms to which they were bonded.

Reactions were monitored a) by thin-layer chromatography on Merck silica gel 60 F254 TLC-plates; detection was either by UV-irradiation at 254/336 nm on untreated silica or by staining with ammoniummolybdatophosphate, ninhydrine, 2,4-dinitrophenylhydrazine, I\(_2\)/SiO\(_2\) or vanilline in H\(_2\)SO\(_4\), accompanied by gentle heating; b) by UV-HPLC on a WATERS 2695 (Elutants: Solvent A= 0.1% CF\(_3\)CO\(_2\)H + 3 % MeCN + 97 % H\(_2\)O; Solvent B= 0.1 % CF\(_3\)CO\(_2\)H + 97 % MeCN + 3 % H\(_2\)O; flow in the range of 0.1 mL/min) using a Chromolith Performance PDA column (100mm length, 3mm diameter) at 220-380nm. Purity by HPLC of \(\geq 98\%\) (at 254nm) was achieved for all samples (unless indicated otherwise) and considered to be sufficient.

Column chromatography was performed using a BUCHI MPLC consisting of two C-605 pump modules, a C-615 pump manager, a C-630 UV-monitor and a C-660 fraction collector on flash-type 40-63µm silica. Petroleum ether (PE) refers to a boiling range of 40-60 °C. EE refers to acetic acid ethyl ester. When solvent gradients were employed, the polarity was increased parabolically with respect to the mixture percentage of the more polar eluent.

Solvents were obtained commercially, then dried by and stored over 3Å-molsieves before use. Absolute solvents were prepared in the usual ways.

\(\text{K}_2\text{CO}_3\) was thoroughly dried by heating the finely ground commercially available material in a crucible over a Bunsen burner for at least 30 min and subsequently allowing to cool down to rt in an evacuated desiccator.

Preparation of single-crystals for XRD by diffusion and slow evaporation: The sample was dissolved in a minimum amount of CH\(_2\)Cl\(_2\) in an oversized glass tube and then placed in a closed vessel under an almost saturated atmosphere of Et\(_2\)O; after standing at rt for an appreciable amount of time or when the solvent level in the sample tube had risen to near the edge, the vessel was opened and the solvent mixture allowed to slowly evaporate.
General procedure for the preparation of ortho-amino substituted aromatic aldehydes via nucleophilic aromatic substitution:

General procedures 1a and 1b: To a mixture of 1 eq. of ortho-haloaldehyde in the reaction solvent, there were added subsequently 1.1-6 eq. of secondary amine and 1.4 eq. of dry K₂CO₃ (respective to the amount of secondary amine nucleophile added; for additionally introduced acidic mixture components, e.g. hydrohalogenide salts of those secondary amines, there was further added a stoichiometrically equal increased amount of K₂CO₃ to compensate for the excess of acid in the reaction mixture) (variation 1a) or 1 eq. of secondary amine and 1.4 eq. of dry K₂CO₃ (variation 1b).

The resulting mixture was heated under reflux for the time indicated. The suspension was cooled to rt and poured into a half-saturated K₂CO₃-solution, extracted with CH₂Cl₂ (three times using 10 mL/100 mg of expected product). The organic phases were combined, washed once with 10 mL brine, the brine re-extracted with 10 mL CH₂Cl₂ and the combined organic phases dried (Na₂SO₄), the solvent roto-evaporated to yield the crude product that was dissolved in CH₂Cl₂. There was added an appropriate amount of 40-63 µm silica gel and the resultant mixture was concentrated on a rotavapor until no more solvent was distilled off. The adsorbed mixture was then loaded as such into an MPLC cartridge for chromatographic separation.

General procedure for the preparation of ortho-amino substituted aromatic aldehydes via Pd-mediated coupling:

General procedure 2: To 1 eq. of ortho-halo-aldehyde I-IV there were added 0.01 eq. of Pd(OAc)₂, 0.03 eq. of rac-BINAP to 1 eq. of secondary amine 5-8 and 1.4 eq. of Cs₂CO₃ (respective to the amount of secondary amine nucleophile added; for additionally introduced acidic mixture components, e.g. hydrohalogenide salts of those secondary amines, there was further added a stoichiometrically equal increased amount of Cs₂CO₃ to compensate for the excess of acid in the reaction mixture) in toluene. The mixture was purged with argon for 15 min and then heated under reflux and argon atmosphere for the time indicated (see experimental details). The resulting suspension was cooled to rt and poured into a half-saturated K₂CO₃-solution, extracted with CH₂Cl₂ (three times using 10 mL/100 mg of expected product). The organic phases were combined, washed once with 10 mL brine, the brine re-extracted with 10 mL CH₂Cl₂ and the combined organic phases dried (Na₂SO₄), the solvent roto-evaporated to yield the crude product that was dissolved in CH₂Cl₂. There was added an appropriate amount of 40-63 µm silica gel and the resultant suspension was concentrated on a rotavapor until no more solvent was distilled off. The adsorbed mixture was then loaded as such into an MPLC cartridge for chromatographic separation.
Methyl 1-(2-formylphenyl)-L-prolinate; (S)-1-(2-Formylphenyl)-pyrrolidine-2-carboxylic acid methyl ester (9a). Prepared following general procedure 2 from 2-bromobenzaldehyde (794 mg, 4.29 mmol) and (S)-pyrrolidine-2-carboxylic acid methyl ester hydrochloride (711 mg, 4.29 mmol). Toluene, 10 mL, 20 h, 95 °C. MPLC gradient PE to PE:EE=80:20. Yield 790 mg (79 %), yellow oil, [α]_D^20 - 365.7 (c 1.17, CHCl₃).

1H-NMR (200MHz, CDCl₃) δ 9.94 (s, 1H, CHO), 7.52 (dd, 1H, J=7.6, J=7.2 Hz, Ar-H-5), 7.21 (dd, 1H, J=7.6, J=6.6 Hz, Ar-H-4), 6.76-6.69 (m, 2H, Ar-H), 4.37 (dd, 1H, J=6.8, J=6.6Hz, α-amino-CH), 3.62-3.51 (br.m, 1H, J=8.4, J=7, J=6.6 Hz, α-amino-CH₂), 3.44 (s, 3H, CH₃), 3.22-3.12 (br.m, 1H, J=6.8 Hz, β-amino-CH₂), 2.31-2.20 (m, 1H, J=7 Hz, β-amino-CH₂).

13C-NMR (50MHz, CDCl₃) δ 190.2 (J), 173.3 (-), 149 (-), 134.3 (J), 132.6 (J), 124.4 (-), 118.3 (J), 115.7 (J), 54.5 (2J), 51.8 (J), 30.1 (2J), 24.6 (2J). GC-MS, m/z (Irel, (%)): 174.07 (100), 156.12 (27), 76.95 (20), 233.13 [M +] (12), 175.23 (12), 129.11 (12), 116.91 (10), 51.1 (8), 103.91 (7), 154.06 (7), 146.1 (6), 128.08 (6), 91.1 (6), 118.12 (5), 130.15 (5), 155.14 (5), 105.1 (5), 132.07 (4), 144.12 (4), 65.17 (3).

2-{Methyl[2-(3,4,5-trimethoxyphenyl)ethyl]amino}benzaldehyde (9b). Prepared following general procedure 2 from 2-bromobenzaldehyde (322 mg, 1.74 mmol) and methyl[2-(3,4,5-trimethoxy-phenyl)-ethyl]amine (391 mg, 1.74 mmol). Toluene, 10 mL, 60 h, 90 °C. MPLC gradient PE to PE:Et₂O=80:20. Yield 350 mg (67 %), yellow oil. 1H-NMR (200MHz, CDCl₃) δ 10.14 (s, 1H, CHO), 7.70 (dd, 1H, J=7.6, J=1.8 Hz) 7.44-7.36 (m, 1H, J=8.8, J=7.2, J=1.8 Hz), 7.04-6.94 (m, 2H, J=8.2, J=7.4 Hz), 6.27 (s, 2H, (OCH₃)₃-Ar-H), 3.75 (s, 6H, m-O-CH₃), 3.74 (s, 3H, p-O-CH₃), 3.37-3.29 (m, 2H, J=15.4, J=8, J=7.4 Hz, β-phenylethylamine-CH₂), 2.89 (s, 3H, N-CH₃), 2.81-2.73 (m, 2H, J=15.4, J=8, J=7.4 Hz, benzyl-CH₂). 13C-NMR (50MHz, CDCl₃) δ 191.4 (J), 155.4 (-), 153.1 (-), 136.4 (-), 134.9 (-), 134.5 (J), 130.1 (J), 128.3 (-), 121.5 (J), 119.3 (J), 105.5 (J), 60.8 (J), 60 (2J), 56 (J), 42.3 (J), 34.2 (2J). GC-MS, two main peaks, m/z (Irel, (%)): 7.32 min:106.03 (100), 135.12 (70), 76.9 (49), 51.07 (30), 79.08 (22), 78.13 (22), 91.09 (19), 118.18 (16), 107.18 (15), 9.29 min: 194.1 (100), 179.11 (81), 64.95 (46), 151.06 (38), 90.95 (35), 135.95 (32), 76.92 (29), 121.04 (17), 51.09 (17).

2-[(9S)-4-Methoxy-9-methyl-6,9-dihydro[1,3]dioxolo[4,5-h]isoquinolin-8(7H)-yl]benzaldehyde (9c). Prepared following general procedure 2 from 2-bromobenzaldehyde(569 mg, 3.08 mmol) and (9S)-4-methoxy-9-methyl-6,7,8,9-tetrahydro[1,3]dioxolo[4,5-h]isoquinoline (680 mg, 3.08 mmol). Toluene, 10 mL, 110 h, 90 °C. MPLC gradient PE to PE:EE=90:10. Yield 359mg (36 %), yellow crystals, mp 129.3 °C, [α]_D^20 + 460.3 (c 0.86, CHCl₃). 1H-NMR (200MHz, CDCl₃) δ 10.27 (s, 1H, CHO), 7.78-7.74 (m, 1H, J=8, J=7.4, J=1.8 Hz), 7.46-7.38 (m, 1H, J=8, J=7.6, J=7.4, J=1.8 Hz), 7.09-7.01 (m, 2H, J=8.2, J=7.6 Hz), 6.25 (s, 1H), 5.93 (d, 1H, J=1.4 Hz, -O-CH₂-O-), 5.88 (d, 1H, J=1.4 Hz, -O-CH₂-O-), 4.49 (q, 1H, J=6.6 Hz, α-amino-CH), 3.82 (s, 3H, O-CH₃), 3.56 (ddd, 1H, J=12.7, J=11, J=4.2 Hz, α-amino-CH₂),...
3.25 (ddd, 1H, J=12.7, J=6.1, J=5.5 Hz, α-amino-CH₂), 2.92-2.75 (m, 1H, J=16.2, J=11, J=6.6 Hz, β-amino-CH₂), 2.66-2.55 (dd, 1H, J=16.2, J=4.2 Hz, benzyl-CH₂), 1.25 (d, 3H, J=6.6 Hz, α-amino-CH₃).

13C-NMR (50MHz, CDCl₃) δ 154.8 (-), 144.6 (-), 142.4 (-), 134.6 (J), 133.2 (-), 129.5 (-), 128.9 (J), 128.3 (-), 122.7 (J), 122.1 (J), 115.3 (-), 106.9 (J), 101.5 (2J), 56.4 (J), 54.7 (J), 45.9 (2J), 27.8 (2J), 17.9 (J). MALDI-MS/MS: m/z (Iₑ, %) TIC, MS²: 306.1 (100): 306.1 (100), 234 (36), 263.1 (17), 278.1 (8); 322.1(3).

2-Pyrrolidin-1-ylbenzaldehyde (9d). Prepared following general procedure 1a from 2-fluorobenzaldehyde (21300 mg, 171.5 mmol) and pyrrolidine (15000 mg, 207 mmol). DMF, 100 mL, 16 h, 150 °C. Distilled in a Kugelrohr apparatus at 0.01 mbar and 120 °C, Yield 26300 mg (87 %), purity by HPLC >99.6 % (254nm), yellow oil. 1H-NMR (200MHz, CDCl₃) δ 10.05 (s, 1H, CHO), 7.69-7.59 (m (dd and dd), 2H, J=8, J=7.4, J=7.2 Hz), 6.93-6.69 (m, 2H), 3.52-3.4 (m, 4H, J~6 Hz, α-amino-CH₂), 1.88-1.6 (br.m, 4H, β-amino-CH₂).

2-Piperidin-1-ylbenzaldehyde (9e). Prepared following general procedure 1b from 2-fluorobenzaldehyde (3280 mg, 26.5 mmol) and piperidine (2250 mg, 26.5 mmol). DMF, 50 mL, 16 h, 150 °C. Crude yield 4903 mg (98 %, reddish oil). Purity by HPLC 96.2 % (254 nm). Distilled in a Kugelrohr apparatus at 0.01 mbar and 120 °C, Yield 4644 mg (93 %), purity by HPLC >99.9 %, yellow oil, Rₜ=0.84 (PE:EE=75:25). 1H-NMR (200MHz, CDCl₃) δ 10.27 (s, 1H, CHO), 7.76 (d, 1H, J=6.6 Hz, Ar-H-6), 7.45 (m, 1H, Ar-H-4), 7.11-6.98 (m, 2H, Ar-H-3, Ar-H-5), 3.01 (br.d, 4H, J~6 Hz, α-amino-CH₂), 1.79-1.65 (br.m, 4H, β-amino-CH₂), 1.65-1.57 (br.m, 2H, γ-amino-CH₂). 13C-NMR (50MHz, CDCl₃) δ 156.9 (-), 135.8 (-), 122.2 (J), 120.1 (J), 118.9 (J), 55.5 (2J), 26.1 (2J), 24 (2J). GC-MS, m/z (Iₑ, (%)): 105.9 (100), 189.2 [M⁺] (69), 172.04 (41), 188.17 (38), 131.99 (35), 76.94 (30), 103.96 (30), 146 (26), 118.09 (18), 160.04 (17).

5-Fluoro-2-pyrrolidin-1-ylbenzaldehyde (9f). Prepared following general procedure 1b from 2,5-difluorobenzaldehyde (1110 mg, 7.8 mmol) and pyrrolidine (554 mg, 7.8 mmol). DMF, 10 mL, 20 h, 60 °C. MPLC gradient PE to PE:EE=80:20, Yield 946 mg (63 %), yellow oil. 1H-NMR (200MHz, CDCl₃) δ 10.05 (s, 1H, CHO), 7.33 (dd, 1H, J=9.2, J=3.3 Hz), 7.11-7.05 (m, 1H), 6.74 (dd, 1H, J=9.2, J=4.3 Hz), 3.3-3.23 (br.m, 4H, α-amino-CH₂), 1.94-1.88 (br.m, 4H, β-amino-CH₂). 13C-NMR (50MHz, CDCl₃) δ 189.4 (J), 167.2 (-), 140.5 (-), 135.8 (-), 122.2 (J), 120.1 (J), 116.4 (J), 53.4 (2J), 23.9 (2J).

3-Fluoro-2-piperidin-1-ylbenzaldehyde (9g). Prepared following general procedure 1a from 2,3-difluorobenzaldehyde (138 mg, 0.97 mmol) and piperidine (248 mg, 2.91 mmol). DMF, 5 mL, 20 h, 100 °C. MPLC gradient PE to PE:EE=80:20, Yield 152 mg (76 %), yellow oil. 1H-NMR (200MHz, CDCl₃) δ 10.35 (s, 1H, CHO), 7.45 (dd, 1H, J=7.4, J=7.1 Hz, Ar-H-6), 7.2-6.9 (m, 2H, J=7.4 Hz, Ar-H-4, Ar-H-5), 3.18-3.01 (m, 4H, α-amino-CH₂), 1.77-1.45 (br.m, 6H, β–, γ-amino-CH₂). 13C-NMR
5-Fluoro-2-piperidin-1-ylbenzaldehyde (9h). Prepared following general procedure 1a from 2,5-difluorobenzaldehyde (138 mg, 0.97 mmol) and piperidine (248 mg, 2.91 mmol). DMF, 5 mL, 52 h, 120 °C. MPLC gradient PE to PE:EE=90:10. Yield 157 mg (79 %), yellow oil. \(^{1}\)H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 10.2 (s, 1H, CHO), 7.42 (dd, 1H, J=8.6, J=3.1 Hz, Ar-H-3), 7.2-6.95 (m, 2H, J=8.9, J=8.6, J=3.1 Hz, Ar-H-4, Ar-H-6), 2.96-2.83 (m, 4H, J=5.4 Hz, \(\alpha\)-amino-CH\(_2\)), 1.8-1.6 (br.m, 4H, \(\beta\)-amino-CH\(_2\)). \(^{13}\)C-NMR (50MHz, CDCl\(_3\)) \(\delta\) 190.1, 155.9, 130.2, 121.8, 121.4, 121.1, 114.1, 55.9, 26.1, 23.8. GC-MS, \(m/z\) (Irel, (%)): 211.05 (100), 91.02 (71), 84.12 (13), 64.97 (13), 212.19 (11), 182.99 (8), 55.13 (6), 125.9 (6).

3-Fluoro-2-morpholin-4-ylbenzaldehyde (9i). Prepared following general procedure 1a from 2,3-difluorobenzaldehyde (157 mg, 1.04 mmol) and morpholine (288 mg, 3.12 mmol). DMF, 5 mL, 20 h, 100 °C. MPLC gradient PE:EE=9:1 to PE:EE=85:15. Yield 115 mg (57 %), yellow oil. \(^{1}\)H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 10.47 (s, 1H, CHO), 7.55 (br.d, 1H, J=7.2 Hz, Ar-H-6), 7.35-7.05 (m, 2H, J=7.2 Hz, Ar-H-4, Ar-H-5), 3.82-3.69 (m, 4H, O-CH\(_2\)), 3.22-3.09 (m, 4H, N-CH\(_2\)). \(^{13}\)C-NMR (50MHz, CDCl\(_3\)) \(\delta\) 191.2, 157.8, 141.5, 134.1, 125.9, 124.2, 122.6, 67.3, 52.7.

5-Fluoro-2-morpholin-4-ylbenzaldehyde (9j). Prepared following general procedure 1a from 2,5-difluorobenzaldehyde (157 mg, 1.04 mmol) and morpholine (288 mg, 3.12 mmol). DMF, 5 mL, 52 h, 120 °C. MPLC gradient PE to PE:EE=80:20. Yield 112 mg (56 %), yellow oil. \(^{1}\)H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 10.31 (s, 1H, CHO), 7.45 (dd, 1H, J=7.7, J=7.4 Hz, Ar-H-3), 7.25-7.01 (m, 2H, J=7.2 Hz, Ar-H-4, Ar-H-5), 3.88-3.79 (m, 4H, O-CH\(_2\)), 3.01-2.89 (m, 4H, N-CH\(_2\)). \(^{13}\)C-NMR (50MHz, CDCl\(_3\)) \(\delta\) 190.1, 161.3, 151.9, 130.5, 122.1, 121.7, 115.4, 66.8, 54.5.

2-Pyrrolidin-1-ylquinoline-3-carbaldehyde (9k). Prepared following general procedure 1b from 2-chloroquinoline-3-carbaldehyde (1270 mg, 6.64 mmol) and pyrrolidine (472 mg, 6.64 mmol). DMF, 15 mL, 14 h, 60 °C. MPLC in PE to PE:EE= 80:20. Yield 948 mg (63 %), orange oil. \(^{1}\)H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 9.94 (s, 1H, CHO), 8.12 (s, 1H, Ar-H-4), 7.61-7.43 (m, 3H), 7.05 (dd, 1H, J=7.6, J=7 Hz), 3.54-3.41 (m, 4H, \(\alpha\)-amino-CH\(_2\)), 1.82-1.76 (m, 4H, \(\beta\)-amino-CH\(_2\)). \(^{13}\)C-NMR (50MHz, CDCl\(_3\)) \(\delta\) 189.5, 154.5, 149.9, 143.5, 133.3, 132.9, 128.2, 126.7, 122.3, 121.1, 50.6, 25.9. GC-MS, \(m/z\) (Irel, (%)): 168.79 (100), 128.08 (99), 226.33 [M\(^+\)] (93), 101.28 (90), 197.50 (80), 156.49 (75), 142.82 (61), 70.06 (61), 75.08 (36), 115.15 (27), 89.14 (17).

2-Morpholin-4-ylquinoline-3-carbaldehyde (9l). Prepared following general procedure 1a from 2-chloroquinoline-3-carbaldehyde (198 mg, 1.03 mmol) and morpholine (270 mg, 3.1 mmol). DMF, 5 mL, 20 h, 80 °C. MPLC gradient PE:EE=88:12 to PE:EE=84:16. Yield 140 mg (56 %), amber oil. \(^{1}\)H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 10.11 (s, 1H, CHO), 8.45 (s, 1H, Ar-H-4), 7.85-7.5 (m, 2H, Ar-H-5, Ar-H-8), 7.41-
7.25 (m, 2H, Ar-H-6, Ar-H-7), 3.93-3.87 (m, 4H, O-CH 2), 3.55-3.42 (br.m, 4H, N-CH 2).

$^{13}$C-NMR (50MHz, CDCl3) $\delta$ 189.9 (J), 158.7 (-), 149.2 (-), 143.1 (J), 132.6 (J), 129.2 (J), 127.5 (-), 124.8 (-), 124.0 (J), 121.9 (J), 66.8 (2J), 51.4 (2J). GC-MS, $m/z$ (Irel, (%)): 129.12 (100), 127.92 (79), 242.01 [M$^+$] (77), 207.03 (71), 183.07 (45), 100.9 (44), 157.15 (39), 102.11 (28), 156.14 (26), 74.8 (26), 144.14 (24), 169.13 (20), 77.13 (20), 195.06 (19), 185.14 (18), 213.13 (17), 85.97 (17), 13.19 (16), 184.18 (16), 225.1 (15).

6-Methoxy-2-morpholin-4-ylquinoline-3-carbaldehyde (9m). Prepared following general procedure 1a from 2-chloro-6-methoxyquinoline-3-carbaldehyde (204 mg, 0.92 mmol) and morpholine (240 mg, 2.76 mmol). DMF, 5 mL, 20 h, 80 °C. MPLC gradient PE:EE=80:20 to PE:EE=60:40. Yield 135 mg (54 %), red oil. $^1$H-NMR (200MHz, CDCl3) $\delta$ 10.2 (s, 1H, CHO), 8.46 (s, 1H, Ar-H-4), 8.02 (s, 1H, Ar-H-5), 7.85 (d, 1H, $J=8.8$ Hz, Ar-H-8), 7.41 (br.d, 1H, $J=8.8$ Hz, Ar-H7), 3.90-3.85 (m, 4H, O-CH 2), 3.44-3.34 (m, 4H, N-CH 2), 2.91 (s, 3H, CH 3). $^{13}$C-NMR (50MHz, CDCl3) $\delta$ 190.3 (J), 162.5 (-), 156.6 (-), 145.2 (-), 141.0 (J), 129.1(J), 125.1 (J), 124.9 (-), 122.2 (-), 106.5 (J), 66.8 (2J), 51.7 (2J), 36.4 (J). GC-MS, $m/z$ (Irel, (%)): 272.14 [M$^+$] (100), 159.14 (56), 187.16 (44), 116.1 (39), 213.07 (39), 199.15 (31), 73.3 (28), 158.18 (25), 174.15 (23), 214.16 (21), 215.18 (20), 115.08 (19), 243.18 (19), 171.16 (17), 186.3 (16).

6-Methoxy-2-(4-methylpiperazin-1-yl)quinoline-3-carbaldehyde (9n). Prepared following general procedure 1a from 2-chloro-6-methoxyquinoline-3-carbaldehyde (222 mg, 1 mmol) and 1-methyl-piperazine (301 mg, 3 mmol). DMF, 5 mL, 40 h, 80 °C. MPLC gradient PE to PE:EE=80:20. Yield 266 mg (93 %), yellow oil that crystallized upon standing, yellow needles, mp 114.2 °C. $^1$H-NMR (200MHz, CDCl3) $\delta$ 10.12 (s, 1H, CHO), 8.31 (s, 1H, Ar-H-4), 7.68 (d, 1H, $J=9.2$ Hz, Ar-H-8), 7.28 (dd, 1H, $J=9.2$, $J=2.8$ Hz, Ar-H-7), 6.98 (d, H, $J=2.8$ Hz, Ar-H-5), 3.82 (s, 3H, O-CH 3), 3.42-3.37 (m, 4H, $J=4.8$ Hz, ArN-CH2), 2.6-2.55 (m, 4H, $J=4.8$ Hz, CH3N-CH2), 2.31 (s, 3H, N-CH 3). $^{13}$C-NMR (50MHz, CDCl3) $\delta$ 190 (J), 157.7 (-), 155.9 (-), 144.7 (-), 139.7 (J), 128.5 (J), 124.3 (J), 124.2 (-), 121.6 (-), 109.8 (J), 55 (J), 54.4 (2J), 50.8 (2J), 45.6 (J). GC-MS, $m/z$ (Irel, (%)): 282.16 (100), 162.04 (80), 208.15 (51), 121.98 (35), 57.11 (34), 178.11 (29), 192.14 (28), 123.08 (28), 226.1 (25), 124.09 (20), 207.11 (19), 150.09 (17), 164.11 (16), 283.25 (14), 108.87 (13), 136.09 (12), 135.07 (11), 147.96 (11), 266.22 (10), 94.82 (10).

6-Pyrrolidin-1-yl[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (9o). Prepared following general procedure 1a from 6-chloro[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (1000 mg, 4.25 mmol) and pyrrolidine (907 mg, 13 mmol). DMF, 10 mL, 20 h, 70 °C. MPLC gradient PE to PE:EE =80: 20. Yield 634 mg (60 %), yellow oil. $^1$H-NMR (200MHz, CDCl3) $\delta$ 10 (s, 1H, CHO), 8.1 (s, 1H, Ar-H-4), 6.95 (s, 1H, Ar-H-8), 6.8 (s, 1H, Ar-H-5), 5.95 (s, 2H, -O-CH2-O-), 3.6-3.45 (m, 4H, α–amino-CH2), 2-1.7 (m, 4H, β–ami-no-CH2). $^{13}$C-NMR (50MHz, CDCl3) $\delta$ 189.5 (J),154.5 (-), 153.3 (-), 149.1 (-), 145 (-), 141.6 (J), 133.2 (-), 117.9 (J), 105.3 (-), 103.6 (J), 101.5 (2J), 50.9 (2J), 25.7 (2J).
6-Piperidin-1-yl[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (9p). Prepared following general procedure 1a from 6-chloro[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (40 mg, 0.17 mmol) and piperidine (20 mg, 0.34 mmol). DMF, 2 mL, 40 h, 80 °C. MPLC gradient PE to PE:EE=70:30. Yield 36 mg (75 %), yellow oil, crystals from n-BuOH, yellow needles, mp 103 °C. $^1$H-NMR (200MHz, CDCl$_3$) δ 10.05 (s, 1H, CHO), 8.20 (s, 1H, Ar-H-8), 7.05 (s, 1H, Ar-H-9), 6.96 (s, 1H, Ar-H-4), 6.01 (s, 2H, -O-CH$_2$-O-), 3.30-3.22 (m, 4H, $\alpha$-amino-CH$_2$), 1.8-1.55 (br.m, 6H, $\beta$, $\gamma$-amino-CH$_2$). $^{13}$C-NMR (50MHz, CDCl$_3$) δ 191.8 (J), 155 (-), 151.5 (-), 145.8 (J), 131.5 (-), 129.3 (-), 126.5 (-), 124.0 (J), 121.9 (J), 101.6 (2J), 54.6 (2J), 28.6 (2J), 26.5 (2J). GC-MS, two main peaks, $m/z$ (Irel, (%)): 283.9 [M$^+$] (100), 84.0 (74), 172 (70), 200 (66), 188.1 (62), 113.8 (53), 227 (52), 212.9 (50), 267(23), 240.9 (21), 141.8 (18), 255 (16). 148.08 (100), 149.18 (8), 90.95 (7), 76.97 (6), 120.09 (6), 117.95 (5), 105.09 (4).

6-Morpholin-4-yl[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (9q). Prepared following general procedure 1a from 6-chloro[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (206 mg, 0.87 mmol) and morpholine (228 mg, 2.61 mmol). DMF, 5 mL, 20 h, 80 °C. MPLC in PE to PE:EE=90:10. Yield 166 mg (66 %), orange oil. $^1$H-NMR (200MHz, CDCl$_3$) δ 10.05 (s, 1H, CHO), 8.25 (s, 1H, Ar-H-4), 7.1 (s, 1H, Ar-H-5), 6.96 (s, 1H, Ar-H-8), 6.02 (s, 2H, -O-CH$_2$-O-), 3.88-3.83 (m, 4H, O-CH$_2$), 3.40-3.33 (m, 4H, N-CH$_2$). $^{13}$C-NMR (50MHz, CDCl$_3$) δ 189.8 (J), 153.3 (-), 146.7 (-), 141 (J), 125.9 (-), 125.2 (-), 120.4 (-), 119.7 (-), 104.7 (J), 103.9 (J), 101.9 (2J), 66.8 (2J), 51.7 (2J).

6-(4-Methylpiperazin-1-yl)[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (9r). Prepared following general procedure 1a from 6-chloro[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (197 mg, 0.97 mmol) and 1-methyl-piperazine (251 mg, 2.9 mmol). DMF, 5 mL, 50 h, 80 °C. MPLC gradient PE to PE:EE=80:20. Yield 230 mg (88 %), yellow oil that crystallized upon standing, yellow needles, mp 114.5 °C. $^1$H-NMR (200MHz, CDCl$_3$) δ 10.05 (s, 1H, CHO), 8.19 (s, 1H, Ar-H-8), 7.17 (s, 1H, Ar-H-5), 6.88 (s, 1H, Ar-H-8), 6.02 (s, 2H, -O-CH$_2$-O-), 3.09-3.03 (m, 4H, ArN-CH$_2$), 2.44-2.36 (m, 4H, CH$_3$N-CH$_2$), 2.2 (br.s, 3H, CH$_3$). $^{13}$C-NMR (50MHz, CDCl$_3$) δ 190.1 (J), 158.8 (-), 153.1 (-), 148.3 (-), 146.5 (-), 140.1 (J), 120.2 (-), 119.9 (-), 104.7(J), 103.9 (J), 101.8 (2J), 55.0 (2J), 51.2 (2J), 46.1 (J). GC-MS, 2 main peaks, $m/z$ (Irel, (%)):14.55 min: 104.95 (100), 76.97 (91), 211.18 (68), 316.23 (51), 171.17 (49), 171.17 (25), 315.18 (22), 50.92 (18), 130.07 (14). 15.24 min: 185.04 (100), 70.05 (47), 83.11 (43), 127.9 (38), 129.1 (23), 173.04 (21), 100.91 (14), 255.1 (13), 198.17 (13), 186.19 (11).

3-Benzyl-2-oxo-4-pyrrolidin-1-yl-2,3-dihydro-1,3-thiazole-5-carbaldehyde (9s). Prepared following general procedure 1a from 3-benzyl-4-chloro-2-oxo-2,3-dihydrothiazole-5-carbaldehyde (196 mg, 0.7 mmol) and pyrrolidine (150 mg, 2.2 mmol). DMF, 5 mL, 20 h, 100 °C. MPLC gradient EE to EE:acetone=80:20. Yield 152 mg (76 %), amber oil. $^1$H-NMR (200MHz, CDCl$_3$) δ 9.64 (s, 1H, CHO),
7.33-7.14 (m, 3H, phenyl Ar-H-3, H-4, H-5), 7.09-6.94 (m, 2H, phenyl Ar-H-2, H-6), 5.01 (s, 2H, benzyl-CH2), 3.43-3.20 (br.m, 4H, J=6 Hz, pyrrolidinyl-α-amino-CH2), 1.99-1.67 (bm, 4H, J=8.8, J=6 Hz, pyrrolidinyl-β-amino-CH2).\(^{13}\)C-NMR (50MHz, CDCl\(_3\)) \(\delta\) 180.5, 169.2, 151.6, 135.3, 128, 124.2, 123.6, 105.1, 56.8, 48.4, 24.8. GC-MS, \(m/z\) (Irel, (%)): 98.1 (100), 55.2 (14.5), 84.0 (7.5), 70.1 (7).

3-Benzyl-4-morpholin-4-yl-2-oxo-2,3-dihydro-1,3-thiazole-5-carbaldehyde (9t). Prepared following general procedure 1a from 3-benzyl-4-chloro-2-oxo-2,3-dihydrothiazole-5-carbaldehyde (168 mg, 0.22 mmol) and morpholine (112 mg, 1.32 mmol). 1,2-dichloroethane, 3 mL, 3 h, 80 °C. MPLC gradient PE to PE:EE=80:20. Yield 200 mg (quant.), amber oil, crystals from CH\(_2\)Cl\(_2\)/Et\(_2\)O by diffusion and slow evaporation, mp 215.6 °C. \(^1\)H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 9.8 (s, 1H, CHO), 7.3-7.05 (m, 5H, Ar-H), 4.84 (s, 2H, benzyl-CH2), 3.12-3.01 (m, 4H, J=5.5 Hz, O-CH\(_2\)), 2.99-2.87 (br.m, 4H, N-CH\(_2\)).\(^{13}\)C-NMR (50MHz, CDCl\(_3\)) \(\delta\) 177.1, 167.6, 152.2, 133.2, 126.4, 125.3, 123.8, 105.4, 52.1, 45.1, 23.6. GC-MS, \(m/z\) (Irel, (%)): 98.1 (100), 55.2 (14.6), 84.0 (7.7), 70.1 (7.1).

3-Methyl-5-morpholin-4-yl-1-phenyl-1H-pyrazole-4-carbaldehyde (9u). Prepared following general procedure 1a from 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (163 mg, 0.74 mmol) and morpholine (193 mg, 2.22 mmol). DMF, 5 mL, 20 h, 100 °C. MPLC gradient PE to PE:EE=80:20. Yield 110 mg (51 %), grey oil. \(^1\)H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 9.89 (s, 1H, CHO), 7.50-7.33 (m, 5H, Ar-H), 3.62 (br.d, 4H, J=4.8 Hz, O-CH\(_2\)), 3.07 (br.d, J=4.8 Hz, N-CH\(_2\)), 2.41 (s, 3H, CH\(_3\)).\(^{13}\)C-NMR (50MHz, CDCl\(_3\)) \(\delta\) 182, 151.1, 150.5, 137.8, 128.1, 127.2, 123.7, 110.8, 65.5, 49.6, 12.4. GC-MS, \(m/z\) (Irel, (%)): 211.8 (100), 240 (85), 271 [M\(^+\)] (80), 90.9 (74), 252.1 (67.5), 225.9 (66), 103.9 (60), 51 (56), 184.1(55), 144.1 (53), 115.9 (46), 198.1 (36).

3-Methyl-5-(4-methylpiperazin-1-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (9v). Prepared following general procedure 1a from 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (155 mg, 0.7 mmol) and 1-methyl-piperazine (210 mg, 2.1 mmol). DMF, 5 mL, 16 h, 100 °C. MPLC gradient PE to PE:EE=70:30. Yield 149 mg (75 %), yellow oil. \(^1\)H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 9.85 (s, 1H, CHO), 7.41-6.94 (m, 5H, Ar-H), 3.22-3.05 (m, 4H), 2.40-2.25 (m, 4H), 2.22 (s, 3H, N-CH\(_3\)), 2.2 (s, 3H, Ar-CH\(_3\)).\(^{13}\)C-NMR (50MHz, CDCl\(_3\)) \(\delta\) 184.5, 152.1, 148.7, 136.7, 125.7, 124.6, 123.9, 108, 69.3, 48, 45.5, 15.5.GC-MS, \(m/z\) (Irel, (%)): 70.1 (100), 77.0 (20), 284.1 [M\(^+\)] (18.5), 83.2 (16.5), 91.0 (14.5), 212 (14), 58.2 (13).

**General procedure for the preperation of heterocycles via cyclization by tert-amino-effect:**

**General procedure 3** To 1 eq. of ortho-aminoaldehyde in \(n\)-BuOH there were added 1-1.08 eq. of C-H-acidic compound. The mixture was refluxed on a silicon oil bath with good stirring at a temperature and for the time given, subsequently cooled to rt and the solvent roto-evaporated to yield the crude product that was dissolved in CH\(_2\)Cl\(_2\). There was added an appropriate amount of 40-63 µm silica gel and the resultant suspension was concentrated on a rotavapor until no more solvent was distilled off. The
adsorbed mixture was then loaded as such into an MPLC cartridge for chromatographic separation.

*General procedure 3a:* Analogous to procedure 3, but before chromatographic separation, the resultant crude product was washed with dH₂O (two times using 2 mL/100 mg of expected product) and once with 5 mL brine, the aqueous phases washed once again with CH₂Cl₂ (using 2 mL/mL of dH₂O) and the combined organic phases dried (Na₂SO₄), the solvent roto-evaporated to yield the crude product that was dissolved in CH₂Cl₂. There was added an appropriate amount of 40-63 µm silica gel and the resultant mixture was concentrated on a rotavapor until no more solvent was distilled off. The adsorbed mixture was then loaded as such into an MPLC cartridge for chromatographic separation.

*General procedure 3b:* Analogous to procedure 3, but the crude product was triturated from the least amount of cold 96 % EtOH.

*General procedure 3c:* Analogous to procedure 3, but the crude product was obtained in a state where further purification was unnecessary.

*General procedure 3d:* Analogous to procedure 3, but to the reaction mixture there was added 1 eq. of anhydrous NH₄OAc before refluxing.

*General procedure 3e:* Analogous to procedure 3a, but upon solvent-solvent-extraction, the aqueous phase was adjusted to a pH near the ionization point of the expected product and the aqueous phase continuously extracted with CH₂Cl₂ to yield the crude product in a state where further chromatographic purification was unnecessary.

*(±)-2,2-Dimethyl-1',2',3',3a'-tetrahydro-5'H-spiro[1,3-dioxane-5,4'-pyrrolo[1,2-a]quinoline]-4,6-dione (13a).* Prepared following general procedure 3c from 2-pyrrolidine-1-yl-benzaldehyde 9d (2326 mg, 13.29 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione 11 (1913 mg, 13.29 mmol). n-BuOH, 20 mL, 75 °C, 2 h. Evaporation of solvent and recrystallization from 96 % EtOH. Yield: 2899 mg (97 %), white solid, mp 187 °C (EtOH, decomp.); single crystals for XRD from abs. EtOH/DMF=5:1, colorless prisms, mp 189 °C (decomp). ¹H-NMR (200MHz, CDCl₃)  δ 7.19 (dd, 1H, J=7.9, J=7.6 Hz), 7.05 (d, 1H, J=7.4 Hz), 6.72-6.61 (m, 2H, J=7.9, J=7.4 Hz), 3.99 (dd, 1H, J=8.8, J=3 Hz), 3.70-3.60 (m, 1H), 3.57 (d, 1H, J=16.4 Hz, benzyl-CH₂), 3.33 (dd, 1H, J=16, J=4.2 Hz), 3.19 (d, 1H, J=16.4 Hz, benzyl-CH₂), 2.29-2.15 (br.m, 1H), 2.12-1.98 (br.m, 2H), 1.8 (s, 3H, CH₃), 1.77 (s, 3H, CH₃), 1.74-1.64 (br.m, 1H). ¹³C-NMR (50MHz, CDCl₃)  δ 170 (-), 164.1 (-), 143.1 (-), 128.2 (J), 127.8 (J), 117 (-), 116.2 (J), 111.6 (J), 104.7 (-), 64.6 (J), 48 (2J), 47.3 (-) 36.5 (2J), 30 (J), 28.5 (2J), 28.2 (J), 23.2 (J).

*(±)-2,2-Dimethyl-2',3',4',4a'-tetrahydro-1'H,6'H-spiro[1,3-dioxane-5,5'-pyrido[1,2-a]quinoline]-4,6-dione (13b).* Prepared following general procedure 3b from 2-piperidin-1-yl-benzaldehyde 9e (180 mg, 0.95 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione 11 (135 mg, 0.97 mmol). n-BuOH, 5 mL, 1 h, 75 °C. Trituration from 5 mL cold 96 % EtOH. Yield 288 mg (96 %), white solid, mp 151.6 °C (decomp.), Rₜ=0.46 (PE:EE=75:25). ¹H-NMR (200MHz, CDCl₃)  δ 7.17 (dd, 1H, J=7.8, J=7.2 Hz), 7.01-6.93 (m, 2H,
$J=8, J=6.4$ Hz), 6.75 (dd, 1H, $J=7.4, J=7.2$ Hz), 4.12 (br.d, 1H, $J=12.3$ Hz), 3.54 (d, 1H, $J=16.5$ Hz, benzyl-$\text{CH}_2$), 3.48-3.44 (m, 1H, $J=8.2$ Hz), 3.14 (d, 1H, $J=16.5$ Hz, benzyl-$\text{CH}_2$), 2.80 (m, 1H, $J=12.2, J=11.7$ Hz), 1.89-1.82 (br.m, 1H), 1.78 (br., 6H, $\text{CH}_3$), 1.74-1.68 (bm, 2H), 1.67-1.35 (br.m, 3H). $^{13}$C-NMR (50MHz, CDCl$_3$) $\delta$ 169.3, 164.8, 144.8, 128.7, 127.6, 119.3, 118.2, 113.3, 105, 61.7, 52.1, 48.6, 34.3, 30.3, 28.1, 28, 24.5, 23.9. GC-MS, two peaks, intensity ratio (rel.%): 35 (15.5 min), 100 (16.7 min); m/z (I$_{rel}$, (%)): Signal 15.5 min.: 213.2 (100), 156.1 (70), 184.2 (65), 129.2 (42), 143.2 (20), 170.2 (19), 77.2 (16). Signal 16.7 min.: 184.2 (100), 213.2 (91), 156.2 (66), 130.2 (60), 144.2 (45), 55.1 (45), 77.2 (34), 170.2 (27), 115.1 (20).

(±)-10-Fluoro-1',3'-dimethyl-2,3,4,4a-tetrahydro-1H,2'H,6H-spiro[pyrido[1,2- a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione (13c). Prepared following general procedure 3 from 3-fluoro-2-piperidin-1-yl-benzaldehyde 9g (50 mg, 0.24 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione 12 (38 mg, 0.25 mmol). n-BuOH, 2 mL, 6 h, 75 °C. MPLC gradient PE to PE:EE=80:20. Yield 77 mg (93 %), whitish solid. $^1$H-NMR (200MHz, CDCl$_3$) $\delta$ 6.92 (dd, 1H, $J=7.5, J=1.6$ Hz), 6.79-6.50 (m, 2H), 4.14-4.01 (m, 1H), 3.44 (d, 1H, $J=17.4$ Hz, benzyl-$\text{CH}_2$), 3.46-3.39 (m, 1H), 3.31 (s, 3H, N-$\text{CH}_3$), 3.19 (s, 3H, N-$\text{CH}_3$), 2.95 (d, 1H, $J=17.4$ Hz, benzyl-$\text{CH}_2$), 2.91–2.79 (br.m, 1H), 1.7-1.1 (br.m, 6H). $^{13}$C-NMR (50MHz, CDCl$_3$) $\delta$ 170.3 (-), 167.5 (-), 151.1 (-), 150.2 (-), 133.8 (-), 130.8 (J), 124.5 (-), 123.9 (J), 119.2 (J), 64.6 (J), 53.1 (-), 51.5 (2J), 35.6 (2J), 29.1 (J), 28.6 (J), 26.8 (2J), 24.9 (2J), 24.1 (2J).GC-MS, m/z (I$_{rel}$, (%)): 345.3 [M +] (100), 189.2 (99), 57.9 (88), 148.2 (68), 83.2 (56), 174.2 (52), 161.2 (33), 135.2 (22).

(±)-10-Fluoro-1',3'-dimethyl-1,2,4,4a-tetrahydro-2'H,6H-spiro[1,4-oxazino[4,3-a]quinoline-5,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione (13d). Prepared following general procedure 3 from 3-fluoro-2-morpholin-4-yl-benzaldehyde 9i (38 mg, 0.18 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione 12 (29 mg, 0.19 mmol). n-BuOH, 2 mL, 6 h, 100 °C. MPLC gradient PE to PE:EE=50:50. Yield 63 mg (quant.), white solid. $^1$H-NMR (200MHz, CDCl$_3$) $\delta$ 6.93 (dd, 1H, $J=7.6, J=1.2$ Hz), 6.89-6.72 (m, 2H), 3.83-3.53 (br.m, 6H), 3.34 (d, 1H, $J=15.8$ Hz, benzyl-$\text{CH}_2$), 3.21 (s, 3H, N-$\text{CH}_3$), 3.2 (s, 3H, N-$\text{CH}_3$), 3.1-3.01 (m, 1H), 2.95 (d, 1H, $J=15.8$ Hz, benzyl-$\text{CH}_2$). $^{13}$C-NMR (50MHz, CDCl$_3$) $\delta$ 170.2 (-), 169.9 (-), 150.8 (-), 134.5 (-), 126.9 (-), 124.1 (J), 121.8 (J), 121.6 (-), 114.2 (J), 67.1 (2J), 66.6 (2J), 62.5 (J), 50.1 (-), 45.8 (2J), 35.1 (2J), 29 (J), 28.9 (J).GC-MS, m/z (I$_{rel}$, (%)): 347.2 [M +] (100), 174.0 (87), 303.2 (80), 147.2 (67), 316.2 (65), 58.1 (51), 260.2 (48).

(±)-1',3'-Dimethyl-1,2,3,3a-tetrahydro-2'H,5H-spiro[benzo[g]pyrrolo[1,2-a]-1,8-naphthyridine-4,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione (13e). Prepared following general procedure 3 from 2-pyrrolidin-1-yl-quinoline-3-carbaldehyde 9k (249 mg, 1.01 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione 12 (172 mg, 1.01 mmol). n-BuOH, 10 mL, 30 h, 75 °C. MPLC gradient PE to PE:EE=80:20. Yield 400 mg (quant.), whitish solid. $^1$H-NMR (200MHz, CDCl$_3$) $\delta$ 7.69 (d, 1H, $J=8.3$ Hz), 7.54 (br.s, 1H, Ar-H-4),
7.48-7.37 (m, 2H, J=8.3, J=7.7, J=1.5 Hz), 7.11 (ddd, 1H, J=7.9, J=6.8, J=1.1 Hz), 4.12-3.96 (m, 2H, J=16.4, J=1.9 Hz, benzylidene-H, α-amino-CH2, α-amino-CH), 3.14 (s, 3H, CH3), 3.01 (d, 1H, J=16.4 Hz, benzylidene-H), 2.07-1.86 (m, 2H, J=5.8, J=4.3, J=2.6 Hz, β-amino-CH2), 1.52-1.33 (m, 2H, J=9.8, J=7.1, J=1.5 Hz, β-amino-CH2).

13C-NMR (50MHz, CDCl3) δ 169.9 (β), 166.6 (β), 152.4 (β), 150.8 (β), 147.1 (β), 133.9 (β), 128.8 (β), 126.8 (β), 125.9 (β), 121.9 (β), 117.1 (β), 64.2 (β), 49 (β), 47.1 (2J), 36.8 (2J), 29.1 (β), 28.5 (2J), 28.4 (2J), 23 (2J).

(±)-2',2'-Dimethyl-1,2,3,3a-tetrahydro-5H-spiro[1,3-benzodioxolo[5,6-g]pyrrolo[1,2-a]-1,8-naphthyridine-4,5'-[1,3]dioxane]-4',6'-dione (13f). Prepared following general procedure 3 from 6-pyrrolidin-1-yl-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde 9o (448 mg, 1.66 mmol) and 2,2-dimethyl[1,3]dioxane-4,6-dione 11 (239 mg, 1.66 mmol). n-BuOH, 10 mL, 20 h, 75 °C. MPLC gradient PE to PE:EE=80:20. Yield 650 mg (99 %), white solid, mp 232.8 °C. 1H-NMR (200MHz, CDCl3) δ 7.42 (s, 1H, Ar-H-4), 7.09 (s, 1H, Ar-H-8), 6.79 (s, 1H, Ar-H-5), 5.93 (s, 2H, -O-CH2-O-), 4.15-3.9 (m, 2H, α-amino-CH2, α-amino-CH), 3.55 (d, 1H, J=17.2 Hz, benzylidene-CH2), 3.6-3.42 (m, 3H), 1.75 (s, 3H, CH3), 1.76 (s, 3H, CH3).13C-NMR (50MHz, CDCl3) δ 169.3 (β), 163.9 (β), 151.1 (β), 144 (-), 133.7 (β), 136 (-), 118.1 (-), 113 (-), 105 (-), 103.9 (β), 102.8 (β), 101 (2J), 64.5 (β), 49.8 (-), 47.4 (2J), 36.2 (2J), 30.1 (β), 28.9 (2J), 28.1 (β), 22.9 (2J).

(±)-2',2'-Dimethyl-1,2,4,4a-tetrahydro-6H-spiro[1,3-benzodioxolo[5,6-g]oxazino[4,3-a]-1,8-naphthyridine-5,5'-[1,3]dioxane]-4',6'-dione (13g). Prepared following general procedure 3 from 6-morpholin-4-yl-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde 9q (140 mg, 0.53 mmol) and 2,2-dimethyl[1,3]dioxane-4,6-dione 11 (75 mg, 0.53 mmol). n-BuOH, 5 mL, 20 h, 75 °C. MPLC gradient PE to PE:EE=80:20. Yield 110 mg (51 %), white solid. 1H-NMR (200MHz, CDCl3) δ 7.59 (s, 1H, Ar-H-4), 7.06 (s, 1H, Ar-H-8), 6.85 (s, 1H, Ar-H-5), 5.93 (s, 2H, -O-CH2-O-), 4.94 (d, 1H, J=13 Hz), 4.02 (m, 2H), 3.71-3.49 (m, 3H), 3.21-2.92 (m, 3H), 1.75 (s, 3H, CH3).13C-NMR (50MHz, CDCl3) δ 170.2 (β), 168.9 (-), 149.7 (-), 144.2 (-), 141.8 (-), 133.8 (β), 123.9 (-), 122.6 (-), 111 (-), 104.8 (β), 103.8 (-), 102.2 (β), 101.8 (2J), 68 (2J), 66.5 (2J), 60.8 (β), 49 (-), 46.4 (-), 44 (2J), 36.2 (2J), 24.5 (β), 23.2 (β).

(±)-1',3'-Dimethyl-1,2,4,4a-tetrahydro-2'H,6'H-spiro[1,3-benzodioxolo[5,6-g][1,4]oxazino[4,3-a]-1,8-naphthyridine-5,5'-pyrimidine]-2',4',6'-[1'H,3'H]-trione (13h). Prepared following general procedure 3 from 6-morpholin-4-yl-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde 9q (50 mg, 0.175 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione 12 (27.5 mg, 0.18 mmol). n-BuOH, 5 mL, 45 h, 75 °C. MPLC gradient PE to PE:EE=50:50. Yield 65 mg (88 %), nearly colorless solid. 1H-NMR (200MHz, CDCl3) δ 7.41 (s,
1H, Ar-H-4), 7.01 (bs, 1H, Ar-H-5), 6.77 (s, 1H, Ar-H-8), 5.96 (s, 2H, O-CH\textsubscript{2}-O-), 4.97 (d, 1H, J=13.5 Hz), 3.99-3.84 (m, 2H), 3.66-3.42 (br.m, 3H), 3.31 (s, 3H, N-CH\textsubscript{3}), 3.2 (s, 3H, N-CH\textsubscript{3}), 3.19-2.91 (br.m, 3H).\textsuperscript{13}C-NMR (50MHz, CDCl\textsubscript{3}) δ 169.4 (-), 166.2 (-), 150.5 (-), 141.9 (-), 140.4 (-), 133.7 (J), 120.3 (-), 119.3 (-), 114.1 (-), 109.3 (-), 104.2 (J), 102.4 (J), 66.9 (2J), 66.4 (2J), 59.4 (J), 49.4 (-), 44.0 (2J), 35.1 (2J), 29.2 (J), 28.6 (J).GC-MS, m/z (I rel, (%)):149.1 (100), 57.2 (37), 167.1 (28), 71.2 (24), 113.2 (12), 83.2 (9).

\((\pm)-2',2'-\text{Dimethyl-2,3,4,4a-tetrahydro-1H,6H-spiro[1,3-benzodioxolo[5,6-g]pyrido[1,2-a]-1,8-naphthyridine-5,5'-[1,3]dioxane]-4',6'-dione}\) (13i). Prepared following general procedure 3 from 6-piperidin-1-yl-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde \textbf{9p} (75 mg, 0.27 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione \textbf{11} (39 mg, 0.28 mmol). n-BuOH, 5 mL, 4 h, 75 °C. MPLC gradient PE to PE:EE=80:20. Yield 108 mg (99 %), white solid.\textsuperscript{1}H-NMR (200MHz, CDCl\textsubscript{3}) δ 7.36 (s, 1H, Ar-H-4), 7.05 (s, 1H, Ar-H-5), 6.8 (s, 1H, Ar-H-8), 5.96 (s, 2H, -O-CH\textsubscript{2}-O-), 4.9-4.83 (d, 1H, J=12.8 Hz, α−amino-CH\textsubscript{2}), 3.58-3.53 (m, 1H, α−amino-CH), 3.52-3.09 (m, 4H, J=16.6, J=12.8 Hz, α−amino-CH\textsubscript{2}, benzyl-CH\textsubscript{2}, β−amino-CH), 2.88-2.72 (br.m, 1H), 1.82 (br.s, 6H, CH\textsubscript{3}), 1.8-1.2 (br.m, 4H, β−, γ−amino-CH\textsubscript{2}).

\textbf{2,2-Dimethyl-5-[(6-piperidin-1-yl-[1,3]dioxolo[4,5-g]quinolin-7-yl)methylene]-1,3-dioxane-4,6-dione} (13i-1). Prepared from 6-piperidin-1-yl-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde \textbf{9p} (75 mg, 0.27 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione \textbf{11} (39 mg, 0.28 mmol) in 2 mL n-BuOH. The mixture was stirred for 30 min at rt until a thick orange to brownish precipitate had developed; the precipitate was filtered off, washed with 3x 0.5 mL n-BuOH and once with 0.5 mL cold MeOH yielding 71 mg (65 %) as an orange solid which was dried under vaccuum and exhibited spectroscopic properties exhibited by the proposed Knoevenagel-type benzylidenic intermediate as well as a little of an impurity, supposedly 13i. Upon standing in CDCl\textsubscript{3} at rt overnight the sample turned colorless. NMR-measurements were repeated and showed only signals corresponding to the cyclized product (characterisation see 13i).\textsuperscript{1}H-NMR (200MHz, CDCl\textsubscript{3}) δ 8.52 (s, 1H, benzylidene-H), 8.50 (s, 1H, Ar-H-4), 7.06 (s, 1H, Ar-H-5), 6.01 (s, 2H, O-CH\textsubscript{2}-O-), 3.29-3.13 (br.m, 4H, α−amino-CH\textsubscript{2}), 1.81-1.54 (br.m, 12H, CH\textsubscript{3}, β−, γ−amino-CH\textsubscript{2}).

\((\pm)-1',3'-\text{Dimethyl-2,3,4,4a-tetrahydro-1H,2'H,6H-spiro[1,3-benzodioxolo[5,6-g]pyrido[1,2-a]-1,8-naphthyridine-5,5'-pyrimidine]-2',4',6'(1'H,3'H)trione}\) (13j). Prepared following general procedure 3 from 6-piperidin-1-yl-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde \textbf{9p} (31 mg, 0.11 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione \textbf{12} (17 mg, 0.11 mmol). n-BuOH, 2 mL, 6 h, 100 °C. MPLC gradient PE to PE:EE=70:30. Yield 43 mg (92 %), white solid.\textsuperscript{1}H-NMR (200MHz, CDCl\textsubscript{3}) δ 7.38 (s, 1H, Ar-H-4), 7.01 (s, 1H, Ar-H-5), 6.79 (s, 1H, Ar-H-8), 5.93 (s, 2H, O-CH\textsubscript{2}-O-), 4.97 (d, 1H, J=14 Hz), 3.66-3.60 (m, 1H, J=11.4, J=2.2 Hz), 3.42-3.16 (m, 4H), 3.29 (s, 3H, N-CH\textsubscript{3}), 3.23 (s, 3H, N-CH\textsubscript{3}), 2.68-2.62 (br.m, 1H), 1.8-1.2 (br.m, 4H).\textsuperscript{13}C-NMR (50MHz, CDCl\textsubscript{3}) δ 169.5 (-), 166 (-), 150.3 (-), 141.6 (-), 140 (-), 133.5
(±)-1',3,3'-Trimethyl-2,3,4,4a-tetrahydro-1'H,2'H,6H-spiro[1,3-benzodioxolo[5,6-g]pyrazino[1,2-a]-1,8-naphthyridine-5,5'-pyrimidine]-2',4',6'-(1'H,3'H)-trione (13k). Prepared following general procedure 3 from 6-(4-methyl-piperazin-1-yl)[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde 9r (50 mg, 0.17 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione 12 (27 mg, 0.18 mmol). n-BuOH, 5 mL, 30 h, 75 °C. MPLC gradient PE to PE:EE= 70:30. Yield 73 mg (quant.), white solid. ¹H-NMR (200MHz, CDCl3) δ 7.38 (s, 1H, Ar-H-4), 7.02 (s, 1H, Ar-H-8), 6.78 (s, 1H, Ar-H-5), 5.93 (s, 2H, -O-CH2-O-), 5.17-5.09 (m, 1H, J=12.5 Hz), 3.89 (dd, 1H, J=10.7, J=2.7 Hz), 3.45 (m, 1H, J=16.8, J=1.2 Hz, benzylic-CH2), 3.40 (s, 1H), 3.30 (s, 3H, (CO)N-CH3), 3.22 (s, 3H, (CO)N-CH3), 3.12 (d, 1H, J=16.8 Hz, benzylic-CH2), 2.97 (br.m, 1H, J=3.1 Hz), 2.8 (d, 1H, J=11.5 Hz), 2.55 (br.d, 1H, J=10.2 Hz), 2.21 (s, 3H, N-CH3), 2.11-2.06 (br.m, 1H, J=11.7, J=3.1 Hz). ¹³C-NMR (50MHz, CDCl3) δ 169.5 (-), 167 (-), 152.1 (-), 150.8 (-), 149.9 (-), 144.9 (-), 144.3 (-), 133.6 (J), 119.2 (-), 114.5 (-), 104.2 (J), 102.4 (J), 101 (2J), 95.9 (J), 55.7 (2J), 53.7 (2J), 50.8 (-), 44.2 (2J), 34 (2J), 29.9 (J), 28.7 (J), 26.9 (J). GC-MS, m/z (Irel, (%)): 149.1 (100), 167.1 (37), 71.2 (30).

(±)-1'-Benzyl-2,2-dimethyl-1',4',5a',6',8',9'-hexahydro-2'H-spiro[1,3-dioxane-5,5'-(1,4)oxazine]-2',4,6-trione (13l). Prepared following general procedure 3 from 3-benzyl-4-morpholin-4-yl-2-oxo-2,3-dihydrothiazole-5-carbaldehyde 9t (25 mg, 0.09 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione 11 (12.8 mg, 0.09 mmol). n-BuOH, 2 mL, 100 h, 75 °C. MPLC gradient PE to PE:EE=90:10. Yield 36 mg (95 %), greyish solid. ¹H-NMR (200MHz, CDCl3) δ 7.31-7.05 (m, 5H, Ar-H), 4.99-4.95 (m, 2H, N-CH2Ph), 4.16-4.09 (bs, 1H, α−amino-CH), 3.69-3.59 (m, 2H), 3.44 (d, 1H, J=16.1 Hz, benzylic-CH2), 3.29 (d, 1H, J=16.1 Hz, benzylic-CH2), 2.92-2.85 (m, 2H), 2.84-2.77 (m, 2H), 1.38 (s, 3H, CH3), 1.37 (s, 3H, CH3). ¹³C-NMR (50MHz, CDCl3) δ 166.7, 166.5, 165.5, 165.2, 131.4, 129.8, 127.9, 127.8, 125.5, 121.8, 103, 67.1, 65.4, 55.7, 51.4, 50.3, 44.1, 37.7, 28.4, 28.1. GC-MS, two major peaks of rel. int. 51 %, 100 %; m/z (Irel, (%)): 100 % rel. int. peak, 16 min, m/z (Irel, (%)): 242.9 (100), 184 (76), 77 (64), 186.2 (56), 51 (48). 51 % rel. int. peak, 22 min, m/z (Irel, (%)): 149 (100), 167 (82), 57.1 (72), 70.2 (63), 150.1 (40).

(±)-1',3,3'-Trimethyl-1-phenyl-1,4,6,7,8,9-hexahydro-2'H,5aH-spiro[pyrazolo[4,3-c]quinolizine-5,5'-pyrimidine]-2',4',6'-(1'H,3'H)-trione (13m). Prepared following general procedure 3 from 3-methyl-1-phenyl-5-piperidin-1-yl-1H-pyrazole-4-carbaldehyde (27 mg, 0.1 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione 12 (16 mg, 0.11 mmol). n-BuOH, 2 mL, 24 h, 100 °C. MPLC gradient PE to PE:EE=80:20. Yield 41 mg (88 %), white solid. ¹H-NMR (200MHz, CDCl3) δ 7.33-7.22 (m, 5H, Ar-H), 4.30 (bs, 1H), 3.91-3.87 (m, 1H), 3.50-3.46 (m, 1H), 3.34 (s, 3H, N-CH3), 3.33 (s, 3H, N-CH3), 3.31 (d, 1H, J=17 Hz),
3.29-3.25 (m, 2H), 3.19 (d, 1H, J = 17 Hz), 3.01-2.93 (m, 1H), 2.35 (s, 3H, Ar-CH₃), 1.9-1.81 (br.m, 1H), 1.6-1.4 (br.m, 2H). ¹³C-NMR (50MHz, CDCl₃) δ 171.7, 169.4, 150, 133.3, 132.5, 129.2, 128.7, 128.3, 127.7, 126.2, 66.2, 52.7, 54.7, 44.4, 37.4, 30.3, 29.9, 28.1, 25.2, 13.4. GC-MS, m/z (Irel, (%)): 240.8 (100), 77 (57), 84 (56), 158.2 (43), 117.1 (42), 212.2 (42), 184.2 (41).

(±)-2,2,3'-Trimethyl-1'-phenyl-1',4',5a',6',8',9'-hexahydrospiro[1,3-dioxane-5,5'-pyrazolo[4',3';5,6]pyrazolo[4',3':5,6]pyrido[2,1-c][1,4]oxazine]-4,6-dione (13n). Prepared following general procedure 3 from 3-methyl-5-morpholin-4-yl-1-phenyl-1H-pyrazole-4-carbaldehyde 9u (25 mg, 0.09 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione 11 (14 mg, 0.1 mmol). n-BuOH, 2 mL, 100 h, 100 °C. MPLC gradient PE to PE:EE=50:50. Yield 27 mg (75 %), colorless solid. ¹H-NMR (200MHz, CDCl₃) δ 7.29-7.15 (m, 5H, Ar-H), 4.23 (br.s, 1H), 4.02-3.95 (m, 2H), 3.88-3.79 (m, 2H), 3.59-3.54 (m, 2H), 3.30 (d, 1H, J=16.9 Hz, benzylic-CH₂), 3.12 (d, 1H, J=16.9 Hz, benzylic-CH₂), 2.41 (s, 3H, Ar-CH₃), 1.39 (s, 3H, CH₃), 1.38 (s, 3H, CH₃). ¹³C-NMR (50MHz, CDCl₃) δ 171.5, 166.4, 135.3, 133.3, 129.2, 128.9, 128.3, 127.5, 126.3, 103.3, 65.3, 54.7, 52.7, 45.3, 41.7, 30.4, 23.5, 22.7, 13.8. GC-MS, two major peaks, m/z (Irel, (%)): 56.1 (100), 104.9 (63), 86.9 (51), 143 (50), 161.1 (38), 217.2 (33); 91 (100), 132 (90), 178.9 (88), 104 (77), 65 (73), 77 (68), 146.1 (66).

(±)-1',3,3'-Trimethyl-1-phenyl-1,4,5a,6,8,9-hexahydro-2'H-spiro[pyrazolo[4',3';5,6]pyrimidine]-2',4',6'(1'H, 3'H)-trione (13o). Prepared following general procedure 3 from 3-methyl-5-morpholin-4-yl-1-phenyl-1H-pyrazole-4-carbaldehyde 9u (27 mg, 0.1 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione 12 (16 mg, 0.1 mmol). n-BuOH, 2 mL, 90 h, 100 °C. MPLC gradient PE to PE:EE=60:40. Yield 24 mg (60 %), white solid. ¹H-NMR (200MHz, CDCl₃) δ 7.33-7.22 (m, 5H, Ar-H), 4.14 (br.s, 1H), 3.75-3.71 (m, 2H), 3.60-3.54 (m, 2H), 3.51 (d, 1H, J=15.8 Hz), 3.41 (d, 1H, J=15.8 Hz), 3.31-3.28 (br.s, 6H, N-CH₃), 2.4 (s, 3H, Ar-CH₃). ¹³C-NMR (50MHz, CDCl₃) δ 169.5, 168.4, 151.3, 134.4, 133.2, 129.2, 128.9, 128.3, 127.5, 126.3, 66.2, 57.8, 52.7, 50.7, 44, 38.1, 28.5, 28.2, 13.8. GC-MS, two major peaks, rel. int. 49 %, 100 %, m/z (Irel, (%)): 100 % rel. int. peak, 16 min: 184.1 (100), 242.3 (98), 77 (92), 186.2 (78), 51.1 (63). 21 min: 149 (100), 167.1 (86), 57.1 (82), 70.2 (75), 150.1 (38).

(12bS)-8-Methoxy-1',3',12b-trimethyl-7,12b-dihydro-2'H,6H,14H-spiro[1,3-dioxolo[6,7]isoquinoline-13,5'-pyrimidine]-2',4',6'-(1'H,3'H)-trione (14). Prepared following general procedure 3b from 2-((S)-9-methoxy-5-methyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)benzaldehyde 9c (100 mg, 0.307 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione 12 (51 mg, 0.33 mmol). n-BuOH, 5 mL, 22 h, 75 °C. Trituration from 5 mL cold 96 % EtOH. Yield 98 mg (69 %), amber solid, mp 215.9 °C, [α]D²⁰ +13.7 (c 0.93, CHCl₃). ¹H-NMR (200MHz, CDCl₃) δ 7.4 (bd, 1H, J=6.6 Hz), 7.2-6.99 (m, 2H, J=7.6, J=7.2, J=6.3 Hz), 6.77 (bd, 1H, J=7.6 Hz), 6.35 (s, 1H), 6.06 (d, 1H, J=1 Hz, -O-CH₂-O-), 5.86 (d, 1H, J=1 Hz, -O-CH₂-O-), 4.37-4.25 (m, 1H, J=18, J=11.4, J=5.5 Hz, 0.84 (56), 158.2 (43), 117.1 (42), 212.2 (42), 184.2 (41).
α-amino-CH₂), 3.9 (s, 3H, O-CH₃), 3.7 (d, 1H, J=16.2 Hz, benzyl-CH₂), 2.93-2.86 (m, 1H, J=15.8, J=10, J=5.5 Hz), 2.81-2.67 (m, 1H, J=15.8, J=11.4, J=4.5 Hz), 1.93 (s, 3H, C₆H₅-CH₂).13C-NMR (50MHz, CDCl₃) δ 166.4 (-), 165.1 (-), 151.9 (-), 148.6 (-), 146.7 (-), 141.5 (-), 134.5 (-), 131.5 (-), 130.8 (J), 129.7 (-), 126.7 (J), 123.8 (J), 118.1 (J), 109.2 (-), 107.6 (J), 102.2 (2J), 56.9 (J), 47.5 (2J), 29.8 (2J), 28.8 (2J), 28.3 (J), 28.2 (J), 20.1 (J). GC-MS, m/z (Irel, (%)): Fragmentation, 2 main peaks: broad, 13.73-13.85 min: 380.13 (100), 306.09 (60), 395.19 (45), 322.14 (23), 294.13 (17), 76.99 (15), 352.13 (11), 204.14 (10), 292.14 (10); 14.15 min: 378.12 (100), 304.11 (59), 72.98 (56), 281.05 (50), 95.86 (48), 393.11 (32).

(+)-1,1',3-Trimethyl-2'- (3,4,5-trimethoxybenzyl)-1',4'-dihydro-2'H,2'H-spiro[pyrimidine-5,3'-quinoline]-2,4,6(1'H,3'H)-trione (15). Prepared following general procedure 3 from 2-{methyl-[2-(3,4,5-trimethoxy-phenyl)ethyl]amino}benzaldehyde 9b (100 mg, 0.304 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione (50 mg, 0.32 mmol). n-BuOH, 5 mL, 30 h, 75 °C. MPLC gradient PE:CH₂Cl₂=88:12 to PE:CH₂Cl₂:Et₂O=70:10:20. Yield 125 mg (88 %), yellow oil that upon standing spontaneously crystallized to a white solid, mp 256.7 °C.1H-NMR (200MHz, CDCl₃) δ 7.19-7.03 (m, 2H, J=8, J=7.4, J=0.8 Hz), 6.72 (dd, 1H, J=7.4, J=0.8 Hz), 6.46 (d, 1H, J=8 Hz), 6.03 (br.s, 2H), 3.77-3.63 (br.m, 2H, J=17.6 Hz), 3.76 (s, 3H, O-CH₃), 3.69 (br.s, 6H, O-CH₃), 3.25 (s, 3H, (CO)₂N-CH₃), 3.15 (s, 3H, (CO)₂N-CH₃), 2.99 (d, 1H, J=17.6 Hz, benzyl-CH₂), 2.57 (dd, 1H, J=15.8, J=12.3, J=4.4 Hz), 2.37-2.24 (m, 2H, J=9.8, J=7.6, J=2.4 Hz), 2.24-2.16

(+)-(3aR*,4S*)-1,2,3,3a,4,5-Hexahydropyrrolo[1,2-a]quinoline-4-carboxylic acid (16a). (+)-(3aR*,4R*)-1,2,3,3a,4,5-Hexahydropyrrolo[1,2-a]quinoline-4-carboxylic acid (17a). Prepared following general procedure 3e from (+)-2,2-dimethyl-1',2',3',3a'-tetrahydro-5'H-spiro[1,3-dioxane-5,4'-pyrrolo[1,2-a]quinoline]-4,6-dione 13a (752mg, 2.56 mmol). H₂O/HCl, 20 mL, pH 1, 95 °C, 50 h. The resultant aqueous suspension was basified to pH 4.2 and extracted continuously with CH₂Cl₂. The organic phases were once washed with 2 mL dH₂O, dried (Na₂SO₄) and rotaryevaporated to yield 457 mg (82 %), purity by HPLC 97.6 % (254 nm), slightly brown solid, recrystallization from 96 % EtOH, blackish to violet plates, mp 116-121°C (decomp.); diastereomer ratio is u:l ≥ 7:1 (de ≥ 75 %) via integration in 1H-NMR. Main isomer (3a,4-u): 1H-NMR (200MHz, CDCl₃) δ 9.97 (bs, 1H, COO-H), 7.03 (dd, 1H, J=8, J=7.4 Hz), 6.94 (d, 1H, J=7.8 Hz), 6.55 (br.d, 1H, J=7.4 Hz), 6.36 (d, 1H, J=7.8 Hz), 3.51-3.38 (ddd, 1H, J=10, J=5, J=2.4 Hz), 3.36-3.27 (br.dd, 1H, J=8.9, J=2.2 Hz), 3.20- 3.08 (ddd, 1H, J=9.9, J=8.9, J=1.6 Hz), 2.98-2.88 (m, 2H, J=15.8, J=12.3, J=4.4 Hz), 2.37-2.24 (m, 1H, J=9.8, J=7.6, J=2.4 Hz), 2.24-2.16
(br.m, 1H, J=12.3, J=5.4 Hz), 2.03-1.79 (br.m, 2H, J=11.7, J=9.2, J=6.9, J=4.9, J=2.3 Hz), 1.61-1.45 (ddd, 1H, J=11.5, J=10, J=7.8 Hz). $^{13}$C-NMR (50MHz, CDCl$_3$) $\delta$ 180.8 (-), 143.7 (-), 128.5 (J), 127.7 (J), 119.4 (-), 115.4 (J), 110.4 (J), 59.3 (J), 47.2 (2J), 43.5 (J), 31.9 (2J), 28.5 (2J), 23.7 (2J). $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 7.01-6.95 (m, 2H, J=7.6 Hz), 6.5-6.46 (dd, 1H, J=7, J=6.4 Hz), 6.39-6.37 (br.d, 1H, J=7.9 Hz), 3.4-3.34 (m, 1H, J=8.8 Hz), 3.33-3.29 (br.m, 1H, J=8.8 Hz), 3.13-3.07 (m, 1H, J=8.8, J=7.6 Hz), 2.89 (br.dd, 1H, J=15.8, J=4.4 Hz, benzyl-CH$_2$), 2.8 (br.dd, 1H, J=15.8, J=12 Hz, benzyl-CH$_2$), 2.17-2.11 (br.m, 2H, J=12, J=9.8, J=7.6 Hz, J=4.4 Hz, $\alpha$-keto-H, $\beta$-amino-CH$_2$), 2.04-1.95 (br.m, 1H, J=12.6, J=6.1 Hz), 1.91-1.81 (br.m, 1H, J=8.5, J=6.4 Hz), 1.56-1.45 (m, 1H, J=7.6 Hz). Minor isomer 17a, (3a,4-$d$): $^1$H-NMR (200MHz, CDCl$_3$) $\delta$ 10.2-9.8 (m (br.s), 1H, COO-H), 7.11 (m, 1H), 6.79 (m, 1H), 6.55 (br.d, 1H, J=7.4 Hz), 6.3 (m, 1H), 3.67-3.61 (br.m, 1H); other signals are not resolved properly. $^{13}$C-NMR (50MHz, CDCl$_3$) $\delta$ 177.2 (-), 144.5 (-), 128.8 (J), 127.3 (J), 120.2 (-), 117.6 (J), 112.3 (J), 58.7 (J), 47.3 (2J), 40 (J), 31.1 (2J), 28.8 (2J), 22.9 (2J). GC-MS, m/z ($\text{I}_{rel}$, (%)): $^1$-l-$ mixture, 2 main peaks: 12.91 min: 223.15 (100), 221.07 (72), 195.13 (49), 167.12 (44). 13.07 min: 223.01 (100), 221.1 (54), 195.16 (41), 167.15 (31). MALDI-MS/MS: m/z ($\text{I}_{rel}$, %) TIC, MS$_2$: 170.1 (100); 385.1 (33): 341.1 (100), 196.1 (67), 385.1 (51), 170 (9), 216 (8); 186 (9); 212.1 (7); 357.1 (6); 401.1 (5); 337.1 (4); 415.1 (4).

(±)-(4a*R*,5S*)-2,3,4,4a,5,6-Hexahydro-1H-pyrido[1,2-a]quinoline-5-carboxylic acid (16b). (±)-(4a*R*,5R*)-2,3,4,4a,5,6-Hexahydro-1H-pyrido[1,2-a]quinoline-5-carboxylic acid (17b). Prepared following general procedure 3e from (±)-2,2-dimethyl-2',3',4',4a'-tetrahydro-1'H,6'H-spiro[1,3-dioxane-5,5'-pyrido[1,2-a]quinoline]-4,6-dione 13b (850 mg, 2.7 mmol). H$_2$O/HCl, 20 mL, pH 1, 95 °C, 16 h. The resultant aqueous suspension was basified to pH 5.4 and continuously extracted with CH$_2$Cl$_2$. The organic phases were once washed with 2 mL dH$_2$O, dried (Na$_2$SO$_4$) and rotoevaporated to yield 588 mg (95 %), purity by HPLC 97.9 % (254 nm), slightly brown semi-solid, diastereomer ratio is $u:l \geq 5:1$ (de $\geq 67 %$) via integration in $^1$H-NMR (~7:1 via integration in $^{13}$C-NMR). Main isomer (4a,5-$u$): $^1$H-NMR (200MHz, CDCl$_3$) $\delta$ 11.2-10.7 (br.s, 1H, COO-H), 7.03 (dd, 1H, J=7.8, J=7.6 Hz), 6.91 (d, 1H, J=7.4 Hz), 6.81-6.68 (m, 1H, J=8.2, J=7.6 Hz), 6.65-6.58 (m, 1H, J=7.2 Hz), 3.85 (d, 1H, J=13.1 Hz, $\alpha$-amino-CH$_2$), 3.14 (dd, 1H, J=9.6, J=7.8 Hz, $\alpha$-amino-CH), 3.01-2.59 (m, 4H, J=16.4, J=15.2, J=12.8, J=9.6, J=7.2 Hz), 1.73-1.18 (br.m, 6H), $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 6.98 (dd, 1H, J=8.9, J=7.3 Hz), 6.89 (d, 1H, J=7.3 Hz), 6.7 (d, 1H, J=8.2 Hz), 6.55 (dd, 1H, J=7.6, J=7.3 Hz), 3.85 (bd, 1H, J=12.9 Hz, $\alpha$-amino-CH$_2$), 3.15 (ddd, 1H, J=9.4, J=8.5, J=5.6 Hz, $\alpha$-amino-CH), 2.95 (dd, 1H, J=15, J=8.5 Hz, benzyl-CH$_2$), 2.8-2.61 (m, 2H, J=15, J=12.9, J=5 Hz benzyl-CH$_2$, $\alpha$-amino-CH$_2$), 2.54-2.48 (ddd, 1H, J=9.4, J=9.1, J=5.1 Hz), 1.80-1.63 (br.m, 3H), 1.57-1.27 (br.m, 3H). $^{13}$C-NMR (50MHz, CDCl$_3$) $\delta$ 180.2 (-), 145.5 (-), 129.9 (J), 127.5 (J), 122.8 (-), 118.3 (J), 113.2 (J), 58 (J), 48.5 (2J), 46 (J), 31.1 (2J), 29.7 (2J), 24.7 (2J), 24.5 (2J). Minor
isomer 17b, (4a,5-): \(^1\)H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 11.2-10.7 (br.s, 1H, COO-H), 7.07-6.90 (m, 2H), 6.81-6.57 (m, 2H), 3.97 (d, 1H, J=14.3 Hz), 3.51-3.44 (br.m, 1H), 3.01-2.59 (m, 4H), 1.73-1.18 (br.m, 6H), other signals not resolved properly. \(^1\)H-NMR (400MHz, CDCl\(_3\)) \(\delta\) 7-6.5 (4 Ar-H), 3.99 (d, 1H, J=14.3 Hz), 3.61-3.49 (ddd,1H, J=8.2, J=4.5, J=4.2 Hz, \(\alpha\)-amino-CH), 2.99-2.89 (m, 1H, J=12 Hz), other signals not resolved. \(^1\)C-NMR (50MHz, CDCl\(_3\)) \(\delta\) 178.4 (-), 144.1 (-), 129.9 (J), 127.5 (J), 121.9 (-), 118.3 (J), 113.5 (J), 57.3 (J), 53.5 (2J), 42.6 (J), 26.9 (2J), 24.7 (2J), 24.6 (2J), 22.9 (2J).


Prepared following general procedure 3 from 2-((S)-4-methoxy-9-methyl-6,9-dihydro-7\(\text{H}\)-[1,3]dioxolo[4,5-h]isoquinolin-8-yl)-benzaldehyde 9c (100 mg, 0.43 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione 11 (70 mg, 0.45 mmol). n-BuOH, 5 mL, 30 h, 75 °C. MPLC gradient PE:CH\(_2\)Cl\(_2\)=88:12 to PE:CH\(_2\)Cl\(_2\):Et\(_2\)O=70:10:20. Yield of parent spiro compound 18 13 mg (16 %), yellow solid, yield of carboxylic acids 61 mg (61 %), de \(\geq 9\) %, red oil. Main isomer, 33 mg: 1H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 7.03 (dd, 1H, J=7.2, J=6.7 Hz), 6.99-6.95 (m, 1H, J=6.4 Hz), 6.73 (d, 1H, J=8.2 Hz), 6.62 (dd, 1H, J=7.2, J=0.8 Hz), 6.22 (s, 1H), 5.91 (d, 1H, J=1.4 Hz, -O-CH\(_2\)-O-), 5.88 (d, 1H, J=1.4 Hz, -O-CH\(_2\)-O-), 3.97-3.87 (m, 1H, J=9.7, J=6, J=3, J=2.9 Hz), 3.81 (br.s, 3H, O-CH\(_3\)), 3.68-3.62 (m, 2H, J=12.3, J=7, J=0.8 Hz), 3.64-3.57 (m, 1H, J=7.2, J=3.5 Hz), 3.12-2.94 (m, 2H, J=15.2, J=10, J=9.5, J=3, J=2.9 Hz, \(\alpha\)-carboxy-benzyl-CH\(_2\), benzyl-CH\(_2\), J=12.3, J=7, J=0.8 Hz), 2.81-2.73 (m, 1H, J=15.2, J=12.3, J=11.9 Hz, \(\alpha\)-carboxy-xy-benzyl-CH\(_2\)), 2.65-2.55 (m, 1H, J=15.2, J=10, 2.9 Hz, benzyl-CH\(_2\)), 1.39 (s, 3H, CH\(_3\)). \(^1\)C-NMR (50MHz, CDCl\(_3\)) \(\delta\) 172.5 (-), 144.9 (-), 144.2 (-), 142.3 (-), 133.6 (-), 129.5 (-), 129.1 (J), 126.9 (J), 121 (-), 118.6 (-), 117 (J), 111.6 (J), 106.4 (J), 101.1 (2J), 59.6 (2J), 56.4 (J), 46.1 (-), 44.5 (J), 38.9 (2J), 28.4 (2J), 21.6 (J). GC-MS, \(m/z\) (Irel, (%)): Fragmentation, main peaks: 8.11 min: 76.91 (100), 83.87 (92), 79.09 (82), 85.87 (58), 51.06 (56), 106.98 (43), 187.92 (28), 28. (26). 8.83 min: 56.95 (100), 70.93 (68), 85.15 (32), 83.86 (30), 54.98 (16), 86.19 (10). 9.73 min: 56.98 (100), 70.95 (68), 85.14 (32). 11.33 min: 57.07 (100), 219.18 (31), 177.09 (30), 163.08 (23), 91 (10), 267.19 (10), 135.11 (8). 11.7 min: 69.87 (100), 81.03 (80), 99.02 (77). 12.08 min: 54.96 (100), 68.93 (88), 57.12 (84), 83.12 (83), 97.15 (70). 12.35 min: 126.98 (100), 155.04 (86), 174.09 (37), 128.14 (21), 99.06 (17), 199.03 (17), 173.07 (17), 227.08 (16), 84.01 (13), 301.15 (14). 13.39 min: 149 (100), 72.99 (17), 281.04 (11). 13.49 min: 54.94 (100), 57.09 (83), 68.98 (77), 83.12 (76), 97.14 (72). Minor isomer, 28 mg: \(^1\)H-NMR (200MHz, CDCl\(_3\)) \(\delta\) 7.05 (dd, 1H, J=7.6, J=6.8 Hz), 6.94-6.9 (m, 2H, J=9 Hz), 6.68 (dd, 1H, J=7.2, J=6.8 Hz), 6.2 (s, 1H), 5.86 (d, 1H, J=1.2 Hz, -O-CH\(_2\)-O-), 5.8 (d, 1H, J=1.2 Hz, -O-CH\(_2\)-O-), 3.97-3.87 (m, 1H, J=9, J=7.2, J=2.9Hz), 3.78 (bs, 3H, OCH\(_3\)), 3.74-3.7 (m, 1H, J=9, J=5.5, J=3.3 Hz), 3.64-3.57 (m, 1H, J=7.2, J=3.5 Hz), 3.12-2.94 (m, 2H, J=14.4, J=12.7, J=11.5, J=9.5, J=3, J=2.9 Hz, \(\alpha\)-carboxy-benzyl-CH\(_2\), benzyl-CH\(_2\)), 2.94-2.87 (br.m, 2H, J=14.4, J=11.5, J=3.3
Hz, α-carboxy-benzyl-CH₂), 1.46 (s, 3H, CH₃). ¹³C-NMR (50MHz, CDCl₃) δ 173 (-), 145.3 (-), 144.9 (-), 142.4 (-), 130.3 (-), 128.7 (J), 127.1 (-), 127 (J), 124 (-), 118.8 (J), 118 (-), 117.3 (J), 107.3 (J), 100.8 (2J), 57.6 (-), 56.3 (J), 45.8 (J), 44.4 (2J), 29.7 (2J), 28.5 (2J), 22.5 (J). GC-MS, fragmentation, main peaks: m/z (Irel, (%)): 9.25 min: 92.13 (100), 91.07 (66), 83.89 (54), 135.06 (37), 85.86 (33), 51.03 (24). 12.08 min: 55.1 (100), 83.15 (92), 57.13 (86), 69.08 (80), 97.14 (71). 12.34 min: 126.99 (100), 155.04 (89), 174.09 (37), 128.13 (20), 199.03 (19), 173.05 (18), 99.09 (18), 227.08 (18), 301.13 (17). 12.85 min: 173.04 (100), 127.05 (90), 174.04 (79), 72.99 (46), 160.02 (44). 13.38 min: 149 (100), 72.99 (16), 281.04 (11). Sample mixture, major isomer: minor isomer is < 4.31 : 1 and > 3.24 : 1, averaged 3.71 : 1 via integration of the methylenedioxy groups in 200 MHz ¹H-NMR; [α]D⁺²° + 122.5 (c 0.4, CHCl₃). Spectroscopically (200 MHz ¹H-NMR) pure minor isomer: [α]D⁺²° + 103.2 (c 0.38, CHCl₃). (±)-(3aR*,4S*)-1,2,3,3a,4,5-Hexahydrobenzo[g]pyrrolo[1,2-a]-1,8-naphthyridine-4-carboxylic acid (21). Prepared following general procedure 3a from 2-pyrrolidin-1-yl-quinoline-3-carbaldehyde 9k (385 mg, 1.7 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione 11 (246 mg, 1.7 mmol). n-BuOH, 10 mL, 240 h, 75 °C. MPLC gradient PE to PE:EE=50:50. Yield 282 mg (62 %), amber to reddish oil. Main isomer: ¹¹H-NMR (200MHz, CDCl₃) δ 7.58 (d, 1H, J=8.3 Hz), 7.38-7.30 (m, 3H, J=7.4 Hz), 7.07-6.99 (m, 1H, J=8.3, J=7.6, J=1 Hz), 3.75-3.50 (m, 3H, J=11.3, J=9.8, J=2.5 Hz), 3.01-2.93 (m, 2H, J=7.4 Hz), 2.35-2.25 (m, 1H, J=9.8, J=7.4, J=2.5 Hz), 2.21-2.05 (m, 1H, J=11.3, J=5.5 Hz), 1.98-1.68 (bm, 3H). ¹³C-NMR (50MHz, CDCl₃) δ 173.4 (-), 153 (-), 147.7 (-), 133.7 (J), 128.7 (J), 126.8 (J), 125.6 (J), 122.9 (-), 121.4 (J), 118.6 (-), 64.8 (2J), 59.8 (J), 46.4 (2J), 43.6 (J), 31.9 (2J), 23.3 (2J). GC-MS, m/z (Irel, (%)): 76.96 (100), 104.93 (79), 197.03 (75). (±)-(4aR*,5S*)-5-Benzoyl-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]-1,8-naphthyridine-5-carbonitrile (24). (±)-(4aR*,5R*)-5-Benzoyl-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoline-5-carbonitrile (25). Prepared following general procedure 3 from 2-piperidin-1-yl-benzaldehyde 9e (299 mg, 1.6 mmol) and 3-oxo-3-phenyl-propionitrile 23 (230 mg, 1.6 mmol). n-BuOH, 5 mL, 75 °C, 40 h. MPLC gradient PE to CH₂Cl₂. Yield: 333 mg (66 %), dark oil. Ratio of (4a,5-u)-isomer to (4a,5-l) is 3:1 via integration in 200 MHz-¹H-NMR. Crystallization from MeOH, yield 110 mg spectroscopically pure (4a,5-u)-diastereomer, violet to dark crystals, mp 109.1 °C, suitable for XRD; Rf=0.75 (CH₂Cl₂). Main isomer, (4a,5-u): ¹¹H-NMR (200MHz, CDCl₃) δ 8.09-8.05 (m, 2H, J=7 Hz, o-benzoyl-H), 7.68-7.59 (m, 1H, J=7.2 Hz, p-benzoyl-H), 7.54-7.44 (m, 2H, J=7.6 Hz, m-benzoyl-H), 7.18 (bddd, 1H, J=8.6, J=7 Hz, m-anilino-Ar-H), 7.05 (bd, 1H, J=7.4 Hz, m-anilino-Ar-H), 6.88 (br.d, 1H, J=8.2 Hz, o-anilino-Ar-H), 6.77 (br.dd, 1H, J=7.4, J=7.2 Hz, p-anilino-Ar-H), 4.01 (br.d, 1H, J=13 Hz, α-amino-CH₂), 3.77 (dd, 1H, J=10, J=9 Hz, α-amino-CH), 3.55 (d, 1H, J=15.8 Hz, benzyl-CH₂), 3.31 (d, 1H, J=15.8 Hz, benzyl-CH₂), 2.78-2.64 (m, 1H, J=13, J=7.3 Hz, α-amino-CH₂), 2.01-1.97 (br.m, 2H, β-amino-CH₂), 1.74-1.56 (br.m, 4H,
β-, γ-ami-no-CH2). 1H-NMR (400MHz, CDCl3) δ 8.1-8.08 (m, 2H, J=8, J=1.2 Hz), 7.68-7.59 (m, 1H, J=7.8, J=7.2, J=2.3, J=1.7 Hz), 7.54-7.44 (m, 2H, J=7.8, J=2.3, J=1.7 Hz), 7.18 (dd, 1H, J=7.3, J=1.7 Hz), 7.05 (br.d, 1H, J=7.6 Hz), 6.88 (d, 1H, J=8.5 Hz), 6.77 (dd, 1H, J=7.3, J=0.9 Hz), 4.04-4.01 (m, 1H, J=12.8 Hz), 3.77 (dd, 1H, J=10.8, J=2 Hz), 3.56 (d, 1H, J=16.1 Hz), 3.33 (d, 1H, J=16.1 Hz), 2.77-2.7 (m, 1H, J=12.8, J=8.5, J=4.4 Hz), 2.01-1.97 (br.m, 2H, J=10.5, J=8.5, J=4.4, J=2 Hz), 1.74-1.56 (m, 4H, J=16.7, J=12, J=9.3, J=7.6, J=5.5 Hz). 13C-NMR (50MHz, CDCl3) δ 193.6 (-), 143.8 (-), 135.3 (-), 133.4 (J), 129.1 (J), 128.8 (intense, J), 128.6 (intense, J), 128.2 (J), 119.3 (-), 118.8 (-), 118.4 (J), 113.8 (J), 60.8 (J), 50.1 (-), 48.8 (2J), 35.7 (2J), 27.4 (2J), 24.3 (2J), 23.5 (2J).

Minor isomer: 1H-NMR (200MHz, CDCl3) δ 8.18-8.13 (m, 2H, J=7.2 Hz, m-benzoyl-Ar-H), 7.52-7.4 (br.m, 2H, o-benzoyl-Ar-H), 7.35-7.30 (m, 1H, p-benzoyl-Ar-H), 7.11-6.99 (m, 2H, m-anilino-Ar-H), 6.90-6.81 (br.m, 2H, o,p-anilino-H), 4.10 (br.d, 1H, J=13 Hz, α-amino-CH2), 3.89-3.83 (d, 1H, J=8.8 Hz, α-amino-CH), 3.52 (d, 1H, J=17 Hz, benzyl-CH2), 2.98 (d, 1H, J=17 Hz, benzyl-CH2), 2.97-2.89 (m, 1H, J=13 Hz, α-amino-CH2), 1.92-1.74 (br.m, 2H, β-amino-CH2), 1.65-1.40 (br.m, 4H, β-γ-amino-CH2). 1H-NMR (400MHz, CDCl3) δ 8.31-8.28 (m, 2H, J=7.3 Hz), 7.71-7.67 (m, 1H, J=7, J=1.2 Hz), 7.59-7.56 (m, 2H, J=7.3, J=1.8 Hz), 7.23-7.2 (m, 1H), 7.16-7.14 (m, 1H), 6.92 (br.d, 1H, J=8.2 Hz), 6.8-6.76 (m, 1H, J=7.6 Hz), 4.23 (br.d, 1H, J=14.3 Hz), 4.14 (br.dd, 1H, J=11.4, J=1.8 Hz), 3.65 (d, 1H, J=17 Hz), 3.16-3.09 (m, 2H, J=17, J=12.3 Hz), 1.92-1.74 (br.m, 2H, J=12.3 Hz), 1.65-1.40 (br.m, 4H, J=15.5, J=12.6, J=8.8, J=8.5, J=3.8 Hz). 13C-NMR (50MHz, CDCl3) δ 191.3 (-), 142.7 (-), 141 (-), 134.2 (J), 130.1 (J), 129.4 (J), 128.9 (J), 128.4 (J), 120.2 (-), 119 (-), 118.1 (J), 113.2 (J), 61.3 (J), 49.5 (2J), 48 (-), 33 (2J), 31.2 (2J), 25.2 (2J), 21.9 (2J).

X-Ray diffraction of 24: C21H20N2O, Mr = 316.39, triclinic, space group P-1 (No. 2), T = 100(2) K, λ = 0.71073 Å; lattice parameters: a = 9.3363(4) Å, b = 9.7901(4) Å, c = 18.6993(8) Å, α = 97.023(1) °, β = 94.791(1) °, γ = 103.322(1) °, V = 1639.63(12) Å³, Z = 4, Dc = 1.282 Mg m⁻³, µ = 0.079 mm⁻¹. Crystal size: 0.59 x 0.54 x 0.48 mm, brown oval, R-Factor: 1.93 %.

Selected distances [Å] and torsion angles [°]: Conformer with pyrido ring in near-coplanar orientation relative to quinoline ring: N 1-C8 = 2.477, N 1-C7 = 2.884, N 1-O1 = 4.172; C 7-C6-C1-N 1 = -5.37, C 6-C1-N 1-C9 = 6.15, C 1-N 1-C9-C8 = -32.99, N 1-C9-C8-C7 = 57.49, C 9-C8-C7-C6 = -56.79, C 8-C7-C6-C1 = 31.78, H 9-C 9-C 8-C 7 = -177.63, H 9-C 9-C 8-C 14 = 55.23, N 1-C 9-C 10-C 11 = -53.52, C 1-N 1-C 9-C 10 = -154.89. Conformer with pyrido ring in near-orthogonal orientation relative to quinoline ring: N 1-C8 = 2.456, N 1-C 7 = 2.921, N 1-O 1 = 3.462; C 7-C 6-C 1-N 1 = 3.81, C 6-C 1-N 1-C 9 = -20.77, C 1-N 1-C 9-C 8 = 50.13, N 1-C 9-C 8-C 7 = -62.49, C 9-C 8-C 7-C 6 = 46.53, C 8-C 7-C 6-C 1 = -18.26, H 9-C 9-C 8-C 7 = -179.19, H 9-C 9-C 8-C 14 = 63.09, H 9-C 9-C 8-C 15 = -57.99, N 1-C 9-C 10-C 11 = -56.60, C 1-N 1-C 9-C 10 = -75.22.

(±)-Ethyl-(4aR*,5S*)-5-((1,3-thiazol-2-ylamino)carbonyl)-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoline-5-carboxylate (27). (±)-Ethyl-(4aR*,5R*)-5-((1,3-thiazol-2-ylamino)carbonyl)-
2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoline-5-carboxylate (28). Prepared following general procedure 3d from 2-piperidin-1-ylbenzaldehyde 9e (488 mg, 2.61 mmol), N-thiazol-2-yl-malonamic acid ethyl ester 26 (559 mg, 2.87 mmol) and (191 mg, 2.61 mmol) of anhydrous NH$_4$OAc. Refluxing abs. EtOH, 10 mL, 65 h. MPLC gradient PE to CH$_2$Cl$_2$. Yield of (4a,5-u) 343 mg (34 %), yellow oil, single crystals for XRD from CH$_2$Cl$_2$/Et$_2$O by diffusion and slow evaporation, mp 181.8 °C; yield of (4a,5-l) 650 mg, white solid, mp 177.6 °C; single crystals for XRD from CH$_2$Cl$_2$/Et$_2$O by diffusion and slow evaporation, mp 191.3 °C; overall 99 %. (4a,5-u): 1H-NMR (200MHz, CDCl$_3$) $\delta$ 10.70-10.45 (br.s, 1H, N-H), 7.47 (br.s, 1H), 7.18-6.97 (br.m, 3H), 6.70-6.61 (br.m, 2H), 4.08-3.93 (br.m, 4H, $J=15.6$, $J=6.8$ Hz, COO-CH$_2$, $\alpha$-amino-CH$_2$, $\alpha$-amino-CH), 3.38 (d, 1H, $J=16.6$ Hz, benzyl-CH$_2$), 3.23 (d, 1H, $J=16.6$ Hz, benzyl-CH$_2$), 2.92-2.82 (m, 1H, $J=10.8$ Hz, $\alpha$-amino-CH$_2$), 1.73 (br.s, 1H), 1.6-1.11 (br.m, 6H), 0.98-0.91 (br.t, 3H, $J=6.8$ Hz, CH$_3$). 13C-NMR (50MHz, CDCl$_3$) $\delta$ 171.5 [COO, (-)], 166 [CONH, (-)], 157.8 [thiazole-Cquat, (-)], 142.6 (-), 137.8 (J), 129.5 (J), 127.3 (J), 120.8 (-), 117.6 (J), 114 (J), 112.9 (J), 62.5 [$\alpha$-amino-CH, (J)], 62.4 [ester-CH$_2$, (2J)], 56.6 [Cquat. phenylethyl] (-), 49.2 [$\alpha$-amino-CH$_2$, (2J)], 27.7 (2J), 25.4 (2J), 24.7 (2J), 21.6 (2J), 13.6 CH$_3$ (J). GC-MS, fragmentation; 3 major peaks; $m/z$ (Irel, (%)): 10.9 min: 106 (100), 117.96 (79), 175.2 (64), 119.12 (49), 146.06 (34), 76.94 (33), 90.93 (26), 103.97 (21), 174.21 (17), 51.1 (15), 70.04 (13), 130.12 (12), 78.13 (9), 132.1 (7), 156.15 (7), 176.23 (7), 158.17 (7), 92.14 (7), 65.11 (6), 147.18 (6). 12.4 min: 103.96 (100), 144.11 (100), 145.15 (82), 77.06 (80), 189.13 (53), 117.05 (38), 131.99 (35), 51.11 (31), 105.11 (26), 76.07 (20), 188.06 (18), 50.19 (15), 78.1 (15), 63.1 (15), 91.08 (14), 90.05 (13), 146.15 (13), 115 (12), 65.14 (12). 14.87 min: 242.14 (100), 214.08 (50), 243.22 (15), 167.13 (12), 168.16 (12), 169.17 (9), 96.07 (7), 240.2 (7), 215.19 (7), 281.08 (5), 166.11 (5), 209.11 (5), 190.99 (4), 132.95 (4), 253.03 (4), 73.03 (4) 196.16 (3), 115.08 (3).

(4a,5-l): 1H-NMR (200MHz, CDCl$_3$) $\delta$ 11.8-11.4 (br.s, 1H, N-H), 7.92 (d, 1H, $J=3.3$ Hz, thiazole-Ar-H), 7.11-7 (m, 2H, $J=7.8$, $J=7.6$ Hz), 6.93 (d, 1H, $J=8.2$ Hz), 6.83 (d, 1H, $J=3.3$ Hz, thiazole Ar-H), 6.72 (br.d, 1H, $J=7.2$ Hz), 4.27-4.16 (m, 3H, $J=7.2$, $J=7$ Hz, COO-CH$_2$, $\alpha$-amino-CH$_2$), 3.91 (br.d, 1H, $J=10.8$ Hz, $\alpha$-amino-CH$_2$), 3.40 (d, 1H, $J=17.9$ Hz, benzyl-CH$_2$), 3.24-3.07 (m, 2H, $J=17.9$ Hz, benzyl-CH$_2$, $\alpha$-amino-CH$_2$), 1.78-1.12 (br.m, 6H, $J=8$, $J=6.6$, $J=4.4$, $J=3.9$ Hz, $\beta$, $\gamma$-amino-CH$_2$), 1.22 (br.t, 3H, $J=7.2$ Hz, CH$_3$). 13C-NMR (50MHz, CDCl$_3$) $\delta$ 169.6 (-), 169.5 (-), 157.5 [thiazole Cquat, (-)], 140.9 (-), 137.4 (J), 130.3 (J), 128 (J), 120.9 (-), 119.8 (J), 114.8 (J), 113.9 (J), 62 (2J), 58.7 (J), 55.3 [Cquat. phenylethyl, (-)], 49.1 (2J), 29.7 (2J), 25.2 (2J), 24.5 (2J), 20.8 (2J), 14 (J), GC-MS, 2 main peaks, $m/z$ (Irel, (%)): 14.05 min: 76.97 (100), 104.96 (90), 211.07 (59), 172.2 (34), 315.28 (31), 51.04 (20), 171.19 (17), 315.22 (15), 130.11 (11), 155.14 (10), 128.13 (9), 154.13 (8), 212.22 (8), 170.2 (7), 90.89 (7), 78.2 (6), 118.21 (6), 217.3 (6), 106.19 (6), 16.26 min: 281.12 (100), 201.14 (58), 352.28 (55), 229.12 (36), 172.07 (36), 269.15 (35), 241.15 (33), 263.03 (27), 113.92 (26), 54.95 (24), 202.16 (23), 213.13 (20), 282.18 (17), 267.15 (16), 173.12 (16), 253.1 (16), 126.24 (15), 227.15 (15), 67.08 (13), 335.27 (12).
X-Ray diffraction of 28: C$_{20}$H$_{23}$N$_3$O$_3$S, $M_r$ = 385.49, monoclinic, space group $P 2_1/n$ (No. 14), $T$ = 298(2) K, $\lambda$ = 0.71073 Å; lattice parameters: $a$ = 12.0875(17) Å, $b$ = 10.4022(15) Å, $c$ = 15.871(2) Å, $\alpha$ = 90.00°, $\beta$ = 106.145(2)°, $\gamma$ = 90.00°, $V$ = 1916.86 Å$^3$, $Z$ = 4, $Z'$: 0, $D_x$ = 1.336 Mg m$^{-3}$, $\mu$ = 0.195 mm$^{-1}$, Crystal size: 0.57 x 0.45 x 0.38 mm, colorless block, $R$-Factor: 4.35 %. Selected distances [Å] and angles [°]: N1-C13 = 1.416, N1-C1 = 1.473, N1-C5 = 1.478, N1-C6 = 2.476, N1-C7 = 2.927, N1-N2 = 2.744, S1-O1 = 2.830; C14-C6-C18 = 106.13, C14-C6-C7 = 108.71, C14-C6-C5 = 114.75; N1-C5-C6-C7 = 60.23, N1-C5-C4-C3 = 55.52, N1-C1-C2-C3 = -57.86, N1-C5-C6-C18 = 179.27, N1-C5-C6-C14 = -62.25.

Methyl (1'S,3a'R)-1,3-dimethyl-2,4,6-trioxo-1',2',3,3',3a',4,6-octahydro-2H,5'H-spiro[pyrimidine-5,4'-pyrrolo[1,2-a]quinoline]-1'-carboxylate (30). Methyl (1'S,3a'S)-1,3-dimethyl-2,4,6-trioxo-1',2',3,3',3a',4,6-octahydro-2H,5'H-spiro[pyrimidine-5,4'-pyrrolo[1,2-a]quinoline]-1'-carboxylate (31). Prepared following general procedure 3 from (S)-1-(2-formylphenyl)-pyrrolidine-2-carboxylic acid methyl ester 9a (100 mg, 0.43 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione 12 (70 mg, 0.45 mmol). $n$-BuOH, 5 mL, 45 h, 75 °C. MPLC gradient PE:CH$_2$Cl$_2$=88:12 to PE:CH$_2$Cl$_2$: Et$_2$O=70:10:20. Yield 117 mg (73 %), de $\geq$ 43 %, amber low melting solid. Main isomer, (1'S,3a'S): $^1$H-NMR (200MHz, CDCl$_3$) $\delta$ 7.09-6.93 (m, 2H, $J$ =8, $J$ =7.8, $J$ =7.6 Hz), 6.65 (dd, 1H, $J$ =7.4, $J$ =1 Hz), 6.36 (d, 1H, $J$ =7.6 Hz), 4.28 (dd, 1H, $J$ =8, $J$ =4.1 Hz, H-1), 4.12 (dd, 1H, $J$ =7.4, $J$ =5.5 Hz, H-3a), 3.67 (s, 3H, COO-CH$_3$), 3.52 (d, 1H, $J$ =16.4 Hz, H-5$u$ = on same side as H3a), 3.31 (s, 3H, N-CH$_3$), 3.12 (s, 3H, N-CH$_3$), 2.91 (d, 1H, $J$ =16.4 Hz, H-5$u$ = on opposite side as H-3a), 2.25-2.12 (m, 1H, $J$ =12.1, $J$ =7.4, $J$ =6.1 Hz, H-3$u$). 13C-NMR (50MHz, CDCl$_3$) $\delta$ 174.6 (-), 170.4 (-), 167.1 (-), 151.1 (-), 141.9 (-), 128.2 (J), 128.1 (J), 118.7 (-), 117.6 (-), 111.5 (J), 128.2 (J), 52.3 (J), 36.7 (s, 3H, COO-CH$_3$), 3.52 (d, 1H, $J$ =16.4 Hz, H-5$u$ = on same side as H3a), 3.31 (s, 3H, N-CH$_3$), 3.12 (s, 3H, N-CH$_3$), 2.91 (d, 1H, $J$ =16.4 Hz, H-5$u$ = on opposite side as H-3a). $^1$C-NMR (50MHz, CDCl$_3$) $\delta$ 174.6 (-), 170.4 (-), 167.1 (-), 151.1 (-), 141.9 (-), 128.2 (J), 128.1 (J), 118.7 (-), 117.6 (J), 111.5 (J), 63.7 (J), 62.2 (J), 52.3 (J), 49 (-), 36.9 (2J), 28.9 (J), 28.5 (J), 28.3 (2J), 26.8 (2J). GC-MS, fragmentation, main peaks: m/z (Irel, (%)): 6.97 min: 142.06 ( 100), 58.09 (96), 69.93 (22), 114 (18), 85.89 (9). 11.33 min: 57.06 (100), 219.16 (38), 177.08 (36), 163.04 (25), 267.15 (11). 12.09 min: 54.96 (100), 68.92 (99), 83.11 (98), 97.11 (74), 111.14 (31). 13.05 min: 167.07 (100), 83.38 (71), 309.12 (46). 13.49 min: 83.07 (100), 54.96 (99), 68.92 (95), 97.12 (85), 111.18 (38), 14.23 min: 160 (100), 188.05 (72), 76.98 (42), 54.02 (30), 72.98 (26), 132.08 (26), 281.04 (24), 96.11 (20).

Minor isomer, (1'S,3a'R): $^1$H-NMR (200MHz, CDCl$_3$) $\delta$ 7.15-7.01 (m, 2H, $J$ =8, $J$ =7.8, $J$ =7.6 Hz), 6.39 (dd, 1H, $J$ =7.4, $J$ =1 Hz), 6.36 (d, 1H, $J$ =7.6 Hz), 4.29 (dd, 1H, $J$ =8, $J$ =4.1 Hz, H-1), 3.82-3.74 (m, 1H, $J$ =6.1 Hz, H-3a), 3.64 (d, 1H, $J$ =16.4 Hz, H-5$u$ = on same side as H3a), 3.31 (s, 3H, N-CH$_3$), 3.21 (s, 3H, N-CH$_3$), 2.95 (d, 1H, $J$ =16.4 Hz, H-5$u$ = on opposite side as H-3a), 2.23-2.12 (m, 1H, $J$ =12.1, $J$ =7.4, $J$ =6.1 Hz, H-3$u$). 13C-NMR (50MHz, CDCl$_3$) $\delta$ 173.2 (-), 169.7 (-), 166.4 (-), 151.4 (-), 141.2 (-), 128.4 (J), 127.6 (J), 121.7 (-), 121.2 (J), 110.8 (J), 66.5 (J), 58.6 (J), 52.2 (J), 51.8 (-), 36.6 (2J), 29.4 (J), 29 (J), 28.4 (2J), 26.4 (2J). Sample mixture, isomer composition major : minor is < 6.25 : 1 but > 4.76 : 1 via averaged integration of the aromatic protons at $\delta$ 6.66, $\delta$ 6.38 and of the aliphatic protons at $\delta$ 4.29 and $\delta$ 4.14 ppm (shifts of the major isomer); [$\alpha$]$_D^{20}$ -34 (c 0.95,
CHCl₃).

Methyl (1'S,3a'S)-2,2-dimethyl-4,6-dioxo-1',2',3',3a'-tetrahydro-5'H-spiro[1,3-dioxane-5,4'-pyrrolo[1,2-a]quinoline]-1'-carboxylate (32).

Methyl (1'S,3a'R)-2,2-dimethyl-4,6-dioxo-1',2',3',3a'-tetrahydro-5'H-spiro[1,3-dioxane-5,4'-pyrrolo[1,2-a]quinoline]-1'-carboxylate (33).

Prepared following general procedure 3 from (S)-1-(2-formylphenyl)-pyrrolidine-2-carboxylic acid methyl ester 9a (150 mg, 0.64 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione 11 (97 mg, 0.67 mmol). n-BuOH, 5 mL, 30 h, 75 °C. MPLC gradient PE:CH₂Cl₂=88:12 to PE:CH₂Cl₂:Et₂O=70:10:20. Yield 177 mg (69 %), de ≥ 80 %, yellowish oil that upon standing spontaneously crystallized the pure (1'S,3a'S)-isomer as a colorless solid, mp 141.6 °C (decomp.). Main isomer, (1'S,3a'S): 1H-NMR (200MHz, CDCl₃) δ 7.09-6.95 (m, 2H, J = 7.8, J = 7.4 Hz, Ar-H-8, Ar-H-6), 6.68-6.61 (m, 1H, J = 7.6, J = 4.9 Hz, H-3a), 3.66 (s, 3H, COO-CH₃), 3.54 (d, 1H, J = 16.4 Hz, H-5d), 3.02 (d, 1H, J = 16.4 Hz, H-5u), 2.35-2.06 (m, 2H, J = 12, J = 8, J = 4 Hz, H-3d, H-2u), 2.01-1.73 (br.m, 2H, J = 12.5, J = 8.5, J = 4.5 Hz, H-3u, H-2d), 1.69 (br., 6H, ketal-CH₃).1H-NMR (400MHz, CDCl₃) δ 7.07 (dd, 1H, J = 7.8, J = 7.6 Hz, Ar-H-8), 6.98 (d, 1H, J = 7.3 Hz), 6.67 (dd, 1H, J = 7.6, J = 7.3 Hz), 6.39 (d, 1H, J = 8.2 Hz), 4.29 (dd, 1H, J = 8.5, J = 3.4 Hz), 4.17 (dd, 1H, J = 7.9, J = 4.7 Hz), 3.68 (s, 3H, COO-CH₃), 3.57 (d, 1H, J = 16.4 Hz), 3.04 (d, 1H, J = 16.4 Hz), 2.31 (ddd, 1H, J = 13.2, J = 12.9, J = 7.9 Hz, H-3d), 2.17 (ddd, 1H, J = 13.2, J = 12.9, J = 8.5 Hz, H-2u), 1.94 (ddd, 1H, J = 16.6 Hz, J = 12.9, J = 3.4 Hz, H-2d), 1.79 (m, 1H, J = 16.7, J = 12.9, J = 4.7 Hz, H-3u). 13C-NMR (50MHz, CDCl₃) δ 174.7 (C-OOCH₃, -), 169.6 (C-OOC₉q, -), 164.6 (C-OOC₉q, -), 141.8 (C-9a, -), 128.4 (C-6, J), 127.7 (C-8, J), 117.7 (C-5a, -), 117.3 (C-7, J), 111.9 (C-9, J), 104.9 (ketal-C₉q, -), 64.6 (C-3a, J), 62.5 (C-1, J), 52.3 (O-CH₃, J), 47.4 (C-4, -), 35.9 (C-5, 2J), 30.4 (ketal-CH₃, J), 28.4 (ketal-CH₃, J), 27.6 (C-2, 2J), 27.2 (C-3, 2J). GC-MS, fragmentation, first two main peaks m/z (Irel, (%)): 11.34 min: 57.05 (100), 219.16 (31), 177.08 (30), 163.09 (19.9), 163.04 (22), 90.98 (10), 267.15 (9); 12.08 min: 54.96 (100), 82.96 (11), 91.01 (9.7), 267.16 (9), 134.95 (9), 119.06 (8), 76.96 (8), 12.08 min: 54.96 (100), 57.11 (79), 83.17 (70), 69.13 (69), 97.15 (57), 111.15 (27). Pure (1'S,3a'S), [α]D²⁰ = -
93.3 (c = 1, CHCl₃). Sample mixture, isomer composition is (1'S,3a'S) : (1’S,3a’R) = 2.58 : 1 via integration of the aromatic protons at δ 6.55 (major isomer) and δ 6.4 ppm (minor isomer), respectively; [α]D²⁰ = -25.2 (c = 0.87, CHCl₃).

(±)-(3aR*,4S*)-4-Nitro-1,2,3,4a,4,5-hexahydropyrrolo[1,2-a]quinoline (35). (±)-(3aR*,4R*)-4-Nitro-1,2,3,4a,4,5-hexahydropyrrolo[1,2-a]quinoline (36). Prepared following general procedure 3d from 2-pyrrolidin-1-yl-benzaldehyde 9d or 3 from [2-((E)-2-nitro-vinyl)-phenyl]-pyrrolidine 37a. Reproducibly obtained as a ((3a,4-u) : (3a,4-l) ≥ 11:1; de ≥ 84-85 %)-mixture. Via 3d: Prepared from 2-pyrrolidin-1-yl-benzaldehyde 9d (552 mg, 0.79 mmol), nitromethane (212 mg, 0.87 mmol) and anhydrous NH₄OAc (240 mg, 0.79 mmol). n-BuOH, 5 mL, 120 h, 118 °C. MPLC gradient PE:CH₂Cl₂=88:12 to PE:CH₂Cl₂:Et₂O=70:10:20. Yield 172 mg (25 %), recrystallization from 96 % EtOH afforded yellow prisms of spectroscopically pure (3a,4-u), mp 120.2 °C. Main isomer (3a,4-u): 1H-NMR (200MHz, CDCl₃) δ 7.06 (dd, 1H, J =8, J =7.4 Hz), 6.96 (d, 1H, J =7.4 Hz), 6.57 (dd, 1H, J =8 Hz), 6.41 (d, 1H, J =8.2 Hz), 4.36 (ddd, 1H, J =12, J =9.6, J =4.7 Hz, α-nitro-CH), 3.67 (ddd, 1H, J =9.6, J =9.4, J =5.5 Hz, α-amino-CH), 3.43-3.3 (m, 2H, J =14.6, J =12, J =11.7, J =10.2, J =9, J =4.7, J =1.6 Hz, α-amino-CH₂, benzyl-CH₂ (H-5 trans to H-4)), 3.25-3.12 (m, 2H, J =14.6, J =11.7, J =10.2, J =9, J =4.7, J =1.6 Hz, α-amino-CH₂, benzyl-CH₂ (H-5 cis to H-4)), 2.21- 1.79 (br.m, 4H, J =10.6, J =6.1, J =2.4, J =1.6 Hz, β-amino-CH₂).1H-NMR (400MHz, CDCl₃) δ 7.18 (dd, 1H, J =7.9, J =7.6 Hz, Ar-H-8), 7.08 (d, 1H, J =7.3 Hz, Ar-H-6), 6.69 (dd, 1H, J =7.6, J =7.3 Hz, Ar-H-7), 6.52 (d, 1H, J =8.2 Hz, Ar-H-9), 4.47 (ddd, 1H, J =9.6, J =6.6 Hz, J =4.7 Hz, α-amino-CH), 3.53-3.46 (m, 2H, J =14.6, J =12, J =9.4, J =9, J =6.2, J =2.4 Hz, α-amino-CH₂, benzyl-CH₂ (H-5 trans to H-4)), 3.34-3.28 (m, 2H, J =14.6, J =11.7, J =9, J =5.3, J =4.7, J =1.6 Hz, α-amino-CH₂, benzyl-CH₂ (H-5 cis to H-4)), 2.3-2.22 (m, 1H, J =11.7, J =5.3, J =1.8 Hz, H-3 trans to H-3a), 2.18-2.14 (m, 1H, J =12.6, J =5.3 Hz, H-2), 2.1-1.97 (m, 1H, J =12.6, J =2.9 Hz, H-2), 1.84-1.74 (m, 1H, J =9.4, J =6.2, J =2.4 Hz, H-3 cis to H-3a). 13C-NMR (50MHz, CDCl₃) δ 143 (-), 128.9 (J), 128.3 (J), 117.3 (-), 116.5 (J), 111.2 (J), 84.3 (J), 60.3 (J), 47.6 (2J), 33.7 (2J), 30.7 (2J), 23.4 (2J). GC-MS, m/z (Irel, (%)): 170.04 (100), 218.12 [M⁺] (41), 172.18 (40), 129.94 (32), 171.21 (29), 144.12 (16), 143.1 (16), 114.98 (11), 77.15 (10), 127.81 (9), 117.09 (7), 141.93 (6), 103.09 (6), 91.09 (5), 116.1 (5), 156.12 (5), 71.69 (5), 88.94 (5), 168.14 (4), 219.22 [M+1] (4).

1-{2-[(E)-2-nitrovinyl]phenyl}pyrrolidine (37a). Prepared according to (20) from 2-pyrrolidine-1-yl-benzaldehyde 9d (1610 mg, 9.17 mmol), anhydrous KF (101 mg, 0.6 mmol), Me₂HN-HCl (1310 mg, 18.34 mmol) and MeNO₂ (20 g, excess) in a 250 mL round-bottom-flask equipped with condenser, drying tube and a Dean-Stark trap. Refluxing toluene, 20 mL, 3 h, 100-110 °C. The solvents were roto-evaporated and the residue taken up in CH₂Cl₂, washed once with 20 mL brine, the brine re-extracted with 10 mL CH₂Cl₂ and the organic phases combined, dried (Na₂SO₄) and roto-evaporated. MPLC
gradient PE to PE:EE=80:20. Yield 1186 mg (59%). Crystals from MTBE/MeOH, dark-red needles, mp 176 °C. 1H-NMR (200MHz, CDCl$_3$) δ 8.33 (d, 1H, $J$=13.4 Hz, benzylidene-H), 7.37 (d, 1H, $J$= 13.4 Hz, β-nitrostyrenyl-H), 7.30-7.17 (m, 2H, Ar-H), 6.83-6.66 (m, 2H, Ar-H), 3.30-3.23 (m, 4H, α,β–amino-CH$_2$). 

1H-NMR (200MHz, CDCl$_3$) δ 8.29 (d, 1H, $J$=13.7 Hz, benzylidene-H), 7.62 (d, 1H, $J$=13.7 Hz, β-nitrostyrenyl-H), 7.41-7.31 (m, 2H, Ar-H), 7.09-6.9 (m, 2H, Ar-H), 2.87-2.91 (m, 4H, α–amino-CH$_2$), 1.76-1.55 (m, 4H, β–amino-CH$_2$), 1.55-1.4 (m, 2H, γ–amino-CH$_2$). 13C-NMR (50MHz, CDCl$_3$) δ 155.3 (-), 137 (J), 136.6 (weak, J), 132.7 (J), 129.2 (J), 124.3 (-), 122.8 (J), 119.7 (J), 54.6 (2J), 26.3 (2J), 24 (2J).

1-{2-[(E)-2-nitrovinyl]phenyl}piperidine (37b). Prepared according to (20) from 2-piperidine-1-yl-benzaldehyde 9d (815 mg, 4.31 mmol), anhydrous KF (68 mg, 1.2 mmol), Me$_2$HN·HCl (703 mg, 8.62 mmol) and MeNO$_2$ (18 g, excess) in a 100 mL round-bottom-flask equipped with condenser, drying tube and a Dean-Stark trap. Refluxing toluene, 20 mL, 2 h, 100-110 °C. The solvents were roto-evaporated and the residue taken up in CH$_2$Cl$_2$, washed twice with 50 mL saturated Na$_2$CO$_3$-solution, then once with 10 mL brine, the brine re-extracted with 10 mL CH$_2$Cl$_2$ and the organic phases combined, dried (Na$_2$SO$_4$) and roto-evaporated. Yield 659 mg (66 %), red oil, $R_f$=0.94 (CH$_2$Cl$_2$), $R_f$=0.74 (PE:EE=90:10). 1H-NMR (200MHz, CDCl$_3$) δ 8.29 (d, 1H, $J$=13.7 Hz, benzylidene-H), 7.62 (d, 1H, $J$=13.7 Hz, β-nitrostyrenyl-H), 7.41-7.31 (m, 2H, Ar-H), 7.09-6.9 (m, 2H, Ar-H), 2.87-2.91 (m, 4H, α–amino-CH$_2$), 1.76-1.55 (m, 4H, β–amino-CH$_2$), 1.55-1.4 (m, 2H, γ–amino-CH$_2$). 13C-NMR (50MHz, CDCl$_3$) δ 155.3 (-), 137 (J), 136.6 (weak, J), 132.7 (J), 129.2 (J), 124.3 (-), 122.8 (J), 119.7 (J), 54.6 (2J), 26.3 (2J), 24 (2J).

1-{2-[((Z)-2-Nitrovinyl)phenyl]pyrrolidine (38a). Prepared from [2-((E)-2-Nitrovinyl)phenyl]pyrrolidine 37a (499 mg, 3.2 mmol). Refluxing n-BuOH, 5 mL, 60 h, 118 °C. MPLC gradient PE:CH$_2$Cl$_2$:Et$_2$O =88:12 to PE:CH$_2$Cl$_2$:Et$_2$O =70:10:20. Yield 102mg (20 %), emerald green oil that isomerizes to the deeply red (E)-isomer under the influence of ambient light and/or temperature. 1H-NMR (200MHz, CDCl$_3$) δ 7.53 (d, 1H, $J$=7.9 Hz, benzylidene-H), 7.25 (d, 1H, $J$=7.9 Hz, β-nitrostyrenyl-H), 7.15-7.06 (m, 1H, $J$=8.5, $J$=7.6, $J$=7.1, $J$=5.3, $J$=3.1 Hz), 6.39 (d, 1H, $J$=3 Hz), 4.05 (t (dd), 2H, $J$=7 Hz), 3.50 (dd, 2H, $J$=6.5, $J$=6.3 Hz), 1.89-1.74 (m, 2H, $J$=7.7, $J$=7 Hz), 1.51-1.39 (m, 2H, $J$=7, $J$=6.3 Hz). 13C-NMR (50MHz, CDCl$_3$) δ 135.9 (-), 128.6 (-), 127.7 (J), 121.4 (J), 120.9 (J), 119.1 (J), 109.4 (J), 101.1 (J), 62.3 (2J), 46.1 (2J), 29.9 (2J), 26.7 (2J); note that the α,β–amino-methylene-carbons have become magnetically nonequivalent, most likely reflecting the increase in steric hindrance of rotation around the C-N-bond; we did not observe this in the corresponding (E)-isomer.

(±)-1,1’-[1,3,5-Trinitropentane-2,4-diyl]bis(2,1-phenylene)di(piperidine (39). Fract. crystallization from PE/MTBE/MeOH. Yield 341 mg (30 %), light-brown solid. Recrystallization from i-PrOH, slightly brown solid, mp 153.3 °C. Single crystals for XRD from CH$_2$Cl$_2$/Et$_2$O by diffusion and slow evaporation, mp 144.9 °C. 1H-NMR (200MHz, CDCl$_3$) δ 7.41 -7.19 (m, 4H, $J$=8, $J$=7.6, $J$=7.1, $J$=5.3, $J$=3.1 Hz), 5.38 (dd, 1H, $J$=13.5, $J$=4.7 Hz), 5.14 (dd, 1H, $J$=9.2, $J$=7.8 Hz), 5.02 (dd, 1H, $J$=13.5, $J$=9.8 Hz), 4.65-4.54 (m, 1H, $J$= 9.2, $J$= 7.8, $J$= 4.7 Hz), 3.01-2.68 (br., 4H), 1.88-1.29 (br., 6H). 13C-NMR (50MHz, CDCl$_3$) δ 153.2 (-), 129.9 (J), 129.5 (-), 126.8 (J), 125.8 (J), 122.9 (J), 94.2 (J), 75.4 (2J), 37.3 (J), 26.5 (2J), 26.2
X-Ray diffraction of 39: C_{27}H_{35}N_{5}O_{6}, M_r = 525.61, triclinic, space group P-1 (No. 2), T = 298(2) K, \lambda = 0.7073 \AA; lattice parameters: a = 9.150(3) \AA, b = 12.096(4) \AA, c = 13.425(4) \AA, \alpha = 75.012(4) ^\circ, \beta = 74.163(4) ^\circ, \gamma = 75.417(4) ^\circ, V = 1354.32 A^3, Z = 2, D_x = 1.289 Mg m^{-3}, \mu = 0.092 mm^{-1}, Crystal size: 0.57 x 0.45 x 0.38 mm, colorless block, R-Factor: 5.71 %. Selected distances [\AA] and angles [^\circ]: N 4-N5 = 5.721, N 5-O5 = 4.094, N 4-O6 = 7.299; C_{16}-C_{1}C_{4} = 115.09; C_{1}-C_{4}-C_{2}-N_{2} = 166.81, C_{16}-C_{1}-C_{4}-C_{2}-N_{2} = -57.55, C_{3}-C_{16}-C_{1}-C_{4} = -166.98.

(±)-Methyl-5-nitro-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoline-5-carboxylate (40). Prepared following general procedure 3d from 2-piperidinylbenzaldehyde 9e (651 mg, 3.45 mmol), nitro-acetic acid methyl ester (450 mg, 3.8 mmol) and NH_{4}OAc (266 mg, 3.5 mmol). EtOH, 5 mL, 60 h, 78 °C. MPLC gradient PE:CH_{2}Cl_{2}=88:12 to PE:CH_{2}Cl_{2}:EE=70:10:20. Obtained as a diastereomer mixture, isomer ratio is ≥ 10:1 (de ≥ 82 %) by integration in ^1H-NMR, yield 153 mg (15 %), yellow oil. Main isomer: ^1H-NMR (200MHz, CDCl_{3}) \delta 7.09-7.02 (m, 1H, J=7.8 Hz), 6.98 (d, 1H, J=7 Hz), 6.70-6.64 (m, 2H, J=8.2, J=7 Hz), 4.24-4.16 (m, 1H, J=11.3 Hz), 3.96-3.89 (br.d, 1H, J=13.5 Hz), 3.76 (s, 3H, CH_{3}), 3.70-3.59 (m, 2H, J=17, J=11.3, J=4.1 Hz), 3.29 (d, 1H, J=17 Hz, benzyl-CH_{2}), 3.02–2.87 (m, 1H, J=13.5 Hz), 1.9-1.78 (br.m, 1H), 1.73-1.41 (bm, 3H, J=13.5 Hz), 1.41-1.33 (m, 1H, J=11.7 Hz, J=4.1 Hz), 1.39-1.31 (m, 1H, J=11.7 Hz, J=4.1 Hz). ^13C-NMR (50MHz, CDCl_{3}) \delta 165.7 (-), 143.5 (-), 129.5 (J), 128.8 (J), 118.7 (J), 118.4 (-), 112.9 (J), 94.3 (-), 60.7 (J), 54.2 (J), 48.5 (2J), 31.8 (2J), 27 (2J), 25.6 (2J), 22.9(2J). GC-MS, m/z (I_{rel}, (%)):91 (100), 158.14 (52), 159.17 (19), 76.94 (15), 131.95 (14), 64.93 (13), 67.98 (12), 154.03 (11), 172.14 (11), 144.12 (10), 105.4 (8), 92.14 (8), 135.11 (8), 120.08 (6), 51.08 (6), 117.06 (5), 173.17 (5), 104.05 (5), 292.15 [M+2] (5).

(±)-Ethyl-4-acetyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-4-carboxylate (41). Prepared following general procedure 3d from 2-pyrrolidinyl-benzaldehyde 9d (610 mg, 3.48 mmol), 3-oxobutyric acid ethyl ester (489 mg, 3.55 mmol) and NH_{4}OAc (268 mg, 3.48 mmol). EtOH, 7 mL, 220 h, 78 °C. MPLC gradient PE to PE:CH_{2}Cl_{2}=50:50. Obtained as a diastereomer mixture, isomer ratio is ≥ 7:1 (de ≥ 75 %) by integration in ^1H-NMR, yield 69 mg (7 %), slightly yellow oil. ^1H-NMR (200MHz, CDCl_{3}) \delta 7.39-7.09 (m, 2H, J=7.4 Hz, Ar-H), 7.05 -6.94 (m, 2H, J=8 Hz), 1.97-1.86 (m, 3H, CH_{2}-CH_{3}), 1.48-1.12 (br.m, 1H, J=15.4 Hz, benzyl-CH_{2}), 1.29 (d, 1H, J=15.4 Hz, benzyl-CH_{2}), 1.99 (br.s, 3H, CO-CH_{3}), 1.48-1.12 (br.m, 4H, J=15.4 Hz, benzyl-CH_{2}), 3.31 (d, 1H, J=15.4 Hz, benzyl-CH_{2}), 1.99 (br.s, 3H, CO-CH_{3}), 1.48-1.12 (br.m, 4H, J=15.4 Hz, benzyl-CH_{2}), 1.29 (d, 1H, J=15.4 Hz, benzyl-CH_{2}). ^13C-NMR (50MHz, CDCl_{3}) \delta 201.9 (-), 167.1 (-), 140.4 (-), 127.2 (J), 123.8(J), 122.3 (J), 113.9 (J), 106.7(-), 68.9 (J), 60.3 (2J), 44 (-), 46.3 (2J), 34.6 (2J), 29.8 (2J), 26.4 (J), 21.9 (2J), 12.5 (J).

(±)-Ethyl-5-acetyl-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoline-5-carboxylate (42). Prepared following general procedure 3d from 2-piperidinylbenzaldehyde 9e (650 mg, 3.45 mmol), 3-oxobutyric acid ethyl ester (400 mg, 3.45 mmol) and NH_{4}OAc (266 mg, 3.45 mmol). EtOH, 10 mL, 250 h, 78 °C. MPLC gradient PE to PE:CH_{2}Cl_{2}=50:50. Obtained as a diastereomer mixture, isomer ratio is ≥ 4:1 (de ≥
60 %) via integration in $^1$H-NMR, yield 34 mg (3 %), yellow oil. Main isomer, $^1$H-NMR (200MHz, CDCl$_3$) $\delta$ 7.03-6.96 (m, 2H, J = 7.2 Hz, J = 6 Hz), 6.68-6.53 (m, 2H, J = 8.4, J = 8.2 Hz), 4.19-4.08 (q, 2H, J = 15.8 Hz, benzyl-CH$_2$), 3.04-2.88 (m, 2H, $\alpha$-amino-CH$_2$, benzyl-CH$_2$), 2.18 (s, 3H, CO-CH$_3$), 1.85-1.35 (br.m, 6H, $\beta\gamma$-amino-CH$_2$), 1.26 (t, 3H, J = 7 Hz, COCH$_2$-CH$_3$).$^{13}$C-NMR (50MHz, CDCl$_3$) $\delta$ 203.1 (-), 169.9 (-), 143.8 (-), 130.1 (-), 128.1 (J), 121.3 (J), 118.1 (J), 113.3 (J), 62.9 (-), 62.3 [2J, CH$_2$-CH$_3$], 54.2 [2J, CH$_2$], 49 [2J, CH$_2$-CH$_3$], 43a, b. Prepared following general procedure 3d from 2-pyrrolidin-1-yl-benzaldehyde 9d (697 mg, 3.69 mmol), 1-methylimidazolidine-2,4-dione (421 mg, 4.1 mmol) and anhydrous NH$_4$OAc (284 mg, 3.7 mmol). Abs. EtOH, 10 mL, 140 h, 78 °C. MPLC gradient PE to PE:EE = 80:20. Yield of cyclized isomer <1%, trace amounts in reaction mixture stain purple in molybdatophosphate at R$\_f$=0.73 (CH$_2$Cl$_2$); obtained 593 mg (59 %) of a 3:2 mixture of 1-Methyl-5-[1-(2-pyrrolidin-1-yl-phenyl)-meth-(Z)-ylidene]-imi-dazolidine-2,4-dione 43a and 1-Methyl-5-[1-(2-pyrrolidin-1-yl-phenyl)-meth-(E)-ylidene]-imidazolidine-2,4-dione 43b as yellow oil that crystallized upon standing in CH$_2$Cl$_2$ the pure (5$Z$)-isomer 43a. GC-MS, m/z (I$_{rel}$, (%)) of a 3:2 mixture Z:E-isomer ratio: 171.2 (100), 170.18 (87), 143.15 (38), 114.95 (24), 77.07 (17), 130.14 (16), 128.12 (13), 142.14 (13), 168.16 (12), 172.2 (12), 89.06 (11), 167.17 (10), 169.15 (9), 63.08 (9), 85.61 (9), 154.16 (9), 56.11 (8), 57.21 (8), 51.11 (8).

(5$Z$)-1-Methyl-5-(2-pyrrolidin-1-ylbenzylidene)imidazolidine-2,4-dione (43a). Main isomer, precipitates in a pure state from CH$_2$Cl$_2$ as a yellow solid, mp 126-131 °C. $^1$H-NMR (200MHz, CDCl$_3$) $\delta$ 9.7-9.2 (br.s, 1H, N-H), 8.01 (d, 1H, J=0.9 Hz, benzylidene-H), 7.32-7.25 (m, 1H, J=7.6 Hz, Ar-H-4), 7.18-7.14 (m, 1H, J=0.9 Hz, Ar-H-6), 7.04-6.96 (m, 2H, J=8, J=7 Hz; Ar-H-5, Ar-H-3), 3.21 (s, 3H, N-CH$_3$), 2.94-2.82 (m, 4H), 1.68-1.46 (br.m, 4H).$^{13}$C-NMR (50MHz, CDCl$_3$) $\delta$ 163.4 (-), 154.4 (-), 154.5 (-), 131.6 (J), 129.4 (-), 126.5 (-), 122.5 (J), 118.7 (J), 116.4 (J), 113 (J), 54.7 (2J), 27.3 (J), 24.8 (2J).

(5$E$)-1-Methyl-5-(2-pyrrolidin-1-ylbenzylidene)imidazolidine-2,4-dione (43b). $^1$H-NMR (200MHz, CDCl$_3$) $\delta$ 9.7-9.2 (br.s, 1H, N-H), 7.32-7.25 (m, 1H), 7.18-7.14 (m, 1H), 7.04-6.98 (m, 2H), 6.96 (d, 1H, J=1.2 Hz, benzylidene-H), 2.97 (s, 3H, N-CH$_3$), 2.96-2.82 (br.m, 4H), 1.68-1.46 (br.m, 4H).$^{13}$C-NMR (50MHz, CDCl$_3$) $\delta$ 165.3 (-), 156.3 (-), 154.5 (-), 131.6 (J), 130.8 (-), 130.4 (-), 129.9 (J), 126.7 (J), 121.7 (J), 118.9 (J), 54.2 (2J), 26.8 (J), 24.5 (2J).

ACKNOWLEDGEMENT

Donation of chemicals from Interbioscreen, Ltd. is gratefully acknowledged. We are thankful to Dr. Martina Marchetti for MALDI analyses.
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