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

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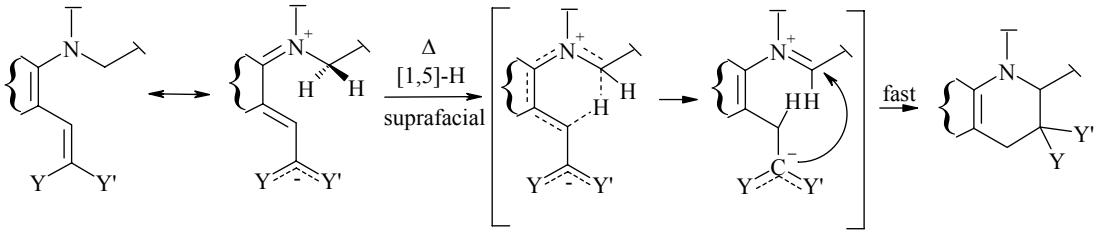
Abstract - Scope and limitations of the T-reaction with emphasis on using chiral, natural products as starting materials to prepare novel chiral heterocycles is studied and the diastereoselective introduction of newly formed stereocenters is explained via proposed mechanisms.

INTRODUCTION

The T-reaction is currently being used with increased frequency for the creation of new C-C bonds in [1,2-*a*]-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,[1] 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[2], generated upon a suprafacial [1,5]-hydrideshift[3] 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.

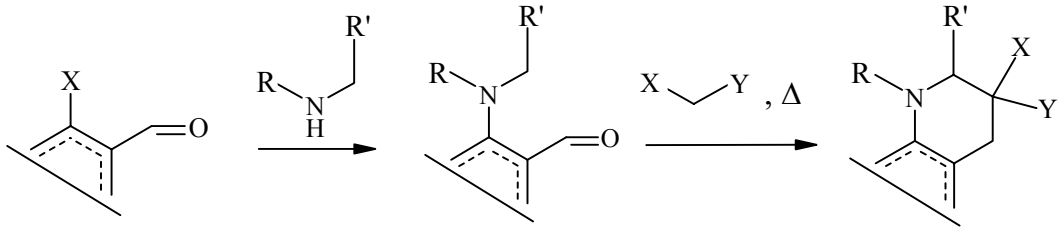


Scheme 1: The *tert*-amino-effect operative in the T-reaction.

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.

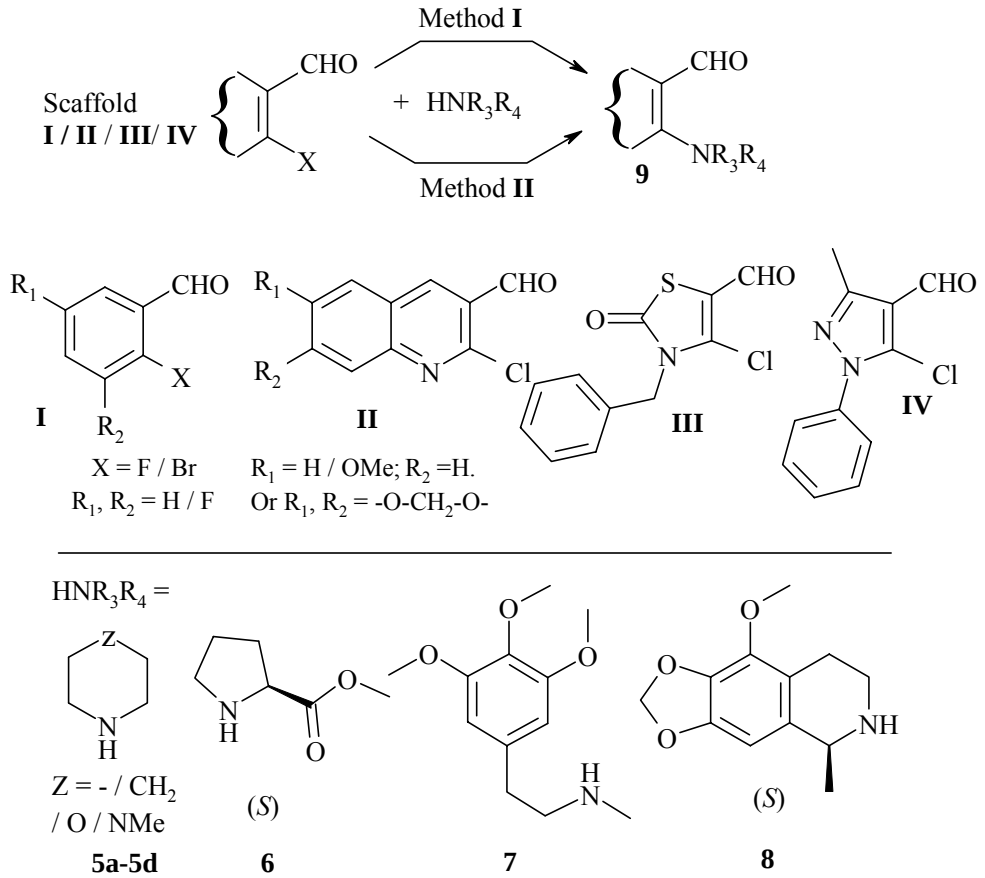
RESULTS AND DISCUSSION

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[4] followed by the tandem[2,5] T-reaction in protic solvents (see schemes). We examined variations on the C-H-acid moiety, namely employing mono- (X = NO_2, Y = H), disubstituted (X, Y= COR, COOR, CONHR, NCOR or CN)[6] and heterocyclic[7] active methylene compounds 2,2-dimethyl-[1,3]-dioxane-4,6-dione (Meldrum's acid, **11**, see Scheme 4) and 1,3-dimethylpyrimidine-2,4,6-trione (*N*,*N*-dimethylbarbituric acid, **12**). When X ≠ Y, new stereogenic centers are formed. With X = Y, follow-up transformations[8] 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[5] 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"[7] high in comparison to open-chain active methylene compounds with similar electron-withdrawing properties is validated.[9,10]



Scheme 3: Methods of *N*-Arylation

Method I: X = Br, R_1 = R_2 = H , 1 eq. HNR_3R_4 (**6** / **7** / **8**), 0.01-0.05 eq. $Pd(OAc)_2$ *cat.*, 0.03-0.15 eq. (±)-BINAP *cat.*, 1.4 eq. Cs_2CO_3, $C_6H_5CH_3$, Δ, Ar. **Method II**: X = F (Scaffold **I**), X = Cl (Scaffold **II**, **III**, **IV**), R_1, R_2 = H / F, 1 eq. HNR_3R_4 (**5**), 1.5 eq. K_2CO_3, DMF or DCE, Δ.

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[11,12] substituted aldehydes or Buchwald-Hartwig Pd-catalyzed aryl amination[13-16] 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 SN_{Ar2}- 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 insensititive nucleophiles (**5a-d**). Both methods allowed for the preparation of non-racemic arylated *tert*-anilines (HNR_3R_4= **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

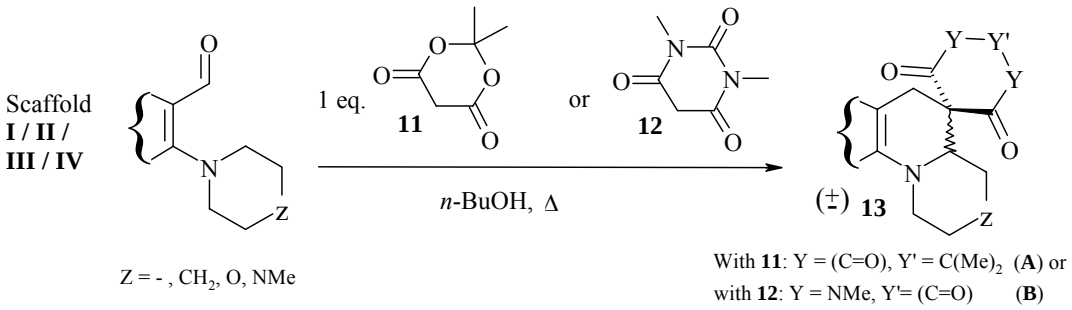
Product	Scaffold	Method	R_1, R_2	HNR_3R_4	Temp [°C], Time [h], isolated yield [%]
9a	**I**	I	H, H	**6**	95, 20, 79
9b	**I**	I	H, H	**7**	90, 60, 67
9c	**I**	I	H, H	**8**	90, 110, 36
9d	**I**	II	H, H	**5a**	150, 16, 87
9e	**I**	II	H, H	**5b**	150, 16, 93
9f	**I**	II	F, H	**5a**	60, 200, 63
9g	**I**	II	H, F	**5b**	100, 20, 76
9h	**I**	II	F, H	**5b**	120, 52, 79
9i	**I**	II	H, F	**5c**	100, 20, 57
9j	**I**	II	F, H	**5c**	120, 52, 56
9k	**II**	II	H, H	**5a**	60, 14, 63
9l	**II**	II	H, H	**5c**	80, 20, 56
9m	**II**	II	OCH_3, H	**5c**	80, 20, 54
9n	**II**	II	OCH_3, H	**5d**	80, 40, 93
9o	**II**	II	-O-CH_2-O-	**5a**	70, 20, 60
9p	**II**	II	-O-CH_2-O-	**5b**	80, 40, 75
9q	**II**	II	-O-CH_2-O-	**5c**	80, 20, 66
9r	**II**	II	-O-CH_2-O-	**5d**	80, 50, 88
9s	**III**	II	-	**5a**	100, 20, 76
9t	**III**	II	-	**5c**	80, 3, quant.[a]
9u	**IV**	II	-	**5c**	100, 20, 51
9v	**IV**	II	-	**5d**	100, 16, 75

[a] Reaction performed in DCE.

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

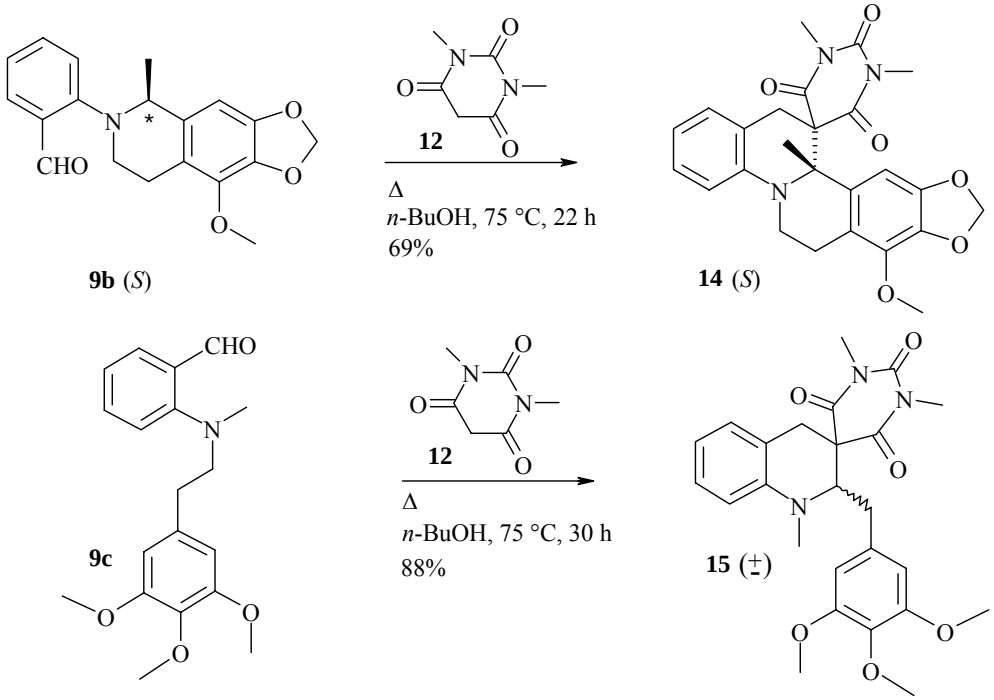
Entry	Scaffold	R_1, R_2	Z	Y-Y'-Y	Temp. [°C], Time [h], isolated yield [%]
13a	**I**	H, H	-	**A**	75, 2, 97
13b	**I**	H, H	CH_2	**A**	75, 1, 96
13c	**I**	H, F	CH_2	**B**	75, 6, 93
13d	**I**	H, F	O	**B**	100, 6, quant.
13e	**II**	H, H	-	**B**	75, 30, quant.
13f	**II**	-O-CH_2-O-	-	**A**	75, 20, 99
13g	**II**	-O-CH_2-O-	O	**A**	75, 20, 51
13h	**II**	-O-CH_2-O-	O	**B**	75, 45, 88
13i	**II**	-O-CH_2-O-	CH_2	**A**	75, 4, 99
13j	**II**	-O-CH_2-O-	CH_2	**B**	100, 6, 92
13k	**II**	-O-CH_2-O-	NCH_3	**B**	75, 30, quant.
13l	**III**	-	O	**A**	75, 100, 95
13m	**IV**	-	CH_2	**B**	100, 24, 88
13n	**IV**	-	O	**A**	100, 100, 75
13o	**IV**	-	O	**B**	100, 90, 60

Employing cyclic C-H acids **11** and **12** (Scheme 4) furnished correspondding racemic *spiro*-substituted fused heterocycles **13** in good to excellent yields, providing derivatives of novel heterocycles [1,3]thiazolo[5',4':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-



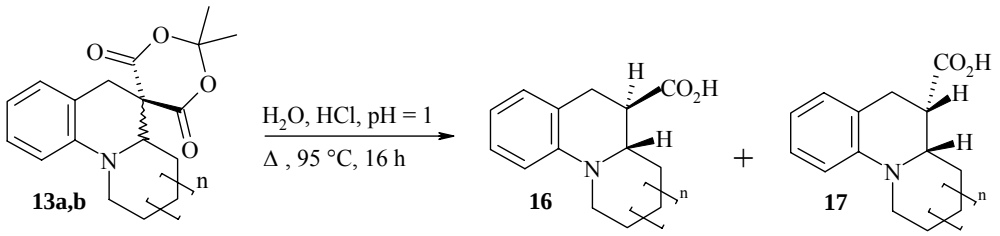
Scheme 4: Tandem-cyclizations of *ortho*-cycloalkylamino substituted aromatic aldehydes via *tert*-amino-effect using Meldrum's or *N*,*N*-dimethylbarbituric acid

[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 decompositon 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 occuring 2-phenylethylamines 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**.

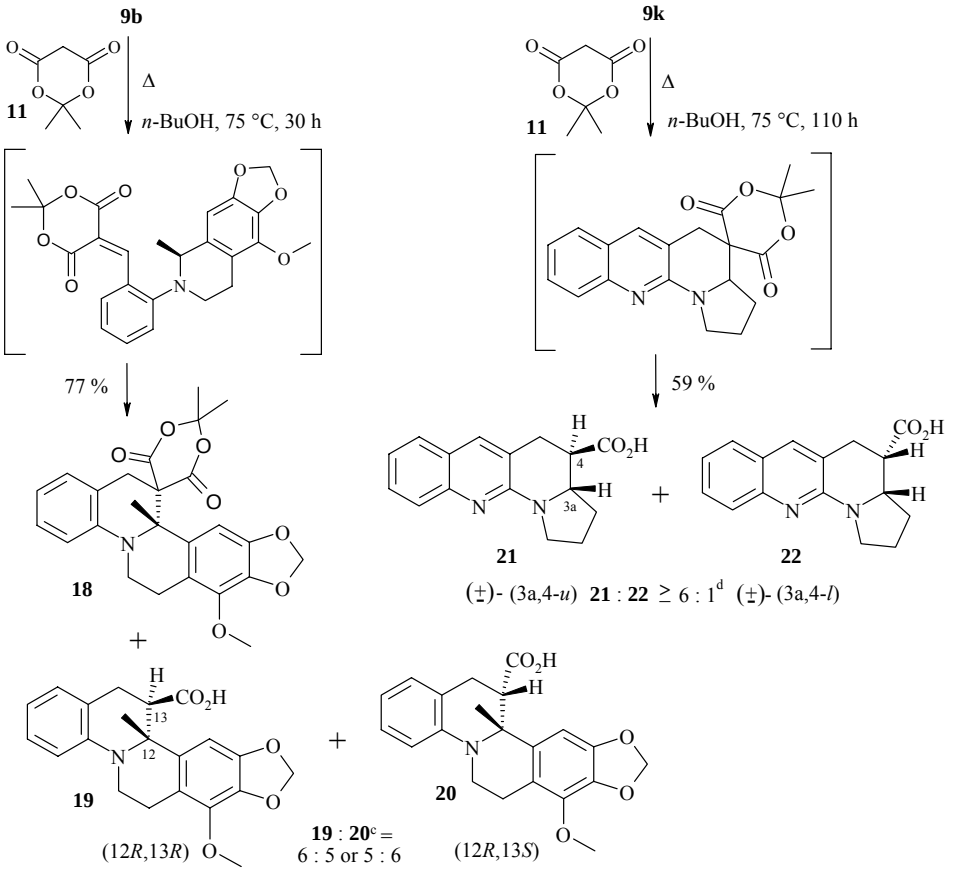


	n	Yield (%)	isomer ratio[b]
16a,17a	0	82	(3a,4-*u*) : (3a,4-*l*) ≥ 5:1
16b,17b	1	95	(4a,5-*u*) : (4a,5-*l*) ≥ 7:1

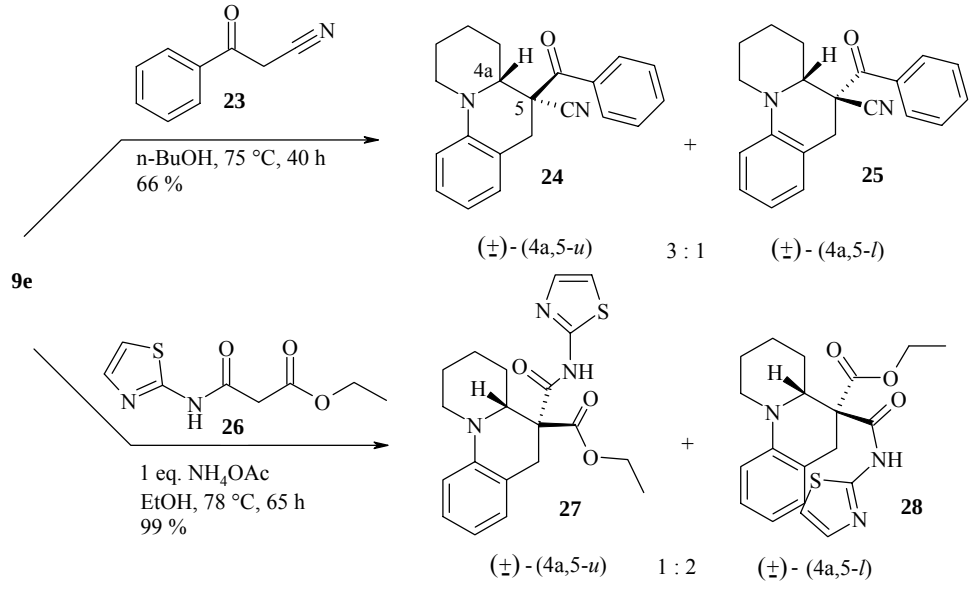
Scheme 6: Diastereoselective ring-opening of *spiro*-fused 1,3-dioxane-4,6-diones.
[b] isomers not adequately separable on SiO_2; isomer ratio determined via ^{1}H-NMR.

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,[18] the preferred diastereomer **16** is that in which the vicinal protons at the two stereocenters are related *trans* to each other, furnishing the -(*u*) diastereomer.[19] This was deduced from the value of the vicinal coupling constants ^{3}J of protons in ^{1}H-NMR at the stereogenic phenylethylenic and bridgehead α-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]isoquino[2,1-*a*]quinoline-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,[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–*u*) isomer **24** with the cyano moiety located *trans* to the bridgehead hydrogen (Scheme 8) as determined by single crystal XRD (Figure 2). Two conformers of the pure (4a,5-*u*)-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).

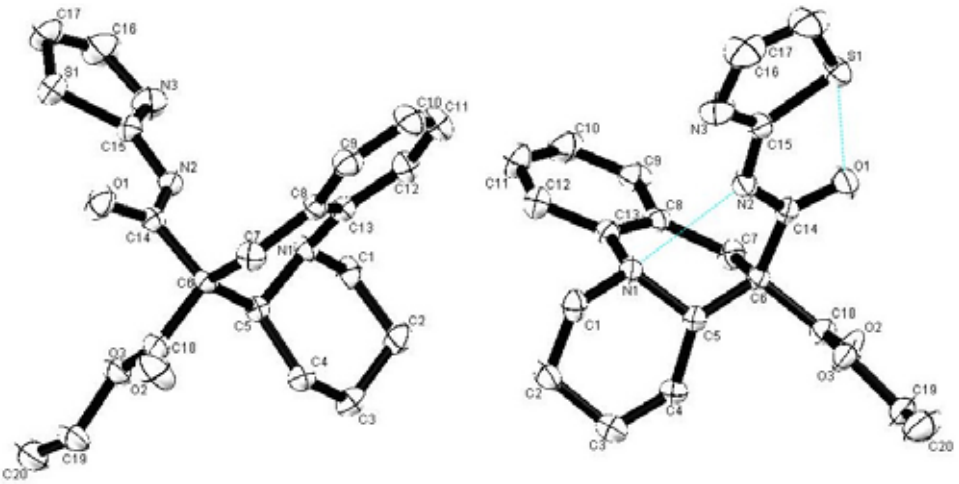


Figure 1: XRD of compound **28**. (50% probability thermal ellipsoids crystallographic numbering, non-stereogenic hydrogens omitted for clarity, dashed lines on right model indicate H-bonding between N_1-N_2 and S_1-O_1.)

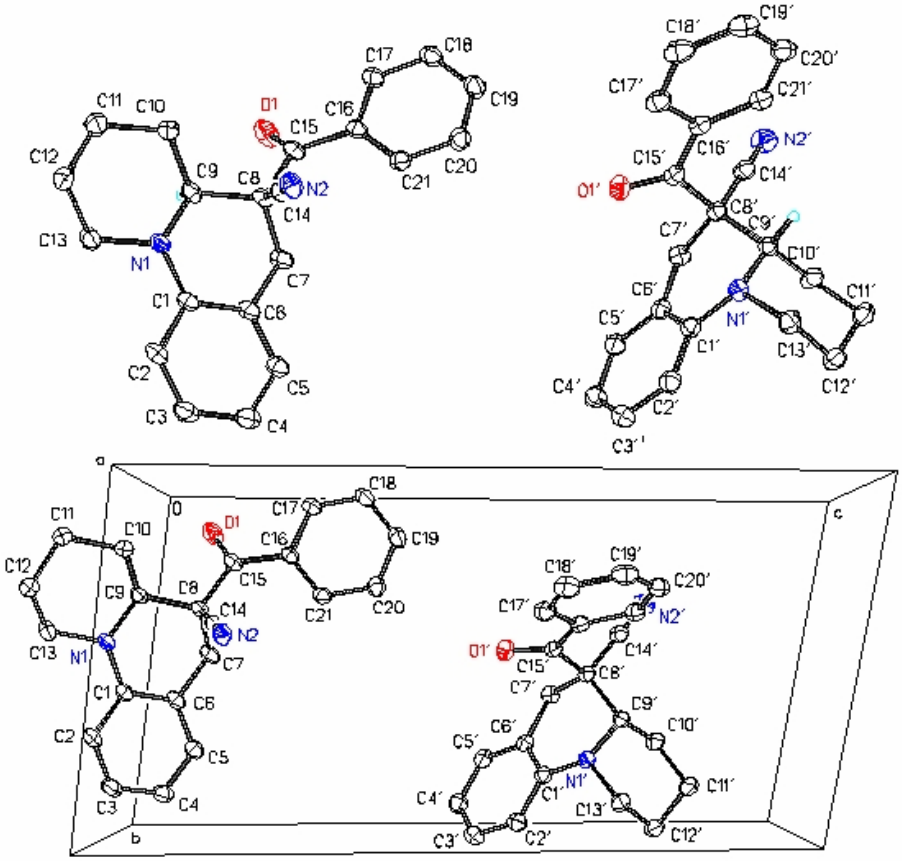
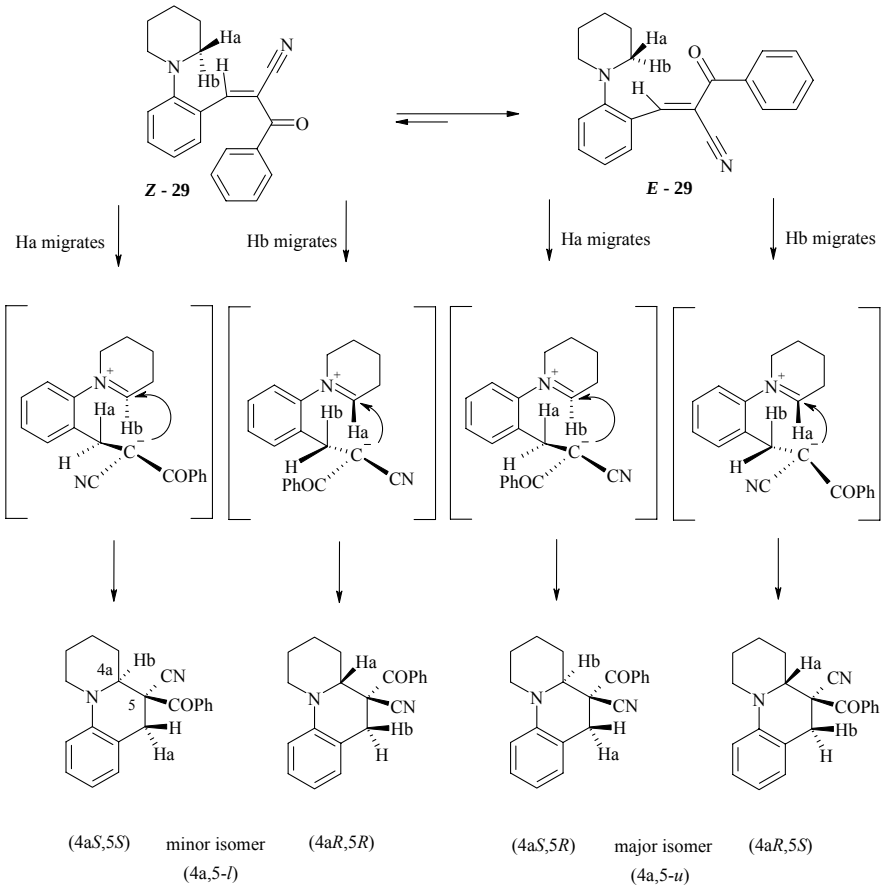


Figure 2: XRD of two conformers of compound **24** (*ORTEP* drawing, 50 % probability, crystallographic numbering, non-stereogenic hydrogens omitted for clarity). In below: Asymmetric unit cell, hydrogens omitted.

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 *Ha* and *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**.

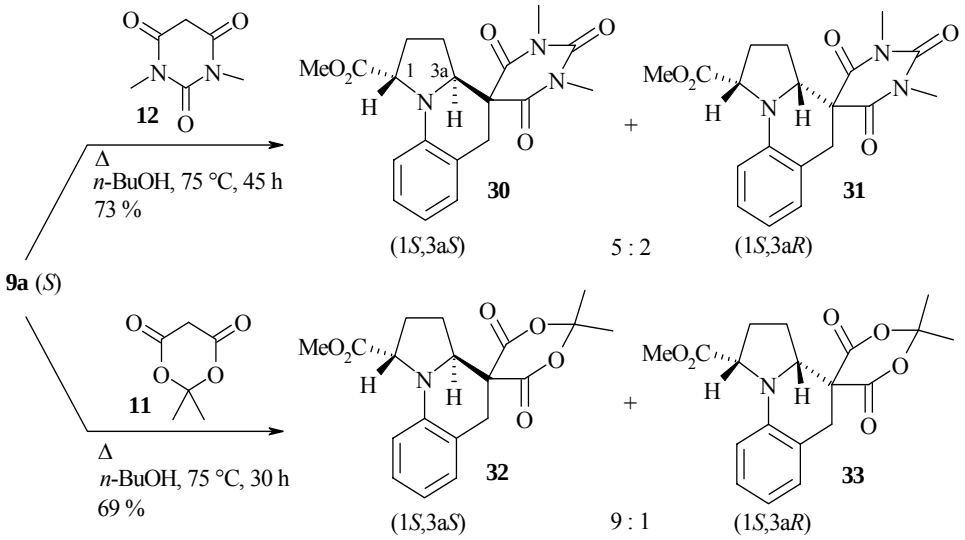


Scheme 9: Overall scheme of supposedly viated pathways of cyclization via *tert*-amino-effect, compounds **23** and **24**

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 H2*u*, further H3a and H3*d* were observed whereas H3a showed no NOE with H3*u* in the main isomer. In contrast, H3a interacted with H5*u* in the minor isomer.



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

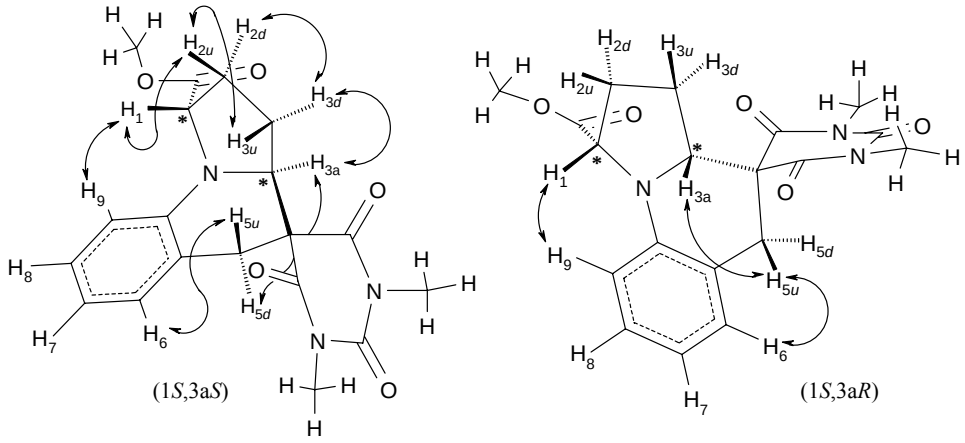
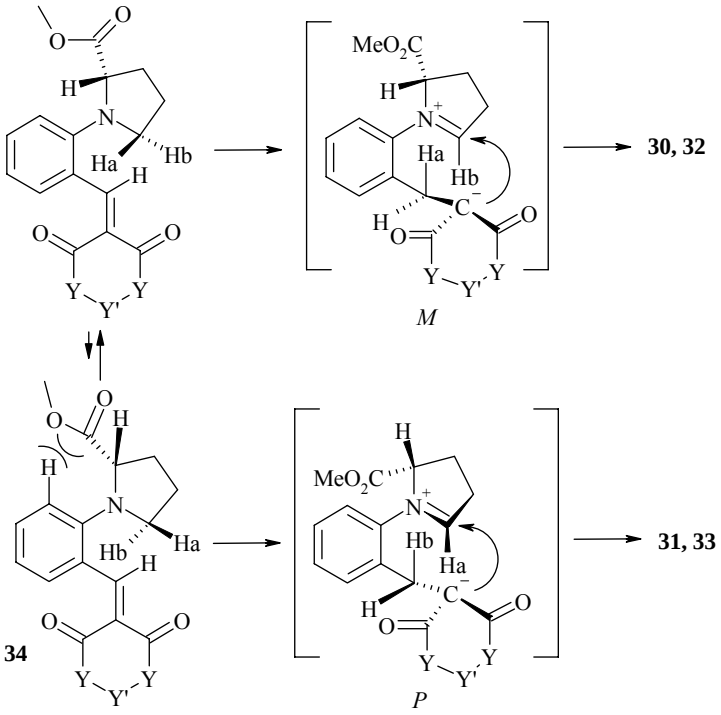


Figure 3: Selected NOE correlations for **30**, **31**. **32**, **33** generate analogous signals.

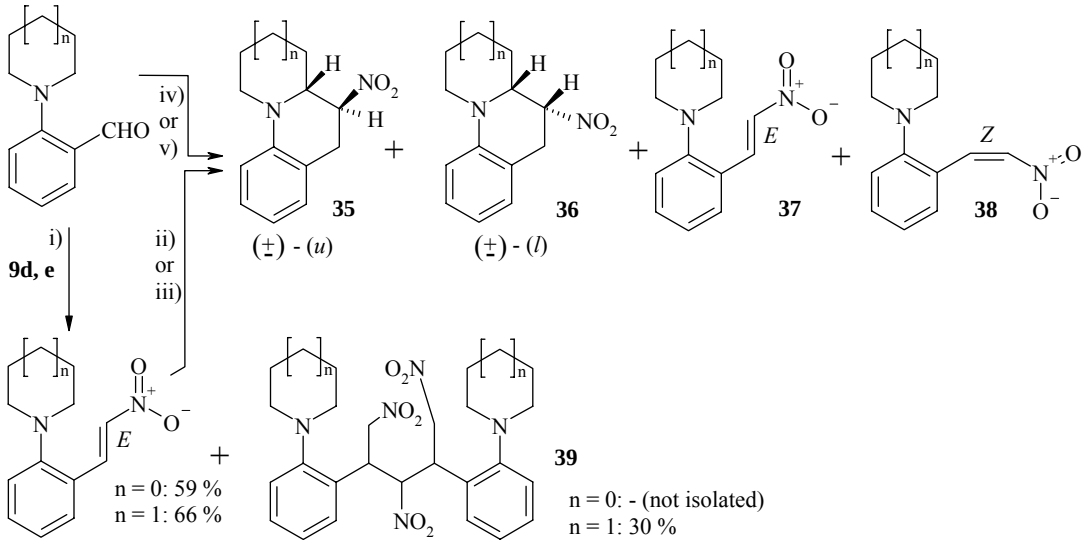
In Scheme 11, a possible mechanism accounting for this stereopreference is hypothesized. Assuming a transient destabilizing interaction[2] occurs in the unsaturated intermediate between the chiral α-amino proton and H9 in the phenyl ring in **34**, such an interaction would disfavor the placement of *Hb* in a coplanar orientation for subsequent hydride-migration. Conversely, the migration of *Ha* does not suffer from a comparable sterical hindrance.



Scheme 11: Explanation of the diastereomeric preference in T-reactions using prolines

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.[8] Lewis acid catalysis using $AlCl_3$ 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-*u*) 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 12: Nitro-functionalized [1,2-*a*]fused hexahydroquinolines via *tert*-amino-effect. i) $MeNO_2$, 0.2 eq. KF, 2 eq. $HNMe_2$.HCl; C_6H_5Me, Δ, 110 °C, 2-3 h, Dean-Stark trap.[20] ii) *n*-BuOH, Δ, 118 °C; 80 h (n=0) or 220 h (n=1). iii) *n*-BuOH, Δ, 118 °C, 90 h, $AlCl_3$ *cat.*/ stoich. iv) 1 eq. NH_4OAc, 1.1 eq. $MeNO_2$, Δ, 118 °C, 120 h. v) 1 eq. NH_4OAc, 1.1 eq. $MeNO_2$, Δ, 118 °C, 60 h, $AlCl_3$ *cat.*

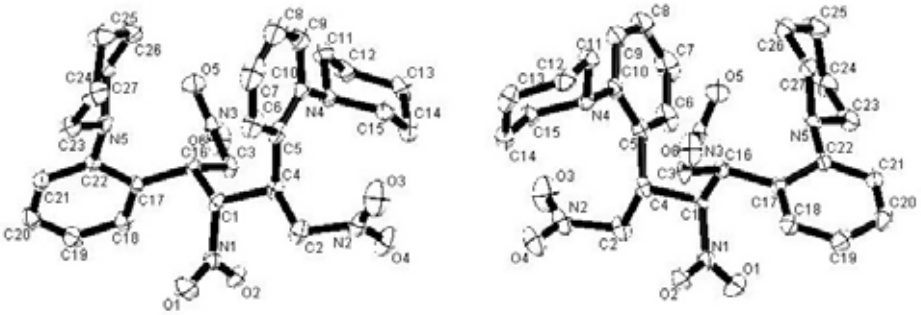


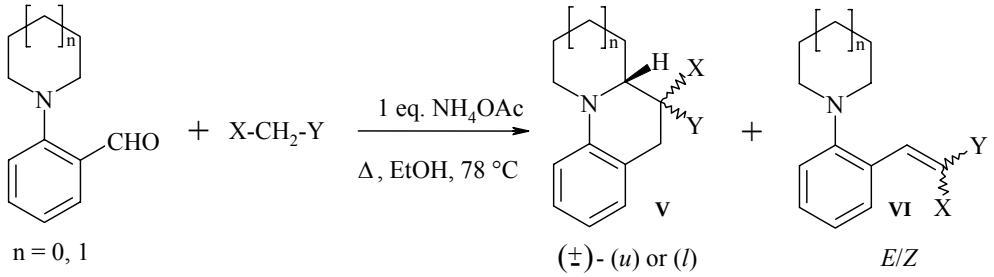
Figure 4: XRD of compound **39** (20 % thermal ellipsoids, hydrogens omitted for clarity, crystallographic numbering, view from two opposite sides)

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

n	Path	Isolated yield of **35** and **36** (%)	Isolated yield of **37** and **38** (%)
0	ii)	39; (3a,4-*u*): (3a,4-*l*) ≥ 12:1.	**37a**: <1; **38a**: 11.
0	iv)	25; (3a,4-*u*): (3a,4-*l*) ≥ 23:2	**37a**: 16; **38a**: 20.
0	v)	27; (3a,4-*u*): (3a,4-*l*) ≥ 25:2	**37a**: 8; **38a**: 19.
1	ii), iii)	traces[e]	**37b**: 40, **38b**: not determined.

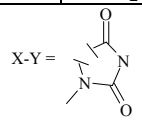
Attempts to utilize methyl nitroacetate, *N*-methylhydantoin or ethyl acetoacetate as C-H acids gave the T-products only in low yield (Scheme 13, Table 4).

[e] 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. [f] Nature of major diastereomer unassessed.

	n	X	Y	Reaction time [h]	Yield of **V** (%)	Yield of **VI** (%)
40	1	NO_2	CO_2Me	60	15 (ratio ≥ 10:1)[f]	59 (*E*/*Z*-mixture)
41	0	MeCO	CO_2Me	220	7 (ratio ≥ 7:1)[f]	60 (*E*/*Z*-mixture)
42	1	MeCO	CO_2Me	250	3 (ratio ≥ 4:1)[f]	49 (*E*/*Z*-mixture)
43	0	X-Y = 		290	traces[e]	59 (*E*:*Z* = 2:3)

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, respecttively, 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 Θ 45° 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 $\nu_{res} \sim J$ (CH/CH_3), $\nu_{res} \sim J/2$ (CH_2) or no signal for C_{quart} 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 N_2-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: $\alpha\,[_{\text{wavelength[nm]}}{}^{\text{temperature[°C]}}] = \alpha$ [589 nm]*100/(L[dm]*c[g/100mL]).

Single crystal X-ray data were collected on a Bruker Smart APEX CCD area detector diffractometer using graphite-monochromated Mo K_α radiation (λ= 0.71073 Å, sealed X-ray tube) and 0.3° ω-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), λ/2 effects, and crystal decay were applied.[21] The structures were solved by direct methods using the program SHELXS97.[22] 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 F_{254} 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_2SO_4, accompanied by gentle heating; b) by UV-HPLC on a WATERS 2695 (Elutants: Solvent A= 0.1% CF_3CO_2H + 3 % MeCN + 97 % H_2O; Solvent B= 0.1 % CF_3CO_2H + 97 % MeCN + 3 % H_2O; 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 ≥ 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.

K_2CO_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_2Cl_2 in an oversized glass tube and then placed in a closed vessel under an almost saturated atmosphere of Et_2O; 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 K_2CO_3 (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 K_2CO_3 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 K_2CO_3 (*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 K_2CO_3-solution, extracted with CH_2Cl_2 (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 CH_2Cl_2 and the combined organic phases dried (Na_2SO_4), the solvent roto-evaporated to yield the crude product that was dissolved in CH_2Cl_2. 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 preperation 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 Cs_2CO_3 (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 Cs_2CO_3 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 K_2CO_3-solution, extracted with CH_2Cl_2 (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 CH_2Cl_2 and the combined organic phases dried (Na_2SO_4), the solvent roto-evaporated to yield the crude product that was dissolved in CH_2Cl_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.

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, $[\alpha]_D^{20}$ - 365.7 (c 1.17, $CHCl_3$)**.** ^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2), 3.44 (s, 3H, CH_3), 3.22-3.12 (br.m, 1H, *J*=6.8 Hz, α-amino-CH_2), 2.31-2.20 (m, 1H, *J*=7 Hz, β-amino-CH_2), 1.98-1.70 (br.m, 3H, β-amino-CH_2).^{13}C-NMR (50MHz, $CDCl_3$) δ 190.2 (J), 173.3 (-), 149 (-), 134.3 (J), 132.6 (J), 124.4 (-), 118.3 (J), 115.7 (J), 62.6 (J), 54.5 (2J), 51.8 (J), 30.1 (2J), 24.6 (2J).GC-MS, *m/z* (I_{rel}, (%)):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:Et_2O=80:20. Yield 350 mg (67 %), yellow oil. ^{1}H-NMR (200MHz, $CDCl_3$) 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, $(OCH_3)_3$-Ar-H), 3.75 (s, 6H, *m*-O-CH_3), 3.74 (s, 3H, *p*-O-CH_3), 3.37-3.29 (m, 2H, *J*=15.4, *J*=8, *J*=7.4 Hz, β-phenylethylamine-CH_2), 2.89 (s, 3H, N-CH_3), 2.81-2.73 (m, 2H, *J*=15.4, *J*=8, *J*=7.4 Hz, benzyl-CH_2).^{13}C-NMR (50MHz, $CDCl_3$) 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* (I_{rel}, (%)): 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-[(9*S*)-4-Methoxy-9-methyl-6,9-dihydro[1,3]dioxolo[4,5-*h*]isoquinolin-8(7*H*)-yl]benzaldehyde (9c). Prepared following general procedure 2 from 2-bromobenzaldehyde(569 mg, 3.08 mmol) and (*S*)-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, $[\alpha]_D^{20}$ + 460.3 (c 0.86, $CHCl_3$).^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2-O-), 5.88 (d, 1H, *J*=1.4 Hz, -O-CH_2-O-), 4.49 (q, 1H, *J*=6.6 Hz, α-amino-CH), 3.82 (s, 3H, O-CH_3), 3.56 (ddd, 1H, *J*=12.7, *J*=11, *J*=4.2 Hz, α-amino-CH_2),

3.25 (ddd, 1H, *J*=12.7, *J*=6.1, *J*=5.5 Hz, α-amino-CH_2), 2.92-2.75 (m, 1H, *J*=16.2, *J*=11, *J*=5.5 Hz, benzyl-CH_2), 2.66-2.55 (dd, 1H, *J*=16.2, *J*=4.2 Hz, benzyl-CH_2), 1.25 (d, 3H, *J*=6.6 Hz, α-amino-CH_3). ^{13}C-NMR (50MHz, $CDCl_3$) δ 191.8 (J), 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* (I_{rel}, %) TIC, MS^2: 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. ^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2), 1.88-1.6 (br.m, 4H, β-amino-CH_2).

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, R_f=0.84 (PE:EE=75:25).^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2), 1.79-1.65 (br.m, 4H, β–amino-CH_2), 1.65-1.57 (br.m, 2H, γ–amino-CH_2).^{13}C-NMR (50MHz, $CDCl_3$) δ 191.3 (J), 156.9 (-), 134.7 (J), 129 (J), 128.5 (-), 121.9 (J), 118.9 (J), 55.5 (2J), 26.1 (2J), 24 (2J).GC-MS, m/z (I_{rel}, (%)):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, 200 h, 60 °C. MPLC gradient PE to PE:EE=80:20, Yield 946 mg (63 %), yellow oil.^{1}H-NMR (200MHz,$CDCl_3$) 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-CH_2), 1.94-1.88 (br.m, 4H, β-amino-CH_2).^{13}C-NMR (50MHz, $CDCl_3$) 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. ^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2), 1.77-1.45 (br.m, 6H, β–, γ–amino-CH_2).^{13}C-NMR

(50MHz,$CDCl_3$) δ 191.6, 162.6, 151.6, 143.3, 133.9, 124.6, 122.3, 54.1, 26.4, 24.

5-Fluoro-2-piperidin-1-ylbenzaldehyde (9h). Prepared following general procedure 1a from 2,5-difluoro-benzaldehyde (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, $CDCl_3$) δ 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, α-amino-CH_2), 1.8-1.6 (br.m, 4H, β-amino-CH_2), 1.59-1.4 (br.m, 2H, γ-amino-CH_2). ^{13}C-NMR (50MHz,$CDCl_3$) δ 190.1, 155.9, 130.2, 121.8, 121.4, 121.1, 114.1, 55.9, 26.1, 23.8. GC-MS, *m/z* (I_{rel}, (%)): 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, Ar-H-4, Ar-H-6) 3.88-3.79 (m, 4H, O-CH_2), 3.01-2.89 (m, 4H, N-CH_2).^{13}C-NMR (50MHz,$CDCl_3$) δ 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, $CDCl_3$) δ 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, α-amino-CH_2), 1.82-1.76 (m, 4H, β-amino-CH_2).^{13}C-NMR (50MHz, $CDCl_3$) δ 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* (I_{rel}, (%)):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 ge-neral 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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* (I_{rel}, (%)): 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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* (I_{rel}, (%)): 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, $CDCl_3$) δ 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-CH_2), 2.6-2.55 (m, 4H, *J*=4.8 Hz, CH_3N-CH_2), 2.31 (s, 3H, N-CH_3). ^{13}C-NMR (50MHz, $CDCl_3$) δ 190 (J), 157.7 (-), 155.9 (-), 144.7 (-), 139.7 (J), 128.5 (J), 124.3 (J), 124.2 (-), 121.6 (-),106 (J), 55 (J), 54.4 (2J), 50.8 (2J), 45.6 (J). GC-MS, *m/z* (I_{rel}, (%)): 282.16 (100), 162.04 (80), 208.15 (51), 121.98 (35), 57.11 (34), 178.11 (29), 192.14 (28), 123.08 (25), 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, $CDCl_3$) δ 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-CH_2-O-), 3.6-3.45 (m, 4H, α–amino-CH_2), 2-1.7 (m, 4H, β–ami-no-CH_2). ^{13}C-NMR (50MHz, $CDCl_3$) δ 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, α-amino-CH_2), 1.8-1.55 (br.m, 6H, β–, γ–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 (-), 122 (-), 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* (I_{rel}, (%)): 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]dio-xolo[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 ^{1}H-NMR (200MHz, $CDCl_3$) δ 9.96 (s, 1H, CHO), 8.19 (s, 1H, Ar-H-4), 7.17 (s, 1H, Ar-H-5), 6.88 (s, 1H, Ar-H-8), 5.98 (s, 2H, -O-CH_2-O-), 3.09-3.03 (m, 4H, ArN-CH_2), 2.44-2.36 (m, 4H, CH_3N-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* (I_{rel}, (%)):14.55 min: 104.95 (100), 76.97 (91), 211.18 (68), 316.23 (51), 172.17 (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-CH_2), 3.43-3.20 (br.m, 4H, *J*~6 Hz, pyrrolidinyl-α-amino-CH_2) 1.99-1.67 (bm, 4H, *J*=8.8, *J*~6 Hz, pyrrolidinyl-β-amino-CH_2).^{13}C-NMR (50MHz, $CDCl_3$) δ 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* (I_{rel}, (%)): 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_2Cl_2/Et_2O by diffusion and slow evaporation, mp 215.6 °C. ^{1}H-NMR (200MHz, $CDCl_3$) δ 9.8 (s, 1H, CHO), 7.3-7.05 (m, 5H, Ar-H), 4.84 (s, 2H, benzyl-CH_2), 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, $CDCl_3$) δ 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* (I_{rel}, (%)): 98.1 (100), 55.2 (14.6), 84.0 (7.7), 70.1 (7.1).

3-Methyl-5-morpholin-4-yl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (9u). Prepared following general procedure 1a from 5-chloro-3-methyl-1-phenyl-1*H*-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, $CDCl_3$) δ 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, $CDCl_3$) δ 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* (I_{rel}, (%)): 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-1*H*-pyrazole-4-carbaldehyde (9v). Prepared following general procedure 1a from 5-chloro-3-methyl-1-phenyl-1*H*-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, $CDCl_3$) δ 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, $CDCl_3$) δ 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* (I_{rel}, (%)): 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_2Cl_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 dH_2O (two times using 2 mL/ 100 mg of expected product) and once with 5 mL brine, the aqueous phases washed once again with CH_2Cl_2 (using 2 mL/mL of dH_2O) and the combined organic phases dried (Na_2SO_4), the solvent roto-evaporated to yield the crude product that was dissolved in CH_2Cl_2. 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 NH_4OAc 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 continuosly extracted with CH_2Cl_2 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). ^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2), 3.33 (dd, 1H, *J*=16, *J*=4.2 Hz), 3.19 (d, 1H, *J*=16.4 Hz, benzyl-CH_2), 2.29-2.15 (br.m, 1H), 2.12-1.98 (br.m, 2H), 1.8 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 1.74-1.64 (br.m, 1H).^{13}C-NMR (50MHz, $CDCl_3$) 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 (2J).

(±)-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.), R_f= 0.46 (PE:EE=75:25). ^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2), 3.48-3.44 (m, 1H, *J*=8.2Hz), 3.14 (d, 1H, *J*=16.5 Hz, benzyl-CH_2), 2.80 (m, 1H, *J*=12.2, *J*=11.7 Hz), 1.89-1.82 (br.m, 1H), 1.78 (br., 6H, CH_3), 1.74-1.68 (bm, 2H), 1.67-1.35 (br.m, 3H). ^{13}C-NMR (50MHz, $CDCl_3$) δ 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-1*H*,2'*H*,6*H*-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, $CDCl_3$) δ 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-CH_2), 3.46-3.39 (m, 1H), 3.31 (s, 3H, N-CH_3), 3.19 (s, 3H, N-CH_3), 2.95 (d, 1H, *J*=17.4 Hz, benzyl-CH_2), 2.91–2.79 (br.m, 1H), 1.7-1.1 (br.m, 6H). ^{13}C-NMR (50MHz, $CDCl_3$) δ 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*,6*H*-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, $CDCl_3$) δ 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-CH_2), 3.21 (s, 3H, N-CH_3), 3.2 (s, 3H, N-CH_3), 3.1-3.01 (m, 1H), 2.95 (d, 1H, *J*=15.8 Hz, benzyl-CH_2).^{13}C-NMR (50MHz, $CDCl_3$) δ 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*,5*H*-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, $CDCl_3$) δ 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*=7.6, *J*=5.8, *J*=4.3, *J*=3.2 Hz, α-amino-CH_2, α-amino-CH), 3.66-3.57 (br.m, 2H, *J*=16.4, *J*=1.9 Hz, benzylic-H, α-amino-CH_2), 3.33 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 3.01 (d, 1H, *J*=16.4 Hz, benzylic-H), 2.07-1.86 (m, 2H, *J*=5.8, *J*=4.3, *J*=2.6 Hz, β-amino-CH_2), 1.52-1.33 (m, 2H, *J*=9.8, *J*=7.1, *J*=1.5 Hz, β-amino-CH_2).^{13}C-NMR (50MHz, CDCl3) δ 169.9 (-), 166.6 (-), 152.4 (-), 150.8 (-), 147.1 (-), 133.9 (J), 128.8 (J), 126.8 (J), 125.9 (J), 122.9 (-), 121.9 (J), 117.1 (-), 64.2 (J), 49 (-), 47.1 (2J), 36.8 (2J), 29.1 (J), 28.5 (2J), 28.4 (J), 23 (2J).

(±)-2',2'-Dimethyl-1,2,3,3a-tetrahydro-5*H*-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. ^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2-O-), 4.15-3.9 (m, 2H, α-amino-CH_2, α -amino-CH), 3.55 (d, 1H, *J*=17.2 Hz, benzylic-CH_2), 3.6-3.42 (br.m, 1H, α-amino-CH_2), 3.15 (d, 1H, *J*=17.2 Hz, benzylic-CH_2), 2.2-2.03 (br.m, 1H, β-amino-CH_2), 2-1.5 (br.m, 3H, β-amino-CH_2), 1.66 (br.s, 6H, CH_3).^{13}C-NMR (50MHz, $CDCl_3$) δ 169.3 (-), 163.9 (-), 151.1 (-), 150 (-), 144 (-), 133.7 (J), 136 (-), 118.1 (-), 113 (-), 105 (-), 103.9 (J), 102.8 (J), 101 (2J), 64.5 (J), 49.8 (-), 47.4 (2J), 36.2 (2J), 30.1 (J), 28.9 (2J), 28.1 (J), 22.9 (2J).

(±)-2',2'-Dimethyl-1,2,4,4a-tetrahydro-6*H*-spiro[1,3-benzodioxolo[5,6-*g*][1,4]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. ^{1}H-NMR (200MHz, $CDCl_3$) δ 7.59 (s, 1H, Ar-H-4), 7.06 (s, 1H, Ar-H-5), 6.85 (s, 1H, Ar-H-8), 5.98 (s, 2H, -O-CH_2-O-), 4.94 (d, 1H, *J*=13 Hz**),** 4.02-3.89 (m, 2H), 3.71-3.49 (m, 3H), 3.21-2.92 (br.m, 3H), 1.76 (s, 3H, CH_3), 1.75 (s, 3H, CH_3).^{13}C-NMR (50MHz, $CDCl_3$) δ 170.2 (-), 168.9 (-), 149.7 (-), 144.2 (-), 141.8 (-), 133.8 (J), 123.9 (-), 122.6 (-), 111 (-), 104.8 (J), 103.8 (-), 102.2 (J), 101.8 (2J), 68 (2J), 66.5 (2J), 60.8 (J), 49 (-), 46.4 (-), 44 (2J), 36.2 (2J), 24.5 (J), 23.2 (J).

(±)-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. ^{1}H-NMR (200MHz, $CDCl_3$) 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_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_3), 3.2 (s, 3H, N-CH_3), 3.19-2.91 (br.m, 3H).^{13}C-NMR (50MHz, $CDCl_3$) 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), 101.1 (2J), 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).

(±)-2',2'-Dimethyl-2,3,4,4a-tetrahydro-1*H*,6*H*-spiro[1,3-benzodioxo-lo[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 **9p** (75 mg, 0.27 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione **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.^{1}H-NMR (200MHz, $CDCl_3$) δ 7.36 (s, 1H, Ar-H4), 7.05 (s, 1H, Ar-H-5), 6.8 (s, 1H, Ar-H-8), 5.96 (s, 2H, -O-CH_2-O-), 4.9-4.83 (d, 1H, *J*=12.8 Hz, α–amino-CH_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_2, benzyl-CH_2, β–amino-CH), 2.88-2.72 (br.m, 1H), 1.82 (br.s, 6H, CH_3), 1.8-1.2 (br.m, 4H, β–, γ–amino-CH_2).

2,2-Dimethyl-5-[(6-piperidin-1-yl[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methy-lene]-1,3-dioxane-4,6-dione (13i-1). Prepared from 6-piperidin-1-yl-[1,3]dioxolo[4,5-*g*]quinoline-7-carbaldehyde **9p** (75 mg, 0.27 mmol) and 2,2-dimethyl-[1,3]dioxane-4,6-dione **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 $CDCl_3$ at rt overnight the sample turned colorless. NMR-measurements were repeated and showed only signals corresponding to the cyclized product (characterisation see **13i**).^{1}H-NMR (200MHz, $CDCl_3$) δ 8.52 (s, 1H, benzylidene-H), 8.50 (s, 1H, Ar-H-4), 7.06 (s, 1H, Ar-H-8), 6.91 (s, 1H, Ar-H-5), 6.01 (s, 2H, -O-CH_2-O-), 3.29-3.13 (br.m, 4H, α -amino-CH_2), 1.81-1.54 (br.m, 12H, CH_3, β-, γ-amino-CH_2).

(±)-1',3'-Dimethyl-2,3,4,4a-tetrahydro-1*H*,2'*H*,6*H*-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 **9p** (31 mg, 0.11 mmol) and 1,3-dimethylpyrimidine-2,4,6-trione **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.^{1}H-NMR (200MHz, $CDCl_3$) 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_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_3), 3.23 (s, 3H, N-CH_3), 2.68-2.62 (br.m, 1H), 1.8-1.2 (br.m, 4H).^{13}C-NMR (50MHz, $CDCl_3$) δ 169.5 (-), 166 (-), 150.3 (-), 141.6 (-), 140 (-), 133.5

(J), 120.3 (-), 119.6 (-), 114.5 (-), 109.6 (-), 104.2 (J), 102.4 (J), 100.6 (2J), 64.7 (2J), 62.8 (J), 45.9 (-), 39.9 (2J), 35.1 (2J), 29.8 (J), 29 (J), 25.8 (2J), 24 (2J). GC-MS, *m/z* (I_{rel}, (%)): 149.1 (100), 57.2 (51), 167.1 (37), 71.2 (30).

(±)-1',3,3'-Trimethyl-2,3,4,4a-tetrahydro-1*H*,2'*H*,6*H*-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-carbal-dehyde **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. ^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2-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-CH_2), 3.40 (s, 1H), 3.30 (s, 3H, (CO)N-CH_3), 3.22 (s, 3H, (CO)N-CH_3), 3.12 (d, 1H, *J*=16.8 Hz, benzylic-CH_2), 2.97 (br.m, 1H, *J*=12.6, *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).^{13}C-NMR (50MHz, $CDCl_3$) 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), 59.6 (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* (I_{rel}, (%)): 91.1 (100), 146.1 (94), 202.2 (34), 65.1 (29), 250.3 (27), 293.3 (19).

(±)-1'-Benzyl-2,2-dimethyl-1',4',5a',6',8',9'-hexahydro-2'*H*-spiro[1,3-dioxane-5,5'-[1,3]thiazolo[5',4':5,6]pyrido[2,1-*c*][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. ^{1}H-NMR (200MHz, $CDCl_3$) δ 7.31-7.05 (m, 5H, Ar-H), 4.99-4.95 (m, 2H, N-CH_2Ph), 4.16-4.09 (bs, 1H, α–amino-CH), 3.69-3.59 (m, 2H), 3.44 (d, 1H, *J*=16.1 Hz, benzylic-CH_2), 3.29 (d, 1H, *J*=16.1 Hz, benzylic-CH_2), 2.92-2.85 (m, 2H), 2.84-2.77 (m, 2H), 1.38 (s, 3H, CH_3), 1.37 (s, 3H, CH_3).^{13}C-NMR (50MHz, $CDCl_3$) δ 166.7, 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* (I_{rel}, (%)):100 % rel. int. peak, 16 min, *m/z* (I_{rel}, (%)): 242.9 (100), 184 (76), 77 (64), 186.2 (56), 51 (48). 51 % rel. int. peak, 22 min, m/z (I_{rel}, (%)): 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*,5a*H*-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-1*H*-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.^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_3), 3.33 (s, 3H, N-CH_3), 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-CH_3), 1.9-1.81 (br.m, 1H), 1.6-1.4 (br.m, 2H). ^{13}C-NMR (50MHz, $CDCl_3$) 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* (I_{rel}, (%)): 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-dio-xane-5,5'-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-1*H*-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.^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2), 3.12 (d, 1H, *J*=16.9 Hz, benzylic-CH_2), 2.41 (s, 3H, Ar-CH_3), 1.39 (s, 3H, CH_3), 1.38 (s, 3H, CH_3).^{13} C-NMR (50MHz, $CDCl_3$) 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* (I_{rel}, (%)): 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]pyrido[2,1-*c*][1,4]oxazine-5,5'-pyrimidine]-2',4',6'(1'*H*, 3'*H*)-trione (13o). Prepared following general procedure 3 from 3-methyl-5-morpholin-4-yl-1-phenyl-1*H*-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.^{1}H-NMR (200MHz, $CDCl_3$) 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), 3.59-3.54 (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-CH_3), 2.4 (s, 3H, Ar-CH_3). ^{13}C-NMR (50MHz, $CDCl_3$) 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* (I_{rel}, (%)):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).

(12b*S*)-8-Methoxy-1',3',12b-trimethyl-7,12b-dihydro-2'*H*,6*H*,14*H*-spiro[1,3-dioxolo[6,7]isoquino[2,1-*a*]quinoline-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-5*H*-[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, $[\alpha]_D^{20}$ + 13.7 (c 0.93, $CHCl_3$). ^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2-O-), 5.86 (d, 1H, *J*=1 Hz, -O-CH_2-O-), 4.37-4.25 (m, 1H, *J*=18, *J*=11.4, *J*=5.5 Hz,

α-amino-CH_2), 3.9 (s, 3H, O-CH_3), 3.7 (d, 1H, *J*=16.2 Hz, benzyl-CH_2), 3.56-3.38 (m, 1H, *J*=18, *J*=10, *J*=4.5 Hz), 3.34 (d, 1H, *J*=16.2 Hz, benzyl-CH_2), 3.05 (br.s, 6H, N-CH_3), 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, C_{quart}-CH_3).^{13}C-NMR (50MHz, $CDCl_3$) 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* (I_{rel}, (%)): 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), 320.09 (38), 191 (36), 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 **12** (50 mg, 0.32 mmol). *n*-BuOH, 5 mL, 30 h, 75 °C. MPLC gradient PE:CH_2Cl_2=88:12 to PE:CH_2Cl_2:Et_2O=70:10:20. Yield 125 mg (88 %), yellow oil that upon standing spontaneously crystallized to a white solid, mp 256.7 °C.^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_3), 3.69 (br.s, 6H, O-CH_3), 3.25 (s, 3H, $(CO)_2$N-CH_3), 3.15 (s, 3H, $(CO)_2$N-CH_3), 2.99 (d, 1H, *J*=17.6 Hz, benzyl-CH_2), 2.57 (dd, 1H, *J*=13.6, *J*=9.6 Hz), 2.48 (s, 3H, N-CH_3), 2.42 (dd, 1H, *J*=13.7, *J*=4.7 Hz).^{13}C-NMR (50MHz, $CDCl_3$) δ 169.7 (-), 169.1 (-), 153.1 (intense, -), 151.7 (-), 142 (-), 136.8 (-), 133.2 (-), 128.7 (J), 127 (J), 120.3 (-), 117.9 (J), 112.7 (J), 106.4 (intense, J), 68.7 (J), 60.8 (J), 56.1 (intense, J), 55.1 (-), 40.3 (J), 36.1 (2J), 29.4 (J), 29 (J), 26.4 (2J). GC-MS, *m/z* (I_{rel}, (%)): 380.12 (100), 306.09 (73), 395.18 (53), 322.11 (42), 76.88 (25), 294.13 (25), 95.84 (21), 281.08 (18).

(±)-(3a*R,4*S**)-1,2,3,3a,4,5-Hexahydropyrrolo[1,2-*a*]quinoline-4-car-boxylic acid (16a)**. **(±)-(3a*R**,4*R**)-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). H_2O/HCl, 20 mL, pH 1, 95 °C, 50 h. The resultant aqueous suspension was basified to pH 4.2 and extracted continuously with CH_2Cl_2. The organic phases were once washed with 2 mL dH_2O, dried (Na_2SO_4) and rotoevaporated 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 ^{1}H-NMR. Main isomer (3a,4-*u*): ^{1}H-NMR (200MHz, $CDCl_3$) 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, $CDCl_3$) δ 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, $CDCl_3$) δ 7.01-6.95 (m, 2H, *J*=7.6 Hz), 6.5-6.46 (dd, 1H, *J*=7, *J*=7.1 Hz), 6.39-6.37 (br.d, 1H, *J*=7.9 Hz), 3.4-3.34 (m, 1H, *J*=9.8, *J*=5.3, *J*=4.7 Hz), 3.33-3.29 (br.m, 1H, *J*=8.8 Hz), 3.13-3.07 (m, 1H, *J*=8.8, *J*=8.5, *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*=6.9, *J*=4.7, *J*= 4.4 Hz, α-keto-H, β-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*=10, *J*=8.5, *J*=6.4 Hz), 1.56-1.45 (m, 1H, *J*=10, *J*=7.6 Hz). Minor isomer **17a**, (3a,4-*l*): ^{1}H-NMR (200MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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* (I_{rel}, (%)): *u*/*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* (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,5*S**)-2,3,4,4a,5,6-Hexahydro-1*H*-pyrido[1,2-*a*]quinoline-5-carboxylic acid (16b). (±)-(4a*R**,5*R**)-2,3,4,4a,5,6-Hexahydro-1*H*-pyri-do[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_2O/HCl, 20 mL, pH 1, 95 °C, 16 h. The resultant aqueous suspension was basified to pH 5.4 and continuously extracted with CH_2Cl_2. The organic phases were once washed with 2 mL dH_2O, dried (Na_2SO_4) and rotoevaporated to yield 588 mg (95 %), purity by HPLC 97.9 % (254 nm), slightly brown semi-solid, diastereomer ratio is *u*:*l* ≥ 5:1 (de ≥ 67 %) via integration in ^{1}H-NMR (~7:1 via integration in ^{13}C-NMR). Main isomer (4a,5-*u*): ^{1}H-NMR (200MHz, $CDCl_3$) δ 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, α-amino-CH_2), 3.14 (dd, 1H, *J*=9.6, *J*=7.8 Hz, α-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, $CDCl_3$) δ 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, α-amino-CH_2), 3.15 (ddd, 1H, *J*=9.4, *J*=8.5, *J*=5.6 Hz, α-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, α-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, $CDCl_3$) δ 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-*l*): ^{1}H-NMR (200MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, α-amino-CH), 2.99-2.89 (m, 1H, *J*=12 Hz), other signals not resolved.^{13}C-NMR (50MHz, $CDCl_3$) δ 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).

(12b*R*,13*R*)-8-Methoxy-12b-methyl-7,12b,13,14-tetrahydro-6*H*-[1,3]dioxolo[6,7]isoquino[2,1-*a*]quinoline-13-carboxylic acid (19). (12b*R*,13*S*)-8-Methoxy-12b-methyl-7,12b,13,14-tetrahydro-6*H*-[1,3]dioxolo[6,7]isoquino[2,1-*a*]quinoline-13-carboxylic acid (20).

Prepared following general procedure 3 from 2-((*S*)-4-methoxy-9-methyl-6,9-dihydro-7*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_2Cl_2=88:12 to PE:CH_2Cl_2:Et_2O=70:10:20. Yield of parent spiro compound **18** 13 mg (16 %), yellow solid, yield of carboxylic acids 61 mg (61 %), de ≥ 9 %, red oil. Main isomer, 33 mg: ^{1}H-NMR (200MHz, $CDCl_3$) δ 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*=5.3, *J*=3.5 Hz), 3.12-2.94 (m, 2H, *J*=15.2, *J*=12.3, *J*=9.5, *J*=3, *J*=2.9 Hz, α-carboxy-benzyl-CH_2, benzyl-CH_2), 2.81-2.73 (m, 1H, *J*=12.3, *J*=11.9 Hz, α-carbo-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). ^{13}C-NMR (50MHz, $CDCl_3$) δ 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* (I_{rel}, (%)): 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), 168.94 (57). 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, $CDCl_3$) δ 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, α-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-CH_2), 1.46 (s, 3H, CH_3). ^{13}C-NMR (50MHz, $CDCl_3$) 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* (I_{rel}, (%)): 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).13.49 min: 54.93 (100), 57.12 (92), 83.13 (80), 68.9 (75), 97.14 (64), 281.05 (36), 111.18 (31). 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 ^{1}H-NMR; $[\alpha]_D^{20}$ + 122.5 (c 0.4, $CHCl_3$). Spectroscopically (200 MHz ^{1}H-NMR) pure minor isomer: $[\alpha]_D^{20}$ + 103.2 (c 0.38, $CHCl_3$).

(±)-(3a*R,4*S**)-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: ^{1}H-NMR (200MHz, $CDCl_3$) 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).^{13}C-NMR (50MHz, $CDCl_3$) 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* (I_{rel}, (%)): 76.96 (100), 104.93 (79), 197.03 (75).

(±)-(4a*R,5*S**)-5-Benzoyl-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinoline-5-carbonitrile (24). (±)-(4a*R**,5*R**)-5-Benzoyl-2,3,4,4a,5,6-hexahydro-1*H*-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 CH_2Cl_2. Yield: 333 mg (66 %), dark oil. Ratio of (4a,5-*u*)-isomer to (4a,5-*l*) is 3:1 via integration in 200 MHz-^{1}H-NMR. Crystallization from MeOH, yield 110 mg spectroscopically pure (4a,5-*u*)-diastereomer, violet to dark crystals, mp 109.1 °C, suitable for XRD; R_f=0.75 (CH_2Cl_2). Main isomer, (4a,5-*u*): ^{1}H-NMR (200MHz, $CDCl_3$) 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 (bdd, 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-CH_2), 3.77 (dd, 1H, *J*=10, *J*=9 Hz, α-amino-CH), 3.55 (d, 1H, *J*=15.8 Hz, benzyl-CH_2), 3.31 (d, 1H, *J*=15.8 Hz, benzyl-CH_2), 2.78-2.64 (m, 1H, *J*=13, *J*=7.3 Hz, α-amino-CH_2), 2.01-1.97 (br.m, 2H, β–amino-CH_2), 1.74-1.56 (br.m, 4H,

β–, γ–ami-no-CH_2). ^{1}H-NMR (400MHz, $CDCl_3$) 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). ^{13}C-NMR (50MHz, $CDCl_3$) 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: ^{1}H-NMR (200MHz, $CDCl_3$) 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-CH_2), 3.89-3.83 (d, 1H**,** *J*=8.8 Hz, α-amino-CH), 3.52 (d, 1H, *J*=17 Hz, benzyl-CH_2), 2.98 (d, 1H, *J*=17 Hz, benzyl-CH_2), 2.97-2.89 (m, 1H, *J*=13 Hz, α-amino-CH_2), 1.92-1.74 (br.m, 2H, β-amino-CH_2), 1.65-1.40 (br.m, 4H, β-,γ-amino-CH_2). ^{1}H-NMR (400MHz, $CDCl_3$) 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). ^{13}C-NMR (50MHz, $CDCl_3$) 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**: $C_{21}H_{20}N_2O$, M_r = 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) A^3, Z = 4, D_x = 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-C_8 = 2.477, N_1-C_7 = 2.884, N_1-O_1 = 4.172; C_7-C_6-C_1-N_1 = -5.37, C_6-C_1-N_1-C_9 = 6.15, C_1-N_1-C_9-C_8 = -32.99, N_1-C_9-C_8-C_7 = 57.49, C_9-C_8-C_7-C_6 = -56.79, C_8-C_7-C_6-C_1 = 31.78, H_9-C_9-C_8-C_7 = -61.38, H_9-C_9-C_8-C_{14} = 177.63, H_9-C_9-C_8-C_{15} = 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-C_8 = 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-(4a*R,5*S**)-5-[(1,3-thiazol-2-ylamino)carbonyl]-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinoline-5-carboxylate (27)**. **(±)-Ethyl-(4a*R**,5*R**)-5-[(1,3-thiazol-2-ylamino)carbonyl]-**

2,3,4,4a,5,6-hexahydro-1*H*-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_4OAc. Refluxing abs. EtOH, 10 mL, 65 h. MPLC gradient PE to CH_2Cl_2. Yield of (4a,5-*u*) 343 mg (34 %), yellow oil, single crystals for XRD from CH_2Cl_2/Et_2O 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_2Cl_2/Et_2O by diffusion and slow evaporation, mp 191.3 °C; overall 99 %. (4a,5-*u*): ^{1}H-NMR (200MHz, $CDCl_3$) δ 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, α-amino-CH_2, α-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, α-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).^{13}C-NMR (50MHz, $CDCl_3$) δ 171.5 [COO, (-)], 166 [CONH, (-)], 157.8 [thiazole-$C_{quart.}$, (-)], 142.6 (-), 137.8 (J), 129.5 (J), 127.3 (J), 120.8 (-), 117.6 (J), 114 (J), 112.9 (J), 62.5 [α-amino-CH, (J)], 62.4 [ester-CH_2, (2J)], 56.6 [$C_{quart.}$ phenylethyl] (-), 49.2 [α-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* (I_{rel}, (%)): 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*):^{1}H-NMR (200MHz, $CDCl_3$) δ 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, α-amino-CH_2), 3.91 (br.d, 1H, *J*=10.8 Hz, α-amino-CH), 3.40 (d, 1H, *J*=17.9 Hz, benzyl-CH_2), 3.24-3.07 (m, 2H, *J*=17.9 Hz, benzyl-CH_2, α-amino-CH_2), 1.78-1.12 (br.m, 6H, *J*=8, *J*=6.6, *J*=4.4, *J*=3.9 Hz, β-,γ-amino-CH_2), 1.22 (br.t, 3H, *J*=7.2 Hz, CH_3).^{13}C-NMR (50MHz, $CDCl_3$) δ 169.6 (-), 169.5 (-), 157.5 [thiazole $C_{quart.}$, (-)], 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 [$C_{quart.}$ 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* (I_{rel}, (%)): 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), 317.3 (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**: $C_{20}H_{23}N_3O_3S$, M_r = 385.49, monoclinic, space group *P* $2_1/n$ (No. 14), *T* = 298(2) K, λ = 0.71073 Å; lattice parameters: *a* = 12.0875(17) Å, *b* = 10.4022(15) Å, *c* = 15.871(2) Å, α= 90.00°, β= 106.145(2) °, γ = 90.00 °, *V* = 1916.86 A^3, *Z* = 4, Z': 0, D_x = 1.336 Mg m^{-3}, μ = 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 [°]: N_1-C_{13} = 1.416, N_1-C_1 = 1.473, N_1-C_5 = 1.478, N_1-C_6 = 2.476, N_1-C_7 = 2.927, N_1-N_2 = 2.744, S_1-O_1 = 2.830; C_{14}-C_6-C_{18} = 106.13, C_{14}-C_6-C_7 = 108.71, C_{14}-C_6-C_5 = 114.75; N_1-C_5-C_6-C_7 = 60.23, N_1-C_5-C_4-C_3 = 55.52, N_1-C_1-C_2-C_3 = -57.86, N_1-C_5-C_6-C_{18} = 179.27, N_1-C_5-C_6-C_{14} = -62.25.

Methyl (1'*S*,3a'*S*)-1,3-dimethyl-2,4,6-trioxo-1,1',2',3,3',3a',4,6-octahy-dro-2*H*,5'*H*-spiro[pyrimidine-5,4'-pyrrolo[1,2-*a*]quinoline]-1'-carboxy-late(30). **Methyl (1'*S*,3a'*R*)-1,3-dimethyl-2,4,6-trioxo-1,1',2',3,3',3a',4,6-octahydro-2*H*,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_2Cl_2=88:12 to PE:CH_2Cl_2: Et_2O=70:10:20. Yield 117 mg (73 %), de ≥ 43 %, amber low melting solid. Main isomer, (1'*S*,3a'*S*): ^{1}H-NMR (200MHz, $CDCl_3$) δ 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*d* = 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*=7.8, *J*=7.2, *J*=4.5 Hz, H-3*d*), 2.08-2.03 (m, 1H, *J*=12.1, *J*=7.4, *J*=4.1 Hz, H-2*u*), 1.99-1.84 (m, 2H, *J*=12.1, *J*=8, *J*=7.8, *J*=7.6, *J*=5.5, *J*=4.5 Hz, H-3*u*, H-2*d*). ^{13}C-NMR (50MHz, $CDCl_3$) δ 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* (I_{rel}, (%)): 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, $CDCl_3$) δ 7.15-7.01 (m, 2H), 6.47 (br.d, 1H, *J*=8 Hz), 6.65 (dd, 1H, *J*=7.4, *J*=1.2 Hz), 4.29-4.24 (m, 1H, H-1), 3.82-3.74 (m, 1H, *J*=6.1 Hz, H-3a), 3.64 (d, 1H, *J*=16.6 Hz, H-5*d*), 3.58 (s, 3H, COO-CH_3), 3.29 (s, 3H, N-CH_3), 3.21 (s, 3H, N-CH_3), 2.95 (d, 1H, *J*=16.6 Hz, H-5*u*), 2.39-2.24 (m, 1H, H-3*d*), 2.23-1.88 (m, 3H, H-2, H-3*u*).^{13}C-NMR (50MHz, $CDCl_3$) δ 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 δ 6.66, δ 6.38 and of the aliphatic protons at δ 4.29 and δ 4.14 ppm (shifts of the major isomer); $[\alpha]_D^{20}$ -34 (c 0.95,

$CHCl_3$).

Methyl (1'*S*,3a'*S*)-2,2-dimethyl-4,6-dioxo-1',2',3',3a'-tetrahydro-5'*H*-spi-ro[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*-spi-ro[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:CH_2Cl_2=88:12 to PE:CH_2Cl_2:Et_2O=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*): ^{1}H-NMR (200MHz, $CDCl_3$) 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*=7.4, *J*=7.2 Hz, Ar-H-7), 6.38 (d, 1H, *J*=8 Hz, Ar-H-9), 4.26 (dd, 1H, *J*=8.3, *J*=3.4 Hz, H-1), 4.14 (dd, 1H, *J*=7.6, *J*=4.9 Hz, H-3a), 3.66 (s, 3H, COO-CH_3), 3.54 (d, 1H, *J*=16.4 Hz, H-5*d*), 3.02 (d, 1H, *J*=16.4 Hz, H-5*u*), 2.35-2.06 (m, 2H, *J*~12, *J*~8, *J*~4 Hz, H-3*d*, H-2*u*), 2.01-1.73 (br.m, 2H, *J*~12.5, *J*~8.5, *J*~4.5 Hz, H-3*u*, H-2*d*), 1.69 (br., 6H, ketal-CH_3).^{1}H-NMR (400MHz, $CDCl_3$) 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-CH_3), 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-3*d*), 2.17 (ddd, 1H, *J*=13.2, *J*=12.9, *J*=8.5 Hz, H-2*u*), 1.94 (ddd, 1H, *J*=16.6 Hz, *J*=12.9, *J*=3.4 Hz, H-2*d*), 1.79 (m, 1H, *J*=16.7, *J*=12.9, *J*=4.7 Hz, H-3*u*). ^{13}C-NMR (50MHz, $CDCl_3$) δ 174.7 (C-$OOCH_3$, -), 169.6 (C-OOC_q, -), 164.6 (C-OOC_q, -), 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-C_q, -), 64.6 (C-3a, J), 62.5 (C-1, J), 52.3 (O-CH_3, J), 47.4 (C-4, -), 35.9 (C-5, 2J), 30.4 (ketal-CH_3, J), 28.4 (ketal-CH_3, J), 27.6 (C-2, 2J), 27.2 (C-3, 2J). GC-MS, fragmentation, first two main peaks *m/z* (I_{rel}, (%)):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), 68.94 (95), 83.12 (86), 97.15 (69), 111.17 (28), 125.18 (11). Minor isomer, (1'*S*,3a'*R*): ^{1}H-NMR (200MHz, $CDCl_3$) δ 7.1-6.96 (m, 2H, *J*=8.6, *J*=8 Hz, Ar-H-8, Ar-H-6), 6.69 (dd, 1H, *J*=7.4, *J*=7.2 Hz, Ar-H-7), 6.53 (d, 1H, *J*=8 Hz, Ar-H-9), 4.32-4.28 (m, 1H, *J*=6.6, *J*=3.5 Hz, H-1), 3.82-3.74 (m, 1H, *J*=9.2, *J*=6.4, *J*=2.7 Hz, H-3a), 3.59 (s, 3H, COO-CH_3), 3.55 (d, 1H, *J*=16.8 Hz, H-5*d*), 3.03 (d, 1H, *J*=16.8 Hz, H-5*u*), 2.21-1.86 (br.m, 4H, *J*=15.4, *J*=12.9, *J*=9.2, *J*=6.6, *J*=6.4, *J*=3.5, *J*=2.7 Hz, H-2, H-3), 1.7 (br., 6H, ketal-CH_3).^{13}C-NMR (50MHz, $CDCl_3$) δ 172.9 (-), 169.5 (-), 163.8 (-), 141.3 (-), 128.5 (J), 127.3 (J), 119.1 (-), 117.4 (J), 111.3 (J), 104.8 (-), 65.8 (J), 58.9 (J), 52.3 (J), 49.4 (-), 34.3 (2J), 30.5 (J), 28.4 (2J), 27.9 (J), 27.3 (2J). GC-MS, fragmentation, first two main peaks, *m/z* (I_{rel}, (%)): 11.33 min: 57.06 (100), 219.18 (24), 177.11 (24), 163.09 (19.9), 55 (11), 82.96 (11), 91.01 (9.71), 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*), $[\alpha]_D^{20}$= -

93.3 (c = 1, $CHCl_3$). 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; $[\alpha]_D^{20}$= - 25.2 (c= 0.87, $CHCl_3$).

(±)-(3a*R,4*S**)-4-Nitro-1,2,3,4a,4,5-hexahydropyrrolo[1,2-*a*]quinoline (35). (±)-(3a*R**,4*R**)-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 NH_4OAc (240 mg, 0.79 mmol). *n*-BuOH, 5 mL, 120 h, 118 °C. MPLC gradient PE:CH_2Cl_2=88:12 to PE:CH_2Cl_2:Et_2O=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*): ^{1}H-NMR (200MHz, $CDCl_3$) 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*=9.4, *J*=9, *J*=6.1, *J*=5.5 Hz, α-amino-CH_2, benzyl-CH_2 (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-CH_2, benzyl-CH_2 (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-CH_2).^{1}H-NMR (400MHz, $CDCl_3$) 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*=12, *J*=9.6, *J*=4.7 Hz**,** α-nitro-CH), 3.8 (ddd, 1H, *J*=9.6, *J*=9.4, *J*=6.6 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-CH_2, benzyl-CH_2 (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-CH_2, benzyl-CH_2 (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). ^{13}C-NMR (50MHz, $CDCl_3$) 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* (I_{rel}, (%)): 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), $Me_2HN{\cdot}HCl$ (1310 mg, 18.34 mmol) and $MeNO_2$ (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 CH_2Cl_2, washed once with 20 mL brine, the brine re-extracted with 10 mL CH_2Cl_2 and the organic phases combined, dried (Na_2SO_4) 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. ^{1}H-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, *J*~6.6 Hz, α,β–amino-CH_2), 1.94-1.85 (m, 4H, β–amino-CH_2). ^{13}C-NMR (500MHz, $CDCl_3$) δ 148.7 (-), 137 (J), 132.2 (J), 130 (J), 127.2 (J), 116.7 (J), 116.2 (-), 113.4 (J), 50.3 (2J), 23.1 (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), $Me_2HN{\cdot}HCl$ (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_2Cl_2, washed twice with 50 mL saturated Na_2CO_3-solution, then once with 10 mL brine, the brine re-extracted with 10 mL CH_2Cl_2 and the organic phases combined, dried (Na_2SO_4) and roto-evaporated. Yield 659 mg (66 %), red oil, R_f=0.94 (CH_2Cl_2), R_f=0.74 (PE:EE=90:10).^{1}H-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).^{13}C-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_2Cl_2=88:12 to PE:CH_2Cl_2:Et_2O =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. ^{1}H-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 Hz), 7.04-6.96 (m, 2H, *J*=8.5, *J*=7.4, *J*=3 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).^{13}C-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 noneqivalent, most likely reflecting the increase in steric hindrance of rotation around the C-N-bond; we did not observe this in the correponding (*E*)-isomer.

(±)-1,1'-[(1,3,5-Trinitropentane-2,4-diyl)bis(2,1-phenylene)]dipiperidine (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_2Cl_2/Et_2O by diffusion and slow evaporation, mp 144.9 °C.^{1}H-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).^{13}C-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

(2J), 23.9 (2J). X-Ray diffraction of **39**: $C_{27}H_{35}N_5O_6$, M_r = 525.61, triclinic, space group *P-1* (No. 2), T = 298(2) K, λ = 0.71073 Å; lattice parameters: a = 9.150(3) Å, b = 12.096(4) Å, c = 13.425(4) Å, α= 75.012(4) °, β= 74.163(4) °, γ = 75.417(4) °, V = 1354.32 A^3, Z = 2, Z' = 0, D_x = 1.289Mg m^{-3}, μ = 0.092 mm^{-1}, *Crystal size*: 0.57 x 0.45 x 0.38 mm, colorless block, *R-Factor*: 5.71 %. Selected distances [Å] and angles [°]: N_4-N_5 = 5.721, N_5-O_5 = 4.094, N_4-O_6 = 7.299; C_{16}-C_1-C_4 = 115.09; C_1-C_{16}-C_3-N_3 = -170.59, C_1-C_4-C_2-N_2 = 166.81, N_5-C_{27}-C_{26}-C_{25} = -57.55, C_3-C_{16}-C_1-C_4 = -166.98.

(±)-Methyl-5-nitro-2,3,4,4a,5,6-hexahydro-1*H*-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_4OAc (266 mg, 3.5 mmol). EtOH, 5 mL, 60 h, 78 °C. MPLC gradient PE:CH_2Cl_2=88:12 to PE:CH_2Cl_2:EE=70:10:20. Obtained as a diastereomer mixture, isomer ratio is ≥ 10:1 (de ≥ 82 %) by integration in ^{1}H-NMR, yield 153 mg (15 %), yellow oil. Main isomer: ^{1}H-NMR (200MHz, $CDCl_3$) δ 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, *J*=2 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, *J*=2.7 Hz, benzyl-CH_2), 3.29 (d, 1H, *J*=17 Hz, benzyl-CH_2), 3.02–2.87 (m, 1H, *J*=13.5, *J*=11.3, *J*=7.2 Hz), 1.9-1.78 (br.m, 1H), 1.73-1.41 (bm, 3H, *J*=11.3, *J*=7.2, *J*=4.1 Hz), 1.41-1.33 (m, 1H, *J*=11.7, *J*=4.1 Hz).^{13}C-NMR (50MHz, $CDCl_3$) δ 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-oxo-butyric acid ethyl ester (489 mg, 3.55 mmol) and NH_4OAc (268 mg, 3.48 mmol). EtOH, 7 mL, 220 h, 78 °C. MPLC gradient PE to PE:CH_2Cl_2=50:50. Obtained as a diastereomer mixture, isomer ratio is ≥ 7:1 (de ≥ 75 %) by integration in ^{1}H-NMR, yield 69 mg (7 %), slightly yellow oil.^{1}H-NMR (200MHz, $CDCl_3$) δ 7.39-7.09 (m, 2H, *J*=7.4 Hz, Ar-H), 7.05 -6.94 (m, 2H, *J*=8 Hz), 4.17-4.06 (m, 5H, *J*=10.6, *J*=7.2, *J*=7, *J*=3.4 Hz), 3.44 (d, 1H, *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), 1.11 (br.m, 3H, CH_2-CH_3).^{13}C-NMR (50MHz, $CDCl_3$) δ 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-1*H*-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_4OAc (266 mg, 3.45 mmol). EtOH, 10 mL, 250 h, 78 °C. MPLC gradient PE to PE:CH_2Cl_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, $CDCl_3$) δ 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*=7 Hz, CO-CH_2), 4.04-3.92 (br.m, 2H, α-amino-CH_2, α-amino-CH), 3.35 (d, 1H, *J*=15.8 Hz, benzyl-CH_2), 3.04-2.88 (m, 2H, α-amino-CH_2, benzyl-CH_2), 2.18 (s, 3H, CO-CH_3), 1.85-1.35 (br.m, 6H, β,γ-amino-CH_2), 1.26 (t, 3H, *J*=7 Hz, $COCH_2$-CH_3).^{13}C-NMR (50MHz, $CDCl_3$) δ 203.1 (-), 169.9 (-), 143.8 (-), 130.1 (-), 128.1 (J), 121.3 (J), 118.1 (J), 113.3 (J), 62.9 (-), 62.3 [α-keto-CH_2, 2J], 60.8 [α-amino-CH, J], 49 [α-amino-CH_2, 2J], 29.2 [benzyl-CH_2, 2J], 28.5 (2J), 25.3 (2J), 25.3 [CO-CH_3, (J)], 22.3 (2J), 14.1 [$COCH_2$-CH_3, (J)].

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_4OAc (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_2Cl_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]-imidazo-lidine-2,4-dione **43b** as yellow oil that crystallized upon standing in CH_2Cl_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_2Cl_2 as a yellow solid, mp 126-131 °C. ^{1}H-NMR (200MHz, $CDCl_3$) δ 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*=8, *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, $CDCl_3$) δ 163.4 (-), 154.4 (-), 153.9 (-), 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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).

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