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Knoevenagel-IMHDA and -IMSDA sequences for the synthesis of chiral condensed O,N-, S,N- and N-heterocycles†

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Domino Knoevenagel-cyclization reactions of styrene substrates, containing an *N*-(*ortho*-formyl)aryl subunit, were carried out with *N*-substituted 2-cyanoacetamides to prepare tetrahydro-4*H*-pyrano[3,4-*c*]quinolone and hexahydrobenzo[*j*]phenanthridine derivatives by competing IMHDA and IMSDA cyclization, respectively. The diastereoselective IMHDA step with α,β-unsaturated amide, thioamide, ester and ketone subunits as a heterodiene produced condensed chiral tetrahydropyran or thiopyran derivatives, which in the case of Meldrum's acid were reacted further with amine nucleophiles in a multistep domino sequence. In order to simplify the benzene-condensed tricyclic core of the targets and get access to hexahydro-1*H*-pyrano[3,4-*c*]pyridine derivatives, a truncated substrate was reacted with cyclic and acyclic active methylene reagents in diastereoselective Knoevenagel-IMHDA reactions to prepare novel condensed heterocyclic scaffolds. The chemo-, regio- and diastereoselectivity of the cyclization step were investigated and structural elucidation was aided by single crystal X-ray analysis.

Introduction

The inverse-electron-demand hetero-Diels–Alder (IEDHDA) reaction is a highly efficient method used to assemble a chiral 3,4-dihydropyran ring (Scheme 1a),[1] which has been recently gaining increasing attention to prepare condensed and spirocyclic heterocyclic scaffolds of pharmacological interest stereoselectively in inter-[2] or intramolecular reactions.[3] For instance, George and co-workers reported the biomimetic intramolecular oxa-HDA reaction of an electron-rich 2*H*-chromene substrate (Scheme 1a), which afforded the polycyclic framework of the natural product busseihydroquinone E.[3c] The analogue thia-HDA reactions have been much less utilized for building the dihydrothiopyran ring and arylidene-thiolactams,[4] amides of thiocinnamic acid[5] and thiochalcones[6] were reported as typical thiodienes as exemplified by Fishwick and co-workers' thia-HDA reaction with *N*,*N*-disubstituted amides of thiocinnamic acid (Scheme 1b).[5] Thermal intramolecular styryl Diels–Alder (IMSDA) reactions often compete with IMHDA reactions in styrene derivatives. Although styrene is considered a poor diene, IMSDA prevails when the heterodiene has low reactivity or conditions are not suitable to enable an IMHDA reaction (Scheme 1c).[7] The initial step of the IMSDA reaction involves the loss of aromaticity but a subsequent 1,3-hydrogen shift restores it by producing condensed tetralin derivatives. For instance, Andrus and co-workers utilized the IMSDA reaction to assemble the tetracyclic deoxypodophyllotoxin core with the styryl functionality acting as the diene and reacting with an electron-deficient alkyne dienophile (Scheme 1c).[8]

The IMHDA and IMSDA reactions can be readily incorporated into domino sequences, which provide access to complex chiral condensed heterocycles of novel scaffolds and pharmacological interest from reasonably simple building blocks. While more than half of the new drugs derived from natural products or related to them in the past four decades,[9] there is still a great demand for synthetic procedures, which can produce novel heterocyclic entities with versatile substitution patterns. Domino IMHDA and IMSDA sequences were proved to be powerful methods to synthesize natural products or novel heterocyclic scaffolds.[10]

Recently we have explored domino Knoevenagel-cyclization sequences involving different cyclisation mechanisms such as

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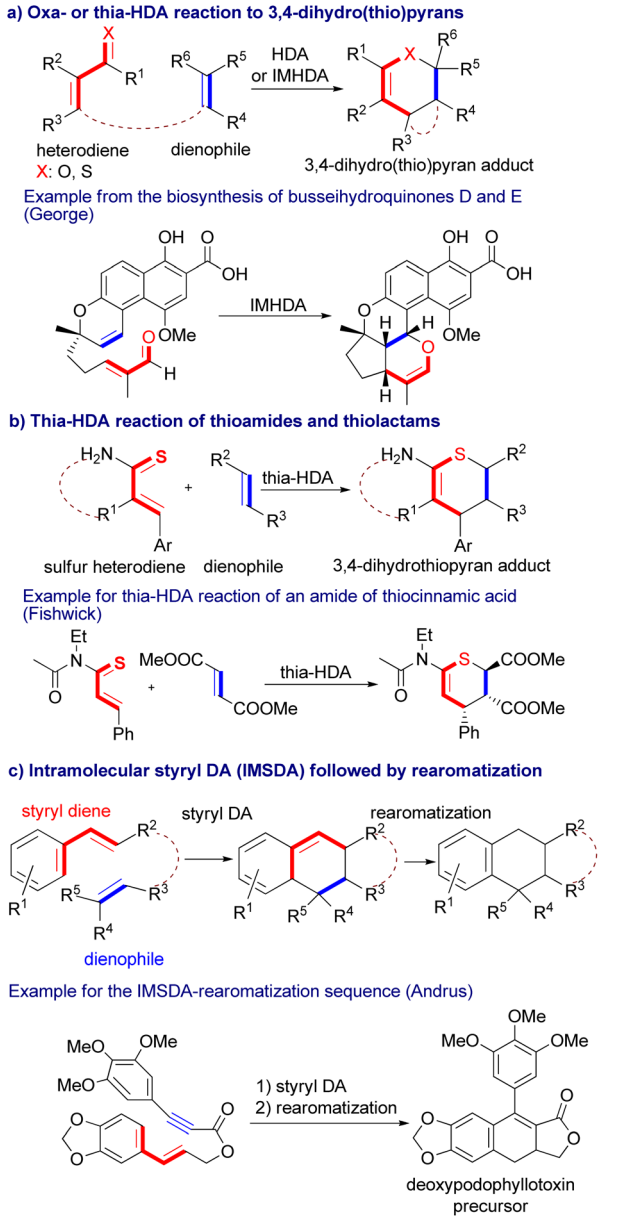


Scheme 1 (a) General scheme for oxa- and thia-HDA and an example for an IMHDA cyclization. (b) General scheme for the thia-HDA reaction of thioamides and thiolactams with an example for amides of thiocinnamic acid. (c) General scheme and a specific example for IMSDA reactions.

IMHDA, IMSDA, [2 + 2] cycloaddition or a multistep inverse Cadogan-type cyclization to produce novel condensed and spirocyclic heterocyclic skeletons of pharmacological relevance.[11]

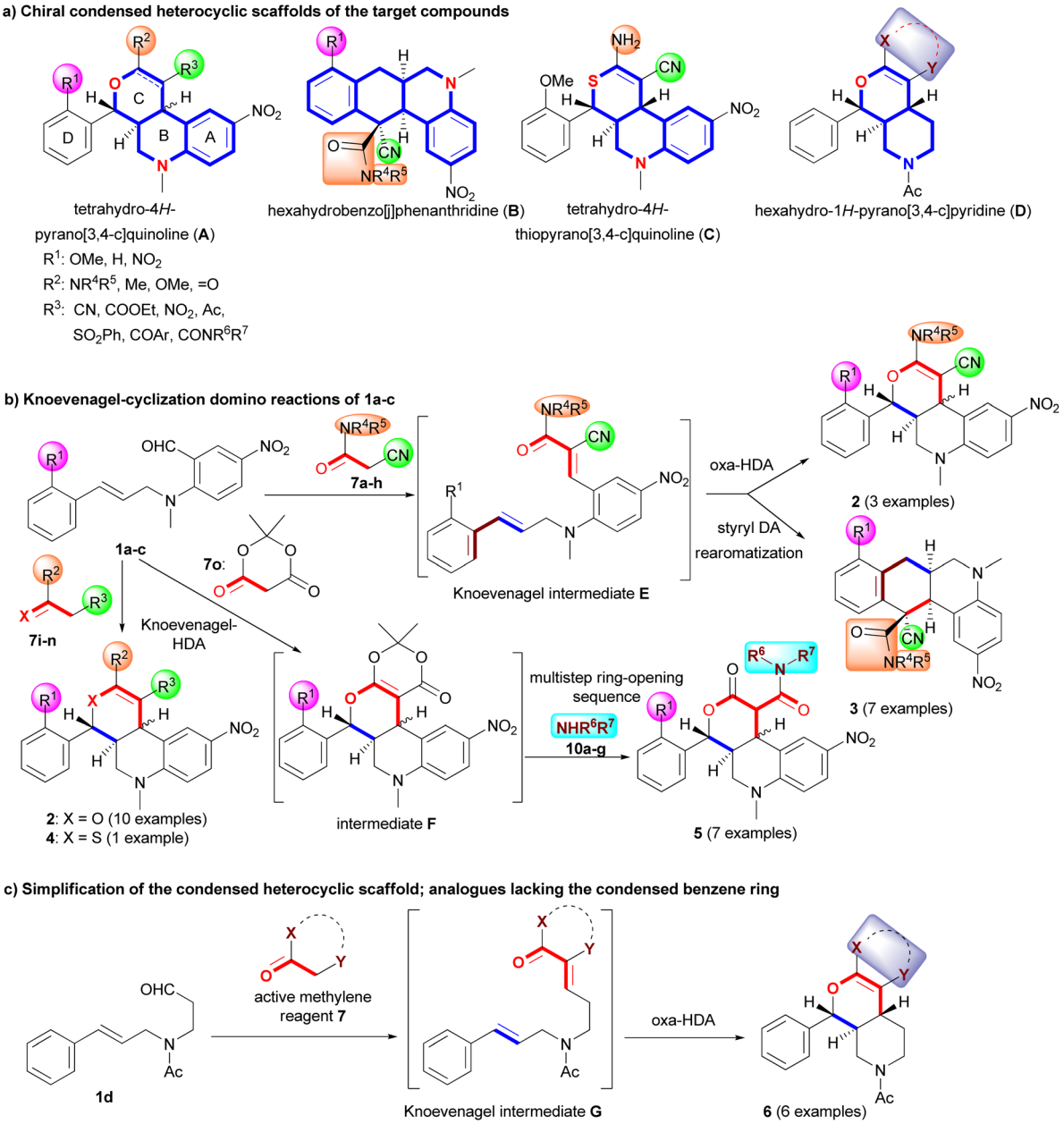
In this work, we envisaged the domino Knoevenagel-cyclization reaction of a styrene substrate (**1a**) with *N*-substituted 2-cyanoacetamides (**7a–h**) to prepare tetrahydro-4*H*-pyrano[3,4-*c*]quinolone (**1a** → **E** → **2**) and hexahydrobenzo[*j*]phenanthridine derivatives (**1a** → **E** → **3**) with different substitution patterns by competing IMHDA and IMSDA cyclization, respectively (Scheme 2a and b). The *N*-substitution of the α,β-unsaturated amide heterodiene governed the mechanism of the cyclization step whether it took place with an oxa-IMHDA reaction (**E** → **2**) with the involvement of the amide carbonyl or an IMSDA-rearomatization sequence using the carbon–carbon double bond as a dienophile (**E** → **3**). When reacting the styrene substrates **1a–c** with active methylene reagents **7i** and **7k–n** containing a ketone or ester carbonyl group, oxa-IMHDA cyclization occurred resulting in further 4*H*-pyrano[3,4-*c*]quinolones with versatile substitution (Scheme 2a and b). With 2-cyanothioacetamide reagent (**7j**), a thia-IMHDA cyclization prevailed affording the novel tetrahydro-4*H*-thiopyrano[3,4-*c*]quinolone skeleton (**7j** → **4**). The domino Knoevenagel-cyclization sequence of **1a** with Meldrum's acid reagent (**7o**) produced the initial oxa-IMHDA intermediate **F**, which was reacted with amine nucleophiles **10a–g** to induce a multistep ring-opening and fragmentation sequence of the 1,3-dioxinone ring resulting in lactone products **5**.

In order to simplify the tricyclic core of **A** by the removal of the condensed benzene ring and get access to the hexahydro-1*H*-pyrano[3,4-*c*]pyridine skeleton **D** (Scheme 2a), the conformationally flexible substrate **1d** was prepared and reacted with cyclic and acyclic active methylene reagents in diastereoselective Knoevenagel-IMHDA reactions affording novel condensed heterocyclic scaffolds **6** (**1d** → **G** → **6**) (Scheme 2c).

Results and discussion

The substrates **1a–d** of the domino cyclization reactions were prepared from commercially available cinnamaldehyde derivatives in a few steps (Scheme S1–S3†).[11b] 2-Cyanoacetamide reagents (**7a–i**) with different substituents at the amide nitrogen were reacted with substrate **1a** in dry EtOH using piperidine as an additive. We found that depending on the substitution of the amide nitrogen of the reagent **7a–h**, the initial Knoevenagel intermediate **E** underwent an IMSDA or IMHDA cyclization resulting in **3** or **2**, respectively (Table 1).

With secondary amide reagents **7a–e** (entries 1–5), the domino diastereoselective Knoevenagel-IMSDA reaction took place exclusively, which afforded *cis*-annulated tetralin derivatives *rac*-(6a*R**,12*S**,12a*S**)-**3aa–3ae** as a single diastereomer with good to excellent yields (57–93%). The three contiguous chirality centers were introduced with full diastereoselectivity and only with the 2-cyano-*N*-allylacetamide reagent, was the epimeric *rac*-(6a*R**,12*R**,12a*S**)-*epi*-**3ag** product observed as a minor product (entry 4). When using tertiary amide reagents (entry 6–8), the IMHDA cyclization mechanism competed with the IMSDA one. With 3-oxo-3-(piperidin-1-yl)propanenitrile (**7f**), only IMHDA cyclization occurred producing the C-10b epimers *rac*-(4*R**,4a*S**,10b*S**)-**2af** (*trans* ring fusion) and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-**2af** (*cis* ring fusion) with 2 : 1 ratio (58%, entry 6). Both IMHDA and IMSDA cyclizations occurred with reagents 3-(morpholin-4-yl)-3-oxopropanenitrile (**7g**) and 3-oxo-3-(pyrrolidin-1-yl) propanenitrile (**7h**), the reactions of which required reflux temperature to be completed (entries 7 and 8). With reagent **7g**, the epimeric mixture of the IMHDA products **2ag** and *epi*-**2ag** was obtained as the major product (67%), while the IMSDA product **3ag** was isolated as a single diastereomer (22%, entry 7). The reagent **7h** afforded the **3ah** diastereoselectively as the major product (76%), while the IMHDA product was obtained as a 1 : 1 epimeric mixture of **2ah** and *epi*-**2ah** (entry 8).

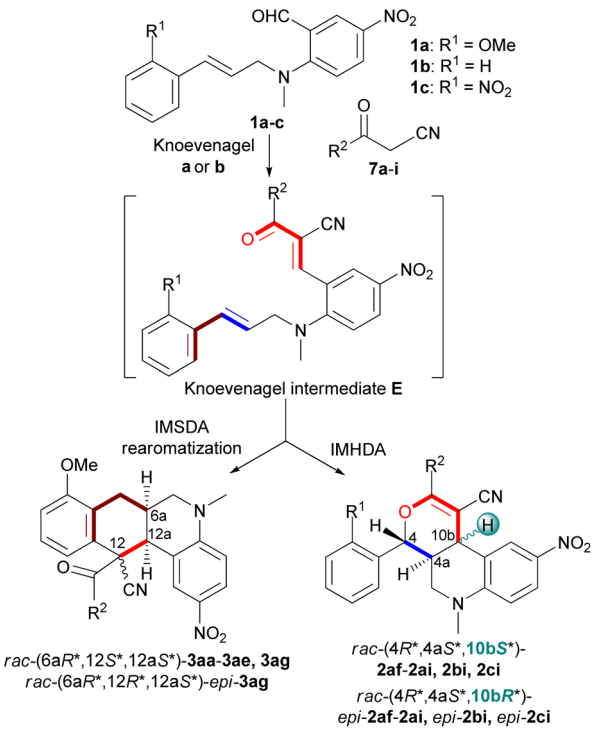


Scheme 2 (a) General structures of the chiral condensed heterocyclic target compounds and (b) domino cyclization sequences of substrates **1a–c** and (c) **1d**.

As a related reagent, benzoylacetonitrile (**7i**) was tested with substrates **1a–c** (entries 9–11) when the heterodiene moiety of the Knoevenagel intermediate **E** contained a more reactive ketone carbonyl group, which reacted exclusively by the IMHDA cyclization mechanism. The products were isolated as a mixture of C-10b epimers favoring the *rac*-(4*R**,4a*S**,10b*S**) diastereomer with *trans* ring annulation over the *rac*-(4*R**,4a*S**,10b*R**) one. The epimeric products were not separated but the major isomer *rac*-(4*R**,4a*S**,10b*S**)-**2ai** crystallized from the solution and thus its planar structure and relative configuration were also confirmed by single crystal X-ray diffraction analysis (CCDC no. 2283893, Fig. 1).

The relative configuration of the IMHDA products **2** was determined by using the $^{3}J_{4a\text{-}H,10b\text{-}H}$ coupling constant and characteristic NOE correlations (Table S1†). For the (4*R**,4a*S**,10b*S**)-**2** having *trans* ring junction, the $^{3}J_{4a\text{-}H,10b\text{-}H}$ coupling constant values fall typically in the range of 9.0–12.0 Hz and 10b-H/4-H NOE correlation indicated the *cis* orientation of the axial methine protons. In contrast, the *cis* ring junction of (4*R**,4a*S**,10b*R**)-*epi*-**2** gave rise to 3.1–4.7 Hz $^{3}J_{4a\text{-}H,10b\text{-}H}$ coupling constant values and 10b-H/4a-H NOE correlation. For tetralin derivatives **3**, the small value of the $^{3}J_{6a\text{-}H,12a\text{-}H}$ coupling constant in the range of 3.7–3.0 Hz allowed determining the *cis* annulation of the tetralin ring, which could be

Table 1 Competing domino Knoevenagel-IMSDA and -IMHDA sequences with 2-cyanoacetamide reagents **7a–h** and benzoylacetonitrile (**7i**)



Entry	1a–c	7a–i	R^2	2-3aa–ai	Y (%)	dr[c]
1	**1a**	**7a**		**3aa**	68	1 : 0
2	**1a**	**7b**		**3ab**	93	1 : 0
3	**1a**	**7c**		**3ac**	78	1 : 0
4	**1a**	**7d**		**3ad**, *epi*-**3ad**	56	5 : 1
5	**1a**	**7e**		**3ae**	57	1 : 0
6	**1a**	**7f**		**2af**, *epi*-**2af**	58	1 : 2
7	**1a**	**7g**		**2ag**, *epi*-**2ag** **3ag**	67 22	4 : 1[d] 1 : 0[d]
8	**1a**	**7h**		**2ah**, *epi*-**2ah** **3ah**	21 76	1 : 4[d] 1 : 0[d]
9	**1a**	**7i**	Ph	**2ai**, *epi*-**2ai**	94	6 : 5
10	**1b**	**7i**	Ph	**2bi**, *epi*-**2bi**	77	3 : 1
11	**1c**	**7i**	Ph	**2ci**, *epi*-**2ci**	70	4 : 1

[a] Piperidine, dry ethanol, rt, overnight. [b] Piperidine, dry ethanol, reflux 4 h. [c] Ratio of isomers *rac*-(6a*R**,12*S**,12a*S**)-3/*rac*-(6a*R**,12*R**,12a*S**)-*epi*-**3** and *rac*-(4*R**,4a*S**,10b*S**)-2/-(4*R**,4a*S**,10b*R**)-*epi*-2 was determined by ^{1}H-NMR integrals. [d] No reaction at room temperature, reaction was carried out at reflux temperature.

also confirmed by the 6aH/12a-H NOE correlation (Fig. S3–S17†). Since the quaternary C-12 chirality center has no proton, its relative configuration could be only assigned on the basis of

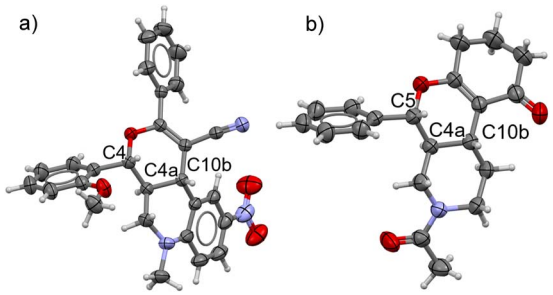
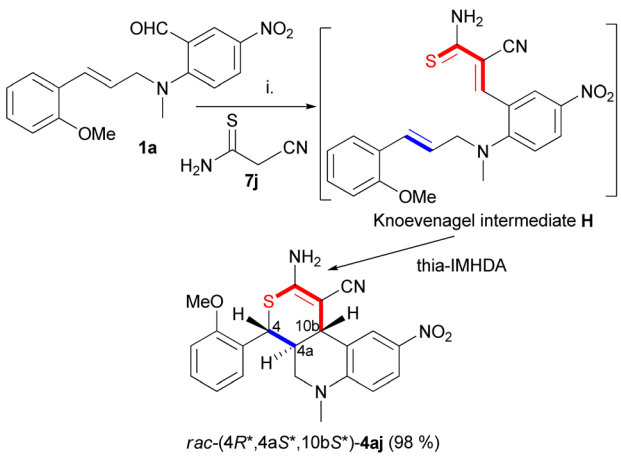


Fig. 1 ORTEP view at 50% probability level of (a) *rac*-(4*R**,4a*S**,10b*S**)-**2ai** (CCDC no. 2283893) and (b) *rac*-(4a*S**,5*R**,9b*R**)-**6p** (CCDC no. 2401371). For *rac*-(4*R**,4a*S**,10b*S**)-**2ai**, the solvent molecule is omitted for clarity.

NOE correlation among the 12a-H and carboxamide substituent (Fig. S11 and S14†). The relative configuration of the C-12 and C-12a chirality centers is governed by the stereospecificity of the cyclization step; an (*E*) configuration of the carbon–carbon double bond of the Knoevenagel intermediate **E** results in the product (6a*R**,12*S**,12a*S**)-**3** with *cis* orientation of the 12a-H and the carboxamide group, while (*Z*) configuration affords (6a*R**,12*R**,12a*S**)-*epi*-**3** with *trans* arrangement of the 12a-H and the carboxamide group.[12]

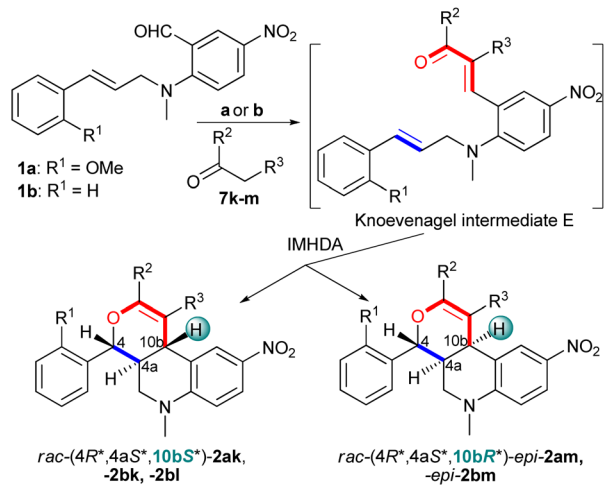
The domino reaction of the sulfur-containing active methylene reagent 2-cyanothioacetamide (**7j**) with **1a** produced the initial Knoevenagel intermediate **E** that contained a reactive α,β-unsaturated thiocarbonyl heterodiene (Scheme 3) favoring the thia-IMHDA cyclization. The thia-IMHDA cyclization (**E** → **4aj**) occurred diastereoselectively with quantitative yield, affording the tetrahydro-4*H*-thiopyrano[3,4-*c*]quinolone derivative *rac*- (4*R**,4a*S**,10b*S**)-**4aj** with *trans* ring junction. The tricyclic *S*,*N*-scaffold of *rac*-**4aj** represents a new condensed heterocyclic entity, which was reported earlier only as part of condensed pentacycles.[4b]

The domino Knoevenagel-cyclization sequence was also extended to active methylene reagents containing ester groups (Table 2). The Knoevenagel intermediate obtained in the reaction



Scheme 3 Domino Knoevenagel-thia-IMHDA reaction of **1a** with 2-cyanoacethioacetamide. (i) Piperidine, dry ethanol, rt, overnight.

Table 2 Domino Knoevenagel-IMHDA reactions with acyclic active methylene reagents containing ester groups



Entry	7k–m	R^2	R^3	2ak–bl	Yields (%)	dr
12	**7k**	Me	COOEt	**2ak**	45	1 : 0[b]
13	**7k**	Me	COOEt	**2bk**	70	1 : 0[b]
14	**7l**	OEt	NO_2	**2bl**	7	1 : 0[a]
15	**7m**	OMe	SO_2Ph	*epi*-**2am**	35	0 : 1[a]
16	**7m**	OMe	SO_2Ph	*epi*-**2bm**	36	0 : 1[a]

[a] Piperidine, dry EtOH, rt. overnight. [b] Piperidine, dry EtOH, reflux 4 h.

of ethyl acetoacetate (**7k**) and substrates **1a** and **1b** had an α,β-unsaturated ketone heterodiene, which reacted in a diastereoselective oxa-IMHDA reaction to afford *rac*-(4*R**,4a*S**,10b*S**)-**2ak** and -**2bk** (entries 12 and 13, Table 2). With ethyl nitroacetate (**7l**) reagent, the ester carbonyl contributed to the heterodiene and only the formation of (4*R**,4a*S**,10b*S**)-**2ak** was observed by an oxa-IMHDA cyclization step with low yield (entry 14). The low yield is probably due to a competing inverse Cadogan-type cyclization sequence initiated by a nitro-IMHDA reaction, which we observed as a novel multistep cascade in the reaction of 2*H*-chromene derivatives with methyl nitroacetate.[11c] In entry 14, this cascade probably did not lead to stable intermediates and products, which lowered the yield by decomposition. With the methyl (phenylsulfonyl)acetate reagent (**7m**), the Knoevenagel intermediates cyclized with the oxa-IMHDA mechanism using the ester carbonyl group for the heterodiene and the *rac*-(4*R**,4a*S**,10b*R**)-*epi*-**2am** and -*epi*-**2bm** products formed with full diastereoselectivity (entries 15 and 16).

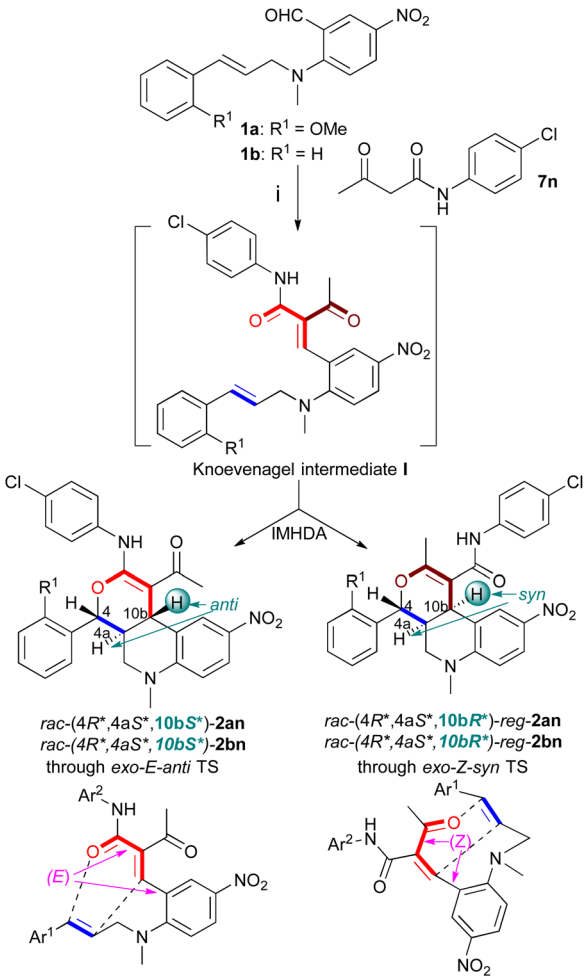
Based on our previous density functional theory (DFT) calculations on related substituted 2*H*-chromene derivatives, the (4*R**,4a*S**,10b*S**)- and (4*R**,4a*S**,10b*R**)-*epi*-diastereomers formed through *exo-E-anti* (entries 12–14) and *exo-Z-syn* (entries 15 and 16) transition states, respectively.[11c]

Since the reagent *N*-(4-chlorophenyl)-3-oxobutanamide (**7n**) can be considered an amide analogue of the methyl acetoacetate (**7k**) forming a conjugating ketone and an amide carbonyl group in the Knoevenagel intermediate obtained with **1a** and **1b**, it was unexpected that both the α,β-unsaturated amide and ketone subunits reacted in oxa-IMHDA cyclization, affording a mixture of regioisomeric products **2an**/*reg*-**2an** and **2bn**/*reg*-**2bn** (entries 17 and 18, Table 3). *Rac*-(4*R**,4a*S**,10b*S**)-**2an** and -**2bn** were produced diastereoselectively as the major product with an oxa-IMHDA reaction of the α,β-unsaturated amide heterodiene of the Knoevenagel intermediate through an *exo-E-anti* transition state. The regioisomeric *rac*-(4*R**,4a*S**,10b*R**)-*reg*-**2an** and -**2bn** formed also diastereoselectively with *cis*-ring annulation and participation of the α,β-unsaturated ketone moiety as a diene of the oxa-IMHDA step. The stereochemistry of the products suggested that the initial Knoevenagel intermediate had (*E*) configuration for the carbon–carbon double bond and *exo-Z-syn* and *exo-E-anti* transition states led to *trans*- and *cis*-ring annulations in the oxa-IMHDA step with participation of amide- or ketone-type heterodienes, respectively. In IMHDA reactions, the *exo*/*endo* notations of the transition state refer to the relative orientation of the heterodiene and linker connecting the heterodiene and the dienophile subunits. If the linker is located below or above the heterodiene, the transition state is *endo*. The *E*/*Z* and *anti*/*syn* notations are defined in the scheme of Table 3.

The Meldrum's acid (**7o**) is a frequently utilized convenient active methylene reagent in domino Knoevenagel-IMHDA reactions to prepare condensed tetrahydro-α-pyrones, since the reactive 1,3-dioxinone moiety of the IMHDA product can be readily removed by fragmenting it with water or alcohols. This approach was exploited in the synthesis of condensed tetrahydropyran-2*H*-2-one natural products,[13] and Tietze and co-workers also used it for the preparation of hirsutin[14] and (+)-camptothecin.[15] However, there are no examples when the fragmentation is initiated by the nucleophilic attack of primary or secondary amines at the lactone carbonyl of the condensed 1,3-dioxinone moiety of the IMHDA product, by which we could introduce a C-1 carboxamide group to the 4-aryl-hexahydro-2*H*-pyrano[3,4-*c*]quinolin-2-one skeleton in a multistep sequence (Table 4).

In this work, we utilized secondary (**10a–d**) and primary amines (**10e–g**) as nucleophiles for the ring-opening of the 1,3-dioxinone moiety of IMHDA intermediate **2ao**, which after attacking the lactam carbonyl induced a loss of an acetone molecule. The products **5a–g** contained a β-dicarbonyl subunit with an enolizable C-1 chirality center (Table 4). The multistep sequences provided access to hexahydro-2*H*-pyrano[3,4-*c*]quinolin-2-one-1-carboxamides with moderate to low yields, which would not be accessible with malonamide reagents due to their low reactivity (Scheme S4†). A competitive ring-opening reaction with water is also feasible, affording the decarboxylated lactones, which may contribute the lower yields and different ratio of diastereomers (Scheme S5†). The IMHDA reaction occurred through the *exo-Z-syn* and *exo-E-anti* transition states leading to *trans*- and *cis*-ring annulations and the labile C-1 chirality center adopted the more stable relative configuration through enolization. This implies four possible diastereomers, from which only one or two were isolated in the reaction. Varying mixtures of diastereomers dia1 and dia2 having *trans* relative configuration of the 1-H and 10b-H, were obtained in the reaction of **1a** with secondary cyclic amine nucleophiles **10a–c**

Table 3 Domino Knoevenagel-IMHDA sequence of substrates **1a,b** with *N*-(4-chlorophenyl)-3-oxobutanamide (**7n**)



Entry	Products		Y (%)	Ratio
17	*rac*-(4*R**,4a*S**,10b*S**)-**2an**	*rac*-(4*R**,4a*S**,10b*R**)-*reg*-**2an**	37	1.4 : 1
18	*rac*-(4*R**,4a*S**,10b*S**)-**2bn**	*rac*-(4*R**,4a*S**,10b*R**)-*reg*-**2bn**	67	1.4 : 1

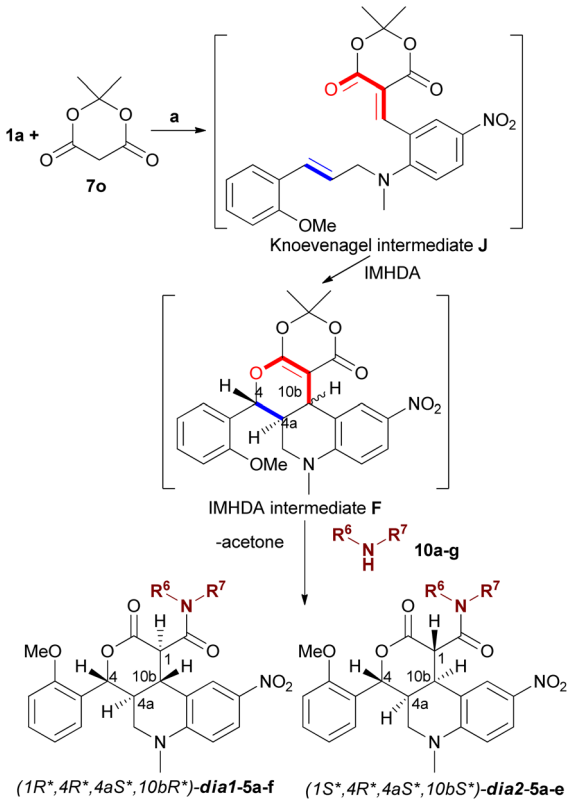
[a] Piperidine, dry EtOH, reflux 4 h.

(entries 19–21) and benzylamine (**10e**) (entry 23), which could be separated by column chromatography in the case of amines **10b**, **10c** and **10e** (Fig. S68–S82 and S86–S92†). With dimethylamine (**10d**), generated *in situ* from the hydrochloride salt, only a single diastereomer dia2-**5d** was isolated with 38% yield (entry 22, Fig. S83–S85†). The $^{3}J_{H,H}$ coupling constants of the methine protons and the NOE correlations were utilized to determine the absolute configuration of the four contiguous chirality centers (Table S2†). When using primary methylamine (**10f**), dia2-**5f** with *trans* orientation of the 1-H and 10b-H protons and *cis* ring junction was isolated (entry 24, Fig. S93 and S94†). The reaction of the primary allylamine (**10g**) afforded a single diastereomer dia2-**5g** with 37% yield (Fig. S95 and S96†).

In order to prepare further simplified hexahydro-1*H*-pyrano [3,4-*c*]pyridine analogues of pharmacological relevance,[16] which lack the condensed benzene ring and represent novel heterocyclic skeletons, the truncated substrate **1d** was prepared from cinnamaldehyde in four steps (Schemes S1–S3† and Table 5). Substrate **1d** had an *N*-acetyl group instead of the *N*-methyl, which increased the stability in the presence of the propanal subunit. The aliphatic substrate **1d** had lower reactivity in the domino Knoevenagel-IMHDA sequences compared to aromatic substrates **1a–c** and thus reactions were carried out with microwave activation at 120 °C. When using the regular thermal conditions of the domino cyclizations, refluxing ethanol in the presence piperidine, the reaction of **1d** and 1,3-cyclohexanedione (**7p**) stopped at the stage of the Knoevenagel intermediate and prolonged reflux resulted in decomposition.

The microwave-assisted domino reaction of **1d** with 1,3-cyclohexanedione (**7p**) and 1,3-cyclopentanedione (**7q**) afforded the *trans*-annulated condensed tricyclic products *rac*-

Table 4 Domino Knoevenagel-IMHDA-ring-opening sequences with Meldrum's acid (**7o**) as an active methylene reagent and different amines (**10a–g**) as nucleophiles

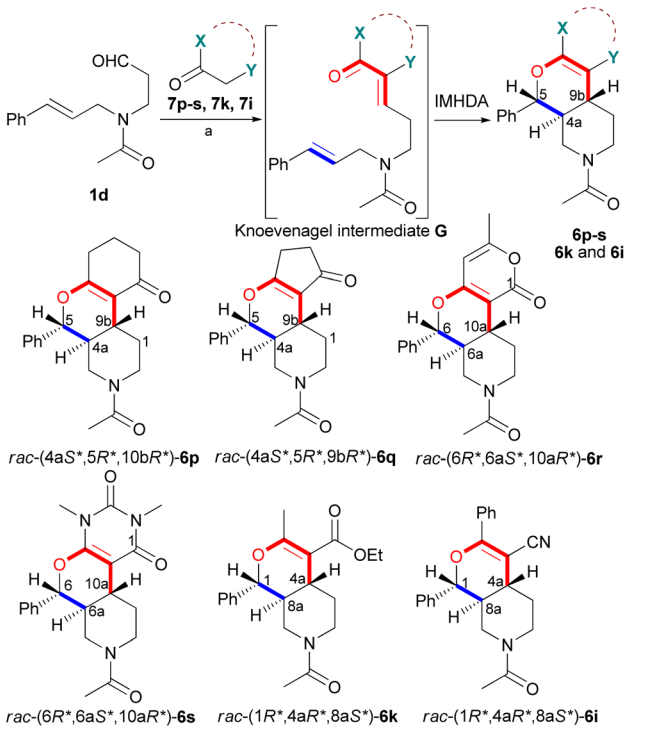


Entry	Amines **10a–g**	**5a–g**	Yield (%)	dr (dia1 : dia2)[b]
19	 **10a**	dia1-**5a**, dia2-**5a**	65	4 : 5[c]
20	 **10b**	dia1-**5b** dia2-**5b**	3 18	1 : 6
21	 **10c**	dia1-**5c** dia2-**5c**	16 9	7 : 4
22	 **10d**	dia2-**5d**	38	0 : 1
23	 **10e**	dia1-**5e** dia2-**5e**	4 21	1 : 5
24	 **10f**	dia2-**5f**	24	0 : 1
25	 **10g**	dia2-**5g**	37	0 : 1

[a] Amine reagent, dry toluene, rt, 4 days. [b] Ratio of diasomers as determined by ^{1}H-NMR integrals. [c] Inseparable diastereomeric mixture.

(4a*S**,5*R**,10b*R**)-**6p** and *rac*-(4a*S**,5*R**,9b*R**)-**6q** as a single diastereomer in excellent and moderate yields, respectively (Table 5, entries 26 and 27). The reactions with cyclic reagents 4-hydroxy-6-methyl-2*H*-pyran-2-one (**7r**) and *N*,*N*-dimethylbarbituric acid (**7s**)

Table 5 Domino Knoevenagel-IMHDA reactions of **1d** with cyclic (**7p–s**) and acyclic (**7k**, **7i**) active methylene reagents



Entry	**7a–r**	Structure of the reagent	Product	Yield (%)
26	**7p**		**6p**	92
27	**7q**		**6q**	42
28	**7r**		**6r**	37
29	**7s**		**6s**	16
30	**7k**		**6k**	63
31	**7i**		**6i**	48

[a] Piperidine, dry EtOH, 120 °C MW 1 h.

resulted in the formation of *rac*-(6a*R**,6a*S**,10a*R**)-**6r** and *rac*-(6a*R**,6a*S**,10a*R**)-**6s**, respectively, which have the same stereochemical orientation as **6p** and **6q**, although the numbering and stereochemical descriptors of the chirality centers are different due to the different tricyclic core (entries 28 and 29). With acyclic reagents **7k** and **7i**, condensed *trans*-annulated bicyclic cores of **6k** and **7i** were produced with full diastereoselectivity. In all the products, the piperidine and dihydropyran rings had *trans* fusion, which was obtained through *exo-Z-syn* transition state of the IMHDA step.

The slow interconversion of the s-*cis* and s-*trans* conformers of the *N*-acetyl subunit augmented by the conformational

flexibility of the piperidine ring resulted in at least two series of signals in the NMR spectra, which made the assignment of relative configuration challenging. In most cases, overlapping signals of different conformers did not allow the assignment of the relative configuration by using only NOE correlations. In the case of **6k** and **6q**, the key ^{1}H-NMR signals did not overlap, and thus the relative configuration could be assigned as *rac*-(1*R**,4a*R**,8a*S**) and *rac*-(4a*S**,5*R**,9b*R**), respectively. The relative configuration of **6p** was also confirmed independently by means of single crystal X-ray diffraction analysis (CCDC no. 2401371) as (4a*S**,5*R**,9b*R**).

In vitro antiproliferative activity of the chiral condensed heterocyclic products was tested on U87 glioblastoma, A2058 melanoma and HT-29 colorectal adenocarcinoma human cancer cell lines, and IC_{50} values were determined for the most active ones by MTT method. *Epi*-**2am**, obtained in the Knoevenagel-IMHDA reaction of **1a** and methyl (phenylsulfonyl) acetate reagent (**7m**), had IC_{50} values of 46 μM and 19 μM against U87 and A2058 cancer cell lines, respectively (positive control for U87: etoposide with an IC_{50} value of 12.0 μM).

Experimental

Materials and methods

Chemicals were purchased Puriss p.a. from commercial suppliers, and solvents were purified by distillation before use. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used, and compounds were visualized by irradiation with UV light. Column chromatography was performed using silica gel Merck 60 (particle size 0.063–0.200 mm). Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The NMR spectra were recorded on Bruker Avance DRX 360 MHz (^{1}H: 360 MHz; ^{13}C: 90 MHz), Bruker Avance II 400 (^{1}H: 400 MHz. ^{13}C: 100 MHz) and Bruker Avance II 500 MHz (^{1}H: 500 MHz. ^{13}C: 125 MHz) spectrometers using TMS as internal standard. The nuclear Overhauser effects were detected with offset-compensated and zero-quantum suppressed ROESY experiments developed by Batta *et al.*[17] Chemical shifts were reported as δ in ppm and $^3J_{H,H}$ coupling constants in Hz. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer and absorption bands are presented as wavenumber in cm^{-1}. Electrospay Quadrupole Time-of-Flight HRMS measurements were performed with a MicroTOF-Q type QqTOF MS instrument equipped with an ESI source from Bruker (Bruker Daltoniks, Bremen, Germany).

X-ray diffraction analysis

X-ray-quality crystals were grown by slow evaporation of the mixture of chloroform/methanol 4 : 1 solution of the compounds. A crystal well-looking in polarized light microscope was fixed under a microscope onto a Mitegen loop using high-density oil. Diffraction intensity data were collected ambient temperature using a Bruker-D8 Venture diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) equipped with INCOATEC IμS 3.0 (Incoatec GmbH, Geesthacht, Germany) dual (Cu and Mo) sealed tube micro sources and a Photon II Charge-Integrating Pixel Array detector (Bruker AXS GmbH, Karlsruhe, Germany) using Mo Kα (λ = 0.71073 Å) radiation.

High-multiplicity data collection and integration were performed using APEX3 (version 2017.3-0, Bruker AXS Inc., 2017, Madison, WI, USA) software. Data reduction and multiscan absorption correction were performed using SAINT (version 8.38A, Bruker AXS Inc., 2017, Madison, WI, USA). The structure was solved using direct methods and refined on F^2 using the SHELXL program[18] incorporated into the APEX3 suite. Refinement was performed anisotropically for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions on parent atoms in the final refinement.

The CIF file was manually merged using Publcif software,[19] while graphics were designed using the Mercury program.[20] Details of the crystal parameters, data collection, and structure refinement are given in Table SX1.† The compounds are racemates, crystallizing in monoclinic centrosymmetric space group no. 14 so the relative configuration of the chirality elements are given. ORTEP views are shown in Fig. SX1–3.† The results of the X-ray diffraction structure determinations were in accordance with the Checkcif functionality of PLATON software (Utrecht University, Utrecht, the Netherlands),[21] without A or B level alert. Structural parameters, such as bond length and angle data (Tables SX2–4†), are in the expected range.

***In vitro* cytostatic activity; cell culturing and media.** Antiproliferative activities of the products were evaluated *in vitro* against A2058 melanoma, HT-29 colorectal adenocarcinoma and U87 human glioblastoma (ATCC HTB-14)[22] cell culture, which were generous gifts from Dr József Tóvári (Department of Experimental Pharmacology, National Institute of Oncology, Budapest, Hungary). Maintaining U87 cell culture, DMEM (Lonza, Basel, Switzerland)) supplemented with 10% FBS (Biosera, Nuaille, France), 2 mM L-glutamine, 100 μg per ml penicillin/streptomycin (50 IU per ml and 50 μg ml^{-1}, respectively, Gibco PEN/STREP (Thermo Fisher Scientific, Waltham, MA, USA), 1 mM pyruvate, and 1% non-essential amino acids (CM DMEM) were used. A2058 and HT-29 cells were cultured in RPMI medium (Lonza, Basel, Switzerland) supplemented with 10% FBS, 2 mM L-glutamine and the above listed PEN/STREP. The cultures were maintained at 37 °C in a humidified atmosphere with 5% CO_2.

For the end-point-type tetrazolium [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, MTT] assay,[23] cells were seeded during the exponential growth phase one day before the experiment. In the case of cytostasis, 5×10^3 cells/100 μl per well were seeded on a 96-well cell culture plate (Sarstedt, Nümbrecht, Germany) in CM DMEM. Cells were treated with the compounds using DMSO stock solutions (c = 20 mM) diluted in DMEM incomplete medium (ICM) (final c = 1% (v/v) for DMSO content) in the concentration range 2.56×10^{-3}–100 μM. Cells were treated with the compounds for 24 h. ICM and ICM containing 0.5% (v/v) DMSO were used as controls. After incubation, cells were washed with ICM three times, and in the last step, CM was added. After culturing the cells for 72 h, 45 μl sterile-filtered MTT (Millex 0.22 μm filter, Millipore, Cork, Ireland) was added (2 mg ml^{-1} in ICM) to the cells. Mitochondrial

enzymes reduce MTT to a formazan derivative (purple crystals). As a positive control etoposide was employed.

After 3.5 h incubation, plates were centrifuged (2000 rpm, 5 min), the supernatant was removed, and formazan crystals were dissolved in DMSO. Absorbance was determined with an ELISA plate reader (Labsystems iEMS reader, Helsinki, Finland) at $\lambda = 540$ and 620 nm. A_{620} values were subtracted from A_{540} values, and cytostatic activity was calculated with the formula: cytostasis% $= 100 \times (1 - A_{\text{treated cells}}/A_{\text{control cells}})$, where $A_{\text{treated cells}}$ and $A_{\text{control cells}}$ are the average absorbance of treated and control cells. The 50% inhibitory concentration (IC_{50}) values were determined from the dose–response curves. The curves were calculated using Microcal OriginPro (version: 2018) software (OriginLab, Northampton, MA, USA).

General methods for the domino Knoevenagel-cyclization reactions

Method A (MW): to a standard 10 ml volume cylindrical Pyrex® reaction vessel, **1d**, **7p–7s**, **7k**, **7i**, piperidine and 2 ml of dry ethanol were added. The vessel was sealed with PEEK snap cap and standard PTFE-coated silicone septum and warmed up to 120 °C and stirred for 1 hour. The solvent was removed *in vacuo*, and the crude was triturated with 3 ml of cold ethanol, and the crystals were filtered and washed with 2 ml of cold ethanol. If no precipitate formed, the crude was purified with column chromatography.

Method B: in a flame-dried three-necked round-bottom flask equipped with a reflux condenser and a $CaCl_2$ drying tube, benzaldehyde derivative **1a** (100 mg) and Meldrum's-acid **7o** (1.2 equivalent) were dissolved in toluene (5 ml). Primary or secondary amines (**10a–g**, 1.2 equivalent) were added to the mixture and stirred for four days at room temperature. After completion, the solvent was removed *in vacuo*, and the crude product was purified by column chromatography.

Methods C and D: in a flame-dried three-necked round-bottom flask equipped with a reflux condenser and a $CaCl_2$ drying tube, benzaldehyde derivative **1a–c** (100 mg) and active methylene reagent **7a–n**, (1.2 equivalent) were dissolved in ethanol (5 ml). Piperidine (1 equivalent) was added to the solution, and it was stirred overnight at room temperature (method C) or refluxed for 4 hours (method D). The mixture was concentrated *in vacuo* and purified by column chromatography.

Synthetic procedures and characterization of the products

***rac*-(6a*R**,12*S**,12a*S**)-12-Cyano-*N*-cyclohexyl-8-methoxy-5-methyl-2-nitro-5,6,6a,7,12,12a-hexahydrobenzo[*j*] phenanthridine-12-carboxamide [*rac*-(6a*R**,12*S**,12a*S**)-3aa].** The reaction of **1a** with **7a** was carried out according to method D. The crude product was purified by column chromatography (hexane/chloroform/acetone 10 : 5 : 1) affording *rac*-(6a*R**,12*S**,12a*S**)-**3aa** as yellow powder (68%), which decomposes above 240 °C. $R_f = 0.46$ (hexane/chloroform/acetone 10 : 5 : 1).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.00–2.02 (m, 10H, 7′-11′-H), 2.69–2.82 (m, 1H, 6a-H), 2.98–3.03 (m, 2H, 7-H), 3.04 (s, 3H, 1′-H), 3.28–3.38 (m, 1H, 6-H_b), 3.59 (t, $J = 12.9$ Hz, 1H, 6-H_a), 3.85 (s, 3H, 2′-H), 3.87–3.94 (m, 1H, 6′-H), 3.96 (d, $J = 3.0$ Hz, 1H, 12a-H), 6.44 (d, $J = 7.9$ Hz, 1H, 5′-H), 6.63 (d, $J = 9.3$ Hz, 1H, 4-H), 6.78–6.94 (m, 2H, 9-H, 11-H), 7.19–7.31 (m, 1H, 10-H), 7.85 (d, $J = 2.5$ Hz, 1H, 1-H), 8.12 (dd, $J = 9.3$, 2.6 Hz, 1H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5 (C-10′), 24.6 (C-9′), 24.7 (C-7), 25.4 (C-8′), 28.0 (C-6a), 32.7 (C-7′), 32.8 (C-11′), 38.6 (C-1′), 41.6 (C-6′), 50.1 (C-12a), 51.8 (C-6), 52.1 (C-12), 55.6 (C-2′), 109.8 (C-4), 110.0 (C-11), 119.5 (C-3′), 119.7 (C-1), 120.6 (C-12b), 122.8 (C-11a), 125.5 (C-10), 126.6 (C-3), 128.4 (C-9), 129.4 (C-7a), 136.2 (C-2), 150.6 (C-4′), 157.7 (C-4a), 165.8 (C-8). IR: (KBr) ν: 2989, 2929, 2848, 1684, 1670, 1601, 1576, 1515, 1492, 1465, 1431, 1303, 1275, 1260, 1224, 1183, 1152, 1106, 1085. HRMS: calcd for $C_{27}H_{31}N_4O_4$ $[M + H]^+$ 475.2345, found 475.2342.

***rac*-(6a*R**,12*S**,12a*S**)-12-Cyano-8-methoxy-5-methyl-2-nitro-*N*-phenyl-5,6,6a,7,12,12a-hexahydrobenzo[*j*] phenanthridine-12-carboxamide [*rac*-(6a*R**,12*S**,12a*S**)-3ab].** The reaction of **1a** with **7b** was carried out according to method C. The crude product was concentrated *in vacuo* and purified by column chromatography (hexane/chloroform/acetone 10 : 5 : 1) affording *rac*-(6a*R**,12*S**,12a*S**)-**3ab** as yellow powder (93%), which decomposes above 253 °C. $R_f = 0.50$ (hexane/chloroform/acetone 10 : 5 : 1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.72–2.80 (m, 1H, 6a-H), 2.97–3.05 (m, 5H, 1′-H, 7-H), 3.30–3.37 (m, 1H, 6-H_b), 3.58 (t, $J = 12.9$ Hz, 1H, 6-H_a), 3.85 (s, 3H, 2′-H), 4.00 (d, $J = 3.1$ Hz, 1H, 12a-H), 4.49 (dd, $J = 14.6$, 5.3 Hz, 1H, 6′-H_a), 4.65 (dd, $J = 14.6$, 5.3 Hz, 1H, 6′-H_b), 6.61 (d, $J = 9.3$ Hz, 1H, 4-H), 6.78–6.88 (m, 3H, 9-H, 11-H, 5′-H), 7.20–7.35 (m, 6H, Ph-H, 10-H), 7.90 (d, $J = 2.6$ Hz, 1H, 1-H), 8.10 (dd, $J = 9.3$, 2.6 Hz, 1H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5 (C-7), 28.0 (C-6a), 38.6 (C-1′), 41.7 (C-12a), 45.1 (C-6′), 51.8 (C-6), 52.2 (C-12), 55.6 (C-2′), 109.9 (C-4), 110.2 (C-11), 119.5 (C-3′), 119.9 (C-9), 120.4 (C-12b), 122.8 (C-11a), 125.4 (C-1), 126.7 (C-3), 128.1 (C-8′, C-10′, C-12′), 128.4 (C-10), 129.0 (C-9′, C-11′), 129.2 (C-7′), 136.3 (C-7a), 136.7 (C-2), 150.6 (C-4′), 157.7 (C-4a), 167.0 (C-8). IR: (KBr) ν: 2923, 2851, 1747, 1680, 1647, 1604, 1523, 1495, 1466, 1434, 1361, 1321, 1303, 1276, 1261, 1185, 1108. HRMS: calcd for $C_{27}H_{25}N_4O_4$ $[M + H]^+$ 469.1875, found 469.1870.

***rac*-(6a*R**,12*S**,12a*S**)-12-Cyano-8-methoxy-5-methyl-2-nitro-*N*-(prop-2-yn-1-yl)-5,6,6a,7,12,12a-hexahydrobenzo[*j*] phenanthridine-12-carboxamide [*rac*-(6a*R**,12*S**,12a*S**)-3ac].** The reaction of **1a** with **7c** was carried out according to method C. The precipitate was filtered and washed with 5 ml of cold ethanol. The filtrate was concentrated *in vacuo* and purified by column chromatography (hexane/chloroform/ethyl acetate 5 : 5 : 1). Unifying the product from crystallization and chromatography afforded *rac*-(6a*R**,12*S**,12a*S**)-**3ac** as yellow powder (78%), which decomposes at 270 °C. $R_f = 0.17$ (hexane/chloroform/ethyl acetate 5 : 5 : 1).

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.66–2.75 (m, 1H, 6a-H), 2.89–2.95 (m, 1H, 7-H), 2.99 (s, 3H, 1′-H), 3.06 (s, 1H, 8′-H), 3.32–3.40 (m, 1H, 6-H_b), 3.44 (dd, $J = 13.0$, 5.2 Hz, 1H, 6-H_a), 3.81 (d, $J = 3.2$ Hz, 1H, 12a-H), 3.85 (s, 3H, 2′-H), 3.91 (dd, $J = 22.7$, 3.2 Hz, 2H, 6′-H), 6.75–6.83 (m, 2H, 4-H, 9-H), 7.02 (d, $J = 8.2$ Hz, 1H, 11-H), 7.30 (t, $J = 8.2$ Hz, 1H, 10-H), 7.68 (d, $J = 2.3$ Hz, 1H, 1-H), 8.03 (dd, $J = 9.3$, 2.3 Hz, 1H, 3-H), 8.67 (t, $J = 5.2$ Hz, 1H, 5′-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 23.9 (C-7),

27.2 (C-6a), 29.4 (C-6′), 38.3 (C-1′), 40.6 (C-12a), 50.9 (C-6), 52.9 (C-12), 55.7 (C-2′), 80.0 (C-7′), 110.1 (C-4), 110.4 (C-11), 119.2 (C-3′), 119.4 (C-12b), 119.7 (C-9), 122.6 (C-7a), 124.9 (C-3), 126.0 (C-1), 128.1 (C-10), 128.9 (C-12a), 134.9 (C-2), 150.8 (C-4a), 157.1 (C-8), 167.5 (C-4′). IR: (KBr) *ν*: 3005, 2988, 2932, 2839, 1683, 1600, 1259, 1182, 1105. HRMS: calcd for $C_{24}H_{23}N_4O_4$ $[M + H]^+$ 431.1719, found 431.1714.

***rac*-(6a*R**,12*S**,12a*S**)- and *rac*-(6a*R**,12*R**,12a*S**)-*N*-Allyl-12-cyano-8-methoxy-5-methyl-2-nitro-5,6,6a,7,12,12a-hexahydrobenzo [*j*]phenanthridine-12-carboxamide [*rac*-(6a*R**,12*S**,12a*S**)-3ad and *rac*-(6a*R**,12*R**,12a*S**)-*epi*-3ad].** The reaction of **1a** with **7d** was carried out according to method C. The crude product was concentrated *in vacuo* and purified by column chromatography (hexane/chloroform/acetone 20 : 5 : 1) affording the mixture of *rac*-(6a*R**,12*S**,12a*S**)-**3ad** and *rac*-(6a*R**,12*R**,12a*S**)-*epi*-**3ad** as yellow powder (56%), R_f = 0.67 (hexane/chloroform/acetone 10 : 5 : 1). The diastereomeric ratio was ∼5 : 1 according to the ^{1}H-NMR integrals.

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.64–2.72 (m, 1H, 6a-H), 2.90–2.95 (m, 2H, 7-H), 2.99 (s, 3H, 1′-H), 3.07 (s, 1H, 5′-H), 3.27–3.36 (m, 2H, 2× 6-H$_b$), 3.36–3.46 (m, 2H, 2× 6-H$_a$), 3.74–3.83 (m, 2H, 6′-H), 3.85 (s, 3H, 2′-H), 3.87 (d, J = 3.7 Hz, 1H, 12a-H, major), 5.01–5.14 (m, 2H, 2× 8′-H), 5.77–5.90 (m, 1H, 2× 7′-H), 6.78 (d, J = 9.5 Hz, 1H, 4-H), 6.84–6.89 (m, 1H, 9-H), 7.01 (dd, J = 8.0, 2.8 Hz, 1H, 11-H), 7.06 (d, J = 7.8 Hz, 1H, 11-H), 7.31 (t, J = 8.1 Hz, 1H, 10-H), 7.64 (d, J = 2.7 Hz, 1H, 1-H), 8.03 (dd, J = 9.3, 2.7 Hz, 1H, 3-H), 8.45 (t, J = 5.7 Hz, 1H, 5′-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.4 and 27.6 (C-7), 28.0 (C-6a), 38.6 (C-1′), 41.8 and 43.2 (C-12a), 43.4 and 44.0 (C-6′), 51.8 (C-6), 52.2 (C-12), 55.6 (C-2′), 109.8 and 110.0 (C-4), 110.1 and 110.7 (C-11), 118.1 (C-3′), 119.0 (C-9), 119.3 (C-3′), 119.9 (C-7′), 120.4 (C-9), 122.8 (C-12b), 124.3 (C-7a), 125.3 (C-1), 125.5 (C-3), 126.6 (C-1), 128.2 (C-3), 128.4 and 129.0 (C-10), 132.7 (C-11a), 132.8 (C-7′), 136.2 (C-2), 150.6 (C-4a), 157.6 (C-8), 167.0 (C-4′). IR: (KBr) *ν*: 2924, 1671, 1601, 1524, 1492, 1467, 1437, 1319, 1290, 1257, 1185, 1109, 1050, 1023. HRMS: calcd for $C_{24}H_{25}N_4O_4$ $[M + H]^+$ 433.1875, found 433.1869.

***rac*-(6a*R**,12*S**,12a*S**)-12-Cyano-*N*-(2-hydroxyethyl)-8-methoxy-5-methyl-2-nitro-5,6,6a,7,12,12a-hexahydrobenzo[*j*] phenanthridine-12-carboxamide [*rac*-(6a*R**,12*S**,12a*S**)-3ae].** The reaction of **1a** with **7e** was carried out according to method C. The crude product was concentrated *in vacuo* and purified by column chromatography (hexane/chloroform/acetone 10 : 5 : 1) affording *rac*-(6a*R**,12S*,12a*S**)-**3ae** as brown oil (57%), R_f = 0.38 (hexane/chloroform/acetone 10 : 5 : 1).

^{1}H NMR (500 MHz, acetone-d_6) δ 2.76–2.84 (m, 1H, 6a-H), 2.97–3.02 (m, 2H, 7-H), 3.07 (s, 3H, 1′-H), 3.40–3.48 (m, 1H, 6′-H$_a$), 3.48–3.54 (m, 1H, 6-H$_b$), 3.60–3.66 (m, 1H, 7′-Ha), 3.68–3.75 (m, 2H, 6-H), 3.81–3.84 (m, 1H, 7′-H$_b$), 3.89 (s, 3H, 2′-H), 3.99 (d, J = 3.4 Hz, 1H, 12a-H), 6.76–6.81 (m, 1H, 4-H), 6.97–7.03 (m, 2H, 11-H and 4-H), 7.23–7.32 (m, 1H, 10-H), 7.50 (s, 1H, 8′-H), 7.82 (d, J = 2.3 Hz, 1H, 1-H), 8.03–8.07 (m, 1H, 3-H). ^{13}C NMR (126 MHz, acetone-d_6) δ 25.1 (C-7), 28.6 (C-6a), 38.7 (C-1′), 42.3 (C-12a), 43.7 (C-6′), 52.3 (C-6), 55.9 (C-12), 56.0 (C-2′), 60.8 (C-7′), 110.7 (C-4), 110.9 (C-11), 120.7 (C-3′), 120.7 (C-12b), 120.9 (C-9), 123.8 (C-11a), 126.0 (C-1), 126.7 (C-3), 128.9 (C-10), 130.7 (C-7a), 136.8 (C-2), 151.8 (C-4′), 158.5 (C-4a), 168.2 (C-8). IR: (KBr) *ν*: 2922, 1675, 1603, 1524, 1490, 1465, 1434, 1320, 1295, 1275, 1259, 1224, 1183, 1108. HRMS: calcd for $C_{23}H_{25}N_4O_5$ $[M + H]^+$ 437.1824, found 437.1822.

***rac*-(4*R**,4a*S**,10b*S**)- and *rac*-(4*R**,4a*S**,10b*R**)-4-(2-Methoxy phenyl)-6-methyl-9-nitro-2-(piperidin-1-yl)-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinoline-1-carbonitrile [*rac*-(4*R**,4a*S**,10b*S**)-2af and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-2af].** The reaction of **1a** with **7f** was carried out according to method C. The precipitate was filtered and washed with 5 ml of cold ethanol. The filtrate was concentrated *in vacuo* and purified by column chromatography (chloroform). Unifying the product from crystallization and chromatography afforded the mixture of *rac*-(4*R**,4a*S**,10b*S**)-**2af** and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-**2af** as yellow powder (58%). The diastereomeric ratio was ∼1 : 2 according to the ^{1}H-NMR integrals. R_f = 0.07 (hexane/acetone 2 : 1).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.44–1.67 (m, 12H, 2× 3″-H, 2× 4″-H, 2× 5″-H), 2.20 (bs, 1H, 4a-H), 2.56–2.64 (m, 1H, 4a-H), 2.79 (dd, J = 11.9, 5.4 Hz, 1H, 5-H$_b$), 2.91 (s, 3H, 3′-H), 2.98 (s, 3H, 3′-H), 3.41–3.50 (m, 5H, 2″-H, 6″-H, 5-H$_a$), 3.53 (d, J = 4.7 Hz, 1H, 10b-H from *epi*-**2af**), 3.58–3.71 (m, 4H, 2″-H, 6″-H), 3.76 (s, 3H, 2′-H), 3.84 (bs, 3H, 2′-H), 5.37 (d, J = 6.6 Hz, 1H, 4-H from *epi*-**2af**), 5.42 (bs, 1H, 4-H from **2af**), 6.62–6.75 (m, 2H, 2× 7-H), 6.75–6.81 (m, 1H, 5‴-H), 6.97–7.13 (m, 3-H, 3‴-H, 2× 5‴-H), 7.23 (d, J = 7.2 Hz, 1H, 3‴-H), 7.30–7.46 (m, 4H, 2× 4‴-H, 2× 6‴-H), 7.95–8.06 (m, 2H, 2× 8-H), 8.08 (d, J = 1.9 Hz, 1H, 10-H), 8.19 (bs, 1H, 10-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 23.8 (2× C-4″), 25.4 and 25.5 (2× C-5″ and 2× C-3″), 27.2 (C-4a), 33.0 (C-10b), 33.1 (C-4a), 38.0 and 38.2 and 38.7 (C-3′), 48.1 (2× C-2″ and 2× C-6″), 48.3 (C-2″ and C-6″), 49.5 and 51.0 and 51.8 (C-6), 54.5 (C-1), 55.4 and 55.6 and 55.8 (C-3′), 60.0 (C-1), 74.5 (2× C-4), 109.5 and 109.7 and 110.0 (C-7), 110.5 and 111.3 and 111.5 (C-9), 118.7 (C-1‴), 119.2 (C-10), 119.3 (C-6‴), 120.5 (C-10b), 120.7 (C-6‴), 120.8 (C-5‴), 121.7 (C-1′), 122.0 (C-1‴), 122.1 (C-1′), 124.8 and 124.9 (C-3‴), 125.3 (2× C-10a), 125.5 (C-10), 125.6 and 125.9 and 126.5 (C-8), 128.6 (C-4‴), 129.0 (C-1‴), 129.8 and 130.4 (C-4‴), 134.6 and 135.3 and 135.6 (C-9), 149.7 (C-6a), 150.9 (C-4a), 151.3 (2× C-6a), 156.0 (C-2‴), 157.3 (C-2‴), 163.0 and 164.6 and 166.9 (C-2). IR: (KBr) *ν*: 3005, 2989, 2936, 2848, 2169, 1574, 1530, 1492, 1453, 1437, 1300, 1275, 1260, 1178, 1112, 1077, 1051. HRMS: calcd for $C_{26}H_{29}N_4O_4$ $[M + H]^+$ 461.2188, found 461.2187.

***rac*-(4*R**,4a*S**,10b*S**)- and *rac*-(4*R**,4a*S**,10b*R**)-4-(2-Methoxyphenyl)-6-methyl-2-morpholino-9-nitro-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinoline-1-carbonitrile [*rac*-(4*R**,4a*S**,10b*S**)-2ag and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-2ag].** The reaction of **1a** with **7g** was carried out according to method D using dry 1,2-dichloroethane as solvent. The crude product was purified by column chromatography (hexane/chloroform/acetone 10 : 5 : 1) affording the mixture of *rac*-(4*R**,4a*S**,10b*S**)-**2ag** and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-**2ag** as the major product and brown oil (67%). The diastereomeric ratio was ∼4 : 1 according to the ^{1}H-NMR integrals, R_f = 0.38 (hexane/chloroform/acetone 10 : 5 : 1).

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.21 (bs, 1H, 4a-H), 2.80 (dd, J = 11.7, 5.3 Hz, 1H, 5-H$_b$), 2.91 (s, 3H, 3′H), 2.98 (s, 1H, 2″-H), 3.48–3.55 (m, 3H, 5-H$_a$, 3″-H), 3.60–3.66 (m, 6H, 5″-H, 6″-H, 10b-

H from *epi*-**2ag**), 3.76 (s, 1H, 2″-H), 3.83 (s, 3H, 2′-H), 5.38 (d, J = 6.7 Hz, 1H, 4-H from *epi*-**2ag**), 5.45 (bs, 1H, 4-H from **2ag**), 6.68 (d, J = 9.2 Hz, 1H, 7-H), 7.01 (t, J = 7.4 Hz, 1H, 5‴-H), 7.10 (d, J = 8.3 Hz, 1H, 3‴-H), 7.36–7.47 (m, 2H, 6‴-H, 4‴-H), 8.01 (dd, J = 9.2, 2.6 Hz, 1H, 8-H), 8.17–8.21 (m, 1H, 10-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 30.7 and 33.0 (C-4a), 38.1 and 38.7 (C-3′), 47.4 (C-1), 47.6 (C-5), 49.4 (C-1), 51.8 and 55.7 (C-2″ and C-6″), 55.8 (C-10b), 65.9 (C-2′), 74.7 (2× C-3″, 2× C-5″), 109.6 and 109.7 (C-7), 111.3 and 111.6 (C-9), 119.3(C-5‴), 120.7 and 120.9 (C-10), 121.8 (C-1′), 124.8 (C-10a), 124.9 (C-8), 125.2 and 125.4 (C-1‴), 126.6 and 129.9 (C-6‴), 130.5 (C-4‴), 135.4 and 135.6 (C-9), 151.3 (C-6a), 156.1 (C-2‴), 166.9 (C-2). IR: (KBr) ν: 3004, 2988, 2848, 2348, 2175, 1602, 1570, 1522, 1491, 1457, 1431, 1397, 1361, 1311, 1275, 1260, 1232, 1220, 1177, 1114. HRMS: calcd for $C_{25}H_{27}N_4O_5$ $[M + H]^+$ 463.1981, found 463.1975.

***rac*-(6a*R**,12*S**,12a*S**)-8-Methoxy-5-methyl-12-(morpholine-4-carbonyl)-2-nitro-5,6,6a,7,12,12a-hexahydrobenzo[*j*]phenanthridine -12-carbonitrile [*rac*-(6a*R**,12*S**,12a*S**)-3ag].** The reaction of **1a** with **7g** was carried out according to method D. The crude product was concentrated *in vacuo* and purified by column chromatography (hexane/chloroform/acetone 10 : 5 : 1) affording *rac*-(6a*R**,12*S**,12a*S**)-**3ag** as the minor product and yellow amorphous solid (22%), R_f = 0.48 (hexane/chloroform/acetone 10 : 5 : 1).

^{1}H NMR (500 MHz, DMSO-d_6) δ 2.69–2.78 (m, 1H, 6a-H), 2.95–3.02 (m, 4H, 7-H, 1′-H), 3.42–3.48 (m, 4H, 10′-H, 6′-H), 3.52–3.59 (m, 2H, 6-H), 3.63 (d, J = 3.4 Hz, 4H, 7′-H, 9′-H), 3.66 (d, J = 4.1 Hz, 1H, 12a-H), 3.85 (s, 3H, 1′-H), 6.76–6.82 (m, 2H, 9-H, 4-H), 7.05 (d, J = 8.0 Hz, 1H, 11-H), 7.37 (t, J = 8.0 Hz, 1H, 10-H), 7.66 (d, J = 2.7 Hz, 1H, 1-H), 8.04 (dd, J = 9.3, 2.7 Hz, 1H, 3-H). ^{13}C-NMR (90 MHz, DMSO-d_6) δ 23.5 (C-7), 27.2 (C-6a), 38.1 (C-1′), 51.0 (C-6), 54.8 (C-12), 55.1 (C-6′, C-10′), 55.6 (C-2′), 65.9 (C-7′, 9′), 110.0 (C-4), 110.7 (C-11), 118.5 (C-3′), 119.0 (C-12b), 119.3 (C-9), 120.8 (C-11a), 125.7 (C-1), 125.9 (C-3), 128.6 (C-7a), 128.7 (C-10), 134.6 (C-2), 150.9 (C-4a), 157.3 (C-4′), 165.1 (C-8). IR: (KBr) ν: 2917, 2857, 1648, 1602, 1580, 1525 1492, 1468, 1434, 1275, 1262, 1109. HRMS: calcd for $C_{25}H_{27}N_4O_5$ $[M + H]^+$ 463.1981, found 463.1974.

***rac*-(4*R**,4a*S**,10b*S**)- and *rac*-(4*R**,4a*S**,10b*R**)-4-(2-Methoxyphenyl)-6-methyl-9-nitro-2-(pyrrolidin-1-yl)-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinoline-1-carbonitrile [*rac*-(4*R**,4a*S**,10b*S**)-2ah and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-2ah].** The reaction of **1a** with **7h** was carried out according to method D. The crude product was concentrated *in vacuo* and purified by column chromatography (chloroform) affording the mixture of *rac*-(4*R**,4a*S**,10b*S**)-**2ah** and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-**2ah** as the minor product as yellow powder (21%). The diastereomeric ratio was ~1 : 4 according to the ^{1}H-NMR integrals, R_f = 0.21 (chloroform).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.77–1.87 (m, 4H, 4″-H, 5″-H), 2.11–2.24 (m, 4H, 3″-H, 6″-H), 2.57–2.67 (m, 1H, 4a-H), 2.70–2.87 (m, 1H, 4a-H), 2.93 (dd, J = 18.4, 6.5 Hz, 1H, 5-H$_b$), 3.05 (s, 3H, 3′-H), 3.08 (d, J = 6.6 Hz, 1H, 10b-H from **2ah**), 3.31–3.40 (m, 1H, 5-H$_b$), 3.63 (d, J = 4.6 Hz, 1H, 10b-H from *epi*-**2ah**), 3.65–3.79 (m, 2H, 2× 5-H$_a$), 3.83–3.90 (m, 6H, 2″-H), 5.14 (d, J = 4.6 Hz, 1H, 4-H from *epi*-**2ah**), 5.30 (bs, 1H, 4-H from **2ah**), 6.64 (d, J = 9.3 Hz, 1H, 7-H), 6.84 (d, J = 8.1 Hz, 1H, 6‴-H), 6.89 (d, J = 8.0 Hz, 1H, 3‴-H), 7.27 (dd, J = 8.8, 7.0 Hz, 2H), 4‴-H, 5‴-H, 7.70 (d, J = 2.6 Hz, 1H, 10-H), 8.10 (dd, J = 9.3, 2.6 Hz, 1H, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.3 (C-3″), 24.5 (C-5″), 27.0 (C-6″), 28.4 and 31.1 (C-4a), 38.6 (C-3′), 41.4 (C-10b), 47.7 (C-1), 49.2 (C-2″), 51.8 and 55.6 (C-2′), 71.5 and 71.6 (C-4), 109.9 (C-7), 110.0 (C-2‴), 118.8 (C-1′), 119.7 (C-5‴), 120.7 (C-10), 122.0 (C-10a), 125.9 (C-8), 126.7 (C-3‴), 127.4 and 127.4 (C-6‴), 128.5 and 128.7 (C-4‴), 136.1 (C-9), 150.9 (C-6a), 157.5 (C-2‴), 165.7 (C-2). IR: (KBr) ν: 2922, 1635, 1601, 1528, 1490, 1466, 1432, 1299, 1274, 1259, 1221, 1181, 1107, 1097. HRMS: calcd for $C_{25}H_{27}N_4O_4$ $[M + H]^+$ 447.2032, found 447.2029.

***rac*-(6a*R**,12*S**,12a*S**)-8-Methoxy-5-methyl-2-nitro-12-(pyrrolidine-1-carbonyl)-5,6,6a,7,12,12a-hexahydrobenzo[*j*] phenanthridine-12-carbonitrile [*rac*-(6a*R**,12*S**,12a*S**)-3ah].** The reaction of **1a** with **7h** was carried out according to method D. The crude product was concentrated *in vacuo* and purified by column chromatography (hexane/dichloromethane/acetone 8 : 5 : 1) affording *rac*-(6a*R**,12*S**,12a*S**)-**3ah** as the major product and yellow amorphous solid (76%), R_f = 0.06 (hexane/dichloromethane/acetone 8 : 5 : 1).

^{1}H NMR (500 MHz, DMSO-d_6) δ 1.80 (bs, 2H, 7′-H), 2.03–2.13 (m, 2H, 6′-H), 2.66–2.73 (m, 1H, 6a-H), 2.91 (dd, J = 18.4, 5.8 Hz, 2H, 7-H$_b$), 3.00 (s, 3H, 1′-H), 3.08 (bs, 1H, 7-H$_a$), 3.37–3.47 (m, 1H, 6-H$_a$), 3.47–3.56 (m, 3H, 6-H$_b$, 8′-H), 3.73 (d, J = 3.8 Hz, 1H, 12a-H), 3.85 (s, 3H, 2′-H), 6.73–6.81 (m, 2H, 9-H, 4-H), 7.03 (d, J = 8.2 Hz, 1H, 11-H), 7.33 (t, J = 8.0 Hz, 1H, 10-H), 7.54 (d, J = 1.9 Hz, 1H, 1-H), 8.01–8.06 (m, 1H, 3-H). ^{13}C NMR (90 MHz, DMSO-d_6) δ 22.6 (C-6′), 23.6 (C-7), 26.1 (C-7′), 27.3 (C-6a), 38.2 (C-1′), 38.6 (C-12a), 46.0 (C-4′), 48.2 (C-8′), 50.9 (C-6), 54.7 (C-12), 55.6 (C-2′), 109.9 (C-4), 110.4 (C-9), 118.9 (C-12b), 119.3 (C-3′), 119.8 (C-11), 121.9 (C-11a), 125.8 (C-3), 126.0 (C-1), 128.4 (C-7a), 128.6 (C-10), 134.6 (C-2), 150.9 (C-4a), 157.0 (C-8), 164.7 (C-4). IR: (KBr) ν: 2918, 2850, 1634, 1600, 1574, 1529, 1489, 1465, 1432, 1399, 1359, 1337, 1318, 1299, 1291, 1259, 1220, 1180, 1152, 11 285, 1107. HRMS: calcd for $C_{25}H_{27}N_4O_4$ $[M + H]^+$ 447.2032, found 447.2036.

***rac*-(4*R**,4a*S**,10b*S**)- and *rac*-(4*R**,4a*S**,10b*R**)-4-(2-Methoxyphenyl)-6-methyl-9-nitro-2-phenyl-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinoline-1-carbonitrile [*rac*-(4*R**,4a*S**,10b*S**)-2ai and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-2ai].** The reaction of **1a** with **7i** was carried out according to method C and the product precipitate during the reaction. The crystals were filtered and washed with 5 ml of cold ethanol, affording the mixture of *rac*-(4*R**,4a*S**,10b*S**)-**2ai** and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-**2ai** as orange powder (94%). R_f = 0.24 (hexane/acetone 3 : 1). The diastereomeric ratio was ~6 : 5 according to ^{1}H-NMR integrals.

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.73–2.78 (m, 1H, 4a-H), 2.86 (dd, J = 11.6, 5.5 Hz, 1H, 5-H$_a$), 2.95 and 3.00 (s, 3H, 3′-H), 3.12 (dd, J = 13.1, 6.8 Hz, 1H, 5-H$_a$), 3.39–3.44 (m, 1H, 5-H$_b$), 3.69 (dd, J = 13.2, 4.4 Hz, 1H, 5-H$_b$), 3.79 (s, 3H, 2′-H), 3.83 (d, J = 5.2 Hz, 1H, 10b-H from *epi*-**2ai**), 3.87 (s, 3H, 2′-H), 3.93 (d, J = 9.0 Hz, 1H, 10b-H from **2ai**), 5.56 (d, J = 6.2 Hz, 1H, 4-H from *epi*-**2ai**), 5.64 (bs, 1H, 4-H from **2ai**), 6.74–6.79 (m, 2H, 7-H), 6.99 (t, J = 7.4 Hz, 1H, 5‴-H), 7.07 (t, J = 7.5 Hz, 1H, 5‴-H), 7.12 (dd, J = 12.5, 8.4 Hz, 2H, 3‴-H), 7.32 (d, J = 7.4 Hz, 1H, 6‴-H), 7.38–7.46 (m, 3H, 2× 4‴-H, 6‴-H), 7.48–7.60 (m, 5H, 2× 3″-H, 5″-H,

2× 4″-H), 7.72–7.77 (m, 4H, 2× 2″-H, 2× 6″-H), 8.02 (dd, J = 9.3, 2.7 Hz, 1H, 8-H), 8.08 (dd, J = 9.2, 2.6 Hz, 1H, 8-H), 8.21 (d, J = 2.7 Hz, 1H, 10-H), 8.53 (dd, J = 2.6, 1.1 Hz, 1H, 10-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 31.6 (C-4a), 32.6 and 37.2 (C-10b), 38.1 and 38.8 (C-3′), 49.4 and 51.6 (C-5), 55.7 and 55.8 (C-2′), 74.3 (C-4), 83.1 and 85.7 (C-1), 110.0 and 110.1 (C-7), 111.3 and 111.6 (C-3‴), 119.2 and 120.0 (C-10a), 120.4 (C-1′), 120.8 and 120.8 (C-5‴), 123.1 (C-10a), 124.9 and 125.2 (C-8), 125.4 (C-1‴), 125.8 (C-10), 126.6 (C-6‴), 128.0 (C-2″, C-6″), 128.5 and 128.6 (C-3″, C-5″), 128.8 (C-2″, C-6″), 130.0 (C-4‴), 130.5(C-6‴), 131.0 and 131.5 (C-4″), 132.6 and 132.8 (C-1″), 135.4 and 135.7 (C-9), 149.6 and 151.8 (C-6a), 156.0 and 169.4 (C-2). IR (KBr) ν: 2916, 2842, 2310, 2205, 1605, 1493, 1313, 1282. HRMS: calcd for $C_{27}H_{23}N_3O_4Na$ $[M + Na]^+$ 476.1586, found 476.1581.

***rac*-(4*R**,4a*S**,10b*S**)- and *rac*-(4*R**,4a*S**,10b*R**)-6-Methyl-9-nitro-2,4-diphenyl-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*] quinoline-1-carbonitrile [*rac*-(4*R**,4a*S**,10b*S**)-2bi and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-2bi].** The reaction of **1b** with **7i** was carried out according to method C and the product precipitate during the reaction. The crystals were filtered and washed with 5 ml of cold ethanol, affording the mixture of *rac*-(4*R**,4a*S**,10b*S**)-**2bi** and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-**2bi** as orange powder (77%), R_f = 0.42 (hexane/acetone 3 : 1). The diastereomeric ratio was ∼3 : 1 according to ^{1}H-NMR integrals.

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.38–2.47 (m, 1H, 4a-H), 2.69 (dd, J = 11.6, 5.6 Hz, 1H, 5-H$_b$), 2.75–2.81 (m, 1H, 4a-H), 2.91 and 3.02 (s, 3H, 2‴-H), 3.06–3.14 (m, 1H, 5-H$_a$), 3.40 (t, J = 11.6 Hz, 1H, 5-H$_b$), 3.66 (dd, J = 12.9, 3.7 Hz, 1H, 5-H$_b$), 3.81 (d, J = 4.2 Hz, 1H, 10b-H from *epi*-**2bi**), 3.84 (d, J = 11.0 Hz, 1H, 10b-H from **2bi**), 5.29 (d, J = 10.0 Hz, 1H, 4-H from **2bi**), 5.39 (bd, J = 5.3 Hz, 1H, 4-H from *epi*-**2bi**), 6.73 (d, J = 9.2 Hz, 1H, 7-H), 6.77 (d, J = 9.4 Hz, 1H, 7-H), 7.38–7.48 (m, 5H, Ph), 7.48–7.60 (m, 9H, Ph, 2× 3″-H, 4″-H, 5″-H), 7.73–7.82 (m, 2H, 2″-H, 6″-H), 8.02 (dd, J = 9.4, 2.3 Hz, 1H, 8-H), 8.07 (dd, J = 9.2, 2.2 Hz, 1H, 8-H), 8.24 and 8.56 (bs, 1H, 10-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 32.3 (C-10b) 32.5 (C-4a), 37.2 (C-10b), 38.0 and 38.9 (C-2‴), 39.5 (C-4a), 49.4 and 51.8 (C-5), 78.5 and 81.4 (C-4), 83.1 and 86.1 (C-1), 110.0 and 110.3 (C-7), 119.2 (C-10), 119.9 and 120.3 (C-1‴), 123.0 (C-10a), 124.9 and 125.0 (C-8), 126.0 (C-10), 127.6 (C-2″, C-6″), 128.0 (C-4″), 128.5 (C-3″, C-5″), 128.6 (C-2″, C-6″), 128.8 (C-3″, C-5″), 129.3 (C-4″), 131.0 and 131.6 (C-4′), 132.5 and 132.8 (C-1′), 135.6 and 135.7 (C-1″), 136.2 and 138.0 (C-9), 149.8 and 151.8 (C-6a), 169.3 (C-2). IR (KBr) ν: 2895, 2310, 2198, 1605, 1520, 1491, 1317, 1284. HRMS: calcd for $C_{26}H_{21}N_3O_3Na$ $[M + Na]^+$ 446.1481, found 446.1475.

***rac*-(4*R**,4a*S**,10b*S**)- and *rac*-(4*R**,4a*S**,10b*R**)-6-Methyl-9-nitro-4-(2-nitrophenyl)-2-phenyl-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinoline-1-carbonitrile [*rac*-(4*R**,4a*S**,10b*S**)-2ci and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-2ci].** The reaction of **1c** with **7i** was carried out according to method C and the product precipitate during the reaction. The crystals were filtered and washed with 5 ml of cold ethanol, affording the mixture of *rac*-(4*R**,4a*S**,10b*S**)-**2ci** and *rac*-(4*R**,4a*S**,10b*R**)-*epi*-**2ci** as orange powder (70%). R_f = 0.30 (hexane/acetone 3 : 1). The diastereomeric ratio was ∼4 : 1 according to ^{1}H-NMR integrals.

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.66–2.75 (m, 1H, 4a-H), 2.91 (dd, J = 11.8, 5.3 Hz, 1H, 5-H$_b$), 2.96 and 3.02 (s, 3H, 2′-H), 3.19–3.27 (m, 1H, 5-H$_b$), 3.58 (t, J = 11.8 Hz, 1H, 5-H$_a$), 3.70 (dd, J = 13.2, 4.5 Hz, 1H, 5-H$_a$), 3.94 (bd, J = 4.1 Hz, 1H, 10b-H from *epi*-**2ci**), 4.00 (d, J = 10.9 Hz, 1H, 10b-H from **2ci**), 5.78 (d, J = 10.0 Hz, 1H, 4-H from **2ci**), 5.91 (bd, J = 3.2 Hz, 1H, 4-H from *epi*-**2ci**), 6.72–6.83 (m, 2H, 2× 7-H), 7.49–7.61 (m, 3H, 2″-H, 4‴-H, 6″-H), 7.67–7.77 (m, 3H, 2× 5‴-H, 6‴-H), 7.77–7.83 (m, 3H, 3″-H, 2× 5″-H), 7.87–7.92 (m, 3H, 3‴-H, 2× 4″-H), 8.01–8.07 (m, 1H, 3‴-H), 8.09 (dd, J = 9.2, 2.4 Hz, 1H, 8-H), 8.14 (d, J = 8.0 Hz, 1H, 8-H), 8.19–8.22 and 8.53–8.57 (m, 1H, 10-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 32.1 and 37.2 (C-10b), 38.1 and 38.7 (C-2′), 39.4 (C-4a), 49.3 and 51.4 (C-5), 75.0 and 75.8 (C-4), 83.8 and 86.5 (C-1), 110.1 and 110.2 (C-7), 119.3 and 119.3 (C-10), 120.1 (C-1′), 122.7 (C-10a), 124.4 (C-3‴), 125.0 and 125.3 (C-8), 128.0 (C-3″, C-5″), 128.5 and 128.6 (C-2″, C-6″), 128.9 (C-3″, C-5″), 129.8 (C-1″), 129.9 (C-4″), 130.1 (C-4″), 130.7 (C-3‴), 131.1 and 131.7 (C-4‴), 132.3 and 132.5 (C-1‴), 133.8 and 134.4 (C-5‴), 135.5 and 135.6 (C-9), 149.4 and 149.7 (C-2‴), 151.6 (C-6a), 168.9 (C-2). IR (KBr) ν: 2912, 2364, 2321, 2207, 1605, 1524, 1314, 1284. HRMS: calcd for $C_{26}H_{20}N_4O_5Na$ $[M + Na]^+$ 491.1331, found 491.1326.

***rac*-(4*R**,4a*S**,10b*S**)-2-Amino-4-(2-methoxyphenyl)-6-methyl-9-nitro-4a,5,6,10b-tetrahydro-4*H*-thiopyrano[3,4-*c*] quinoline-1-carbonitrile [*rac*-(4*R**,4a*S**,10b*S**)-4aj].** The reaction of **1a** with **7j** was carried out according to method C. The crude product was concentrated *in vacuo* and purified by column chromatography (hexane/chloroform/acetone 10 : 5 : 1) affording *rac*-(4*R**,4a*S**,10b*S**)-**4aj** as yellow amorphous solid (98%), which decomposed above 250 °C. R_f = 0.11 (hexane/chloroform/acetone 5 : 5 : 1).

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.51–2.58 (m, 1H, 4a-H), 2.88 (s, 3H, 4′-H), 2.93 (dd, J = 11.7, 5.4 Hz, 1H, 5-H$_b$), 3.11–3.19 (m, 1H, 5-H$_a$), 3.64 (d, J = 11.0 Hz, 1H, 10b-H), 3.84 (s, 3H, 3′-H), 4.75 (d, J = 10.6 Hz, 1H, 4-H), 6.64–6.71 (m, 3H, 2′-H, 7-H), 6.94–7.00 (m, 1H, 5″-H), 7.08 (d, J = 7.7 Hz, 1H, 3″-H), 7.29–7.36 (m, 1H, 4″-H), 7.41 (dd, J = 7.6, 1.6 Hz, 1H, 6″-H), 8.01 (dd, J = 9.1, 2.6 Hz, 1H, 8-H), 8.19 (dd, J = 2.6, 1.2 Hz, 1H, 10-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 37.6 (C-4′), 40.4 (C-10b), 41.0 (C-4), 41.8 (C-4a), 54.0 (C-5), 55.7 (C-3′), 68.1 (C-1), 109.5 (C-7), 111.7 (C-3′), 119.9 (C-10), 120.4 (C-1′), 120.9 (C-5″), 123.4 (C-1″), 124.3 (C-8), 125.5 (C-10a), 128.7 (C-6″), 129.5 (C-4″), 135.8 (C-9), 151.5 (C-6a), 157.0 (C-2″), 160.0 (C-2). IR: (KBr) ν: 3734, 3440, 3005, 2989, 1601, 1560, 1524, 1491, 1462, 1452, 1436, 1418, 1362, 1313, 1275, 1260, 1217, 1194, 1159. HRMS: calcd for $C_{21}H_{21}N_4O_3S$ $[M + H]^+$ 409.1334, found 409.1330.

***rac*-(4*R**,4a*S**,10b*S**)-Ethyl 4-(2-methoxyphenyl)-2,6-dimethyl-9-nitro-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*] quinoline-1-carboxylate [*rac*-(4*R**,4a*S**,10b*S**)-2ak].** The reaction of **1a** with **7k** was carried out according to method D. The precipitate was filtered and washed with 5 ml of cold ethanol, affording *rac*-(4*R**,4a*S**,10b*S**)-**2ak** as yellow powder (45%), mp 252–255 °C, R_f = 0.91 (hexane/ethyl acetate 2 : 1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 3H, 4′), 2.13 (bs, 1H, 4a-H), 2.39 (s, 3H, 5′-H), 2.76 (dd, J = 11.2, 5.8 Hz, 1H, 5-H$_b$), 2.92 (s, 3H, 7′-H), 3.39 (t, J = 11.2 Hz, 1H, 5-H$_a$), 3.73 (d, J = 12.0 Hz, 1H, 10b-H), 3.86 (s, 3H, 6′-H), 4.15–4.37 (m, 2H, 3′-H), 5.29 (bs, 1H, 4-H), 6.48 (d, J = 9.1 Hz, 1H, 7-H), 6.94 (d, J = 8.4 Hz, 1H, 3″-H), 7.01 (t, J = 7.4 Hz, 1H, 5″-H), 7.33 (t, J =

7.1 Hz, 2H, 6″-H, 4″-H), 7.63–7.70 (m, 1H, 10-H), 8.02 (dd, J = 9.1, 2.4 Hz, 1H, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.4 (C-4′), 20.4 (C-5′), 38.1 (C-7′), 38.8 (C-10b), 43.5 (C-4a), 52.7 (C-5), 55.7 (C-6′), 60.4 (C-3′), 71.4 (C-4), 102.4 (C-1), 109.4 (C-7), 110.9 (C-3″), 120.4 (C-10), 121.4 (C-5″), 124.4 (C-8), 126.7 (C-1″), 127.0 (C-6″), 129.9 (C-4″), 137.3 (C-9), 152.0 (C-6a), 167.2 (C-2), 168.3 (C-1′). IR (KBr) ν: 2925, 2852, 2370, 2318, 1702, 1616, 1513, 1490. HRMS: calcd for $C_{24}H_{26}N_2O_6Na$ $[M + Na]^+$ 461.1689, found 461.1683.

***rac*-(4*R**,4a*S**,10b*S**)-Ethyl 2,6-dimethyl-9-nitro-4-phenyl-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinoline-1-carboxylate [*rac*-(4*R**,4a*S**,10b*S**)-2bk].** The reaction of **1b** with **7k** was carried out according to method D. The precipitate was filtered and washed with 5 ml of cold ethanol, affording *rac*-(4*R**,4a*S**,10b*S**)-**2bk** as yellow powder (70%), mp 239–241 °C, R_f = 0.47 (hexane/acetone 3 : 1).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3H, 4′-H), 2.11–2.23 (m, 1H, 4a-H), 2.40 (s, 3H, 5′-H), 2.68 (dd, J = 11.6, 5.9 Hz, 1H, 5-H_b), 2.91 (s, 3H, 6′-H), 3.25 (t, J = 11.6 Hz, 1H, 5-H_a), 3.70 (d, J = 11.2 Hz, 1H, 10b-H), 4.15–4.35 (m, 2H, 3′-H), 4.65 (d, J = 10.2 Hz, 1H, 4-H), 6.50 (d, J = 9.0 Hz, 1H, 7-H), 7.29–7.36 (m, 2H, 2″-H, 6″-H), 7.36–7.47 (m, 3H, 3″-H, 4″-H, 5″-H), 7.63–7.71 (m, 1H, 10-H), 8.02 (dd, J = 9.0, 2.5 Hz, 1H, 8-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.4 (C-4′), 20.2 (C-5′), 38.1 (C-6′), 38.7 (C-10b), 42.9 (C-4a), 53.4 (C-5), 60.5 (C-3′), 80.7 (C-4), 102.6 (C-1), 109.5 (C-7), 120.4 (C-10), 124.4 (C-8), 126.7 (C-10a), 126.9 (C-2″, C-6″), 129.1 (C-3″, C-5″), 129.3 (C-4″), 137.3 (C-1″), 137.6 (C-9), 151.9 (C-6a), 166.6 (C-2), 168.1 (C-1′). IR (KBr) ν: 2977, 2911, 2318, 1700, 1613, 1515, 1490, 1316, 1281. HRMS: calcd for $C_{23}H_{24}N_2O_5Na$ $[M + Na]^+$ 431.1583, found 431.1582.

***rac*-(4*R**,4a*S**,10b*S**)-2-Ethoxy-6-methyl-1,9-dinitro-4-phenyl-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinoline [*rac*-(4*R**,4a*S**, 10b*S**)-2bl].** The reaction of **1b** with **7l** was carried out according to method D. The precipitate was filtered and washed with 2 ml of cold ethanol affording *rac*-(4*R**,4a*S**,10b*S**)-**2bl** as yellow powder (7%), which decomposes above 240 °C. R_f = 0.25 (hexane/acetone 3 : 1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.1 Hz, 3H, 3′-H), 2.48–2.65 (m, 1H, 4a-H), 2.88 (dd, J = 11.3, 5.9 Hz, 1H, 5-H_b), 2.96 (s, 3H, 4′-H), 3.35 (t, J = 11.3 Hz, 1H, 5-H_a), 4.13 (d, J = 11.2 Hz, 1H, 10b-H), 4.36–4.56 (m, 2H, 2′-H), 5.29 (d, J = 10.1 Hz, 1H, 4-H), 6.58 (d, J = 9.1 Hz, 1H, 7-H), 7.30–7.39 (m, 2H, 2″-H, 6″-H), 7.39–7.51 (m, 3H, 3″-H, 4″-H, 5″-H), 7.73 (dd, J = 2.6, 1.1 Hz, 1H, 10-H), 8.08 (dd, J = 9.1, 2.6 Hz, 1H, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.2 (C-3′), 38.2 (C-4′), 40.7 (C-4a), 40.9 (C-10b), 52.2 (C-5), 63.2 (C-2′), 85.2 (C-4), 110.3 (C-7), 113.6 (C-1), 119.9 (C-4), 122.8 (C-10a), 125.3 (C-6), 127.5 (C-2″, C-6″), 129.4 (C-3″, C-5″), 130.5 (C-4″), 133.1 (C-1″), 137.7 (C-9), 151.0 (C-6a), 161.6 (C-2). IR (KBr) ν: 2929, 1730, 1606, 1305, 1284. HRMS: calcd for $C_{21}H_{21}N_3O_6Na$ $[M + Na]^+$ 434.1328, found 434.1323.

***rac*-(4*R**,4a*S**,10b*R**)-2-Methoxy-4-(2-methoxyphenyl)-6-methyl-9-nitro-1-(phenylsulfonyl)-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinolone [*rac*-(4*R**,4a*S**,10b*R**)-*epi*-2am].** The reaction of **1a** with **7m** was carried out according to method C, and the product precipitated during the reaction. The crystals were filtered and washed with 5 ml of cold ethanol, affording *rac*-(4*R**,4a*S**,10b*R**)-*epi*-**2am** as yellow powder (35%), mp 211–213 °C, R_f = 0.38 (hexane/chloroform 1 : 3).

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.57 (s, 1H, 4a-H), 2.69 (d, J = 13.3 Hz, 1H, 5-H_b), 2.95 (s, 3H 3″-H), 3.45 (s, 3H, 1″-H), 3.57 (s, 3H, 2″-H), 3.85 (dd, J = 13.3, 4.4 Hz, 1H, 5-H_a), 4.39 (d, J = 3.4 Hz, 1H, 10b-H), 5.21 (bs, 1H, 4-H), 6.72 (d, J = 9.3 Hz, 1H, 7-H), 6.98 (t, J = 7.3 Hz, 1H, 5‴-H), 7.04 (d, J = 7.3 Hz, 1H, 6‴-H), 7.28 (d, J = 7.3 Hz, 1H, 3‴-H), 7.36–7.45 (m, 1H, 4‴-H), 7.60–7.74 (m, 3H, 3′-H, 4′-H, 5′-H), 7.93–8.06 (m, 3H, 2′-H, 6′-H, 8-H), 8.24 (bs, 1H, 10-H). ^{13}C-NMR (90 MHz, DMSO-d_6) δ 34.5 (C-4a), 35.2 (C-10b), 38.7 (C-3″), 50.0 (C-5), 54.9 (C-2″), 55.3 (C-1″), 91.6 (C-1), 109.6 (C-7), 111.5 (C-6‴), 120.7 (C-5‴), 122.5 (C-1‴), 124.0 (C-10a), 124.8 (C-8), 126.2 (C-10), 126.7 (C-2′, C-6′), 128.8 (C-3′, C-3‴, C-5′), 130.6 (C-4‴), 132.4 (C-4″), 135.9 (C-9), 144.2 (C-1′), 149.5 (C-6a), 156.9 (C-2‴), 161.1 (C-2). IR (KBr) ν: 2952, 2833, 1605, 1493, 1327, 1304, 1281. HRMS: calcd for $C_{27}H_{26}N_2O_7SNa$ $[M + Na]^+$ 545.1358, found 545.1353.

***rac*-(4*R**,4a*S**,10b*R**)-2-Methoxy-6-methyl-9-nitro-4-phenyl-1-(phenylsulfonyl)-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinoline [*rac*-(4*R**,4a*S**,10b*R**)-*epi*-2bm].** The reaction of **1b** with **7m** was carried out according to method C, and the product precipitated during the reaction. The crystals were filtered and washed with 5 ml of cold ethanol, affording *rac*-[4*R**,4a*S**,10b*R**]-*epi*-**2bm** as yellow powder (36%). Mp 218–219 °C, R_f = 0.38 (hexane/acetone 3 : 1).

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.43–2.48 (m, 1H, 4a-H), 2.63 (d, J = 12.9 Hz, 1H, 5-H_b), 2.94 (s, 3H, 2‴-H), 3.49 (s, 3H, 1‴-H), 3.82 (dd, J = 12.9, 3.5 Hz, 1H, 5-H_a), 4.43 (d, J = 3.5 Hz, 1H, 10b-H), 4.95 (d, J = 11.0 Hz, 1H, 4-H), 6.75 (d, J = 9.3 Hz, 1H, 7-H), 7.28–7.36 (m, 2H, 2″-H, 3″-H), 7.42 (bs, 3H, 3″-H, 4″-H, 5″-H), 7.62 (t, J = 7.4 Hz, 2H, 3′-H, 5′-H), 7.65–7.73 (m, 1H, 4′-H), 7.94–8.05 (m, 3H, 2′-H, 6′-H, 8-H), 8.35 (bs, 1H, 10-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 35.3 (C-10b), 35.6 (C-4a), 40.2 (C-2‴), 50.0 (C-5), 55.1 (C-1‴), 81.4 (C-4), 92.1 (C-1), 110.2 (C-7), 122.9 (C-10a), 124.6 (C-8), 126.7 (C-10), 126.9 (C-2′, C-6′), 127.3 (C-2″, C-6″), 128.8 (C-3″, C-4″, C-5″), 129.3 (C-3′, C-5′), 132.4 (C-4′), 136.3 (C-9), 136.3 (C-1‴), 144.0 (C-1′), 149.5 (C-6a), 161.0 (C-2). IR (KBr) ν: 2949, 2863, 2318, 1603, 1330, 1304, 1287. HRMS: calcd for $C_{26}H_{24}N_2NaO6_S$ $[M + Na]^+$ 515.1253, found 515.1247.

***rac*-1-{(4*R**,4a*S**,10b*S**)-2-[(4-Chlorophenyl)amino]-4-(2-methoxyphenyl)-6-methyl-9-nitro-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinolin-1-yl}ethanone [*rac*-(4*R**,4a*S**,10b*S**)-2an] and *rac*-(4*R**,4a*S**,10b*R**)-*N*-(4-chlorophenyl)-4-(2-methoxyphenyl)-2,6-dimethyl-9-nitro-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinoline-1-carboxamide [*rac*-(4*R**,4a*S**,10b*R**)-reg-2an].** The reaction of **1a** with **7n** was carried out according to method D and the product precipitate during the reaction. The crystals were filtered and washed with 5 ml of cold ethanol. The filtrate was concentrated *in vacuo* and purified by column chromatography (hexane/acetone 3 : 1). Unifying the product from crystallization and chromatography afforded the mixture of *rac*-(4*R**,4a*S**,10b*S**)-**2an** and *rac*-(4*R**,4a*S**,10b*R**)-*reg*-**2an** as yellow powder (37%). R_f = 0.26 (hexane/acetone 3 : 1). The regioisomer ratio was ~10 : 7 according to the ^{1}H-NMR integrals.

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.11 and 2.24 (s, 3H, 2′-H), 2.27–2.35 (m, 1H, 4a-H), 2.74 (d, J = 13.0 Hz, 2H, 2× 5-H_b), 2.78–2.84 (m, 2H, 5-H_a, 4a-H), 2.91 and 2.96 (s, 3H, 5′-H), 3.72 (s, 3H, 4′-H), 3.79–3.90 (m, 4H, 5-H_a, 4′-H), 4.06 (d, J = 9.5 Hz, 1H, 10b-

H from **2an**), 4.22 (d, J = 3.1 Hz, 1H, 10b-H from *reg*-**2an**), 5.27 (bd, J = 10.9 Hz, 2H, 2× 4-H), 6.66 and 6.74 (d, J = 9.3 Hz, 1H, 7-H), 6.98–7.07 and 7.06–7.14 (m, 2H, 3‴-H, 5‴-H), 7.20–7.26 (m, 4H, 2″-H, 3″-H, 5″-H, 6″-H), 7.34–7.43 (m, 5H, 2″-H, 3″-H, 4‴-H, 5″-H, 6″-H), 7.63 (d, J = 8.8 Hz, 2H, 2× 6‴-H), 7.69–7.75 (m, 1H, 10-H), 7.95 (dd, J = 9.3, 2.5 Hz, 1H, 8-H), 8.00–8.05 (m, 2H, 8-H, 10-H), 10.07 (s, 1H, 2′-H), 13.80 (s, 1H, 3′-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 18.5 (C-3′), 26.0 (C-2′), 33.9 (C-10b), 35.0 (C-4a), 37.9 (C-5′), 38.4 (C-10b), 38.5 (C-5′), 50.2 and 52.2 (C-5), 55.6 and 55.7 (C-4′), 89.4 and 106.5 (C-1), 109.3 and 109.8 (C-7), 111.3 (C-3‴), 119.4 (C-10), 120.9 (C-5‴), 121.5 (C-6‴), 122.4 (C-10a), 122.8 (C-2″, C-3″, C-5″, C-6″), 124.3 (C-8), 124.4 (C-1‴), 124.7 (C-8), 125.0 (C-10), 125.1 (C-10a), 127.0 (C-4″), 127.6 (C-1‴), 128.5 (C-3″, C-5″), 128.9 (C-2″, C-6″), 130.0 and 130.4 (C-4‴), 135.6 and 135.7 (C-9), 136.2 and 137.9 (C-1″), 149.9 and 152.0 (C-6a), 156.9 and 158.3 (C-2‴), 161.0 and 167.6 (C-2), 193.1 (C-2″). IR (KBr) ν: 2916, 2310, 1601, 1492, 1315. HRMS: calcd for $C_{28}H_{26}ClN_3O_5Na$ $[M + Na]^+$ 542.1459, found 542.1453.

***rac*-1-{(4*R**,4a*S**,10b*S**)-2-[(4-Chlorophenyl)amino]-6-methyl-9-nitro-4-phenyl-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinolin-1-yl}ethanone [*rac*-(4*R**,4a*S**,10b*S**)-2bn] and *rac*-(4*R**,4a*S**,10b*R**)-*N*-(4-chlorophenyl)-2,6-dimethyl-9-nitro-4-phenyl-4a,5,6,10b-tetrahydro-4*H*-pyrano[3,4-*c*]quinoline-1-carboxamide [*rac*-(4*R**, 4a*S**,10b*R**)-reg-2bn].** The reaction of **1b** with **7n** was carried out according to method D and the product precipitate during the reaction. The crystals were filtered and washed with 5 ml of cold ethanol. The filtrate was concentrated *in vacuo* and purified by column chromatography (hexane/acetone 3 : 1). Unifying the product from crystallization and chromatography afforded the mixture of *rac*-(4*R**,4a*S**,10b*S**)-**2bn** and *rac*-(4*R**,4a*S**,10b*R**)-*reg*-**2bn** as yellow powder (67%). R_f = 0.40 (hexane/acetone 3 : 1). The regioisomer ratio was ~10 : 7 according to the ^{1}H-NMR integrals.

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.14 (s, 3H, 2′-H), 2.20–2.28 (m, 4H, 2× 3′-H, 2× 4a-H), 2.63–2.71 (m, 3H, 4a-H, 2× 5-H$_b$), 2.88 and 2.97 (s, 3H, 4′-H), 3.33–3.38 (m, 1H, 5-H$_a$), 3.79 (dd, J = 13.4, 4.3 Hz, 1H, 5-H$_a$), 4.03 (d, J = 11.0 Hz, 1H, 10b-H from **2bn**), 4.26 (d, J = 3.4 Hz, 1H, 10b-H from *reg*-**2bn**), 4.86 (d, J = 10.1 Hz, 1H, 4-H from **2bn**), 4.93 (d, J = 11.4 Hz, 1H, 4-H from *reg*-**2bn**), 6.64 (d, J = 9.2 Hz, 1H, 7-H), 6.75 (d, J = 9.3 Hz, 1H, 7-H), 7.22 (s, 3H, 2× 3″-H, 5″-H), 7.36 (d, J = 8.8 Hz, 3H, 3″-H, 2× 5″-H), 7.37–7.47 (m, 12H, 2× Ph-H, 2″-H, 6″-H), 7.65 (d, J = 8.8 Hz, 2H, 2‴-H, 6‴-H), 7.73–7.76 (m, 1H, 10-H), 7.94 (dd, J = 9.1, 2.5 Hz, 1H, 8-H), 7.99–8.04 (m, 2H, 10-H, 8-H), 10.14 (s, 1H, 2′-H), 13.82 (s, 1H, 3′-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 18.7 (C-2′), 26.0 (C-3′), 34.0 (C-10b), 35.3 (C-4a), 37.5 (C-10b), 37.8 and 38.7 (C-4′), 40.6 (C-4a), 50.3 and 52.5 (C-5), 79.4 and 80.1 (C-4), 89.6 and 106.6 (C-1), 109.8 and 109.9 (C-7), 119.4 (C-10), 121.8 (C-2″ and C-6″), 122.6 (C-10a), 122.9 (C-2‴ and C-6‴), 124.3 and 124.7 (C-8), 125.0 (C-10), 125.1 (C-10a), 127.1 (C-4″), 127.3 (C-3‴ and C-5‴), 127.7 (C-4″), 128.4 (C-3″, C-5″), 128.6 (C-3″, C-5″), 128.9 (C-2‴ and C-6‴ and C-4‴), 129.2 (C-4‴), 135.8 and 135.9 (C-9), 136.2 and 136.8 (C-1‴), 137.5 and 137.8 (C-1″), 150.0 and 152.1 (C-6a), 157.8 (C-1′), 160.8 and 167.4 (C-2), 193.3 (C-1′). IR (KBr) ν: 3032, 2911, 2310, 1617, 1602, 1494, 1316, 1282. HRMS: calcd for: $C_{27}H_{24}ClN_3O_4Na$ $[M + Na]^+$ 512.1353, found 512.1348.

***rac*-(1*R**,4*R**,4a*S**,10b*R**)- and *rac*-(1*S**,4*R**,4a*S**,10b*S**)-4-(2-Methoxyphenyl)-6-methyl-9-nitro-1-(piperidine-1-carbonyl)-4,4a,5,6-tetrahydro-1*H*-pyrano[3,4-*c*]quinolin-2(10b*H*)-one [*rac*-(1*R**,4*R**,4a*S**,10b*R**)-dia1-5a and *rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-5a].** The reaction of **1a** with **7o** and amine **10a** was carried out according to method B, and the crude product was purified by flash column chromatography (hexane/ethyl acetate 2 : 1) affording the mixture of *rac*-(1*R**,4*R**,4a*S**,10b*R**)-dia1-**5a** and *rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-**5a** as orange oil (65%). R_f = 0.49 (hexane/ethyl acetate 1 : 2). The diastereomeric ratio was ~4 : 5 according to ^{1}H-NMR integrals.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.39–1.67 (m, 4H, 5″-H, 4″-H), 2.05–2.15 (m, 4H, 5″-H, 3″-H), 2.17–2.24 (m, 1H, 4a-H), 2.41–2.51 (m, 1H, 4a-H), 2.93 (s, 3H, 3′-H), 3.08 (s, 3H, 3′-H), 3.17–3.26 (m, 2H, 6″-H), 3.36–3.47 (m, 2H, 6″-H), 3.52 (dd, J = 12.7, 10.1 Hz, 1H, 5-H$_b$), 3.61 (dd, J = 12.8, 5.8 Hz, 1H, 5-H$_a$), 3.63–3.69 (m, 1H, 5-H$_b$), 3.72–3.79 (m, 1H, 5-H$_a$), 3.82–3.87 (m, 6H, 2× 2′-H, 2″-H$_a$), 3.88 (d, J = 9.8 Hz, 1H, 1-H from dia2-**5a**), 3.92 (dd, J = 9.8, 5.2 Hz, 1H, 10b-H from dia2-**5a**), 3.96 (d, J = 10.5 Hz, 1H, 1-H from dia1-**5a**), 4.03 (dd, J = 11.5, 10.5 Hz, 1H, 10b-H from dia1-**5a**), 4.08–4.17 (m, 1H, 1-H), 5.74 (d, J = 10.5 Hz, 1H, 2″-H$_a$), 5.84 (d, J = 3.1 Hz, 1H, 4-H from dia2-**5a**), 6.44 (d, J = 10.4 Hz, 1H, 4-H from dia1-**5a**), 6.57 (d, J = 9.3 Hz, 1H, 7-H), 6.89 (d, J = 8.2 Hz, 1H, 7-H), 6.95 (d, J = 8.3 Hz, 1H, 3‴-H), 7.02 (t, J = 7.5 Hz, 1H, 3‴-H), 7.12 (t, J = 7.5 Hz, 1H, 5‴-H), 7.30–7.39 (m, 3H, 2× 4‴-H, 6‴-H), 7.54 (dd, J = 7.6, 1.6 Hz, 1H, 6‴-H), 7.72–7.76 (m, 1H, 10-H), 7.78 (d, J = 2.6 Hz, 1H, 10-H), 7.93–7.99 (m, 1H, 8-H), 8.01 (ddd, J = 9.2, 2.6, 1.1 Hz, 1H, 8-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 24.37 and 24.66 (C-5″), 25.59 (C-4″), 26.10 and 26.28 (C-3″), 33.93 (C-4a), 34.20 (C-10b), 37.41 (C-4a), 38.46 (C-10b), 38.98 and 39.27 (C-3′), 43.95 (C-4″), 46.83 (C-1), 47.00 (C-2″), 47.72 (C-2″), 48.01 (C-5), 50.37 and 51.61 (C-6″), 51.70 (C-1), 55.58 and 55.82 (C-2′), 77.67 and 78.86 (C-4), 109.31 and 109.54 (C-7), 110.41 and 111.31 (C-3‴), 121.20 and 121.25 (C-5‴), 121.35 (C-10a), 121.78 (C-10), 122.22 (C-10a), 124.62 (C-1‴), 124.86 (C-10), 125.23 and 125.56 (C-8), 126.18 (C-1‴), 127.69 and 128.29 (C-6‴), 129.77 and 130.65 (C-4‴), 137.04 and 137.09 (C-9), 149.55 and 150.31 (C-6a), 155.36 and 157.13 (C-2‴), 165.96 and 166.77 (C-1′), 166.84 and 167.08 (C-2). IR: (KBr) ν: 2925, 1721, 1637, 1601, 1578, 1520, 1492, 1437, 1312, 1275, 1261, 1240, 1183, 1164, 1107, 1084, 1024. HRMS: calcd for $C_{26}H_{30}N_3O_6$ $[M + H]^+$ 480.2134, found 480.2129.

***rac*-(1*R**,4*R**,4a*S**,10b*R**)-4-(2-Methoxyphenyl)-6-methyl-9-nitro-1-(pyrrolidine-1-carbonyl)-4,4a,5,6-tetrahydro-1*H*-pyrano[3,4-*c*]quinolin-2(10b*H*)-one [*rac*-(1*R**,4*R**,4a*S**,10b*R**)-dia1-5b].** The reaction of **1a** with **7o** and amine **10b** was carried out according to method B, and the crude product was purified by flash column chromatography (hexane/ethyl acetate 2 : 1) affording *rac*-(1*R**,4*R**,4a*S**,10b*R**)-dia1-**5b** as the minor product and orange oil (3%), R_f = 0.46 (hexane/ethyl acetate 1 : 2).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.00–2.26 (m, 4H, 3″-H, 4″-H), 2.39–2.51 (m, 1H, 4a-H), 2.89–3.00 (m, 4H, 5-H$_b$, 3′-H), 3.42 (t, J = 11.8 Hz, 1H, 5-H$_a$), 3.63–3.72 (m, 1H, 2″-H$_a$), 3.72–3.81 (m, 1H, 2″-H$_b$), 3.86 (s, 5H, 5″-H$_a$, 2′-H), 3.96 (d, J = 10.2 Hz, 1H, 1-H), 4.05 (dd, J = 11.8, 10.2 Hz, 1H, 10b-H), 4.09–4.19 (m, 1H, 5″-H$_b$),

5.76 (d, J = 10.5 Hz, 1H, 4-H), 6.46 (d, J = 9.2 Hz, 1H, 7-H), 6.96 (dd, J = 8.4, 1.1 Hz, 1H, 3‴-H), 6.98–7.08 (m, 1H, 5‴-H), 7.32–7.43 (m, 2H, 4‴-H and 6‴-H), 7.77 (dd, J = 2.6, 1.4 Hz, 1H, 10-H), 8.01 (dd, J = 9.2, 2.5 Hz, 1H, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.68 (C-4″), 26.13 (C-3″), 37.46 (C-4a), 38.50 (C-10b), 39.30 (C-3′), 47.03 (C-5″), 47.75 (C-2″), 51.64 (C-5), 51.72 (C-1), 55.84 (C-2′), 78.78 (C-4), 109.32 (C-7), 111.31 (C-3‴), 121.28 (C-5‴), 121.81 (C-10), 122.24 (C-10a), 124.63 (C-1‴), 125.28 (C-8), 128.31 (C-6‴), 130.67 (C-4‴), 137.15 (C-9), 150.30 (C-6a), 157.14 (C-2‴), 166.75 (C-1′), 166.85 (C-2). IR: (KBr) ν: 2988, 1715, 1642, 1603, 1580, 1520, 1492, 1463, 1437, 1275, 1260, 1022. HRMS: calcd for $C_{25}H_{28}N_3O_6$ [M + H]$^+$ 466.1978, found 466.1973.

***rac*-(1*S**,4*R**,4a*S**,10b*S**)-4-(2-Methoxyphenyl)-6-methyl-9-nitro-1-(pyrrolidine-1-carbonyl)-4,4a,5,6-tetrahydro-1*H*-pyrano[3,4-*c*]quinolin-2(10b*H*)-one [*rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-5b].** The reaction of **1a** with **7o** and amine **10b** was carried out according to method B, and the crude product was purified by flash column chromatography (hexane/ethyl acetate 2 : 1) affording *rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-**5b** as the major product and orange oil (18%), R_f = 0.46 (hexane/ethyl-acetate 1 : 2).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.61–1.78 (m, 2H, 4″-H), 1.80–1.91 (m, 2H, 3″-H), 2.61–2.73 (m, 3H, 2″-H, 4a-H), 3.10 (d, J = 2.9 Hz, 3H, 3′-H), 3.47–3.65 (m, 6H, 2″-H, 5″-H, 5-H), 3.65 (d, J = 10.0 Hz, 1H, 1-H), 3.84 (s, 3H, 2′-H), 3.86 (dd, J = 10.0, 4.5 Hz, 1H, 10b-H), 5.86 (d, J = 3.1 Hz, 1H, 4-H), 6.57 (d, J = 9.2 Hz, 1H, 7-H), 6.90 (dd, J = 8.3, 1.1 Hz, 1H, 3‴-H), 7.13 (ddd, J = 7.6, 6.8, 1.1 Hz, 1H, 5‴-H), 7.34 (td, J = 7.9, 1.7 Hz, 1H, 4‴-H), 7.58 (dd, J = 7.7, 1.7 Hz, 1H, 6‴-H), 7.74–7.80 (m, 1H, 10-H), 8.02 (dd, J = 9.2, 2.7 Hz, 1H, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.54 (C-4″), 25.95 (C-3″), 33.70 (C-4a), 34.19 (C-10b), 39.05 (C-3′), 46.44 (C-2″), 47.36 (C-5″), 49.82 (C-1), 50.35 (C-5), 55.60 (C-2′), 77.74 (C-4), 109.54 (C-7), 110.39 (C-3″), 121.17 (C-10a), 121.29 (C-5‴), 124.56 (C-10), 125.60 (C-8), 126.15 (C-1‴), 127.77 (C-6‴), 129.80 (C-4‴), 137.01 (C-9), 149.55 (C-6a), 155.33 (C-2‴), 166.20 (C-1′), 167.01 (C-2). IR: (KBr) ν: 2916, 1724, 1635, 1603, 1489, 1430, 1274, 1259, 1183, 1111, 1088. HRMS: calcd for $C_{25}H_{28}N_3O_6$ [M + H]$^+$ 466.1978, found 466.1974.

***rac*-(1*R**,4*R**,4a*S**,10b*R**)-4-(2-Methoxyphenyl)-6-methyl-1-(morpholine-4-carbonyl)-9-nitro-4,4a,5,6-tetrahydro-1*H*-pyrano[3,4-*c*]quinolin-2(10b*H*)-one [*rac*-(1*R**,4*R**,4a*S**,10b*R**)-dia1-5c].** The reaction of **1a** with **7o** and amine **10c** was carried out according to method B, and the crude product was purified by flash column chromatography (hexane/ethyl acetate 2 : 1) affording *rac*-(1*R**,4*R**,4a*S**,10b*R**)-dia1-**5c** as the major product and orange oil (16%), R_f = 0.51 (hexane/ethyl acetate 1 : 2).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.48 (ddt, J = 14.9, 10.9, 4.2 Hz, 1H, 4a-H), 2.91–2.99 (m, 4H, 3′-H, 5-H$_b$), 3.42 (t, J = 11.7 Hz, 1H, 5-H$_a$), 3.81–3.89 (m, 5H, 2′-H, 2″-H), 3.88–4.01 (m, 6H, 3″-H, 4″-H, 5″-H), 4.10 (dd, J = 11.7, 10.0 Hz, 1H, 10b-H), 4.15 (d, J = 10.0 Hz, 1H, 1-H), 5.73 (d, J = 10.3 Hz, 1H, 4-H), 6.46 (dd, J = 9.3, 1.4 Hz, 1H, 7-H), 6.97 (d, J = 8.3 Hz, 1H, 3‴-H), 7.03 (t, J = 7.5 Hz, 1H, 5‴-H), 7.33 (dd, J = 7.6, 1.7 Hz, 1H, 6‴-H), 7.35–7.42 (m, 1H, 4‴-H), 7.68–7.77 (m, 1H, 10-H), 7.92–8.06 (m, 1H, 8-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 37.41 (C-4a), 38.36 (C-10b), 39.29 (C-3′), 43.56 (C-6″), 47.69 (C-2″), 48.60 (C-1), 51.66 (C-5), 55.87 (C-2′), 66.62 (C-3″ and C-5″), 78.89 (C-4), 109.36 (C-7), 111.37 (C-3‴), 121.33 (C-5‴), 121.58 (C-10), 122.05 (C-10a), 124.48 (C-1‴), 125.40 (C-8), 128.29 (C-6‴), 130.77 (C-4‴), 137.10 (C-9), 150.33 (C-6a), 157.15 (C-2‴), 166.44 (C-1′), 166.92 (C-2). IR: (KBr) ν: 2989, 1717, 1633, 1601, 1577, 1523, 1491, 1459, 1275, 1260, 1112, 1046. HRMS: calcd for $C_{25}H_{28}N_3O_7$ [M + H]$^+$ 482.1927, found 482.1922.

***rac*-(1*S**,4*R**,4a*S**,10b*S**)-4-(2-Methoxyphenyl)-6-methyl-1-(morpholine-4-carbonyl)-9-nitro-4,4a,5,6-tetrahydro-1*H*-pyrano[3,4-*c*]quinolin-2(10b*H*)-one [*rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-5c].** The reaction of **1a** with **7o** and amine **10c** was carried out according to method B, and the crude product was purified by flash column chromatography (hexane/ethyl acetate 2 : 1) affording *rac*-(1*S**,4*R**,4a*S**,10b*S**)- dia2-**5c** as the minor product and orange oil (9%), R_f = 0.6 (hexane/ethyl acetate 1 : 2).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.69–2.76 (m, 1H, 4a-H), 3.10–3.16 (m, 4H, 6″-H$_b$, 3′-H), 3.19–3.25 (m, 1H, 5″-H$_b$), 3.43–3.70 (m, 4H, 5-H, 5″-H$_a$, 6″-H$_a$), 3.71–3.79 (m, 4H, 3″-H, 2″-H), 3.83 (d, J = 9.8 Hz, 1H, 1-H), 3.86 (s, 3H, 2′-H), 3.98 (dd, J = 9.8, 4.7 Hz, 1H, 10b-H), 5.88 (d, J = 3.0 Hz, 1H, 4-H), 6.60 (d, J = 9.2 Hz, 1H, 7-H), 6.93 (d, J = 8.1 Hz, 1H, 3‴-H), 7.09–7.18 (m, 1H, 5‴-H), 7.35–7.40 (m, 1H, 4‴-H), 7.46–7.56 (m, 1H, 6‴-H), 7.77–7.82 (m, 1H, 10-H), 8.04 (ddd, J = 9.2, 2.7, 0.7 Hz, 1H, 8-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 33.91 (C-4a), 33.99 (C-10b), 39.01 (C-3′), 43.18 (C-2″), 46.75 (C-1), 47.22 (C-6″), 50.40 (C-5), 55.64 (C-2′), 66.50 (C-5″), 66.83 (C-3″), 77.92 (C-4), 109.69 (C-7), 110.55 (C-3‴), 121.21 (C-10a), 121.26 (C-5‴), 124.84 (C-10), 125.69 (C-8), 126.03 (C-1‴), 127.54 (C-6‴), 129.94 (C-4‴), 137.22 (C-9), 149.53 (C-6a), 155.40 (C-2‴), 166.29 (C-1′), 166.85 (C-2). IR: (KBr) ν: 2919, 1722, 1643, 1602, 1579, 1523, 1493, 1463, 1437, 1320, 1293, 1268, 1240, 1185, 1169, 1109, 1084, 1009. HRMS: calcd for $C_{25}H_{28}N_3O_7$ [M + H]$^+$ 482.1927, found 482.1923.

***rac*-(1*S**,4*R**,4a*S**,10b*S**)-4-(2-Methoxyphenyl)-*N*,*N*,6-trimethyl-9-nitro-2-oxo-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline-1-carboxamide [*rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-5d].** The reaction of **1a** with **7o** and amine **10d** was carried out according to method B, and the crude product was purified by flash column chromatography (hexane/ethyl acetate 2 : 1) affording *rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-**5d** as orange oil (38%), R_f = 0.11 (hexane/ethyl acetate 1 : 1).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.67–2.75 (m, 1H, 4a-H), 2.79 (s, 3H, 4′-H), 3.04 (s, 3H, 3′-H), 3.11 (s, 3H, 6′-H), 3.51–3.60 (m, 1H, 5-H$_b$), 3.63 (dd, J = 12.6, 5.7 Hz, 1H, 5-H$_a$), 3.84 (s, 3H, 5′-H), 3.89 (bs, 2H, 1-H, 10b-H), 5.86 (d, J = 3.1 Hz, 1H, 4-H), 6.54–6.61 (m, 1H, 7-H), 6.87–6.96 (m, 1H, 3″-H), 7.12–7.18 (m, 1H, 5″-H), 7.33–7.44 (m, 1H, 4″-H), 7.54 (dd, J = 7.7, 1.8 Hz, 1H, 6″-H), 7.72–7.81 (m, 1H, 10-H), 7.98–8.11 (m, 1H, 8-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 33.77 (C-4a), 34.18 (C-10b), 36.32 (C-4′), 38.10 (C-3′), 38.97 (C-6′), 47.22 (C-1), 50.36 (C-5), 55.59 (C-5′), 77.76 (C-4), 109.54 (C-7), 110.44 (C-3″), 121.10 (C-10c), 121.24 (C-5″), 124.54 (C-10), 125.61 (C-8), 126.20 (C-1″), 127.62 (C-4″), 129.79 (C-6″), 137.11 (C-9), 149.55 (C-6a), 155.34 (C-1′), 166.99 (C-2″), 167.93 (C-2). IR: (KBr) ν: 2989, 1720, 1649, 1601, 1488, 1461, 1275, 1259, 1179, 1132, 1085. HRMS: calcd for $C_{23}H_{26}N_3O_6$ [M + H]$^+$ 440.1821, found 440.1816.

***rac*-(1*S**,4*R**,4a*S**,10b*S**)-*N*-Benzyl-4-(2-methoxyphenyl)-6-methyl-9-nitro-2-oxo-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline-1-carboxamide [*rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-5e].**

The reaction of **1a** with **7o** and amine **10e** was carried out according to method B, and the crude product was purified by flash column chromatography (hexane/ethyl acetate 2 : 1) affording *rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-**5e** as the minor product (orange oil, 4%), $R_f = 0.43$ (hexane/ethyl-acetate 1 : 1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83–2.89 (m, 1H, 4a-H), 3.08 (s, 3H, 5′-H), 3.33 (dd, $J = 12.8$, 7.6 Hz, 1H, 5-H_b), 3.62–3.68 (m, 1H, 5-H_a), 3.74 (d, $J = 6.7$ Hz, 1H, 1-H), 3.80 (s, 3H. 4′-H), 4.00–4.05 (m, 1H, 10b-H), 4.46–4.53 (m, 1H, 3″-H_b), 4.59–4.65 (m, 1H, 3″-H_a), 5.70 (d, $J = 5.9$ Hz, 1H, 4-H), 6.59 (d, $J = 9.2$ Hz, 1H, 7-H), 6.83–6.89 (m, 1H, 4‴-H), 6.91–6.96 (m, 1H, 3‴-H), 7.00–7.08 (m, 1H, 5‴-H), 7.22–7.26 (m, 1H, 6‴-H), 7.26–7.31 (m, 3H, 3″-H, 5″-H), 7.31–7.36 (m, 2H, 2″-H, 6″-H), 7.36–7.40 (m, 1H, 4‴-H), 7.97–8.03 (m, 1H, 10-H), 8.03–8.11 (m, 2H, 8-H, 2′-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 32.85 (C-4a), 32.98 (C-10b), 39.08 (C-5′), 44.47 (C-5), 50.63 (C-3′), 51.05 (C-1), 55.63 (C-4′), 78.54 (C-4), 109.59 (C-7), 111.00 (C-3‴), 120.26 (C-10a), 121.20 (C-5‴), 124.17 (C-4″), 125.60 (C-1‴), 125.67 (C-6‴), 127.87 (C-2″ and C-6″), 128.92 (C-1″), 130.13 (C-3″ and C-5″), 130.26 (C-4‴), 137.66 (C-9), 149.99 (C-6a), 156.10 (C-2‴), 165.27 (C-1′), 168.16 (C-2). IR: (KBr) ν: 2989, 1725, 1653, 1601, 1578, 1525, 1492, 1462, 1275, 1260, 1189, 1023. HRMS: calcd for $C_{28}H_{28}N_3O_6$ $[M + H]^+$ 502.1978, found 502.1977.

***rac*-(1*R**,4*R**,4a*S**,10b*R**)-*N*-Benzyl-4-(2-methoxyphenyl)-6-methyl-9-nitro-2-oxo-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*] quinoline-1-carboxamide [*rac*-(1*R**,4*R**,4a*S**,10b*R**)-dia1-5e].** The reaction of **1a** with **7o** and amine **10e** was carried out according to method B, and the crude product was purified by flash column chromatography (hexane/ethyl acetate 2 : 1) affording *rac*-(1*R**,4*R**,4a*S**,10b*R**)-dia1-**5e** as the major product (orange oil, 21%), $R_f = 0.18$ (hexane/ethyl acetate 2 : 1).

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.66 (dd, $J = 9.3$, 4.7 Hz, 1H, 4a-H), 3.07 (s, 3H, 5′-H), 3.40 (dd, $J = 13.2$, 9.3 Hz, 1H, 5-H_b), 3.62–3.70 (m, 2H, 10b-H, 5-H_b), 3.82 (s, 3H, 4′-H), 3.86 (d, $J = 9.3$ Hz, 1H, 1-H), 4.22 (dd, $J = 15.1$, 5.0 Hz, 1H, 3′-H_b), 4.45 (dd, $J = 15.1$, 5.0 Hz, 1H, 3′-H_a), 5.76 (d, $J = 4.0$ Hz, 1H, 4-H), 6.76 (d, $J = 9.3$ Hz, 1H, 7-H), 7.07–7.17 (m, 4H, 3‴-H, 5‴-H, 2″-H, 6″-H), 7.17–7.24 (m, 3H, 3″-H, 5″-H, 6‴-H), 7.33–7.42 (m, 2H, 4‴-H, 4″-H), 7.72 (d, $J = 2.7$ Hz, 1H, 10-H), 8.00 (dd, $J = 9.3$, 2.7 Hz, 1H, 8-H), 8.57 (t, $J = 5.8$ Hz, 1H, 2′-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 32.73 (C-4a), 33.32 (C-10b), 38.51 (C-5′), 42.32 (C-3′), 49.52 (C-5), 50.61 (C-1), 55.60 (C-4′), 76.36 (C-4), 109.87 (C-7), 111.18 (C-3‴), 120.03 (C-10a), 120.37 (C-5‴), 123.92 (C-10), 125.19 (C-8), 126.63 (C-1‴), 126.81 (C-4″), 127.05 (C-2″ and C-6″), 128.06 (C-3″ and C-5″), 129.61 (C-4‴), 135.24 (C-9), 138.41 (C-1″), 150.06 (C-6a), 155.46 (C-2‴), 166.82 (C-1′), 166.87 (C-2). IR: (KBr) ν: 2989, 1735, 1669, 1640, 1605, 1578, 1532, 1488, 1467, 1454, 1431, 1371, 1312, 1275, 1260, 1184, 1114, 1025. HRMS: calcd for $C_{28}H_{28}N_3O_6$ $[M + H]^+$ 502.1978, found 502.1976.

***rac*-(1*S**,4*R**,4a*S**,10b*S**)-4-(2-Methoxyphenyl)-*N*,6-dimethyl-9-nitro-2-oxo-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline-1-carboxamide [*rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-5f].** The reaction of **1a** with **7o** was carried out in the presence of amine **10f** according to method B, which was formed *in situ* in the reaction of 24 mg (1.2 equivalent) methylamine hydrochloride and 51 mg K_2CO_3 (1.2 equivalent). The crude product was purified by flash column chromatography (hexane/ethyl acetate 2 : 1) affording *rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-**5f** as orange oil (24%), $R_f = 0.19$ (hexane/ethyl acetate 1 : 1).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.62 (d, $J = 4.6$ Hz, 3H, 3′-H), 2.66 (dd, $J = 8.6$, 4.7 Hz, 1H, 4a-H), 3.04 (s, 3H, 4′-H), 3.32 (dd, $J = 13.3$, 8.6 Hz, 1H, 5-H_b), 3.58 (dd, $J = 8.4$, 4.6 Hz, 1H, 10b-H), 3.64 (dd, $J = 13.2$, 4.9 Hz, 1H, 5-H_a), 3.86–3.79 (m, 4H, 5′-H, 1-H), 5.72 (d, $J = 4.9$ Hz, 1H, 4-H), 6.74 (d, $J = 9.4$ Hz, 1H, 7-H), 7.04–7.10 (m, 2H, 3′-H, 5′-H), 7.37–7.43 (m, 2H, 4′-H, 6′-H), 7.70 (d, $J = 2.6$ Hz, 1H, 10-H), 7.97 (dd, $J = 9.2$, 2.6 Hz, 1H, 8-H), 8.11 (d, $J = 4.6$ Hz, 1H, 2′-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 33.0 (C-4a), 33.7 (C-4′), 36.8 (C-10b), 49.6 (C-5), 50.8 (C-3′), 53.0 (C-1), 55.6 (C-5′), 76.1 (C-4), 109.6 (C-3″), 109.7 (C-5″), 110.0 (C-7), 111.1 (C-10), 120.0 (C-10a), 120.5 (C-8), 125.4 (C-4″), 126.6 (C-1″), 127.2 (C-6″), 135.3 (C-9), 150.2 (C-6a), 155.6 (C-1′), 166.9 (C-2″), 167.7 (C-2). IR: (KBr) ν: 2990, 1716, 1650, 1599, 1484, 1460, 1279, 1242, 1182, 1137, 1080. HRMS: calcd for $C_{22}H_{24}N_3O_6$ $[M + H]^+$ 426.1665, found 426.1664.

***rac*-(1*S**,4*R**,4a*S**,10b*S**)-*N*-Allyl-4-(2-methoxyphenyl)-6-methyl-9-nitro-2-oxo-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*] quinoline-1-carboxamide [*rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-5g].** The reaction of **1a** with **7o** and amine **10g** was carried out according to method B, and the crude product was purified by flash column chromatography (hexane/ethyl acetate 2 : 1) affording *rac*-(1*S**,4*R**,4a*S**,10b*S**)-dia2-**5g** as orange oil (37%), $R_f = 0.12$ (hexane/ethyl acetate 2 : 1).

^{1}H-NMR (400 MHz, acetone-d_6) δ 2.77 (dt, $J = 9.4$, 4.3 Hz, 1H, 4a-H), 3.15 (s, 3H, 7′-H), 3.54 (dd, $J = 12.9$, 9.6 Hz, 1H, 5-H_b), 3.75 (dd, $J = 13.0$, 5.3 Hz, 1H, 5-H_a), 3.80 (d, $J = 2.6$ Hz, 2H, 3′-H_a), 3.84 (ddd, $J = 7.2$, 3.6, 1.4 Hz, 1H, 3′-H_b), 3.88 (s, 3H, 7′-H), 3.89 (dd, $J = 4.5$, 1.6 Hz, 1H, 10b-H), 4.94–5.01 (m, 1H, 1-H), 5.08–5.15 (m, 1H, 5′-H_b), 5.73–5.82 (m, 1H, 5′-H_a), 5.83 (d, $J = 3.9$ Hz, 1H, 4′-H), 6.76 (d, $J = 9.3$ Hz, 1H, 4-H), 7.03–7.13 (m, 1H, 7-H), 7.38 (td, $J = 8.1$, 1.7 Hz, 1H, 5″-H), 7.48 (dd, $J = 7.5$, 1.4 Hz, 1H, 3′-H), 7.79 (d, $J = 2.7$ Hz, 1H, 6″-H), 7.95–8.01 (m, 2H, 10-H, 8-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 32.7 (C-4a), 33.1 (C-1), 39.1 (C-6′), 42.7 (C-5), 50.6 (C-10b), 50.9 (C-3′), 55.6 (C-7′), 78.5 (C-4), 109.5 (C-7), 110.9 (C-3′), 117.0 (C-5′), 120.1 (C-1′), 121.1 (C-5″), 124.1 (C-10), 125.5 (C-10a), 125.6 (C-8), 127.9 (C-6″), 130.2 (C-4″), 133.5 (C-4′), 137.1 (C-9), 149.9 (C-6a), 156.1 (C-2″), 165.3 (C-1′), 168.2 (C-2). IR: (KBr) ν: 2920, 2849, 1745, 1682, 1648, 1600, 1525, 1499, 1469, 1430, 1355, 1317, 1304, 1276, 1260, 1189, 1101. HRMS: calcd for $C_{24}H_{26}N_3O_6$ $[M + H]^+$ 452.1821, found 452.1825.

***rac*-(4a*S**,5*R**,10b*R**)-3-Acetyl-5-phenyl-3,4,4a,5,7,8,9,10b-octahydro-1*H*-chromeno[3,4-*c*]pyridin-10(2*H*)-one [*rac*-(4a*S**,5*R**, 10b*R**)-6p].** The reaction of **1d** with **7p** was carried out according to method A and the crude product was purified by column chromatography (chloroform/acetone 10 : 1) affording *rac*-(4a*S**,5*R**,10b*R**)-**6p** as pale-yellow oil (92%), $R_f = 0.23$ (chloroform/acetone 10 : 1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94–1.13 (m, 2H, 1-H), 1.70 (s, 3H, 2′-H), 1.71–1.82 (m, 2H, 4a-H), 1.88–2.00 (m, 4H, 2× 9-H), 2.04 (s, 3H, 2′-H), 2.21–2.28 (m, 1H, 10b-H), 2.28–2.36 (m, 1H, 10b-H), 2.36–2.56 (m, 8H, 2× 7-H, 2× 8-H), 2.57–2.67 (m, 1H, 1-H_a), 2.67–2.76 (m, 1H, 4-H_b), 2.89–3.04 (m, 2H, 4-H_a, 4-H_b), 3.09–3.23 (m, 2H, 2-H_a, 2-H_b), 3.78–3.91 (m, 1H, 2-H_a), 4.10–4.19 (m, 1H, 4-H_a), 4.59 (d, $J = 10.3$ Hz, 2H, 2× 5-H), 4.65–4.74 (m,

1H, 4-H_a), 7.29–7.36 and 7.39–7.49 (m, 2× 5 H, 2× Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 and 21.2 (C-7), 21.7 and 29.0 (C-2′), 29.0 and 29.4 (C-1), 30.0 (C-8), 37.3 and 37.4 (C-10), 37.4 and 37.5 (C-9b), 42.0 and 43.2 (C-4), 43.7 and 45.6 (C-4a), 46.7 and 48.3 (C-2), 81.1 and 82.0 (C-5), 113.9 and 114.2 (C-9a), 126.9, 127.2, 129.1, 129.4 and 129.5 (2× Ph), 136.5 and 136.9 (C-1″), 168.9 and 169.3 (C-1′), 172.0 and 172.5 (C-6a), 197.7 and 198.0 (C-10). IR: (KBr) ν: 2924, 2854, 1646, 1604, 1454, 1387, 1277, 1256, 1228, 1188, 1162, 1084. HRMS: calcd for $C_{20}H_{24}NO_3$ $[M + H]^+$ 326.1756, found 326.1758.

***rac*-(4a*S**,5*R**,9b*R**)-3-Acetyl-5-phenyl-1,3,4,4a,5,7,8,9b-octahydrocyclopenta[5,6]pyrano[3,4-*c*]pyridin-9(2*H*)-one [*rac*-(4a*S**,5*R**,9b*R**)-6q].** The reaction of **1d** with **7q** was carried out according to method A and the crude product was purified by column chromatography (chloroform/acetone 10 : 1) affording *rac*-(4a*S**,5*R**,9b*R**)-**6q** as pale-yellow oil (42%), R_f = 0.29 (chloroform/acetone 10 : 1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13–1.32 (m, 2H, 1-H_a, 1-H_b), 1.68–1.77 (m, 4H, 2′-H, 4a-H), 2.04 (s, 3H, 2′-H), 2.16–2.26 (m, 1H, 4-H_b), 2.41–2.54 (m, 6H, 2× 7-H, 2× 9b-H), 2.54–2.64 (m, 4H, 2× 8-H), 2.70–2.78 (m, 2H, 2-H_a, 1-H_b), 2.78–2.92 (m, 1H, 1-H_a), 3.03–3.13 (m, 1H, 2-H_b), 3.17–3.31 (m, 1H, 2-H_b), 3.84–3.95 (m, 1H, 2-H_a), 4.17–4.28 (m, 1H, 4-H_a), 4.69–4.80 (m, 1H, 4-H_a), 4.80–4.91 (m, 2H, 2× 5-H), 7.25–7.55 (m, 10H, 2× Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 and 21.7 (C-2′), 26.1 and 26.2 (C-8), 27.4 and 28.1 (C-1), 33.8 and 36.0 (C-7), 36.1 (C-9b), 41.6 and 42.3 (C-4), 42.9 and 44.2 (C-4a), 46.5 and 47.9 (C-2), 83.5 and 84.4 (C-5), 115.8 and 116.1 (C-9a), 126.9, 127.2, 129.1, 129.2, 129.3, 129.6, 129.7, 136.1, 136.5 (2× Ph), 168.9 and 169.3 (C-1′), 184.0 and 184.5 (C-6a), 203.1 and 203.3 (C-9). IR: (KBr) ν: 2923, 1681, 1618, 1425, 1396, 1280, 1248, 1224, 1131, 1063. HRMS: calcd for $C_{19}H_{22}NO_3$ $[M + H]^+$ 312.1599, found 312.1602.

***rac*-(6*R**,6a*S**,10a*R**)-8-Acetyl-3-methyl-6-phenyl-6a,7,8,9,10,10a-hexahydropyrano[3′,4′:5,6]pyrano[3,4-*c*]pyridin-1(6*H*)-one [*rac*-(6*R**,6a*S**,10a*R**)-6r].** The reaction of **1d** with **7r** was carried out according to method A and the crude product was purified by column chromatography (chloroform/ethyl acetate 10 : 1) affording *rac*-(6*R**,6a*S**,10a*R**)-**6r** as pale yellow oil (37%), R_f = 0.53 (chloroform/ethyl acetate 10 : 1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07–1.28 (m, 2H, 2× 10-H_b), 1.74–1.87 (m, 2H, 2× 10a-H), 1.94–2.10 (m, 4H, 2′-H and 7-H_b), 2.15–2.23 (m, 6H, 2′-H and 3′-H), 2.54–2.71 (m, 2H, 10-H_a and 7-H_b), 2.71–2.81 (m, 1H, 9-H_b), 3.06–3.18 (m, 1H, 9-H_b), 3.18–3.30 (m, 1H 9-H_a), 3.85–3.97 (m, 1H, 9-H_a), 4.16–4.26 (m, 1H, 7-H_a), 4.74 (d, J = 10.4 Hz, 2H, 2× -6-H), 5.78 (s, 1H, 4-H), 7.28–7.53 (m, 10H, 2× Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 (C-2′), 21.0 and 21.5 (C-3′), 28.0 and 28.7 (C-10), 30.8 and 36.8 (C-10a), 41.7 (C-7), 42.8 (C-6a), 42.9 (C-7), 44.7 (C-6a), 46.4 and 47.9 (C-9), 81.2 and 82.0 (C-6), 99.6 (C-10b), 100.0 and 100.2 (C-4), 126.2, 126.8, 127.1, 128.5, 129.0, 129.1, 129.5, 129.6, 131.6, 136.0 and 136.3 (2× Ph), 161.0 (C-1), 163.3 and 165.7 (C-4a), 168.8 and 169.2 (C-1′). IR: (KBr) ν: 3063, 2922, 2172, 1705, 1648, 1572, 1496, 1446, 1407, 1360, 1283, 1230, 1144, 1034. HRMS: calcd for $C_{20}H_{22}NO_4$ $[M + H]^+$ 340.1548, found 340.1552.

***rac*-(6*R**,6a*S**,10a*R**)-8-Acetyl-2,4-dimethyl-6-phenyl-4,6,6a,7,8, 9,10,10a-octahydro-1*H*-pyrido[4′,3′:4,5]pyrano[2,3-*d*]pyrimidine-1,3(2*H*)-dione [*rac*-(6*R**,6a*S**,10a*R**)-6s].** The reaction of **1d** with **7s** was carried out according to method A and the crude product was purified by column chromatography (chloroform/ethyl acetate 5 : 1) affording *rac*-(6*R**,6a*S**,10a*R**)-**6s** as pale-yellow oil (16%), R_f = 0.07 (chloroform/ethyl acetate 5 : 1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–1.60 (m, 1H, 10-H_b), 2.12 (s, 3H, 2′-H), 2.14–2.17 (m, 3H, 2′-H), 2.27–2.41 (m, 2H, 2× 10-H_a), 2.62 (t, J = 13.0 Hz, 1H, 7-H_b), 2.73–2.81 (m, 1H, 7-H_a), 3.03–3.10 (m, 2H, 2× 10a-H), 3.17 (t, J = 13.3 Hz, 1H, 7-H_b), 3.23 (s, 3H, 3′-H), 3.25–3.31 (m, 4H, 3′-H, 9-H_b), 3.31–3.36 (m, 7H, 2× 4′-H, 9-H_a), 3.42 (d, J = 14.0 Hz, 1H, 10-H_b), 3.85 (d, J = 13.5 Hz, 1H, 9-H_b), 4.27 (d, J = 14.2 Hz, 1H, 9-H_a), 4.68 (d, J = 13.3 Hz, 1H, 7-H_a), 5.18 (d, J = 11.2 Hz, 1H, 6-H), 5.26 (d, J = 11.0 Hz, 1H, 6-H), 7.27–7.56 (m, 10H, 2× Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 and 21.7 (C-2′), 28.0 (C-4′), 28.3 (C-10), 28.8 (C-3′), 29.3 (C-10), 29.8 and 30.1 (C-10a), 37.5 and 38.1 (C-6a), 41.3 (C-7), 46.2 (C-9), 80.2 and 80.8 (C-6), 90.1 and 90.8 (C-10b), 127.0, 127.6, 128.1, 128.7, 129.4, 129.4, 130.3, 136.1 and 136.9 (2× Ph), 151.0 (C-3), 155.7 (C-10), 162.4 (C-4a), 169.2 and 169.8 (C-1′). IR: (KBr) ν: 2920, 1704, 1629, 1487, 1427, 1372, 1301, 1261, 1244, 1185. HRMS: calcd for $C_{20}H_{24}N_3O_4$ $[M + H]^+$ 370.1766, found 370.1771.

***rac*-(1*R**,4a*R**,8a*S**)-Ethyl 7-acetyl-3-methyl-1-phenyl-4a,5,6,7,8,8a-hexahydro-1*H*-pyrano[3,4-*c*]pyridine-4-carboxylate [*rac*-(1*R**,4a*R**,8a*S**)-6k].** The reaction of **1d** with **7k** was carried out according to method A and the crude product was purified by column chromatography (chloroform/ethyl acetate 10 : 4) affording *rac*-(1*R**,4a*R**,8a*S**)-**6k** as pale-yellow oil (63%), R_f = 0.49 (chloroform/ethyl acetate 10 : 4).

^{1}H NMR (500 MHz, acetone-d_6) δ 0.95–1.06 (m, 1H, 5-H_b), 1.09–1.20 (m, 1H, 5-H_b), 1.31 (t, J = 7.1 Hz, 6H, 2× 5′-H), 1.60–1.68 (m, 4H, 7′-H, 8a-H), 1.74–1.83 (m, 1H, 8a-H), 1.98 (s, 3H, 7′-H), 2.04–2.12 (m, 1H, 6-H_b), 2.13–2.17 (m, 3H, 1′-H), 2.20–2.32 (m, 1H, 6-H_b), 2.32–2.38 (m, 2H, 2× 5-H_a), 2.50–2.66 (m, 1H, 6-Ha), 2.85 (t, J = 12.4 Hz, 1H, 8-H_b), 3.07–3.15 (m, 1H, 8-H_b), 3.21 (d, J = 13.1 Hz, 1H, 8-H_a), 3.96 (d, J = 13.5 Hz, 1H, 8-H_a), 4.06–4.13 (m, 1H, 6-H_a), 4.16–4.28 (m, 4H, 2× 4′-H), 4.62 (d, J = 13.3 Hz, 1H, 6-H_a), 4.74–4.79 (m, 2H, 2× 1-H), 7.30–7.65 (m, 10H, 2× Ph). ^{13}C NMR (125 MHz, acetone-d_6) δ 14.7 and 19.7 (C-5′), 21.1 and 21.6 (C-7′), 30.6 and 31.3 (C-5), 39.3 (2 × C-4a), 42.0 and 43.3 (C-6), 44.4 and 45.6 (C-8a), 46.9 and 48.5 (C-8), 60.1 (C-4′), 80.8 and 81.4 (C-1), 106.5 and 106.7 (C-4), 128.0, 2× 129.4, 129.5, 129.6, and 2× 139.0 (2× Ph) 161.6 and 161.7 (C-3), 167.9 and 168.0 (C-2′), 168.5 and 168.9 (C-6′). IR: (KBr) ν: 3033, 2979, 2926, 2863, 1955, 1884, 1704, 1645, 1446, 1368, 1263, 1166, 1090, 1024. HRMS: calcd for $C_{20}H_{26}NO_4$ $[M + H]^+$ 344.1861, found 344.1860.

***rac*-(1*R**,4a*R**,8a*S**)-7-Acetyl-1,3-diphenyl-4a,5,6,7,8,8a-hexahydro-1*H*-pyrano[3,4-*c*]pyridine-4-carbonitrile [*rac*-(1*R**,4a*R**,8a*S**)-6i].** The reaction of **1d** with **7i** was carried out according to method A and the crude product was purified by column chromatography (chloroform/ethyl acetate 10 : 1) affording *rac*-(1*R**,4a*R**,8a*S**)-**6i** as pale-yellow oil (48%), R_f = 0.28 (chloroform/ethyl acetate 10 : 1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37–1.55 (m, 2H, 2× 5-H_a), 1.71–1.82 (m, 5H, 3′-H, 2× 9a-H), 2.06 (s, 3H, 3′-H), 2.13–2.23 (m, 1H, 8-H_b), 2.23–2.36 (m, 2H, 2× 5-H_b), 2.46–2.63 (m, 3H, 2×

4a-H, 8-H_b), 2.65–2.79 (m, 1H, 6-H_b), 3.02–3.16 (m, 1H, 6-H_b), 3.20–3.34 (m, 1H, 6-H_a), 3.89–4.04 (m, 1H, 8-H_a), 4.22–4.36 (m, 1H, 8-H_a), 4.87 (d, J = 10.3 Hz, 2H, 2× 1-H), 7.29–7.48 (m, 14H, 2× Ph), 7.75 (d, J = 7.7 Hz, 2H, 2× 4′-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 and 21.7 (C-3′), 29.7 and 30.5 (C-5), 38.2 (C-4a), 41.4 (C-8a), 41.7 (C-8), 42.7 (C-8a), 43.4 (C-8), 46.1 and 47.7 (C-6), 81.8 and 82.7 (C-1), 86.2 and 86.8 (C-4), 118.3 and 118.6 (C-1″), 126.8, 127.1, 128.1, 128.4, 129.1, 129.2, 129.5, 129.6, 130.9, 131.0, 132.7, 132.8, 136.2 and 136.5 (4× Ph), 165.2 and 165.5 (C-3), 169.0 and 169.3 (C-2′). IR: (KBr) ν: 3055, 3037, 3016, 3002, 2961, 2906, 2863, 2192, 1642, 1606, 1448, 1425, 1359, 1267, 1227, 1152, 1028. HRMS: calcd for $C_{23}H_{23}N_2O_2$ $[M + H]^+$ 359.1759, found 359.1755.

Conclusions

A styrene substrate, containing an *N*-(*ortho*-formyl)aryl subunit, was reacted with *N*-substituted 2-cyanoacetamides in domino Knoevenagel-cyclization reactions, which produced tetrahydro-4*H*-pyrano[3,4-*c*]quinolone and hexahydrobenzo[j] phenanthridine derivatives selectively by competing IMHDA and IMSDA cyclizations, respectively. We found that the *N*-substitution of the α,β-unsaturated amide heterodiene governed the mechanism of the cyclization step whether it took place with an oxa-IMHDA reaction with the involvement of the amide carbonyl or an IMSDA-rearomatization sequence using the carbon–carbon double bond as a dienophile.

The diastereoselective IMHDA step of the domino reactions took place with α,β-unsaturated amide, thioamide, ester and ketone subunits of the Knoevenagel intermediate as a heterodiene and it produced condensed chiral tetrahydropyran or -thiopyran derivatives with versatile substitution pattern. In the case of Meldrum's acid, the IMHDA product was transformed further with amine nucleophiles to induce a multistep ring-opening and fragmentation sequence of the 1,3-dioxinone ring, resulting in lactone products. Competing IMHDA pathways with contribution of amide or ester carbonyls to the heterodiene subunit were identified in the domino reactions with *N*-(4-chlorophenyl)-3-oxobutanamide.

A truncated substrate, lacking the condensed benzene ring, was reacted with cyclic and acyclic active methylene reagents to get access to the tricyclic and bicyclic substituted hexahydro-1*H*-pyrano[3,4-*c*]pyridine derivatives of novel skeletons in diastereoselective Knoevenagel-IMHDA reactions through *exo-Z-syn* transition state of the IMHDA step.

One of products, obtained by Knoevenagel-IMHDA reaction with methyl (phenylsulfonyl)acetate reagent, showed *in vitro* antiproliferative activity against human glioblastoma cell line with an IC_{50} value of 46 μM.

Data availability

CCDC 2283893 for *rac*-(4*R**,4a*S**,10b*S**)-**2ai** and 2401371 for *rac*-(4a*S**,5*R**,9b*R**)-**6p** contain the supplementary crystallographic data for this paper. These data can be obtained free from **www.ccdc.cam.ac.uk/data_request/cif**, or by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. The data supporting this article are included in the Experimental section and the ESI.†

Author contributions

Conceptualization, A. P., S. B. K. and T. K.; methodology, M. K., S. B. K., L. B. H. and S. B.; software, A. B.; validation, M. K., A. K.-S., A. B.; formal analysis, M. K., A. K.-Á.; investigation, M. K. and S. B. K.; resources, T. K. and A. K.; data curation, M. K, S. B. K. and T. K.; writing – original draft preparation, M. K. and S. B. K.; writing – review and editing, A. P., A. K. and T. K.; visualization, T. K., M. K.; supervision, T. K.; project administration, A. P., S. B. K. and T. K.; funding acquisition, T. K. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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