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Pseudo-Five-Component Stereoselective Synthesis of Highly Functionalized 3-Azabicyclo[3.3.1]nona-2,7-dienes

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Abstract—The reaction of aromatic aldehydes with malononitrile, ethyl or butyl cyanoacetate and acetylacetone in the presence of NaOH under mild conditions (EtOH, 25°C) led to the formation of new series of (1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*)-2-amino-6,9-diaryl-7-acetyl-8-methyl-4-oxo-5-cyano-3-azabicyclo[3.3.1]nona-2,7-diene-1-carboxylic acids esters. A plausible mechanism of the cascade reaction was proposed.

Keywords: methylene active nitriles, cyanoacetic ester, multicomponent reactions (MCRs), cascade reactions, 3-azabicyclo[3.3.1]nonane, 2-amino-4*H*-pyrans

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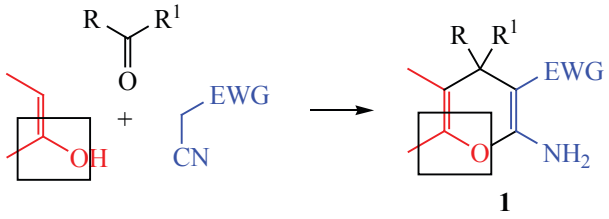
Multicomponent reactions (MCRs) based on methylene active nitriles are one of the most popular approaches used to design polyfunctional heterocyclic molecules (for reviews, see [1–17]). Such multicomponent and/or cascade processes provide rational access to libraries of O, S, N-containing heterocycles for biological screening. The advantages of such reactions include ease of implementation, efficiency, atom-economy and selectivity [1, 6, 17]. Especially significant are multicomponent reactions of malononitrile/cyanoacetic ester with aldehydes/ketones and CH-acids (enolysable carbonyl compounds, phenols, naphthols, etc.), leading to the formation of 2-amino-4*H*-pyran or -chromene derivatives **1** (Scheme 1). In turn, compounds **1** are of interest as low molecular weight ligands of various protein targets with a wide spectrum of biological action, and also serve as a starting materials in the synthesis of more complex polycyclic systems (for reviews, see [7, 9, 14, 18–27]).

Continuing our research in the field of synthesis of polyfunctional molecules based on cyanoacetic acid derivatives [28–32], we focused our attention on the multicomponent reaction of malononitrile, aldehydes, and acetylacetone with cyanoacetic esters, which has not yet been studied. Both the reaction of unsaturated nitriles **2** with acetylacetone and the three-component cyclocondensation of carbonyl compounds and acetylacetone with the aforementioned methylene active nitriles are well known and have been repeatedly reported in various versions (for example, see [33–45]). Such transformations usually proceed as tandem processes: Knoevenagel reaction → Michael reaction → heterocyclization, and lead to 5-acetyl-6-methyl-2-amino-4*H*-pyrans **3** (Scheme 2). At the same time, an unusual course of the reaction has been also described: for example, in some cases, along with 2-amino-4*H*-pyrans **3**, pyrano[2,3-*b*]pyridines **4** and **5** [46–48] or dipyrans **6** [49] were also isolated as by-products. The formation of such compounds formally assumes the participation in the reaction of 2 equiv. of aldehyde and 2 equiv. of malononitrile. A related transformation has

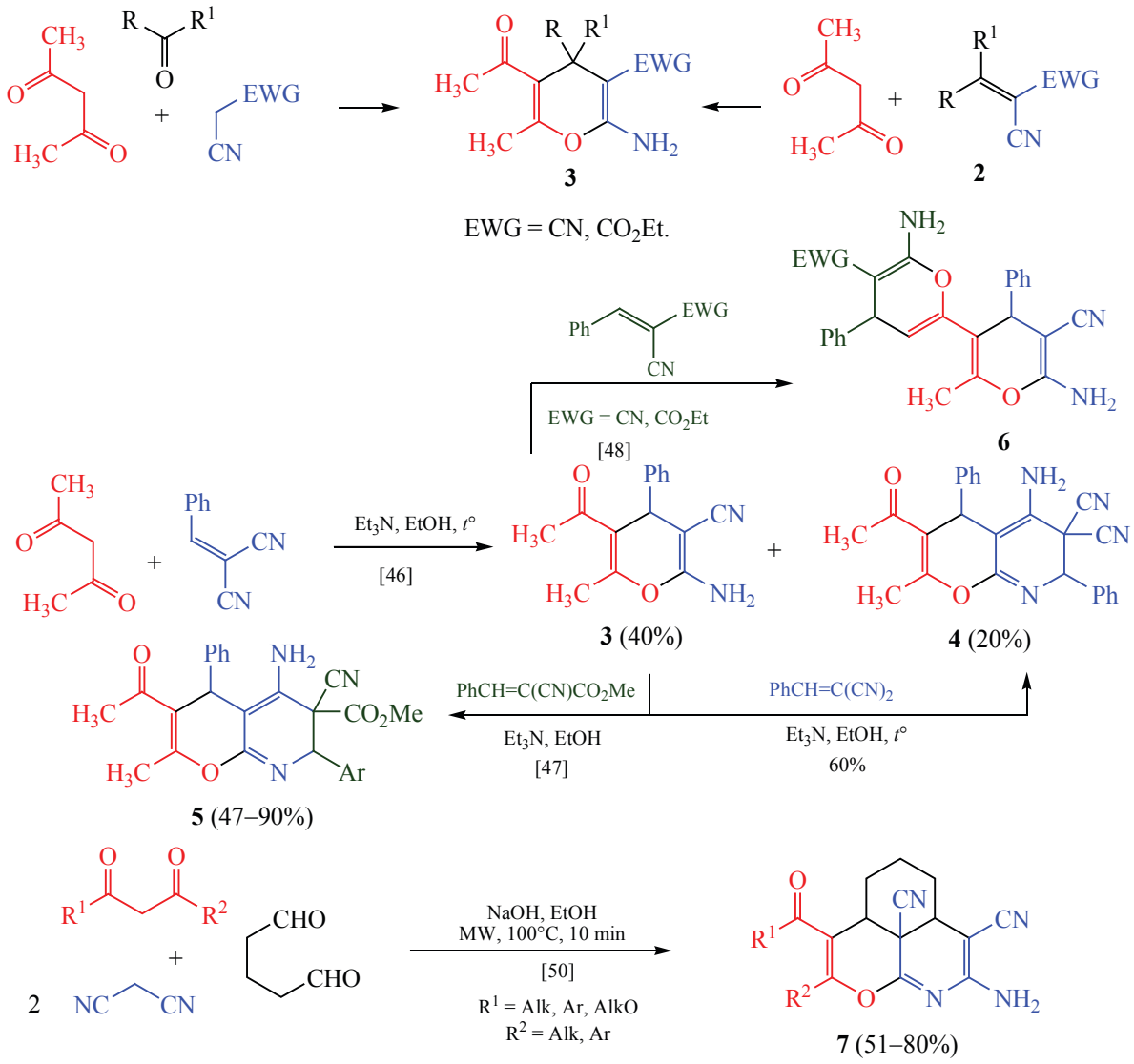
Scheme 1.



1

EWG = CN, CO_2R, etc.

Scheme 2.



been reported in [50]: for example, the condensation of glutaraldehyde with 1,3-dicarbonyl compounds and 2 equiv. of malononitrile gave rise hexahydropyrano-[4,3,2-*ij*]isoquinolines **7** (Scheme 2).

The initial task of this work was to study a multi-component variant of cross-heterocyclization with formation of pyrano[2,3-*b*]pyridines **5**. Some compounds with a pyranopyridine fragment (for review, see [51]) are known to be promising antiallergic and anticancer drugs, as well as pyran analogs of tacrine (pyranotacrines), a drug for the treatment and therapy of Alzheimer's disease [42, 52–57].

We found that the sequential reaction of malononitrile with aldehydes, cyanoacetic esters, and acetylacetone in the presence of alkali in EtOH at 25°C leads to the formation of 2-amino-6,9-diaryl-7-acetyl-8-methyl-4-oxo-5-cyano-3-azabicyclo[3.3.1]nona-2,7-diene-1-carboxylic acid esters **8a**–**8h** (Scheme 3, Table 1). Their structure was proved by the NMR, IR spectroscopy, and HPLC-MS data, as well as single crystal X-ray diffraction analysis (Fig. 1). Compound **8a** crystallizes in the centrosymmetric space group *P*21/*c*. The NMR spectra do not exhibit signal doubling characteristic of diastereomeric products. According to these data, compounds **8** are racemic mixtures with (1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*) configuration. The obtained azabicyclic products are colorless crystalline or pale colored fine-crystalline powdery substances, insoluble in ethanol, but soluble in DMSO.

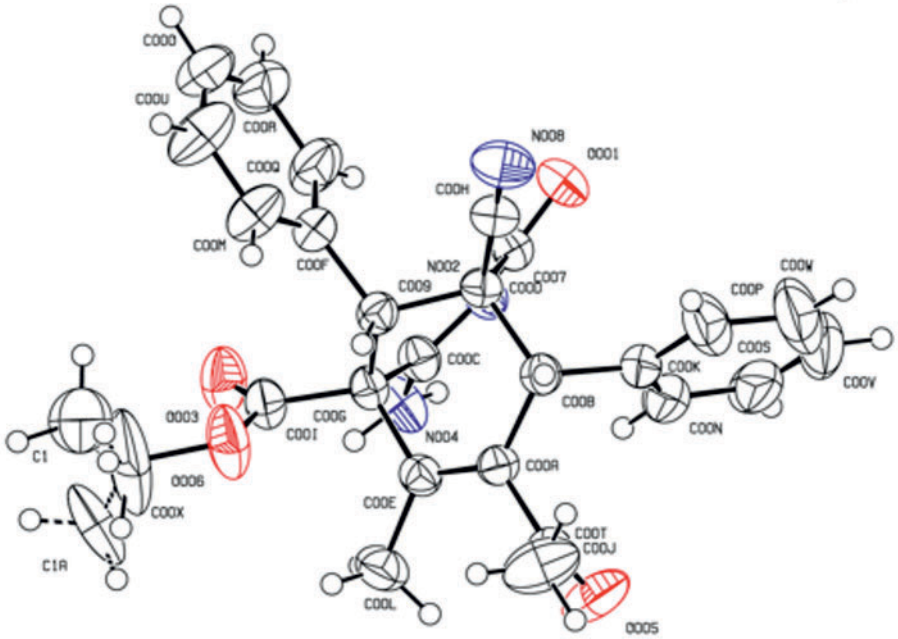
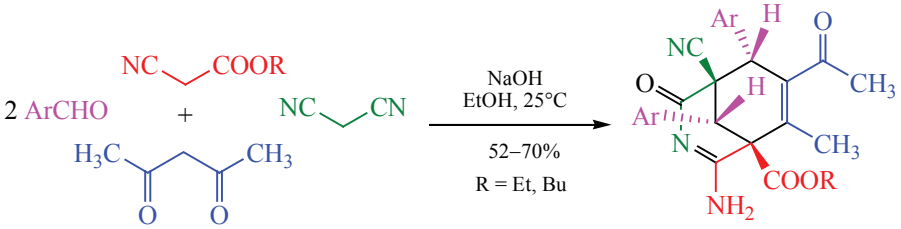


Fig. 1. General view of the molecule of ethyl 2-amino-7-acetyl-5-cyano-8-methyl-4-oxo-6,9-diphenyl-3-azabicyclo[3.3.1]nona-2,7-diene-1-carboxylate **8a** in the crystal.

Scheme 3.



8a–8h

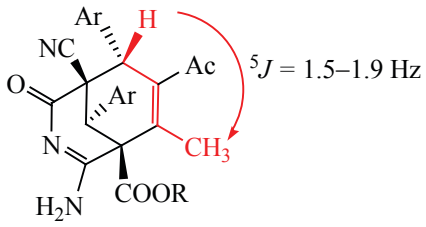
The ^{1}H NMR spectra of compounds **8a**–**8h** show a characteristic pattern for two aromatic substituents and one ester fragment. The signal of the protons of the acetyl group is found in the 1.98–2.07 ppm region; the C^8CH_3 protons resonate at 1.90–1.99 ppm. The signal of the C^9H proton is recorded as a singlet at 4.17–4.86 ppm, while the C^6H proton resonates in the weaker field (4.95–5.46 ppm). An interesting feature of the spectra is the long-range interaction between the H^6 and C^8CH_3 protons with a coupling constant of ^5J = 1.5–1.9 Hz, observed in some cases (**8a**, **8d**, **8e**) (Scheme 4). In other cases, the H^6 and C^8CH_3 signals are observed in the form of clearly broadened singlets (unresolved doublets). In our opinion, the presence of signals splitting of homoallylic protons is due to the specific rigid configuration of the bridging heterocyclic system.

Table 1. Yields and melting points for compounds **8a**–**8h**

Comp. no.	R	Ar	Yield, %	mp, °C
8a	Et	Ph	70	210
8b	Et	4-ClC_6H_4	67	254
8c	Et	3-$NO_2C_6H_4$	54	239
8d	Et	2,4-$Cl_2C_6H_3$	61	237
8e	*n*-Bu	Ph	63	218
8f	*n*-Bu	4-ClC_6H_4	62	226
8g	*n*-Bu	4-$MeOC_6H_4$	52	223
8h	*n*-Bu	3-$NO_2C_6H_4$	54	239

Due to conjugation and hindered rotation around a single bond, the amino group protons are not magnetically equivalent and are registered as broadened singlets at 8.45–8.83 and 9.17–9.61 ppm. A similar splitting

Scheme 4.



8

has been observed by us earlier in the NMR spectra of 3,7-diazabicyclo[3.3.1]non-3-enes with a similar fragment O=C–N=C–NH$_2$ [58]. The IR spectra of compounds **8** show characteristic bands of stretching vibrations of N–H bond (3407–3450 cm^{-1}), three bands of different C=O groups (acetyl 1726–1753 cm^{-1}, ester 1695–1708 cm^{-1}, and amide 1646–1669 cm^{-1}). The presence of one unconjugated cyano group is confirmed by the presence of a weak absorption band in the range of 2246–2251 cm^{-1}.

Literary search on the synthesis of compounds with 3-azabicyclo[3.3.1]nona-2,7-diene fragment revealed that a number of derivatives occur in nature as *Aristotelia chilensis* alkaloids [59]; the known synthetic approaches to the synthesis of 3-azabicyclo[3.3.1]nona-2,7-dienes are few in number, and are mainly based on the Ritter reaction of (–)-β-pinene [60, 61] or (–)-α-pinene [62] with nitriles, as well as on the rearrangement of azaspirocyclohexadienones [63] and the multicomponent reaction of 2 equiv. of malononitrile with dimedone and glutaraldehyde [50]. Of particular interest is the work [64], which describes the preparation of bridged 3-azabicyclo[3.3.1]nona-2,7-dienes **9** by reacting 2-amino-5-acetyl-6-methyl-4-phenyl-4*H*-pyran-3-carbonitrile **3** with benzylidenemalononitrile (Scheme 5); it is also postulated that structure **9** corresponds to the true structure of compounds **4** and **6**.

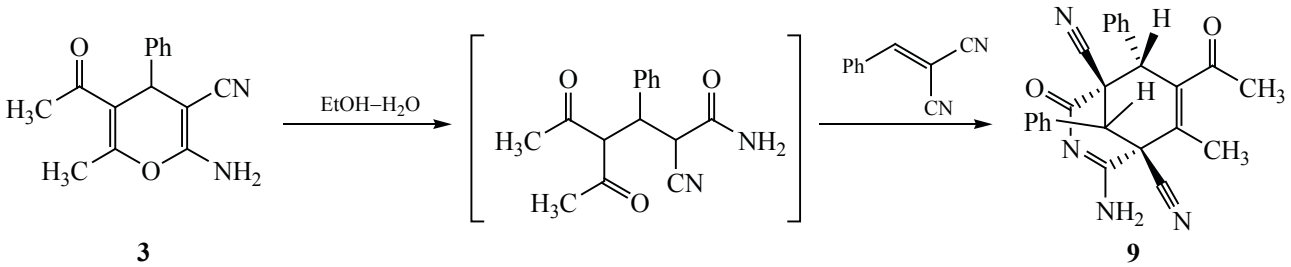
In light of the above results, we can assume the following probable mechanism for the cascade multicomponent reaction leading to the preparation of compounds **8** (Scheme 6). At the first stage, a Knoevenagel condensation between malononitrile and aldehydes takes place with the formation of ArCH=C(CN)$_2$. Further Michael addition reaction of arylidenemalononitriles with acetylacetone followed by heterocyclization results in the formation of 4*H*-pyrans **3**. The latter undergo nucleophilic cleavage of the ring with the formation of acyclic intermediates **10**. Simultaneously, the cyanoacetic ester reacts with the second equivalent of aldehyde to form the corresponding Knoevenagel product. Further Michael addition of anion **10** and carbocyclization with the elimination of water and the formation of cyclohexene **11** is likely to occur. Subsequent intramolecular cyclization with the participation of amide and nitrile groups leads to the formation of the final product **8**. In our opinion, the stereoselectivity of the process in the absence of chirality inducers is due to the spatial repulsion of bulky aryl substituents at the stage of formation of **10**: it is obvious that Michael addition at this stage is more favorably from the sterically least hindered side of the molecule.

In conclusion, a new stereoselective multicomponent reaction of malononitrile with aromatic aldehydes, acetylacetone and cyanoacetic esters was discovered; structure of the obtained 3-azabicyclo[3.3.1]nona-2,7-dienes was studied in detail, including the single crystal X-ray diffraction method. A plausible mechanism of the cascade process was proposed.

EXPERIMENTAL

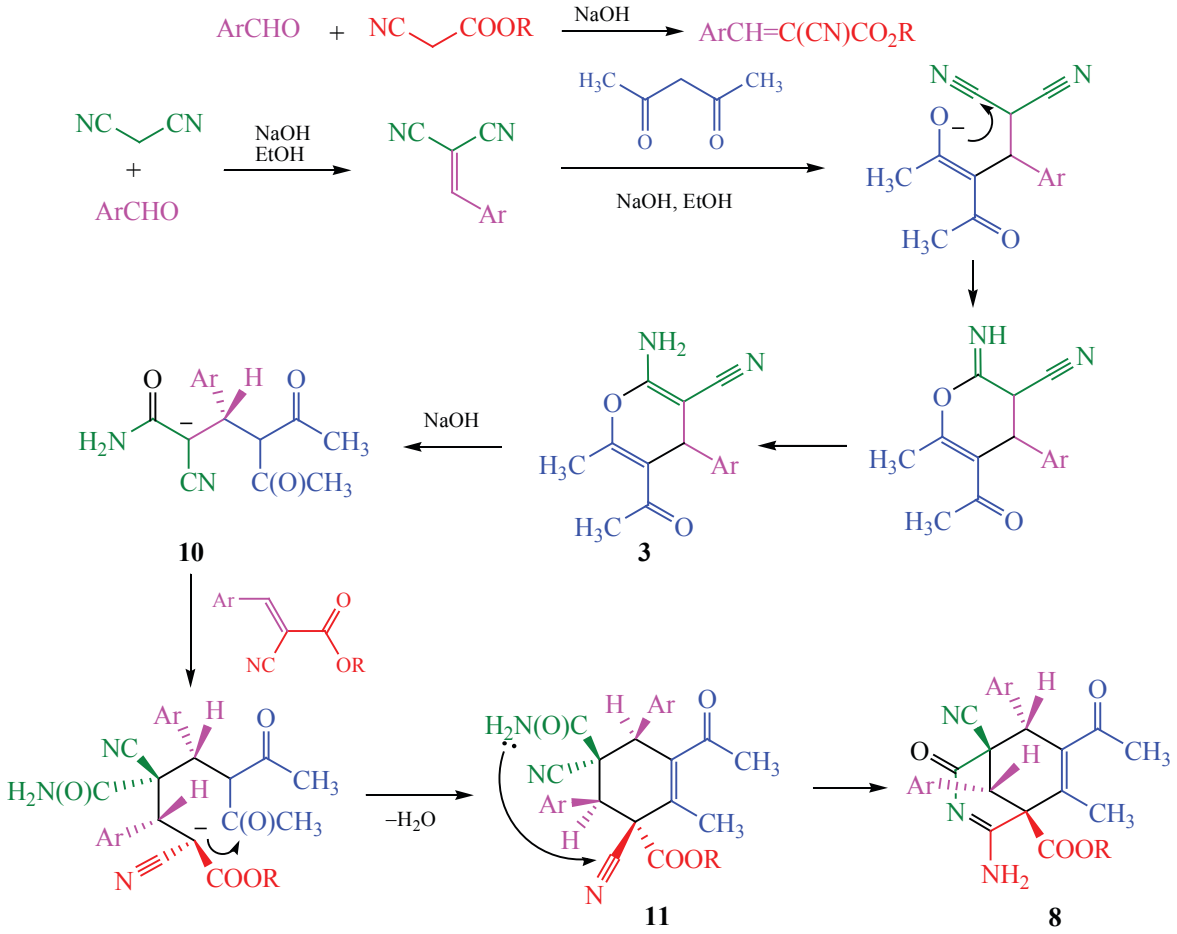
^{1}H, ^{13}C NMR spectra were recorded on a Bruker AC-300 (300.13 and 75.47 MHz, respectively) and Varian Agilent VNMRS 400 MHz (400.08 and 100.61 MHz, respectively) instruments from DMSO-d_6 solutions. Residual solvent signals were used as a standard. IR spectra were recorded on a Bruker FT-IR spectrometer

Scheme 5.



3 **9**

Scheme 6.



from KBr pellets. Elemental analysis was performed on a Carlo Erba 1106 instrument. HPLC-MS analysis was performed on an Agilent 1200 liquid chromatograph equipped with a UV detector with a diode array, a light scattering detector (ELSD) and a mass detector [Rapid Resolution HT Cartrige column 4.6 × 30 mm, 1.8 μm, Zorbax SB-C18, ES-API ionization; mobile phase: H_2O + 0.1% HCOOH/MeCN + 0.1% HCOOH, changing gradient from 100 to 0% water, flow rate is 2.9 mL/min. Melting points were determined on a Kofler table and were not corrected. The purity of the obtained compounds was monitored by TLC on Silufol UV-254 plates, acetone–hexane (1 : 1) eluent, iodine vapor developer, UV detector.

(1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*)-2-Amino-6,9-diaryl-7-acetyl-8-methyl-4-oxo-5-cyano-3-azabicyclo[3.3.1]-nona-2,7-diene-1-carboxylic acids esters 8a–8h (*general procedure*). To a solution of 0.1 g (2.5 mmol) of NaOH in 15 mL of 96% ethanol were added 5 mmol of aromatic aldehyde and 0.33 g (5 mmol) of malononitrile. The resulting mixture was stirred at 25°C for 15 min, then another 5 mmol of aldehyde, 5 mmol of the corresponding cyanoacetate, and 0.51 mL (5 mmol) of acetylacetone were added. A day later, the precipitated crystals were filtered off, and if necessary, they were recrystallized from a DMSO–EtOH mixture (1 : 1).

Ethyl (1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*)-2-amino-7-acetyl-5-cyano-8-methyl-4-oxo-6,9-diphenyl-3-azabicyclo[3.3.1]nona-2,7-diene-1-carboxylate (8a). Yield 70%, mp 210°C. ^{1}H NMR spectrum (300 MHz), δ, ppm: 0.83 t (3H, $OCH_2C\underline{H}_3$, ^3J = 7.0 Hz), 1.97 br. s (3H, Me), 1.99 s [3H, C(O)Me], 3.87–3.92 m (2H, $OC\underline{H}_2CH_3$), 4.29 s (1H, H^9), 5.04 d (1H, H^6, ^5J = 1.5 Hz), 7.23–7.43 m (10H, Ph), 8.54 br. s (1H, NH_2), 9.35 br. s (1H, NH_2). ^{13}C NMR spectrum (75 MHz), δ_C, ppm: 13.2 ($OCH_2\underline{C}H_3$), 16.4 ($C^8\underline{C}H_3$), 29.8 [C(O)$\underline{C}H_3$], 50.6 (C^5 or C^1), 51.5 (C^1 or C^5), 53.5 (C^6 or C^9), 54.7 (C^9 or C^6), 61.9 ($O\underline{C}H_2CH_3$), 118.6 (C≡N), 128.2 (CH Ar), 128.3

(CH Ar), 128.4 (CH Ar), 128.8 (CH Ar), 129.3 (CH Ar), 129.4 (CH Ar), 134.4 (C^7), 135.4 (C^1 Ar), 135.6 (C^1 Ar), 139.2 (C^8), 167.7 (COOEt), 168.5 (C^2 or C^4), 170.1 (C^4 or C^2), 202.1 ($\underline{C}(O)CH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 456.2 $[M + H]^+$. Found, %: C 71.00; H 5.70; N 9.10. $C_{27}H_{25}N_3O_4$. Calculated, %: 71.19; H 5.53; N 9.22. *M* 455.51.

Ethyl (1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*)-2-amino-7-acetyl-5-cyano-8-methyl-4-oxo-6,9-bis(4-chlorophenyl)-3-azabicyclo[3.3.1]nona-2,7-diene-1-carboxylate (8b). Yield 67%, mp 218°C. IR spectrum, ν, cm^{-1}: 3449 s (N–H), 2246 w (C≡N), 1738 s [$C(O)CH_3$], 1695 s (CO_2Et), 1647 s (C=O amide). ^{1}H NMR spectrum (300 MHz), δ, ppm: 0.89 t (3H, $OCH_2C\underline{H}_3$, ^3J = 6.9 Hz), 1.95 br. s (3H, Me), 2.01 s [3H, C(O)Me], 3.94 q (2H, $OC\underline{H}_2CH_3$, ^3J = 6.9 Hz), 4.33 s (1H, H^9), 5.06 br. s (1H, H^6), 7.20 d (2H, H Ar, ^3J = 7.8 Hz), 7.26–7.28 m (4H, H Ar), 7.46 d (2H, H Ar, ^3J = 8.3 Hz), 8.59 br. s (1H, NH_2), 9.31 br. s (1H, NH_2). ^{13}C NMR spectrum (75 MHz), δ_C, ppm: 13.2 ($OCH_2\underline{C}H_3$), 16.4 ($C^8\underline{C}H_3$), 29.8 [$C(O)\underline{C}H_3$], 49.6 (C^5 or C^1), 50.5 (C^1 or C^5), 53.1 (C^6 or C^9), 54.5 (C^9 or C^6), 62.1 ($O\underline{C}H_2CH_3$), 118.2 (C≡N), 128.3 (C Ar), 128.9 (2C Ar), 130.0 (C Ar), 133.6 (C^4 Ar), 134.2 (C^4 Ar), 134.4 (C^1 Ar), 134.5 (C^1 Ar), 138.7 (C^8), 167.3 (COOEt), 168.3 (C^2 or C^4), 169.7 (C^4 or C^2), 202.0 [$\underline{C}(O)CH_3$]. Mass spectrum, *m*/*z* (I_{rel}, %): 524.0 $[M + H]^+$, 526.0 $[M + H]^+$. Found, %: C 61.80; H 4.50; N 7.96. $C_{27}H_{23}Cl_2N_3O_4$. Calculated, %: 61.84; H 4.42; N 8.01. *M* 524.40.

Ethyl (1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*)-2-amino-7-acetyl-5-cyano-8-methyl-6,9-bis(3-nitrophenyl)-4-oxo-3-azabicyclo[3.3.1]nona-2,7-diene-1-carboxylate (8c). Yield 65%, mp 231°C. IR spectrum, ν, cm^{-1}: 3426 s (N–H), 2246 w (C≡N), 1753 s [$C(O)CH_3$], 1701 s (CO_2Et), 1669 s (C=O amide), 1530 [$\nu_{as}(NO_2)$], 1351 [$\nu_s(NO_2)$]. ^{1}H NMR spectrum (300 MHz), δ, ppm: 0.84 t (3H, $OCH_2C\underline{H}_3$, ^3J = 7.1 Hz), 1.99 br. s (3H, Me), 2.07 s [3H, C(O)Me], 3.94 q (2H, $OC\underline{H}_2CH_3$, ^3J = 7.1 Hz), 4.67 s (1H, H^9), 5.31 br. s (1H, H^6), 7.64–7.77 m (4H, H Ar), 8.10–8.14 m (2H, H Ar), 8.19 d (2H, H Ar, ^3J = 8.3 Hz), 8.27 d (2H, H Ar, ^3J = 8.3 Hz), 8.79 br. s (1H, NH_2), 9.61 br. s (1H, NH_2). ^{13}C NMR spectrum (75 MHz), δ_C, ppm: 13.2 ($OCH_2\underline{C}H_3$), 16.4 ($C^8\underline{C}H_3$), 29.9 [C(O)$\underline{C}H_3$], 49.5 (C^5 or C^1), 50.3 (C^1 or C^5), 52.8 (C^6 or C^9), 54.2 (C^9 or C^6), 62.3 ($O\underline{C}H_2CH_3$), 117.9 (C≡N), 121.5 (C Ar), 122.0 (C Ar), 123.5 (C Ar), 124.0 (C Ar), 130.4 (C Ar), 130.9 (C Ar), 133.9 (C Ar), 134.8 (C Ar), 137.2 (C Ar), 137.4 (C Ar), 138.3 (C^8), 147.4 (C-NO_2 Ar), 147.7 (C–NO_2 Ar), 167.1 (COOEt), 168.6 (C^2 or C^4), 169.2 (C^4 or C^2), 202.1 [$\underline{C}(O)CH_3$]. Mass spectrum, *m*/*z* (I_{rel}, %): 546.2 $[M + H]^+$. Found, %: C 59.38; H 4.40; N 12.75. $C_{27}H_{23}N_5O_8$. Calculated, %: 59.45; H 4.25; N 12.84. *M* 545.50.

Ethyl (1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*)-2-amino-7-acetyl-5-cyano-8-methyl-4-oxo-6,9-bis(2,4-dichlorophenyl)-3-azabicyclo[3.3.1]nona-2,7-diene-1-carboxylate (8d). Yield 61%, mp 237°C. IR spectrum, ν, cm^{-1}: 3420 s (N–H), 2251 w (C≡N), 1743 s [$C(O)CH_3$], 1699 s (CO_2Et), 1648 s (C=O amide). ^{1}H NMR spectrum (300 MHz), δ, ppm: 0.90 t (3H, $OCH_2C\underline{H}_3$, ^3J = 7.1 Hz), 1.98 d (3H, Me, ^5J = 1.9 Hz), 2.05 s [3H, C(O)Me], 3.91–4.04 m (2H, $OC\underline{H}_2CH_3$), 4.86 s (1H, H^9), 5.46 d (1H, H^6, ^5J = 1.9 Hz), 6.62 d (1H, H Ar, ^3J = 8.3 Hz), 7.22 d (1H, H Ar, ^3J = 8.8 Hz), 7.35 d. d (1H, H Ar, ^3J = 8.3, ^4J = 2.0 Hz), 7.54 d. d (1H, H Ar, ^3J = 8.8, ^4J = 2.0 Hz), 7.68 d (1H, H Ar, ^4J = 2.0 Hz), 7.78 d (1H, H Ar, ^4J = 2.0 Hz), 8.83 br. s (1H, NH_2), 9.60 br. s (1H, NH_2). ^{13}C NMR spectrum (75 MHz), δ_C, ppm: 13.1 ($OCH_2\underline{C}H_3$), 16.7 ($C^8\underline{C}H_3$), 29.8 [$C(O)\underline{C}H_3$], 45.6 (C^5 or C^1), 46.5 (C^1 or C^5), 51.2 (C^6 or C^9), 53.7 (C^9 or C^6), 62.5 ($O\underline{C}H_2CH_3$), 117.2 (C≡N), 127.4 (C Ar), 128.4 (C Ar), 129.0 (C Ar), 129.4 (C Ar), 129.9 (C Ar), 131.3 (CH Ar), 131.6 (CH Ar), 132.4 (C Ar), 134.1 (CH Ar), 134.5 (CH Ar), 134.6 (CH Ar), 135.3 (C Ar), 136.3 (CH Ar), 138.6 (C^8), 166.8 (COOEt), 168.3 (C^2 or C^4), 169.2 (C^4 or C^2), 201.8 [$\underline{C}(O)CH_3$]. Mass spectrum, *m*/*z* (I_{rel}, %): 592.0 $[M + H]^+$, 593.8 $[M + H]^+$, 594.8 $[M + H]^+$, 597.8 $[M + H]^+$. Found, %: C 54.60; H 3.70; N 7.06. $C_{27}H_{21}Cl_4N_3O_4$. Calculated, %: 54.66; H 3.57; N 7.08. *M* 593.29.

Butyl (1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*)-2-amino-7-acetyl-5-cyano-8-methyl-4-oxo-6,9-diphenyl-3-azabicyclo[3.3.1]nona-2,7-diene1-carboxylate (8e). Yield 63%, mp 218°C. ^{1}H NMR spectrum (300 MHz), δ, ppm: 0.76 t [3H, $O(CH_2)_3C\underline{H}_3$, ^3J = 7.2 Hz], 1.03–1.28 m (4H, $OCH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.95 d (3H, Me, ^5J = 1.5 Hz), 1.98 s [3H, C(O)Me], 3.82–3.88 m (2H, $OC\underline{H}_2$), 4.29 s (1H, H^9), 5.05 d (1H, H^6, ^5J = 1.5 Hz), 7.18–7.34 m (10H, 2 Ph), 8.51 br. s (1H, NH_2), 9.30 br. s (1H, NH_2). ^{13}C NMR spectrum (75 MHz), δ_C, ppm: 13.5 ($OCH_2CH_2CH_2\underline{C}H_3$), 16.4 ($C^8\underline{C}H_3$), 18.5 ($OCH_2CH_2\underline{C}H_2CH_3$), 29.5 ($OCH_2\underline{C}H_2CH_2CH_3$), 29.8 [$C(O)\underline{C}H_3$], 50.5 ($C^5$ or C^1), 51.4 (C^1 or C^5), 53.5 (C^6 or C^9), 54.7 (C^9 or C^6), 65.6 ($O\underline{C}H_2CH_2CH_2CH_3$), 118.6 (C≡N), 128.15 (C Ar), 128.24 (C Ar), 128.8 (C Ar), 129.3 (C Ar), 129.6 (C Ar), 134.2 (C^7), 135.4 (C^1 Ar), 135.6 (C^1 Ar), 139.1 (C^8), 167.8 (COOBu), 168.4 (C^2 or C^4),

170.0 (C^4 or C^2), 202.1 [$\underline{C}(O)CH_3$]. Mass spectrum, *m*/*z* (I_{rel}, %): 409.0 [*M* – BuOH + H]$^+$, 456.0 [*M* – BuO + HCOOH]$^+$, 484.0 [*M* + H]$^+$, 487.0 [*M* – BuOH + DMSO]$^+$, 562.0 [*M* + H + DMSO]$^+$. Found, %: C 72.01; H 6.13; N 8.65. $C_{29}H_{29}N_3O_4$. Calculated, %: 72.03; H 6.04; N 8.69. *M* 483.56.

Butyl (1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*)-2-amino-7-acetyl-5-cyano-8-methyl-4-oxo-6,9-bis(4-chlorophenyl)-3-azabicyclo[3.3.1]nona2,7-diene-1-carboxylate (8f). Yield 62%, mp 226°C. IR spectrum, ν, cm^{-1}: 3450 s (N–H), 2250 m (C≡N), 1730 s [C(O)CH_3], 1695 s (CO_2Bu), 1648 s (C=O amide). ^{1}H NMR spectrum (300 MHz), δ, ppm: 0.78 t [3H, O(CH_2)$_3$C$\underline{H}_3$, ^3J = 7.1 Hz], 1.04–1.34 m (4H, OCH_2C$\underline{H}_2$C$\underline{H}_2$CH_3), 1.94 br. s (3H, Me), 2.01 s [3H, C(O)Me], 3.88 t (2H, OC$\underline{H}_2$, ^3J = 6.3 Hz), 4.34 s (1H, H^9), 5.06 br. s (1H, H^6), 7.19 d (2H, H Ar, ^3J = = 7.8 Hz), 7.24–7.36 m (4H, H Ar), 7.45 d (2H, H Ar, ^3J = 8.3 Hz), 8.55 br. s (1H, NH_2), 9.28 br. s (1H, NH_2). ^{13}C NMR spectrum (75 MHz), δ_C, ppm: 13.4 (OCH_2CH_2CH_2C$\underline{H}_3$), 16.4 (C^{8}C$\underline{H}_3$), 18.4 (OCH_2CH_2C$\underline{H}_2$CH_3), 29.5 (OCH_2C$\underline{H}_2$CH_2CH_3), 29.8 [C(O)C$\underline{H}_3$], 49.5 (C^5 or C^1), 50.5 (C^1 or C^5), 53.1 (C^6 or C^9), 54.6 (C^9 or C^6), 65.7 (O$\underline{C}$H$_2$CH$_2$CH$_2$CH$_3$), 118.2 (C≡N), 128.6 (2CH Ar), 128.9 (2CH Ar), 129.4 (2CH Ar), 132.4 (2CH Ar), 133.0 (C^4 Ar), 133.6 (C^4 Ar), 134.2 (C^1 Ar), 134.4 (C^1 Ar), 138.7 (C^8), 167.5 ($\underline{C}$OOBu), 168.3 (C^2 or C^4), 169.6 (C^4 or C^2), 201.9 [$\underline{C}(O)CH_3$]. Mass spectrum, *m*/*z* (I_{rel}, %): 552.2 [*M* + H]$^+$, 553.2 [*M* + H]$^+$, 554.2 [*M* + H]$^+$, 556.2 [*M* + H]$^+$. Found, %: C 63.14; H 5.03; N 7.46. $C_{29}H_{27}Cl_2N_3O_4$. Calculated, %: 63.05; H 4.93; N 7.61. *M* 552.45.

Butyl (1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*)-amino-7-acetyl-5-cyano-8-methyl-6,9-bis(4-methoxyphenyl)-4-oxo-3-azabicyclo[3.3.1]nona-2,7-diene-1-carboxylate (8g). Yield 52%, mp 223°C. IR spectrum, ν, cm^{-1}: 3407 s (N–H), 2248 w (C≡N), 1726 s [C(O)CH_3], 1704 s (CO_2Bu), 1646 s (C=O amide). ^{1}H NMR spectrum (400 MHz), δ, ppm: 0.76 t [3H, O(CH_2)$_3$C$\underline{H}_3$, ^3J = 7.0 Hz], 1.06–1.28 m (4H, OCH_2C$\underline{H}_2$C$\underline{H}_2$CH_3), 1.90 br. s (3H, Me), 1.98 s [3H, C(O)Me], 3.71 br. s (6H, MeO), 3.83–3.87 m (2H, OC$\underline{H}_2$), 4.17 s (1H, H^9), 4.95 br. s (1H, H^6), 6.77–6.85 m (4H, H Ar), 6.89 d (2H, H Ar, ^3J = 7.8 Hz), 7.08 d (2H, H Ar, ^3J = 8.3 Hz), 8.45 br. s (1H, NH_2), 9.17 br. s (1H, NH_2). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 13.4 (OCH_2CH_2CH_2C$\underline{H}_3$), 16.3 (C^{8}C$\underline{H}_3$), 18.4 (OCH_2CH_2C$\underline{H}_2$CH_3), 29.5 (OCH_2C$\underline{H}_2$CH_2CH_3), 29.7 [C(O)C$\underline{H}_3$], 49.8 (C^5 or C^1), 50.7 (C^1 or C^5), 53.8 (C^6 or C^9), 54.86 (C^9 or C^6), 54.93 (OCH_3), 55.0 (OCH_3), 65.5 (O$\underline{C}$H$_2$CH$_2$CH$_2$CH$_3$), 113.6 (2CH Ar), 114.0 (2CH Ar), 118.7 (C≡N), 127.1 (2CH Ar), 127.4 (2CH Ar), 133.5 (C^1 Ar), 133.7 (C^1 Ar), 139.3 (C^8), 158.9 (C^4 Ar), 159.3 (C^4 Ar), 167.9 ($\underline{C}$OOBu), 168.5 (C^2 or C^4), 170.62 (C^4 or C^2), 202.1 ($\underline{C}(O)CH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 544.0 [*M* + H]$^+$. Found, %: C 68.40; H 6.29; N 7.67. $C_{31}H_{33}N_3O_6$. Calculated, %: 68.49; H 6.12; N 7.73. *M* 543.61.

Butyl (1*S*,5*R*,6*R*,9*R*)/(1*R*,5*S*,6*S*,9*S*)-amino-7-acetyl-5-cyano-8-methyl-6,9-bis(3-nitrophenyl)-4-oxo-3-azabicyclo[3.3.1]nona-2,7-diene-1-carboxylate (8h). Yield 54%, mp 239°C. IR spectrum, ν, cm^{-1}: 3420 s (N–H), 2248 w (C≡N), 1739 s [C(O)CH_3], 1708 s (CO_2Bu), 1652 s (C=O amide), 1530 [$\nu_{as}(NO_2)$], 1350 [$\nu_s(NO_2)$]. ^{1}H NMR spectrum (400 MHz), δ, ppm: 0.71 t [3H, O(CH_2)$_3$C$\underline{H}_3$, ^3J = 7.3 Hz], 1.01–1.28 m (4H, OCH_2C$\underline{H}_2$C$\underline{H}_2$CH_3), 1.98 br. s (3H, Me), 2.07 s (3H, C(O)Me), 3.81–3.93 m (2H, OC$\underline{H}_2$), 4.69 s (1H, H^9), 5.32 br. s (1H, H^6), 7.63–7.77 m (4H, H Ar), 8.12–8.16 m (2H, H Ar), 8.19 d (2H, H Ar, ^3J = 7.3 Hz), 8.27 d (2H, H Ar, ^3J = 8.3 Hz), 8.79 br. s (1H, NH_2), 9.60 br. s (1H, NH_2). ^{13}C NMR spectrum (101 MHz), δ_C, ppm: 13.3 (OCH_2CH_2CH_2C$\underline{H}_3$), 16.5 (C^{8}C$\underline{H}_3$), 18.4 (OCH_2CH_2C$\underline{H}_2$CH_3), 29.5 (OCH_2C$\underline{H}_2$CH_2CH_3), 29.9 [C(O)C$\underline{H}_3$], 49.5 (C^5 or C^1), 50.3 (C^1 or C^5), 52.9 (C^6 or C^9), 54.2 (C^9 or C^6), 66.0 (O$\underline{C}$H$_2$CH$_2$CH$_2$CH$_3$), 117.9 (C≡N), 123.5 (2CH Ar), 124.0 (2CH Ar), 130.1 (2CH Ar), 131.0 (CH Ar), 134.7 (CH Ar), 137.3 (C^1 Ar), 137.5 (C^1 Ar), 138.3 (C^8), 147.4 (NO_2C^3 Ar), 147.7 (NO_2C^3 Ar), 167.3 ($\underline{C}$OOBu), 168.6 (C^2 or C^4), 169.2 (C^4 or C^2), 202.1 [$\underline{C}(O)CH_3$]. Mass spectrum, *m*/*z* (I_{rel}, %): 574.0 [*M* + H]$^+$. Found, %: C 60.70; H 4.82; N 12.17. $C_{29}H_{27}N_5O_8$. Calculated, %: 60.73; H 4.74; N 12.21. *M* 573.55.

Single crystal X-ray diffraction analysis of compound **8a** ($C_{27}H_{25}N_3O_4$) was performed on an automatic four-circle diffractometer Agilent Super Nova, Dual, Cu at zero, Atlas S2 at 293(2) K. The structure was solved by a direct method using the Olex2 [65] and ShelXD [66] software package and refined with the SHELXL package [67]. The structure was refined by full-matrix least squares in the anisotropic approximation for non-hydrogen atoms with respect to F^2. The crystals are monoclinic, crystal size 0.287 × 0.204 × 0.151 mm, *M* 455.50, space group *P*21/*c* (no. 14); the unit cell parameters: *a* 13.7124(3), *b* 11.4209(2), *c* 16.5473(3) Å, β 113.641(3)°, *V* 2373.95(9) Å^3, *Z* 4, d_{calc} 1.274 g/cm^3, μ(CuK_α) 0.704 mm^{-1}, *F*(000) 960.0; θ 7.038°–152.43°,

reflection index intervals: $-17 \le h \le 14$, $-14 \le k \le 14$, $-20 \le l \le 20$; number of measured reflections 40056, number of independent reflections 4956 (R_{int} 0.0293, R_{sigma} 0.0133), number of reflections with $I > 2\sigma(I)$ 4956, number of refined parameters 330, R-factor [$I > 2\sigma(I)$]: R_1 0.0466 (wR_2 0.1345); R-factors for all reflections: R_1 0.0514 (wR_2 0.1397); GOOF by F^2 1.015, $\Delta\rho_{max}/\Delta\rho_{min}$ 0.24/–0.21 e/Å^3. X-Ray diffraction data for compound **8a** were deposited at the Cambridge Crystallographic Data Center (CCDC 2065543).

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

SUPPLEMENTARY INFORMATION

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