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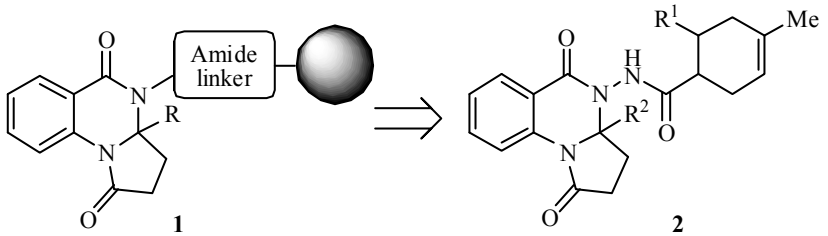
SYNTHESIS OF NOVEL 4-AMINOTETRAHYDROPYRROLO[1,2-*a*]QUINAZOLINE DERIVATIVES

Decarboxylation of substituted monohydrazides of 6-arylcyclohex-3-ene-1,1-dicarboxylic acids proceeds stereospecifically and leads to 1,6-*cis*-disubstituted cyclohex-3-enes. Due to the presence of anthranilic acid moiety these decarboxylated hydrazides undergo formation of pyrrolo[1,2-*a*]quinazolines when treated with 2-oxoglutaric acid. The present paper describes the first example of chemoselective synthesis of amide-linked conjugates between cyclohexene moiety and tetrahydropyrrolo[1,2-*a*]quinazolines.

Keywords: cyclohexene carboxylic acid hydrazides, 2-oxoglutaric acid, pyrrolo-[1,2-*a*]quinazolines, amide linker, stereospecific decarboxylation.

Polyheterocyclic structures containing fused quinazolines are attractive molecular scaffolds due to their broad spectrum of biological activities. A vivid renaissance can be observed in the investigations dealing with pyrrolo[1,2-*a*]-quinazolines **1**. Structures containing this heterocyclic core have been very recently studied as thyroid stimulating hormone receptor agonists [1] and for other applications. Most of synthetic approaches towards pyrrolo[1,2-*a*]quinazolines available prior 1991 have been reviewed [2]. A survey of very recent literature shows the condensation between 2-nitrobenzamides and appropriate dielectrophiles in the presence of $SnCl_2$ [3] or Fe [4] as reducing agents as the preferred method. Additionally, following the *gold rush* pyrrolo[1,2-*a*]quinazolines can be efficiently obtained *via* reaction of anthranilic amides and substituted pent-4-ynoic acids [5]. Other more conventional contemporary methods among others include reaction between nitrile-containing enaminones and anthranilate esters [6] and condensation of 2-oxoglutaric acid [7] and other 4-oxocarboxylic acids [8] with anthranilic amides.

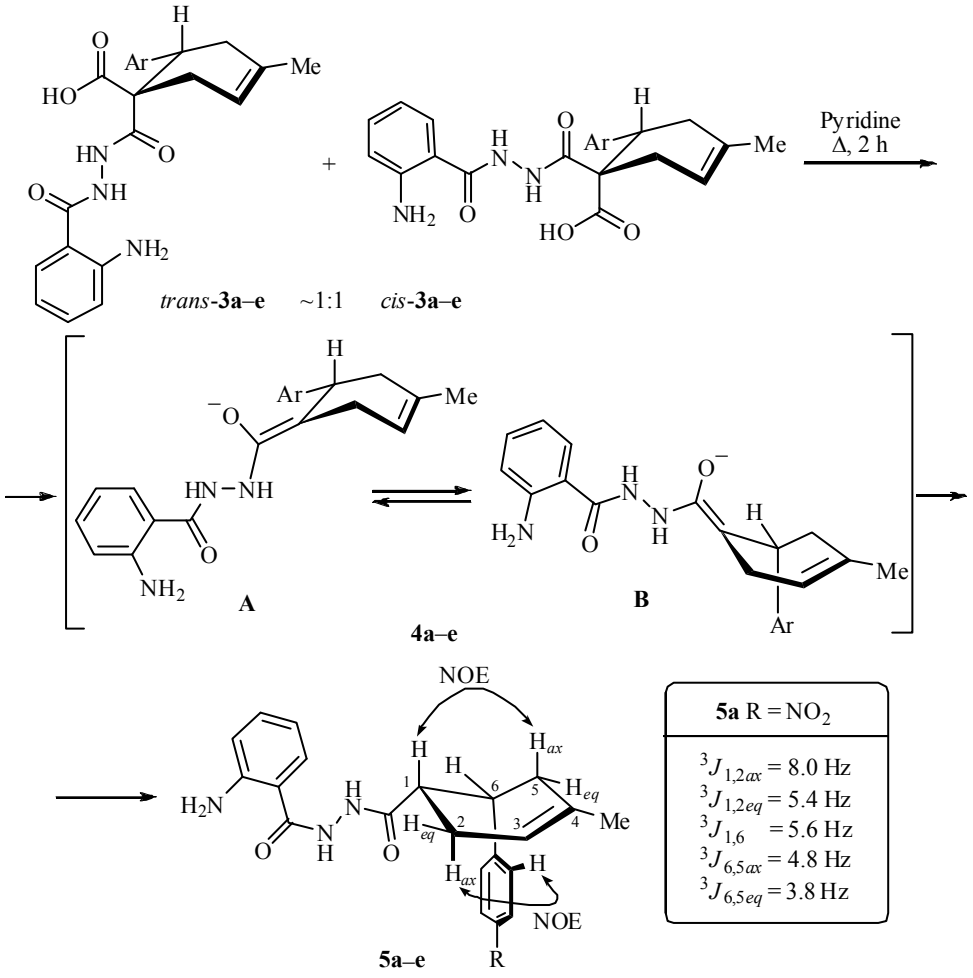


To the best of our knowledge there are only two reports dealing with the synthesis of partially hydrogenated analogs of 4-aminopyrrolo[1,2-*a*]quinazolines. One of the described processes employs anthranilic acid hydrazide, but does not achieve full chemoselectivity, as phthalazino[1,2-*b*]quinazoline is also obtained [9]. A more recent approach uses gold(I)-catalyzed cascade reactions and produces either pyridazinoquinazolinones or derivatives of the title compounds depending on the relative nucleophilicity of nitrogen atoms in variously substituted 2-amino-benzohydrazides [10]. Hence, we proceeded to the synthesis of novel derivatives

of 4-aminopyrrolo[1,2-*a*]quinazolines **2** that can be viewed as amide-linked conjugates (general structure **1**) between the above mentioned fused heterocyclic system and a cyclohexene as a carbocycle of choice.

It is worth to mention that cyclohexene fragment, and, particularly, differently substituted cyclohexene carboxylic acids, are interesting molecular platforms in terms of medicinal chemistry. Thus, the latter fragment orients pharmacophores of well-known drugs Oseltamivir and Tilidine in the correct special arrangement required for their biological activities. Very recently, cyclohexene carboxylic acid derivatives have been successfully studied as full niacin receptor agonists [11]. Additionally, 3-cyclohexene-1-carboxylic acid has been used as a valuable precursor in synthesis of novel cyclohexenyl nucleosides with substantial antiviral activities [12]. Furthermore, synthetic efforts towards substituted cyclohexene carboxylic acids [13] and their structure elucidation [14] have taken place due to their role both in different biosynthetic processes [15] and in fragrance industry [16].

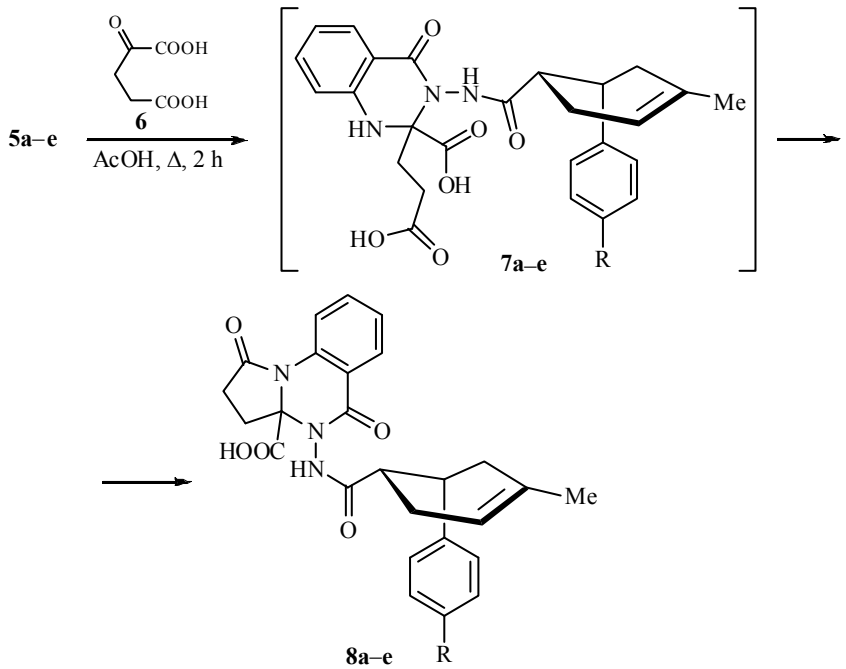
Consequently, we would like to report here an investigation of diastereoselective process towards 2-aminobenzoic acid *N*'-(6-aryl-4-methylcyclohex-3-enecarbonyl)hydrazides **5a**–**d** [17] and their condensation with 2-oxoglutaric acid that chemoselectively generates only 4-amino-1,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*]quinazoline derivatives of type **2**.



3, **4 a–e** Ar = 4-RC_6H_4; **a** R = NO_2, **b** R = F, **c** R = Cl, **d** R = Br, **e** R = H

It is well known that 1,1-dicarboxylic acid derivatives possessing at least one free carboxylic group undergo decarboxylation upon heating in a basic or an acidic medium. Less is known about the diastereoselectivity of such a process and about the influence of neighboring substituents in the cyclohexene systems. Careful investigation of decarboxylation of 1,1-dicarbonyl compounds **3a**–**e** described earlier [17] led us to propose a diastereoselectivity model for the above mentioned process.

Thus, decarboxylation of a nearly 1:1 mixture of dicarbonyl compounds *cis*-**3** and *trans*-**3** led to good isolated yields of **5a**–**e** as pure diastereoisomers. We propose that decarboxylation in a weakly basic pyridine medium produces at equilibrium concentration enolate **4a**–**e** which might exist in two conformations **A** and **B**. Apparently, there is a conformational preference for the form **B** where aryl group occupies a *pseudo-axial* position [18]. Such arrangement diminishes 1,3-allylic strain between the substituent at C-6 atom and substituents on exocyclic double bond [19, 20]. Finally, the protonation of the enolate occurs from the face opposite to that of the aryl group. The overall process leads to 1,6-*cis*-disubstituted cyclohexene derivatives **5a**–**e**. Conformational analysis of products **5a**–**e** including nuclear Overhauser effects and examination of coupling constant fully confirms the above mentioned model. It was found that pyridine is a far better solvent for this process than acetic acid or DMF that were described earlier. It is interesting to note that the yields of compounds **5a**–**e** correlate with the increase of the Hammett constant (σ_{para}) of the substituents in the phenyl ring: NO_2 > Br ≈ Cl > F > H [21].



Com-pound	R	Yield, % (mixture of diastereoisomers)	*dr*
8a	NO_2	83	2.5:1
8b	F	88	1:1
8c	Cl	89	1:1
8d	Br	87	1:1
8e	H	78	1.5:1

With linear precursors in hand, we turned to the construction of pyrrolo[1,2-*a*]-quinazoline moiety. The target compounds **8a**–**e** were obtained in good to excellent yields *via* condensation reaction of linear hydrazides **5a**–**e** with 2-oxoglutaric acid (**6**) in refluxing acetic acid as the reaction medium. Thus, for the first time *N*-substituted 4-amino-1,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*]quinazoline ring system is generated in a chemoselective process without a concurrent formation of phthalazino[1,2-*b*]quinazoline derivatives. The downside of this process is one's inability to control the relative configuration at C-3a atom. Therefore, products **8a**–**e** are obtained and characterized as a mixture of diastereo-isomers, except for compound **8a** which gave separable 2.5:1 mixture of isomers. In the latter case, it was possible to prove that the 1,6-*cis*-arrangement of cyclo-hexene unit is retained, as the analysis of coupling constants and 2D NOESY cross-peaks in product **8a** reveals a pattern similar to that in compound **5a**. It is worth to note that the above mentioned condensation between hydrazides **5a**–**e** and keto-acid **6** was faster and cleaner than that attempted with their carboxyl group-containing parent compounds **3a**–**e**. These latter reacted much slower and produced diastereomeric mixtures of both decarboxylated compounds and their analogs that still contain a free carboxylic group at cyclohexene ring.

In summary, we have demonstrated that due to 1,3-allylic strain 6-arylcyclohex-3-ene-1,1-dicarboxylic acid derivatives produce 1,6-*cis*-substituted cyclohexene derivatives upon decarboxylation. The obtained tetrahydro-1*H*-pyrrolo[1,2-*a*]-quinazoline precursors give the respective title compounds in good isolated yields when treated with 2-oxoglutaric acid.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 spectrometer (300 and 75 MHz, respectively) in DMSO-d_6, residual solvent peak were used as an internal reference (2.50 ppm for ^{1}H NMR, 39.5 ppm for ^{13}C NMR). Elemental analyses were performed on Carlo-Erba Instruments EA 1108 Elemental Analyzer. Melting points were determined on Stuart SMP10 melting point apparatus and are uncorrected. The progress of the reactions was monitored by TLC using Merck silica gel 60 F_{254} plates, detection by UV light and/or I_2 camera. Commercial reagents were used without purification.

Preparation of hydrazides 5a–e (General Method). A solution of compound **3a**–**e** (*cis*/*trans* diastereomeric mixture) (10 mmol) in pyridine (50 ml) was gently refluxed for 2 h. Then it was cooled to ambient temperature and poured into water (150 ml). The precipitate was filtered and recrystallized from EtOH.

***cis*-2-Amino-*N*'-{[4-methyl-6-(4-nitrophenyl)cyclohex-3-en-1-yl]carbonyl}benzohydrazide (5a)**. Yield 3.74 g (95%). Yellowish solid. Mp 223–224°C. ^{1}H NMR spectrum δ, ppm (*J*, Hz): 9.92 (1H, br. s, NH); 9.88 (1H, br. s, NH); 8.08 (2H, d, *J* = 8.7, H-3',5' Ar); 7.57 (2H, d, *J* = 8.7, H-2',6' Ar); 7.50 (1H, d, *J* = 7.2, H Ar); 7.17 (1H, dd, *J* = 8.1, *J* = 7.2, H Ar); 6.72 (1H, d, *J* = 7.2, H Ar); 6.51 (1H, dd, *J* = 8.1, *J* = 7.2, H Ar); 6.40 (2H, br. s, NH_2); 5.51 (1H, br. s, 3-CH); 3.56 (1H, ddd, *J* = 5.6, *J* = 4.8, *J* = 3.8, 6-CH); 2.89 (1H, ddd, *J* = 8.0, *J* = 5.6, *J* = 5.4, 1-CH); 2.47 (1H, dd, *J* = 17.7, *J* = 3.8) and 2.36 (1H, dd, *J* = 17.7, *J* = 4.8, 5-CH_2); 2.14 (1H, dd, *J* = 17.7, *J* = 5.4) and 2.01 (1H, dd, *J* = 17.7, *J* = 8.0, 2-CH_2); 1.76 (3H, br. s, CH_3). ^{13}C NMR spectrum, δ, ppm: 172.2 (CO); 168.2 (CO); 151.0 (C); 149.8 (C); 146.0 (C); 132.7 (C); 132.2 (CH); 129.6 (CH); 128.2 (CH); 122.8 (CH); 119.9 (CH); 116.3 (CH); 114.6 (CH); 112.6 (C); 42.4 (CH); 41.2 (CH); 34.5 (CH_2); 24.4 (CH_2); 23.3 (CH_3). Found, %: C 63.80; H 5.49; N 14.07. $C_{21}H_{22}N_4O_4$. Calculated, %: C 63.95; H 5.62; N 14.20.

***cis*-2-Amino-*N*'-{[6-(4-fluorophenyl)-4-methylcyclohex-3-en-1-yl]carbonyl}benzohydrazide (5b)**. Yield 2.94 g (80%). White solid. Mp 102–104°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.92 (1H, br. s, NH); 9.80 (1H, br. s, NH); 7.52 (1H, d, *J* = 8.0, H Ar); 7.31 (2H,

dd, *J* = 8.8, *J* = 5.8, H-3',5' Ar); 7.17 (1H, t, *J* = 8.0, H Ar); 7.02 (2H, t, *J* = 8.8, H-2',6' Ar); 6.73 (1H, d, *J* = 8.0, H Ar); 6.52 (1H, t, *J* = 8.0, H Ar); 6.39 (2H, br. s, NH_2); 5.47 (1H, br. s, 3-CH); 3.49–3.36 (1H, m, 6-CH); 2.83–2.77 (1H, m, 1-CH); 2.45 (1H, br. d, *J* = 18.3) and 2.31 (1H, br. d, *J*=18.3, 5-CH_2); 2.16–1.94 (2H, m, 2-CH_2); 1.74 (3H, br. s, CH_3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 172.6 (CO); 168.2 (CO); 160.8 (d, *J* = 242.0, C); 149.8 (C); 138.7 (d, *J* = 3.0, C); 133.0 (C); 132.2 (CH); 130.0 (d, *J* = 8.0, CH); 128.3 (CH); 119.9 (CH); 116.3 (CH); 114.5 (CH); 114.3 (d, *J* = 21.0, CH); 112.8 (C); 41.4 (CH); 39.7 (CH); 35.3 (CH_2); 24.5 (CH_2); 23.3 (CH_3). Found, %: C 68.24; H 6.00; N 11.28. $C_{21}H_{22}FN_3O_2$. Calculated, %: C 68.65; H 6.04; N 11.44.

***cis*-2-Amino-*N*'-{[6-(4-chlorophenyl)-4-methylcyclohex-3-en-1-yl]carbonyl}benzohydrazide (5c)**. Yield 3.42 g (89%). White solid. Mp 231–233°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.91 (1H, br. s, NH); 9.81 (1H, br. s, NH); 7.51 (1H, d, *J* = 8.0, H Ar); 7.32–7.24 (4H, m, H Ar'); 7.17 (1H, t, *J* = 8.0, H Ar); 6.72 (1H, d, *J* = 8.0, H Ar); 6.52 (1H, t, *J* = 8.0, H Ar); 6.38 (2H, br. s, NH_2); 5.47 (1H, br. s, 3-CH); 3.45–3.37 (1H, m, 6-CH); 2.84–2.77 (1H, m, 1-CH); 2.44, (1H, br. d, *J* = 17.1) and 2.30 (1H, br. d, *J* =17.1, 5-CH_2); 2.15–1.94 (2H, m, 2-CH_2); 1.74 (3H, br. s, CH_3). ^{13}C NMR spectrum, δ, ppm: 172.5 (CO); 168.2 (CO); 149.8 (C); 141.6 (C); 132.9 (C); 132.3 (CH); 130.8 (C); 130.1 (CH); 128.3 (CH); 127.6 (CH); 119.9 (CH); 116.3 (CH); 114.5 (CH); 112.8 (C); 41.3 (CH); 40.3 (CH); 35.0 (CH_2); 24.4 (CH_2); 23.3 (CH_3). Found, %: C 65.31; H 5.71; N 10.69. $C_{21}H_{22}ClN_3O_2$. Calculated, %: C 65.71; H 5.78; N 10.95.

***cis*-2-Amino-*N*'-{[6-(4-bromophenyl)-4-methylcyclohex-3-en-1-yl]carbonyl}benzohydrazide (5d)**. Yield 3.60 g (84%). White solid. Mp 205–207°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.90 (1H, br. s, NH); 9.81 (1H, br. s, NH); 7.52 (1H, d, *J* = 8.0, H Ar); 7.38 (2H, d, *J* = 8.5, H Ar'); 7.24 (2H, d, *J* = 8.5, H Ar'); 7.17 (1H, t, *J* = 8.0, H Ar); 6.72 (1H, d, *J* = 8.0, H Ar); 6.51 (1H, t, *J* = 8.0, H Ar); 6.38 (2H, br. s, NH_2); 5.46 (1H, br. s, 3-CH); 3.42–3.36 (1H, m, 6-CH); 2.84–2.76 (1H, m, 1-CH); 2.43 (1H, br. d, *J* = 17.0) and 2.29 (1H, br. d, *J* =17.0, 5-CH_2); 2.14–1.94 (2H, m, 2-CH_2); 1.73 (3H, br. s, CH_3). ^{13}C NMR spectrum, δ, ppm: 172.5 (CO); 168.2 (CO); 149.8 (C); 142.1 (C); 132.9 (C); 132.2 (CH); 130.6 (CH); 130.5 (CH); 128.2 (CH); 119.9 (CH); 119.3 (C); 116.3 (CH); 114.5 (CH); 112.7 (C); 41.3 (CH); 39.9 (CH); 34.9 (CH_2); 24.4 (CH_2); 23.3 (CH_3). Found, %: C 58.94; H 5.02; N 9.73. $C_{21}H_{22}BrN_3O_2$. Calculated, %: C 58.89; H 5.18; N 9.81.

***cis*-2-Amino-*N*'-{[4-methyl-6-phenylcyclohex-3-en-1-yl]carbonyl}benzohydrazide (5e)**. Yield 2.38 g (68%). White solid. Mp 108–110°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.91 (1H, br. s, NH); 9.77 (1H, br. s, NH); 7.52 (1H, d, *J* = 8.2, H Ar); 7.30–7.10 (6H, m, H Ar, H Ph); 6.72 (1H, d, *J* = 8.2, H Ar); 6.51 (1H, t, *J* = 8.2, H Ar); 6.38 (2H, br. s, NH_2); 5.46 (1H, br. s, 3-CH); 3.42–3.36 (1H, m, 6-CH); 2.86–2.79 (1H, m, 1-CH); 2.42–2.36 (2H, m, 5-CH_2); 2.12–2.05 (2H, m, 2-CH_2); 1.74 (3H, br. s, CH_3). ^{13}C NMR spectrum, δ, ppm: 172.7 (CO); 168.2 (CO); 149.8 (C); 142.8 (C); 133.2 (C); 132.2 (CH); 128.3 (CH); 128.2 (CH); 127.8 (CH); 126.1 (CH); 119.9 (CH); 116.3 (CH); 114.6 (CH); 112.8 (C); 41.4 (CH); 40.4 (CH); 35.2 (CH_2); 24.9 (CH_2); 23.4 (CH_3). Found, %: C 71.83; H 6.58; N 11.87. $C_{21}H_{23}N_3O_2$. Calculated, %: C 72.18; H 6.63; N 12.03.

Preparation of compounds 8a–e (General Method). A solution of hydrazide **5a–e** (10.0 mmol) and 2-oxoglutaric acid (**6**) (1.75 g, 12.0 mmol) in glacial AcOH (75 ml) was gently refluxed for 2 h. The resulting reaction mixture was cooled to ambient temperature, the precipitate was filtered and recrystallized from glacial AcOH (350 ml). Analytical samples of the obtained compounds **8a–e** were additionally recrystallized from appropriate solvent.

4-({[4-Methyl-6-(4-nitrophenyl)cyclohex-3-en-1-yl]carbonyl}amino)-1,5-dioxo-2,3,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3a(1*H*)-carboxylic acid (8a). Yield 4.18 g (83%). Yellowish solid. Mp >310 °C (decomp.). Analytical sample of one pure diastereoisomer was obtained by crystallization from *n*-BuOH. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 14.33 (1H, br. s, COOH); 10.28 (1H, s, NH); 8.17 (1H, d, *J* = 8.0, H Ar); 8.06–8.01 (3H, m, H Ar, H Ar'); 7.71 (1H, t, *J* = 8.0, H Ar); 7.57 (2H, d, *J* = 8.7, H Ar'); 7.39 (1H, d, *J* = 8.0, H Ar); 5.52 (1H, br. s, 3'-CH); 3.69 (1H, dt, *J* = 4.9, *J* = 3.1, 6'-CH); 3.13 (1H, ddd, *J* = 9.0, *J* = 5.3, *J* = 4.9, 1'-CH); 2.81–2.62 (2H, m) and 2.61–2.38 (2H, m, 2,3-CH_2); 2.37–2.22 (2H, m, 5'-CH_2); 2.09 (1H, dd, *J* = 18.0, *J* = 5.3) and 1.97 (1H, dd, *J* = 18.0, *J* = 9.0,

2'-CH_2); 1.76 (3H, br. s, CH_3). ^{13}C NMR spectrum, δ, ppm: 174.4 (CO); 172.7 (CO); 171.1 (CO); 161.6 (CO); 150.9 (C); 146.1 (C); 135.7 (C); 134.4 (CH); 133.0 (C); 129.7 (CH); 128.7 (CH); 125.5 (CH); 122.7 (CH); 120.1 (CH); 119.1 (CH); 118.6 (C); 81.4 (C); 40.9 (CH); 40.1 (CH); 35.0 (CH_2); 29.9 (CH_2); 26.0 (CH_2); 24.1 (CH_2); 23.3 (CH_3). Found, %: C 61.88; H 4.78; N 10.99. $C_{26}H_{24}N_4O_7$. Calculated, %: C 61.90; H 4.80; N 11.11.

4-({[6-(4-Fluorophenyl)-4-methylcyclohex-3-en-1-yl]carbonyl}amino)-1,5-dioxo-2,3,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3a(1*H*)-carboxylic acid (8b). Yield 4.20 g (88%). White solid. Mp 288–302°C (EtOH). ^{1}H and ^{13}C NMR spectra are described as 1:1 mixture of racemic (3a*R**,1'*S**,6'*R**)- and (3a*S**,1'*S**,6'*R**)-diastereoisomers. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 14.28 (1H, br. s, COOH); 10.18 (0.5H, s, NH); 9.86 (0.5H, s, NH); 8.17 (0.5H, d, *J* = 8.9, H Ar); 8.13 (0.5H, d, *J* = 8.5, H Ar); 8.02 (0.5H, d, *J* = 8.0, H Ar); 7.90 (0.5H, d, *J* = 7.7, H Ar); 7.73–7.64 (1H, m, H Ar); 7.41–7.27 (3H, m, H Ar); 7.12 (1H, t, *J* = 8.9, H Ar); 6.98 (1H, t, *J* = 8.9, H Ar); 5.48 (0.5H, br. s, 3'-CH); 5.41 (0.5H, br. s, 3'-CH); 3.59–3.54 (0.5H, m, CH); 3.26–3.20 (0.5H, m, CH); 3.15–3.09 (0.5H, m, CH); 3.06–2.98 (0.5H, m, CH); 2.80–2.60 (2H, m, CH_2); 2.59–2.14 (4H, m, 2CH_2); 2.06–1.96 (2H, m, CH_2); 1.74 (1.5H, br. s, CH_3); 1.69 (1.5H, br. s, CH_3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 174.8 (CO); 174.7 (CO); 172.8 (CO); 172.7 (CO); 171.1 (CO); 171.0 (CO); 161.7 (CO); 160.9 (d, *J* = 242.0, C); 160.8 (d, *J* = 242.0, C); 160.6 (CO); 139.6 (d, *J* = 3.0, C); 138.5 (d, *J* = 3.0, C); 135.7 (C); 135.6 (C); 134.3 (CH); 134.1 (CH); 133.3 (C); 133.1 (C); 130.1 (d, *J* = 8.0, CH); 129.7 (d, *J* = 8.0, CH); 128.6 (CH); 128.3 (CH); 125.4 (CH); 125.3 (CH); 120.1 (CH); 119.0 (bs, 2CH); 118.7 (C); 118.6 (C); 118.5 (CH); 114.8 (d, *J* = 21.0, CH); 114.2 (d, *J* = 21.0, CH); 81.4 (C); 80.8 (C); 41.2 (CH); 40.6 (CH); 39.4 (br, 2CH); 35.8 (CH_2); 33.4 (CH_2); 29.9 (CH_2); 29.8 (CH_2); 26.9 (CH_2); 26.4 (CH_2); 26.0 (CH_2); 24.0 (CH_2); 23.5 (CH_3); 23.3 (CH_3). Found, %: C 65.12; H 4.99; N 8.69. $C_{26}H_{24}FN_3O_5$. Calculated, %: C 65.40; H 5.07; N 8.80.

4-({[6-(4-Chlorophenyl)-4-methylcyclohex-3-en-1-yl]carbonyl}amino)-1,5-dioxo-2,3,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3a(1*H*)-carboxylic acid (8c). Yield 4.40 g (89%). White solid. Mp 302–304 °C (EtOH). ^{1}H and ^{13}C NMR spectra are described as 1:1 mixture of racemic (3a*R**,1'*S**,6'*R**)- and (3a*S**,1'*S**,6'*R**)-diastereoisomers ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 14.26 (1H, br. s, COOH); 10.20 (0.5H, s, NH); 9.88 (0.5H, s, NH); 8.17 (0.5H, d, *J* = 8.0, H Ar); 8.14 (0.5H, d, *J* = 8.0, H Ar); 8.02 (0.5H, d, *J* = 8.0, H Ar); 7.90 (0.5H, d, *J* = 8.0, H Ar); 7.73–7.64 (1H, m, H Ar); 7.41–7.26 (4H, m, H Ar); 7.21 (1H, d, *J* = 8.4, H Ar); 5.48 (0.5H, br. s, 3'-CH); 5.42 (0.5H, br. s, 3'-CH); 3.58–3.52 (0.5H, m, CH); 3.27–3.20 (0.5H, m, CH); 3.17–3.10 (0.5H, m, CH); 3.07–3.00 (0.5H, m, CH); 2.81–2.60 (2H, m, CH_2); 2.59–2.13 (4H, m, 2CH_2); 2.10–1.91 (2H, m, CH_2); 1.74 (1.5H, br. s, CH_3); 1.69 (1.5H, br. s, CH_3). ^{13}C NMR spectrum, δ, ppm: 174.8 (CO); 174.6 (CO); 172.7 (CO); 172.6 (CO); 171.1 (CO); 171.0 (CO); 161.7 (CO); 160.6 (CO); 142.4 (C); 141.5 (C); 135.7 (C); 135.6 (C); 134.3 (CH); 134.1 (CH); 133.2 (C); 133.1 (C); 131.0 (C); 130.7 (C); 130.2 (CH); 129.8 (CH); 128.7 (CH); 128.4 (CH); 128.1 (CH); 127.5 (CH); 125.4 (CH); 125.3 (CH); 120.1 (CH); 119.1 (CH); 119.0 (CH); 118.7 (C); 118.6 (CH); 118.5 (C); 81.4 (C); 80.8 (C); 41.0 (CH); 40.5 (CH); 39.7 (CH); 39.6 (CH); 35.5 (CH_2); 33.3 (CH_2); 29.9 (CH_2); 29.8 (CH_2); 26.7 (CH_2); 26.4 (CH_2); 26.0 (CH_2); 24.0 (CH_2); 23.5 (CH_3); 23.3 (CH_3). Found, %: C 63.41; H 4.78; N 8.41. $C_{26}H_{24}ClN_3O_5$. Calculated, %: C 63.22; H 4.90; N 8.51.

4-({[6-(4-Bromophenyl)-4-methylcyclohex-3-en-1-yl]carbonyl}amino)-1,5-dioxo-2,3,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3a(1*H*)-carboxylic acid (8d). Yield 4.68 g (87%). White solid. Mp >310 °C (decomp.) (EtOH). ^{1}H and ^{13}C NMR spectra are described as 1:1 mixture of racemic (3a*R**,1'*S**,6'*R**)- and (3a*S**,1'*S**,6'*R**)-diastereoisomers ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 14.26 (1H, br. s, COOH); 10.20 (0.5H, s, NH); 9.88 (0.5H, s, NH); 8.17 (0.5H, d, *J* = 7.4, H Ar); 8.14 (0.5H, d, *J* = 8.4, H Ar); 8.02 (0.5H, d, *J* = 7.5, H Ar); 7.90 (0.5H, d, *J* = 7.7, H Ar); 7.73–7.64 (1H, m, H Ar); 7.49 (1H, d, *J* = 8.5, H Ar); 7.41–7.31 (2H, m, H Ar); 7.25 (1H, d, *J* = 8.7, H Ar); 7.21 (1H, d, *J* = 8.5, H Ar); 5.49 (0.5H, br. s, 3'-CH); 5.42 (0.5H, br. s, 3'-CH); 3.57–3.51 (0.5H, m, CH); 3.26–3.18 (0.5H, m, CH); 3.17–3.10 (0.5H, m, CH); 3.07–3.00 (0.5H, m, CH); 2.80–2.55 (2H, m, CH_2); 2.44–2.14 (4H, m, CH_2); 2.11–1.93 (2H, m, CH_2); 1.74 (1.5H, br. s, CH_3); 1.69

(1.5H, br. s, CH_3). ^{13}C NMR spectrum, δ, ppm: 174.7 (CO); 174.5 (CO); 172.6 (CO); 172.5 (CO); 171.0 (CO); 170.9 (CO); 161.6 (CO); 160.5 (CO); 142.7 (C); 141.9 (C); 135.6 (C); 135.5 (C); 134.2 (CH); 134.0 (CH); 133.2 (C); 133.0 (C); 130.9 (CH); 130.6 (CH); 130.4 (CH); 130.1 (CH); 128.6 (CH); 128.3 (CH); 125.4 (CH); 125.3 (CH); 120.0 (CH); 119.4 (C); 119.2 (C); 119.0 (CH); 118.9 (CH); 118.7 (CH); 118.6 (C); 118.5 (C); 81.4 (C); 80.7 (C); 40.9 (CH); 40.4 (CH); 39.6 (br, 2CH); 35.4 (CH_2); 33.2 (CH_2); 29.8 (CH_2); 29.7 (CH_2); 26.6 (CH_2); 26.3 (CH_2); 25.9 (CH_2); 24.0 (CH_2); 23.4 (CH_3); 23.3 (CH_3). Found, %: C 57.76; H 4.34; N 7.67. $C_{26}H_{24}BrN_3O_5$. Calculated, %: C 58.00; H 4.49; N 7.80.

4-({[4-Methyl-6-phenylcyclohex-3-en-1-yl]carbonyl}amino)-1,5-dioxo-2,3,4,5-tetrahydropyrrolo[1,2-*a*]quinazoline-3a(1*H*)-carboxylic acid (8e). Yield 3.58 g (78%). White solid. Mp 200–201°C (EtOH–H_2O, 2:1).^1H and ^{13}C NMR spectra are described as 1.5:1 mixture of racemic (3a*R**,1'*S**,6'*R**)- and (3a*S**,1'*S**,6'*R**)-diastereoisomers. ^1H NMR spectrum, δ, ppm (*J*, Hz): 14.23 (1H, br. s, COOH); 10.14 (0.6H, s, NH); 9.84 (0.4H, s, NH); 8.17 (0.6H, d, *J* = 8.1, H Ar); 8.12 (0.4H, d, *J* = 8.1, H Ar); 8.03 (0.6H, d, *J* = 8.1, H Ar); 7.90 (0.4H, d, *J* = 8.1, H Ar); 7.73–7.63 (1H, m, H Ar); 7.41–7.25 (4H, m, H Ar); 7.22–7.10 (2H, m, H Ar); 5.48 (0.6H, br. s, HC=); 5.41 (0.4H, br. s, HC=); 3.57–3.51 (0.6H, m, CH); 3.24–3.11 (0.8H, m, 2CH); 3.08–3.00 (0.6H, m, CH); 2.78–2.59 (2H, m, CH_2); 2.58–2.12 (4H, m, $2CH_2$); 2.06–1.91 (2H, m, CH_2); 1.75 (1.8H, br. s, CH_3); 1.69 (1.2H, br. s, CH_3). ^{13}C NMR spectrum, δ, ppm: 175.2 (CO); 175.1 (CO); 173.1 (CO); 173.0 (CO); 171.5 (CO); 171.4 (CO); 162.1 (CO); 161.0 (CO); 143.8 (C); 142.9 (C); 136.1 (C); 136.0 (C); 134.7 (CH); 134.5 (CH); 133.9 (C); 133.6 (C); 129.0 (CH); 128.8 (CH); 128.7 (CH); 128.6 (CH); 128.3 (CH); 128.0 (CH); 126.8 (CH); 126.5 (CH); 125.9 (CH); 125.8 (CH); 120.4 (CH); 119.5 (CH); 119.4 (CH); 119.1 (C); 119.0 (C); 118.9 (CH); 81.9 (C); 81.2 (C); 41.6 (CH); 40.9 (CH); 40.6 (CH); 40.5 (CH); 36.1 (CH_2); 33.6 (CH_2); 30.3 (CH_2); 30.2 (CH_2); 27.5 (CH_2); 26.7 (CH_2); 26.4 (CH_2); 24.8 (CH_2); 24.0 (CH_3); 23.8 (CH_3). Found, %: C 67.79; H 5.36; N 9.19. $C_{26}H_{25}N_3O_5$. Calculated, %: C 67.96; H 5.48; N 9.14.

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