Synthesis of Novel Annelated Systems Based on the Interaction and Reactivity Estimation of Amino-1,5-benzodiazepin-2-ones with Dimethyl-2-oxoglutaconate

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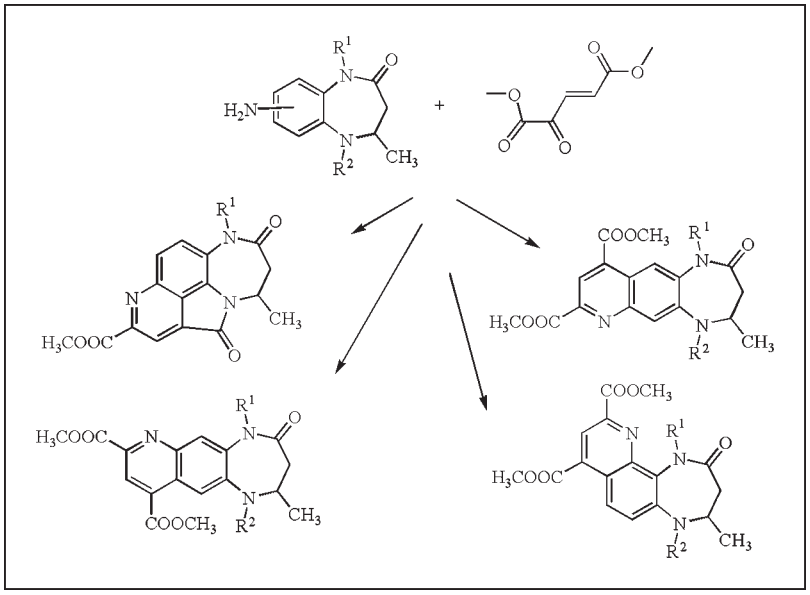

A number of substituted tetracyclic 4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole and tricyclic 1*H*-[1,4]diazepino[2,3-*g*] or [2,3-*h*]quinoline derivatives were prepared from 7- (or 8, or 9)amino-1,5-benzodiazepin-2-ones by the Doebner–von Miller quinoline synthesis. The structure of the cyclized products depends on the position of the primary amino group and on the substituents of the diazepine ring of the starting compounds. The regiochemical outcome of the reaction was estimated by calculating average local ionization energies on the molecular surface at the Density Functional Theory (DFT) level of theory.

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INTRODUCTION

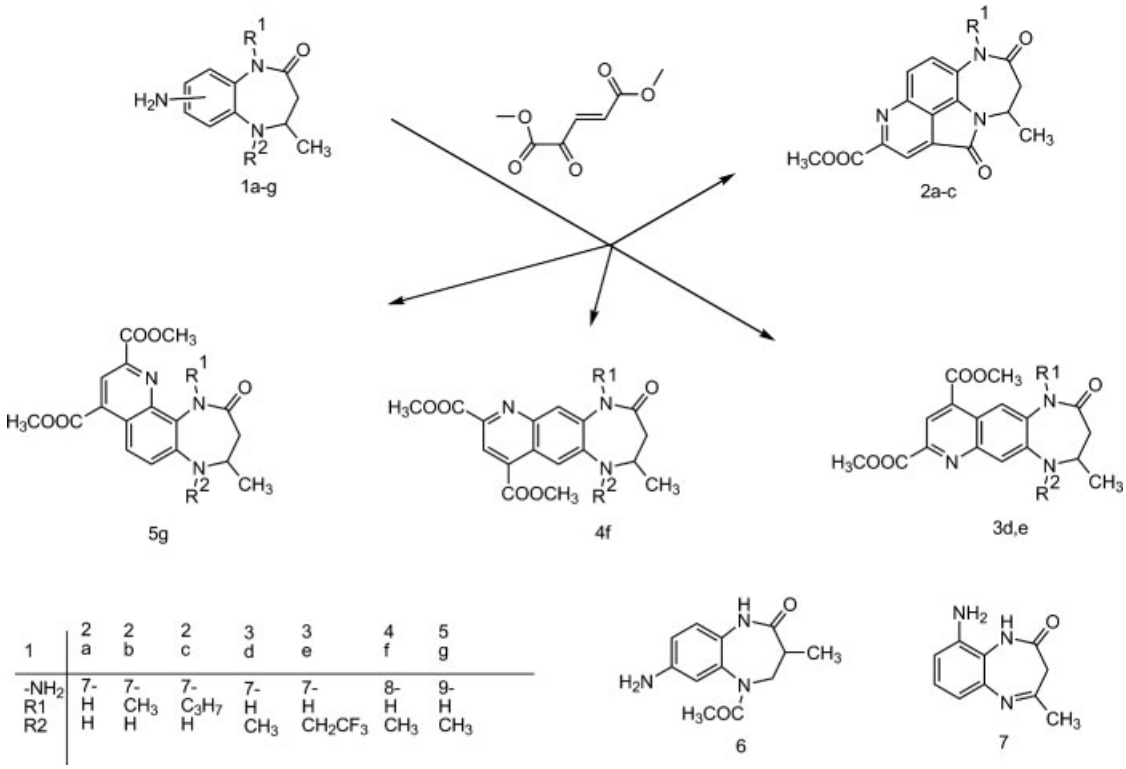
Benzodiazepines and their polycyclic derivatives are known as medically active synthetic substances [1]. Quinoline ring system derivatives are important as antimalarial agents. In addition, quinolines are present as structural subunits of naturally occurring products, such as quinonoid alcohol dehydrogenase coenzyme [2,3]. Numerous papers have described the synthesis of polycyclic 1,5-benzodiazepine derivatives with a pyridine ring annelated to the heptatomic diazepine nucleus [4]. It is known that some of such derivatives exhibit widespread biological activities. As a continuation of our interest in polycyclic 1,5-benzodiazepines we investigated the combination of the diazepine and quinoline heterocycles in the common polyheterocyclic system where the pyridine ring is annelated to the aromatic ring of bicyclic benzodiazepine.

The classical Skraup-Doebner-von Miller synthesis is among the most general approaches to the quinoline ring system [2,3]. The key substrates for this condensation reaction are aromatic amines and α,β-unsaturated ketones [2]. In this article, we report our results on the preparation of tetracyclic diazepinopyridoindoles and tricyclic diazepinoquinolines.

RESULTS AND DISCUSSION

In this study, 7-(or 8, or 9)amino-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **1a–g** were used as starting amine components to prepare annelated derivatives

Scheme 1



1	2 a	2 b	2 c	3 d	3 e	4 f	5 g
-NH_2	7-	7-	7-	7-	7-	8-	9-
R1	H	CH_3	C_3H_7	H	H	H	H
R2	H	H	H	CH_3	CH_2CF_3	CH_3	CH_3

(Scheme 1). Cyclocondensation was accomplished by the reaction of amines with dimethyl-2-oxoglutaconate [5] (modified Doebner-von Miller sequence) in a single step. Thus, the treatment of amines **1a–g** with 1.5 equiv of dimethyl-2-oxoglutaconate in dichloromethane at room temperature for 24 h and then for additional 24 h after the addition of 3*M* hydrogen chloride solution in glacial acetic acid gave cyclic derivatives **2a–c, 3d,e, 4f,** and **5g**. The yields of compounds ranged from poor to moderate (16–51%).

For the application of this cyclization methodology, first we employed amines **1a–c,** which did not possess an alkyl group on the N_5 atom of the heterocyclic diazepine ring. The reaction of **1a–c** with dimethyl-2-oxoglutaconate afforded tetracyclic tetrahydro-4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole derivatives **2a–c**. During the first stage of this reaction, the amino group added to the carbon atom of unsaturated ketone at β-position with respect to the ketonic function and cyclization occurred to give the cyclized piperidinol [3]. The addition of the acid catalyst effected the dehydration and aromatization of the latter together with intramolecular acylation of the diazepine ring N_5 atom by the cyclic ester group and an indole ring was formed [6]. The pyridine ring closure in 7-aminoderivatives **1a–c** took place at the 6-position of the benzodiazepine moiety.

When 7-amino-5-alkylsubstituted benzodiazepinones **1d,e** were treated with oxoglutaconate, the cyclocondensation proceeded at the 8-position of the bicyclic heterocycle and linear tricyclic diazepinoquinolines **3d,e** were obtained. The TLC analysis did not indicate the formation of isomeric products. On the other hand, the reaction of amine **6** with oxoglutaconate under parallel reaction conditions did not take place, and about 30% of the starting N_5-acetylsubstituted amine **6** was recovered.

Analogically, the cyclocondensation of 8-amino **1f** and 9-aminoderivative **1g** with oxoglutaconate under the same conditions gave linear [1,4]diazepino[2,3-*g*]quinoline **4f** and angular [1,4]diazepino[2,3-*h*]quinoline **5g**, respectively (in low yields). The isolation of the reaction products was rather complicated because the formation of polymeric products of unknown structure was observed. The attempts to prepare a new tricyclic derivative from 9-amino-2,3-dihydro-1,5-benzodiazepin-2-one **7** were not straightforward. In the reaction of **7** with oxoglutaconate, the isolated product was not identified. In the ^{1}H NMR spectrum, the observed signals at 8.79 (pyridine ring), doublets at 8.73 and 7.91 (benzene ring), and singlets at 4.09 and 4.10 ppm ($COOCH_3$ groups) confirmed the presence of the 2,4-substituted quinoline structure fragment (compare with **5g**), but there were no signals dependant on diazepine unit

protons. Our early studies showed that in acidic medium the split of the N_5—C_4 bond of dihydro-1,5-benzodiazepinones or their transformation to a five-membered cycle could occur [7].

The synthesis of the starting materials **1a** [8] and **1d,f** [9] was described in our previous studies. Derivatives **1b,c,e,g, 6** and **7** were then easily obtained from the corresponding nitroderivatives **8b,c,e,g,** 5-acetyl-3-methyl-7-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**9**) and 2,3-dihydro-4-methyl-9-nitro-1*H*-1,5-benzodiazepin-2-one (**10**) [10] by catalytic hydrogenation. 1,4-Dimethyl-7-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**8b**) and 4-methyl-7-nitro-5-(2,2,2-trifluorethyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**8e**) were prepared according to the procedure described in our previous work [11]. Compound **8c** was synthesized by alkylation of 4-methyl-7-nitro-1,3,4,5,-tetrahydro-2*H*-1,5-benzodiazepin-2-one [12] with 1-bromopropane under phase-transfer catalysis conditions. 4,5-Dimethyl-9-nitroderivative **8g** was prepared by reductive alkylation of dihydronitroderivative **10** with sodium borohydride and formic acid. Compound **9** was synthesized by nitration of 5-acetyl-3-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one [13]. The starting aminobenzodiazepinones carrying various alkyl groups at the N_1 and N_5 atoms of the diazepine heterocycle ring were chosen for their acute solubility in organic solvents.

The structures attributed to the compounds described in this article are consistent with the results of elemental analysis, IR, ^{1}H and ^{13}C NMR spectral data. In this connection, the ^{1}H NMR spectra of linear and angular condensed regioisomeric systems are particularly significant. The signals of two benzene ring protons form two doublets or two singlets for compounds **2a–c, 5g** and **3d,e, 4f**, respectively. These assignments are unambiguously confirmed when NOE is observed between amide group (N—H) or methyl group (N—CH_3) protons and the nearest benzene ring proton (16–25% and 11–24%, respectively). Furthermore, we can point out that the ^{1}H NMR spectra of **2a–c** confirm the structure attributed to these tetracyclic systems because no signals for heterocyclic amine (N—H) group and for one of OCH_3 group protons were detected. Moreover, the diazepine CH proton signals were shifted downfield by about 0.9 ppm with respect to those of the starting compounds **1a–c**. It is interesting to note that the vicinal spin-spin coupling constants of seven-membered ring protons for **2a–c** were very low (2.1–2.4 and 5.3–5.4 Hz) in comparison with those of precursors **1b,c** (7.5–7.7 and 5.2 Hz) or 5-acetyl-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (13.0 Hz) [14]. This observation suggests that the conformation of the seven-membered ring in tetracyclic derivatives **2a–c** is exchanged. ^{13}C NMR spectral data agree with the proposed structures.

The quinoline derivatives are highly colored compounds and ethanolic solutions of **3d,e** and **4f** exhibit deep colors accompanied with fluorescence.

Generally, we have described the synthesis of novel heterocyclic systems from various N_1- and N_5-substituted amino-1,5-benzodiazepinones employing the Doebner-von Miller quinoline synthesis. It is confirmed that the formation of a new pyridine ring takes place at the adjacent position with respect to the primary amine group of the starting compound. However, the regiochemical outcome of cyclization reaction for asymmetrically substituted aromatic amines is unpredictable [3,15]. To get more insight into the nature of the studied cyclization process, the theoretical investigation of the electronic structure of the starting compounds was carried out.

Considering the reaction mechanism of the Doebner-von Miller quinoline synthesis, it was shown [2,3,15] that cyclization reaction involves a stepwise mechanism. The cyclocondensation step is based on the electrophilic addition to the carbon atom of the aromatic ring [2,15]. This step determinates the regiochemical features of the reaction. Hence, our goal was to estimate the most reactive aromatic sites for electrophilic attack. One of the best indicators of electrophilic attraction is provided by local ionization energy map calculations based on molecular electron density surfaces [16–22].

In this study, we computed local ionization energy maps for a series of N_1- and N_5-substituted amino-1,5-benzodiazepinones **1a,b,d,f,g** and **6**. First, a conformational search was performed using Molecular Mechanics Force Field to identify the lowest energy conformer for each structure [23]. The lowest energy conformer structures were further optimized using quantum mechanics at the DFT level of theory with B3LYP functional and 6-31G* basis set [24]. This basis set then was used to calculate the local ionization energy map on three dimension surfaces corresponding to the contour of constant electronic density equal to 0.025 electron/bohr^3 [17,23–25]. The surface of value 0.025 electron/bohr^3 displays the surface that indicates electron density on the π-electron surface of aromatic compounds. The literature [17,25] suggests that this contour gives physically reasonable molecular dimensions and reflects molecular features such as bond formation, electron lone pairs, *etc*.

We present two distinct and typical local ionization energy maps, which are most important for the interpretation of the observed regiochemistry. Figure 1 demonstrates the optimized geometry structures of **1a** and **6** heterocycles and shows the computed local ionization energy maps onto the molecular surfaces of these heterocycles. The dark gray regions on the surface area around the aromatic ring represent localizations on the

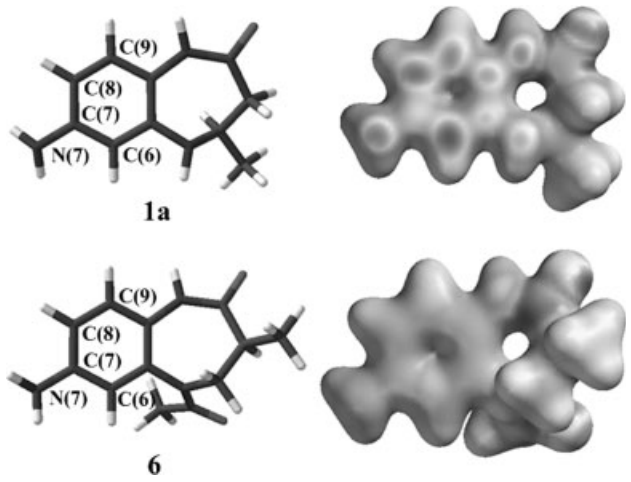


Figure 1. Optimized geometry structures and local ionization energy surface maps on the molecular surfaces defined by the contour of constant electron density equal 0.025 electron/bohr^3 for compounds **1a** and **6**. Color ranges in kcal/mol: from dark gray 259.43 to bright gray 593.62.

molecular surface where electron removal occurs easily (with minimal energy). For **1a** the lowest average localization of local ionization energies are found at adjacent positions with respect to the aromatic primary amino group. The results indicate the affinity to electrophiles at the adjacent positions of the aromatic carbon atoms. Analogical tendencies in localization of the lowest average local ionization energies are observed for heterocycles **1b,d,f,g** (not shown in Fig. 1). Otherwise, the pictured evenly gray molecular surface above the aromatic ring area for **6** shows that the aromatic ring is deactivated toward the electrophilic attack. Experimentally, the reaction of amine **6** with oxoglutaconate does not lead to the cyclized product. These findings reveal the deactivating tendency of the acetyl group in **6** for the pending reaction. In Table 1, the smallest local ionization energy values (I_{min}) and total energy values for optimized geometry structures **1a,b,d,f,g** and **6** are presented. I_{min} values are the points at which the smallest amount of energy is required to remove the electron from the surface and show the most reactive sites toward electrophiles. The lowest average local ionization energy localizations (Fig. 1) for 7-amino substituted **1a** are found on the molecular surface over the aromatic C_6 and C_8 atoms. Furthermore, as shown in Table 1, the I_{min} values for **1a,b** are lower for C_6 position than for C_8. This suggests a higher electrophilic affinity and propensity of ring cyclization at C_6 position. In the experiments with 7-aminoderivatives **1a–c**, the pyridine ring closure is observed at C_6 position. The lowest I_{min} values for 7-amino-5-methylsubstituted **1d** located above the C_8 atom show the C_8-directing ring closure tendency. Accordingly, the experimental cyclocondensation of compound **1d** proceeds at C_8 position. In the case of 7-amino-5-acetylsubstituted derivative **6**, I_{min} values are higher than those for compounds **1a,b,d,f,g**. The calculated I_{min} values for 8-aminosubstituted **1f** show that the lowest value is located above the C_7 carbon atom and is consistent with the tendency of the ring closure at the C_7 position. The same consequence of calculated and experimental results is in accordance with 9-aminoderivative **1g** where I_{min} values are located at C_8 position of the aromatic ring. Thus, in general, the obtained results are in agreement with experimental data.

In conclusion, quantum-chemical calculations show that cyclization reaction behavior is governed by the easiness of electron removal (ionization) from definite π-electron density surface regions of molecules. Local ionization energy maps and I_{min} values are indicative tools for the calculation of the relative activating and deactivating tendencies of the aromatic ring in the studied compounds.

EXPERIMENTAL

Melting points were determined in open capillaries method on a MEL-TEMP 1202D apparatus and are uncorrected. The IR spectra (potassium bromide) were taken on a Perkin Elmer Spectrum GX FTIR spectrometer. The electronic absorption spectra were obtained on Nicolet evoliution 300

Table 1

Calculated total energies (a.u.) of optimized geometries and smallest local ionization energy values I_{min} (kcal/mol) on the molecular surfaces defined by the contour of constant electron density equal 0.025 electron/bohr^3 on carbon atoms of the aromatic ring and the nitrogen atom of the primary amino group for compounds **1a,b,d,f,g** and **6**.

	Compounds					
	1a	**1b**	**1d**	**1f**	**1g**	**6**
Total energy, a.u.	−628.5704	−667.6857	−667.6856	−667.6741	−667.6892	−781.0432
I_{min}, kcal/mol	358.58(N_7)	287.79(N_7)	368.50(N_7)	287.79(N_8)	293.09(N_9)	436.99(N_7)
	358.28(C_6)	301.39(C_6)	379.90(C_6)	329.76(C_6)	315.23(C_6)	431.22(C_6)
	399.40(C_7)	353.28(C_7)	399.40(C_7)	313.62(C_7)	328.84(C_7)	441.37(C_7)
	380.49(C_8)	320.30(C_8)	368.96(C_8)	352.82(C_8)	314.77(C_8)	436.61(C_8)
	381.64(C_9)	328.61(C_9)	375.88(C_9)	320.30(C_9)	360.89(C_9)	439.52(C_9)

spectrophotometer, and the fluorescence emission spectra were recorded on Hitachi MPF-4 Fluorescence spectrophotometer in ethanol. Except where noted otherwise, ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in deuteriochloroform on a Varian Unity Inova 300 spectrometer at 302 K. The chemical shifts are referenced to tetramethylsilane (δ (^{1}H) = 0) and the solvent signal deuteriochloroform (δ (^{13}C) = 77.0 ppm), deuteriodimethylsulfoxide (δ (^{13}C) = 49.5 ppm). The values of chemical shifts are expressed in ppm and coupling constants (J) in Hz. The CH_3, CH_2, CH and C_{quart} groups in ^{13}C NMR were differentiated by means of the APT method. The reactions were controlled by the TLC method and performed on a Merck precoated silica gel aluminum roll ($60F_{254}$) with chloroform-ethyl acetate-methanol (v/v, 14:7:1) as the eluent and was visualized with UV light. Dry column vacuum chromatography [26] was performed with silica gel Chemapol L 5/40 mesh.

General Procedure for the Synthesis of 2a–c, 3d,e, 4f and 5g. To a stirred solution of the appropriate aminobenzodiazepinone **1a–g** (5.0 mmol) in 100–300 mL of dry dichloromethane, 1.28 g (7.5 mmol) of dimethyl-2-oxoglutaconate was added. The mixture was stirred at room temperature for 24 h. Then 4 mL (12.0 mmol) of 3*M* hydrogen chloride solution in glacial acetic acid was added and the intensively colored mixture was stirred at room temperature for additional 24 h. In some occasions, the precipitate was formed. The mixture was treated with a saturated aqueous sodium hydrogencarbonate solution until the aqueous phase became alkaline (pH 7–8), then the organic phase was washed with water. After drying over magnesium sulfate and the removal of the solvent in vacuum, the dark semisolid residue was subjected to purification. Recrystallization from a proper solvent gave pure compounds **3d** and **3e**. Dark oily residues were subjected to dry column vacuum chromatography (silicagel) using the dichloroethane-ethyl acetate system for gradient elution. Organic fractions with $R_f \sim 0.35$ were collected and after removal of the solvent gave compounds **2a–c** and fractions collected with $R_f \sim 0.50$ gave compounds **4f** and **5g**. Pure compounds were obtained by recrystallization from a proper solvent.

Methyl 6-methyl-4,8-dioxo-6,7,8,9-tetrahydro-4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole-2-carboxylate (2a). Brightly yellow crystals (chloroform, 30% yield), mp 299–302°C [6]; ^{1}H NMR: δ 1.52 (d, J = 6.6 Hz, 3H, CH_3), 3.07 (dd, J = 2.3, 14.8 Hz, 1H, CH_2), 3.18 (ddd, J = 1.3, 5.3, 14.8 Hz, 1H, CH_2), 4.13 (s, 3H, OCH_3), 4.99 (m, 1H, CH), 7.33 (d, J = 9.1 Hz, 1H, 10-H), 7.97 (d, J = 9.1 Hz, 1H, 11-H), 8.47 (br s, 1H, NH), 8.74 (s, 1H, 3-H); ^{13}C NMR (dimethylsulfoxide-d_6): δ 19.12 (6-CH_3), 42.53 (7-C), 44.06 (6-C), 52.81 (OCH_3), 117.82 (3-C), 120.72, 120.98, 123.17, 123.81 (11-C), 127.79 (10-C), 133.31, 141.47, 148.49, 163.08 (CO), 164.92 (CO), 171.04 ppm (8-CO).

Methyl 6,9-dimethyl-4,8-dioxo-6,7,8,9-tetrahydro-4*H*-[1,4]-diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole-2-carboxylate (2b). Orange crystals (chloroform, 29% yield), mp 231–233°C [6]; ^{1}H NMR: δ 1.49 (d, J = 6.7 Hz, 3H, CH_3), 3.00 (dd, J = 2.1, 14.2 Hz, 1H, CH_2), 3.18 (dd, J = 5.4, 14.3 Hz, 1H, CH_2), 3.59 (s, 3H, 9-OCH_3), 4.13 (s, 3H, OCH_3), 4.90 (m, 1H, CH), 7.65 (d, J = 9.3 Hz, 1H, 10-H), 8.01 (d, J = 9.3 Hz, 1H, 11-H), 8.72 (s, 1H, 3-H); ^{13}C NMR: δ 19.29 (6-CH_3), 34.31 (9-CH_3), 42.60 (C-7), 46.30 (C-6), 53.52 (OCH_3), 119.29 (d, J = 173.0 Hz, 3-C), 121.57, 124.44, 124.87 (d, J = 166.7 Hz, 11-C), 126.83, 127.17 (d, J = 160.6 Hz, 10-C), 134.31, 142.31, 150.19, 164.48 (CO), 165.19 (CO), 169.92 ppm (8-CO).

Methyl 6-methyl-4,8-dioxo-9-propyl-6,7,8,9-tetrahydro-4*H*-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole-2-carboxylate (2c). Orange crystals (mixture of diethyl ether and ethyl acetate, yield 25%), mp 163–165°C; IR: 1725, 1702, 1660 cm^{-1}; ^{1}H NMR: δ 1.00 (t, J = 7.4 Hz, 3H, CH_3), 1.49 (d, J = 6.7 Hz, 3H, CH_3), 1.65–1.89 (m, 2H, CH_2), 2.99 (dd, J = 2.4, 14.0 Hz, 1H, CH_2), 3.13 (dd, J = 5.4, 13.9 Hz, 1H, CH_2), 3.96–4.12 (m, 2H, CH_2), 4.13 (s, 3H, OCH_3), 4.89 (m, 1H, CH), 7.64 (d, J = 9.4 Hz, 1H, 10-H), 8.00 (d, J = 9.4 Hz, 1H, 11-H), 8.72 (s, 1H, 3-H); ^{13}C NMR: δ 11.29 (9-CH_3), 19.26 (6-CH_3), 21.72 (9$''$-CH_2), 42.60 (7-C), 46.56 (6-C), 48.34 (9$'$-CH_2), 53.56 (OCH_3), 119.22 (3-C), 121.90, 123.75, 124.91 (11-C), 127.28 (10-C), 127.38, 134.21, 142.37, 150.04, 164.67 (CO), 165.23 (CO), 169.65 ppm (8-CO). *Anal*. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.30; H, 5.31; N, 11.64.

Dimethyl 4,5-dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[2,3-*g*]quinoline-8,10-dicarboxylate (3d). Yellow crystals (ethyl acetate, 46% yield), mp 203–205°C; IR: 3319, 3196, 1723, 1670 cm^{-1}; UV-vis: λ_{max} ($\varepsilon \times 10^{-3}$) 245 (30.5), 290 (21.2), 355 (6.2) nm (M^{-1}cm^{-1}); ^{1}H NMR: δ 1.31 (d, J = 6.1 Hz, 3H, CH_3), 2.44 (dd, J = 8.9, 13.4 Hz, 1H, CH_2), 2.72 (dd, J = 4.8, 13.4 Hz, 1H, CH_2), 3.02 (s, 3H, CH_3), 3.94 (m, 1H, CH), 4.06 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 7.83 (s, 1H, 6-H), 8.49 (s, 1H, 11-H), 8.59 (s, 1H, 9-H), 8.67 (br s, 1H, NH); ^{13}C NMR: δ 17.26 (4-CH_3), 39.33 (5-CH_3), 40.89 (3-C), 52.84 (OCH_3), 53.32 (OCH_3), 60.62 (4-C), 116.04 (d, J = 165.2 Hz, 11-C), 120.01 (d, J = 162.3 Hz, 6-C), 121.06 (d, J = 171.2 Hz, 9-C), 122.48, 133.99, 136.70, 145.02, 146.59, 147.87, 165.35 (CO), 165.97 (CO), 172.41 ppm (2-CO). *Anal*. Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.64; H, 5.30; N, 11.90.

Dimethyl 4-methyl-2-oxo-5-(2,2,2-trifluorethyl)-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[2,3-*g*]quinoline-8,10-dicarboxylate (3e). Yellow crystals (ethyl acetate, 51% yield), mp 236–238°C; IR: 3320, 1745, 1727, 1693 cm^{-1}; UV-vis: λ_{max} ($\varepsilon \times 10^{-3}$) 245 (18.2), 284 (12.5), 365 (4.7) nm (M^{-1}cm^{-1}); ^{1}H NMR: δ 1.21 (d, J = 6.1 Hz, 3H, CH_3), 2.36 (dd, J = 11.3, 13.4 Hz, 1H, CH_2), 2.61 (ddd, J = 1.4, 5.4, 13.4 Hz, 1H, CH_2), 3.78 (m, 1H, CH), 4.06 (s, 3H, OCH_3), 4.06–4.20 (m, 2H, 5-CH_2), 4.10 (s, 3H, OCH_3), 8.06 (s, 1H, 6-H), 8.44 (br s, 1H, NH), 8.60 (s, 1H, 11-H), 8.67 (s, 1H, 9-H); ^{13}C NMR: δ 16.45 (4-CH_3), 41.05 (3-C), 52.50 (q, J = 32.9 Hz, 5-CH_2), 52.98 (OCH_3), 53.41 (OCH_3), 60.12 (4-C), 116.89 (11-C), 122.27 (9-C), 124.08, 124.47 (q, J = 280.2 Hz, CF_3), 125.11 (6-C), 134.43, 138.63, 142.49, 147.01, 147.37, 165.09 (CO), 165.76 (CO), 172.15 ppm (2-CO). *Anal*. Calcd. for $C_{19}H_{18}F_3N_3O_5$: C, 53.65; H, 4.27; N, 9.88. Found: C, 53.48; H, 4.36; N, 10.01.

Dimethyl 1,2-dimethyl-4-oxo-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[2,3-*g*]quinoline-8,10-dicarboxylate (4f). Yellow crystals (isopropanol, 16% yield), mp 255–258°C; IR: 3198, 3122, 1715, 1683 cm^{-1}; UV-vis: λ_{max} ($\varepsilon \times 10^{-3}$) 245 (31.1), 295 (14.7), 410 (9.0) nm (M^{-1}cm^{-1}); fluorescence: λ_{ex} 300 and 410, λ_{em} 550 nm; ^{1}H NMR: δ 1.37 (d, J = 6.2 Hz, 3H, CH_3), 2.47 (dd, J = 8.3, 13.5 Hz, 1H, CH_2), 2.75 (dd, J = 4.4, 13.4 Hz, 1H, CH_2), 3.09 (s, 3H, CH_3), 3.94 (m, 1H, CH), 4.07 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 7.85 (s, 1H, 6-H), 8.30 (br s, 1H, NH), 8.45 (s, 1H, 11-H), 8.66 (s, 1H, 9-H); ^{13}C NMR: δ 17.90 (2-CH_3), 39.47 (1-CH_3), 40.74 (3-C), 52.70 (OCH_3), 53.19 (OCH_3), 60.66 (2-C), 113.58 (11-C), 121.31 (6-

C), 122.47 (9-C), 125.65, 132.23, 136.38, 145.13, 145.20 (2-C), 165.44 (CO), 166.19 (CO), 172.21 ppm (4-CO). *Anal.* Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.63; H, 5.29; N, 11.65.

Dimethyl 4,5-dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[2,3-*h*]quinoline-8,10-dicarboxylate (5g). Dark red crystals (tert-butylmetyl ether, 20% yield), mp 161–163°C; IR: 3273, 1730, 1708, 1672 cm^{-1}; ^1H NMR: δ 1.38 (d, J = 6.4 Hz, 3H, CH_3), 2.56 (ddd, J = 1.0, 7.6, 13.8 Hz, 1H, CH_2), 2.84 (dd, J = 4.4, 13.9 Hz, 1H, CH_2), 3.07 (s, 3H, CH_3), 4.02 (m, 1H, CH), 4.05 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 7.54 (d, J = 9.4 Hz, 1H, 6-H), 8.52 (s, 1H, 9-H), 8.53 (d, J = 9.4 Hz, 1H, 7-H), 9.24 (br s, 1H, NH); ^{13}C NMR: δ 18.37 (4-CH_3), 39.39 (5-CH_3), 42.04 (3-C), 52.88 (OCH_3), 53.06 (OCH_3), 61.07 (4-C), 120.32 (d, J = 171.6 Hz, 9-C), 120.99 (d, J = 168.5 Hz, 7-C), 121.06, 124.35, 124.98 (d, J = 159.6 Hz, 6-C), 135.61, 139.74, 140.55, 146.31, 165.27 (CO), 166.01 (CO), 171.72 ppm (2-CO). *Anal.* Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.79; H, 5.40; N, 11.93.

General procedure for the synthesis of 1b,c,e,g, 6 and 7. In a hydrogenation apparatus, equipped with a magnetic stirrer, the catalyst 10% palladium on carbon (10% of the weight of the starting nitroderivative) was added to a solution of suitable nitrobenzodiazepinone **8b,c,e,g, 9** and **10** (20.0 mmol) in 150–200 mL of methanol and the mixture was hydrogenated at room temperature and atmospheric pressure. After the consumption of 1.34 L (60 mmol) of hydrogen the catalyst was filtered off. The filtrate was concentrated to dryness in vacuum and the resultant solid residue was crystallized from a proper solvent.

7-Amino-1,4-dimethyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1b). Synthesized from **8b** [11]. Yellowish crystals (ethyl acetate, 77% yield), mp 149–151°C; ^1H NMR: δ 1.24 (d, J = 6.2 Hz, 3H, CH_3), 2.28 (dd, J = 7.7, 12.7 Hz, 1H, 3-CH_2), 2.51 (dd, J = 5.2, 12.6 Hz, 1H, 3-CH_2), 3.13 (br s, 1H, NH), 3.28 (s, 3H, 1-CH_3), 3.66 (br s, 2H, NH_2), 4.00 (m, 1H, CH), 6.18 (d, J = 2.5 Hz, 1H, 6-H), 6.36 (dd, J = 2.5, 8.4 Hz, 1H, 8-H), 6.91 (d, J = 8.4 Hz, 1H, 9-H); ^{13}C NMR: δ 23.19 (4-CH_3), 35.45 (1-CH_3), 40.24 (3-C), 56.80 (4-C), 108.31, 109.43, 123.62, 127.90, 140.15, 144.72, 171.37 ppm (CO). *Anal.* Calcd. for $C_{11}H_{15}N_3O$: C, 64.34; H, 7.37; N, 20.47. Found: C, 64.38; H, 7.30; N, 20.66.

7-Amino-4-methyl-1-propyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1c). Synthesized from **8c**. Beige colored crystals (mixture of methanol and diethyl ether, 71% yield), mp 143-145°C; IR: 3407, 3345, 3330, 3233, 1666–1609 cm^{-1}; ^1H NMR: δ 0.84 (t, J = 7.4 Hz, 3H, CH_3), 1.23 (d, J = 6.2 Hz, 3H, CH_3), 1.50 (m, 2H, CH_2), 2.23 (dd, J = 7.5, 12.6 Hz, 1H, 3-CH_2), 2.48 (dd, J = 5.2, 12.6 Hz, 1H, 3-CH_2), 3.05 (br s, 1H, NH), 3.64 (br s, 2H, NH_2), 3.73 (m, 2H, CH_2), 3.98 (m, 1H, CH), 6.18 (d, J = 2.5 Hz, 1H, 6-H), 6.35 (dd, J = 2.5, 8.4 Hz, 1H, 8-H), 6.93 (d, J = 8.4 Hz, 1H, 9-H); ^{13}C NMR: δ 11.22 (CH_3), 21.13 (CH_2), 23.11 (4-CH_3), 40.38 (3-C), 49.26 (CH_2), 56.89 (4-C), 108.52, 109.51, 124.08, 126.60, 141.20, 144.74, 171.20 ppm (CO). *Anal.* Calcd. for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 67.23; H, 8.32; N, 17.89.

7-Amino-4-methyl-5(2,2,2-trifluoroethyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1e). Synthesized from **8e** [11]. Yellowish crystals (mixture of diethyl ether and hexane, 95% yield), mp 156–158°C; IR: 3454, 3371, 3174, 1677 cm^{-1}; ^1H NMR: δ 1.08 (d, J = 6.1 Hz, 3H, CH_3), 2.22–2.40 (m, 2H, CH_2), 3.3–3.7 (br s, 2H, NH_2), 3.53 (dq, J = 8.9, 15.4 Hz, 1H, 5-CH_2), 3.83 (dq, J = 8.6, 15.4 Hz, 1H, 5-CH_2), 4.02 (m, 1H, CH), 6.42–6.46 (m, 2H, 6-H, 8-H), 6.81 (m, 1H, 9-H), 7.83 (br s, 1H, NH); ^{13}C NMR: δ 17.05 (4-CH_3), 41.07 (3-C), 52.80 (q, J = 32.4 Hz, 5-CH_2), 61.37 (4-C), 111.82, 112.00, 123.68, 124.49, 126.69, 140.05, 144.93, 173.44 ppm (CO). *Anal.* Calcd. for $C_{12}H_{14}F_3N_3O$: C, 52.75; H, 5.16; N, 15.38. Found: C, 52.87; H, 5.24; N, 15.30.

9-Amino-4,5-dimethyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1g). Synthesized from **8g**. Cream crystals (methanol, 70% yield), mp 213–215°C; IR: 3453, 3367, 3198, 1678 cm^{-1}; ^1H NMR: δ 1.09 (d, J = 6.1 Hz, 3H, CH_3), 2.24 (dd, J = 10.0, 12.6 Hz, 1H, CH_2), 2.42 (ddd, J = 1.2, 5.4, 12.6 Hz, 1H, CH_2), 2.77 (s, 3H, CH_3), 3.86 (m, 1H, CH), 3.95 (br s, 2H, NH_2), 6.45–6.51 (m, 2H, 6-H, 8-H), 6.98 (dd, J = 8.0, 8.0 Hz, 1H, 7-H), 8.34 (br s, 1H, NH); ^{13}C NMR: δ 15.78 (4-CH_3), 38.65 (5-CH_3), 41.52 (3-C), 62.83 (4-C), 110.53, 111.84, 119.72, 126.29, 139.59, 142.66, 174.76 ppm (CO). *Anal.* Calcd. for $C_{11}H_{15}N_3O$: C, 64.34; H, 7.37; N, 20.47. Found: C, 64.47; H, 7.29; N, 20.59.

5-Acetyl-7-amino-3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (6). Synthesized from **9**. Yellow crystals (acetonitrile, 89% yield), mp 191–193°C; IR: 3438, 3348, 3233, 1673, 1653 cm^{-1}; ^1H NMR: δ 1.11 (d, J = 6.7 Hz, 3H, CH_3), 1.86 (br s, 3H, CH_3), 2.75 (m, 1H, CH), 3.46 (dd, J = 6.9, 13.5 Hz, 1H, CH_2), 3.83 (br s, 2H, NH_2), 4.56 (dd, J = 12.3, 13.1 Hz, 1H, CH_2), 6.51 (d, J = 2.5 Hz, 1H, 6-H), 6.67 (dd, J = 2.5, 8.4 Hz, 1H, 8-H), 6.94 (d, J = 8.5 Hz, 1H, 9-H), 7.90 (br s, 1H, NH); ^{13}C NMR: δ 12.51 (4-CH_3), 22.66 (5-CH_3), 34.88(3-C), 54.74 (4-C), 115.06, 115.39, 124.35, 126.05, 135.66, 145.29, 170.38, 175.20 ppm. *Anal.* Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.62; H, 6.41; N, 18.13.

9-Amino-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one (7). Synthesized from 10 [10] Yellowish crystals (methanol, 90% yield), mp 170–172°C; ^1H NMR: δ 2.39 (s, 3H, CH_3), 3.16 (s, 2H, CH_2), 3.81 (br s, 2H, NH_2), 6.66 (dd, J = 1.4, 7.8 Hz, 1H, 8-H or 6-H), 6.83 (dd, J = 1.3, 8.1 Hz, 1H, 6-H or 8-H), 7.05 (t, J = 7.9 Hz, 1H, 7-H), 8.00 (m, 1H, NH); ^{13}C NMR: δ 28.00, 43.80, 113.38, 117.81, 125.54, 138.41, 141.09, 163.09, 166.45 ppm. *Anal.* Calcd. for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.57; H, 5.79; N, 22.37.

4-Methyl-7-nitro-1-propyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (8c). To a solution of 2.2 g (10.0 mmol) of 4-methyl-7-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one [12] in 150 mL of benzene, 0.5 g (1.50 mmol) of tetrabutylammonium bromide, 15 mL 50% aqueous sodium hydroxide and 1.8 mL (20.0 mmol) of 1-bromopropane were added. The reaction was performed according to the procedure method A previously described by us [11]. The working-up of the reaction mixture gave 1.6 g (61%) of **8c**. Yellowish crystals (ethyl acetate), mp 116–118°C; IR: 3296, 1651, 1517, 1344 cm^{-1}; ^1H NMR: δ 0.85 (t, J = 7.4 Hz, 3H, CH_3), 1.32 (d, J = 6.3 Hz, 3H, CH_3), 1.54 (m, 2H, CH_2), 2.28 (dd, J = 7.4, 12.9 Hz, 1H, 3-CH_2), 2.57 (dd, J = 5.2, 12.9 Hz, 1H, 3-CH_2), 3.55 (br s, 1H, NH), 3.86 (m, 2H, CH_2), 4.12 (m, 1H, CH), 7.29 (d, J = 8.8 Hz, 1H, 9-H), 7.76 (d, J = 2.6 Hz, 1H, 6-H), 7.89 (dd, J = 2.5, 8.8 Hz, 1H, 8-H); ^{13}C NMR: δ 11.08 (CH_3), 21.13(CH_2), 23.01(4-CH_3), 40.29 (3-C), 49.67 (CH_2), 57.32 (4-C), 117.23, 117.84, 123.27, 140.29, 140.78, 145.10, 170.57 ppm (CO). *Anal.* Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.61; H, 6.63; N, 16.12.

4,5-Dimethyl-9-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (8g). To a solution of 2.2 g (10.0 mmol) of dihydro-9-nitroderivative **10** [10] in 50 mL of formic acid, 3.25 g

(70.0 mmol) of sodium borohydride was added. The reaction was performed following the procedure previously described by us [11]. The working-up of the reaction mixture gave 1.3 g (57%) of **8g**. Yellow crystals (ethyl acetate), mp 184–186°C; IR: 3192, 3122, 1686, 1636, 1529, 1345 cm^{-1}; ^1H NMR: δ 1.19 (d, J = 6.1 Hz, 3H, CH_3), 2.25 (dd, J = 9.8, 13.0 Hz, 1H, CH_2), 2.55 (ddd, J = 1.4, 5.7, 13.0 Hz, 1H, CH_2), 2.88 (s, 3H, 5-CH_3), 3.95 (m, 1H, CH), 7.24 (dd, J = 8.1, 8.1 Hz, 1H, 7-H), 7.37 (dd, J = 1.4, 8.1 Hz, 1H, 6-H), 7.77 (dd, J = 1.5, 8.2 Hz, 1H, 8-H), 8.80 (br s, 1H, NH); ^{13}C NMR: δ 15.93 (4-CH_3), 39.41 (5-CH_3), 41.37 (3-C), 62.77 (4-C), 119.42, 124.36, 127.95, 130.04, 140.28, 143.11, 171.89 ppm (CO). *Anal*. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.35; H, 5.65; N, 17.71.

5-Acetyl-3-methyl-7-nitro-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (9). A solution of 2.2 g (10.0 mmol) of 5-acetyl-3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one [13] in 30 mL of conc. sulfuric acid, and a solution of 2.2 g (20.0 mmol) of potassium nitrate in 25 mL of conc. sulfuric acid were precooled to −18°C and were combined. The reaction mixture was kept at −18°C for 1 h, then at 4°C for 5 h and at room temperature for 24 h. After that the reaction mixture was poured on ice and extracted with ethyl acetate (3 × 70 mL). The organic phase was washed successively with water and a saturated aqueous sodium hydrogencarbonate solution (3 × 40 mL), dried over magnesium sulfate and concentrated in vacuum to dryness. Recrystallization of the solid residue from ethyl acetate gave 1.3 g (50%) of yellowish crystals of **9**, mp 212–214°C; IR: 3208, 3156, 1697, 1650, 1523, 1347 cm^{-1}; ^1H NMR: δ 1.22 (br d, 3H, CH_3), 1.88 (br s, 3H, CH_3), 2.82 (br m, 1H, CH), 3.63 (br m, 1H, CH_2), 4.67 (br m, 1H, CH_2), 7.34 (d, J = 8.7 Hz, 1H, 9-H), 8.17 (br d, 1H, 6-H), 8.29 (br dd, 1H, 9-H), 9.05 ppm (br s, 1H, NH). *Anal*. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.93; H, 4.79; N, 16.17.

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