

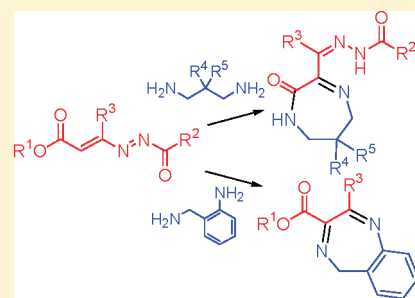
Divergent Regioselective Synthesis of 2,5,6,7-Tetrahydro-1*H*-1,4-diazepin-2-ones and 5*H*-1,4-Benzodiazepines

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Supporting Information

ABSTRACT: A novel and simple one-pot synthesis of 3-substituted 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones from 1,2-diaza-1,3-dienes (DDs) and *N*-unsubstituted aliphatic 1,3-diamines is described. Here we also report a procedure to selectively obtain alkyl 5*H*-1,4-benzodiazepine-3-carboxylates from the DDs and 2-aminobenzylamine. Both processes occur by means of sequential 1,4-conjugated addition followed by regioselective 7-exo cyclization. The behavior of *N*-methyl- and *N,N'*-dimethyl-1,3-diaminopropanes toward the DDs furnished pyrazol-3-ones and bis- α -aminohydrazones, respectively.



INTRODUCTION

The exploration of privileged structures in drug discovery has gained increasing interest and relevance.¹ Among the small molecules employed in this field, molecular scaffolds that mimic peptide secondary structures are particularly useful for the identification and development of therapeutic agents.^{1,2} For example, 1,4-benzodiazepine is a privileged scaffold or fragment that has been studied extensively and frequently appeared in the biologically active molecules and drugs.³ In particular, a large number of 1,4-benzodiazepines act as anxiolytic, antidepressant, anticonvulsant, and antihypnotic agents⁴ and some of them exhibit antitumor activity.⁵

The seven-membered 1,4-diazepin-2-one ring mimics β - and γ -turn secondary structures^{6–8} and exhibits anticonvulsant activity,⁹ antibacterial activity against multidrug-resistant *Mycobacterium tuberculosis* strains,¹⁰ antitumor properties,¹¹ and lymphocyte function-associated antigen-1 (LFA-1) antagonists.¹² For these reasons, the development of new strategies for the synthesis of 1,4-diazepin-2-ones is ever evolving.

The most reported synthetic approaches to 1,4-benzodiazepine skeletons include reaction of 2-aminobenzoic acids and their derivatives or 2-aminobenzophenones with α -amino acids,¹³ cyclocondensation of 2-halobenzoic acid derivatives or 2-halobenzophenones with diamines,¹⁴ and Pictet–Spengler reaction of *N,N'*-dimethyl-*N*-phenyl-1,2-ethanediamine with aldehydes.¹⁵

The diazepinone ring is reported in the literature to be prepared from linear precursors by intramolecular reductive amination,^{8,16–18} lactam formation,^{19–21} and transamidation.²² Also, the preparation of 1,4-diazepin-2-ones involves iminophosphorane intermediates by means of intramolecular aza-Wittig reaction or hydrolysis of the iminophosphoranes to the corresponding amino derivatives followed by intramolecular cyclocondensation.²³ The limit of these procedures is that they involve some preparative difficulties and require several steps.

1,2-Diaza-1,3-dienes²⁴ (DDs) are versatile intermediates and react with a wide range of nucleophiles at its highly electrophilic center (at C-4),²⁵ leading to a wide variety of heterocyclic rings.^{24,26} In particular, we went back to our previous investigations on the reaction of DDs **1** with 1,2-diamines to obtain 1,2,5,6-tetrahydro-2-pyrazinones **I**²⁷ or pyrazines **II**,²⁷ depending from the conditions used, and with 1,3-diamines (in the molar ratio 2:1) that furnished the corresponding bis- α -aminohydrazones **III**,²⁸ respectively (Scheme 1).

On the basis of these experiences, and in continuation of our ongoing interest in the discovery of reactions for the synthesis of new heterocycles from azo-ene systems, we have designed a novel method for the preparation of 1,4-diazepin-2-ones **A** and/or 1,4-diazepines **B** from DDs **1** and 1,3-diamines **2** in the molar ratio 1:1 (Scheme 2). Our analysis of the seven-membered heterocyclic core emphasizes strategic disconnections along the C(2)–N(1) and C(3)–N(4) bonds. This reveals two subunits that trace the lower-half to the pertinent diamines **2**, and the upper half to the α,β -dications **C** and **D**, that further can be correlated to the 4-alkoxycarbonyl azoene system of the DDs **1**. The high electrophilicity at the carbon terminus of the heterodiene system²⁵ permits the formation of C(3)–N(4) junction in **A** and in **B**, by means of a 1,4-Michael-type addition with one of the nitrogens in diamine **2**.

At this point, two different C(2)–N(1) junctions can be obtained by means of a subsequent intramolecular 7-exo cyclization of the second nitrogen of the diamine that can occur on the carboxylic function of **C**, giving 1,4-diazepin-2-ones **A**, or on the hydrazone function of **E**, furnishing 1,2-diazepines **B**, respectively.

To the best of our knowledge, only one example²⁹ for the synthesis of 1,4-diazepin-2-ones was reported in literature, using

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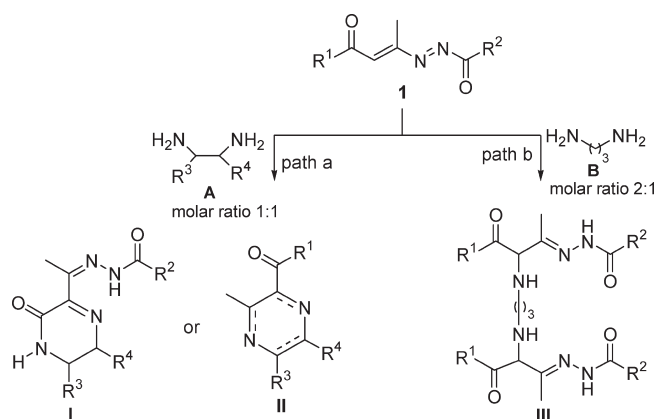
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this disconnection approach. In 1969, in fact, McDougal and Malik attempted to prepare simple 1,4-diazepine starting from glyoxal sodium hydrogen sulfite and 2,4-diaminopentane; instead they obtained *cis*-dimethylhexahydro-1,4-diazepin-2-one.²⁹ The authors tried unsuccessfully to enlarge the scope of this methodology by using both 1,3-diamines and 1,2-dicarbonyl or α -halogen carbonyl derivatives. The same method was then used by Knapp et al.³⁰ starting from the same glyoxal derivative with *N,N*-dimethylpropane-1,3-diamine, obtaining the expected 1,4-dimethyl-1,4-diazepan-2-one but in very poor yield while employing harsh reaction conditions. Thus, the reaction had limited scope. On the other hand, only relatively few methods are reported for the synthesis of 1,4-diazepines, starting from diamine derivatives and bis-electrophiles, and often they are unsatisfactory.^{29,31}

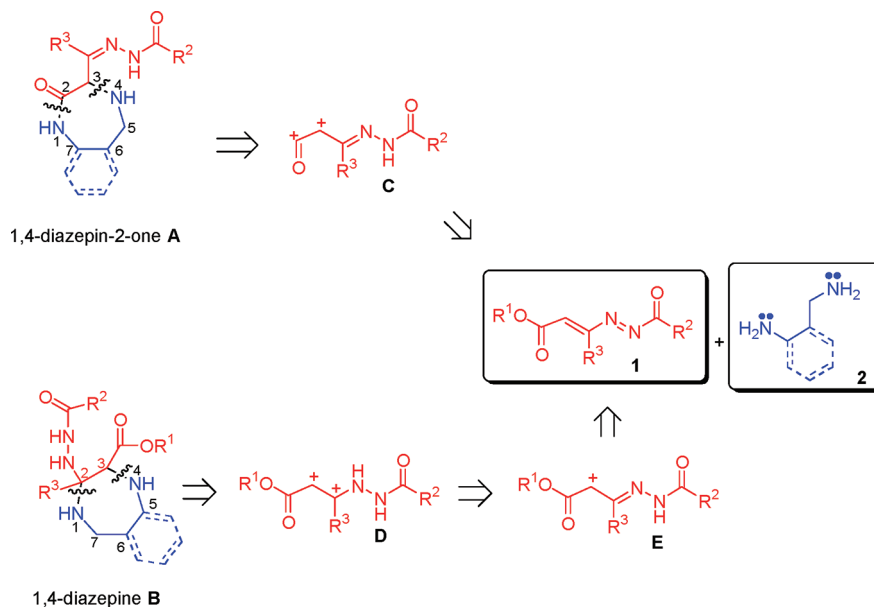
RESULTS AND DISCUSSION

Therefore, with the aim to synthesize 1,4-diazepin-2-ones or 1,4-diazepines, initially we explored the reaction of DDs 1a–c³² with aliphatic 1,3-diamines 2a–c at room temperature

Scheme 1. Reactivity of 1,2-Diaza-1,3-dienes 1 with 1,2-Diamines A and with 1,3-Diamines B (in the molar ratio 1:2)



Scheme 2. Retrosynthetic Strategy for the Preparation of 1,4-Diazepin-2-ones A or 1,4-Diazepines B



in diethyl ether (Scheme 3). To avoid the formation of bis- α -aminohydrazone,³¹ we carried out the reaction in equimolar ratio and by adding reagents 1 to 2.

Under these conditions, the disappearance of the typical red color of the starting DDs indicated the completion of the reaction rapidly (1 min), and TLC revealed one as major spot. The products were isolated as solids, simply by partial evaporation of the reaction solvent, and identified to be the α -aminohydrazone 3a–d (Scheme 3, path a, Table 1). As compounds 3 are not very stable in solution, their spectroscopic NMR analyses must be done promptly. Their formation takes place by means of an aza-Michael addition by one of the two nitrogens in 2a–c to the terminus carbon of the azo-ene system of the DDs 1.

When DDs 1a–f were allowed to react with the same aliphatic 1,3-diamines 2a–c in 1:1 molar ratio, in ethanol rather than in diethyl ether, we directly obtained the expected 3-substituted 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones 4a–o, which precipitated out from the reaction medium with satisfactory yields (48–67%) (Scheme 3, path b, Table 2).

Scheme 3. Synthesis of α -Aminohydrazone 3a–d and of 3-Substituted 2,5,6,7-Tetrahydro-1*H*-1,4-diazepin-2-ones 4a–o

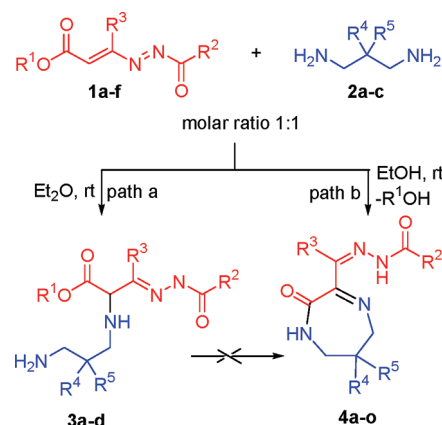


Table 1. Synthesis of α -Aminohydrazone 3a–d

entry	1,2-diaza-1,3-dienes 1				1,3-diamines 2			products 3	
	1	R ¹	R ²	R ³	2	R ⁴	R ⁵	3	yield (%) ^a
1	1a	Et	Ot-Bu	Me	2a	H	H	3a	90
2	1b	Me	NHPh	Me	2a	H	H	3b	100
3	1c	Me	Ot-Bu	Me	2b	H	Me	3c	98
4	1c	Me	Ot-Bu	Me	2c	Me	Me	3d	90

^aYield of pure isolated products 3 based on DDs 1.

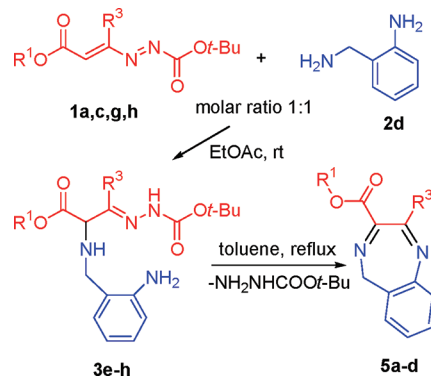
Table 2. One-Pot Synthesis of 3-Substituted 2,5,6,7-Tetrahydro-1H-1,4-diazepin-2-ones 4a–o

entry	1,2-diaza-1,3-dienes 1				1,3-diamines 2			products 4	
	1	R ¹	R ²	R ³	2	R ⁴	R ⁵	4	time (h) yield (%) ^a
1	1a	Et	Ot-Bu	Me	2a	H	H	4a	3.0 58
2	1b	Me	NHPh	Me	2a	H	H	4b	2.5 48
3	1d	Me	OBn	Me	2a	H	H	4c	2.0 44
4	1e	Me	NH ₂	Me	2a	H	H	4d	2.0 57
5	1f	Me	NH ₂	Et	2a	H	H	4e	2.5 48
6	1b	Me	NHPh	Me	2b	H	Me	4f	4.0 63
7	1c	Me	Ot-Bu	Me	2b	H	Me	4g	4.0 62
8	1d	Me	OBn	Me	2b	H	Me	4h	4.0 40
9	1e	Me	NH ₂	Me	2b	H	Me	4i	6.0 57
10	1f	Me	NH ₂	Et	2b	H	Me	4j	2.0 61
11	1b	Me	NHPh	Me	2c	Me	Me	4k	3.0 63
12	1c	Me	Ot-Bu	Me	2c	Me	Me	4l	2.5 62
13	1d	Me	OBn	Me	2c	Me	Me	4m	8.0 42
14	1e	Me	NH ₂	Me	2c	Me	Me	4n	1.0 54
15	1f	Me	NH ₂	Et	2c	Me	Me	4o	4.0 65

^aYield of isolated pure product 4 based on DD 1.

In this case, the initial 1,4-addition of the amino group in 1,3-diamines 2a–c takes place at the terminus carbon of the heterodiene DDs 1a–f to form hydrazones 3, followed by regioselective nucleophilic attack of the second amino group at the ester function, with the loss of an alcohol molecule. Then spontaneous oxidation of the C–N bond furnishes 2,5,6,7-tetrahydro-1H-1,4-diazepin-2-ones 4a–o. The role of the air in this process was confirmed, performing the same reaction under inert atmosphere: in fact, under these conditions, no products 4 were detected, but we obtained complicated reaction mixtures. Probably, the presence of three conjugated double bonds confers stability to these compounds 4. It should be noted that synthesis of these interesting molecules are limited in the literature.³³ All attempts to convert α -aminohydrazone 3a–d into the corresponding 4 failed, giving complicated reaction mixtures, and this is ascribed to the poor stability of compounds 3 in solution.

The 7-exo cyclization has been confirmed by comparing the ¹H chemical shifts of the hydrogens bound to the nitrogens involved in this process. In particular, the amine NH₂ in the 1,4-adducts 3 show a chemical shift at ~2.20 ppm; on the contrary, the amide NH in the diazepinone derivatives 4 is at 8.19–8.65 ppm. Also, the multiplicity of this diagnostic signal in the latter that appears as a triplet confirms unequivocally that the nitrogen responsible for the ring closure process derives from the starting reagents 2. With respect to the analogous six-membered compounds obtained

Scheme 4. Synthesis of α -Aminohydrazone 3e–h and of Alkyl 5H-1,4-Benzodiazepine-3-carboxylates 5a–dTable 3. Synthesis of α -Aminohydrazone 3e–h and Alkyl 5H-1,4-Benzodiazepine-3-carboxylates 5a–d

entry	1,2-diaza-1,3-dienes 1			products 3		products 5		
	1	R ¹	R ³	3	yields (%) ^a	5	time (h)	yields (%) ^b
1	1a	Et	Me	3e	72	5a	4.0	47
2	1c	Me	Me	3f	96	5b	5.0	53
3	1g	Me	Et	3g	95	5c	4.0	62
4	1h	<i>i</i> -Pr	Me	3h	66	5d	3.0	71

^aYield of pure isolated products 3 based on DDs 1. ^bYield of pure isolated products 5 based on α -aminohydrazone 3.

from DDs and 1,2-diamines,²⁷ there is a good agreement in the diagnostic signals both at ¹H and ¹³C NMR.

In order to obtain the 1,4-benzodiazepine core, we examined the reaction of DDs 1a,c,g,h and 2-aminobenzylamine 2d, in 1:1 molar ratio. The best conditions we found involved the use of 1-*tert*-butoxycarbonyl-DDs in ethyl acetate at room temperature, obtaining the corresponding α -aminohydrazone 3e–h in good to excellent yields (66–96%) simply by precipitation from the reaction medium (Scheme 4, Table 3).

Compounds 3 are formed by means of an aza-Michael addition of the more nucleophilic benzylic nitrogen of the diamine 2d at the terminus carbon of the azo-ene system of DDs 1. Compounds 3e–h in toluene under reflux were converted into the corresponding alkyl 5H-1,4-benzodiazepine-3-carboxylates 5a–d in satisfactory yields (47–71%) (Scheme 4, Table 3). Their formation involves a regioselective ring closure by the anilinic nitrogen on the hydrazone function and the subsequent spontaneous loss of *tert*-butyl carbamate moiety.

The peculiar regioselectivity observed in the ring closure process of these reactions depends on the differential nucleophilicity of the involved nitrogen atoms in aliphatic (2a–c) or aromatic (2d) 1,3-diamines, respectively, together with the diverse nucleophilic affinity of ester and hydrazone groups. Also the different strain of monocyclic 1,4-diazepin-2-ones 4 compared with that of bicyclic 1,4-benzodiazepines 5 could play an important role.

Then, we studied the behavior of N-monosubstituted 1,3-diamine toward DDs. When the reactions between DDs 1a,b,g,i and N-methyl-1,3-diaminopropane 2e were carried out in dichloromethane at room temperature, in a 1:1 molar ratio,

Scheme 5. Synthesis of 4-[(3-Aminopropyl)-(methyl)amino]-1*H*-pyrazol-3-ones **6a–d and Bis- α -aminohydrazones **7a,b****

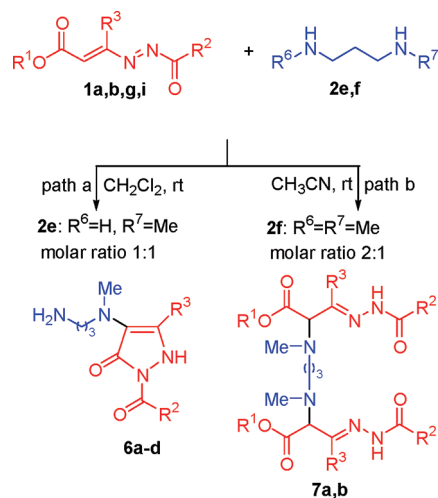


Table 4. Synthesis of 4-[(3-Aminopropyl)(methyl)amino]-1*H*-pyrazol-3-ones **6a–d and Bis- α -aminohydrazones **7a,b****

entry	1,2-diaza-1,3-dienes 1			1,3-diamines 2			products 6		products 7
	1	R¹	R²	2	R⁶	R⁷	6	time yield (h) (%) ^a	yield (%) ^b
1	1a	Et	<i>O</i> - <i>t</i> -Bu	Me	2e	H	Me	6a 0.1	54
2	1b	Me	NHPh	Me	2e	H	Me	6b 0.2	50
3	1g	Me	<i>O</i> - <i>t</i> -Bu	Et	2e	H	Me	6c 0.1	91
4	1i	Et	OMe	Me	2e	H	Me	6d 0.1	60
5	1a	Et	<i>O</i> - <i>t</i> -Bu	Me	2f	Me	Me		7a 98
6	1b	Me	NHPh	Me	2f	Me	Me		7b 98

^aYield of pure isolated products **6** based on DDs **1**. ^bYield of pure isolated products **7** based on DDs **1**.

pyrazol-3-ones **6a–d** were obtained as sole products in good to excellent yields (Scheme 5, Table 4).

The mechanism for the formation of pyrazol-3-one ring provides the preliminary formation of nonisolable α -aminohydrazones that can occur by the 1,4-addition of the more nucleophilic secondary nitrogen or of the less nucleophilic NH₂ of diamine **2e**. The subsequent intramolecular nucleophilic attack of the hydrazonic nitrogen atom on the ester group with loss of an alcohol molecule and tautomerism can furnish structures I or II of pyrazolone ring, respectively (Figure 1).²⁴

The exact structure of pyrazol-3-ones **6** was determined by NOE experiments on compound **6a**, chosen as example, that showed considerable NOE enhancement of N-CH₃ at 2.52 ppm by irradiation of CH₃ at 2.16 ppm and *vice versa*: this evidence suggests the proximity of these two groups, in agreement with 4-[(3-aminopropyl)(methyl)amino]-1*H*-pyrazol-3-ones of structure I (Figure 1) obtained by the initial nucleophilic attack of the secondary nitrogen. Hence, in this case, the lack of the hydrogen bond to the tertiary nitrogen derived from the diamine **2e** probably drives the different regioselectivity of the ring closure to pyrazol-3-ones, preventing the formation of the C=N bond. Pyrazoles are molecules of interest because they

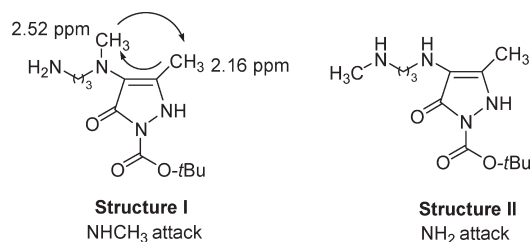


Figure 1. NOE experiments on compound **6a.**

often recur in organic, biological and medicinal chemistry and they have been applied also in the analytical and agricultural fields.³⁴

Then we extended this study to the reactions of *N,N'*-dimethyl-1,3-diaminopropane **2f** with DDs **1a,b**. We explored several conditions without much success, except when carried out in acetonitrile at room temperature, in a 2:1 molar ratio: bis- α -aminohydrazones **7a,b** were obtained in 5 min, in very good yields (Scheme 5, Table 4).³¹

Under conditions employed for the formation of 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones **4**, the reactions of DDs with diamines **2e,f** furnished complicated reaction mixtures.

CONCLUSION

In summary, we have reported novel regioselective syntheses of 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones and alkyl 5*H*-1,4-benzodiazepine-3-carboxylates, starting from DDs and aliphatic as well as aromatic 1,3-diamines, respectively. Also, the reactivity of *N*-unsubstituted, *N*-mono-, or *N,N'*-disubstituted 1,3-diamines were compared in the transformation process, that gave 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones and 5*H*-1,4-benzodiazepines, 4-[(3-aminopropyl)(methyl)amino]-1*H*-pyrazol-3-ones, and bis- α -aminohydrazones, respectively.

Therefore, the utility of the described syntheses to obtain interesting heterocyclic scaffolds, together with mild and simple reaction conditions (no dry solvents or inert atmosphere) makes them well suitable for the generation of combinatorial libraries that might be useful in the chemical biology research.

EXPERIMENTAL SECTION

General Remarks. All the commercially available reagents and solvents were used without further purification. 1,2-Diaza-1,3-dienes **1a–i** were synthesized as a mixture of *E/Z* isomers as previously reported.³² Chromatographic purification of compounds was carried out on silica gel (60–200 μ m). TLC analysis was performed on preloaded (0.25 mm) glass-supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% Ce(SO₄) \cdot 4H₂O, 2.5% (NH₄)₆Mo₇O₂₄ \cdot 4H₂O in 10% sulfuric acid followed by heating on a hot plate. All ¹H NMR and ¹³C NMR spectra were recorded at 400 and 100.56 MHz, respectively. Proton and carbon spectra were referenced internally to solvent signals, using values of δ = 2.50 ppm for proton (middle peak) and δ = 39.50 ppm for carbon (middle peak) in DMSO-*d*₆ and δ = 7.27 ppm for proton and δ = 77.00 ppm for carbon (middle peak) in CDCl₃. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, q = quartet, qi = quintet, sex = sextet, sept = septet, m = multiplet, and br = broad signal. All coupling constants (*J*) are given in hertz. FT-IR spectra were obtained as Nujol mulls. Mass spectra were

recorded in the EI (70 eV) or ESI mode. Melting points were determined in open capillary tubes and are uncorrected.

General Procedure for the Synthesis of α -Aminohydrazones **3a–h.** To a solution of aliphatic 1,3-diamines **2a–c** (1.0 mmol) in diethyl ether (2 mL) or 2-aminobenzylamine **2d** (1.0 mmol) in ethyl acetate (2 mL) magnetically stirred at room temperature, a solution of 1,2-diaza-1,3-dienes **1a–c,g,h** (1.0 mmol) in diethyl ether (3 mL) in the case of aliphatic 1,3-diamines **2a–c** or ethyl acetate (3 mL) in the case of 2-aminobenzylamine **2d** was added. At the disappearance of the red color of **1a–c,g,h** that occurred within 1 min, products **3a–d** were crystallized by partial evaporation of the solvent under reduced pressure, while products **3e–h** directly crystallized from the reaction solvent. Compounds **3** are not very stable in solution, and in some cases, it is difficult to record ^{13}C NMR spectra. Spectroscopic data for α -aminohydrazones **3a–d** are given below.

tert-Butyl 2-[2-[(3-Aminopropyl)amino]-3-ethoxy-1-methyl-3-oxopropylidene]hydrazinecarboxylate (3a**).** White powder from diethyl ether; mp 140–2 °C. ^1H NMR (DMSO- d_6): δ = 1.15 (t, J = 7.2 Hz, 3H), 1.41 (s, 9H), 1.47–1.50 (m, 2H), 1.73 (s, 3H), 2.25 (br s, 2H), 2.31–2.48 (m, 4H), 3.30 (s, 1H), 3.81 (s, 1H), 4.09 (dq, J = 7.2 Hz, J = 2.4 Hz, 2H), 9.56 (s, 1H). ^{13}C NMR (DMSO- d_6): δ = 12.8 (q), 14.0 (q), 28.1 (q), 29.6 (t), 45.3 (t), 45.4 (t), 60.5 (t), 67.5 (d), 79.2 (s), 149.7 (s), 152.9 (s), 170.9 (s). IR: ν_{max} = 3229, 1744, 1732, 1712, 1678 cm^{-1} . MS: m/z (%) = 316 [M^+] (12), 298 (12), 286 (6), 272 (16), 260 (49), 236 (45), 216 (100), 204 (84), 185 (54), 172 (60), 155 (76), 143 (52), 130 (70), 111 (52). Anal. calcd for $\text{C}_{14}\text{H}_{28}\text{N}_4\text{O}_4$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.28; H, 8.79; N, 17.91.

Methyl 2-[(3-Aminopropyl)amino]-3-[(anilino)carbonyl]hydrazono]butanoate (3b**).** White powder from diethyl ether; mp 110–2 °C. ^1H NMR (DMSO- d_6): δ = 1.54–1.59 (m, 2H), 1.83 (s, 3H), 2.46–2.57 (m, 4H), 2.65–2.70 (m, 2H), 3.66 (s, 3H), 3.67 (s, 1H), 4.05 (s, 1H), 6.99 (t, J = 7.2 Hz, 1H), 7.28 (t, J = 7.6 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 8.73 (s, 1H), 9.68 (br s, 1H). ^{13}C NMR (DMSO- d_6): δ = 13.1 (q), 29.5 (t), 45.3 (t), 45.4 (t), 51.9 (q), 67.1 (d), 119.2 (d), 122.3 (d), 128.5 (d), 138.9 (s), 146.8 (s), 153.2 (s), 171.5 (s). IR: ν_{max} = 3372, 3194, 1745, 1693 cm^{-1} . MS: m/z (%) = 321 [M^+] (1), 264 (7), 185 (7), 176 (63), 165 (11), 149 (18), 136 (24), 119 (100), 111 (40). Anal. calcd for $\text{C}_{15}\text{H}_{23}\text{N}_5\text{O}_3$: C, 56.06; H, 7.21; N, 21.79. Found: C, 56.28; H, 7.19; N, 21.91.

tert-Butyl 2-[2-[(3-Amino-2-methylpropyl)amino]-3-methoxy-1-methyl-3-oxopropylidene]hydrazinecarboxylate (3c**).** White powder from diethyl ether; mp 111–3 °C. ^1H NMR (DMSO- d_6): δ = 0.80–0.83 (m, 3H), 1.38–1.40 (m, 1H), 1.44 (s, 9H), 1.76 (s, 3H), 2.18–2.47 (m, 6H), 3.63 (s, 3H), 3.85 (br s, 1H), 3.86 (s, 1H), 9.62 (br s, 1H). ^{13}C NMR (DMSO- d_6): δ = 12.9 (q), 15.1 (q), 28.1 (q), 35.7 (d), 45.2 (t), 51.8 (9), 64.9 (t), 67.6 (d), 79.2 (s), 149.5 (s), 152.9 (s), 171.4 (s). IR: ν_{max} = 3370, 3198, 1743, 1698 cm^{-1} . MS: m/z (%) = 316 [M^+] (8), 286 (11), 263 (15), 251 (51), 216 (100), 184 (44), 171 (51), 158 (86), 130 (60), 110 (40). Anal. calcd for $\text{C}_{14}\text{H}_{28}\text{N}_4\text{O}_4$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.18; H, 8.81; N, 18.01.

tert-Butyl 2-[2-[(3-Amino-2,2-dimethylpropyl)amino]-3-methoxy-1-methyl-3-oxopropylidene]hydrazinecarboxylate (3d**).** White powder from diethyl ether; mp 116–8 °C. ^1H NMR (DMSO- d_6): δ = 0.88 (s, 6H), 1.51 (s, 9H), 1.81 (s, 3H), 2.20–2.27 (m, 4H), 2.47–2.49 (m, 2H), 2.63 (s, 1H), 3.73 (s, 3H), 4.01 (s, 1H), 7.57 (s, 1H). (It is impossible to obtain a good ^{13}C NMR spectrum, because of the poor stability of the compound in solution.) IR: ν_{max} = 3224, 1738, 1718, 1702, 1662 cm^{-1} . MS: m/z (%) = 330 [M^+] (7), 312 (10), 295 (8), 269 (13), 258 (33), 238 (34), 202 (100), 185 (32), 167 (60), 142 (64), 130 (70), 111 (75). Anal. calcd for $\text{C}_{15}\text{H}_{30}\text{N}_4\text{O}_4$: C, 55.52; H, 9.15; N, 16.96. Found: C, 55.47; H, 9.21; N, 17.01.

tert-Butyl 2-[2-[(2-Aminobenzyl)amino]-3-ethoxy-1-methyl-3-oxopropylidene]hydrazinecarboxylate (3e**).** White powder from ethyl acetate; mp 122–4 °C. ^1H NMR (CDCl_3): δ = 1.27 (t, J = 7.2 Hz,

3H), 1.52 (s, 9H), 1.78 (s, 3H), 2.27 (br s, 1H), 3.71 and 3.79 (AB-system, J = 12.0 Hz, 2H), 4.12 (s, 1H), 4.18–4.25 (m, 2H), 4.52 (br s, 2H), 6.64–6.69 (m, 2H), 7.01 (d, J = 7.2 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 7.51 (s, 1H). ^{13}C NMR (CDCl_3): δ = 12.3 (q), 14.1 (q), 20.2 (q), 50.4 (t), 61.4 (t), 67.0 (d), 81.2 (s), 115.6 (d), 117.7 (d), 123.0 (s), 128.5 (d), 130.3 (d), 146.5 (s), 147.2 (s), 152.3 (s), 170.7 (s). IR: ν_{max} = 3475, 3378, 3138, 1749, 1726, 1618 cm^{-1} . MS: m/z (%) = 364 [M^+] (1), 258 (3), 232 (19), 202 (12), 188 (8), 159 (40), 143 (17), 130 (50), 121 (65), 106 (100). Anal. calcd for $\text{C}_{18}\text{H}_{28}\text{N}_4\text{O}_4$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.28; H, 7.79; N, 15.19.

tert-Butyl 2-[2-[(2-Aminobenzyl)amino]-3-methoxy-1-methyl-3-oxopropylidene]hydrazinecarboxylate (3f**).** White powder from ethyl acetate; mp 120–2 °C. ^1H NMR (DMSO- d_6): δ = 1.44 (s, 9H), 1.78 (s, 3H), 2.59 (br s, 1H), 3.49 and 3.55 (AB-system, J = 12.4 Hz, 2H), 3.65 (s, 3H), 5.13 (s, 1H), 4.50 (br s, 2H), 6.48 (t, J = 7.6 Hz, 1H), 6.62 (d, J = 7.6 Hz, 1H), 6.92–6.98 (m, 2H), 9.65 (s, 1H). ^{13}C NMR (DMSO- d_6): δ = 13.4 (q), 28.1 (q), 48.8 (t), 52.0 (q), 66.3 (d), 79.3 (s), 114.7 (d), 115.8 (d), 122.3 (s), 127.9 (d), 129.7 (d), 147.3 (s), 147.4 (s), 152.9 (s), 171.4 (s). IR: ν_{max} = 3496, 3372, 3149, 1749, 1738, 1624 cm^{-1} . MS: m/z (%) = 350 [M^+] (3), 322 (4), 256 (6), 218 (25), 188 (18), 174 (14), 159 (31), 144 (19), 130 (63), 121 (93), 106 (100). Anal. calcd for $\text{C}_{17}\text{H}_{26}\text{N}_4\text{O}_4$: C, 58.27; H, 7.48; N, 15.99. Found: C, 58.33; H, 7.65; N, 15.73.

Methyl N-(2-Aminobenzyl)-3-[(tert-butoxycarbonyl)hydrazono]norvalinate (3g**).** White powder from ethyl acetate; mp 84–6 °C. ^1H NMR (CDCl_3): δ = 1.02 (t, J = 7.6 Hz, 3H), 1.50 (s, 9H), 1.74 (br s, 1H), 2.18–2.24 (m, 2H), 3.64–3.78 (m, 2H), 3.72 (s, 3H), 4.05 (s, 1H), 4.53 (br s, 2H), 6.60–6.66 (m, 2H), 6.97–7.06 (m, 2H), 7.90 (s, 1H). ^{13}C NMR (CDCl_3): δ = 9.3 (q), 20.1 (t), 28.1 (q), 50.3 (t), 52.1 (q), 65.2 (d), 81.2 (s), 115.6 (d), 117.6 (d), 122.7 (s), 128.5 (d), 130.1 (d), 146.4 (s), 151.4 (s), 152.5 (s), 171.5 (s). IR: ν_{max} = 3440, 3338, 3223, 1744, 1726, 1624 cm^{-1} . MS: m/z (%) = 364 [M^+] (1), 233 (13), 202 (17), 188 (14), 173 (16), 158 (14), 144 (9), 130 (23), 121 (83), 106 (100). Anal. calcd for $\text{C}_{18}\text{H}_{28}\text{N}_4\text{O}_4$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.42; H, 7.89; N, 15.23.

tert-Butyl 2-[2-[(2-Aminobenzyl)amino]-3-isopropoxy-1-methyl-3-oxopropylidene]hydrazinecarboxylate (3h**).** White powder from ethyl acetate; mp 144–6 °C. ^1H NMR (CDCl_3): δ = 1.23 and 1.25 (2d, J = 6.4 Hz, 6H), 1.50 (s, 9H), 1.75 (s, 3H), 2.12 (br s, 1H), 3.69 and 3.78 (AB-system, J = 12.4 Hz, 2H), 4.05 (s, 1H), 4.38 (br s, 2H), 5.07 (sept, J = 6.4 Hz, 1H), 6.63–6.67 (m, 2H), 6.98–7.08 (m, 2H), 7.64 (2s, 1H). ^{13}C NMR (CDCl_3): δ = 12.3 (q), 21.6 (q), 28.1 (q), 50.3 (t), 67.1 (d), 69.1 (d), 81.2 (s), 115.6 (d), 117.7 (d), 119.8 (s), 128.5 (d), 130.3 (d), 146.5 (s), 147.2 (s), 152.4 (s), 170.2 (s). IR: ν_{max} = 3465, 3375, 3135, 1752, 1735, 1617 cm^{-1} . MS: m/z (%) = 378 [M^+] (1), 289 (3), 247 (10), 233 (4), 216 (11), 202 (7), 189 (4), 174 (8), 159 (24), 142 (6), 130 (20), 121 (46), 106 (100). Anal. calcd for $\text{C}_{19}\text{H}_{30}\text{N}_4\text{O}_4$: C, 60.30; H, 7.99; N, 14.80. Found: C, 60.44; H, 7.85; N, 14.93.

General Procedure for the Synthesis of 2,5,6,7-Tetrahydro-1H-1,4-diazepin-2-ones **4a–o.** To a solution of diamines **2a–c** (1.0 mmol) in EtOH (2 mL) magnetically stirred at room temperature was added a solution of 1,2-diaza-1,3-dienes **1a–f** (1.0 mmol) in EtOH (3 mL). The disappearance of the red color of **1a–f** occurred within 1 min, and, at this point of the reaction, the TLC analysis revealed the presence of α -aminohydrazones **3** as major products. After 1.0–8.0 h, compounds **3** were converted into the corresponding 2,5,6,7-tetrahydro-1H-1,4-diazepin-2-ones **4a–o** that in part crystallized from the reaction medium, while the remaining part was obtained by flash chromatography (silica, 10% methanol–90% ethyl acetate as eluant). Spectroscopic data for 2,5,6,7-tetrahydro-1H-1,4-diazepin-2-ones **4a–o** are given below.

tert-Butyl 2-[1-(2-Oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-ethylidene]hydrazinecarboxylate (4a**).** White powder from ethanol; mp 248–50 °C. ^1H NMR (DMSO- d_6): δ = 1.41 (s, 9H), 1.81 (q, J = 6.8 Hz, 2H), 2.02 (s, 3H), 2.85 (q, J = 6.0 Hz, 2H), 3.53 (t, J = 6.4 Hz, 2H),

8.19 (t, $J = 6.0$ Hz, 1H), 10.05 (s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 11.5$ (q), 28.0 (q), 28.1 (t), 36.0 (t), 47.7 (t), 79.8 (s), 147.1 (s), 152.2 (s), 166.5 (s), 167.2 (s). IR: $\nu_{\text{max}} = 3230, 1739, 1708, 1678, 1648\text{ cm}^{-1}$. MS: m/z (%) = 268 [M^+] (1), 212 (29), 195 (24), 167 (49), 150 (13), 139 (100), 111 (94). Anal. calcd for $\text{C}_{12}\text{H}_{20}\text{N}_4\text{O}_3$: C, 53.72; H, 7.51; N, 20.88. Found: C, 53.88; H, 7.59; N, 20.61.

1-(2-Oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone *N*-Phenylsemicarbazone (**4b**). White powder from ethanol; mp 182–4 °C. ^1H NMR (DMSO- d_6): $\delta = 1.85$ (q, $J = 6.4$ Hz, 2H), 2.07 (s, 3H), 2.91 (q, $J = 6.0$ Hz, 2H), 3.59 (t, $J = 6.0$ Hz, 2H), 7.03 (t, $J = 7.6$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 8.42 (t, $J = 6.0$ Hz, 1H), 8.57 (s, 1H), 10.28 (br s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 10.9$ (q), 28.0 (t), 36.0 (t), 48.0 (t), 118.3 (d), 122.7 (d), 129.0 (d), 138.3 (s), 143.9 (s), 152.4 (s), 165.8 (s), 166.3 (s). IR: $\nu_{\text{max}} = 3362, 3255, 3183, 1697, 1668, 1612\text{ cm}^{-1}$. MS: m/z (%) = 287 [M^+] (17), 195 (4), 167 (64), 140 (100), 111 (79). Anal. calcd for $\text{C}_{14}\text{H}_{17}\text{N}_5\text{O}_2$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.39; H, 6.09; N, 24.51.

Benzyl 2-[1-(2-Oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)ethylidene]hydrazinecarboxylate (**4c**). White powder from ethanol; mp 230–2 °C. ^1H NMR (DMSO- d_6): $\delta = 1.80$ (q, $J = 6.4$ Hz, 2H), 2.02 (s, 3H), 2.90 (q, $J = 6.0$ Hz, 2H), 3.53 (t, $J = 6.4$ Hz, 2H), 5.16 (s, 2H), 7.32–7.41 (m, 5H), 8.21 (t, $J = 6.8$ Hz, 1H), 10.43 (br s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 11.6$ (q), 28.1 (t), 36.0 (t), 47.8 (t), 66.1 (t), 127.9 (d), 128.0 (d), 128.4 (d), 136.4 (s), 148.0 (s), 153.3 (s), 165.4 (s), 167.1 (s). IR: $\nu_{\text{max}} = 3398, 3229, 1740, 1711, 1685, 1646\text{ cm}^{-1}$. MS: m/z (%) = 302 [M^+] (3), 225 (5), 211 (3), 196 (2), 167 (95), 152 (4), 139 (100), 111 (92). Anal. calcd for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.61; H, 6.03; N, 18.61.

1-(2-Oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone Semicarbazone (**4d**). White powder from ethanol; mp 233–5 °C. ^1H NMR (DMSO- d_6): $\delta = 1.82$ (q, $J = 6.8$ Hz, 2H), 1.99 (s, 3H), 2.87 (q, $J = 6.4$ Hz, 2H), 3.54 (t, $J = 6.4$ Hz, 2H), 5.82 and 6.51 (2br s, 2H), 8.23 (t, $J = 6.4$ Hz, 1H), 9.89 (s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 10.8$ (q), 28.0 (t), 36.0 (t), 47.8 (t), 142.8 (s), 156.3 (s), 165.8 (s), 166.6 (s). IR: $\nu_{\text{max}} = 3460, 3192, 1718, 1704, 1683, 1635\text{ cm}^{-1}$. MS: m/z (%) = 211 [M^+] (1), 167 (83), 151 (44), 139 (85), 111 (100). Anal. calcd for $\text{C}_8\text{H}_{13}\text{N}_5\text{O}_2$: C, 45.49; H, 6.20; N, 33.16. Found: C, 45.38; H, 6.39; N, 33.01.

1-(2-Oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-propanone Semicarbazone (**4e**). White powder from ethanol; mp 196–8 °C. ^1H NMR (DMSO- d_6): $\delta = 0.90$ (t, $J = 7.6$ Hz, 3H), 1.80 (q, $J = 6.4$ Hz, 2H), 2.58 (q, $J = 7.6$ Hz, 2H), 2.84 (q, $J = 6.4$ Hz, 2H), 3.53 (t, $J = 6.4$ Hz, 2H), 5.86 and 6.56 (2br s, 2H), 8.20 (t, $J = 6.4$ Hz, 1H), 10.02 (s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 10.0$ (q), 16.8 (t), 28.0 (t), 36.1 (t), 47.8 (t), 146.9 (s), 156.4 (s), 165.8 (s), 165.9 (s). IR: $\nu_{\text{max}} = 3463, 3201, 1708, 1687, 1654\text{ cm}^{-1}$. MS: m/z (%) = 225 [M^+] (1), 181 (81), 164 (21), 153 (45), 110 (100). Anal. calcd for $\text{C}_9\text{H}_{15}\text{N}_5\text{O}_2$: C, 47.99; H, 6.71; N, 31.09. Found: C, 48.03; H, 6.79; N, 31.11.

1-(6-Methyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone *N*-Phenylsemicarbazone (**4f**). Pink powder from ethanol; mp 178–80 °C. ^1H NMR (DMSO- d_6): $\delta = 0.91$ (d, $J = 7.2$ Hz, 3H), 2.06 (s, 3H), 2.15 (sex., $J = 6.0$ Hz, 1H), 2.61 (dt, $J = 14.8$ Hz, $J = 5.6$ Hz, 1H), 2.98 (dt, $J = 14.8$ Hz, $J = 5.6$ Hz, 1H), 3.20 (dd, $J = 9.0$ Hz, $J = 8.4$ Hz, 1H), 3.70 (dd, $J = 10.2$ Hz, $J = 6.0$ Hz, 1H), 7.03 (t, $J = 7.6$ Hz, 1H), 7.32 (t, $J = 8.4$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 8.53 (t, $J = 6.0$ Hz, 1H), 8.59 (s, 1H), 10.04 (br s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 11.0$ (q), 16.5 (q), 34.6 (d), 42.9 (t), 55.0 (t), 118.3 (d), 122.7 (d), 129.0 (d), 138.4 (s), 144.0 (s), 152.4 (s), 165.8 (s), 169.3 (s). IR: $\nu_{\text{max}} = 3451, 3327, 3195, 3066, 1705, 1654\text{ cm}^{-1}$. MS: m/z (%) = 301 [M^+] (23), 209 (6), 181 (63), 167 (11), 154 (100), 139 (22), 125 (69), 111 (57). Anal. calcd for $\text{C}_{15}\text{H}_{19}\text{N}_5\text{O}_2$: C, 59.79; H, 6.36; N, 23.24. Found: C, 59.89; H, 6.49; N, 23.11.

tert-Butyl 2-[1-(6-Methyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)ethylidene]hydrazinecarboxylate (**4g**). Pink powder from ethanol; mp 242–4 °C. ^1H NMR (DMSO- d_6): $\delta = 0.87$ (d, $J = 6.8$

Hz, 3H), 1.44 (s, 9H), 1.98 (s, 3H), 2.13 (sex., $J = 5.6$ Hz, 1H), 2.54 (dt, $J = 14.4$ Hz, $J = 4.8$ Hz, 1H), 2.89 (dt, $J = 14.4$ Hz, $J = 6.0$ Hz, 1H), 3.11 (dd, $J = 10.8$ Hz, $J = 7.2$ Hz, 1H), 3.62 (dd, $J = 10.4$ Hz, $J = 5.6$ Hz, 1H), 8.32 (t, $J = 6.0$ Hz, 1H), 10.06 (s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 11.5$ (q), 16.4 (q), 28.0 (q), 34.6 (d), 42.8 (t), 54.8 (t), 79.9 (s), 147.1 (s), 152.2 (s), 165.5 (s), 167.3 (s). IR: $\nu_{\text{max}} = 3397, 3240, 1746, 1723, 1685, 1651\text{ cm}^{-1}$. MS: m/z (%) = 283 [M^+] (1), 267 (3), 226 (25), 209 (20), 181 (45), 153 (100), 139 (19), 125 (49), 110 (35). Anal. calcd for $\text{C}_{13}\text{H}_{22}\text{N}_4\text{O}_3$: C, 55.30; H, 7.85; N, 19.84. Found: C, 55.18; H, 7.99; N, 19.66.

Benzyl 2-[1-(6-Methyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)ethylidene]hydrazinecarboxylate (**4h**). White powder from ethanol; mp 110–2 °C. ^1H NMR (DMSO- d_6): $\delta = 0.89$ (d, $J = 6.8$ Hz, 3H), 2.02 (s, 3H), 2.14 (sex., $J = 5.6$ Hz, 1H), 2.48–2.61 (m, 1H), 2.92 (dt, $J = 14.4$ Hz, $J = 7.6$ Hz, 1H), 3.15 (dd, $J = 8.8$ Hz, $J = 8.0$ Hz, 1H), 3.65 (dd, $J = 10.6$ Hz, $J = 6.4$ Hz, 1H), 5.18 (s, 2H), 7.33–7.40 (m, 5H), 8.36 (t, $J = 6.8$ Hz, 1H), 10.47 (br s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 11.6$ (q), 16.4 (q), 34.6 (d), 42.8 (t), 54.8 (t), 66.1 (t), 127.9 (d), 128.0 (d), 128.4 (d), 136.4 (s), 148.1 (s), 153.3 (s), 165.4 (s), 167.1 (s). IR: $\nu_{\text{max}} = 3390, 3221, 1744, 1717, 1682, 1645\text{ cm}^{-1}$. MS: m/z (%) = 316 [M^+] (1), 239 (9), 224 (20), 196 (56), 183 (12), 167 (75), 151 (19), 139 (31), 126 (35), 108 (100). Anal. calcd for $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_3$: C, 60.75; H, 6.37; N, 17.71. Found: C, 60.64; H, 6.43; N, 17.65.

1-(6-Methyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone Semicarbazone (**4i**). Pink powder from ethanol; mp 148–50 °C. ^1H NMR (DMSO- d_6): $\delta = 0.89$ (d, $J = 6.8$ Hz, 3H), 1.99 (s, 3H), 2.15 (sex., $J = 5.2$ Hz, 1H), 2.56 (dt, $J = 14.8$ Hz, $J = 4.4$ Hz, 1H), 2.92 (dt, $J = 14.8$ Hz, $J = 8.0$ Hz, 1H), 3.14 (dd, $J = 8.4$ Hz, $J = 8.0$ Hz, 1H), 3.65 (dd, $J = 10.6$ Hz, $J = 6.0$ Hz, 1H), 5.92 and 6.66 (2br s, 2H), 8.35 (t, $J = 6.0$ Hz, 1H), 9.90 (s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 10.8$ (q), 16.5 (q), 34.6 (d), 42.9 (t), 54.9 (t), 142.9 (s), 156.4 (s), 165.8 (s), 166.7 (s). IR: $\nu_{\text{max}} = 3451, 3193, 1725, 1705, 1694, 1655\text{ cm}^{-1}$. MS: m/z (%) = 225 [M^+] (1), 209 (2), 181 (68), 165 (4), 153 (100), 139 (6), 125 (43), 110 (14). Anal. calcd for $\text{C}_9\text{H}_{15}\text{N}_5\text{O}_2$: C, 47.99; H, 6.71; N, 31.09. Found: C, 48.08; H, 6.79; N, 31.16.

1-(6-Methyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-propanone Semicarbazone (**4j**). Pink powder from ethanol; mp 190–2 °C. ^1H NMR (DMSO- d_6): $\delta = 0.89$ (d, $J = 8.4$ Hz, 3H), 1.03 (t, $J = 7.2$ Hz, 3H), 2.16 (sex., $J = 6.0$ Hz, 1H), 2.48–2.61 (m, 3H), 2.92 (dt, $J = 14.8$ Hz, $J = 7.2$ Hz, 1H), 3.18 (dd, $J = 9.0$ Hz, $J = 9.2$ Hz, 1H), 3.62 (dd, $J = 8.0$ Hz, $J = 6.0$ Hz, 1H), 5.90 and 6.63 (2br s, 2H), 8.33 (t, $J = 5.6$ Hz, 1H), 10.05 (s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 10.0$ (q), 16.4 (q), 16.9 (t), 34.6 (d), 43.0 (t), 54.9 (t), 146.9 (s), 156.4 (s), 165.8 (s), 165.9 (s). IR: $\nu_{\text{max}} = 3399, 3191, 1703, 1687\text{ cm}^{-1}$. MS: m/z (%) = 240 [M^+] (1), 224 (4), 195 (24), 179 (42), 164 (37), 149 (23), 138 (32), 126 (78), 111 (100). Anal. calcd for $\text{C}_{10}\text{H}_{17}\text{N}_5\text{O}_2$: C, 50.20; H, 7.16; N, 29.27. Found: C, 50.33; H, 7.09; N, 29.44.

1-(6,6-Dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone *N*-Phenylsemicarbazone (**4k**). Pink powder from ethanol; mp 216–8 °C. ^1H NMR (DMSO- d_6): $\delta = 0.91$ (s, 6H), 2.04 (s, 3H), 2.58 (d, $J = 6.0$ Hz, 2H), 3.28 (s, 2H), 7.01 (t, $J = 7.2$ Hz, 1H), 7.30 (t, $J = 7.2$ Hz, 2H), 7.40 (d, $J = 7.6$ Hz, 2H), 8.57 (s, 1H), 8.65 (t, $J = 6.0$ Hz, 1H), 10.38 (br s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 10.9$ (q), 24.4 (q), 39.9 (s), 48.5 (t), 60.4 (t), 118.3 (d), 122.7 (d), 128.9 (d), 138.4 (s), 144.0 (s), 152.4 (s), 165.6 (s), 166.4 (s). IR: $\nu_{\text{max}} = 3325, 3196, 3086, 1702, 1662, 1599\text{ cm}^{-1}$. MS: m/z (%) = 315 [M^+] (17), 285 (1), 223 (5), 195 (43), 176 (15), 167 (100), 153 (11), 139 (29), 119 (32), 110 (30). Anal. calcd for $\text{C}_{16}\text{H}_{21}\text{N}_5\text{O}_2$: C, 60.94; H, 6.71; N, 22.21. Found: C, 61.02; H, 6.85; N, 22.43.

tert-Butyl 2-[1-(6,6-Dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)ethylidene]hydrazinecarboxylate (**4l**). Pink powder from ethanol; mp 220–4 °C. ^1H NMR (DMSO- d_6): $\delta = 0.88$ (s, 6H), 1.44 (s, 9H), 1.98 (s, 3H), 2.52 (d, $J = 6.4$ Hz, 2H), 3.22 (s, 2H), 8.45 (t, $J = 6.0$ Hz, 1H), 10.06 (s, 1H). ^{13}C NMR (DMSO- d_6): $\delta = 11.5$ (q), 24.4

(q), 28.0 (q), 39.9 (s), 48.5 (t), 60.1 (t), 79.8 (s), 147.2 (s), 152.2 (s), 165.4 (s), 167.3 (s). IR: ν_{\max} = 3255, 1746, 1720, 1688, 1651 cm^{-1} . MS: m/z (%) = 296 [M^+] (1), 281 (2), 240 (19), 223 (18), 195 (31), 179 (6), 167 (100), 153 (18), 139 (35), 124 (20), 110 (45). Anal. calcd for $\text{C}_{14}\text{H}_{24}\text{N}_4\text{O}_3$: C, 56.74; H, 8.16; N, 18.90. Found: C, 56.88; H, 8.23; N, 18.66.

Benzyl 2-[1-(6,6-Dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)ethylidene]hydrazinecarboxylate (4m). Pink powder from ethanol; mp 90–2 °C. ^1H NMR (DMSO- d_6): δ = 0.90 (s, 6H), 2.03 (s, 3H), 2.55 (d, J = 6.0 Hz, 2H), 3.25 (s, 2H), 5.19 (s, 2H), 7.33–7.42 (m, 5H), 8.51 (t, J = 6.0 Hz, 1H), 10.48 (br s, 1H). ^{13}C NMR (DMSO- d_6): δ = 11.7 (q), 24.5 (q), 39.9 (s), 48.6 (t), 60.2 (t), 66.2 (t), 128.0 (d), 128.1 (d), 128.5 (d), 136.4 (s), 148.2 (s), 153.5 (s), 165.4 (s), 167.2 (s). IR: ν_{\max} = 3399, 3223, 1749, 1717, 1690 cm^{-1} . MS: m/z (%) = 330 [M^+] (1), 239 (6), 206 (19), 191 (100), 128 (19), 108 (49). Anal. calcd for $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.69; H, 6.55; N, 17.02.

1-(6,6-Dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-ethanone Semicarbazone (4n). Scarlet powder from ethanol; mp 208–10 °C. ^1H NMR (DMSO- d_6): δ = 0.91 (s, 6H), 1.99 (s, 3H), 2.55 (d, J = 6.4 Hz, 2H), 3.25 (s, 2H), 5.92 and 6.67 (2br s, 2H), 8.49 (t, J = 6.0 Hz, 1H), 9.88 (br s, 1H). ^{13}C NMR (DMSO- d_6): δ = 10.8 (q), 24.5 (q), 39.8 (s), 48.5 (t), 60.2 (t), 142.9 (s), 156.3 (s), 165.6 (s), 166.7 (s). IR: ν_{\max} = 3450, 3294, 3204, 1690, 1655 cm^{-1} . MS: m/z (%) = 240 [M^+] (1), 224 (3), 209 (3), 195 (54), 178 (10), 167 (100), 153 (8), 139 (21), 124 (19), 113 (48). Anal. calcd for $\text{C}_{10}\text{H}_{17}\text{N}_5\text{O}_2$: C, 50.20; H, 7.16; N, 29.27. Found: C, 50.29; H, 7.19; N, 29.46.

1-(6,6-Dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-yl)-1-propanone Semicarbazone (4o). Scarlet powder from ethanol; mp 176–8 °C. ^1H NMR (DMSO- d_6): δ = 0.89 (s, 6H), 0.92 (t, J = 7.2 Hz, 3H), 2.45–2.59 (m, 4H), 3.23 (s, 2H), 5.88 and 6.62 (2br s, 2H), 8.45 (t, J = 6.4 Hz, 1H), 10.05 (s, 1H). ^{13}C NMR (DMSO- d_6): δ = 10.1 (q), 16.9 (t), 24.4 (q), 39.8 (s), 48.5 (t), 60.2 (t), 146.9 (s), 156.4 (s), 165.9 (s), 166.1 (s). IR: ν_{\max} = 3432, 3203, 3159, 1711, 1664, 1596 cm^{-1} . MS: m/z (%) = 253 [M^+] (1), 209 (91), 181 (100), 167 (23), 153 (32), 139 (19), 110 (92). Anal. calcd for $\text{C}_{11}\text{H}_{19}\text{N}_5\text{O}_2$: C, 52.16; H, 7.56; N, 27.65. Found: C, 52.27; H, 7.48; N, 27.49.

General Procedure for the Synthesis of Alkyl 5H-1,4-Benzodiazepine-3-carboxylates 5a–d. A solution of α -aminohydrazone 3e–h (1.0 mmol) in toluene (5 mL) was refluxed for 3.0–5.0 h, until the corresponding alkyl 5H-1,4-benzodiazepine-3-carboxylates 5a–d were formed. After flash chromatography (silica, 10% ethyl acetate–90% cyclohexane as eluant), compounds 5a–c were obtained as oils, while 5d was crystallized from cyclohexane–ethyl acetate. Spectroscopic data for alkyl 5H-1,4-benzodiazepine-3-carboxylates 5a–d are given below.

Ethyl 2-Methyl-5H-1,4-benzodiazepine-3-carboxylate (5a). Red oil. ^1H NMR (CDCl_3): δ = 1.34 (t, J = 7.2 Hz, 3H), 2.54 (s, 3H), 4.30 (q, J = 7.2 Hz, 2H), 4.63 (br s, 2H), 7.22–7.39 (m, 4H). ^{13}C NMR (CDCl_3): δ = 14.0 (q), 25.6 (q), 54.5 (t), 62.4 (t), 125.7 (d), 127.1 (d), 128.1 (d), 128.8 (s), 128.9 (d), 146.8 (s), 154.9 (s), 162.6 (s), 163.2 (s). IR: ν_{\max} = 1731, 1633 cm^{-1} . ESI $^+$: m/z = 231 [$\text{M} + \text{H}$] $^+$. Anal. calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.98; H, 6.29; N, 12.01.

Methyl 2-Methyl-5H-1,4-benzodiazepine-3-carboxylate (5b). Orange oil. ^1H NMR (CDCl_3): δ = 2.43 (s, 3H), 3.72 (s, 3H), 4.62 (br s, 2H), 7.12–7.27 (m, 4H). ^{13}C NMR (CDCl_3): δ = 25.6 (q), 53.0 (q), 54.5 (t), 125.6 (d), 127.1 (d), 128.0 (d), 128.6 (s), 128.9 (d), 146.7 (s), 154.3 (s), 162.9 (s), 163.1 (s). IR: ν_{\max} = 1749, 1729, 1640 cm^{-1} . ESI $^+$: m/z = 217 [$\text{M} + \text{H}$] $^+$. Anal. calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.88; H, 5.33; N, 13.02.

Methyl 2-Ethyl-5H-1,4-benzodiazepine-3-carboxylate (5c). Orange oil. ^1H NMR (CDCl_3): δ = 1.27 (t, J = 7.2 Hz, 3H), 2.88 (q, J = 7.6 Hz, 2H), 3.85 (s, 3H), 4.82 (br s, 2H), 7.25–7.41 (m, 4H). ^{13}C NMR (CDCl_3): δ = 11.1 (q), 31.5 (t), 53.1 (q), 54.6 (t), 125.7 (d), 127.0 (d),

128.1 (d), 128.8 (s), 129.0 (d), 147.9 (s), 154.5 (s), 163.1 (s), 168.0 (s). IR: ν_{\max} = 1752, 1738, 1640 cm^{-1} . MS: m/z (%) = 230 [M^+] (34), 191 (4), 171 (6), 145 (30), 130 (100), 117 (33). Anal. calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.66; H, 6.28; N, 12.31.

Isopropyl 2-Methyl-5H-1,4-benzodiazepine-3-carboxylate (5d). Yellow powder from cyclohexane–ethyl acetate; mp 112–4 °C. ^1H NMR (CDCl_3): δ = 1.28 (d, J = 6.0 Hz, 6H), 2.48 (s, 3H), 4.25 (br s, 2H), 5.1 (sept, J = 6.4 Hz, 1H), 7.20–7.36 (m, 4H). ^{13}C NMR (CDCl_3): δ = 21.4 (q), 25.4 (q), 54.3 (t), 70.2 (d), 125.6 (d), 126.9 (d), 128.0 (d), 128.7 (s), 128.8 (d), 146.7 (s), 155.2 (s), 162.1 (s), 163.1 (s). IR: ν_{\max} = 1724, 1645, 1605 cm^{-1} . MS: m/z (%) = 244 [M^+] (37), 229 (4), 202 (11), 186 (16), 157 (26), 130 (100), 116 (19), 103 (10). Anal. calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.99; H, 6.49; N, 11.51.

General Procedure for the Synthesis of 4-[(3-Aminopropyl)-(methyl)amino]-1H-pyrazol-3-ones 6a–d. To a solution of *N*-methyl-1,3-diaminopropane 2e (1.0 mmol) in dichloromethane (2 mL) magnetically stirred at room temperature was added a solution of 1,2-diaza-1,3-dienes 1a,b,g,i (1.0 mmol) in dichloromethane (3 mL). The disappearance of the red color of 1a,b,g,i occurred within 0.1–0.2 h and products 6a–d directly crystallized from the reaction solvent. Spectroscopic data for 4-[(3-aminopropyl)(methyl)amino]-1H-pyrazol-3-ones 6a–d are given below.

tert-Butyl 4-[(3-Aminopropyl)(methyl)amino]-3-methyl-5-oxo-2,5-dihydro-1H-pyrazole-1-carboxylate (6a). Pink powder from dichloromethane; mp 95–7 °C. ^1H NMR (CDCl_3): δ = 1.49–1.57 (m, 4H), 1.61 (s, 9H), 2.16 (s, 3H), 2.52 (s, 3H), 2.77–2.83 (m, 2H), 2.85–2.92 (m, 2H), 8.94 (br s, 1H). ^{13}C NMR (CDCl_3): δ = 15.8 (q), 24.1 (t), 38.0 (t), 40.7 (t), 54.7 (q), 82.5 (s), 113.0 (s), 150.6 (s), 150.7 (s), 160.4 (s). IR: ν_{\max} = 3443, 3219, 1732, 1648 cm^{-1} . MS: m/z (%) = 284 [M^+] (1), 256 (4), 226 (6), 211 (8), 184 (32), 167 (15), 153 (18), 140 (100), 126 (64), 111 (29). Anal. calcd for $\text{C}_{13}\text{H}_{24}\text{N}_4\text{O}_3$: C, 54.91; H, 8.51; N, 19.70. Found: C, 54.88; H, 8.59; N, 19.81.

4-[(3-Aminopropyl)(methyl)amino]-3-methyl-5-oxo-*N*-phenyl-2,5-dihydro-1H-pyrazole-1-carboxamide (6b). Pink powder from dichloromethane; mp 132–4 °C. ^1H NMR (DMSO- d_6): δ = 1.58–1.61 (m, 2H), 2.00 (s, 3H), 2.04 and 2.31 (2br s, 2H), 2.61 (s, 3H), 2.63–2.93 (m, 4H), 6.99 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 8.03 (br s, 1H), 12.66 (s, 1H). ^{13}C NMR (DMSO- d_6): δ = 16.3 (q), 25.1 (t), 38.3 (t), 43.1 (t), 54.5 (q), 108.4 (s), 118.8 (d), 122.2 (d), 128.9 (d), 139.2 (s), 148.3 (s), 149.8 (s), 160.1 (s). IR: ν_{\max} = 3338, 3184, 1725, 1690, 1662, 1599 cm^{-1} . MS: m/z (%) = 303 [M^+] (2), 277 (9), 234 (7), 221 (14), 210 (26), 188 (53), 176 (37), 166 (23), 151 (22), 140 (70), 119 (100), 111 (62). Anal. calcd for $\text{C}_{15}\text{H}_{21}\text{N}_5\text{O}_2$: C, 59.39; H, 6.98; N, 23.09. Found: C, 59.48; H, 6.89; N, 23.01.

tert-Butyl 4-[(3-Aminopropyl)(methyl)amino]-3-ethyl-5-oxo-2,5-dihydro-1H-pyrazole-1-carboxylate (6c). Pink powder from dichloromethane; mp 128–30 °C. ^1H NMR (CDCl_3): δ = 1.17 (t, J = 7.2 Hz, 3H), 1.42 (br s, 2H), 1.48–1.50 (m, 2H), 1.62 (s, 9H), 2.50–2.55 (m, 5H), 2.61–2.82 (m, 2H), 2.87–2.94 (m, 2H), 8.96 (br s, 1H). ^{13}C NMR (CDCl_3): δ = 13.6 (q), 22.7 (t), 26.9 (t), 37.4 (t), 39.5 (t), 53.9 (q), 82.2 (s), 112.3 (s), 150.8 (s), 155.8 (s), 160.3 (s). IR: ν_{\max} = 3316, 3186, 1729, 1638 cm^{-1} . MS: m/z (%) = 298 [M^+] (3), 267 (8), 235 (30), 197 (19), 180 (24), 168 (29), 134 (42), 128 (49), 115 (100). Anal. calcd for $\text{C}_{14}\text{H}_{26}\text{N}_4\text{O}_3$: C, 56.35; H, 8.78; N, 18.78. Found: C, 56.42; H, 8.69; N, 18.66.

Methyl 4-[(3-Aminopropyl)(methyl)amino]-3-methyl-5-oxo-2,5-dihydro-1H-pyrazole-1-carboxylate (6d). Pink powder from dichloromethane; mp 150–2 °C. ^1H NMR (CDCl_3): δ = 1.52–1.64 (m, 4H), 2.19 (s, 3H), 2.59 (s, 3H), 2.89–2.96 (m, 4H), 3.89 (s, 3H), 8.69 (br s, 1H). ^{13}C NMR (CDCl_3): δ = 15.2 (q), 24.2 (t), 38.9 (t), 41.5 (t), 53.0 (q), 55.7 (q), 112.3 (s), 151.5 (s), 151.6 (s), 160.4 (s). IR: ν_{\max} = 3450, 3282, 1739, 1648 cm^{-1} . MS: m/z (%) = 242 [M^+] (21), 211 (29), 198

(36), 184 (10), 166 (21), 154 (7), 140 (100), 111 (19). Anal. calcd for $C_{10}H_{18}N_4O_3$: C, 49.57; H, 7.49; N, 23.13. Found: C, 49.48; H, 7.53; N, 23.25.

General Procedure for the Synthesis of Bis- α -aminohydrazones 7a, b. To a solution of 1,2-diaza-1,3-dienes **1a,b** (2.0 mmol) in acetonitrile (3 mL) magnetically stirred at room temperature, a solution of *N,N'*-dimethyl-1,3-diaminopropane **2f** (1 mmol) in acetonitrile (2 mL) was added. At the disappearance of the red color of **1a,b** that occurred within 5 min, products **7a,b** were obtained simply by evaporation of the reaction solvent; **7a** was obtained as yellow oil, while **7b** was crystallized from diethyl ether–petroleum ether (bp 40–60 °C). Spectroscopic data for bis- α -aminohydrazones **7a,b** are given below.

Di-tert-Butyl 5,11-Bis(ethoxycarbonyl)-4,6,10,12-tetramethyl-2,3,6,10,13,14-hexaazapentadeca-3,12-diene-1,15-dioate (7a). Yellow oil. 1H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 6H), 1.47 (s, 18H), 1.60–1.64 (m, 2H), 1.85 (s, 6H), 2.25 (s, 6H), 2.39–2.45 (m, 4H), 3.90 (s, 2H), 4.12–4.19 (m, 4H), 7.63 (br s, 2H). ^{13}C NMR ($CDCl_3$): δ = 12.2 (q), 13.8 (q), 27.8 (q), 38.4 (t), 51.8 (t), 53.2 (t), 60.2 (q), 73.7 (d), 80.5 (s), 148.0 (s), 152.3 (s), 169.8 (s). IR: ν_{max} = 3390, 3205, 1740, 1685 cm^{-1} . MS: *m/z* (%) = 586 [M^+] (6), 513 (3), 343 (12), 312 (24), 286 (40), 274 (32), 244 (13), 213 (100). Anal. calcd for $C_{27}H_{50}N_6O_8$: C, 55.27; H, 8.59; N, 14.32. Found: C, 55.38; H, 8.69; N, 14.21.

Dimethyl 1,15-Dianilino-4,6,10,12-tetramethyl-1,15-dioxo-2,3,6,10,13,14-hexaazapentadeca-3,12-diene-5,11-dicarboxylate (7b). Yellow powder from diethyl ether–light petroleum (bp 40–60 °C); mp 68–70 °C. 1H NMR ($CDCl_3$): δ = 1.65–1.69 (m, 2H), 2.00 (s, 6H), 2.34 (s, 6H), 2.54–2.63 (m, 4H), 3.74 (s, 6H), 4.00 (s, 2H), 7.02–7.04 (m, 2H), 7.25–7.31 (m, 4H), 7.43–7.47 (m, 4H), 8.06 (s, 2H), 8.95 (br s, 2H). ^{13}C NMR ($CDCl_3$): δ = 13.5 (q), 38.5 (t), 50.1 (t), 51.5 (t), 51.9 (q), 73.7 (d), 119.1 (d), 123.3 (d), 128.9 (d), 137.9 (s), 146.7 (s), 153.5 (s), 170.6 (s). IR: ν_{max} = 3368, 3193, 1742, 1690, 1651 cm^{-1} . MS: *m/z* (%) = 596 [M^+] (1), 356 (4), 326 (3), 294 (100). Anal. calcd for $C_{29}H_{40}N_8O_6$: C, 58.37; H, 6.76; N, 18.78. Found: C, 58.58; H, 6.89; N, 18.95.

ASSOCIATED CONTENT

Supporting Information. Figures giving 1H NMR and ^{13}C NMR spectral data for compounds **3a–h**, **4a–o**, **5a–d**, **6a–d**, and **7a,b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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