A combined experimental and theoretical study of the synthesis of quinazolino[3,2-*a*][1,5]benzodiazepin-13-ones

Regina Janciene,[a]* Ausra Vektariene,[b] Gema Mikulskiene,[a] Tomas Javorskis,[a] Gytis Vektaris,[b] and Algirdas Klimavicius[a]

[a]Vilnius University Institute of Biochemistry, Mokslininku 12, LT-08662 Vilnius, Lithuania
[b]Vilnius University Institute of Theoretical Physics and Astronomy, A. Gostauto 12, LT-01108 Vilnius, Lithuania
E-mail: regina.janciene@bchi.vu.lt

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Abstract

A simple and efficient general approach to various tetracyclic 6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-ones has been demonstrated by reductive N-heterocyclization of 5-alkyl- or benzoyl-1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones. These 2-nitrobenzoylamides were obtained by acylation of the starting 5-alkyl- or benzoyl-1,5-benzodiazepin-2-ones with 2-nitrobenzoyl chloride. A theoretical understanding of the features of the reductive N-heterocyclization reaction was provided by means of quantum chemical reactivity descriptors calculations.

Keywords: Dihydroquinazolino[3,2-*a*][1,5]benzodiazepine, 1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one, reductive heterocyclization, quantum-chemistry calculations

Introduction

Naturally occurring alkaloids such as asperlicins, circumdatins, benzomalvins and sclerotigenin incorporating a quinazolino[1,4]benzodiazepine system in their structure have been isolated from different sources.[1] These alkaloids display various biological activities. In a quest to find additional potential quinazoline-based derivatives, various substituted quinazolinones[2,3] and compounds encompassing a quinazolino[1,4]benzodiazepine moiety in their skeleton[4-7] have been developed.

As a part of our ongoing research activity,[8-10] we were interested in the synthesis of some quinazolino[1,5]benzdiazepine derivatives as possible analogues of natural products. The main synthetic routes to compounds with quinazolino[1,4]benzodiazepine moiety utilize the

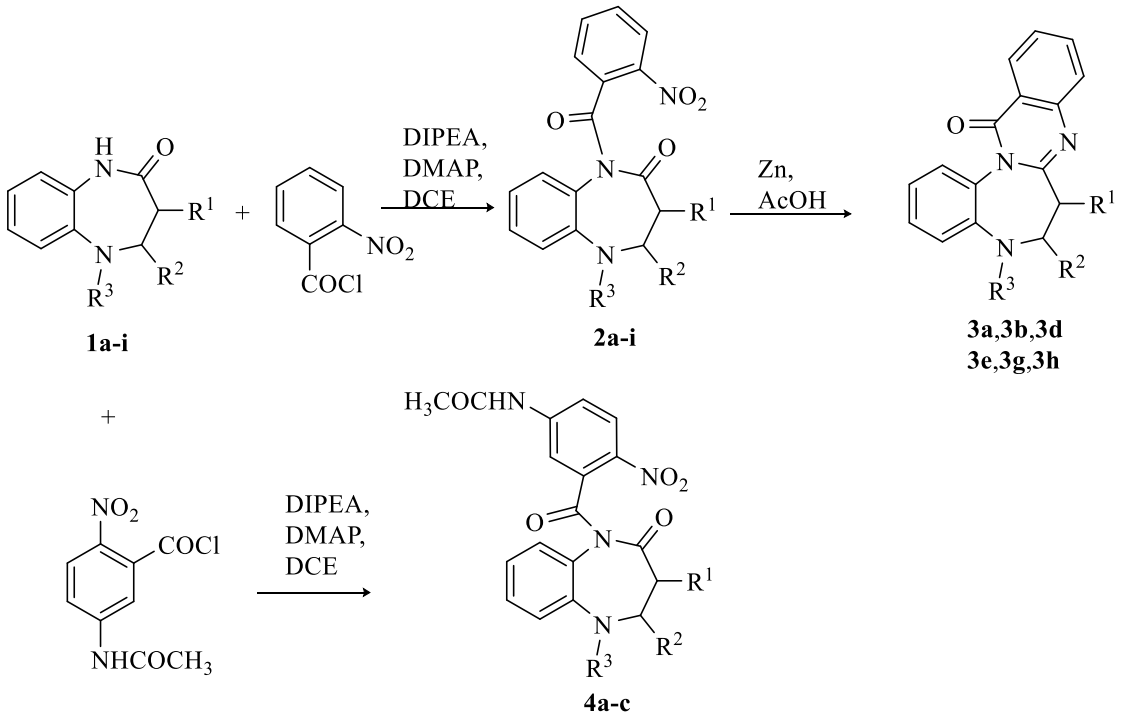
implementations of 2-azidobenzoylamides in aza-Wittig methodology[4,5,11] and transition metal-induced reductive N-heterocyclization[2,3,6,7,12] for the construction of a variety of heterocyclic compounds. Although these methods have emerged as versatile strategies, they have some disadvantages such as cost and availability of the reagents such as 2-azidobenzoyl chloride and noble metal catalysts.

As a continuation of our interest in polycyclic 1,5-benzodiazepines, we investigated the synthesis of novel quinazolino[3,2-*a*][1,5]benzodiazepine derivatives with potential biological activity.[13,14] The heteroannelation was achieved by coupling the bicyclic 1,5-benzodiazepinones with 2-nitrobenzoyl chloride followed by a reductive N-heterocyclization. The structural features of both quinazolino[3,2-*a*][1,5]benzodiazepines and *N*-(2-nitrobenzoyl)-1,5-benzodiazepin-2-ones are discussed herein. Also, in the present study, the initial assessment of possible reaction intermediates was carried out and quantum-chemical reactivity descriptors were calculated to clarify the outcome of the reductive N-heterocyclization of nitrobenzoylamides.

Results and Discussion

A simple synthetic route for the preparation of 6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepines **3** is depicted in Scheme 1. The first step of this strategy comprises the interaction of the starting 5-(benzoyl, benzyl, methyl) substituted-tetrahydro-1,5-benzodiazepin-2-ones with 2-nitrobenzoyl- or 5-acetylamino-2-nitrobenzoyl chlorides.

Thus, benzoylation of lactams **1a-i** with freshly prepared 2-nitrobenzoyl chloride in the presence of *N*,*N*-diisopropylethylamine (DIPEA) and the catalytic amount of 4-dimethylaminopyridine (DMAP) in dry dichlorethane (DCE) at room temperature afforded corresponding nitro benzoylamides **2a-i**. The compounds of structure **2** were isolated in acceptable 42-65% yields after chromatographic purification. It should be noted that several experimental parameters were explored with the aim to obtain much higher yields of products **2**. The attempts to achieve a better yield of this transformation by increasing the reaction temperature (refluxing in different solvents) and prolonging the reaction time and usage of various quantities of the catalyst (DMAP) and acid chloride were not successful. Continuing our interest in this benzoylation reaction, we investigated the interaction of 1,5-benzodiazepin-2-ones **1a-c** with 5-acetylamino-2-nitrobenzoyl chloride under analogous conditions. This interaction led to acetylamino-substituted amides **4a-c** in 20-25% yields. We think that rather low yields of isolated products **4a-c** is a result of their very poor solubility in usual solvents (DCE, $CHCl_3$, ethyl acetate, benzene) and their complicated separation from the side products (e.g., DIPEA·HCl salt). In addition, 5-acetylamino-2-nitrobenzoyl chloride was prepared according to the procedure[15] and used without further purification.



Compound	R^1	R^2	R^3
1a,2a,3a,4a	H	H	COC_6H_5
1b,2b,3b,4b	H	CH_3	COC_6H_5
1c,2c,4c	CH_3	H	COC_6H_5
1d,2d,3d	H	H	$CH_2C_6H_5$
1e,2e,3e	H	CH_3	$CH_2C_6H_5$
1f,2f	CH_3	H	$CH_2C_6H_5$
1g,2g,3g	H	H	CH_3
1h,2h,3h	H	CH_3	CH_3
1i,2i	CH_3	H	CH_3

Scheme 1. Synthesis of quinazolino[3,2-*a*][1,5]benzodiazepin-13-ones.

As the second step in this investigation, we studied the reductive N-heterocyclization of precursors **2a-i** and **4a-c**. Recently, only a few examples of the catalytic reductive cyclization of N-(2-nitrobenzoyl)amides to the corresponding quinazolino[1,5]benzodiazepines have been reported by us.[16] Herein, we report the use of zinc dust in glacial acetic acid at room temperature for the reduction of nitro compounds **2** and **4**. As planned in Scheme 1, this process in the case of compounds **2a,b,d,e,g,h** was nicely accompanied by a simultaneous N-heterocyclization to give 6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepines **3a**,**b**,**d**,**e**,**g**,**h**. It should be noted that during this process the formation of the corresponding amino derivatives was not observed (TLC). The polycyclic compounds **3a**,**b**,**e,h** were obtained in good 68-97% yields, whereas compounds **3d**

and **3g** were isolated only in 30-32% yields. Due to their poor solubility and instability in heterocyclization reaction conditions (acetic acid), acetylamino-substituted amides **4a-c** were unsuitable models for the study of this reaction.

Starting compounds **1a-c** were easily obtained by the benzoylation of the corresponding 1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones according to the procedure.[17] Precursors **1d-i** were previously described by us.[18]

The structures of the studied compounds were investigated using IR and NMR spectroscopy. The IR spectra of amides **2a-i** and **4a-c** show typical bands at 3361-3383 cm^{-1} for the NH (compounds **4a-c**), 1645-1729 cm^{-1} for two or three C=O and 1500-1530 cm^{-1} and 1332-1350 cm^{-1} for the NO_2 stretching vibrations. All examined quinazolinones **3** showed one or two (compounds **3a,b**) bands in the region of carbonyl group absorption at 1641-1691 cm^{-1} and C=N bond absorption peak at 1609-1611 cm^{-1}.

For easier comparison of NMR data, the arbitrary numbering of atoms is presented in Figure 1 **(A** – for compounds **2a-i, B** – for compounds **3a**, **3b**, **3d, 3e, 3g, 3h** and **C** – for compounds **4a-c**).

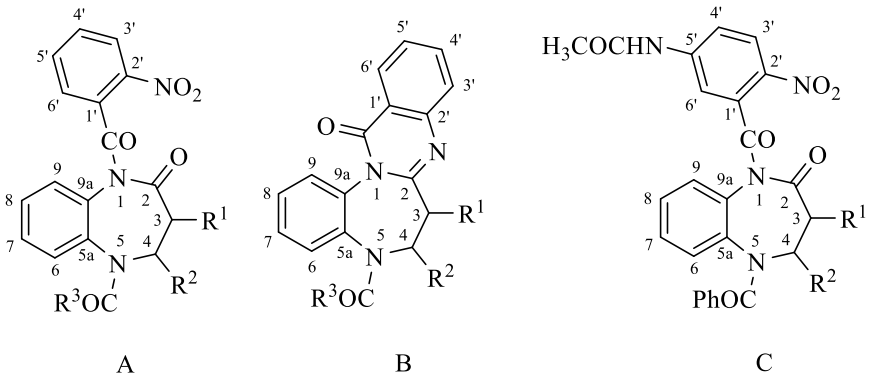


Figure 1. Arbitrary numbering for the analysis of NMR data.

The ^{1}H NMR spectra of starting compounds **1a-c**, as well as of previously described **1d-i,**[18] exhibited the signals of aliphatic protons (CH_3, CH_2 or CH groups) of the heptatomic ring, the characteristic NH singlet at about 9.0 ppm and the resonances of aromatic protons in the range of 6.7–7.2 ppm integrated for nine protons. ^{13}C NMR spectra of **1a-c**, in addition to the unambiguously assigned aromatic and aliphatic carbon resonances, revealed two appropriate downfield lying lines at 170.2–171.0 ppm (5-CO) and 173.6–175.7 ppm (C-2).

The missing NH singlet and the appearance of four additional aromatic protons in ^{1}H NMR spectra pointed to the formation of compounds **2a-i**. The characteristic most downfield signal in the aromatic region at ~ 8.3 ppm was ascribed to CH-3′ using the HMBC spectra. ^{13}C NMR spectra of **2a-c,** compared to spectra of **1a-c**, showed the typical resonances with almost the same chemical shift values (169.7–170.9 ppm) for 5-CO, upfield shifted 1.9–3.0 ppm for C-2 and the new signals at ~134.7 ppm, ~144.5 ppm and ~167.7 ppm assigned to C-1′, C-2′ and 1-CO,

respectively. The presence of diastereotopic methylene protons (5-CH_2) which resonances formed characteristic AB quartet at ~ 4.3 ppm and ~ 4.5 ppm in ^{1}H NMR spectra and the absence of the resonance of 5-CO group carbon in ^{13}C NMR spectra were intrinsic to compounds **2d-f** compared to **2a-c**. ^{1}H and ^{13}C NMR spectra of compounds **2g-i** showed the presence of 5-CH_3 group which resonated at 2.8 ppm and 39.4 ppm, respectively. Broadened resonances of aliphatic and some of aromatic moieties were observed in the case of compounds **2d, 2g, 2h** in ^{1}H and ^{13}C NMR spectra possibly due to the slow dynamic processes of heterocycle ring compared to the NMR time scale.

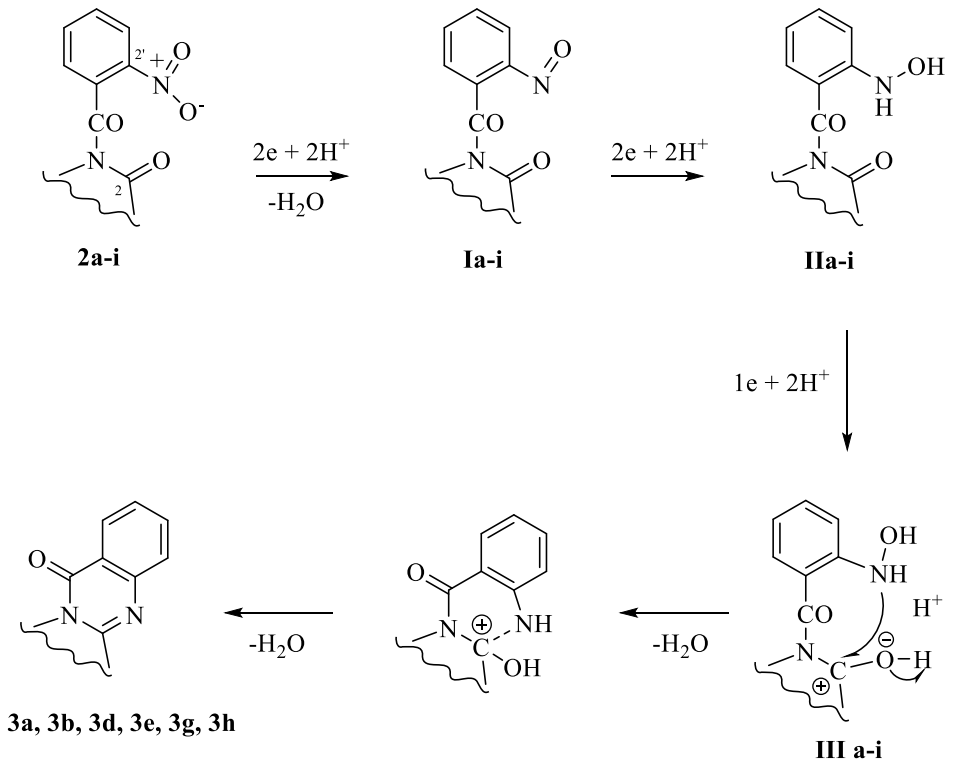
The above mentioned facts can be applied to prove the structure of compounds **4a-c**. In addition, two new resonances, singlets at 2.1 ppm ($COCH_3$) and 10.7 ppm (5′-NH), were observed in ^{1}H NMR spectra of compounds **4a-c**. The resonances in ^{13}C NMR spectra of compounds **4a-c** at 136.5 ppm, 137.8 ppm and 145.4 ppm were attributed to 1′-, 2′-, 5′- aryl ring carbons, respectively, and the resonance at 169.6 ppm was attributed to 5′-NHCO carbon atom. These assignments were made by detailed analysis of HMBC spectra.

The essential feature of the formation of the compounds of structure **3** was the missing signal of C-2 (carbonyl group) at ~172.8 ppm and the appearance of resonance at ~ 154.0 ppm (**3a,b**) and ~156.1 ppm (**3d,e,g,h**) attributed to C=N group carbon compared to the corresponding ^{13}C NMR spectra of compounds **2**. The resonances of 1-CO group were shifted upfield by approximately 7 ppm and were observed in the range of 160.6-160.9 ppm, the resonances of C-1' carbon were shifted upfield ~ 13.4 ppm and those of C-2' downfield ~ 2.2 ppm. The most deshielded proton (at ~ 8.3 ppm) in the aromatic region was assigned to CH-6′ in ^{1}H NMR spectra in the case of compounds **3**.

It should be noted that the reductive cyclization carried out with derivatives **2c**,**f**,**i** under analogous conditions was unsuccessful. Nitro derivatives **2c**,**f**,**i** (~50%) and starting lactams **1c**,**f,i** (~20%), as a result of partial hydrolysis of nitrobenzoylamides **2**, were obtained, while the corresponding amino compounds were not isolated. Thus, 1-nitrobenzoylated derivatives **2c**,**f**,**i** bearing the methyl substituent in the 3-position of the diazepine nucleus behaved differently in comparison with nitrobenzoylamides **2a, 2b, 2d, 2e, 2g, 2h** which had no substituents or had the methyl substituent in the 4-position of heptatomic moiety. These differences can not be explained entirely by the steric hindrance caused by 3-methyl group. The steric influence of 3-methyl group was not observed in our previous study of the synthesis of imidazo[1,2-*a*] and thiazolo[3,2-*a*][1,5]benzodiazepine derivatives.[8,9] Moreover, it is well known that the steric hindrance effects of bulky methyl group most often affects reactivity behaviors in the less flexible aromatic system or in the molecular systems bearing conjugated delocalized π bonding.[19,20] While in this reductive heterocyclization the heptatomic diazepine ring bearing 3-methyl group can easily change configuration due to flexible σ bonding system. In this way molecular self-regulation of reacting molecular system (in our case 1-nitrobenzoylated derivatives **2c**,**f**,**i**) could lead to the geometry changes that avoids the steric hindrance effects of reacting centre.

It is worth mentioning that the mechanism for the reduction of nitro compounds has been the subject of many investigations and there is considerable evidence that this reaction proceeds stepwise through a number of intermediates including nitroso and hydroxylamine derivatives that were detected in the reaction mixture.[21,22] However, the theoretical understanding of the reduction occurring with simultaneous heterocyclization process is not established well. To identify which reaction step is important for the initiation of heterocyclization reaction, we focused our efforts on the estimation of possible reaction intermediates by means of quantum-chemical reactivity descriptors calculations.

We suggested the possible reaction mechanism scenario for this heterocyclization and presented it in Scheme 2.



Scheme 2. Mechanism of reductive heterocyclization of nitroamides **2a-i.**

We assumed that the studied reductive cyclization reaction starts in a similar way to the reduction reaction of aromatic nitro compounds to amines.[21,22] After the nitro group is activated by metal mediated electrons and two hydrogen atoms, the elimination of water molecule occurs leading to nitroso intermediates **Ia-i** which after the reductive addition of two hydrogen atoms form hydroxylamine intermediates **IIa-i**. The formation of hydroxylamine intermediates **IIa-i** enables the nucleophilic attack of the 2'-N atom on the C(2) atom of the protonated carbonyl group. After the reductive addition of a hydrogen atom, intermediates **IIIa-i** possessing the weak interaction between the C(2) and 2'-N atoms are formed. The subsequent elimination of two

water molecules afforded the C=N double bond and final products **3a**, **3b**, **3d**, **3e**, **3g, 3h**. The presented reaction mechanism (Scheme 2) demonstrates that the initiation of heterocyclization reaction becomes possible after intermediate **III** is formed. Thus, the insight into the electronic structure of intermediate **III** can be of great importance for the explanation of different reactivity pattern of nitrobenzoylamides **2a-i** in the reductive heterocyclization reaction. To confirm our assumptions, the theoretical investigation results of intermediates **IIIa-i** by means of quantum chemical reactivity descriptors calculations are presented in this article. Frontier molecular orbitals densities[23] and Mulliken (M), natural (N) and electrostatic potential derived charges (ESP)[19,23-29] reflect the different behavior of these intermediates in the reductive heterocyclization process.

It is known that frontier orbital densities on atoms allow the estimation of donor-acceptor interactions that exist between different atoms in the same molecule.[24] According to the frontier orbital reactivity theory, the majority of chemical reactions take place at the position and in the orientation where the overlap of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the respective reactants can reach the maximum.[19,24-28] The charge distribution in the molecule most frequently predicts the interaction of electrostatic forces.[19,23-28] Mulliken charges and natural charges show how much electron density is associated with each atom's orbitals. The ESP charges at the atom are chosen to best describe the electrostatic potential surrounding the molecule. The molecular ESP charges on the molecular electron density iso-surface are a good indicator for the interpretation of chemical reactivity.[25-27,29] Hence, it gives a suitable description of molecular properties, such as strong noncovalent interactions that are predominantly electrostatic in nature.

In our earlier quantum chemical reactivity descriptors studies of the substituted 1,5-benzodiazepine-2-thiones interaction with bromoketones, the performance of the AM1 method and DFT B3LYP functional with two different basis sets (6-31G* and 6-31+G*) was compared and it was stated that both methods provided very similar results.[29] The advantage of the AM1 model is that it is less time consuming. However, the DFT B3LYP model allows the calculation of more molecular quantum properties, offers better accuracy in the estimation of reactivity descriptors, ensures high reliability, and includes a broader diversity of descriptors. Hence, in the present computational study of heterocyclization reaction we used the AM1 and DFT B3LYP 6-31G* methods. The first optimization of plausible intermediate structures was carried out with AM1 method. Consequently, the AM1 geometry optimized structures were used as initial coordinates for energy optimization at the DFT level using the B3LYP functional and 6-31G* basis sets.[30] The vibrational frequencies were computed for optimized intermediate structures and checked to present no imaginary vibrational frequency to ensure that they were local minima points on the potential energy surface.[20,31] The HOMO and LUMO densities were calculated according to the methods described in the literature.[23]

The calculated reactivity descriptors – M, N and ESP charges, HOMO and LUMO densities, for 3,4,5-substituted intermediates **IIIa-i** on the C(2) and 2'-N atoms are the most significant for the reaction progress. They are presented in Table 1. To get the overall insight to the observed

reactivity, the typical and the most important for the reaction progress HOMO and LUMO shapes of **IIIa-c** were selected from all calculated results of **IIIa-i** and pictured in Figure 2. Computation reveals that HOMOs of **IIIa-i** consist of identical shapes. Figure 2 demonstrates that the HOMO shapes for **IIIa-c** consist of out of plane π orbitals located on the benzene ring of benzoylamide moiety and the lone pair orbital situated on the nitrogen 2'-N atom of the hydroxylamine group. The data presented in Table 1 supports the results of the pictured HOMO shapes showing that HOMO density values for 2'-N atom of all studied intermediates differ slightly and are in the range of 0.24-0.38, whereas differences in the shapes of LUMO of **IIIa-i** are observed. As shown in Figure 2, the LUMOs of 3,4- unsubstituted and 4-methyl substituted **IIIa-b** mainly consists of the antibonding out of plane π orbital located on the C(2)-O bond of the diazepine skeleton. The minor contribution to the LUMO shape occupancy of **IIIa-b** is located between the nitrogen N(1) atom of the diazepine skeleton and the carbon atom of 1-CO group in benzoylamide moiety. The magnitudes of densities and the phase of HOMO on the nitrogen 2'-N atom and on the C(2) atom of LUMO demonstrate the tendency in phase overlap between those molecular orbitals and allow bonding interaction between C(2) and 2'-N atoms for **IIIa-b**. The LUMO shapes of the 3-methyl substituted **IIIc** mainly consist of the antibonding out of plane π orbital located on the carbonyl group of benzoylamide moiety and partly on the benzene ring annulated with the diazepine cycle (Figure 2). Meanwhile, the C(2)-O bond on diazepine skeleton does not have noticeable shape for **IIIc**. Thus, in this case, the bonding overlap between the nitrogen 2'-N atom and the carbon C(2) atom is not promoted. This phenomenon is also revealed by the calculated values of LUMO densities for C(2) atom of **IIIa-i** presented in Table 1. There is a significant difference between the two intermediate groups: LUMO density values for **IIIa,b,d,e,g,h** are in the range of 0.35-0.53, whereas those for **IIIc,f,i** in the range of 0.05-0.15.

The results presented in Table 1 show that the calculated M, N and ESP charges for **IIIc,f,i** bearing 3-methylgroup in heptatomic nucleus do not differ from those for the rest investigated intermediates **IIIa,b,d,e,g,h**. Therefore, it is possible to suggest that the charges do not play a significant role for this reaction step, whereas the calculated HOMO and LUMO shapes and density values suggest that heterocyclization reaction is controlled by frontier molecular orbitals. Moreover, our computational results reveal that the position of the substituents on the diazepine skeleton have the effect on the LUMO density changes on the **IIIa-i**. This suggests that the presence of the electron donating 3-methyl substituent decreases the electrophilicity of the C(2) atom and evokes resistance for further intramolecular rearrangements.

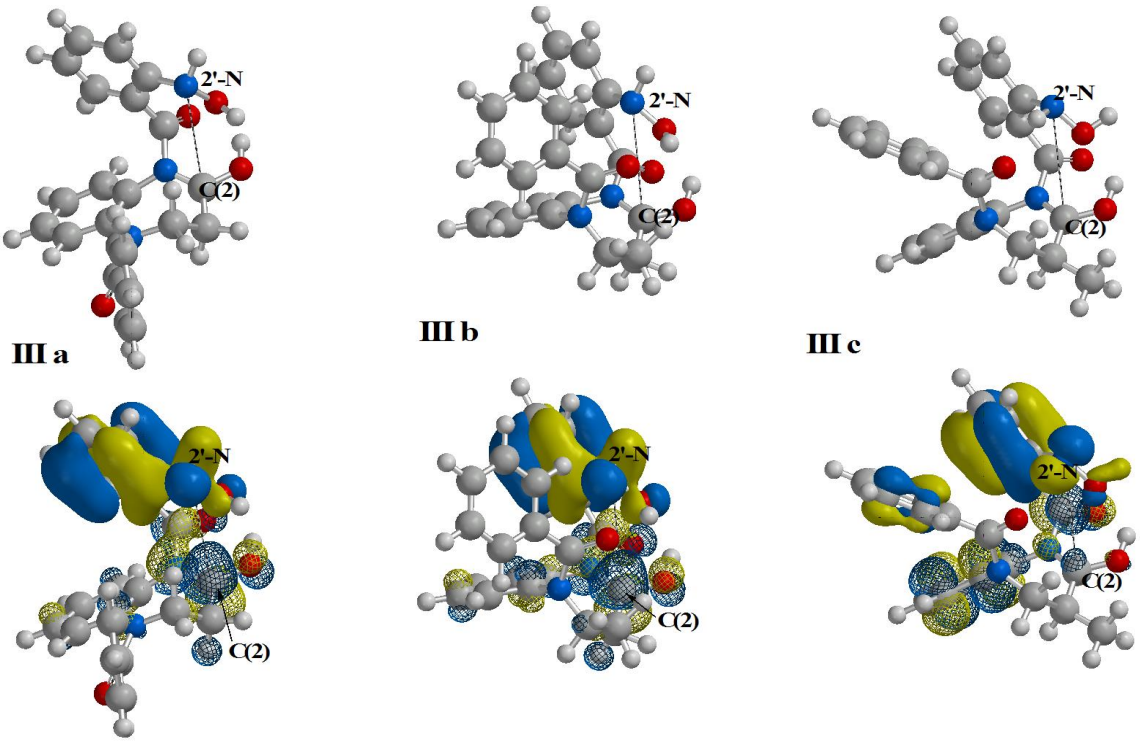


Figure 2. The optimal geometry of intermediates **IIIa-c** and HOMO(solid), LUMO(mesh) shapes.

Table 1. Calculated M, N and ESP charges, HOMO, LUMO densities for intermediates **IIIa-i** on C(2) and 2'-N atoms

Intermediate	2'-N				C(2)			
	ESP	M	N	HOMO	ESP	M	N	LUMO
IIIa	-0.552	-0.408	-0.329	0.235	0.479	0.612	0.764	0.391
IIIb	-0.381	-0.399	-0.321	0.289	0.585	0.651	0.784	0.415
IIIc	-0.537	-0.402	-0.338	0.293	0.419	0.677	0.789	0.048
IIId	-0.512	-0.469	-0.405	0.374	0.326	0.605	0.850	0.528
IIIe	-0.384	-0.357	-0.289	0.314	0.667	0.631	0.748	0.350
IIIf	-0.367	-0.402	-0.306	0.316	0.491	0.650	0.740	0.098
IIIg	-0.436	-0.432	-0.391	0.376	0.651	0.641	0.757	0.453
IIIh	-0.259	-0.410	-0.352	0.290	0.610	0.621	0.745	0.413
IIIi	-0.330	-0.411	-0.353	0.298	0.478	0.629	0.754	0.150

In conclusion, a series of new 6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-ones was successfully synthesized using the reductive N-heterocyclization of 1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones. It was established that the course of this heterocyclization depended on the presence of substituents in the heptatomic ring of the starting heterocycles. The possible heterocyclization reaction mechanism was suggested. It was shown that the initiation of heterocyclization reaction in the reduction process became possible with the formation of intermediate **IIIa-i**. The calculated reactivity descriptors (frontier molecular orbitals densities, Mulliken, natural and electrostatic potential derived charges) of intermediates **IIIa-i** suggest that heterocyclization reaction is an intermolecular rearrangement strongly controlled by frontier molecular orbitals, whereas charges do not play a significant role for this reaction step. Moreover, our computational results reveal that the position of the substituent on the diazepine skeleton affect the changes in LUMO densities of **IIIa-i**, therefore this reactivity descriptor can be useful for characterization and prediction of the studied heterocyclization process.

Experimental Section

General. Melting points were determined in open capillaries on a MEL-TEMP 1202D apparatus and are uncorrected. The IR spectra (potassium bromide) were taken on a Perkin Elmer Spectrum GX FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 300 and Bruker Ascend^{tm} 400 at 302 K. Chemical shifts (δ) are reported relative to tetramethylsilane (TMS) with the solvent reference: $CDCl_3$ (δ 7.26 ppm), DMSO-d_6 (δ 2.50 ppm) for ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm), DMSO-d_6 (δ 39.50 ppm) for ^{13}C NMR. The values of chemical shifts are expressed in ppm and coupling constants (*J*) in Hz. The assignments of ^{13}C NMR spectra were made with the aid of APT and HMBC experiments. Elemental analyses (C, H, N) were performed on an Elemental Analyser CE-440. 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 (ν/ν, 14:7:1) as the eluent and was visualized with UV light. Dry column vacuum chromatography[32] was performed with silica gel 60 (0.015-0.040 mm, Merck).

General procedure for the synthesis of 1-(2-nitrobenzoyl)-3-R^1-4-R^2-5-R^3-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones (2a-i). Freshly prepared o-nitrobenzoylchloride (0.8 mL, 6 mmol) in dry DCE (6 mL) was added dropwise to a stirred solution of appropriate benzodiazepinone **1a-i** (5 mmol) in dry DCE (40-60 mL) containing DIPEA (1.05 mL, 6 mmol) and catalytic amount of DMAP at room temperature. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with DCE (60 mL), washed with 1n HCl, 5% $NaHCO_3$ and water. After drying and removal of the solvent in vacuum, the oily residues were firstly subjected to dry column vacuum chromatography (silicagel) using the benzene-DCE system for gradient elution and recrystallized from dichloromethane-diethyl ether mixture to give **2a-i**.

5-Benzoyl-1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (2a). White crystals, yield 1.14 g (55%), mp 213-215 °C. IR: *v* 1727, 1706, 1652 (CO), 1524, 1350 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 2.50 (1H, ddd, *J* 1.4, 4.7, 13.6 Hz, 3-CH_2), 2.71 (1H, dt, *J* 6.8, 13.9 Hz, 3-CH_2), 3.74 (1H, ddd, *J* 1.6, 6.8, 12.9 Hz, 4-CH_2), 4.64 (1H, dt, *J* 4.8, 13.7 Hz, 4-CH_2), 6.83 (1H_{arom}, dd, *J* 1.1, 7.9 Hz, CH), 7.17-7.45 (8H_{arom}, m, CH), 7.63 (1H_{arom}, ddd. *J* 1.4, 7.5, 8.4 Hz, CH), 7.73 (1H_{arom}, dd, *J* 1.3, 8.0 Hz, CH), 7.76 (1H_{arom}, dt, *J* 1.2, 7.5 Hz, 5′-CH), 8.29 (1H_{arom}, dd, *J* 1.1, 8.3 Hz, 3′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 35.0 (C-3), 47.3 (C-4), 124.3 (CH), 126.8 (CH), 128.2 (*m*-CH_{Ph}), 128.3 (CH), 129.1 (*o*-CH_{Ph}), 129.1 (CH), 129.7 (2CH), 129.8 (CH), 130.8 (*p*-CH_{Ph}), 133.9 (*i*-C_{Ph}), 134.2 (C-5a or C-9a), 134.6 (C-1′), 134.6 (CH), 137.0 (C-9a or C-5a), 144.6 (C-2′), 167.6 (1-CO), 170.9 (5-CO), 171.1 (C-2). Anal. Calcd. for $C_{23}H_{17}N_3O_5$ (415.40): C, 66.50; H, 4.12; N, 10.12%. Found: C, 66.31; H, 4.22; N, 10.35%.

5-Benzoyl-4-methyl-1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (2b). White crystals, yield 1.20 g (56%), mp 205-207 °C. IR: *v* 1729, 1707, 1651 (CO), 1525, 1349 (NO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.24 (3H, d, *J* 6.2 Hz, 4-CH_3), 2.37 (1H, dd, *J* 12.1, 13.1 Hz, 3-CH_2), 2.45 (1H, dd, *J* 5.7, 13.2 Hz, 3-CH_2), 5.16 (1H, qt, *J* 5.9, 11.5 Hz, 4-CH_2), 6.80 (1H_{arom}, d, *J* 7.1 Hz, CH), 7.18-7.78 (11H_{arom}, m, CH), 8.28 (1H_{arom}, dd, *J* 0.9, 8.3 Hz, 3′-CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 18.0 (4-CH_3), 42.5 (C-3), 53.7 (C-4), 124.3 (CH), 126.9 (CH), 128.1 (*o*-CH_{Ph}), 128.6 (CH), 128.8 (*m*-CH_{Ph}), 129.0 (CH), 129.3 (CH), 129.8 (CH), 130.5 (*p*-CH_{Ph}), 131.0 (CH), 134.6 (*i*-C_{Ph}), 134.6 (CH), 134.7 (C-5a or C-9a), 134.8 (C-1′), 134.8 (C-9a or C-5a), 144.5 (C-2′), 167.8 (1-CO), 169.8 (5-CO), 170.7 (C-2). Anal. Calcd. for $C_{24}H_{19}N_3O_5$ (429.43): C, 67.13; H, 4.46; N, 9.79%. Found: C, 67.31; H, 4.59; N, 9.61%.

5-Benzoyl-3-methyl-1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (2c). White crystals, yield 1.01 g (47%), mp 211-213 °C. IR: *v* 1726, 1706, 1645 (CO), 1525, 1344 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.08 (3H, d, *J* 6.5 Hz, 3-CH_3), 2.85 (1H, pd, *J* 6.4, 12.7 Hz, 3-CH), 3.69 (1H, dd, *J* 6.3, 12.8 Hz, 4-CH_2), 4.30 (1H, t, *J* 12.9 Hz, 4-CH_2), 6.85 (1H_{arom}, dd, *J* 1.1, 7.9 Hz, CH), 7.19-7.81 (11H_{arom}, m, CH), 8.31 (1H_{arom}, dd, *J* 1.1, 8.3 Hz, 3′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.4 (3-CH_3), 37.4 (C-3), 54.3 (C-4), 124.3 (CH), 126.7 (CH), 128.1 (*m*-CH_{Ph}), 128.2 (CH), 129.1 (*o*-CH_{Ph}), 129.2 (CH), 129.3 (CH), 129.6 (CH), 129.7 (CH), 130.8 (*p*-CH_{Ph}), 133.5 (*i*-C_{Ph}), 134.2 (C-5a or C-9a), 134.6 (CH), 134.9 (C-1′), 137.7 (C-9a or C-5a), 144.5 (C-2′), 167.8 (1-CO), 170.7 (5-CO), 173.8 (C-2). Anal. Calcd. for $C_{24}H_{19}N_3O_5$ (429.43): C, 67.13; H, 4.46; N, 9.79%. Found: C 66.89; H 4.31; N 10.01%.

5-Benzyl-1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (2d). Yellowish solid, yield 0.84 g (42%), mp 59-61 °C. IR: *v* 1725, 1699 (CO), 1527, 1348 (NO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.27 (1H, br, 3-CH_2), 2.62 (1H, br, 3-CH_2), 2.89 (1H, br, 4-CH_2), 3.47 (1H, br, 4-CH_2), 4.08 (1H, br, 5-CH_2), 4.49 (1H, br, 5-CH_2), 7.22-7.62 (11H_{arom}, m, CH), 7.73 (1H_{arom}, dt, *J* 1.2, 7.5 Hz, 5′-CH), 8.27 (1H_{arom}, dd, *J* 0.4, 8.3 Hz, 3′-CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 35.9 (C-3), 53.6 (C-4), 57.2 (5-CH_2), 120.8 (CH), 123.8 (CH), 124.2 (CH), 126.4 (CH), 127.5 (*p*-CH_{Ph}), 128.3 (*m*-CH_{Ph}), 128.4 (CH), 128.6 (*o*-CH_{Ph}), 129.3 (CH), 129.7 (CH), 132.0 (C-5a or C-9a), 134.3 (CH), 135.5 (C-1′), 137.3 (*i*-C_{Ph}), 143.9 (C-9a or C-5a), 144.7 (C-

2′), 167.3 (1-CO), 172.4 (C-2). Anal. Calcd. for $C_{23}H_{19}N_3O_4$ (401.42): C 68.82; H, 4.77; N, 10.47%. Found: C, 69.02; H, 4.61; N, 10.19%.

5-Benzyl-4-methyl-1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (2e). Orange crystals, yield 1.3 g (62%), mp 165-166 °C. IR: *v* 1725, 1700 (CO), 1527, 1346 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.95 (3H, d, *J* 6.1 Hz, 4-CH_3), 2.22-2.35 (1H, m, 3-CH_2), 3.77 (1H, m, 4-CH), 4.42 and 4.27 (2H, ABq, *J* 14.0 Hz, 5-CH_2), 7.21-7.61 (11H_{arom}, m, CH), 7.73 (1H_{arom}, dt, *J* 1.2, 7.5 Hz, 5′-CH), 8.26 (1H_{arom}, dd, *J* 0.9, 8.3 Hz, 3′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.2 (4-CH_3), 43.9 (C-3), 53.3 (5-CH_2), 57.2 (C-4), 123.9 (CH), 124.2 (2CH), 126.6 (CH), 127.3 (*p*-CH_{Ph}), 127.9 (CH), 128.3 (*m*-CH_{Ph}) 128.5 (*o*-CH_{Ph}), 128.8 (CH), 129.3 (CH), 133.4 (C-5a or C-9a), 134.4 (CH), 135.6 (C-1′), 137.4 (*i*-CH_{Ph}), 141.1 (C-9a or C-5a), 144.7 (C-2′), 167.4 (1-CO), 172.2 (C-2). Anal. Calcd. for $C_{24}H_{21}N_3O_4$ (415.44): C, 69.39; H, 5.10; N, 10.11%. Found: C, 69.15; H, 4.89; N, 10.38%.

5-Benzyl-3-methyl-1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (2f). Yellow crystals, yield 1.34 g (65%), mp 127-128 °C. IR: *v* 1723, 1698 (CO), 1526, 1346 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.87 (3H, d, *J* 6.1 Hz, 4-CH_3), 2.73-2.90 (1H, m, 3-CH and 1H, m, 4-CH), 3.06 (1H, dd, *J* 9.6, 11.7 Hz, 4-CH), 4.03 and 4.51 (2H, ABq, *J* 13.6 Hz, 5-CH_2), 7.22-7.62 (11H_{arom}, m, CH), 7.74 (1H_{arom}, dt, *J* 1.2, 7.5 Hz, 5′-CH), 8.28 (1H_{arom}, dd, *J* 1.2, 8.3 Hz, 3′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.7 (3-CH_3), 38.5 (C-3), 57.5 (5-CH_2), 61.9 (C-4), 120.7 (CH), 124.0 (CH), 124.6 (CH), 126.6 (CH), 127.7 (*p*-CH_{Ph}), 128.6 (*m*-CH_{Ph}) 128.8 (CH), 128.9 (*o*-CH_{Ph}), 129.5 (CH), 129.9 (CH), 131.9 (C-5a or C-9a), 134.7 (CH), 136.1 (C-1′), 137.7 (*i*-CH_{Ph}), 144.8 (C-9a or C-5a), 145.1 (C-2′), 167.7 (1-CO), 175.2 (C-2). Anal. Calcd. for $C_{24}H_{21}N_3O_4$ (415.44): C, 69.39; H, 5.10; N, 10.11%. Found: C, 69.13; H, 4.93; N, 10.35%.

5-Methyl-1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (2g). Sandy crystals, yield 0.81 g (50%), mp 154-156 °C. IR: *v* 1717, 1702 (CO), 1526, 1348 (NO_2) cm^{-1}.^1H NMR (300 MHz, $CDCl_3$): δ_H 2.32 (1H, br, 3-CH_2), 2.58 (1H, br, 3-CH_2), 2.86 (3H, s, 5-CH_3), 2.97 (1H, br, 4-CH_2), 3.56 (1H, br, 4-CH_2), 7.19-7.62 (6H_{arom}, m, CH), 7.72 (1H_{arom}, dt, *J* 1.2, 7.5 Hz, 5′-CH), 8.24 (1H_{arom}, dd, *J* 1.0, 8.3 Hz, 3′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 36.0 (C-3), 40.5 (5-CH_3), 56.4 (C-4), 119.4 (CH), 123.4 (CH), 124.1 (CH), 127.0 (CH), 128.4 (CH), 129.3 (CH), 129.6 (CH), 131.3 (C-5a or C-9a), 134.3 (CH), 135.4 (C-1′), 144.1 (C-9a or C-5a), 144.6 (C-2′), 167.3 (1-CO), 172.3 (C-2). Anal. Calcd. for $C_{17}H_{15}N_3O_4$ (325.32): C, 62.76; H, 4.65; N, 12.92%. Found: C, 62.52; H, 4.81; N, 13.11%.

4,5-Dimethyl-1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (2h). Yellowish crystals, yield 0.93 g (55%), mp 120-122 °C. IR: *v* 1726, 1702 (CO), 1528, 1346 (NO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.97 ((0.7)3H, br, 4-CH_3), 1.34 ((0.3)3H, br, 4-CH_3), 2.05 ((0.3)2H, br, 3-CH_2), 2.29 ((0.7)2H, br, 3-CH_2), 2.87 (3H, s, 5-CH_3), 3.15 ((0.3)1H, br, 4-CH), 3.80 ((0.7)1H, br, 4-CH), 7.22-7.61 (6H_{arom}, m, CH), 7.72 (1H_{arom}, dt, *J* 1.0, 7.5 Hz, 5′-CH), 8.23 (1H_{arom}, br, 3′-CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.3[19.8] (4-CH_3), 37.2[38.3] (5-CH_3), [42.4]44.0 (C-3), 60.6 (C-4), 119.5*, 122.6*, 122.9*, 123.9*, 124.1 (CH), 127.3 [126.6] (CH), 126.6*, 126.7*, 127.3*, 128.0*, 128.3*, 128.4*, 128.5*, 128.6*, 128.8*, 129.3 (CH), 129.4*, [131.2]132.6 (C-9a), 134.3 (CH), 135.5 (C-1′), 141.4[146.0] (C-5a), 144.6 (C-2′),

[167.1]167.4 (1-CO), [170.7]172.2 (C-2). Values of chemical shift gave in angle brackets correspond to the minor isomer, * marked values are chemical shifts of undefined resonances. Anal. Calcd. for $C_{18}H_{17}N_3O_4$ (339.35): C, 63.71; H, 5.05; N, 12.38%. Found: C, 63.52; H, 4.88; N, 12.12%.

3,5-Dimethyl-1-(2-nitrobenzoyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (2i). Brown crystals, yield 0.85 g (50%), mp 167-169 ºC. IR: *v* 1728, 1697 (CO), 1530, 1347 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.93 (3H, d, *J* 6.4 Hz, 3-CH_3), 2.69-2.82 (1H, m, 3-CH), 2.82 (3H, s, 5-CH_3), 2.92 (1H, dd, *J* 6.7, 9.8 Hz, 4-CH_2), 3.16 (1H, dd, *J* 9.8, 12.0 Hz, 4-CH_2), 7.17-7.61 (6H_{arom}, m, CH), 7.73 (1H_{arom}, dt, *J* 1.2, 7.5 Hz, 5′-CH), 8.24 (1H_{arom}, dd, *J* 1.1, 8.3 Hz, 3′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.4 (3-CH_3), 38.2 (C-3), 40.3 (5-CH_3), 64.4 (C-4), 118.9 (CH), 123.1 (CH), 124.1(CH), 126.9 (CH), 128.4 (CH), 129.3 (CH), 129.5 (CH), 130.8 (C-5a or C-9a), 134.4 (CH), 135.7 (C-1′), 144.4 (C-9a or C-5a), 145.1 (C-2′), 167.4 (1-CO), 172.2 (C-2). Anal. Calcd. for $C_{18}H_{17}N_3O_4$ (339.35): C, 63.71; H, 5.05; N, 12.38%. Found: C, 63.49; H, 5.27; N, 12.55%.

General procedure for the synthesis of N-{3-[(5-benzoyl-4-R^2-3-R^1-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)carbonyl]-4-nitrophenyl}acetamides 4a-c. A suspension of 5-acetylamino-2-nitrobenzoic acid (1.45 g, 6.5 mmol) and thionyl chloride (7.7 g, 4.7 ml, 65 mmol) in dry chloroform (50 ml) was carefully refluxed until reaction mixture turned clear (~7h). The solvent was evaporated under vacuum, then dry benzene (30 ml) was added and distilled out. After repeating this procedure twice, dark oil was dissolved in dry DCE (10 ml) and added dropwise at room temperature to a stirred solution of appropriate benzodiazepine **1a-c** (5 mmol) in dry DCE (60-80ml) containing DIPEA (1.05ml, 6mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 24h and then filtered with suction. Yellow solid is washed with big amount of cold chloroform and dried.

N-{3-[(5-Benzoyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)carbonyl]-4-nitrophenyl}acetamide (4a). Sandy crystals, yield 0.59 g (25%), mp 268-271 ºC. IR: *v* 3368 (NH), 1730, 1711, 1655 (CO), 1500, 1332 (NO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.12 (3H, s, $COCH_3$), 2.55 (1H, t, *J* 5.6 Hz, 3-CH_2), 2.67 (1H, dt, *J* 6.5, 13.7 Hz, 3-CH_2), 3.66 (1H, dd, *J* 6.4, 13.0 Hz, 4-CH_2), 4.37 (1H, t, *J* 13.1 Hz, 4-CH_2), 6.94-7.90 (11H_{arom}, m, CH), 8.30 (1H_{arom}, dd, *J* 9.2 Hz, 3′-CH), 10.72 (1H, s, 5′-NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 24.3 (CO<u>CH</u>$_3$), 34.6 (C-3), 47.2 (C-4), 115.3 (CH), 118.6 (CH), 126.1(CH), 127.9 (*o*-CH_{Ph}), 128.1 (CH), 128.7 (*m*-CH_{Ph}), 129.4 (C-5a or C-9a), 129.6 (CH), 130.1 (CH), 130.4 (*p*-CH_{Ph}), 133.6 (*i*-CH_{Ph}), 135.0 (CH), 136.2 (C-1′), 136.6 (C-9a or C-5a), 137.9 (C-2′), 145.5 (C), 167.1 (1-CO), 169.6 (5-CO), 169.8 (<u>CO</u>CH_3), 171.6 (C-2). Anal. Calcd. for $C_{25}H_{20}N_4O_6$ (472.45): C, 63.56; H, 4.27; N, 11.86%. Found: C, 63.32; H, 4.02; N, 12.02%.

N-{3-[(5-Benzoyl-4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)carbonyl]-4-nitrophenyl}acetamide (4b). Sandy crystals, yield 0.61 g (25%), mp 291-294 ºC. IR: *v* 3383 (NH), 1711, 1652 (CO), 1497, 1336 (NO_2) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H 1.13 (3H, d, *J* 5.9 Hz, 4-CH_3), 2.12 (3H, s, $COCH_3$), 2.36 (1H, t, *J* 12.9 Hz, 3-CH_2), 2.48-2.55 (1H, 3-CH_2 overlapped with solvent signal), 4.93 (1H, br, 4-CH_2), 6.93-7.88 (11H_{arom}, m, CH), 8.31 (1H_{arom},

d, *J* 9.2 Hz, 3′-CH), 10.71 (1H, s, 5′-NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 17.5 (4-CH_3), 24.2 (CO$\underline{CH}_3$), 41.8 (C-3), 53.54 (C-4), 115.2 (CH), 118.5 (CH), 126.1(CH), 127.8 (*o*-CH_{Ph}), 128.5 (*m*-CH_{Ph}), 128.5 (CH), 128.8 (C-5a or C-9a), 129.3 (CH), 130.1 (*p*-CH_{Ph}), 131.2 (CH), 134.4 (*i*-CH_{Ph}), 134.4 (CH), 135.1 (C-9a or C-5a), 136.2 (C-1′), 137.9 (C-2′), 145.4 (C-5′), 167.2 (1-CO), 168.8 (5-CO), 169.6 ($\underline{CO}CH_3$), 171.0 (C-2). Anal. Calcd. for $C_{26}H_{22}N_4O_6$ (486.48): C, 64.19; H, 4.56; N, 11.52%. Found: C, 63.98; H, 4.71; N, 11.33%.

N-{3-[(5-Benzoyl-3-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)carbonyl]-4-nitrophenyl}acetamide (4c). Sandy crystals, yield 0.85 g (35%), mp 297-299 ºC. IR: *v* 3361 (NH), 1709, 1648 (CO), 1501, 1334 (NO_2) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.93 (3H, d, *J* 6.3 Hz, 3-CH_3), 2.12 (3H, s, $COCH_3$), 2.83 (1H, m, 3-CH), 3.64 (1H, dd, *J* 6.4, 12.6 Hz, 4-CH_2), 4.03 (1H, t, *J* 12.5 Hz, 4-CH_2), 6.96-7.86 (11H_{arom}, m, CH), 8.31 (1H_{arom}, d, *J* 9.2 Hz, 3′-CH), 10.71 (1H, s, 5′-NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.2 (3-CH_3), 24.3 (CO$\underline{CH}_3$), 37.0 (C-3), 53.9 (C-4), 115.2 (CH), 118.5 (CH), 126.1(CH), 127.9 (*o*-CH_{Ph}), 128.1 (CH), 128.7 (*m*-CH_{Ph}), 129.1 (C-5a or C-9a), 129.5 (CH), 129.7 (CH), 130.4 (*p*-CH_{Ph}), 133.1 (*i*-CH_{Ph}), 134.9 (CH), 136.5 (C-1′), 137.3 (C-2′), 137.8 (C-9a or C-5a), 145.4 (C-5′), 167.3 (1-CO), 169.5 (5-CO), 169.6 ($\underline{CO}CH_3$), 174.0 (C-2). Anal. Calcd. for $C_{26}H_{22}N_4O_6$ (486.48): C, 64.19; H, 4.56; N, 11.52%. Found: C, 64.39; H, 4.69; N, 11.71%.

General procedure for the synthesis of 3-R^1-4-R^2-5-R^3-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-ones 3a,3b, 3d, 3e, 3g, 3h. Zn dust (1.63 g, 25 mmol) was added to a solution of appropriate nitrobenzoylamide **2a-i (**2.5 mmol) in glacial acetic acid (20-30 mL) and the reaction mixture was stirred at room temperature for 2-3 h. After completion of reduction, as observed by TLC monitoring, the reaction mixture was filtered. The filtrate was concentrated to dryness in vacuum. The residue was dissolved in dichloromethane, the solution washed with 5% $NaHCO_3$ and water, dried and evaporated to dryness in vacuum. Compounds **3a, 3b, 3e, 3h** were obtained after the oily residues were subjected to dry column vacuum chromatography (silicagel) using the DCE-ethyl acetate system for gradient elution and recrystallized from dichloromethane-diethyl ether mixture. Compounds **3d** and **3g** after chromatographic purification were obtained as clear oils. They were held in a refrigerator for a long time and solidified. Hexane-diethyl ether mixture was added and solid material was separated by filtration, washed with cold diethyl ether and dried.

The reduction of compounds **2c, 2f** and **2i** did not occur. Crystallization of the oily reaction residues from dichloromethane-diethyl ether mixture gave unchanged **2c** (51%), **2f** (53%) and **2i** (50%). Filtrate was concentrated and starting benzodiazepines **1c** (18%, ethyl acetate), **1f** (25%, benzene) and **1i** (23%, benzene) were isolated after chromatographic separation of the obtained residues. Mixed samples with authentic compounds did not show depression of the melting point.

5-Benzoyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (3a). Grayish crystals, yield 0.84 g (91%), mp 219-221 ºC. IR: *v* 1691, 1641 (CO), 1609 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.89 (1H, dt, *J* 6.1, 13.6 Hz, 3-CH_2), 3.13 (1H, dd, *J* 4.4, 13.9 Hz, 3-CH_2), 3.81 (1H, dd, *J* 6.0, 12.8 Hz, 4-CH_2), 4.76 (1H, dt, *J* 5.0, 13.4 Hz, 4-CH_2), 6.84 (1H_{arom}, d,

J 7.8 Hz, CH), 7.16-7.29 (6H_{arom}, m, CH), 7.39 (1H_{arom}, t. *J* 7.8 Hz, CH), 7.53 (1H_{arom}, t, *J* 7.5 Hz, CH), 7.63 (1H_{arom}, d, *J* 7.7 Hz, CH), 7.73 (1H_{arom}, d, *J* 7.9 Hz, CH), 7.82 (1H_{arom}, t, *J* 7.5 Hz, CH), 8.37 (1H_{arom}, d, *J* 7.8 Hz, 6′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 33.8 (C-3), 49.4 (C-4), 121.1 (C-1′), 127.2 (CH), 127.3 (CH), 127.4 (CH), 128.0 (*o*-CH_{Ph}), 128.8 (CH), 129.1 (*m*-CH_{Ph}), 129.6 (CH), 129.7 (CH), 130.6 (*p*-CH_{Ph}), 133.1 (*i*-C_{Ph}), 134.2 (C-5a or C-9a), 135.0 (CH), 136.6 (C-9a or C-5a), 147.1 (C-2′), 154.1 (C-2), 160.9 (1-CO), 170.9 (5-CO). Anal. Calcd. for $C_{23}H_{17}N_3O_2$ (367.40): C, 75.19; H, 4.66; N, 11.44%. Found: C, 74.95; H, 4.49; N, 11.65%.

5-Benzoyl-6-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (3b). Yellowish crystals, yield 0.65 g (68%), mp 214-216 ºC. IR: *v* 1686, 1649 (CO), 1611 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.34 (3H, d, *J* 6.2 Hz, 4-CH_3), 2.56 (1H, dd, *J* 12.7, 13.4 Hz, 3-CH_2), 3.09 (1H, dd, *J* 5.0, 13.8 Hz, 3-CH_2), 5.19-5.31 (1H, 4-CH), 6.81 (1H_{arom}, d, *J* 7.5 Hz, CH), 7.13-7.25 (6H_{arom}, m, CH), 7.41 (1H_{arom}, dt. *J* 1.2, 8.1 Hz, CH), 7.53 (1H_{arom}, dd, *J* 1.1, 15.0 Hz, CH), 7.72 (1H_{arom}, d, *J* 7.6 Hz, CH), 7.82 (1H_{arom}, dt, *J* 1.5, 8.3 Hz, CH), 8.36 (1H_{arom}, dd, *J* 1.2, 8.0 Hz, 6′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.9 (4-CH_3), 41.5 (C-3), 55.7 (C-4), 121.1 (C-1′), 127.2 (CH), 127.3 (CH), 127.4 (CH), 127.9 (*o*-CH_{Ph}), 128.2 (CH), 128.7 (CH), 128.7 (*m*-CH_{Ph}), 129.3 (CH), 130.3 (*p*-CH_{Ph}), 131.0 (CH), 133.8 (*i*-C_{Ph}), 134.6 (C-5a or C-9a), 135.0 (CH), 147.0 (C-2′), 153.8 (C-2), 160.8 (1-CO), 169.8 (5-CO). Anal. Calcd. for $C_{24}H_{19}N_3O_2$ (381.43): C, 75.57; H, 5.02; N, 11.02%. Found: C, 75.32; H, 4.81; N, 11.27%.

5-Benzyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (3d). Grayish solid, yield 0.27 g (30%), mp 70-73 ºC. IR: *v* 1686 (CO), 1610 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.79-2.90 (1H, m, 3-CH_2), 2.96-3.07 (1H, m, 3-CH_2 and 1H, m, 4-CH_2), 3.60-3.69 (1H, m, 4-CH_2), 4.08 and 4.44 (2H, ABq, *J* 13.7 Hz, 5-CH_2), 7.13-7.85 (12H_{arom}, m, CH), 8.37 (1H_{arom}, dd, *J* 1.4, 8.0 Hz, 6′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 34.6 (C-3), 56.2 (C-4), 57.0 (5-CH_2), 120.9 (CH), 121.1 (C-1′), 123.4 (CH), 126.5 (CH), 126.8 (CH), 127.2 (CH), 127.5 (*p*-CH_{Ph}), 128.0 (*o*-CH_{Ph}), 128.1 (CH), 128.5 (*m*-CH_{Ph}), 129.8 (CH), 130.8 (C-5a or C-9a), 134.6 (CH), 137.3 (*i*-C_{Ph}), 143.7 (C-9a or C-5a), 146.5 (C-2′), 156.3 (C-2), 160.6 (1-CO). Anal. Calcd. for $C_{23}H_{19}N_3O$ (353.42): C, 78.16; H, 5.42; N, 11.89%. Found: C, 78.47; H, 5.61; N, 11.63%.

5-Benzyl-6-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (3e). Sandy crystals, yield 0.73 g (80%), mp 183-185 ºC. IR: *v* 1682 (CO), 1609 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.08 (3H, d, *J* 6.1 Hz, 4-CH_3), 2.48 (1H, dd, *J* 1.1, 13.1 Hz, 3-CH_2), 2.93 (1H, dd, *J* 5.6, 13.4 Hz, 3-CH_2), 3.92 (1H, tt, *J* 5.9, 11.7 Hz, 4-CH_2), 4.24 and 4.35 (2H, ABq, *J* 14.1 Hz, 5-CH_2), 7.05-7.84 (12H_{arom}, m, CH), 8.39 (1H_{arom}, d, *J* 7.9 Hz, 6′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.4 (4-CH_3), 42.9 (C-3), 53.3 (5-CH_2), 59.0 (C-4), 121.0 (C-1′), 123.6 (CH), 123.8 (CH), 126.6 (CH), 126.7 (CH), 127.1 (CH), 127.4 (*p*-CH_{Ph}), 127.8 (*m*-CH_{Ph}), 127.9 (CH), 128.3 (*o*-CH_{Ph}), 129.0 (CH), 132.2 (C-5a or C-9a), 134.5 (CH), 137.3 (*i*-C_{Ph}), 140.8 (C-5a or C-9a), 147.0 (C-2′), 155.9 (C-2), 160.7 (1-CO). Anal. Calcd. for $C_{24}H_{21}N_3O$ (367.44): C, 78.45; H, 5.76; N, 11.44%. Found: C, 78.66; H, 5.92; N, 11.17%.

5-Methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (3g). Sandy solid, yield 0.22 g (32%), mp 104-107 ºC. IR: *v* 1687 (CO), 1610 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.76 (3H, s, 5-CH_3), 2.82 (1H, dd, *J* 7.0, 12.9 Hz, 3-CH_2), 2.99 (1H, dd, *J* 5.7, 13.3

Hz, 3-CH_2), 3.06 (1H, ddd, *J* 0.7, 6.8, 9.8 Hz, 4-CH_2), 3.68 (1H, ddd, *J* 5.4, 9.8, 12.7 Hz, 4-CH_2), 7.18-7.81 (7H_{arom}, m, CH), 8.31 (1H_{arom}, d, *J* 8.2 Hz, 6′-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 34.7 (C-3), 40.4 (5-CH_3), 58.8 (C-4), 119.5 (CH), 121.2 (C-1′), 122.8 (CH), 126.4 (CH), 126.8 (CH), 127.4 (CH), 128.2 (CH), 129.8 (CH), 129.8 (C-5a or C-9a), 134.6 (CH), 144.1 (C-9a or C-5a), 146.5 (C-2′), 156.2 (C-2), 160.7 (1-CO). Anal. Calcd. for $C_{17}H_{15}N_3O$ (277.32): C, 73.63; H, 5.45; N, 15.15%. Found: C, 73.94; H, 5.68; N, 11.41%.

5,6-Dimethyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (3h). Yellowish solid, yield 0.58 g (80%), mp 57-60 ºC. IR: *v* 1687 (CO), 1610 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.05 ((0.8)3H, d, *J* 6.1 Hz, 4-CH_3), 1.45 ((0.2)3H, d, *J* 6.1 Hz, 4-CH_3), 2.47 (1H, dd, *J* 11.6, 13.5 Hz, 3-CH_2), 2.77 ((0.8)3H, s, 5-CH_3), 2.79 ((0.2)3H, s, 5-CH_3), 2.96 ((0.2)1H, dd, *J* 6.3, 13.6 Hz, 3-CH_2), 3.03 ((0.8)1H, dd, *J* 5.5, 13.5 Hz, 3-CH_2), 3.25 ((0.2)1H, dp, *J* 1.3, 6.3 Hz, 4-CH), 3.94 ((0.8)1H, pd, *J* 6,0, 11.8 Hz, 4-CH), 7.16-7.81 (7H_{arom}, m, CH), 8.31 (1H_{arom}, d, *J* 8.2 Hz, 6′-CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.4[19.5] (4-CH_3), 37.3[38.3] (5-CH_3), [41.0]42.9 (C-3), 62.4[62.8] (C-4), [120.0]121.2 (C-1′), 122.5[122.8] (CH), 123.0 (CH), 126.4 (CH), 126.7 (CH), [127.3]127.4 (CH), [127.8]128.0 (CH), 129.1[129.5] (CH), 130.8 (C-C5a or C-9a), 134.5 (CH), 141.6 (C-9a or C-5a), [146.2]146.5 (C-2′), [154.1]156.0 (C-2), [159.0]160.7 (1-CO). Values of chemical shift gave in angle brackets correspond to the minor isomer. Anal. Calcd. for $C_{18}H_{17}N_3O$ (291.35): C, 72.20; H, 5.88; N, 14.42%. Found: C, 71.95; H, 6.09; N, 14.15%.

5-Benzoyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1a). Compound **1a** was synthesized according to procedure[17] from 3.2 g (20 mmol) of 1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one and 2.55 ml (22 mmol) of benzoyl chloride, and 1.78 ml (22 mmol) of pyridine. Yield 4.6 g (86%) **1a**, white crystals, mp 198-200 ºC (from ethyl acetate). IR: *v* 3204, 3153, 3104 (NH), 1682, 1627 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.68 (1H, br, 3-CH_2), 2.88 (1H, br, 3-CH_2), 3.88 (1H, br, 4-CH_2), 4.87 (1H, br, 4-CH_2), 6.72 (1H_{arom}, d, *J* 7.8 Hz, CH), 6.82-7.24 (8H_{arom}, m, CH), 9.44 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 33.0 (C-3), 49.0 (C-4), 122.3 (C-9), 125.8 (C-7), 127.9 (*o*-CH_{Ph}), 128.2 (*m*-CH_{Ph}), 128.4 (C-6), 130.2 (C-8 or *p*-CH_{Ph}), 130.3 (*p*-CH_{Ph} or C-8), 134.5 (*i*-C_{Ph} or C-9a or C-5a), 135.0 (C-5a or C-9a or *i*-C_{Ph}), 135.0 (C-9a or C-5a or *i*-C_{Ph}), 171.0 (5-CO), 174.1 (C-2). Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (266.30): C, 72.16; H, 5.30; N, 10.52%. Found: C, 72.41; H, 5.47; N, 10.71%.

5-Benzoyl-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1b). Compound **1b** was synthesized analogously as **1a** from 3.6 g (20 mmol) of 4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one.[17] Yield 4.5 g (81%) **1b**, white crystals, mp 212-214 ºC (from ethyl acetate). IR: *v* 3178, 3068 (NH), 1686, 1646 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.34 (3H, d, *J* 6.2 Hz, 4-CH_3), 2.44-2.61 (2H, m, 3-CH_2), 5.36 (1H, m, 4-CH), 6.71 (1H_{arom}, d, *J* 7.7 Hz, CH), 6.87 (1H_{arom}, t, *J* 7.5 Hz, CH), 7.07-7.24 (7H_{arom}, m, CH), 9.11 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.8 (4-CH_3), 40.6 (C-3), 55.7 (C-4), 122.3 (C-9), 126.0 (C7), 127.8 (*o*,*m*-CH_{Ph}), 128.8 (C-6), 129.9 (C-8), 131.7 (*p*-CH_{Ph}), 132.9 (*i*-C_{Ph}), 135.5 (C-9a or C-5a), 136.0 (C-5a or C-9a), 170.2 (5-CO), 173.6 (C-2). Anal. Calcd. for $C_{17}H_{16}N_2O_2$ (280.32): C, 72.84; H, 5.75; N, 9.99%. Found: C, 72.51; H, 5.87; N, 9.71%.

5-Benzoyl-3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (1c). Compound **1c** was synthesized analogously as **1a** from 3.6 g (20 mmol) of 3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one.[17] Yield 4.2 g (75%) **1c,** white crystals, mp 171-173 ºC (from ethyl acetate). IR: *v* 3196, 3060 (NH), 1681, 1642 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.24 (3H, d, *J* 7.1 Hz, 3-CH_3), 2.92 (1H, m, 3-CH), 3.87 (1H, dd, *J* 5.8, 12.8 Hz, 4-CH_2), 4.48 (1H, t, *J* 12.8 Hz, 4-CH_2), 6.71 (1H_{arom}, d, *J* 7.6 Hz, CH), 6.86 (1H_{arom}, t, *J* 7.2 Hz, CH), 7.10-7.24 (7H_{arom}, m, CH), 8.78 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.8 (3-CH_3), 34.9 (C-3), 56.7 (C-4), 122.5 (C-9), 126.0 (C-7), 127.9 (*o*-CH_{Ph}), 128.2 (*m*-CH_{Ph}), 128.4 (C6), 130.2 (*p*-CH_{Ph}), 130.2 (C-8), 132.9 (*i*-C_{Ph}), 135.1 (C-9a or C-5a), 135.3 (C-5a or C-9a), 171.0 (5-CO), 175.7 (C-2). Anal. Calcd. for $C_{17}H_{16}N_2O_2$ (280.32): C, 72.84; H 5.75; N, 9.99%. Found: C, 73.01; H, 5.61; N, 9.83%.

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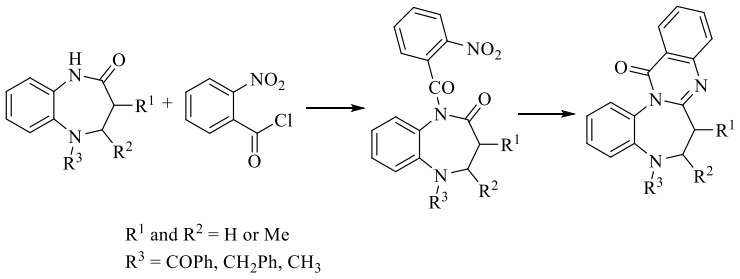
Graphical Abstract

A combined experimental and theoretical study of the synthesis of quinazolino[3,2-a][1,5]benzodiazepin-13-ones *Regina Janciene, Ausra Vektariene, Gema Mikulskiene, Tomas Javorskis, Gytis Vektaris, Algirdas Klimavicius*	 R^1 and R^2 = H or Me R^3 = COPh, CH_2Ph, CH_3

