Monatsh Chem (2011) 142:609–618
DOI 10.1007/s00706-011-0496-4

ORIGINAL PAPER

Experimental and theoretical investigation of substituent effects in a two-pathway reaction of tetrahydro-1,5-benzodiazepine-2-thiones with 4-substituted 2-bromoacetophenones

Regina Janciene · Ausra Vektariene · Zita Stumbreviciute · Benedikta Puodziunaite

Received: 3 March 2011 / Accepted: 30 March 2011 / Published online: 4 May 2011

Abstract The interaction of 5-acetyl(or formyl)-3-R^1-(CH_3, H)-4-R^2(CH_3, Ph, H)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepine-2-thiones with 2-bromo-4′-X(CH_3, OCH_3, Br, H)-acetophenones leads to a mixture of products: 5,6-dihydro-4*H*-[1,3]thiazolo[3,2-*a*][1,5]benzodiazepinium salts and *S*-[2-oxo-2-(4-X-phenyl)ethyl] 3-(1*H*-benzimidazol-1-yl)propane(or butane-)thioate hydrobromides. The course of the concurrent reactions depends on the presence of substituents of the starting thiones and on the nature of the 4-substituent of the bromoacetophenones. Semiempirical Austin method 1 (AM1) and density functional theory (DFT) B3LYP computational studies for the interpretation of two concurrent reaction pathways are presented.

Keywords 5-Acyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepine-2-thiones · Cyclizations · Density functional theory · Structure–activity relationships · Semiempirical calculations

Introduction

In recent years, great effort has been applied in the benzodiazepine area to develop new members of this family. Among the new compounds are those containing different heterocyclic rings annulated to the basic 1,5-benzodiazepine system [1].

In previous papers [2–4] we reported a cyclofunctionalization strategy of the 1,5-benzodiazepine system, which exploited the reactivity of the C=S bond of the heptatomic nucleus by interaction with α-halogen carbonyl compounds. Tricyclic thiazolo[1,5]benzodiazepines were obtained from 1,3,4,5-tetrahydro-1,5-benzodiazepine-2-thiones by treatment with bromoacetaldehyde diethylacetal [2], chloroacetone [3], and 2-bromo(or 2,4′-dibromo)acetophenones [4]. In a recent paper [4] we reported that treatment of the aromatic bromoketones with thiolactams, carrying *N*(5)-acetyl substituents, gives rise to two concurrent reactions leading to the corresponding thiazolobenzodiazepinium bromides and *N*-substituted benzimidazole derivatives as a result of hydrolysis of starting compounds followed by rearrangement. The bromoacetophenone reaction carried out on *N*(5)-formyl- or *N*(5)-anilinocarbonyl-substituted 1,5-benzodiazepine-2-thiones afforded only tricyclic thiazolobenzodiazepines.

To extend our study, we present herein a detailed investigation of the interaction of 5-acyl-1,5-benzodiazepine-2-thiones with 4-substituted aromatic bromoketones. The influence of substituents in the heptatomic nucleus of the starting thiolactams and of the nature of 4-substituents of aromatic ketones on the course of the studied interaction was also elaborated. The estimation of local structure–reactivity descriptors was performed using DFT and AM1 computations.

Results and discussion

5-Acetyl(or formyl)-3-R^1-4-R^2-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepine-2-thiones **1**–**6**, previously described by us in [2] (compounds **2**, **5**, **6**), [3] (compound **1**), and [4] (compound **4**), were used as starting compounds to prepare

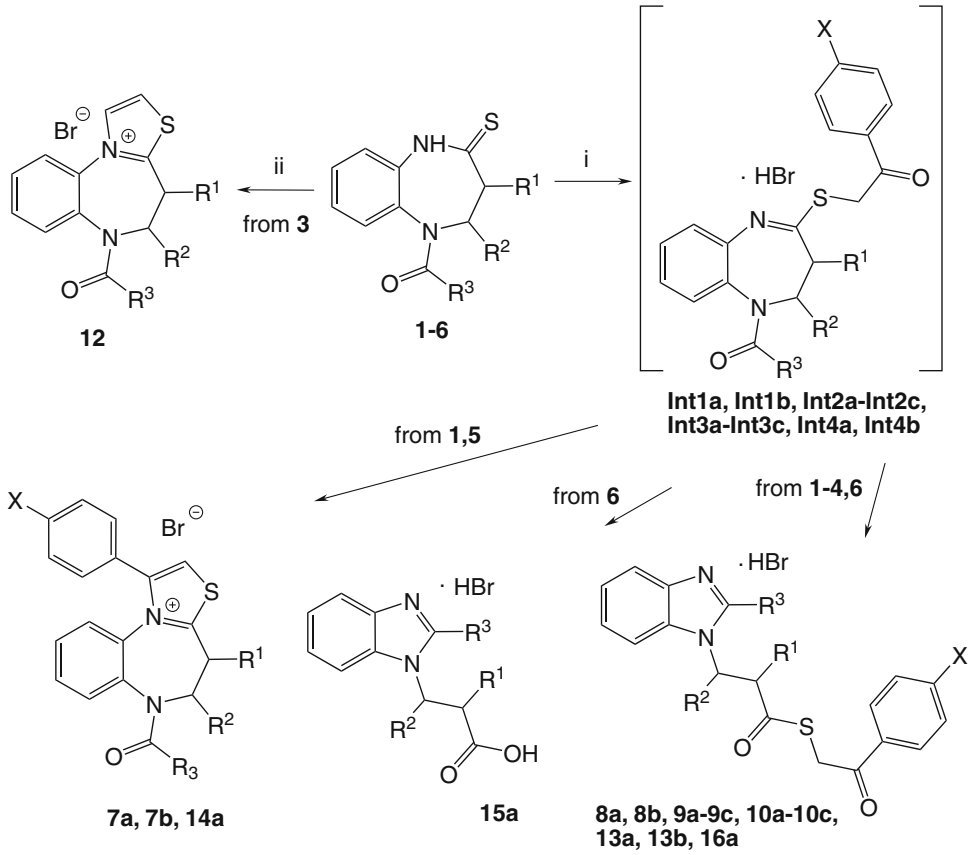
R. Janciene (✉) · Z. Stumbreviciute · B. Puodziunaite
Institute of Biochemistry, Vilnius University, Vilnius, Lithuania
e-mail: regina.janciene@bchi.vu.lt

A. Vektariene
Institute of Theoretical Physics and Astronomy, Vilnius University, Vilnius, Lithuania

cyclocondensation derivatives. Thione **3** was synthesized by acylation of 2,3,4,5-tetrahydro-4-phenyl-1*H*-1,5-benzodiazepin-2-thione [5] using the procedure described in [4]. The reaction of thiolactams **1**–**6** with slight excess of the appropriate 4-substituted bromoacetophenone [X = CH_3 (**a**), OCH_3 (**b**), H (**c**)] was performed in refluxing butan-2-one according to the procedure previously described by us [4]. The reaction sequence is illustrated in Scheme 1.

Thus, the treatment of 5-acetyl-3-methylbenzodiazepine-2-thione (**1**) with 2-bromo-4′-methylacetophenone [X = CH_3 (**a**)] or 2-bromo-4′-methoxyacetophenone [X = OCH_3 (**b**)] gave a mixture of products: tricyclic thiazolobenzodiazepinium bromides **7a** and **7b** (60% and 37% yields) and *N*-substituted 2-methylbenzimidazole derivatives **8a** and **8b** (31% and 40% yields). In this case, two reactions are equally possible. Analogously, two products were obtained by treatment of thiolactam **1** with 2,4′-dibromoacetophenone [X = Br (**d**)] or 2-bromoacetophenone [X = H (**c**)] [4]. The reaction of 5-acetyl-4-methyl(or phenyl)benzodiazepine-2-thiones **2** and **3** with 4-substituted bromoacetophenones (X = OCH_3, CH_3) and 2-bromoacetophenone (X = H) afforded only 2-methylbenzimidazole derivatives **9a**–**9c** and **10a**–**10c** in moderate yields (25–66%), whereas tricyclic benzodiazepines were not formed. Thus, one of the concurrent reactions dominated, namely the rearrangement of the heptatomic diazepine ring to five-membered imidazole. In our previous papers [2, 3], we described synthesis of thiazolo[1,5] benzodiazepines from 4-methyl-substituted thiolactam **2**

Scheme 1



X = CH_3 (a), OCH_3 (b), H (c)

i: $BrCH_2COPh$-X(p), $C_2H_5COCH_3$, reflux, 2-3 h

ii: $BrCH_2CH(OC_2H_5)_2$, $C_2H_5COCH_3$, reflux, 1 h

	R^1	R^2	R^3
1, Int1a, Int1b, 7a, 7b, 8a, 8b	CH_3	H	CH_3
2, Int2a-Int2c, 9a-9c	H	CH_3	CH_3
3, Int3a-Int3c, 10a-10c, 11, 12	H	Ph	CH_3
4, Int4a, Int4b, 13a, 13b	H	H	CH_3
5, 14a	CH_3	H	H
6, 15a, 16a	H	H	H

by treatment with α-bromoacetaldehyde diethylacetal or chloroacetone. In those reactions, the corresponding benzimidazole derivatives were not separated. Analogously, cyclocondensation of 4-phenyl-substituted thiolactam **3** with bromoacetaldehyde diethylacetal afforded only tricyclic thiazole **12**.

The isolation of compounds **9a–9c** and **10a–10c** was rather intricate due to the resinification of the reaction mixtures. It is noteworthy that the conversion of the staring thioamides into the corresponding amides was observed by thin-layer chromatography (TLC) in all cases. Thus, in the reaction of thiolactam **3** with the corresponding bromoacetophenones [X = CH_3 (**a**), OCH_3 (**b**), H (**c**)], 5-acetyl-1,3,4,5-tetrahydro-4-phenyl-2*H*-1,5-benzodiazepin-2-one **11** [6] was isolated (in 11–15% yields) from the reaction resin residue. Attempts to optimize the cyclization reaction conditions were not successful. Synthesis of **9b** performed in acetone or benzene solutions proceeded slowly, and only the *S*-alkyl intermediate **Int1b** was detected (TLC analysis). The experiment performed in refluxing toluene (compound **10b**) led to replacement of sulfur by the oxygen atom in starting compound **3**, whereas the reaction in dichloroethane afforded the same result as in butan-2-one. The formation of *S*-alkylated 1,5-benzodiazepine derivatives as intermediates was observed in all experiments by TLC monitoring of reaction progress. In our previous paper [4], the structure of *S*-alkyl intermediates formed in the first step of the condensation–cyclization reaction was confirmed.

Furthermore, we can point out that the reaction of thiolactam **4**, carrying no substituents in the 3- and 4-positions of the diazepine nucleus, proceeded differently as compared with that of thiolactam **1**. By treating compound **4** with 2-bromo-4′-methyl (or methoxy) acetophenones [X = CH_3 (**a**), OCH_3 (**b**)], benzimidazole derivatives **13a** and **13b** were the only products of the reaction, while the reaction of compound **4** with 2-bromo (or 2,4′-dibromo) acetophenones [X = H (**c**), Br (**d**)] yielded a mixture of the corresponding tricyclic thiazolobenzodiazepine and benzimidazole derivatives [4]. We can presume that these cycloaddition reactions are also influenced by the nature of the 4-substituents of bromoacetophenones.

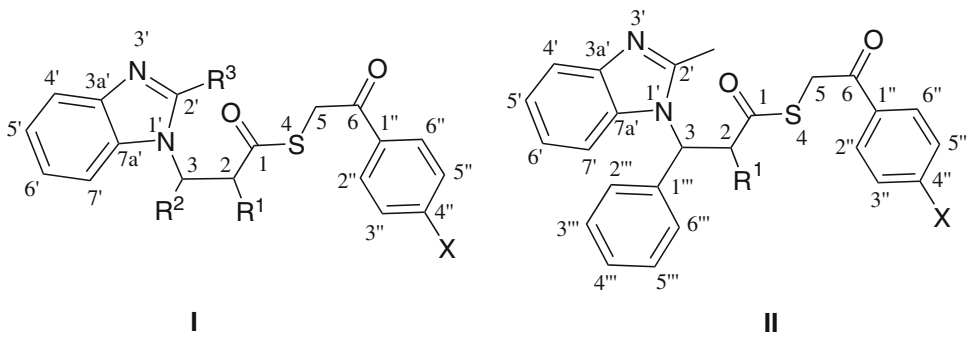
Finally, the reaction of 5-formyl-substituted thiolactams **5**, **6** [2, 7] with 4-substituted acetophenones also proceeded differently. The treatment of 3-methylbenzodiazepine-2-thione **5** with 2-bromo-4′-methylacetophenone [X = CH_3 (**a**)] gave the thiazolobenzodiazepine **14a**. A trace of the corresponding benzimidazole derivative was detected by TLC analysis, but was not isolated. Reaction of thiolactam **6** with the same bromoacetophenone gave two benzimidazole derivatives **15a** and **16a** in 27% and 30% yields.

The structure of the studied compounds was investigated using infrared (IR) and ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra. For the description of NMR spectra, we used the arbitrary numbering of atoms as in Scheme 2 (**I** for compounds **8a**, **8b**, **9a–9c**, **13a**, **13b**, **15a**, and **16a**; **II** for compounds **10a–10c**).

Spectral signals were consistent with the analogous structures previously proposed by us in [4]. The existence of a singlet signal of the proton of 2-CH group in the ^{1}H NMR spectra of compounds **7a**, **7b**, and **14a** (8.34, 8.50, and 8.33 ppm) confirms the formation of the thiazole nucleus. The signal of the aromatic H-10 proton of compound **7b** at 7.3 ppm is shifted upfield with respect to the signals of the same proton of compound **12** (H-10, 8.44 ppm) and 1-methylthiazolobenzodiazepines [3], probably due to the anisotropic effect of the benzene ring in 1-position. The low-field-shifted H-2′ proton signals at 9.55 (CD_3OD) and 10.09 ppm ($CDCl_3$) in the ^{1}H NMR spectra of compounds **15a** and **16a** are characteristic of the benzimidazole ring.

Consequently, the presented study of the interaction of 5-acyl-3-R^1-4-R^2-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepine-2-thiones **1–6** with 4-substituted aromatic bromoketones suggests that two concurrent reactions take place: the cyclization reaction resulting in the formation of tricyclic thiazolo[1,5]benzodiazepinium salts **7a**, **7b**, **14a** and acidic hydrolysis leading to rearrangement of the diazepine heterocycle to five-membered imidazole derivatives **8a**, **8b**, **9a–9c**, **10a–10c**, **13a**, **13b**, **16a**. The course of the studied interaction (i.e., whether both reactions occur simultaneously or one of them dominates) depends on the presence of substituents of the starting thiones **1–6** in 3- and

Scheme 2



4-positions ($R^1 = CH_3$, H, $R^2 = CH_3$, Ph, H) and on the nature of the 4-substituent of the bromoacetophenones.

Our earlier investigations [4] of the reaction mechanism in terms of the reaction potential-energy surface calculations showed that the first step of the studied interaction is common to both pathways and proceeds through the formation of the intermediates (**Int**, Scheme 1). In this work, with the aim of estimating the regiochemical outcome of the pending interaction, we extended our computational investigations to selected reaction intermediate structures **Int1a**-**Int1d**, **Int1x**, **Int2a**-**Int2c**, **Int3a**-**Int3c**, **Int4a**-**Int4d** [X = CH_3 (**a**), OCH_3 (**b**), H (**c**), Br (**d**)]. The optimal geometry structure of **Int1b** is presented in Fig. 1 as an example.

It is evident that the intermediate structure consists of the 1,5-benzodiazepine-2-thione skeleton and the 4-substituted acetophenone moiety. Such molecular geometry allows us to estimate the influence of all substituents on the regiochemical outcomes of the studied cyclization processes. The C(3)=O and C(2)-S carbon atoms and the N(1)-C(2) bond are the most important molecular sites for initialization of the two concurrent reaction pathways. We focused our attention on the estimation of reactivity indexes for these atoms. We calculated optimal geometries of reaction intermediate structures **Int1a**-**Int1d**, **Int1x**, **Int2a**-**Int2c**, **Int3a**-**Int3c**, **Int4a**-**Int4d** and their local reactivity indexes at two different levels of theory: density functional theory (DFT) and the Hartree–Fock–Roothaan semiempirical methodology using the Austin method 1 (AM1) approach.

From a theoretical point of view, there are some kinetic and quantum mechanics studies of the reactivity of benzofused heterocycles that qualitatively predict the reactive sites of these compounds [8–10]. It was demonstrated [11–14] that DFT B3LYP is a reliable method for calculation of the geometries and energies of benzofused heterocycles. Nevertheless, analysis of aromatic compounds and large bioorganic heterocyclic systems shows that AM1 Hamiltonian approximations based Fukui functions and other reactivity descriptors correctly determine reactivity features in the active sites of molecules [15, 16].

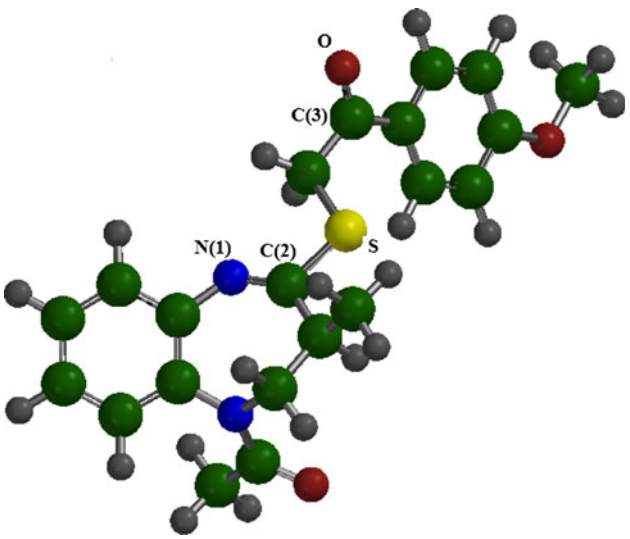


Fig. 1 Optimal geometry of **Int1b**

It is worth noting that a molecular electrostatic potential based on the molecular electron density surface is a good indicator for the interpretation of chemical reactivity. It gives a suitable description of molecular properties, such as strong noncovalent interactions that are predominantly electrostatic in nature. It has been shown [13, 14, 17] that the shell close to the van der Waals surface gives physically reasonable molecular dimensions and reflects molecular features, such as bond formation and electron lone pairs. Therefore, we calculated atom-centered point charges fitted to the electrostatic potential (ESP) on the shell held near the surface of a molecule at the van der Waals radii [17, 18].

Moreover, the hard and soft acids and bases (HSAB) principle has been very useful to predict the reactivity of chemical systems. The HSAB principle has been used by Parr and Yang [19] in terms of DFT concepts for expression of local reactivity indexes such as the Fukui function. The Fukui function is a local reactivity descriptor that indicates the best way to change the number of electrons in a molecule. Hence, it indicates the propensity of the electronic density to deform at a given position, i.e., to accept or donate electrons [20]. We calculated the condensed Fukui function [19, 21, 22] for nucleophilic attack [f+(r)] on the particular atoms of intermediates [C(2) and C(3)] as the most important for the interpretation of the outcome of the reaction.

In this work, based on the optimized geometries of reaction intermediate structures **Int1**–**Int4**, we calculated local reactivity descriptors: bond length (BL), bond order (BO), ESP-derived charges, and f+(r). The calculations were carried out using the semiempirical AM1 method and DFT B3LYP functional with two different basis sets (6-31G* and 6-31+G*). BL and BO values for the fragment N(1)-C(2) are presented in Table 1, while ESP charges and f+(r) for the fragment N(1)-C(2)-C(3) of **Int1a**–**Int1d**, **Int1x**, **Int2a**–**Int2c**, **Int3a**–**Int3c**, **Int4a**–**Int4d** are presented in Table 2.

The results of our computation of the intermediates reveal that the presence of substituents (R^1 and R^2) on the diazepine skeleton, as well as 4-substituents on the aromatic bromoketones, influences the values of all calculated reactivity descriptors. The nature of the substituents determines the electron density displacement on the molecular surface of the intermediates. Hence, changes in electron density displacement cause N(1)-C(2) bond weakening or strengthening. This allows us to predict the

further possible course of the pending reaction. In the case of **Int2a–Int2c** and **Int3a–Int3c**, the weakening and lengthening of the N(1)-C(2) bond compared with that in **Int1a–Int1d**, **Int1x** suggest that the hydrolysis reaction pathway could be more probable (Table 1). Otherwise, the strengthening of the N(1)-C(2) bond in **Int1a–Int1d**, **Int1x**, **Int4c**, **Int4d** compared with that in **Int2a–Int2c**, **Int3a–Int3c** could be compatible with the reaction pathway corresponding to formation of tricyclic thiazoles. For example, the BO value ~1.93 for **Int1x** represents a strong double bond and correlates well with synthesis results showing the exceptional formation of the tricyclic thiazole derivative [3], while **Int2c** with BO value ~1.70 undergoes the hydrolysis reaction leading to N(1)-C(2) bond cleavage.

Table 1 Calculated N(1)-C(2) bond length (BL) and bond order (BO) values of **Int1a–Int1d**, **Int1x**, **Int2a–Int2c**, **Int3a–Int3c**, **Int4a–Int4d**

Int	AM1		B3LYP 6-31G*		B3LYP 6-31+G*	
	BL (Å)	BO	BL (Å)	BO	BL (Å)	BO
1a	1.291	1.830	1.275	1.729	1.276	1.755
1b	1.283	1.826	1.274	1.729	1.277	1.781
1c[a]	1.290	1.831	1.274	1.736	1.277	1.746
1d[a]	1.290	1.829	1.274	1.720	1.277	1.770
1x[b]	1.270	1.842	1.273	1.924	1.274	1.930
2a	1.295	1.750	1.279	1.703	1.282	1.701
2b	1.295	1.744	1.280	1.700	1.281	1.701
2c	1.296	1.742	1.281	1.685	1.280	1.701
3a	1.295	1.750	1.280	1.700	1.283	1.690
3b	1.295	1.759	1.281	1.700	1.281	1.698
3c	1.295	1.754	1.279	1.704	1.279	1.702
4a	1.295	1.799	1.280	1.705	1.278	1.701
4b	1.300	1.800	1.276	1.702	1.277	1.695
4c[a]	1.300	1.829	1.275	1.731	1.281	1.751
4d[a]	1.295	1.805	1.277	1.733	1.281	1.753

[a] Synthesis presented in [4]

[b] **Int1x**, intermediate of interaction of 5-acetyl-3-methyl-1,5-benzodiazepine-2-thione (**1**) with chloroacetone [3]

The ESP charge distribution illustrates the most favorable sites for nucleophilic or electrophilic attack and confirms the results described above with new evidence (Table 2). A decrease of positive ESP charge on the C(3) carbon atom and an increase of positive ESP charge on the C(2) atom in **Int2a–Int2c**, **Int3a–Int3c**, **Int4a**, **Int4b** as compared with the corresponding values in **Int1x** allow the start of the hydrolysis reaction at the C(2) reacting site with the formation of the rearrangement products, i.e., benzimidazole derivatives. An increased positive ESP charge on the C(3) atom in **Int1x** is compatible with the enhanced power of this atom for nucleophilic attack as compared with the C(2) atom. This is in full accordance with the course of the reaction of 1,5-benzodiazepinethiones with aliphatic halogen ketones, which proceeds through **Int1x** and gives only one product, the tricyclic thiazolobenzodiazepine

Table 2 Calculated ESP charges and Fukui functions [f+(r)] for fragment N(1)-C(2)-C(3) of **Int1a–Int1d**, **Int1x**, **Int2a–Int2c**, **Int3a–Int3c**, **Int4a–Int4d**

Int	AM1			B3LYP 6-31G*					B3LYP 6-31+G*		
	ESP charges			ESP charges			f+(r)		ESP charges		
	N(1)	C(2)	C(3)	N(1)	C(2)	C(3)	C(2)	C(3)	N(1)	C(2)	C(3)
1a	−0.53	+0.50	+0.48	−0.42	+0.41	+0.39	0.18	0.17	−0.43	+0.39	+0.38
1b	−0.52	+0.54	+0.54	−0.29	+0.33	+0.35	0.21	0.18	−0.36	+0.34	+0.39
1c[a]	−0.52	+0.60	+0.61	−0.40	+0.39	+0.38	0.17	0.06	−0.37	+0.38	+0.41
1d[a]	−0.49	+0.44	+0.46	−0.42	+0.39	+0.38	0.14	0.15	−0.38	+0.39	+0.39
1x[b]	−0.56	+0.49	+0.61	−0.40	+0.33	+0.68	0.02	0.13	−0.41	+0.32	+0.75
2a	−0.57	+0.58	+0.48	−0.51	+0.54	+0.41	0.18	0.06	−0.47	+0.54	+0.39
2b	−0.49	+0.57	+0.50	−0.52	+0.51	+0.40	0.28	0.07	−0.45	+0.56	+0.40
2c	−0.58	+0.59	+0.46	−0.48	+0.50	+0.40	0.17	0.07	−0.46	+0.52	+0.41
3a	−0.60	+0.76	+0.43	−0.60	+0.76	+0.43	0.18	0.01	−0.61	+0.76	+0.43
3b	−0.60	+0.75	+0.48	−0.60	+0.54	+0.41	0.19	0.06	−0.62	+0.56	+0.39
3c	−0.57	+0.77	+0.43	−0.51	+0.51	+0.38	0.20	0.07	−0.52	+0.53	+0.38
4a	−0.56	+0.64	+0.55	−0.50	+0.50	+0.41	0.23	0.03	−0.53	+0.51	+0.38
4b	−0.47	+0.48	+0.34	−0.44	+0.50	+0.36	0.16	0.08	−0.46	+0.52	+0.37
4c[a]	−0.55	+0.58	+0.56	−0.46	+0.45	+0.43	0.14	0.10	−0.45	+0.51	+0.52
4d[a]	−0.57	+0.63	+0.64	−0.49	+0.47	+0.44	0.24	0.16	−0.50	+0.50	+0.48

[a] Synthesis presented in [4]

[b] **Int1x**, intermediate of interaction of 5-acetyl-3-methyl-1,5-benzodiazepine-2-thione (**1**) with chloroacetone [3]

derivative [3]. Moreover, for **Int1x**, the Fukui function values for nucleophilic attack [f+(r)] on the C(2) and C(3) atoms are 0.02 and 0.13 and show greater reactivity of C(3). For **Int2a–Int2c**, **Int3a–Int3c**, **Int4a**, **Int4b**, the f+(r) values on the C(2) atom are increased by ten or more times compared with C(3). This fact indicates a greater possibility for the formation of only one benzimidazole derivative. When f+(r) values on C(2) and C(3) are similar (**Int1a**, **Int1b**, **Int4c**, **Int4d**), both reactions proceed equally.

It is worth mentioning that the use of both the AM1 and DFT B3LYP methods in this study provides the opportunity to compare the performance of these two approaches for the interpretation of reactivity descriptors. Both methods provide very similar results: BL, BO, and ESP charge values, despite some numerical differences, are qualitatively similar and in reasonable agreement with the relevant experimental results. Hence, both of them can be employed for prediction of reactivity tendencies of the interaction of substituted 1,5-benzodiazepine-2-thiones with 4-substituted aromatic bromoketones. The advantage of the AM1 model is that it is less time consuming, but it gives a sufficiently high correlation with experiment and seems adequate as a simple reactivity screening tool. However, the DFT 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.

Conclusions

Investigation of the interaction of 5-acyl-3-R^1-4-R^2-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepine-2-thiones **1–6** with 4-substituted 2-bromoacetophenones shows that the progress of two competitive transformations apparently depend on the presence of substituents in 3- and 4-positions of the starting thiones **1–6** and as well as on the nature of the 4-substituent of the bromoacetophenones. The semi-empirical AM1 and DFT B3LYP computational studies of local reactivity descriptors of the optimal geometry of intermediate structures **Int1a–Int1d**, **Int1x**, **Int2a–Int2c**, **Int3a–Int3c**, **Int4a–Int4d** reveal that the substitution of the diazepine skeleton and aromatic bromoketones affects the electronic density on the molecular space. The changes of electronic density are reflected by differences in bond length, bond order, ESP charge, and Fukui function values for intermediates and explain the features of the studied interaction. Computational studies reported herein may be a powerful tool for interpretation of experimental results and a valuable additional tool in the design of synthetic pathways to novel fused heterocycles.

Experimental

Melting points were determined in open capillaries on a MEL-TEMP 1202D apparatus. The IR spectra (potassium bromide) were taken on a PerkinElmer Spectrum GX Fourier-transform infrared (FTIR) spectrometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian Unity Inova 300 spectrometer at 302 K. Chemical shifts are referenced to tetramethylsilane [$\delta(^1\text{H}) = 0$] and the solvent signal for deuteriochloroform [$\delta(^{13}\text{C}) = 77.0$ ppm] and deuteriomethanol [$\delta(^{13}\text{C}) = 49.0$ ppm]. The NMR peaks corresponding to the minor isomer of compounds **7a** and **14a** are given in square brackets. The assignment of the resonances in the NMR spectra was based on the chemical shift theory and signal intensity arguments, multiplicities, and comparison with structurally related compounds, as well as on attached proton test (APT), nuclear Overhauser effect (NOE), correlation spectroscopy (COSY), and ^{1}H, ^{13}C two-dimensional (2D) NMR experiments for some compounds. The reactions were controlled by the TLC method performed on a Merck precoated silica gel aluminum roll ($60F_{254}$) with chloroform–ethyl acetate–methanol (v/v, 14:7:1) as eluent and visualized with ultraviolet (UV) light. Elemental analyses (C, H, N) were performed on an Elemental Analyser CE-440, and results were found to be in good agreement (±0.25%) with calculated values.

The first optimization of intermediate structures was carried out with AM1 [18]. Consequently, the AM1 geometry optimized structures were used as initial coordinates for geometry optimization at the DFT level using the B3LYP functional and the 6-31G* and 6-31+G* basis sets using the GAMESS package [20]. 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. The optimized structures were minima on the potential-energy surface profile, and their harmonic vibrational frequencies were positive. On the basis of the obtained coordinates, visualization of optimized geometries and evaluation of local reactivity descriptors was performed using SPARTAN'06 [18].

*General procedure for preparation of compounds **7a, 7b, 8a, 8b, 9a–9c, 10a–10c, 13a, 13b, 14a, 15a, 16a***

To a stirred solution of an appropriate 1,5-benzodiazepine-2-thione derivative **1–6** (5.0 mmol) in 50–80 cm^3 butan-2-one, 2-bromo-4′-methyl (or methoxy) acetophenone or bromoacetophenone (7.5 mmol) was added. The mixture was refluxed for 1–3 h; the optimal reaction time was determined by TLC monitoring. Then, the mixture was stored overnight in a refrigerator. The work-up of the

reaction mixture and separation of products in each case was performed distinctively.

6-Acetyl-5,6-dihydro-4-methyl-1-(4-methylphenyl)-4H-[1,3]thiazolo[3,2-a][1,5]benzodiazepin-11-ium bromide (**7a**, $C_{21}H_{21}BrN_2OS$)

The precipitate formed was collected by filtration. Recrystallization from methanol-diethyl ether afforded 1.29 g (60%) **7a**. M.p.: 272–274 °C; ^{1}H NMR (CD_3OD, two rotamers in a ratio of 70:30): $\delta = 1.71$ (d, $J = 6.5$ Hz, 3H, 4-CH_3), 2.08 (s, 3H, 6-CH_3), [2.32 (s, 3H, 6-CH_3), 2.35 (s, 3H, 4′-CH_3)], 2.38 (s, 3H, 4′-CH_3), 3.56 (m, 1H, CH), 3.93 (dd, $J = 6.3$, 12.5 Hz, 1H, CH_2), [4.2–4.4 (m, 2H, CH_2)], 4.70 (t, $J = 12.6$ Hz, 1H, CH_2), 7.03–7.81 (m, 8H, arom), 8.34 (s, 1H, H-2) ppm; ^{13}C NMR (CD_3OD): $\delta = 14.72$ (4-CH_3), 21.37 (4′-CH_3), 23.03 (6-CH_3), 36.19 (C-4), 58.81 (C-5), 121.82 (C-2), 125.63, 129.13, 130.85 (4C), 130.99 (2C), 132.11, 133.82, 137.09, 143.07 (C-4′), 150.55 (C-1), 172.24 (6-CO),181.09 (C-3a) ppm; IR: $\bar{\nu} = 1{,}671$ cm^{-1}.

S-[2-(4-Methylphenyl)-2-oxoethyl] 2-methyl-3-(2-methyl-1H-benzimidazol-1-yl)propanethioate hydrobromide (**8a**, $C_{21}H_{23}BrN_2O_2S$)

To the cooled filtrate obtained after isolation of **7a** from the reaction mixture, diethyl ether was added. The precipitate formed was collected by filtration. Recrystallization from dichloromethane-diethyl ether gave 0.69 g (31%) **8a**. M.p.: 159–161 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.47$ (d, $J = 7.0$ Hz, 3H, 2-CH_3), 2.42 (s, 3H, 4″-CH_3), 3.03 (s, 3H, 2′-CH_3), 3.51 (m, 1H, 2-H), 4.25 and 4.33 (AB-q, $J = 16.8$ Hz, 2H, 5-CH_2), 4.39 (dd, $J = 5.1$, 14.7 Hz, 1H, 3-CH_2), 4.65 (dd, $J = 9.8$, 14.7 Hz, 1H, 3-CH_2), 7.27 (m, 2H, H-3″,5″), 7.46–7.55 (m, 2H, H-5′,6′), 7.60 (m, 1H, H-7′), 7.83 (m, 2H, H-2″,6″), 7.89 (m, 1H, H-4′) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.96$ (2′-CH_3), 16.31 (2-CH_3), 21.69 (4″-CH_3), 37.03 (C-5), 46.70 (C-2), 47.19 (C-3), 111.44 (C-4′), 115.30 (C-7′), 126.27 (C-6′), 126.63 (C-5′), 128.48 (C-2″,6″), 129.52 (C-3″,5″), 129.90, 130.95, 132.62, 145.07 (C-4″), 150.56 (C-2′), 191.00 (C-6), 199.14 (C-1) ppm; IR: $\bar{\nu} =$ 2,800–2,614, 1,693, 1,678 cm^{-1}.

6-Acetyl-5,6-dihydro-1-(4-methoxyphenyl)-4-methyl-4H-[1,3]thiazolo[3,2-a][1,5]benzodiazepin-11-ium bromide (**7b**, $C_{21}H_{21}BrN_2O_2S$)

The compound was isolated by following the procedure described for **7a**. Recrystallization from methanol-diethyl ether yielded 0.82 g (37%) **7b**. M.p.: 231–233 °C; ^{1}H NMR ($CDCl_3$, two rotamers in a ratio of 78:22): $\delta = 1.71$ (d, $J = 6.6$ Hz, 3H, 4-CH_3), [1.82 (d, $J = 6.4$ Hz, 3H, 4-CH_3)], 2.02 (s, 3H, 6-CH_3), [2.35 (s, 3H, 6-CH_3)], 3.60 (m, 1H, CH), 3.76–3.83 (m, 1H, CH_2), 3.83 (s, 3H, 4′-CH_3), [4.2–4.3 (br m, 2H, CH_2)], 4.67 (t, $J = 12.8$ Hz, 1H, CH_2), 6.89 (m, 2H, H-3′,5′), 7.17 (m, 2H, H-2′,6′), 7.30 (br dd, 1H, H-10), 7.38 (br dt, 1H, H-9), 7.49 (br dd, 1H, H-7), 7.62 (br dt, 1H, H-8), 8.50 (s, 1H, H-2), [8.54 (br s, 1H, H-2)] ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.83$ (4-CH_3), 22.73 (6-CH_3), 35.03 (C-4), 55.39 (4′-CH_3), 57.28 (C-5), 114.58 (C-3′,5′), 118.73, 123.33 (C-2), 128.96 (C-10), 129.71 (C-9), 129.76 (C-7), 131.03 (C-2′,6′), 132.30 (C-8), 132.78, 135.31, 147.64 (C-1), 161.36 (C-4′), 169.46 (6-CO), 178.13 (C-3a) ppm; IR: $\bar{\nu} = 1{,}676$ cm^{-1}.

S-[2-(4-Methoxyphenyl)-2-oxoethyl] 2-methyl-3-(2-methyl-1H-benzimidazol-1-yl)propanethioate hydrobromide (**8b**, $C_{21}H_{23}BrN_2O_3S$)

The compound was isolated by following the procedure described for **8a**. Recrystallization from dichloromethane gave 0.93 g (40%) **8b**. M.p.: 150–152 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.47$ (d, $J = 7.0$ Hz, 3H, 2-CH_3), 3.01 (s, 3H, 2′-CH_3), 3.52 (m, 1H, H-2), 3.87 (s, 3H, 4″-CH_3), 4.23 and 4.28 (AB-q, $J = 16.6$ Hz, 2H, 5-CH_2), 4.45 (dd, $J = 5.0$, 14.8 Hz, 1H, 3-CH_2), 4.65 (dd, $J = 10.0$, 14.8 Hz, 1H, 3-CH_2), 6.93 (m, 2H, H-3″,5″), 7.44–7.54 (m, 2H, H-5′,6′), 7.64 (m, 1H, H-7′), 7.86 (m, 1H, H-4′), 7.90 (m, 2H, H-2″,6″) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 12.00$ (2′-CH_3), 16.26 (2-CH_3), 36.76 (C-5), 46.66 (C-2), 47.22 (C-3), 55.55 (4″-CH_3), 111.58 (C-4′), 113.98 (C-3″,5″), 115.09 (C-7′), 126.19 (C-6′), 126.52 (C-5′), 128.02, 129.84, 130.73 (C-2″,6″), 130.95, 150.58 (C-2′), 164.09 (C-4″), 189.92 (C-6), 199.28 (C-1) ppm; IR: $\bar{\nu} =$ 2,800–2,636, 1,680, 1,667 cm^{-1}.

S-[2-(4-Methylphenyl)-2-oxoethyl] 3-(2-methyl-1H-benzimidazol-1-yl)butanethioate hydrobromide (**9a**, $C_{21}H_{23}BrN_2O_2S$)

Diethyl ether was added to a cooled reaction mixture until it became turbid, and the solution was decanted from the resin precipitated. Addition of diethyl ether to the cooled solution and partition from the precipitated resin was repeated until the formation of the solid precipitate, which was collected by filtration. Recrystallization from dichloromethane-diethyl ether afforded 0.69 g (31%) **9a**. M.p.: 104–106 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.80$ (d, $J = 7.0$ Hz, 3H, 3-CH_3), 2.35 (s, 3H, 4″-CH_3), 3.06 (s, 3H, 2′-CH_3), 3.30 (dd, $J = 4.0$, 16.7 Hz, 1H, 2-CH_2), 3.70 (dd, $J = 10.5$, 16.7 Hz, 1-H, 2-CH_2), 4.16 and 4.30 (AB-q, $J = 16.8$ Hz, 2H, 5-CH_2), 5.22 (m, 1H, H-3), 7.20 (m, 2H, H-3″,5″), 7.41–7.51 (m, 2H, H-5′,6′), 7.71 (m, 1H, H-7′), 7.74 (m, 2H, H-2″,6″), 7.89 (m, 1H, H-4′) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 12.36$ (2′-CH_3), 19.29 (3-CH_3), 21.53 (4″-CH_3), 36.88 (C-5), 46.58 (C-2), 53.35 (C-3), 112.73 (C-4′), 115.38 (C-7′), 125.90 (C-6′), 126.11 (C-5′), 128.28 (C-2″,6″), 128.95, 129.33 (C-3″,5″), 130.25, 132.38, 144.85 (C-4″), 150.17 (C-2′), 191.16 (C-6), 194.24 (C-1) ppm; IR: $\bar{\nu} = 2{,}800$–$2{,}518$, 1,692, 1,669 cm^{-1}.

S-[2-(4-Methoxyphenyl)-2-oxoethyl] 3-(2-methyl-1H-benzimidazol-1-yl)butanethioate hydrobromide (**9b**, $C_{21}H_{23}BrN_2O_3S$)

The compound was isolated by following the procedure described for **9a**. Recrystallization from dichloromethane afforded 1.53 g (66%) **9b**. M.p.: 118–120 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.83$ (d, $J = 7.1$ Hz, 3H, 3-CH_3), 3.10 (s, 3H, 2′-CH_3), 3.28 (dd, $J = 4.0$, 16.6 Hz, 1H, 2-CH_2), 3.71 (dd, $J = 10.5$, 16.6 Hz, 1H, 2-CH_2), 3.88 (s, 3H, 4″-CH_3), 4.18 and 4.36 (AB-q, $J = 16.7$ Hz, 2H, 5-CH_2), 5.22 (m, 1H, H-3), 6.94 (m, 2H, H-3″,5″), 7.48–7.55 (m, 2H, H-5′,6′), 7.69 (m, 1H, H-7′), 7.90 (m, 2H, H-2″,6″), 8.02 (m, 1H, H-4′) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 12.35$ (2′-CH_3), 19.38 (3-CH_3), 36.87 (C-5), 46.69 (C-2), 50.38 (C-3), 55.58 (4″-CH_3), 112.55 (C-7′), 114.04 (C-3″,5″), 115.89 (C-4′), 126.06 (C-6′), 126.35 (C-5′), 128.00, 129.00, 130.53, 130.77 (C-2″,6″), 150.26 (C-2′), 164.18 (C-4″), 189.97 (C-6), 194.31 (C-1) ppm; IR: $\bar{\nu} = 2{,}800$–$2{,}522$, 1,688, 1,672 cm^{-1}.

S-[2-Oxo-2-phenylethyl)] 3-(2-methyl-1H-benzimidazol-1-yl)butanethioate hydrobromide (**9c**, $C_{20}H_{21}BrN_2O_2S$)

The compound was isolated by following the procedure described for **9a**. Recrystallization from dichloromethane afforded 0.67 g (31%) **9c**. M.p.: 77–79 °C; ^{1}H NMR ($CDCl_3$): $\delta = 1.83$ (d, $J = 7.1$ Hz, 3H, 3-CH_3), 3.09 (s, 3H, 2′-CH_3), 3.31 (dd, $J = 4.1$, 16.6 Hz, 1H, 2-CH_2), 3.72 (dd, $J = 10.5$, 16.6 Hz, 1H, 2-CH_2), 4.22 and 4.38 (AB-q, $J = 16.9$ Hz, 2H, 5-CH_2), 5.23 (m, 1H, H-3), 7.43–7.53 (m, 4H, H-5′,6′,3″,5″), 7.70 (m, 1H, H-7′), 7.90 (m, 2H, H-2″,6″), 7.97 (m, 1H, H-4′) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 12.42$ (2′-CH_3), 19.37 (3-CH_3), 37.11 (C-5), 46.70 (C-2), 50.42 (C-3), 112.61 (C-7′), 115.77 (C-4′), 126.03 (C-6′), 126.30 (C-5′), 128.31 (2C), 128.82 (2C), 129.03, 130.50, 133.99 (C-4″), 134.98 (C), 150.27 (C-2′), 191.61 (C-6), 194.21 (C-1) ppm; IR: $\bar{\nu} = 2{,}800$–$2{,}525$, 1,697, 1,681 cm^{-1}.

S-[2-(4-Methylphenyl)-2-oxoethyl] 3-(2-methyl-1H-benzimidazol-1-yl)-3-phenylpropanethioate hydrobromide (**10a**, $C_{26}H_{25}BrN_2O_2S$)

The compound was isolated by following the procedure described for **9a**. Recrystallization from ethyl acetate afforded 0.89 g (35%) **10a**. M.p.: 127–129 °C; ^{1}H NMR ($CDCl_3$): $\delta = 2.41$ (s, 3H, 4″-CH_3), 3.15 (s, 3H, 2′-CH_3), 3.82–4.02 (m, 2H, 2-CH_2), 4.23 and 4.41 (br AB-q, 2H, 5-CH_2), 6.31 (m, 1H, H-3), 7.17–7.47 (m, 8H, arom), 7.83 (m, 2H, H-2″,6″), 8.00 (m, 1H, H-4′) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.14$ (2′-CH_3), 21.74 (4″-CH_3), 37.56 (C-5), 44.47 (C-2), 55.81 (C-3), 112.90 (C-7′), 115.99 (C-4′), 126.08 (C-2‴,6‴), 126.20 (C-6′), 126.50 (C-5′), 128.57 (C-2″,6″), 129.50, 129.58 (C-3″,5″), 129.68, 129.80 (C-3‴,5‴), 130.60, 132.47, 133.72, 145.16 (C-4″), 150.93 (C-2′), 190.92 (C-6), 194.26 (C-1) ppm; IR: $\bar{\nu} = 2{,}800$–$2{,}513$, 1,691, 1,676 cm^{-1}.

The resin partitioned after isolation of **10a** was kept in a refrigerator. After long standing (for 7–10 days), crystals were formed. The crystals were taken up with cold acetone, collected by filtration, and recrystallized from dioxane to yield 0.15 g (11%) 5-acetyl-1,3,4,5-tetrahydro-4-phenyl-2*H*-1,5-benzodiazepin-2-one (**11**); m.p.: 198–200 °C (Ref. [6] 200–202 °C). A mixed sample with authentic compound **11** did not show depression of the melting point.

S-[2-(4-Methoxyphenyl)-2-oxoethyl] 3-(2-methyl-1H-benzimidazol-1-yl)-3-phenylpropanethioate hydrobromide (**10b**, $C_{26}H_{25}BrN_2O_3S$)

The compound was isolated by following the procedure described for **9a**. Recrystallization from ethyl acetate afforded 0.81 g (31%) **10b**. M.p.: 106–108 °C; ^{1}H NMR ($CDCl_3$): $\delta = 3.16$ (s, 3H, 2′-CH_3), 3.88 (s, 3H, 4″-CH_3), 3.88 (dd, $J = 4.6$, 16.3 Hz, 1H, 2-CH_2), 4.00 (dd, $J = 10.5$, 16.3 Hz, 1H, 2-CH_2), 4.23 and 4.38 (AB-q, $J = 16.7$ Hz, 2H, 5-CH_2), 6.33 (dd, $J = 4.6$, 10.5 Hz, 1H, H-3), 6.94 (m, 2H, H-3″,5″), 7.18–7.22 (m, 2H, arom), 7.28 (m, 1H, arom), 7.34–7.50 (m, 5H, arom), 7.92 (m, 2H, H-2″,6″), 8.00 (m, 1H, H-4′) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 12.40$ (2′-CH_3), 37.02 (C-5), 44.18 (C-2), 55.55 (C-3), 55.76 (4″-CH_3), 112.85 (C-7′), 114.03 (C-3″,5″), 115.68 (C-4′), 125.94 (C-2‴,6‴), 126.11 (C-5′), 126.42 (C-6′), 127.95 (C-4′), 129.45, 129.53 (C-4), 129.66 (C-3‴,5‴), 130.37, 130.77 (C-2″,6″), 133.71, 150.91 (C-2′), 164.17 (C-4″), 189.81 (C-6), 194.32 (C-1) ppm; IR: $\bar{\nu} = 2{,}800$–$2{,}518$, 1,679, 1,662 cm^{-1}.

Analogously, compound **11** was isolated from the partitioned resin by following the procedure described for **10a** in 0.18 g (13%) yield.

S-(2-Oxo-2-phenylethyl) 3-(2-methyl-1H-benzimidazol-1-yl)-3-phenylpropanethioate hydrobromide (**10c**, $C_{25}H_{23}BrN_2O_2S$)

The compound was isolated by following the procedure described for **9a**. Recrystallization from acetone afforded 0.62 g (25%) **10c**. M.p.: 147–150 °C; ^{1}H NMR ($CDCl_3$): $\delta = 3.15$ (s, 3H, 2′-CH_3), 3.87 (dd, $J = 4.5$, 16.2 Hz, 1H, 2-CH_2), 3.99 (dd, $J = 10.5$, 16.3 Hz, 1H, 2-CH_2), 4.27 and 4.44 (AB-q, $J = 17.0$ Hz, 2H, 5-CH_2), 6.25 (dd, $J = 4.6$, 10.5 Hz, 1H, H-3), 6.94 (m, 2H, H-3″,5″), 7.26 (m, 1H, arom), 7.36 (m, 1H, arom), 7.36–7.51 (m, 5H, arom), 7.62 (m, 1H, arom), 7.94 (m, 2H, H-2″,6″), 8.01 (m, 1H, H-4′) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 12.44$ (2′-CH_3), 37.37 (C-5), 44.24 (C-2), 55.70 (C-3), 112.79 (C-7′), 115.87 (C-4′), 125.91 (2C), 126.10 (C-5′), 126.41 (C-6′), 128.38 (2C), 128.88 (2C), 129.51 (C), 129.58 (CH), 129.71 (2C), 130.64 (C), 133.74 (C), 134.08 (CH), 134.97, 150.91 (C-2′), 191.35 (C-6), 194.18 (C-1) ppm; IR: $\bar{\nu} = 2{,}800$–$2{,}512$, 1,698, 1,677 cm^{-1}.

Analogously, compound **11** was isolated from the partitioned resin by following the procedure described for **10a** in 0.21 g (15%) yield.

S-[2-(4-Methylphenyl)-2-oxoethyl] 3-(2-methyl-1H-benzimidazol-1-yl)propanethioate hydrobromide (**13a**, $C_{20}H_{21}BrN_2O_2S$)

The compound was isolated by following the procedure described for **9a**. Recrystallization from chloroform afforded 1.10 g (51%) **13a**. M.p.: 98–100 °C; ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3H, 4″-CH_3), 3.08 (s, 3H, 2′-CH_3), 3.37 (br t, 2H, 2-CH_2), 4.35 (s, 3H, 5-CH_2), 4.73 (br t, 2H, 3-CH_2), 7.28 (m, 2H, H-3″,5″), 7.49 (m, 1H, H-5′), 7.52 (m, 1H, H-6′), 7.63 (m, 1H, H-7′), 7.84 (m, 2H, H-2″,6″), 7.89 (m, 1H, H-4′) ppm; ^{13}C NMR ($CDCl_3$): δ = 12.05 (2′-CH_3), 21.69 (4″-CH_3), 37.04 (C-5), 40.66 (C-2), 41.15 (C-3), 111.42 (C-7′), 115.23 (C-4′), 126.29 (C-6′), 126.63 (C-5′), 128.49 (C-2″,6″), 129.54 (C-3″,5″), 129.93, 130.71, 132.65, 145.11 (C-4″), 150.69 (C-2′), 191.33 (C-6), 194.64 (C-1) ppm; IR: $\bar{\nu}$ = 2,800–2,556, 1,698, 1,686 cm^{-1}.

S-[2-(4-Methoxyphenyl)-2-oxoethyl] 3-(2-methyl-1H-benzimidazol-1-yl)propanethioate hydrobromide (**13b**, $C_{20}H_{21}BrN_2O_3S$)

The compound was isolated by following the procedure described for **9a**. Recrystallization from chloroform afforded 1.11 g (49%) **13b**. M.p.: 179–181 °C; ^{1}H NMR ($CDCl_3$): δ = 3.08 (s, 3H, 2′-CH_3), 3.36 (br t, 2H, 2-CH_2), 3.89 (s, 3H, 4″-CH_3), 4.34 (s, 3H, 5-CH_2), 4.71 (br t, 2H, 3-CH_2), 6.96 (m, 2H, H-3″,5″), 7.47–7.56 (m, 2H, H-5′,6′), 7.61 (m, 1H, H-7′), 7.91 (m, 1H, H-4′), 7.93 (m, 2H, H-2″,6″) ppm; ^{13}C NMR ($CDCl_3$): δ = 12.01 (2′-CH_3), 36.87 (C-5), 40.57 (CH_2), 41.06 (CH_2), 55.60 (4″-CH_3), 111.27 (C-7′), 114.08 (C-3″,5″), 115.39 (C-4′), 126.33 (C-6′), 126.69 (C-5′), 128.08, 129.98, 130.64, 130.82 (C-2″,6″), 150.66 (C-2′), 164.23 (C-4″), 190.11 (C-6), 194.65 (C-1) ppm; IR: $\bar{\nu}$ = 2,800–2,526, 1,691, 1,677 cm^{-1}.

6-Formyl-5,6-dihydro-4-methyl-1-(4-methylphenyl)-4H-[1,3]thiazolo[3,2-a][1,5]benzodiazepin-11-ium bromide (**14a**, $C_{20}H_{19}BrN_2OS$)

The compound was isolated by following the procedure described for **7a**. Recrystallization from methanol-diethyl ether afforded 0.69 g (33%) **14a**. M.p.: 243–245 °C; ^{1}H NMR (CD_3OD, two rotamers in a ratio of 60:40): δ = [1.72 (d, J = 5.6 Hz, 3H, 4-CH_3)], 1.74 (d, J = 6.4 Hz, 3H, 4-CH_3), [2.39 (s, 3H, 4′-CH_3)], 2.40 (s, 3H, 4′-CH_3), [3.70 (m, 1H, H-4)], 3.77 (m, 1H, H-4), 3.95 (dd, J = 5.8, 12.4 Hz, 1H, 5-CH_2), [4.30 (dd, J = 7.2, 12.2 Hz, 1H, 5-CH_2)], [4.38 (t, J = 12.1 Hz, 1H, 5-CH_2)], 4.56 (t, J = 12.1 Hz, 1H, 5-CH_2), 7.07–7.78 (m, 8H, arom), 8.33 (s, 1H, H-2), [8.34 (s, 1H, H-2)], [8.39 (s, 1H, H-6)], 8.53 (s, 1H, H-6) ppm; ^{13}C NMR (CD_3OD, two rotamers in a ratio of 60:40): δ = [14.33 (4-CH_3)], 14.81 (4-CH_3), 21.43 (4′-CH_3), 36.47 (C-4), [36.52 (C-4)], 56.95 (C-5), [59.75 (C-5)], 121.58, [121.66, 125.72], 125.77, [128.73], 129.34, 130.43, 130.62, 130.82 (2C), 130.86, 130.95 (3C), 131.94, [132.49], 133.53, 133.85, 134.01, [134.89, 135.26], 135.70, [142.82 (C-4′)], 142.85 (C-4′), 150.91 (C-1), [150.99 (C-1)], 164.22 (C-6), [165.10 (C-6), 180.14 (C-3a)], 180.99 (C-3a) ppm; IR: $\bar{\nu}$ = 1,682 cm^{-1}.

3-(1H-Benzimidazol-1-yl)propanoic acid hydrobromide (**15a**, $C_{10}H_{11}BrN_2O_2$)

The compound was isolated by following the procedure described for **7a**. Recrystallization from methanol-diethyl ether afforded 0.34 g (27%) **15a**. M.p.: 212–214 °C; ^{1}H NMR (CD_3OD): δ = 3.11 (t, J = 6.3 Hz, 2H, 2-CH_2), 4.86 (t, J = 6.3 Hz, 2H, 3-CH_2), 7.68–7.75 (m, 2H, H-5′,6′), 7.90 (m, 1H, arom), 8.05 (m, 1H, arom), 9.55 (s, 1H, H-2′) ppm; ^{13}C NMR (CD_3OD): δ = 33.67, 44.10, 114.26, 115.85, 127.98, 128.30, 132.19, 132.35, 142.85 (C-2′), 173.58 (C-1) ppm.

S-[2-(4-Methylphenyl)-2-oxoethyl] 3-(1H-benzimidazol-1-yl)propanethioate hydrobromide (**16a**, $C_{19}H_{19}BrN_2O_2S$)

The compound was isolated by following the procedure described for **8a**. Recrystallization from dichloroethane-diethyl ether afforded 0.63 g (30%) **16a**. M.p.: 90–92 °C; ^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3H, 4″-CH_3), 3.52 (br t, 2H, 2-CH_2), 4.34 (s, 3H, 5-CH_2), 4.99 (br t, 2H, 3-CH_2), 7.23 (m, 2H, H-3″,5″), 7.48–7.57 (m, 2H, H-5′,6′), 7.71 (m, 1H, H-7′), 7.80 (m, 1H, H-2″,6″), 8.00 (m, 1H, H-4′), 10.09 (s, 1H, H-2′) ppm; ^{13}C NMR ($CDCl_3$): δ = = 21.67 (4″-CH_3), 36.92 (5-CH_2), 42.38 (2-CH_2), 42.55 (3-CH_2), 112.15 (C-7′), 115.82 (C-4′), 126.71 (C-6′), 126.94 (C-5′), 128.50 (C-2″,6″), 129.44 (C-3″,5″), 130.44, 130.66, 132.66, 140.78 (C-2′), 144.90 (C-4″), 191.81 (C-6), 195.04 (C-1) ppm; IR: $\bar{\nu}$ = 2,800–2,608, 1,692, 1,676 cm^{-1}.

6-Acetyl-5,6-dihydro-5-phenyl-4H-[1,3]thiazolo[3,2-d][1,5]benzodiazepin-11-ium bromide (**12**, $C_{19}H_{17}BrN_2OS$)

The reaction of 2.96 g benzodiazepine-2-thione **3** (10 mmol) with 5 cm^3 α-bromoacetaldehyde diethylacetal (32 mmol) was performed according to the general procedure described in [2] and yielded 2.56 g (64%) **12**. M.p.: 245–248 °C (methanol-diethyl ether); ^{1}H NMR (CD_3OD): δ = 1.79 (s, 3H, 6-CH_3), 3.57 (dd, J = 13.0, 14.9 Hz, 1H, CH_2), 4.31 (dd, J = 5.4, 14.9 Hz, 1H, CH_2), 6.48 (dd, J = 5.3, 13.0 Hz, 1H, CH), 7.36–7.61 (m, 5H, arom), 7.60 (dd, J = 1.6, 7.7 Hz, 1H, H-7), 7.85 (dt, J = 1.6, 7.7 Hz, 1H, H-8), 7.92 (dt, J = 1.6, 7.7 Hz, 1H, H-9), 8.04 (dd, J = 1.6, 7.9 Hz, 1H, H-10), 8.44 (d, J = 4.0 Hz, 1H, H-2), 8.87 (d, J = 4.0 Hz, 1H, H-1) ppm; ^{13}C NMR (CD_3OD): δ = 23.14 (C-6), 33.61 (C-4), 66.28 (C-5), 126.04, 127.14, 128.14 (2C), 129.83, 129.97 (2C), 132.43, 133.93, 134.10,

134,65, 135.49, 137.99, 139.61, 172.29, 172.54 ppm; IR: $\bar{\nu}$ = 1,668, 1,660 cm^{-1}.

5-Acetyl-1,3,4,5-tetrahydro-4-phenyl-2H-1,5-benzodiazepine-2-thione (**3**, $C_{17}H_{16}N_2OS$)
Acetylation of 2.54 g 2,3,4,5-tetrahydro-4-phenyl-2*H*-1,5-benzodiazepine-2-thione (10 mmol) [5] with 1.5 cm^3 acetic anhydride (15 mmol) and work-up were conducted using a procedure from [4]. Yield 2.1 g (71%) **3**. M.p.: 226–228 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$): δ = 1.78 (s, 3H, CH_3), 3.20 (t, J = 13.0 Hz, 1H, CH_2), 3.29 (ddd, J = 1.3, 4.9, 12.9 Hz, 1H, CH_2), 6.33 (dd, J = 5.0, 13.0 Hz, 1H, CH_2), 7.18 (dd, J = 1.3, 7.8 Hz, 1H, arom), 7.28–7.32 (m, 6H, arom), 7.36 (dd, J = 1.5, 7.8 Hz, 1H, arom), 7.49 (dt, J = 1.4, 7.7 Hz, 1H, arom), 10.45 (br s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 23.15 (CH_3), 47.78 (CH_2), 63.74 (CH), 122.62, 126.63 (C-2″,6″), 127.68, 128.00, 128.59 (C-3″,5″), 129.60, 131.55, 133.63, 136.37, 139.87, 170.09 (CO), 203.36 (CS) ppm; IR: $\bar{\nu}$ = 3,300, 3,149, 1,658 cm^{-1}.

References

1. Di Braccio M, Grossi G, Roma G, Vargiu L, Mura M, Marongiu ME (2001) Eur J Med Chem 36:935
2. Janciene R, Vektariene A, Stumbreviciute Z, Kosychova L, Klimavicius A, Puodziunaite BD (2004) Heteroat Chem 15:363
3. Janciene R, Stumbreviciute Z, Podeniene D, Puodziunaite BD, Black S, Husbands SM (2006) J Heterocycl Chem 43:979
4. Janciene R, Stumbreviciute Z, Vektariene A, Kosychova L, Sirutkaitis R, Palaima A, Staniulyte Z, Puodziunaite BD (2008) Heteroat Chem 19:72
5. Janciene R, Kosychova L, Bukelskiene V, Domkus V, Stumbreviciute Z, Ragaleviciene V, Puodziunaite B (2002) Arzneim Forsch 52:475
6. For reviews see: Krapcho J, Turk CF (1967) US Patent 3321468; (1968) Chem Abstr 68:21970
7. Puodzhyunaite BA, Yanchene RA, Stumbryavichyute ZA (1988) Chem Heterocycl Compd 24:786
8. Okujama T, Kunugiza KT (1974) Bull Chem Soc Jpn 47:1267
9. Jursic BS (1998) J Mol Struct (Theochem) 427:165
10. Jursic BS (1996) Can J Chem 74:114
11. Nathaniel R, Mineva T, Nikolova R, Bojilova A (2006) Int J Quantum Chem 106:1357
12. Jursic BS, Zdravskovski Z (1995) Int J Quantum Chem 54:161
13. Ehresmann B, Martin B, Horn AHC, Clark T (2003) J Mol Model 9:342
14. Vektariene A, Vektaris G, Svoboda J (2009) Arkivoc vii:311
15. Fayet G, Rotureau P, Joubert L, Adamo C (2010) J Mol Model 16:805
16. Khandogin J, York DM (2004) Proteins: Struct, Funct, Bioinf 56:724
17. Chirlian LE, Francl MM (1987) J Comput Chem 8:894
18. Spartan'06, Wavefunction Inc, Irvine, CA. In: Shao Y, Molnar LF, Jung Y, Kussmann J, Ochsenfeld C, Brown ST, Gilbert ATB, Slipchenko LV, Levchenko SV, O'Neill DP, DiStasio Jr RA, Lochan RC, Wang T, Beran GJO, Besley NA, Herbert JM, Lin CY, Van Voorhis T, Chien SH, Sodt A, Steele RP, Rassolov VA, Maslen PE, Korambath PP, Adamson RD, Austin B, Baker J, Byrd EFC, Dachsel H, Doerksen RJ, Dreuw A, Dunietz BD, Dutoi AD, Furlani TR, Gwaltney SR, Heyden A, Hirata S, Hsu C-P, Kedziora G, Khalliulin RZ, Klunzinger P, Lee AM, Lee MS, Liang WZ, Lotan I, Nair N, Peters B, Proynov EI, Pieniazek PA, Rhee YM, Ritchie J, Rosta E, Sherrill CD, Simmonett AC, Subotnik JE, Woodcock III HL, Zhang W, Bell AT, Chakraborty AK, Chipman DM, Keil FJ, Warshel A, Hehre WJ, Schaefer HF, Kong J, Krylov AI, Gill PMW, Head-Gordon M (2006) Phys Chem Chem Phys 8:3172
19. Parr RG, Yang W (1989) Functional Theory of Atoms and Molecules. Oxford University Press, New York
20. Schmidt MW, Baldridge KK, Boatz JA, Elbert ST, Gordon MS, Jensen JH, Koseki S, Matsunaga N, Nguyen KA, Su SJ, Windus TL, Dupuis M, Montgomery JA (1993) J Comput Chem 14:1347
21. Parr RG, Yang W (1984) J Am Chem Soc 106:4049
22. Ayres PW, Parr RG (2000) J Am Chem Soc 122:2010