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Tetrahedron
Tetrahedron 61 (2005) 7294–7303

A comparison of ring-chain tautomerism in heterocycles derived from 2-aminobenzenesulfonamide and anthranilamide

Olga A. Maloshitskaya,[a] Jari Sinkkonen,[a] Valery V. Alekseyev,[b] Kirill N. Zelenin[b] and Kalevi Pihlaja[a,*]

[a]*Department of Chemistry, Structural Chemistry Group, University of Turku, FI-20014 Turku, Finland*
[b]*Russian Military Medical Academy, 194044 St. Petersburg, Russian Federation*

Received 1 February 2005; revised 11 April 2005; accepted 28 April 2005

Available online 13 June 2005

Dedicated to the Memory of the late Professor Kirill N. Zelenin

Abstract—A number of anthranilamide and 2-aminobenzenesulfonamide derivatives with aromatic aldehydes and 1,3-dicarbonyl compounds were synthesized. Substituted benzaldehyde derivatives of neither aminoamides showed tautomerism in solutions. Reaction products of 2-aminobenzenesulfonamide with *p*-substituted benzoylacetic aldehydes and *p*-substituted benzoylacetones undergo ring-chain tautomerism with a good linear correlation between the ring-chain equilibrium constants (log K, where $K=$[ring]/[chain]) and the Hammett–Brown σ^+ parameters of the aromatic substituents. The equilibrium constant was measured for the reaction products of 2-aminobenzenesulfonamide with unsubstituted benzoylacetaldehyde at several temperatures which enabled the enthalpy and entropy of this reaction to be evaluated.

1. Introduction

Ring-chain tautomerism of 1,3-*N*,*N* heterocycles is currently drawing considerable attention.[1–3] Tautomeric equilibria have been described in the simplest six-membered 1,3-*N*,*N* heterocycles, 2-arylhexahydropyrimidines,[4] as well as in more complex systems which contain this structural sub-unit, such as monocyclic 2-aryl-4-methylhexahydropyrimidines,[2] *N*-alkyl-2-aryl hexahydropyrimidines[5] and condensed heterocycles. In the latter case, the hexahydropyrimidine moiety was condensed to a saturated cycloalkane (2-aryldecahydroquinazolines[6]) or to a benzo ring (2-aryltetrahydroquinazolines[3,5]). Aryl groups at C-2 were in above cases *para*-substituted phenyls (ArX). It is known that the equilibrium constants ($K_x=$[ring]/[chain]) for ring-chain equilibria depend on the electronic properties of substituents X as described by the Hammett–Brown constants σ^+: $\log K_x=\rho\sigma^+ +\log K_H$.

Variations of structural factors other than substituents X on the aryl ring can also influence the ring-chain equilibria in heterocyclic systems. An interesting case of ring-chain tautomerism of imines derived from a 1,3-diamine (2-aminomethylaniline) and β-dicarbonyl compounds has been reported.[7,8] It was shown that their linear (open-chain) tautomers were relatively more stable than the analogous imines obtained from monocarbonyl compounds. This was explained by conjugation between the imine and carbonyl double bonds in β-dicarbonyl derivatives.

In general, the greater the proportion of the enol tautomer in the starting β-dicarbonyl compound, the more stable is the enamine tautomer of its imino derivative.[9] In the case of imines derived from 1,3-diamines and β-dicarbonyl compounds, the enamine form corresponds to the linear (open-chain) tautomer. Moreover, ring-chain tautomeric equilibria of β-dicarbonyl derivatives containing a *para*-substituted phenyl ring (e.g., benzoylacetic aldehyde and benzoylacetone derivatives) also correlate with the σ^+ constants of the aryl substituents.[10]

Thus, molecular design of ring-chain tautomeric systems based on 1,3-*N*,*N*-heterocycles obtained from 1,3-diamines consists of variations both in the amine component (substitutions and ring fusions) and the carbonyl component (mono- vs. β-dicarbonyl compounds).

Imines derived from 2-aminobenzenesulfonamide and anthranilamide resemble structurally compounds discussed

Keywords: Ring-chain tautomerism; Anthranylamide; 2-Aminobenzenesulfonamide; 1,3-Dicarbonyl compounds.
* Corresponding author. Tel./fax: +358-2-3336750; e-mail: kpihlaja@utu.fi

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doi:10.1016/j.tet.2005.04.074

above. It remains to be proved, whether the ring-chain tautomerism is possible after replacing the conformationally labile –CH_2NH– fragment in 1,3-diamine derivatives with structurally more rigid amide or sulfonamide moiety. There are a few publications reporting both cyclic and open-chain tautomers for the condensation products of anthranilamide with substituted benzaldehydes.[11–14] The cyclization of linear isomers was reported to occur upon heating or acidification, but the possibility of reversible cyclization has not been previously studied, although ring-chain tautomerism has been observed in structurally related systems.[3]

The possibility of ring-chain tautomerism in 2-aminobenzenesulfonamide derivatives leading to benzo-1,2,4-thiadiazines is of considerable practical importance because many benzenesulfonamide derivatives and thiadiazines are known to possess pharmacological activity.[15,16] So far, only a few cyclic products derived from 2-aminobenzenesulfonamide and carbonyl compounds have been described in the literature.[15]

2. Results and discussion

Structures of all substances were determined by NMR spectra measured in DMSO-d_6. Tautomeric equilibria were considered as being reached when the ratio of tautomers did not change over five days (at room temperature) or in 2 h (at 80 °C) from the previous determination. Chemical shifts were assigned, in addition to the information from basic proton and carbon spectra, using gradient-selected DQF-COSY, HSQC, and HMBC (see Section 4).

2.1. Reaction of anthranilamide and 2-aminobenzenesulfonamide with aromatic aldehydes

We found that reaction products **4** derived from anthranilamide (Scheme 1) undergo irreversible cyclization to derivatives **5** regardless of the electronic properties of substituents R. Note that the latter are energetically more stable according to semiempirical MNDO calculations.[13] Contrary to what has been reported,[13] we found that melting a mixture of solid anthranilamide with *p*-nitrobenzaldehyde for 10 min initially affords the linear product **4a** (tlc control), which cyclized giving **5a** upon recrystallization from ethanol. Similar effects of recrystallization have been described previously.[12] Alternatively, cyclization of **4a** into **5a** can be achieved by heating its DMSO solution to 80 °C for 3 h. Under these conditions, however, the rate of cyclization seems to depend on the electronic properties of substituents R. Thus, the previously unknown compound **4b** (R = NMe_2) was stable in DMSO at 80 °C and cyclized only in the presence of traces of trifluoroacetic acid.

Only cyclic products **6** could be obtained from the reaction of 2-aminobenzenesulfonamide with substituted benzaldehydes (Scheme 1). The electronic properties of substituents R had no effect on the course of this reaction. Even the salicylaldehyde derivative **6c**, in which the ring form is sterically hindered by the *ortho* substitution, did not show a trace of the open-chain isomer.

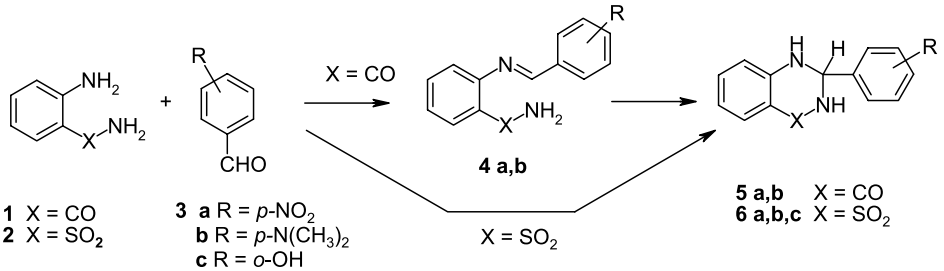
Thus, ring-chain tautomerism could not be observed in the reaction products of substituted benzaldehydes with either anthranilamide or 2-aminobenzenesulfonamide.

2.2. Reactions of anthranilamide and 2-aminobenzenesulfonamide with β-dicarbonyl compounds

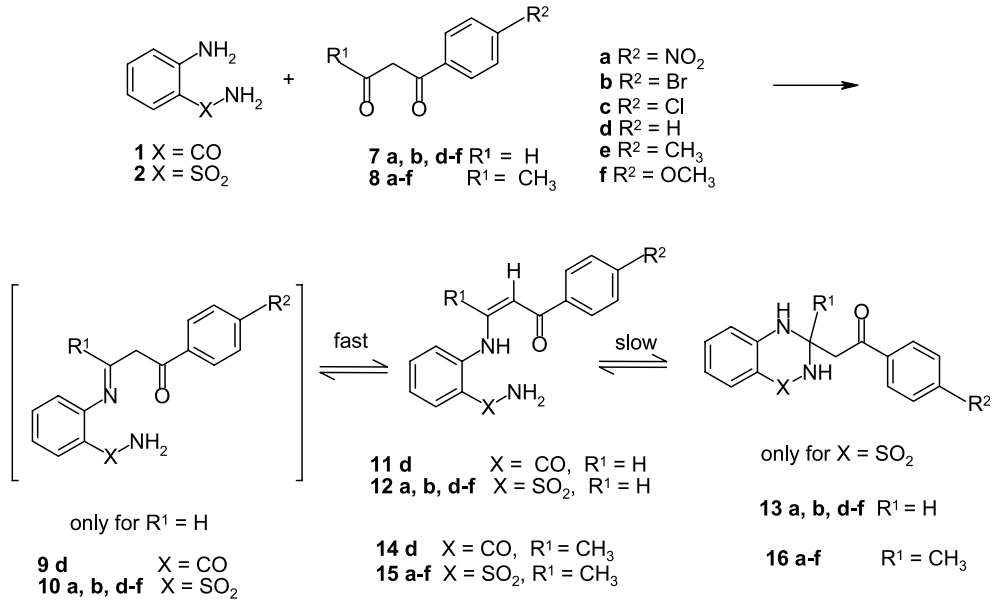
2.2.1. Reactions with *p*-substituted benzoylacetic aldehydes. Anthranilamide and 2-aminobenzenesulfonamide reacted with the title compounds as shown in Scheme 2 (R^1 = H). Reaction products **11** and **12** precipitated from methanolic solutions. In DMSO solutions they exist exclusively in the linear form (as a 10:1 mixture of *Z*- and *E*-isomers, as follows from the observed CH=CH coupling constants, J = 8.0 Hz for *Z*- and J = 12.4 Hz for *E*-isomer). The predominance of the *Z*-isomer can be explained by the hydrogen bonding between NH proton and C=O carbonyl oxygen (Scheme 2). The share of *E*-isomer reversibly increased upon heating the solutions of both **11** and **12**. This reversible *E*–*Z* isomerization indicates a tautomeric equilibrium between *Z*- and *E*-isomers, which is possible via the ketimine structures **9** and **10**, respectively. The ketimine structures are present in the equilibrium mixture at a negligibly low concentration.

A difference in the chemical behaviour between anthranilamide and 2-aminobenzenesulfonamide derivatives became apparent when they were left standing in solutions. No cyclization occurs in solutions of anthranilamide derivative **11**. Contrary, when solutions of **12** were left at room temperature, the transformation into the cyclic form **13** gradually happened, and the ring-chain equilibria were reached in few months (Scheme 2). The equilibria can be reached in 2–3 weeks if solutions are acidified with traces of trifluoroacetic acid, or in 1–2 days by heating solutions without acidification.

Compositions of the equilibrium mixtures obtained by heating the unsubstituted benzoylacetaldehyde derivative **12d** in DMSO-d_6 at different temperatures are shown in



Scheme 1.



Scheme 2.

Table 1 (K_{equil}=[ring]/[$E+Z$ chains]). Using $\Delta G=-RT\ln K$ ($=\Delta H-T\Delta S$), a very good linear correlation follows:

$$\Delta G[\mathrm{J\ mol^{-1}}] = (22.7\ \mathrm{K^{-1}} \pm 0.9\ \mathrm{K^{-1}})T - (9.9 \pm 0.3)10^3, \quad r = 0.997. \tag{1}$$

In other words the enthalpy $\Delta H=-(9.9\pm0.4)$ kJ mol^{-1} and the entropy $\Delta S=-(22.7\pm0.9)$ J mol^{-1} K^{-1} for the tautomerization between **12d** and **13d**.

Compositions of tautomeric mixtures **12**⇌**13** (Table 2) equilibrated in DMSO at 80 °C (Eq. 2) or upon acidification with traces of trifluoroacetic acid at 22 °C (Eq. 3) showed a good linear correlation with the σ^+ substituent constants:

$$\log K = -(0.41 \pm 0.06)\sigma^+ + (0.19 \pm 0.03), \quad r = 0.970(\mathrm{DMSO}, 80\ ^\circ\mathrm{C}). \tag{2}$$

$$\log K = -(0.52 \pm 0.07)\sigma^+ + (0.47 \pm 0.04), \quad r = 0.974(\mathrm{DMSO + TFA},\ 22\ ^\circ\mathrm{C}) \tag{3}$$

Table 2. Tautomeric equilibrium constants for substituted **12a**,**b**,**d–f**⇌**13a**,**b**,**d–f** and **15a–f**⇌**16a–f**

R	σ^+	K_{equil} for **12**⇌**13**, DMSO-d_6		K_{equil} for **15**⇌**16**, DMSO-d_6; 22 °C
		22 °C	80 °C	
NO_2	0.79	0.99	0.66	0.06
Br	0.15	2.39	1.29	0.16
Cl	0.11	—	—	0.16
H	0	3.64	1.92	0.24
CH_3	−0.31	4.69	2.19	0.33
OCH_3	−0.78	6.29	2.86	0.48

K_{equil}=[13]/[12, $E+Z$].

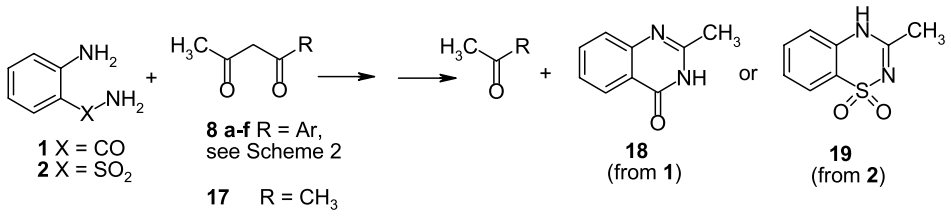
Yields and melting points of compounds **12a**,**b**,**d–f** are presented in Table 3, NMR data of *Z*-**12a**,**b**,**d–f** in Tables 4 and 5, NMR data of *E*-**12a**,**b**,**d–f** in Table 6, and NMR data of **13a**,**b**,**d–f** in Tables 7 and 8.

2.2.2. Reactions with β-diketones. *Reactions with acetylacetone* (Scheme 3). It has been reported previously[13] that the condensation of anthranilamide with acetylacetone resulted in the formation of compound **18** due to loss of an acetone molecule (Scheme 3). When repeating this experiment, we also discovered in the reaction mixture a condensation product of anthranilamide with acetone which shows a fast decomposition of the intermediate product. Acetylacetone reacted with 2-aminobenzenesulfonamide in a similar manner to form compound **19**. Its structure is confirmed by presence of only one methyl group and by absence of CO signal in carbon spectra. Spectral characteristics of **19** were identical to those published earlier.

Table 1. Temperature dependence of equilibrium constants for tautomeric equilibrium between **12d** and **13d** in DMSO-d_6

T, K	295	329	348	363	393	420
K_{equil}	3.64	2.47	1.91	1.79	1.35	1.09

K_{equil}=[**13d**]/[**12d**, $E+Z$].



Scheme 3.

According to the literature,[17] benzothiadiazine **19**, obtained by a different way, exists as the 4*H*-, and not 2*H*-isomer.

Reactions with p-substituted benzoylacetones (Scheme 2, $R^1=CH_3$). The condensation product of anthranilamide with benzoylacetone is exclusively an open-chain *Z*-enamine **14d**. When dissolved in DMSO, this compound decomposes on heating (in a few hours) or on acidification with traces of trifluoroacetic acid (in a week) to form acetophenone and compound **18** (Scheme 3). The same decomposition product **18** is obtained in reaction of anthranilamide with acetylacetone. No signals could be observed for the cyclic isomer of **14d**.

Similarly, when 2-benzenesulfonamide reacted with various substituted benzoylacetones in methanol, the products **15a–f** precipitated from the solutions. In DMSO-d_6 solutions they exist as open-chain *Z*-enamines (for yields and melting points, see Table 3). The *Z*-configuration of the products was confirmed by NOESY spectra, which showed the CH_3-group and the CH-proton to be close in space (measured for **15d**). In DMSO-d_6 solutions of **15**, however, ring-chain tautomeric equilibria **15** ⇌ **16** (Scheme 2) slowly evolved either at room temperature (during several months) or at 80 °C (during several hours), but unfortunately decomposition accompanied the tautomerization (Scheme 3). Decomposition product is the same as was obtained in reaction with acetylacetone. By acidification of DMSO solutions of **15** with traces of TFA, ring-chain tautomeric equilibria were reached at room temperature in a few days (similarly to compounds **12**) without considerable decomposition. Additional precautions were taken against possible hydrolysis by using dried DMSO and storing NMR tubes in a desiccator. When measures were taken against decomposition and hydrolysis, a reasonable linear dependence of the ring-chain equilibrium constants against Hammett σ^+ was observed (see Table 2 and Eq. 4).

$$\log K = -(0.59\pm0.06)\sigma^+ - (0.71\pm0.03), \quad r = 0.982 \tag{4}$$

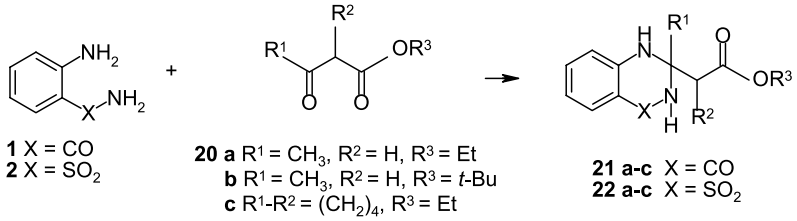
NMR data of **15a–f** are given in Tables 9 and 10, and that of **16a–e** in Tables 11–13.

It was suggested previously[8] that the relative stabilities of ring and chain forms in structurally similar ring-chain tautomeric systems can be compared by measuring the intercepts c of their ($\log K$ vs. σ^+) lines. Thus, the tautomeric ring forms **16** of the benzoylacetone derivatives ($c=-0.71$, Eq. 4) are relatively less stable than the tautomeric ring forms **13** ($c=+0.47$, Eq. 3) of the benzoylacetaldehyde derivatives under the same conditions (room temperature, traces of trifluoroacetic acid).

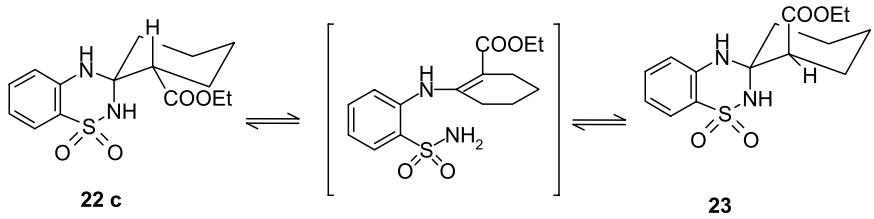
2.2.3. Reactions with β-ketoacid esters. Both anthranilamide and 2-benzenesulfonamide when reacting with β-ketoesters formed only cyclic products. The structure of compound **22a** has already been proved.[13] Cyclic isomers of condensation products of anthranilamide with ethyl acetoacetate are thought to be more stable than linear forms based on semiempirical MNDO calculations.[13] We proved that compound **22b** is also cyclic (Scheme 4).

Anthranilamide reacted with 2-carbethoxycyclohexanone **20c** to form two spirocyclic diastereomers in a 3:1 ratio. The diastereomer ratio is constant with time. The chair-conformation of the cyclohexane ring is confirmed by NOESY spectra. From ^{1}H NMR data it follows that the predominant stereoisomer has an axially oriented carbethoxy group and an equatorial H-2 (no diaxial H,H-coupling constants were observed in the H-2 multiplet, the largest constant being only 5 Hz). The axial orientation of the bulky COOEt substituent may be explained by formation of intramolecular hydrogen bonds.

Reaction of 2-benzenesulfonamide with acetoacetic esters has been previously studied,[18] and a ketoimine structure similar to **10** (Scheme 2) was erroneously assigned to the reaction products based on the IR spectra. We discovered that acetoacetic ester derivatives **22a**,**b** have cyclic structures, and no open-chain isomers were formed with time. The 2-carbethoxycyclohexanone derivative **22c** was obtained initially as a single diastereomer, in which the



Scheme 4.



Scheme 5.

COOEt group was equatorial and H-2 was axial (the coupling constants $J_{ax,ax}=11.0$ Hz and $J_{ax,eq}=3.5$ Hz were observed for the H-2 multiplet). The chair conformation of the cyclohexane ring is confirmed by NOESY spectra, which showed the H-2_{ax}, H-4_{ax} and H-6_{ax} to be close in space. However, a second diastereomer **23** slowly accumulated in solution, and the amounts of **22c** and **23** became equal after 1.5 months (Scheme 5). The build-up of **23** suggests a ring-(chain)-ring tautomeric interconversion via an open-chain form which is obviously present in a very low concentration, i.e. below the detection limits of NMR.

The presence of tautomerism in the 2-carbethoxycyclohexanone derivative and its absence in the acetoacetic ester derivatives agrees well with the observations made previously[9] on the imine derivatives of 1,3-ketoesters. It was shown then that the enamine forms of cyclic ketoesters are more stable than those of acetoacetic esters. In our case, the enamine form corresponds to the open-chain tautomer.

3. Conclusion

We have confirmed that the linear and cyclic forms of the reaction products from anthranilamide with various substituted benzaldehydes, which have been sporadically studied over the last decades, are indeed structural isomers, and not tautomers.

Replacement of monocarbonyl compounds with β-dicarbonyl compounds is known to stabilize the linear tautomers in various ring-chain equilibria due to double bond conjugation. It was proved that the products obtained from β-dicarbonyl compounds with anthranilamide show no signs of ring-chain tautomerism. On the other hand, ring-chain tautomerism was for the first time observed in the derivatives of 2-aminobenzenesulfonamide with β-dicarbonyl compounds. In a series of *p*-substituted benzoyl acetaldehydes and -acetones, the tautomeric equilibria depended linearly on the Hammett–Brown constants of the substituents on the 2-aryl group. To our knowledge, this is the first case of ring-chain tautomerism in aminoamide derivatives.

4. Experimental

4.1. NMR measurements

NMR-spectra were acquired using Bruker Avance 500 and 600 spectrometers (equipped with BBI-5 mm-Zgrad-ATM and BBO-5 mm-Zgrad probes) operating at 500.13 and 600.13 MHz for ^{1}H and 125.77 and 150.90 MHz for ^{13}C, respectively. Spectra were recorded at 25 °C using DMSO-d_6 and $CDCl_3$ as a solvent with a non-spinning sample in 5 mm NMR-tubes. Spectra were processed by a PC with Windows XP operating system and XWin NMR software. Proton and carbon spectra were referenced internally to TMS signal using value 0.00 ppm.

^{1}H NMR spectra and ^{13}C NMR proton-decoupled spectra were acquired with single-pulse excitation and 30° flip angle. 1 Hz exponential weighting was applied prior to Fourier transformation (in carbon spectra).

Gradient selected DQF-COSY spectra were acquired with cosygpmfqf pulse program (pulse programs refer to original ones installed by Bruker). Gradient selected NOESY spectra were acquired with noesygpph pulse program. Gradient selected ^{1}H–^{13}C HSQC spectra were acquired with hsqcetgpsisp.2 pulse program (using shaped pulses). Gradient selected ^{1}H–^{13}C HMBC spectra were acquired with hmbcgplpndqf pulse program.

4.2. General synthetic procedures

4.2.1. Reaction of anthranilamide with *p*-dimethylaminobenzaldehyde. Three millimoles of anthranilamide was dissolved in 4 ml of dry methanol and added to a solution of 3 mmol of *p*-dimethylaminobenzaldehyde in 4 ml of dry methanol. Reaction mixture was refluxed during 5 h and cooled to a room temperature. Crystals of two types precipitated: white thin plates (ring form) and heavy yellow cubes (chain form). Crystals were manually separated and spectroscopically characterized.

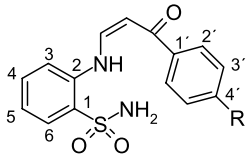
4.2.1.1. 2-(4′-Dimethylaminobenzylidenimino)anthranilamide (4b). Yield 15%, cubic yellow crystals, mp 192 °C. HRMS: $C_{16}H_{16}N_3O$ $(M-H)^+$ calcd 266.1293; obsd 266.1288. δ_H(DMSO-d_6): 3.04 (6H, s, $N(CH_3)_2$), 6.82 (2H, d, $J_{3'4'}=8.8$ Hz, H-3′, H-5′), 7.19 (1H, d, $J_{34}=7.6$ Hz, H-3), 7.28 (1H, t, $J_{45}=J_{56}=7.6$ Hz, H-5), 7.52 (1H, td, $J_{34}=J_{45}=7.0$, $J_{46}=1.2$ Hz, H-4), 7.61 (1H, br s, NH), 7.76 (2H, d, $J_{3'2'}=8.8$ Hz, H-2′, H-6′), 8.01 (1H, dd, $J_{56}=7.4$ Hz, $J_{46}=1.2$ Hz, H-6), 8.42 (1H, s, CH), 9.25 (1H, br s, NH). $\delta_C(CDCl_3)$: 39.59 ($N(CH_3)_2$), 111.48 (C-3′, C-5′), 119.25 (C-3), 122.90 (C-1′), 124.93 (C-5), 126.59 (C-1), 130.05 (C-6), 130.69 (C-2′, C-6′), 132.16 (C-4), 150.25 (C-2), 152.82 (C-4′), 161.31 (CH=N), 166.95 (C=O).

4.2.1.2. 2-(4′-Dimethylaminophenyl)-1,2,3,4-tetrahydroquinazolin-4-one (5b). Yield 50%, white plates, mp 228 °C. HRMS: $C_{16}H_{17}N_3O$ $M^{+\cdot}$ calcd 267.1372; obsd 267.1359. δ_H(DMSO-d_6): 2.90 (6H, s, $N(CH_3)_2$), 5.64 (1H, s, CH), 6.66 (1H, t, $J_{56}=J_{67}=7.3$ Hz, H-6), 6.71 (2H, d, $J_{2'3'}=8.7$ Hz, H-3′, H-5′), 6.73 (1H, m, H-8), 6.92 (1H, br s,

Table 3. Yields and physical properties of 2-aminosubstituted benzenesulfonamides **12a**,**b**,**d–f** and **15a–f**

	Yield %	Melting point °C	Colour	$M^{+\cdot}$	HRMS	
					Calculated	Observed
12a	60	198	Orange crystals	$C_{15}H_{13}N_3SO_5$	347.0576	347.0573
12b	69	186	Yellow cubic crystals	$C_{15}H_{13}N_2SO_3Br$	379.9830	379.9817
12c	87	145	Pale yellow crystals	$C_{15}H_{14}N_2SO_3$	302.0725	302.0717
12d	56	175	Yellow crystals	$C_{16}H_{16}N_2SO_3$	316.0882	316.0881
12e	75	179	Yellow crystals	$C_{16}H_{16}N_2SO_4$	332.0831	332.0823
15a	69	202	Dark orange crystals	$C_{16}H_{15}N_3SO_5$	361.0732	361.0725
15b	61	183	Yellow cubic crystals	$C_{16}H_{15}N_2SO_3Br$	393.9987	393.9975
15c	67	170	Pale yellow plate crystals	$C_{16}H_{14}N_2SO_3Cl$ (M−H)	349.0414	349.0420
15d	70	196	Pale yellow plate crystals	$C_{16}H_{16}N_2SO_3$	316.0882	316.0878
15e	51	204	Yellow crystals	$C_{17}H_{18}N_2SO_3$	330.1038	330.1023
15f	58	175	Pale yellow cubic crystals	$C_{17}H_{17}N_2SO_4$ (M−H)	345.0909	345.0910

Table 4. Proton spectra of 4′-substituted 2-(3-oxo-3-phenyl-*Z*-prop-1-enylamino) benzenesulfonamides **12a**,**b**,**d–f**



		CHCO, d	$J_{CH=CH}$	H-5, t	J_{45}	J_{35}	H-4, t	J_{34}	H-3, d	H-6, d	J_{56}
12a	NO_2	6.30	9.0	7.28	7.5	—	7.63	7.5	7.67	7.88	7.5
12b	Br	6.23	8.4	7.23	7.5	1.2	7.61	7.2	7.64	7.87	7.6
12d	H	6.26	8.0	7.23	7.2	1.6	7.62	m	7.62	7.88	7.6
12e	CH_3	6.22	8.4	7.21	7.2	2.0	7.60	m	7.60	7.85	7.6
12f	OCH_3	6.21	8.5	7.21	—	—	7.59	m	7.69	7.87	8.0
		J_{46}	NH_2, s	NC*H*, dd	J_{NH-CH}	H-3′,5′, d	$J_{2'3'}$	H-2′,6′, d	NH, d	X	
12a	NO_2	—	7.68	7.94	11.5	8.50	8.0	8.33	12.51	—	
12b	Br	0.8	7.65	7.84	12.4	7.71	8.8	7.93	12.43	—	
12d	H	1.0	7.66	7.82	12.0	7.52	8.0	7.99	12.43	7.58	
12e	CH_3	0.8	7.61	7.78	12.0	7.31	8.4	7.89	12.37	2.37	
12f	OCH_3	—	7.62	7.74	11.5	7.03	8.5	7.98	12.37	3.84	

Table 5. Carbon spectra of 4′-substituted 2-(3-oxo-3-phenyl-*Z*-prop-1-enylamino) benzenesulfonamides **12a**,**b**,**d–f**

		*C*HCO	C-3	C-5	C-6	C-1	C-4	C-2
12a	NO_2	95.74	117.56	123.27	128.27	131.07	133.59	137.65
12b	Br	95.43	117.23	122.82	128.26	130.79	133.56	137.51
12d	H	95.79	117.09	122.62	128.33	130.70	133.57	138.09
12e	CH_3	95.76	116.98	122.45	128.26	130.58	133.54	138.14
12f	OCH_3	95.73	116.83	122.30	128.29	130.49	133.55	138.24
		*C*HNH	C-2′,6′	C-3′,5′	C-4′	C-1′	CO	X
12a	NO_2	145.88	128.65	123.78	143.57	149.14	187.00	—
12b	Br	144.77	129.38	131.63	125.83	137.91	187.89	—
12d	H	144.23	127.32	128.63	131.91	138.52	189.17	—
12e	CH_3	143.84	127.41	129.18	135.93	142.02	188.89	21.07
12f	OCH_3	143.35	129.49	113.83	162.28	131.23	188.18	55.40

NH), 7.22 (1H, dt, $J_{78}=J_{67}=7.7$ Hz, $J_{75}=1.3$ Hz, H-7), 7.30 (2H, d, $J_{2'3'}=8.8$ Hz, H-2′, H-6′), 7.61 (1H, d, $J_{56}=6.8$ Hz, H-5), 8.07 (NH). δ_C(DMSO-d_6): 40.21 ($N(CH_3)_2$), 66.70 (CH), 111.97 (C-3′, C-5′), 114.43 (C-8),115.08 (C-4a), 117.00 (C-6), 127.39 (C-5), 127.79 (C-2′, C-6′), 128.62 (C-1′), 133.20 (C-7), 148.29 (C-8a), 150.74 (C-4′), 163.92 (CO).

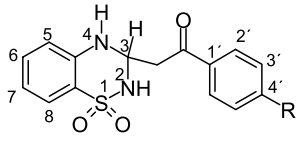
4.2.2. 3-(2′-Hydroxyphenyl)-4*H*-2,3-dihydrobenzo-1,2,4-thiadiazine-1,1-dioxide (6c). A solution of 2 mmol of 2-aminobenzenesulfonamide in 5 ml of dry methanol was added to a solution of 2 mmol of salicylic aldehyde in 2 ml of dry methanol. Reaction was completed in several hours (tlc control). Solvent was evaporated, solid recrystallized from methanol. Yield 56%, white crystals, mp 155 °C HRMS: $C_{13}H_{12}N_2O_3S$ $M^{+\cdot}$ calcd 276.0569; obsd 276.0566. δ_H(DMSO-d_6): 6.14 (1H, br. s, CH), 6.74 (1H, t, $J_{67}=J_{78}=7.6$ Hz, H-7), 6.87–6.90 (2H, m, H-5, H-5′), 6.92 (1H, d, $J_{3'4'}=8.0$ Hz, H-3′), 7.19 (1H, s, NH), 7.23 (1H, td, $J_{3'4'}=J_{4'5'}=7.6$, $J_{4'6'}=1.6$ Hz, H-4′), 7.28 (1H, td,

Table 6. Spectra of 4′-substituted 2-(3-oxo-3-phenyl-*E*-prop-1-enylamino)benzenesulfonamides **12a**,**b**,**d–f** (detected signals)

			Proton signals				
		%	CH–CO, d	J_{CH-CH}	H-5, m	NH_2, br s	CH–N*H*, t
12a	NO_2	10	6.84	12.5	n.d.	7.77	n.d.
12b	Br	11	6.82	12.8	7.21	7.76	8.15
12d	H	10	6.84	12.4	7.20	7.77	8.15
12e	CH_3	8	6.83	12.8	7.18	7.74	8.11
12f	OCH_3	10	6.86	12.5	n.d.	n.d.	8.12
			Proton signals		Carbon signals		
		%	NH, d	J_{CH-NH}	*C*H–CO	CHNH	CO
12a	NO_2	10	9.34	12.5	100.87	144.95	186.31
12b	Br	11	9.21	12.8	100.77	143.72	186.72
12d	H	10	9.17	12.8	101.22	143.16	187.85
12e	CH_3	8	9.10	12.4	101.26	142.67	187.38
12f	OCH_3	10	9.09	12.5	101.24	142.18	186.47

n.d., not detected.

Table 7. Proton spectra of 4′-substituted 3-(2-phenyl-2-oxoethyl)-2*H*,4*H*-benzothiadiazine-1,1-dioxides **13a**,**b**,**d–f**



		H-a, dd (CH_2)	H-b, dd (CH_2)	J_{gem}	J_{CH-CH2}	CH, m	H-7, t	J_{78}	J_{57}	H-5, d	J_{56}	
13a	NO_2	3.59	3.73	17.1	5.4	5.32	6.74	7.2	n.d.	6.81	7.8	
13b	Br	3.47	3.63	16.8	6.0	5.29	6.74	7.2	1.2	6.81	7.8	
13d	H	3.50	3.66	17.0	6.3	5.31	6.73	7.2	1.2	6.82	8.4	
13e	CH_3	3.43	3.60	16.8	6.3	5.28	6.73	7.2	1.2	6.82	7.8	
13f	OCH_3	3.40	3.59	16.8	6.3	5.30	6.73	7.2	n.d.	6.83	8.4	
		H-6, t	J_{67}	J_{68}	H-8, d	NH, s	NH–SO_2, d	J_{NH-CH}	H-2′,6′ d	$J_{2'3'}$	H-3′,5′ d	X
13a	NO_2	7.31	7.8	1.2	7.49	7.21	7.71	12	8.22	8.4	8.41	—
13b	Br	7.31	7.8	1.2	7.48	7.17	7.67	12	7.92	8.4	7.80	—
13d	H	7.30	8.0	1.5	7.48	7.20	7.65	12	7.99	7.5	7.58	7.69
13e	CH_3	7.30	7.2	1.8	7.48	7.16	7.64	11	7.89	7.8	7.38	2.40
13f	OCH_3	7.30	7.2	1.2	7.49	7.16	7.65	11	7.98	8.4	7.09	3.86

Table 8. Carbon spectra of 4′-substituted 3-(2-phenyl-2-oxoethyl)-2*H*,4*H*-benzothiadiazine-1,1-dioxides **13a**,**b**,**d–f**

		CH_2	CH	C-5	C-7	C-8a	C-8	C-6
13a	NO_2	43.02	62.24	115.25	115.87	121.08	123.73	132.98
13b	Br	42.45	62.38	115.89	116.48	121.06	123.71	132.93
13d	H	42.45	62.49	115.93	116.47	121.13	123.68	132.89
13e	CH_3	42.32	62.51	115.90	116.42	121.06	123.68	132.89
13f	OCH_3	42.08	62.67	115.94	116.45	121.09	123.71	132.91
		C-4a	C-3′,5′	C-2′,6′	C-4′	C-1′	CO	X
13a	NO_2	140.94	123.98	129.52	143.43	150.06	194.96	—
13b	Br	143.49	131.93	130.10	127.71	135.40	194.95	—
13d	H	143.54	128.83	128.07	133.57	136.42	195.68	—
13e	CH_3	143.55	129.37	128.31	133.95	144.04	195.14	21.19
13f	OCH_3	143.60	114.04	130.50	163.47	129.49	194.01	55.61

$J_{56}=J_{67}=7.6$ Hz, $J_{68}=1.4$ Hz, H-6), 7.51 (1H, d, $J_{78}=8.0$ Hz, H-8), 7.64 (1H, dd, $J_{5'6'}=7.6$, $J_{4'6'}=1.2$ Hz, H-6′), 7.71 (1H, m, NH), 9.96 (1H, br s, OH). δ_C(DMSO-d_6): 61.75 (CH), 115.28 (C-3′), 116.11 (C-5), 116.28 (C-7), 118.92 (C-5′), 121.35 (C-8a), 123.27 (C-1′), 123.68 (C-8), 128.10 (C-6′), 129.82 (C-4′), 132.57 (C-6), 144.12 (C-4a), 154.39 (C-2′).

4.2.3. Procedure A (compounds 11d, 12a,b,d–f, 14d, 15a–f). A solution of 2 mmol of β-dicarbonyl compounds in 5 ml of dry methanol was added to a solution of 2 mmol of aminoamide in 5 ml of dry methanol at room temperature. In several days a precipitate developed. It was filtered off, washed with methanol, and recrystallized from methanol if necessary.

Table 9. Proton spectra of 4′-substituted 2-(1-methyl-3-oxo-3-phenyl-*Z*-prop-1-enylamino)benzenesulfonamides **15a–f**

		CH_3	CH–CO	H-5, t	J_{45}	J_{35}	H-3, d	J_{34}	H-4, t	H-6, d
15a	NO_2	2.10	6.27	7.50	7.5	n.d.	7.55	7.5	7.67	7.95
15b	Br	2.06	6.17	7.45	7.6	0.8	7.50	7.8	7.63	7.93
15c	Cl	2.07	6.19	7.46	8.0	n.d.	7.51	8.0	7.64	7.93
15d	H	2.08	6.20	7.44	7.5	n.d.	7.50	n.d.	7.63	7.95
15e	CH_3	2.06	6.17	7.43	7.5	1.0	7.49	8.0	7.62	7.92
15f	OCH_3	2.07	6.16	7.42	7.5	7.5	7.47	7.5	7.62	7.94
		J_{56}	J_{46}	NH_2, s	H-3′, H-5′, d	$J_{2'3'}$	H-2′, H-6′, d	NH, s	X	
15a	NO_2	7.5	n.d.	7.55	8.32	8.7	8.19	12.87	—	
15b	Br	7.8	1.6	7.49	7.70	8.0	7.89	12.72	—	
15c	Cl	8.0	1.0	7.52	7.54	8.5	7.98	12.73	—	
15d	H	n.d.	1.0	7.52	7.50	n.d.	7.96	12.77	7.53	
15e	CH_3	1.5	1.5	7.48	7.28	8.0	7.86	12.69	2.37	
15f	OCH_3	7.5	n.d.	7.48	7.02	9.0	7.95	12.67	3.83	

Table 10. Carbon spectra of 4′-substituted 2-(1-methyl-3-oxo-3-phenyl-*Z*-prop-1-enylamino)benzenesulfonamides **15a–f**

		CH_3	*C*HCO	C-5	C-6	C-3	C-4	C-2	C-1
15a	NO_2	20.06	95.61	126.43	127.52	128.53	132.60	135.20	137.89
15b	Br	20.09	95.15	126.08	127.57	128.44	132.59	135.60	137.80
15c	Cl	20.13	95.22	126.10	127.58	128.48	132.63	135.63	137.81
15d	H	20.14	95.53	125.93	127.60	128.42	132.62	135.83	137.75
15e	CH_3	20.02	95.33	125.68	127.46	128.22	132.48	135.81	137.56
15f	OCH_3	20.15	95.34	125.64	127.59	128.25	132.59	136.06	137.59
		CH_3C=	C-2′,6′	C-3′,5′	C-4′	C-1′	CO	X	
15a	NO_2	163.15	128.22	123.55	144.55	148.70	184.46	—	
15b	Br	161.83	129.09	131.38	125.00	138.28	185.76	—	
15c	Cl	161.82	128.92	128.48	136.03	137.95	185.66	—	
15d	H	161.22	127.04	128.42	131.25	139.26	187.26	—	
15e	CH_3	160.61	127.01	128.89	136.49	141.11	186.95	20.92	
15f	OCH_3	161.80	129.09	113.63	160.19	131.84	186.54	55.34	

Table 11. Proton spectra of 4′-substituted 3-methyl-3-(2-phenyl-2-oxoethyl)-2*H*,4*H*-benzothiadiazine-1,1-dioxides **16d–f**

		CH_3, s	H-a, d (CH_2)	H-b, d (CH_2)	J_{gem}	H-7, t	J_{78}	H-5, d	J_{56}	NH,s
16d	H	1.78	3.62	3.85	17.5	6.73	7.2	6.84	8.0	7.11
16e	CH_3	1.69	3.54	3.74	16.8	6.71	7.6	6.78	8.0	7.09
16f	OCH_3	1.70	3.53	3.72	16.3	6.72	7.2	6.80	8.4	7.08
		H-6, t	J_{67}	J_{68}	H-8, d	$NH–SO_2$, s	H-2′, H-6′	H-3′, H-5′	X	
16d	H	7.28	8.0	1.6	7.5(m)	7.83	7.93	7.5(m)	7.6	
16e	CH_3	7.3m	7.6	n.d.	7.6(m)	7.75	7.81	7.3(m)	2.36	
16f	OCH_3	7.27	7.2	1.8	7.48(m)	7.77	7.94(m)	7.02	3.84	

Compounds **7a**,**b**,**d–f** and **8b–f** were obtained from corresponding acetophenones by Claisen condensation using standard synthetic protocol (e.g., see Ref. 19), and compound **8a**—according to Ref. 20.

4.2.3.1. *N*-(3-Oxo-3-phenyl-*cis*-prop-1-enyl)anthranilamide (11d). Yield 45%, yellow crystals, mp 199 °C. HRMS: $C_{16}H_{14}N_2O_2$ $M^{+\cdot}$ calcd 266.1055, obsd 266.1047. δ_H(DMSO-d_6): 6.13 (1H, d, $J_{CH–CH}$=8.0 Hz, C*H*–CO), 7.10 (1H, t, $J_{56}=J_{45}$=7.2 Hz, H-5), 7.45–7.65 (6H, m, H-3, H-4, H-3′, H-4′, H-5′, NH from NH_2), 7.71 (1H, d, J_{56}= 7.6 Hz, H-6), 7.80 (1H, dd, $J_{CH–CH}$=8.0, $J_{CH–NH}$=12,6 Hz, C*H*–NH), 7.96 (2H, d, $J_{2'3'}$=7.2 Hz, H-2′, H-6′), 8.09 (1H, broad s, NH from NH_2), 13.09 (1H, d, $J_{NH–CH}$=12.8 Hz, NH). δ_C(DMSO-d_6): 94.54 (*C*H–CO), 115.09 (C-3), 121.42 (C-1), 121.86 (C-5), 127.06 (C-2′, C-6′), 128.44 (C-3′, C-5′), 128.85 (C-6), 131.51 (C-4′), 132.07 (C-4), 138.80 (C-1′), 140.46 (C-2), 143.54 (CH–NH), 169.47 (CO–NH_2), 188.32 (*C*O–Ph).

4.2.3.2. *N*-(3-Oxo-3-phenyl-*trans*-prop-1-enyl)anthranilamide (*trans*-11d). Conc. 16%, detected signals: δ_H (DMSO-d_6): 6.75 (1H, d, $J_{CH–CH}$=12.4 Hz, C*H*–CO), 7.05 (1H, m, H-5), 8.23 (1H, t, $J_{CH–CH}=J_{CH–NH}$= 13.0 Hz, C*H*–NH), 8.29 (1H, broad s, NH from NH_2), 11.49 (1H, d, $J_{NH–CH}$=13.2 Hz, NH). δ_C(DMSO-d_6): 100.06 (*C*H–CO), 142.59 (*C*H–NH), 170.55 (CO–NH_2), 187.58 (*C*O–Ph).

4.2.3.3. *N*-(1-Methyl-3-oxo-3-phenyl-*cis*-prop-1-enyl)-anthranilamide (14d). Yield 60%, light-yellow crystals, mp 160 °C. HRMS: $C_{17}H_{16}N_2O_2$ $M^{+\cdot}$ calc 280.1212, obsd

Table 12. Carbon spectra of 4′-substituted 3-methyl-3-(2-phenyl-2-oxoethyl)-2*H*,4*H*-benzothiadiazine-1,1-dioxides **16d–f**

		CH_3	CH_2	N–*C*–N	C-5	C-7	C-8a	C-8	C-6
16d	H	26.54	46.08	69.87	116.34	116.48	120.24	123.56	132.97
16e	CH_3	26.42	45.86	69.80	116.26	116.37	120.10	123.52	132.95
16f	OCH_3	26.37	45.58	69.90	116.24	116.32	120.13	123.46	132.86
		C-4a	C-3′,5′	C-2′,6′	C-4′	C-1′	CO	X	
16d	H	142.38	128.63	127.93	133.24	137.24	196.98	—	
16e	CH_3	142.34	129.20	128.10	134.77	143.69	196.47	21.12	
16f	OCH_3	142.32	113.76	130.33	163.20	130.12	195.42	55.46	

Table 13. Spectra of 4′-substituted 3-methyl-3-(2-phenyl-2-oxoethyl)-2*H*,4*H*-benzothiadiazine-1,1-dioxides **16a–c** (concentration less than 20%, detected signals)

		Proton signals								
		CH_3, s	H-a, d (CH_2)	H-b, d (CH_2)	J_{gem}	H-7, t	$J_{78}=J_{67}$	H_5, d	J_{56}	NH, s
16a	Cl	1.70	3.52	3.79	16.8	6.71	7.2	6.77	7.6	7.13
16b	Br	1.70	3.51	3.78	16.8	6.71	7.2	6.77	8.4	7.13
16c	NO_2	1.74	3.56	3.92	17.0	6.72	7.5	6.78	n.d.	7.19
		Carbon signals								
		CH_3	CH_2	N–*C*–N	C=O					
16a	Cl	n.d.	45.87	69.53	195.69					
16b	Br	26.40	45.89	69.54	194.32					

280.1208. δ_H(DMSO-d_6): 3.00 (3H, s, CH_3), 6.06 (1H, s, C*H*–CO), 7.29 (1H, dt, $J_{56}=J_{45}=7.2$ Hz, $J_{35}=1.0$ Hz, H-5), 7.39 (1H, d, $J_{34}=8.0$ Hz, H-3), 7.45–7.51 (5H, m, H-4, H-3′, H-4′, H-5′, NH from NH_2), 7.54 (1H, dd, $J_{56}=$ 7.5 Hz, $J_{46}=1.5$ Hz, H-6), 7.91 (3H, m, H-2′, H-6′, NH from NH_2), 12.88 (1H, s, NH). δ_C(DMSO-d_6): 20.08 (CH_3), 94.45 (*C*H–CO), 125.13 (C-5), 126.16 (C-3), 126.78 (C-2′, C-6′), 127.05 (C-6), 128.25 (C-3′, C-5′), 128.98 (C-4), 130.90 (C-4′), 131.52 (C-1), 136.06 (C-2), 139.41 (C-1′), 160.95 (=*C*–CH_3), 168.82 (CO–NH_2), 186.53 (*C*O–Ph).

4.2.4. Procedure B (compounds 21a–c, 22a–c). 2 mmol of aminoamide was dissolved in 6 mmol of β-ketoester, and one drop of concentrated HCl was added on stirring. A white solid developed in approx. 15 min. It was washed with cold hexane and recrystallized from hexane–benzene.

4.2.4.1. 2-(2-Methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)acetic acid, ethyl ester (21a). Yield 47%, white powder, mp 109 °C (lit. 103 °C, Ref. 13).

4.2.4.2. 2-(2-Methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)acetic acid, *tert*-butyl ester (21b). Yield 72%, white powder, mp 163 °C. HRMS: $C_{15}H_{21}N_2O_3$ $(M+H)^+$ calcd 277.1552; obsd 277.1562. δ_H(DMSO-d_6): 1.31 (9H, s, $(CH_3)_3C$), 1.48 (3H, s, CH_3), 2.50 (1H, m, H-a from CH_2), 2.58 (1H, d, $J_{gem}=13.8$ Hz, H-b from CH_2), 6.64 (1H, t, $J_{67}=J_{56}=7.2$ Hz, H-6), 6.67 (1H, d, $J_{78}=7.8$ Hz, H-8), 6.70 (1H, br s, NH), 7.22 (1H, t, $J_{78}=J_{67}=7.2$ Hz, H-7), 7.57 (1H, d, $J_{56}=7.8$ Hz, H-5), 7.94 (1H, br s, NH). δ_C(DMSO-d_6): 27.42 ($(CH_3)_3C$), 27.85(CH_3), 47.18 (CH_2CO), 67.69 (N–*C*–N), 80.10 ($(CH_3)_3C$), 113.55 (C-4a), 114.13 (C-8), 116.57 (C-6), 127.02 (C-5), 133.20 (C-7), 146.30 (C-8a), 162.44 (CO), 168.60 (COO).

4.2.4.3. 4′-Oxo-1′,2′,3′,4′-tetrahydrospiro[cyclohexane-1,2′-quinazoline]-2-carboxylic acid, ethyl ester (21c) (a mixture of two diastereomers). Yield 73%, white powder, mp 146 °C, HRMS: $C_{16}H_{20}N_2O_3$ $M^{+\cdot}$ calcd 288.1474; obsd 288.1472. Major component (carbethoxy group in axial position): δ_H ($CDCl_3$): 1.20 (3H, t, $J_{CH3-CH2}=$ 7.2 Hz, CH_3CH$_2$), 1.46 (2H, m, both H-4 or H-4 and H-5), 1.64 (2H, m, both H-5 or H-4 and H-5), 1.78 (1H, m, H-6ax), 1.91 (1H, m, H-3 ax or eq), 1.99.(1H, m, H-3 ax or eq), 2.25 (1H, m, H-6eq), 2.91 (1H, m, $J_{2eq3ax}=5.2$ Hz, H-2e), 4.06 (2H, m, CH_2CH$_3$), 5.36 (1H, s, NH), 6.67 (1H, d, $J_{7'8'}=$ 7.8 Hz, H-8′), 6.80 (1H, t, $J_{5'6'}=J_{6'7'}=7.2$ Hz, H-6′), 7.06 (1H, br.d, NH), 7.26 (1H, td, $J_{6'7'}=J_{7'8'}=7.8$ Hz, $J_{5'7'}=$ 1.2 Hz, H-7′), 7.85 (1H, m, H-5′). δ_C($CDCl_3$): 14.05 (*C*H$_3$CH$_2$), 21.30 (C-5), 22.27 (br, C-4), 25.01 (C-3), 36.22 (br, C-6), 49.86 (br, C-2), 60.91 (CH$_3$*C*H$_2$), 69.18 (N–*C*–N), 114.71 (C-4′a), 115.38 (C-8′), 118.79 (C-6′), 128.07 (C-5′), 134.00 (C-7′), 145.59 (C-8′a), 164.07 (CO), 173.04 (COO). Minor component (carbethoxy group in equatorial position, concentration approx. 30%): δ_H ($CDCl_3$): 1.15 (3H, t, $J_{CH3-CH2}=7.2$ Hz, CH_3CH$_2$), 1.24 1.40 (2H, m, H-5ax, H-4ax), 1.65–2.05 (5H, m, cyclohexane H), 2.35 (1H, m, H-6eq), 2.77 (1H, $J_{H\text{-}2ax-H\text{-}3ax}=9.0$ Hz, $J_{H\text{-}2ax-H\text{-}3eq}=3.6$ Hz, H-2ax), 4.00 (2H, m, CH_2CH$_3$), 4.86 (1H, s, NH), 6.65 (1H, d, $J_{7'8'}=7.8$ Hz, H-8′), 6.74 (1H, br.d, NH), 6.78 (1H, m, H-6′), 7.26 (1H, m, H-7′), 7.84 (1H, m, H-5′). δ_C($CDCl_3$): 14.00 (*C*H$_3$CH$_2$), 21.24 (C-5), 22.67 (br, C-4), 25.15 (C-3), 37.73 (br, C-6), 51.79 (br, C-2), 60.93 (CH$_3$*C*H$_2$), 69.20 (N–*C*–N), 114.75 (C-4′a), 115.06 (C-8′), 118.68 (C-6′), 128.20 (C-5′), 133.90 (C-7′), 145.34 (C-8′a), 163.70 (CO), 172.34 (COO).

4.2.4.4. 2-Methyl-2-(2*H*,4*H*-1,1-dioxo-benzo-1,2,4-thiadiazin-3-yl)acetic acid, ethyl ester (22a). Yield 47%, white powder, mp 110 °C (lit. 109 °C, Ref. 18). δ_H(DMSO-d_6): 1.18 (3H, t, $J=7.2$ Hz, CH_3CH$_2$), 1.63 (3H, s, CH_3),

2.83 (1H, d, J_{gem}=15.6 Hz, H-a from CO–CH_2), 3.02 (1H, d, J_{gem}=15.6 Hz, H-b from CO–CH_2), 4.08 (2H, m, CH_2CH$_3$), 6.72 (1H, t, J_{67}=J_{78}=7.2 Hz, H-7), 6.79 (1H, d, J_{56}=8.4 Hz, H-5), 7.08 (1H, broad s, NH), 7.28 (1H, dt, J_{56}=J_{67}=8.4 Hz, J_{68}=1.8 Hz, H-6), 7.45 (1H, d, J_{78}=7.2 Hz, H-8), 7.72 (1H, s, SO$_2$N*H*). δ_C(DMSO-d_6): 13.90 (*C*H$_3$CH$_2$), 26.08 (CH$_3$), 43.33 (*C*H$_2$CO), 59.89 (*C*H$_2$CH$_3$), 68.95 (N–*C*–N), 116.10 (C-5), 116.38 (C-7), 120.01 (C-8a), 123.42 (C-8), 132.87 (C-6), 142.15 (C-4a), 168.97 (CO).

4.2.4.5. 2-Methyl-2-(2*H*,4*H*-1,1-dioxo-benzo-1,2,4-thiadiazin-3-yl)acetic acid, *tert*-butyl ester (22b). Yield 77%, white powder, mp 151 °C. HRMS: $C_{14}H_{20}N_2O_4S$ $M^{+\cdot}$ calcd 312.1144; obsd 312.1155. δ_H(DMSO-d_6): 1.40 (9H, s, (C*H*$_3$)$_3$C), 1.62 (3H, s, CH$_3$), 2.72 (1H, d, J_{gem}=15.0 Hz, H-a from CO–CH_2), 2.93 (1H, d, J_{gem}=15.0 Hz, H-b from CO–CH_2), 6.72 (1H, t, J_{67}=J_{78}=7.2 Hz, H-7), 6.80 (1H, d, J_{56}=8.4 Hz, H-5), 7.04 (1H, broad s, NH), 7.28 (1H, dt, J_{56}=J_{67}=7.8 Hz, J_{68}=1.8 Hz, H-6), 7.45 (1H, dd, J_{78}=8.4 Hz, J_{68}=1.2 Hz, H-8), 7.67 (1H, s, SO$_2$N*H*). δ_C(DMSO-d_6): 26.02 (CH$_3$), 27.61 ((*C*H$_3$)$_3$C), 44.37 (*C*H$_2$CO), 69.01 (N–*C*–N), 80.22 ((CH$_3$)$_3$*C*), 116.15 (C-5), 116.38 (C-7), 120.11 (C-8a), 123.45 (C-8), 132.84 (C-6), 142.16 (C-4a), 168.40 (CO).

4.2.4.6. 2′-Carbethoxy-2*H*,4*H*-spiro(benzo-1,2,4-thiadiazine-3,1′-cyclohexane(-1,1-dioxide (22c) (equatorial carbethoxy group). Yield 68%, white powder, mp 161 °C. HRMS: $C_{15}H_{20}N_2O_4S$ $M^{+\cdot}$ calcd 324.1144; obsd 324.1152. δ_H(DMSO-d_6): 1.18 (3H, t, $J_{CH3-CH2}$=7.2 Hz, C*H*$_3$CH$_2$), 1.34 (2H, m, H-6′ax, H-4′ax), 1.56 (1H, m, H-5′ax or H-5′eq), 1.66 (2H, m, H-4′eq, H-5′eq or H-5′ax), 1.76 (1H, m, H-3′ax), 1.83 (1H, m, H-3′eq), 2.64 (1H, dm, J_{gem}=14.0 Hz, H-6′eq), 2.78 (1H, dd, $J_{2'ax3'ax}$=11.0 Hz, $J_{2'ax3'eq}$=3.5 Hz, H-2′ax), 4.12 (2H, m, CH_2CH$_3$), 6.74 (dt, J_{78}=J_{67}=7.5 Hz, J_{57}=1.0 Hz, H-7), 6.79 (1H, d, J_{56}=8.0 Hz, H-5), 6.86 (1H, broad s, NH), 7.29 (1H, dt, J_{67}=J_{56}=7.8 Hz, J_{68}=1.5 Hz, H-6), 7.37 (1H, s, SO$_2$N*H*), 7.45 (1H, dd, J_{78}=7.8 Hz, J_{68}=1.3 Hz, H-8). δ_C(DMSO-d_6): 13.82 (*C*H$_3$CH$_2$), 20.90 (C-5′), 23.44 (br, C-4′), 25.71 (C-3′), 34.01 (br, C-6′), 49.72 (br, C-2′), 60.76 (*C*H$_2$CH$_3$), 71.07 (N–*C*–N), 116.48 (C-5), 117.01 (C-7), 120.30 (C-8a), 123.64 (C-8), 133.15 (C-6), 142.36 (C-4a), 174.32 (br, CO).

4.2.4.7. 2′-Carbethoxy-2*H*,4*H*-spiro(benzo-1,2,4-thiadiazine-3,1′-cyclohexane)-1,1-dioxide (23) (axial carbethoxy group), interpreted signals. δ_H(DMSO-d_6): 1.13 (3H, t, $J_{CH3-CH2}$=7.2 Hz, C*H*$_3$CH$_2$), 1.45–1.85 (4H, m, cyclohexane ring), 1.76 (1H, m, H-3′ax or H-3′eq), 1.93 (1H, m, H-3′ax or H-3′eq), 1.96 (1H, m, H-6′eq), 2.29 (1H, td, $J_{6'ax-5'ax}$=J_{gem}=13.2 Hz, $J_{6'ax-5'eq}$=4.2 Hz, H-6′ax), 3.73 (1H, m, H-2′eq), 4.06 (2H, m, CH_2CH$_3$), 6.70 (1H, dt, J_{78}=J_{67}=7.5 Hz, J_{57}=0.6 Hz, H-7), 6.84–6.92 (m, NH, H-5), 7.25 (1H, dt, J_{67}=J_{56}=7.8 Hz, J_{68}=1.5 Hz, H-6), 7.44 (1H, dd, J_{78}=7.8 Hz, J_{68}=1.3 Hz, H-8). δ_C(DMSO-d_6): 13.90 (*C*H$_3$CH$_2$), 20.00 (C-5′), 23.44 (br, C-4′), 24.36 (C-3′), 32.56 (br, C-6′), 45.22 (C-2′), 59.89 (*C*H$_2$CH$_3$), 70.70 (N–*C*–N), 116.29, 116.36 (C-5, C-7), 120.01 (C-8a), 123.47 (C-8), 132.80 (C-6), 142.32 (C-4a), 172.12 (br, CO).

Acknowledgements

We thank Dr. V. Ovcharenko for HRMS spectra and fruitful discussions.

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