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Synthesis and Intramolecular Heterocyclization of β-Amino Ketone Thiosemicarbazones

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Abstract—Intramolecular heterocyclization of thiosemicarbazones derived from saturated and conjugated β-amino ketones afforded previously unknown dihydro-1,3,4-thiadiazole derivatives. A probable scheme of the transformation of multicenter intermediate includes generation and intramolecular cyclization of a thiol thiosemicarbazone tautomer without participation of conjugated double carbon–carbon bond in the substrate.

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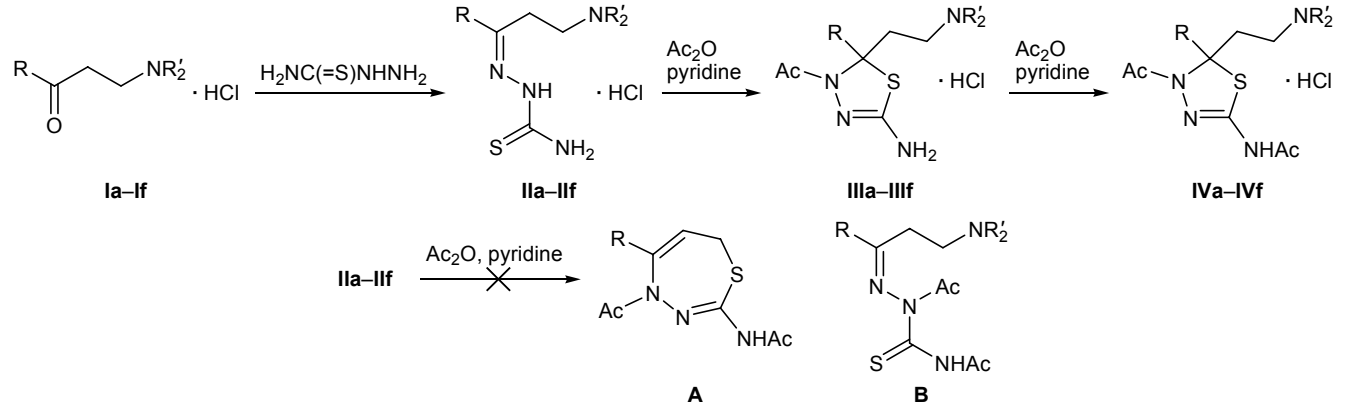
Saturated and unsaturated Mannich bases exhibit antimicrobial [1] and antiviral [2] activity and are promising as substrates for the design of efficient agents for cancer therapy [3]. Introduction of various pharmacophoric fragments into molecules of Mannich bases could essentially change their activity and extend their medicinal and biological potential. Thiosemicarbazones and their cyclic derivatives, dihydrothiadiazoles, are also important as biologically active compounds [4].

The present work was aimed at synthesizing compounds of the thiourea and dihydrothiadiazole series containing a tertiary aminoalkyl group, including heterocyclic amine fragments. As starting compounds we used saturated and unsaturated β-amino ketones **Ia**–**If** which were converted in up to 87% yield into the corresponding thiosemicarbazone hydrochlorides **IIa**–**IIf** by treatment with thiosemicarbazide in the presence of a catalytic amount of aqueous HCl (Scheme 1). The structure of thiosemicarbazones **IIa**–**IIf** was confirmed by IR and ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectra of **IIa**–**IIf** contained triplets at δ 2.43–2.56 ppm from protons in the aminomethylene fragment, while compounds **IIc**–**IIf** characteristically displayed two doublets at δ 6.81–6.87 ppm (J = 16.0 Hz) from the vinylic protons. The C=N and C=S carbon atoms resonated in the ^{13}C NMR spectra at δ_C 143.2–146.2 and 179.2–184.6 ppm, respectively.

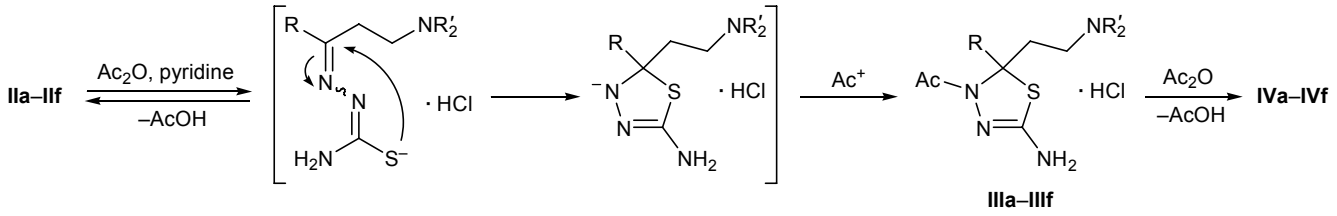
Thiosemicarbazones **IIa**–**IIf** were subjected to heterocyclization by the action of acetic anhydride in

Scheme 1.



R = Ph, R′ = Me (**a**), R′$_2$N = morpholin-4-yl (**b**); R = (*E*)-PhCH=CH, R′ = Me (**c**), R′$_2$N = morpholin-4-yl (**d**); R = (*E*)-2-(2-furyl)ethenyl, R′ = Me (**e**), R′$_2$N = morpholin-4-yl (**f**).

Scheme 2.



pyridine. This reaction may be expected to produce several structures, in particular five-membered dihydro-1,3,4-thiadiazole ring (**IVa**–**IVf**) via intramolecular heterocyclization, thiadiazepine system **A** as a result of elimination of secondary amine and subsequent cyclization, and acylated thiosemicarbazone **B**. Analysis of the product structure, reaction course, and our previous data [5, 6] showed that heterocyclization of thiosemicarbazones **IIa**–**IIf** is regioselective and that the products are mono- and bis-acylated dihydro-1,3,4-thiadiazole derivatives **IIIa**–**IIIf** and **IVa**–**IVf**, depending on the reaction time. The IR spectra of **IIIa**–**IIIf** contained two absorption bands in the region 3400–3300 cm^{-1} due to stretching vibrations of the primary amino group. The presence in the ^1H NMR spectra of **IIIc**–**IIIf** of doublets at δ 6.52–6.65 ppm (J = 16 Hz) from vinylic protons indicated *trans* configuration of the exocyclic double C=C bond. Diastereotopic protons in the α-methylene group resonated at δ 2.49–3.06 ppm as doublets of triplets. The ^{13}C NMR spectra of **IIIa**–**IIIf** contained a signal at δ_C 82.9–83.1 ppm from quaternary carbon atom, which rules out formation of alternative structures **A** and **B**.

In the IR spectra of **IVa**–**IVf** we observed an absorption band at 3300–3100 cm^{-1}, which corresponded to stretching vibrations of the amide NH group. Compounds **IVa**–**IVf** displayed in the ^1H NMR spectra two singlets belonging to methyl protons in two acetyl groups, and the corresponding carbonyl carbon signals were located at δ_C 167.2–169.3 ppm in the ^{13}C NMR spectra.

A probable mechanism of the observed heterocyclization is illustrated by Scheme 2. Initial enolization of thiosemicarbazone **II** is favored by deprotonation under the action of acylating agent. Next follows thiadiazole ring closure as a result of intramolecular nucleophilic attack by the thiolate ion on the C=N carbon atom. The cyclic structure is stabilized by acylation, and the subsequent acylation of **III** at the exocyclic amino group yields compounds **IV**.

To conclude, we were the first to report on the synthesis of saturated and unsaturated β-amino ketone thiosemicarbazones and their intramolecular heterocyclization with formation of previously unknown functionally substituted dihydro-1,3,4-thiadiazoles.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Varian 400 spectrometer at 400 and 100 MHz, respectively, using DMSO-d_6 as solvent and TMS as internal reference. The IR spectra were measured in KBr on an FSM-1201 instrument. The progress of reactions and the purity of products were monitored by HPLC using a Waters Alliance chromatograph equipped with a Waters 2996 diode array detector and a Waters SunFire C18 column (150×2.1 mm, grain size 3.5 μm); eluent 24% MeCN–58% H_2O pH 2.3–8% MeOH–10% $C_7H_{13}SO_3Na$ (c = 0.1 M).

Thiosemicarbazones IIa–IIf (*general procedure***).** A solution of 0.05 mol of ketone **Ia**–**If** and 0.06 mol of thiosemicarbazide in 20 ml of propan-2-ol containing a catalytic amount of hydrochloric acid was heated for 15–120 min under reflux. The mixture was cooled, and the precipitate was filtered off and recrystallized from propan-2-ol.

3-Dimethylamino-1-phenylpropan-1-one thiosemicarbazone hydrochloride (IIa). Yield 67%, mp 160–162°C. IR spectrum, ν, cm^{-1}: 3374, 3354 (NH_2), 3235 (NH), 2660 (NH^+), 1200 (C=S). ^1H NMR spectrum, δ, ppm: 2.71 s (6H, Me), 2.82 t (2H, C**H**$_2$CH$_2$N$^+$, J = 10.8 Hz), 3.39 t (2H, CH$_2$N$^+$, J = 10.2 Hz), 7.54 m (5H, Ph), 8.62 s (1H, NH), 10.53 s (2H, NH_2), 11.63 s (1H, NH^+). Found, %: C 50.55; H 6.28; N 20.08. $C_{12}H_{19}ClN_4S$. Calculated, %: C 50.25; H 6.68; N 19.93.

3-(Morpholin-4-yl)-1-phenylpropan-1-one thiosemicarbazone hydrochloride (IIb). Yield 75%, mp 155–157°C. IR spectrum, ν, cm^{-1}: 3456, 3345 (NH_2), 3196 (NH), 2557 (NH^+), 1191 (C=S). ^1H NMR spectrum, δ, ppm: 2.85 t (2H, C**H**$_2$CH$_2$N$^+$, J = 9.5 Hz), 3.41 m (2H, CH$_2$N$^+$, J = 9.8 Hz), 3.91 m (4H, OCH$_2$C**H**$_2$), 4.20 t (4H, CH$_2$O, J = 7.8 Hz), 7.56 m (5H, Ph), 8.75 s (1H, NH), 10.05 s (2H, NH_2), 11.26 s

(1H, NH^+). Found, %: C 51.33; H 6.94; N 17.43. $C_{14}H_{21}ClN_4OS$. Calculated, %: C 51.13; H 6.44; N 17.04.

5-Dimethylamino-1-phenylpent-1-en-3-one thiosemicarbazone hydrochloride (IIc). Yield 87%, mp 159–161°C. IR spectrum, ν, cm^{-1}: 3398, 3349 (NH_2), 3194 (NH), 2650 (NH^+), 1679 (C=C), 1197 (C=S). ^{1}H NMR spectrum, δ, ppm: 2.81 s (6H, Me), 3.01 t (2H, C**H**$_2$$CH_2N^+$, J = 12.3 Hz), 3.43 t (2H, CH_2N^+, J = 11.1 Hz), 6.81 d (1H, 2-H, J = 16.0 Hz), 6.87 d (1H, 1-H, J = 16.0 Hz), 7.54 m (5H, Ph), 8.92 s (1H, NH), 10.56 s (2H, NH_2), 11.34 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 25.3 (**C**$H_2CH_2N^+$), 27.1 (**C**H_2N^+), 117.9 (C^2), 127.3 (C^1); 126.2, 127.4, 127.6, 128.2, 128.4, 137.4 (C_{arom}); 152.5 (C=N), 179.7 (C=S). Found, %: C 53.92; H 7.14; N 18.04. $C_{14}H_{21}ClN_4S$. Calculated, %: C 53.75; H 6.77; N 17.91.

5-(Morpholin-4-yl)-1-phenylpent-1-en-3-one thiosemicarbazone hydrochloride (IId). Yield 59%, mp 181–183°C. IR spectrum, ν, cm^{-1}: 3376, 3256 (NH_2), 3178 (NH), 2520 (NH^+), 1686 (C=C), 1204 (C=S). ^{1}H NMR spectrum, δ, ppm: 2.85 t (2H, C**H**$_2$$CH_2N^+$, J = 12.8 Hz), 3.41 m (2H, CH_2N^+, J = 12.8 Hz), 3.91 m (4H, C**H**$_2$$CH_2O$), 4.20 m (4H, CH_2O), 6.77 d (1H, 2-H, J = 16.0 Hz), 6.83 d (1H, 1-H, J = 16.0 Hz), 7.54 m (5H, Ph), 8.91 s (1H, NH), 10.14 s (2H, NH_2), 10.98 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 26.3 (**C**$H_2CH_2N^+$), 29.1 (CH_2N^+), 47.1 (**C**H_2CH_2O), 69.2 (CH_2O), 118.2 (C^2) 129.8 (C^1); 125.1, 126.3, 124.6, 127.1, 127.9, 137.4 (C_{arom}); 151.3 (C=N), 181.9 (C=S). Found, %: C 54.97; H 6.68; N 15.51. $C_{16}H_{23}ClN_4OS$. Calculated, %: C 55.11; H 6.53; N 15.79.

5-Dimethylamino-1-(2-furyl)pent-1-en-3-one thiosemicarbazone hydrochloride (IId). Yield 85%, mp 170–173°C. IR spectrum, ν, cm^{-1}: 3396, 3276 (NH_2), 3168 (NH), 2580 (NH^+), 1659 (C=C), 1195 (C=S). ^{1}H NMR spectrum, δ, ppm: 2.86 s (6H, Me), 3.15 t (2H, C**H**$_2$$CH_2N^+$, J = 10.3 Hz), 3.39 t (2H, CH_2N^+, J = 10.8 Hz), 6.13 d (1H, 2-H, J = 16.0 Hz), 6.21 d (1H, 1-H, J = 16.0 Hz), 6.29–6.41 m (2H, 3′-H, 4′-H), 7.34 d (1H, 5′-H, J = 1.8 Hz), 8.98 s (1H, NH), 10.25 s (2H, NH_2), 10.89 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 25.3 (**C**$H_2CH_2N^+$), 27.1 (CH_2N^+), 111.4 (C^2), 117.5 (C^1), 117.1 ($C^{4'}$), 114.3 ($C^{3'}$), 146.1 ($C^{2'}$), 153.1 ($C^{5'}$), 156.1 (C=N), 180.4 (C=S). Found, %: C 48.03; H 6.35; N 19.01. $C_{12}H_{19}ClN_4OS$. Calculated, %: C 47.59; H 6.32; N 18.50.

1-(2-Furyl)-5-(morpholin-4-yl)pent-1-en-3-one thiosemicarbazone hydrochloride (IIf). Yield 85%, mp 174–176°C. IR spectrum, ν, cm^{-1}: 3349, 3276 (NH_2), 3178 (NH), 2525 (NH^+), 1658 (C=C), 1178 (C=S). ^{1}H NMR spectrum, δ, ppm: 3.02 t (2H, C**H**$_2$$CH_2N^+$, J = 9.6 Hz), 3.24 t (2H, CH_2N^+, J = 9.8 Hz), 3.89 m (4H, C**H**$_2$$CH_2O$), 4.04 m (4H, CH_2O), 6.07 d (1H, 2-H, J = 16.0 Hz), 6.19 d (1H, 1-H, J = 16.0 Hz), 6.31–6.39 m (2H, 3′-H, 4′-H), 7.31 d (1H, 5′-H, J = 1.9 Hz), 8.89 s (1H, NH), 11.04 s (2H, NH_2), 11.03 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 26.1 (**C**$H_2CH_2N^+$), 29.6 (CH_2N^+), 45.4 (**C**H_2CH_2O), 68.7 (CH_2O), 112.1 (C^2), 118.9 (C^1), 117.9 ($C^{4'}$), 116.1 ($C^{3'}$), 151.4 ($C^{2'}$), 154.2 ($C^{5'}$), 154.7 (C=N), 179.8 (C=S). Found, %: C 48.43; H 6.41; N 16.14. $C_{14}H_{21}ClN_4O_2S$. Calculated, %: C 48.76; H 6.14; N 16.25.

Dihydro-1,3,4-thiadiazoles IIIa–IIIf (*general procedure***).** A solution of 0.015 mol of compound **IIa–IIf** and 0.06 mol of acetic anhydride in 30 ml of pyridine was stirred for 25–50 min. The solvent was distilled off under reduced pressure, and the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol.

4-Acetyl-5-[2-(dimethylamino)ethyl]-5-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-amine hydrochloride (IIIa). Yield 47%, mp 181–182°C. IR spectrum, ν, cm^{-1}: 3486, 3405 (NH_2), 2593 (NH^+), 1641 (C=C), 1602 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.12 s (3H, COMe), 2.74 d.t (2H, 5-CH_2, J = 12.1, 4.0 Hz), 2.91 t (2H, CH_2N^+, J = 11.9 Hz), 3.18 s (6H, MeN^+), 7.49 m (5H, Ph), 8.90 s (2H, NH_2), 10.43 s (1H, NH^+). Found, %: C 51.27; H 6.58; N 16.89. $C_{14}H_{21}ClN_4OS$. Calculated, %: C 51.13; H 6.44; N 17.04.

4-Acetyl-5-[2-(morpholin-4-yl)ethyl]-5-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-amine hydrochloride (IIIb). Yield 45%, mp 173–175°C. IR spectrum, ν, cm^{-1}: 3479, 3412 (NH_2), 2636 (NH^+), 1668 (C=C), 1609 (C=N), 1538. ^{1}H NMR spectrum, δ, ppm: 2.13 s (3H, COMe), 2.76 d.t (2H, 5-CH_2, J = 13.6, 4.1 Hz), 3.05 t (2H, CH_2N^+, J = 12.8 Hz), 3.62 m (4H, C**H**$_2$$CH_2O$), 4.02 m (4H, CH_2O), 7.59 m (5H, Ph), 8.50 s (2H, NH_2), 10.87 s (1H, NH^+). Found, %: C 51.43; H 6.49; N 15.37. $C_{16}H_{23}ClN_4O_2S$. Calculated, %: C 51.18; H 6.25; N 15.11.

4-Acetyl-5-[2-(dimethylamino)ethyl]-5-(2-phenylethenyl)-4,5-dihydro-1,3,4-thiadiazol-2-amine hydrochloride (IIIc). Yield 52%, mp 195–196° C. IR spectrum, ν, cm^{-1}: 3495, 3426 (NH_2), 2593 (NH^+), 1623 (C=C), 1559 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.08 s (3H, COMe), 2.46 d.t (2H, 5-CH_2, J = 13.6, 4.2 Hz), 3.07 t (2H, CH_2N^+, J = 13.9 Hz), 3.18 s (6H, MeN^+), 6.52 d (1H, 5-CH=, J = 16.0 Hz), 6.78 d (1H,

=C**H**Ph, J = 16.0 Hz), 7.75 m (5H, Ph), 9.30 s (2H, NH_2), 10.51 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 25.3 (Me), 31.9 (5-CH_2), 54.6 (CH_2N), 81.3 (C^5), 126.1 (5-CH=), 128.4 (=**C**HPh); 127.4, 127.9, 128.4, 129.5, 129.8, 135.4 (C_{arom}); 146.5 (C^2), 167.9 (C=O). Found, %: C 54.42; H 6.68; N 16.02. $C_{16}H_{23}ClN_4OS$. Calculated, %: C 54.15; H 6.53; N 15.79.

4-Acetyl-5-[2-(morpholin-4-yl)ethyl]-5-(2-phenylethenyl)-4,5-dihydro-1,3,4-thiadiazol-2-amine hydrochloride (IIId). Yield 51%, mp 161–162°C. IR spectrum, ν, cm^{-1}: 3459, 3436 (NH_2), 2606 (NH^+), 1617 (C=C), 1568 (C=N). ^1H NMR spectrum, δ, ppm: 2.11 s (3H, COMe), 2.71 d.t (2H, 5-CH_2, J = 13.5, 4.0 Hz), 3.07 t (2H, CH_2N^+, J = 13.2 Hz), 3.87 m (4H, C**H**$_2$$CH_2O$), 4.13 m (4H, CH_2O), 6.57 d (1H, 5-CH=, J = 16.0 Hz), 6.78 d (1H, =C**H**Ph, J = 16.0 Hz), 7.47 m (5H, Ph), 9.02 s (2H, NH_2), 10.41 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 24.5 (Me), 31.9 (5-CH_2), 53.8 (CH_2N^+), 46.5 (**C**H_2CH_2O), 62.4 (CH_2O), 79.4 (C^5), 126.8 (5-CH=), 129.5 (=**C**HPh); 126.4, 126.3, 126.4, 127.3, 128.1, 134.9 (C_{arom}), 151.6 (C^2), 168.7 (C=O). Found, %: C 54.16; H 6.24; N 13.96. $C_{18}H_{25}ClN_4O_2S$. Calculated, %: C 54.47; H 6.35; N 14.11.

4-Acetyl-5-[2-(dimethylamino)ethyl]-5-[2-(2-furyl)ethenyl]-4,5-dihydro-1,3,4-thiadiazol-2-amine hydrochloride (IIIe). Yield 61%, mp 184–187°C. IR spectrum, ν, cm^{-1}: 3419, 3386 (NH_2), 2623 (NH^+), 1618 (C=C), 1585 (C=N). ^1H NMR spectrum, δ, ppm: 2.09 s (3H, COMe), 2.45 d.t (2H, 5-CH_2, J = 14.1, 3.9 Hz), 3.04 t (2H, CH_2N^+, J = 14.6 Hz), 3.12 s (6H, MeN^+), 6.02 d (1H, 5-CH=, J = 16.0 Hz), 6.28 d (1H, =C**H**Fu, J = 16.0 Hz), 6.32–6.37 m (2H, 3′-H, 4′-H), 7.38 d (1H, 5′-H, J = 1.8 Hz), 9.10 s (2H, NH_2), 10.58 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 25.9 (Me), 27.8 (5-CH_2), 29.1 (CH_2N^+), 87.1 (C^5), 114.2 (5-CH=), 124.6 (=**C**HFu), 117.3 ($C^{4'}$), 117.9 ($C^{3'}$), 146.2 ($C^{2'}$), 159.4 ($C^{5'}$), 154.1 (C^2), 169.4 (C=O). Found, %: C 49.09; H 6.03; N 16.41. $C_{14}H_{21}ClN_4O_2S$. Calculated, %: C 48.76; H 6.14; N 16.25.

4-Acetyl-5-[2-(2-furyl)ethenyl]-5-[2-(morpholin-4-yl)ethyl]-4,5-dihydro-1,3,4-thiadiazol-2-amine hydrochloride (IIIe). Yield 57%, mp 168–171°C. IR spectrum, ν, cm^{-1}: 3426, 3396 (NH_2), 2645 (NH^+), 1618 (C=C), 1578 (C=N). ^1H NMR spectrum, δ, ppm: 2.13 s (3H, COMe), 2.45 d.t (2H, 5-CH_2, J = 16.1, 3.9 Hz), 3.09 t (2H, CH_2N^+, J = 15.9 Hz), 3.89 m (4H, C**H**$_2$$CH_2O$), 4.12 m (4H, CH_2O), 6.21 d (1H, 5-CH=, J = 16.0 Hz), 6.31 d (1H, =C**H**Fu, J = 16.0 Hz), 6.28–6.36 m (2H, 3′-H, 4′-H), 7.49 d (1H, 5′-H, J = 1.8 Hz), 8.86 s (2H, NH_2), 10.62 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 25.6 (Me), 29.1 (5-CH_2), 32.1 (CH_2N^+), 46.8 (**C**H_2CH_2O), 67.9 (CH_2O), 79.4 (C^5), 116.2 (5-CH=), 124.2 (=**C**HFu), 118.1 ($C^{4'}$), 119.2 ($C^{3'}$), 152.3 ($C^{2'}$), 156.2 ($C^{5'}$), 148.9 (C^2), 168.1 (C=O). Found, %: C 50.02; H 6.09; N 14.69. $C_{16}H_{23}ClN_4O_3S$. Calculated, %: C 49.67; H 5.99; N 14.48.

Dihydro-1,3,4-thiadiazoles IVa–IVf (*general procedure*). A solution of 0.015 mol of **IIa**–**IIf** or **IIIa**–**IIIf** and 0.06 mol of acetic anhydride in 30 ml of pyridine was stirred for 4–6 h. The solvent was distilled off under reduced pressure, and the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol.

***N*-{4-Acetyl-5-[2-(dimethylamino)ethyl]-5-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl}acetamide hydrochloride (IVa).** Yield 67%, mp 175–177°C. IR spectrum, ν, cm^{-1}: 3486 (NH), 2647 (NH^+), 1623 (C=C), 1590 (C=N), 1540 (amide II). ^1H NMR spectrum, δ, ppm: 2.07 s and 2.11 s (3H each, COMe), 2.69 d.t (2H, 5-CH_2, J = 15.9, 4.0 Hz), 2.95 t (2H, CH_2N^+, J = 15.4 Hz), 3.17 s (6H, Me), 7.61 m (5H, Ph), 8.91 s (1H, NH), 10.43 s (1H, NH^+). Found, %: C 51.94; H 6.64; N 15.55. $C_{16}H_{23}ClN_4O_2S$. Calculated, %: C 51.81; H 6.25; N 15.11.

***N*-{4-Acetyl-5-[2-(morpholin-4-yl)ethyl]-5-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl}acetamide hydrochloride (IVb).** Yield 67%, mp 183–185°C. IR spectrum, ν, cm^{-1}: 3479 (NH), 2596 (NH^+), 1654 (C=C), 1594 (C=N), 1520 (amide II). ^1H NMR spectrum, δ, ppm: 2.11 s and 2.17 s (3H each, COMe), 2.76 d.t (2H, 5-CH_2, J = 15.9, 4.1 Hz), 3.05 t (2H, CH_2N^+), 3.62 m (4H, C**H**$_2$$CH_2O$), 4.02 m (4H, CH_2O), 7.59 m (5H, Ph), 8.91 s (1H, NH), 10.87 s (1H, NH^+). Found, %: C 52.67; H 6.31; N 13.49. $C_{18}H_{25}ClN_4O_3S$. Calculated, %: C 52.36; H 6.10; N 13.57.

***N*-{4-Acetyl-5-[2-(dimethylamino)ethyl]-5-(2-phenylethenyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl}-acetamide hydrochloride (IVc).** Yield 78%, mp 195–196°C. IR spectrum, ν, cm^{-1}: 3495 (NH), 2642 (NH^+), 1619 (C=C), 1556 (C=N), 1534 (amide II). ^1H NMR spectrum, δ, ppm: 2.05 s and 2.16 s (3H each, COMe), 2.61 d.t (2H, 5-CH_2, J = 15.8, 4.2 Hz), 3.01 t (2H, CH_2N^+, J = 15.1 Hz), 3.15 s (6H, Me), 6.54 d (1H, 5-CH=, J = 16.0 Hz), 6.62 d (1H, =C**H**Ph, J = 16.0 Hz), 7.80 m (5H, Ph), 8.58 s (1H, NH) 10.51 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 24.4 and 25.6 (Me), 31.8 (5-CH_2), 53.4 (CH_2N^+), 82.9 (C^5), 124.5 (5-CH=), 127.2 (=**C**HPh); 128.2, 128.3, 128.5, 129.1, 129.9, 136.0 (C_{arom}); 148.7 (C^2), 166.4 and 167.3 (C=O).

Found, %: C 54.78; H 6.70; N 14.01. $C_{18}H_{25}ClN_4O_2S$. Calculated, %: C 54.47; H 6.35; N 14.11.

***N*-{4-Acetyl-5-[2-(morpholin-4-yl)ethyl]-5-(2-phenylethenyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl}-acetamide hydrochloride (IVd).** Yield 73%, mp 187–189°C. IR spectrum, ν, cm^{-1}: 3459 (NH), 2634 (NH^+), 1621 (C=C), 1559 (C=N), 1550 (amide II). ^1H NMR spectrum, δ, ppm: 2.11 s and 2.18 s (3H each, COMe), 2.69 d.t (2H, 5-CH_2, J = 16.1, 4.0 Hz), 3.14 t (2H, CH_2N^+, J = 15.9 Hz), 3.71 m (4H, C**H**$_2$$CH_2O$), 4.09 m (4H, CH_2O), 6.53 d (1H, 5-CH=, J = 16.0 Hz), 6.65 d (1H, =C**H**Ph, J = 16.0 Hz), 7.35 m (5H, Ph), 8.91 s (1H, NH), 10.41 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 23.7 and 26.4 (Me), 32.5 (5-CH_2), 52.9 (CH_2N^+), 45.9 (**C**$H_2$$CH_2O$), 63.5 ($CH_2O$), 81.5 ($C^5$), 127.1 (5-CH=), 129.3 (=**C**HPh); 126.1, 126.5, 126.9, 127.4, 127.6, 135.4 (C_{arom}); 151.2 (C=N), 168.9 and 169.1 (C=O). Found, %: C 55.15; H 6.46; N 12.65. $C_{20}H_{27}ClN_4O_3S$. Calculated, %: C 54.72; H 6.20; N 12.76.

***N*-{4-Acetyl-5-[2-(dimethylamino)ethyl]-5-[2-(2-furyl)ethenyl]-4,5-dihydro-1,3,4-thiadiazol-2-yl}-acetamide hydrochloride (IVe).** Yield 78%, mp 184–187°C. IR spectrum, ν, cm^{-1}: 3419 (NH), 2632 (NH^+), 1621 (C=C), 1578 (C=N), 1542 (amide II). ^1H NMR spectrum, δ, ppm: 2.13 s and 2.16 s (3H each, COMe), 2.36 d.t (2H, 5-CH_2, J = 15.8, 3.9 Hz), 2.95 t (2H, CH_2N^+, J = 15.6 Hz), 3.10 s (6H, Me), 6.24 d (1H, 5-CH=, J = 16.0 Hz), 6.32 d (1H, =C**H**Fu, J = 16.0 Hz), 6.31–6.36 m (2H, 3′-H, 4′-H), 7.36 d (1H, 5′-H, J = 1.9 Hz), 8.98 s (1H, NH) 10.56 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 24.3 and 25.1 (Me), 26.1 (5-CH_2), 28.4 (CH_2N^+), 86.7 (C^5), 113.9 (5-CH=), 121.1 (=**C**HFu), 116.3 ($C^{4'}$), 117.1 ($C^{3'}$), 145.9 ($C^{2'}$), 159.3 ($C^{5'}$), 157.9 (C=N), 169.1 and 169.4 (C=O). Found, %: C 49.51; H 6.42; N 14.39. $C_{16}H_{23}ClN_4O_3S$. Calculated, %: C 49.67; H 5.99; N 14.48.

***N*-{4-Acetyl-5-[2-(2-furyl)ethenyl]-5-[2-(morpholin-4-yl)ethyl]-4,5-dihydro-1,3,4-thiadiazol-2-yl}-acetamide hydrochloride (IVf).** Yield 68%, mp 168–171°C. IR spectrum, ν, cm^{-1}: 3426 (NH), 2656 (NH^+), 1626 (C=C), 1586 (C=N), 1545 (amide II). ^1H NMR spectrum, δ, ppm: 2.14 s and 2.16 s (3H each, COMe), 2.41 d.t (2H, 5-CH_2, J = 16.2, 3.9 Hz), 3.04 t (2H, CH_2N^+, J = 16.0 Hz), 3.68 m (4H, C**H**$_2$$CH_2O$), 4.13 m (4H, CH_2O), 6.19 d (1H, 5-CH=, J = 16.0 Hz), 6.28 d (1H, =C**H**Fu, J = 16.0 Hz), 6.29–6.34 m (2H, 3′-H, 4′-H), 7.41 d (1H, 5′-H, J = 1.9 Hz), 9.05 s (1H, NH), 10.59 s (1H, NH^+). ^{13}C NMR spectrum, δ_C, ppm: 22.7 and 23.4 (Me), 28.4 (5-CH_2), 31.6 (CH_2N^+), 47.1 (**C**$H_2$$CH_2O$), 68.4 ($CH_2O$), 78.9 ($C^5$), 115.1 (5-CH=), 123.4 (=**C**HFu), 117.4 ($C^{4'}$), 118.5 ($C^{3'}$), 151.2 ($C^{2'}$), 154.5 ($C^{5'}$), 149.3 (C=N), 169.2 and 169.7 (C=O). Found, %: C 50.65; H 5.54; N 13.48. $C_{18}H_{25}ClN_4O_4S$. Calculated, %: C 50.40; H 5.87; N 13.06.

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