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БИСТИАДИАЗОЛАМИНЫ: СИНТЕЗ, СТРОЕНИЕ, СВОЙСТВА

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В данной работе выполнено прогнозирование спектров биологической (в том числе антибактериальной) активности шести двухъядерных гетероциклических аминов, в которых два 1,3,4-тиадиазольных фрагмента объединены метиленовым, этиленовым, пропиленовым, бутиленовым, пентиленовым и этениленовым спейсерами. Данные исследования показали высокую вероятность проявления ценных биологических свойств (таких как Cl^--транспортный ингибитор АТФазы, мукомембранный протектор, ингибитор убихинол-цитохром-с-редуктазы) и, следовательно, важность синтеза этих соединений. Ранее данные продукты были получены, но методы синтеза оказались либо невоспроизводимыми, либо требовали использования дорогостоящих реактивов. В связи с этим нами была усовершенствована методика синтеза исследуемых соединений: продукты были получены взаимодействием тиосемикарбазида с соответствующей дикарбоновой кислотой в среде оксихлорида фосфора. Синтезированные молекулы были охарактеризованы данными ИК, электронной, ЯМР спектроскопии, масс-спектрометрии, элементного анализа и рентгеноспектрального микроанализа. Методом рентгеноструктурного анализа впервые установлена структура бис(5-амино-1,3,4-тиадиазол-2-ил)метана в виде соли – двойного гидрохлорида моногидрата. Полный набор данных рентгеноструктурного анализа был депонирован в Кембриджской базе данных (депонент CCDC 2087791), и его можно получить на сайте https://www.ccdc.cam.ac.uk/structures/ или по электронной почте: deposit@ccdc.cam.ac.uk. Геометрические параметры (длина связи, углы между атомами и гетероциклическими плоскостями) всех соединений были рассчитаны методом теории функционала плотности. Квантово-химические данные для бис(5-амино-1,3,4-тиадиазол-2-ил)метана соответствуют данным рентгеноструктурного анализа.

Ключевые слова: гетероциклы, прогноз, квантовая химия, синтез, рентгеноструктурный анализ

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BISTHIADIAZOLEAMINES: SYNTHESIS, STRUCTURE AND PROPERTIES

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In this work the prediction of spectra of biological (including antibacterial) activity of six binuclear heterocyclic amines, in which two 1,3,4-thiadiazole fragments were united metylene, ethylene, propylene, butylene, pentylene and ethenylene spacers, was performed. These researches have demonstrated a high probability of the exhibition of valuable biological properties (such as Cl^--transporting ATPase inhibitor, mucomembranous protector, ubiquinol-cytochrome-c reductase inhibitor) and, therefore, the significance of these compounds synthesis. Previously, these products were obtained, but the synthesis methods were either not reproducible or required the use of expensive reagents. Therefore, the method of investigated compounds synthesis was improved. The products were synthesized by interaction of thiosemicarbazide with corresponding dicarboxylic acid in phosphorus oxychloride medium. The obtained molecules were characterized by IR, electronic, NMR spectroscopy, mass-spectrometry, data of elemental analysis and X-ray spectral microanalysis. For the first time the structure of bis(5-amino-1,3,4-thiadiazole-2-yl)methane as double hydrochloride monohydrate was established by X-ray crystallography. A full set of X-ray diffraction data was deposited in the Cambridge Structural Database (deposit CCDC 2087791) and it can be gotten from the site https://www.ccdc.cam.ac.uk/structures/, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, or e-mail: deposit@ccdc.cam.ac.uk. Geometric parameters (bond length, angles between atoms and heterocyclic planes) of all compounds were calculated using method DFT. Quantum chemical data for bis(5-amino-1,3,4-thiadiazole-2-yl)methane correspond X-ray analysis data.

Key words: heterocycles, prediction, quantum chemistry, synthesis, X-ray diffraction analysis

INTRODUCTION

It is well known, in process of time antibacterial drugs resistance increases. Therefore, one of the important tasks of modern pharmaceutical chemistry is the search and development of the most effective and less toxic drugs. The obtaining of new medicinal substances is a very difficult and time-long process. In order to reduce the time spent on the search for a molecule with the desired properties and the least toxic effect, programs are used to predict of the presence of biological, including antibacterial, properties according to the structural formula of a compound.

In their structure many pharmaceutical substances contain heterocyclic fragments which act as pharmacophores. The 1,3,4-thiadiazole fragment, which is part of many drugs, such as diacarb, etazole, metazolamide, tizanidine, megazole, is the most interesting for chemical modification. Therefore, as objects of study in this work, we selected bis(1,3,4-thiadiazole)-amines, in which heterocyclic fragments are united by methylene, ethylene, propylene, butylene, pentylene, and ethenylene spacers. To determine the advisability of these molecules obtaining, biological properties were predicted.

EXPERIMENTAL PART

General Information

The prediction biological activity spectra were carried out using programs PASS (Prediction of Activity Spectra for Substances) [1] and Anti-Bac-Pred, which available on the Internet: http://www.way2drug.com/PASSonline/ and http://way2drug.com/antibac/.

Thiosemicarbazide ("Vekton") was recrystallizated from water with absorbent carbon (m.p. 180 °C). Malonic, succinic, glutaric, adipic, pimelic, and fumaric acids ("Vekton") were used as a commercial product without further purification.

IR spectra were collected with a AVATAR 360 FT-IR spectrometer. UV/Vis spectra were recorded

with a HITACHI U-2001 spectrophotometer. The determination of the carbon, hydrogen, nitrogen and sulfur percentage in the samples was carried out on a FLASH EA1112 Termo Quest analyzer. A Vega 3 SBH scanning electron microscope was used to obtain the surface physics of the samples. MALDI-TOF mass-spectra were collected with a AXIMA Confidence (SHIMADZU). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 500 (500.17 MHz, ^{1}H; 125.77 MHz, ^{13}C) spectrometer and referenced to residual DMSO-*d*$_6$ (2.50 ppm, ^{1}H; 39.5 ppm, ^{13}C). Chemical shifts are reported in ppm, and multiplicities are indicated by s (singlet), t (triplet), and m (multiplet). To assign the signals of the obtained compounds, the ^{1}H, ^{13}C HSQC spectrum was recorded. X-Ray analysis was carried out with the monocrystal diffractometer Xcalibur Ruby with CCD-detector. All calculations were performed using software packages SHELXS [2], SHELXL [3], CrysAlis PRO [4], Mercury [5], publCIF [6] и OLEX2 [7]. CCDC 2087791 contains the supplementary crystallographic data for bis(5-amino-1,3,4-thiadiazole-2-yl)methane as double hydrochloride monohydrate. These data can be obtained free of charge *via* https://www.ccdc.cam.ac.uk/structures/, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, or e-mail: deposit@ccdc.cam.ac.uk.

Quantum chemical calculations were performed by the density functional theory using hybrid functional B3LYP and basis set 6-31G (d,p) [8]. The preparation of the initial geometry, processing and visualization of the results of calculations were performed using programs ChemCraft [9] and Mercury [5].

*General Procedure for the Synthesis of Bis-thiadiazoleamines (**1**-**6**)*

The mixture of thiosemicarbazide (0.77 g, 8.4 mmol) and correspond dicarboxylic acid (4.2 mmol) was dissolved in 10 mL of phosphorus oxychloride. The reaction mass temperature was raised step-by-step to 60 °C during 30 min, kept 20-25 min. Then reaction mixture was poured out on the ice, impurities were filtered. The target product was extracted from filtrate by 40% NaOH solution addition to pH = 7. The precipitation was filtered, washed by ice-water to remove inorganic impurities, then by organic solvents, and dried.

*The synthesis of bis(5-amino-1,3,4-thiadiazole-2-yl)methane (**1**)*

Following the general procedure, compound **1** was obtained as white powder. Yield: 0.365 g (40.6%); m.p. 258-260 °C; ^{1}H NMR (500.17 MHz, [D$_6$]DMSO): δ = 7.16 (s, 4H, -N*H*$_2$), 4.41 ppm (s, 2H, -C*H*$_2$-); ^{13}C NMR (125.77 MHz, [D$_6$]DMSO): δ = 169.69, 154.30, 30.90 ppm; IR (KBr): $\tilde{\nu}$ = 3269 (N–H$_s^{as}$), 3094 (N–H$_s^{s}$), 2940 (CH$_2$–CH$_{2s}$), 1635 (N–H$_d$), 1513 (C=N$_s$), 1401 (CH$_2$–CH$_{2d}$), 1322, 1170, 1131, 903, 623, 424 cm^{-1}; MALDI-TOF MS (CHCA): *m/z* (%): 215.43 (22) [*M*+H]$^+$, 237.45 (100) [*M*+Na]$^+$, 253.44 (24) [*M*+K]$^+$ (calcd for $C_5H_6N_6S_2$ 214.01).

*The synthesis of bis(5-amino-1,3,4-thiadiazole-2-yl)ethane (**2**)*

Following the general procedure, compound **2** was obtained as white powder. Yield: 0.57 g (59.0%); m.p. 184-186 °C; ^{1}H NMR (500.17 MHz, [D$_6$]DMSO): δ = 7.04 (s, 4H, -N*H*$_2$), 2.81-2.78 ppm (t, 4H, -C*H*$_2$-); ^{13}C NMR (125.77 MHz, [D$_6$]DMSO): δ = 169.04, 156.86, 29.41 ppm; IR (KBr): $\tilde{\nu}$ = 3237 (N–H$_s^{as}$), 3101 (N–H$_s^{s}$), 2789 (CH$_2$–CH$_{2s}$), 1640 (N–H$_d$), 1529 (C=N$_s$), 1400 (CH$_2$–CH$_{2d}$), 1333, 1149, 1053, 688, 639, 422 cm^{-1}; MALDI-TOF MS (DHB): *m/z* (%): 229.44 (100) [*M*+H]$^+$, 251.46 (54) [*M*+Na]$^+$, 267.44 (24) [*M*+K]$^+$ (calcd for $C_6H_8N_6S_2$ 228.03); elemental analysis calcd (%) for $C_6H_8N_6S_2$: C 31.57, H 3.53, N 36.81, S 28.09; found: C 31.89, H 3.28, N 36.98, S 27.85.

*The synthesis of bis(5-amino-1,3,4-thiadiazole-2-yl)propane (**3**)*

Following the general procedure, compound **3** was obtained as white powder. Yield: 0.84 g (82.5%); m.p. 268-270 °C; ^{1}H NMR (500.17 MHz, [D$_6$]DMSO): δ = 7.04 (s, 4H, -N*H*$_2$), 2.87-2.84 (t, 4H, -C*H*$_2$-CH$_2$-C*H*$_2$-), 2.00-1.94 ppm (m, 2H, -CH$_2$-C*H*$_2$-CH$_2$-); IR (KBr): $\tilde{\nu}$ = 3276 (N–H$_s^{as}$), 3097 (N–H$_s^{s}$), 2860 (CH$_2$–CH$_{2s}$), 1622 (N–H$_d$), 1521 (C=N$_s$), 1398 (CH$_2$–CH$_{2d}$), 1204, 1055, 694, 653, 583, 430 cm^{-1}; MALDI-TOF MS (DHB): *m/z* (%): 243.48 (100) [*M*+H]$^+$, 265.50 (54) [*M*+Na]$^+$ (calcd for $C_7H_{10}N_6S_2$ 242.04).

*The synthesis of bis(5-amino-1,3,4-thiadiazole-2-yl)butane (**4**)*

Following the general procedure, compound **4** was obtained as white powder. Yield: 0.175 g (16.27%); m.p. 210-212 °C; ^{1}H NMR (500.17 MHz, [D$_6$]DMSO): δ = 7.00 (s, 4H, -N*H*$_2$), 2.83-2.81 (t, 4H, -C*H*$_2$-CH$_2$-CH$_2$-C*H*$_2$-), 1.67-1.65 ppm (m, 4H, -CH$_2$-C*H*$_2$-C*H*$_2$-CH$_2$-); IR (KBr): $\tilde{\nu}$ = 3272 (N–H$_s^{as}$), 3099 (N–H$_s^{s}$), 2860 (CH$_2$–CH$_{2s}$), 1635 (N–H$_d$), 1523 (C=N$_s$), 1396 (CH$_2$–CH$_{2d}$), 1342, 1233, 1184, 1057, 697, 589, 444 cm^{-1}; MALDI-TOF MS (DHB): *m/z* (%): 257.58 (100) [*M*+H]$^+$, 279.59 (46) [*M*+Na]$^+$, 295.59 (16) [*M*+K]$^+$ (calcd for $C_8H_{12}N_6S_2$ 256.06); elemental analysis calcd (%) for $C_8H_{12}N_6S_2$: C 37.48, H 4.72, N 32.78, S 25.01; found: C 37.80, H 4.47, N 32.95, S 24.78.

*The synthesis of bis(5-amino-1,3,4-thiadiazole-2-yl)pentane (**5**)*

Following the general procedure, compound **5** was obtained as white powder. Yield: 0.97 g (85.4%); m.p. 239-240 °C; ^{1}H NMR (500.17 MHz, [D$_6$]DMSO):

δ = 6.98 (s, 4H, -NH_2), 2.79-2.76 (t, 4H, -CH_2-CH_2-CH_2-CH_2-CH_2-), 1.67-1.61 (m, 4H, -CH_2-CH_2-CH_2-CH_2-CH_2-), 1.40-1.34 ppm (m, 2H, -CH_2-CH_2-CH_2-CH_2-CH_2-); ^{13}C NMR (125.77 MHz, [D_6]DMSO): δ = 168.61, 158.74, 29.81, 29.12, 28.15 ppm; IR (KBr): $\tilde{\nu}$ = 3296 (N–H_s^{as}), 3104 (N–H_s^{s}), 2860 (CH_2–CH_{2s}), 1617 (N–H_d), 1521 (C=N_s), 1395 (CH_2–CH_{2d}), 1342, 1198, 1055, 692, 564, 410 cm^{-1}; MALDI-TOF MS (DHB): *m/z* (%): 271.55 (74) [*M*+H]$^+$, 293.56 (100) [*M*+Na]$^+$, 309.53 (6) [*M*+K]$^+$ (calcd for $C_9H_{14}N_6S_2$ 270.07).

*The synthesis of bis(5-amino-1,3,4-thiadiazole-2-yl)ethene (**6**)*

Following the general procedure, compound **6** was obtained as yellow powder. Yield: 0.05 g (5.26%); m.p. 253-255 °C; ^{1}H NMR (500.17 MHz, [D_6]DMSO): δ = 7.13 (s, 4H, -NH_2), 1.07 ppm (s, 2H, -C*H*=); IR (KBr): $\tilde{\nu}$ = 3282 (N–H_s^{as}), 3111 (N–H_s^{s}), 1257, 1238 (=C–H_d), 1628 (N–H_d), 1508 (C=N_s), 1238, 1129, 1067, 928, 699 cm^{-1}; UV/Vis (DMSO, c = 3.01·10^{-4} mol·L^{-1}): λ_{max} (lgε) = 365 (3.67) nm; MALDI-TOF MS (DHB): *m/z* (%): 227.42 (40) [*M*+H]$^+$, 249.42 (100) [*M*+Na]$^+$ (calcd for $C_6H_6N_6S_2$ 226.01).

Mass- and NMR spectra of compounds **1-6** are presented in Supporting Information http://journals.isuct.ru/ctj/article/view/3980 (Figs. S1-S11).

RESULTS AND DISCUSSION

At the first stage of work using chemoinformatics methods and special computer programs such as PASS and Anti-Bac-Pred we predicted biological (including antibacterial) properties of six molecules: bis(5-amino-1,3,4-thiadiazole-2-yl)methane (**1**), -ethane (**2**), -propane (**3**), -butane (**4**), -pentane (**5**) and -ethene (**6**).

It was determined that the compounds **1** and **2** can exhibit properties of Cl$^-$-transporting ATPase inhibitor with possibility 72.6%, the molecules **4** and **5** potentially are ubiquinol-cytochrome-*c* reductase inhibitors, *i.e.* **1**, **2**, **4** and **5** can be use as regulators diverse metabolic pathways. Also, **4** and **5** are mucomembranous protectors with possibility 72-73%. The compound **3** can exhibit antidiabetic properties potentially. The molecule **6** can be Mcl-1 antagonist with possibility 88.1% that is **6** would be able to use as cancer drugs (Table 1) [10-17].

Antibacterial research *in silico* of compounds **1-6** showed that all molecules can exhibit antimicrobial activity to gram-negative bacteria *Shigella sp.* with possibility 60-63%.

Thus, these studies confirm the feasibility of the molecules **1-6** synthesis.

Earlier, the authors [18,19] proposed synthesis methods of bis(5-amino-1,3,4-thiadiazole-2-yl)methane (**1**), -ethane (**2**), -propane (**3**), -butane (**4**) and -pentane (**5**). However, the first way we can't reproduce as Ashutosh B. *et al.* [18] obtained bis(5-amino-1,3,4-thiadiazole-2-yl)alkanes by interaction dichlorine anhydrides of dicarboxylic acids with thiosemicarbazide in sulfuric acid medium. The formation of dichlorine anhydrides occurred in thionyl chloride. The last one, as it turned out, destroys thiosemicarbazide and distillation of thionyl chloride excess result in hydrolysis of dichlorine anhydrides to dicarboxylic acids. The second method, proposed by Epishina M.A. *et al*. [19], involves the use expensive reagents.

Table 1

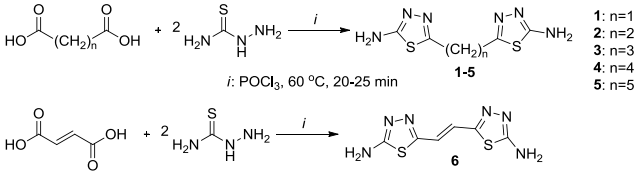
The spectrum of biological activity of molecules 1-6

***Таблица 1.* Спектр биологической активности молекул 1-6**

Compound	P_a	P_i	Activity
1	0.726	0.012	Cl$^-$-transporting ATPase inhibitor
2	0.726	0.012	Cl$^-$-transporting ATPase inhibitor
3	0.722	0.005	Antidiabetic
4	0.724	0.046	Mucomembranous protector
5	0.710	0.065	Ubiquinol-cytochrome-*c* reductase inhibitor
6	0.733	0.042	Mucomembranous protector

We attempted to carry out the synthesis in a hydrochloric acid medium, varying the temperature and time of reaction [20]. But yields were unsatisfactory.

In this regard, we obtained compounds **1-5** by interaction equimolar amounts of corresponding dicarboxylic acids with thiosemicarbazide in phosphorus oxychloride medium. Reaction mixture temperature was increased step-by-step to 60 °C for 30 min, then was kept – 20-25 min. A further increase in temperature led to the appearance of the mercaptans smell, which indicated the destruction of thiosemicarbazide. Moreover, for the first time using this method bis(5-amino-1,3,4-thiadiazole-2-yl)ethene (**6**) was obtained (Scheme).



Scheme. Synthesis scheme of bisthiadiazoleamines **1-6**

Схема. Синтез бистиадиазоламинов **1-6**

The synthesized compounds structures were confirmed by data of IR, NMR spectroscopy, mass-spectrometry, elemental, X-ray spectral microanalysis and X-ray crystallography.

IR spectra of all obtained molecules (Fig. S12, Supporting Information) are similar and have bands in region 3237-3296, 3094-3104 и 1617-1640 cm^{-1} that can be characterized as asymmetrical, symmetrical stretching and deformation vibrations of the N–H bonds of the amine groups. The bands at 2789-2940 and 1395-1401 cm^{-1} correspond to stretching and deformation vibrations of the alkyl spacer, at 1513-1529 cm^{-1} – stretching vibrations of the C=N bond of the heterocyclic fragments.

The comparison of IR spectra of compounds **2** and **6** (Fig. S13, Supporting Information) showed that in spectrum of bis(5-amino-1,3,4-thiadiazole-2-yl)ethene two bands are in region 1257 and 1238 cm^{-1}, which correspond to vibrations of the =C–H bonds of the ethenylene spacer. In the same time, in spectrum of bis(5-amino-1,3,4-thiadiazole-2-yl)ethane only one band is in this region.

UV-Vis spectra of bisthiadiazolealkanes **1**-**5** have not pronounced absorption band, only shoulder is in region 275-280 nm. UV-Vis spectrum of compound **6** (Fig. S14, Supporting Information) has absorption band in region 365 nm, the present of which can explain by emergence of a conjugated system of double bonds.

The obtained compounds **1**-**6** were characterized by mass-spectrometry data. For example, Fig. S6 (Supporting Information) shows mass-spectrum of bis(5-amino-1,3,4-thiadiazole-2-yl)ethene, in which two signals at 227.42 and 249.42 Da correspond to $[M+H]^+$ and $[M+Na]^+$ molecular ions, respectively. Isotopic distribution corresponds to the theoretically values.

^1H, ^{13}C NMR spectra were recorded for the synthesized compounds **1**-**6**. So, in ^1H NMR spectrum of bis(5-amino-1,3,4-thiadiazole-2-yl)pentane (Fig. 1) triplet at 2.79-2.76 ppm and multiplets at 1.67-1.61, 1.40-1.34 ppm characterize proton resonance of alkyl spacer. The NH_2-groups protons signal is present at 6.98 ppm. Integral signal intensities confirm these assignments.

In ^{13}C NMR spectrum of bis(5-amino-1,3,4-thiadiazole-2-yl)pentane (Fig. 2) three signals at 29.81, 29.12 and 28.15 ppm correspond to resonance C atoms of alkyl spacer and two signals at 168.61 and 158.74 ppm is related to C atoms of thiadiazole cycle.

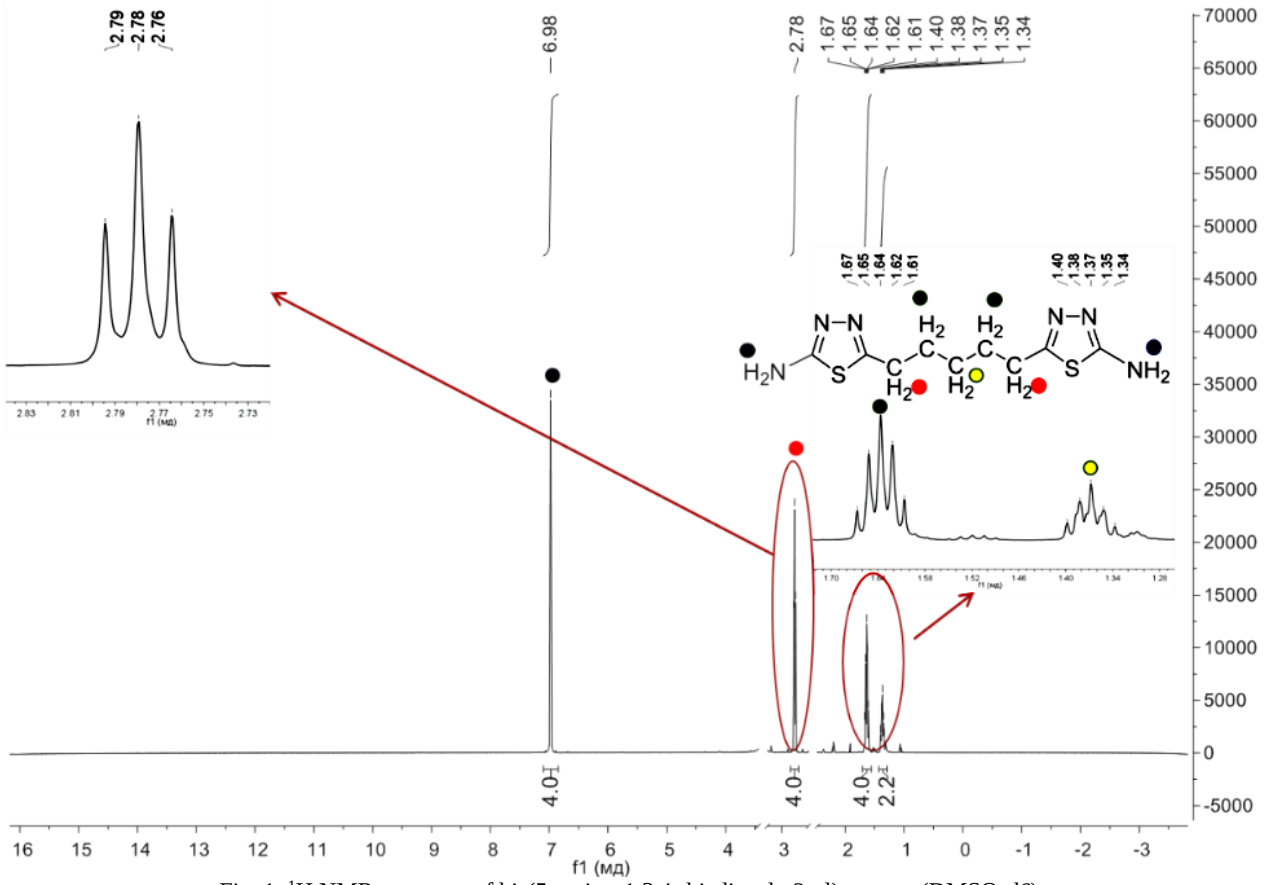


Fig. 1. ^1H NMR spectrum of bis(5-amino-1,3,4-thiadiazole-2-yl)pentane (DMSO-*d6*)
Рис. 1. ^1H ЯМР спектр бис(5-амино-1,3,4-тиадиазол-2-ил)пентана (ДМСО-*d6*)

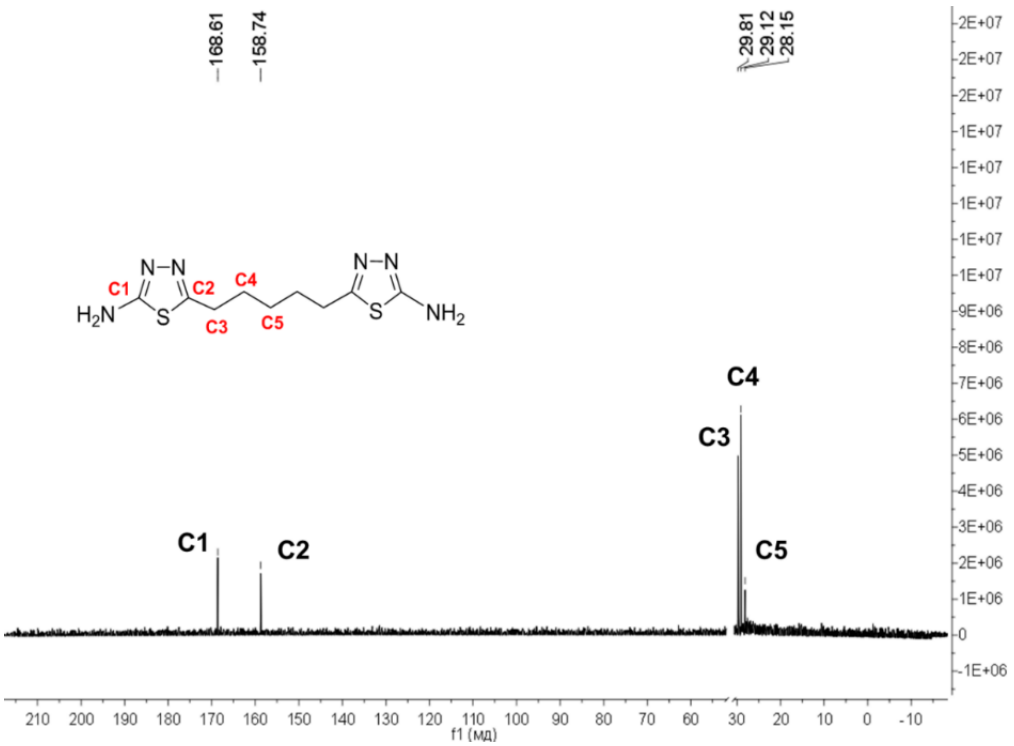


Fig. 2. ^{13}C NMR spectrum of bis(5-amino-1,3,4-thiadiazole-2-yl)pentane (DMSO-*d6*)
Рис. 2. ^{13}C ЯМР спектр бис(5-амино-1,3,4-тиадиазол-2-ил)пентана (ДМСО-*d6*)

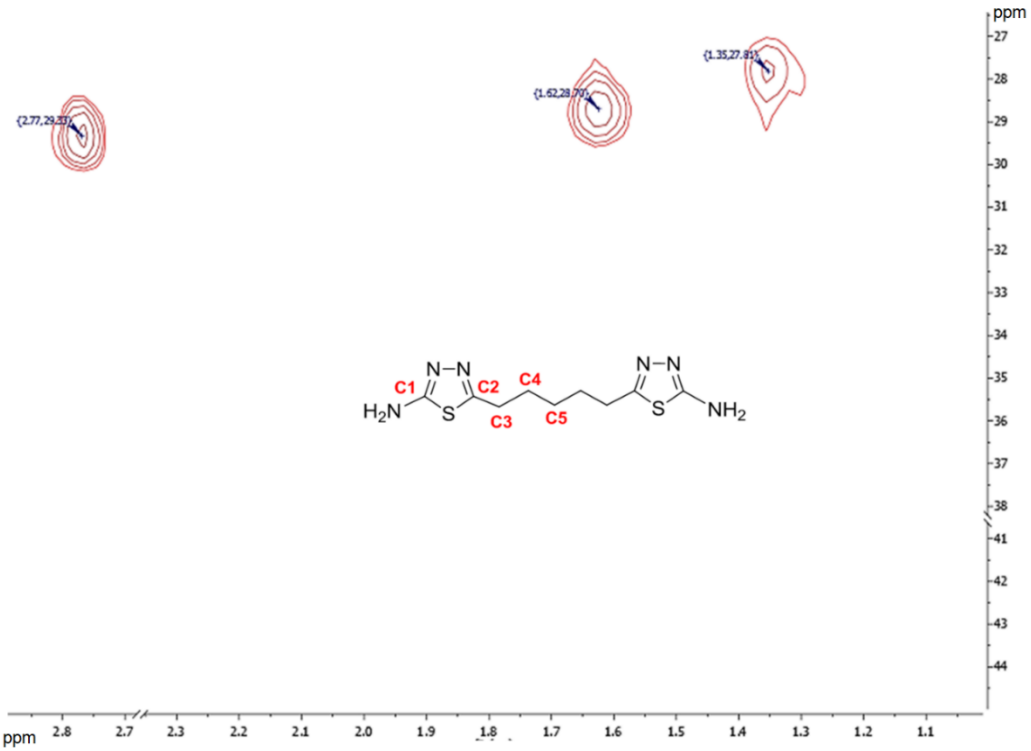


Fig. 3. Cross peaks of 2D ^{1}H-^{13}C HSQC of NMR spectrum of bis(5-amino-1,3,4-thiadiazole-2-yl)pentane (DMSO-*d6*)
Рис. 3. Кросс-пики 2D ^{1}H-^{13}C HSQC ЯМР спектра бис(5-амино-1,3,4-тиадиазол-2-ил)пентана (ДМСО-*d6*)

2D ^{1}H-^{13}C HSQC NMR spectrum was carried out for assignment of signals. The spectrum showed a noticeable correlation between the signals C3, C4 and C5 atoms (29.33, 28.70 and 27.81 ppm) and the protons giving rise to the signal at 2.77, 1.62 and 1.35 ppm, respectively (Fig. 3).

The structure of bis(5-amino-1,3,4-thiadiazole-2-yl)methane (**1**) was established by single crystal

X-ray analysis, which showed the molecule exists as double hydrochloride monohydrate (Fig. 4), because the crystal was grown by slowly evaporating a saturated solution in dilute hydrochloric acid.

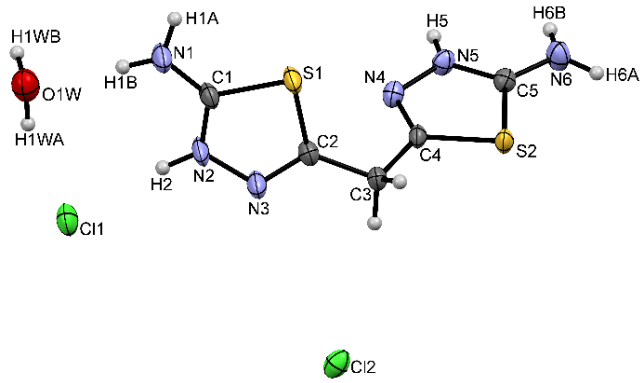


Fig. 4. Asymmetric unit of **1** showing the non-hydrogen atoms as 50 % probability thermal ellipsoids

Рис. 4. Ассиметричная единица **1** (неводородные атомы представлены как тепловые колебания эллипсоидов с 50 % вероятностью)

The unit cell of **1** contains four nonplanar cations, which are not linked directly to each other by hydrogen bonds (Fig. S15, Supporting Information). Each anion links two cations *via* intermolecular N–H···Cl hydrogen bonds (Table S1, Supporting Information). Water molecules also stabilize the crystal packing through the formation of O–H···Cl and N–H···O hydrogen bonds. All OH, NH and NH_2 groups are involved in hydrogen bonding forming a complex three-dimensional network.

Crystal data, data collection and structure refinement details are summarized in Table S2 (Supporting Information).

To establish the geometric structure of the obtained products, quantum chemical calculations were performed at the DFT level using the hybrid B3LYP functional and the basis set 6-31G (d, p).

The comparison of the geometric parameters according to X-ray crystallography data and quantum chemical calculations in the molecule **1** showed that the bond lengths and angles are in agreement (Table 2).

The optimization of the molecules **1**-**6** geometry showed that in the bis(5-amino-1,3,4-thiadiazole-2-yl)ethene **6**, in comparison with other bisthiadiazolealkanes **1**-**5**, there is a decrease in the bond lengths in the heterocyclic fragment. Due to the flexible alkyl bridge, thiadiazole fragments are located at an angle, and in a row from bistiadiazolemethane to bistiadiazolepropane a decrease the angle between planar thiadiazole fragments is observed; with a further increase in the length of the alkyl chain, an increase of the angle occurs. Due to the presence of a double bond, the bis(5-amino-1,3,4-thiadiazole-2-yl)ethene molecule is planar (Table 3).

Atom coordinates for **1-6** are presented in Supporting Information (Tables S3-S8).

Table 2

Selected geometric parameters (Å) for 1

***Таблица 2.* Избранные геометрические параметры 1 (Å)**

Bond length	X-ray analysis	Quantum chemical calculations
C1–N1	1.304(3)	1.373
C1–S1	1.725(2)	1.763
C1–N2	1.323(3)	1.307
N1–H1A	0.890(2)	1.013
N1–H1B	0.820(2)	1.010
S1–C2	1.745(2)	1.773
C2–C3	1.495(3)	1.503
C2–N3	1.284(3)	1.296
N2–H2	0.860(2)	-
N2–N3	1.373(3)	1.370
S2–C4	1.750(2)	1.774
S2–C5	1.731(2)	1.763
C3–H3A	0.970	1.095
C3–H3B	0.970	1.095
C3–C4	1.493(2)	1.504
H5–N5	0.830(2)	-
C4–N4	1.284(3)	1.296
N4–N5	1.374(2)	1.370
C5–N5	1.321(3)	1.307
C5–N6	1.310(3)	1.372
N6–H6A	0.880(3)	1.013
N6–H6B	0.760(3)	1.010
Angle	X-ray analysis	Quantum chemical calculations
N1–C1–S1	124.5(2)	122.3
N1–C1–N2	125.5(2)	123.3
S1–C1–N2	110.0(1)	114.3
C1–S1–C2	88.04(9)	85.6
S1–C2–C3	122.4(1)	123.0
S1–C2–N3	115.1(1)	113.4
C3–C2–N3	122.5(2)	123.5
C1–N2–N3	117.0(2)	112.5
C4–S2–C5	87.7(9)	85.5
C2–C3–C4	113.9(2)	114.1
C2–N3–N2	109.9(2)	114.2
S2–C4–C3	120.6(1)	122.9
S2–C4–N4	115.3(1)	113.4
C3–C4–N4	124.2(2)	123.7
C4–N4–N5	109.8(2)	114.2
S2–C5–N5	110.1(1)	114.3
S2–C5–N6	124.9(2)	122.3
N5–C5–N6	125.0(2)	123.3
N4–N5–C5	117.2(2)	112.5

Table 3

The angles between planar thiadiazole fragments

***Таблица 3.* Величины углов между плоскими тиадиазольными фрагментами**

Compound	Angle, °
1	108.85
2	88.13
3	53.32
4	85.18
5	114.03
6	180

CONCLUSION

Thus, the prediction of biological (including antibacterial) activity spectra of bis(5-amino-1,3,4-thiadiazole-2-yl)methane **1**, -ethane **2**, -propane **3**, -butane **4**, -pentane **5** and -ethene **6** was carried out. Based on the obtained results about the feasibility of the molecules **1**-**6** synthesis the method was improved. The produced molecules were characterized by IR, electronic, NMR spectroscopy, mass-spectrometry, data of elemental analysis and X-ray spectral microanalysis. The structure of bis(5-amino-1,3,4-thiadiazole-2-yl)methane was established by X-ray crystallography. Geometric parameters of all compounds were calculated using method DFT.

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