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Antiviral drug Triazavirin, selectively labeled with ^{2}H, ^{13}C, and ^{15}N stable isotopes. Synthesis and properties

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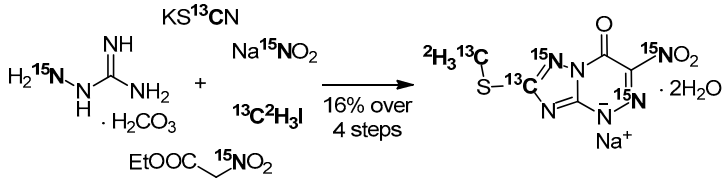


Isotope-labeled antiviral drug Triazavirin containing ^{2}H, ^{13}C, and ^{15}N atoms in its structure has been synthesized. $^{13}C^{2}H_3I$ and $KS^{13}CN$ served as donors of ^{13}C isotopes. The use of ^{13}C-MeI containing ^{2}H atoms made it possible to additionally incorporate deuterium labels into the structure of the compound. The ^{15}N atoms were incorporated using ^{15}N-enriched sodium nitrite, aminoguanidine carbonate, and ethyl nitroacetate. The resulting $^{2}H_3$,$^{13}C_2$,$^{15}N_3$-Triazavirin was characterized by NMR spectroscopy.

Keywords: azoloazines, antiviral activity, NMR spectroscopy, spin-spin coupling constants, stable isotopes.

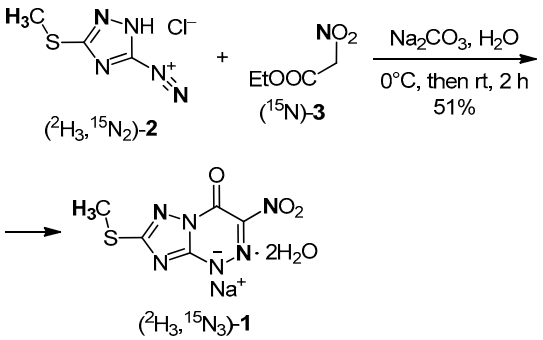
Triazavirin (TZV) (**1**) is used to treat diseases caused by various types of influenza A and B viruses, including the pandemic H5N1 (avian influenza virus).[1–6] Research to expand the spectrum of action of this drug is ongoing. The data obtained make it possible to classify TZV as a first-line drug in the treatment of tick-borne viral encephalitis.[7] In addition, TZV (**1**) is undergoing clinical trials as an antiviral agent against the pandemic strain of coronavirus COVID-19.[8–10]

To evaluate the new data obtained on the activity of TZV, more complete information on the mechanism of its action, bioavailability, and biological transformation would be required. To solve these problems, it is advisable to use compounds enriched in stable isotopes (^{2}H, ^{13}C, and ^{15}N) which can be used as internal standards for chromato-mass spectrometry.[11,12] This strategy makes it possible to investigate blood, serum, and other biological fluids for the presence of the studied biologically active compounds and their metabolites. The ability to analyze the concentrations of a compound and its metabolites is necessary for pharmacokinetic studies and in the selection of effective doses of drugs.

Previously, we proposed the synthesis of labeled TZV ($^{2}H_3$,$^{15}N_3$)-**1** containing ^{2}H and ^{15}N atoms in its structure (Scheme 1, labeled atoms are indicated in bold). The incorporation of stable isotopes was based on the reaction of the diazonium salt (^{2}H,$^{15}N_2$)-**2** with ethyl nitroacetate (^{15}N)-**3**.[13] It is important to note that this compound was used as an internal standard in studying the effect of TZV (**1**) on the aggregation of natural peptides prone to self-association, as exemplified by the β-amyloid peptide (βAP) fragment accumulating in the brains of patients with Alzheimer's disease, and the cytolytic peptide of bee venom melittin.[14]

This work presents the preparation of labeled TZV ($^{2}H_3$,$^{13}C_2$,$^{15}N_3$)-**1** containing two additional ^{13}C atoms (Scheme 2). In this case, the inclusion of ^{13}C isotopes in the structures of biologically active compounds makes it possible to additionally involve the method of ^{13}C NMR spectroscopy for the study of metabolic and pharmacokinetic pathways.[15,16]

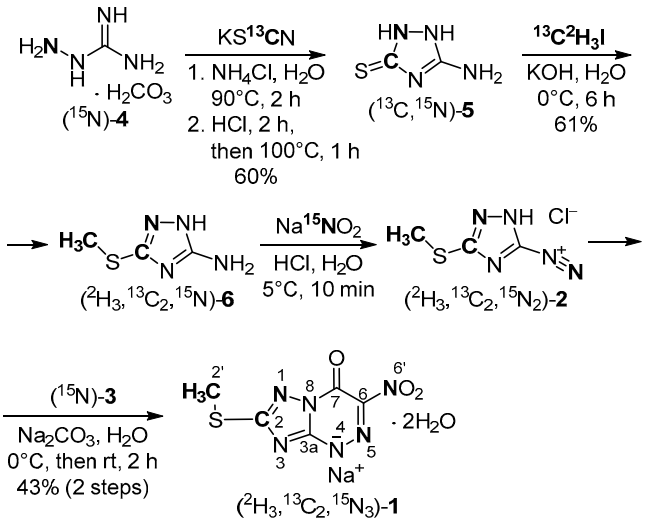
Scheme 1



Enriched potassium thiocyanate and ($^2H_3$,^{13}C)-MeI were used as donors of ^{13}C atoms. Treatment of aminoguanidine carbonate (^{15}N)-**4** (^{15}N, 98%) with labeled KSCN (^{13}C, 95–98%) gave 5-amino-3-mercaptotriazole (^{13}C,^{15}N)-**5** in 60% yield (Scheme 2). The presence of ^{13}C and ^{15}N atoms in the structure of (^{13}C,^{15}N)-**5** was confirmed by the registration of the molecular ion $[M+H]^+$ peak with a monoisotopic mass of 119.0233 Da in the high-resolution mass spectrum. The reaction of compound (^{13}C,^{15}N)-**5** with labeled MeI (99.5% ^2H, 99% ^{13}C) gave aminotriazole ($^2H_3$,$^{13}C_2$,^{15}N)-**6** in 61% yield. The incorporation of additional ^2H and ^{13}C labels in this case was proved by mass spectrometry ($[M+H]^+$ *m*/*z* 137.0612). The reaction of aminotriazole ($^2H_3$,$^{13}C_2$,^{15}N)-**6** with ^{15}N-nitrous acid generated from enriched $NaNO_2$ (98%, ^{15}N) resulted in the formation of diazonium salt ($^2H_3$,$^{13}C_2$,$^{15}N_2$)-**2**. Subsequent treatment with ethyl nitroacetate (^{15}N)-**3** (^{15}N, 98%) afforded isotopically enriched triazolotriazine sodium salt dihydrate ($^2H_3$,$^{13}C_2$,$^{15}N_3$)-**1** in 43% yield.

Studying compound ($^2H_3$,$^{13}C_2$,$^{15}N_3$)-**1** by NMR spectroscopy it was found that in the ^{13}C NMR spectrum the signals of all carbon atoms have additional splitting characterized by the constants of the spin-spin interaction ^{13}C–^{15}N ($J_{C–N}$) with labeled ^{15}N atoms. The quantitative measurement of $J_{C–N}$ was carried out on the basis of a set of one-dimensional ^{13}C NMR experiments recorded with selective decoupling from ^2H and ^{15}N atoms (Figs. S3–S5, Supplementary information file). The values of the measured ^{13}C–^{15}N coupling constants are presented in Table 1. The presence of spin-spin interactions between the ^{13}C-2 and ^{13}C-2' atoms with the ^{15}N-1 atom was additionally confirmed by the data of the ^{13}C–^{15}N HMBC two-dimensional spectrum in which the corresponding cross peaks are present (Fig. 1). Analysis of the ^{13}C–^{15}N HMBC two-dimensional spectrum also showed the presence of a long-range constant ($^4J_{C–N}$) which is due to the interaction between ^{13}C-2 and ^{15}N-5 atoms. In addition, a set of cross peaks with the corresponding $J_{C–N}$ constants between the C-3a, C-6, and C-7 atoms with a natural content of the ^{13}C isotope and ^{15}N-enriched N-1, N-5, and N-6' atoms was observed in the ^{13}C–^{15}N HMBC spectrum.

Scheme 2



Analysis of the ^{13}C–^{15}N HMBC spectrum also indicated the possible signal frequencies of the N-3, N-4, and N-8 atoms with the natural abundance of the ^{15}N isotope (Fig. 1, Table 1). Using the one-dimensional ^{13}C NMR spectrum acquired with decoupling from ^2H and ^{15}N atoms, the geminal coupling constant ^{13}C–^{13}C ($^2J_{C–C}$) between the labeled ^{13}C-2 and ^{13}C-2' atoms was recorded (Table 1). At the same time, the recording of the one-dimensional ^{13}C NMR spectrum with decoupling only from ^{15}N atoms made it possible to estimate the ^2H–^{13}C ($^1J_{C–D}$) heteronuclear interaction. The presence of the $^1J_{C–D}$ constant in the signal of the C-2' atom (Table 1) unambiguously proves the presence of deuterium atoms in

Table 1. Chemical shifts and SSCC of signals in the ^{13}C and ^{15}N NMR spectra of compound ($^2H_3$,$^{13}C_2$,$^{15}N_3$)-**1**

^{13}C NMR spectrum (175 MHz, DMSO-d_6)		^{15}N NMR spectrum (71 MHz, DMSO-d_6)	
Atom	δ, ppm (*J*, Hz)*	Atom	δ, ppm, *J*, Hz
C-2	166.4 dddd $^3J_{C2–D}$ < 1*** $^2J_{C2–C2'}$ = 1.2** $^1J_{C2–N1}$ = 4.7 (×) $^4J_{C2–N5}$ ~ 0.4 (×)	N-1	259.1 dd $^3J_{N1–C2'}$ = 2.6 $^1J_{N1–C2}$ = 4.7
C-2'	13.3 sept dd $^1J_{C2'–D}$ = 21.6 $^2J_{C2'–C2}$ = 1.2** $^3J_{C2'–N1}$ = 2.6 (×)	N-3*[4] N-4*[4]	233.0 s 294.0 s
C-3a	160.7 dd $^2J_{C3a–N5}$ = 2.1 (×) $^2J_{C3a–N1}$ = 0.4	N-5	397.0 d $^2J_{N5–N6'}$ = 6.3
C-6	145.1 ddd $^1J_{C6–N5}$ = 1.8 (×) $^1J_{C6–N6'}$ 23.4 (×) $^3J_{C6–N1}$ 1.6 (×)	N-6'	367.9 d $^2J_{N5-N6'}$ = 6.3
C-7	143.5 dddd $^3J_{C7–C2}$ = 7.0 $^2J_{C7–N5}$ = 1.3 $^2J_{C7–N6'}$ = 5.3 (×) $^2J_{C7–N1}$ = 3.6 (×)	N-8*[4]	226.0 s

* The sign (×) denotes the coupling constants which lead to the appearance of cross peaks in the ^{13}C–^{15}N HMBC spectrum (Fig. 1).

** ^{13}C–^{13}C SSCC were measured with simultaneous decoupling from ^2H-2' and ^{15}N-1 nuclei.

*** SSCC was not observed due to the large half-width of the corresponding ^{13}C signal. Previously, the value of $^3J_{C2–D}$ was estimated at 0.7 Hz.[13]

*[4] The signals of atoms with a natural abundance of the ^{15}N isotope were detected in the ^{13}C–^{15}N HMBC spectrum.

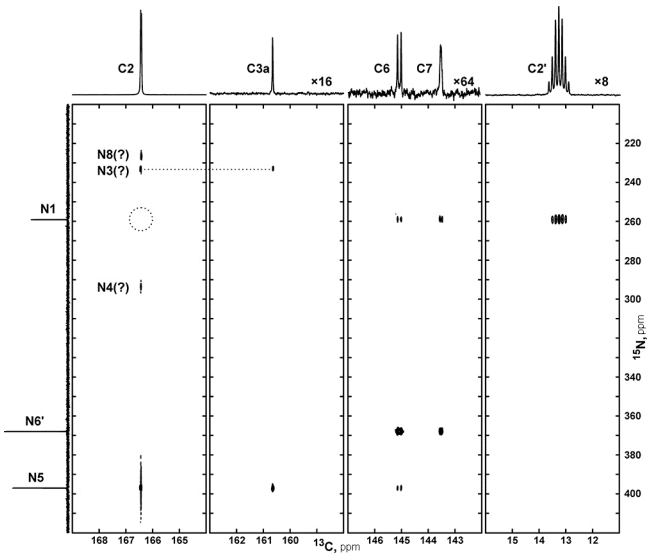


Figure 1. Fragments of the ^{13}C–^{15}N HMBC spectrum of compound ($^{2}H_3$,$^{13}C_2$,$^{15}N_3$)-**1** and the corresponding segments of the one-dimensional ^{13}C and ^{15}N NMR spectra. The intensity of the fragments of the one-dimensional ^{13}C NMR spectrum shown in the panels on the right is increased relative to the fragment on the left panel. The ^{13}C–^{15}N HMBC spectrum showing correlations of ^{15}N nuclei with ^{13}C-2 nucleus was obtained with selective decoupling from ^{15}N-1 nucleus (the signal area is denoted by a dotted circle).

the structure of ($^{2}H_3$,$^{13}C_2$,$^{15}N_3$)-**1**. The signal of the 2'-$^{13}C^{2}H_3$ group was observed as a doublet in the one-dimensional ^{2}H NMR spectrum at ~2.65 ppm (Fig. S1, Supplementary information file). The upfield component of the doublet was partially overlapped by the signal from the solvent DMSO-d_6.

The one-dimensional ^{15}N NMR spectrum of compound ($^{2}H_3$,$^{13}C_2$,$^{15}N_3$)-**1** showed three signals of labeled ^{15}N nitrogen atoms (Table 1, Fig. 1) presented as a doublet of doublets at 259.1 ppm (N-1) and two doublets at 397.0 and 367.9 ppm (N-5 and N-6', respectively). The assignment of signals in the one-dimensional ^{15}N NMR spectrum was carried out on the basis of measuring the ^{13}C–^{15}N coupling constant and analysis of chemical shifts.[13] The ^{15}N–^{15}N spin-spin interaction is reflected in the structure of the signals of the N-5 and N-6' atoms. The multiplicity of the resonance signal of the ^{15}N-1 atom is explained by the presence of two ^{13}C–^{15}N coupling constants with labeled carbon atoms. This conclusion was confirmed by acquiring one-dimensional ^{15}N NMR spectra recorded with selective decoupling from the ^{13}C-2 and ^{13}C-2' atoms (Fig. S2, Supplementary information file). These experiments made it possible to quantitatively measure the direct constant $^{1}J_{C2–N1}$ (Table 1).

To conclude, we have developed methods that allow, in addition to the ^{2}H and ^{15}N atoms, to selectively incorporate ^{13}C isotopes into the structure of the antiviral drug Triazavirin. As a result, a sample was obtained containing three types of stable isotopes at once which was characterized by NMR spectroscopy. The practical use of labeled Triazavirin can significantly expand the possibilities in a comprehensive study of the bioavailability, pharmacokinetics, and metabolic pathways of this antiviral drug using mass spectrometry and NMR spectroscopy. This, in turn, can contribute to a more rational choice of treatment strategies.

Experimental

^{1}H, ^{13}C, and ^{15}N NMR (700, 175, and 71 MHz, respectively) and ^{13}C–^{15}N HMBC spectra of compound ($^{2}H_3$,$^{13}C_2$,$^{15}N_3$)-**1** were acquired on a Bruker Avance 700 spectrometer equipped with a triple resonance sensor (^{1}H, ^{13}C, ^{15}N) in DMSO-d_6, using residual solvent signals (2.50 ppm for ^{1}H nuclei) or solvent signals (40.11 ppm for ^{13}C nuclei) as internal standard; liquid NH_3 (for ^{15}N nuclei) was used as external standard. For measuring ^{13}C–^{13}C and ^{13}C–^{15}N SSCCs, a previously developed method[17] of nonlinear approximation of line shapes in one-dimensional ^{13}C NMR spectra recorded with and without decoupling from ^{2}H and ^{15}N nuclei was used. For selective decoupling of ^{15}N nuclei, adiabatic pulses (WURST-20) with a length of 10–20 ms and an inversion range of ~ 1 kHz (14 ppm) for ^{15}N nuclei were used. The decoupling of the ^{2}H nuclei was carried out by the WALTZ-16 wideband sequence. The ^{13}C–^{15}N HMBC two-dimensional spectra were recorded using delays for the transfer of magnetization between the ^{13}C and ^{15}N nuclei in the range of 50–100 ms. In some cases, selective decoupling of the ^{15}N-1 nucleus was achieved using saturation of the corresponding ^{15}N frequency during magnetization transfer and ^{13}C detection. ^{1}H, ^{13}C, and ^{15}N NMR spectra for compounds (^{13}C,^{15}N)-**5** and ($^{2}H_3$,^{13}C,^{15}N)-**6** were registered on a Bruker Avance II spectrometer (400, 100, and 41 MHz, respectively), DMSO-d_6 solvent. TMS was used as internal standard (for ^{13}C, ^{1}H nuclei), liquid ammonia was used as the external standard (for ^{15}N nuclei). High-resolution mass spectra were recorded on a Finnigan LTQ FT mass spectrometer equipped with a 7 Tesla superconducting magnet and an Ion Max electrospray ionizer. Melting points were determined in open capillaries on a Stuart SMP3 apparatus.

Ethyl nitroacetate (^{15}N)-**3**[13] (^{15}N enrichment 98%) and aminoguanidine (^{15}N)-**4**[18] (^{15}N enrichment 98%) were synthesized according to the previously described methods. Labeled MeI (^{2}H, 99.5% and ^{13}C, 99%) was supplied by Aldrich. Enriched with stable isotopes sodium nitrate (^{15}N, 98%) and potassium thiocyanate (^{13}C, 95–98%) were supplied by Cambridge Isotope Laboratories.

5-Amino-3-mercapto-1,2,4-(3-^{13}C,2-^{15}N)triazole ((^{13}C,^{15}N)-5). (^{15}N)-Aminoguanidine carbonate (^{15}N)-**4** (0.56 g, 4.00 mmol) KS^{13}CN (^{13}C, 95–98%; 0.40 g, 4.00 mmol), NH_4Cl (0.05 g, 0.80 mmol), and water (0.18 ml) were mixed together. The mixture was heated and stirred at 90°C for 2 h, then concentrated HCl (2.70 mmol, 0.46 ml) was added dropwise over 2 h and heating was continued at 100°C for 1 h. Then, a solution of KOH (0.25 g, 4.40 mmol) in H_2O (0.25 ml) was added to the reaction mixture. The mixture was heated at 100°C for 2 h, cooled, filtered, and the filtrate was acidified with concentrated HCl to pH 2. The formed precipitate was filtered off and washed with H_2O. The resulting labeled product (^{13}C,^{15}N)-**5** (0.283 g, 60%, ^{13}C 95–98%, ^{15}N 98%) was used in further syntheses without purification. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.74 (2H,

br. s, NH_2); 12.06 (1H, br. s, NH); 12.25 (1H, dd, $^1J_{H–N}$ = 107.6, $^2J_{H–C}$ = 10.0, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 152.5 (CNH_2, $^2J_{C–C}$ = 5.5); 162.8 (CS, $^1J_{C–N}$ = 12.5). ^{15}N NMR spectrum, δ, ppm (*J*, Hz): 192.2 ($^1J_{C–N}$ = 12.5). Found, *m*/*z*: 119.0233 $[M+H]^+$. $C^{13}CH_5N_3{}^{15}NS$. Calculated, *m*/*z*: 119.0233.

5-Amino-3-($^2H_3$)methylsulfanyl-1,2,4-(3-^{13}C,2-^{15}N)-triazole (($^2H_3$,^{13}C,^{15}N)-6). Labeled 5-amino-3-mercapto-1,2,4-triazole (^{13}C,^{15}N)-**5** (0.118 g, 1.00 mmol) was added to a solution of KOH (0.062 g, 1.10 mmol) in H_2O (2.00 ml). The solution was then cooled to 0°C, $^{13}C^2H_3I$ (^2H 99.5%, ^{13}C 99%; 0.160 g, 1.10 mmol) was added, and the mixture was stirred for 6 h. After evaporation of H_2O under reduced pressure at a temperature not exceeding 60°C to about half of the initial volume, the formed precipitate was filtered off, washed with ice-cold H_2O, and dried. The obtained 5-amino-3-methylmercapto-1,2,4-triazole ($^2H_3$,^{13}C,^{15}N)-**6** (0.082 g, 61%, ^2H 99.5%, ^{13}C 99%, ^{15}N 98%) was used in further syntheses without purification. ^1H NMR spectrum, δ, ppm: 5.94 (2H, br. s, NH_2); 11.88 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 13.0 (sept, $^1J_{C–D}$ = 21.4, C^2H_3); 156.3 (CS); 157.9 (CNH_2). The SSCC for $^{13}C–^{15}N$ was not observed due to signal broadening. ^{15}N NMR spectrum, δ, ppm: 261.4. Found, *m*/*z*: 137.0612 $[M+H]^+$. $C^{13}C_2H_4{}^2H_3N_3{}^{15}NS$. Calculated, *m*/*z*: 137.0612.

2-($^2H_3$)Methylsulfanyl-6-(^{15}N)nitro(2-^{13}C,1,5-$^{15}N_2$)[1,2,4]-triazolo[5,1-*c*][1,2,4]triazin-7(4*H*)-one sodium salt dihydrate (($^2H_3$,$^{13}C_2$,$^{15}N_3$)-1). Labeled 5-amino-3-methylmercapto-1,2,4-triazole ($^2H_3$,$^{13}C_2$,^{15}N)-**6** (0.2 g, 1.47 mmol) was added to a mixture of H_2O (2.00 ml) and concentrated HCl (0.25 ml). The resulting mixture was cooled to –5°C, and a solution of $Na^{15}NO_2$ (0.111 g, 1.50 mmol) in H_2O (1.00 ml) was added dropwise. The reaction mixture was stirred for 10 min and added to a cooled (0°C) solution of ethyl ^{15}N-nitroacetate ((^{15}N)-**3**) (0.30 ml) in 17% aqueous Na_2CO_3 (4.00 ml). The reaction mixture was stirred for 2 h at room temperature, the formed precipitate was filtered and recrystallized from 50% AcOH. Yield 0.185 g (43%, ^2H 99%, ^{13}C 99%, ^{15}N 98%), yellow crystals, mp >300°C. Found, *m*/*z*: 259.0090 [M+H]. $C_3{}^{13}C_2H^2H_3N_3{}^{15}N_3O_3SNa$. Calculated, *m*/*z*: 259.0124. Found, %: C 20.99; H 3.41; N 29.31. $C_3{}^{13}C_2{}^2H_3N_3{}^{15}N_3O_3SNa{\cdot}2H_2O$. Calculated, %: C 21.09; H 3.42; N 29.58.

Supplementary information file containing ^2H, ^{13}C, and ^{15}N NMR spectra of compound ($^2H_3$,$^{13}C_2$,$^{15}N_3$)-**1** is available at the journal website at http://link.springer.com/journal/10593.

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