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2-[2-(Phenylcarbamoyl)hydrazinylidene]propanoates: synthesis, structure and *in vitro* study of the activity against influenza virus

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Experimental

Physicochemical studies were performed using the equipment of the Center for Collective Use "Physicochemical methods for the study of nitro compounds, coordination, biologically active substances and nanostructured materials" of the Interdisciplinary Resource Center for collective use "Modern physicochemical methods for the formation and study of materials for the needs of industry, science and education" Herzen State Pedagogical University of Russia. The ^{1}H, ^{13}C{^{1}H}, ^{1}H—^{1}H dqf-COSY, ^{1}H—^{1}H NOESY, ^{1}H—^{13}C HMQC, HMBC, ^{1}H—^{15}N HMBC NMR spectra were recorded on a JEOL ECX400A spectrometer operating at 399.78 MHz (^{1}H) and 100.53 (^{13}C) or 40.52 MHz (^{15}N) in DMSO-d_6 using residual signals of the nondeuterated solvent (δ_H 2.5, δ_C 39.6) as the references. Chemical shifts of ^{15}N were determined relative to $MeNO_2$. The vibrational spectra were measured on a Shimadzu IR-Prestige-21 Fourier-transform IR spectrometer in KBr pellets (resolution was 2 cm^{-1}). Elemental analysis was performed on a Euro Vector EA 3000 analyzer (CHN Dual).

The starting alkyl 3-nitroacrylates **1a,b** were synthesized according to a procedure described previously.[1]

Methyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate (2a). A solution of nitroacrylate **1a** (300 mg, 2.3 mmol) in glacial acetic acid (5 mL) was added dropwise to a solution of *N*-phenylhydrazinecarboxamide (346 mg, 2.3 mmol) in glacial acetic acid (5 mL). The resulting mixture was stirred for 3 h at room temperature. After removing the solvent, the residue was crystallized from methanol. Yield 510 mg (78%), white powder, mp 110–113°C (MeOH). IR (KBr), ν/cm^{-1}: 3359 (s), 3323 (m), 3247 (br. s, NH), 1728 (s, O–C=O), 1653 (s, N-C=O), 1551 (s), 1384 (s, NO_2). ^{1}H NMR (DMSO-d_6), δ, (*J*, Hz): 3.68 (3H, s, CH_3O); 4.20 (1H, pseudo q, <^{3}J> 5.5, H^{C}); 4.87 (1H, d. d, ^{2}J 14.7, ^{3}J 6.1, H^{A}); 4.93 (1H, d. d, ^{2}J 14.7, ^{3}J 5.6, H^{B}); 5.67 (1H, br. s, N^{1}H); 6.92 (1H, t, <*J*> 7.3, H^{p}); 7.22 (2H, t, <*J*> 7.8, H^{m}); 7.42 (2H, d, <*J*> 7.8, H^{o}); 7.65 (1H, br. s, N^{2}H); 8.47 (1H, br. s, N^{3}H). ^{13}C NMR (DMSO-d_6), δ: 53.0 (CH_3O); 60.6 (CH^{C}); 74.6 (CH_2NO_2); 118.8 (C^{o}); 122.4 (C^{p}); 129.2 (C^{m}); 139.9 (C^{i}); 156.7 (N-C=O); 170.3 (O-C=O). ^{15}N NMR (DMSO-d_6), δ: -308.1 (N^{1}); -274. 9 (N^{3}); -265.0 (N^{2}); 5.5 (NO_2). Found (%): C 46.35; H 4.83; N 19.65. $C_{11}H_{14}N_4O_5$. Calculated (%): C 46.81; H 5.00; N 19.85.

Ethyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate (2b) was synthesized as described for compound **2a** starting from nitroacrylate **1b** (300 mg, 2.07 mmol) and *N*-phenyl-hydrazinecarboxamide (312 mg, 2.07 mmol) in glacial acetic acid. After removing the solvent, the residue was crystallized from ethanol. Yield 470 mg (77%), white powder, mp 77–85°C (EtOH). IR (KBr), ν/cm^{-1}: 3361 (m), 3237 (br. m, NH), 1748 (s, O–C=O), 1669 (s, N-C=O), 1549 (s), 1380 (m, NO_2). ^{1}H NMR (DMSO-d_6), δ, (*J*, Hz): 1.17 (3H, t, ^{3}J = 7.1, CH_3CH$_2$O,); 4.10 (1H, d. q, ^{2}J = 10.7, ^{3}J = 7.1), 4.15 (1H, d. q, ^{2}J = 10.7, ^{3}J = 7.1, CH_3CH_2O); 4.17 (1H, pseudo q, <*J*> 5.6, H^{C}); 4.87 (1H, d. d, ^{2}J 14.7, ^{3}J 5.7, H^{A}); 4.92 (1H, d. d, ^{2}J 14.7, ^{3}J 5.5, H^{B}); 5.63 (1H, br. s, N^{1}H); 6.92 (1H, t, <*J*> 7.3, H^{p}); 7.22 (2H, t, <*J*> 7.8, H^{m}); 7.42 (2H, d, <*J*> 7.8, H^{o}); 7.63 (1H, br. s, N^{2}H); 8.48 (1H, br. s, N^{3}H). ^{13}C NMR (DMSO-d_6), δ: 14.4 (CH_3CH$_2$O); 60.7 (CH^{C}); 61.9 (CH_2O); 74.7 (CH_2NO_2); 118.8 (C^{o}); 122.4 (C^{p}); 129.2 (C^{m}); 139.9 (C^{i}); 156.7 (N-C=O); 169.8 (O-C=O). Found (%): C 48.15; H 5.27; N 18.52. $C_{12}H_{16}N_4O_5$. Calculated (%): C 48.65; H 5.44; N 18.91.

[1] V. V. Pelipko, S. V. Makarenko, R. I. Baichurin, V. M. Berestovitskaya, K. S. Kovalenko, *Russ. J. Org.Chem*., 2017, **53**, 1799.

Methyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate (3a). To a solution of compound **2a** (200 mg, 0.71 mmol) in ethanol (10 mL) was added a solution of potassium hydroxide (40 mg, 0.71 mmol) in water (5 mL). The reaction mixture was stirred for 3 h at room temperature, then evaporated to the minimum amount of solvent. The precipitate was filtered off and dried. The solid residue was recrystallized from MeOH. Yield 110 mg (66%), white powder, mp 172–174°C (MeOH), [lit. yield 87%, mp 180–182°].[2] IR (KBr), ν/cm^{-1}: 3209 cp, 3135 (m, NH), 1726 (s, O–C=O), 1687 (s, N–C=O), 1598 (s, C=N). ^{1}H NMR (DMSO-d_6), δ, (*J*, Hz): 3.73 (3H, s, CH_3O); 2.03 (3H, s, CH_3); 7.01 (1H, t, <*J*> = 7.4, H^p); 7.28 (2H, t, <*J*> = 7.7, H^m); 7.51 (2H, d, <*J*> = 7.7, H^o); 8.82 (1H, s, N^{3}H); 10.16 (1H, br. s, N^{2}H). ^{13}C NMR (DMSO-d_6), δ: 13.1 (CH_3); 52.8 (CH_3O); 119.8 (C^o); 123.4 (C^p); 129.3 (C^m); 138.2 (C=N); 139.0 (C^i); 152.7 (N–C=O); 165.3 (O–C=O). Found (%): C 56.75; H 5.83; N 18.21. $C_{11}H_{13}N_3O_3$. Calculated (%): C 56.16; H 5.57; N 17.86.

Ethyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate (3b) was synthesized as described for compound **3a** starting from compound **2b** (200 mg, 0.68 mmol) and potassium hydroxide (38 mg, 0.68 mmol). The solid residue was recrystallized from EtOH. Yield 120 mg (71%), white powder, mp 162–164°C (EtOH). IR (KBr), ν/cm^{-1}: 3207 (m), 3128 (m, NH), 1709 (s, O–C=O), 1682 (s, N–C=O), 1596 (s, C=N). ^{1}H NMR (DMSO-d_6), δ, (*J*, Hz): 1.25 (3H, t, ^3J = 7.1, C$\underline{H}_3$CH$_2$O); 2.02 (3H, s, CH_3); 4.19 (2H, q, ^3J = 7.1, CH$_3$C$\underline{H}_2$O); 7.01 (1H, t, <*J*> = 7.4, H^p); 7.28 (2H, t, <*J*> = 7.6, H^m); 7.50 (2H, d, <*J*> = 7.7, H^o); 8.80 (1H, br. s, N^{3}H); 10.16 (1H, br. s, N^{2}H). ^{13}C NMR (DMSO-d_6), δ: 13.0 (CH_3); 14.6 ($\underline{C}H_3CH_2O$); 61.5 (CH_2O); 119.7 (C^o); 123.4 (C^p); 129.4 (C^m); 138.4 (C=N); 139.0 (C^i); 152.7 (N–C=O); 164.8 (O–C=O). ^{15}N NMR (DMSO-d_6), δ: -271. 9 (N^3); -40.7 (N^2). Found (%): C 57.49; H 6.08; N 16.44. $C_{12}H_{15}N_3O_3$. Calculated (%): C 57.82; H 6.07; N 16.86.

[2] H. Hrebabecky, J. Beranek, *Collection of Czechoslovak Chemical Communications,* 1975, **40**, 2364.

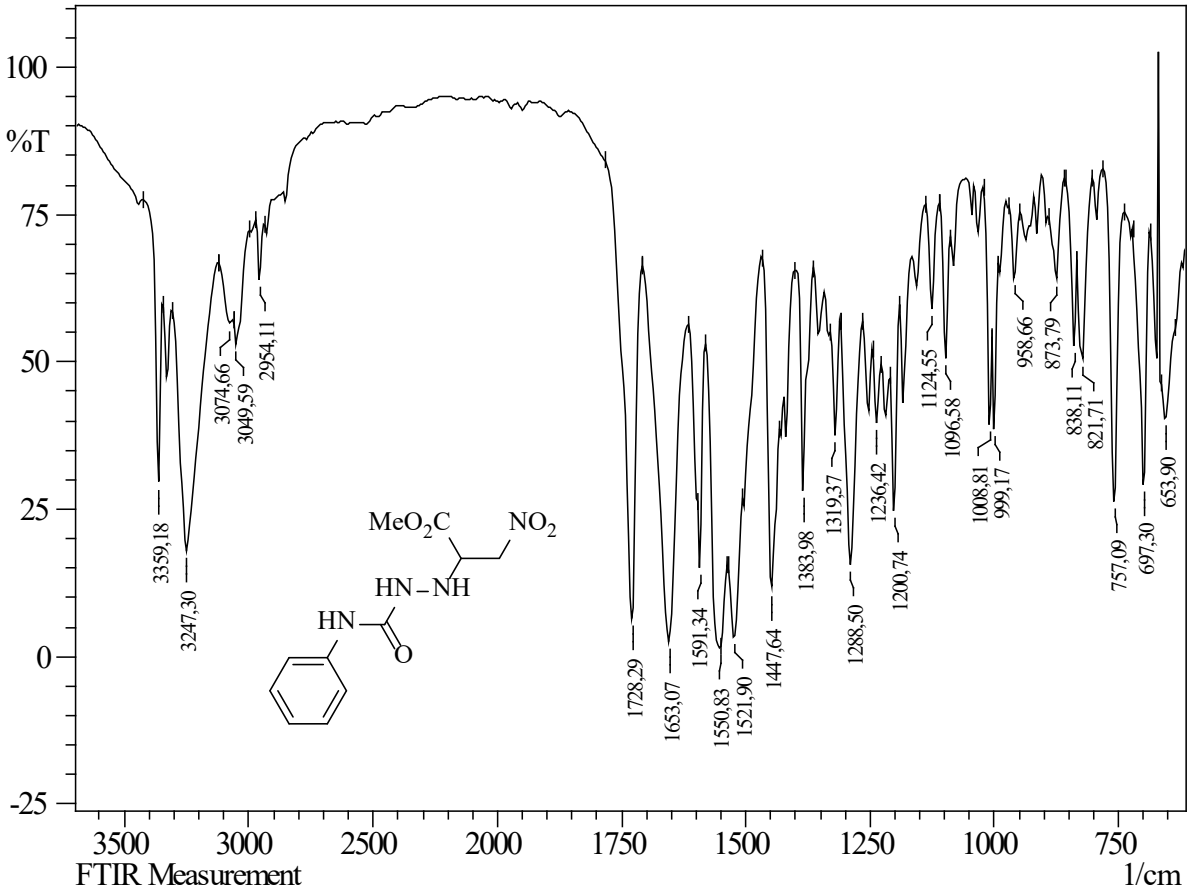

Figure S1. IR spectrum of methyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2a** in KBr

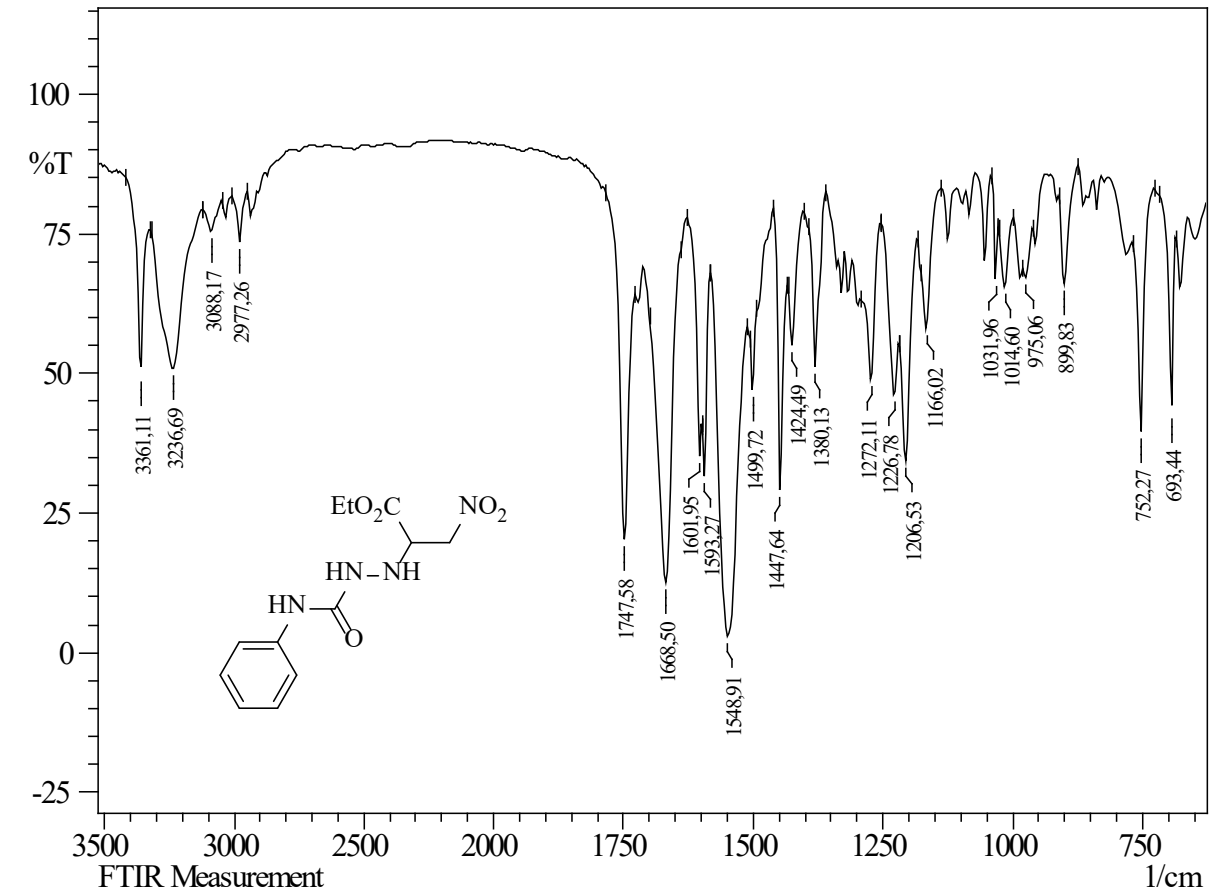

Figure S2. IR spectrum of ethyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2b** in KBr

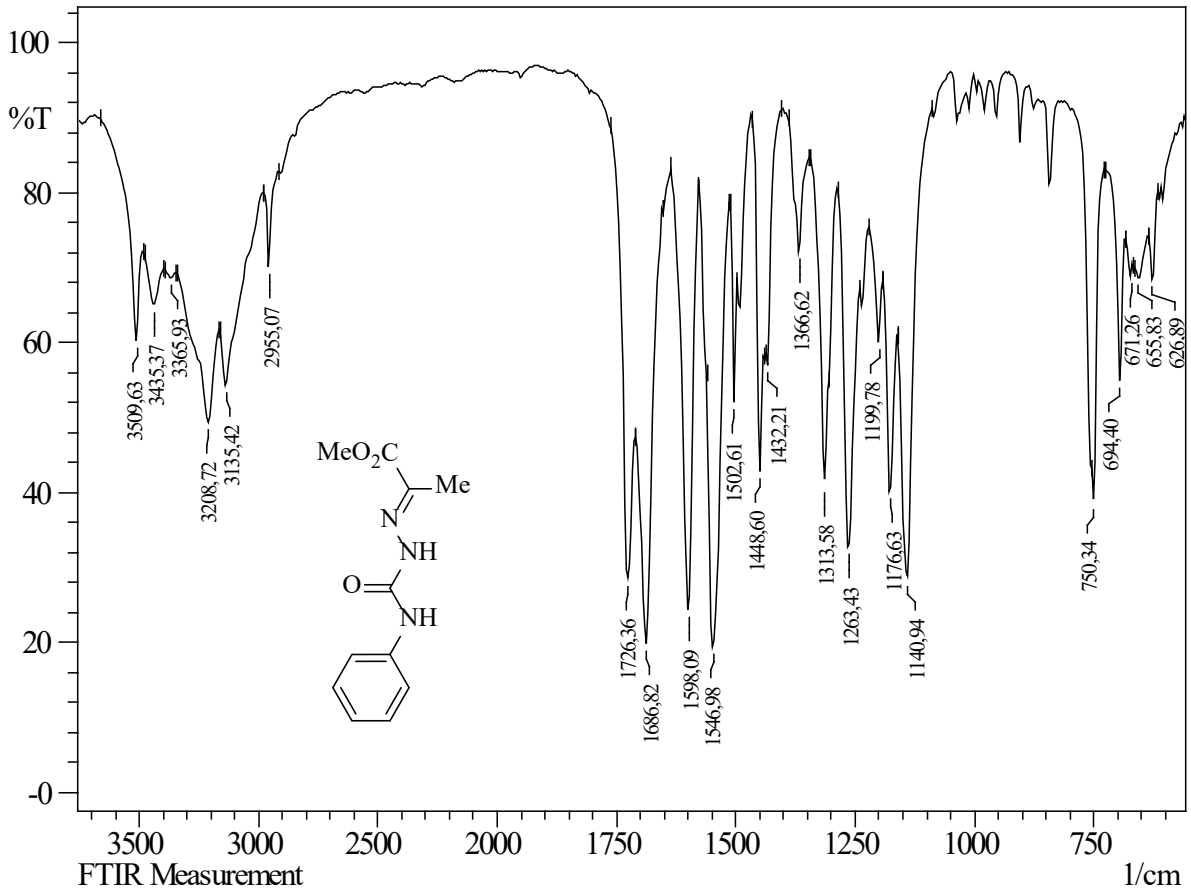

Figure S3. IR spectrum of methyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3a** in KBr

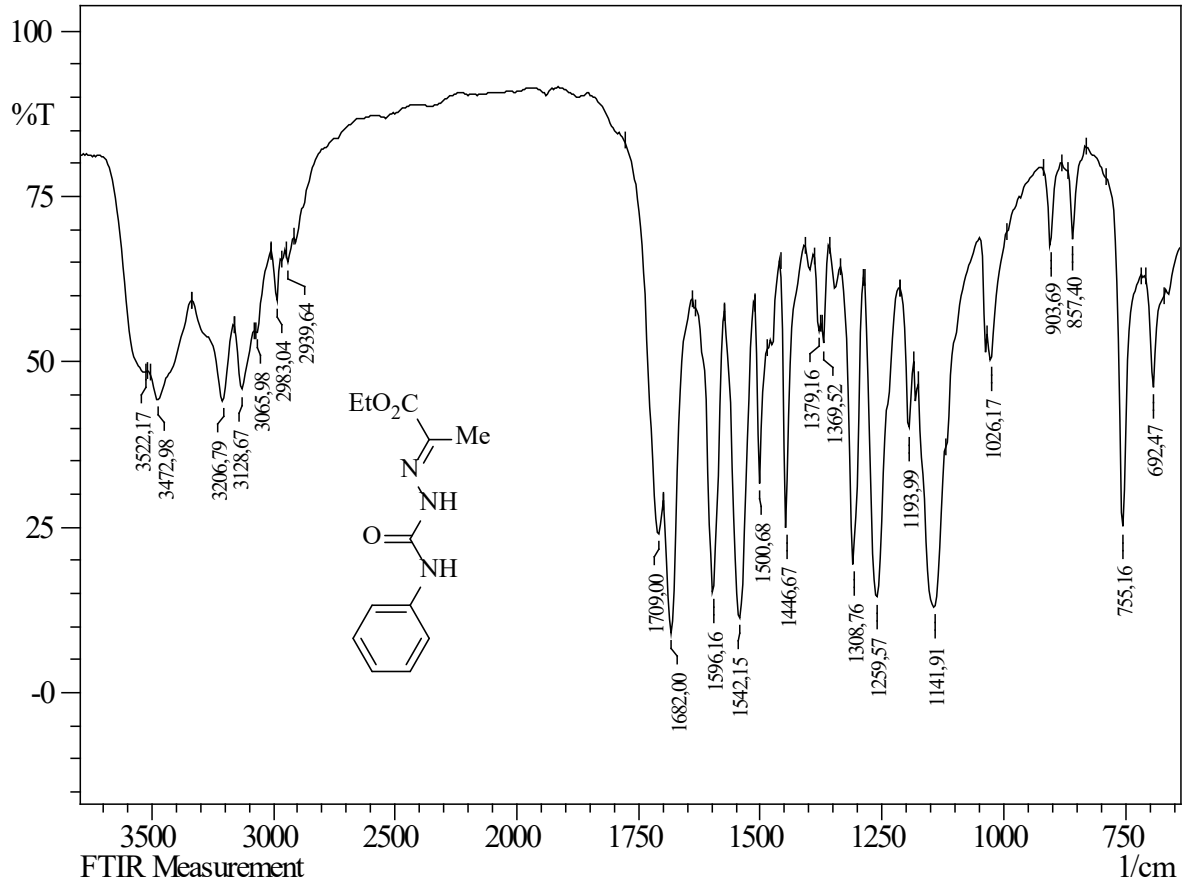

Figure S4. IR spectrum ethyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3b** in KBr

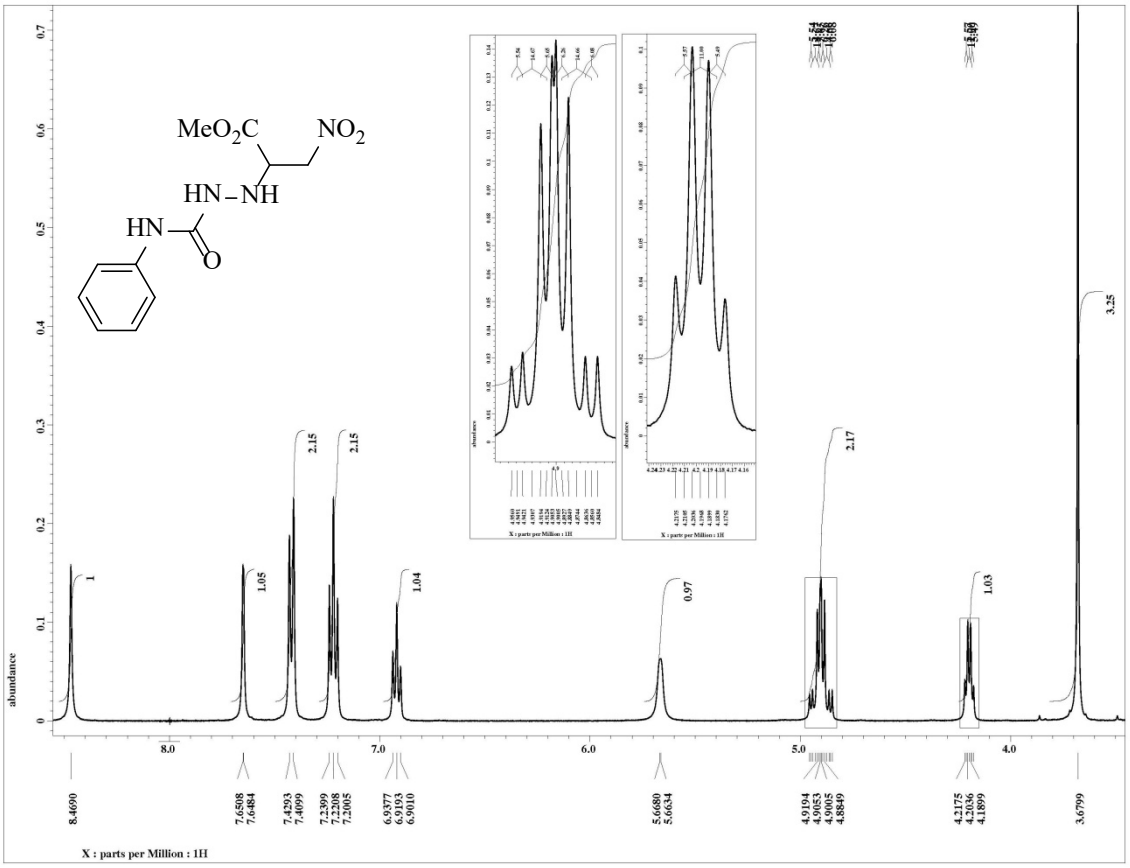

Figure S5. ^{1}H NMR spectrum of methyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2a** in DMSO-d_6

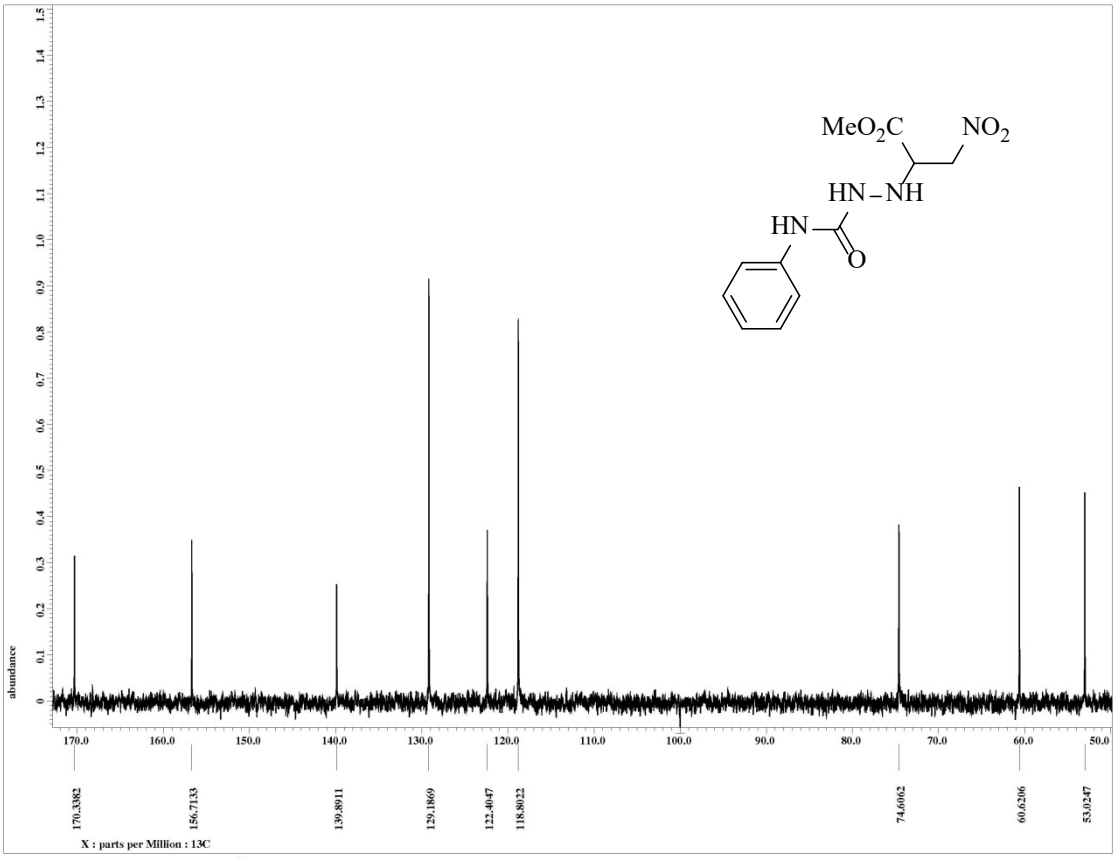

Figure S6. ^{13}C{^{1}H} NMR spectrum of methyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2a** in DMSO-d_6

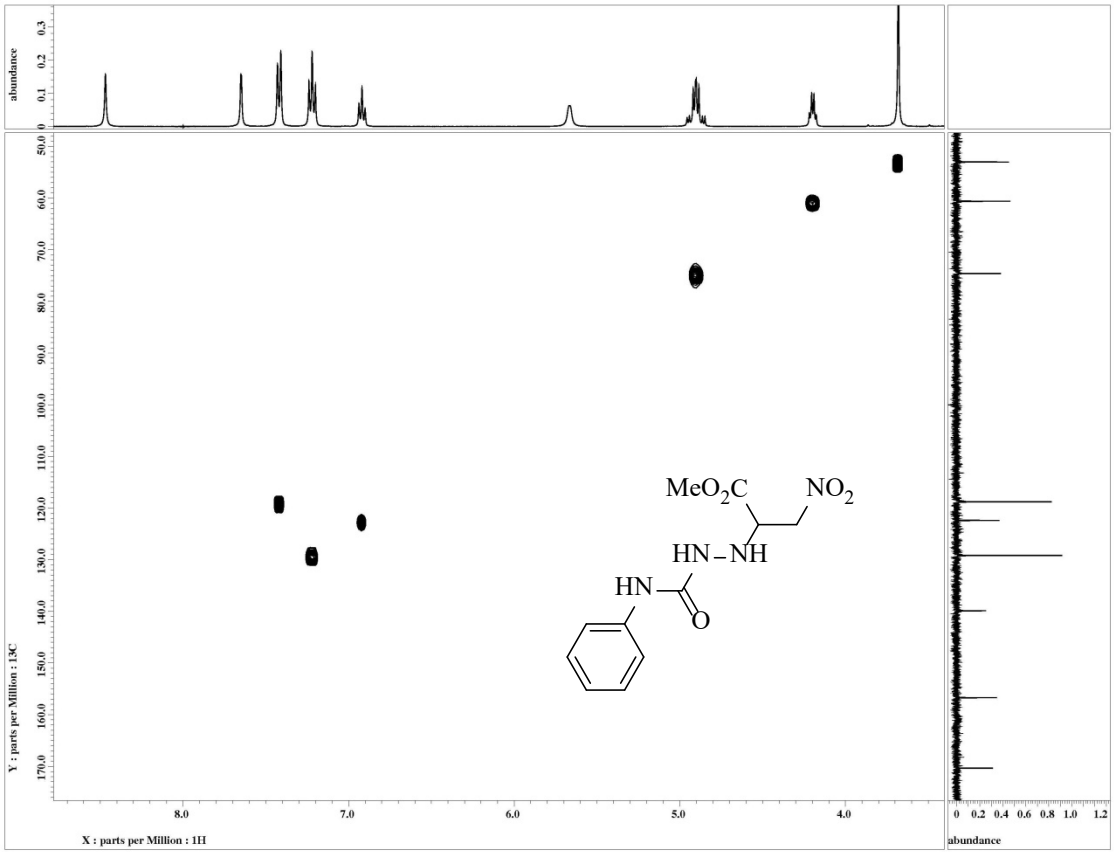

Figure S7. ^{1}H-^{13}C HMQC spectrum of methyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2a** in DMSO-d_6

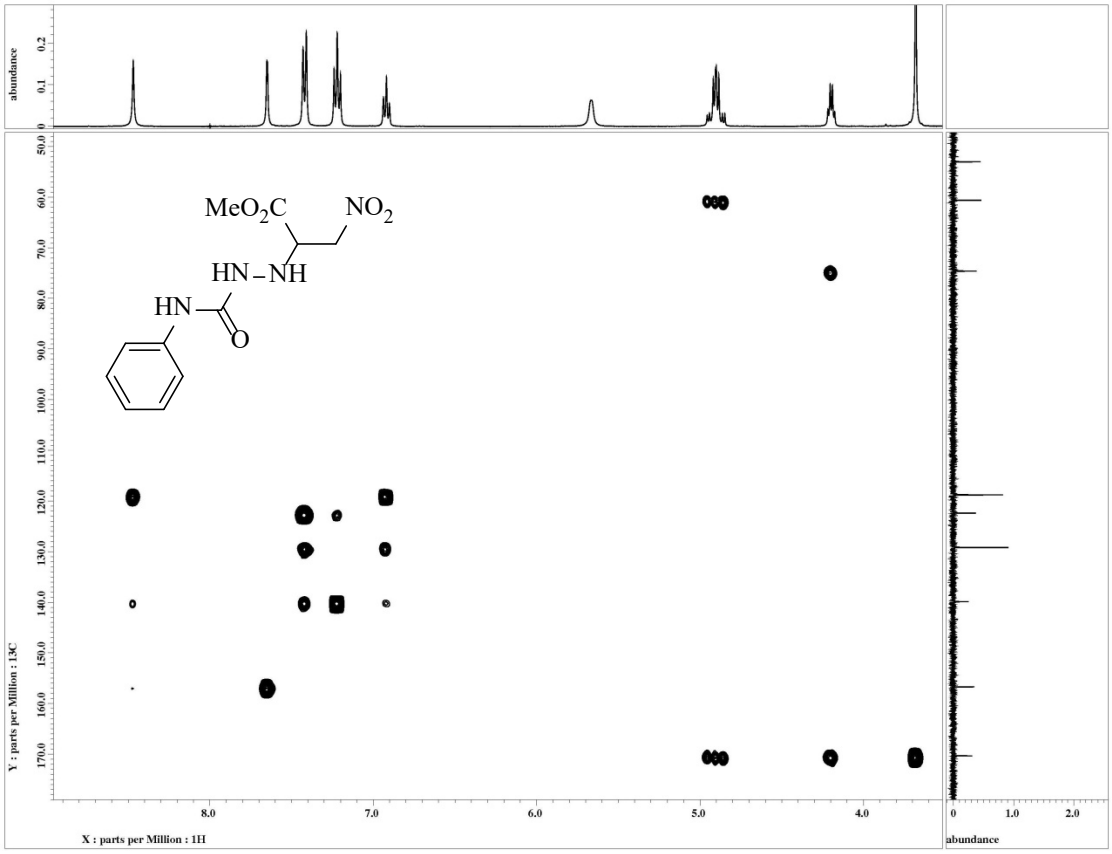

Figure S8. ^{1}H-^{13}C HMBC spectrum of methyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2a** in DMSO-d_6

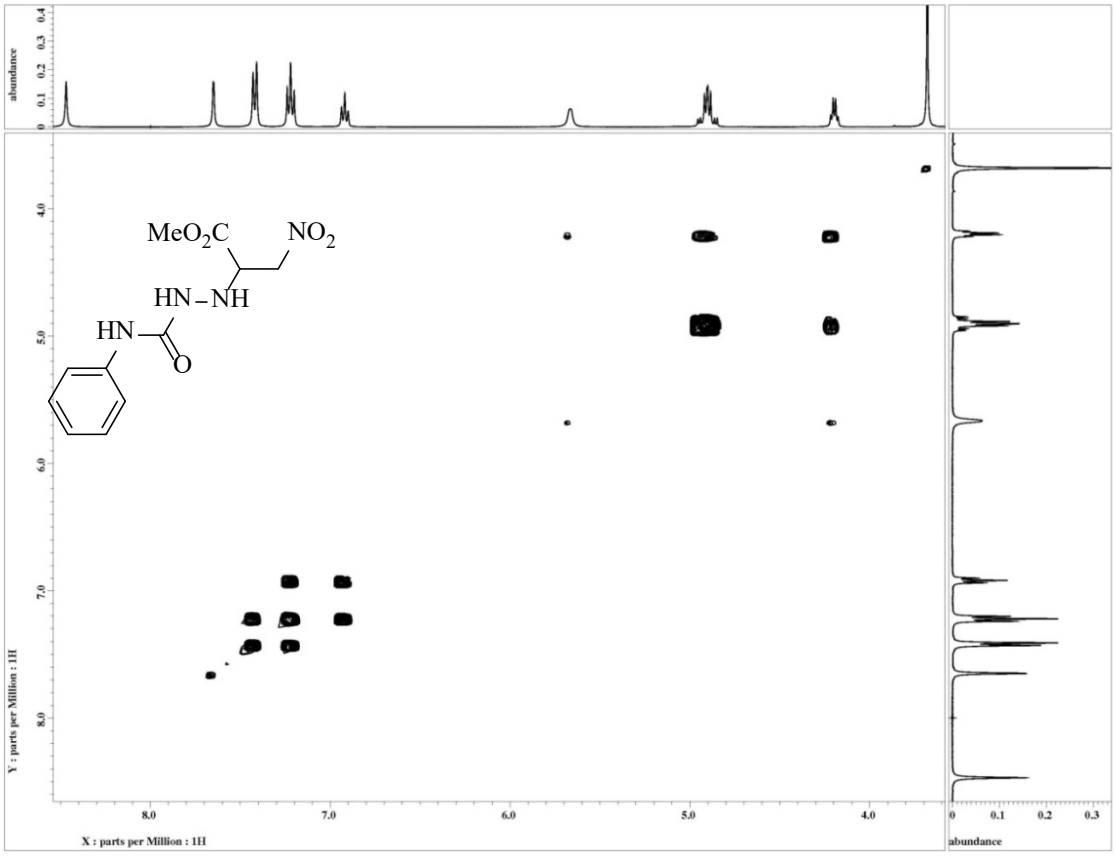

Figure S9. ^{1}H-^{1}H dqf-COSY spectrum of methyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2a** in DMSO-d_6

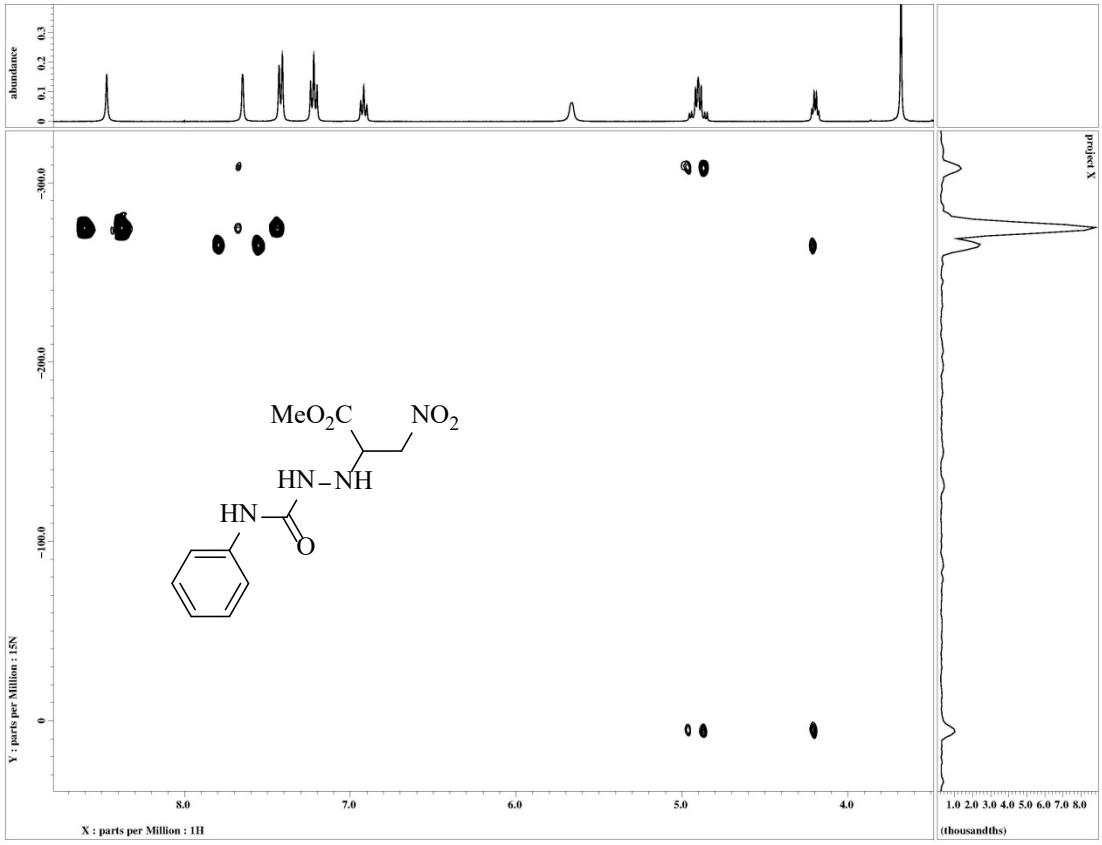

Figure S10. ^{1}H-^{15}N HMBC spectrum of methyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2a** in DMSO-d_6

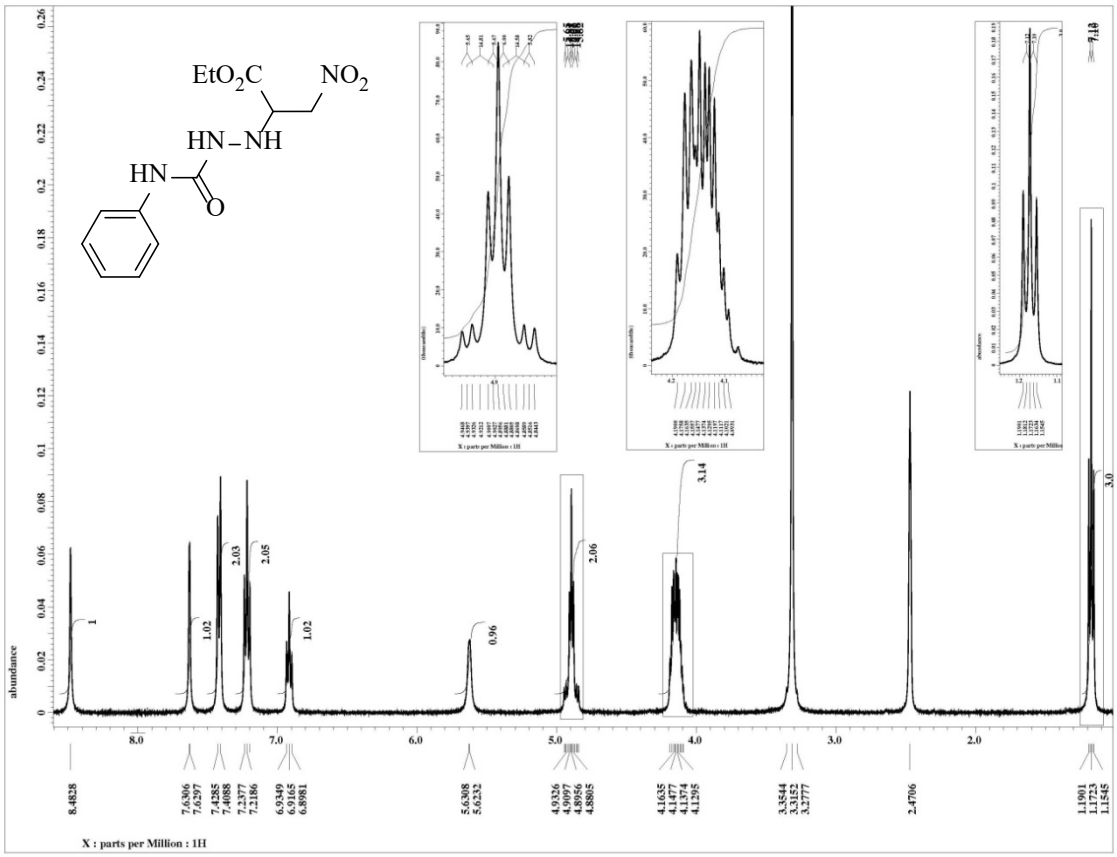

Figure S11. ^{1}H NMR spectrum of ethyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2b** in DMSO-d_6

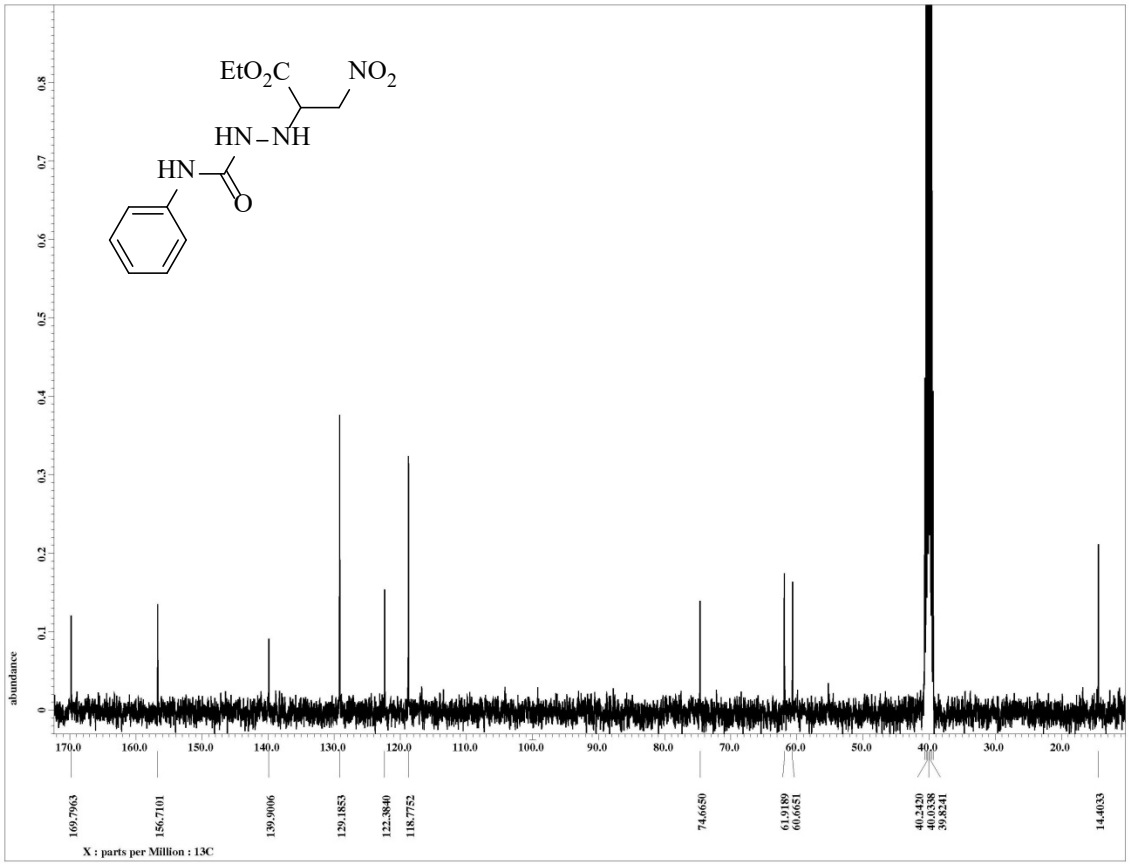

Figure S12. ^{13}C{^{1}H} NMR spectrum of ethyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2b** in DMSO-d_6

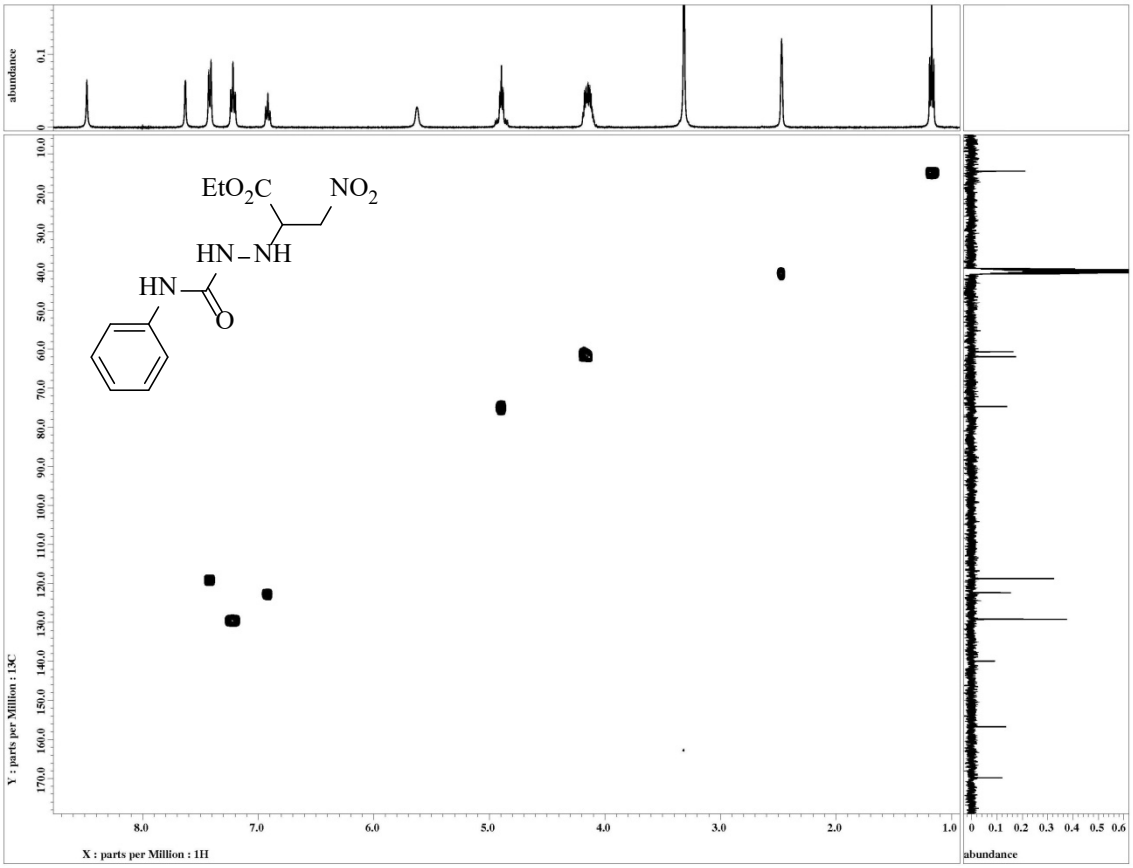

Figure S13. ^{1}H-^{13}C HMQC spectrum of ethyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2b** in DMSO-d_6

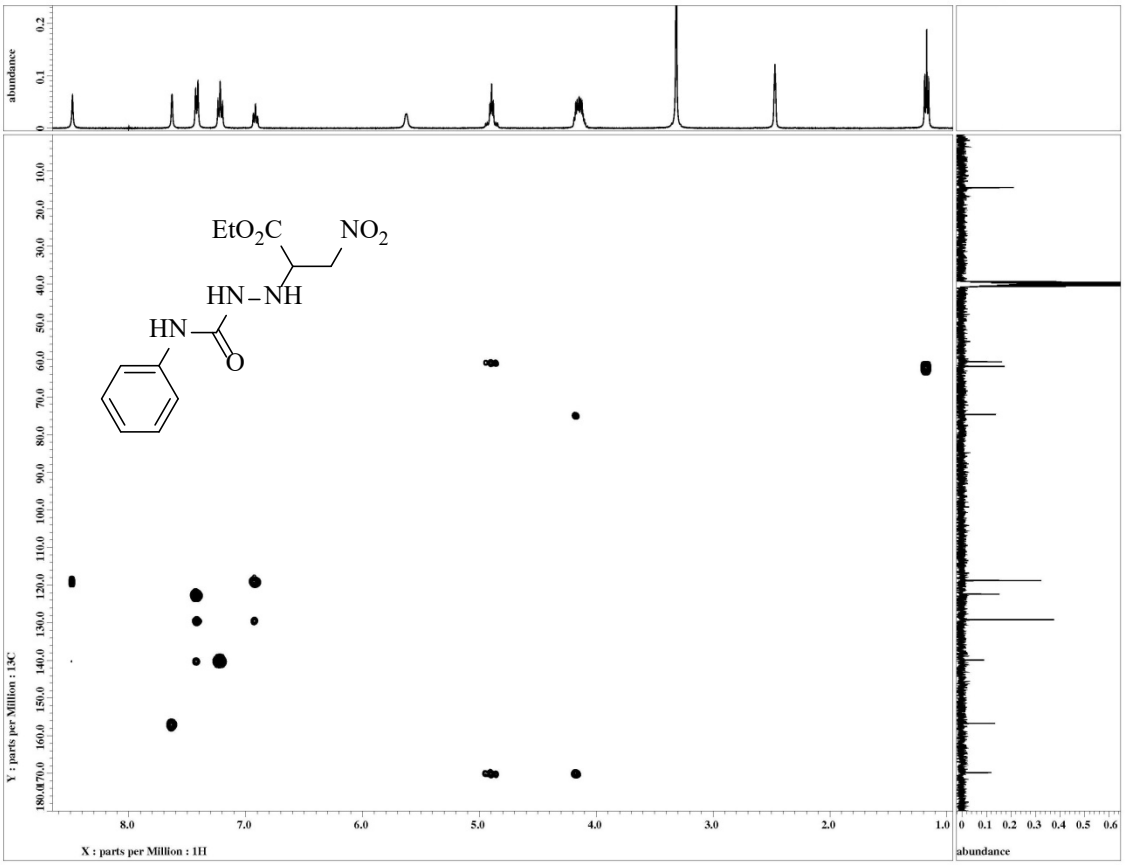

Figure S14. ^{1}H-^{13}C HMBC spectrum of ethyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2b** in DMSO-d_6

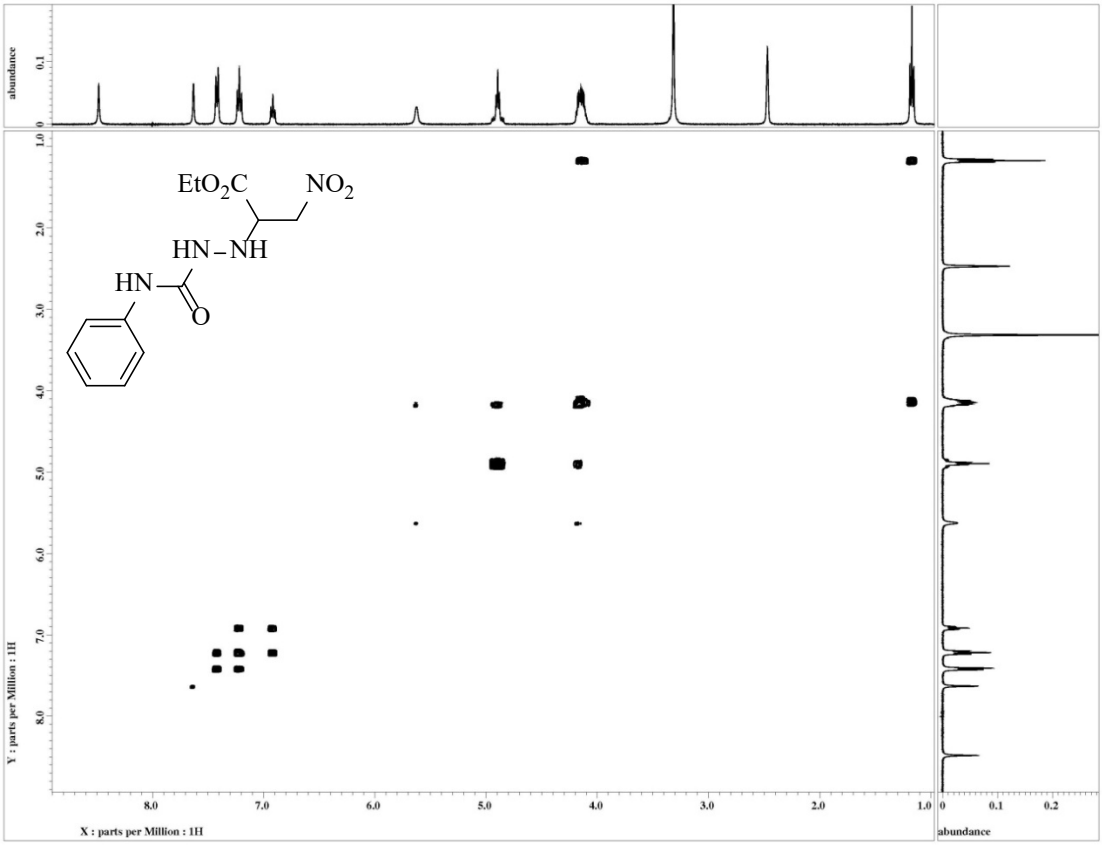

Figure S15. ^{1}H-^{1}H dqf-COSY spectrum of ethyl 3-nitro-2-[2-(phenylcarbamoyl)hydrazinyl]propanoate **2a** in DMSO-d_6

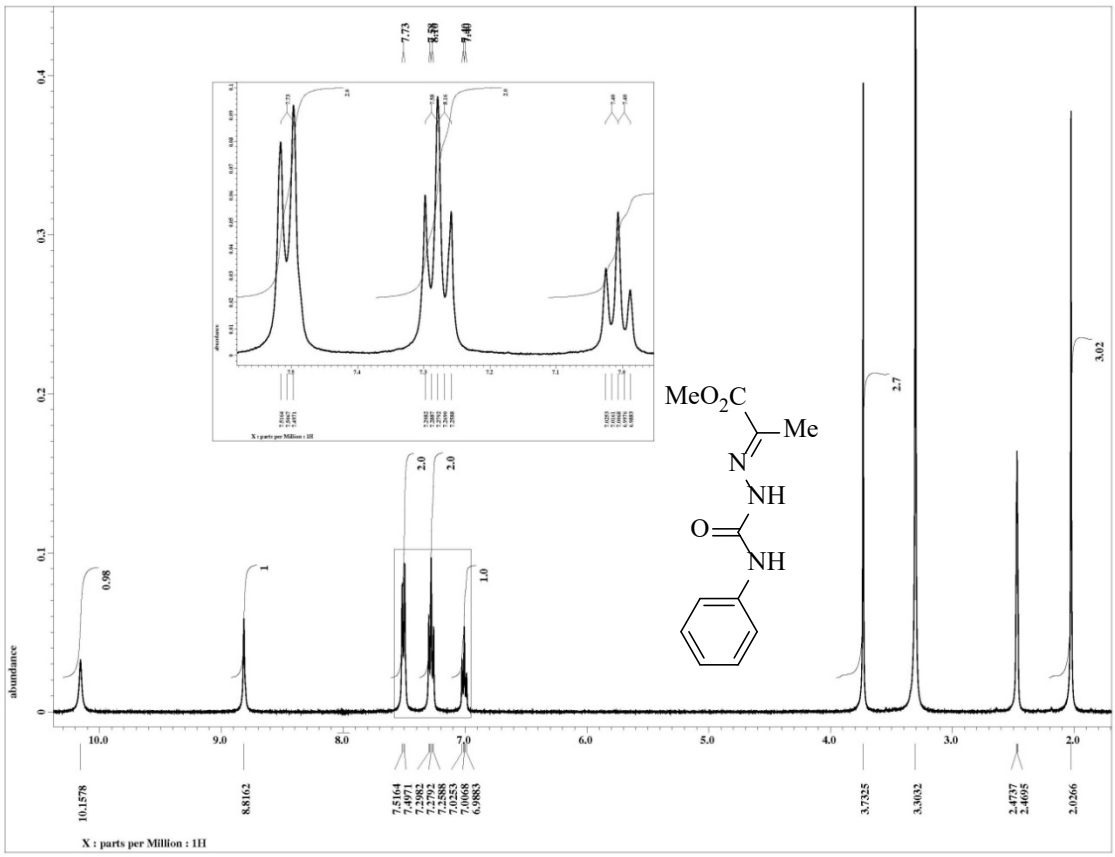

Figure S16. ^{1}H NMR spectrum of methyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3a** in DMSO-d_6

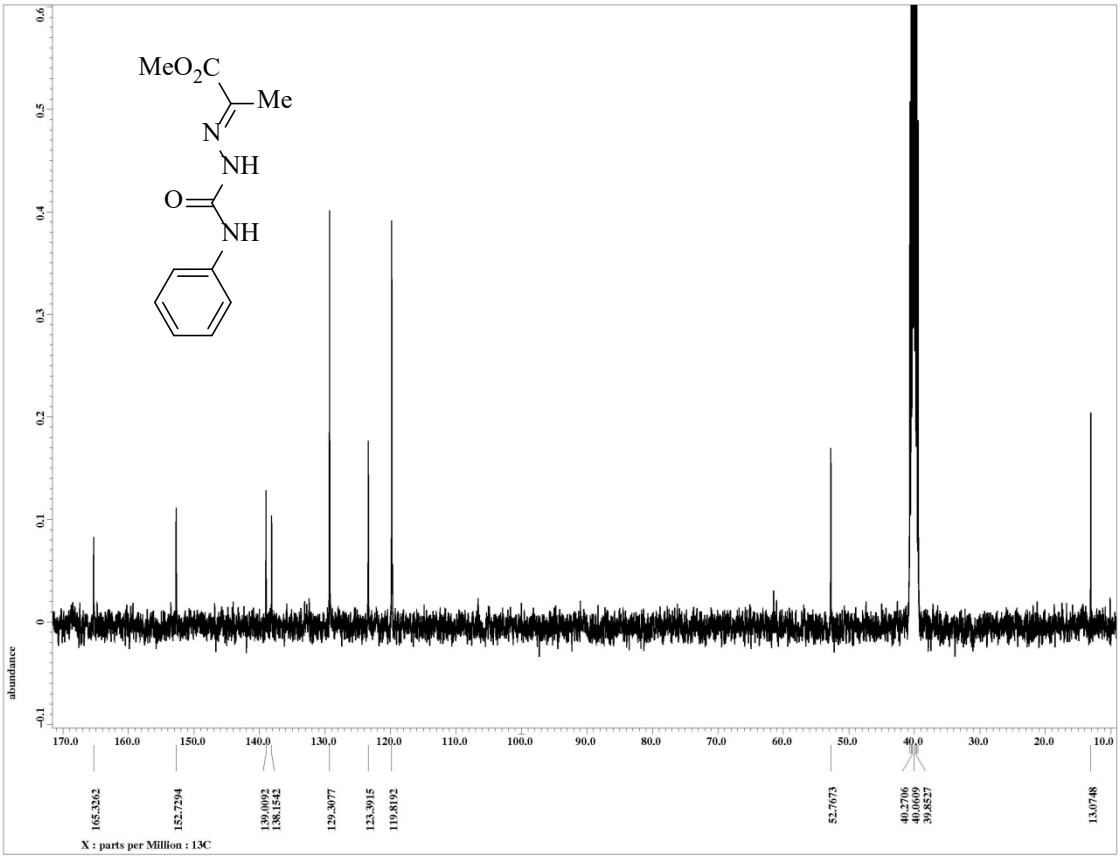

Figure S17. $^{13}C\{^{1}H\}$ NMR spectrum of methyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3a** in DMSO-d_6

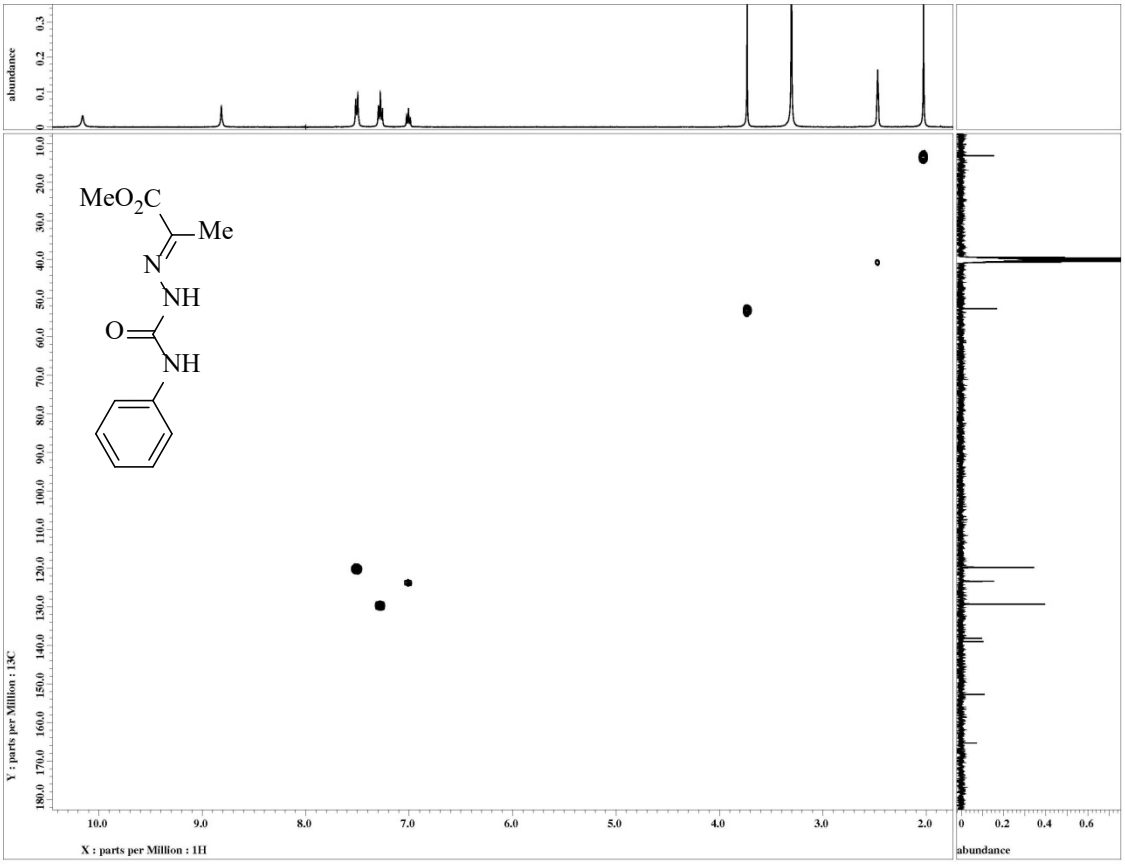

Figure S18. ^{1}H-^{13}C HMQC spectrum of methyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3a** in DMSO-d_6

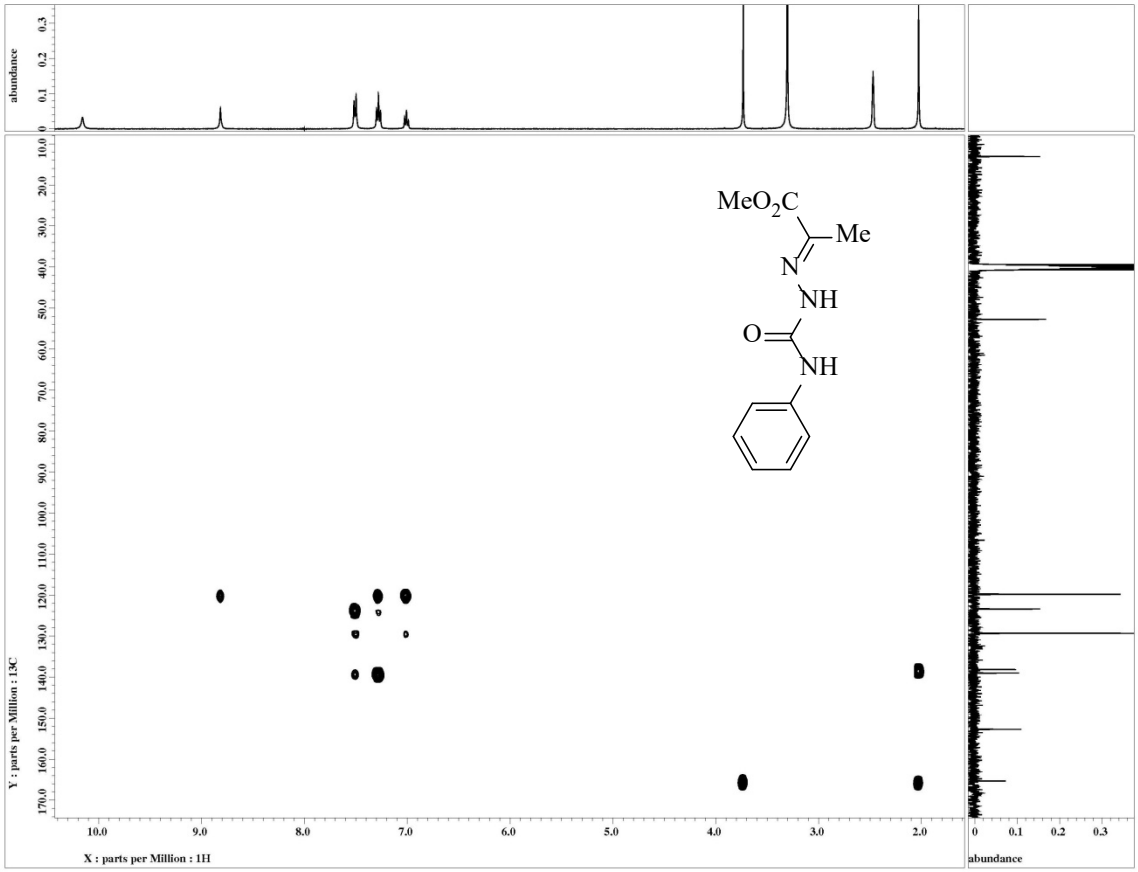

Figure S19. ^{1}H-^{13}C HMBC spectrum of methyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3a** in DMSO-d_6

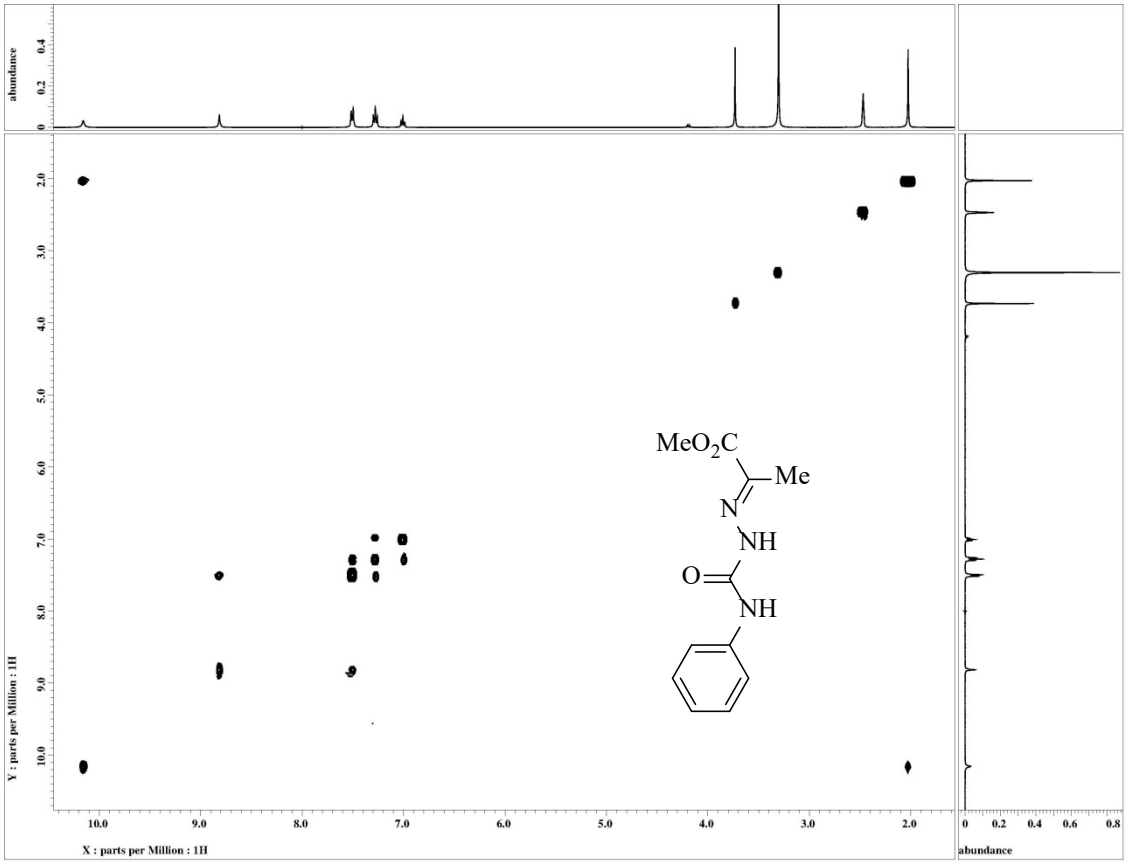

Figure S20. ^{1}H-^{1}H NOESY spectrum of methyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3a** in DMSO-d_6

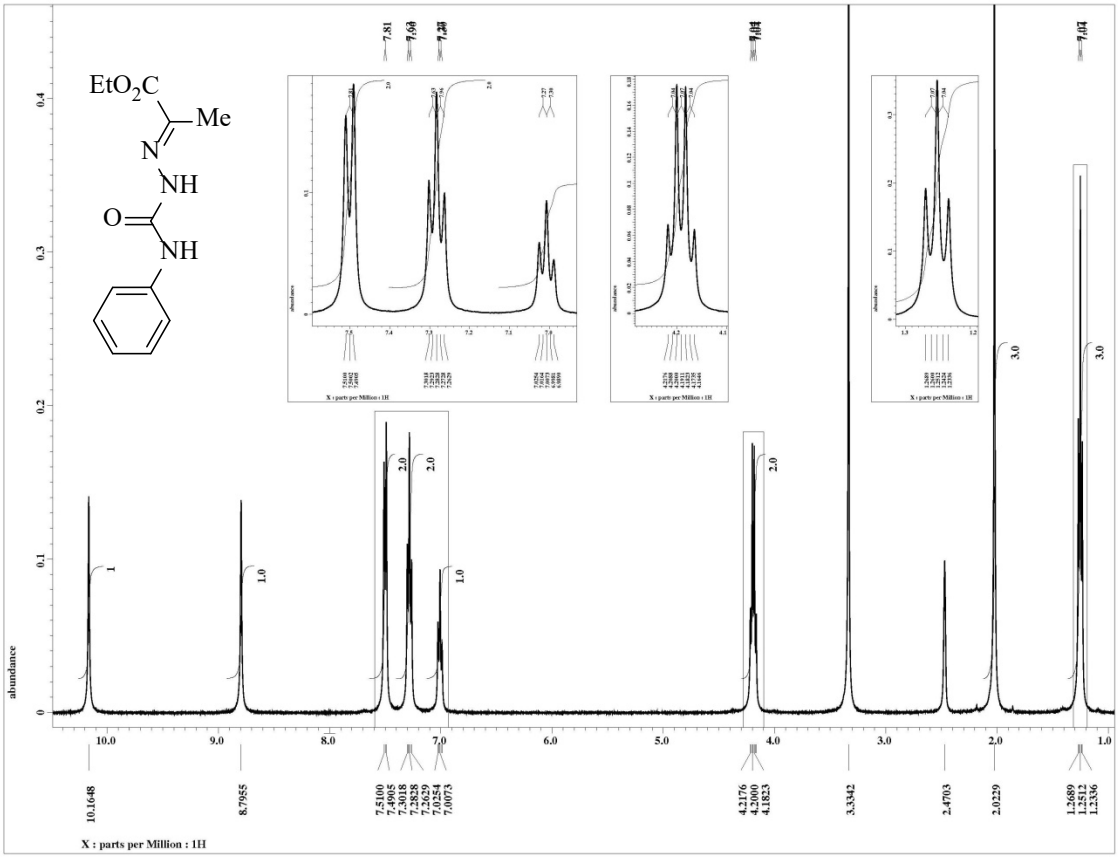

Figure S21. ^{1}H NMR spectrum of ethyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3b** in DMSO-d_6

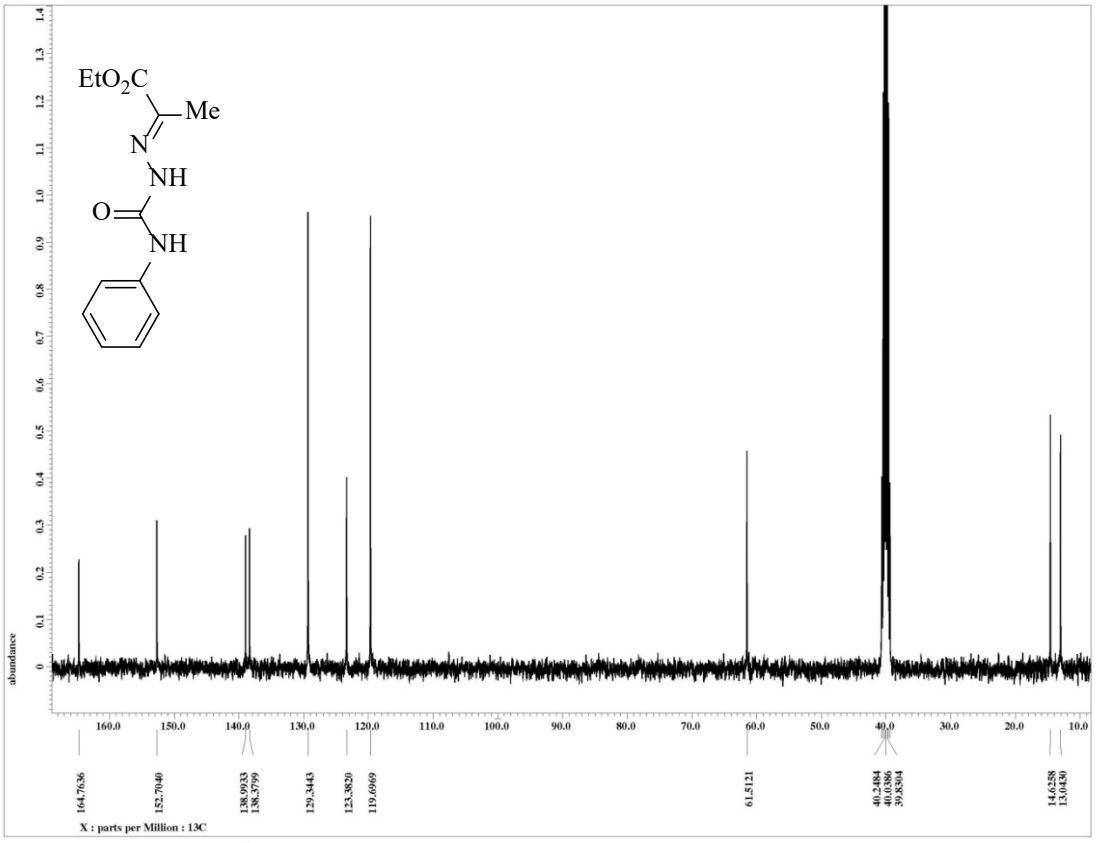

Figure S22. ^{13}C{^{1}H} NMR spectrum of ethyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3b** in DMSO-d_6

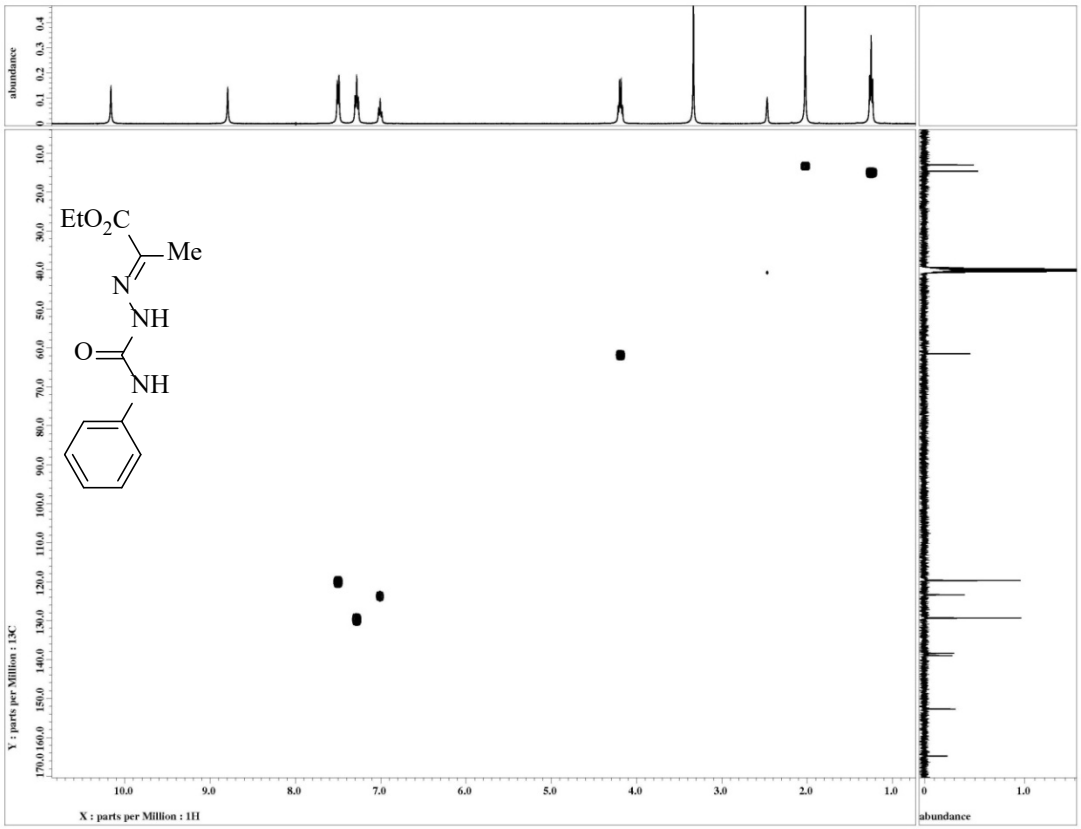

Figure S23. ^{1}H-^{13}C HMQC spectrum of ethyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3b** in DMSO-d_6

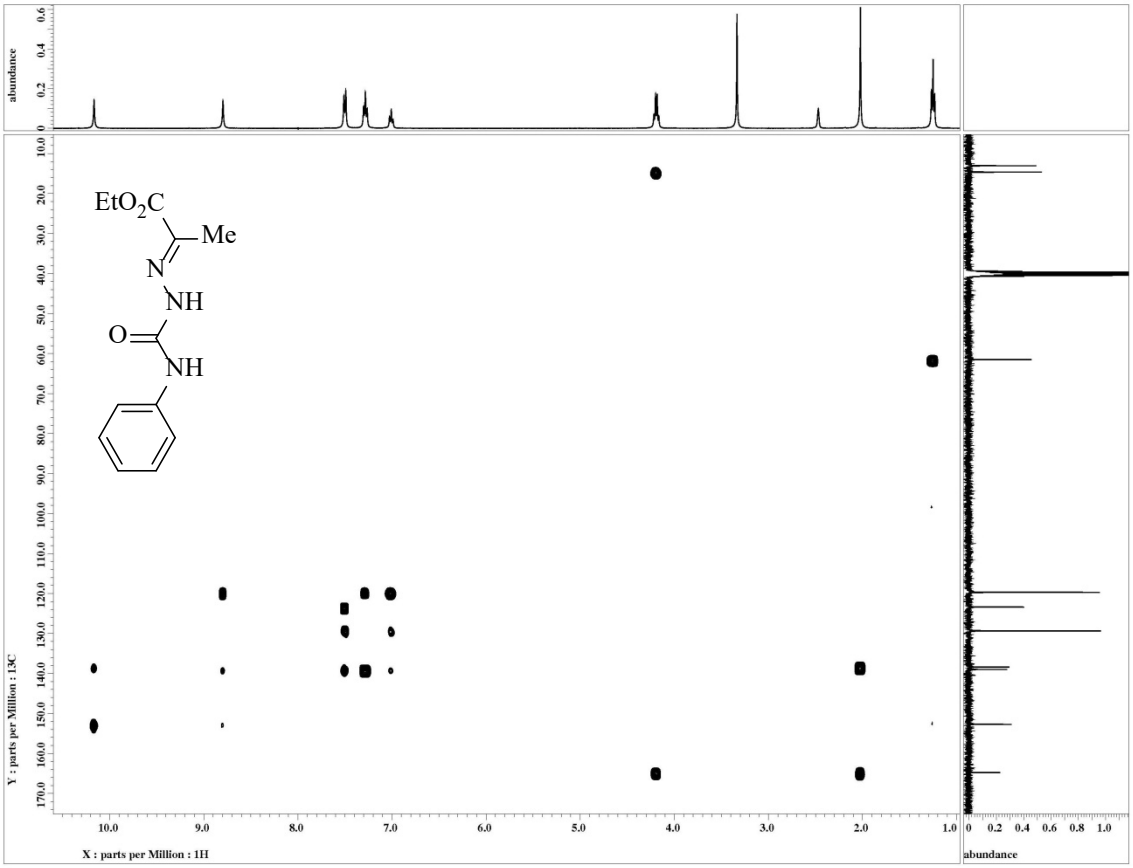

Figure S24. ^{1}H-^{13}C HMBC spectrum of ethyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3b** in DMSO-d_6

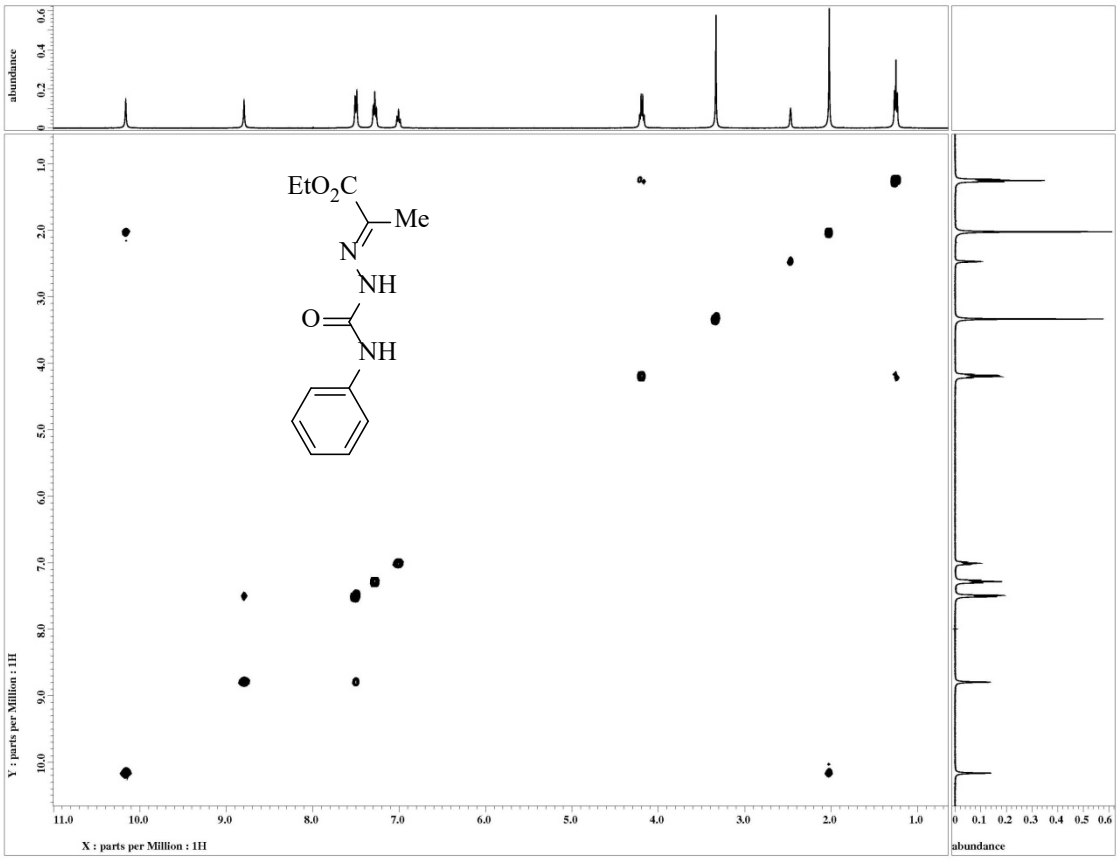

Figure S25. ^{1}H-^{1}H NOESY spectrum of ethyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3b** in DMSO-d_6

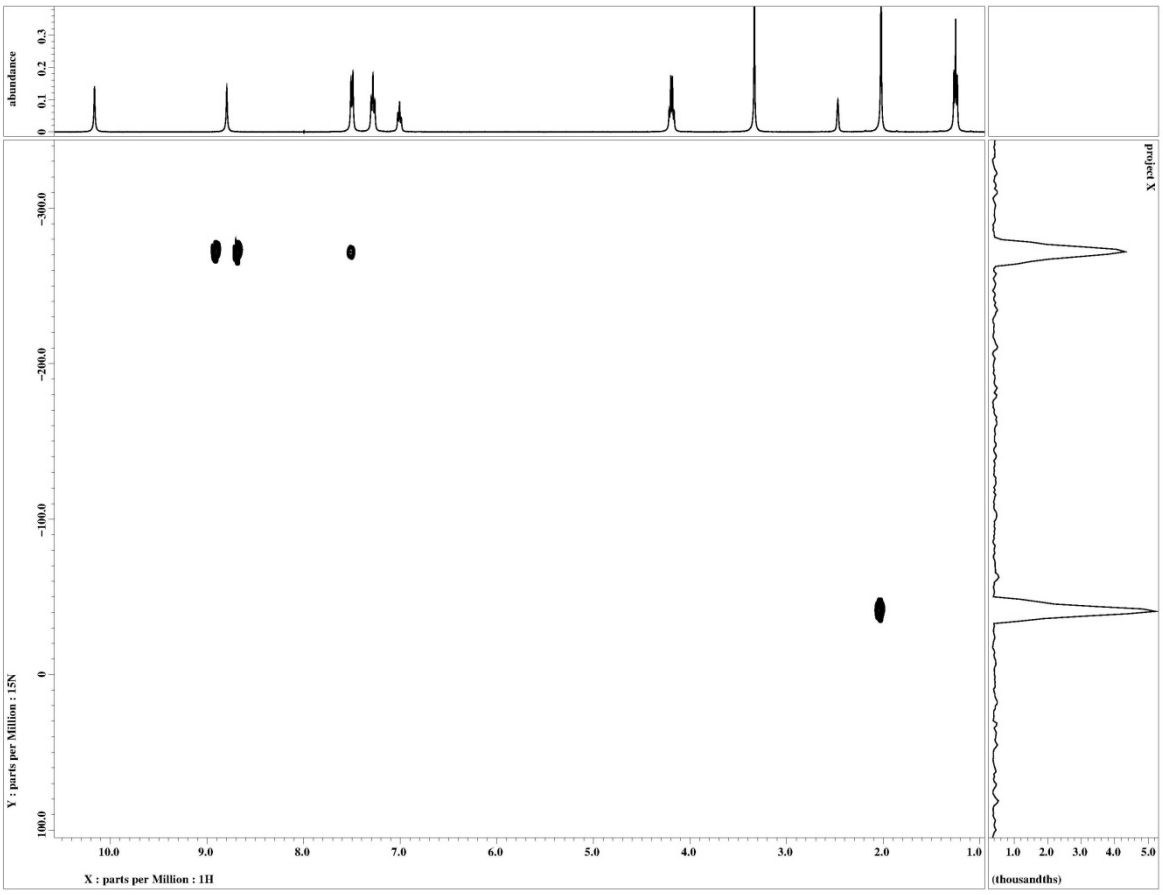

Figure S26. ^{1}H-^{15}N HMBC spectrum of ethyl (2*E*)-2-[2-(phenylcarbamoyl)hydrazinylidene]propanoate **3b** in DMSO-d_6

X-ray diffraction study of compounds 3b was performed on a Bruker D8 QUEST automatic three-circle diffractometer at 108 K (graphite monochromator, λMoK_α = 0.71073 Å, ω- and φ-scan with a step of 0.5°) at the Distributed Spectral-Analytical Center of Shared Facilities for Study of Structure, Composition and Properties of Substances and Materials of FRC Kazan Scientific Center of RAS. Single crystals of a suitable size were glued to the top of a glass fiber in a random orientation. The preliminary unit cell parameters were determined using three runs at different φ angle positions with 12 frames per run (φ-scan technique). The X-ray diffraction data were collected and indexed and the unit cell parameters were determined and refined using the APEX2 software package. The empirical absorption correction based on the crystal shape and an additional spherical correction were applied and systematic errors were corrected using the SADABS software. The structure was solved by direct method using the SHELXT-2014/5 program and refined by the full-matrix least-squares method based on F^2 using the SHELXL-2018/3 program as implemented in WinGX-2020.1. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms at carbon and nitrogen atoms were positioned geometrically and refined using a riding model, at the oxygen atoms were solved from difference Fourier maps and refined at isortopic approximation. Intermolecular interactions were analyzed and the figures were generated with the PLATON and Mercury 2020.3 programs, respectively. Crystallographic data for the structures of **3b** were deposited with the Cambridge Crystallographic Data Centre. The X-ray diffraction data collection and structure refinement statistics and the corresponding CCDC number are given in Table S1.

Table S1. Principal crystallographic parameters of compound **3b** based on X-ray diffraction data

Parameter	**3b**
Molecular formula	$3(C_{12}H_{15}N_3O_3)\cdot C_6H_6\cdot 3H_2O$
Sum Formula	$C_{42}H_{57}N_9O_{12}$
Molecular weight	879.97
Crystal system	triclinic
Space group	*P*-1 (No. 2)
Z	2
Unit cell parameters	
a/Å	11.9472(13)
b/Å	14.1979(16)
c/Å	14.4757(16)
α	71.480(4),
β/deg	78.904(4)
γ	74.986(4)
V/Å^3	2232.5(4)
d_{calc}/g cm^{-3}	1.309
Absorption coefficient, μ/mm^{-1}	0.097
F(000)	936
Θ (min, max)/deg	1.5, 28.0
Ranges of indices	
h	$-15 \le h \le 15$
k	$-18 \le k \le 18$
l	$-19 \le l \le 19$
Number of reflections	
total	91642
unique	10683
R_{int}	0.1744
Completeness up to θ = 28.0°	0.991
$T_{max/min}$	0.7456 / 0.5131
Number of observed reflections (I > 2σ(I))	5828
Number of reflections/of contraints/number of parameters	10683/0/598
GOOF	1.113
R [$I > 2\sigma(I)$]	
R_1	0.0661
wR_2	0.1665
R (based on all reflections)	
R_1	0.1347
wR_2	0.1939
Residual electron density (ρ_{max}/ρ_{min})/e Å^{-3}	0.49 / -0.54
CCDC	2293177

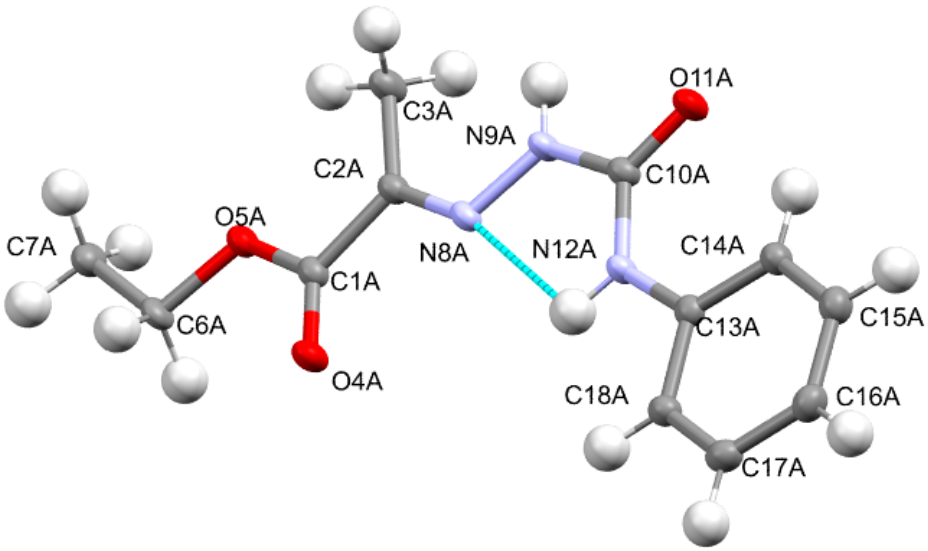

Figure S27. Geometry of one of the independent molecules of ethyl (2*E*)-2-[2-(phenyl-carbamoyl)hydrazinylidene]propanoate **3b** in a crystal. The anisotropic displacement ellipsoids are shown at 50% probability level. The benzene solvate molecule and water molecules are not shown. The intramolecular hydrogen bond is shown by dotted line.

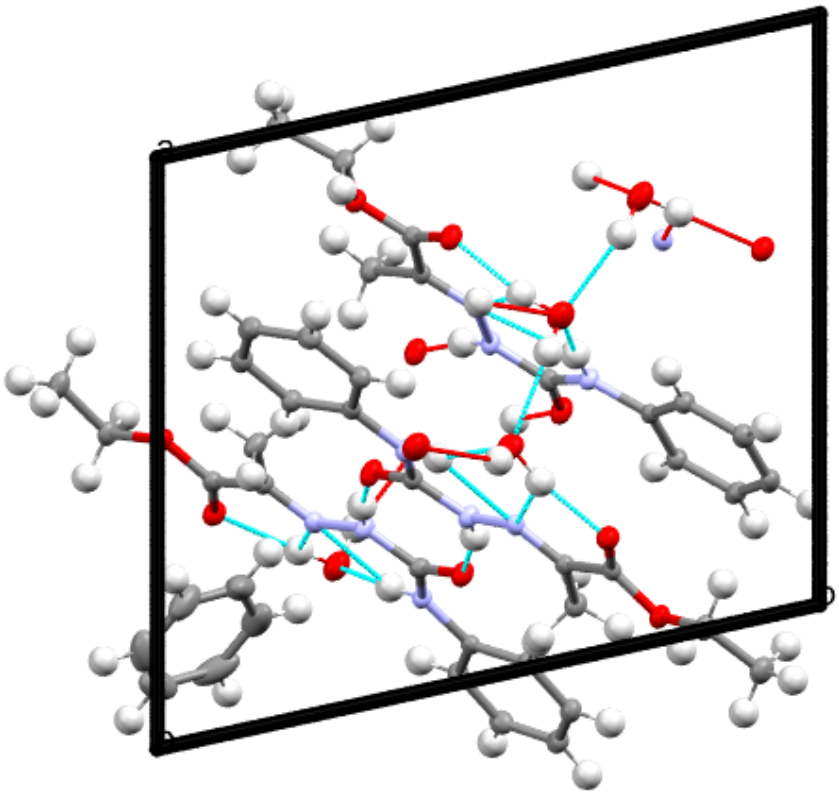

Figure S28. A fragment of **3b** crystal packing. The projection along axis *c*. Hydrogen bonds are shown by dotted lines.

Table S2. Torsion angles (τ) in the molecule of compound **3b**

Angle	τ/deg	Angle	τ/deg	Angle	τ/deg
O4A–C1A–C2A–C3A	-177.2(2)	O4B–C1B–C2B–C3B	176.9(2)	O4C–C1C–C2C–C3C	180.0(2)
O4A–C1A–C2A–N8A	3.2(3)	O4B–C1B–C2B–N8B	-4.8(3)	O4C–C1C–C2C–N8C	-0.3(3)
O5A–C1A–C2A–C3A	1.7(3)	O5B–C1B–C2B–C3B	-3.8(3)	O5C–C1C–C2C–C3C	-0.1(3)
O5A–C1A–C2A–N8A	-177.9(2)	O5B–C1B–C2B–N8B	174.5(2)	O5C–C1C–C2C–N8C	179.6(2)
C2A–C1A–O5A–C6A	-178.4(2)	C2B–C1B–O5B–C6B	-176.9(2)	C2C–C1C–O5C–C6C	-177.8(2)
O4A–C1A–O5A–C6A	0.5(3)	O4B–C1B–O5B–C6B	2.5(3)	O4C–C1C–O5C–C6C	2.2(3)
C1A–C2A–C3A–H3A1	115.2	C1B–C2B–C3B–H3B1	113.5	C1C–C2C–C3C–H3C1	120.9
C1A–C2A–C3A–H3A2	-4.8	C1B–C2B–C3B–H3B2	-6.6	C1C–C2C–C3C–H3C2	0.9
C1A–C2A–C3A–H3A3	-124.8	C1B–C2B–C3B–H3B3	-126.5	C1C–C2C–C3C–H3C3	-119.1
N8A–C2A–C3A–H3A1	-65.2	N8B–C2B–C3B–H3B1	-64.5	N8C–C2C–C3C–H3C1	-58.8
N8A–C2A–C3A–H3A2	174.8	N8B–C2B–C3B–H3B2	175.4	N8C–C2C–C3C–H3C2	-178.8
N8A–C2A–C3A–H3A3	54.7	N8B–C2B–C3B–H3B3	55.5	N8C–C2C–C3C–H3C3	61.2
C1A–C2A–N8A–N9A	179.3(2)	C1B–C2B–N8B–N9B	-178.9(2)	C1C–C2C–N8C–N9C	-179.1(2)
C3A–C2A–N8A–N9A	-0.3(3)	C3B–C2B–N8B–N9B	-0.7(3)	C3C–C2C–N8C–N9C	0.5(3)
H6A1–C6A–C7A–H7A1	62.3	H6B1–C6B–C7B–H7B1	62.2	H6C1–C6C–C7C–H7C1	64.5
H6A1–C6A–C7A–H7A2	-57.6	H6B1–C6B–C7B–H7B2	-57.8	H6C1–C6C–C7C–H7C2	-55.5
H6A1–C6A–C7A–H7A3	-177.7	H6B1–C6B–C7B–H7B3	-177.8	H6C1–C6C–C7C–H7C3	-175.5
H6A2–C6A–C7A–H7A1	-177.4	H6B2–C6B–C7B–H7B1	-178.0	H6C2–C6C–C7C–H7C1	-175.6
H6A2–C6A–C7A–H7A2	62.6	H6B2–C6B–C7B–H7B2	62.0	H6C2–C6C–C7C–H7C2	64.4
H6A2–C6A–C7A–H7A3	-57.4	H6B2–C6B–C7B–H7B3	-58.0	H6C2–C6C–C7C–H7C3	-55.6
O5A–C6A–C7A–H7A1	-57.6	O5B–C6B–C7B–H7B1	-57.9	O5C–C6C–C7C–H7C1	-55.5
O5A–C6A–C7A–H7A2	-177.5	O5B–C6B–C7B–H7B2	-177.9	O5C–C6C–C7C–H7C2	-175.5
O5A–C6A–C7A–H7A3	62.4	O5B–C6B–C7B–H7B3	62.1	O5C–C6C–C7C–H7C3	64.5
H6A1–C6A–O5A–C1A	59.0	H6B1–C6B–O5B–C1B	70.2	H6C1–C6C–O5C–C1C	60.1
H6A2–C6A–O5A–C1A	-61.3	H6B2–C6B–O5B–C1B	-49.5	H6C2–C6C–O5C–C1C	-59.8
C7A–C6A–O5A–C1A	178.9(2)	C7B–C6B–O5B–C1B	-169.6(2)	C7C–C6C–O5C–C1C	-179.9(2)
N9A–C10A–N12A–H12A	4.9	N12B–C10B–N9B–N8B	-0.2(3)	N12C–C10C–N9C–N8C	1.3(3)
N9A–C10A–N12A–C13A	-175.1(2)	N12B–C10B–N9B–H9B	179.8	N12C–C10C–N9C–H9C	-178.7
O11A–C10A–N12A–H12A	-175.7	O11B–C10B–N9B–N8B	-179.7(2)	O11C–C10C–N9C–N8C	-178.9(2)
O11A–C10A–N12A–C13A	4.3(4)	O11B–C10B–N9B–H9B	0.3	O11C–C10C–N9C–H9C	1.1

N12A–C10A–N9A–N8A	2.9(3)	N9B–C10B–N12B–C13B	-179.9(2)	N9C–C10C–N12C–C13C	178.0(2)
N12A–C10A–N9A–H9A	-177.0	N9B–C10B–N12B–H12B	0.1	N9C–C10C–N12C–H12C	-2.0
O11A–C10A–N9A–N8A	-176.5(2)	O11B–C10B–N12B–C13B	-0.4(4)	O11C–C10C–N12C–C13C	-1.8(4)
O11A–C10A–N9A–H9A	3.5	O11B–C10B–N12B–H12B	179.6	O11C–C10C–N12C–H12C	178.2
C10A–N12A–C13A–C14A	-5.7(4)	C18B–C13B–C14B–H14B	-179.5	C18C–C13C–C14C–H14C	179.8
C10A–N12A–C13A–C18A	173.5(2)	C18B–C13B–C14B–C15B	0.4(4)	C18C–C13C–C14C–C15C	-0.2(4)
H12A–N12A–C13A–C14A	174.3	N12B–C13B–C14B–H14B	-0.9	N12C–C13C–C14C–H14C	-1.9
H12A–N12A–C13A–C18A	-6.4	N12B–C13B–C14B–C15B	179.1(2)	N12C–C13C–C14C–C15C	178.1(2)
N12A–C13A–C14A–H14A	-2.0	C14B–C13B–C18B–C17B	-0.5(4)	C14C–C13C–C18C–C17C	0.5(4)
N12A–C13A–C14A–C15A	177.9(2)	C14B–C13B–C18B–H18B	179.5	C14C–C13C–C18C–H18C	-179.4
C18A–C13A–C14A–H14A	178.8	N12B–C13B–C18B–C17B	-179.2(2)	N12C–C13C–C18C–C17C	-177.7(2)
C18A–C13A–C14A–C15A	-1.3(4)	N12B–C13B–C18B–H18B	0.7	N12C–C13C–C18C–H18C	2.3
N12A–C13A–C18A–C17A	-177.1(2)	C14B–C13B–N12B–C10B	10.7(4)	C14C–C13C–N12C–C10C	176.8(2)
N12A–C13A–C18A–H18A	2.8	C14B–C13B–N12B–H12B	-169.3	C14C–C13C–N12C–H12C	-3.2
C14A–C13A–C18A–C17A	2.1(4)	C18B–C13B–N12B–C10B	-170.6(2)	C18C–C13C–N12C–C10C	-4.9(4)
C14A–C13A–C18A–H18A	-177.9	C18B–C13B–N12B–H12B	9.4	C18C–C13C–N12C–H12C	175.1
C13A–C14A–C15A–H15A	179.4	C13B–C14B–C15B–H15B	179.8	C13C–C14C–C15C–H15C	-180.0
C13A–C14A–C15A–C16A	-0.6(4)	C13B–C14B–C15B–C16B	-0.3(4)	C13C–C14C–C15C–C16C	0.1(4)
H14A–C14A–C15A–H15A	-0.6	H14B–C14B–C15B–H15B	-0.3	H14C–C14C–C15C–H15C	-0.0
H14A–C14A–C15A–C16A	179.4	H14B–C14B–C15B–C16B	179.7	H14C–C14C–C15C–C16C	-180.0
C14A–C15A–C16A–H16A	-178.5	C14B–C15B–C16B–H16B	-179.9	C14C–C15C–C16C–H16C	179.8
C14A–C15A–C16A–C17A	1.6(4)	C14B–C15B–C16B–C17B	0.1(4)	C14C–C15C–C16C–C17C	-0.2(4)
H15A–C15A–C16A–H16A	1.5	H15B–C15B–C16B–H16B	0.0	H15C–C15C–C16C–H16C	-0.2
H15A–C15A–C16A–C17A	-178.4	H15B–C15B–C16B–C17B	-179.9	H15C–C15C–C16C–C17C	179.9
C15A–C16A–C17A–H17A	179.3	C15B–C16B–C17B–H17B	179.8	C15C–C16C–C17C–H17C	-179.5
C15A–C16A–C17A–C18A	-0.7(4)	C15B–C16B–C17B–C18B	-0.2(4)	C15C–C16C–C17C–C18C	0.5(4)
H16A–C16A–C17A–H17A	-0.6	H16B–C16B–C17B–H17B	-0.1	H16C–C16C–C17C–H17C	0.5
H16A–C16A–C17A–C18A	179.3	H16B–C16B–C17B–C18B	179.9	H16C–C16C–C17C–C18C	-179.5
C16A–C17A–C18A–C13A	-1.1(4)	C16B–C17B–C18B–C13B	0.4(4)	C16C–C17C–C18C–C13C	-0.7(4)
C16A–C17A–C18A–H18A	178.9	C16B–C17B–C18B–H18B	-179.6	C16C–C17C–C18C–H18C	179.3
H17A–C17A–C18A–C13A	178.9	H17B–C17B–C18B–C13B	-179.7	H17C–C17C–C18C–C13C	179.3
H17A–C17A–C18A–H18A	-1.1	H17B–C17B–C18B–H18B	0.4	H17C–C17C–C18C–H18C	-0.7
C2A–N8A–N9A–C10A	-179.7(2)	C2B–N8B–N9B–C10B	175.2(2)	C2C–N8C–N9C–C10C	179.3(2)
C2A–N8A–N9A–H9A	0.3	C2B–N8B–N9B–H9B	-4.8	C2C–N8C–N9C–H9C	-0.7

Table S3. Angles (τ) in the molecule of compound **3b**

Angle	τ/deg	Angle	τ/deg	Angle	τ/deg
C2A–C1A–O4A	125.7(2)	C2B–C1B–O4B	125.2(2)	C2C–C1C–O4C	125.0(2)
C2A–C1A–O5A	110.5(2)	C2B–C1B–O5B	112.1(2)	C2C–C1C–O5C	112.3(2)
O4A–C1A–O5A	123.7(2)	O4B–C1B–O5B	122.7(2)	O4C–C1C–O5C	122.7(2)
C1A–C2A–C3A	121.6(2)	C1B–C2B–C3B	121.3(2)	C1C–C2C–C3C	121.3(2)
C1A–C2A–N8A	113.0(2)	C1B–C2B–N8B	112.7(2)	C1C–C2C–N8C	112.9(2)
C3A–C2A–N8A	125.4(2)	C3B–C2B–N8B	126.0(2)	C3C–C2C–N8C	125.8(2)
C2A–C3A–H3A1	109.4	C2B–C3B–H3B1	109.5	C2C–C3C–H3C1	109.5
C2A–C3A–H3A2	109.5	C2B–C3B–H3B2	109.5	C2C–C3C–H3C2	109.5
C2A–C3A–H3A3	109.5	C2B–C3B–H3B3	109.4	C2C–C3C–H3C3	109.5
H3A1–C3A–H3A2	109.5	H3B1–C3B–H3B2	109.5	H3C1–C3C–H3C2	109.5
H3A1–C3A–H3A3	109.5	H3B1–C3B–H3B3	109.5	H3C1–C3C–H3C3	109.5
H3A2–C3A–H3A3	109.5	H3B2–C3B–H3B3	109.5	H3C2–C3C–H3C3	109.5
H6A1–C6A–H6A2	108.7	H6B1–C6B–H6B2	108.5	H6C1–C6C–H6C2	108.6
H6A1–C6A–C7A	110.5	H6B1–C6B–C7B	110.2	H6C1–C6C–C7C	110.3
H6A1–C6A–O5A	110.5	H6B1–C6B–O5B	110.2	H6C1–C6C–O5C	110.3
H6A2–C6A–C7A	110.4	H6B2–C6B–C7B	110.2	H6C2–C6C–C7C	110.3
H6A2–C6A–O5A	110.5	H6B2–C6B–O5B	110.2	H6C2–C6C–O5C	110.3
C7A–C6A–O5A	106.3(2)	C7B–C6B–O5B	107.5(2)	C7C–C6C–O5C	107.0(2)
C6A–C7A–H7A1	109.4	C6B–C7B–H7B1	109.5	C6C–C7C–H7C1	109.5
C6A–C7A–H7A2	109.5	C6B–C7B–H7B2	109.5	C6C–C7C–H7C2	109.5
C6A–C7A–H7A3	109.5	C6B–C7B–H7B3	109.5	C6C–C7C–H7C3	109.5
H7A1–C7A–H7A2	109.5	H7B1–C7B–H7B2	109.5	H7C1–C7C–H7C2	109.5
H7A1–C7A–H7A3	109.5	H7B1–C7B–H7B3	109.5	H7C1–C7C–H7C3	109.5
H7A2–C7A–H7A3	109.5	H7B2–C7B–H7B3	109.5	H7C2–C7C–H7C3	109.5
N12A–C10A–N9A	116.7(2)	N9B–C10B–N12B	117.3(2)	N9C–C10C–N12C	116.0(2)
N12A–C10A–O11A	125.0(2)	N9B–C10B–O11B	118.7(2)	N9C–C10C–O11C	119.3(2)
N9A–C10A–O11A	118.3(2)	N12B–C10B–O11B	124.0(2)	N12C–C10C–O11C	124.7(2)
C10A–N12A–H12A	116.4	C14B–C13B–C18B	119.1(2)	C14C–C13C–C18C	119.1(2)
C10A–N12A–C13A	127.2(2)	C14B–C13B–N12B	124.5(2)	C14C–C13C–N12C	116.9(2)
H12A–N12A–C13A	116.4	C18B–C13B–N12B	116.4(2)	C18C–C13C–N12C	123.9(2)
N12A–C13A–C14A	124.2(2)	C13B–C14B–H14B	120.2	C13C–C14C–H14C	119.7
N12A–C13A–C18A	116.4(2)	C13B–C14B–C15B	119.6(2)	C13C–C14C–C15C	120.6(2)
C14A–C13A–C18A	119.5(2)	H14B–C14B–C15B	120.2	H14C–C14C–C15C	119.7
C13A–C14A–H14A	120.3	C14B–C15B–H15B	119.2	C14C–C15C–H15C	119.7
C13A–C14A–C15A	119.5(2)	C14B–C15B–C16B	121.6(2)	C14C–C15C–C16C	120.5(2)
H14A–C14A–C15A	120.3	H15B–C15B–C16B	119.2	H15C–C15C–C16C	119.8
C14A–C15A–H15A	119.4	C15B–C16B–H16B	120.6	C15C–C16C–H16C	120.5
C14A–C15A–C16A	121.2(2)	C15B–C16B–C17B	118.7(2)	C15C–C16C–C17C	119.0(2)
H15A–C15A–C16A	119.4	H16B–C16B–C17B	120.6	H16C–C16C–C17C	120.5
C15A–C16A–H16A	120.4	C16B–C17B–H17B	119.6	C16C–C17C–H17C	119.4
C15A–C16A–C17A	119.2(2)	C16B–C17B–C18B	120.7(2)	C16C–C17C–C18C	121.2(2)
H16A–C16A–C17A	120.4	H17B–C17B–C18B	119.6	H17C–C17C–C18C	119.4
C16A–C17A–H17A	119.9	C13B–C18B–C17B	120.2(2)	C13C–C18C–C17C	119.6(2)
C16A–C17A–C18A	120.1(2)	C13B–C18B–H18B	119.9	C13C–C18C–H18C	120.2
H17A–C17A–C18A	120.0	C17B–C18B–H18B	119.9	C17C–C18C–H18C	120.2
C13A–C18A–C17A	120.4(2)	C2B–N8B–N9B	117.9(2)	C2C–N8C–N9C	118.2(2)
C13A–C18A–H18A	119.8	C10B–N9B–N8B	120.7(2)	C10C–N9C–N8C	120.5(2)
C17A–C18A–H18A	119.8	C10B–N9B–H9B	119.6	C10C–N9C–H9C	119.8
C2A–N8A–N9A	118.0(2)	N8B–N9B–H9B	119.6	N8C–N9C–H9C	119.8
C10A–N9A–N8A	120.4(2)	C10B–N12B–C13B	126.7(2)	C10C–N12C–C13C	127.3(2)
C10A–N9A–H9A	119.8	C10B–N12B–H12B	116.6	C10C–N12C–H12C	116.3
N8A–N9A–H9A	119.8	C13B–N12B–H12B	116.6	C13C–N12C–H12C	116.4
C1A–O5A–C6A	116.9(2)	C1B–O5B–C6B	115.4(2)	C1C–O5C–C6C	116.0(2)

Table S4. Bond lengths (*d*) in the molecule of compound **3b**

Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å
C1A–C2A	1.491(3)	C1B–C2B	1.494(3)	C1C–C2C	1.491(3)
C1A–O4A	1.212(3)	C1B–O4B	1.211(3)	C1C–O4C	1.211(2)
C1A–O5A	1.329(3)	C1B–O5B	1.336(2)	C1C–O5C	1.327(3)
C2A–C3A	1.493(3)	C2B–C3B	1.496(3)	C2C–C3C	1.494(3)
C2A–N8A	1.287(3)	C2B–N8B	1.276(3)	C2C–N8C	1.282(3)
C3A–H3A1	0.980	C3B–H3B1	0.980	C3C–H3C1	0.980
C3A–H3A2	0.980	C3B–H3B2	0.980	C3C–H3C2	0.980
C3A–H3A3	0.980	C3B–H3B3	0.980	C3C–H3C3	0.980
C6A–H6A1	0.990	C6B–H6B1	0.990	C6C–H6C1	0.990
C6A–H6A2	0.990	C6B–H6B2	0.990	C6C–H6C2	0.990
C6A–C7A	1.494(3)	C6B–C7B	1.497(3)	C6C–C7C	1.495(3)
C6A–O5A	1.454(2)	C6B–O5B	1.446(2)	C6C–O5C	1.448(3)
C7A–H7A1	0.980	C7B–H7B1	0.980	C7C–H7C1	0.980
C7A–H7A2	0.980	C7B–H7B2	0.980	C7C–H7C2	0.980
C7A–H7A3	0.980	C7B–H7B3	0.980	C7C–H7C3	0.980
C10A–N12A	1.343(3)	C10B–N9B	1.366(3)	C10C–N9C	1.370(3)
C10A–N9A	1.378(3)	C10B–N12B	1.345(3)	C10C–N12C	1.355(3)
C10A–O11A	1.232(2)	C10B–O11B	1.234(2)	C10C–O11C	1.225(3)
N12A–H12A	0.880	C13B–C14B	1.384(3)	C13C–C14C	1.391(3)
N12A–C13A	1.414(3)	C13B–C18B	1.397(3)	C13C–C18C	1.390(3)
C13A–C14A	1.384(3)	C13B–N12B	1.418(3)	C13C–N12C	1.409(3)
C13A–C18A	1.395(3)	C14B–H14B	0.950	C14C–H14C	0.950
C14A–H14A	0.950	C14B–C15B	1.379(3)	C14C–C15C	1.379(3)
C14A–C15A	1.386(3)	C15B–H15B	0.950	C15C–H15C	0.950
C15A–H15A	0.950	C15B–C16B	1.373(3)	C15C–C16C	1.382(3)
C15A–C16A	1.382(3)	C16B–H16B	0.950	C16C–H16C	0.950
C16A–H16A	0.950	C16B–C17B	1.384(3)	C16C–C17C	1.380(3)
C16A–C17A	1.382(3)	C17B–H17B	0.950	C17C–H17C	0.950
C17A–H17A	0.950	C17B–C18B	1.374(3)	C17C–C18C	1.387(3)
C17A–C18A	1.385(3)	C18B–H18B	0.950	C18C–H18C	0.950
C18A–H18A	0.950	N8B–N9B	1.360(2)	N8C–N9C	1.358(3)
N8A–N9A	1.359(2)	N9B–H9B	0.880	N9C–H9C	0.880
N9A–H9A	0.880	N12B–H12B	0.880	N12C–H12C	0.880

Viruses and Cells

Influenza virus A/Puerto Rico/8/34 (H1N1), was obtained from the collection of viruses of St. Petersburg Pasteur Institute. Prior to the experiment, virus was propagated in the allantoic cavity of 10–12 day old chicken embryos for 48 h at 36°C. MDCK cells (ATCC # CCL-34) were grown in 96-wells plates in alpha-MEM medium with 10% fetal bovine serum.

Cytotoxicity Assay

MDCK cells were seeded onto 96-well culture plates (10^4 cells per well) and incubated at 36°C in 5% CO_2 until continuous monolayer formation. To assess the toxicity of compounds, a series of their three-fold dilutions at concentrations of 300 to 3,7 μg/mL in Eagle's MEM medium were prepared. The dilutions were added to the wells of the plates. Cells were incubated for 72 h at 36°C under 5% CO_2. Further, cells were washed 2 times with saline (0.9% NaCl) and 100 μL/well of MTT solution (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) at a concentration of 0.5 mg/mL in MEM was added. The plates were incubated for 2 h at 36°C, the liquid was removed and DMSO (0.1 mL per well) was added. The optical density (OD) of the cells was measured on a Thermo Multiskan FC spectrophotometer (Thermo Fisher Scientific,Waltham, MA, USA) at a wavelength of 540 nm. Based on the obtained data, the CC_{50}, the concentration of the compound that destroys 50% of the cells in culture, was calculated for each specimen.

CPE Reduction Assay

The compounds in appropriate concentrations were added to MDCK cells (0.1 mL per well). MDCK cells were further infected with either A/Puerto Rico/8/34 (H1N1) influenza virus (MOI 0.01). Plates were incubated for 72 h at 36°C at 5% CO_2. After that, cell viability was assessed by MTT test as described above. The cytoprotective activity of compounds was considered as their ability to increase the values of OD compared to control wells (with virus only, no drugs). Based on the results obtained, the values of IC_{50}, i.e., the concentration of compounds that results in 50% cells protection, were calculated using GraphPad Prism software. Values of IC_{50} obtained in micrograms/mL were then calculated into micromoles. Based on the obtained data, the selectivity index (SI), the ratio of CC_{50} to IC_{50}, was calculated for each compound.