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Graphical Abstract

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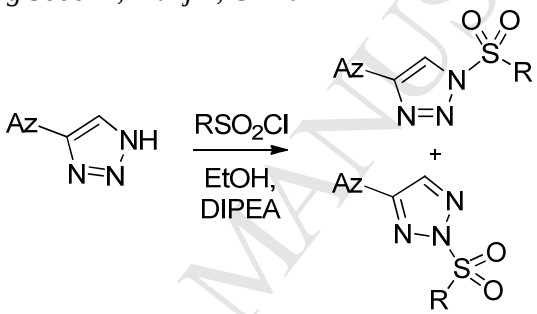

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ABSTRACT

The reactions of *N*-unsubstituted triazoles with sulfonyl chlorides afforded mixtures of regioisomeric 1- and 2-sulfonyl-1,2,3-triazoles. In some cases, pure regioisomers were obtained by crystallization of mixtures of isomers. 1,2,3-Triazoles bearing thiadiazole, isoxazole and benzene rings react with mesyl chloride and tosyl chloride to form mainly 1-substituted 1,2,3-triazoles. Conversely, reactions of triazoles **1a,b** and oxadiazolyl triazole **1h** with more bulky 1-(2,4-dimethylphenyl)sulfonyl chloride affords mainly 2-substitued products. Oxadiazole **1b** furnishes an equal mixture of the regioisomeric products **3** and **4** as a result of the reaction with mesyl and tosyl chlorides. Higher temperatures increase the ratio of isomers in favor of the 2-substituted triazole. The ratio of isomers depends on both the nature of the azolyl ring and on the size of the substituent in the sulfonyl chloride. Based on the results of experimental and theoretical data, 1-substituted and 2-substituted 1,2,3-triazoles can be considered as the kinetic and thermodynamic products.

1. Introduction

The discovery in 2002 by the Sharpless/Fokin and Meldal groups of the CuAAC reaction opened the way to 1,2,3-triazole derivatives of various structures available for testing their material and biological properties.[1,2] Further applications were found in medicinal chemistry, biology, and analytical chemistry.[3] Due to the capacity for ring rearrangements and transformations, 1,2,3-triazoles are widely used in organic synthesis.[4-11] 1-Sulfonyl-1,2,3-triazoles were found to be convenient chemical reagents to generate azavinyl carbenoids that in turn can undergo reactions with compounds bearing double and triple bonds and are capable of inserting into C–H, N–H, O–H and C–C bonds.[3,4] This approach is recognized by many scientists as a powerful method to prepare, starting from 1-sulfonyl-1,2,3-triazoles, a huge variety of other heterocyclic compounds and valuable organic compounds such as azoles, [1] fused indoles, *N*-sulfonylamidines, cycloalkanes, enamines, dienes, ketones, and sulfonamides.[12-14]

The introduction of an azolyl fragment to 1,2,3-triazole could increase both the stability of the intermediate azavinyl carbenes and open the possibility for the reaction to proceed even without catalyst.[15] On the other hand, 4-azolyl-1,2,3-triazoles evoke special interest in medicinal chemistry as close structural analogs of 4-azolylpyrazoles that recently have been discovered as novel types of anticancer compounds.[16]

The noncatalyzed[17-19] and copper catalyzed[20] 1,3-dipolar cycloaddition of alkynes to azides with sulfonyl azides were often used for the synthesis of 1-sulfonyl substituted 1,2,3-triazoles. However, this was never used for the synthesis of 1-sulfonyl-4-azolyl-1,2,3-triazoles, most probably because the azolyl acetylenes are poorly available chemicals.

Cycloaddition reactions of enamines and 1,3-dicarbonyl compounds to azides present a promising approach to 1,4,5-substituted-1,2,3-triazoles that however has been less studied than the CuAAC method.[13] Recently we have shown that reactions of β-azolyl enamines with aryl and alkyl azides

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represent a convenient, regioselective and general method to prepare 4-azolyl-1,2,3-triazoles in which these enamines are the synthetic equivalents of azolyl alkynes.[21] Unfortunately, we did not manage to expand our approach to reactions of β-azolyl enamines with sulfonyl azides for the synthesis of 1-sulfonyl-4-azolyl-1,2,3-triazole. The formation of *N*-unsubstituted-4-azolyl-1,2,3-triazoles took place in high yields instead of the expected 1-sulfonyl-1,2,3-triazoles.[21]

We turned our attention to reactions of sulfonyl chlorides with *N*-unsubstituted-1,2,3-triazoles. Though this reaction is recognized as a traditional method to prepare 1-sulfonyl triazoles[14] the publications with data on reactivity of 1,2,3-triazoles with sulfonyl chlorides are innumerous.[22, 23, 24-30] The parent 1,2,3-triazole, 4-phenyl- and 4-ethoxycarbonyl-1,2,3-triazole are shown to react with tosyl chloride under basic conditions to form mainly 1-tosyl-1,2,3-triazoles with a small impurity of 2-substituted triazoles.[22-24] Conversely, 4-nitro-1,2,3-triazole reacts with 2,4,6-trimethylbenzene-1-sulfonyl chloride to give a mixture of 1-substituted- and 2-substituted-1,2,3-triazoles in almost equal quantity.[25] To the best of our knowledge, no systematic experimental or theoretical studies were made to elucidate the factors governing the direction of the reaction. Neither the effect of the structure of 1,2,3-triazoles nor that of the nature of the sulfonyl chloride and the reaction temperature on the ratio of isomers formed in the reaction have been studied. It should be noted that reactions of 4-azolyl-*N*-unsubstituted 1,2,3-triazoles with sulfonyl chlorides were not previously reported in the scientific or patent literature. To prepare 1- and 2-sulfonyl substituted 1,2,3-triazoles we have studied the reactions of 1,2,3-triazol-4-yl-1,2,3-thiadiazoles **1a,b**, 1,2,3-triazol-4-yl-1,2,4-oxadiazole **1c,d** and 1,2,3-triazol-4-yl-isoxazole **1e** with mesyl (**2a**), tosyl (**2b**), 2,4-dimethyl- (**2c**) and 4-fluorobenzene-1-sulfonyl (**2d**) chlorides.

2. Results and Discussion

N-Unsubstituted-1,2,3-triazoles **1a–e** were obtained from reactions of tosyl azide with enamines bearing in β-position 1,2,3-thiadiazole, 1,2,4-oxadiazole and isoxazole rings.[21]

We have found that reactions of *NH*-triazoles **1a–e** with sulfonyl chlorides **2a**–**d** proceed smoothly at room temperature in anhydrous ethanol in the presence of DIPEA (diisopropylethylamine) to afford mixtures of 1- (**3a–n**) and 2-sulfonyl-4-azolyl-1,2,3-triazoles (**4a–n**) of various ratios in good yields (Table 1). The formation of 1,5-disubstituted 1,2,3-triazoles **5** was not registered by TLC and NMR spectra. Unfortunately, the mixtures of regioisomers **3a–n** and **4a–n** could not to be separated by column chromatography with silica gel. However, crystallization of mixtures of products **3a/4a**, and **3i/4i** from ethyl acetate allowed us to prepare pure 1-sulfonyl substituted triazoles bearing in position 4 1,2,3-thiadiazole ring **3a** and isoxazole **3j** of 90% purity (Table 1). On the other hand, crystallization of mixtures **3c/4c** and **3i/4i** (double crystallization) led to formation of pure 2-sulfonyl substituted 1,2,3-thiadiazol-5-yl-1,2,3-triazole **4c** and 1,2,4-oxadiazol-5-yl-1,2,3-triazole **4i**, respectively. In general, the nature of the azole ring significantly affects the ratio of **3:4**. This ratio decreases in the following order 1,2,3-thiadiazole > isoxazole > 1,2,4-oxadiazole (compare data for the reaction of mesyl chloride (Table 1, entries 1, 4, 7, 10); for the reaction of tosyl chloride (Table 1, entries 2, 5, 8, 11, 13)). Comparing data of entries 1–6 for reactions of 1,2,3-thiadiazoles **3a–f**, entries 6–9 for oxadiazoles **3g–i** with sulfonyl chlorides **2a–d** and entries 10–14 or reaction of isoxazoles **1d,e** with sulfonyl chlorides **2a–d** allow us to conclude that the ratios of **3:4** decrease with increase of the molecular size of the sulfonyl chlorides in favor of 2-substitued-1,2,3-triazoles. The replacement of the cyano group by an ester function (Table 1, entries 11 and 13) also favors the formation of 2-sulfonyl substituted 1,2,3-triazoles.

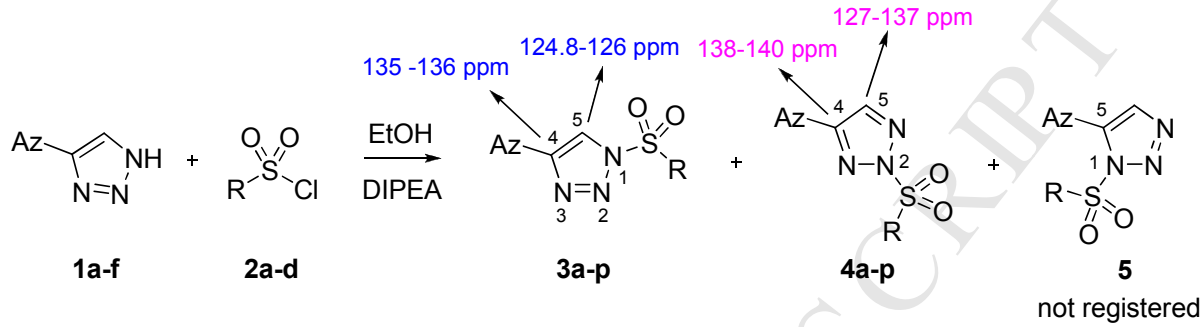
For comparison with the triazoles **1a-e**, we have reacted model 4-phenyl-1,2,3-triazole (**1f**) with 1.2 equivalent of tosyl chloride (**1b**) and DIPEA in ethanol at room temperature. After column chromatography, a 89% yield of a 7:3 mixture of the 1- and 2-sulfonylated 4-phenyltriazoles **3o/4o** was obtained. A longer reaction time was observed in the case of 2,4-dimethylbenzene-1-sulfonyl chloride (**2c**) and the expected compound was isolated as a 3:2 mixture of 1- and 2-sulfonylated 4-phenyltriazoles **3p/4p** with an overall yield of 74%. Both experiments confirm the conclusion made on the reactivity of 4-azolyl-1,2,3-triazoles in reaction with azides: a more hindered sulfonyl chloride reagent favors the 2-substituted isomer. On the other hand, the outcome of the mesylation reaction of 4-phenyl-1,2,3-triazole was time dependent as we could see if we studied the reaction by taking ^{1}H NMR spectra at time intervals. Already after 10 minutes at room temperature in either deuterated chloroform or methanol, the conversion is around 70%, with a mixture of 1- and 2-substituted regioisomers formed in about the same 7:3 ratio, next to about 30% of the starting material. Unexpectedly, longer reaction times lead to less conversion and at the same time the ratio of the regioisomers changes in favor of the 2-substituted compound. This can be explained by hydrolysis of the sulfonylated products formed under the influence of traces of water or other nucleophiles, which occurs faster for the 1-substituted isomer. This phenomenon may be a reason for different ratios of 1- and 2-sulfonylated triazoles found in the literature.[20, 31]

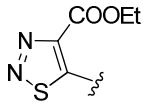
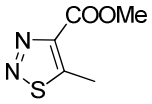
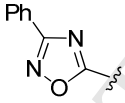
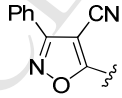
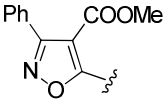
To prepare pure 2-sulfonyl-1,2,3-triazole **4i** we treated the mixture of isomers **3i**/**4i** with a solution of acetic acid in water at 60 °C similar to the protocol published by Yamauchi et al.[31] However, unsubstituted triazole **1c**, instead of desired **4i**, was prepared in good yield due to hydrolysis in water/acid mixture. Obviously, 1-sulfonyl-4-azol-yl-1,2,3-triazoles are very sensitive to water.

The structures of compounds **3a–p** and **4a–p** were confirmed by a combination of ^{1}H and ^{13}C NMR spectroscopy, mass-spectrometry, and by X-ray analysis data for single crystals of pure samples of triazoles **3a** and **4c**. NMR spectra of all compounds exhibit signals that are similar to the signals belonging to both the starting compounds, e.g. the hydrogen and carbon atoms of azolyl triazoles **1** and sulfonyl chlorides **2**. Based on the spectra of the pure isomers, and their HSQC and HMBC spectra, the singlet signals in low field at 8.81–9.39 and 8.39–8.90 ppm in ^{1}H NMR spectra, and the signals in regions 124.8–126.0, 135.0–136.0, 129.0–137.0 and 138.0–140.0 ppm in ^{13}C NMR spectra were assigned to protons of C5–H and carbons of C–4 and C–5 of 1-sulfonyl- and 2-sulfonyl-1,2,3-triazoles, respectively. The NMR spectra of mixtures **3a–p** and **4a–p** demonstrate that all compounds belong to the same structural type. Thus, the ^{1}H NMR spectra contain two singlets of C5–H protons at 9.35–9.39 and 8.74–8.90 ppm (**3,4a–f**), 8.86–8.88 and 8.43–8.55 ppm (**3,4g–i**), 8.79–9.20 and 8.39–8.58 (**3,4j–n**), 8.32–8.34 and 8.06–8.07 (**3,4o,p**) and two singlets of methyl groups of substituents R in sulfonyl fragments at 2.40–3.67 ppm in different intensity ratio. ^{13}C NMR spectra of mixtures **3,4a–p** exhibit a set of double signals. In the HMBC spectrum of compound **3a** the peak at 14.3 ($CH_2\underline{C}H_3$) correlates with the peak at 4.59

($C\underline{H}_2CH_3$), the peak at 62.7 ($\underline{C}H_2CH_3$) with the peak at 1.52 ($CH_2C\underline{H}_3$), the peak at 135.9 (C4) with the peak at 9.36 (C5–H), the peak at 160.9 (C=O) with the peak at 4.59 ($C\underline{H}_2CH_3$). The structures of prepared compounds **3** and **4** are further supported by X-ray analysis (Fig.1 and Fig.2) for the crystals of triazoles **3a** and **4c**. According to the X-ray data, compound **3a** crystallizes in a centrosymmetric space group. All heavy atoms of the azolyl-triazole fragment are in plane with only 0.02 Å deviation of the plane. The ester group is placed approximately in the plane of the bis-heterocycle and the mesyl attached to N1 of the triazole ring. All bond lengths and angles are in good agreement with the standard values. In the molecular packing, a short contact between C(1) and C(4) with d = 3.28 Å is observed. All atoms of the azolyl-triazolyl fragment of compound **4c** similarly to **3a** are in the plane. In contrast to **3a**, the sulfonyl fragment is attached to N2 of the triazole and has an approximately perpendicular orientation of the R-sulfonyl moiety to the plane of the bis-heterocycle.

Table 1. Yields and ratios of regioisomers **3** and **4** in their mixtures prepared by reaction of 4-azolyl-1,2,3-triazoles with sulfonyl chlorides



Entry	**3, 4**	Az	R	Ratio of **3**:**4**[a]	Yield, %[b]
1	**3a**, **4a**		Me	90:10	64
				100:0[c]	49[c]
2	**3b**, **4b**		4-MeC_6H_4	75:25	93
3	**3c**, **4c**		2,4-$(Me)_2C_6H_3$	33:67	90
				0:100[c]	50[c]
4	**3d**, **4d**		Me	79:21	86
5	**3e**, **4e**		4-MeC_6H_4	69:31	92
6	**3f**, **4f**		4-FC_6H_4	63:37	83
7	**3g**, **4g**		Me	50:50	63
8	**3h**, **4h**		4-MeC_6H_4	50:50	85
9	**3i**, **4i**		2,4-$(Me)_2C_6H_3$	12:88	80
				5:95[c]	
				0:100[d]	26[d]
10	**3j**, **4j**		Me	70:30	58
				90:10[c]	40[c]
11	**3k**, **4k**		4-MeC_6H_4	55:45	95
12	**3l**, **4l**		2,4-$(Me)_2C_6H_3$	59:41	91
13	**3m**, **4m**		4-MeC_6H_4	45:55	86
14	**3n**, **4n**		4-FC_6H_4	37:63	83
15	**3o**, **4o**	Ph	4-MeC_6H_4	70:30	89
16	**3p**, **4p**	Ph	2,4-$(Me)_2C_6H_3$	60:40	74

[a] Determined by ^{1}H NMR analysis; [b] Isolated yield; [c] After crystallization; [d] After double crystallization

To find optimal conditions for the syntheses of each isomer formed in the reaction, we have studied the ratio of products **3i**/**4i** formed from azolyl triazole **1c** and sulfonyl chloride **2c** depending on the nature of the solvent and temperature (Table 2). We have not found any significant change in the ratio of isomers for the reaction in different solvents. Conversely, the amount of 2-substited isomer **4i** increases at higher temperatures. On the other hand, the content of 1-substituted 1,2,3-triazoles increases with lowering of the reaction temperature. In order to get some insight into this different reactivity behavior density functional theory calculations (M06-2X[32-34]) for the starting azoles **1a–e** as well as the regioisomeric products **3a**, **4a**, **5a**; **3g**, **4g**, **5g**; **3m**,

4m, and **5m** have been performed. Since the reaction is base catalyzed, the anions of the starting materials have been used in

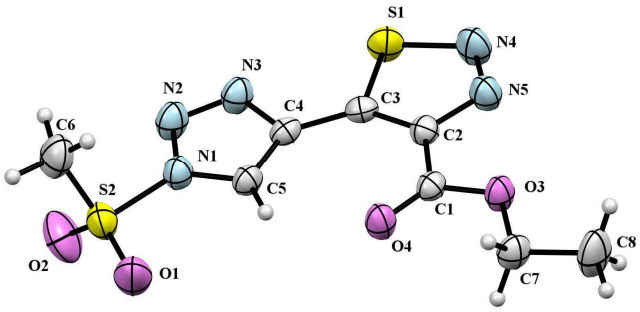


Fig.1. ORTEP of the compound **3a** according XRD data

the calculations. Different conformations resulting from torsion around C1–C2, C3–C4, and N1–S2 (**3a**, **3g**, **3m**), N2–S1 (**4a**, **4g**, **4m**) or N3–S2 (**5a**, **5g**, **5m**) were considered. Solvent effects (EtOH) were taken into account by the SMD solvation model.[35] In complete agreement with the X-ray data for **3a** and **4c** the calculated lowest energy conformations of **3a** and **4a** are characterized by an approximately planar arrangement of both the heterocyclic rings and the ester group [τ(S1–C3–C4–C5) ~180°, τ(C3–C2–C1–O4) ~ 1°; for atom numbering, see Fig. 1) and an approximately perpendicular orientation of the R-sulfonyl moiety. Substitution at N3 is strongly disfavored since products of type **5** are less stable than those of type **3** and **4** by ca. 6 kcal mol^{-1}. Generally, on thermodynamic grounds, substitution at N2, i.e. formation of compounds of type **4**, should preferentially occur [$\Delta\Delta G$ = -1.32 (**4a**), -1.95 (**4g**), and -0.34 kcal mol^{-1} (**4m**)]. As an alternative to product stability the reactivity of the reactants also have been considered. Specifically, the charges q at the possible reactive sites N1, N2, N3 obtained by several population analyses (Mulliken,[36] NPA,[37] Hirshfeld,[38] and ESP-derived charges (CHelpG[39])) were used as reactivity indices. The results are presented in Table 1 in the Supplementary data. Although both basis sets used as well as method of population analysis affect the individual values generally the smallest charges are found at N2 while those at N1 and N3 are similar and significantly more negative. Recently, conceptual density functional theory has become an important tool to assess the reactivity of different molecules and/or different sites within one molecule.[40-42]

Table 2. Effect of solvent and temperature on the ratio of sulfonyltriazoles **3i** and **4i**

Entry	Ratio **3i:4i**[a]	Solvent	Temperature, °C	Yield, %
1	13:87	1,4-dioxane	20	62
2	14:86	$CHCl_3$	20	91
3	8:92	CH_3CN	20	73
4	9:91	Et_2O	20	94
5	33:67	EtOH	0	73
6	12:88	EtOH	20	79
7	9:91	EtOH	40	78
8	7:93	EtOH	60	70

[a] Determined by ^{1}H NMR analysis

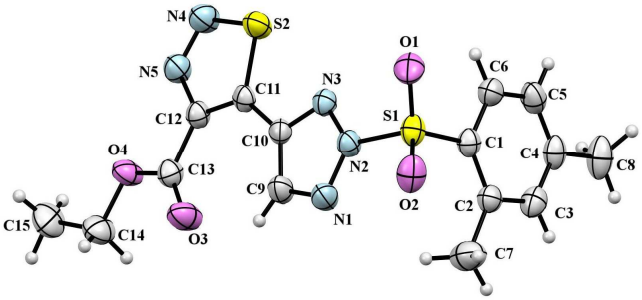


Fig. 2. ORTEP of the compound **4c** according XRD data

Table 3 (See Supplementary data) lists the Fukui index f^- describing the nucleophilicities of the relevant nitrogen atoms. While in a charged-controlled reaction addition of the sulfonyl chloride preferentially should occur at N1 or N3 (this latter attack can be safely ruled out on thermodynamic grounds), in an orbital-controlled reaction formation of 2-sulfonyl derivatives will be preferred.

3. Conclusions

4-Azolyl- and 4-phenyl-1,2,3-triazoles **3a-p/4a-p** have been shown to react with sulfonyl chlorides **2a-d** at N1 and N2 of the triazole ring to form mixtures of 1-sulfonyl- and 2-sulfonyl substituted 4-azolyl(phenyl)-1,2,3-triazoles. No reaction at N3 could be observed. The ratio of isomeric products depends on the nature of both the azole ring and the sulfonyl chlorides. 1,2,3-Thiadiazole **1a** and isoxazole **1d** react with mesyl chloride (**2a**) and tosyl chloride (**2b**) to form mainly 1-substituted 1,2,3-triazoles. Conversely, reaction of **1a** and oxadiazolyl triazole **1c** with more bulky 1-(2,4-dimethylphenyl)sulfonyl chloride (**2c**) has been shown to give mainly 2-substituted product, most probably because of more steric hindrance in compounds bearing a 2,4-dimethylphenyl group than tosyl and mesyl moieties. Density functional calculations indicate that, in agreement with experimental observations, the third isomers **5** should not be formed. Based on calculated product stabilities, 2-sulfonyl-4-azolyl-1,2,3-triazoles are the preferred products. However, under kinetic control, a delicate balance between nitrogen charges and nucleophilicities either can lead to 1- and/or 2-sulfonyl derivatives.

4. Experimental Section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance II spectrometer in $CDCl_3$ or DMSO-d_6 (400 and 100 MHz, respectively) using Me_4Si as an internal standard. Mass experiments were performed on Shimadzu GCMS-QP2010 Ultra gas chromatograph operating at an ionization potential of 70 eV (EI) or Thermo Finnigan LCQ Advantage apparatus (ESI). Microanalyses were performed on PerkinElmer Series II CHNS/O 2400 elemental analyzer. The melting point was defined on Stuart SMP 3 apparatus.

The progress of the reactions and the purity of the compounds were monitored by TLC on TLC Silica gel 60 F_{245} Aluminum sheets (Merck KGaA) in EtOAc-hexane (1:2) system.

4.2. X-ray diffraction study

*4.2.1. X-ray diffraction study of **3a**.*

Single crystals of **3a** were obtained by recrystallization from EtOAc. X-ray diffraction data for single crystals of **3a** were

collected on an Xcalibur3 X-ray diffractometer equipped with a CCD detector (λ-Mo-Kα, graphite monochromator, ω-scanning technique). The structure was determined by the direct method using the SHELXS97 program[43] and refined by the SHELXL97 program using the least-squares method in the anisotropic form (isotropic for H atoms). Prismatic colorless crystal 0.20x0.15x0.10 mm. Crystal system is monoclinic, a = 25.9490(11) Å, b = 6.6154(3) Å, c = 16.6949(6) Å, β =120.056(4)°, V =2480.55(19) Å^3, Completeness 99.9%., space group C2/c, formula is $C_8H_9N_5O_4S_2$ (for Z= 8), μ(Mo Kα) = 0.448, 5969 reflections measured, 3077 unique (R_{int} = 0.0249) which were used in all calculations. The final wR_2 was 0.1316 (all data) and R_1 was 0.0385 (I>=2σ (I)), GooF = 1.009. Largest diff. peak and hole 0.458 and -0.360 ēÅ^{-3}.

*4.2.2. X-ray diffraction study of **4c**.*

Single crystals of **4c** were obtained by crystallization from EtOAc. A suitable crystal was selected and examined on a Xcalibur, Eos diffractometer. The crystal was kept at 293(2) K during data collection. Using Olex2,[44] the structure was estimated with the Superflip[45] structure solution program using Charge Flipping and refined with the ShelXL[43] refinement package using Least Squares minimisation. $C_{15}H_{15}N_5O_4S_2$, M =393.44, triclinic, a = 4.9502(4) Å, b = 12.0870(7) Å, c = 15.2704(9) Å, α = 104.228(5)°, β = 98.802(6)°, γ = 97.850(6)°, V = 860.63(10) Å^3, T = 293(2), space group P-1 (no. 2), Z = 2, μ(Mo Kα) = 0.343, 7744 reflections measured, 4662 unique (R_{int} = 0.0336) which were used in all calculations. The final wR_2 was 0.1270 (all data) and R_1 was 0.0592 (>2sigma(I)).

Deposition numbers for compounds **3a** (CCDC 1400853) and **4c** (CCDC 1400852) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.3. Quantum chemical calculations

Quantum chemical calculations were done with Gaussian09,[46] GAMESS,[47,48] and Jaguar.[49]

4.4. General synthetic procedure, exemplified by the regioisomeric mixture of ethyl 5-(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (3a) and ethyl 5-(2-(methylsulfonyl)-2*H*-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (4a).

A mixture of triazole **1a** (0.575 g, 2.55 mmol), mesyl chloride (**2a**) (0.35 g, 0.23 mL, 3.06 mmol) and DIPEA (0.39 g, 0.506 mL, 3.06 mmol) in anhydrous ethanol (4 mL) was stirred at room temperature for 1 h. The formed precipitate was filtered off and washed with anhydrous ethanol to give a mixture of isomeric 1- and 2-sulfonyl-1,2,3-triazoles **3a** and **4a** in 90:10 ratio.

Crystallization of the mixture of triazoles **3a**/**4a** gives pure 1-sulfonyl substituted triazole **3a**, the mixture of **3c**/**4c** gives 2-sulfonyl substituted triazole **4c**, and the mixture of **3i**/**4i** gives 2-sulfonyl substituted triazole **4i** (double recrystallization).

3a/**4a**. Colourless crystals, yield 64%, 0.49 g, mp 140–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (3H, t, J 8.0 Hz, $OCH_2C\underline{H}_3$), 3.53 (**4a**), 3.63 (**3a**) (3H, 2s, $SO_2C\underline{H}_3$), 4.59 (2H, qv., J 8.0 Hz, J 16.0 Hz, $OC\underline{H}_2CH_3$), 8.87 (**4a**), 9.36 (**3a**) (1H, 2s, C5–H); MS m/z EI (70 eV), (I, %): 303 (M^+, 5), 152 (68), 79 (100), 69 (98); Anal. Calcd for $C_8H_9N_5O_4S_2$ (303.32): C, 31.68; H, 2.99; N, 23.09; S, 21.14. Found: C, 31.82; H, 3.22; N, 23.36; S, 21.46.

3a. Colourless crystals, yield 49%, 0.30 g, mp 169–171 °C (from EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (3H, t, J 8.0 Hz, $OCH_2C\underline{H}_3$), 3.63 (3H, s, $SO_2C\underline{H}_3$), 4.59 (2H, qv., J 8.0 Hz, J 16.0 Hz, $OC\underline{H}_2CH_3$), 9.36 (s, 1H, C5–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 43.0, 63.0, 125.1, 136.1, 147.4, 150.7, 161.2; Anal. Calcd for $C_8H_9N_5O_4S_2$ (303.32): C, 31.68; H, 2.99; N, 23.09; S, 21.14. Found: C, 31.79; H, 2.82; N, 23.28; S, 21.19.

*4.4.1. Ethyl 5-(1-tosyl-1H-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (**3b**) and ethyl 5-(2-tosyl-2H-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (**4b**).*

Colourless crystals, yield 93%, 0.46 g, mp 152–159 °C; **3b**/**4b** ratio is 75:25; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45–1.54 (3H, m, $OCH_2C\underline{H}_3$), 2.45 (**4b**), 2.47 (**3b**) (3H, 2s, $SO_2C_6H_4C\underline{H}_3$), 4.52–4.62 (2H, m, $OC\underline{H}_2CH_3$), 7.38–7.43 (2H, m, $H_{arom.}$), 8.01–8.07 (2H, m, $H_{arom.}$), 8.74 (**4b**), 9.35 (**3b**) (1H, 2s, C5-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.7, 14.0, 20.7, 21.2, 61.9, 62.1, 125.5, 126.0, 128.1, 128.6, 128.8, 130.9, 131.0, 134.0, 135.6, 136.7, 138.0, 139.4, 145.1, 146.5, 148.0, 151.9, 159.5, 160.3; MS m/z EI (70 eV), (I, %): 379 (M^+, 7), 155 (40), 152 (38), 91 (100); Anal. Calcd for $C_{14}H_{13}N_5O_4S_2$ (379.41): C, 44.32; H, 3.45; N, 18.46; S, 16.90. Found: C, 44.65; H, 3.69; N, 18.63; S, 16.71.

*4.4.2. Ethyl 5-(1-(2,4-dimethylphenylsulfonyl)-1H-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (**3c**) and ethyl 5-(2-(2,4-dimethylphenylsulfonyl)-2H-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (**4c**).*

Colourless crystals, yield 90%, 0.41 g, mp 153–156 °C; **3c**/**4c** ratio is 33:67; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46–1.56 (3H, m, $OCH_2C\underline{H}_3$), 2.41, 2.68 (**3c**) (3H, 2s, $SO_2C_6H_3(C\underline{H}_3)_2$), 2.40, 2.67 (**4c**) (3H, 2s, $SO_2C_6H_3(C\underline{H}_3)_2$), 4.53–4.62 (2H, m, $OC\underline{H}_2CH_3$), 7.16–7.28 (2H, m, $H_{arom.}$), 8.14–8.18 (1H, m, $H_{arom.}$), 8.75 (**4c**), 9.36 (**3c**) (1H, 2s, C5–H); MS m/z EI (70 eV), (I, %): 393 (M^+, 8), 169 (100), 152 (60), 105 (81); Anal. Calcd for $C_{15}H_{15}N_5O_4S_2$ (393.44): C, 45.79; H, 3.84; N, 17.80; S, 16.30. Found: C, 46.03; H, 3.62; N, 18.12; S, 16.38.

4c. Colourless crystals, yield 50%, 0.23 g, mp 176–178 °C (from EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (3H, t, J 8.0 Hz, $OCH_2C\underline{H}_3$), 2.40 (3H, s, $SO_2C_6H_3C\underline{H}_3$), 2.67 (3H, s, $SO_2C_6H_3C\underline{H}_3$), 4.55 (2H, qv., J 8.0 Hz, J 16.0 Hz, $OC\underline{H}_2CH_3$), 7.16 (1H, s, $H_{arom.}$), 7.24 (1H, d, J 8.0 Hz, $H_{arom.}$), 8.15 (1H, d, J 8.0 Hz, $H_{arom.}$), 8.75 (1H, s, C5–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.0, 20.0, 20.5, 61.9, 125.1, 126.6, 127.3, 131.3, 134.0, 135.3, 137.9, 143.3, 146.5, 151.9, 160.3; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 20.7, 21.6, 62.8, 127.9, 130.5, 131.8, 134.1, 137.9, 138.9, 140.2, 147.6, 148.6, 149.5, 160.5; Anal. Calcd for $C_{15}H_{15}N_5O_4S_2$ (393.44): C, 45.79; H, 3.84; N, 17.80; S, 16.30. Found: C, 45.91; H, 3.65; N, 17.60; S, 16.38.

*4.4.3. Methyl 5-(1-(methylsulfonyl)-1H-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (**3d**) and methyl 5-(2-(methylsulfonyl)-2H-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (**4d**).*

Colourless crystals, yield 86%, 0.12 g, mp 176–177 °C; **3d**/**4d** ratio is 79:21; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54 (**4d**), 3.64 (**3d**) (3H, 2s, $SO_2C\underline{H}_3$), 4.14 (3H, s, $COOC\underline{H}_3$), 8.90 (**4d**), 9.39 (**3d**) (1H, 2s, C5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.8, 42.9, 53.4, 53.5, 125.0, 129.4, 135.9, 138.3, 145.8, 146.9, 150.8, 154.0, 160.9, 161.4; MS m/z EI (70 eV), (I, %): 289 (M^+, 8), 152 (66), 79 (100), 59 (97); Anal. Calcd for $C_7H_7N_5O_4S_2$ (289.29): C, 29.06; H, 2.44; N, 24.21; S, 22.17. Found: C, 28.75; H, 2.29; N, 24.42; S, 22.41.

*4.4.4. Methyl 5-(1-tosyl-1H-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (**3e**) and methyl 5-(2-tosyl-2H-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (**4e**).*

Colourless crystals, yield 92%, 0.16 g, mp 134–137 °C; **3e**/**4e** ratio is 69:31; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (**4e**), 2.47 (**3e**)

(3H, 2s, $SO_2C_6H_4C\underline{H}_3$), 4.08 (**4e**), 4.13 (**3e**) (3H, 2s, $COOC\underline{H}_3$), 7.38–7.44 (2H, m, $H_{arom.}$), 8.02–8.08 (2H, m, $H_{arom.}$), 8.76 (**4e**), 9.36 (**3e**) (1H, 2s, C5–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.0, 53.3, 53.4, 124.9, 125.9, 129.0, 129.2, 130.5, 130.7, 132.0, 132.3, 135.7, 138.3, 139.2, 146.7, 147.7, 148.1, 149.6, 151.2, 160.9, 161.4; MS *m/z* EI (70 eV), (I, %): 365 (M^+, 7), 155 (30), 91 (100), 65 (30); Anal. Calcd for $C_{13}H_{11}N_5O_4S_2$ (365.39): C, 42.73; H, 3.03; N, 19.17; S, 17.55. Found: C, 43.03; H, 2.86; N, 18.95; S, 17.66.

*4.4.5. Methyl 5-(1-(4-fluorophenylsulfonyl)-1H-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (**3f**) and methyl 5-(2-(4-fluorophenylsulfonyl)-2H-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (**4f**).*

Colourless crystals, yield 83%, 0.081 g, mp 129–132 °C; **3f/4f** ratio is 63:37; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (**4f**), 4.12 (**3f**) (3H, 2s, $COOC\underline{H}_3$), 7.29–7.35 (2H, m, $H_{arom.}$), 8.15–8.23 (2H, m, $H_{arom.}$), 8.77 (**4f**), 9.36 (**3f**) (1H, 2s, C5–H); ^{13}C NMR (100 MHz, $CDCl_3$): 53.3, 53.4, 117.5, 117.7, 125.0, 131.0, 131.3, 132.2, 132.3, 135.8, 146.4, 148.4, 149.3, 150.9, 160.8, 161.4, 167.2, 167.3; MS m/z EI (70 eV), (I, %): 369 (M^+, 10), 277 (20), 159 (57), 95 (100); Anal. Calcd for $C_{12}H_8FN_5O_4S_2$ (369.35): C, 39.02; H, 2.18; N, 18.96; S, 17.36. Found: C, 39.14; H, 2.24; N, 18.90; S, 17.58.

*4.4.6. 5-(1-(Methylsulfonyl)-1H-1,2,3-triazol-4-yl)-3-phenyl-1,2,4-oxadiazole (**3g**) and 5-(2-(methylsulfonyl)-2H-1,2,3-triazol-4-yl)-3-phenyl-1,2,4-oxadiazole (**4g**).*

Colourless crystals, yield 63%, 0.40 g, mp 122–127 °C; **3g/4g** ratio is 50:50; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (**4g**), 3.67 (**3g**) (3H, 2s, $SO_2C\underline{H}_3$), 7.50–7.59 (3H, m, $H_{arom.}$), 8.17–8.20 (2H, m, $H_{arom.}$), 8.55 (**4g**), 8.86 (**3g**), (1H, 2s, C5–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.9, 42.9, 125.4, 125.9, 126.0, 127.7, 128.9, 129.0, 129.1, 131.5, 131.7, 131.8, 137.7, 137.9, 147.6, 149.3, 167.1, 167.2, 169.2, 169.3; MS *m/z* EI (70 eV), (I, %): 291 (M^+, 10), 212 (21), 145 (47), 79 (Ms, 100); Anal. Calcd for $C_{11}H_9N_5O_3S$ (291.29): C, 45.36; H, 3.11; N, 24.04; S, 11.01. Found: C, 45.13; H, 3.25; N, 24.11; S, 11.09.

*4.4.7. 3-Phenyl-5-(1-tosyl-1H-1,2,3-triazol-4-yl)-1,2,4-oxadiazole (**3h**) and 3-phenyl-5-(2-tosyl-2H-1,2,3-triazol-4-yl)-1,2,4-oxadiazole (**4h**).*

Colourless crystals, yield 85%, 0.29 g, mp 177–180 °C; **3h/4h** ratio is 50:50; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (**4g**), 2.48 (**3h**) (3H, 2s, $SO_2C_6H_5C\underline{H}_3$), 7.40–7.45 (2H, m, $H_{arom.}$), 7.48–7.56 (3H, m, $H_{arom.}$), 8.06–8.10 (2H, m, $H_{arom.}$), 8.14–8.17 (2H, m, $H_{arom.}$), 8.43 (**4h**), 8.86 (**3h**) (1H, 2s, C5–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 21.9, 125.4, 126.0, 126.1, 127.5, 127.6, 128.9, 129.0, 129.1, 129.3, 130.5, 130.8, 131.6, 131.7, 132.0, 132.1, 133.9, 137.5, 137.9, 147.8, 148.4, 167.4, 167.6, 169.0, 169.2; MS *m/z* EI (70 eV), (I, %): 367 (M^+, 9), 155 (40), 145 (33), 91 (100); Anal. Calcd for $C_{17}H_{13}N_5O_3S$ (367.38): C, 55.58; H, 3.57; N, 19.06; S, 8.73. Found: C, 55.39; H, 3.89; N, 18.96; S, 8.64.

*4.4.8. 5-(1-(2,4-Dimethylphenylsulfonyl)-1H-1,2,3-triazol-4-yl)-3-phenyl-1,2,4-oxadiazole (**3i**) and 5-(2-(2,4-dimethylphenylsulfonyl)-2H-1,2,3-triazol-4-yl)-3-phenyl-1,2,4-oxadiazole (**4i**).*

Colourless crystals, yield 80%, 0.71 g, mp 150–153 °C; **3i/4i** ratio is 12:88; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (**4i**), 2.43 (**3i**) (3H, 2s, $SO_2C_6H_3(C\underline{H}_3)_2$), 2.68 (**3i**), 2.69 (**4i**) (3H, 2s, $SO_2C_6H_3(C\underline{H}_3)_2$), 7.17–7.29 (2H, m, $H_{arom.}$), 7.49–7.56 (3H, m, $H_{arom.}$), 8.14–8.22 (3H, m, $H_{arom.}$), 8.43 (**4i**), 8.88 (**3i**) (1H, 2s, C5–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 20.7, 21.6, 21.7, 125.5, 126.0, 126.1, 127.5, 127.6, 127.9, 128.1, 128.9, 129.0, 130.4, 131.6, 131.7, 131.9, 133.8, 134.1, 134.4, 137.1, 137.5, 140.2, 140.3, 147.8, 148.3, 167.4, 167.6, 169.0, 169.2; MS *m/z* EI (70 eV), (I, %): 381 (M^+, 10), 169 (13), 105 (100), 77 (40); Anal. Calcd for $C_{18}H_{15}N_5O_3S$ (381.41): C, 56.68; H, 3.96; N, 18.36; S, 8.41. Found: C, 56.91; H, 4.21; N, 18.23; S, 8.59.

4i: Colourless crystals, yield 26%, 0.23 g, mp 176–178 °C (from EtOAc, double recrystallization); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (3H, s, $SO_2C_6H_3(C\underline{H}_3)_2$), 2.69, (3H, s, $SO_2C_6H_3(C\underline{H}_3)_2$), 7.17 (1H, s, $H_{arom.}$), 7.26 (1H, d, *J* 8.0 Hz, $H_{arom.}$), 7.49–7.55 (3H, m, $H_{arom.}$), 8.15 (2H, d, *J* 8.0 Hz, $H_{arom.}$), 8.20 (1H, d, *J* 8.0 Hz, $H_{arom.}$), 8.43 (1H, s, C5–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 21.6, 126.0, 127.6, 127.9, 128.9, 130.5, 131.6, 131.9, 134.1, 137.1, 137.5, 140.4, 147.7, 167.5, 169.2; Anal. Calcd for $C_{18}H_{15}N_5O_3S$ (381.41): C, 56.68; H, 3.96; N, 18.36; S, 8.41. Found: C, 56.59; H, 3.87; N, 18.30; S, 8.47.

*4.4.9. 5-(1-(Methylsulfonyl)-1H-1,2,3-triazol-4-yl)-3-phenylisoxazole-4-carbonitrile (**3j**) and 5-(2-(methylsulfonyl)-2H-1,2,3-triazol-4-yl)-3-phenylisoxazole-4-carbonitrile (**4j**).*

Colourless crystals, yield 40%, 0.16 g, mp 150–153 °C (from EtOAc); **3j/4j** ratio is 90:10; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (**4j**), 3.69 (**3j**) (3H, 2s, $SO_2C\underline{H}_3$), 7.54–7.62 (3H, m, $H_{arom.}$), 8.01–8.04 (2H, m, $H_{arom.}$), 8.53 (**4j**), 8.81 (**3j**) (1H, 2s, C5-H); ^{13}C NMR (100 MHz, $CDCl_3$): 41.8, 42.9, 110.8, 111.1, 123.7, 125.4, 125.6, 127.5, 129.4, 129.5, 131.8, 131.9, 133.8, 134.2, 134.9, 136.2, 137.6, 146.3, 161.8, 162.0, 166.3, 166.6; MS *m/z* EI (70 eV), (I, %): 315 (M^+, 8), 236 (32), 169 (20), 79 (Ms, 100); Anal. Calcd for $C_{13}H_9N_5O_3S$ (315.31): C, 49.52; H, 2.88; N, 22.21; S, 10.17. Found: C, 49.19; H, 3.17; N, 22.45; S, 9.98.

*4.4.10. 3-Phenyl-5-(1-tosyl-1H-1,2,3-triazol-4-yl)isoxazole-4-carbonitrile (**3k**) and 3-phenyl-5-(2-tosyl-2H-1,2,3-triazol-4-yl)isoxazole-4-carbonitrile (**4k**).*

Colourless crystals, yield 95%, 0.25 g, mp 198-201 °C; **3k/4k** ratio is 55/45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (**4k**), 2.49 (**3k**) (3H, 2s, $SO_2C_6H_4C\underline{H}_3$), 7.41–7.46 (2H, m, $H_{arom.}$), 7.52–7.60 (3H, m, $H_{arom.}$), 7.98–8.01 (2H, m, $H_{arom.}$), 8.07–8.12 (2H, m, $H_{arom.}$), 8.40 (**4k**), 8.79 (**3k**) (1H, 2s, C5–H); ^{13}C NMR (100 Mz, $CDCl_3$): δ 21.9, 22.0, 110.7, 111.1, 123.6, 125.5, 127.5, 125.7, 129.2, 129.3, 129.4, 129.5, 130.6, 130.8, 131.7, 131.8, 134.0, 136.1, 137.4, 147.9, 148.5, 161.7, 161.8, 166.3, 166.6; MS *m/z* EI (70 eV), (I, %): 391 (M^+, 9), 139 (100), 91 (93), 77 (29); Anal. Calcd for $C_{19}H_{13}N_5O_3S$ (391.40): C, 58.30; H, 3.35; N, 17.89; S, 8.19; Found: C, 58.59; H, 3.08; N, 17.76; S, 8.37.

*4.4.11. 5-(1-(2,4-Dimethylphenylsulfonyl)-1H-1,2,3-triazol-4-yl)-3-phenylisoxazole-4-carbonitrile (**3l**) and 5-(2-(2,4-dimethylphenylsulfonyl)-2H-1,2,3-triazol-4-yl)-3-phenylisoxazole-4-carbonitrile (**4l**).*

Colourless crystals, yield 91%, 0.124 g, mp 142–145 °C; **3l/4l** ratio is 59:41; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (**4l**), 2.43 (**3l**) (3H, 2s, $SO_2C_6H_3(C\underline{H}_3)_2$), 2.70 (**3l**), 2.75 (**4l**) (3H, 2s, $SO_2C_6H_3(C\underline{H}_3)_2$), 7.19–7.29 (2H, m, $H_{arom.}$), 7.53–7.60 (3H, m, $H_{arom.}$), 7.97–8.02 (2H, m, $H_{arom.}$), 8.15–8.20 (1H, m, $H_{arom.}$), 8.39 (**4l**), 8.81 (**3l**) (1H, 2s, C5–H); ^{13}C NMR (100 Mz, $CDCl_3$): δ 20.8, 20.9, 21.6, 21.7, 110.7, 111.1, 123.2, 123.6, 125.5, 125.7, 127.5, 127.9, 128.2, 129.3, 129.4, 130.3, 131.6, 131.7, 131.9, 133.9, 134.2, 134.4, 135.8, 137.1, 140.4, 140.7, 147.9, 148.4, 161.7, 161.8, 166.3, 166.7; MS *m/z* EI (70 eV), (I, %): 405 (M^+, 11), 169 (30), 105 (100), 77 (66); Anal. Calcd for $C_{20}H_{15}N_5O_3S$ (405.43): C, 59.25; H, 3.73; N, 17.27; S, 7.91; Found: C, 59.55; H, 3.45; N, 17.35; S, 8.17.

*4.4.12. Methyl 3-phenyl-5-(1-tosyl-1H-1,2,3-triazol-4-yl)isoxazole-4-carboxylate (**3m**) and methyl 3-phenyl-5-(2-tosyl-2H-1,2,3-triazol-4-yl)isoxazole-4-carboxylate (**4m**).*

Colourless crystals, yield 86%, 0.18 g, mp 95–99 °C; **3m/4m** ratio is 45:55; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (**4m**), 2.50 (**3m**) (3H, 2s, $SO_2C_6H_4C\underline{H}_3$), 3.80 (3H, s, $CO_2C\underline{H}_3$), 7.41–7.55 (5H, m, $H_{arom.}$), 7.62–7.66 (2H, m, $H_{arom.}$), 8.08–8.11 (2H, m, $H_{arom.}$), 8.57 (**4m**), 9.19 (**3m**) (1H, 2s, C5–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 21.9, 52.2, 52.3, 109.1, 110.8, 125.9, 127.5, 127.9, 128.2, 128.3, 129.0, 129.1, 129.2, 130.1, 130.2, 130.5, 130.7, 132.2, 132.4, 134.2, 135.1, 138.4, 139.0, 147.6, 148.1, 161.6, 162.0, 162.6, 162.7, 162.8, 163.6; MS *m/z* EI (70 eV), (I, %): 424 (M^+, 6), 155 (40), 143 (29), 91 (100); Anal. Calcd for $C_{20}H_{16}N_4O_5S$ (424.43): C, 56.60; H, 3.80; N, 13.20; S, 7.55. Found: C, 56.85; H, 4.07; N, 13.09; S, 7.63.

*4.4.13. Methyl 5-(1-(4-fluorophenylsulfonyl)-1H-1,2,3-triazol-4-yl)-3-phenylisoxazole-4-carboxylate (**3n**) and methyl 5-(2-(4-fluorophenylsulfonyl)-2H-1,2,3-triazol-4-yl)-3-phenylisoxazole-4-carboxylate (**4n**).*

Colourless crystals, yield 83%, 0.074 g, mp 135–137 °C; **3n/4n** ratio is 37:63; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (**4n**), 3.77 (**4n**) (3H, 2s, $CO_2C\underline{H}_3$), 7.26–7.35 (2H, m, $H_{arom.}$), 7.45–7.53 (3H, m, $H_{arom.}$), 7.59–7.63 (2H, m, $H_{arom.}$), 8.21–8.26 (2H, m, $H_{arom.}$), 8.58 (**4n**), 9.20 (**3n**) (1H, 2s, C5–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, 52.3, 109.8, 111.0, 117.6, 117.7, 126.0, 128.4, 129.2, 131.2, 131.4, 132.2, 132.3, 134.5, 135.3, 138.7, 139.3, 161.5, 162.0, 162.5, 162.6, 162.8, 163.4, 166.9, 167.3; MS *m/z* EI (70 eV), (I, %): 428 (M^+, 35), 143 (87), 95 (100), 77 (50); Anal. Calcd for $C_{19}H_{13}FN_4O_5S$ (428.39): C, 53.27; H, 3.06; N, 13.08; S, 7.48. Found: C, 53.48; H, 3.17; N, 13.11; S, 7.33.

*4.4.14. 4-Phenyl-1-tosyl-1H-1,2,3-triazole (**3o**) and 4-phenyl-2-tosyl-2H-1,2,3-triazole (**4o**).*

Colourless crystals, yield 89%, 0.09 g, mp 110–112 °C; **3o**/**4o** ratio is 70:30; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (**4o**), 2.44 (**3o**) (3H, 2s, $SO_2C_6H_4C\underline{H}_3$), 7.32–7.45 (5H, m, $H_{arom.}$), 7.81–7.83 (2H, m, $H_{arom.}$), 7.98–8.03 (2H, m, $H_{arom.}$), 8.07 (**4o**), 8.32 (**3o**) (1H, 2s, C5–H); ^{13}C NMR (100 Mz, $CDCl_3$): δ 21.6, 21.7, 118.8, 126.5, 125.9, 128.0, 128.5, 128.4, 128.7, 129.7, 128.9, 129.8, 129.0, 130.0, 130.3, 132.8, 132.9, 135.6, 146.5, 147.1, 151.3; MS (ESI^+): m/z: 322 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{13}N_3O_2S$ (299.35): C, 60.18; H, 4.38; N, 14.04; S, 10.71. Found: C, 60.49; H, 4.58; N, 13.99; S, 10.89.

*4.4.15. 1-(2,4-Dimethylphenylsulfonyl)-4-phenyl-1H-1,2,3-triazole (**3p**) and 1-(2,4-dimethylphenylsulfonyl)-4-phenyl-1H-1,2,3-triazole (**4p**).*

Colourless crystals, yield 74%, 0.08 g, mp 120–123 °C; **3p**/**4p** ratio is 60:40; ^{1}H NMR (400 MHz, $CDCl_3$): δ): δ 2.37 (**4p**), 2.38 (**3p**) (3H, 2s, $SO_2C_6H_4C\underline{H}_3$), δ 2.61 (**3p**), 2.67 (**4p**) (3H, 2s, $SO_2C_6H_4C\underline{H}_3$), 7.11–7.26 (2H, m, $H_{arom.}$), 7.42–7.44 (2H, m, $H_{arom.}$), 7.80–7.84 (2H, m, $H_{arom.}$), 8.11–8.15 (2H, m, $H_{arom.}$), 8.06 (**4p**), 8.34 (**3p**) (1H, 2s, C5–H); ^{13}C NMR (100 Mz, $CDCl_3$): δ 20.2, 20.7, 21.5, 21.6, 126.2, 126.8, 127.7, 127.9, 128.5, 129.1, 130.0, 130.2, 131.3, 131.4, 131.6, 133.4, 133.9, 134.2, 135.2, 138.2, 139.9, 144.6, 146.8, 151.1 ; MS (ESI^+): m/z: 336 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{15}N_3O_2S$ (313.37): C, 61.32; H, 4.82; N, 13.41; S, 10.23; Found: C, 61.57: H, 5.02; N, 13.20; S, 10.30.

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Supplementary Material

Supplementary data associated with this article can be found in t

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Supplementary Data

Reactivity of 1,2,3-triazoles towards sulfonyl chlorides. A novel approach to 1- and 2-sulfonyl-4-azolyl-1,2,3-triazoles

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Table of contens

1. Density functional calculations

Table 3 Atomic charges q obtained by various population analyses [M06-2X/6-31G(d,p)] and Fukui index f^-.

		q[a]				f^-
		Mulliken	NPA	Hirshfeld	CHelpG	
1a	N1	-0.374 (-0.257)	-0.367 (-0.374)	-0.226 (-0.227)	-0.379 (-0.395)	0.071
	N2	-0.144 (-0.013)	-0.118 (-0.129)	-0.151 (-0.156)	-0.217 (-0.236)	0.199
	N3	-0.400 (-0.242)	-0.328 (-0.334)	-0.183 (-0.178)	-0.319 (-0.321)	0.011
1c	N1	-0.375 (-0.254)	-0.369 (-0.373)	-0.232 (-0.232)	-0.435 (-0.457)	0.060
	N2	-0.155 (-0.022)	-0.137 (-0.147)	-0.162 (-0.166)	-0.154 (-0.159)	0.244
	N3	-0.407 (-0.372)	-0.309 (-0.312)	-0.206 (-0.204)	-0.434 (-0.456)	0.005
1d	N1	-0.369 (-0.248)	-0.362	-0.224 (-0.224)	-0.391 (-0.412)	0.070
	N2	-0.141 (0.040)	-0.124	-0.151 (-0.154)	-0.209 (-0.223)	0.203
	N3	-0.408 (-0.359)	-0.304	-0.186 (-0.181)	-0.311 (-0.308)	0.008

1e	N1	-0.371 (-0.248)	-0.361	-0.223 (-0.223)	-0.412 (-0.427)	0.066
	N2	-0.143 (-0.017)	-0.125	-0.152 (-0.155)	-0.155 (-0.163)	0.206
	N3	-0.394 (-0.357)	-0.299	-0.197 (-0.196)	-0.411 (-0.428)	0.007

[a]values in parentheses refer to M06-2x/6-311+G(2df,2p) results.

Table 4. Relative Gibbs free energies (kcal mol^{-1}) in the gas phase and EtOH solution of reactant conformations and product regioisomers/conformations[a]

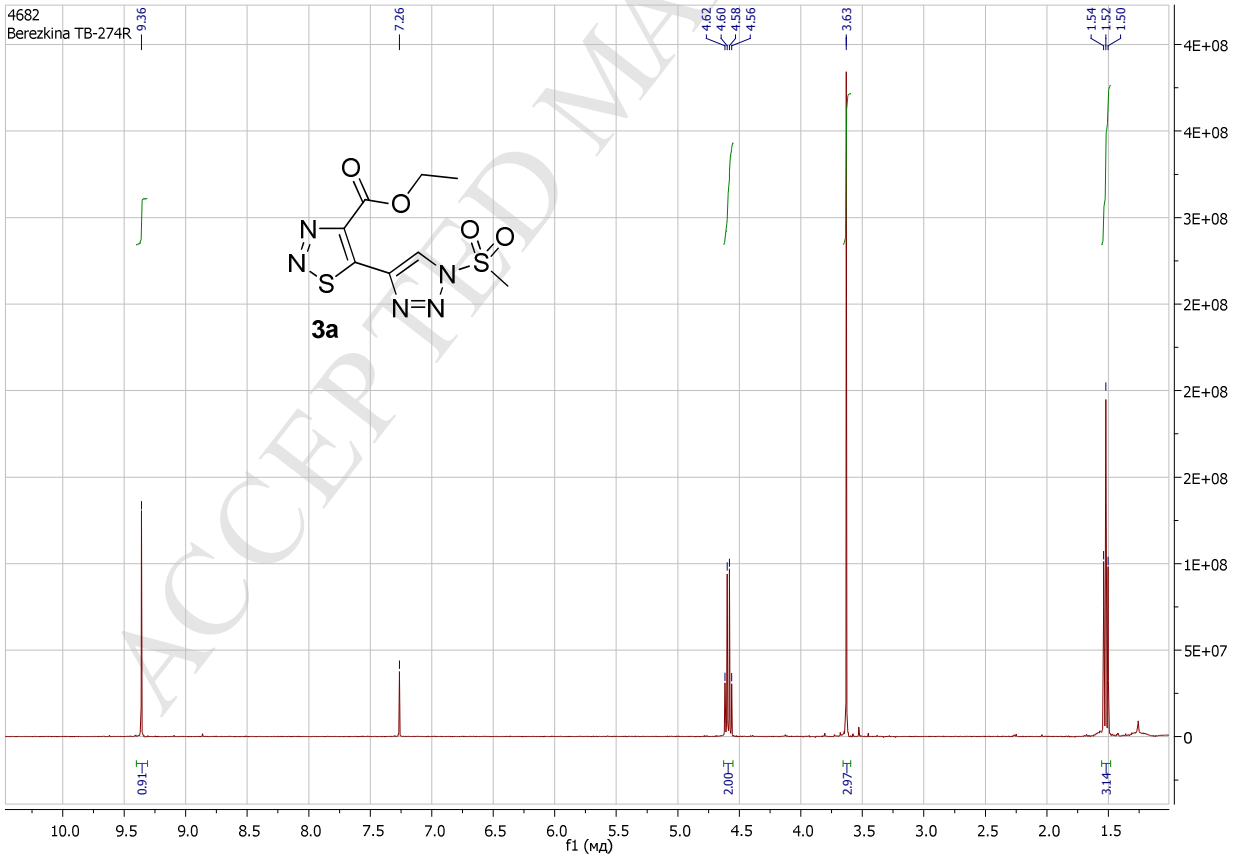
Compd	ΔG		τ_1	τ_2	τ_3
	Gas phase	EtOH			
1a$^-$	0.00	0.00	23.5	-131.0	
	-1.63	-3.52	180.0	-180.0	
	-2.20	-4.06	180.0	0.0	
1b$^-$	0.00	0.00	0.0		
	-0.62	-0.15	-180.0		
1c$^-$	0.00	0.00	0.4		
	-0.25	0.02	-179.8		
3a	6.16	2.81	54.3	-154.8	123.7
	2.45	0.64	-171.4	176.0	126.1
	0.00	0.00	178.9	-1.0	124.5
	5.09	1.73	51.6	-150.9	-126.8
4a	4.46	2.09	36.0	-132.9	-107.9
	6.24	4.39	33.0	-134.4	44.2

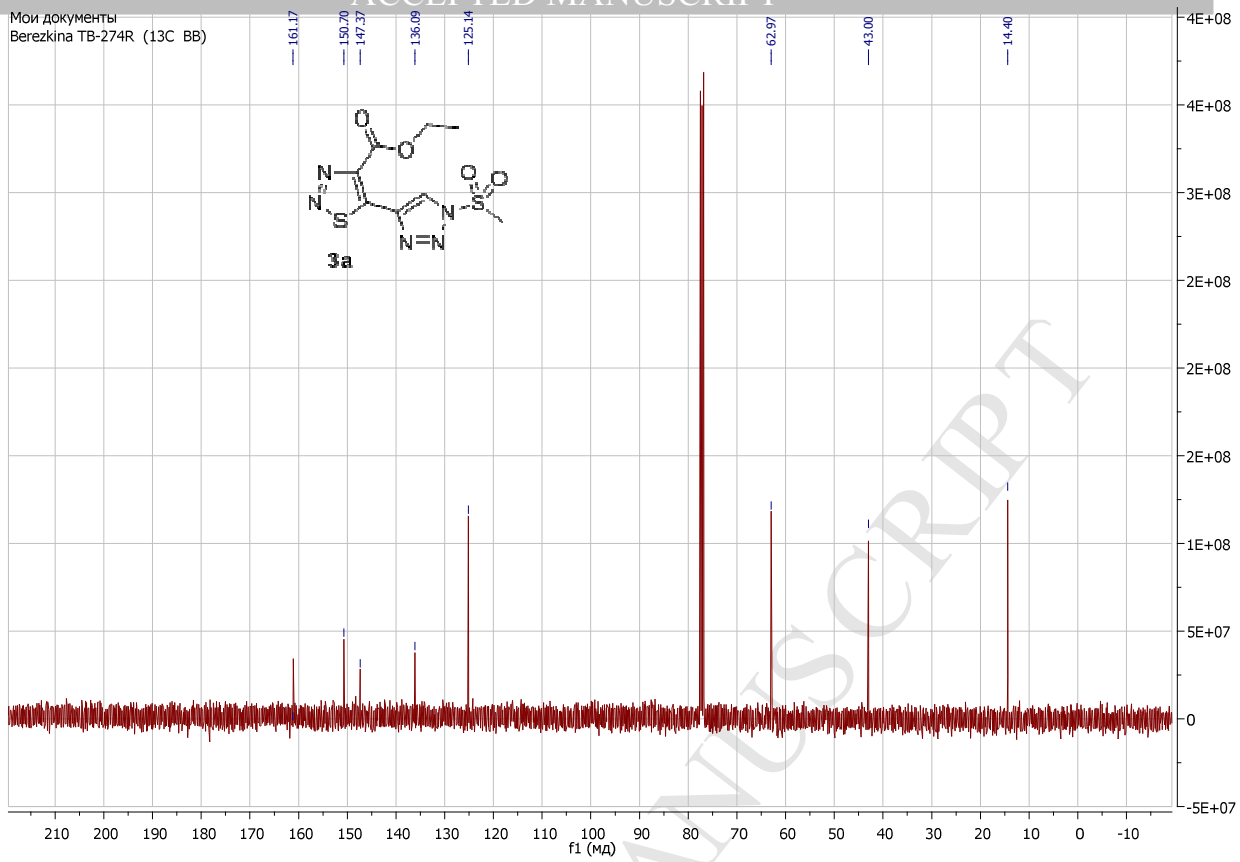
	3.78	0.56	-145.2	168.9	-87.3
	3.84	1.09	-144.0	170.7	57.2
	3.57	2.42	54.5	17.3	89.6
	-0.47	-1.32	170.2	1.7	75.4
5a	7.06	5.12	54.1	-171.4	-54.6
	7.99	6.22	-80.4	-174.5	-60.7
	7.32	5.08	52.0	6.3	-54.2
	4.99	4.82	60.9	2.4	61.4
	7.89	7.74	-127.0	-20.0	-20.4
3g	0.81	0.20	0.2		125.8
	0.00	0.00	-179.7		125.9
4g	0.01	-0.70	0.6		94.2
	-1.34	-1.95	1.0		111.4
	-0.85	-0.89	-179.1		90.5
	-1.15	-0.74	-178.7		128.0
5g	5.42	5.91	27.5		106.0
	5.20	5.96	-152.1		-18.4
	5.69	5.98	-133.9		97.2
3m	0.48	0.00	-0.7		-127.2
	0.63	0.20	1.7		126.7
	0.00	0.82	-179.3		-125.1
	0.19	1.16	178.2		125.0
4m	-0.60	0.54	7.5		145.5

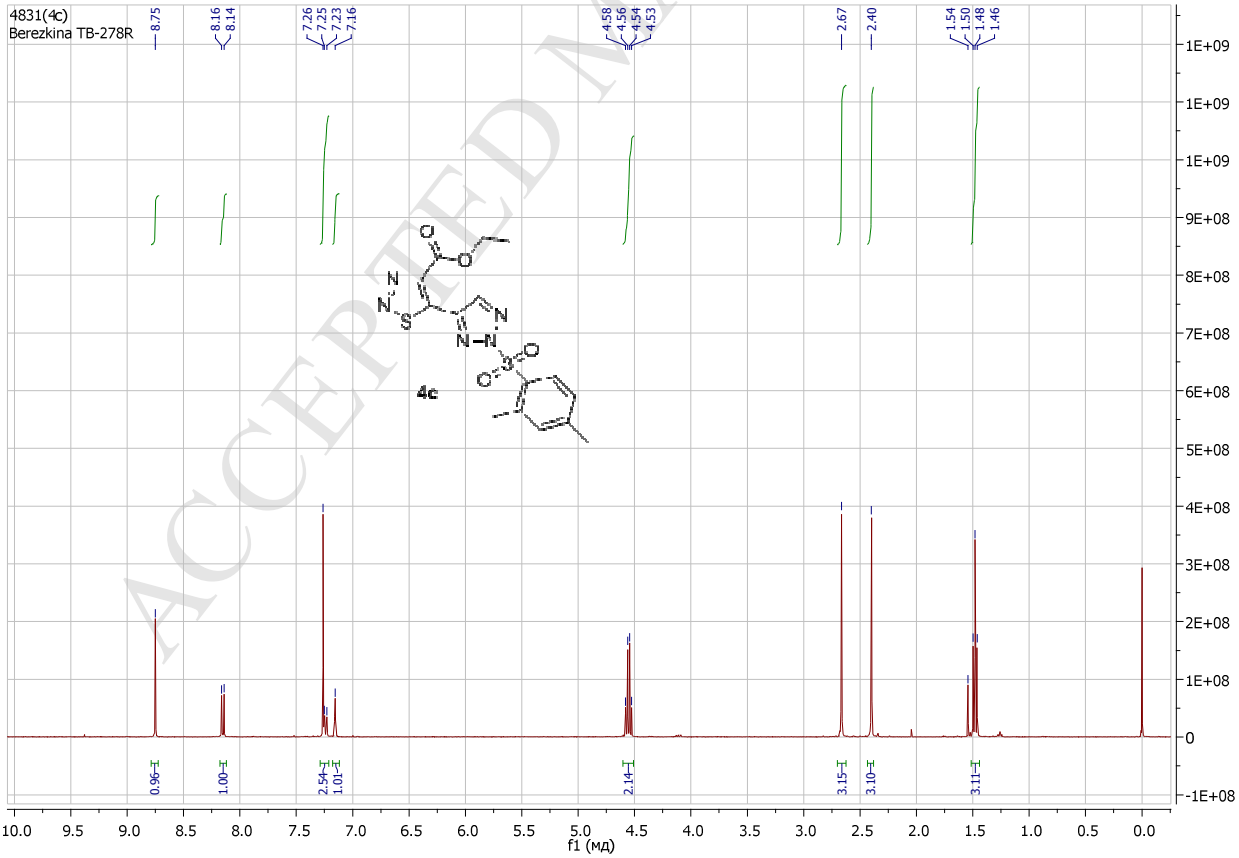
	-0.49	-0.34	-180.0		88.6
5m	5.86	6.29	-132.9		96.5
	5.47	6.55	-145.4		-22.6
	6.00	6.02	132.8		-97.1
	5.13	7.51	47.1		71.1

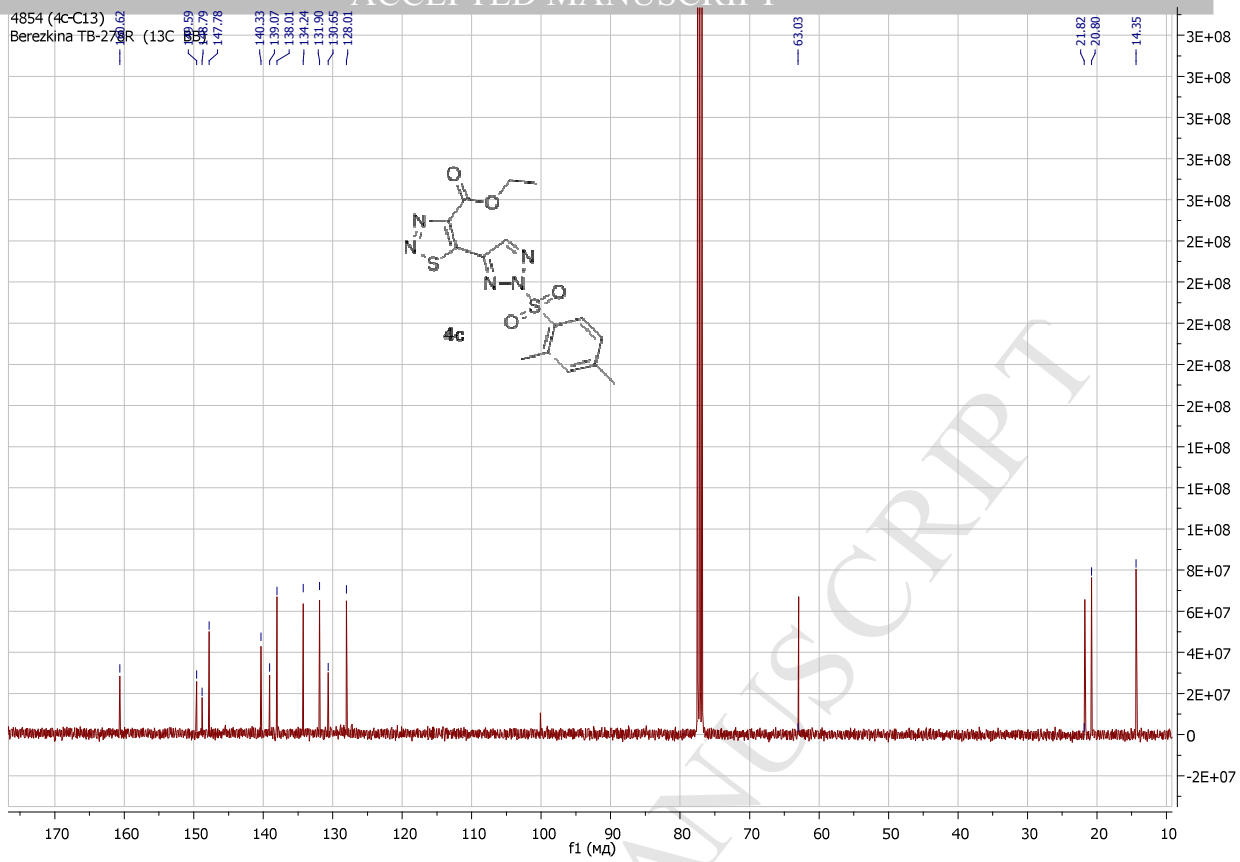
[a] anionic forms of reactants (N-deprotonated triazole ring). For products, within each series **3a** – **5a**, **3g** – **5g**, and **3m** – **5m** Gibbs free energies are given relative to the lowest energy conformation of **3a**, **3g**, **3m**, respectively. Torsional angles τ_1, τ_2, and τ_3 describe the orientations of the two heterocyclic rings [τ_1 = τ(S1–C3–C4–C5) in compounds of series **a**, oxygen instead of S1 for compounds **1b**, **1c**, and products of series **g** and **m**], the ester moiety [τ_2 = τ(C3–C2–C1–O4)], and the substituent of the sulfonyl group [τ_3 = τ(X–Y–S2–C6) with X=C5, Y=N1 for **3**, X=N1, Y=N2 for **4**; and X=N2, Y=N3 for **5**]. For atom numbering see Fig. 1

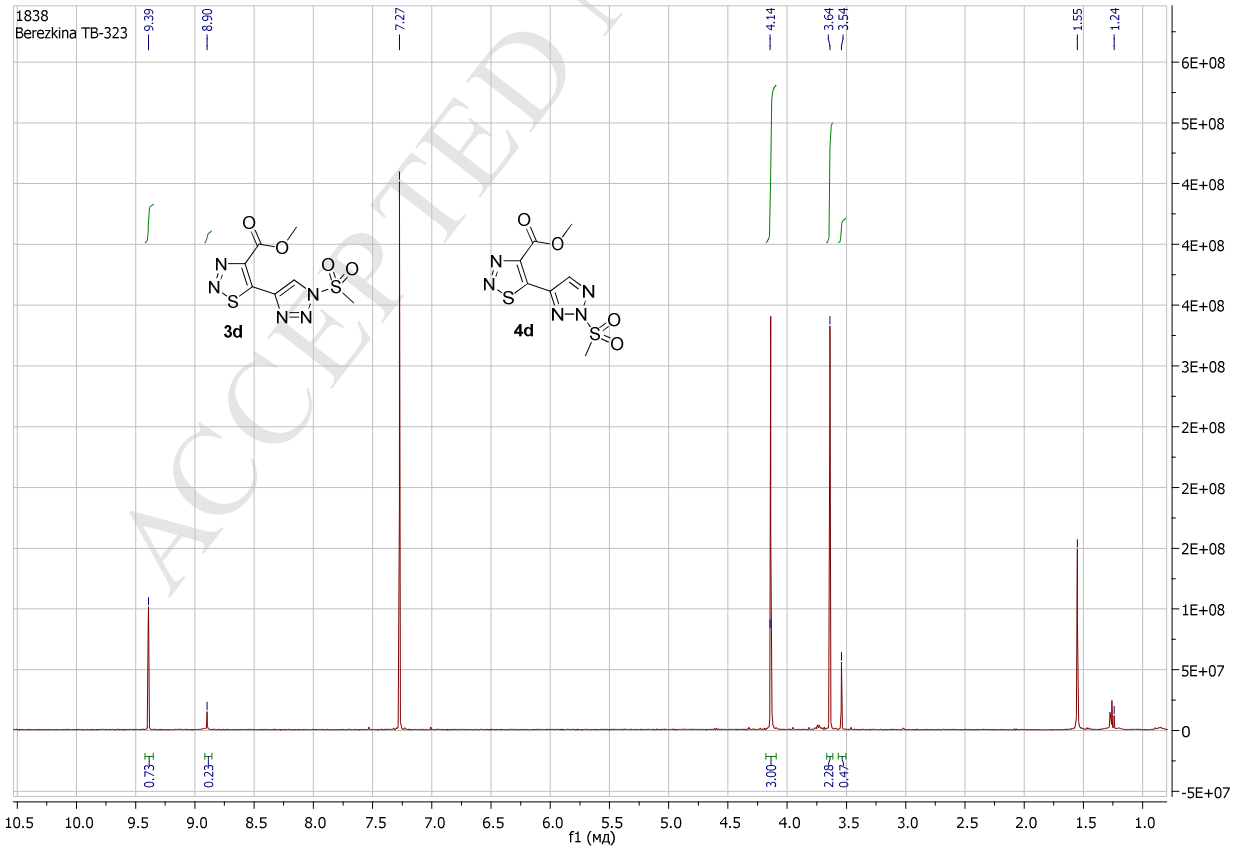
2. NMR spectra

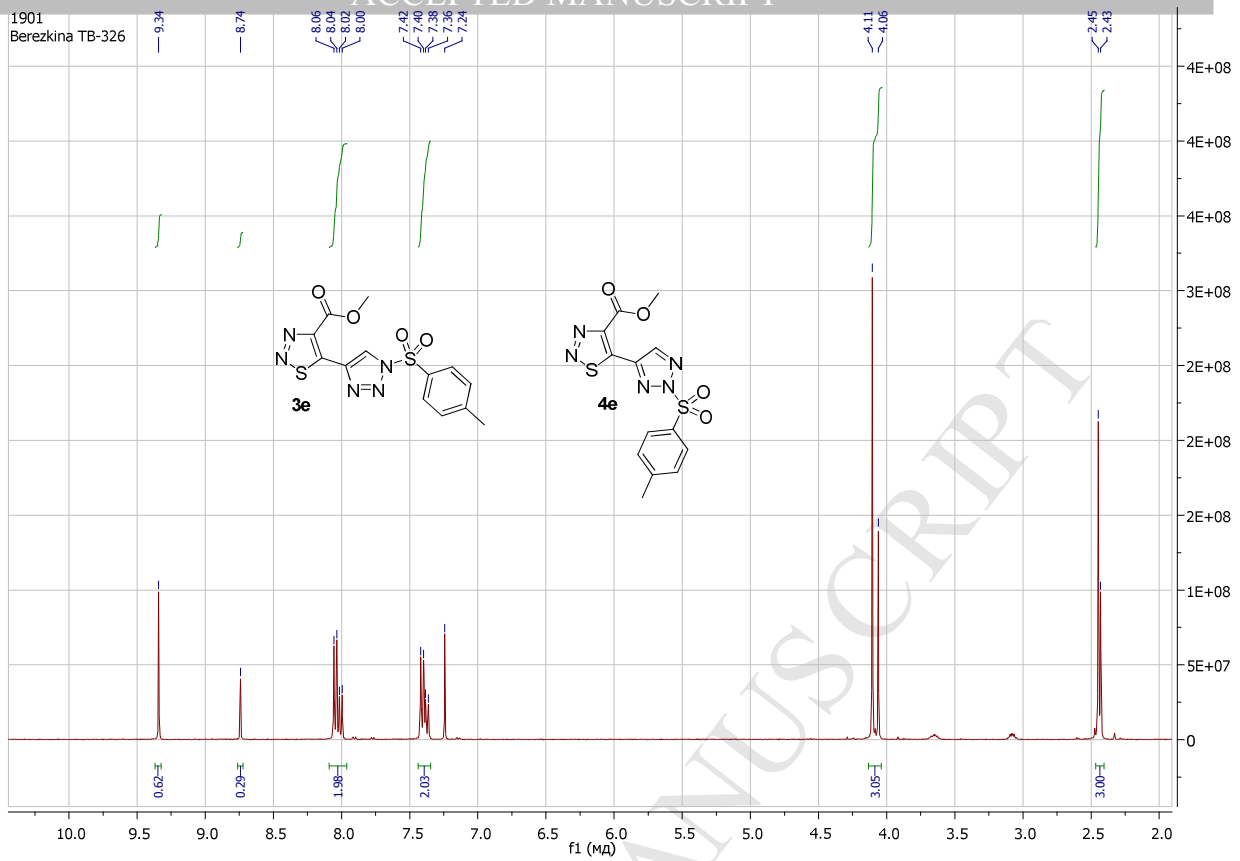


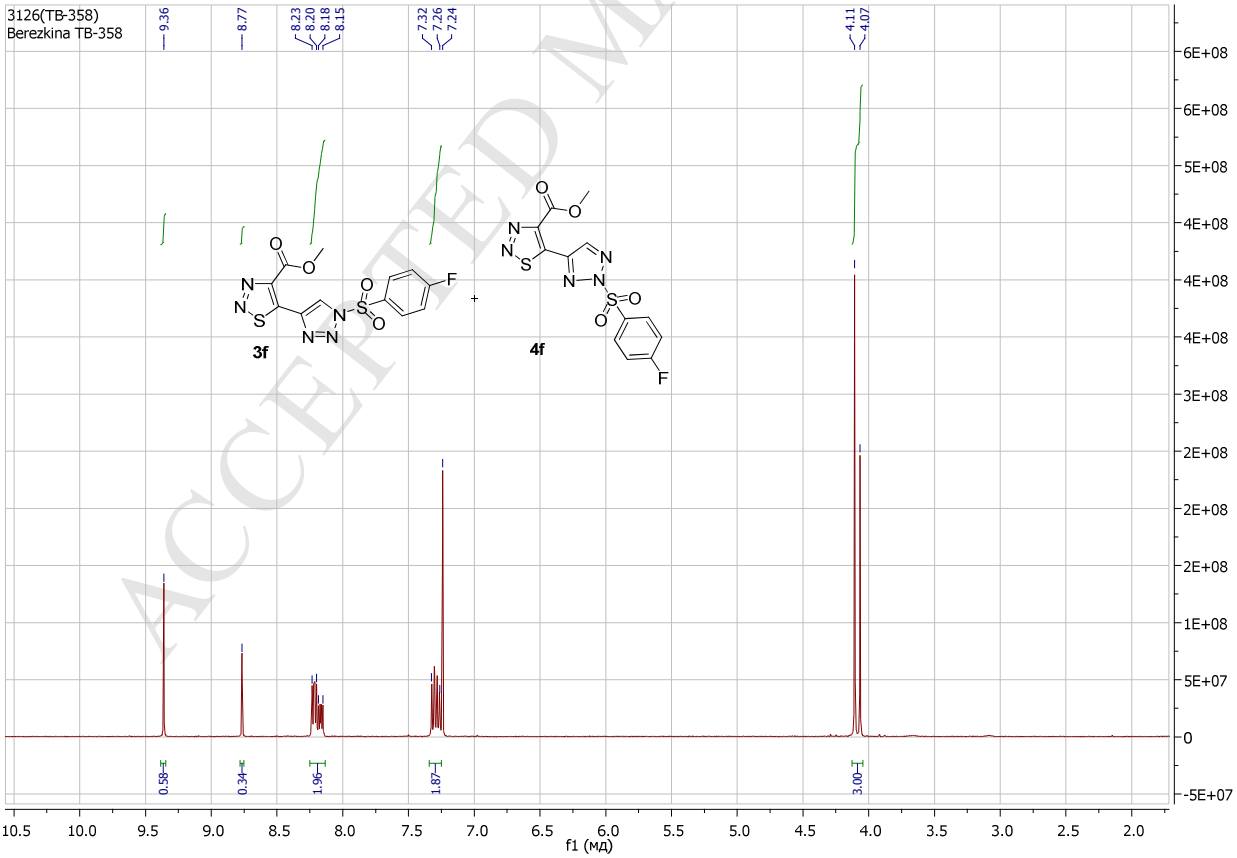


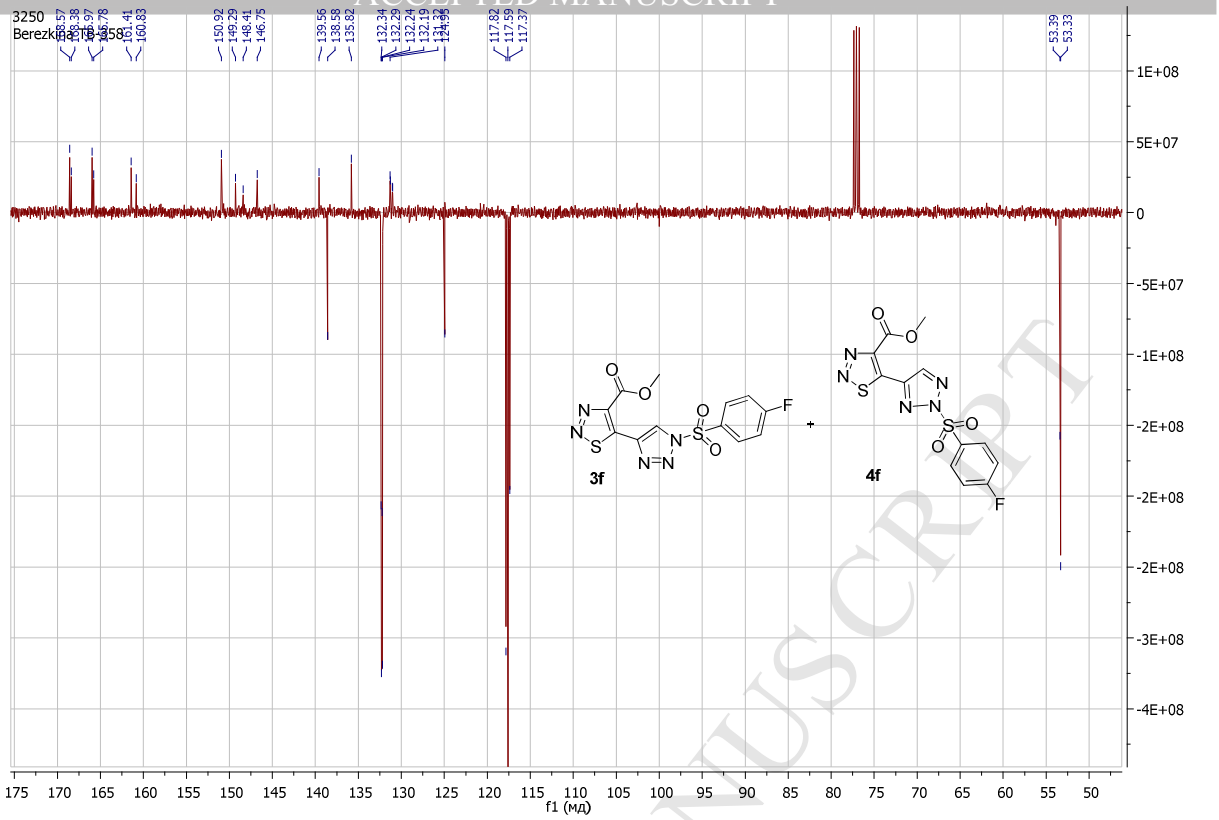


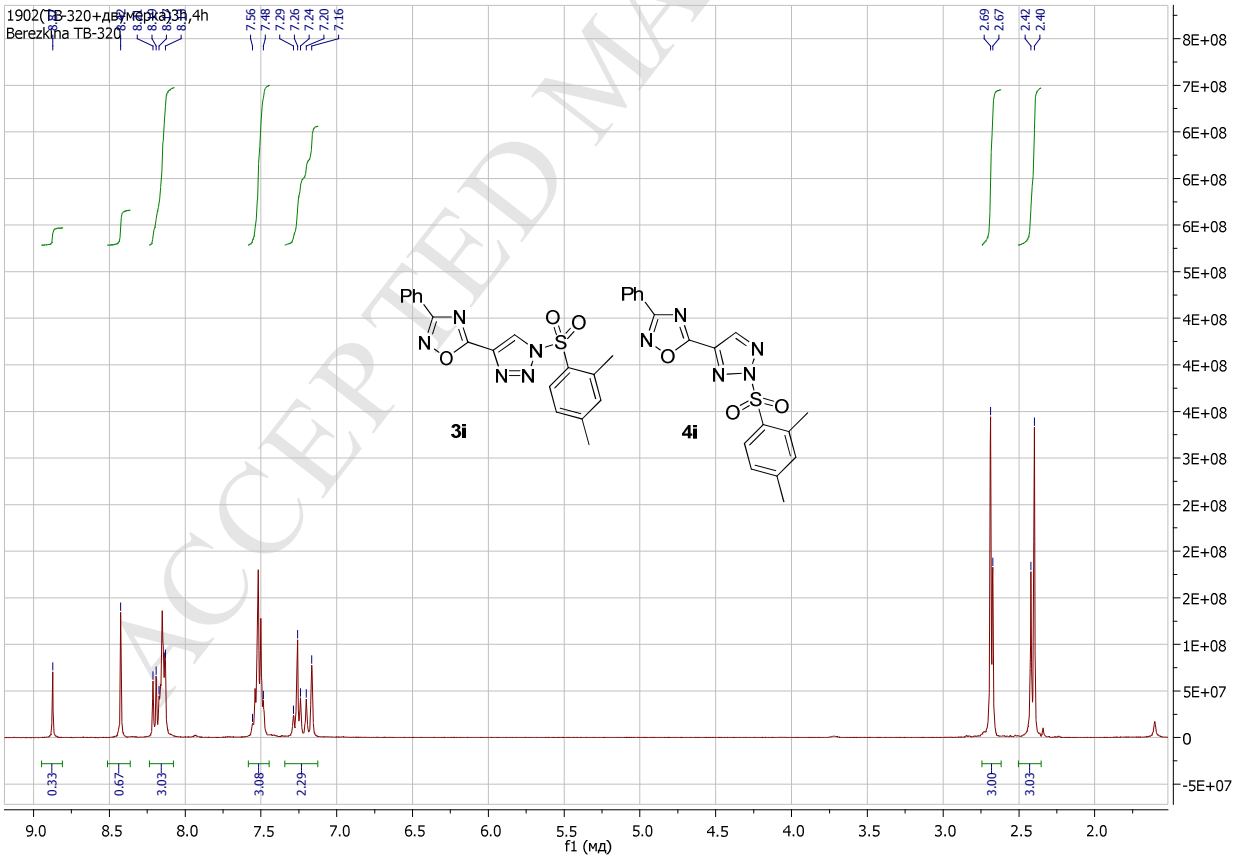


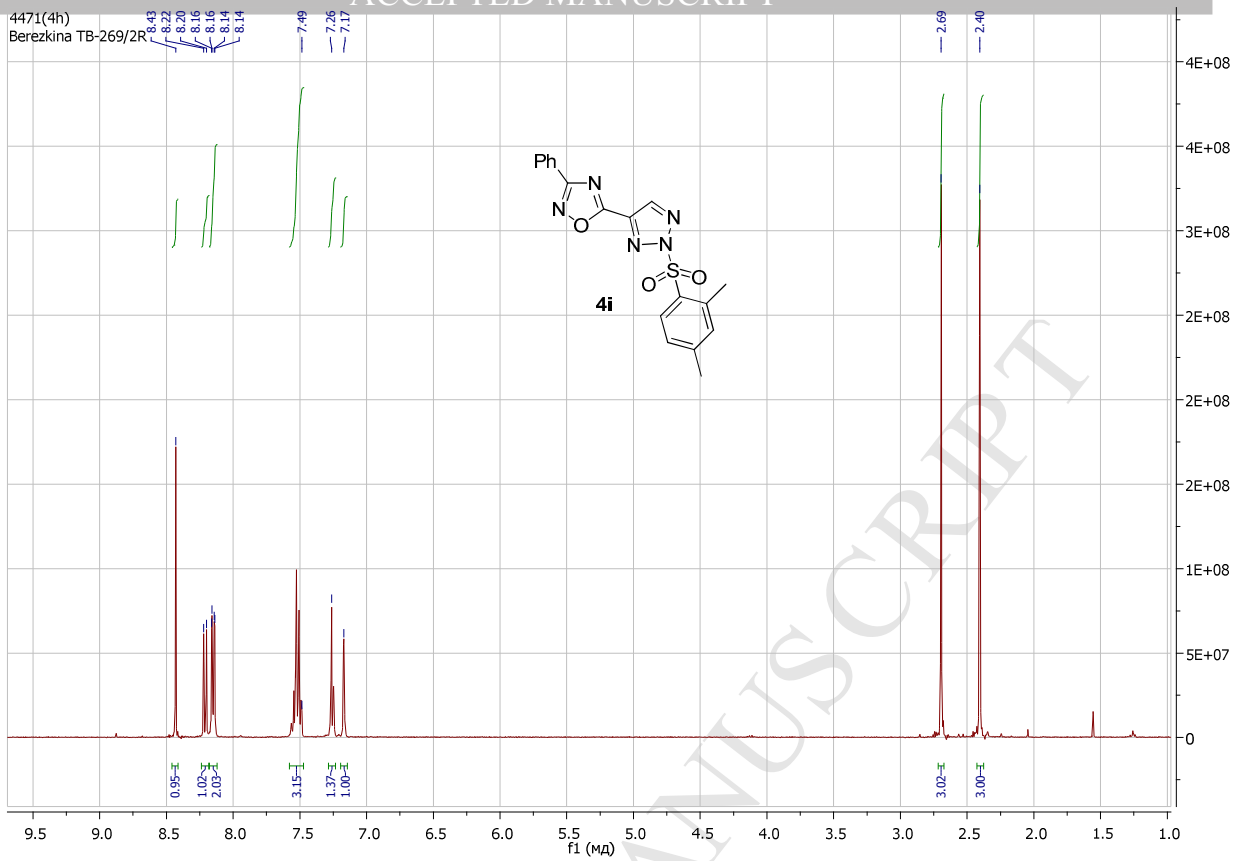


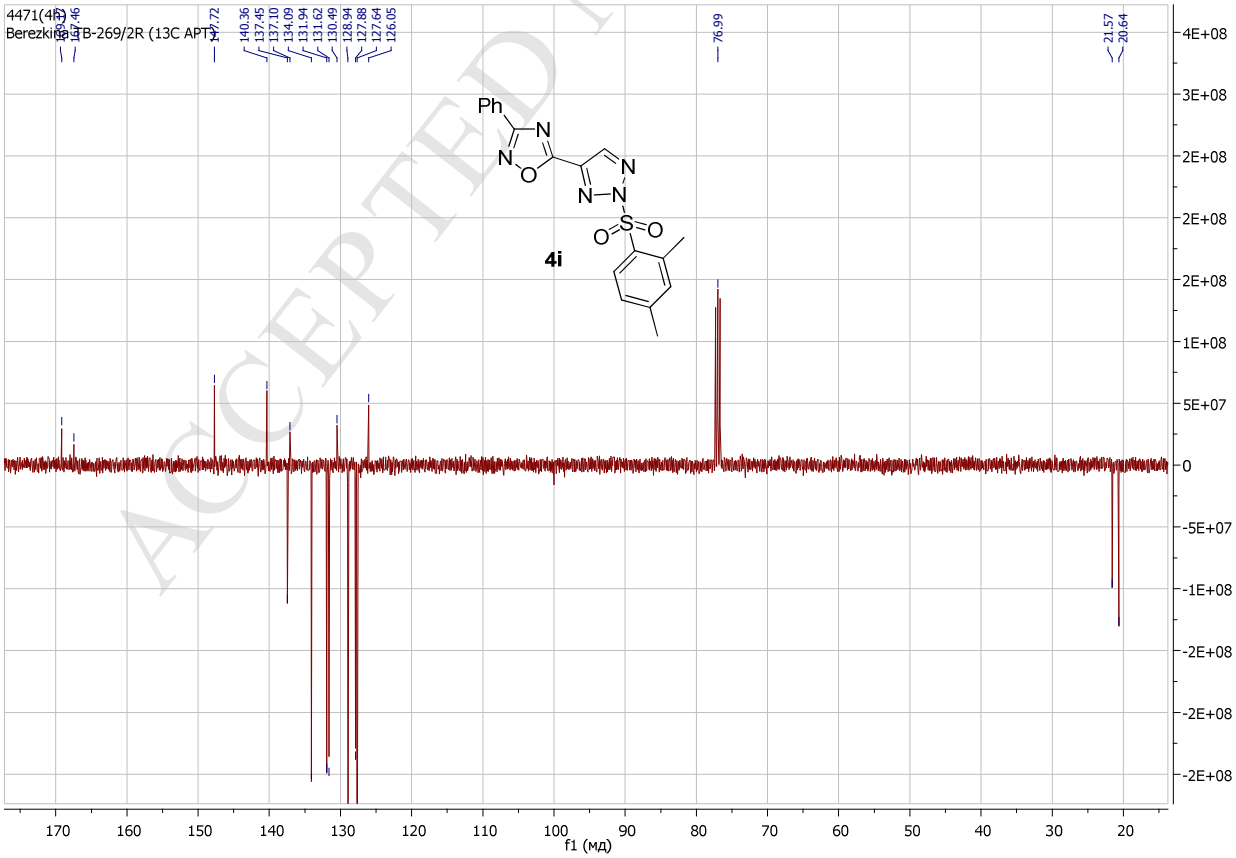


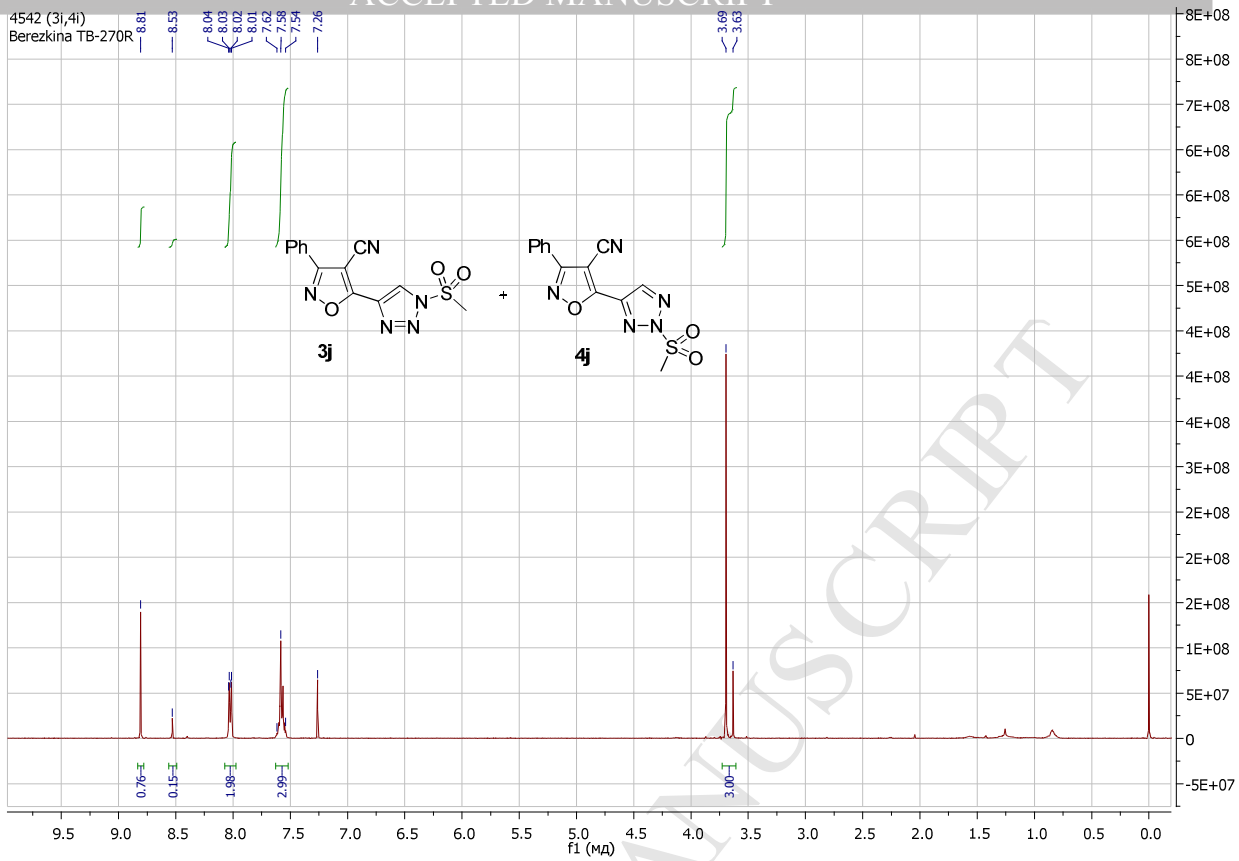


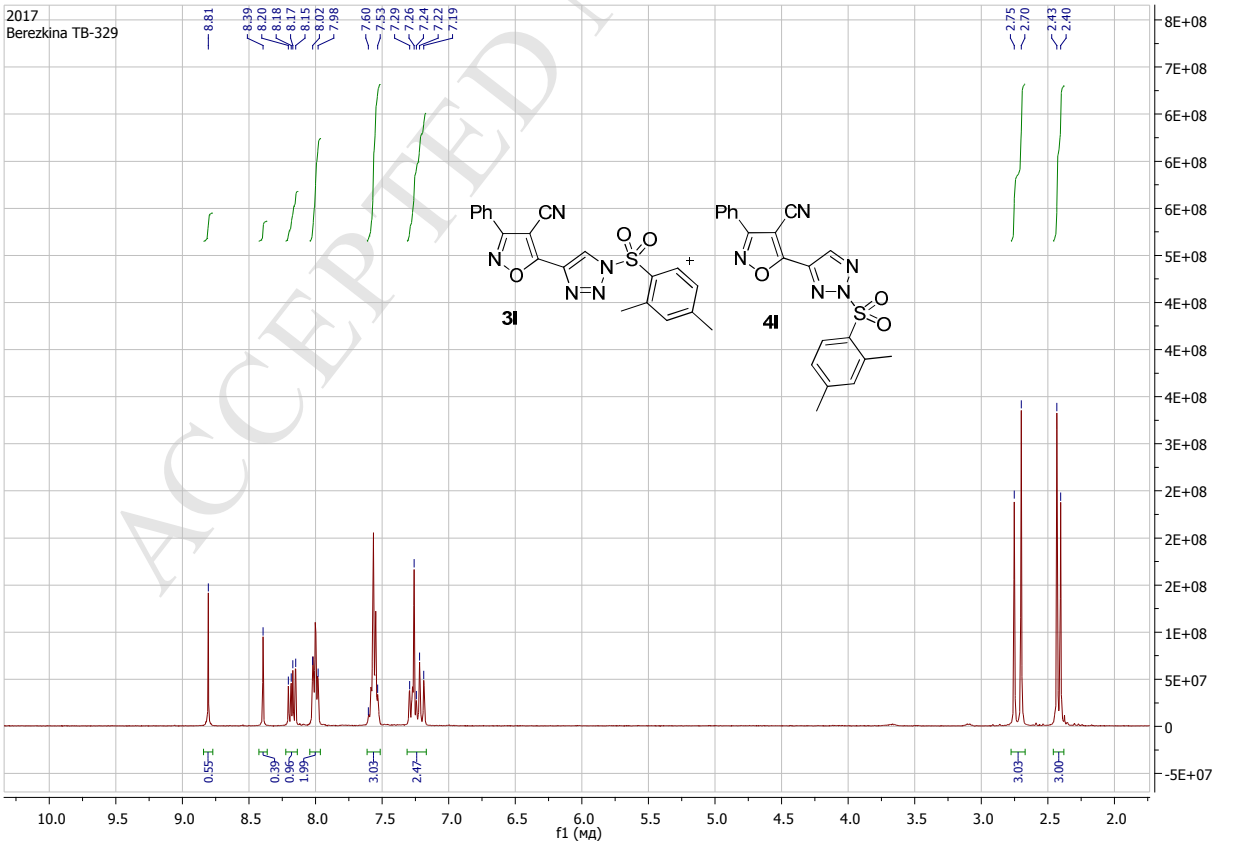


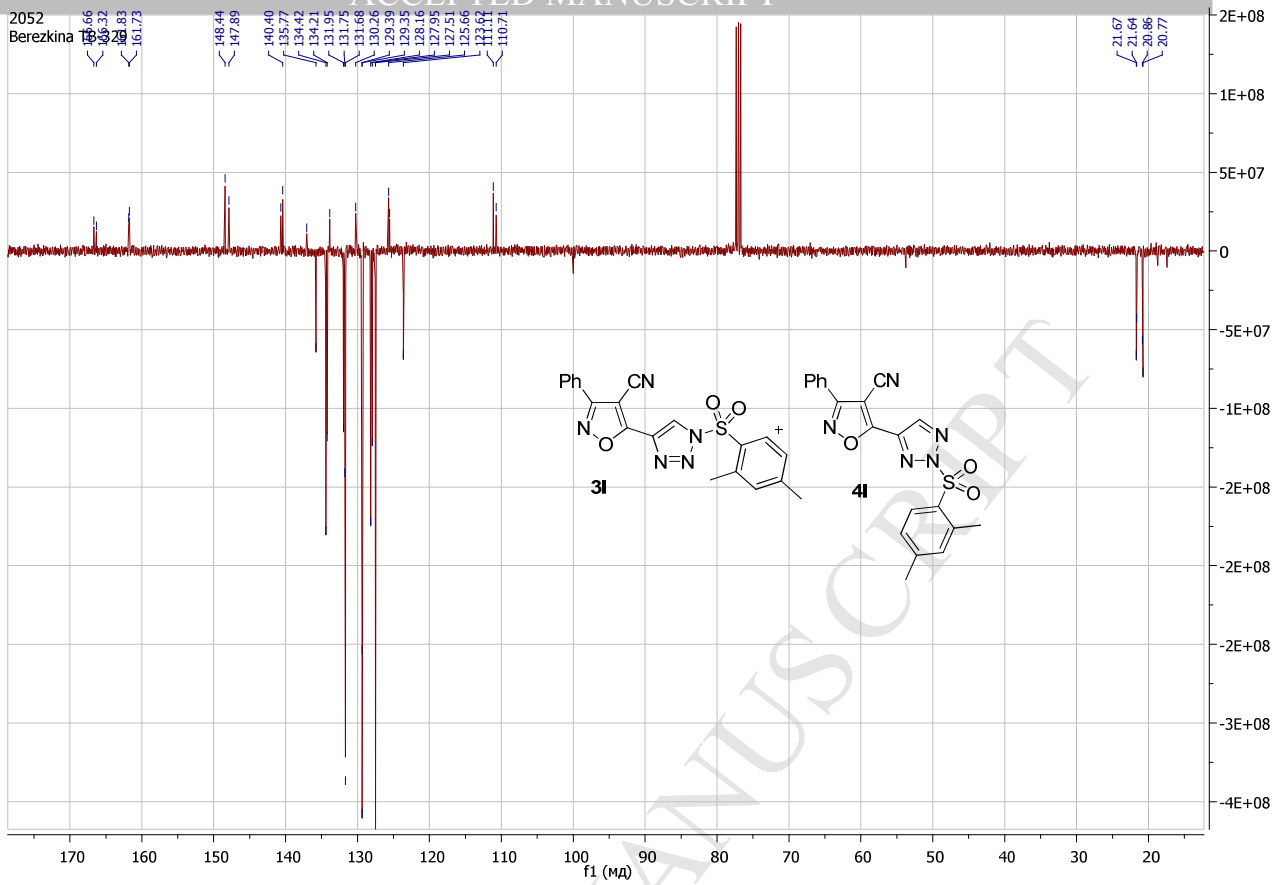


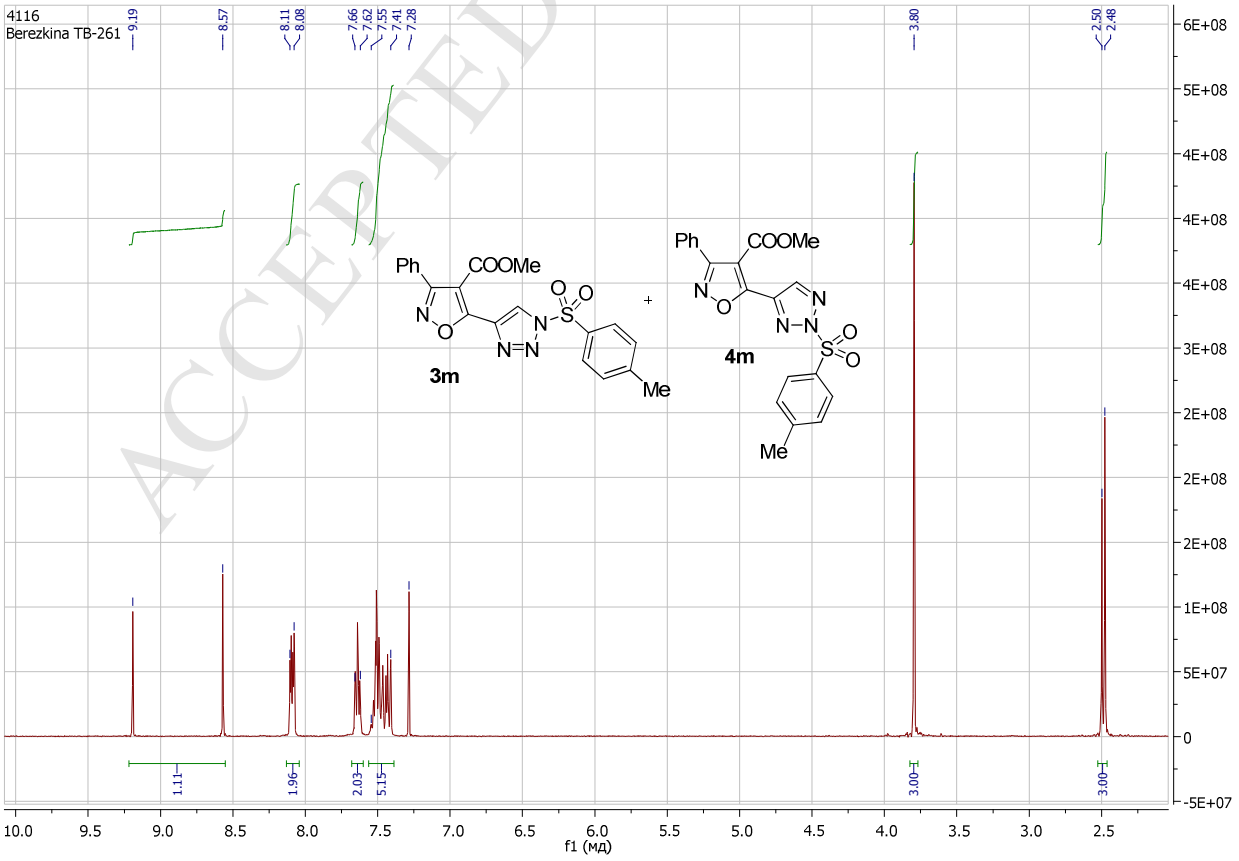


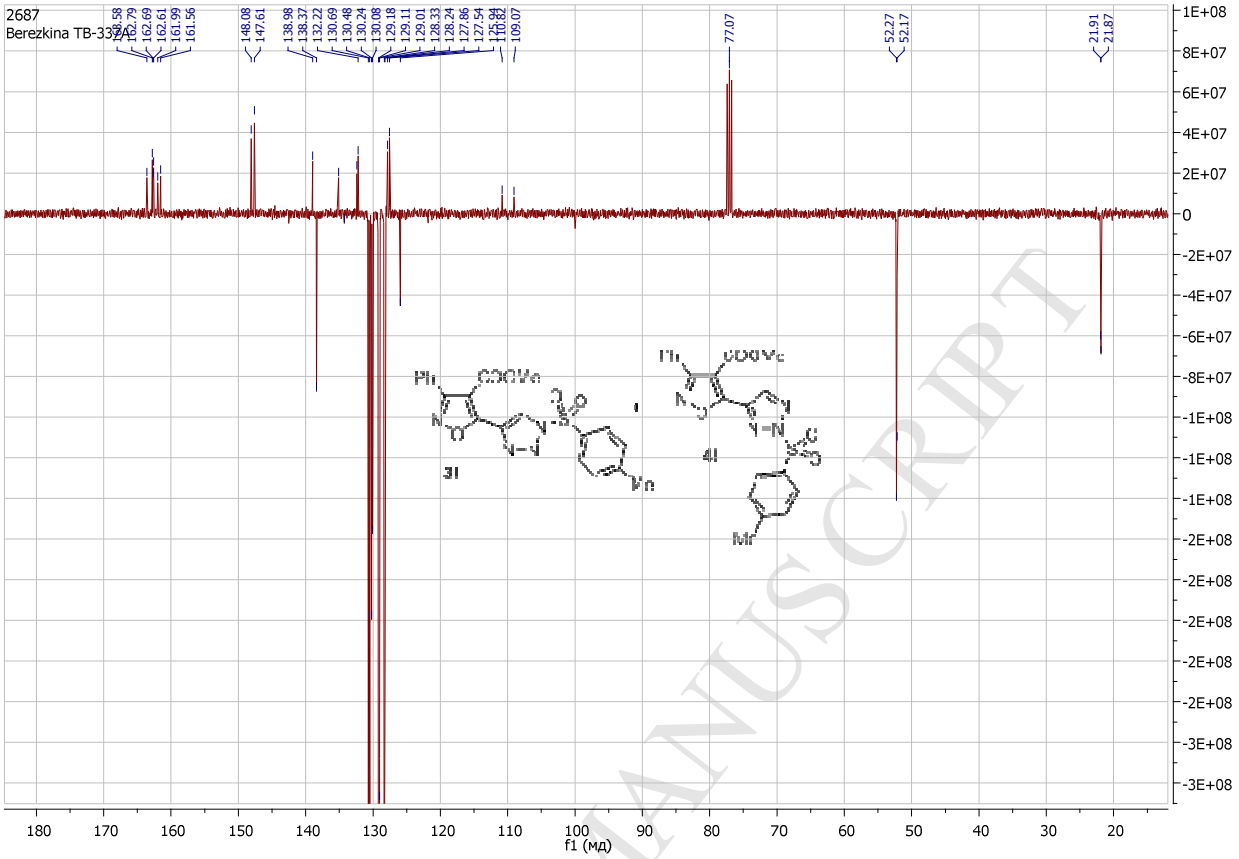


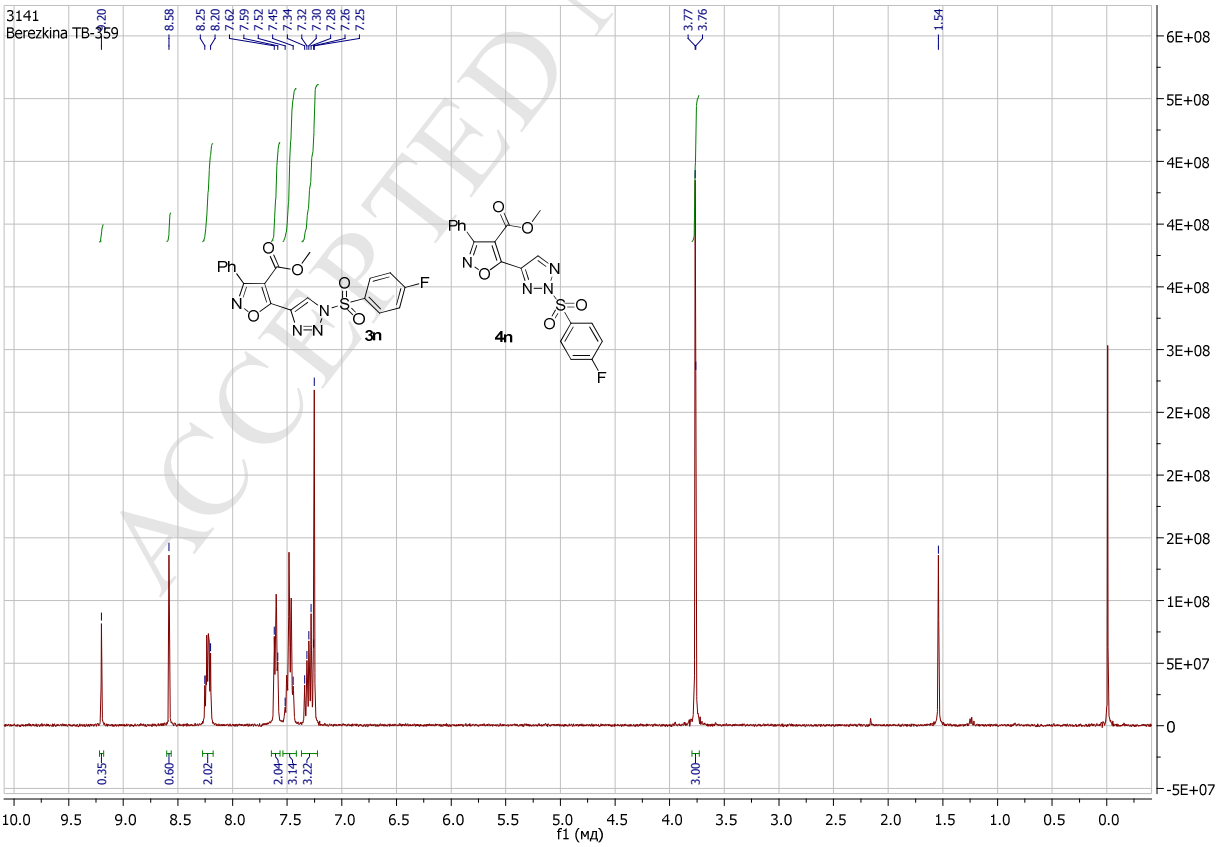


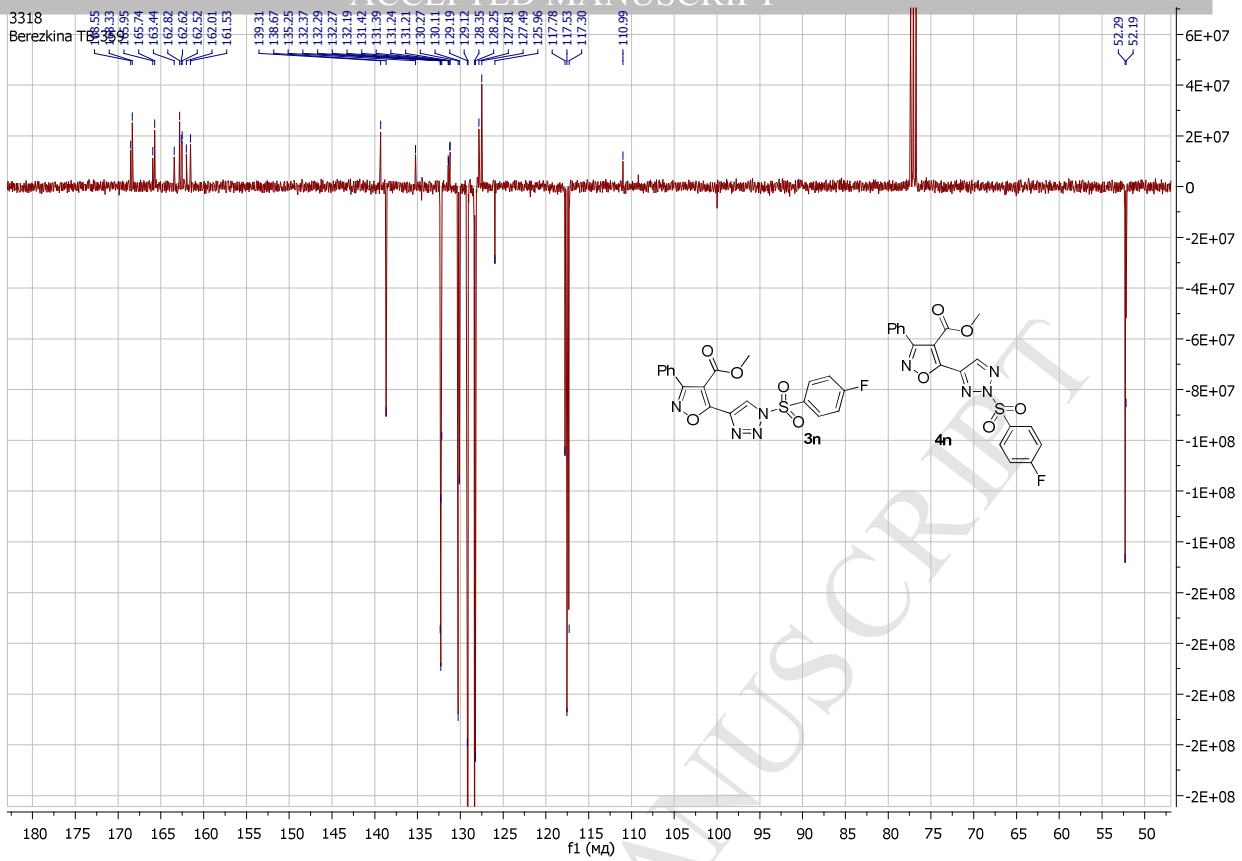




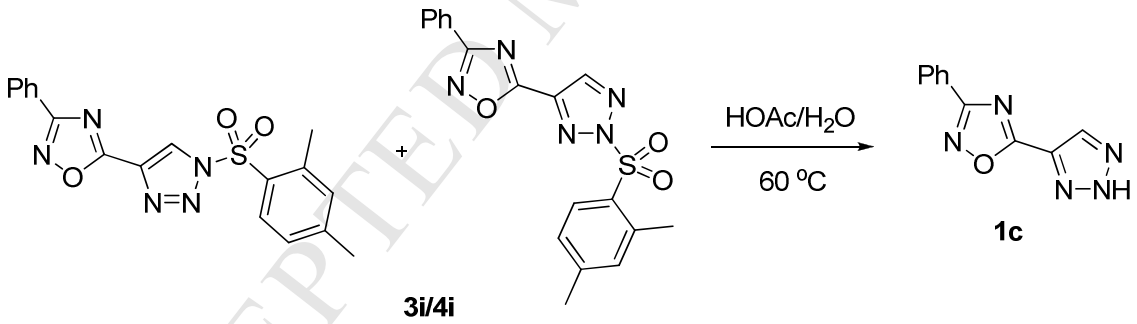








3. Hydrolysis of 2-sulfonyl-1,2,3-triazole **3i**/**4i**



A mixture of compounds **3i**/**4i** (0.12 g, 0.3 mmol) was dissolved in HOAc (5 mL) and H_2O (0.5 mL). The reaction mixture was stirred at 60 °C for 4 h, and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexane 1/3) to yield **1c** as colorless solid (0.04g, 60%). Mp 210-213°C. The spectral data were as described in the literature.[21]