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Reactions of Hydroxyphenyl-Substituted 1,2,4-Triazoles with Electrophylic Reagents

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Abstract—Reactions of hydroxyphenyl substituted 1,2,4-triazoles with various electrophylic reagents were studied. Despite of the presence of several nucleophilic centers in the molecule, the reactions were shown to proceed regioselectively, with the formation of N-substituted 3-(2-hydroxyphenyl)-1,2,4-triazoles. As a result of the reactions of alkylation, tosylation, sulfoamination and aminomethylation by Mannich reaction earlier unknown potential biologically active N-derivatives of 1,2,4-triazole were obtained.

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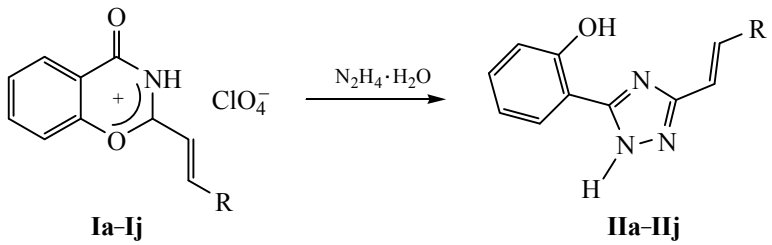
Interest to 1,2,4-triazoles and to their derivatives is caused by a wide spectrum of properties of these compounds useful for practical applications. Among 1,2,4-triazoles there are herbicides [1], nematocides [2], tranquilizers [3], substances with analget and antihypoxit action [4]. Moreover, hydroxyphenyl-substituted 1,2,4-triazoles easily formed from 4-oxo-1,3-benzoxazinium perchlorates [5] under the action of hydrazine-hydrate [6] contain in their structures several reaction centers that expands their synthetic opportunities and therefore they are interesting objects for further chemical transformations. Because of the ability of 1,2,4-triazoles and their derivatives to tautomeric transformations there are problems connected with selectivity of the reaction course and identification of the formed isomeric compounds. Therefore the purpose of the present work was the preparation of new 1,2,4-triazoles and the study of their reactions for the expansion of the base of potential biologically active substances.

At heating a suspension of 4-oxo-1,3-benzoxazinium perchlorates (**Ia–Ij**) [5, 7] with hydrazine hydrate [6] in glacial acetic acid recyclization of salts **I** occurs with the formation of before not described arylvinyl- and hetarylvinyl derivatives of hydroxyphenyl substituted-1,2,4-triazoles (**IIa–IIj**) not known before (Scheme 1).

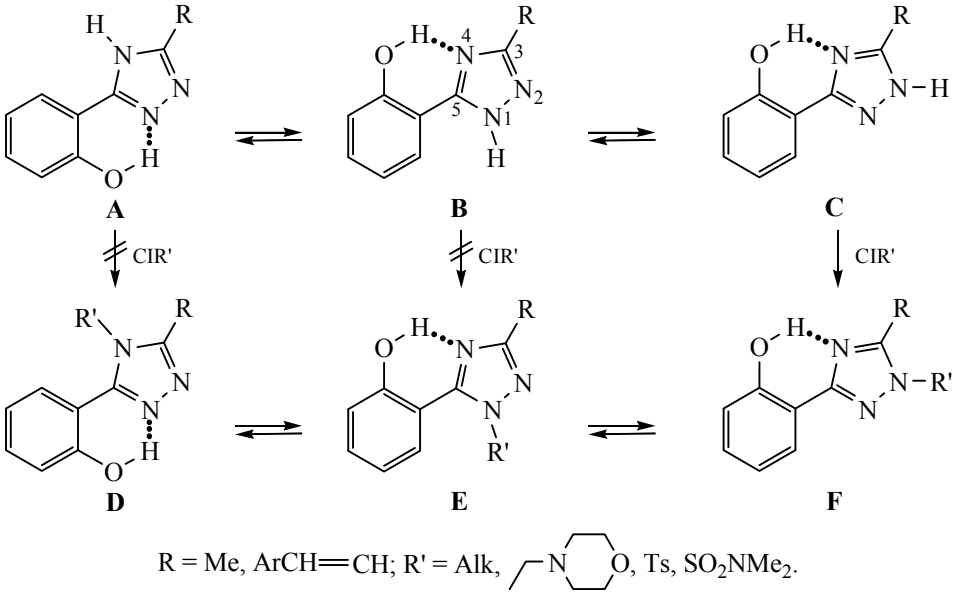
Scheme 1.



Ia–Ij **IIa–IIj**

R = 4-$MeOC_6H_4$ (**a**), 3,4-$(MeO)_2C_6H_3$ (**b**), R = 4-$MeSC_6H_4$ (**c**), R = 4-ClC_6H_4 (**d**), R = 4-BrC_6H_4 (**e**), R = 2-thienyl (**f**), R = 1-methylindol-3-yl (**g**), R = 3-methylthienyl (**h**), R = 2-pyridinyl (**i**), R = 5-methylfuryl (**j**).

Scheme 2.

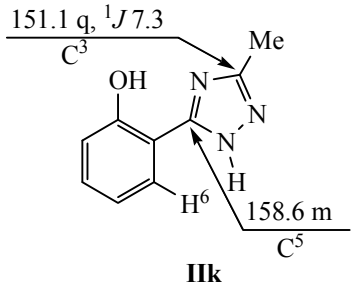


R = Me, ArCH═CH; R' = Alk, , Ts, SO_2NMe_2.

Formation of just 5-(2-hydroxyphenyl)-1*H*-1,2,4-triazoles (**A**) rather than compounds with isomeric structures (**B, C**) (Scheme 2) in this reaction has been proved earlier [8] and is confirmed by us on the basis of the data of ^{13}C NMR spectroscopy and gas phase quantum-chemical DFT-calculations in B3LYP/6-31G basis.

In the ^{13}C NMR spectrum of 5-(2-hydroxyphenyl)-3-methyl-substituted 1,2,4-triazole **IIk** the signal of carbon C^3 (Scheme 3) of triazole ring appears as a quadruplet due to the long-range spin–spin coupling with the protons of CH_3 group (155.1 ppm, ^2J = 7.3 Hz), and the signal of carbon C^5 of triazole ring looks like a multiplet at 158.6 ppm as a result of long-range spin–spin coupling with two proton groups (CH^6 of phenol substituent and NH), that indicates the existence of compound **IIk** in the solution in DMSO as isomeric form **A**.

Scheme 3.



IIk

The data of gas-phase quantum-chemical DFT-calculations in B3LYP/6-31G basis also specify the preferable formation of the the triazole **IIa** as the energetically most favorable isomer **A**, as follows from the energy values for tautomeric forms **A** (–609655.52 kcal mol^{-1}), **B** (–609644.72 kcal mol^{-1}) and **C** (–609655.02 kcal mol^{-1}) (Scheme 2).

The structure of the synthesized arylvinyl- and heterylvinyl-substituted 1,2,4-triazoles **IIa–IIi** has been established also by means of the elemental analysis, IR, and ^1H NMR spectroscopy. In the IR spectra of triazoles **IIb, IId, IIe,** and **IIg** to the hydroxy group correspond the bands in the area of 3210–3190 cm^{-1}, while in the case of compounds **IIc, IIf** and **IIh–IIj** because of strong intramolecular hydrogen bonding this band is not found in this area. In the IR spectra of arylvinyl- and hetarylvinyl-substituted 1,2,4-triazoles (unlike those of earlier synthesized methyl- and phenylvinyl-substituted triazoles [6]) there are strong absorption bands at 1660–1610 cm^{-1} of the double bond conjugated with phenyl group, and a set of bands of moderate intensity in the region of 1600–1580 cm^{-1}, caused by the sskeleton vibrations of aromatic and hetero-cyclic rings. The presence of strong hydrogen bond between phenol hydroxyl and nitrogen atom of the heterocycle is indicated also by the essential downfield shift in the ^1H NMR spectra of 1,2,4-triazoles **II** of the signal of OH group proton (11.55–14.38 ppm) in comparison with free phenols (4.00–7.50 ppm) [9]. In addition, in

the ^{1}H NMR spectra of azoles **IIa–IIj** doubling of the peaks of triazole ring NH protons and phenol OH protons occurs owing to restricted rotation around C(phenol)–C(triazole) bond caused by intramolecular hydrogen bonds.

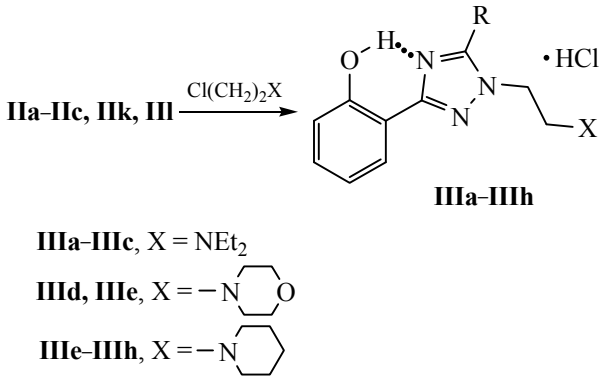
Because of the possible tautomeric transformations of 1,2,4-triazoles **II** in solutions (Scheme 2) it was necessary to elucidate in what tautomeric form and, hence, with the formation of what isomer [*N*-derivative of 5-(2-hydroxyphenyl)-4*H*- (**D**), 5-(2-hydroxyphenyl)-1*H*- (**E**) or 3-(2-hydroxyphenyl)-1*H*-1,2,4-triazole) (**F**)] proceeds the reactions of 1,2,4-triazoles with various electrophylic reagents.

The distignishing of the structure of the formed isomer is of principal significance because the character of substitution should influence essentially the biological activity of the formed compounds.

As a result of reaction of triazoles **IIa–IIc, IIk** and **III** with dialkylaminoethyl chlorides [(2-chloroethyl) diethylamine, 4-(2-chloroethyl)morpholine and 1-(2-chloroethyl)piperidine] at boiling in acetone in the presence of NaOH were synthesized triazoles **IIIa–IIIi** (Scheme 4). To increase the solubility of compounds **IIIa–IIIi** in water and in water–organic media they were isolated from the reaction mixtures in the form of hydrochlorides.

Despite the presence in the molecules hydroxyphenyl-substituted triazoles of several nucleophilic centers, in this reaction (Scheme 4) were isolated in 43–56% yield only *N*-derivatives of 3-(2-hydroxy-phenyl)-1*H*-1,2,4-triazole **IIIa–IIIh**, as follows from the data of ^{1}H (COSY) and ^{13}C NMR spectroscopy. From the analysis of a two-dimentional ^{1}H (COSY) NMR spectrum (Fig. 1) of compound **IIIa** in the region of 6.91–11.05 ppm, it is possible to conclude that the proton of phenol hydroxyl is coupled

Scheme 4.



II: R = 4-MeOC$_6$H$_4$CH=CH (**a**), R = 3,4-(MeO)$_2$C$_6$H$_3$·CH=CH (**b**); R = 4-MeSC$_6$H$_4$CH=CH (**c**), R = Me (**k**), R = Ph–CH=CH (**l**); **III**: R = PhCH=CH (**a**), R = 4-MeO·C$_6$H$_4$CH=CH (**b**), R = 4-MeSC$_6$H$_4$CH=CH (**c**), R = Me (**d**), R = 3,4-(MeO)$_2$C$_6$H$_3$ (**e**), R = PhCH=CH (**f**), R = 4-MeO·C$_6$H$_4$CH=CH (**g**), R = 3,4-(MeO)$_2$C$_6$H$_3$CH=CH (**h**).

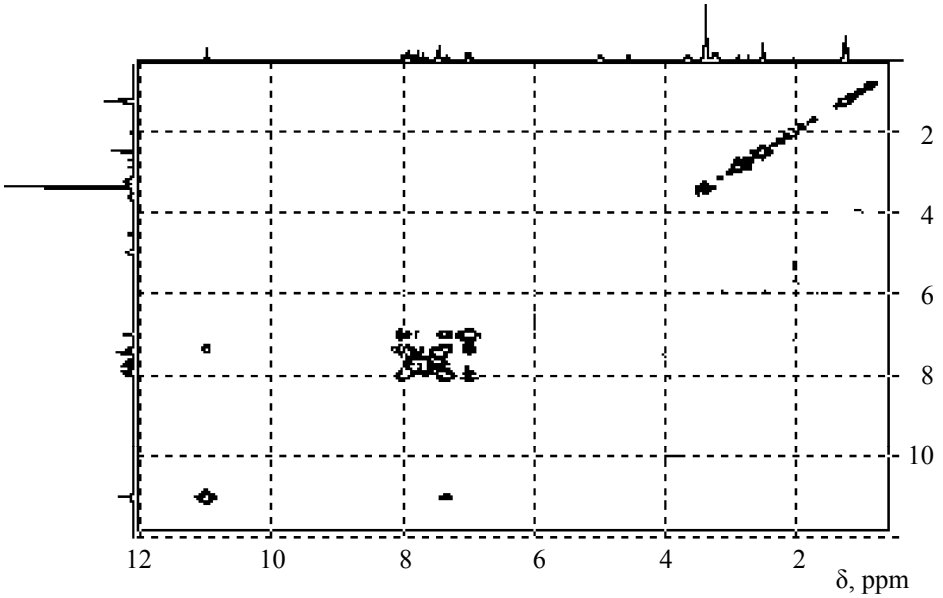


Fig. 1. Two-dimensional ^{1}H NMR (COSY) spectrum of 2-{1-[2-(diethylamino)ethyl]-5-[2-phenylvinyl]-1*H*-1,2,4-triazol-3-yl} phenol hydrochloride (**IIIa**).

with the proton at the carbon C^3, as follows from the existence of the corresponding correlation peaks.

For revealing direction of 1,2,4-triazoles alkylation with alkylaminoethyl chlorides, the spectrum of ^{13}C NMR monoresonance of compound **IIIb** was registered. In the spectrum the signal of carbon C^3 of triazole ring appears as a doublet due to the long-range spin–spin coupling with the proton H^6 of phenolic substituent (159.32 ppm, ^3J = 4.4 Hz), and the signal of carbon C^5 of triazole ring is a multiplet due to the spin–spin coupling with two groups of protons (CH vinyl and CH_2, 152.86 ppm, ^2J = 4.8 Hz, ^3J = 1.2 Hz), that proves the reaction course with the formation of 3-(2-hydroxyphenyl)-1*H*-1,2,4-triazole *N*-derivative. It is known that phenothiazine derivatives show high antioxidant, antiradical, neuroprotecting and antineoplastic activity [10–14]. With the purpose of synthesis of the compounds containing pheno-thiazine fragment we developed a way of introduction of this fragment into 2-hydroxyphenyl-1,2,4-triazoles. By boiling 1,2,4-triazoles **IIb** and **IIf** with 2-chloro-10-(chloroacetyl)-10*H*-phenothiazine in acetone in the presence of potassium carbonate we prepared in high yield new heterocyclic compounds **IVa** and **IVb** (Scheme 5) whose structure was proved by the data of elemental analysis, IR, and ^1H NMR spectroscopy.

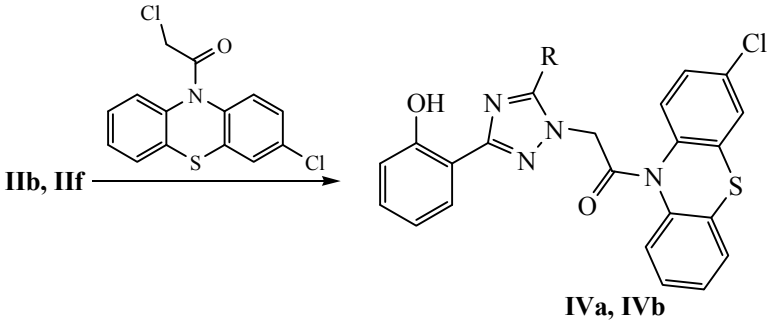
In the ^1H NMR spectra of the phenothiazine derivatives **IVa** and **IVb** in the range of 6.90–8.01 ppm the multiplets of aromatic protons were observed, and because of absence of symmetry elements in these compounds the signals of protons of prochiral CH_2 group at 20°C appear at 5.36–5.75 ppm in the form of two broad doublets, that, possibly, is caused by the restricted amide rotation around C–N bond.

The Mannich aminometylation of 1,2,4-triazoles **IIb** and **III** affords morpholinomethyl-substituted 1,2,4-triazoles **Va** and **Vb** (Scheme 6). In the IR spectra of compounds **Va, Vb**, owing to strong intramolecular hydrogen bond the absorption of hydroxy groups at 3300–3100 cm^{-1} did not appear, but there were absorption bands at 1630–1560 cm^{-1} caused by skeleton vibrations of aromatic and heterocyclic rings. The ^1H NMR spectra of azoles **Va** and **Vb** contain the four-proton triplets in the range of 2.68–3.65 ppm, characteristic of the morpholine fragment. There is a signal at 5.31–5.36 ppm of the NCH_2 group protons as a singlet due to free rotation around C–N bond, unlike the phenothiazine derivative **IV**. In the range of 6.99–8.09 ppm the multiplets were observed of aromatic protons. Similarly to the spectra of triazoles **IIa–IIj** the signal of phenol hydroxyl of compounds **IVa, IVb** and **Va, Vb** is shifted from the region of 4.0–7.5 ppm characteristic of free phenols [9] downfield to 11.05–13.20 ppm owing to strong intramolecular hydrogen bonding.

The direction of triazoles **IIb** and **III** aminometilation has been revealed by an example of compound **Va**. In its ^{13}C NMR monoresonance spectrum the signal of C^3 carbon nucleus of triazole ring is a doublet as a result of long-range spin–spin coupling with the proton H^6 of the phenol substituent (δ_C 160.2 ppm, ^3J = 4.5 Hz), and the signal of carbon C^5 nucleus is a multiplet as a result of long-range spin–spin coupling with two proton groups (CH vinyl and CH_2, δ_C 154.25 ppm, ^2J = 5 Hz, ^3J = 2.6 Hz), that proves the formation in the Mannich reaction of 1-morpholinomethyl-5R-substituted derivatives **Va, Vb**.

We developed the methods of synthesis of *N*-tosyl- and *N*-sulfamoyl-substituted 1,2,4-triazoles **VIa–VId** and **VIIa–VIId**. The target products are formed at heating of 1,2,4-triazoles **IIa–IIc, IIe,** and **IIk** in pyridine with tosyl or sulfamoyl chloride (Scheme 6).

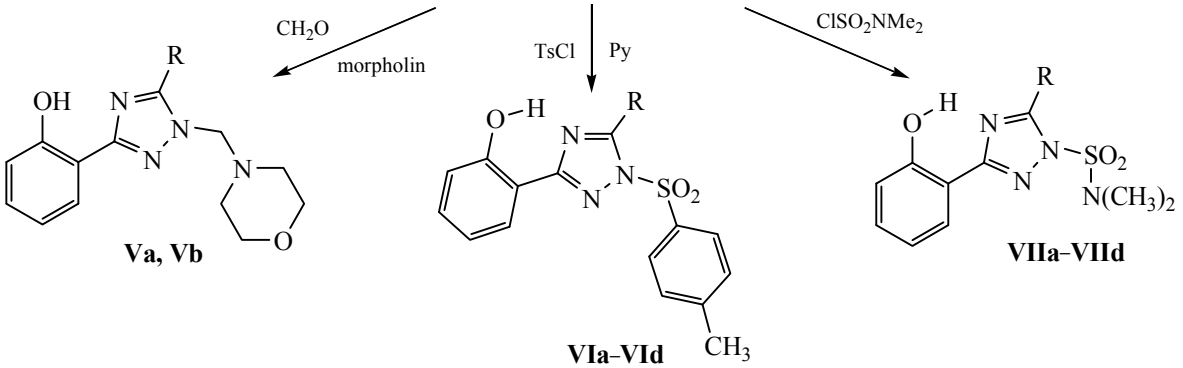
Scheme 5.



II: R = 3,4-$(MeO)_2C_6H_3$=CH– (**b**), R = 2-thienylvinyl (**f**); IV: R = 3,4-$(MeO)_2C_6H_3$CH=CH– (a), R = 2-thienylvinyl (**b**).

Scheme 6.

IIa–IIc, IIe, IIk, IIl



II: R = 4-$MeOC_6H_4CH$=CH (**a**), 3,4-$(MeO)_2C_6H_3CH$=CH (**b**), R = 4-$MeSC_6H_4CH$=CH (**c**), R = 4-BrC_6H_4CH=CH (**e**), R = CH_3 (**k**), R = PhCH=CH (**l**); **V**: R = 4-$MeOC_6H_4CH$=CH (**a**), R = 3,4-$(MeO)_2C_6H_3CH$=CH (**b**); **VI**: R = Me (**a**), R = PhCH=CH (**b**), R = 3,4-$(MeO)_2C_6H_3CH$=CH (**c**), R = 4-BrC_6H_4CH=CH (**d**); **VII**: R = Me (**a**), R = PhCH=CH (**b**), R = 3,4-$(MeO)_2C_6H_3CH$=CH (**c**), R = 4-$MeSC_6H_4CH$=CH (**d**).

The tosyl and sulfamoyl groups do not allow to elucidate the position of replacement in 1,2,4-triazole ring at the identification of isomers by means of ^{13}C NMR spectroscopy. Therefore we applied X-ray structural is shown analysis. In Fig. 2 the molecular structure of compound **VIId** according to X-ray structural analysis that, like the products of alkylation and aminometylation, corresponds to *N*-substituted 3-(2-hydroxyphenyl)-1*H*-1,2,4-triazole.

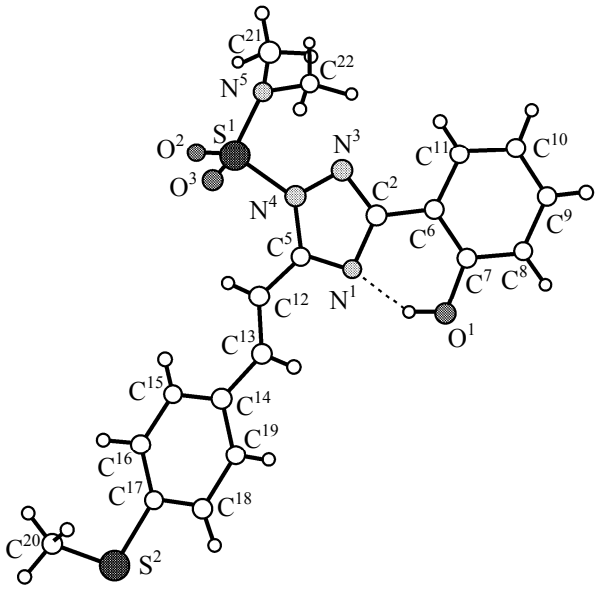


Fig. 2. Molecular structure of 3-(2-hydroxyphenyl)-*N*,*N*-dimethyl-5-{2-[4-(methylthio)phenyl]vinyl}-1*H*-1,2,4-triazol-1-sulfonamide (**VIId**) by the data of X-ray structural analysis.

The compositions and structures of the obtained compounds **VI** and **VII** are confirmed by the data of elemental analysis, IR, ^1H NMR spectroscopy, and also by the data of X-ray structural analysis of compound **VIId**.

In a crystal the molecule actually is flat, except for SO_2NMe_2 group. The torsion angle describing position of the phenol substituent relatively to triazole ring equals 5.1°, and **the** dihedral angle between the planes of *p*-methylthiophenylvinylidene fragment and triazole ring is 10.2°. Hydroxy group in the crystal participates in the formation of strong enough intramolecular O–H···N hydrogen bond with $H^1O\cdots N^1$ distance 1.90 Å. The analysis of the crystal packing showed that all intermolecular contacts correspond to usual van der Waals interactions. The basic bond lengths and bond angles are listed in Table 3.

The 2D ^1H NMR (COSY) spectrum of compound **VIIa** is well consistent with the data of X-ray structural analysis. It is seen from Fig. 3 that the proton of the phenol hydroxyl interacts with the proton [CH_3] of the aromatic ring, that follows from the appearance of the respective correlation peaks, hence, occurs the formation of N- rather than O-substituted 1,2,4-triazoles.

From the investigation carried out it is possible to conclude that the reactions of hydroxyphenyl-substituted 1,2,4-triazoles **II** with electrophylic reagents proceed regioselectively with the formation of 3-(2-hydroxyphenyl)-1*H*-1,2,4-triazole *N*-derivatives.

We established that sulfamoyl substituted 1,2,4-triazoles **VIIa** and **VIId** display antibacterial activity toward *Staphylococcus aureus* 209-P.

EXPERIMENTAL

The elemental analysis of the synthesized compounds was carried out on an automatic CHN analyzer Perkin Elmer 240. The IR spectra were registered on a Specord 75IR from suspensions in mineral oil, The ^{13}C and ^{1}H NMR and 2D ^{1}H NMR (COSY) spectra were obtained on a Varian Unity spectrometer (300 MHz) at 20°C.

Triazoles **IIk** and **IIIl** have been described in [6]. Yields, melting points (solvent for crystallization) and the data of the elemental analysis of the synthesized compounds **II–VII** are listed in Table 2, the data of IR and a ^{1}H NMR spectroscopy of compounds **II–VII** are collected in Table 3.

2-(3-Methyl-1*H*-1,2,4-triazol-5-yl)phenol (IIk). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm, *J*, Hz: 12.92 q (1C, Me, *J* = 129.2), 114.51 m (1C, C_{ar}), 117.6 m (1C, C_{ar}), 120.05 m (1C, C_{ar}), 127.08 d (1C, C_{ar}, *J* = 5.6), 131.58 m (1C, C_{ar}), 155.09 q (1C, $C_{triazole}$, *J* = 7.3), 157.10 m (1C, C_{ar}), 158.55 m (1C, $C_{triazole}$, ^{2}J = 5.2).

2-{3-[2-(4-Methoxyphenyl]-1*H*-1,2,4-triazol-5-yl}-phenol (IIa). A suspension of 10 mmol of perchlorate **Ia** in 10 ml of glacial AcOH and 20 mmol of hydrazine-hydrate was boiled for several minutes. The reaction mixture was cooled to room temperature and after 6–8 h keeping was diluted with water, the formed crystals were filtered and washed with water. Crystals of light brown color, yield 2.4 g.

Table 1. Principal bond lengths (Å) and bond angles (deg) in the molecule of 3-(2-hydroxyphenyl)-*N*,*N*-dimethyl-5-{2-[4-(methylthio)phenyl]vinyl}-1*H*-1,2,4-triazol-1-sulfonamide (**VIId**)

Bond	*d*, Å	Bond angles	ω, deg	Bond angles	ω, deg
O^1–C^7	1.354(3)	$O^2S^1O^3$	124.5(13)	$C^2N^3N^4$	102.2(2)
C^2–N^3	1.327(3)	$O^2S^1N^5$	116.8(10)	$C^5N^4N^3$	110.5(2)
C^2–C^6	1.465(4)	$O^3S^1N^5$	106.4(5)	$C^5N^4S^1$	130.5819
N^3–N^4	1.376(3)	$O^2S^1N^4$	103(2)	$N^3N^4S^1$	117.70(17)
C^9–C^{10}	1.383(4)	$O^3S^1N^4$	97.7(3)	$N^1C^5N^4$	108.4(2)
C^{10}–C^{11}	1.367(4)	$N^5S^1N^4$	104.51(12)	$N^1C^5C^{12}$	126.8(2)
C^{12}–C^{13}	1.321(4)	$C^5N^1C^2$	104.3(2)	$N^4C^5C^{12}$	124.8(2)
		$N^3C^2N^1$	114.5(2)	$C^{22}N^5C^{21}$	115.2(2)
		$N^3C^2C^6$	123.2(2)	$C^{22}N^5S^1$	118.0(2)
		$N^1C^2C^6$	122.2(2)	$C^{21}N^5S^1$	120.6(2)

Compound **IIb–IIj** were prepared similarly [6].

2-{3-[2-(3,4-Dimethoxyphenyl)vinyl]-1*H*-1,2,4-triazol-5-yl}phenol (IIb), brown crystals.

2-(3{(2-[4-(Methylthio)phenyl]vinyl}-1*H*-1,2,4-triazol-5-yl)phenol (IIc), yellow crystals.

2-{3-[2-(4-Chlorophenyl)vinyl]-1*H*-1,2,4-triazol-5-yl}phenol (IId), colorless crystals.

2-{3-[2-(4-Bromophenyl)vinyl]-1*H*-1,2,4-triazol-5-yl}phenol (IIe) colorless crystals.

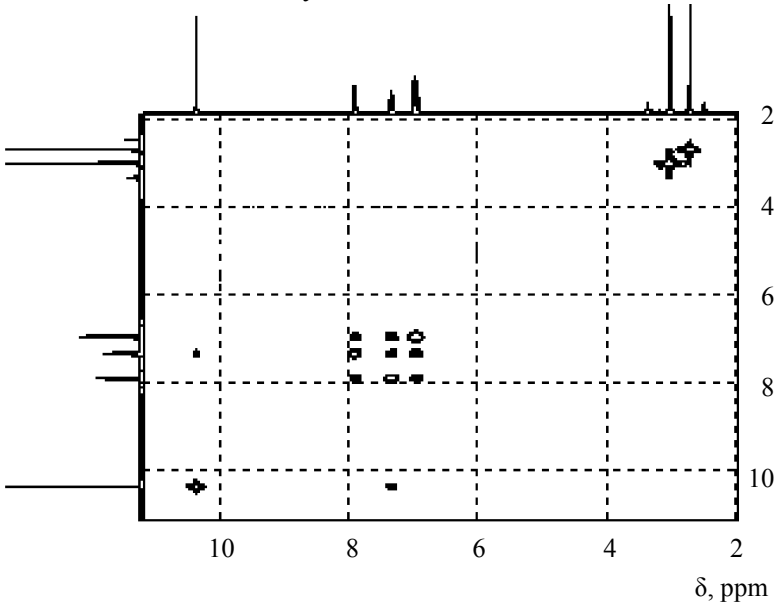


Fig. 3. Two-dimensional ^{1}H NMR (COSY) spectrum of 3-(2-hydroxyphenyl)-*N*,*N*,5-trimethyl-1*H*-1,2,4-triazol-1-sulfonamide (**VIIa**).

Table 2. Yields, melting points and data of elemental analyses of compounds **II–VII**

Comp. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	N	Hal/S		C	H	N	Hal/S
IIa	81	186–188 (BuOH)	69.20	5.00	14.10	–	$C_{17}H_{15}N_3O_2$	69.62	5.00	14.10	–
IIb	56	200–202 (BuOH)	66.00	5.00	13.10	–	$C_{18}H_{17}N_3O_3$	66.87	5.26	13.00	–
IIv	61	198–200 (BuOH)	64.70	5.20	13.90	10.70	$C_{17}H_{15}N_3OS$	64.65	5.05	14.14	10.70
IId	49	198–200 (BuOH)	64.70	4.20	14.00	11.70	$C_{16}H_{12}ClN_3O$	64.54	4.03	14.12	11.93
IIe	57	210–212 (BuOH)	56.30	3.10	12.50	23.00	$C_{16}H_{12}BrN_3O$	56.14	3.51	12.28	23.39
IIf	34	202–204 (*i*-PrOH)	62.60	4.70	15.10	11.10	$C_{14}H_{11}N_3OS$	62.45	4.09	15.61	11.90
IIg	45	235–236 (BuOH)	72.00	5.30	17.50	–	$C_{19}H_{16}N_4O$	72.15	5.06	17.72	–
IIh	50	204–206 (BuOH)	63.30	4.70	14.50	11.10	$C_{15}H_{13}N_3OS$	63.60	4.59	14.84	11.31
IIi	38	228–230 (BuOH)	68.30	4.70	21.40	–	$C_{15}H_{12}N_4O$	68.18	4.55	21.21	–
IIj	36	186–188 (BuOH)	67.70	4.50	15.80	–	$C_{15}H_{13}N_3O_2$	67.42	4.87	15.73	–
IIIa	55	146–147 (MeOH)	66.10	3.90	14.30	8.70	$C_{22}H_{27}ClN_4O$	66.25	6.78	14.05	8.91
IIIb	51	175–177 (BuOH)	64.10	6.90	13.40	8.60	$C_{23}H_{29}ClN_4O_2$	64.41	6.77	13.07	8.28
IIIc	49	70–72 (MeCN)	62.30	6.80	12.40	7.70/7.50	$C_{23}H_{29}ClN_4OS$	62.09	6.52	12.60	7.99/7.20
IIId	48	140–142 (*i*-PrOH)	55.60	6.20	17.00	11.10	$C_{15}H_{21}ClN_4O_2$	55.47	6.47	17.00	10.94
IIIe	42	163–165 (MeOH)	60.20	6.00	12.10	7.10	$C_{24}H_{29}ClN_4O_4$	60.95	6.14	11.85	7.51
IIIf	52	198–200 (*i*-PrOH)	66.40	6.90	14.20	9.00	$C_{22}H_{27}ClN_4O$	66.25	6.78	14.05	8.91
IIIg	43	192–193 (MeOH)	65.70	6.30	12.50	7.90	$C_{24}H_{29}ClN_4O_2$	65.38	6.58	12.71	8.06
IIIh	55	197–199 (BuOH)	63.70	6.70	11.70	7.40	$C_{25}H_{31}ClN_4O_3$	63.76	6.59	11.90	7.55
IVa	97	187–189 (BuOH)	64.50	4.30	9.50	5.80/5.30	$C_{32}H_{25}ClN_4O_4S$	64.38	4.19	9.39	5.95/5.36
IVb	75	146–147 (BuOH)	65.90	3.60	10.90	6.90/6.20	$C_{28}H_{19}ClN_4O_2S$	65.82	3.72	10.97	6.95/6.27
Va	55	160–162 (MeOH)	67.00	6.40	14.50	–	$C_{22}H_{24}N_4O_3$	67.35	6.12	14.29	–
Vb	53	146–148 (*i*-PrOH)	65.10	6.50	12.90	–	$C_{23}H_{26}N_4O_4$	65.40	6.16	13.27	–
VIa	54	177–179 (BuOH)	58.50	4.20	12.90	10.00	$C_{16}H_{15}N_3O_3S$	58.36	4.56	12.77	9.73
VIb	47	122–124 (BuOH)	66.40	4.70	9.80	7.80	$C_{23}H_{19}N_3O_3S$	66.19	4.56	10.07	7.67
VIc	43	152–154 (BuOH)	62.70	4.90	8.90	6.60	$C_{25}H_{23}N_3O_5S$	62.89	4.82	8.81	6.72
VId	43	160–162 (BuOH)	55.80	3.50	8.60	16.2/6.30	$C_{23}H_{18}BrN_3O_5S$	55.65	3.63	8.47	16.1/6.45
VIIa	59	123–125 (BuOH)	46.10	4.90	19.90	11.30	$C_{11}H_{14}N_4O_3S$	46.10	4.96	19.86	11.35
VIIb	46	175–176 (BuOH)	58.30	4.80	15.20	8.60	$C_{18}H_{18}N_4O_3S$	58.38	4.86	15.14	8.65
VIIc	52	169–171 (BuOH)	55.90	5.20	13.10	7.50	$C_{20}H_{22}N_4O_5S$	55.81	5.12	13.02	7.44
VIId	52	150–152 (BuOH)	54.90	4.50	13.60	15.10	$C_{19}H_{20}N_4O_3S_2$	54.81	4.81	13.46	15.38

Table 3. Data of IR and ^{1}H NMR spectroscopy of compounds **II–VII**

Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, solvent, δ, ppm, *J*, Hz
IIa	1640, 1630, 1610, 1560 (C=C_{vinyl}, C=C_{ap}, C=N)	DMSO-d_6, 3.83 s (3H, OMe), 7.27 and 7.67 d.d (2H, CH_{vinyl}, *J* 7.9), 6.92–7.95 m (8H, H_{ar}), 11.98, 11.65 s (1H, NH), 14.21 s (1H, OH)
IIb	3200 (OH); 1640 (C=C); 1610, 1590 (C=C, C=N)	Acetone-d_6, 3.81 s (3H, OMe), 3.83 s (3H, OMe), 6.92–7.91 m (9H, H_{ar}, CH-vinyl), 11.21, 11.62 s (1H, NH), 14.28 s (1H, OH)
IIc	1630, 1610 (C=C); 1570 (C=C, C=N)	Acetone-d_6, 2.55 s (3H, SMe), 7.01–8.09 m (10H, H_{ar}, CH-vinyl), 11.45, 11.73 s (1H, NH); 13.72 s (1H, OH)
IId	3190 (OH); 1650, 1630 (C=C); 1560 (C=C, C=N)	DMSO-d_6, 6.92–7.99 m (10H, H_{ar}, CH-vinyl), 11.18, 11.61 s (1H, NH), 14.38, 14.42 s (1H, OH)
IIe	3210 (OH); 1650 (C=C); 1600, 1550 (C=C, C=N)	DMSO-d_6, 6.99–8.19 m (10H, H_{ar}, CH-vinyl), 11.21, 11.58 s (1H, NH), 14.28 s (1H, OH)
IIf	1620, 1610 (C=C); 1560 (C=C, C=N)	DMSO-d_6, 6.82–7.95 m (9H, H_{ar}, CH-vinyl), 11.08, 11.43 s (1H, NH), 13.95, 14.24 s (1H, OH)

Table 3. (Contd.)

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, solvent, δ, ppm, *J*, Hz
IIg	3200 (OH); 1640, 1610 (C=C); 1590 (C=C, C=N)	DMSO-d_6, 3.90 s (3H, Me), 6.86–7.92 m (11H, H_{ar}, CH-vinyl), 11.33, 11.80 s (1H, NH); 13.88, 14.19 s (1H, OH)
IIh	1630, 1610 (C=C); 1560 (C=C, C=N)	DMSO-d_6, 2.27 s (3H, Me), 6.62–7.98 m (8H, H_{ar}, CH-vinyl), 11.01, 11.43 s (1H, NH), 13.85, 14.22 s (1H, OH)
IIi	1660 (C=N); 1600, 1580 (C=C); 1520 (C=C, C=N)	DMSO-d_6, 6.91–8.58 m (10H, H_{ar}, CH-vinyl), 11.09, 11.55 s (1H, NH)
IIj	1630, 1610 (C=C); 1560 (C=C, C=N)	DMSO-d_6, 2.38 s (3H, Me), 6.09–7.92 m (8H, H_{ar}, CH-vinyl), 11.19, 11.49 s (1H, NH), 14.21 s (1H, OH)
IIIa	1630 (C=N); 1590, 1540 (C=C)	DMSO-d_6, 1.36 t (6H, Me, *J* 7.2), 3.23 m (4H, CH_2), 3.61 t (2H, CH_2, *J* 6.8), 5.08 t (2H, CH_2, *J* 7.2), 6.91–7.99 m (11H, H_{ar}, CH-vinyl), 10.90 s (1H, N^+H), 12.28 s (1H, OH)
IIIb	1650, 1650, 1570, 1520 (C=C_{vinyl}, C=C_{ap}, C=N)	Acetone-d_6, 1.42 t (6H, Me, *J* 7.48), 2.47 s (3H, OMe), 3.28 m (4H, CH_2), 3.70 t (2H, CH_2, *J* 6.9), 5.19 t (2H, CH_2, *J* 7.4), 6.91–8.07 m (10H, H_{ar}, CH_{vinyl}), 11.15 s (1H, N^+H), 13.23 s (1H, OH)
IIIc	1640, 1630 (C=N); 1590, 1560 (C=C)	DMSO-d_6, 1.41 t (6H, Me, *J* 7.50), 2.37 s (3H, SMe), 3.31 m (4H, CH_2), 3.71 t (2H, CH_2, *J* 6.9); 5.09 t (2H, CH_2, *J* 7.2), 6.99, 8.01 m (10H, H_{ar}, CH-vinyl)
IIId	1640, 1630 (C=N); 1560, 1530 (C=C)	DMSO-d_6, 2.67 s (3H, Me), 3.12 t (2H, CH_2, *J* 7.5), 3.55 t (4H, CH_2, *J* 7.7), 3.95 t (4H, CH_2, *J* 5.5), 4.8 t (2H, CH_2, *J* 5.8), 6.83–7.89 m (4H, H_{ar}), 10.87 s (1H, N^+H), 12.70 s (1H, OH)
IIIe	1630, 1610 (C=N); 1530 (C=C)	DMSO-d_6, 3.18 t (2H, CH_2, *J* 6.9), 3.45 t (2H, CH_2, *J* 5.7), 3.68 t (2H, CH_2, *J* 5.9), 3.81 s (3H, OMe) 3.83 s (3H, OMe), 3.95 t (4H, CH_2), 5.07 t (2H, CH_2), 6.89–7.95 m (9H, H_{ar}, CH-vinyl), 10.92 s (1H, N^+H), 12.71 s (1H, OH)
IIIf	1640, 1620 (C=N); 1580, 1550 (C=C)	DMSO-d_6, 1.48–2.01 m (6H, CH_2), 2.99 t (2H, CH_2, *J* 7.7), 3.59 t (4H, CH_2, *J* 7.0), 5.09 t (2H, CH_2, *J* 7.2), 6.89–7.93 m (11H, H_{ar}, CH-vinyl), 10.88 s (1H, N^+H), 11.99 s (1H, OH)
IIIg	1630, 1620 (C=N); 1580, 1560 (C=C)	DMSO-d_6, 1.48–2.02 m (6H, CH_2), 2.98 t (2H, CH_2, *J* 7.5), 3.52 m (4H, CH_2), 3.83 s (3H, OMe); 5.05 t (2H, CH_2, *J* 7.0), 6.78–7.95 m (10H, H_{ar}, CH-vinyl), 10.95 s (1H, N^+H), 11.91 s (1H, OH)
IIIh	1630, 1610 (C=N); 1570, 1520 (C=C)	DMSO-d_6, 1.48–1.99 m (6H, CH_2), 2.96 t (2H, CH_2, *J* 7.7), 3.51 m (4H, CH_2), 3.81 s (3H, OMe), 3.95 s (3H, OMe), 5.09 t (2H, CH_2, *J* 7.0), 6.95–7.95 m (9H, H_{ar}, CH-vinyl), 10.98 s (1H, N^+H), 12.00 s (1H, OH)
IVa	1710 (C=O); 1630, 1600 (C=N); 1550 (C=C)	DMSO-d_6, 3.60 s (3H, OMe), 3.70 s (3H, OMe), 5.75 d.br (2H, CH_2, *J* 5.6), 7.00–8.01 m (16H, H_{ar}, CH-vinyl), 11.05 s (1H, OH)
IVb	1710 (C=O); 1630, 1605 (C=N); 1510 (C=C)	DMSO-d_6, 5.60 d (2H, CH_2, *J* 5.6), 6.90–7.98 m (16H, H_{ar}, CH-vinyl), 11.10 s (1H, OH)
Va	1630, 1620 (C=N); 1590, 1570 (C=C)	DMSO-d_6, 2.73 t (4H, CH_2, *J* 6.9), 3.65 t (4H, CH_2, *J* 7.3), 3.89 s (3H, OMe), 5.31 s (2H, CH_2) 6.99–8.09 m (10H, H_{ar}, CH-vinyl), 13.20 s (1H, OH)
Vb	1600 (C=N); 1580, 1560 (C=C)	DMSO-d_6, 2.68 t (4H, CH_2, *J* 7.2), 3.60 t (4H, CH_2, *J* 7.2), 3.80 s (3H, OMe), 3.88 s (3H, OMe), 5.36 s (2H, CH_2), 6.99–8.09 m (9H, H_{ar}, CH-vinyl), 11.15 s (1H, OH)
VIa	3190 (OH); 1615 (C=N); 1540 (C=C)	DMSO-d_6, 2.21 s (3H, Me), 2.30 s (3H, Me), 7.21–7.70 m (8H, H_{ar}), 13.61 s (1H, OH)
VIb	3200 (OH); 1630 (C=N); 1530 (C=C)	DMSO-d_6, 2.28 s (3H, Me), 6.99–7.88 m (15H, H_{ar}, CH-vinyl), 13.90 s (1H, OH)
VIc	3180 (OH); 1630, 1615 (C=N); 1550 (C=C)	DMSO-d_6, 2.32 s (3H, Me), 3.80 s (3H, OMe), 3.84 s (3H, OMe), 6.85–7.82 m (13H, H_{ar}, CH-vinyl), 13.80 s (1H, OH)
VId	3190 (OH); 1640 (C=N); 1540 (C=C)	DMSO-d_6, 2.28 s (3H, Me), 7.06–7.89 m (14H, H_{ar}, CH-vinyl), 13.92 s (1H, OH)
VIIa	1630 (C=N); 1590, 1580 (C=C)	DMSO-d_6, 2.76 s (3H, Me), 3.08 s (6H, NMe_2), 6.88–7.91 m (4H, H_{ar}), 10.32 s (1H, OH)
VIIb	1620, 1600 (C=N); 1590 (C=C)	DMSO-d_6, 3.12 s (6H, NMe_2), 6.92–7.98 m (11H, H_{ar}, CH-vinyl), 10.38 s (1H, OH)
VIIc	1620, (C=N); 1590, 1560 (C=C)	DMSO-d_6, 3.11 s (6H, NMe_2), 3.82 s (3H, OMe), 3.85 s (3H, OMe), 6.87–8.01 m (9H, H_{ar}, CH-vinyl), 10.44 s (1H, OH)
VIId	1630, 1600 (C=N); 1590 (C=C)	DMSO-d_6, 2.47 s (3H, SMe), 3.08 s (6H, NMe_2), 6.91–7.92 m (10H, H_{ar}, CH-vinyl), 10.38 s (1H, OH)

Table 4. Crystallographic data and parameters of X-ray structural experiment for compound **VIIa**

Parameter	Value
Formula	$C_{19}H_{20}N_4O_3S_2$
Molecular mass	416
Crystal system	Monoclinic
Space group	$P2_1/c$
a, Å	6.4415(10)
b, Å	17.069(3)
c, Å	17.592(3)
β, deg	92.423(14)
V, Å^3	1932.5(6)
$F(000)$	872
Z	4
d_{calc}, g cm^{-3}	1.432
μ, cm^{-1}	3.04
Measured reflexes/total reflexes	10662/4578
R_{int}	0.0388
Reflexes with $I \geq 2\sigma(I)$	2408
Number of refined parameters	296
R_1 ($I \geq 2\sigma(I)$)	0.0576
wR_2 (over all reflexes)	0.1381

2-{3-[2-(2-Thienyl)vinyl]-1*H*-1,2,4-triazol-5-yl}-phenol (IIf) brown crystals.

2-{3-[2-(1-Methyl-1*H*-indo-3-yl)vinyl]-1*H*-1,2,4-triazol-5-yl}phenol (IIg) colorless crystals.

2-{3-[2-(3-methyl-2-thienyl)vinyl]-1*H*-1,2,4-triazol-5-yl}phenol (IIh) yellow-brown crystals.

2-{3-[2-Pyrid-2-ylvinyl]-1*H*-1,2,4-triazol-5-yl}-phenol (IIi) brown crystals.

2-{3-[2-(5-Methyl-2-furyl)vinyl]-1*H*-1,2,4-triazol-5-yl}phenol (IIj) yellow crystals.

2-{1-[2-(Diethylamino)ethyl]-5-[2-phenylvinyl]-1*H*-1,2,4-triazol-3-yl}phenol hydrochloride (IIIa). To a solution of 10 mmol of compound **III** in 15 ml of acetone was added 20 mmol of NaOH and 10 mmol of (2-chloroethyl)diethylamine hydrochloride. The reaction mixture was boiled for 1.5 h, and water was poured to it. The formed out oil was separated, dissolved in 20 ml of acetone and 6 ml of 7% HCl solution was added to it. The product was kept for 12 h at room temperature, then the precipitate formed was filtered off and washed with water. Colorless crystals.

Compounds **IIIb–IIIh** were prepared similarly.

2-(1-[2-(Diethylamino)ethyl]-5-{2-[4-(methoxy)-phenyl]vinyl}-1*H*-1,2,4-triazole-3-yl)phenol hydrochloride (IIIb), colorless crystals. ^{13}C NMR spectrum (DMSO-d_6), δ, ppm, J, Hz: 8.30 q (2C, CH_3, J = 128.2), 42.43 t (1C, CH_2, J = 114.2), 46.39 t (2C, CH_2, J = 143.0), 49.40 t (1C, CH_2, J = 143.5), 55.21 q (1C, OCH_3, J = 144.7), 108.37 d (1C, C_{vinyl}, J = 5.8), 113.79 d (1C, C_{ar}, J = 6.6), 114.18 d (2C, C_{ar}, J = 8.4), 116.88 m (1C, C_{ar}), 119.3 m (1C, C_{ar}), 126.44 d (1C, C_{ar}, J = 9.4,), 127.86 t (1C, C_{ar}, J = 5.8),129.60 d (2C, C_{ar}, J = 8.1), 130.98 m (1C, C_{ar}), 137.78 m (1C, C_{vinyl}), 152.86 m (1C, $Ct_{triazole}$, ^2J = 4.8 Hz, ^3J = 1.2), 156.26 m (1C, C_{ar}), 159.29 d (1C, $C_{triazole}$, J = 4.4,), 160.41 m (1C, C_{ar}).

2-(1-[2-(Diethylamino)ethyl]-5-{2-[4-(methylthio)phenyl]-vinyl}-1*H*-1,2,4-triazole-3-yl)phenol hydrochloride (IIIc), colorless crystals.

2-[5-Methyl-1-(2-morpholin-4-ylethyl)-1*H*-1,2,4-triazol-3-yl]phenol hydrochloride (IIId), colorless crystals.

2-[5-[2-(3,4-Dimethoxyphenyl)vinyl]-1-(2-morpholin-4-ylethyl)-1*H*-1,2,4-triazol-3-yl]phenol hydrochloride (IIIe), colorless crystals.

2-[5-[2-Phenylvinyl]-1-(2-piperidin-1-ylethyl)-1*H*-1,2,4-triazol-3-yl]phenol hydrochloride (IIIf), colorless crystals.

2-[5-[2-(4-Methoxyphenyl)vinyl]-1-(2-piperidin-1-ylethyl)-1*H*-1,2,4-triazol-3-yl]phenol hydrochloride (IIIg), colorless crystals.

2-[5-[2-(3,4-Dimethoxyphenyl)vinyl]-1-(2-piperidin-1-ylethyl)-1*H*-1,2,4-triazol-3-yl]phenol hydrochloride **(IIIh),** colorless crystals.

2-{1-[2-(2-Chloro-10*H*-phenothiazin-10-yl)-2-oxoethyl]-5-[2-(3,4-dimethoxyphenyl)vinyl]-1*H*-1,2,4-triazol-3-yl}phenol (IVa). To a solution of 10 mmol of compound **IIb** in 15 ml of acetone was added 40 mmol of calcined potassium carbonate, and the mixture was boiled for 15 mines, then cooled, and 10 mmol of 3-chloro-10-(chloroacetyl)-10*H*-phenothiazine was added. The reaction mixture was refluxed for 1.5 h, then diluted with water. The separated precipitate was filtered off and washed with water. Light brown crystals were obtained.

2-{1-[2-(2-Chloro-10*H*-phenothiazin-10-yl)-2-oxoethyl]-5-[2-(2-thienyl)vinyl]-1*H*-1,2,4-triazol-3-yl}phenol (IVb) was prepared similarly, brown crystals.

2- [5-[2-(4-Methoxyphenyl)vinyl]-1-(mopholin-4-ylmethyl)-1*H*-1,2,4-triazol-3-yl]phenol (Va). A mixture containing 10 mmol of compound **IIa**, 20 ml of benzene, 10 mmol of morpholine and 20 mmol of form-

aldehyde was refluxed for 6 h. Then the solvent was evaporated and the residue was crystallized to isolate light brown crystals. ^{13}C NMR spectrum (acetone-d_6), δ, ppm, *J*, Hz: 48.9 t (2C, C_{morph}, *J* = 138.1), 51.1 q (1C, CH_3, *J* = 144.4), 53.2 t (1C, CH_2, *J* = 143.0), 69.55 m (2C, CH_2, *J* = 152.8), 108.3 m (1C, C_{ar}), 115.1 m (1C, C_{vinyl}), 117.6 m (2C, C_{ar}), 118.7 m (1C, C_{ar}), 120 t (1C, C_{ar}, *J* = 6.3), 127 d (1C, C_{ar}, *J* = 7.0), 128.3 m (2C, C_{ar}), 128.8 t (1C, C_{ar}, *J* = 7.3), 131.4 t (1C, C_{ar}, *J* = 5.3), 139.8 m (1C, C_{vinyl}), 154.25 m (1C, $C_{triazole}$, ^2J = 5.0, ^3J = 2.6), 157 m (1C, C_{ar}), 158 m (1C, C_{ar}), 160.2 d (1C, $C_{triazole}$, *J* = 4.5).

2-[5-[2-(3,4-dimethoxyphenyl)vinyl]-1-morpholin-4-ylmethyl)-1*H*-1,2,4-triazol-3-yl]phenol (Vb), beige crystals.

2-{5-Methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-1,2,4-triazol-3-yl}phenol (VIa). To a solution of 10 mmol of compound **IIk** in 3.5 ml of pyridine was added 10 mmol of TsCl. The reaction mixture was heated to boiling, then cooled, and left standing for 24 h, and then water was poured to it. The precipitate formed was filtered off and washed with water. Colorless crystals formed.

Compounds **VIb–VId** were prepared similarly.

2-{1-[(4-Methylphenyl)sulfonyl]-5-[2-phenylvinyl]-1*H*-1,2,4-triazol-3-yl}phenol (VIb), colorless crystals.

2-{5-[2-(3,4-dimethoxyphenyl)vinyl]-1-[(4-methylphenyl)sulfonyl]-1*H*-1,2,4-triazol-3-yl}phenol (VIc), light-brown crystals.

2-{5-[2-(4-Bromophenyl)vinyl]-1-[(4-methylphenyl)sulfonyl]-1*H*-1,2,4-triazol-3-yl}phenol (VId), colorless crystals.

3-(2-Hydroxyphenyl)-*N*,*N*,5-trimethyl-1*H*-1,2,4-triazol-1-sulfonamide (VIIa). To a solution of 10 mmol of compound **IIk** in 3.5 ml of pyridine was added 10 mmol of dimethylsulfamoyl chloride. The reaction mixture was heated to boiling, cooled, and kept for 24 h at a room temperature, and then 12 ml of water was poured to it. The separated crystals were filtered off, washed with water, and the colorless crystals were collected.

Compounds **VIIb–VIId** were prepatred similarly.

3-(2-Hydroxyphenyl)-*N*,*N*-dimethyl-5-[2-phenylvinyl]-1*H*-1,2,4-triazol-1-sulfonamide (VIIb), colorless crystals.

5-[2-(3,4-dimethoxyphenyl)vinyl]-3-(2-hydroxyphenyl)-*N*,*N*-dimethyl-1*H*-1,2,4-triazol-1-sulfonamide (VIIc), beige crystals.

3-(2-Hydroxyphenyl)-*N*,*N*-dimethyl-5-{2-[4-(methylthio)phenyl]vinyl}-1*H*-1,2,4-triazol-1-sulfonamide (VIId), yellow crystals.

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