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Graphical Abstract

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Synthesis and study of prototropic tautomerism of 2-(2-hydroxyphenyl)-1-hydroxyimidazoles

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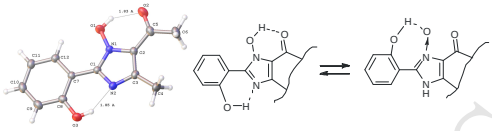

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ABSTRACT

Novel 2-(2-hydroxyphenyl) substituted imidazoles have been synthesized. A prototropic tautomerism of the 1-hydroxyimidazole derivatives has been studied. X-ray diffraction analysis and IR-spectroscopy have revealed that in the solid state the title compounds exist as the N-hydroxy tautomers. The ^{1}H and ^{13}C NMR spectra of the new imidazole derivatives are discussed. It has been shown that in chloroform solutions 5-carbonylsubstituted 2-(2-hydroxyphenyl)-1-hydroxyimidazoles exist in the N-hydroxy tautomeric form. A transition to DMSO results in the existence of the 1-hydroxyimidazoles under study as the N-oxide tautomers.

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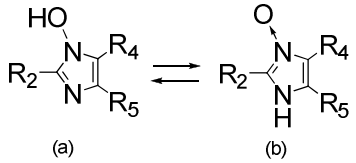
1. Introduction

1-Hydroxyimidazole derivatives are known not only as valuable intermediates in the syntheses of imidazoles[1] but also as biologically active compounds. For example, it has been shown that 1-hydroxyimidazole derivatives display insecticidal and herbicidal properties,[2] exhibit antiprotozoal activity.[3,4]

It is supposed that 1-hydroxyimidazoles exist in either N-hydroxy or N-oxide tautomeric form.



Scheme 1. Prototropic tautomerism of 1-hydroxyimidazoles.

Studying the prototropic tautomerism for potentially biologically active compounds constitutes an important part in Drug Discovery.[5] Recently some new studies dealing with coordination properties of 1-hydroxyimidazoles have appeared.[6-9] Undoubtedly, the data concerning the tautomeric forms of the compounds under consideration are also important for this line of investigation.

The prototropic tautomerism of 1-hydroxyimidazoles and their benzannelated analogues has not been much investigated.

The tautomerism of these compounds was discussed in papers published in the 1960s.[10-15] This discussion was summarized in A.R. Katrizky's paper[15] in which the results of previous papers have been considered. It has also been shown by the example of 1-hydroxy-2,4,5-triphenylimidazole and 1-hydroxybenzimidazole that these compounds existed predominantly as N-hydroxytautomers in non-polar solvents. An increase in the solvent polarity resulted in an increase of the N-oxide form content. The main conclusions were based on the similarity of the absorption spectra of the compounds under consideration and some model compounds (N- and O-methyl derivatives), and the comparison of their pKa values in aqueous solutions.[15]

In later papers[16,17] the position of coalescent signal in the ^{15}N NMR spectra for 1-hydroxybenzimidazole and 2-phenyl-1-hydroxybenzimidazole made it possible to determine the ratio of the tautomeric forms in the equilibrium. It was shown that the equilibrium shifted to the N-oxide tautomer with the decrease of the solvent (DMSO, MeOH, CF_3CH_2OH) pKa,[16] which corresponded to the Katrizky's data.[15]

However, in Castellano's paper[18] it was supposed that the solvent polarity far not always significantly influences on the tautomer ratio. By ^1H NMR spectroscopy it was shown that the predominance of one or another tautomeric form of 6-nitro- and 6-ethoxycarbonyl-1-hydroxybenzimidazol-2-carboxylic acids derivatives was related to proton-donor (proton-acceptor) properties of the solvent. The hydrogen-bond-acceptor (HBA) solvents stabilized the N-hydroxy tautomer, while hydrogen-bond-donor (HBD) solvents, the N-oxide one. In solvents that could act as both, the stabilization of one or another form depended on the acid-base properties. In less polar solvents (such as chloroform) the predominance of one of the tautomers depended on intramolecular interactions.[18]The prototropic tautomerism of 1-hydroxybenzimidazoles in the solid state was also considered by means of IR-spectroscopy and X-ray analysis data.[18]

Unambiguous evidence for the occurence of the N-hydroxyimidazole tautomeric form in the solid state may be obtained from the X-ray structural analysis data (see, e.g., papers).[19-25] In the report[24] the X-ray data for 1-hydroxyimidazole derivatives were considered with regard to their tautomeric form stabilization.

The stabilization of a tautomer in the crystal state is achieved due to inter- and intra-molecular interactions and depends on a nature of imidazole ring substituents. Interestingly, it has been reported that in the molecule of 1,1'-dihydroxy-2,2'-biimidazole derivative one imidazole ring existed in the N-hydroxy form while the second imidazole ring was found to occur in the N-oxide form.[25]

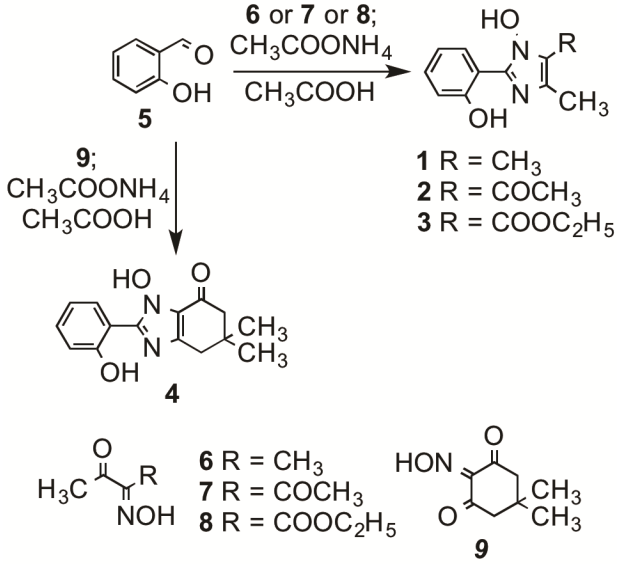
Previously we have studied the prototropic tautomerism of 2-(3-chromenyl)-1-hydroxyimidazoles.[23] By X-ray diffraction analysis it was shown that in the crystal state these compounds exist in the N-oxide tautomeric form. According to the ^1H NMR spectroscopic data in relatively dilute solutions regardless of their nature, 4,5-dimethyl-2-chromenyl-1-hydroxyimidazole existed as the N-hydroxy tautomer. An introduction of the carbonyl group in position 5 of 1-hydroxyimidazole shifts the equilibrium to the N-oxide tautomer; in this case the proton-donor (proton-acceptor) properties of the solvent have an impact on the equilibrium. The weaker the proton-donor properties of the solvent are, the greater is the shift of the tautomeric equilibrium in solution to the N-oxide form.

In order to continue study of the 1-hydroxyimidazole derivatives capable of formation of intramolecular hydrogen bonds (IMHB) here we present an investigation of 2-(2-hydroxyphenyl)-1-hydroxyimidazoles with a carbonyl-containing substituent in position 5 of the heterocycle.

2. Results and Discussion

2.1. Synthesis of compounds

One of the most widespread and convenient methods to synthesize 1-hydroxyimidazoles is a cyclization of starting aldehydes with α-hydroxyiminoketones and ammonium acetate[1,2,4,7,23,24,26-30] in alcohols or glacial acetic acid.



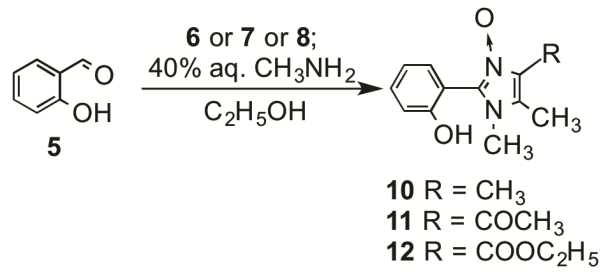
Scheme 2. Synthesis of 1-hydroxyimidazoles **1**-**4**.

Novel 1-hydroxyimidazole derivatives **1**-**4** were synthesized by condensation of salicylic aldehyde **5** with the corresponding

oximes **6-9** and ammonium acetate in glacial acetic acid at 40-45°C. Starting oximes **7-9** were obtained by nitrosation of the corresponding diketones as described earlier.[23] Butanedione monoxime **6** is commercially available.

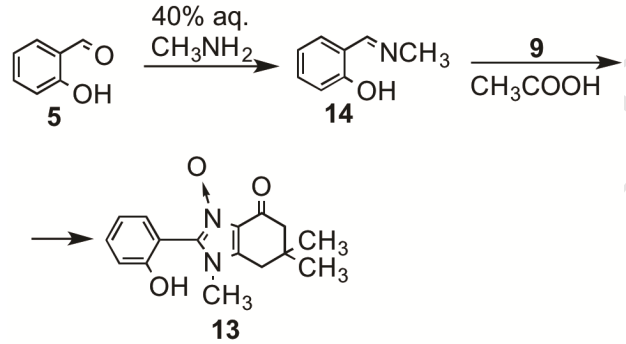
One of the methods to study prototropic tautomerism is to compare the spectral data of the compounds under consideration with a model molecule that has a structure corresponding to a definite tautomer (see, e.g., papers[15-18,23,31] and also a review).[32]

1-Methylimidazole 3-oxides were chosen as model structures for the N-oxide tautomer. Imidazole N-oxides **10-12** were obtained by condensation of salicylic aldehyde **5** with corresponding oximes **6-8** and methyl amine (as a 40% aqueous solution) in ethyl alcohol at room temperature.



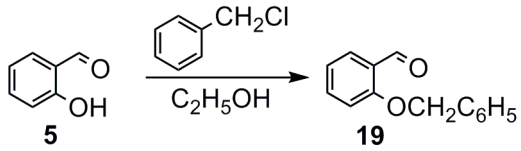
Scheme 3. Synthesis of imidazole N-oxides **10-12.**

N-Oxide **13** was obtained in two steps. Reaction of salicylic aldehyde **5** with aqueous solution of methyl amine led to azomethine **14**. The condensation of the latter with oxime **9** in glacial acetic acid at room temperature resulted in target compound **13**.



Scheme 4. Synthesis of imidazole N-oxide **13**.

Methoxyimidazoles were synthesized as model structures for N-hydroxytautomer. Apparently, N-methoxysubstituted imidazoles **15-18** cannot be obtained by direct methylation due to a possible methylation of the hydroxy group in the phenyl substituent. Therefore, in order to obtain N-methoxyimidazoles **15-18** this group has been protected.

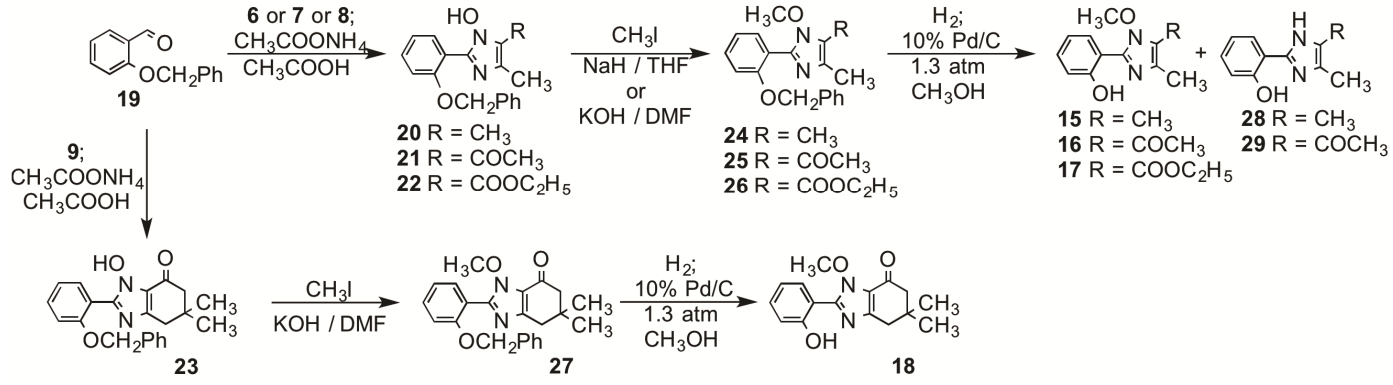


Scheme 5. Protection of hydroxyl group.

The condensation of aldehyde **19** with oximes **6-9** and ammonium acetate in glacial acetic acid led to 2-(2-benzyloxyphenyl)-1-hydroxyimidazoles **20-23**. Technically, in molecules **20-23** the methylation can proceed either at hydroxyl in position 1 or at the N(3) nitrogen atom of the imidazole ring. It is known that the methylation of such structures goes selectively at the hydroxy group in position 1 (see, e.g., Refs.).[15,18] The methylation of compounds **20-23** was carried out by the interaction with methyl iodide either in THF in the presence of sodium hydride (synthesis of **24**) or in DMF in the presence of potassium hydroxide (syntheses of **25-27**). N-Methoxyimidazoles **24-27** were the only products of this reaction.

The benzyl group of 2-(2-benzyloxyphenyl)-1-methoxyimidazoles **24-27** was removed by catalytic hydrogenation with hydrogen on the palladium catalyst in methanol at room temperature and small excessive pressure.

It should be mentioned that in the case of 5-methyl- and 5-acetyl-1-methoxyimidazoles **24** and **25** the reduction reaction resulted in mixture of target N-methoxy derivatives **15** or **16** and imidazoles **28** or **29** without methoxy groups. A decrease in the reaction time in the case of compounds **26** or **27** resulted in N-methoxysubstituted imidazoles **17** and **18** with an admixture of starting compounds **26** and **27**.

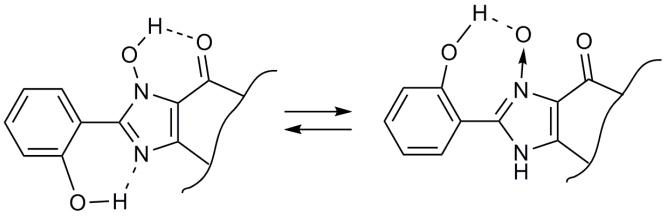


Scheme 6. Synthesis of 1-methoxyimidazoles **15-18**.

2.2. Study of prototropic tautomerism in the solid state.

It is supposed (see, e.g., Refs.[1,10-15,23-25]) that 1-hydroxyimidazoles may exist in the two tautomeric forms (Scheme 1). Taking into consideration possible hydrogen

bonding in the molecules under study, the following utmost forms of the prototropic tautomers of 2-(2-hydroxyphenyl)substituted 1-hydroxyimidazoles **2-4** could be proposed:



Scheme 7. Utmost forms of prototropic tautomers of 5-carbonylsubstituted 2-(2-hydroxyphenyl)-1-hydroxyimidazoles.

The structure of 5-acetyl substituted 1-hydroxyimidazole **2** was determined by an X-ray diffraction study (Figure 1).The planar molecule involves two intramolecular hydrogen bonds O1-H…O2 and O3-H…N2 closing 6-membered cycles. The O…H and N…H distances correspond to a hydrogen bond of medium strength.

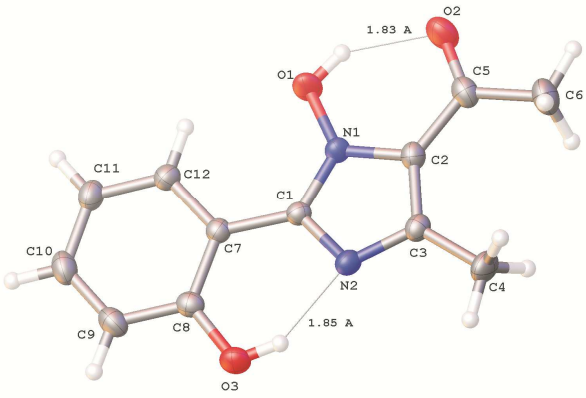


Figure 1. Compound **2**. Structure of formula units: thermal displacement ellipsoids are drawn at the level of 50% probability.

In the crystal the molecules are combined in centrosymmetrically related stacks with the “head-to-tail” mutual arrangement (Figure 2). The stacks are running along the *a*-axis. In a stack the molecules are linked by π-π stacking interactions. All other intermolecular contacts in crystal packing of **2** correspond to van der Waals interactions.

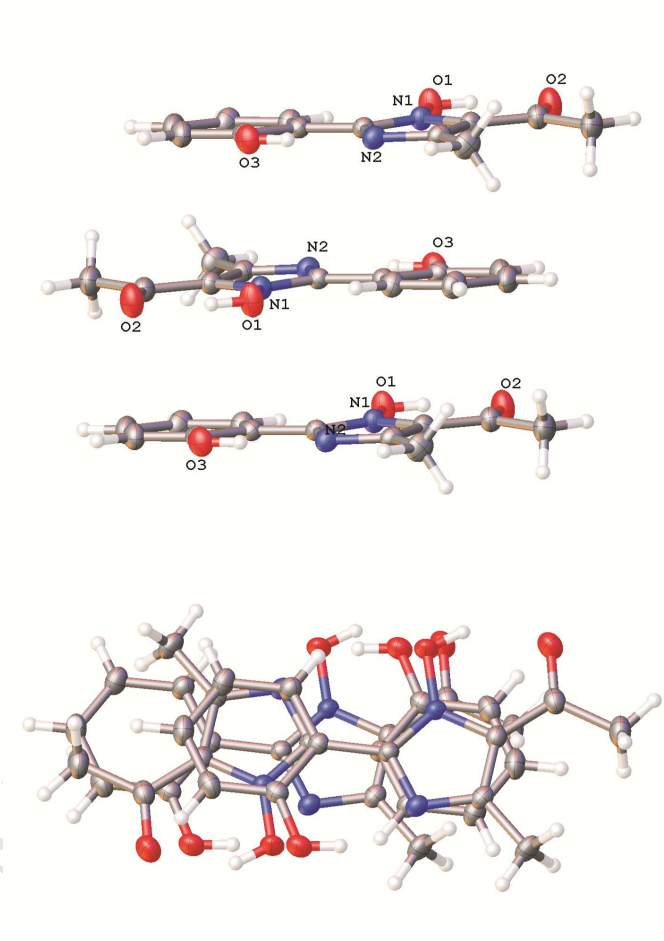


Figure 2. Fragments of crystal packing of compound **2** in different projections.

A confirmation of the presence or absence of intramolecular hydrogen bonding may also be found in the IR spectra of compounds **1-4**, **10-13**, **15-18**, **29** (Table 1).

Table 1. Frequencies (cm^{-1}) of characteristic absorption bands[a] in IR-spectra of 5-carbonylsubstituted 2-(2-hydroxyphenyl)imidazoles.

	11	**2**	**2×H_2O**	**16**	**29**	**12**	**3**	**17**	**13**	**4**	**18**
C=O	1670	1662	1672	1662	1648	1730	1709	1708	1678	1666	1662
N-O (N-oxide)	1304	-	1304	-	-	1300	-	-	1304	-	
OCH_3	-	-	-	2942	-	-	-	2939	-	-	2870
OH/NH (N-OH)		3023 (OH)	3116 (NH)		3089 (NH)		2981 (OH)			3132	

[a]For complete IR spectra see Supplementary Information.

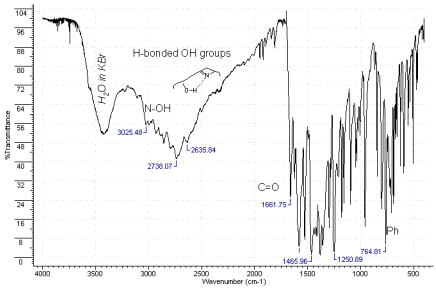


Figure 3. IR spectrum of 1-hydroxyimidazole **2**.

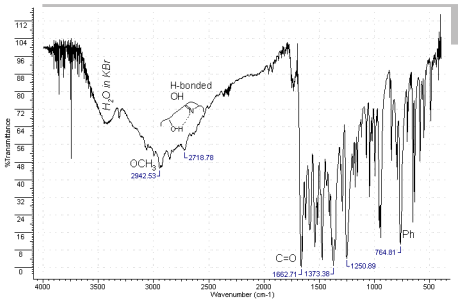


Figure 4. IR spectrum of 1-methoxyimidazole **16.**

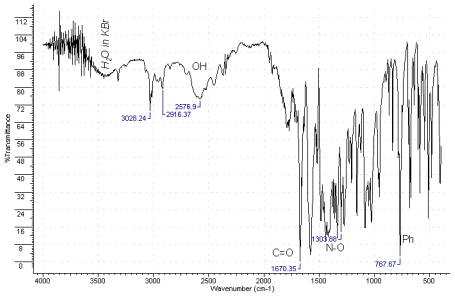


Figure 5. IR spectrum of imidazole N-oxide **11**.

The intramolecular hydrogen bond between the hydroxy group of the phenyl substituent and the “pyridine type” nitrogen atom of the imidazole ring may be clearly observed in the IR spectra of N-methoxy substituted compounds **15-18**. A broad band of a medium intensity at 2500-2800 cm^{-1} can be attributed to the H-bonded hydroxy group.

A band corresponding to this kind of intramolecular hydrogen bond (IMHB) is lacking in the spectra of imidazole N-oxides **10-13**. In these compounds the band for the OH-group vibrations (probably H-bonded with the oxygen atom of the N-oxide moiety) apparently has a lower intensity and is observed at 2500-2650 cm^{-1}.

As for N-hydroxyimidazoles **2**, **3** and **4**, a broad band of a medium intensity appears at 2500-2800 cm^{-1} (**2**), 2300-2500 cm^{-1} (**3**); 2550-2700 cm^{-1} (**4**). This band is similar to the one for the hydroxy group of the phenyl substituent in the spectra of N-methoxyimidazoles **15-18**.

The shapes of the absorption bands corresponding to the two fragments of the second hydrogen bond are also worth discussing. The H-bonded hydroxy group of imidazole appears as broad strong band with maximum absorption at 3023 cm^{-1} for 5-acetylimidazole **2**, at 2981 cm^{-1} for 5-ethoxycarbonylimidazole **3** and at 3132 cm^{-1} for benzimidazole **4**. A significant shift of the band towards higher energies may be explained by a stronger IMHB in compound **4** with the fixed carbonyl group.

It should be noted that in the IR-spectra of N-methoxyderivatives **16-18** and N-oxides **11-13** the C=O group stretching vibrations appear as strong narrow bands. Unlike that in the IR-spectra of N-hydroxyimidazoles **3** and **4** this band is evidently broadened. Broadening of the band may be explained by its involvement in hydrogen bonding. It is interesting that in the case of N-hydroxyimidazole **2** this band is not significantly broadened which may be attributed to a higher lability of this H-bond because of rotational flexibility of acetyl group.

Relative positions of the bands corresponding to the carbonyl groups in the series of compounds **2**, **11**, **16**; **3**, **12**, **17** and **4**, **13**, **18** are also noteworthy. First of all, according to the electronic effect of the electron-donating ethoxy group the bands for C=O in the series **3**, **12**, **17** are shifted ($\Delta \approx 40$-60 cm^{-1}) to higher frequencies (lower wavelengths) with respect to the position of bands for the series **2**, **11**, **16** and **4**, **13**, **18**. Secondly, in all these three series the position of the absorption band for the carbonyl group in 1-hydroxyimidazoles is closer to that in N-methoxyimidazoles and is shifted to lower frequencies with respect to imidazole N-oxides (Table 1).

Obviously, these relative positions of the carbonyl group bands allow us to estimate the total electronic effect of the differently N-substituted imidazole ring with respect to the electron-withdrawing substituent in position 5. Thus, a heterocycle containing the N-oxide moiety appears to be more electron-withdrawing than the N-hydroxy- or N-methoxy-substituted one.

According to the IR-spectroscopic data it may be supposed that in the solid state 1-hydroxyimidazoles **2**, **3** and **4** exist in the N-hydroxy tautomeric form stabilized by two intramolecular hydrogen bonds (IMHB).

In order to verify the assumption of H-bond lability in N-hydroxyimidazole **2** an infrared spectrum of its hydrate (see Experimental) has been recorded.

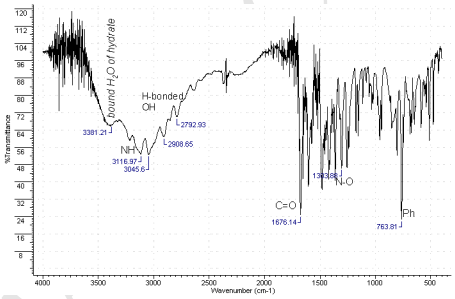


Figure 6. IR spectrum of hydrate of 1-hydroxyimidazole **2**.

In contrast to the band for H_2O adsorbed by KBr (a broad band of medium intensity at 3450 cm^{-1}), the band for bound water of hydrate **2** appears as a strong broad band at approx. 3380 cm^{-1}.

Interestingly, the band for the carbonyl group of hydrate **2** is 10 cm^{-1} shifted to higher frequencies (1672 cm^{-1}). At the same time the intensity of the absorption band for the “N-hydroxygroup” at 3000-3100 cm^{-1} increases, whereas the intensity of the absorption band for the OH-group of the phenyl substituent decreases. It seems that N-hydroxyimidazole **2** containing bound water exists in the N-oxide tautomeric form and the band at 3000-3100 cm^{-1} corresponds to the NH-group vibrations. By the way, the band for the NH-group in imidazole **29** is intense and it is situated at 3089 cm^{-1} like the band in hydrate **2** (See Supplementary).

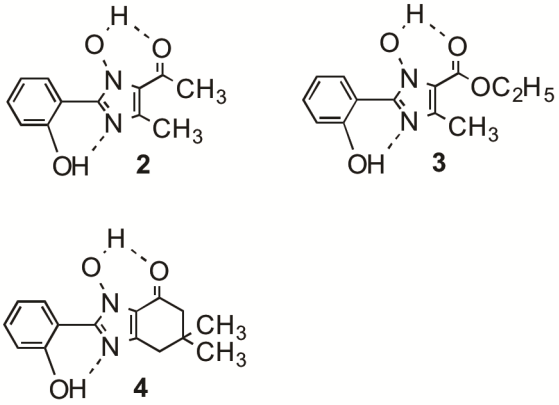
The fact that hydrate **2** exists as the N-oxide is also confirmed by the band at 1304 cm^{-1} which may be attributed to the N->O stretch. A similar band is also present in the IR-spectrum of N-oxide **11** but it is lacking in the spectra of N-methoxyimidazole **16** and anhydrous 1-hydroxyimidazole **2**.

It is worth mentioning that one should regard the assignment of the N->O stretch with great caution. Different authors note that depending on the N-oxide structure the band for the N->O group may appear between 1200 and 1320 cm^{-1}: 1205 cm^{-1},[33] 1215 cm^{-1},[34] 1223 cm^{-1},[18] 1249 cm^{-1}, 1310 cm^{-1}, 1320 cm^{-1}.[35]

We may only suppose that in the case under consideration this band appears at 1304 cm^{-1} for N-oxides **11** and **13**, and at 1300 cm^{-1} for N-oxide **12**. The unambiguous assignment is precluded by a large number of bands in this region.

Thus, according to the analysis of IR spectra it may be concluded that in the solid state anhydrous 5-carbonyl substituted

2-(2-hydroxyphenyl)-1-hydroxyimidazoles exist as the N-hydroxy tautomers, which corresponds to the X-ray diffraction data. The presence of the bound water in the molecule of 1-hydroxyimidazole (hydrate) leads to a transition into the N-oxide tautomer.



Scheme 8. Stabilization of prototropic tautomers of anhydrous 5-carbonylsubstituted 2-(2-hydroxyphenyl)-1-hydroxyimidazoles by IMHB.

2.3. Study of prototropic tautomerism in solution.

2.3.1. Solutions in deuterated chloroform.

Prototropic tautomerism of N-hydroxyimidazoles and their benzannulated analogues in solution may be efficiently studied by means of NMR spectroscopy.[16-18,23,32] It was possible to record the ^{1}H NMR spectra in DMSO-d_6 for all of the compounds. Unfortunately, not all of the imidazole derivatives under consideration are soluble in chloroform, so only the spectra of compounds **2**, **4**, **11**, **13**, **16** and **18** were recorded in $CDCl_3$.

First we consider NMR spectra of 5-acetyl substituted imidazole derivatives in $CDCl_3$ (Table 2).

Table 2.^{1}H NMR spectra in $CDCl_3$ (δ, ppm)[a].

	16	**2**	**11**	**18**	**4**	**13**
N-OH	-	13.93	-	-		-
OH	12.46	12.40	12.60	12.55		12.50
H-3'	7.07 (dd)	7.03 (dd)	7.10 (dd)	7.07 (d)	7.06 (d)	7.16 (d)
H-4'	7.35 (t)	7.33 (t)	7.43 (t)	7.36 (t)	7.36 (t)	7.46 (t)
H-5'	6.95 (t)	6.94 (t)	6.94 (t)	6.95 (t)	6.96 (t)	6.96 (t)
H-6'	8.17 (dd)	8.32 (br.s)	7.20 (dd)	8.20 (d)	8.27 (d)	7.20 (d)
OCH_3/ NCH_3	4.00	-	3.62	4.14	-	3.66
$COCH_3$	2.59	2.57	2.81	-	-	-
4-CH_3	2.56	2.57	2.60	-	-	-
CH_2	-	-	-	2.75	2.75	2.77
CH_2	-	-	-	2.47	2.48	2.46
$2CH_3$	-	-	-	1.16	1.19	1.21

[a]For coupling constants or widths at half height see Experimental.

In $CDCl_3$ two OH protons of compound **2** appear as broadened singlets at 13.93 ppm (N-OH; width at half height $\nu_{½} \approx$ 15 Hz) and at 12.40 ppm ($\nu_{½} \approx$ 62 Hz). At the same time the signal of water from the solvent is observed at 1.64 ppm ($\nu_{½} \approx$ 67 Hz).

Apparently, the reason of OH signal broadening may be connected with the processes of an intermolecular hydrogen exchange. This exchange is evident from the EXSY spectrum of **2**, which reveals cross-peaks of these protons not only with water ([13.96, 1.66]; [12.43, 1.66]) but also with each other ([13.96, 12.43]) (see Supplementary).

It should be noted that OH proton of the phenyl substituent in imidazole N-oxide **11** is observed as a rather narrow signal at 12.60 ppm ($\nu_{½} \approx$ 15 Hz). For 1-methoxyimidazole **16** the OH signal is very broadened ($\nu_{½} \approx$ 360 Hz) and is observed at 12.45 ppm.

It should be also noted that the position of the signal of the CH_3 protons of the acetyl group for N-hydroxyimidazole **2** (2.57 ppm) is closer to the position of the signal of methoxyderivative **16** (2.59 ppm) than to the one of N-oxide **11** (2.81 ppm). It is of interest that in the ^{1}H NMR spectrum one can observe the overlap of signals for two methyl groups (2.574 ppm and 2.571 ppm). At the same time the ^{13}C NMR spectrum reveals two signals (28.1 ppm and 16.8 ppm) that correspond to cross-peaks in 2D HMQC spectrum: [2.57, 28.1] for $COCH_3$ and [2.57, 16.8] for CH_3 in position 4, respectively (see Supplementary).

A comparison of the ^{1}H NMR spectra of the model compounds (i.e., imidazole N-oxide **11** and 1-methoxyimidazole **16**) reveals a difference in the chemical shifts of protons in position 6 of the hydroxyphenyl substituent (H6'). For imidazole N-oxide **11** this signal appears at 7.20 ppm. Being a part of ABC spin system, it is observed as a doublet of doublets with the *ortho*- and *meta*- coupling constants (^3J = 7.9 Hz, ^4J = 1.7 Hz). In the case of N-methoxyimidazole **16** the H6' signal is shifted to lower field (8.17 ppm), being a doublet of doublets, too (^3J = 8.1 Hz, ^4J = 1.6 Hz). This kind of deshielding occurs due to the effect of the neighbouring anisotropic imidazole moiety.

It may be supposed that such deshielding is a consequence of the IMHB formation between the 2-hydroxy group of the phenyl substituent and the "pyridine-type" nitrogen atom of imidazole, which results in a stabilization of a planar structure of the molecule (see X-ray data). In model imidazole N-oxide **11** such type of bonding is impossible. IMHB between the phenyl OH-group and the N-oxide moiety oxygen atom leads to the formation of the non-planar seven-numbered cycle and the corresponding shift of the H6' proton to a higher field. Similarly in the spectra of compounds **21** (hydroxyimidazole) and **25** (methoxyimidazole) bearing bulky benzyloxy substituents (that prevent the planarity of the structures) the signals of the H6' protons are observed at 7.76 ppm (**21**) and 7.27-7.47 ppm (**25**).

In the ^{1}H NMR spectra of 2-(2-hydroxyphenyl)substituted 1-hydroxyimidazole **2** the H6' proton is observed as a broadened signal at 8.32 ppm ($\nu_{½} \approx$ 19 Hz).

The ^{1}H NMR spectra at different temperatures (293 K, 273 K, 263 K, 253 K, 243 K) were also recorded (Table 3).

Table 3. Chemical shifts of characteristic protons in ^{1}H NMR spectra of compound **2** in $CDCl_3$ at different temperatures (δ, ppm)[a].

	293 K	273 K	263 K	253 K	243 K	Δδ
N-OH	13.93 (br)	13.98 (br s; $\nu_{½}\approx$40Hz)	14.01 (s; $\nu_{½}\approx$16Hz)	14.04 (s)	14.06 (s)	0.13
OH	12.41 (br)	12.54 (br s; $\nu_{½}\approx$56Hz)	12.56 (br s; $\nu_{½}\approx$28Hz)	12.64 (s)	12.70 (s)	0.30
H-6'	8.32 (br. s; $\nu_{½}\approx$19Hz)	8.34 (br. s; $\nu_{½}\approx$30Hz)	8.36 (br. s; $\nu_{½}\approx$20Hz)	8.37 (d; J = 8.1Hz)	8.38 (d; J = 8.1Hz)	0.06

[a]For complete spectral data see Supplementary Information.

A decrease in temperature leads to a change in the H6' proton signal. At 253 K and 243 K it is observed as a doublet with the coupling constant 8.1 Hz.

At lower temperatures the rotation processes including both the rotation around phenyl-imidazole bond and the rotation of acetyl group are slowed down. As a result the most energetically favorable structure is achieved. Most likely it is an N-hydroxy tautomeric form stabilized by the two hydrogen bonds (Scheme 8) fixing the planarity of the molecule.

A possibility of the intermolecular proton exchange between the two OH-groups and the water molecules required an investigation of an influence of a concentration on inter- and intramolecular interactions in 1-hydroxyimidazole **2** solution to be carried out. The existence of intermolecular exchange is confirmed by the presence of three cross-peaks in the NOESY (EXSY) spectrum ([13.96, 1.66], [12.43, 1.66], [13.96, 12.43]) (see Supplementary). The intensity of the cross-peak corresponding to the N-OH – H_2O interaction is higher than the intensity of that corresponding to the C_6H_4-OH – H_2O interaction, which evidences a higher rate of the intermolecular exchange in the former case. Apparently, it is explained by a higher acidity of the N-OH proton. For reference, pKa of phenol is 10.0, whereas pKa of 1-hydroxy-2,4,5-trimethylimidazole is 8.39 (in water).[15] On dilution the chemical shifts of protons remain practically unchanged, but the character of the H6' proton signal and both OH-groups is altered (Table 4).

Table 4. Chemical shifts of characteristic protons in ^{1}H NMR spectra of solutions with differing concentrations of compound **2** in $CDCl_3$(δ, ppm)[a].

	Starting solution 0.067 mol/L	Dilution 1 0.034 mol/L	Dilution 2 0.017 mol/L	Dilution 3 0.007 mol/L
N-OH	13.93 (br; $\nu_{½}$≈45Hz)	13.94 (br. s; $\nu_{½}$≈19Hz)	13.95 (s)	13. 95 (s)
OH	12.41 (br; $\nu_{½}$≈60Hz)	12.40 (br. s; $\nu_{½}$≈35Hz)	12.40 (br. s; $\nu_{½}$≈20Hz)	12.40 (br. s; $\nu_{½}$≈18Hz)
H-6'	8.32 (br. s; $\nu_{½}$≈20Hz)	8.34 (br. d; *J*=7.9Hz)	8.35 (br. d; *J*=8.0Hz)	8.35 (d; *J*=8.0Hz)
Signal of H_2O	1.66 $\nu_{½}$≈60Hz	1.56 $\nu_{½}$≈18Hz	1.56 $\nu_{½}$≈9Hz	1.56 $\nu_{½}$≈3Hz

[a]For complete spectral data see Supplementary Information.

The H6' proton in diluted solution is observed as a doublet (^3J = 8.0 Hz). The OH signals are narrowed. The chemical shift for water is shifted from 1.66 ppm in the starting solution to 1.56 ppm in a diluted one (which corresponds to the chemical shift for water in pure chloroform[36]), its $\nu_{½}$ decreasing from 60 Hz to 3 Hz. Narrowing of the signals under consideration is an evidence of decrease of the intermolecular proton exchange between the hydroxyl groups and water molecules due to the decrease of the concentration.

Thus in a diluted solution the influence of the neighbouring molecules (including water) on the violation of the molecule planarity reduces. As a result, the acetyl moiety is not withdrawn from the phenyl-imidazole plane. It leads to narrowing of the H-6' and N-OH proton signals due to the fact that hindrances for the formation of a planar six-membered cycle are eliminated.

The lower effect of dilution on the phenyl-OH proton signal pattern probably evidences that the IMHB C_6H_4-OH – N is stronger and less dependent on external factors than IMHB N-OH – O=C. This corresponds to the assumptions made on the basis of the IR-spectra analysis.

As a whole, the ^{1}H NMR spectra of 1-hydroxyimidazole **4** with fixed carbonyl group in position 5 of imidazole and its model compounds **13** and **18** are similar to the ones considered above.

The "reference" H6' proton signal in $CDCl_3$ is observed at 8.27 ppm (^3J = 8.2 Hz) for compound **4**. The similar signal for model N-oxide **13** is observed at 7.20 ppm (^3J = 7.9 Hz, ^4J = 1.4 Hz). For N-methoxyimidazole **18** it is observed at 8.20 ppm (^3J = 8.1 Hz). The observed deshielding of the H6' protons for compounds **4** and **18** is due to a fixation of the benzimidazole moiety in the plane of the hydroxyphenyl substituent by IMHB between the OH-group of the substituent in position 2 and "pyridine-type" nitrogen atom of the imidazole ring.

2.3.2. Solutions in DMSO-d_6.

A solubility of 1-hydroxyimidazoles **1-4** and their model N-oxides **10-13** and N-methoxyimidazoles **15-18** in DMSO-d_6 allowed to record the NMR spectra for all the compounds under consideration (Table 5).

Table 5. Chemical shifts of characteristic protons in ^{1}H NMR spectra in DMSO-d_6(δ, ppm)[a].

	15	***1***	***10***	***16***	***2***	***11***	***17***	***3***	***12***	***18***	***4***	***13***
N-OH	-	14.66 (br)	-	-	13.79 (br)	-	-		-	-		-
OH	12.95 (br. s)	12.54 (br)	13.78 (br. s)	12.16 (s)	13.59 (br)	12.62 (br. s)	12.18 (s)	12.89 (br)	13.04 (br. s)	12.14 (s)	12.75 (br)	12.86 (br)
H-6'	8.00 (dd)	7.47 (br. d)	7.45 (d)	8.02 (d)	7.55 (br.s)	7.42-7.52 (m)	8.03 (d)	8.00 (br.s)	7.42-7.53 (m)	8.04 (dd)	8.11 (br.s)	7.56 (d)

[a]For complete spectral data see Experimental.

The electronic effect of a substituent in heterocycle position 5 on the proton shielding is typical for the ^{1}H NMR spectra of N-methoxysubstituted **15-18** in DMSO-d_6. One can observe a downfield shift when passing from the electron-donating substituent (methyl group) to the electron-withdrawing ones.

Thus, maximum differences in the spectra are observed for compounds **15** and **18**. The low field shift of the H6' proton signal for all methoxy derivatives should be particularly mentioned together with the differences in signals for the protons of the phenyl moiety (H4') and the OH-group. As a comparison, in the ^{1}H NMR spectra of model N-methylimidazole oxides **10-13** (where a planarity of imidazole and phenyl fragments is violated) the phenyl protons are observed in a rather narrow range in accordance with the 2-hydroxygroup effect. Therefore, there is an IMHB between the OH-proton and the "pyridine-type" nitrogen atom in solutions of N-methoxy derivatives **15-18** in DMSO-d_6. This IMHB stabilizes the planar structure of their molecules.

As a result, the H6' proton is deshielded due to anisotropic and –M effects of the heterocycle. The H4' proton is also sensitive to the effect of the imidazole ring substituent variability. The differences in chemical shifts of the OH-group proton for compound **15** (12.95 ppm) and 5-carbonylsubstituted derivatives **16-18** (12.14 – 12.18 ppm) should also be mentioned. This shift to lower field indicates an increase of IMHB strength in compound **15**. It seems that the strength of this IMHB depends

on the N(3) atom basicity, that is the largest in compound **15** due to the position 5 methyl substituent electron-donating properties. It is noteworthy that the signal of the OH-proton is slightly broadened especially in the case of compounds **15** and **16** ($\nu_{½} \approx$ 9-20 Hz). It may be explained by intermolecular exchange with water which is confirmed by the presence of corresponding cross-peak in the NOESY (EXSY) spectrum of compound **16** (see Supplementary).

In the molecules of imidazole N-oxides **10**-**13** the phenyl and imidazole moieties do not lie in the same plane. As a result, the H6' proton deshielding is not observed. The shift of the OH-proton to a lower field also attracts attention, especially for compound **10**. This shift cannot be explained by only a specific interaction with a bipolar solvent. From our point of view, it is possible that the structures of imidazole N-oxides **10**-**13** are stabilized by IMHB between the OH-group and the N-oxide moiety oxygen atom. This IMHB results in the formation of non-planar seven-membered cycle. The maximum shift to lower field of the OH proton of compound **10** is explained by the maximum electron-donating effect of the N-oxide oxygen atom in 4,5-dimethylsubstituted derivative **10**. It should be mentioned that the signal of the OH-group proton is broadened ($\nu_{½} \approx$ 8-90 Hz) and that in the NOESY (EXSY) spectrum of compound **11** one can observe a cross-peak corresponding to the intermolecular exchange of this proton with water (see Supplementary).

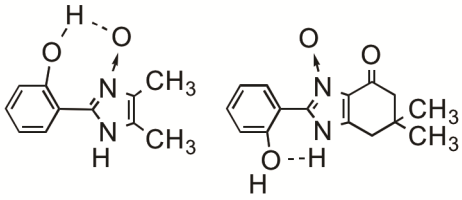
The analysis of the ^{1}H NMR spectra of 1-hydroxyimidazoles **1**-**4** in DMSO-d_6 makes it possible to separate these compounds into two groups. The first group contains compounds **3** and **4** with low-field signals for the H6' protons, *i.e.* a broadened ($\nu_{½} \approx$ 30 Hz) signal at 8.00 ppm for compound **3** and a broadened ($\nu_{½} \approx$ 20 Hz) signal at 8.11 ppm for N-hydroxyimidazole **4**. The second group consists of compounds **1** and **2** with the H6' proton signal in higher field (7.47 ppm for **1** and 7.55 ppm for **2**) evidencing a non-planar structure.

Apparently, for compounds **3** and **4** the shift of the H6' proton signals to a lower field indicates that the 2-hydroxyphenyl and imidazole moieties of the molecules are near coplanar. Whereas, in the low-field area (12.00 – 15.00 ppm) only one signal at 12.75 ppm ($\nu_{½} \approx$ 95 Hz) is observed for compound **4**, with the integrated intensity corresponding to two protons. This signal is shifted to a lower field as compared with that of the OH-proton of N-methoxyimidazole **18** (12.14 ppm) where the IMHB with the "pyridine-type" nitrogen atom exists. This may be interpreted as an evidence of a certain difference in the IMHB formation in planar molecules of **4** and **18**.

As it was already mentioned, the IMHB occurs between the OH group and the "pyridine-type" nitrogen atom in compound **18**. However, this kind of the IMHB does not explain the downfield shift of the "acidic" proton in compound **4**. In order to explain this we assumed that the NH-imidazole N-oxide is formed in this case. The corresponding proton should display a rather high acidity under the influence of the "pyridine-type" nitrogen atom and the cyclic carbonyl substituent. In this case one may expect the formation of IMHB between the NH group and the oxygen atom in position 2 of the phenyl substituent (the "closed" form of N-oxide).

In the ^{1}H NMR spectrum of non-planar compound **1** the signals of the OH-protons are observed at 12.54 ppm and 14.66 ppm. The second signal is shifted to a lower field compared to that for the OH-proton of N-oxide **10**. The corresponding hydrogen atom can interact with the oxygen atom of the N-oxide moiety via IMHB in the non-planar structure.

For the molecule of compound **1** it is possible if hydroxy-oxide tautomerism is taken into consideration. Then in the oxide (the "open" form of N-oxide) the signal at 12.54 ppm can be attributed to the NH-proton (in ^{1}H NMR spectrum of 2-(2-hydroxyphenyl)-4,5-dimethylimidazole **28** the NH-proton is observed at 12.50 ppm while the OH proton of 2-hydroxyphenyl substituent is observed at 12.88 ppm). In the series of 1-hydroxyimidazoles a replacement of the CH_3 group by the $COCH_3$ one in position 5 along with the remaining non-planarity of the molecules results in the converging of signals of protons at the heteroatoms (12.54 ppm and 14.66 ppm for compound **1**; 13.59 ppm and 13.79 ppm for compound **2**). This regularity is a result of the varying electronic effect of the methyl and acetyl groups on the N-oxide oxygen atom and the "pyrrole-type" nitrogen atom of the "open" form of NH-imidazole N-oxide. For the planar "closed" forms of N-oxides (compounds **3** and **4**) the signals of "mobile" protons are observed as one signal (12.89 ppm for **3** and 12.75 ppm for **4**, respectively).



1 *"open" form* **4** *"closed" form*

Scheme 9. Two forms of N-oxide tautomer in DMSO solutions.

The NMR spectra of 5-acetylsubstituted 1-hydroxyimidazole **2** recorded in mixture of solvents ($CDCl_3$-DMSO-d_6 1:1) are similar to those in DMSO-d_6 and testify the "open" NH-imidazole N-oxide tautomeric form (See Supplementary).

2.3.3. ^{13}C NMR spectra.

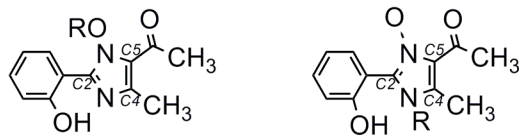
The preliminary conclusion based on the analysis of ^{1}H NMR spectra is confirmed by ^{13}C NMR data (Table 7).

Table 6. ^{13}C NMR of 5-acetylsubstituted imidazole derivatives (δ, ppm).

	in $CDCl_3$			in $CDCl_3$ – DMSO-d_6 (1:1)	in DMSO-d_6		
	16	***2***	***11***	***2***	***16***	***2***	***11***
C-2	141.7	139.4	137.5	135.7	141.3	136.0	136.9
C-4	141.6	142.2	134.3	134.3	141.2	134.7	135.7
C-5	123.6	120.6	127.3	127.2	124.0	127.2	126.5
$\underline{C}OCH_3$	186.9	192.0	190.9	190.0	187.2	190.0	190.3
$CO\underline{C}H_3$	30.0	28.1	31.0	30.9	30.3	30.6	31.0
4-CH_3	16.7	16.8	10.6	12.7	16.8	12.7	10.7
NCH_3/ OCH_3	66.5	--	32.9	--	67.4	--	33.5
C-1'	110.7	110.8	111.2	112.7	111.6	112.5	112.0
C-2'	158.8	158.4	159.8	158.7	158.1	158.7	159.5
C-3'	118.0	117.6	121.3	118.9	117.7	119.2	120.7
C-4'	132.0	131.9	132.8	132.8	132.4	132.9	133.0
C-5'	119.4	119.2	119.0	120.7	119.9	120.0	119.3
C-6'	125.9	127.4	129.0	128.6	127.2	128.7	130.6

The imidazole ring C-atoms are most sensitive to the definite tautomeric form existence. Changes in the nature of the heterocycle nitrogen atoms cause a shift of the signals of these atoms in positions 4 and 5 of the imidazole ring. For the sake of convenience we find it possible to numerate the C-atoms in the

cycle of imidazole N-oxides in the same way as in N-methoxy(N-hydroxy)derivatives:



R = H; CH_3

Scheme 10. Numeration of carbon atoms in imidazole ring.

It is noteworthy that the change of a solvent has practically no impact on the position of ^{13}C nuclei signals of heterocycle for the model structures.

In the ^{13}C NMR spectrum of 1-hydroxyimidazole **2** in $CDCl_3$ the signals for ^{13}C nuclei of imidazole ring atoms are observed at 139.4 ppm (C-2), 142.2 ppm (C-4) and 120.6 ppm (C-5). These values are closer to the ones in the spectrum of N-methoxyimidazole **16**, so we may conclude that N-hydroxyimidazole **2** exists in the N-hydroxy tautomeric form in chloroform.

On the contrary, in DMSO-d_6 the chemical shifts of ^{13}C nuclei attributed to imidazole ring (135.7 ppm (C-2), 134.7 ppm (C-4), 127.2 ppm (C-5)) are close to those of imidazole N-oxide **11**. This result evidences the existence of N-hydroxyimidazole **2** as the N-oxide tautomer in this solvent.

Signals with practically the same chemical shifts are observed in the ^{13}C NMR spectrum of 1-hydroxyimidazole **2** recorded in a mixture of solvents ($CDCl_3$ – DMSO-d_6 1:1). So, under these conditions compound **2** also exists as the N-oxide tautomer.

The same regularity is observed for the signals of the ^{13}C nuclei of substituents in positions 4 and 5 of the imidazole ring. This is especially clear in the case of the 4-CH_3 group directly bonded to the imidazole ring. In the ^{13}C NMR spectrum of N-hydroxyimidazole **2** in $CDCl_3$ this signal (16.8 ppm) corresponds to the one in the spectrum of N-methoxyimidazole **16** (16.7 ppm) rather than the one of imidazole N-oxide **11** (10.6 ppm). As for the spectra recorded in DMSO-d_6, the chemical shift of ^{13}C nuclei of 4-CH_3 group of N-hydroxyimidazole **2** (12.7 ppm) is closer to that in imidazole N-oxide **11** (10.7 ppm) and differs from the chemical shift of ^{13}C nuclei of 4-CH_3 group of N-methoxyimidazole **16** (16.8 ppm).

3. Conclusions

In the solid state 5-carbonylsubstituted 1-hydroxyimidazoles **2-4** exist in the N-hydroxy tautomeric form stabilized by two hydrogen bonds. The presence of hydrate water in the sample of 5-acetylsubstituted 1-hydroxyimidazole **2** leads to the N-oxide tautomeric form.

In $CDCl_3$ 1-hydroxyimidazoles **2** and **4** also exist as the N-hydroxy tautomers stabilized by two hydrogen bonds. The presence of water affects the hydrogen bonding but has no impact on the transition from one tautomeric form into another.

In polar aprotic DMSO-d_6 (strong hydrogen bond acceptor) 1-hydroxyimidazoles **1-4** exist as the N-oxide tautomers of the different nature. It is supposed that 5-methyl- and 5-acetyl substituted N-hydroxyimidazoles **1** and **2** exist as the N-oxide tautomers stabilized by IMHB between the hydroxy group of the phenyl substituent and the oxygen atom of the N-oxide moiety. This kind of hydrogen bond withdraws the phenyl substituent from the phenyl-imidazole plane. It is also supposed that due to the acceptor properties of DMSO N-hydroxyimidazoles **3** and **4** containing bulky ethoxycarbonyl substituent (**3**) or fixed carbonyl group (**4**) in position 5 of imidazole ring transfer to the N-oxide tautomeric form either. The planar structure of this form is stabilized by IMHB between the hydrogen atom at the "pyrrole-type" nitrogen atom and the oxygen atom of the hydroxy group of the phenyl substituent.

4. Experimental

4.1. General

Chemicals were purchased from commercial sources and were used without further purification. The NMR experiments were carried out using a Bruker Avance™ 300 spectrometer operating at 300.13 MHz for ^1H and 75.47 MHz for ^{13}C or using a Bruker Avance™ 600 spectrometer operating at 600.22 MHz for ^1H and 150.93 MHz for ^{13}C. The spectrometers were equipped with unverse gradient probe-head. Chemical shifts are given relative to the residual proton signal of solvent (7.27 ppm for $CDCl_3$ or 2.50 ppm for DMSO-d_6) for ^1H and relative to $CDCl_3$ (77.0 ppm) or to DMSO-d_6 (35.9 ppm) for ^{13}C. All 1D ^1H and ^{13}C experiments as well as 2D experiments (COSY, HSQC, HMBC, EXSY) were performed using standard pulse sequences from the Bruker library. The assignment of the signals in ^1H and ^{13}C NMR spectra has been performed by use of 2D COSY, HMQC and HMBC techniques. The mixing time in EXSY experiment is equal to 0.5 s. Mass-spectra were recorded with a LKB-2000 mass spectrometer. Infrared spectra of solids were recorded with Shimadzu IRAffinity-1 FTIR spectrophotometer in a KBr matrix.

4.2. Detailed experimental procedure and characterization data

*4.2.1. 2-(2-Hydroxyphenyl)-4,5-dimethyl-1H-imidazol-1-ol (**1**).*

A mixture of aldehyde **5** (3.00 g, 0.0245 mol), oxime **6** (2.50 g, 0.0245 mol) and ammonium acetate (2.30 g, 0.0300 mol) in glacial acetic acid (30 mL) was stirred at 40-45°C for 4 h, cooled to room temperature and left to stand overnight. The solvent was removed under reduced pressure. The residue was treated with ether. The obtained solid was heated at reflux in acetonitrile and filtered off warm yielding 4.00 g (80%) of product **1** as white solid. M.p. 251-253 °C.

^1H NMR (300 MHz, DMSO-d_6): δ= 14.66 (br. s, 1H, OH), 12.54 (br. s, 1H, OH), 7.47 (br. d, J = 8.0 Hz, 1H, H6'), 7.30 (t, 1H, H4'), 6.80-6.90 (m, 2H, H3' and H5'), 2.21 (s, 3H, 5-CH_3), 2.11 (s, 3H, 4-CH_3) ppm.

^{13}C NMR (75.47 Hz, DMSO-d_6): δ= 158.2 (C2'), 134.0 (C2), 131.4 (C6'), 127.4 (C4'), 123.9 (C4), 122.2 (C5), 119.4 (C5'), 118.1 (C3'), 112.9 (C1'), 9.6 (4-CH_3), 6.9 (5-CH_3) ppm.

MS(EI): m/z=204$[M]^+$. Anal. $C_{11}H_{12}N_2O_2$ (204): calcd. C 64.71, H 5.88, N 13.73; found C 64.37, H 5.93, N 13.55.

*4.2.2. 1-(1-Hydroxy-2-(2-hydroxyphenyl)-4-methyl-1H-imidazol-5-yl)ethanone (**2**)*

A mixture of aldehyde **5** (2.50 g, 0.0205 mol), oxime **7** (3.00 g, 0.0233 mol) and ammonium acetate (2.00 g, 0.0260 mol) in glacial acetic acid (30 mL) was stirred at 45-55°C for 60 h. Reaction mixture was poured into water (100 mL), triturated, and the precipitate was filtered off and recrystallized from water yielding 1.91 g (41%) of product **2** as a beige solid; m.p. 172-173 °C.

^1H NMR (600 MHz, $CDCl_3$, 293 K, [0.067 mol/l]): δ= 13.93 (br. s, $\nu_{½}$ = 47 Hz, 1H, N-OH), 12.40 (br. s, $\nu_{½}$ = 62 Hz, 1H, OH),

8.32 (br. s, $\nu_{½}$ = 19 Hz, 1H, H6'), 7.33 (t, 1H, H4'), 7.03 (dd, *J* = 8.3, 1.2 Hz, 1H, H3'), 6.94 (t, 1H, H5'), 2.57 (s, 6H, $2CH_3$) ppm.

^{13}C NMR (150.94 MHz, $CDCl_3$): δ= 192.0 (C=O), 158.4 (C-2'), 142.2 (C-4), 139.4 (C-2), 131.8 (C-4'), 127.4 (C-6'), 120.6 (C-5), 119.2 (C-5'), 117.6 (C-3'), 110.8 (C-1'), 28.1 ($CO\underline{C}H_3$), 16.8 (4-CH_3) ppm.

^{1}H NMR (600 MHz, DMSO-d_6): δ= 13.79 (br. s, 1H, N-OH), 13.59 (br. s, 1H, OH), 7.55 (br. s, $\nu_{½}$ = 68 Hz, 1H, H6'), 7.41 (t, 1H, H4'), 6.96 (t, 1H, H5'), 6.93 (d, *J* = 8.3 Hz, 1H, H3'), 2.66 (s, 3H, $COCH_3$), 2.48 (s, 3H, CH_3) ppm.

^{13}C NMR (150.94 MHz, DMSO-d_6): δ= 190.0 (C=O), 158.7 (C-2'), 136.0 (C-2), 134.7 (C-4), 132.9 (C-4'), 128.7 (C-6'), 127.2 (C-5), 120.0 (C-5'), 119.2 (C-3'), 112.5 (C-1'), 30.6 ($CO\underline{C}H_3$), 12.7 (4-CH_3) ppm.

MS(EI): *m/z*=232[M]$^+$. Anal. $C_{12}H_{12}N_2O_3\times0.25H_2O$ (236.5): calcd. C 60.89, H 5.28, N 11.84; found C 61.15, H 5.22, N 11.88.

*4.2.3. Ethyl 1-hydroxy-2-(2-hydroxyphenyl)-4-methyl-1H-imidazole-5-carboxylate (**3**).*

A mixture of aldehyde **5** (3.10 g, 0.0254 mol), oxime **8** (4.00 g, 0.0252 mol) and ammonium acetate (2.00 g, 0.0260 mol) in glacial acetic acid (30 mL) was stirred at room temperature for 5 h and left to stand for 3 d. The reaction mixture was poured into water (100 mL), the precipitate was filtered off and washed with ether. The obtained solid was heated at reflux in acetonitrile, cooled to room temperature, and filtered off, yielding 1.3 g (20%) of chromatographically pure product **3** as white solid. M.p. 236-237 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ= 12.89 (br. s, 2H, 2OH), 8.00 (br. s, $\nu_{½}$ = 32 Hz, 1H, H-6'), 7.35 (t, 1H, H4'), 6.89-6.97 (m, 2H, H3' and H5'), 4.21 (q, 2H, $OC\underline{H}_2CH_3$), 2.45 (s, 3H, 4-CH_3), 1.32 (t, 3H, $OCH_2C\underline{H}_3$) ppm.

^{13}C NMR (75.47 Hz, DMSO-d_6): δ= 158.5 (C=O), 157.9 (C2'), 137.5 (C2), 135.5 (C4), 131.7 (C4'), 127.3 (C6'), 118.6 (C5'), 118.1 (C3'), 117.9 (C5), 111.8 (C1'), 60.3 ($O\underline{C}H_2CH_3$), 14.2 ($OCH_2\underline{C}H_3$), 11.5 (4-CH_3) ppm.

MS(EI): *m/z*=262[M]$^+$. Anal. $C_{13}H_{14}N_2O_4$ (262): calcd. C 59.54, H 5.34, N 10.69; found C 59.44, H 5.26, N 10.65.

*4.2.4. 1-Hydroxy-2-(2-hydroxyphenyl)-5,5-dimethyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-7(4H)-one (**4**).*

A mixture of aldehyde **5** (2.30 g, 0.0184 mol), oxime **9** (3.10 g, 0.0184 mol) and ammonium acetate (1.50 g, 0.0190 mol) in glacial acetic acid (30 mL) was stirred at 40-45°C for 4 h, cooled to room temperature and left to stand overnight. The precipitate was filtered off and then heated at reflux in acetonitrile (40 mL) and filtered off warm, yielding 2.50 g (50%) of chromatographically pure product **4** as a yellow solid. M.p. 262-264 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.27 (d, *J* = 8.2 Hz, 1H, H6'), 7.36 (t, 1H, H4'), 7.06 (d, *J* = 8.1 Hz, 1H, H3'), 6.96 (t, 1H, H5'), 2.75 (s, 2H, CH_2), 2.48 (s, 2H, CH_2), 1.16 (s, 6H, $2CH_3$) ppm.

^{1}H NMR (300 MHz, DMSO-d_6): δ= 12.75 (br. s, 2H, 2OH), 8.11 (br. s, $\nu_{½}$ = 24 Hz; 1H, H6'), 7.36 (t, 1H, H4'), 6.90-7.00 (m, 2H, H3' and H5'), 2.74 (s, 2H, CH_2), 2.41 (s, 2H, CH_2), 1.08 (s, 6H, $2CH_3$) ppm.

^{13}C NMR (75.47 Hz, DMSO-d_6): δ= 185.6 (C=O), 157.9 (C2'), 145.6 (C2), 142.3 (C4), 131.9 (C5), 127.2 (C4'), 122.2 (C6'), 118.8 (C5'), 117.8 (C3'), 111.6 (C1'), 52.4 (CH_2), 37.1 ($\underline{C}(CH_3)_2$), 35.3 (CH_2), 27.8 ($2CH_3$) ppm.

MS(EI): *m/z*=272[M]$^+$. Anal. $C_{15}H_{16}N_2O_3$ (272): calcd. C 66.18, H 5.88, N 10.29; found C 66.09, H 5.94, N 10.23.

*4.2.5. 2-(2-Hydroxyphenyl)-1,4,5-trimethyl-1H-imidazole 3-oxide (**10**).*

40% Aqueous solution of methyl amine (2.50 g), containing 1.0 g (0.033 mol) of methyl amine was added dropwise to a mixture of aldehyde **5** (3.60 g, 0.0295 mol) and oxime **6** (3.6 g, 0.0295 mol) in ethanol (15 mL). The resulting mixture was stirred at room temperature for 1 h and left to stand overnight. The precipitate was filtered off, washed with ethanol and recrystallized from toluene, yielding 3.80 g (60%) of product **10** as a light-yellow solid. M.p. 218-220 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ= 13.78 (br.s, $\nu_{½}$ = 50 Hz, 1H, OH), 7.45 (d, *J* = 7.5 Hz, 1H, H6'), 7.39 (t, 1H, H4'), 6.90-7.00 (m, 2H, H3' and H5'), 3.61 (s, 3H, NCH_3), 2.27 (s, 3H, 5-CH_3), 2.16 (s, 3H, 4-CH_3) ppm.

^{13}C NMR (75.47 Hz, DMSO-d_6): δ= 159.3 (C2'), 134.8 (C2), 131.5 (C6'), 129.2 (C4'), 124.3 (C4), 123.1 (C5), 120.1 (C5'), 118.0 (C3'), 112.4 (C1'), 32.6 (NCH_3), 8.8 (4-CH_3), 6.9 (5-CH_3) ppm.

MS(EI): *m/z*=218[M]$^+$. Anal. $C_{12}H_{14}N_2O_2$ (218): calcd. C 66.06, H 6.42, N 12.84; found C 66.15, H 6.53, N 12.82.

*4.2.6. 4-Acetyl-2-(2-hydroxyphenyl)-1,5-dimethyl-1H-imidazole 3-oxide (**11**).*

Similarly to **10** from aldehyde **5** (2.80 g, 0.0230 mol), oxime **7** (3.00 g, 0.0230 mol) and 40% aq. CH_3NH_2 (2.00 g) product **11** (2.70 g; 48%) was obtained. Yellowish solid, m.p. 216-218 °C (methanol).

^{1}H NMR (600 MHz, $CDCl_3$, 293 K): δ= 12.60 (br. s, $\nu_{½}$ = 14.5 Hz, 1H, OH), 7.43 (t, 1H, H4'), 7.20 (dd, *J* = 7.9, 1.7 Hz, 1H, H6'), 7.10 (dd, *J* = 8.4 Hz, 1.1 Hz, 1H, H3'), 6.94 (t, 1H, H5'), 3.62 (s, 3H, NCH_3), 2.81 (s, 3H, $COCH_3$), 2.60 (s, 3H, 4-CH_3) ppm.

^{13}C NMR (150.94 MHz, $CDCl_3$): δ= 190.9 (C=O), 159.8 (C-2'), 137.5 (C-2), 134.3 (C-4), 132.8 (C-4'), 129.0 (C-6'), 127.3 (C-5), 121.3 (C-3'), 119.0 (C-5'), 111.2 (C-1'), 32.9 (NCH_3), 31.0 ($CO\underline{C}H_3$), 10.6 (4-CH_3) ppm.

^{1}H NMR (600 MHz, DMSO-d_6, 293 K): δ= 12.62 (s, 1H, OH), 7.42-7.52 (m, 2H, H6' and H4'), 6.95-7.05 (m, 2H, H3' and H5'), 3.65 (s, 3H, NCH_3), 2.74 (s, 3H, $COCH_3$), 2.56 (s, 3H, 4-CH_3) ppm.

^{13}C NMR (150.94 MHz, DMSO-d_6): δ= 190.3 (C=O), 159.5 (C-2'), 136.9 (C-2), 135.7 (C-4), 133.0 (C-4'), 130.6 (C-6'), 126.5 (C-5), 120.7 (C-3'), 119.3 (C-5'), 112.0 (C-1'), 33.5 (NCH_3), 31.0 ($CO\underline{C}H_3$), 10.7 (4-CH_3) ppm.

MS(EI): *m/z*=246[M]$^+$. Anal. $C_{13}H_{14}N_2O_3$ (246): calcd. C 63.41, H 5.69, N 11.38; found C 63.35, H 5.65, N 11.19.

*4.2.7. 4-(Ethoxycarbonyl)-2-(2-hydroxyphenyl)-1,5-dimethyl-1H-imidazole 3-oxide (**12**).*

40% aqueous solution of methyl amine (1.08 g), containing 0.43 g (0.0139 mol) of methyl amine was added dropwise to a mixture of aldehyde **5** (1.53 g, 0.0126 mol) and oxime **8** (2.00 g, 0.0126 mol) in ethanol (5 mL). The resulting mixture was stirred at room temperature for 1 h and left to stand for 3 d. The solvent was removed under reduced pressure and the obtained oil was treated with small amount of ether. Thus obtained precipitate was

filtered off and recrystallized from ethyl acetate yielding 0.45 g (13%) of product **12** as a beige solid. M.p. 162-164 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ= 13.04 (br. s, $\nu_{½}$ = 90 Hz, 1H, OH), 7.42-7.53 (m, 2H, H4' and H6'), 6.95-7.03 (m, 2H, H3' and H5'), 4.33 (q, 2H, OC$\underline{H}_2$CH$_3$), 3.64 (s, 3H, NCH$_3$), 2.55 (s, 3H, 4-CH$_3$), 1.32 (t, 3H, OCH$_2$C$\underline{H}_3$) ppm.

^{13}C NMR (75.47 Hz, DMSO-d_6): δ= 159.4 (C=O), 158.2 (C2'), 137.5 (C2), 135.3 (C4), 132.4 (C4'), 129.9 (C6'), 120.2 (C3'), 118.6 (C5), 118.5 (C5'), 111.5 (C1'), 60.6 (O$\underline{C}$H$_2$CH$_3$), 33.3 (NCH$_3$), 14.1 (OCH$_2$$\underline{C}H_3$), 10.4 (4-CH$_3$) ppm.

MS(EI): *m/z*=276[M]$^+$. Anal. $C_{14}H_{16}N_2O_4\cdot0.5H_2O$ (285): calcd. C 58.95, H 5.96, N 9.82; found C 58.51, H 5.25, N 9.68.

*4.2.8. 2-(2-Hydroxyphenyl)-1,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-benzo[d]imidazole 3-oxide (**13**).*

A mixture of azomethine **14** (1.60 g, 0.0118 mol) and oxime **9** (2.00 g, 0.0118 mol) in glacial acetic acid (50 mL) was stirred at room temperature for 4 h. The reaction mixture was poured into water (50 mL), the product was extracted with chloroform (15 mL×2), the extract was sequentially washed with potassium carbonate solution (3%) and water, then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The obtained oil was treated with ether yielding 0.9 g (26%) of product **13** as a beige solid. M.p. 230-232 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ= 12.50 (br. s, $\nu_{½}$ = 30 Hz, 1H, OH), 7.46 (t, 1H, H4'), 7.20 (dd, *J* = 7.9, 1.4 Hz, 1H, H6'), 7.16 (d, *J* = 8.3 Hz, 1H, H3'), 6.96 (t, 1H, H5'), 3.66 (s, 3H, NCH$_3$), 2.77 (s, 2H, CH$_2$), 2.46 (s, 2H, CH$_2$), 1.21 (s, 6H, 2CH$_3$) ppm.

^{1}H NMR (300 MHz, DMSO-d_6): δ= 12.86 (br. s, 1H, OH), 7.56 (d, *J* = 7.2 Hz, 1H, H6'), 7.48 (t, 1H, H4'), 6.96-7.04 (m, 2H, H3' and H5'), 3.66 (s, 3H, NCH$_3$), 2.89 (s, 2H, CH$_2$), 2.43 (s, 2H, CH$_2$), 1.12 (s, 6H, 2CH$_3$) ppm.

^{13}C NMR (75.47 Hz, DMSO-d_6): δ= 184.9 (C=O), 159.4 (C2'), 141.9 (C2), 138.8 (C4), 132.6 (C4'), 129.8 (C6'), 121.9 (C5), 120.3 (C3'), 118.6 (C5'), 111.2 (C1'), 52.0 (CH$_2$), 34.4 ($\underline{C}$(CH$_3$)$_2$), 33.8 (CH$_2$), 33.5 (NCH$_3$), 27.9 (2CH$_3$) ppm.

MS(EI): *m/z*=286[M]$^+$. Anal. $C_{16}H_{18}N_2O_3$ (286): calcd. C 67.13, H 6.29, N 9.79; found C 66.98, H 6.26, N 9.68.

*4.2.9. 2-((Methylimino)methyl)phenol (**14**).*

To aldehyde **5** (12.20 g, 0.10 mol) while stirring at room temperature 40% aqueous solution of methyl amine (13.00 g) containing 5.20 g (0.17 mol) was added dropwise. The mixture was stirred at room temperature for 6 h, then sodium chloride (3.6 g) was added. The product was extracted with ether (20 mL×2), the extract was dried over anhydrous potassium carbonate. The solvent was removed under reduced pressure, yielding 11.00 g (82%) of product **14** as a yellow liquid which was used without further purification. ^{1}H NMR (300 MHz, CDCl$_3$): δ= 13.48 (br. s, 1H, OH), 8.27 (s, 1H, NCH), 7.15-7.35 (m, 2H, H-Ar), 6.77-7.00 (m, 2H, H-Ar), 3.42 (s, 3H, CH$_3$) ppm.

*4.2.10. 2-(1-Methoxy-4,5-dimethyl-1H-imidazol-2-yl)phenol (**15**).*

To imidazole **24** (0.80 g, 0.0026 mol) dissolved in methanol (20 mL) was added 10% palladium on carbon (0.1 g) and the reaction mixture was hydrogenated at room temperature and 1.3 atm for 8 h. The catalyst was filtered off and washed with methanol. The solvent was removed from the filtrate under reduced pressure and the residue was subjected to column chromatography (silica gel, chloroform), yielding 0.34 g (60%) of pure product **15** (m.p. 95-97 °C) and 0.11 g (23%) of pure by-product **28** (m.p. 220-222 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ= 12.95 (br. s, $\nu_{½}$ = 20 Hz, 1H, OH), 8.00 (dd, *J* = 8.3, 1.7 Hz, 1H, H6'), 7.25 (t, 1H, H4'), 6.90-6.97 (m, 2H, H3' and H5'), 3.99 (s, 3H, OCH$_3$), 2.26 (s, 3H, 5-CH$_3$), 2.13 (s, 3H, 4-CH$_3$) ppm.

^{13}C NMR (75.47 Hz, DMSO-d_6): δ= 156.5 (C2'), 136.3 (C2), 129.7 (C4'), 126.4 (C4), 124.1 (C6'), 120.6 (C5), 119.0 (C3'), 116.8 (C5'), 111.8 (C1'), 66.0 (OCH$_3$), 12.3 (4-CH$_3$), 6.9 (5-CH$_3$) ppm.

MS(EI): *m/z*=218[M]$^+$. Anal. $C_{12}H_{14}N_2O_2$ (218): calcd. C 66.06, H 6.42, N 12.84; found C 66.23, H 6.62, N 12.95.

By-product: *(2-(4,5-dimethyl-1H-imidazol-2-yl)phenol* (**28**).^{1}H NMR (300 MHz, DMSO-d_6): δ= 7.71 (d, *J* = 7.3 Hz, 1H, H-Ar), 7.11-7.20 (m, 1H, H-Ar), 6.82-6.92 (m, 2H, H-Ar), 2.15 (s, 6H, 2CH$_3$) ppm. MS(EI): *m/z*=188[M]$^+$.

*4.2.11. 1-(2-(2-hydroxyphenyl)-1-methoxy-4-methyl-1H-imidazol-5-yl)ethanone (**16**).*

Similarly to **15** from imidazole **25** (0.40 g, 0.0012 mol) 0.17 g (58%) of product **16** (m.p. 116-117 °C) and 0.10 g (39%) of by-product **29** (m.p. 264-266 °C) were obtained.

^{1}H NMR (600 MHz, CDCl$_3$, 293 K): δ= 12.46 (br. s, 1H, OH), 8.17 (dd, *J* = 8.1, 1.6 Hz, 1H, H6'), 7.35 (t, 1H, H4'), 7.07 (dd, *J* = 8.4, 1.2 Hz, 1H, H3'), 6.95 (t, 1H, H5'), 4.00 (s, 3H, OCH$_3$), 2.59 (s, 3H, COCH$_3$), 2.56 (s, 3H, 4-CH$_3$) ppm.

^{13}C NMR (150.94 MHz, CDCl$_3$): δ= 186.9 (C=O), 158.8 (C-2'), 141.7 (C-2), 141.6 (C-4), 132.0 (C-4'), 125.9 (C-6'), 123.6 (C-5), 119.4 (C-5'), 118.0 (C-3'), 110.7 (C-1'), 66.5 (OCH$_3$), 30.0 (CO$\underline{C}$H$_3$), 16.7 (4-CH$_3$) ppm.

^{1}H NMR (600 MHz, DMSO-d_6, 293 K): δ= 12.16 (s, 1H, OH), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H, H6'), 7.39 (t, 1H, H4'), 6.98-7.04 (m, 2H, H3' and H5'), 3.98 (s, 3H, OCH$_3$), 2.54 (s, 3H, COCH$_3$), 2.49 (s, 3H, 4-CH$_3$) ppm.

^{13}C NMR (150.94 MHz, DMSO-d_6): δ= 187.2 (C=O), 158.1 (C-2'), 141.3 (C-2), 141.2 (C-4), 132.4 (C-4'), 127.2 (C-6'), 124.0 (C-5), 120.0 (C-5'), 117.8 (C-3'), 111.6 (C-1'), 67.4 (OCH$_3$), 30.3 (CO$\underline{C}$H$_3$), 16.8 (4-CH$_3$) ppm.

MS(EI): *m/z*=246[M]$^+$. Anal. $C_{13}H_{14}N_2O_3$ (246): calcd. C 63.41, H 5.69, N 11.38; found C 62.95, H 5.99, N 11.38.

By-product: *(1-(2-(2-hydroxyphenyl)-4-methyl-1H-imidazol-5-yl)ethanone* (**29**) ^{1}H NMR (300 MHz, DMSO-d_6): δ= 13.15 (br. s, 1H, NH), 12.30 (br. s, 1H, OH), 7.83 (d, *J* = 7.3 Hz, 1H, H-Ar), 7.24-7.34 (m, 1H, H-Ar), 6.90-7.00 (m, 2H, H-Ar), 2.54 (s, 3H, COCH$_3$), 2.45 (s, 3H, CH$_3$) ppm. MS(EI): *m/z*=216[M]$^+$.

*4.2.12. Ethyl 2-(2-hydroxyphenyl)-1-methoxy-4-methyl-1H-imidazole-5-carboxylate(**17**).*

To imidazole **26** (1.00 g, 0.0027 mol) dissolved in methanol (20 mL) was added 10% palladium on carbon (0.10 g) and the mixture was hydrogenated at room temperature and 1.3 atm for 4 h. The catalyst was filtered off and washed with methanol. The solvent was removed from the filtrate under reduced pressure and the residue was subjected to column chromatography (silica gel, chloroform), yielding 0.15 g (20%) of pure product **17** (m.p. 119-121 °C) and 0.55 g of starting imidazole **26**.

^{1}H NMR (300 MHz, DMSO-d_6): δ= 12.18 (s, 1H, OH), 8.03 (d, *J* = 8.2 Hz, 1H, H6'), 7.38 (t, 1H, H4'), 6.95-7.03 (m, 2H, H3' and H5'), 4.34 (q, 2H, OC$\underline{H}_2$CH$_3$), 4.03 (s, 3H, OCH$_3$), 2.44 (s, 3H, 4-CH$_3$), 1.35 (s, 3H, OCH$_2$C$\underline{H}_3$) ppm.

^{13}C NMR (75.47 Hz, DMSO-d_6): δ= 158.1 (C=O), 157.5 (C2'), 141.1 (C2), 140.9 (C4), 131.7 (C4'), 126.4 (C6'), 119.3 (C5'), 117.2 (C3'), 115.1 (C5), 111.2 (C1'), 66.7 (OCH_3), 60.4 ($O\underline{C}H_2CH_3$), 15.3 (4-CH_3), 14.0 ($OCH_2\underline{C}H_3$) ppm.

MS(EI): *m/z*=276[M]$^+$. Anal. $C_{14}H_{16}N_2O_4$ (276): calcd. C 60.87, H 5.80, N 10.14; found C 60.46, H 5.78, N 9.85.

*4.2.13. 2-(2-Hydroxyphenyl)-1-methoxy-5,5-dimethyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-7(4H)-one (**18**).*

To imidazole **27** (1.00 g, 0.0027 mol) dissolved in methanol (20 mL) was added 10% palladium on carbon (0.10 g) and the mixture was hydrogenated at room temperature and 1.3 atm for 4 h. The obtained precipitate was filtered off together with the catalyst and suspended in chloroform. The catalyst was filtered off and solvent was removed from the filtrate under reduced pressure yielding 0.27 g of product **18** as a white solid; m.p. 169-170 °C. In order to obtain additional amount of **18**, the solvent from the filtrate after the reaction was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, chloroform), yielding 0.15 g of product **18**, m.p. 169-170 °C and 0.22 g of starting material **27**. Total yield of product **18** 0.42 g (55%).

^{1}H NMR (300 MHz, $CDCl_3$): δ= 12.55 (br. s, $\nu_{½}$ = 24 Hz, 1H, OH), 8.20 (d, *J* = 8.1 Hz, 1H, H6'), 7.36 (t, 1H, H4'), 7.07 (d, *J* = 8.3 Hz, 1H, H3'), 6.95 (t, 1H, H5'), 4.14 (s, 3H, OCH_3), 2.75 (s, 2H, CH_2), 2.47 (s, 2H, CH_2), 1.16 (s, 6H, $2CH_3$) ppm.

^{1}H NMR (300 MHz, DMSO-d_6): δ= 12.14 (s, 1H, OH), 8.04 (dd, *J* = 8.0, 1.6 Hz, 1H, H6'), 7.40 (t, 1H, H4'), 6.96-7.05 (m, 2H, H3' and H5'), 4.09 (s, 3H, OCH_3), 2.74 (s, 2H, CH_2), 2.45 (s, 2H, CH_2), 1.09 (s, 6H, $2CH_3$) ppm.

^{13}C NMR (75.47 Hz, DMSO-d_6): δ= 185.4 (C=O), 157.6 (C2'), 148.2 (C2), 142.9 (C4), 132.1 (C4'), 126.6 (C6'), 120.4 (C5), 119.4 (C5'), 117.2 (C3'), 111.1 (C1'), 66.6 (OCH_3), 52.1 (CH_2), 37.7 (CH_2), 35.3 ($\underline{C}(CH_3)_2$), 27.8 ($2CH_3$) ppm.

MS(EI): *m/z*=286[M]$^+$. Anal. $C_{16}H_{18}N_2O_3$ (286): calcd. C 67.13, H 6.29, N 9.79; found C 66.96, H 6.19, N 9.61.

*4.2.14. 2-(Benzyloxy)benzaldehyde (**19**).*

To a solution of aldehyde **5** (12.2 g, 0.10 mol) in ethanol (40 mL) a solution of benzyl chloride (13.9 g, 0.11 mol) in ethanol (50 mL) was added. The reaction mixture was stirred at reflux for 1.5 h and filtered without cooling. From the filtrate the solvent was removed under reduced pressure. The residue was dissolved in sodium hydroxide solution (0.5 M, 60 mL), refluxed for 20 min, cooled to room temperature and filtered off, yielding 16.2 g (77%) of product **19** as a beige solid. M.p. 38-40 °C.

*4.2.15. 2-(2-(Benzyloxy)phenyl)-4,5-dimethyl-1H-imidazol-1-ol (**20**).*

A mixture of aldehyde **19** (5.00 g, 0.0236 mol), oxime **6** (2.40 g, 0.0238 mol) and ammonium acetate (2.70 g, 0.0351 mol) in glacial acetic acid (45 mL) was stirred at 45-50 °C for 5.5 h then cooled to room temperature. The reaction mixture was poured into water (140 mL), the product was extracted with chloroform (30 mL×2), the extract was sequentially washed with water and sodium bicarbonate solution (2%, 50 mL). The obtained precipitate was filtered off, yielding 6.5 g (94%) of chromatographically pure product **20** as a white solid. M.p. 160-162 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ= 11.73 (br. s, 1H, OH), 7.20-7.60 (m, 7H, H-Ar), 6.86-7.20 (m, 2H, H-Ar), 5.18 (s, 2H, $C\underline{H}_2$Ph), 2.08 (s, 3H, CH_3), 2.00 (s, 3H, CH_3) ppm. MS (EI): *m/z*=294[M]$^+$.

*4.2.16. 1-(2-(2-(Benzyloxy)phenyl)-1-hydroxy-4-methyl-1H-imidazol-5-yl)ethanone (**21**).*

A mixture of aldehyde **19** (5.00 g, 0.0236 mol), oxime **7** (3.0 g, 0.0236 mol) and ammonium acetate (2.7 g, 0.0351 mol) in glacial acetic acid (45 mL) was stirred at 45-50 °C for 16 h. The reaction mixture is then poured into water (150 mL), triturated and the obtained precipitate is filtered off yielding 6.6 g (88%) of product **21** as beige solid. M.p. 180-182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 12.79 (br. s, 1H, OH), 7.76 (br. s, 1H, H-Ar), 7.25-7.50 (m, 6H, H-Ar), 6.95-7.10 (m, 2H, H-Ar), 5.14 (s, 2H, $C\underline{H}_2$Ph), 2.54 (s, 3H, $COCH_3$), 2.49 (s, 3H, CH_3) ppm. MS (EI): *m/z*=322[M]$^+$.

*4.2.17. Ethyl 2-(2-(benzyloxy)phenyl)-1-hydroxy-4-methyl-1H-imidazole-5-carboxylate(**22**).*

A mixture of aldehyde **19** (5.30 g, 0.0250 mol), oxime **8** (4.0 g, 0.0252 mol) and ammonium acetate (2.6 g, 0.0338 mol) in glacial acetic acid (40 mL) was stirred at room temperature for 9 h and left to stand for 4 d. The reaction mixture was poured into water (150 mL), the product was extracted with chloroform (40 mL×2), the extract was washed with 2% solution of potassium carbonate and with water and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, the residue was subjected to column chromatography (silica gel, eluent – chloroform, chloroform-methanol 100:1 – 10:1) to yield 3.0 g (34%) of product **22** as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 11.03 (br. s, 1H, OH), 7.52-7.66 (m, 1H, H-Ar), 7.28-7.45 (m, 6H, H-Ar), 7.00-7.11 (m, 2H, H-Ar), 5.17 (s, 2H, $C\underline{H}_2$Ph), 4.43 (q, *J*=7.34 Hz, 2H, $C\underline{H}_2CH_3$), 2.50 (s, 3H, CH_3), 1.42 (t, *J*=6.97 Hz, 3H, $CH_2C\underline{H}_3$) ppm. MS (EI): *m/z*=352[M]$^+$.

*4.2.18. 2-(2-Benzyloxy)phenyl)-1-hydroxy-5,5-dimethyl-4,5,6,7-tetrhydro-1H-benzo[d]imidazole-7(4H)-one (**23**).*

A mixture of aldehyde **19** (6.36 g, 0.0300 mol), oxime **9** (5.07 g, 0.0300 mol) and ammonium acetate (3.33 g, 0.0432 mol) in glacial acetic acid (50 mL) was stirred at room temperature for 3 h and left to stand for 3 d. Then the reaction mixture was poured into water (150 mL), the obtained precipitate was filtered off, heated at reflux in acetonitrile and filtered off without cooling to yield 6.64 g of chromatographically pure product **23** as a yellowish solid; m.p. 218-220 °C. Cooling of the filtrate led to the formation of precipitate which was also filtered off yielding 1.74 g of product **23** as a yellowish crystalline solid; m.p. 221-222 °C. Total yield 8.38 g (77%). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 11.74 (br.s, 1H, OH), 7.36-7.49 (m, 4H, H-Ar), 7.22-7.35 (m, 3H, H-Ar), 7.11-7.19 (m, 1H, H-Ar), 6.98-7.09 (m, 1H, H-Ar), 5.18 (s, 2H, $C\underline{H}_2$Ph), 2.68 (s, 2H, CH_2), 2.37 (s, 2H, CH_2), 1.08 (s, 6H, $2CH_3$) ppm. MS (EI): *m/z*=362[M]$^+$.

*4.2.19. 2-(2-(Benzyloxy)phenyl)-1-methoxy-4,5-dimethyl-1H-imidazole (**24**).*

To a mixture of hydroxyimidazole **20** (1.50 g, 0.0050 mol) and sodium hydride (0.12 g, 0.0050 mol) in THF (20 mL) at 0°C methyl iodide (0.71 g, 0.0050 mol) was added dropwise while stirring. Then the ice-bath was removed and the reaction mixture was stirred at room temperature for 1 h and poured into water (40 mL). The product was extracted by ethyl acetate (25 mL), the extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, chloroform) to yield 0.40 g (26%) of product **24** as light-yellow thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.49 (dd, *J* 7.7 Hz, 1.8 Hz, 1H, H-Ar), 7.22-7.40 (m, 6H, H-Ar), 6.95-7.06 (m, 2H, H-Ar), 5.12 (s, 2H, $C\underline{H}_2$Ph), 3.69 (s, 3H,

OCH_3), 2.22 (s, 3H, CH_3), 2.20 (s, 3H, CH_3) ppm. MS (EI): *m/z*=308$[M]^+$.

*4.2.20. 1-(2-(2-(Benzyloxy)phenyl)-1-methoxy-4-methyl-1H-imidazol-5-yl)ethanone (**25**).*

To a mixture of hydroxyimidazole **21** (1.50 g, 0.0046 mol) and powdered potassium hydroxide (0.31 g, 0.0055 mol) in DMF (10 mL) at 0°C methyl iodide (1.60 g, 0.0115 mol) was added dropwise while stirring. Then the ice-bath was removed and the reaction mixture was stirred at room temperature for 2 h and poured into water (30 mL). The product was extracted by tetrachloromethane (10 mL×3), the combined extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, chloroform) to yield 1.00 g (65%) of product **25** as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.49-7.55 (m, 1H, H-Ar), 7.27-7.47 (m, 6H, H-Ar), 7.00-7.10 (m, 2H, H-Ar), 5.14 (s, 2H, C$\underline{H_2}$Ph), 3.76 (s, 3H, OCH_3), 2.57 (s, 3H, $COCH_3$), 2.54 (s, 3H, CH_3) ppm. MS (EI): *m/z*=336$[M]^+$.

*4.2.21. Ethyl 2-(2-(benzyloxy)phenyl)-1-methoxy-4-methyl-1H-imidazole-5-carboxylate (**26**).*

Similarly to **25** from hydroxyimidazole **22** (2.00 g, 0.0057 mol) 1.00 g (48%) of product **26** was obtained as yellow crystallizing oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ= 7.29-7.53 (m, 7H, H-Ar), 6.97-7.10 (m, 2H, H-Ar), 5.15 (s, 2H, C$\underline{H_2}$Ph),4.40 (q, 2H, OC$\underline{H_2}$$CH_3$), 3.85 (s, 3H, OCH_3), 2.55 (s, 3H, CH_3),1.42 (t, 3H, $OCH_2C\underline{H_3}$) ppm. MS (EI): *m/z*=366$[M]^+$.

*4.2.22. 2-(2-(Benzyloxy)phenyl)-1-methoxy-5,5-dimethyl-4,5,6,7-tetrahydro-1H-benzo[d] imidazole-7(4H)-one (**27**).*

To a mixture of hydroxyimidazole **23** (3.62 g, 0.0100 mol) and powdered potassium hydroxide (0.65 g, 0.0116 mol) in DMF (15 mL) at 0°C methyl iodide (1.50 g, 0.0106 mol) was added dropwise while stirring. Then the ice-bath was removed and the reaction mixture was stirred at room temperature for 1.5 h and poured into water (60 mL). The product was extracted by tetrachloromethane (40 mL×2), the combined extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was triturated with ether yielding 2.27 g (60%) of chromatographically pure product **27** as white solid. M.p. 117-118 °C.^{1}H NMR (300 MHz; $CDCl_3$): δ= 7.40-7.54 (m, 2H, H-Ar), 7.22-7.37 (m, 5H, H-Ar), 7.00-7.10 (m, 2H, H-Ar), 5.16 (s, 2H, C$\underline{H_2}$Ph), 3.93 (s, 3H, OCH_3), 2.79 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 1.17 (s, 6H, $2CH_3$) ppm. MS (EI): *m/z*=376$[M]^+$.

4.3. X-Ray Determination

Crystals of $C_{12}H_{12}N_2O_3$ (compound **2**) were grown from a toluene solution. A suitable single crystal was subjected to X-ray measurements on aCCD area SMART-APEX-II diffractometer under a stream of cooled nitrogen using graphite-monochramated Mo-K_α radiation. The crystal was kept at 173.15 K during data collection. The structure was solved by direct methods and refined in anisotropic approximation using Olex2 software.[21] Positions of hydrogen atoms were calculated geometrically with the exception of the OH group hydrogen atoms that were determined objectively. The hydrogen atoms were refined using "riding" model.

A summary of the crystallographic data and structure determination parameters is provided in Table 8.

The experimental data for structure **2** were deposited with the Cambridge Crystallographic Data Centre (CCDC registration number is 1056064). Copies of data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2, EZ, UK (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table 7. Crystal data and structure refinement for compound **2**.

Empirical formula	$C_{12}H_{12}N_2O_3$
Formula weight	232.24
Temperature/K	173.15
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.9232(6)
b/Å	11.0300(8)
c/Å	12.3616(9)
α/°	90.00
β/°	91.3900(10)
γ/°	90.00
Volume/Å^3	1080.00(14)
Z	4
ρ_{calc}g/cm^3	1.428
μ/mm^{-1}	0.105
F(000)	488.0
Crystal size/mm^3	0.38 × 0.3 × 0.28
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.96 to 61.08
Index ranges	$-11 \le h \le 11$, $-15 \le k \le 15$, $-17 \le l \le 17$
Reflections collected	12523
Independent reflections	3276 [R_{int} = 0.0220, R_{sigma} = 0.0191]
Data/restraints/parameters	3276/0/158
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0414, wR_2 = 0.1120
Final R indexes [all data]	R_1 = 0.0519, wR_2 = 0.1209
Largest diff. peak/hole / e Å^{-3}	0.33/-0.24

Acknowledgements

This work was supported by the Ministry of Education and Science of Russia under a state contract.

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Supplementary Data

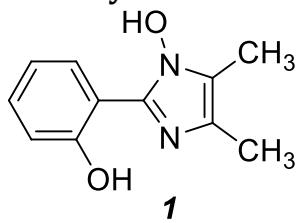
Copies of IR; ^{1}H and ^{13}C spectra.

Supplementary Information.

1. Copies of IR spectra of compounds
2. Copies of NMR spectra of compounds
3. NMR spectra of compound **2** at different temperatures.
4. NMR spectra of compound **2** at different concentrations.
5. NMR spectra of compound **2** in mixture of solvents.

1. Copies of IR spectra of compounds (KBr).

2-(2-Hydroxyphenyl)-4,5-dimethyl-1H-imidazol-1-ol (**1**).



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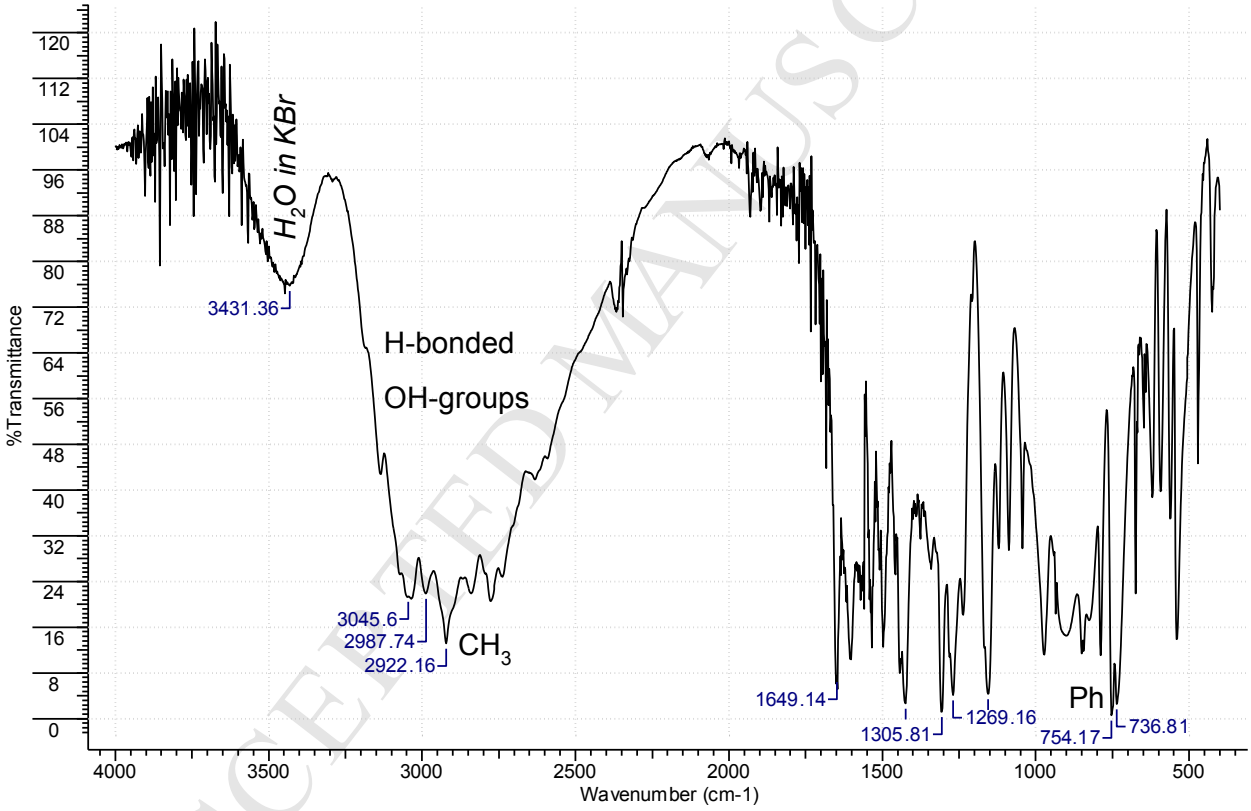
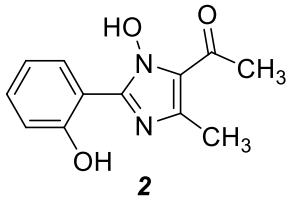


1-(1-Hydroxy-2-(2-hydroxyphenyl)-4-methyl-1H-imidazol-5-yl)ethanone (2).



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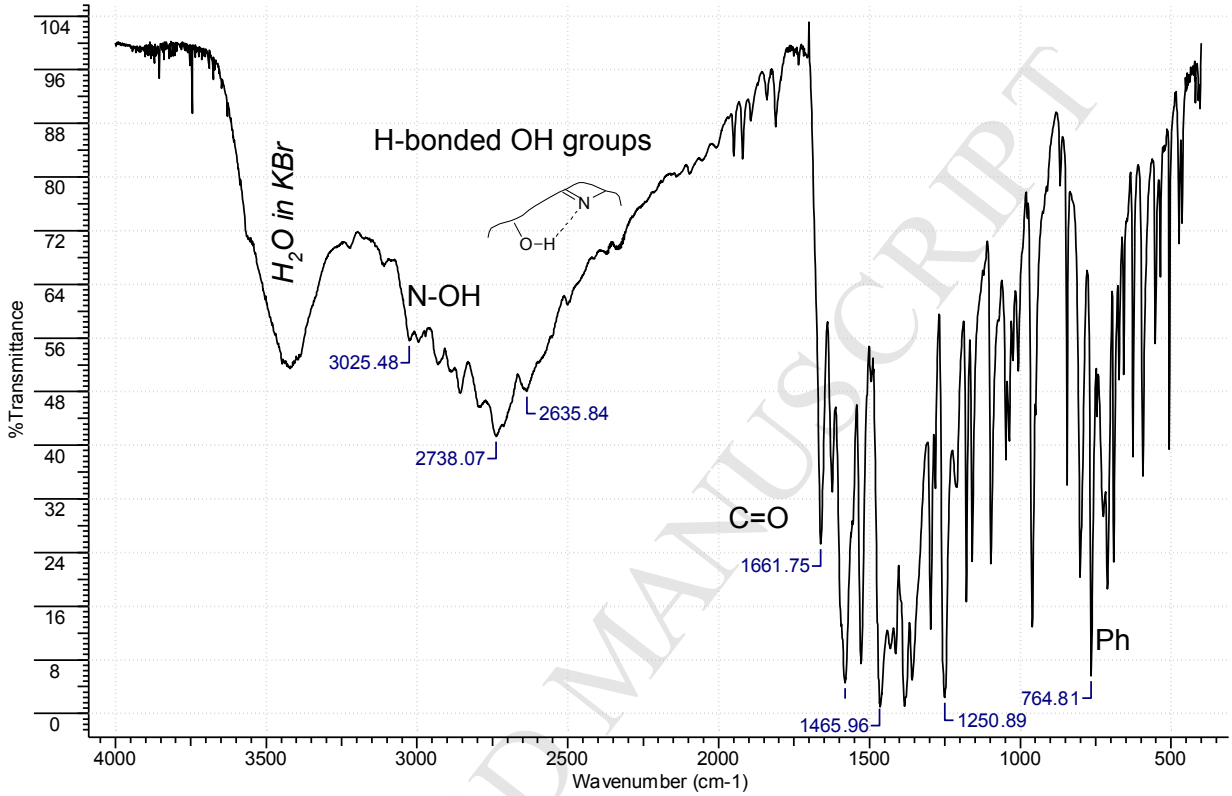
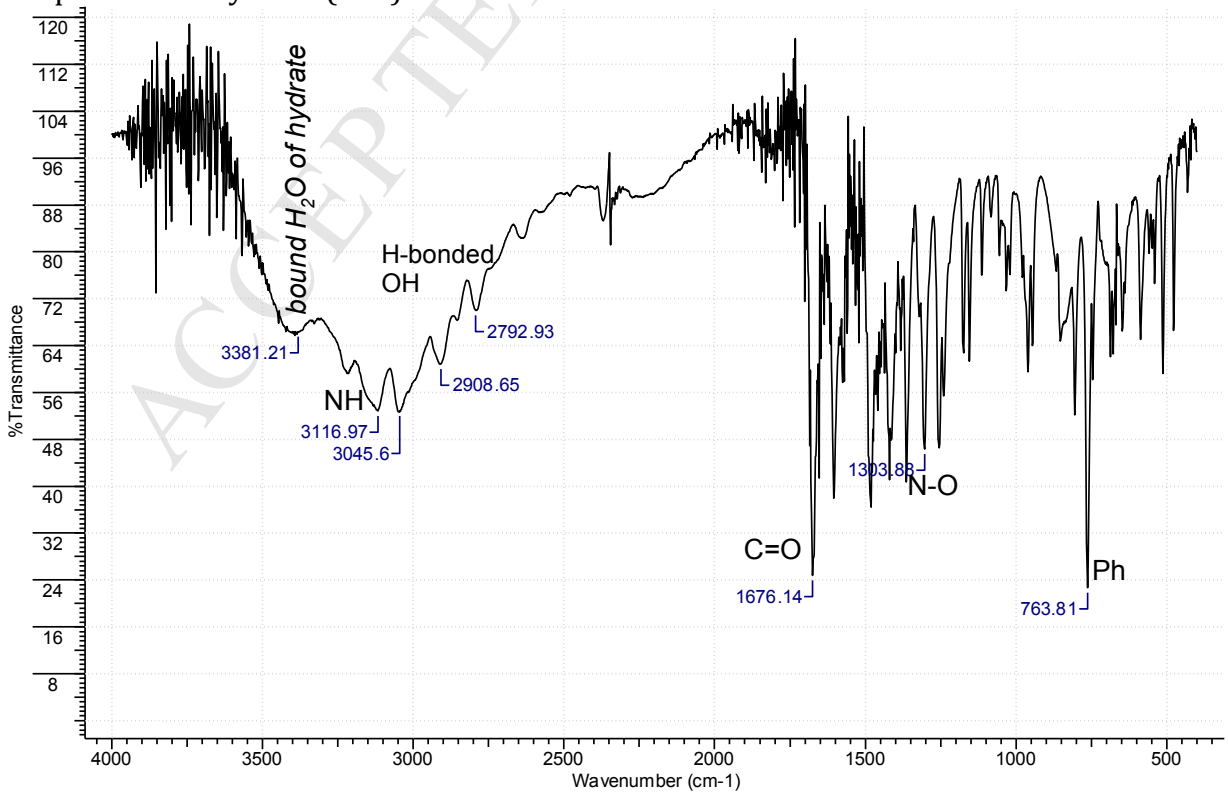
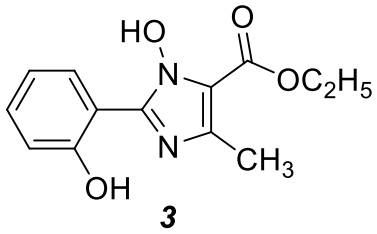


IR spectrum of hydrate (KBr):



Ethyl 1-hydroxy-2-(2-hydroxyphenyl)-4-methyl-1H-imidazole-5-carboxylate (3).



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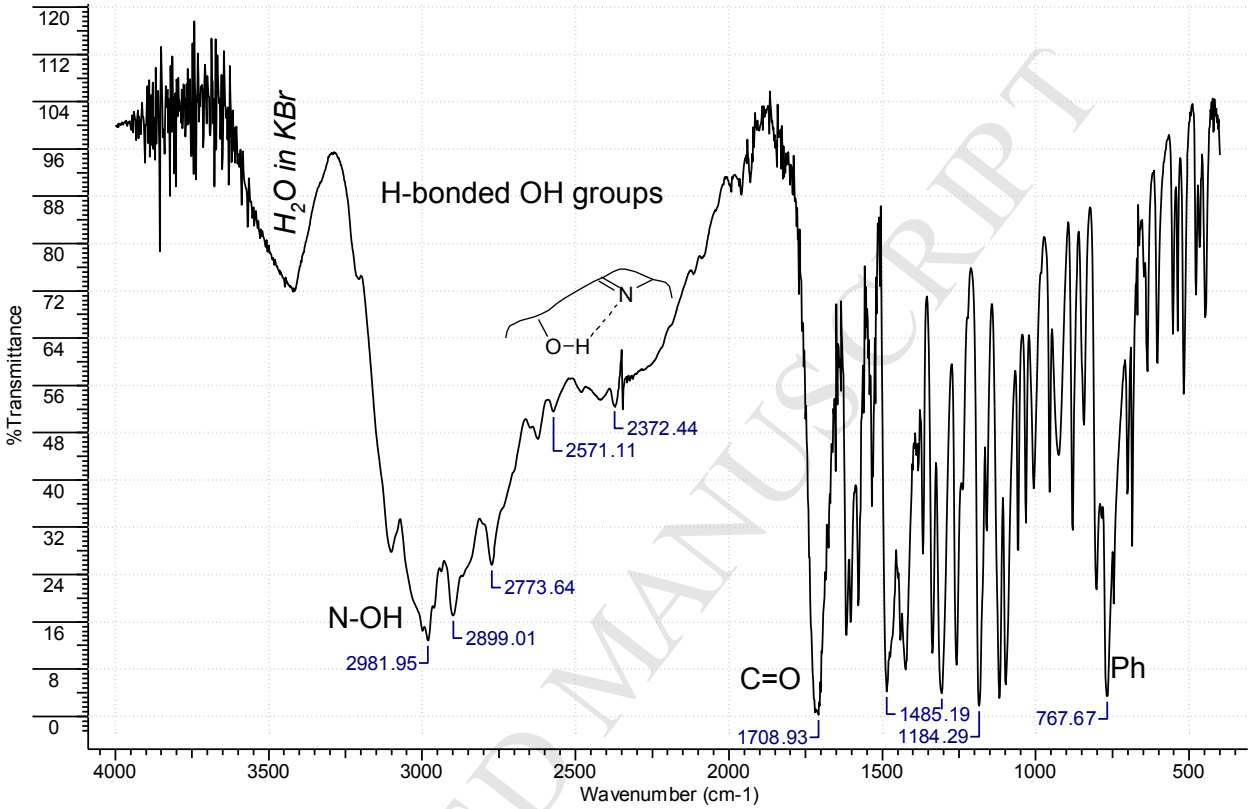
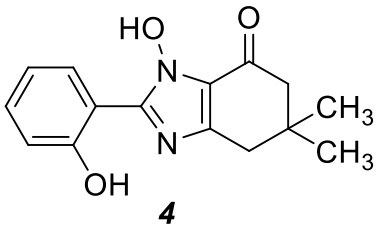


1-Hydroxy-2-(2-hydroxyphenyl)-5,5-dimethyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-7(4H)-one (**4**).



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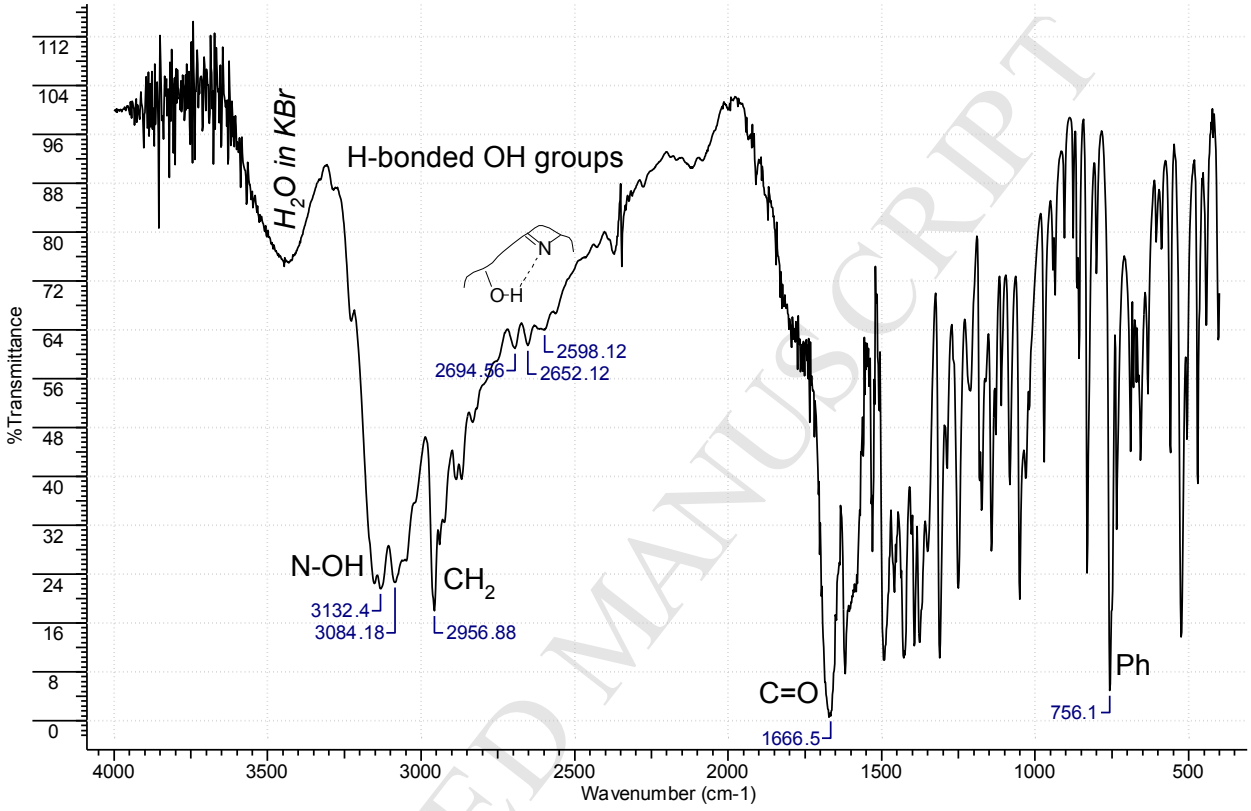
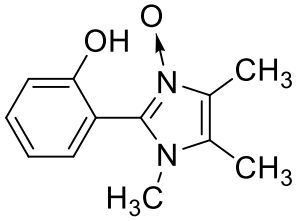


2-(2-Hydroxyphenyl)-1,4,5-trimethyl-1H-imidazole 3-oxide (10).



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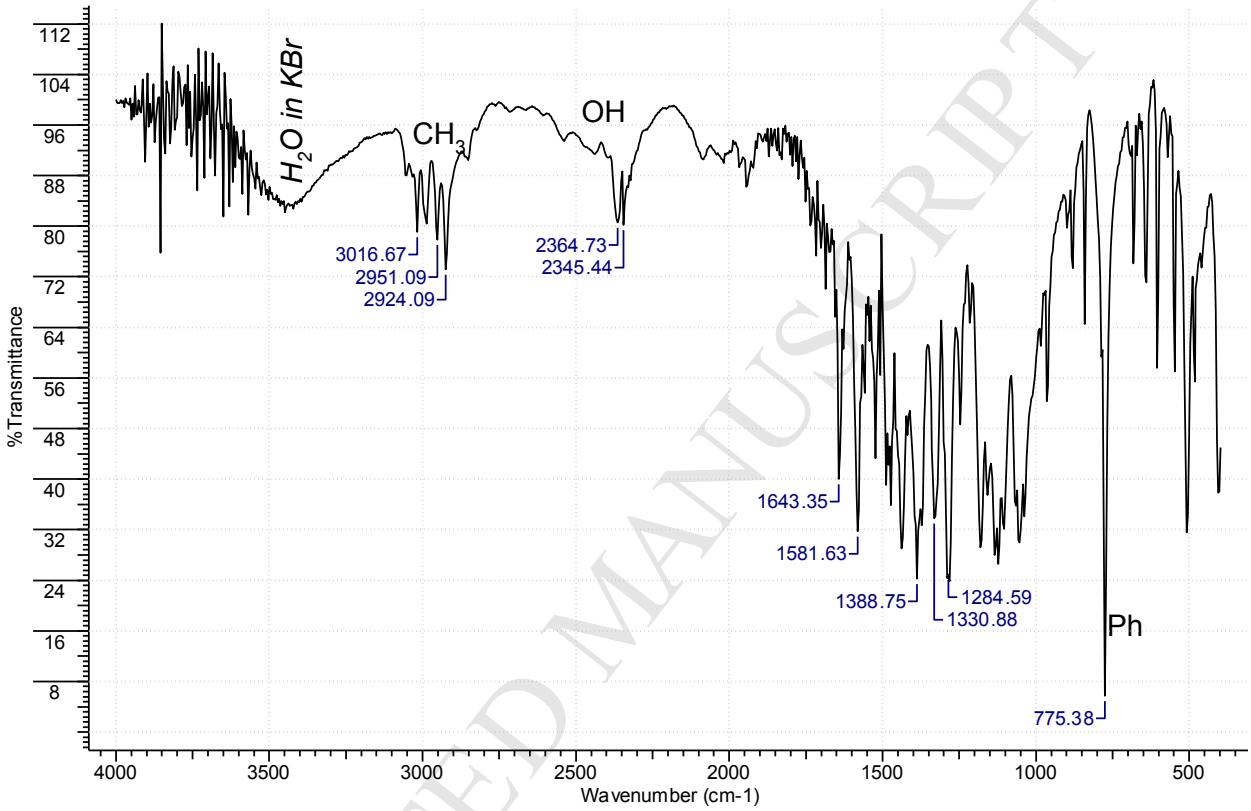
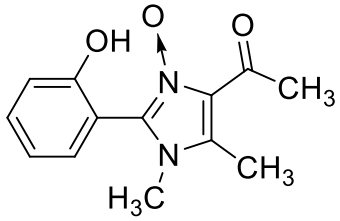


4-Acetyl-2-(2-hydroxyphenyl)-1,5-dimethyl-1H-imidazole 3-oxide (11).



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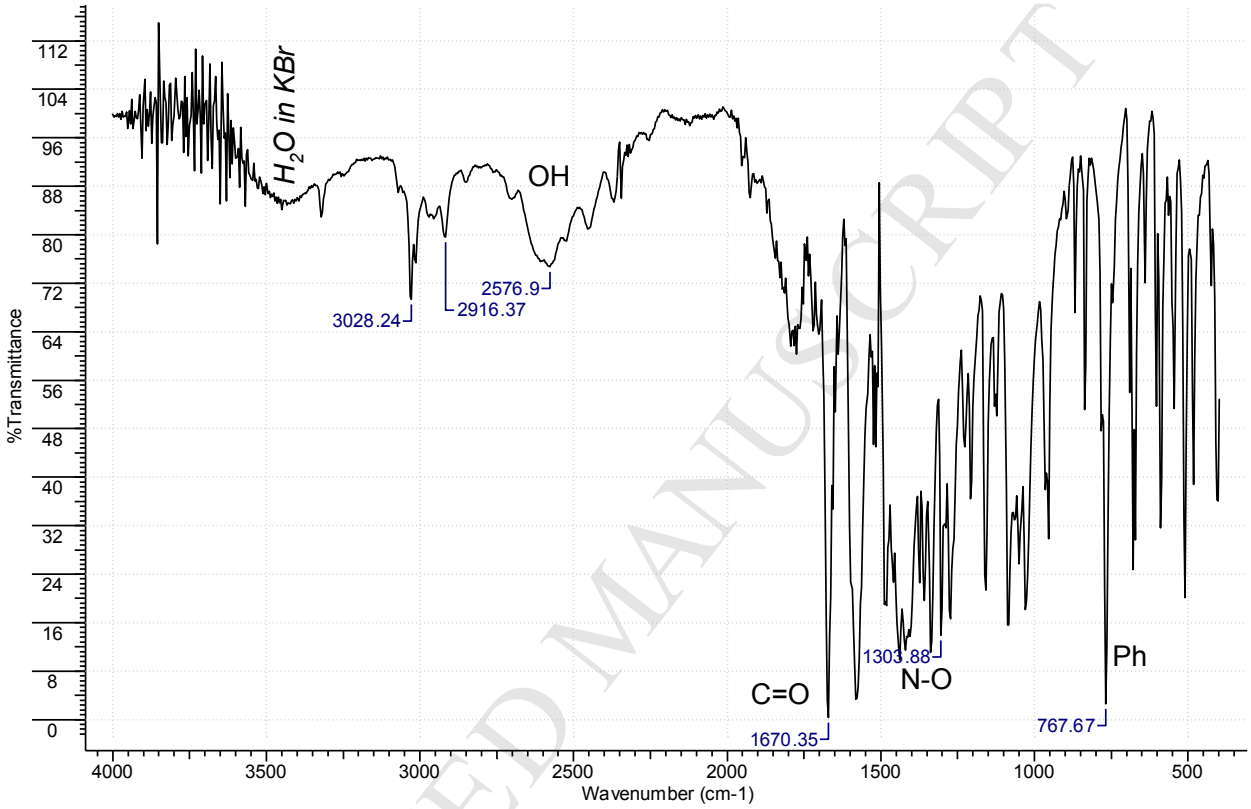
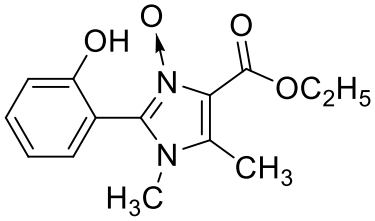


4-(Ethoxycarbonyl)-2-(2-hydroxyphenyl)-1,5-dimethyl-1H-imidazole 3-oxide (12).



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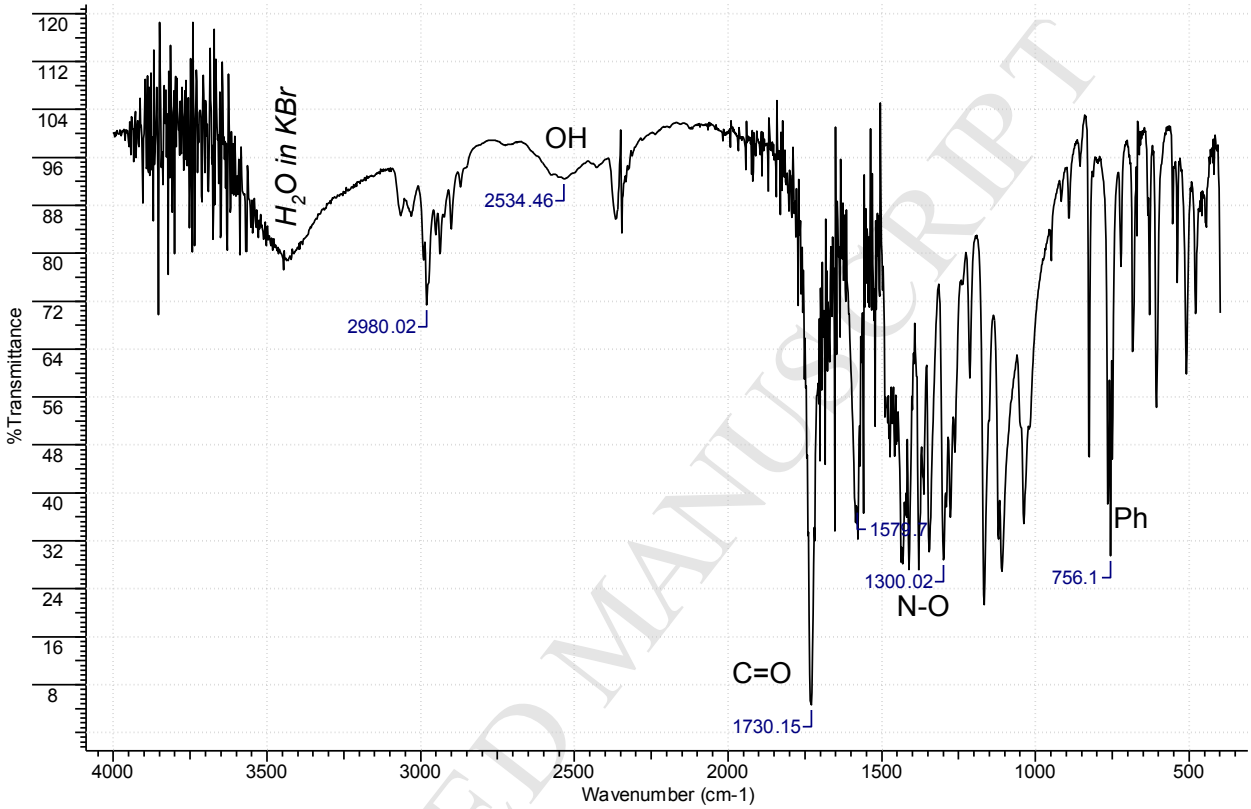
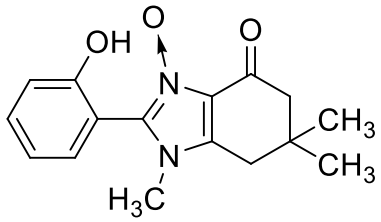


2-(2-Hydroxyphenyl)-1,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-benzo[d]imidazole 3-oxide (**13**).



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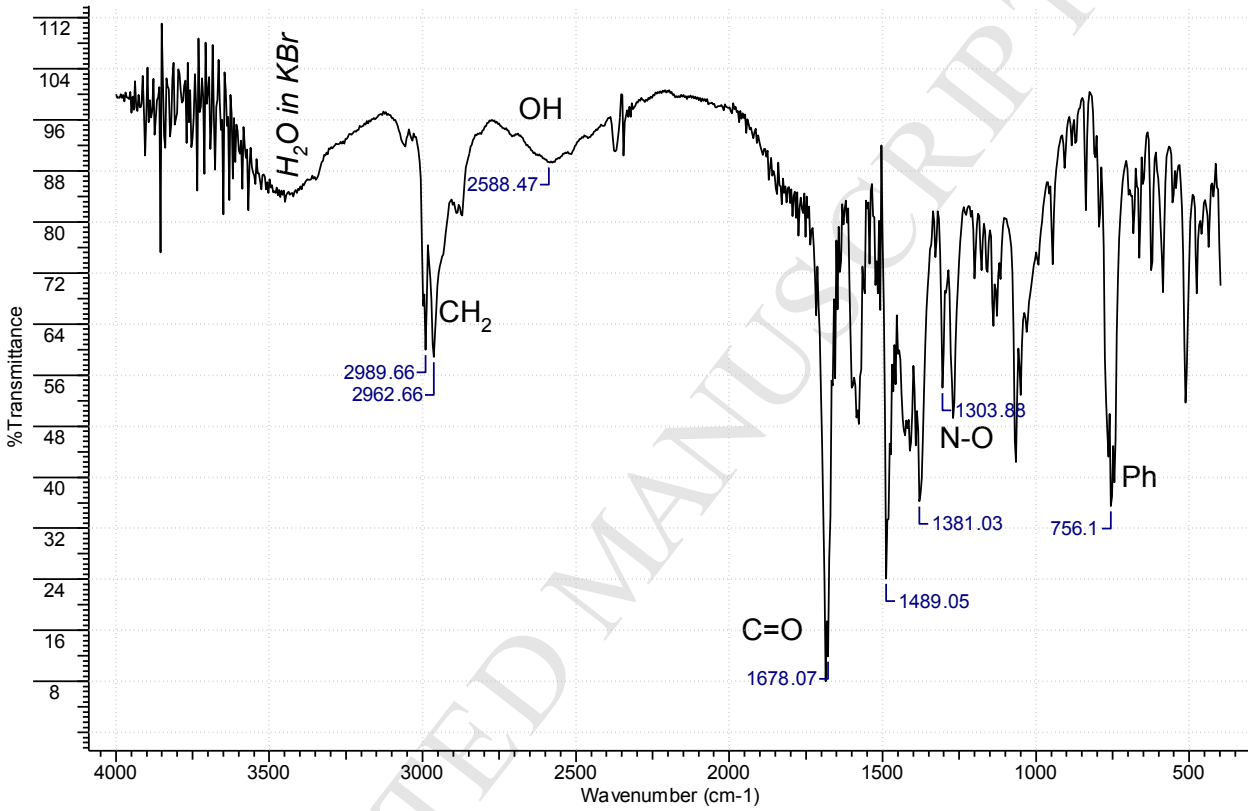
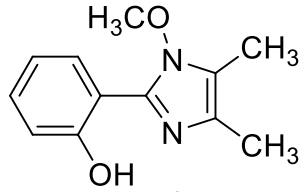


2-(1-Methoxy-4,5-dimethyl-1H-imidazol-2-yl)phenol (15).



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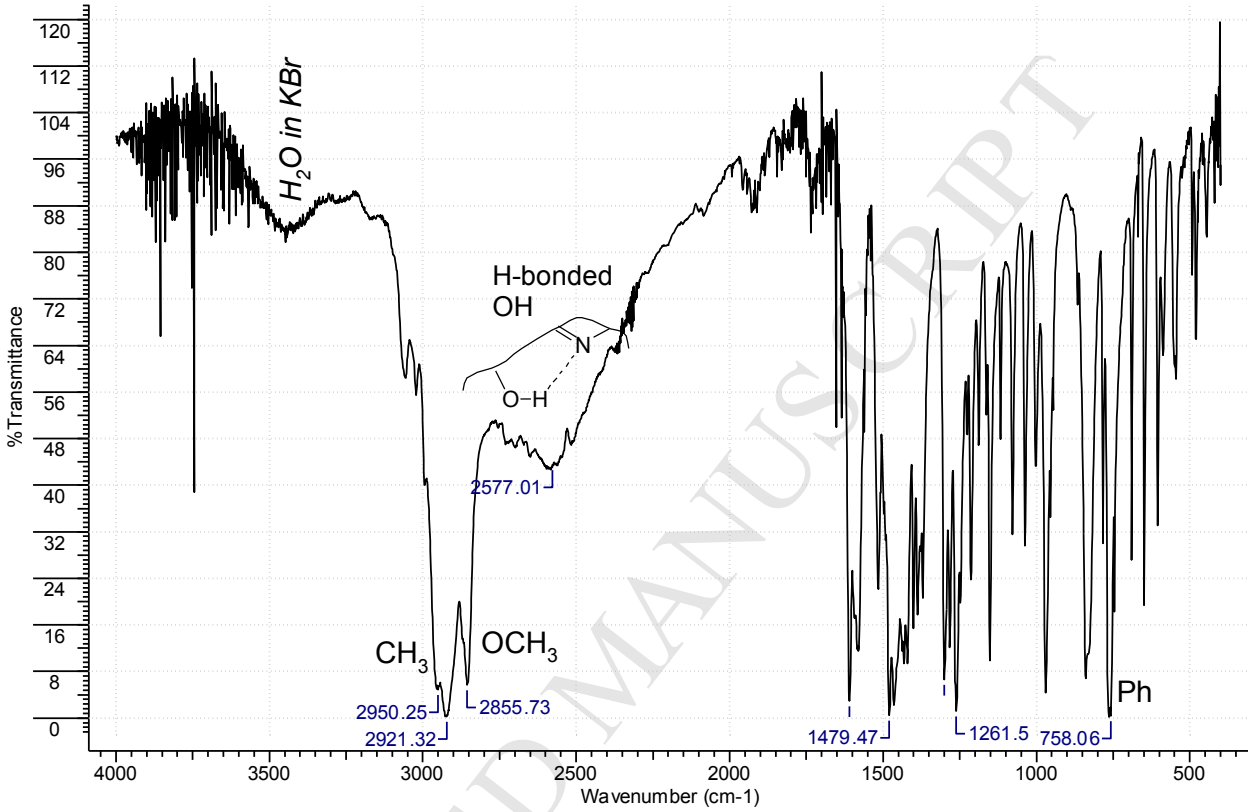
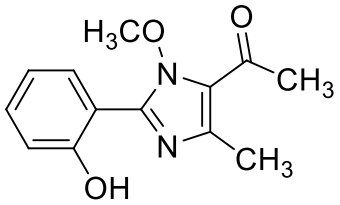


1-(2-(2-hydroxyphenyl)-1-methoxy-4-methyl-1H-imidazol-5-yl)ethanone (16).



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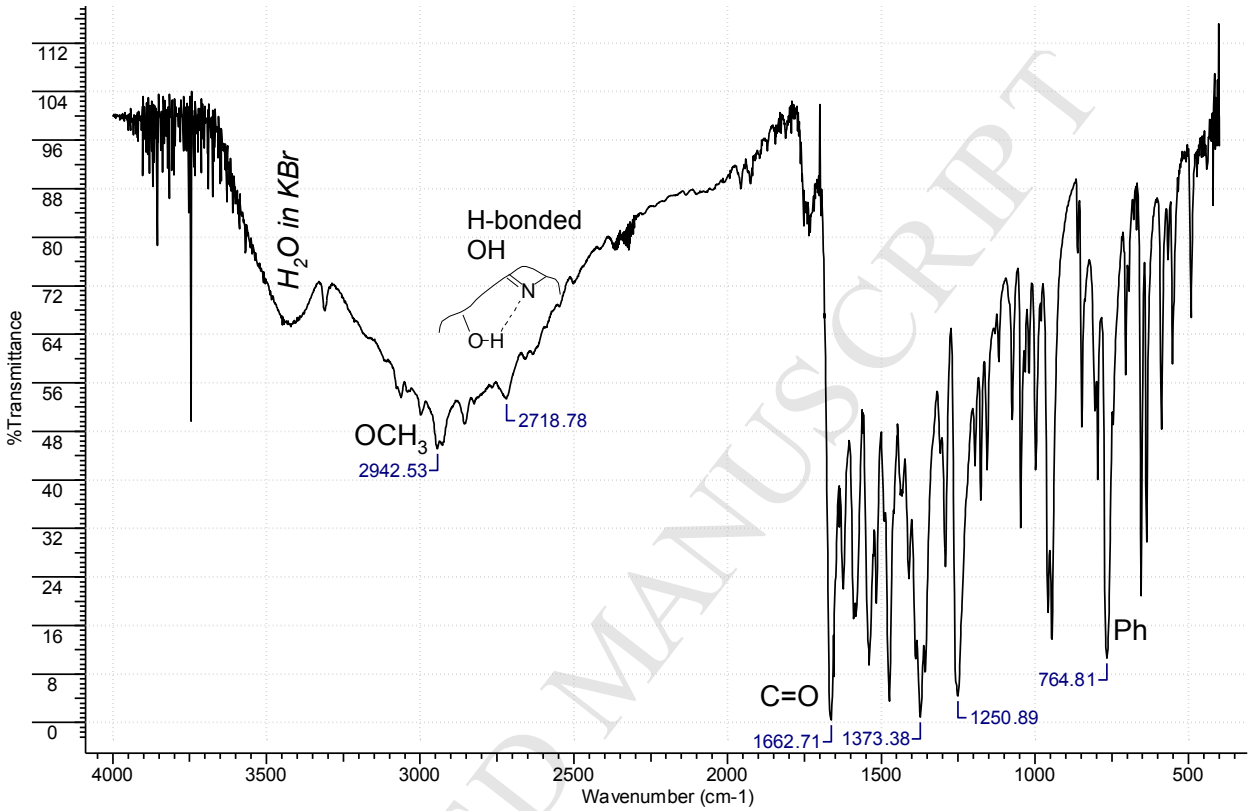
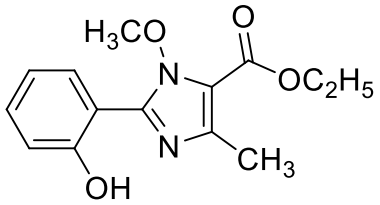
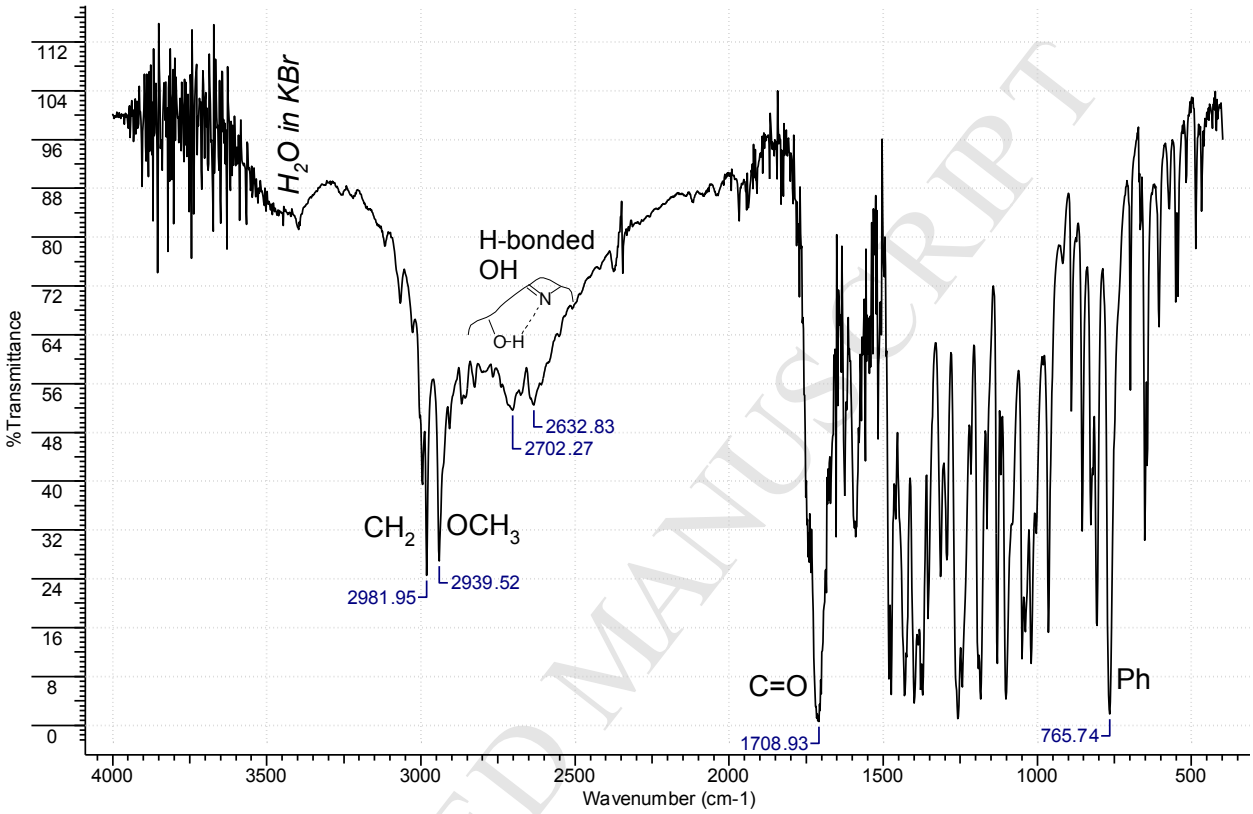


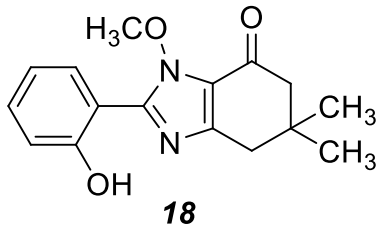
Ethyl 2-(2-hydroxyphenyl)-1-methoxy-4-methyl-1H-imidazole-5-carboxylate (17).



17



2-(2-Hydroxyphenyl)-1-methoxy-5,5-dimethyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-7(4H)-one (**18**).



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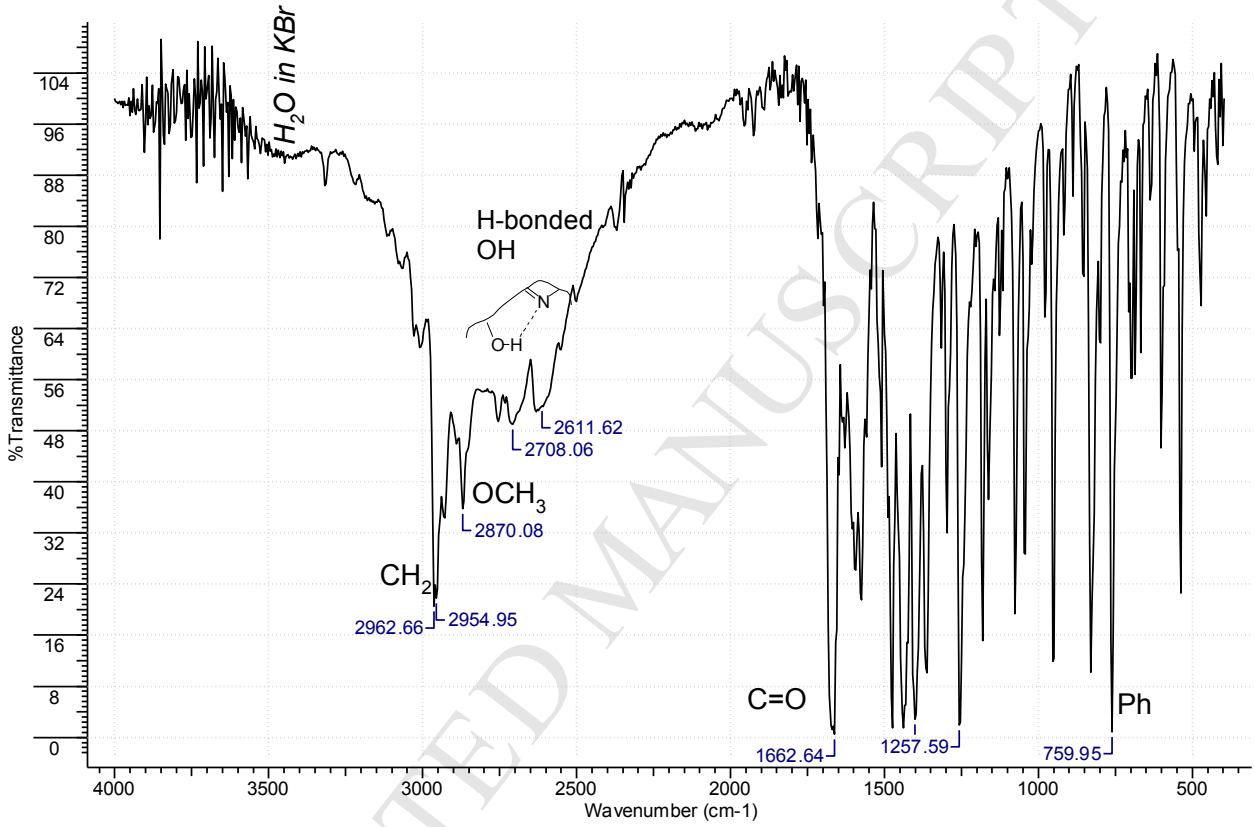
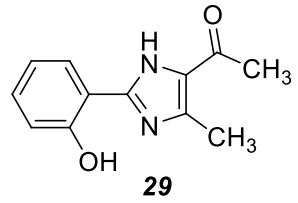


(1-(2-(2-hydroxyphenyl)-4-methyl-1H-imidazol-5-yl)ethanone (29)



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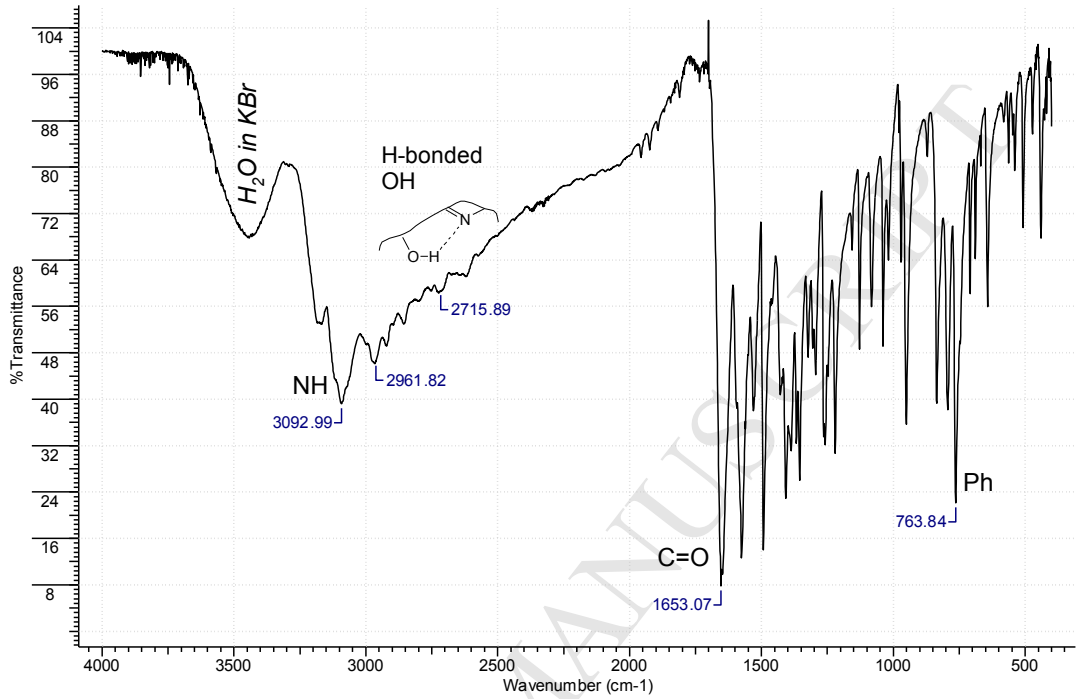
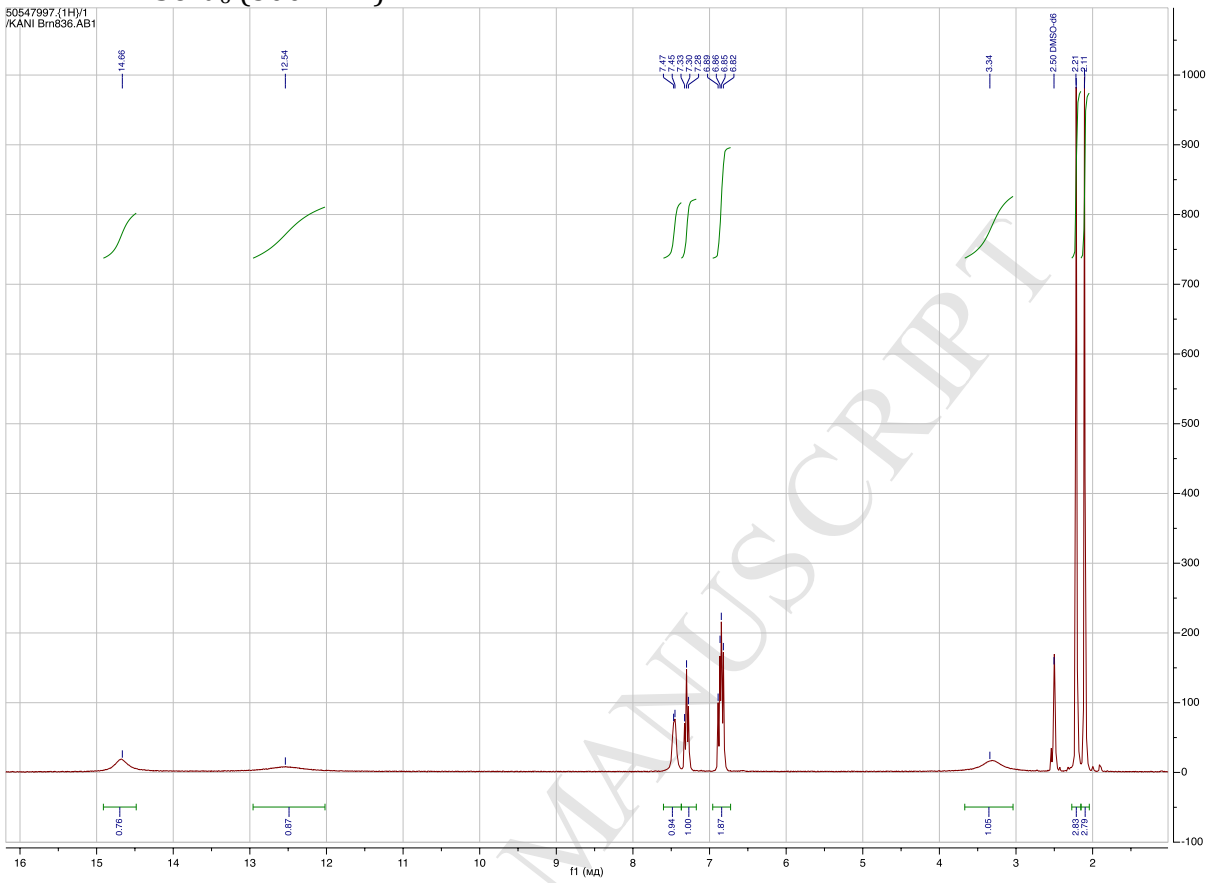


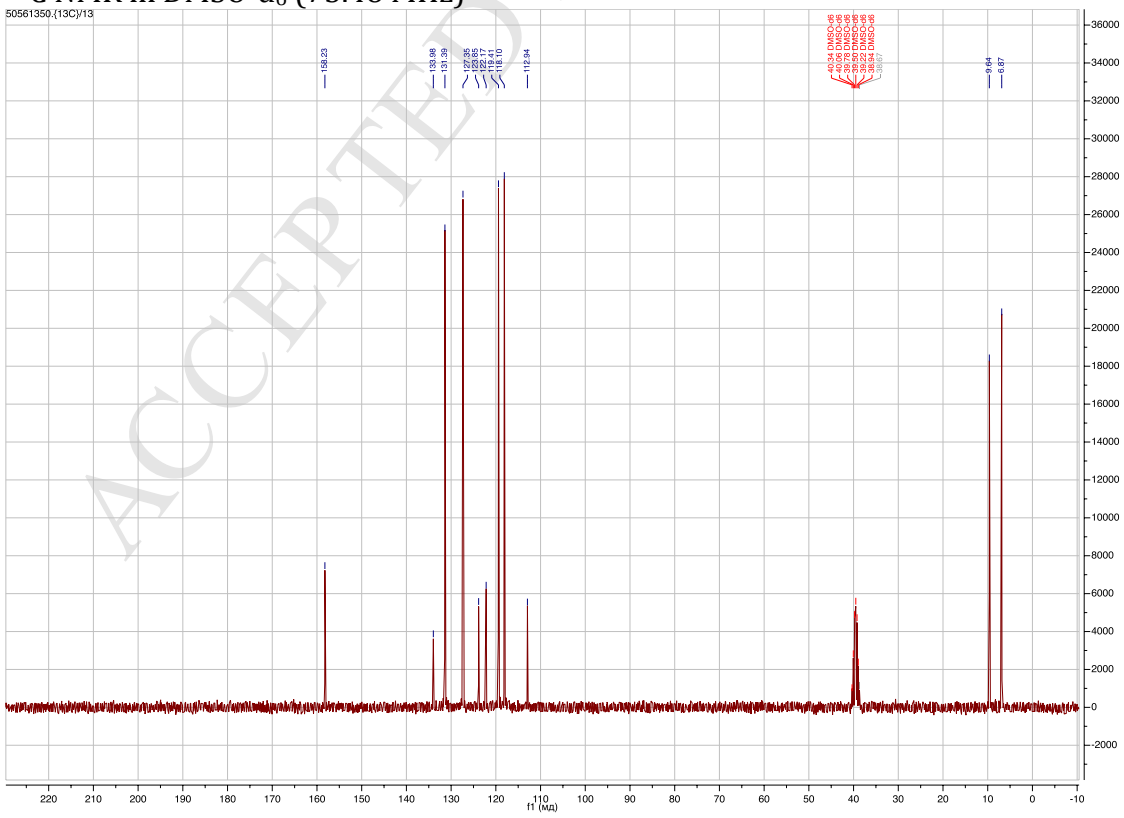
2. Copies of NMR spectra of compounds.

2-(2-Hydroxyphenyl)-4,5-dimethyl-1H-imidazol-1-ol (1).

^{1}H NMR in DMSO-d$_6$ (300 MHz)

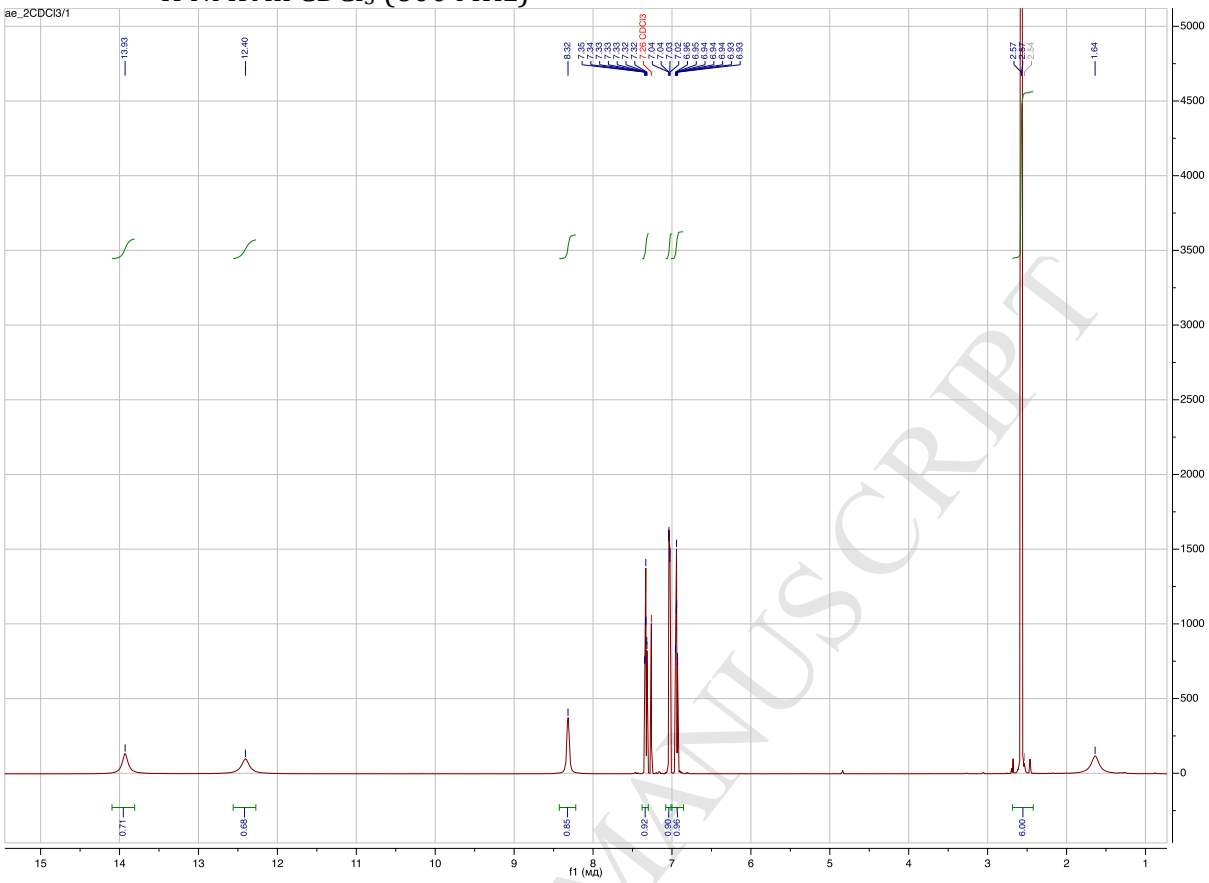


^{13}C NMR in DMSO-d$_6$ (75.48 MHz)

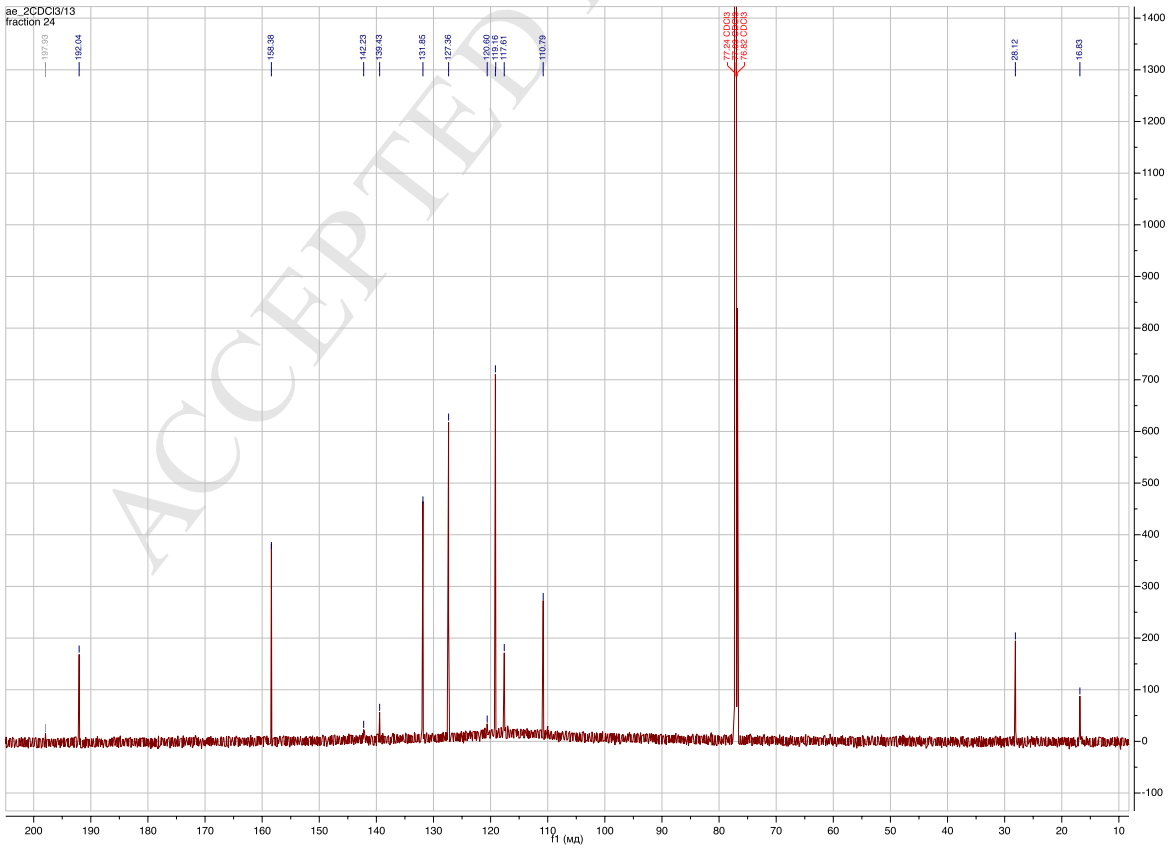


1-(1-Hydroxy-2-(2-hydroxyphenyl)-4-methyl-1H-imidazol-5-yl)ethanone (2).

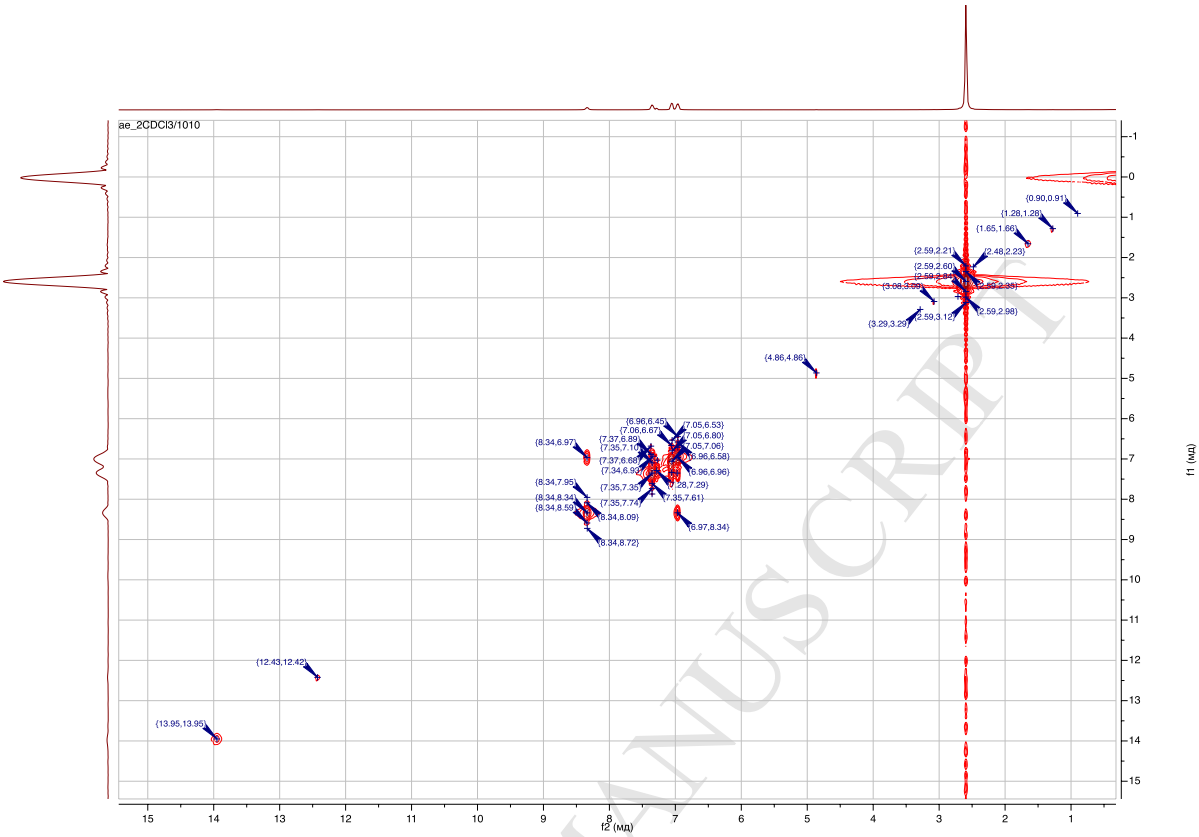
^{1}H NMR in $CDCl_3$ (600 MHz)



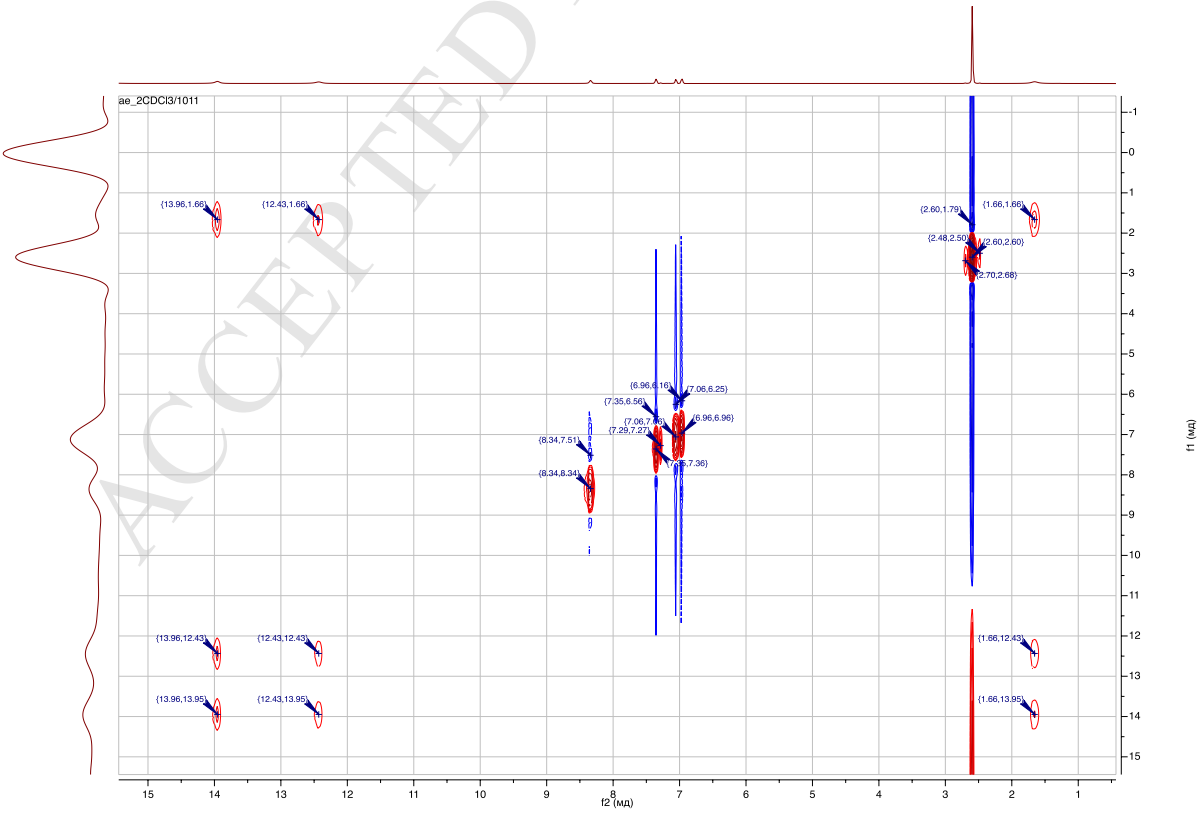
^{13}C NMR in $CDCl_3$ (150.94 MHz)



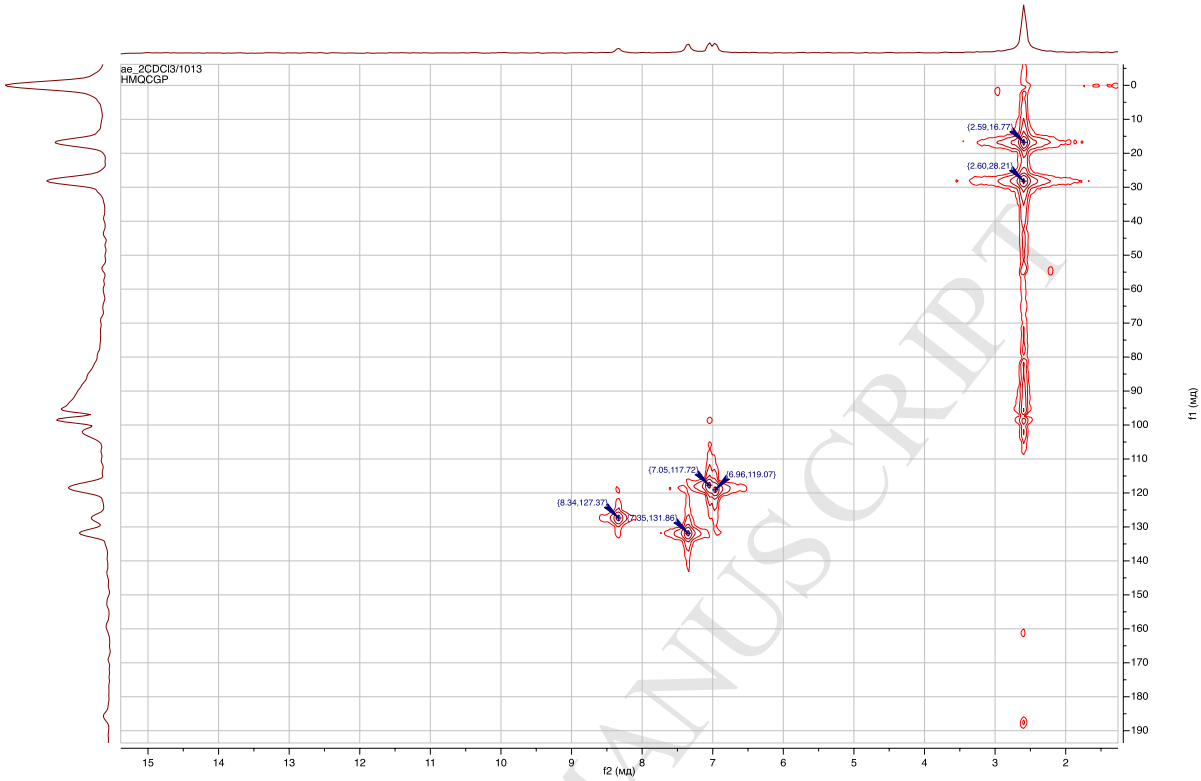
2D COSY NMR in $CDCl_3$ (600 MHz)



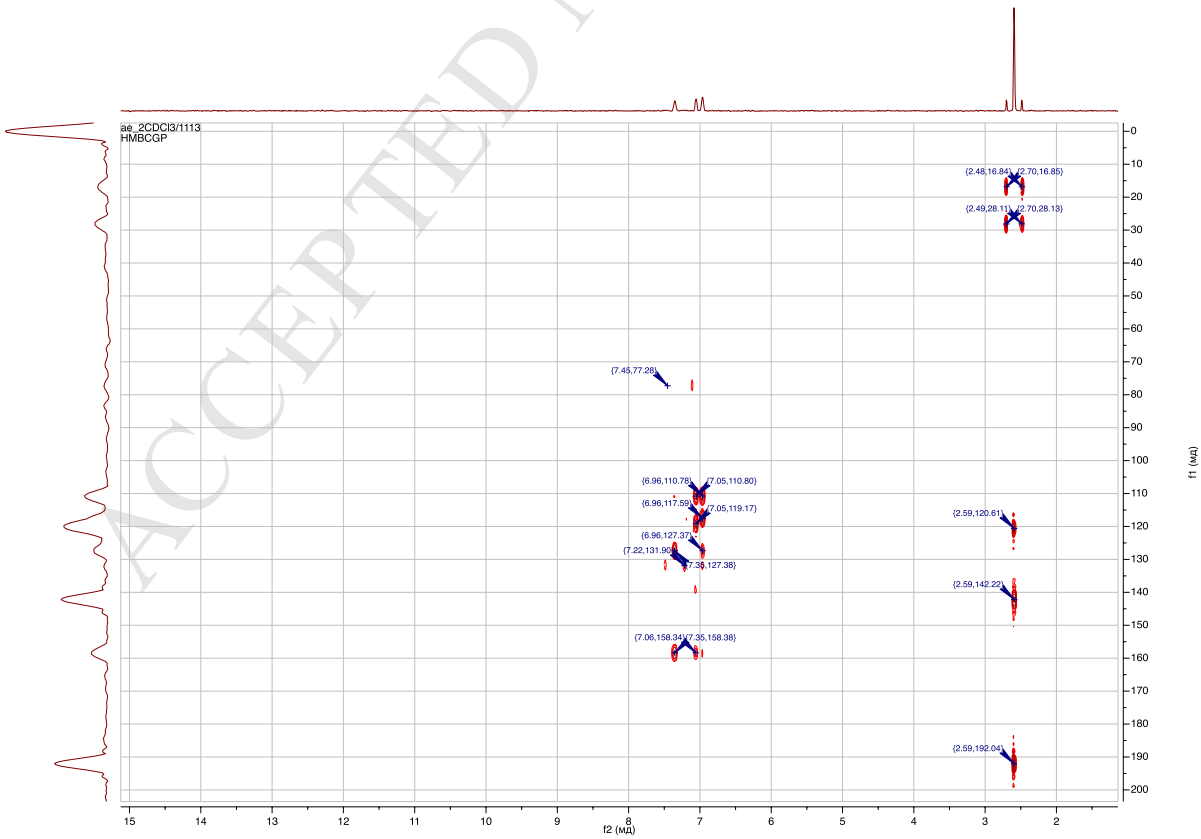
2D NOESY NMR in $CDCl_3$ (600 MHz)



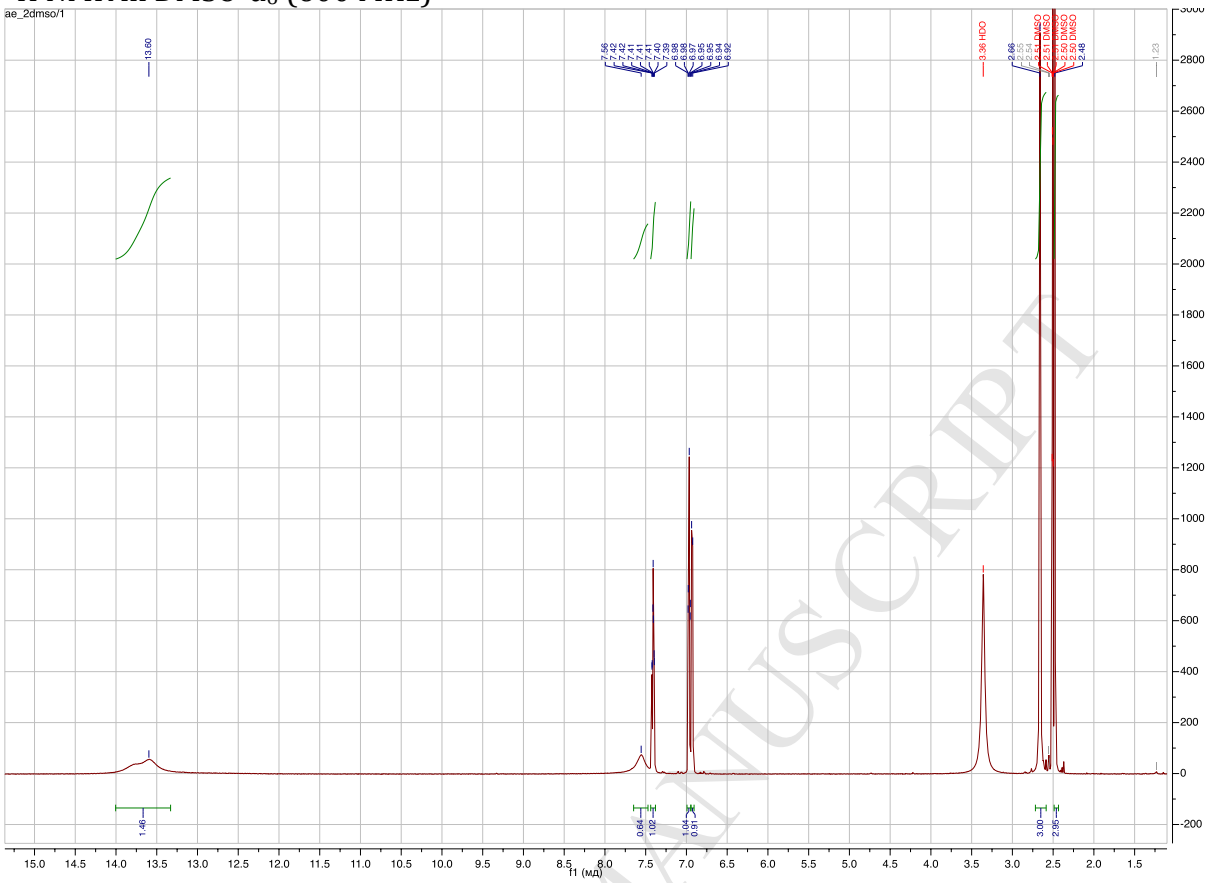
2D HMQC NMR in $CDCl_3$ (600 MHz)



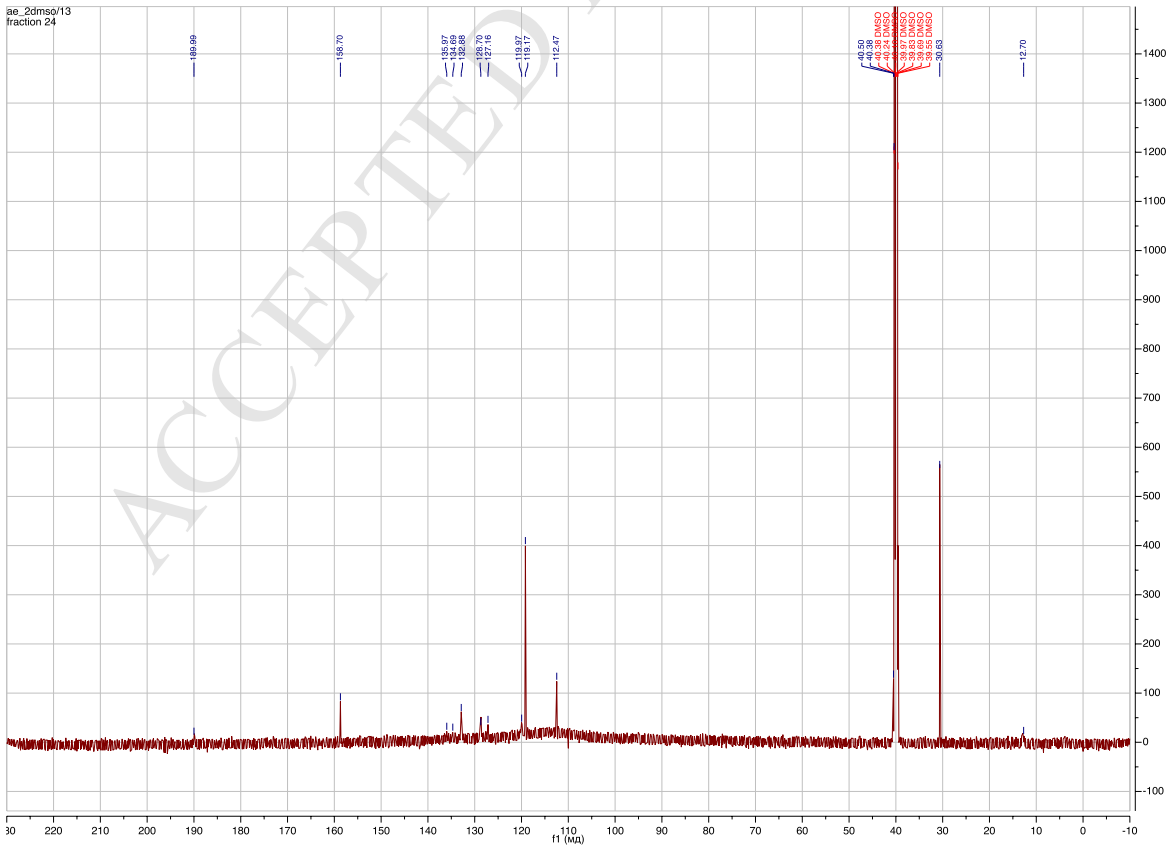
2D HMBC NMR in $CDCl_3$ (600 MHz)



^{1}H NMR in DMSO-d_6 (600 MHz)

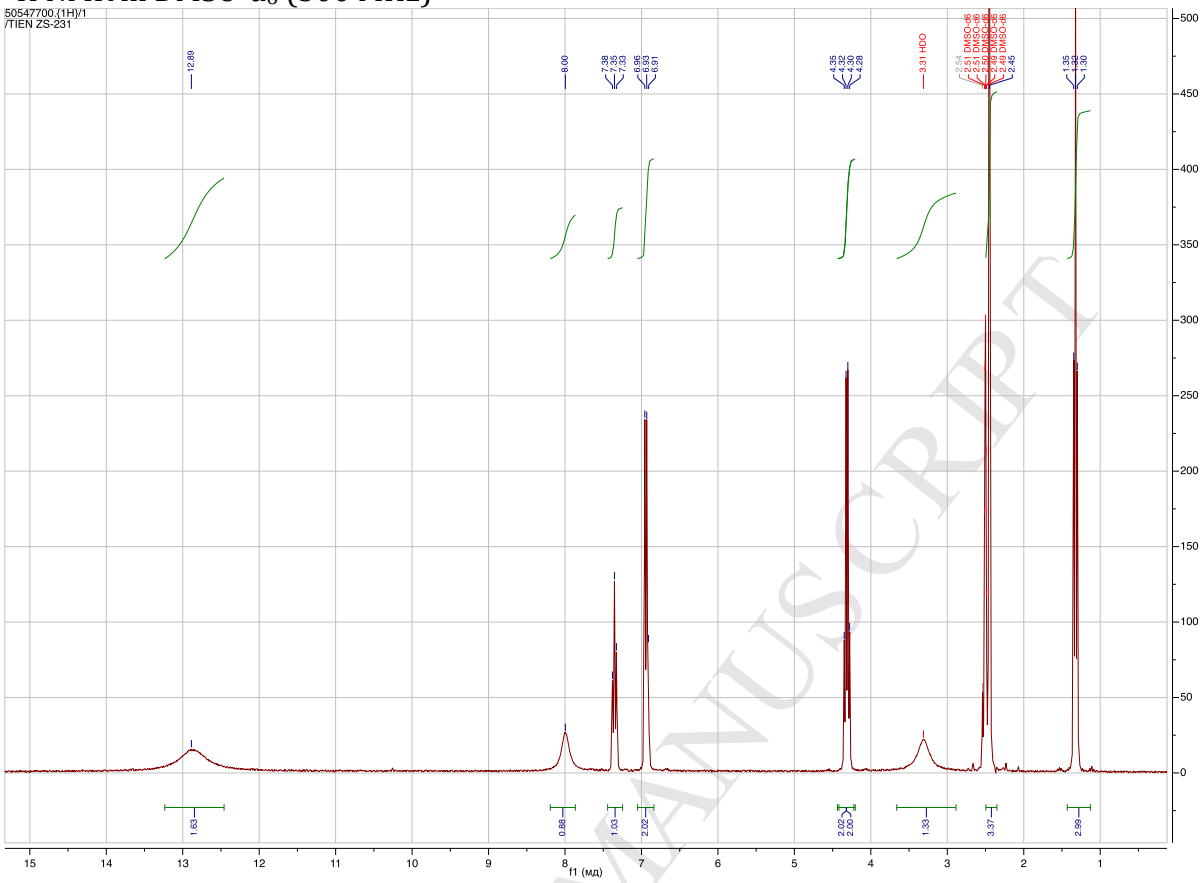


^{13}C NMR in DMSO-d_6 (151 MHz)

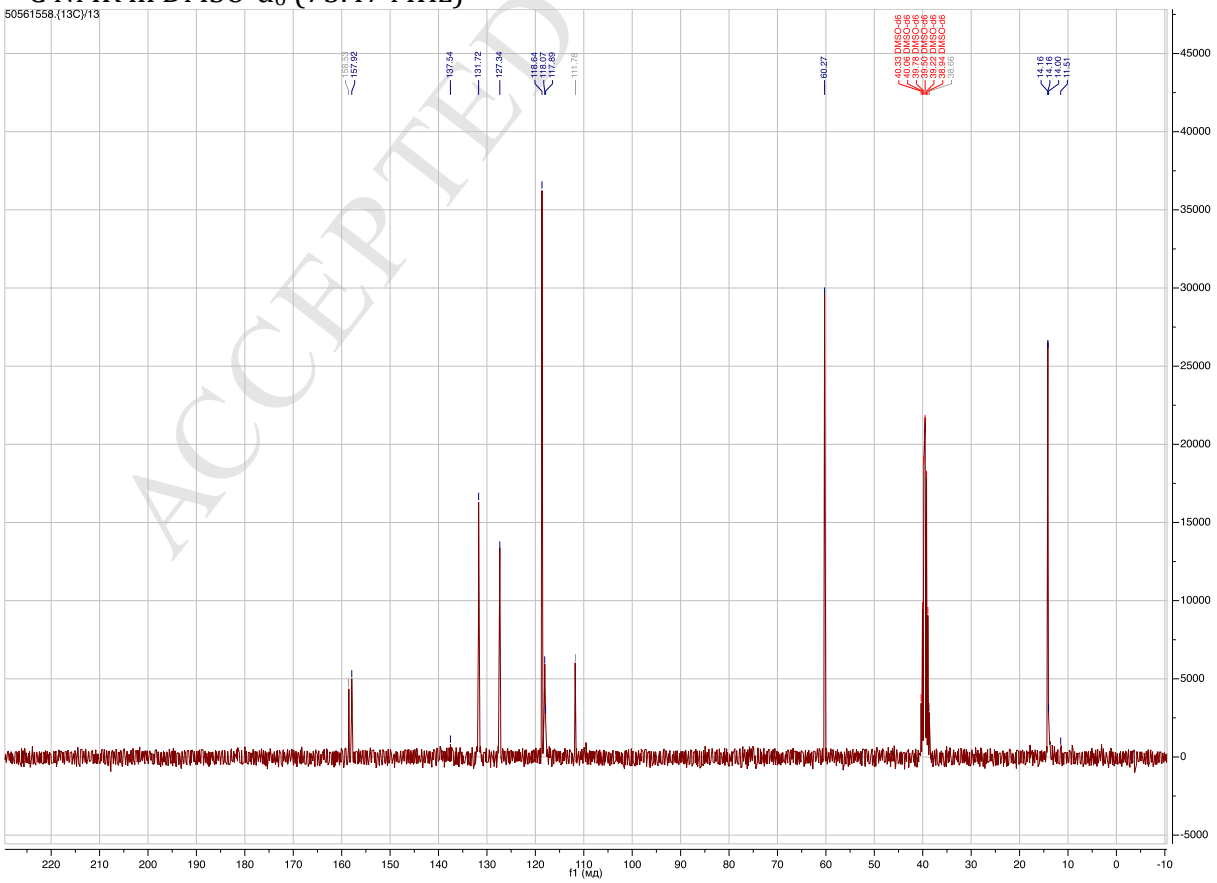


Ethyl 1-hydroxy-2-(2-hydroxyphenyl)-4-methyl-1H-imidazole-5-carboxylate (3).

^{1}H NMR in DMSO-d$_6$ (300 MHz)

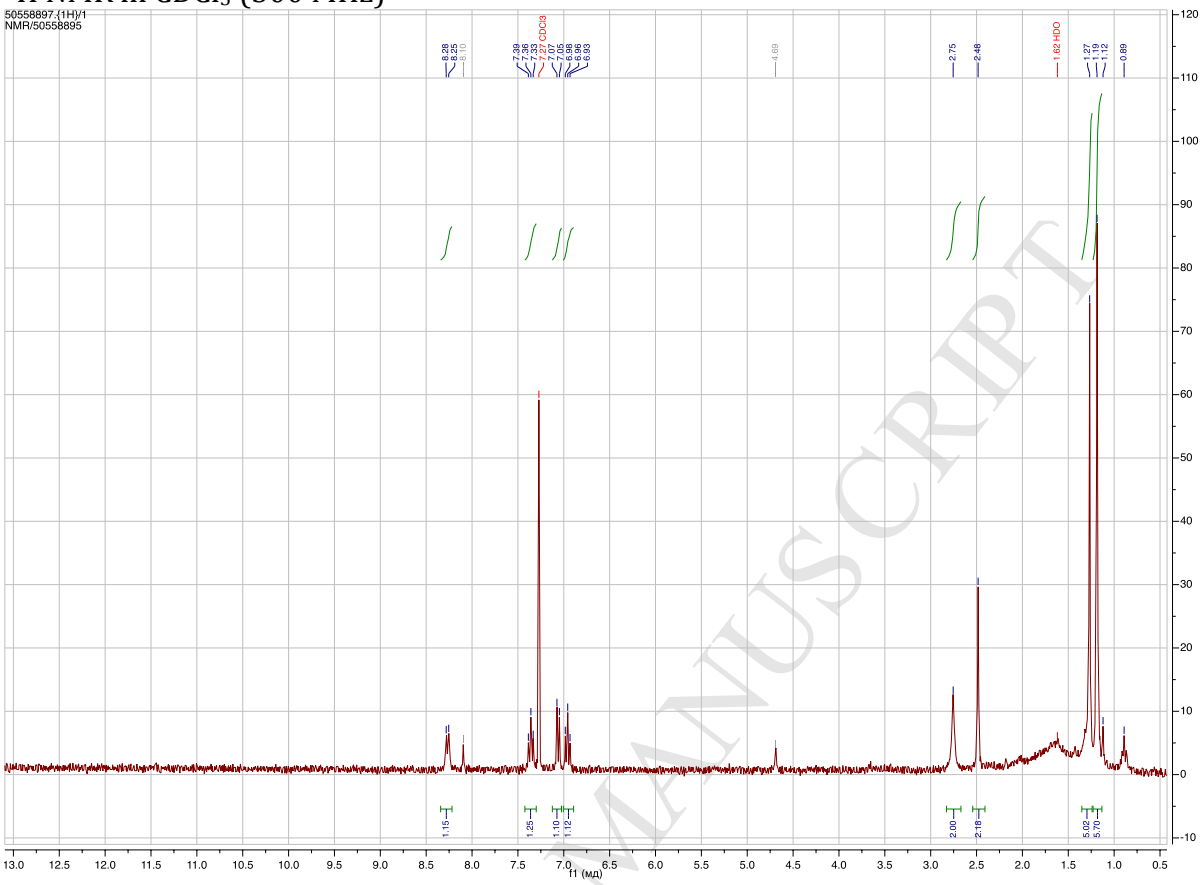


^{13}C NMR in DMSO-d$_6$ (75.47 MHz)

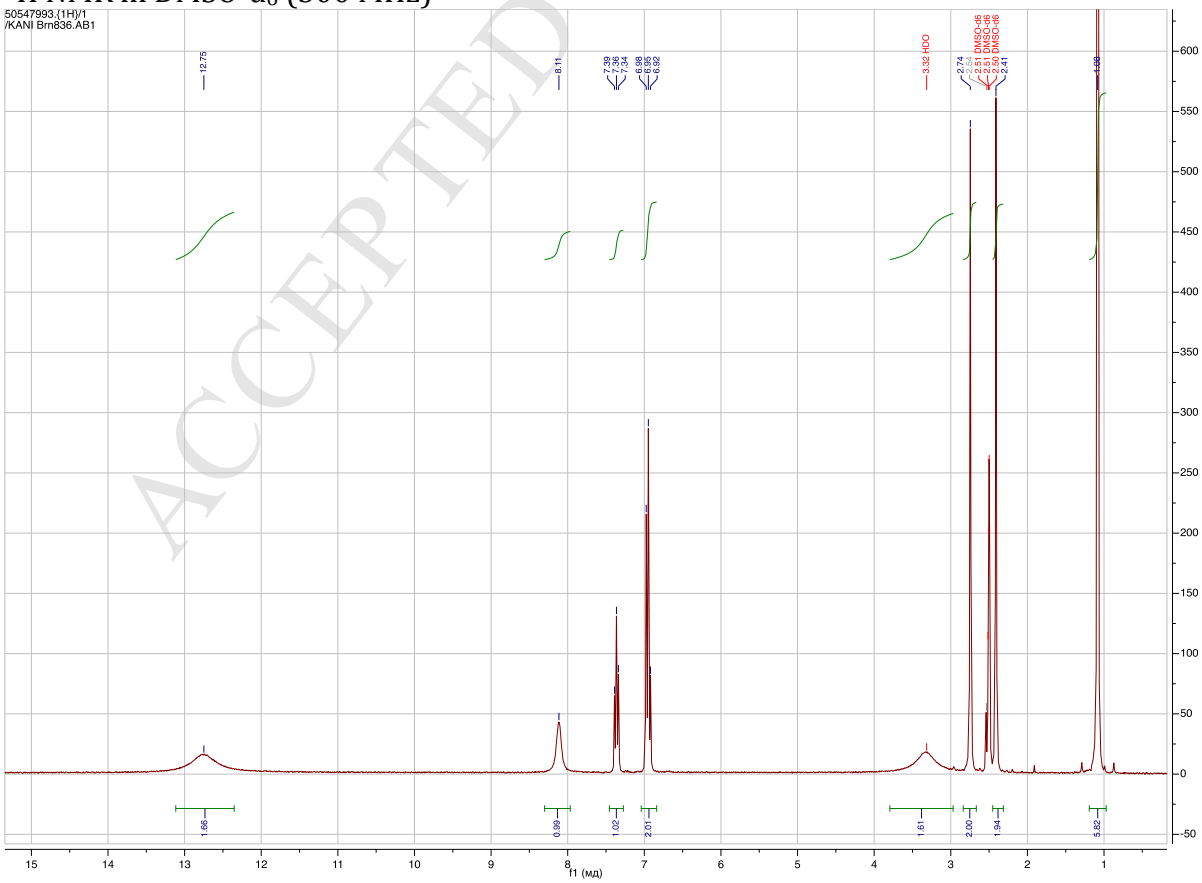


1-Hydroxy-2-(2-hydroxyphenyl)-5,5-dimethyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-7(4H)-one (**4**).

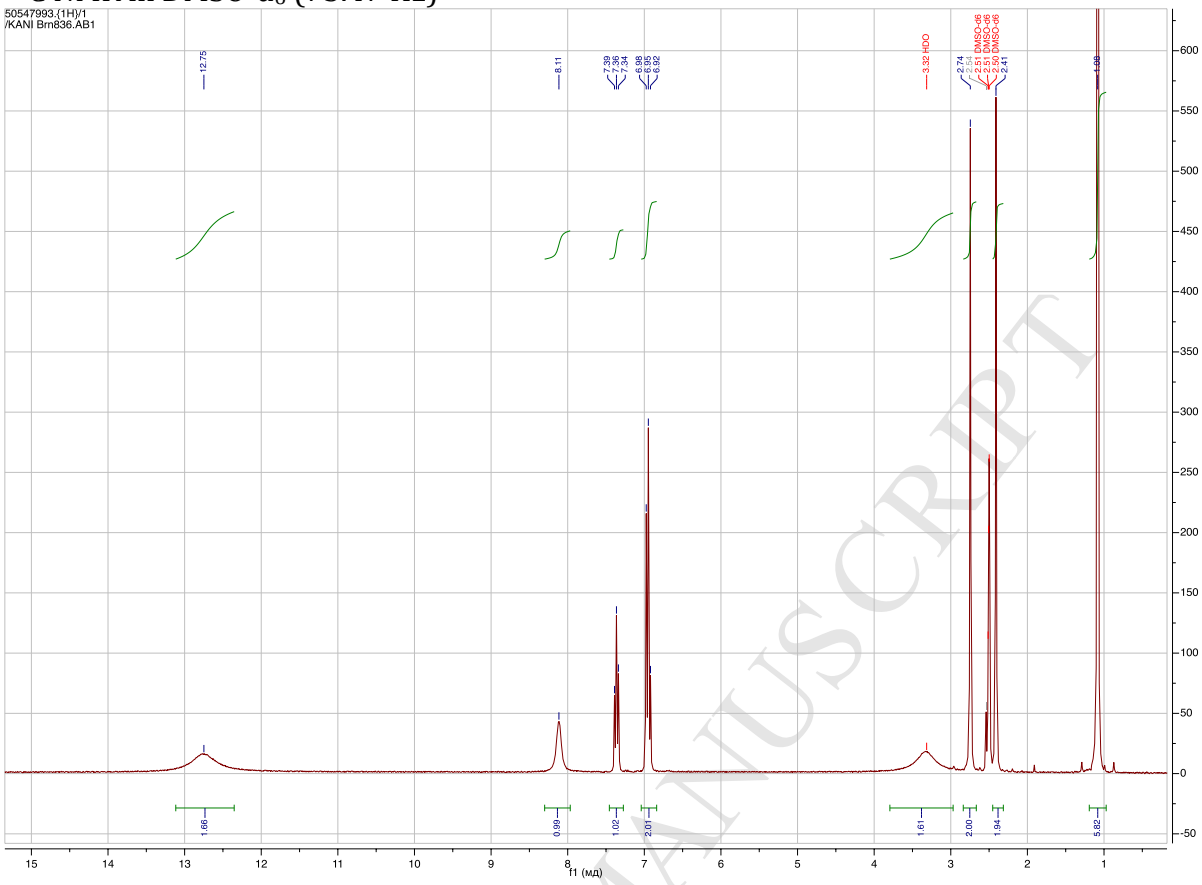
^{1}H NMR in $CDCl_3$ (300 MHz)



^{1}H NMR in DMSO-d_6 (300 MHz)

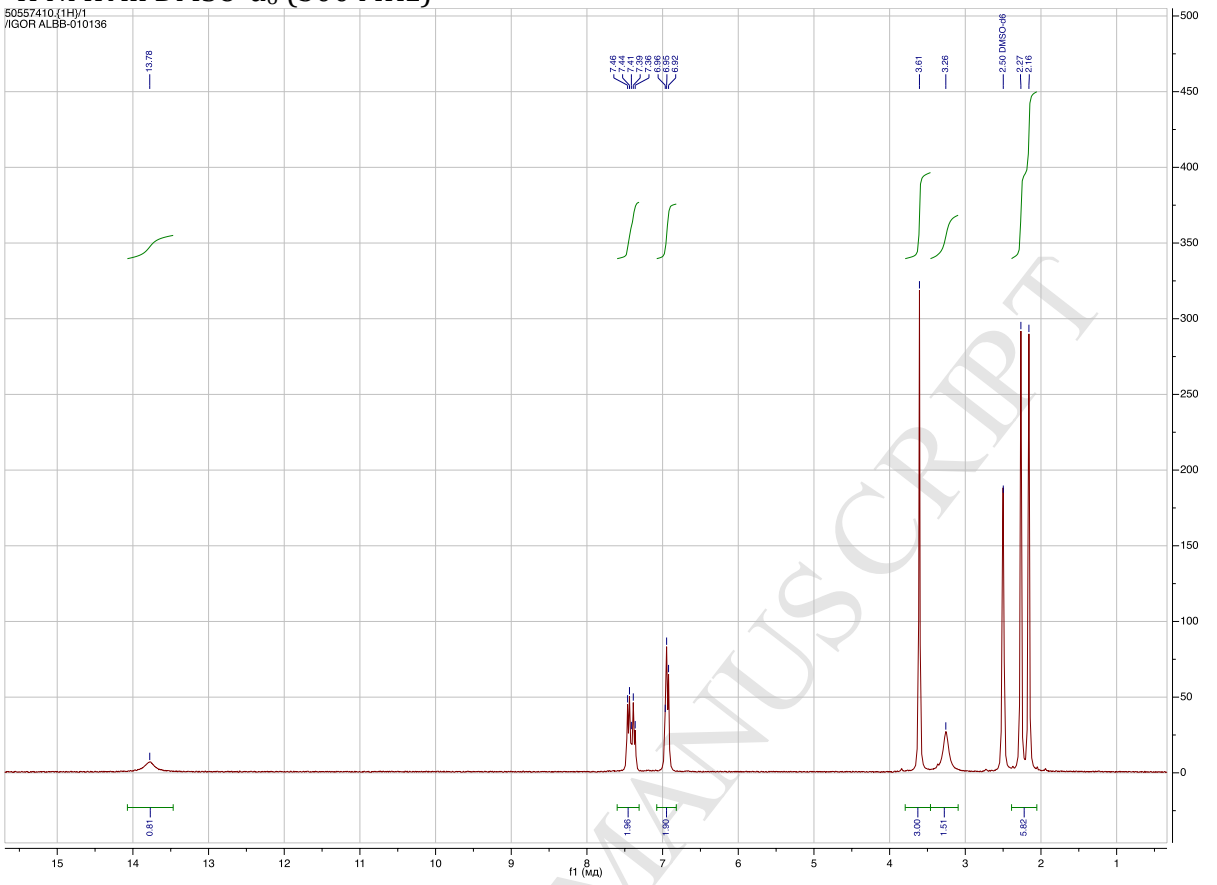


^{13}C NMR in DMSO-d_6 (75.47 Hz)

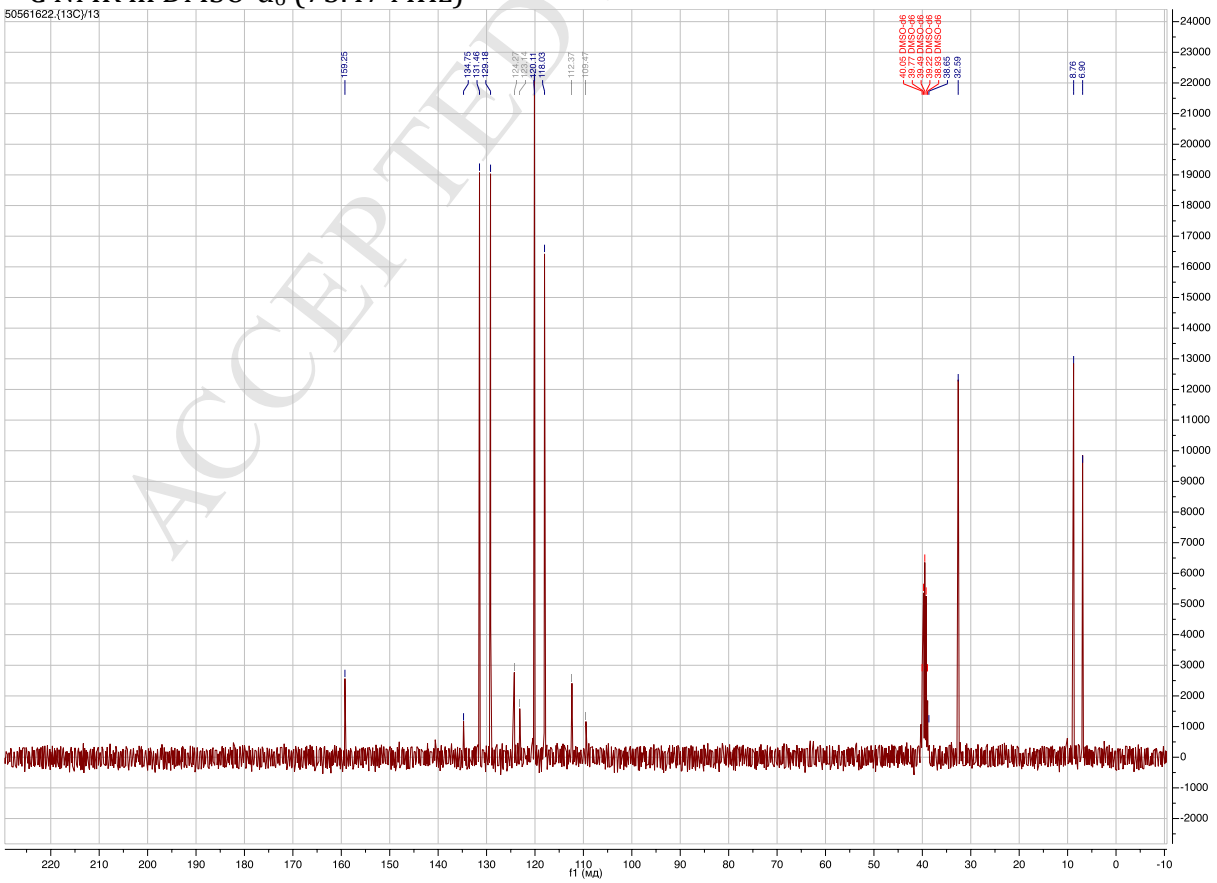


2-(2-Hydroxyphenyl)-1,4,5-trimethyl-1H-imidazole 3-oxide (10).

^{1}H NMR in DMSO-d$_6$ (300 MHz)

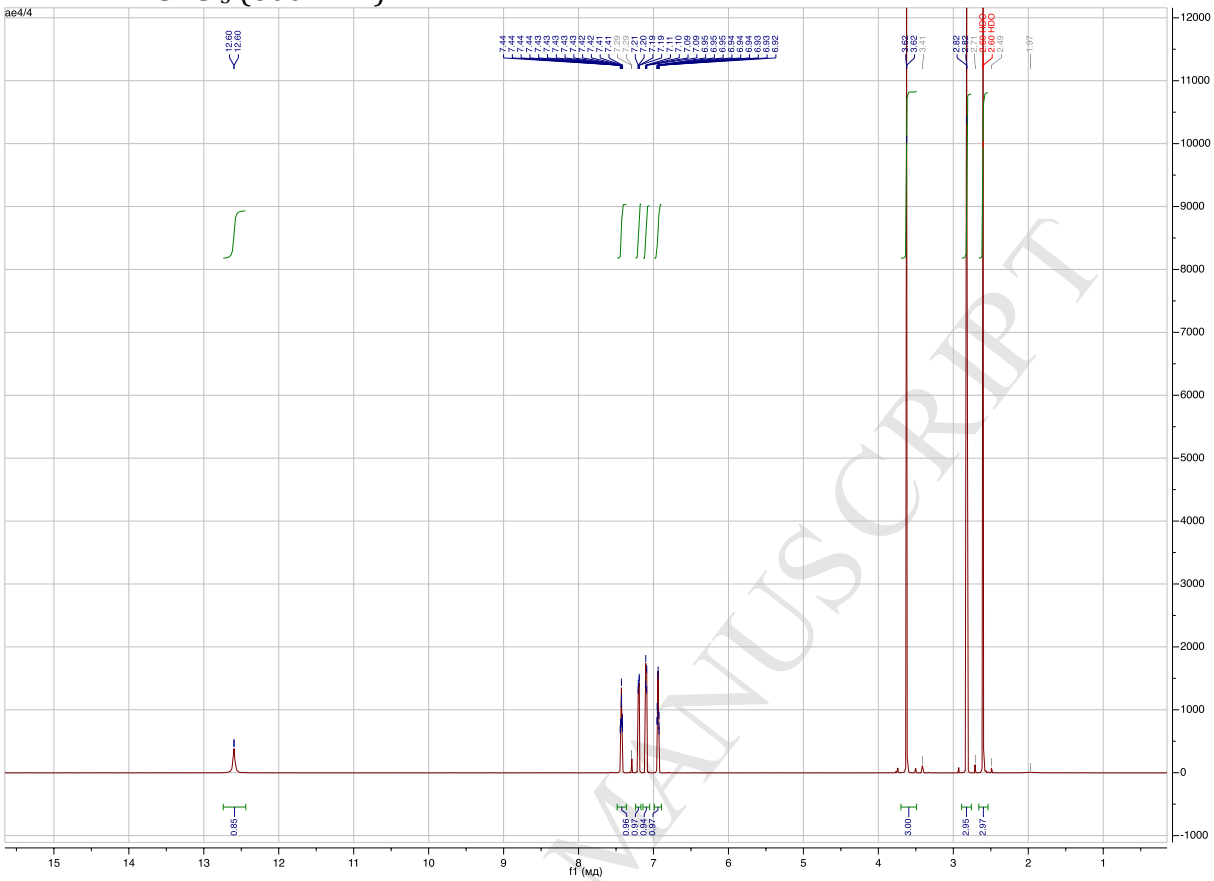


^{13}C NMR in DMSO-d$_6$ (75.47 MHz)

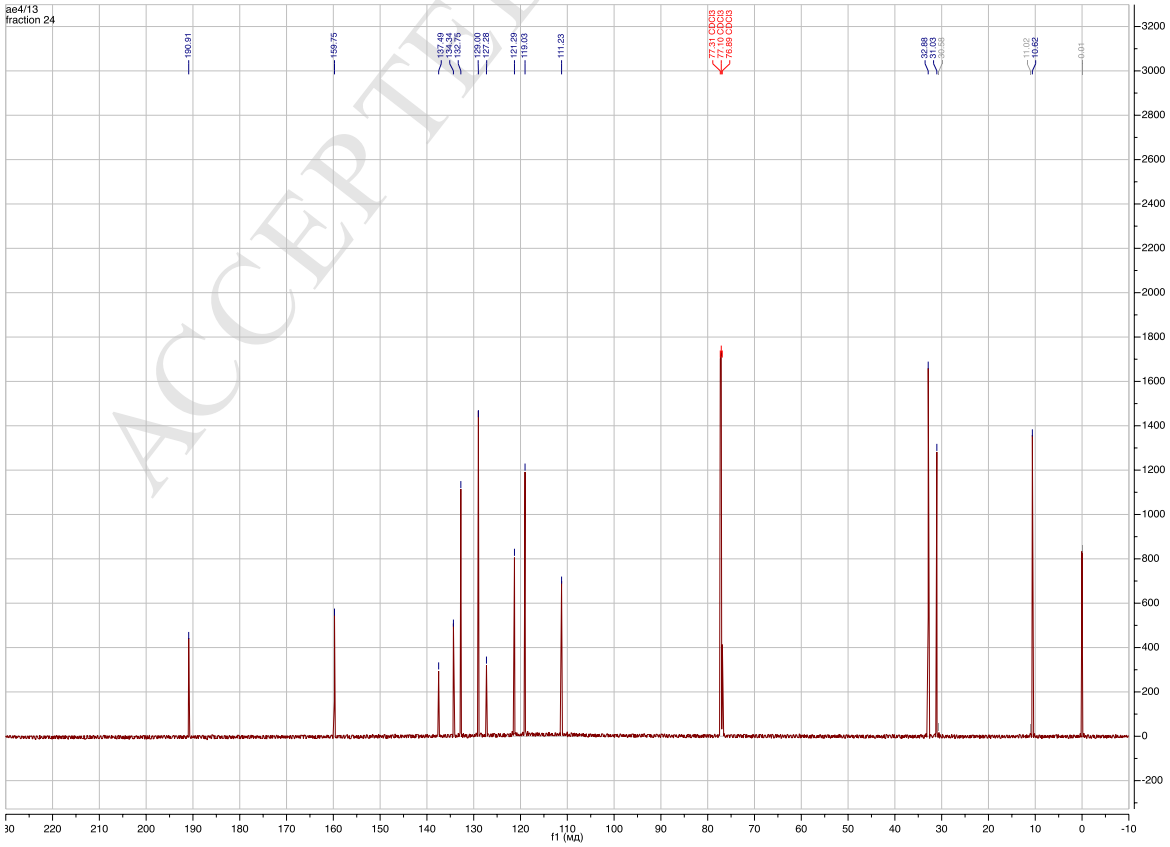


4-Acetyl-2-(2-hydroxyphenyl)-1,5-dimethyl-1H-imidazole 3-oxide (11).

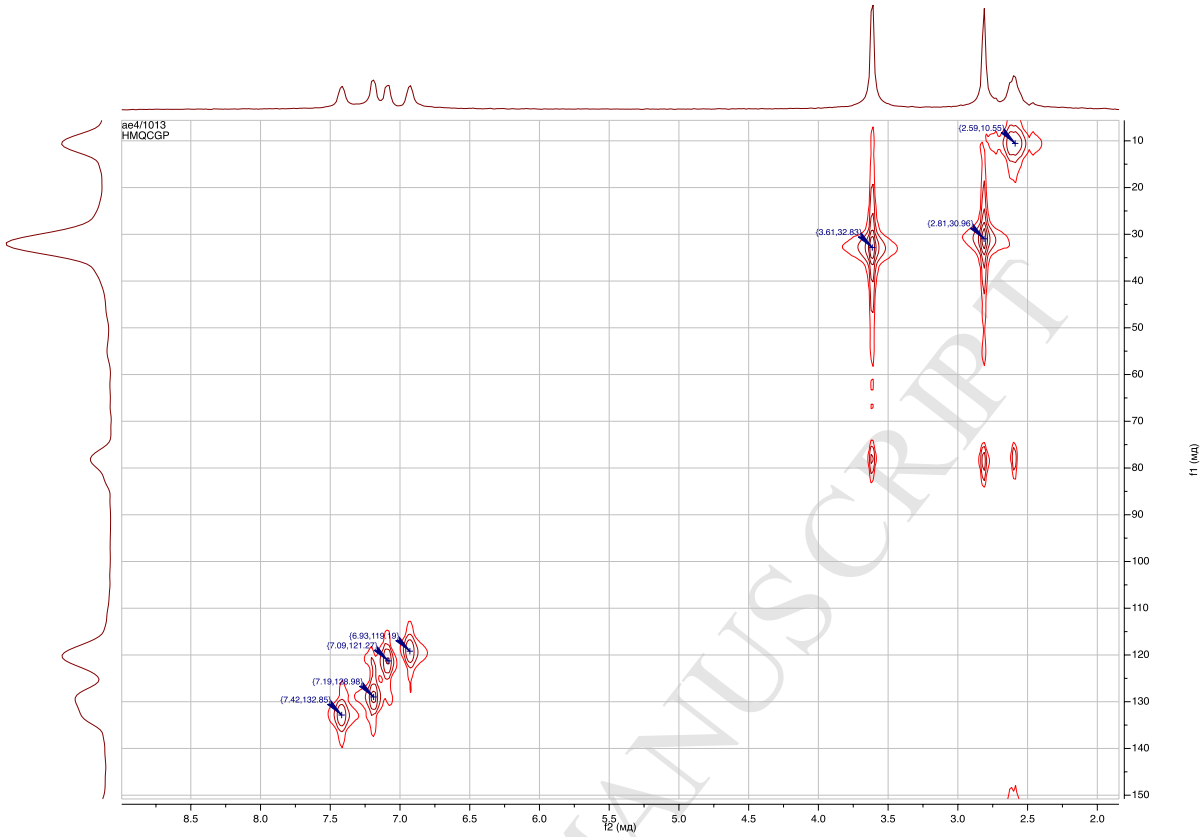
^{1}H NMR in $CDCl_3$ (600 MHz)



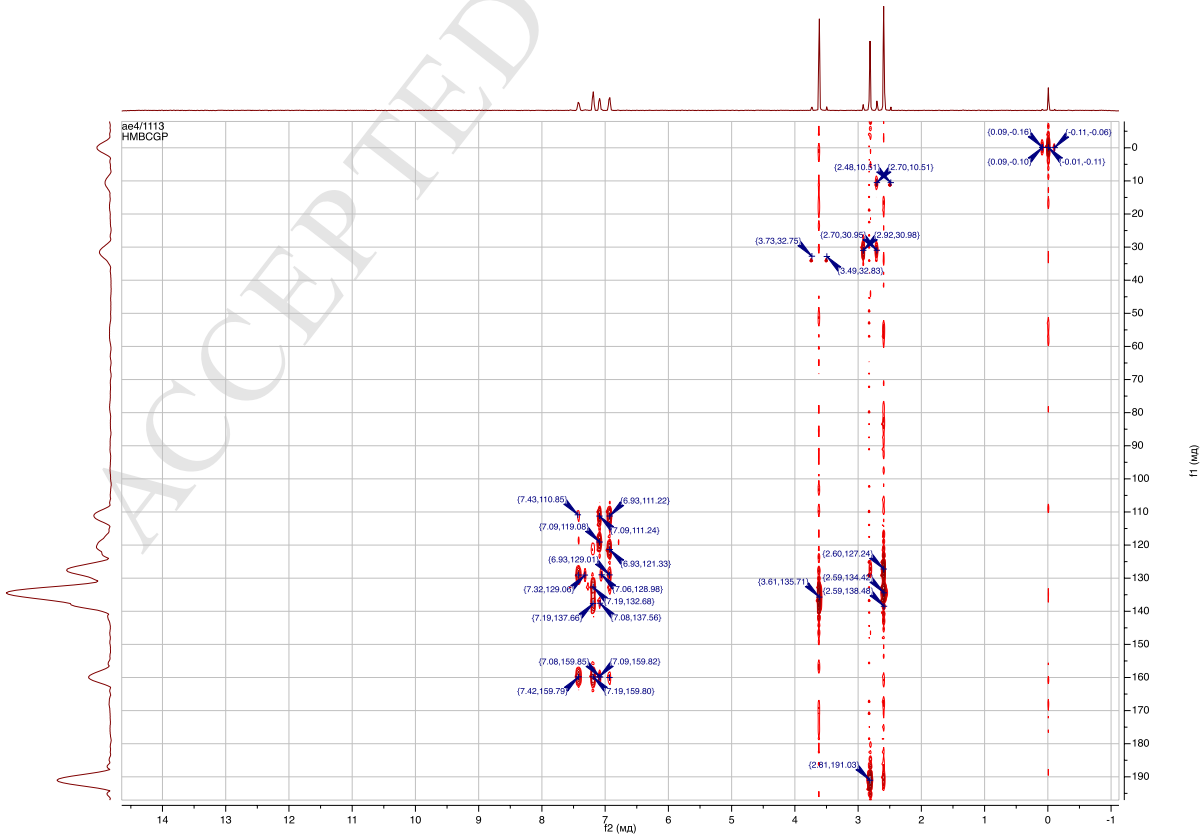
^{13}C NMR in $CDCl_3$ (150.94 MHz)



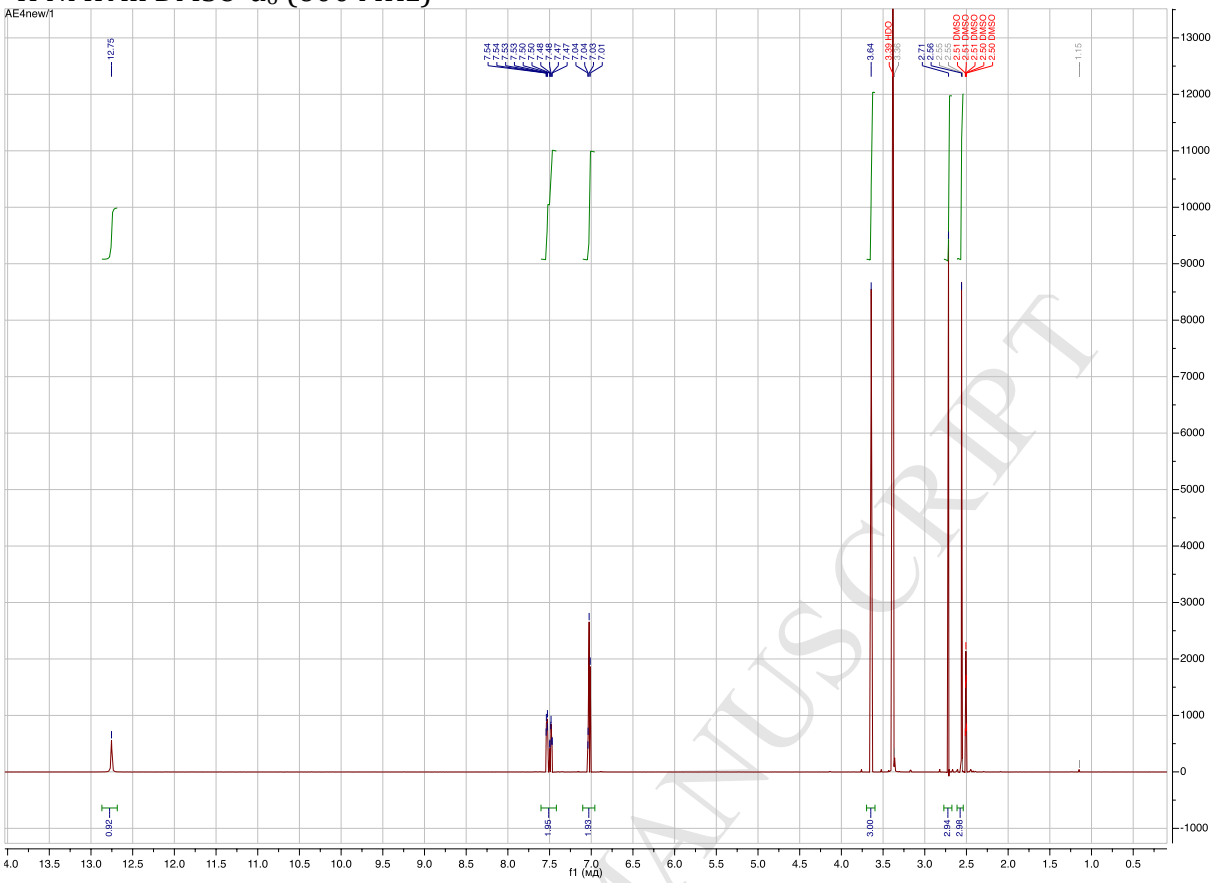
2D HMQC NMR in $CDCl_3$ (600 MHz)



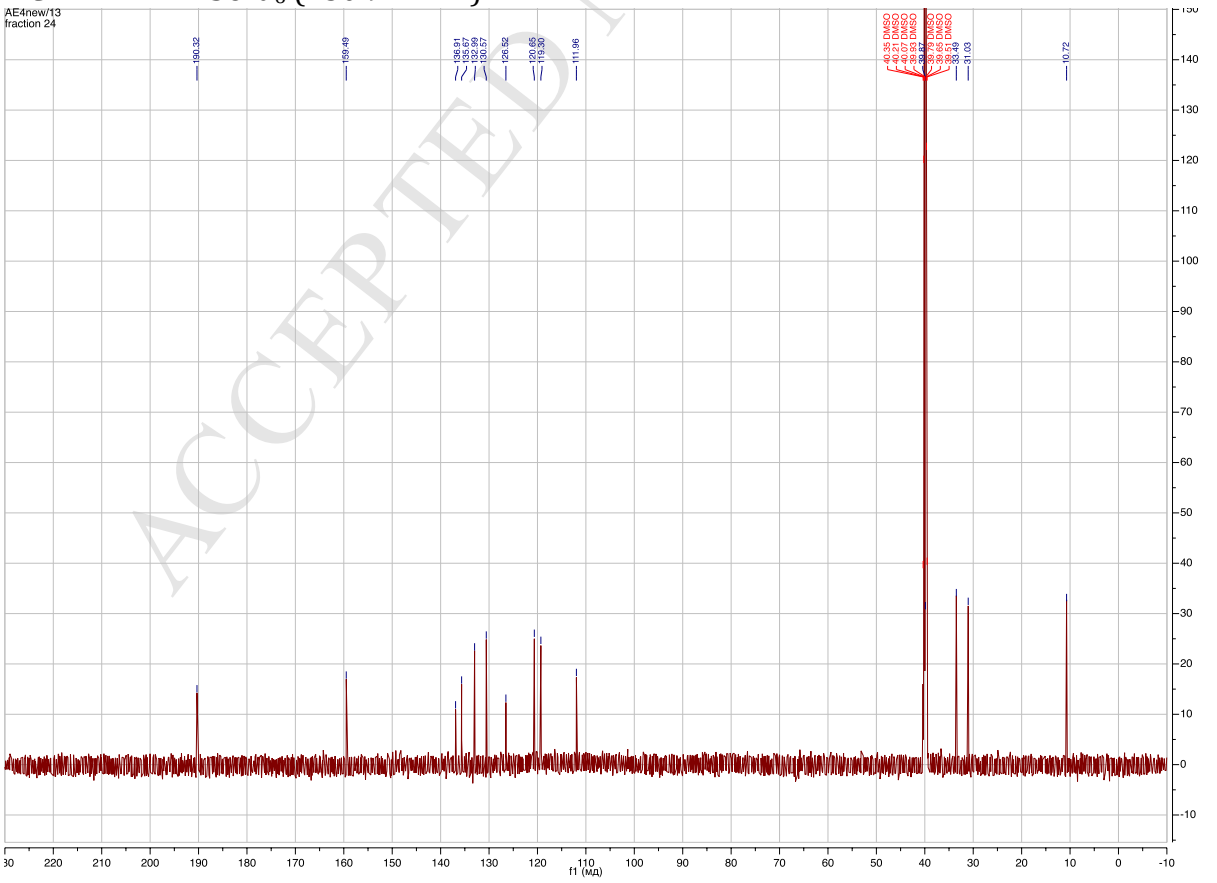
2D HMBC NMR in $CDCl_3$ (600 MHz)



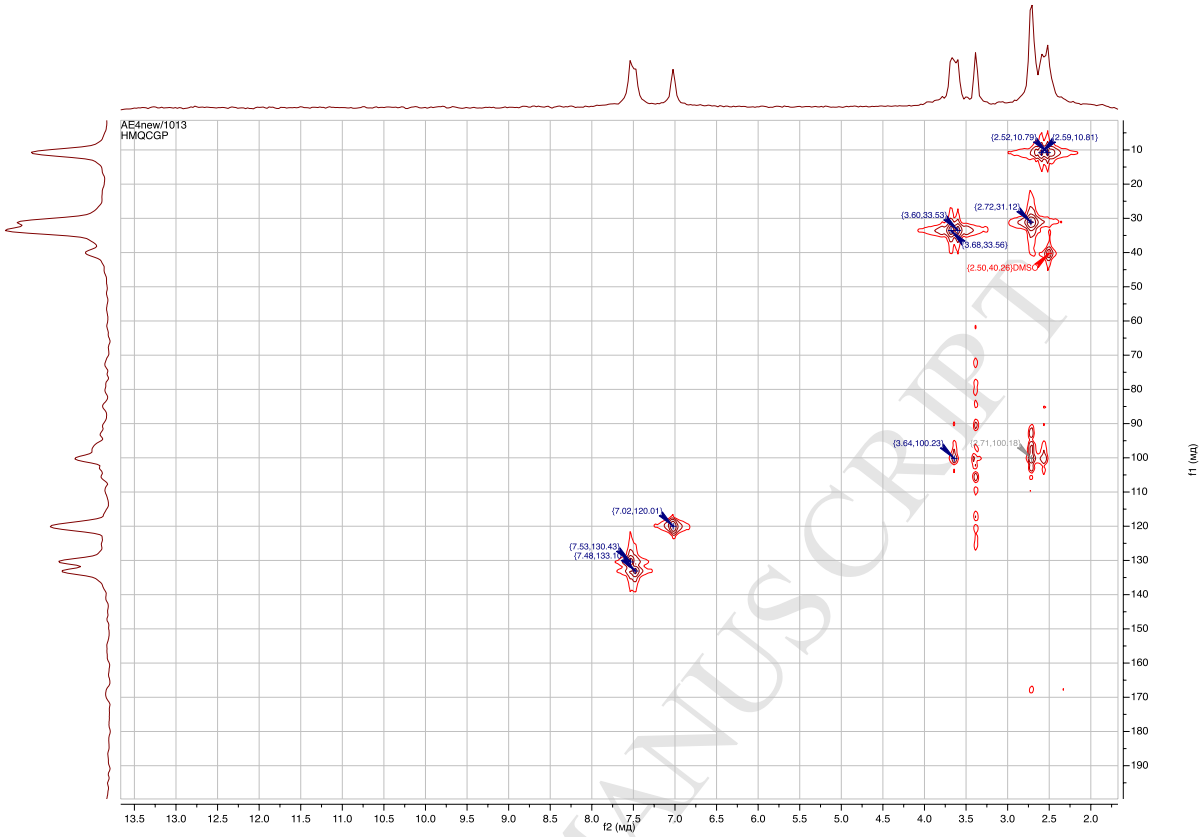
^{1}H NMR in DMSO-d$_6$ (600 MHz)



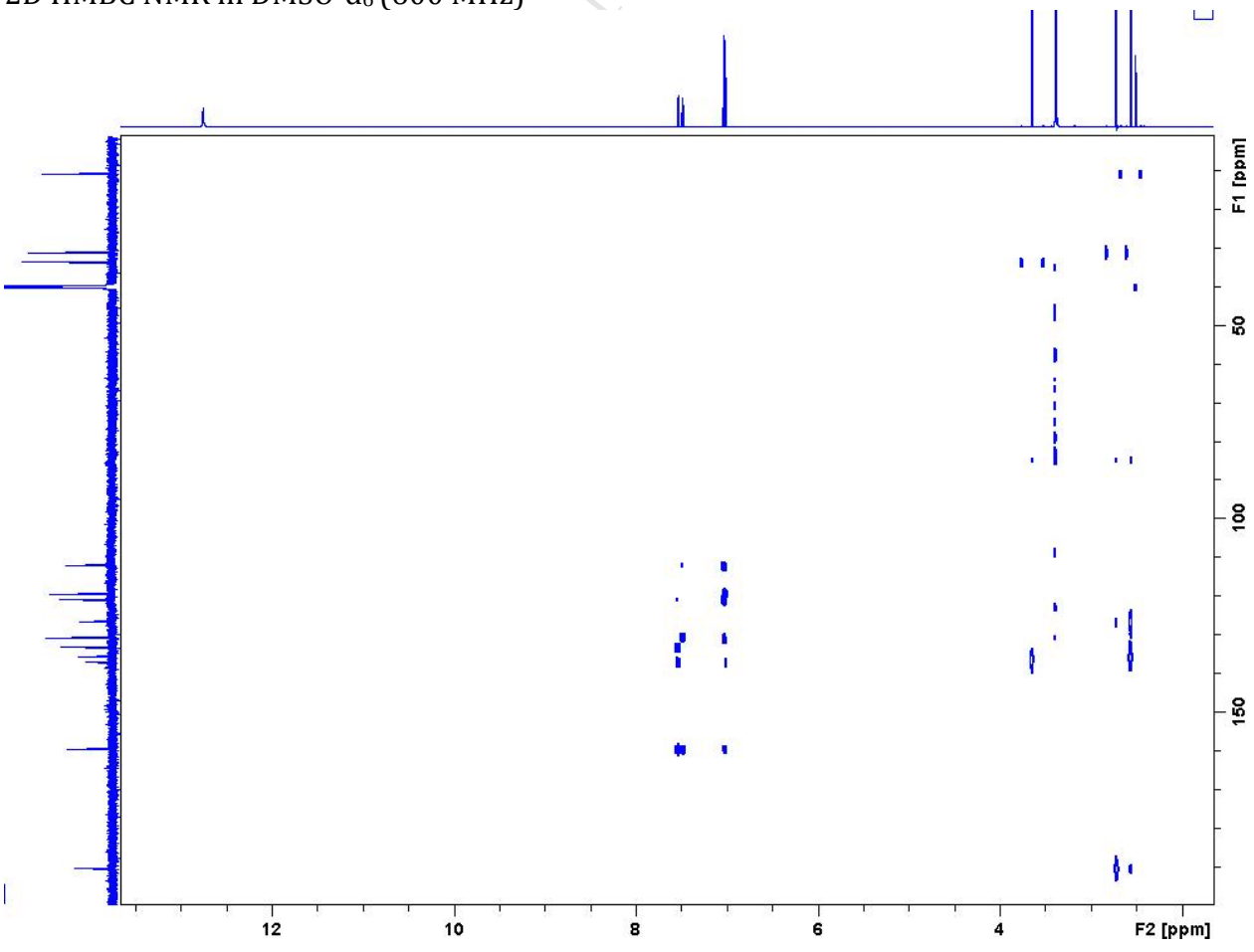
^{13}C NMR in DMSO-d$_6$ (150.94 MHz)



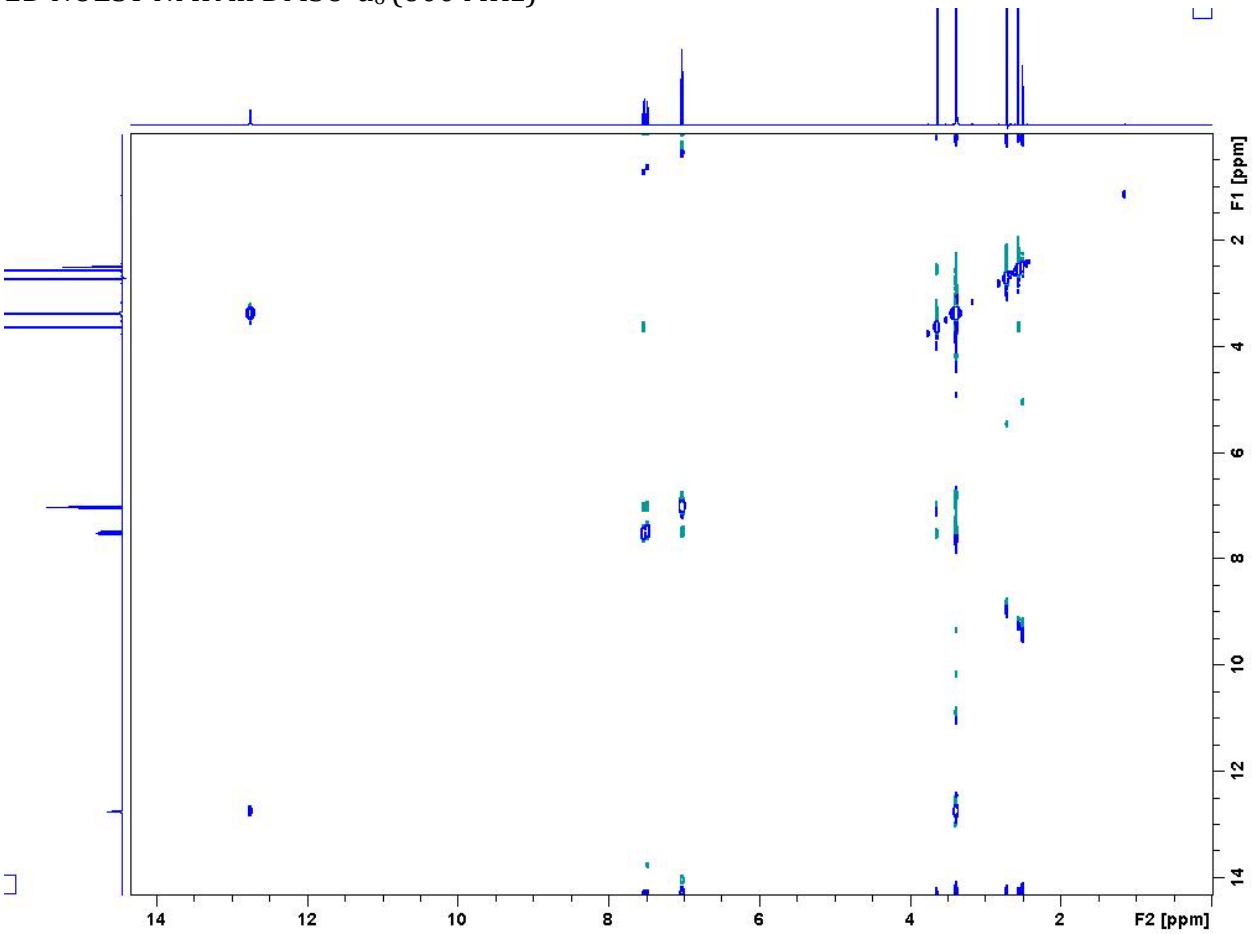
2D HMQC NMR in DMSO-d_6 (600 MHz)



2D HMBC NMR in DMSO-d_6 (600 MHz)

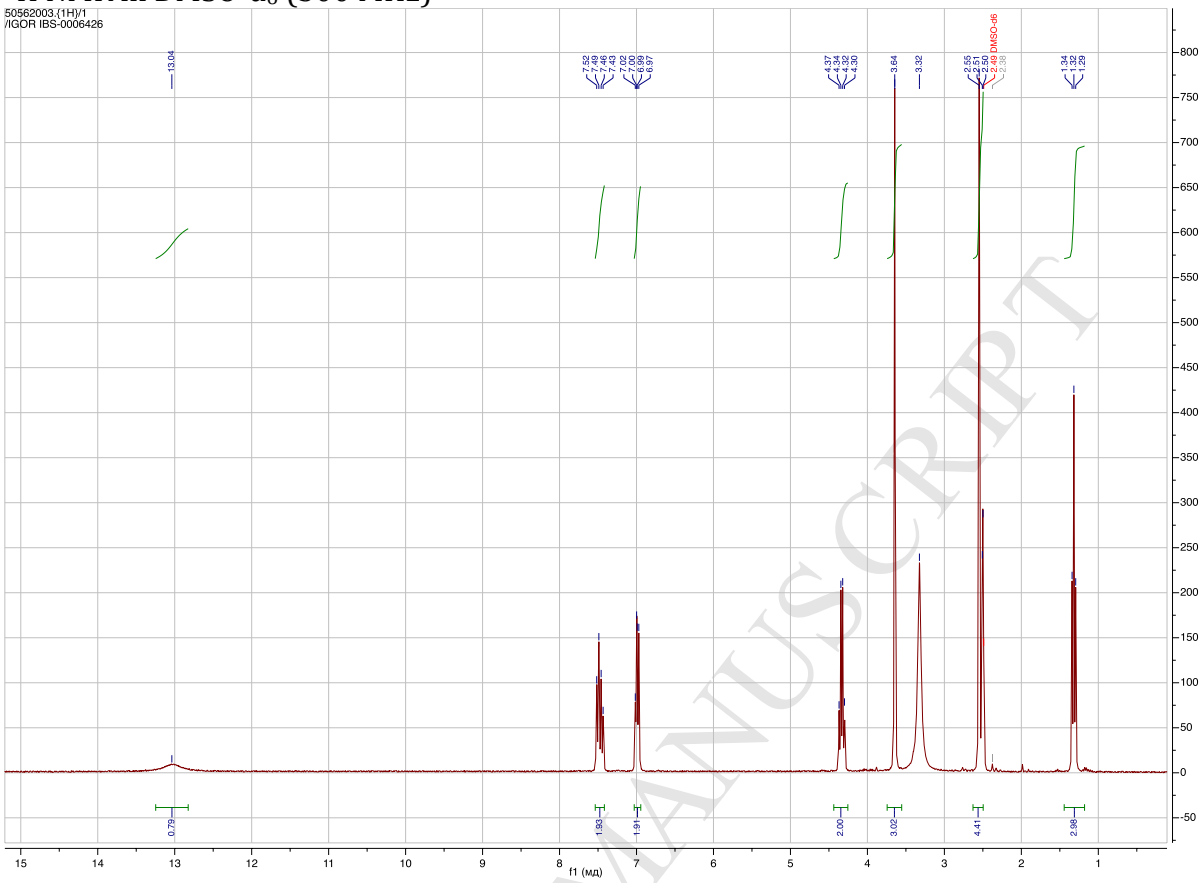


2D NOESY NMR in DMSO-d_6 (600 MHz)

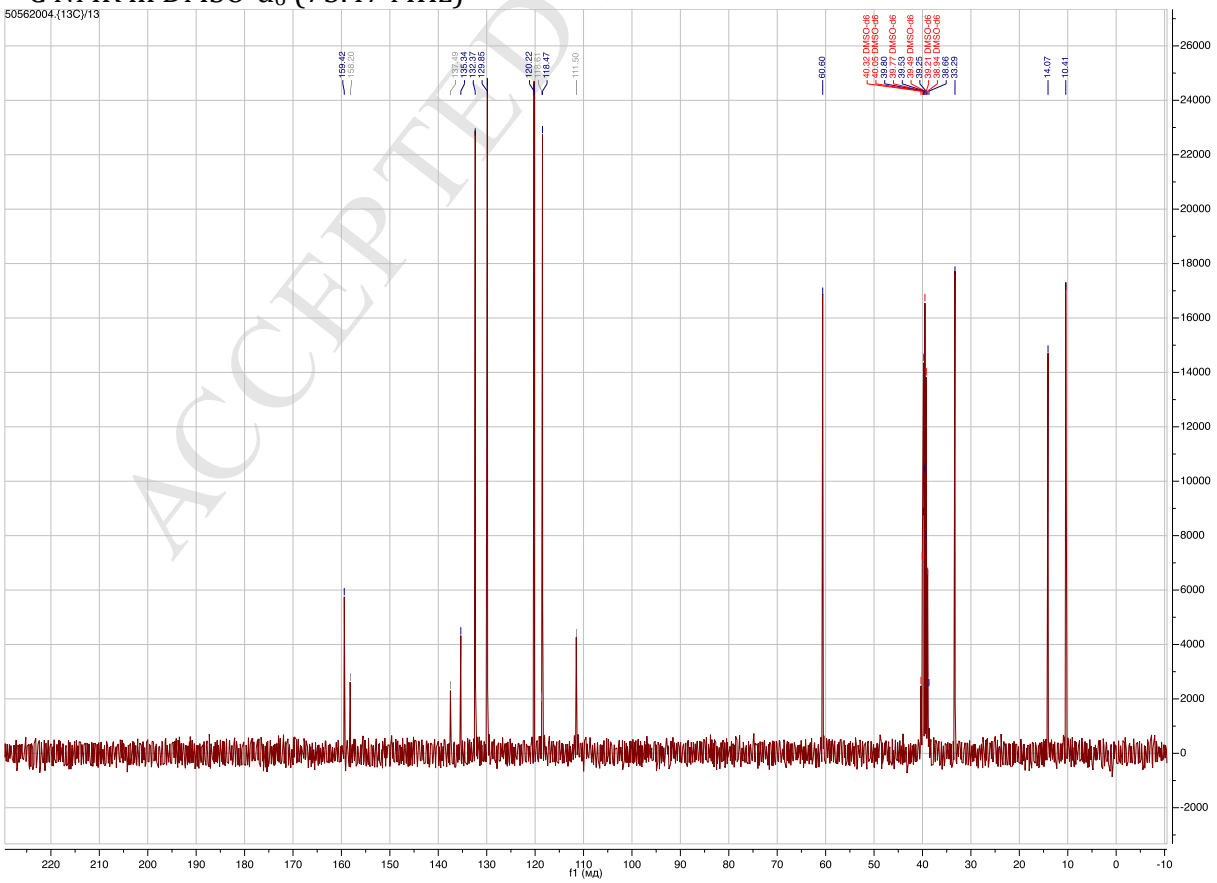


4-(Ethoxycarbonyl)-2-(2-hydroxyphenyl)-1,5-dimethyl-1H-imidazole 3-oxide (12).

^{1}H NMR in DMSO-d$_6$ (300 MHz)

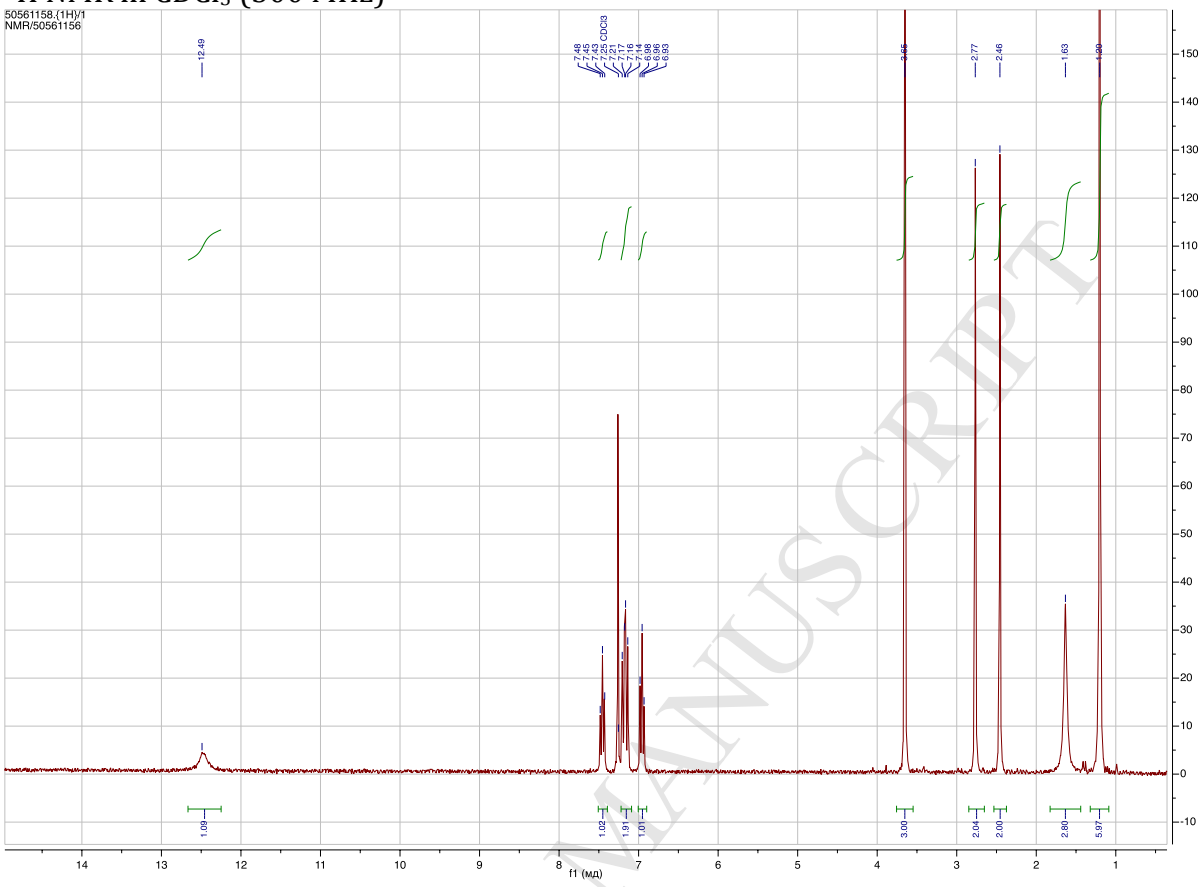


^{13}C NMR in DMSO-d$_6$ (75.47 MHz)

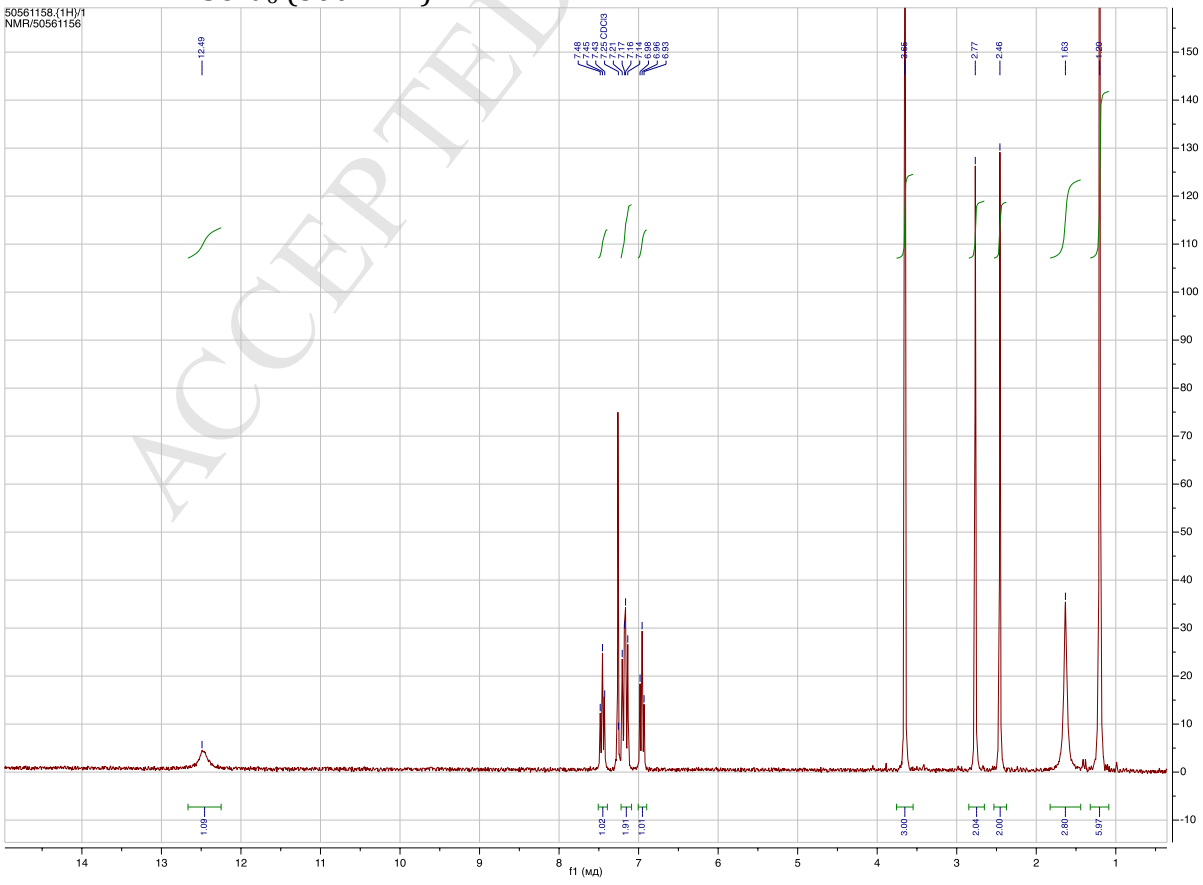


2-(2-Hydroxyphenyl)-1,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-benzo[d]imidazole 3-oxide (**13**).

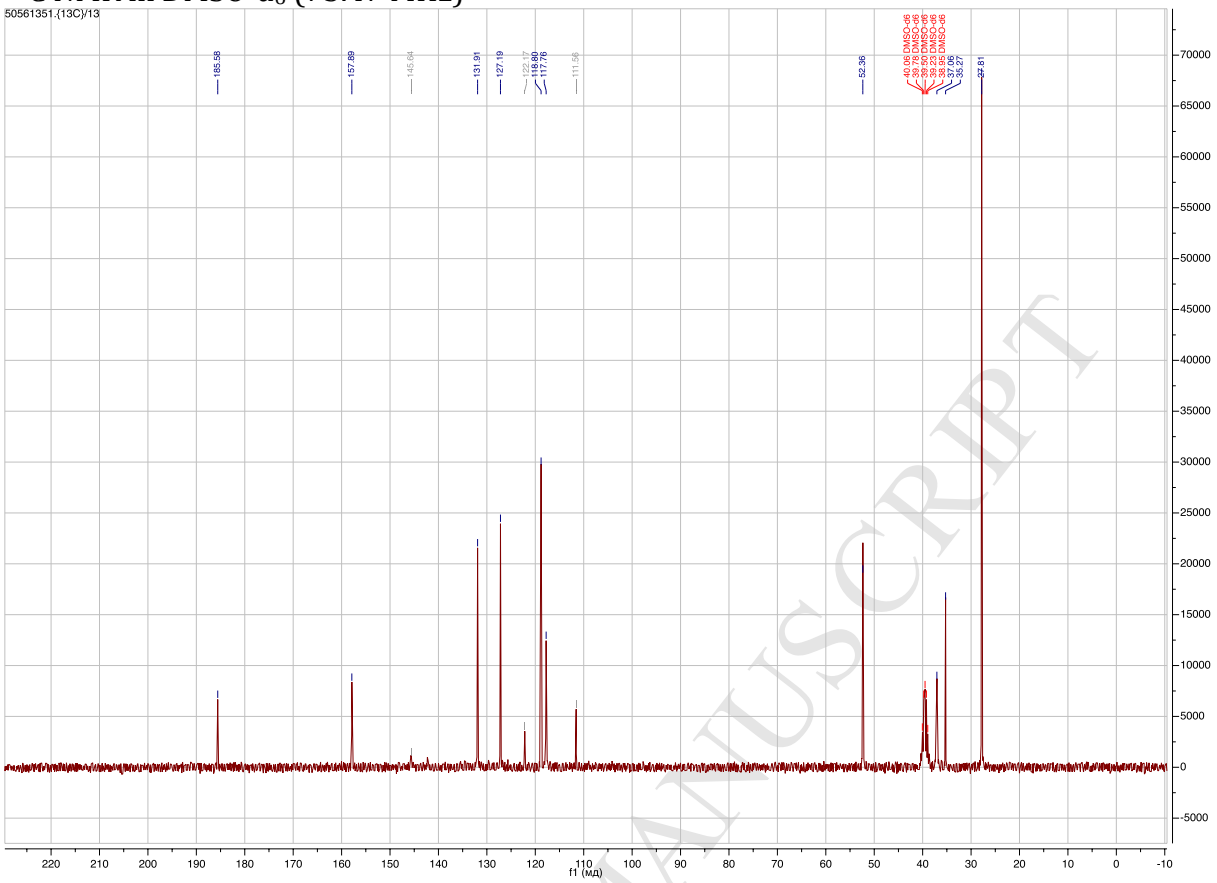
^{1}H NMR in $CDCl_3$ (300 MHz)



^{1}H NMR in DMSO-d_6 (300 MHz)

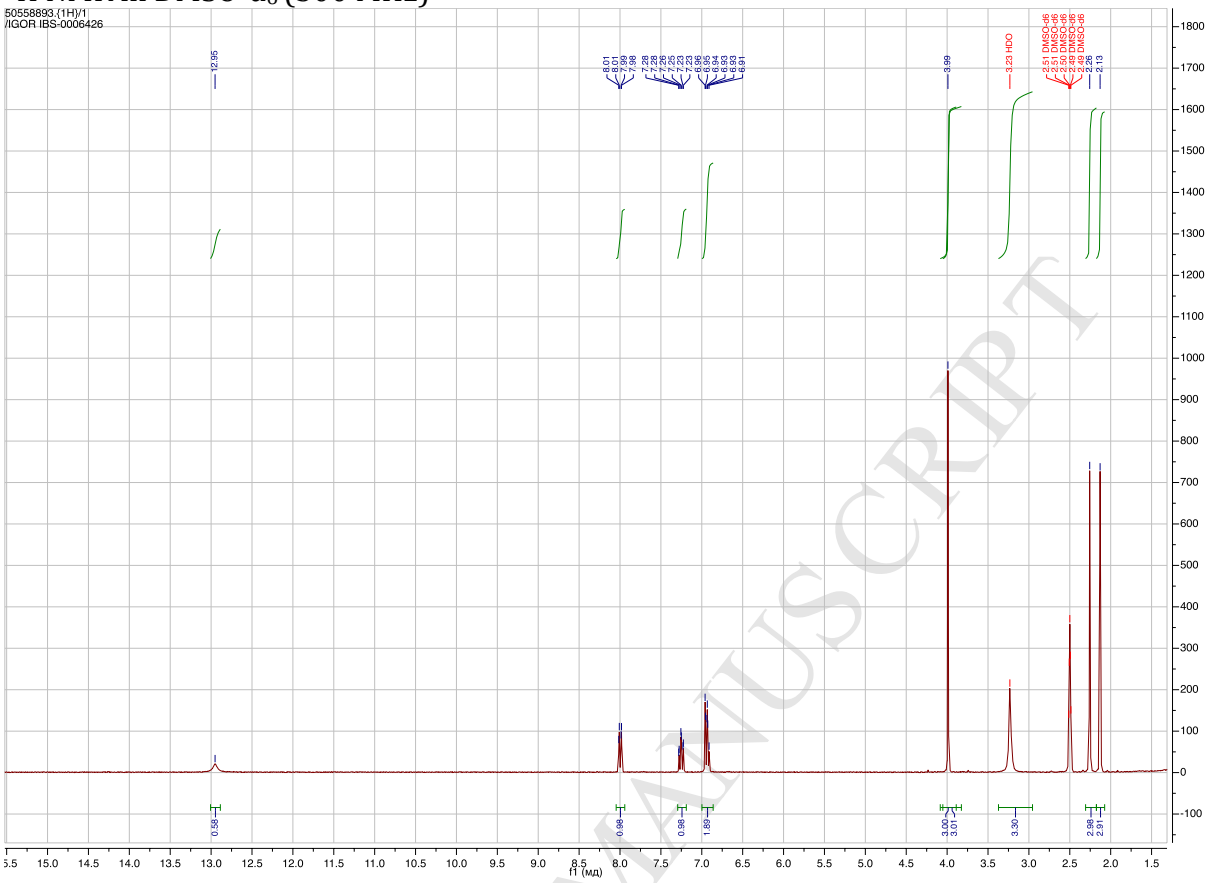


^{13}C NMR in DMSO-d_6 (75.47 MHz)

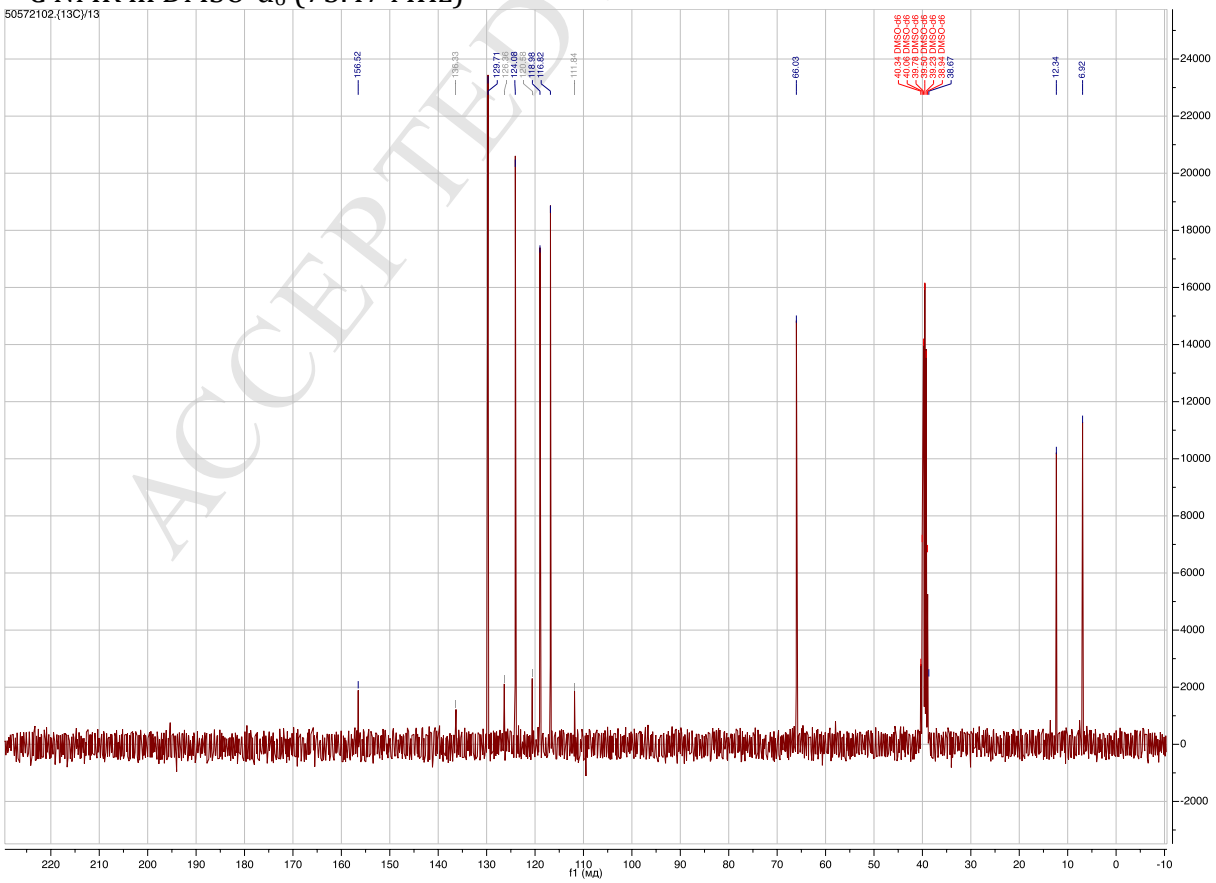


2-(1-Methoxy-4,5-dimethyl-1H-imidazol-2-yl)phenol (15).

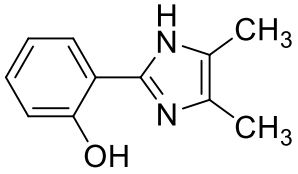
^{1}H NMR in DMSO-d$_6$ (300 MHz)



^{13}C NMR in DMSO-d$_6$ (75.47 MHz)

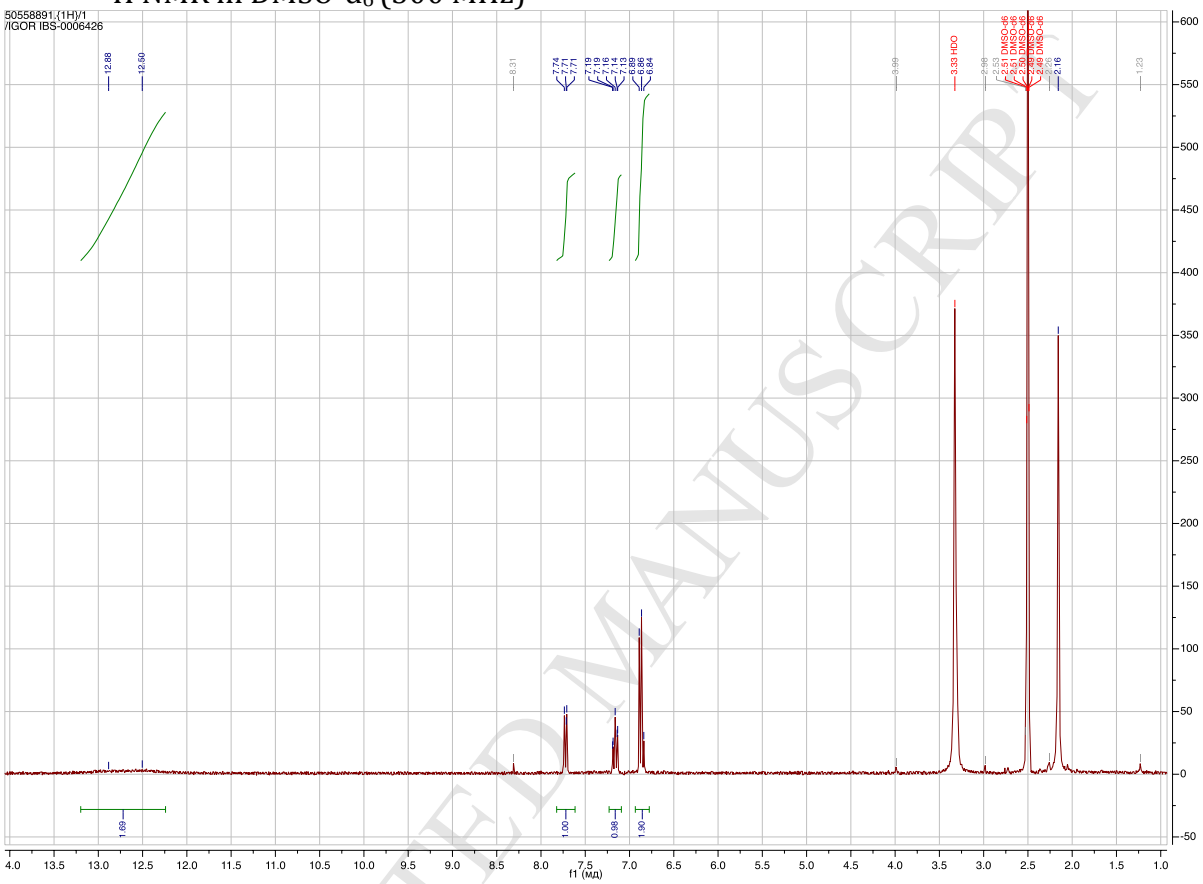


(2-(4,5-dimethyl-1H-imidazol-2-yl)phenol (28).



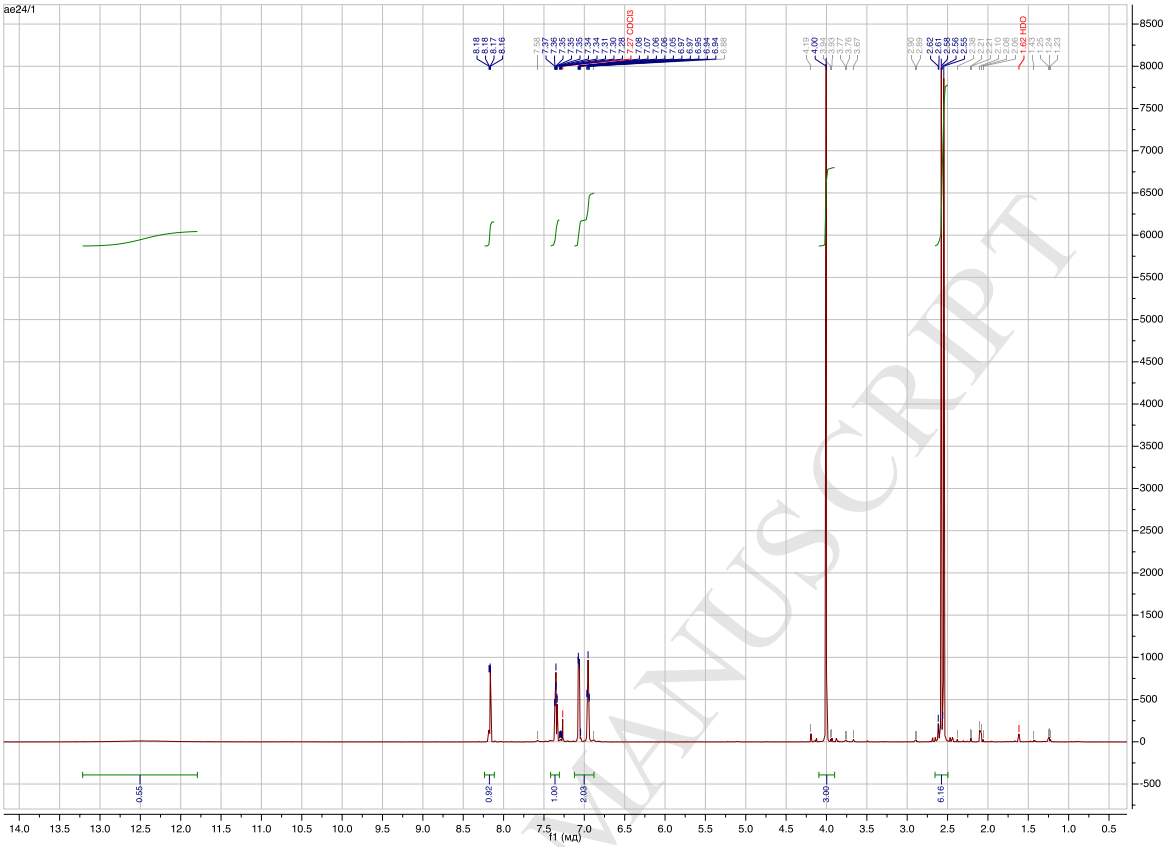
28

^{1}H NMR in DMSO-d$_6$ (300 MHz)

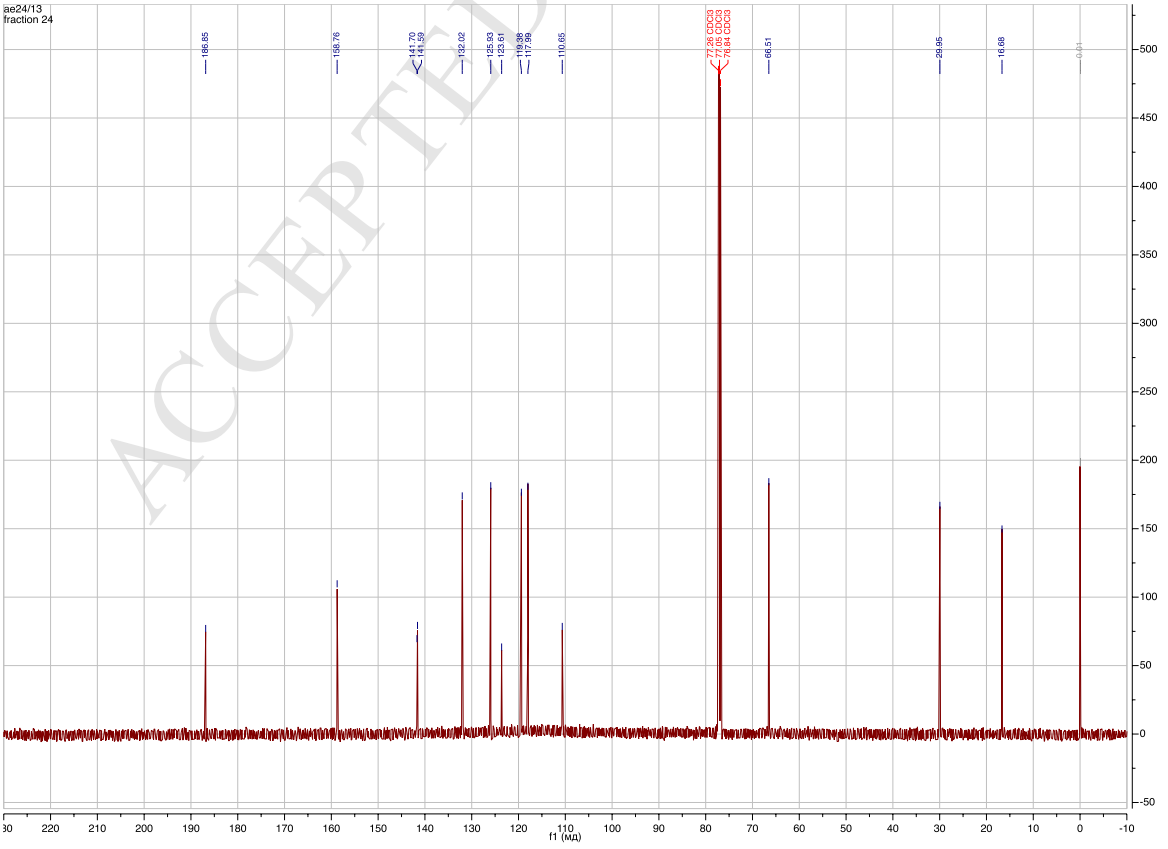


1-(2-(2-hydroxyphenyl)-1-methoxy-4-methyl-1H-imidazol-5-yl)ethanone (16).

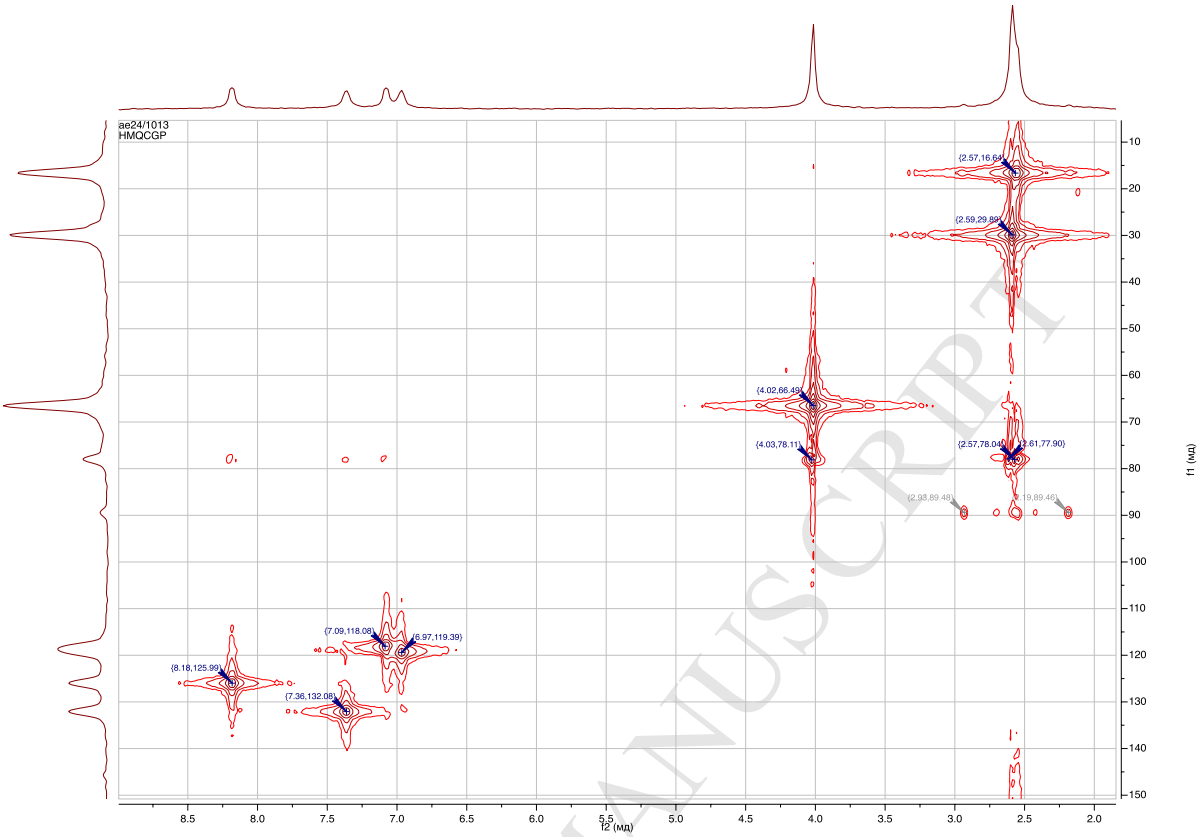
^{1}H NMR in $CDCl_3$ (600 MHz)



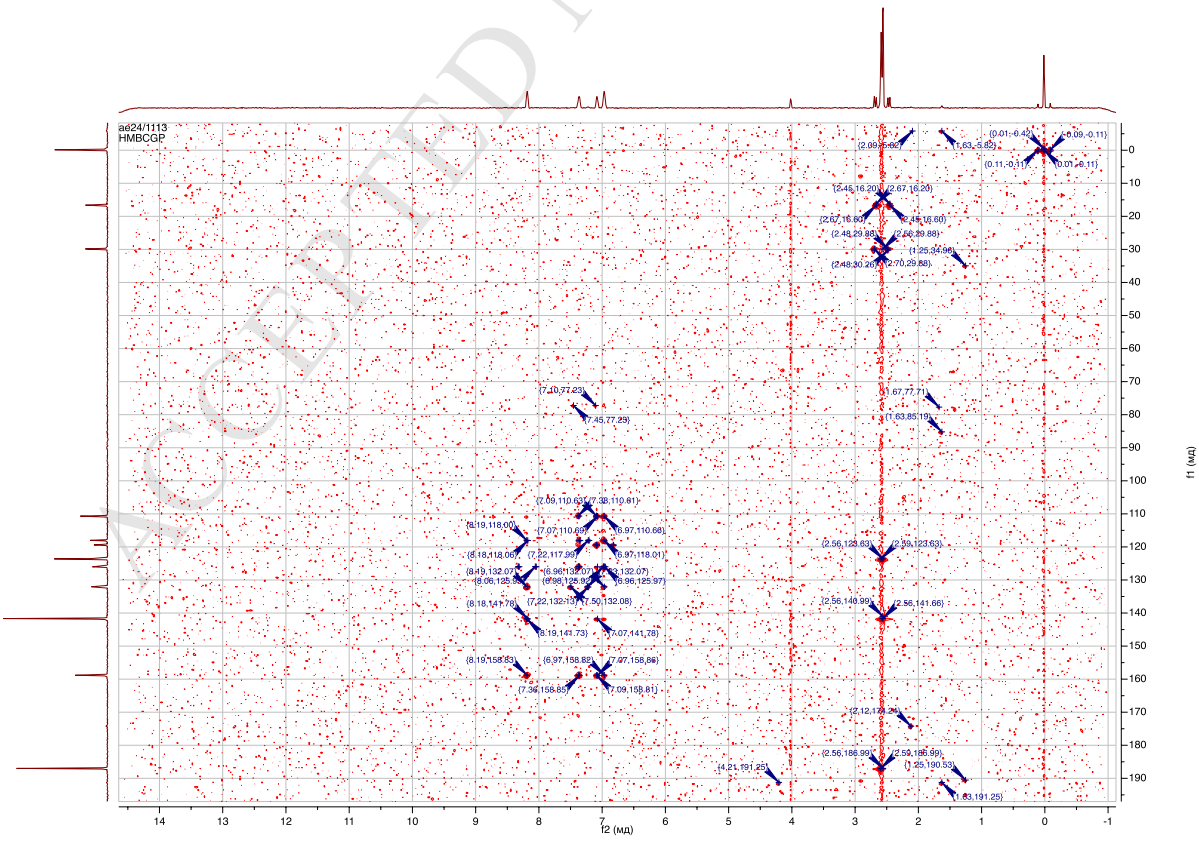
^{13}C NMR in $CDCl_3$ (150.97 MHz)



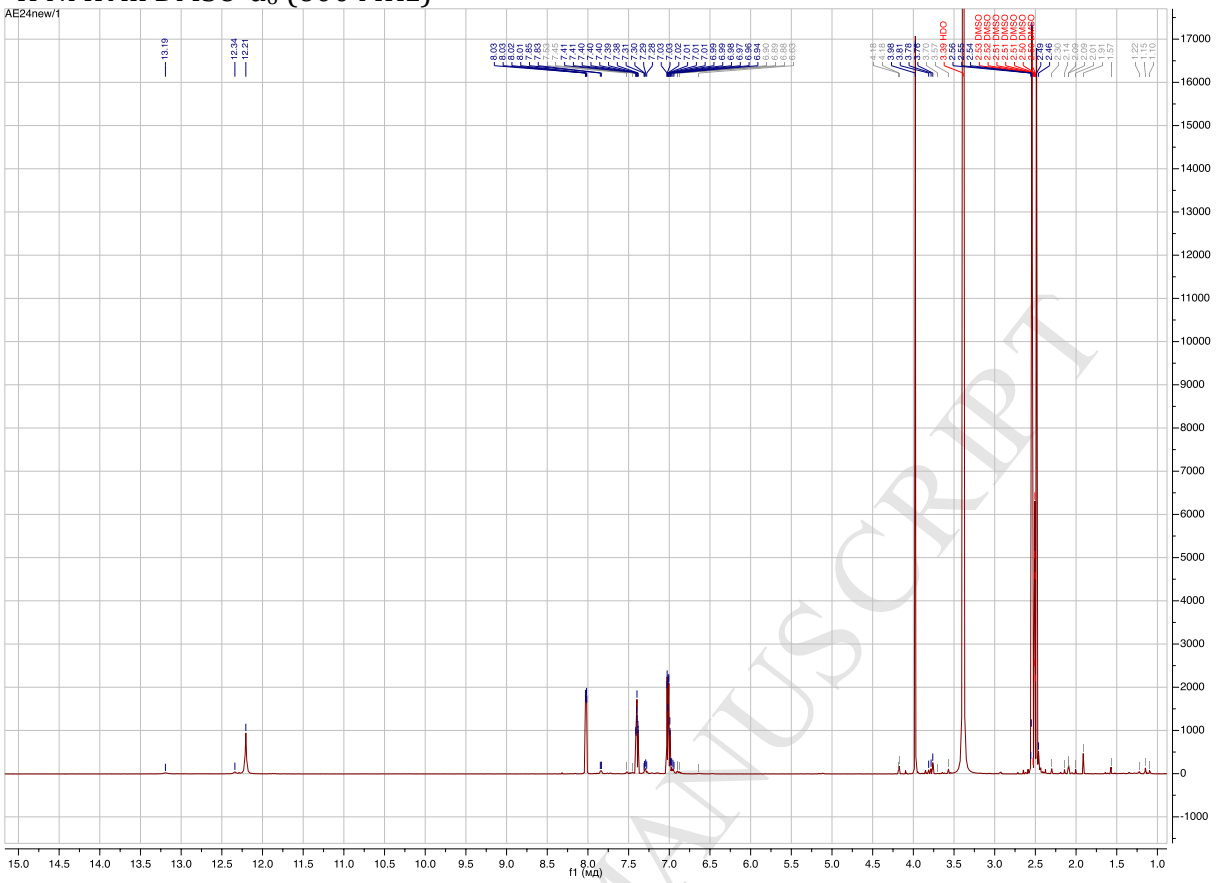
2D HMQC NMR in $CDCl_3$ (600 MHz)



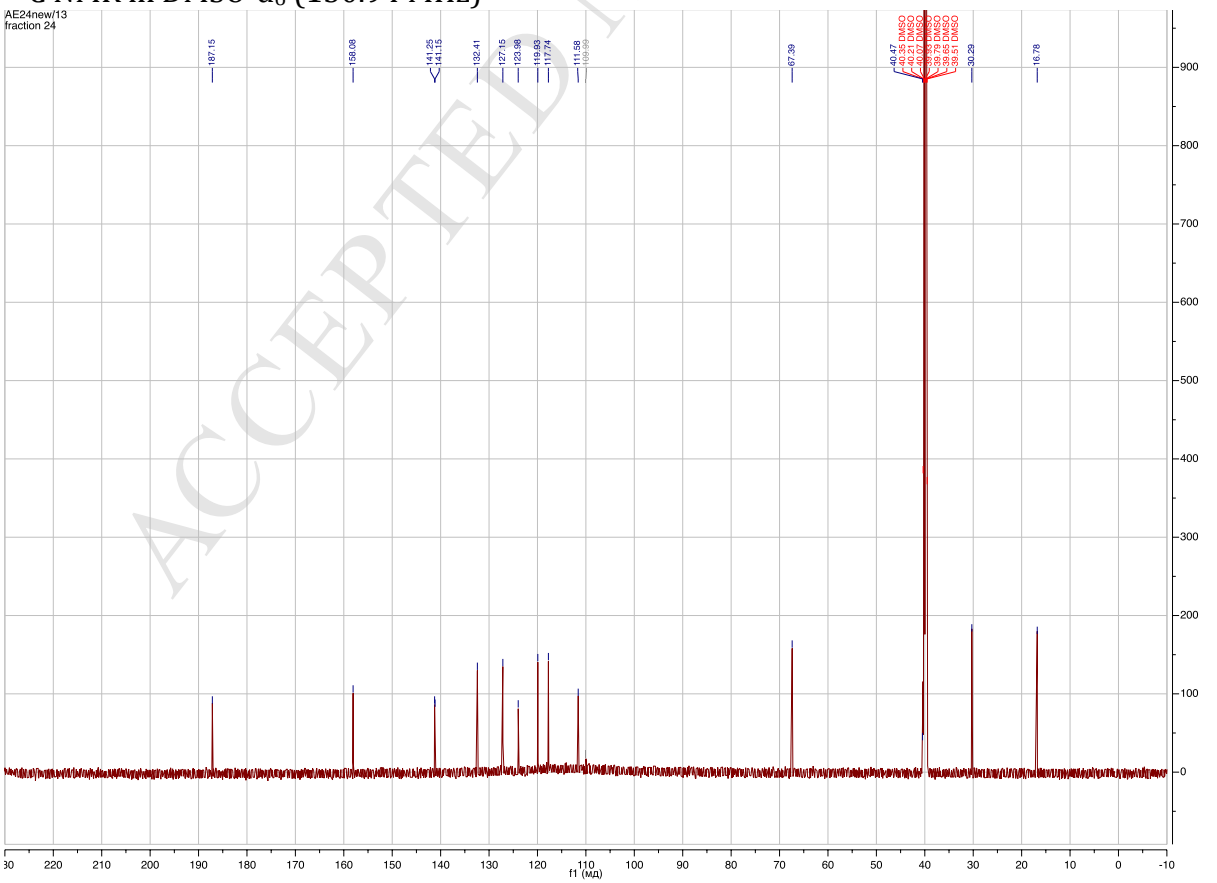
2D HMBC NMR in $CDCl_3$ (600 MHz)



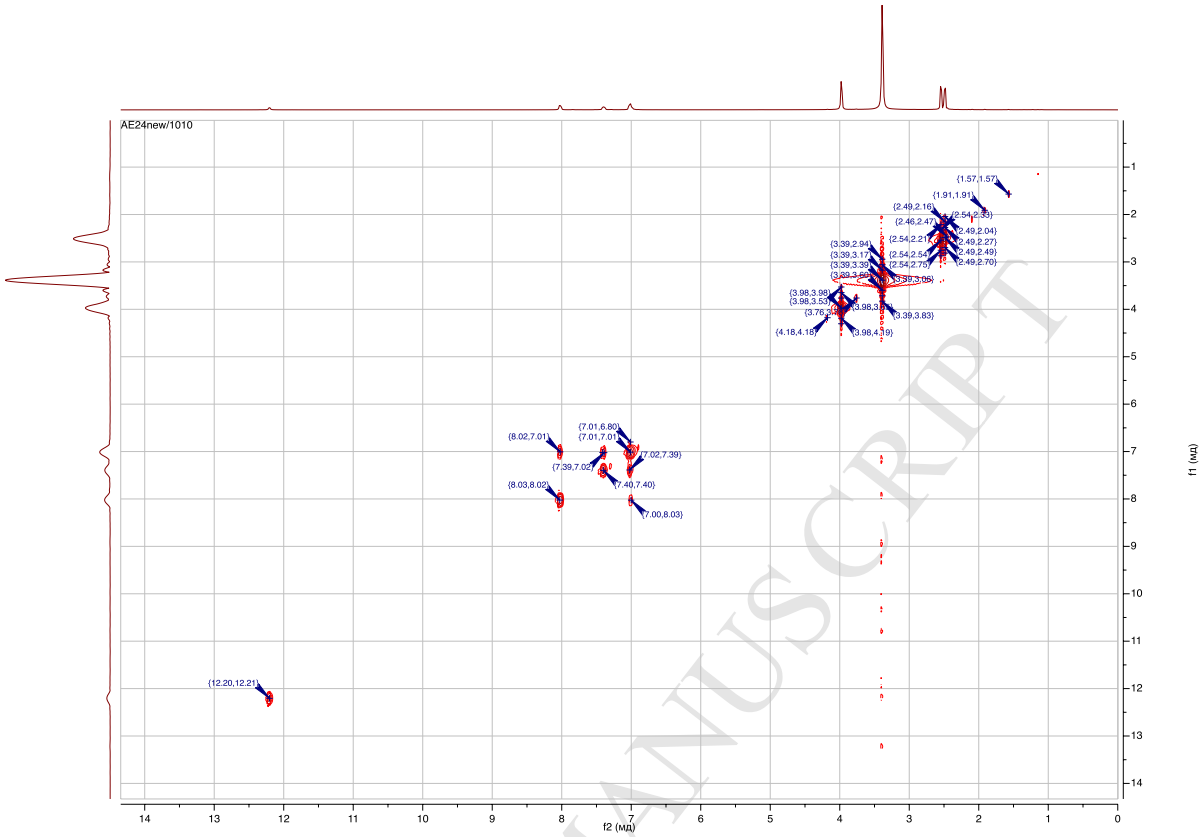
^{1}H NMR in DMSO-d_6 (600 MHz)



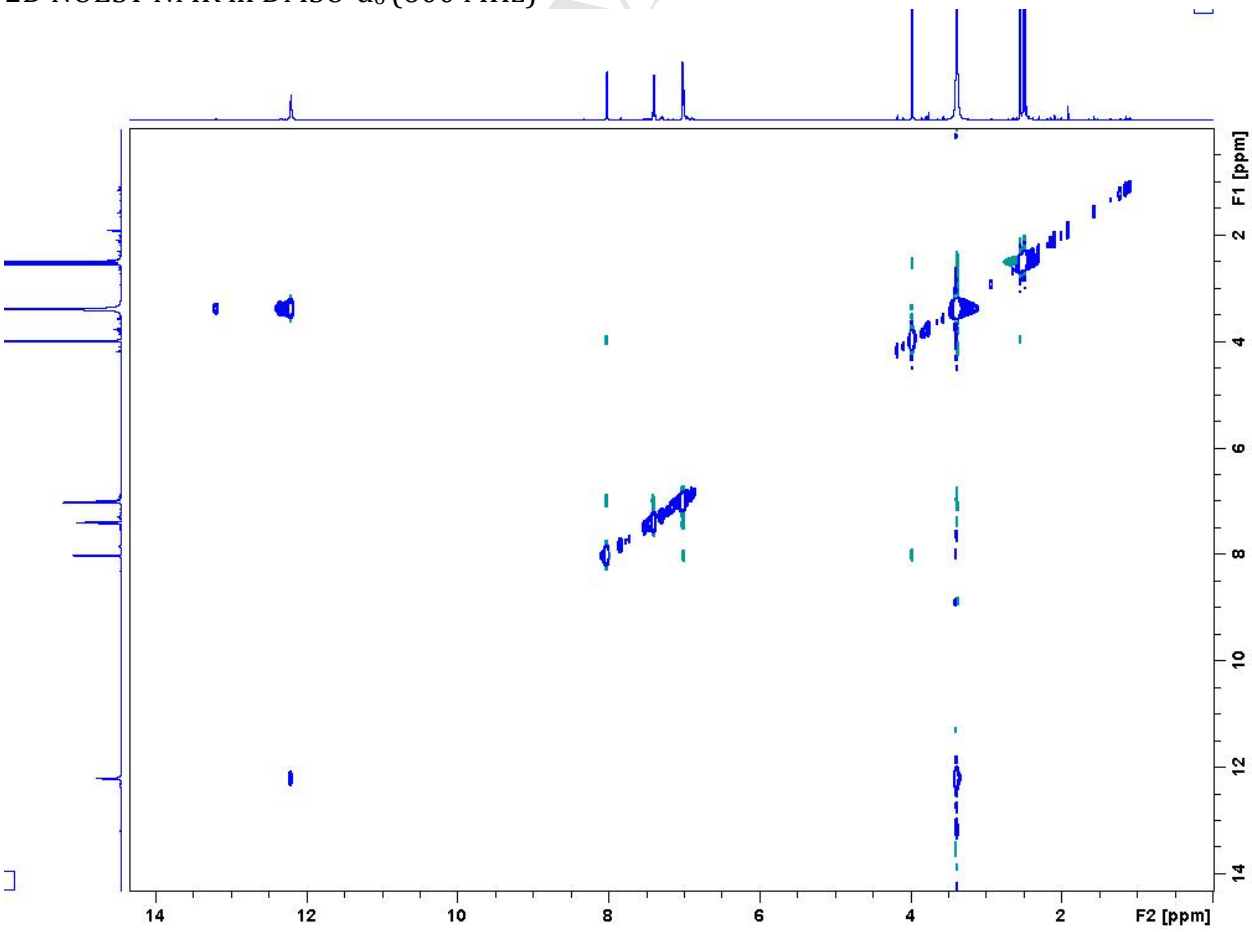
^{13}C NMR in DMSO-d_6 (150.94 MHz)



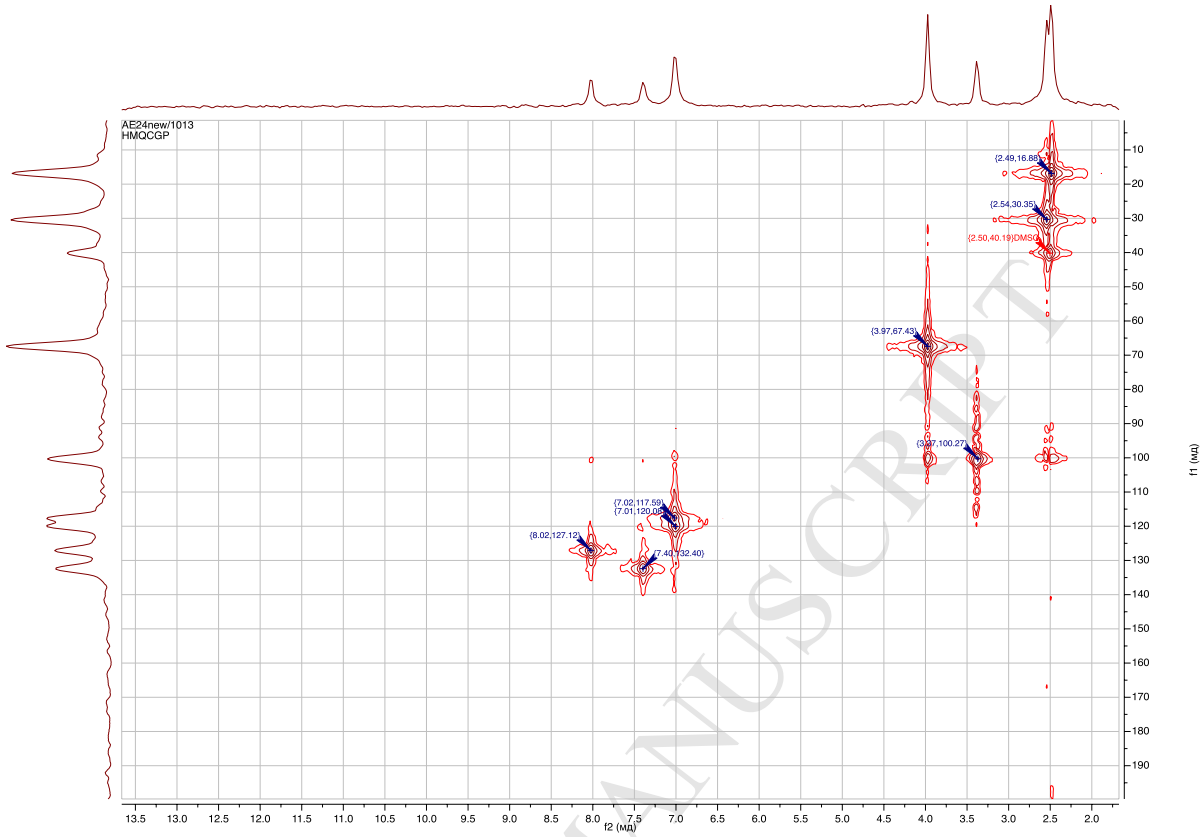
2D COSY NMR in DMSO-d_6 (600 MHz)



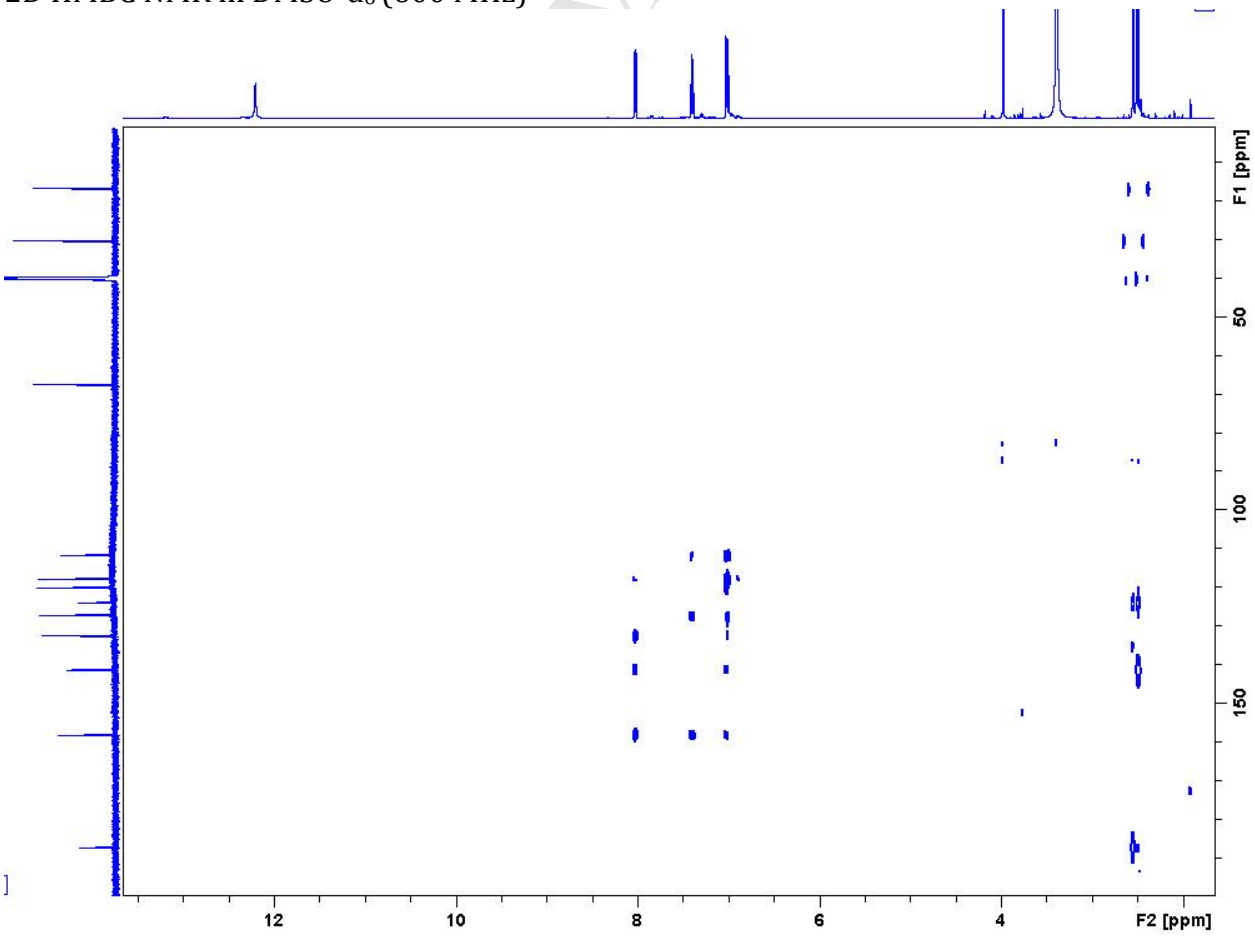
2D NOESY NMR in DMSO-d_6 (600 MHz)



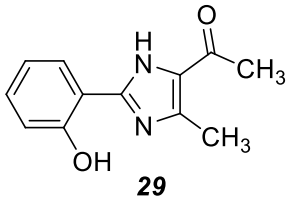
2D HMQC NMR in DMSO-d_6 (600 MHz)



2D HMBC NMR in DMSO-d_6 (600 MHz)

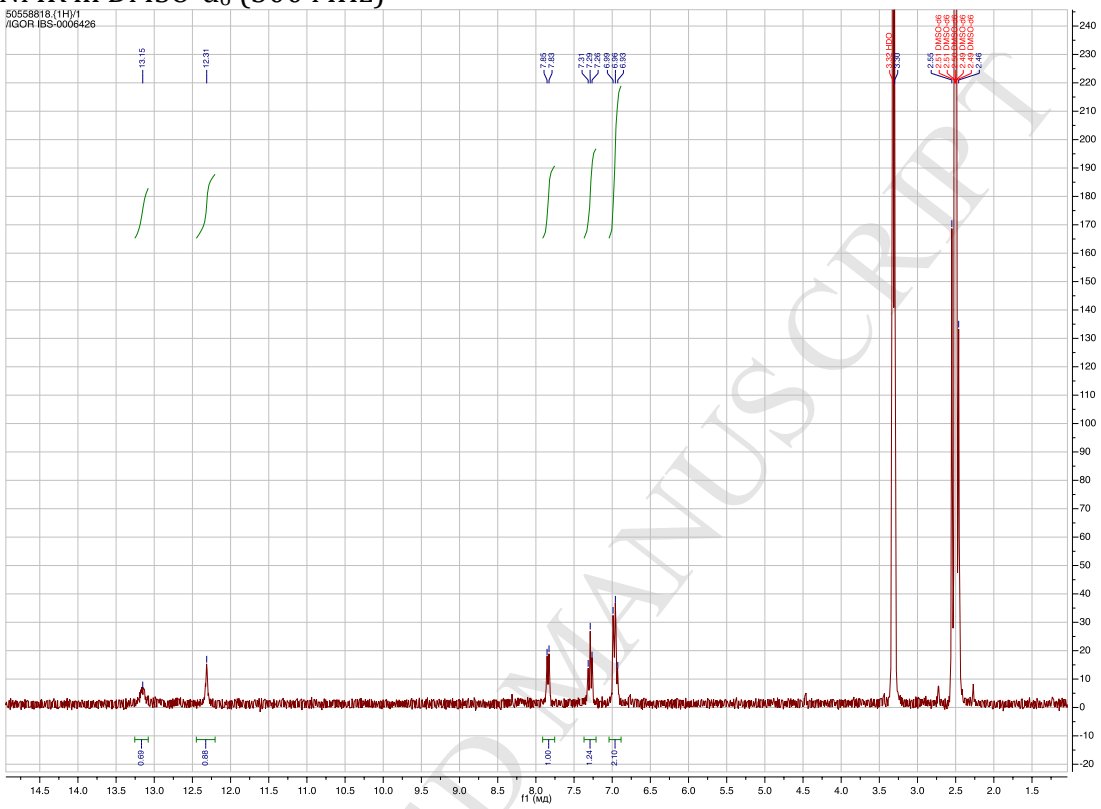


(1-(2-(2-hydroxyphenyl)-4-methyl-1H-imidazol-5-yl)ethanone (29)



29

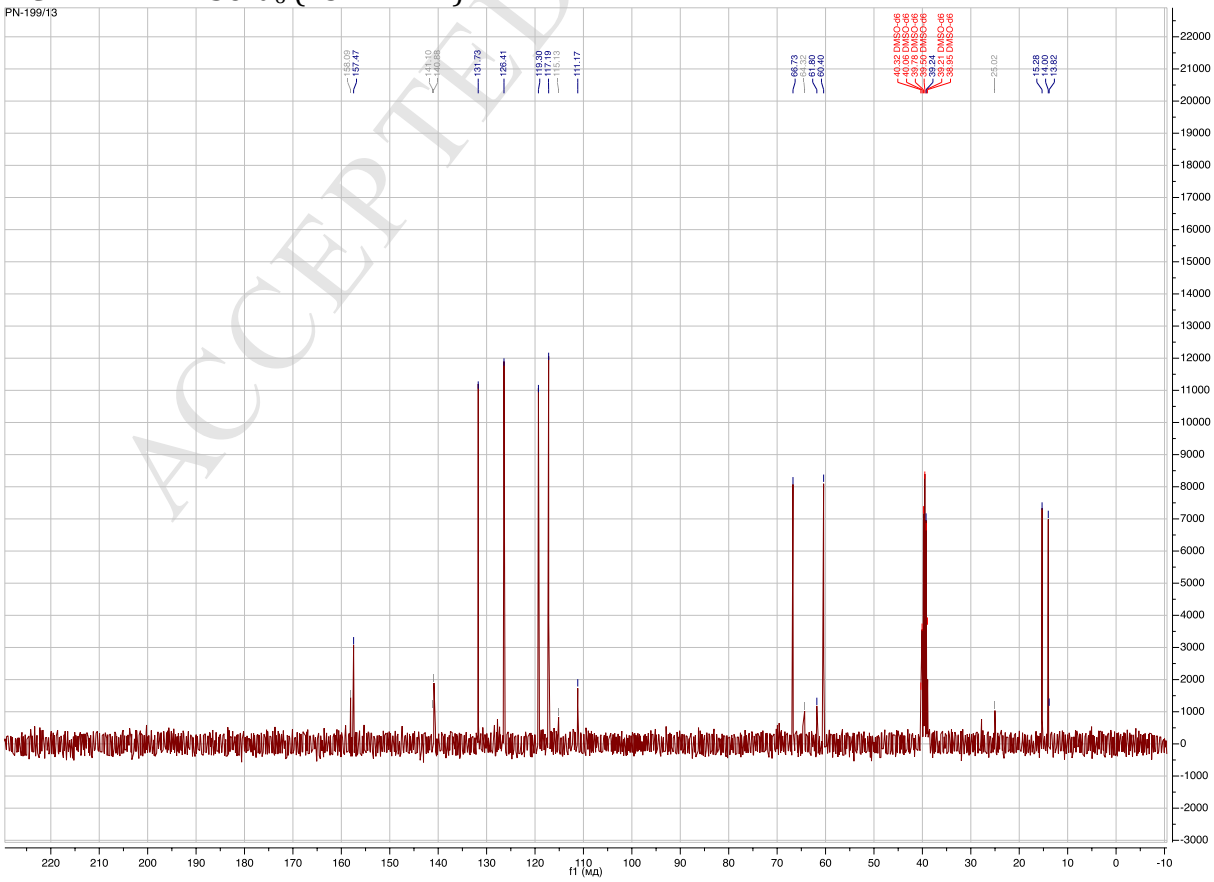
^{1}H NMR in DMSO-d_6 (300 MHz)



Ethyl 2-(2-hydroxyphenyl)-1-methoxy-4-methyl-1H-imidazole-5-carboxylate (17).

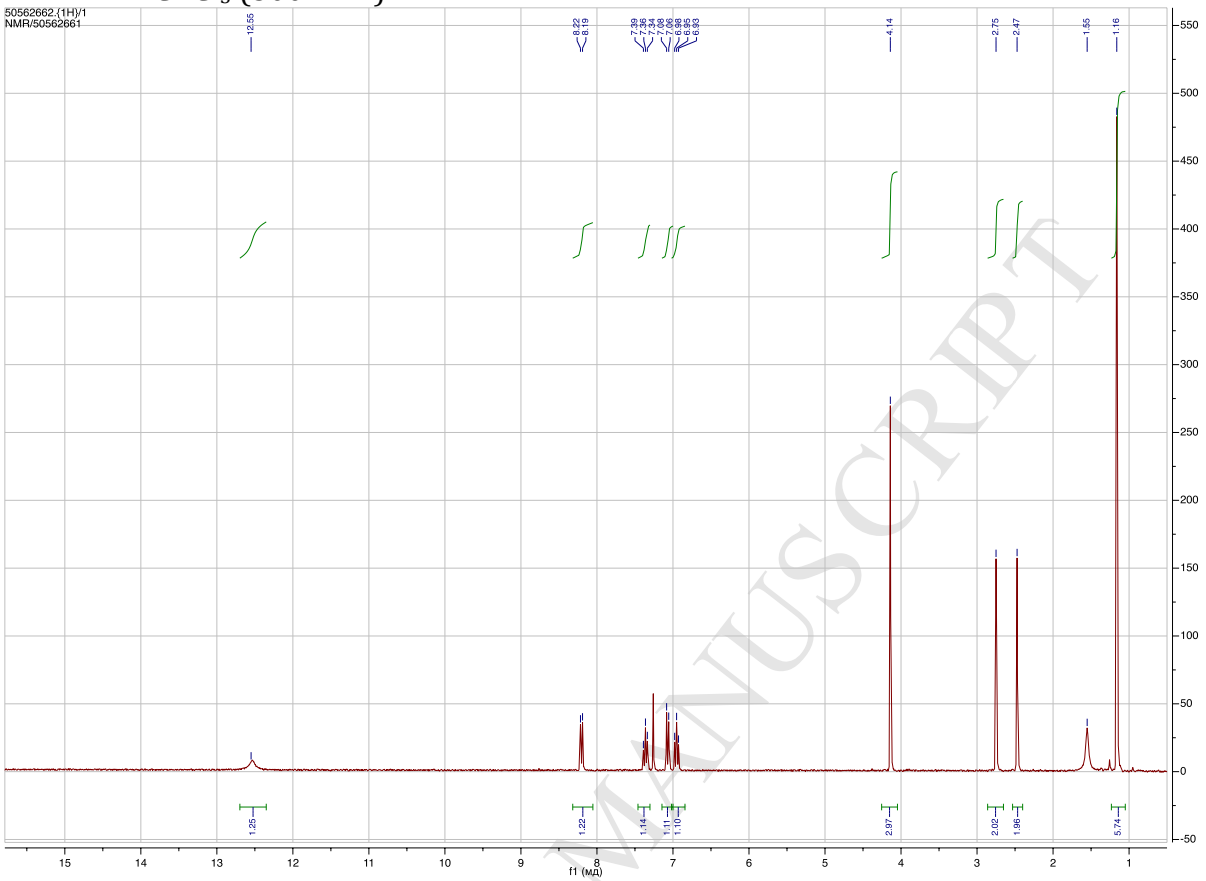
^{1}H NMR in DMSO-d$_6$ (300 MHz)

^{13}C NMR in DMSO-d$_6$ (75.47 MHz)

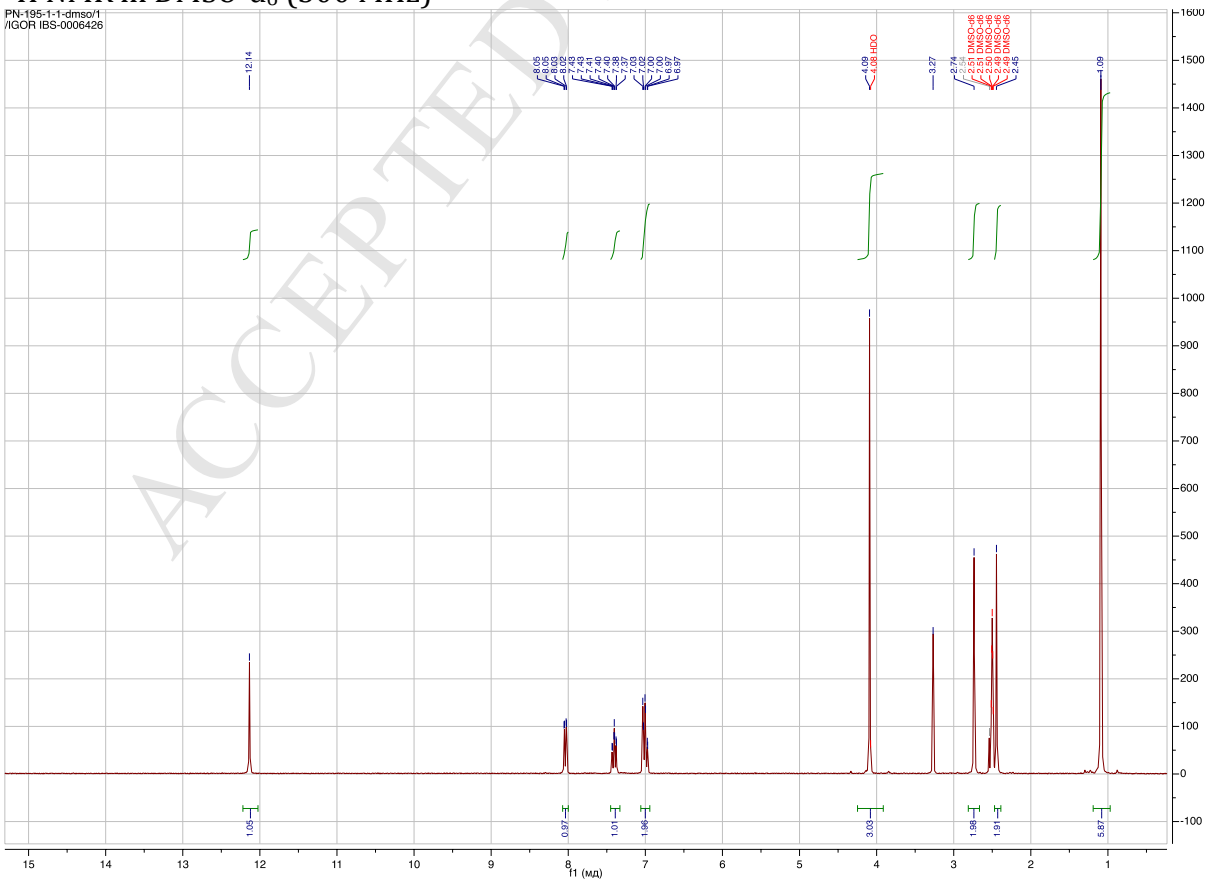


2-(2-Hydroxyphenyl)-1-methoxy-5,5-dimethyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole-7(4H)-one (**18**).

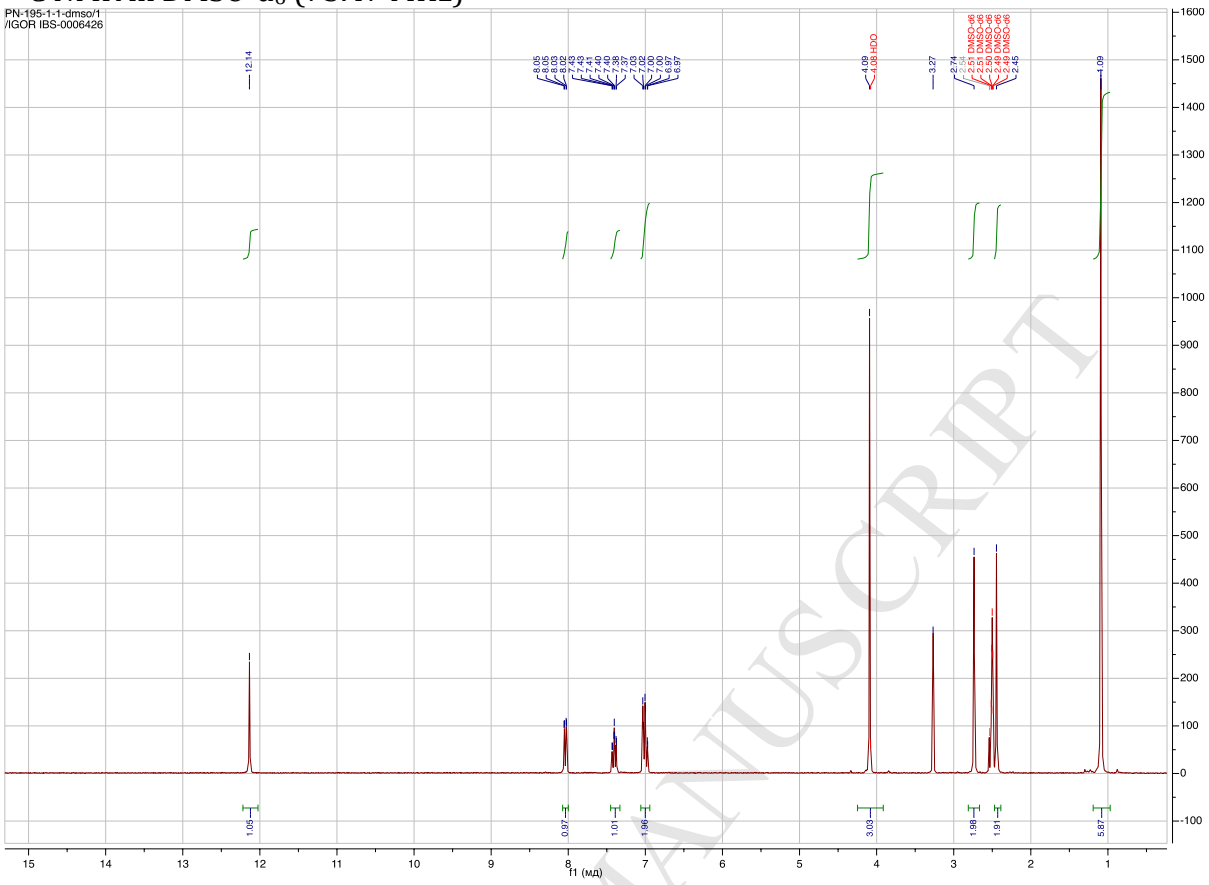
^{1}H NMR in $CDCl_3$ (300 MHz)



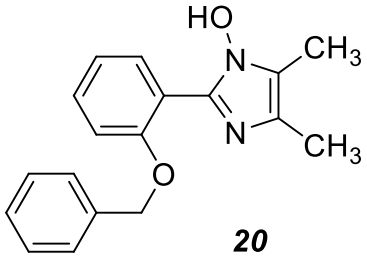
^{1}H NMR in DMSO-d_6 (300 MHz)



^{13}C NMR in DMSO-d_6 (75.47 MHz)

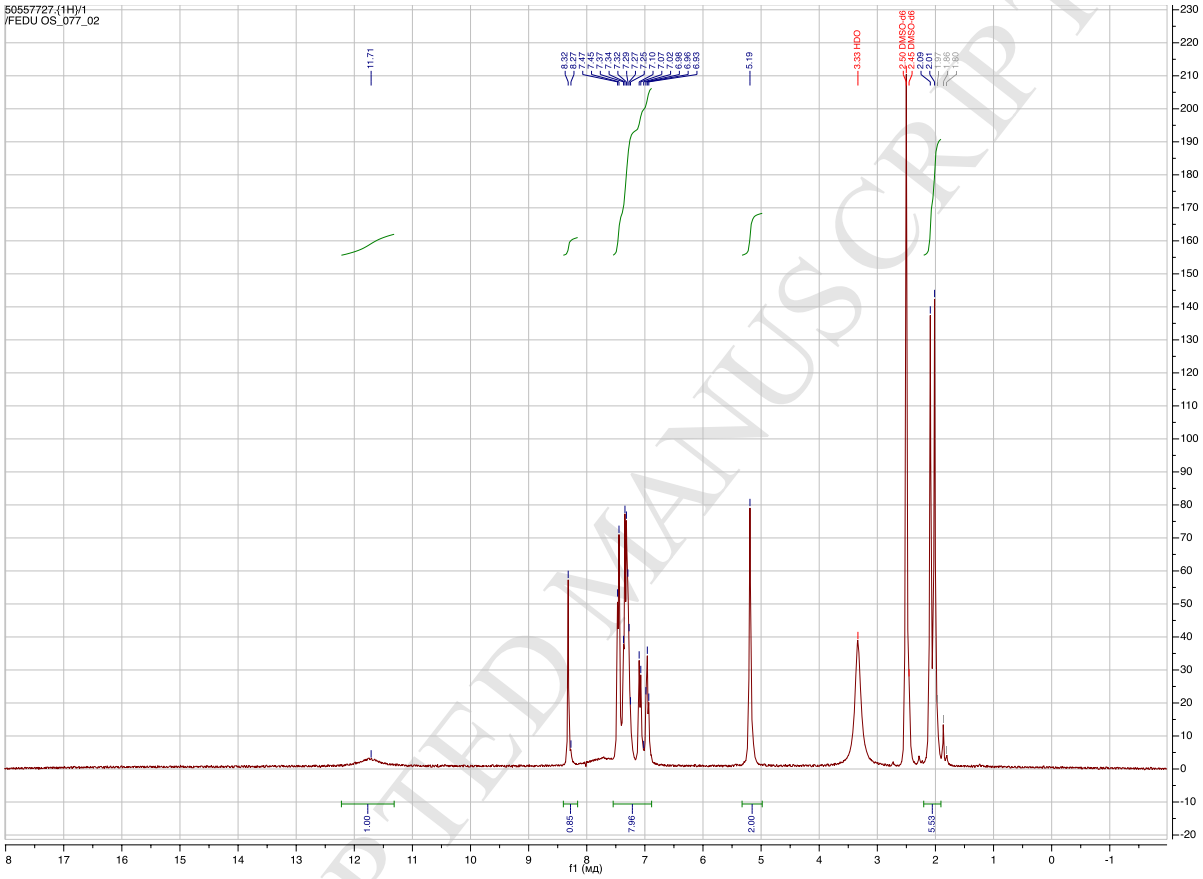


2-(2-(Benzyloxy)phenyl)-4,5-dimethyl-1H-imidazol-1-ol (20).

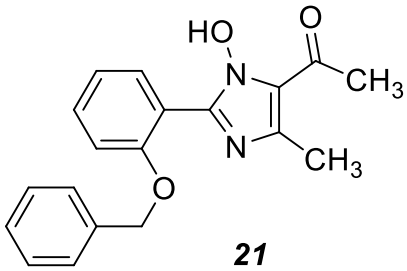


20

^{1}H NMR in DMSO-d_6 (300 MHz)

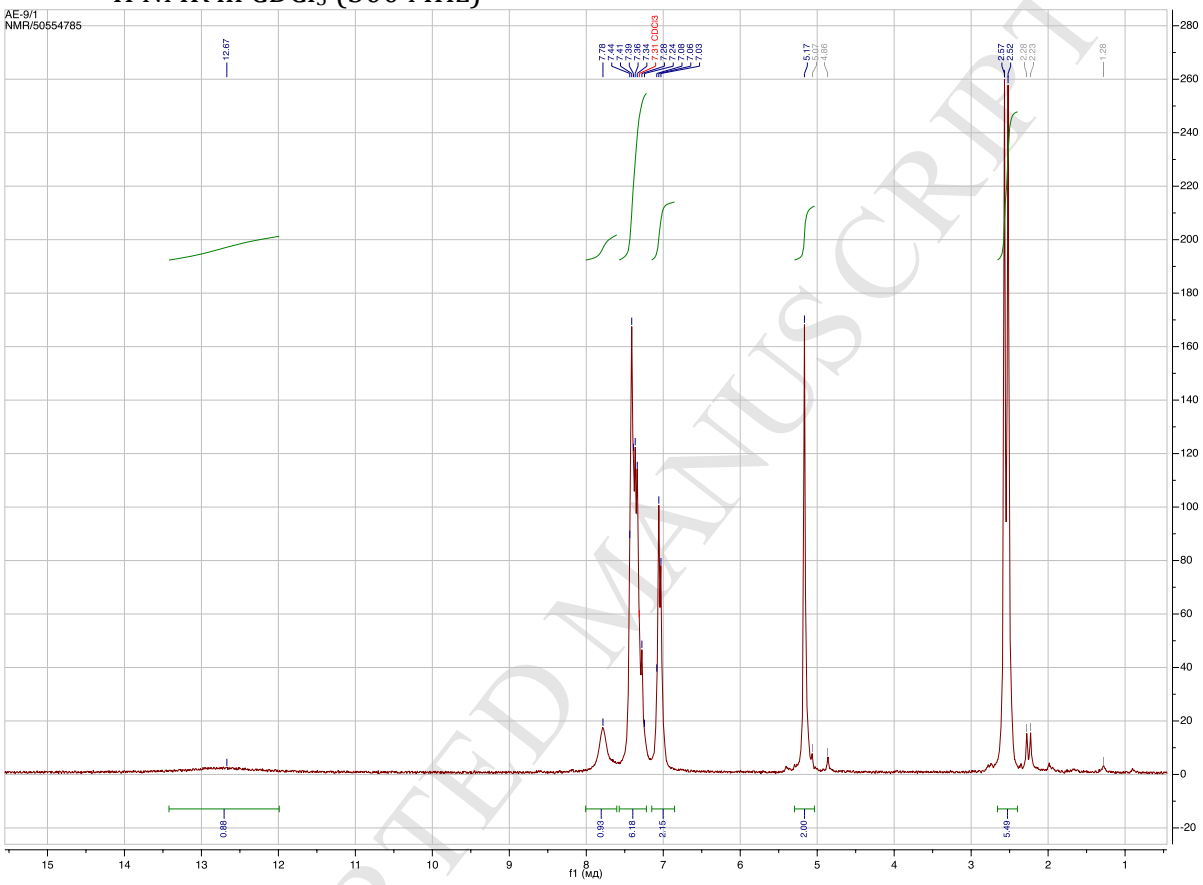


1-(2-(2-(Benzyloxy)phenyl)-1-hydroxy-4-methyl-1H-imidazol-5-yl)ethanone (21).

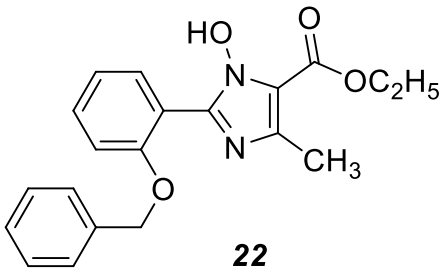


21

^{1}H NMR in $CDCl_3$ (300 MHz)

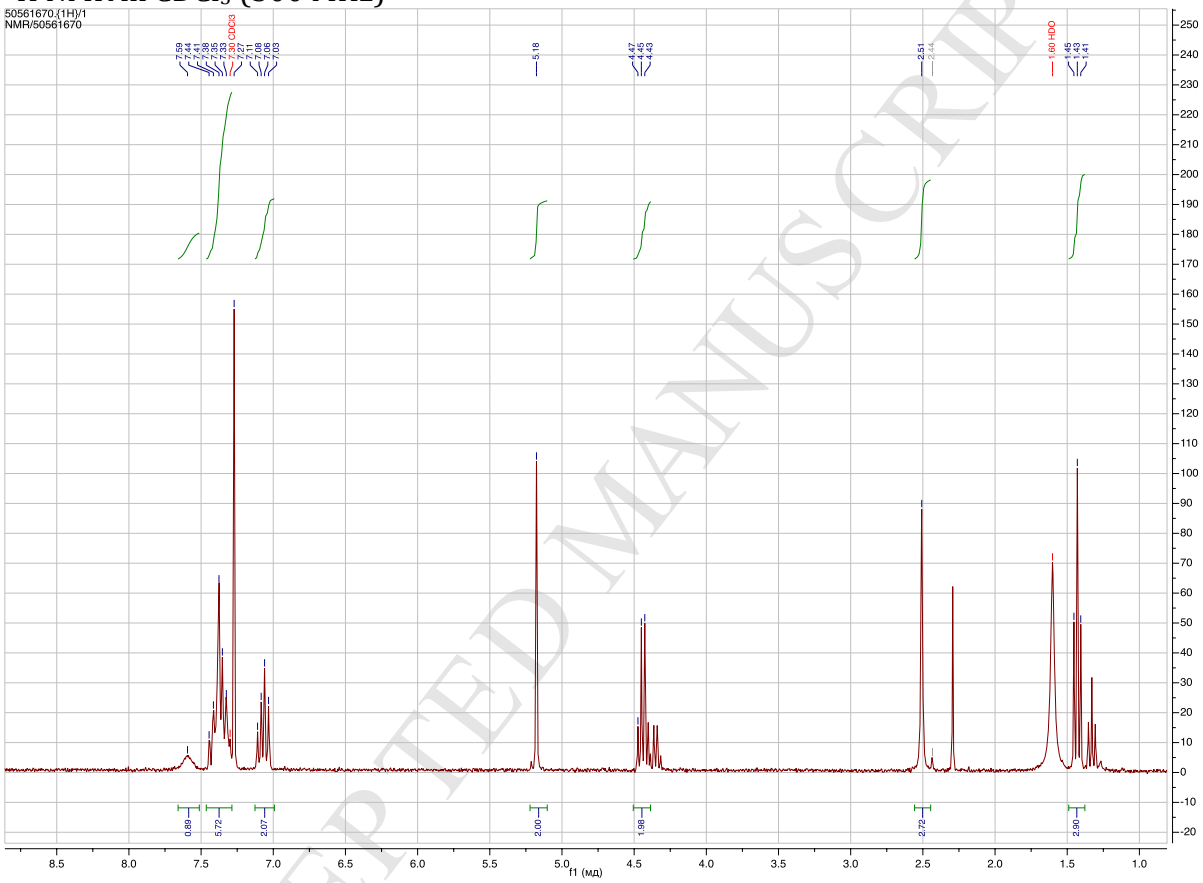


Ethyl 2-(2-(benzyloxy)phenyl)-1-hydroxy-4-methyl-1H-imidazole-5-carboxylate (22).

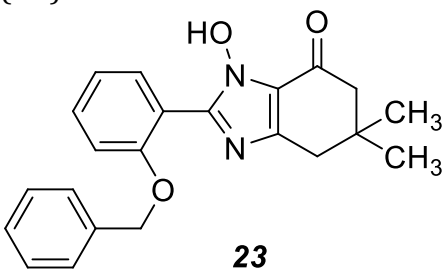


22

^{1}H NMR in $CDCl_3$ (300 MHz)

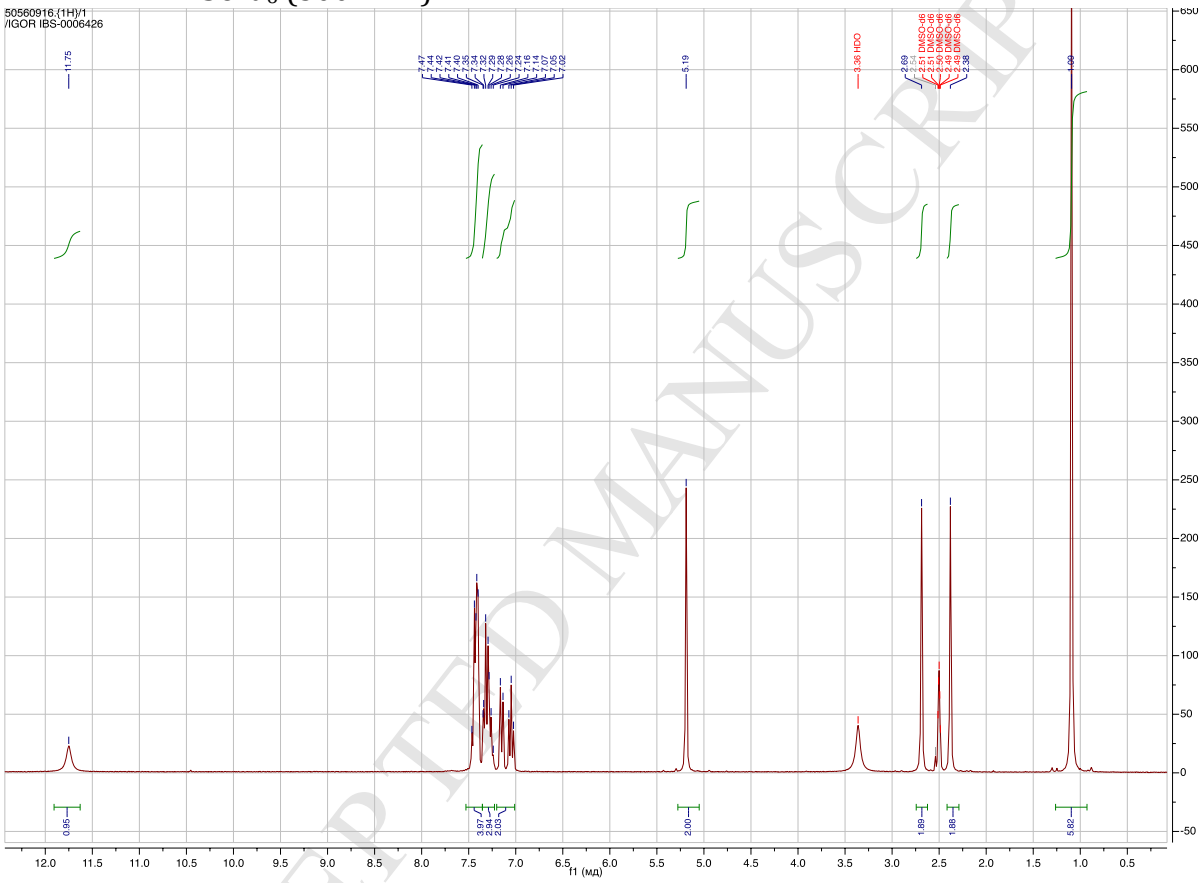


2-(2-Benzyloxy)phenyl)-1-hydroxy-5,5-dimethyl-4,5,6,7-tetrhydro-1H-benzo[d]imidazole-7(4H)-one (**23**).

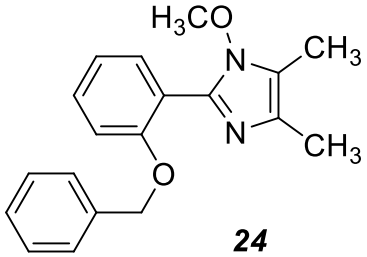


23

^{1}H NMR in DMSO-d$_6$ (300 MHz)

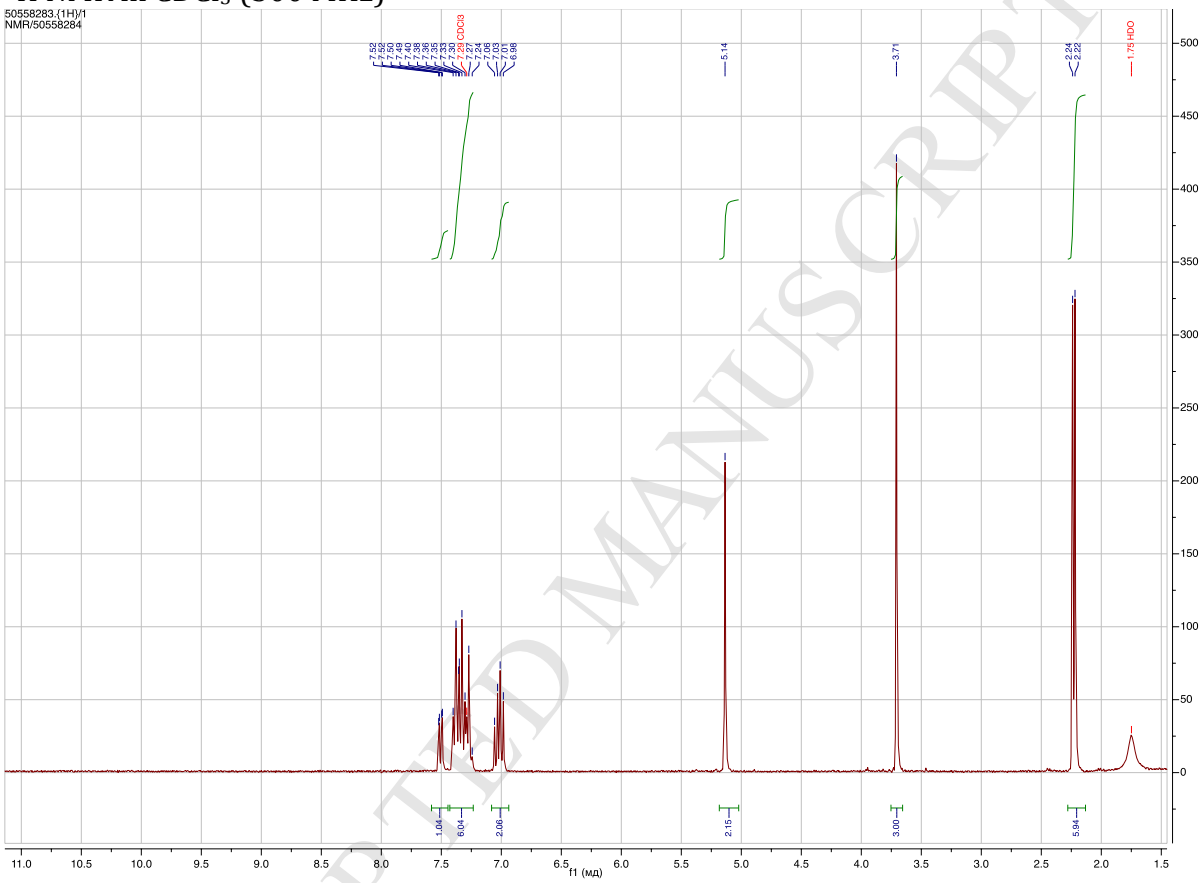


2-(2-(Benzyloxy)phenyl)-1-methoxy-4,5-dimethyl-1H-imidazole (24).

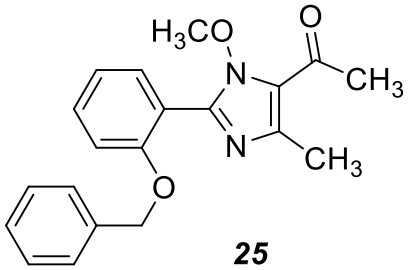


24

^{1}H NMR in $CDCl_3$ (300 MHz)

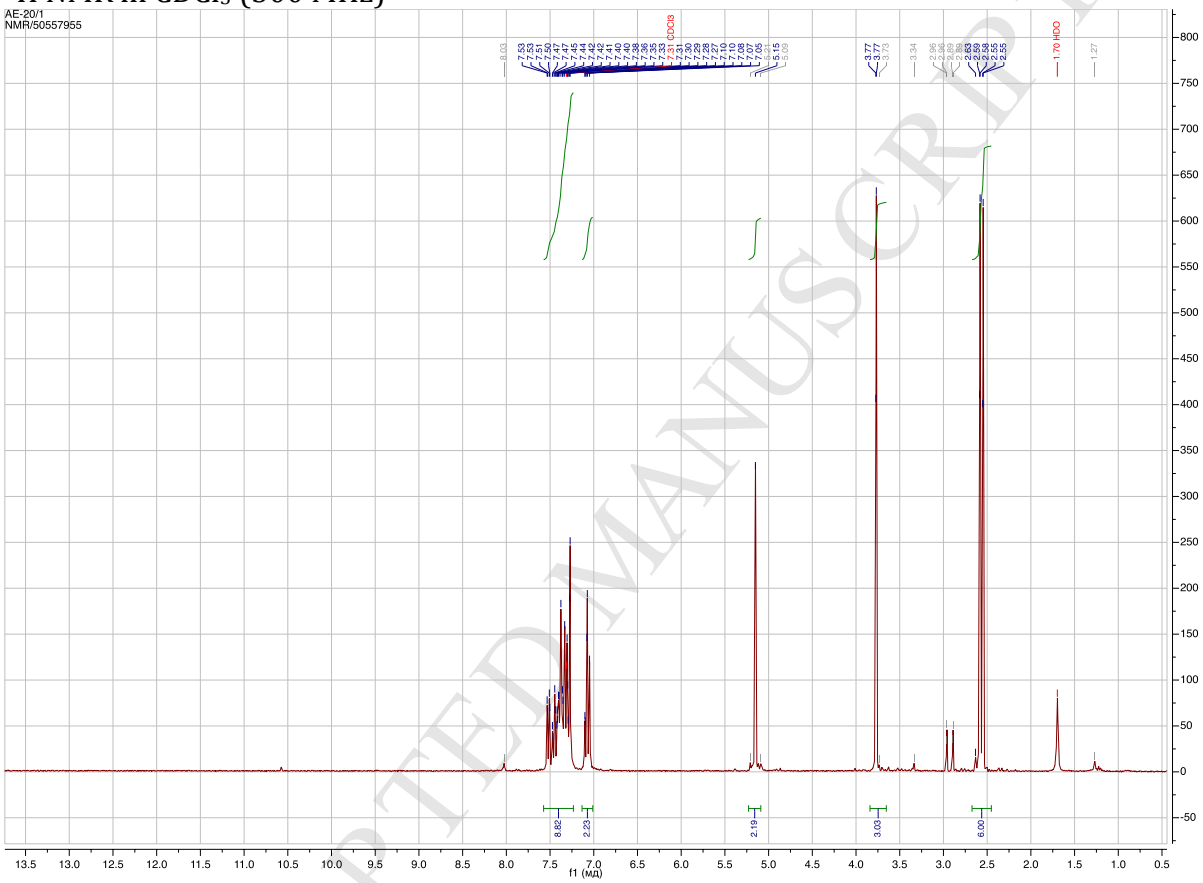


1-(2-(2-(Benzyloxy)phenyl)-1-methoxy-4-methyl-1H-imidazol-5-yl)ethanone (**25**).

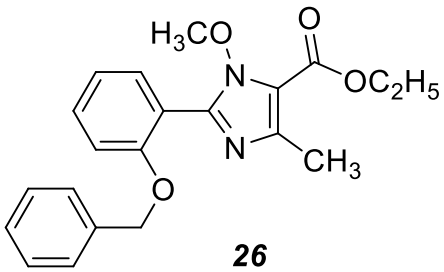


25

^{1}H NMR in $CDCl_3$ (300 MHz)

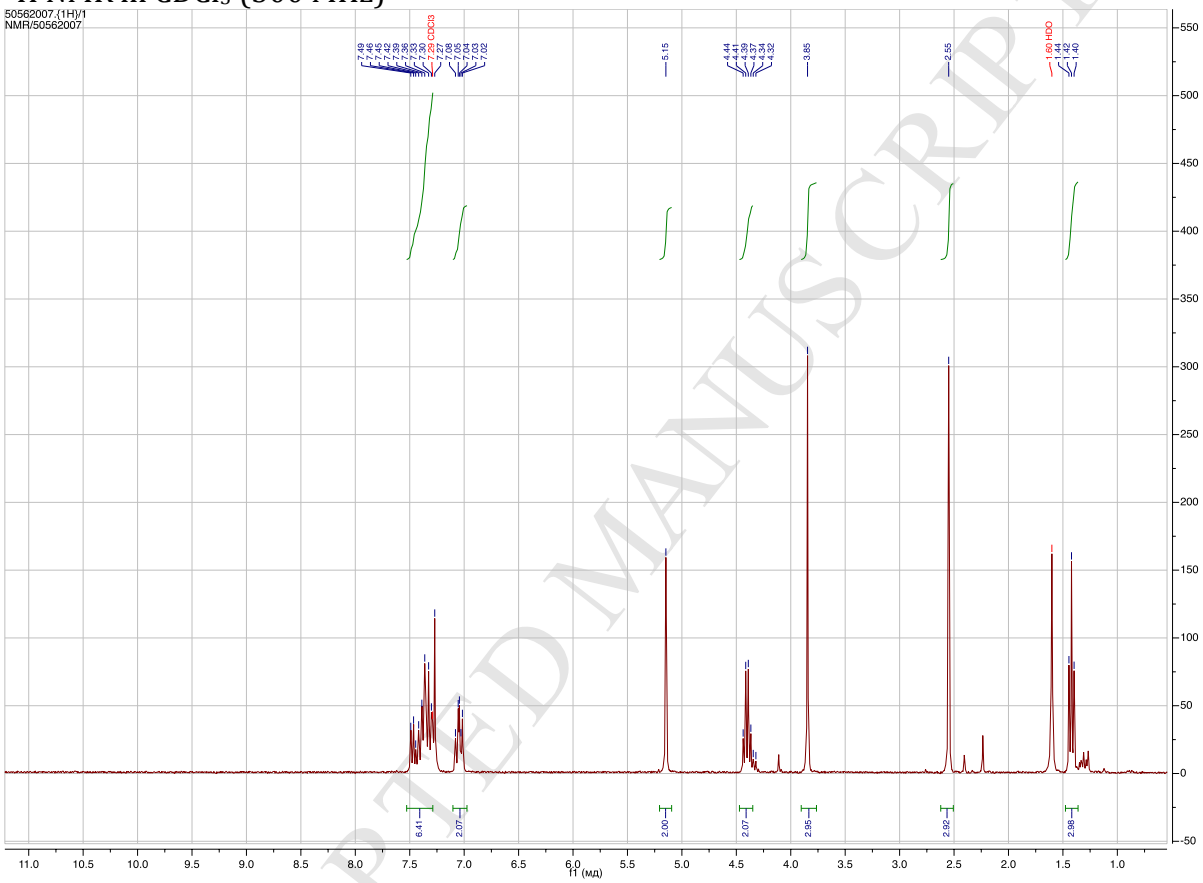


Ethyl 2-(2-(benzyloxy)phenyl)-1-methoxy-4-methyl-1H-imidazole-5-carboxylate (26).

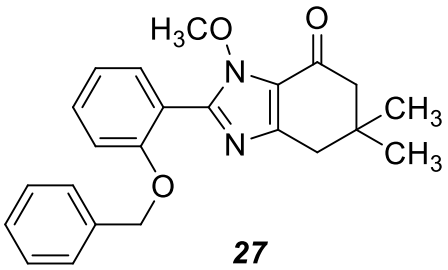


26

^{1}H NMR in $CDCl_3$ (300 MHz)

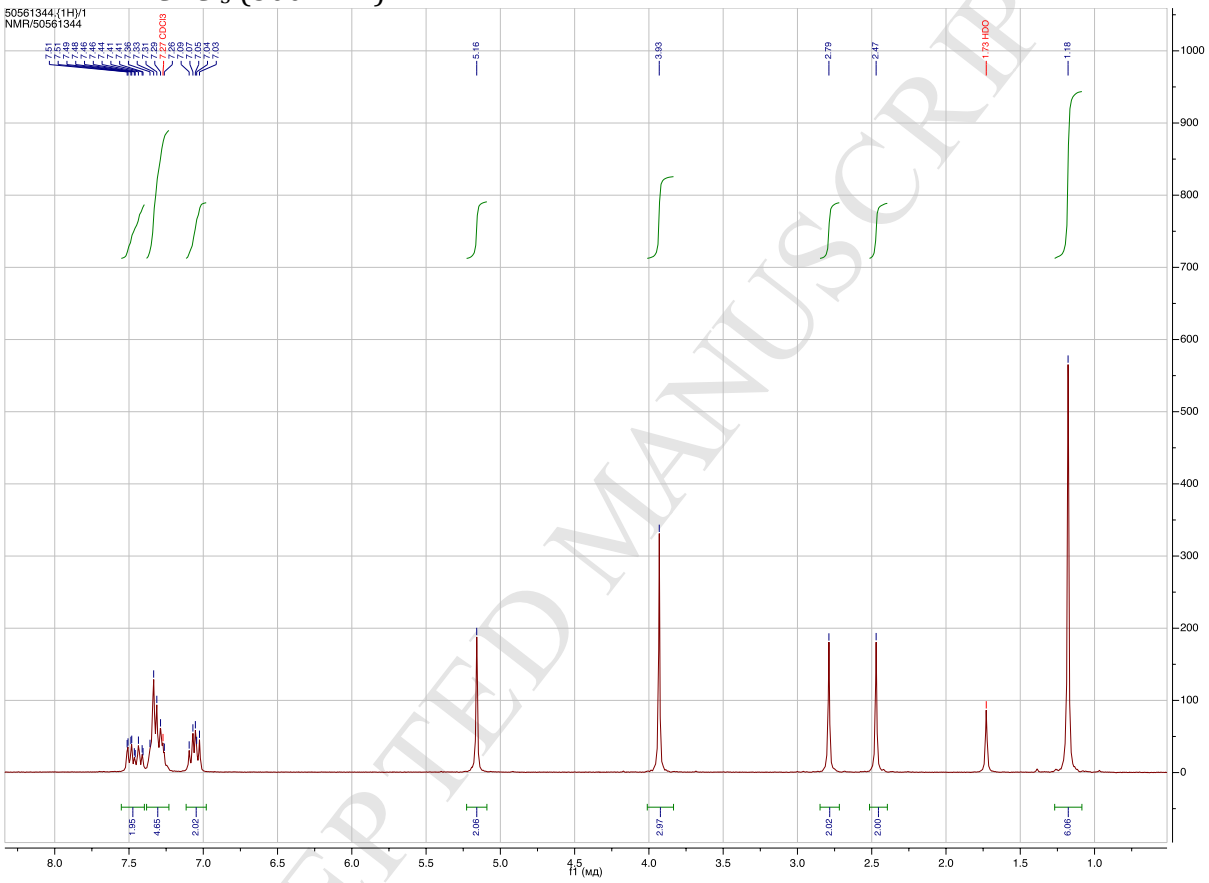


2-(2-(Benzyloxy)phenyl)-1-methoxy-5,5-dimethyl-4,5,6,7-tetrahydro-1H-benzo[d] imidazole-7(4H)-one (**27**).



27

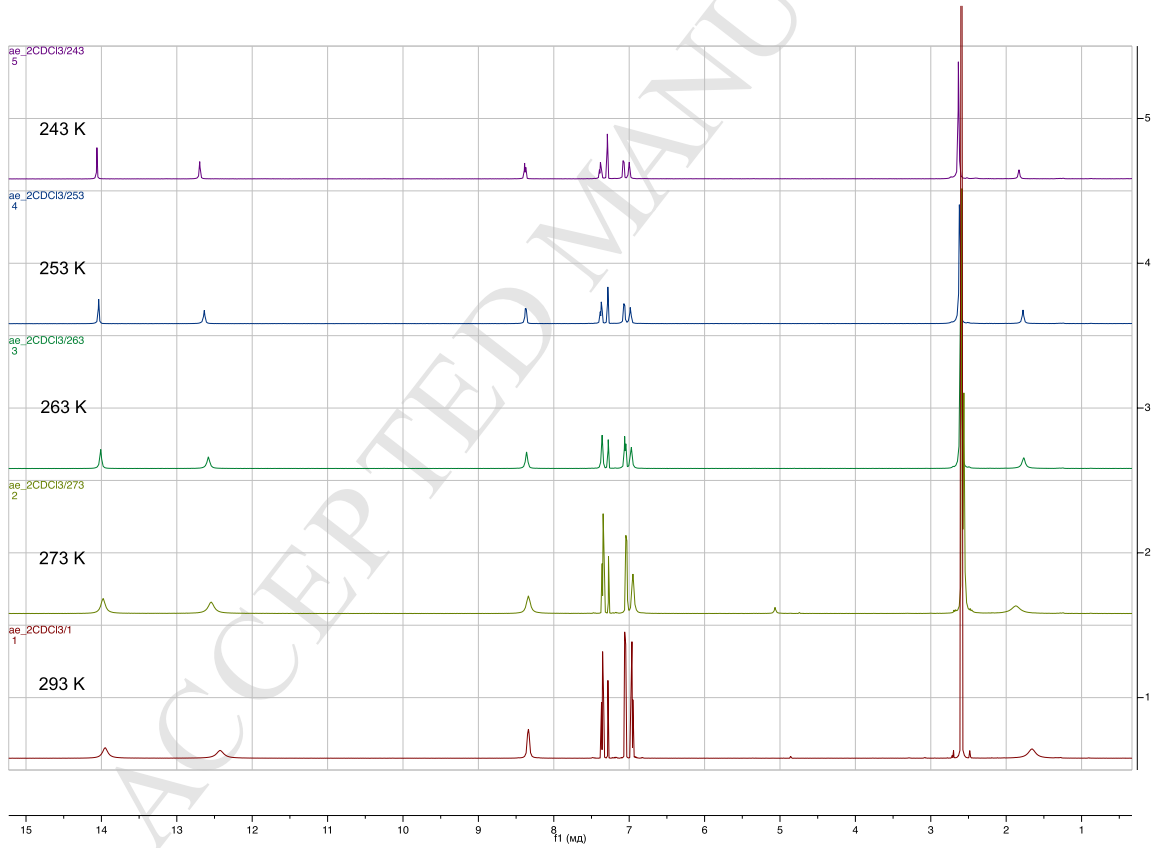
^{1}H NMR in $CDCl_3$ (300 MHz)



3. NMR spectra of compound 2 at different temperatures.

Table S1. ^{1}H NMR spectra of compound **2** in $CDCl_3$ at different temperatures (δ, ppm).

	293 K	273 K	263 K	253 K	243 K	Δδ
N-OH	13.93 (br)	13.98 (br s; $\nu_{½}$≈40Hz)	14.01 (s; $\nu_{½}$≈16Hz)	14.04 (s)	14.06 (s)	0.13
OH	12.41 (br)	12.54 (br s; $\nu_{½}$≈56Hz)	12.56 (br s; $\nu_{½}$≈28Hz)	12.64 (s)	12.70 (s)	0.30
H-3'	7.03 (d)	7.04 (d)	7.05 (d)	7.06 (d)	7.07 (d)	0.04
H-4'	7.33 (t)	7.35 (t)	7.36 (t)	7.37 (t)	7.38 (t)	0.05
H-5'	6.94 (t)	6.95 (br. s)	6.97 (br. t)	6.98 (t)	7.00 (t)	0.06
H-6'	8.32 (br. s; $\nu_{½}$≈19Hz)	8.34 (br. s; $\nu_{½}$≈30Hz)	8.36 (br. s; $\nu_{½}$≈20Hz)	8.37 (d; J = 8.1Hz)	8.38 (d; J = 8.1Hz)	0.06
$COCH_3$	2.57 (s)	2.59 (s)	2.60 (s)	2.62 (s)	2.63 (s)	0.06
4-CH_3	2.57 (s)	2.56 (s)	2.59 (s)	2.61 (s)	2.62 (s)	0.05



^{1}H NMR (600 MHz, $CDCl_3$, 293 K): δ= 13.93 (br. s, $\nu_{½}$ = 47 Hz, 1H, N-OH); 12.40 (br. s, $\nu_{½}$ = 62 Hz, 1H, OH); 8.32 (br. s, $\nu_{½}$ = 19 Hz, 1H, H6'); 7.33 (t, 1H, H4'); 7.03 (dd, J = 8.3, 1.2 Hz, 1H, H3'); 6.94 (t, 1H, H5'); 2.57 (s, 6H, $2CH_3$) ppm.

^{1}H NMR (600 MHz, $CDCl_3$, 273 K): δ= 13.98 (br. s, $\nu_{½}$ = 40 Hz, 1H, N-OH); 12.54 (br. s, $\nu_{½}$ = 56 Hz, 1H, OH); 8.36 (br. s, $\nu_{½}$ = 30 Hz, 1H, H6'); 7.35 (t, 1H, H4'); 7.05 (d, J = 8.3 Hz, 1H, H3'); 6.95 (br. s, $\nu_{½}$ = 22 Hz, 1H, H5'); 2.59 (s, 3H, $COCH_3$); 2.56 (s, 3H, CH_3) ppm.

^{1}H NMR (600 MHz, $CDCl_3$, 263 K): δ= 14.01 (s, $\nu_{½}$ = 16 Hz, 1H, N-OH); 12.56 (br. s, $\nu_{½}$ = 28 Hz, 1H, OH); 8.36 (br. s, $\nu_{½}$ = 20 Hz, 1H, H6'); 7.36 (t, 1H, H4'); 7.05 (d, *J* = 8.3 Hz, 1H, H3'); 6.97 (t, 1H, H5'); 2.60 (s, 3H, $COCH_3$); 2.59 (s, 3H, CH_3) ppm.

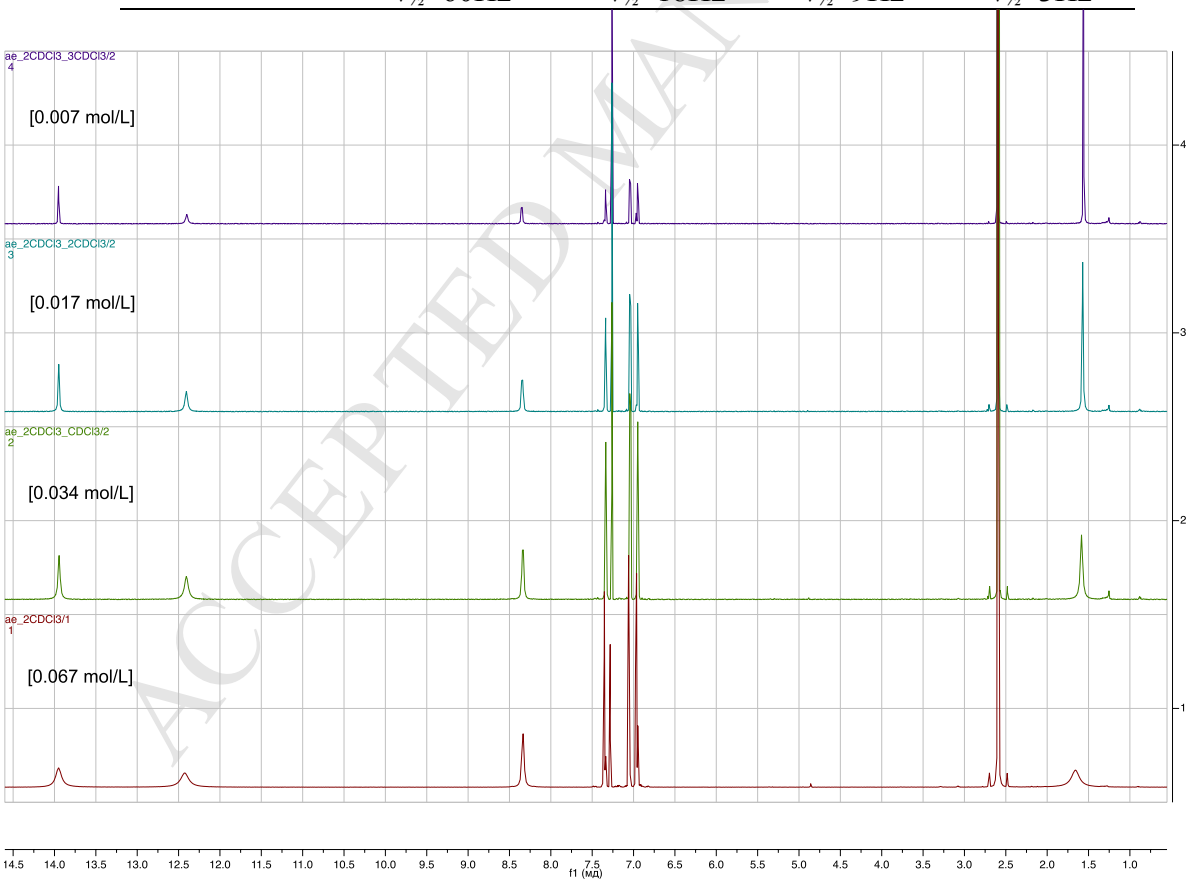
^{1}H NMR (600 MHz, $CDCl_3$, 253 K): δ= 14.04 (s, 1H, N-OH); 12.64 (s, $\nu_{½}$ = 12 Hz; 1H, OH); 8.37 (d, *J* = 8.1 Hz, 1H, H6'); 7.37 (t, 1H, H4'); 7.06 (d, *J* = 8.3 Hz, 1H, H3'); 6.98 (t, 1H, H5'); 2.62 (s, 3H, $COCH_3$); 2.61 (s, 3H, CH_3) ppm.

^{1}H NMR (600 MHz, $CDCl_3$, 243 K): δ= 14.06 (s, 1H, N-OH); 12.70 (s, 1H, OH); 8.38 (d, *J* = 8.0 Hz, 1H, H6'); 7.38 (t, 1H, H4'); 7.07 (d, *J* = 8.3 Hz, 1H, H3'); 7.00 (t, 1H, H5'); 2.63 (s, 3H, $COCH_3$); 2.62 (s, 3H, CH_3) ppm.

4. NMR spectra of compound 2 at different concentrations.

Table S2. ^{1}H NMR spectra of solutions with differing concentrations of compound **2** in $CDCl_3$ (δ, ppm).

	Starting solution 0.067 mol/L	Dilution 1 0.034 mol/L	Dilution 2 0.017 mol/L	Dilution 3 0.007 mol/L
N-OH	13.93 (br; $\nu_{1/2}$≈45Hz)	13.94 (br. s; $\nu_{1/2}$≈19Hz)	13.95 (s)	13. 95 (s)
OH	12.41 (br; $\nu_{1/2}$≈60Hz)	12.40 (br. s; $\nu_{1/2}$≈35Hz)	12.40 (br. s; $\nu_{1/2}$≈20Hz)	12.40 (br. s; $\nu_{1/2}$≈18Hz)
H-3'	7.03 (d)	7.03 (d)	7.04 (dd)	7.04 (dd)
H-4'	7.33 (t)	7.33 (t)	7.33 (t)	7.34 (t)
H-5'	6.94 (t)	6.95 (t)	6.95 (t)	6.95 (t)
H-6'	8.32 (br. s; $\nu_{1/2}$≈20Hz)	8.34 (br. d; *J*=7.9Hz)	8.35 (br. d; *J*=8.0Hz)	8.35 (d; *J*=8.0Hz)
$COCH_3$	2.57 (s)	2.59 (s)	2.60 (s)	2.60 (s)
4-CH_3	2.57 (s)	2.59 (s)	2.59 (s)	2.60 (s)
Signal of H_2O	1.66 $\nu_{1/2}$≈60Hz	1.56 $\nu_{1/2}$≈18Hz	1.56 $\nu_{1/2}$≈9Hz	1.56 $\nu_{1/2}$≈3Hz



^{1}H NMR (600 MHz, $CDCl_3$, [0.067 mol/l]): δ= 13.93 (br. s, $\nu_{1/2}$ = 47 Hz, 1H, N-OH); 12.40 (br. s, $\nu_{1/2}$ = 62 Hz, 1H, OH); 8.32 (br. s, $\nu_{1/2}$ = 19 Hz, 1H, H6'); 7.33 (t, 1H, H4'); 7.03 (dd, *J* = 8.3, 1.2 Hz, 1H, H3'); 6.94 (t, 1H, H5'); 2.57 (s, 6H, $2CH_3$) ppm.

^{1}H NMR (600 MHz, $CDCl_3$, [0.034 mol/l]): δ= 13.94 (br. s, $\nu_{½}$ = 18 Hz, 1H, N-OH); 12.40 (br. s, $\nu_{½}$ = 35 Hz); 8.34 (d, *J* = 7.9 Hz; 1H, H6'); 7.33 (t, 1H, H4'); 7.03 (d, *J* = 8.4 Hz; 1H, H3'); 6.95 (t, 1H, H5'); 2.59 (s, 6H, $2CH_3$) ppm.

^{1}H NMR (600 MHz, $CDCl_3$, [0.017 mol/l]): δ= 13.95 (s, 1H, N-OH); 12.40 (br. s, $\nu_{½}$ = 20 Hz); 8.35 (d, *J* = 8.0 Hz; 1H, H6'); 7.33 (t, 1H, H4'); 7.04 (dd, *J* = 8.3, 1.2 Hz; 1H, H3'); 6.95 (t, 1H, H5'); 2.60 (s, 3H, $COCH_3$); 2.59 (s, 3H, CH_3) ppm.

^{1}H NMR (600 MHz, $CDCl_3$, [0.007 mol/l]): δ= 13.95 (s, 1H, N-OH); 12.40 (br. s, $\nu_{½}$ = 18 Hz, 1H, OH); 8.35 (d, *J* = 8.0 Hz; 1H, H6'); 7.34 (t, 1H, H4'); 7.04 (dd, *J* = 8.3, 1.2 Hz; 1H, H3'); 6.95 (t, 1H, H5'); 2.60 (s, 3H, $COCH_3$); 2.59 (s, 3H, CH_3) ppm.

5. NMR spectra of compound 2 in mixture of solvents $CDCl_3$-DMSO-d_6 (1:1).

Table 3S. ^1H NMR spectra in mixture of $CDCl_3$ and DMSO-d_6 (1:1) at different temperatures (δ, ppm).

	293 K	273 K	253 K
N-OH	13.67 (br. s)	13.68 (s)	13.68 (s)
OH	13.55 (br. s)	13.56 (s)	13.56 (s)
H-3'	6.84 – 6.89 (m)	6.82 – 6.89 (m)	6.82 – 6.89 (m)
H-4'	7.32 (t)	7.32 (t)	7.32 (t)
H-5'	6.84 – 6.89 (m)	6.82 – 6.89 (m)	6.82 – 6.89 (m)
H-6'	7.45 (br.s; $\nu_{½}$≈70Hz)	7.40 (d; *J*=7.8Hz)	7.40 (d; *J*=7.8Hz)
$COCH_3$	2.65 (s)	2.63 (s)	2.63 (s)
4-CH_3	2.46 (s)	2.45 (s)	2.45 (s)
Signal of H_2O	3.33 ($\nu_{½}$≈35Hz)	3.62 ($\nu_{½}$≈13Hz)	3.62 ($\nu_{½}$≈7Hz)

The NMR spectra in mixture of solvents ($CDCl_3$-DMSO-d_6 1:1) at 293 K, 273 K and 253 K were recorded for 5-acetylsubstituted 1-hydroxyimidazole **2** (Table 3S).

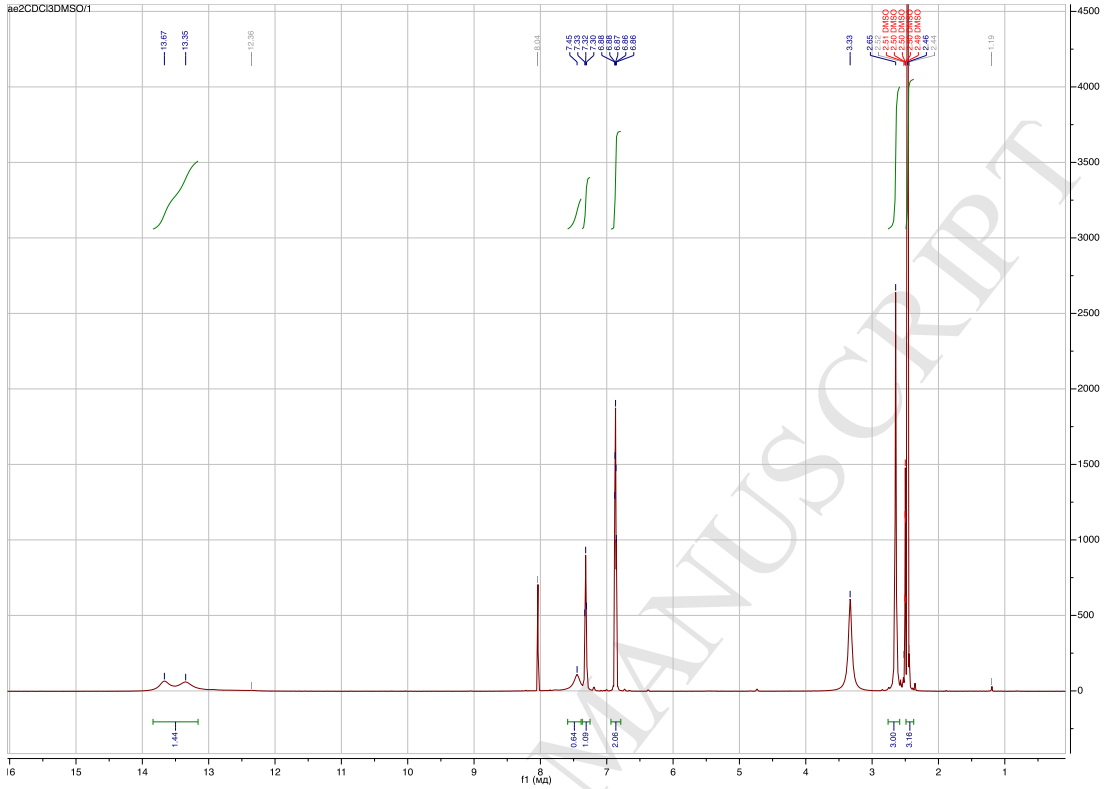
First, it should be mentioned that in this medium at room temperature the signal of the "reference" H6' proton is considerably broadened ($\nu_{½}$ ≈ 70 Hz) and is observed at 7.45 ppm. Cooling the sample results in the doublet (^3J = 7.8 Hz). It seems that the broadening of this signal is related to a rotation of the anisotropic parts of the molecule about the phenyl-imidazole bond that slow down with the temperature decrease.

Secondly, the positions and shapes of the OH and the water proton signals are also noteworthy. At 293 K the water protons give a broadened ($\nu_{½}$ ≈ 35 Hz) signal at 3.33 ppm. Cooling results in its narrowing ($\nu_{½}^{273}$ ≈ 13 Hz; $\nu_{½}^{253}$ ≈ 7 Hz) and shifting to 3.62 ppm. The protons bonded to the heteroatoms are observed at room temperature as broad signals at 13.67 ppm and 13.55 ppm. However on cooling the signals become narrower but their positions remain unchanged. The change in the position and width of the water protons signal allows to conclude that cooling of the sample reduces the intermolecular exchange between the water and OH-protons.

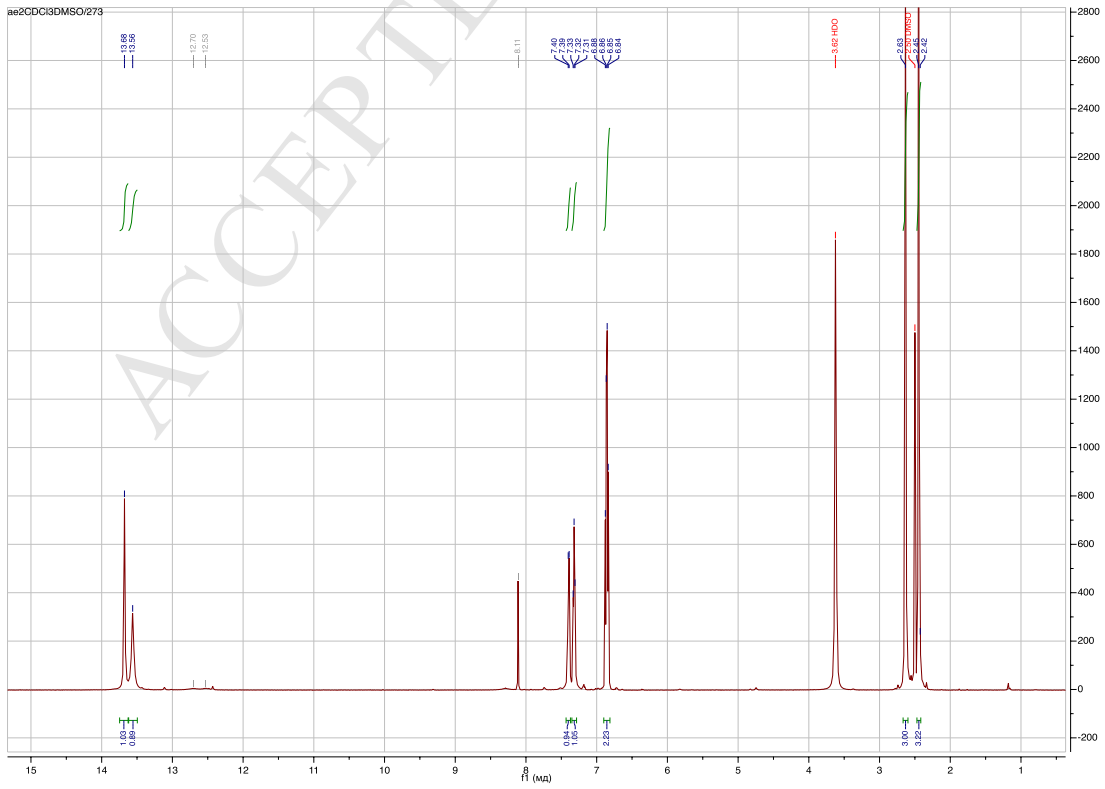
The absence of a low-field shift of the H6' proton signal (7.45 ppm) and the nonequivalence of the signals of the protons bonded to the heteroatoms testify the "open" NH-imidazole N-oxide tautomeric form.

Copies of NMR spectra of compound 2 in mixture of solvents $CDCl_3$ – DMSO-d_6 (1:1)

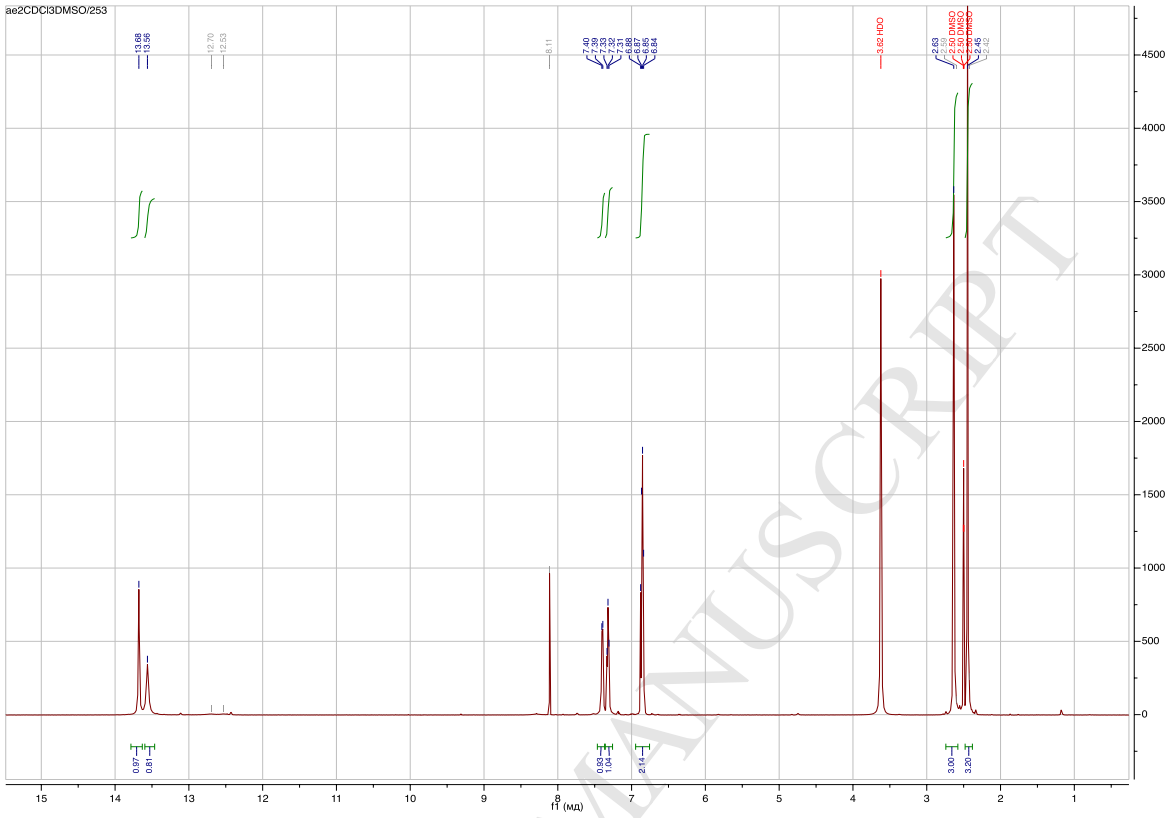
^{1}H NMR spectrum (293 K, 600 MHz): δ= 13.67 (br. s, 1H, N-OH); 13.55 (br. s, 1H, OH); 7.45 (br. s, $\nu_{½}$ = 70 Hz, 1H, H6'); 7.32 (t, 1H, H4'); 6.84-6.89 (m, 2H, H3' and H5'); 2.65 (s, 3H, $COCH_3$); 2.46 (s, 3H, CH_3) ppm.



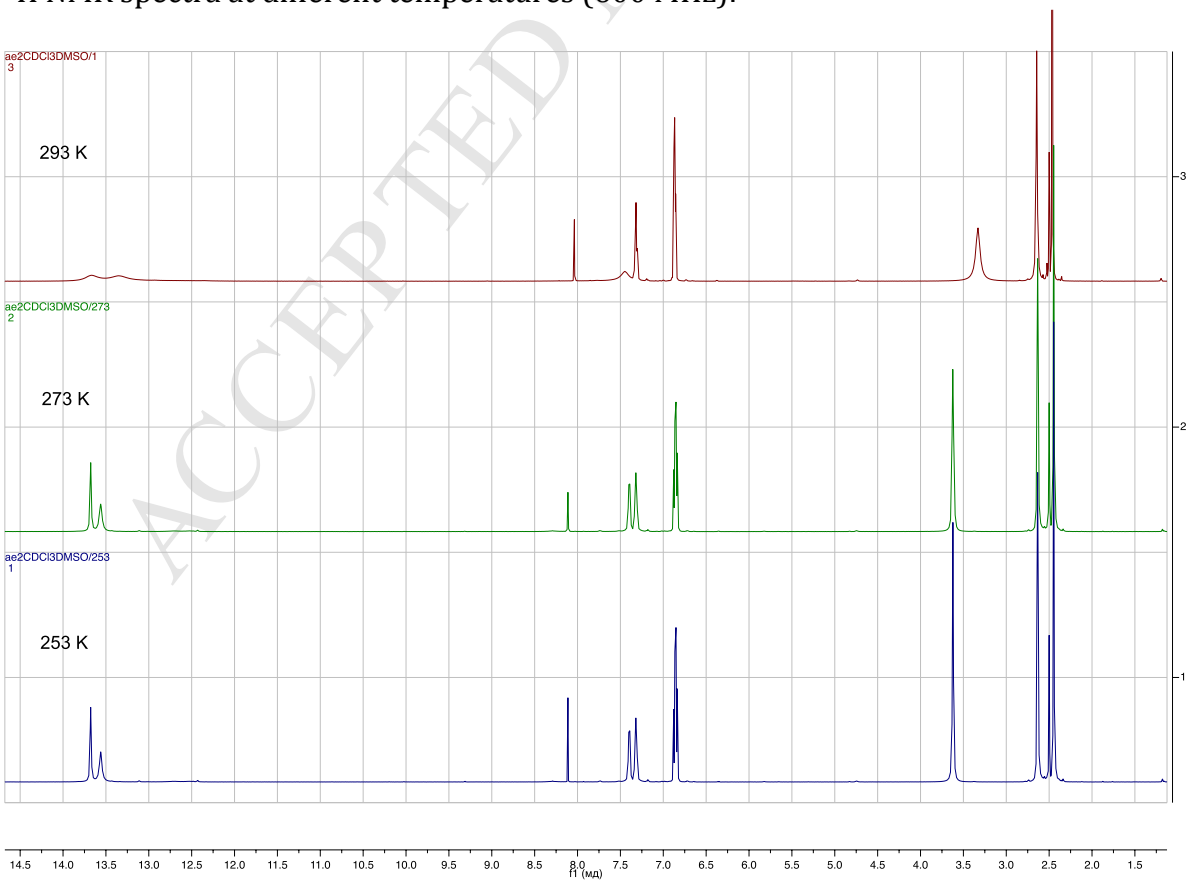
^{1}H NMR spectrum (273 K, 600 MHz): δ= 13.68 (s, 1H, N-OH); 13.56 (s, 1H, OH); 7.40 (d, *J* = 7.8 Hz, 1H, H6'); 7.32 (t, 1H, H4'); 6.82-6.89 (m, 2H, H3' and H5'); 2.63 (s, 3H, $COCH_3$); 2.45 (s, 3H, CH_3) ppm.



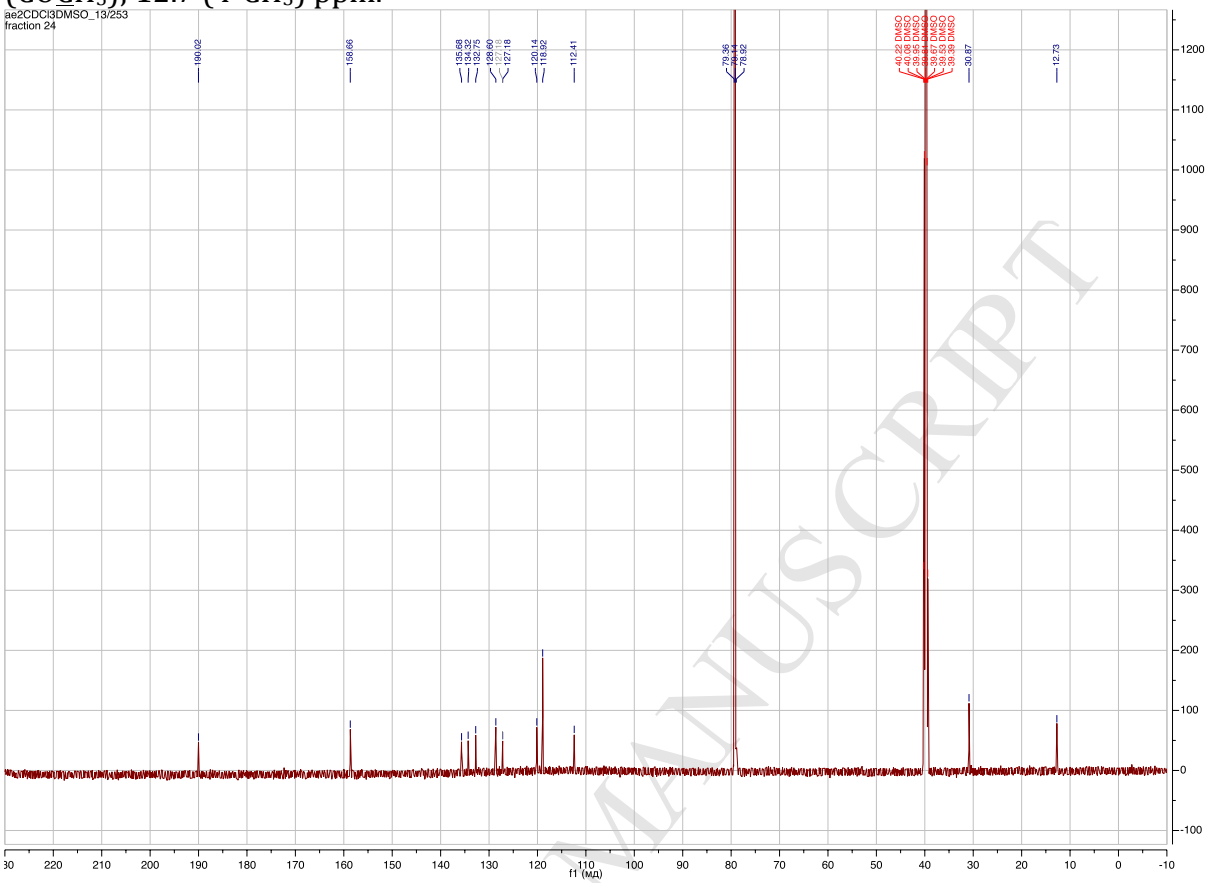
^{1}H NMR spectrum (253 K, 600 MHz): δ= 13.68 (s, 1H, N-OH); 13.56 (s, 1H, OH); 7.40 (d, *J* = 7.8 Hz, 1H, H6'); 7.32 (t, 1H, H4'); 6.82-6.89 (m, 2H, H3' and H5'); 2.63 (s, 3H, $COCH_3$); 2.45 (s, 3H, CH_3) ppm.



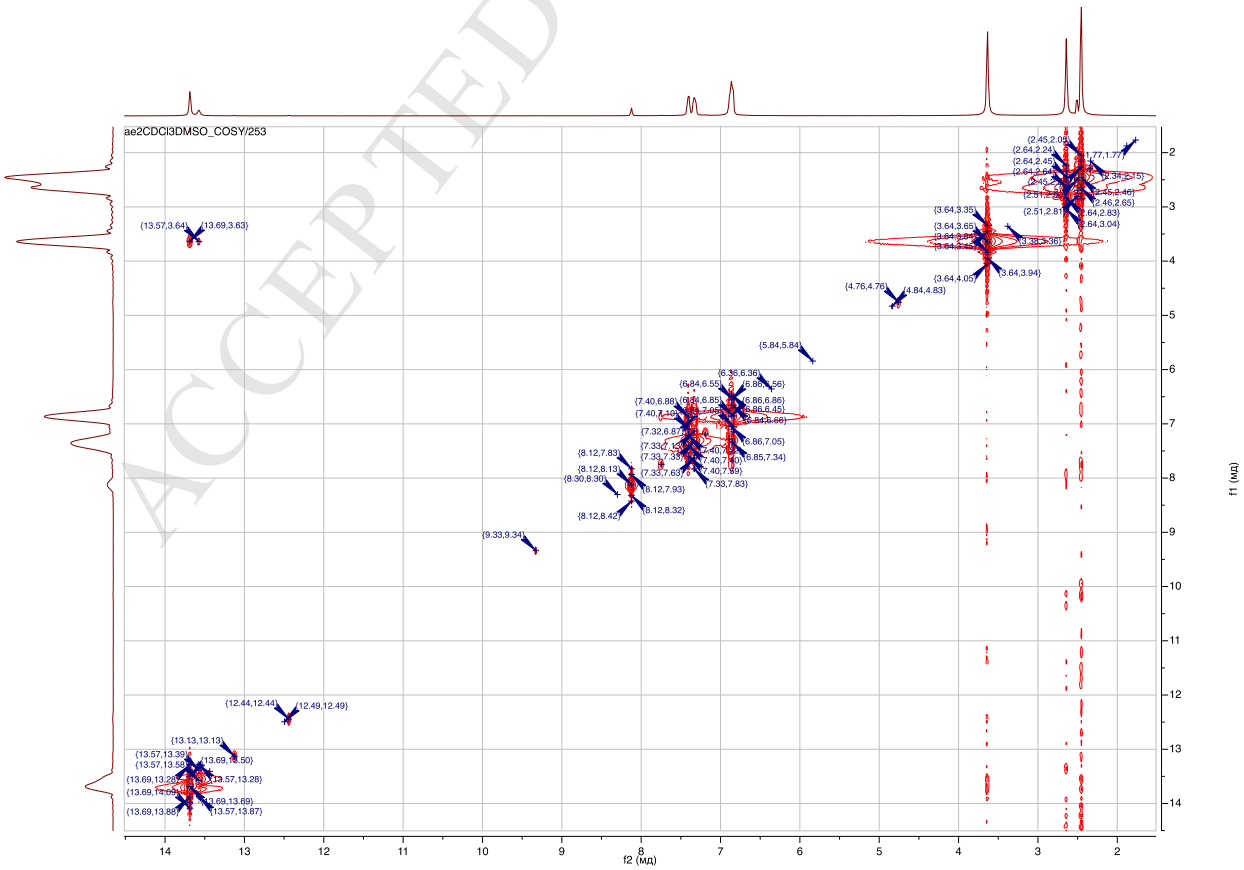
^{1}H NMR spectra at different temperatures (600 MHz):



^{13}C NMR spectrum (253 K, 600 MHz): δ= 190.0 (C=O); 158.7 (C-2'); 135.9 (C-2); 134.3 (C-4); 132.8 (C-3'); 128.6 (C-6'); 127.2 (C-5); 120.7 (C-5'); 118.9 (C-3'); 112.7 (C-1'); 30.9 ($CO\underline{C}H_3$); 12.7 (4-CH_3) ppm.



2D COSY NMR (253 K):



2D HMQC NMR (253 K):