# Accepted Manuscript


Synthesis and study of prototropic tautomerism of 2-(3-chromenyl)-1-hydroxyimidazoles

Polina A. Nikitina, Ludmila G. Kuz,mina, Valery P. Perevalov, Iosif I. Tkach

PII: S0040-4020(13)00250-0

DOI: 10.1016/j.tet.2013.02.039

Reference: TET 24034

To appear in: *Tetrahedron*

Received Date: 3 December 2012

Revised Date: 24 January 2013

Accepted Date: 11 February 2013

Please cite this article as: Nikitina PA, Kuz,mina LG, Perevalov VP, Tkach II, Synthesis and study of prototropic tautomerism of 2-(3-chromenyl)-1-hydroxyimidazoles, *Tetrahedron* (2013), doi: 10.1016/j.tet.2013.02.039.

## Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

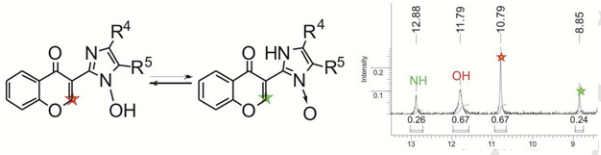
**Synthesis and Study of Prototropic Tautomerism of 2-(3-Chromenyl)-1-Hydroxyimidazoles**

Leave this area blank for abstract info.

Polina A. Nikitina[a], Ludmila G. Kuzmina[b], Valery P. Perevalov[a], Iosif I. Tkach[a,*]

[a]*D.Mendeleyev University of Chemical Technology of Russia, Miusskaya sq., 9, Moscow, 125047, Russia*

[b]*Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Science, Leninskii pr., 31, Moscow, 117907, Russia*



Tetrahedron
journal homepage: www.elsevier.com

# Synthesis and study of prototropic tautomerism of 2-(3-chromenyl)-1-hydroxyimidazoles

Polina A. Nikitina[a] , Ludmila G. Kuz'mina[b], Valery P. Perevalov[a] , and Iosif I. Tkach[a,*]

[a]*Department of Fine Organic Synthesis and Chemistry of Dyes, D.Mendeleyev University of Chemical Technology of Russia, Miusskaya sq., 9, Moscow, 125047, Russia*
[b]*Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Science, Leninskii pr., 31, Moscow, 117907, Russia*

ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
Prototropic tautomerism
1-Hydroxyimidazole
Imidazole N-oxide
2-(3-Chromenyl)imidazole
NMR spectroscopy
X-ray diffraction

ABSTRACT

A series of novel derivatives of imidazole containing a chromenyl moiety in position 2 of the ring has been synthesized.
A characteristic response of the chromenyl ring H-2 proton to its environment allows the study of the prototropic tautomerism of novel 1-hydroxyimidazoles in solution using $^{1}$H NMR spectroscopy. It has been shown that the predominance of one or another tautomer depends on the nature of the substituents of the imidazole ring, and the proton-donating/proton-withdrawing properties of a solvent.
X-ray diffraction data for two of the compounds has revealed that in the solid state these 1-hydroxyimidazole derivatives exist as N-oxide tautomers.

## 1. Introduction

1-Hydroxyimidazole derivatives exhibit various kinds of biological activity. They display insecticidal[1,2,3] and bacteriostatic properties;[4,5] antiviral[6,7] and antihypertensive[8] activities; they are also considered as potent AMPA receptor agonists[9] and so on. 1-Hydroxyimidazoles are also valuable intermediates for the synthesis of imidazole derivatives (see, e.g., reviews;[10,11] papers[12-16]).

It is supposed that 1-hydroxyimidazole derivatives exist in either N-hydroxy (a) or N-oxide (b) tautomeric form:

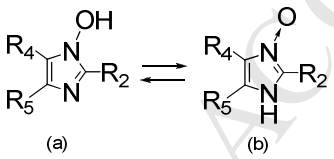



**Figure 1.** Prototropic tautomerism of 1-hydroxyimidazoles.

Prototropic tautomerism of aryl-substituted 1-hydroxyimidazoles was discussed in a series of papers published in 1960s[17-21]. In the paper of A.R. Katrizky,[21] the results of previous publications have been critically considered. For 2,4,5-triphenylimidazole 3-oxide and benzimidazole 3-oxide, it has been shown that these compounds exist predominantly in the N-hydroxy- form in nonpolar solvents, the content of the NH-form being increased as the polarity of a solvent increases. The main conclusions were based on the similarity of the absorption spectra of the compounds under consideration, and model compounds (N- and O-methyl derivatives), and the comparison of their pKa values in aqueous solution.

A few studies of the prototropic tautomerism of related compounds (1-hydroxybenzimidazole derivatives) are also known.[22-25] The prototropic tautomerism of 6-nitro- and 6-ethoxycarbonyl-1-hydroxybenzimidazol-2-carboxylic acids derivatives has been studied by $^{1}$H and $^{13}$C NMR spectroscopy,

* Corresponding author. Tel.: +7-499-978-8842; e-mail: iosif_tkach@mail.ru

quantum-chemical calculations, and X-ray structural analysis.[25] The main conclusion is that only the N-hydroxy form of these compounds may exist in the solid state. In solution, a predominance of one of the tautomeric forms has been explained by a trend of the solvent forming hydrogen bonds (hydrogen-bond-donor HBD or hydrogen-bond-acceptor HBA) rather than solvent polarity.

To the best of our knowledge, other papers concerning prototropic tautomerism in 1-hydroxyimidazoles are lacking. Apparently, it is explained by the use of these compounds mainly as intermediates in the syntheses of imidazoles. Recently, however, research interest in the biological activity of 1-hydroxyimidazoles (see, e.g.,[3,9]) and their coordinating properties[26,27] has increased. From this point of view, it is reasonable to return to the investigation of prototropic tautomerism of 1-hydroxyimidazoles.

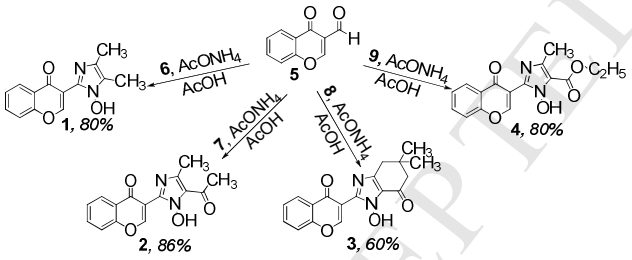
In our opinion, the study of 1-hydroxyimidazole derivatives capable of intramolecular hydrogen-bond formation may be of particular interest. In this work, we investigate 2-(3-chromenyl)-substituted 1-hydroxyimidazoles containing (or not containing) the carbonyl group in position 5 of the imidazole ring.

## 2. Results and Discussion

### *2.1. Synthesis of 2-Chromenyl Substituted 1-Hydroxyimidazoles*

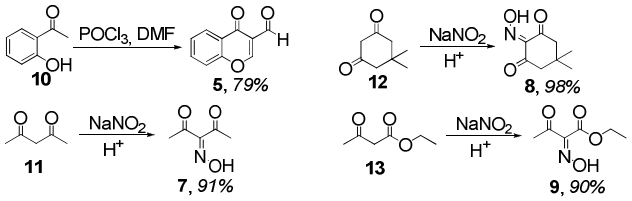
One of the most convenient and wide-spread methods to synthesise 1-hydroxyimidazoles is the cyclization of α-hydroxyiminoketones with aldehydes and ammonium acetate (see, e.g.,[3, 27-29]). The reaction is carried out either in alcohol or in glacial acetic acid. The temperature of the reaction may vary.

Novel 1-hydroxyimidazoles **1-4** were obtained by condensation of 4-oxo-4H-chromenyl-3-carbaldehyde **5** with ammonium acetate and the corresponding oxime **6-9** in glacial acetic acid at room temperature.



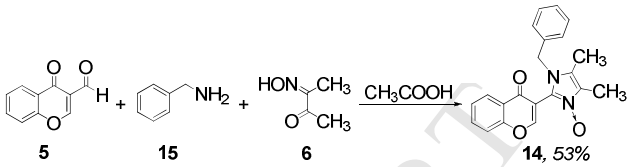

**Scheme 1.** Synthesis of 2-chromenyl-substituted 1-hydroxyimidazoles

Starting aldehyde **5** was obtained by treatment of hydroxyacetophenone **10** with phosphorous-oxychloride in dimethyl formamide.[30] Starting oximes **7-9** were obtained by nitrosation of the corresponding diketones **11-13** by techniques close to those described in literature.[31,32] Butandione monoxime **6** is commercially available.



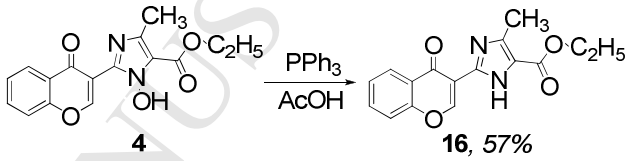

**Scheme 2.** Synthesis of starting compounds.

In order to compare properties of 1-hydroxyimidazoles with 1-substituted imidazole 3-oxide, novel 2-chromenyl-substituted imidazole 3-oxide **14** was synthesized. Condensation was carried out in glacial acetic acid at room temperature, with benzylamine **15** being used as the amine constituent.




**Scheme 3.** Synthesis of imidazole N-oxide **14**.

As is known, 1-hydroxyimidazoles may be easily reduced into the corresponding imidazoles by refluxing with triphenylphosphine in glacial acetic acid. This was demonstrated on 1-hydroxyimidazole **4**:




**Scheme 4.** Reduction of 1-hydroxyimidazole **4**.

All novel imidazole derivatives (**1-4**, **14**) were characterized by $^{1}H$ and $^{13}C$ NMR spectroscopy and mass spectrometry, elemental analysis, and melting point data.

### *2.2. Study of Prototropic Tautomerism of 2-Chromenyl Substituted 1-Hydroximidazoles in Solution*

Prototropic tautomerism of heterocyclic compounds in solution is widely studied by means of NMR spectroscopy (see, e.g.,[25, 33, 34]). This method may be useful and informative in the case of 1-hydroxy-2-chromenylimidazoles **1** – **4**. It will be shown in the further discussion that chemical shifts of the proton at the C-2 atom ($H_{C2}$) of the chromenyl moiety are different for the N-hydroxy- and N-oxide tautomers.

In order to escape the possible (though unlikely) influence of the C-H-acidity at the C-2 atom ($H_{C2}$) of the chromenyl ring and following exchange processes, the NMR spectra of protonated compounds **1** – **4** and **14** were recorded in $CD_3CN$ with the addition of ~10 equivalents of trifluoromethanesulfonic acid, and in trifluoroacetic acid. In both cases the $H_{C2}$ signal appears as a narrow singlet (Table 1), which precludes the exchange process.

**Table 1.** Chemical shifts for the $H_{C2}$ proton of protonated forms of compounds **1-4** and **14**.

| Solvent | **1** | **2** | **3** | **4** | **14** |
|---|---|---|---|---|---|
| $CD_3CN + CF_3SO_3H$ | 9.29 | 9.36 | 9.47 | 9.40 | 8.82 |
| $CF_3COOH$ | 9.44 | 9.59 | 9.70 | 9.57 | 8.40 |

In the $^{1}H$ NMR spectra recorded in deuterated chloroform, the $H_{C2}$ signal is found either at 10.62 ppm (compound **1**), or at 8.93 ppm (compound **3**), or it appears as two signals in the 8.65 – 8.85 and 10.66 – 10.79 ppm ranges, that correspond to different tautomeric forms (Table 2 and Figure 2). The low-field signals in the 11.2 – 13.2 ppm range are attributed to the OH (NH) group protons. A comparison of the positions of the signals for $H_{C2}$ in

compounds **1** – **4** with that in compound **14** makes it possible to conclude that the signals in the ranges 10.62 – 10.79 and 11.22 – 12.16 ppm correspond to the $H_{C2}$ and OH-group protons of the N-hydroxy tautomer (a), whereas the signals in the 8.65 – 8.93 and 12.73 – 13.15 ppm ranges refer to the $H_{C2}$ and NH protons of the N-oxide form of imidazole (b). Thus, in deuterochloroform 4,5-dimethylimidazole **1** exists exclusively as the N-hydroxytautomer (a), whereas 5-carbonyl-substituted imidazoles (**2** – **4**) exist either as the N-oxide tautomer (b) (compound **3**) or as an equilibrium mixture of the tautomers (compounds **2** and **4**) where the N-hydroxy- form (a) prevails (integration of signals in the NMR spectra allows a rough estimation of the tautomer ratio to make, *viz*, (a) : (b) ≈ 2 : 1). For compound **4**, a transition of one tautomer into another one proceeds rather quickly, which is indicated by a broad $H_{C2}$ signal in the range 9.0 – 9.3 ppm (coalescence point). Lowering the temperature to 242K allows us to observe the signals of both tautomers of this compound. It should be noted that, for compound **3** in chloroform, the integrated intensity of the $H_{C2}$ signal is slightly understated. However, the $^1$H NMR spectrum at decreased temperatures does not reveal any "new" signals that could be attributed to another tautomeric form (a).

**Table 2.** Chemical shifts[a] of characteristic protons in various solvents.

| | $CDCl_3$ | | [$D_6$]DMSO | | $CD_3CN$ | $CD_3OD$ |
|---|---|---|---|---|---|---|
| | H-2 | OH (NH) | H-2 | OH (NH) | H-2 | H-2 |
| **1** | 10.79 | 11.22 (OH) | 10.62 | 11.89 (OH) | 10.48 | 10.15 |
| **2** | 8.85 | 12.88 (NH) | 8.74 | 11.94 (NH) | non soluble | non soluble |
| | 10.79 | 11.79 (OH) | | | | |
| **3** | 8.93 | 12.73 (NH) | 8.76 | 11.60 (NH) | 9.23 (br) | 9.57 (br) |
| **4** | 8.65[b] | 13.15[b] (NH) | 8.73 | 11.92 (NH) | 9.25 (br) | 9.60 (br) |
| | 10.66[b] | 12.16[b] (OH) | | | | |
| **14** | 8.70 | - | 8.69 | - | 8.41 | 8.40 |

[a] δ, ppm

[b] The spectrum was recorded at 242K.

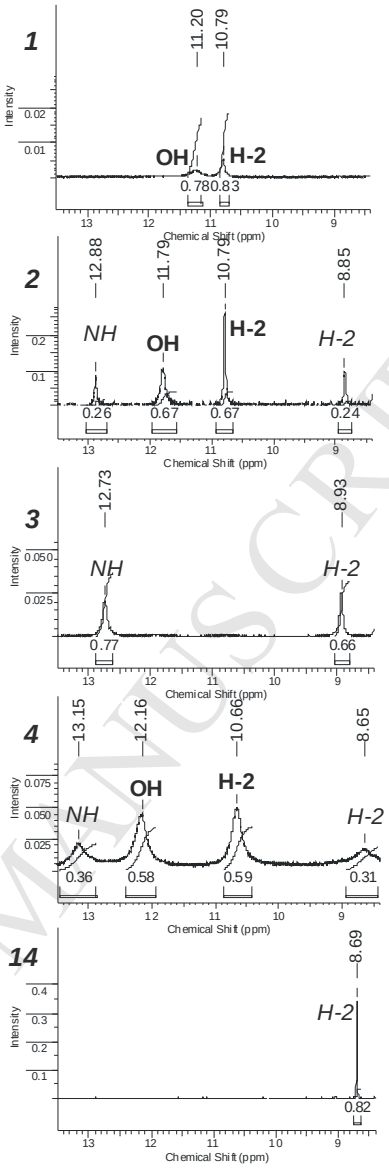



**Figure 2.** 8.5 – 13.5 range of $^1$H NMR spectra of compounds **1-4**, **14** registered in $CDCl_3$.

In more polar aprotic ([$D_6$]DMSO and $CD_3CN$) and protic ($CD_3OD$) solvents, the situation is roughly similar. Thus, according to the agreement of the chemical shifts for $H_{C2}$ of compounds **2** – **4** and N-oxide **14**, it may be established that, in strongly polar aprotic [$D_6$]DMSO, 5-carbonyl-substituted imidazoles (**2** - **4**) exist as N-oxide tautomers (b), while, in the case of 4,5-dimethylimidazole **1**, the signal of the similar proton is shifted downfield by near 2 ppm (hydroxytautomer (a)). In less polar acetonitrile, the signal of $H_{C2}$ for compound **1** appears at 10.48 ppm, which qualitatively coincides with the position of this signal in $CDCl_3$ and [$D_6$]DMSO (hydroxytautomer (a)). For compounds **3** and **4,** the $H_{C2}$ signals are broadened and they appear in the range 9.2 – 9.3 ppm (an intermediate between positions for compounds **1** and **14**, see Table 2), which indicates the existence of the tautomeric equilibria.

In polar protic $CD_3OD$, the situation is quite similar to that observed in acetonitrile. Unfortunately, it was impossible to record the NMR spectra of compounds **3**, **4** in $CD_3CN$ and $CD_3OD$ at a lower temperature because of their poor solubility in these solvents.

So, 4,5-dimethylimidazole **1** exists in solution as the N-hydroxytautomer regardless of the nature of the solvent. In a hydrogen-bond acceptor, [$D_6$]DMSO, 5-carbonyl substituted imidazoles **2** – **4** exist in the N-oxide form. In a weak hydrogen-bond donor, $CDCl_3$, compound **3** containing a fixed carbonyl group in 5 position also exists as a N-oxide tautomer. Evidently, it can be explained by the favourable conditions for conjugation in enaminone moiety, that is additionally stabilized by the intramolecular hydrogen bond between N-H proton and carbonyl oxygen in the chromenyl part of the molecule.

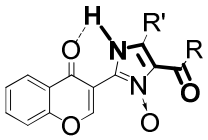



**Figure 3.** Enaminone structure.

The weakening of conjugation due to the possibility of carbonyl group rotation in compounds **2** and **4** in $CDCl_3$, and also the increase in proton-donating ability of a solvent ($CD_3CN$ and $CD_3OD$), that loosens the intramolecular hydrogen bond (compounds **2** and **4**), favours the occurence of the second (N-hydroxy) tautomer (a). This leads to the mixture of tautomers in solution.

Thus, for this series of compounds, the N-oxide form prevails only in molecules stabilized by conjugation in the enaminone structure in the absence of strong proton-donating solvent properties.

It should be mentioned that a high sensitivity of the $H_{C2}$ proton of the chromenyl ring towards the influence of atom environment is typical not only for 1-hydroxyimidazole derivatives but also for imidazoles themselves.

In the $^1$H NMR spectrum of compound **16**, recorded in deuterated chloroform, the $H_{C2}$ proton signal appears as two singlets at 9.19 and 9.09 ppm (the ratio of integrated intensities is 1 : 1.2). The signals of aliphatic protons are also doubled. Specifically, the methyl group in the 4(5) position of the imidazole ring reveals two singlets at 2.64 and 2.56 ppm (the ratio of integrated intensities is 1 : 1.2). Obviously, it is related to the migration of the proton between the nitrogen atoms of imidazole ring, rather than possible conformers obtained as a result of the rotation around the bond between two heterocycles, otherwise in the latter case the signal of the methyl group protons should not be split.

*2.3. Study of Prototropic Tautomerism of 2-Chromenyl Substituted 1-Hydroxyimidazoles in Solid State*

X-ray analysis data have been obtained for compounds **1** and **3**.

The structures of formula units are shown in Figures 4 and 7.

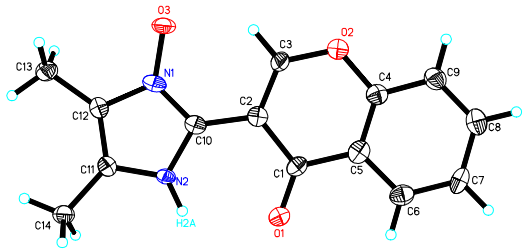



**Figure 4.** Compound **1**. Molecular structure thermal atomic displacement parameter are given at the 50% probability level.

Selected bond lengths are listed in Table 3.

**Table 3.** Selected bond lengths (Å) in molecules.

| | Compound **1** | Compound **3** |
|---|---|---|
| O1–C1 | 1.238(4) | 1.230(2) |
| O2-C3 | 1.362(4) | 1.343(2) |
| O2-C4 | 1.382(4) | 1.367(2) |
| O3-N1 | 1.349(4) | 1.321(2) |
| O4-C13 | - | 1.219(2) |
| N1-C10 | 1.346(5) | 1.339(2) |
| N1-C12 | 1.399(5) | 1.393(2) |
| N2-C11 | 1.373(5) | 1.354(2) |
| N2-C10 | 1.371(5) | 1.364(2) |
| C1-C2 | 1.469(5) | 1.463 |
| C1-C5 | 1.467(5) | 1.474(2) |
| C2-C3 | 1.366(5) | 1.350(2) |
| C2-C10 | 1.446(5) | 1.454(2) |
| C4-C5 | 1.388(5) | 1.383(2) |
| C4-C9 | 1.398(2) | 1.398(2) |
| C5-C6 | 1.405(5) | 1.406(2) |
| C6-C7 | 1.373(5) | 1.372(3) |
| C7-C8 | 1.414(6) | 1.396(3) |
| C8-C9 | 1.379(6) | 1.363(3) |
| C11-C12 | 1.363(5) | 1.372(2) |
| C11-C14 | 1.504(5) | - |
| C11-C16 | - | 1.479(2) |
| C12-C13 | 1.482(5) | 1.450(2) |
| C13-C14 | - | 1.509(2) |
| C14-C15 | - | 1.537(3) |
| C15-C16 | - | 1.540(2) |

Molecules of **1** are packed in infinite chains through hydrogen bonds of the type O3…H2–N2 (see Figures 4 and 5). Geometric parameters of these bonds are as follows: O3…H2 2.312 Å, angle at H2 atom 130°, angle at O3 atom 134.1°. These parameters correspond to a rather weak interaction.

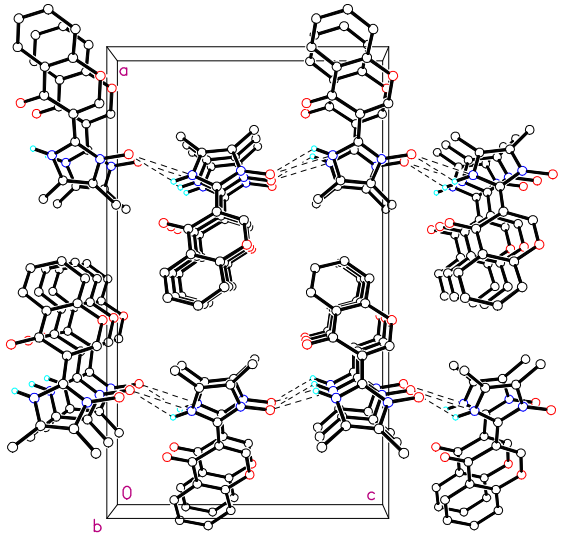



**Figure 5.** Fragment of crystal packing for compound **1**.

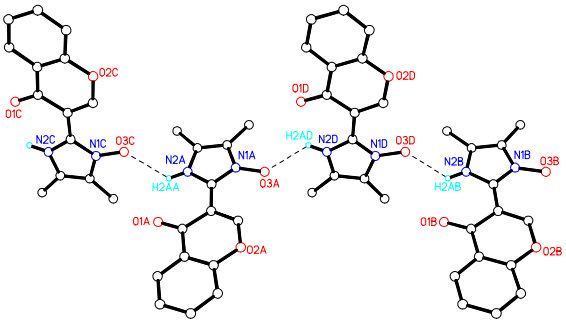



**Figure 6.** System of hydrogen bonds in crystals of compound **1**; labels A, B, C and D in atom denotation indicate different molecules.

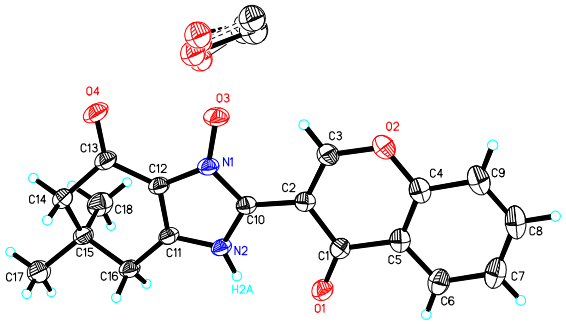



**Figure 7.** Compound **3**. Structure of formula units; thermal atomic displacement parameters are given at the level of 30% probabililty.

As a whole, compound **3** is planar, with the exception of saturated fragment C13…C18. The C13-C12-C11-C16 fragment is planar, whereas atoms C14 and C15 are displaced from the plane of the planar fragment by 0.243 and -0.466 Å, respectively. Methyl groups at C17 and C18 have equatorial and axial orientations, respectively.

Some bond length alternation is observed in the C4…C9 benzene ring. In the crystal, the molecules are linked by hydrogen bonds (Figure 8).

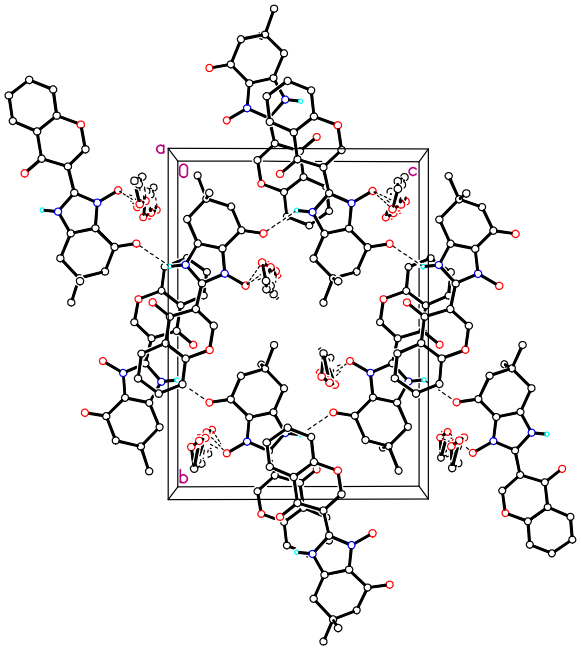



**Figure 8.** Fragment of crystal packing of compound **3**.

It is seen from the projection of the crystal packing that solvate methanol molecules are situated in the cavities between the main molecules in the vicinity of the O3 atom of the main molecules. In all orientations of the disordered solvent molecules, their hydroxyl groups (O1S) are turned towards the O3 atoms. This means that solvent molecules are involved in crystal packing due to hydrogen bonds. The distances between the oxygen atoms of disordered methanol and the O3 atom lies within the range 2.535 – 2.887 Å, typical for hydrogen bonds O–H…O.

Figure 9 shows the system of hydrogen bonds within the crystal. The molecules are combined in endless chains due to hydrogen bonding O4…H2A–N2. The distances O4…N2 and O4…H2A (2.915(2) 2.21 Å, respectively) correspond to N–H…O hydrogen bond, although the angle at H2A hydrogen atom is equal to 139°. This indicates that the location of the hydrogen atom is not optimal, and this hydrogen bond should be rather weak. In the chain, the molecules that have labels C and D, as well A and B in atom denotation are related by translation along the *c*-axis. Pairs of molecules with labels A and C, as well as D and B are related via $2_1$ axes.

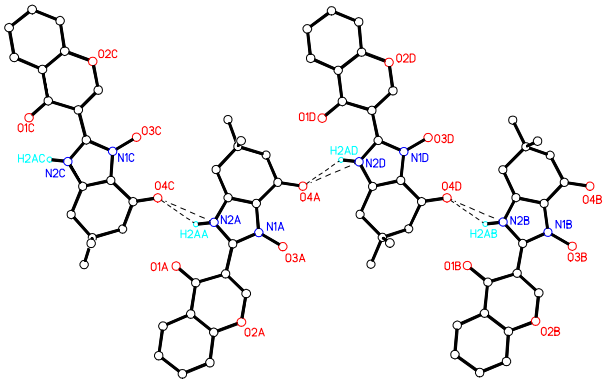


**Figure 9.** System of hydrogen bonds in crystal of compound **3**; labels A, B, C and D in atom denotation indicate different molecules.

According to the X-ray analysis data, both compounds **1** and **3,** in the solid state exist as N-oxide tautomers, the difference in topology of the intermolecular bonds in these molecules being rather interesting.

Thus, in the crystal form, molecules of compound **1** are bound into long chains via hydrogen bonds between the oxygen atom of the N-oxide group and the NH-moiety of the adjacent molecule (that is, they are ordered by imidazole fragments).

As for compound **3**, its NH-moiety is bound by hydrogen bonds with the carbonyl in the 5 position of the imidazole ring of the adjacent molecule, the N-oxide oxygen atom being excluded from formation of the H-bond.

In both cases the carbonyl oxygen atom of the chromenyl moiety does not participate in the formation of chains.

### 3. Conclusion

In the crystal state, substituted imidazoles **1** and **3** exist in the N-oxide tautomeric form. However, the crystal packing of these two compounds is different.

A rather close packing of the molecules in the crystal, and the presence of long chains for 4,5-dimethylimidazole derivative **1** are caused by hydrogen bonds between the imidazole N-oxide moieties of the molecules.

The presence of a bulky annulated ring in the 4,5 positions of the imidazole moiety of compound **3** prevents the formation of an ordered chain structure.

In relatively dilute solution, regardless of the polarity and proton-donor (proton-acceptor) properties of the solvent, in the case of 4,5-dimethyl-2-chromenyl-1-hydroxyimidazole **1** the tautomeric equilibrium between N-hydroxy- (a) and N-oxide (b) forms is shifted to the N-hydroxy tautomer that is apparently more thermodynamically favourable. The introduction of a carbonyl group in position 5 of the 1-hydroxyimidazole shifts the equilibrium to the N-oxide tautomer (b), that becomes more energetically favorable due to the conjugation between the endocyclic amino group of the imidazole moiety and the carbonyl group (an enaminone chain). The more effective this conjugation is (fixed carbonyl group, absence or very weak proton-donating properties of the solvent), the more the tautomeric equilibrium is shifted to the N-oxide form (b).

### 4. Experimental Section

#### 4.1. General

Chemicals were purchased from commercial sources and were used without further purification. $^{1}$H and $^{13}$C NMR spectra were recorded with Bruker VP-200 or Bruker AvanceTM-300 spectrometers with the residual solvents as internal standards. Mass-spectra were recorded with a LKB-2000 mass spectrometer. Infrared spectra of solids were recorded with Shimadzu IRAffinity-1 FTIR spectrophotometer as film obtained from chloroform solution or with Nicolet Magna 750 IR spectrophotometer in a KBr matrix.

#### 4.2. The detailed experimental procedures and characterization data.

*4.2.1. 3-(1-Hydroxy-4,5-dimethyl-1H-imidazol-2-yl)-4H-chromen-4-one (**1**).*

A mixture of aldehyde **5** (4.0 g, 0.023 mol), oxime **6** (2.3 g, 0.023 mol) and ammonium acetate (2.5 g, 0.032 mol) in glacial acetic acid (30 mL) was stirred at room temperature for 12 hours and left to stand overnight. The precipitate was filtered off and washed with ether. The filtrate was poured into water (100 mL), and the precipitate filtered off and dried. The precipitates were combined (5.8 g) and recrystallized from toluene yielding 4.7 g (80%) of product **1** as yellow solid as the mono-hydrate; m.p. 178-180°C. After drying under reduced pressure over $P_2O_5$ m.p. is 203-204°C.

$^{1}$H NMR (300 MHz, $CDCl_3$, 299K): δ = 11.20 (br. s, 1H, OH); 10.79 (br. s, 1H, $H_{Ar}$-2); 8.30 (dd J = 8.07 Hz, 1H, $H_{Ar}$-5); 7.73 - 7.82 (m, 1H, $H_{Ar}$-7); 7.60 (d, J = 8.07 Hz, 1H, $H_{Ar}$-8); 7.45 - 7.53 (m, 1H, $H_{Ar}$-6); 2.28 (s, 3H, $CH_3$); 2.25 (s, 3H, $CH_3$) ppm.

$^{1}$H NMR (300 MHz, [$D_6$]DMSO, 302K): δ = 11.89 (br. s, 0.7H, OH); 10.62 (br. s, 0.7H, $H_{Ar}$-2); 8.10 - 8.25 (m, 1H, H-Ar); 7.67 - 7.92 (m, 2H, H-Ar); 7.50 - 7.60 (m, 1H, H-Ar); 2.18 (s, 3H, $CH_3$); 2.06 (s, 3H, $CH_3$) ppm.

$^{1}$H NMR (300 MHz, $CF_3COOH$, 296K): δ = 9.44 (s, 1H, $H_{Ar}$-2); 8.12 - 8.21 (m, 1H, H-Ar); 7.80 - 7.90 (m, 1H, H-Ar); 7.50 - 7.68 (m, 2H, H-Ar); 2.29 (s, 3H, $CH_3$); 2.26 (s, 3H, $CH_3$) ppm.

$^{1}$H NMR (300 MHz, $CD_3CN$, 300K): δ = 10.48 (s, 1H, $H_{Ar}$-2); 8.23 (d, J = 8.07 Hz, 1H, H-Ar); 7.75 - 7.85 (m, 1H, H-Ar); 7.50 - 7.66 (m, 2H, H-Ar); 2.22 (s, 3H, $CH_3$); 2.11 (s, 3H, $CH_3$) ppm.

$^{1}$H NMR (300 MHz, $CD_3CN$+$CF_3SO_3H$, 301K): δ = 9.29 (s, 1H, $H_{Ar}$-2); 8.27 - 8.35 (m, 1H, H-Ar); 7.92 - 8.04 (m, 1H, H-Ar); 7.62 - 7.82 (m, 2H, H-Ar); 2.34 (s, 3H, $CH_3$); 2.30 (s, 3H, $CH_3$) ppm.

$^{1}$H NMR (300 MHz, $CD_3OD$, 300K): δ = 10.15 (s, 1H, $H_{Ar}$-2); 8.24 - 8.31 (m, 1H, H-Ar); 7.80 - 7.89 (m, 1H, H-Ar); 7.64 - 7.71 (m, 1H, H-Ar); 7.50 - 7.58 (m, 1H, H-Ar); 2.29 (s, 3H, $CH_3$); 2.20 (s, 3H, $CH_3$) ppm.

$^{13}$C NMR (75.48 MHz, [$D_6$]DMSO): δ = 173.8, 155.3, 155.3, 155.2, 134.6, 125.9, 125.2, 124.2, 123.0, 121.5, 120.9, 118.6, 10.4, 6.9 ppm.

MS (EI): m/z = 256 $[M]^+$.

Anal. $C_{14}H_{12}N_2O_3 \cdot H_2O$ (274): calcd. C 61.31, H 5.11, N 10.22; found C 61.11, H 5.07, N 9.89.

Anal. $C_{14}H_{12}N_2O_3$ (256): calcd. C 65.63, H 4.69, N 10.94; found C 65.78, H 4.73, N 10.90.

IR $\nu_{max}$ (KBr) 3400-3000 (br), 2924, 1650, 1637, 1613, 1572, 1463, 1372, 1300, 1261, 1225, 1208, 1163, 1086, 849, 794, 757, 703, 675, 591, 519 $cm^{-1}$.

$\nu_{max}$ (film) 3400-3000 (br), 2924, 1650, 1633, 1614, 1572, 1464, 1373, 1300, 1263, 1227, 1209, 1163, 1087, 849, 789, 758, 704, 675, 638, 590, 518 $cm^{-1}$.

*4.2.2. 3-(5-Acetyl-1-hydroxy-4-methyl-1H-imidazol-2-yl)-4H-chromen-4-one (**2**).*

A mixture of aldehyde **5** (4.0 g, 0.023 mol), oxime **7** (3.0 g, 0.023 mol) and ammonium acetate (2.5 g, 0.032 mol) in glacial acetic acid (30 mL) was stirred at room temperature for 11 hours and left to stand for 3 days. The precipitate was filtered off and washed with ether yielding 5.6 g (86%) of chromatographically pure product **2** as a white solid. After recrystallization from glacial acetic acid and drying under reduced pressure over alkali m.p. is 214-216°C.

$^1$H NMR (300 MHz, $CDCl_3$, 296K): δ = 12.88 (s, 0.3H, NH); 11.79 (s, 0.7H, OH); 10.79 (s, 0.7H, H-2); 8.85 (s, 0.3H, H-2); 8.20 - 8.45 (m, 1H, H-Ar); 7.72 - 7.90 (m, 1H, H-Ar); 7.54 - 7.67 (m, 2H, H-Ar); 2.86 (s, 3H, $CH_3$); 2.60 (s, 3H, $CH_3$) ppm.

$^1$H NMR (300 MHz, [$D_6$]DMSO, 301K): δ = 11.94 (br. s, 0.5 H, NH); 8.74 (br. s, 0.5 H, $H_{Ar}$-2); 8.10 - 8.22 (m, 1H, H-Ar); 7.85 - 7.95 (m, 1H, H-Ar); 7.72 - 7.80 (m, 1H, H-Ar); 7.55 - 7.63 (m, 1H, H-Ar); 2.56 (s, 3H, $CH_3$); 2.42 (s, 3H, $CH_3$) ppm.

$^1$H NMR (300 MHz, $CF_3COOH$, 296K): δ = 9.59 (s, 1H, $H_{Ar}$-2); 8.12 - 8.22 (m, 1H, H-Ar); 7.85 - 7.94 (m, 1H, H-Ar); 7.56 - 7.72 (m, 2H, H-Ar); 2.80 (s, 3H, $CH_3$); 2.69 (s, 3H, $CH_3$) ppm.

$^1$H NMR (300 MHz, $CD_3CN$+$CF_3SO_3H$, 296K): δ = 9.36 (s, 1H, $H_{Ar}$-2); 8.25 - 8.34 (m, 1H, H-Ar); 7.92 - 8.02 (m, 1H, H-Ar); 7.62 - 7.80 (m, 2H, H-Ar); 2.71 (s, 3H, $CH_3$); 2.67 (s, 3H, $CH_3$) ppm.

$^{13}$C NMR (75.48 MHz, [$D_6$]DMSO): δ = 188.6, 173.9, 157.6, 156.2, 155.5, 135.0, 126.3, 126.1, 125.3, 123.8, 123.2, 123.0, 118.7, 29.8, 14.5 ppm.

MS (EI): m/z = 284 $[M]^+$.

Anal. $C_{15}H_{12}N_2O_4$ (284): calcd. C 63.38, H 4.23, N 9.86; found C 63.49, H 4.29, N 9.58.

IR $\nu_{max}$ (film) 3267, 1659, 1639, 1613, 1565, 1559, 1497, 1464, 1410, 1302, 1275, 1224, 1204, 1171, 1146, 957, 916, 855, 802, 760, 687, 605, 530 $cm^{-1}$.

*4.2.3. 1-Hydroxy-5,5-dimethyl-2-(4-oxo-4H-chromen-3-yl)-4,5,6,7-tetrahydro-1H-benzo[d]imidazol-7(4H)-one (**3**).*

A mixture of aldehyde **5** (4.5 g, 0.026 mol), oxime **8** (4.4 g, 0.026 mol) and ammonium acetate (2.2 g, 0.029 mol) in glacial acetic acid (35 mL) was stirred at room temperature for 11 hours and left to stand for 3 days. The precipitate was filtered off and washed with ether yielding 5.0 g (60%) of product **3** as a yellow solid. After recrystallization from toluene and drying under reduced pressure over paraffin m.p. is 205-206°C.

$^1$H NMR (300 MHz, $CDCl_3$, 302K): δ = 12.73 (br. s, 1H, NH); 8.93 (br. s, 1H, $H_{Ar}$-2); 8.25 - 8.42 (m, 1H, H-Ar); 7.74 - 7.87 (m, 1H, H-Ar); 7.45 - 7.67 (m, 2H, H-Ar); 2.69 (s, 2H, $CH_2$); 2.42 (s, 2H, $CH_2$); 1.12 (s, 6H, 2$CH_3$) ppm.

$^1$H NMR (300 MHz, $CDCl_3$, 262K): δ = 12. 96 (br. s, 1H, NH); 8.97 (br. s, 1H, $H_{Ar}$-2); 8.28 - 8.36 (m, 1H, H-Ar); 7.78 - 7.86 (m, 1H, H-Ar); 7.50 - 7.66 (m, 2H, H-Ar); 2.69 (s, 2H, $CH_2$); 2.42 (s, 2H, $CH_2$); 1.11 (s, 6H, 2$CH_3$).

$^1$H NMR (300 MHz, [$D_6$]DMSO, 300K): δ = 11.63 ( br. s, 0.8H, NH); 8.76 (br. s, 0.8H, $H_{Ar}$-2); 8.10 - 8.17 (m, 1H, H-Ar); 7.84 - 7.94 (m, 1H, H-Ar); 7.71 - 7.76 (m, 1H, H-Ar); 7.53 - 7.62 (m, 1H, H-Ar); 2.67 (s, 2H, $CH_2$); 2.36 (s, 2H, $CH_2$); 1.08 (s, 6H, 2$CH_3$) ppm.

$^1$H NMR (300 MHz, $CF_3COOH$, 296K): δ = 9.70 (s, 1H, $H_{Ar}$-2); 8.15 - 8.24 (m, 1H, H-Ar); 7.85 - 7.96 (m, 1H, H-Ar); 7.55 - 7.72 (m, 2H, H-Ar); 3.00 (s, 2H, $CH_2$); 2.64 (s, 2H, $CH_2$); 1.15 (s, 6H, 2$CH_3$) ppm.

$^1$H NMR (300 MHz, $CD_3CN$, 300K): δ = 9.23 (br. s, 1H, $H_{Ar}$-2); 8.25 - 8.36 (m, 1H, H-Ar); 7.85 - 7.98 (m, 1H, H-Ar); 7.53 - 7.76 (m, 2H, H-Ar); 2.70 (s, 2H, $CH_2$); 2.37 (s, 2H, $CH_2$); 1.10 (s, 6H, 2$CH_3$) ppm.

$^1$H NMR (300 MHz, $CD_3CN$+$CF_3SO_3H$, 301K): δ = 9.47 (s, 1H, $H_{Ar}$-2); 8.26 - 8.33 (m, 1H, H-Ar); 7.92 - 8.03 (m, 1H, H-Ar); 7.62 - 7.81 (m, 2H, H-Ar); 2.98 (s, 2H, $CH_2$); 2.56 (s, 2H, $CH_2$); 1.18 (s, 6H, 2$CH_3$) ppm.

$^1$H NMR (300 MHz, $CD_3OD$, 296K): δ = 9.57 (br. s, 1H, $H_{Ar}$-2); 8.22 - 8.30 (m, 1H, H-Ar); 7.82 - 7.90 (m, 1H, H-Ar); 7.50 - 7.72 (m, 2H, H-Ar); 2.83 (s, 2H, $CH_3$); 2.46 (s, 2H, $CH_3$); 1.15 (s, 6H, 2$CH_3$) ppm.

$^{13}$C NMR (75.48 MHz, [$D_6$]DMSO): δ = 185.7, 173.5, 158.2, 155.5, 134.9, 126.3, 125.3, 124.8, 123.4, 122.9, 119.3, 118.6, 114.3, 52.4, 38.3, 35.3, 28.0 ppm.

MS (EI): m/z = 324 $[M]^+$.

Anal. $C_{18}H_{16}N_2O_4$ (324): calcd. C 66.67; H 4.94; N 8.64; found C 66.68; H 5.06; N 8.48.

IR $\nu_{max}$ (KBr) 3104, 2954, 2859, 2600-2200 (br), 1662, 1613, 1557, 1464, 1405, 1312, 1291, 1173, 1142, 1073, 912, 861, 768, 652 $cm^{-1}$.

$\nu_{max}$ (film) 3300-3100 (br), 2959, 2700-2400 (br), 1665, 1616, 1570, 1464, 1370, 1310, 1219, 1176, 1140, 1076, 914, 855, 760, 640 $cm^{-1}$.

*4.2.4. Ethyl 1-hydroxy-4-methyl-2-(4-oxo-4H-chromen-3-yl)-1H-imidazole-5-carboxylate (**4**).*

A mixture of aldehyde **5** (2.1 g, 0.012 mol), oxime **9** (1.91 g, 0.012 mol) and ammonium acetate (1.85 g, 0.024 mol) in glacial acetic acid (20 mL) was stirred at 40-50°C for 3 hours and left to stand overnight. The reaction mixture was poured into water (60 mL), the product was extracted with chloroform (15 mL × 2), the extract was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The obtained oil was treated with ether yielding 3.0 g (80%) of product **4** as a yellowish solid. M.p. 172-173°C (toluene).

$^1$H NMR (300 MHz, $CDCl_3$, 242K): δ = 13.15 (br. s, 0.4H, NH); 12.16 (br. s, 0.6H, OH); 10.66 (br. s, 0.6H, $H_{Ar}$-2); 8.65 (br. s, 0.3H, $H_{Ar}$-2); 8.19 (d, J = 7,34 Hz, 1H, H-Ar); 7.70 - 7.83 (m, 1H, H-Ar); 7.42 - 7.60 (m, 2H, H-Ar); 4.18 - 4.40 (m, 2H, OC**H**$_2$$CH_3$); 2.49 (s, 3H, $CH_3$); 1.30 (t, 3H, $OCH_2C$**H**$_3$) ppm.

$^1$H NMR (300 MHz, $CDCl_3$, 299K): δ = 12.19 (br. s, 0.7 H, OH); 8.27 (d, J = 8.1 Hz, 1H, H-Ar); 7.70 - 7.83(m, 1H, H-Ar); 7.42 - 7.60 (m, 2H, H-Ar); 4.35 (q, 2H, OC**H**$_2$$CH_3$); 2.47 (s, 3H, $CH_3$); 1.36 (t, 3H, $OCH_2C$**H**$_3$) ppm.

$^1$H NMR (300 MHz, [$D_6$]DMSO, 301K): δ = 11.92 (br. s, 0.8H, NH); 8.73 (s, 1H, $H_{Ar}$-2); 8.05 - 8.20 (m, 1H, H-Ar); 7.80 - 7.92 (m, 1H, H-Ar); 7.64 - 7.75 (m, 1H, H-Ar); 7.49 - 7.60 (m, 1H, H-Ar); 4.20 - 4.40 (m, 2H, OC**H**$_2$$CH_3$); 2.33 (s, 3H, $CH_3$); 1.20 - 1.35 (m, 3H, $CH_2C$**H**$_3$) ppm.

$^1$H NMR (300 MHz, $CF_3COOH$, 296K): δ = 9.57 (s, 1H, $H_{Ar}$-2); 8.13 - 8.20 (m, 1H, H-Ar); 7.82 - 7.93 (m, 1H, H-Ar); 7.54 - 7.71 (m, 2H, H-Ar); 4.55 (q, 2H, OC**H**$_2$$CH_3$); 2.68 (s, 3H, $CH_3$); 1.39 (t, 3H, $OCH_2C$**H**$_3$) ppm.

$^1$H NMR (300 MHz, $CD_3CN$, 298K): δ = 9.25 (br. s, 1H, $H_{Ar}$-2); 8.22 - 8.30 (m, 1H, H-Ar); 7.84 - 7.93 (m, 1H, H-Ar); 7.54 - 7.73 (m, 2H, H-Ar); 4.25 - 4.36 (m, 2H, OC**H**$_2$$CH_3$); 2.40 (s, 3H, $CH_3$); 1.29 - 1.38 (m, 3H, $CH_2C$**H**$_3$) ppm.

$^1$H NMR (300 MHz, $CD_3CN$+$CF_3SO_3H$, 301K): δ = 9.40 (s, 1H, $H_{Ar}$-2); 8.25 - 8.32 (m, 1H, H-Ar); 7.91 - 8.01 (m, 1H, H-Ar); 7.60 - 7.78 (m, 2H, H-Ar); 4.47 (q, 2H, OC**H**$_2$$CH_3$); 2.65 (s, 3H, $CH_3$); 1.35 - 1.45 (m, 3H, $CH_2C$**H**$_3$) ppm.

$^1$H NMR (300 MHz, $CD_3OD$, 300K): δ = 9.61 (s, 1H, $H_{Ar}$-2); 8.21 - 8.29 (m, 1H, H-Ar); 7.81 - 7.89 (m, 1H, H-Ar); 7.64 - 7.70 (m, 1H, H-Ar); 7.52 - 7.59 (m, 1H, H-Ar); 4.38 (q, 2H, OC**H**$_2$$CH_3$); 2.52 (s, 3H, $CH_3$); 1.39 (t, 3H, $CH_2C$**H**$_3$) ppm.

$^{13}$C NMR (75.48 MHz, [$D_6$]DMSO): δ = 188.6, 173.7, 158.9, 158.0, 155.6, 134.8, 134.7, 128.1, 126.2, 125.3, 125.0, 123.4, 118.6, 59.9, 15.4, 14.2 ppm.

MS (EI): m/z = 314 $[M]^+$.

Anal. $C_{16}H_{14}N_2O_5$ (314): calcd. C 61.15; H 4.46; N 8.92; found C 61.18; H 4.54; N 8.76.

IR $\nu_{max}$ (film) 3300-3150 (br), 2982, 2700-2400 (br), 1717, 1655, 1616, 1576, 1463, 1314, 1260, 1219, 1180, 1165, 1148, 1101, 1059, 1018, 923, 852, 762, 708, 664, 610, 523 $cm^{-1}$.

*4.2.5. 4-Oxo-4H-chromene-3-carbaldehyde (**5**).*[30]

Freshly distilled phosphorous-oxychloride (27.5 mL, 46.06 g, 0.30 mol) was added dropwise to DMF (60 mL) at 5-10°C and stirring. The mixture was stirred for 15 minutes and then the solution of *o*-hydroxyacetophenone **10** (13.60 g, 0.1 mol) in DMF (40 mL) was added dropwise at 0-5°. The reaction mixture was stirred at low temperature for 30 minutes and then heated and stirred at 50-55°C for 4 hours. The mixture was cooled to room temperature, poured into ice-water (approx. 400 mL) and stirred for 1.5 hour. The precipitate was filtered off, washed with water and cooled ethanol (100 mL) yielding 13.8 g (79%) of product **5** as yellowish solid. M.p. 152-154°C (toluene). Lit. m.p. 152-153°C.[30]

*4.2.6. Pentan-2,3,4-trione 3-oxime (**7**).*[31]

Pentane-2,4-dione **11** (25.0 g, 0.25 mol) was dissolved in 7% sulfuric acid (250 mL) at 15°C. Then a solution of sodium nitrite (17.3 g, 0.25 mole) in water (75 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 hours, the product was extracted with ethyl acetate(50 mL × 3), the extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure yielding 29.3 g (91%) of **7** as a pale yellow oil which crystallizes if left to stand undisturbed. M.p. 73-75°C. Lit. m.p. 75°C.[31] **7** was used without further purification.

*4.2.7. 5,5-Dimethyl-1,2,3-trione 2-oxime (**8**).*[32]

5,5-Dimethyl-1,3-cyclohexanedione **12** (50.0 g, 0.357 mol) was suspended in a 15% solution of potassium hydroxide (118 mL) and sodium nitrite (24.6 g, 0.357 mol) was added. The suspension obtained was diluted with water (20 mL) and cooled to 0°C. Then 15% sulfuric acid (212 mL) was added dropwise at 0-10°C. The mixture was stirred at a low temperature for 30 minutes and then the precipitate was filtered off and dried under reduced pressure over alkali to yield 58.8 g (97.5%) of **8** as yellow solid; m.p. 85-88°C. Lit. m.p. 87°C.[32] **8** was used without further purification.

*4.2.8. Ethyl 2-(hydroxyimino)-3-butanoate (**9**).*[32]

A solution of ethyl acetoacetate **13** (40 mL, 41.0 g, 0.315 mol) in glacial acetic acid (52 mL) was cooled to 5°C and a solution of sodium nitrite (32 g, 0.462 mol) in water (70 mL) was added dropwise at 5-10°C. The mixture was stirred for 1 hour at 8±2°C then a 18% solution of sodium chloride (150 mL) was added and the mixture was stirred for 20 minutes more. Then it was extracted with chloroform (75 mL × 2), the extract was sequentially washed with 18% solution of sodium chloride, 10% solution of sodium hydrocarbonate, 18% solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield 45.0 g (90%) of **9** as yellow oil. **9** was used without further purification.

*4.2.9. 1-Benzyl-4,5-dimethyl-2-(4-oxo-4H-chromen-3-yl)-1H-imidazole 3-oxide (**14**).*

A mixture of aldehyde **5** (2.0 g, 0.011 mol), oxime **6** (1.2 g, 0.011 mol) and benzylamine **15** (1.2 g, 0.011 mol) in glacial acetic acid (15 mL) was stirred at room temperature for 3 hours and left to stand for 10 days. The reaction mixture was poured into water (100 mL), the precipitate was filtered off, washed with water and dried giving 3.6 g of a pale yellow solid. The product was sequentially refluxed first in toluene then in acetonitrile yielding 2.0 g (53%) of chromatographically pure **14** as an off-white solid. M.p. 209-210°C.

$^1$H NMR (300 MHz, $CDCl_3$, 300K): δ = 8.69 (s, 1H, $H_{Ar}$-2); 8.18 - 8.28 (m, 1H, H-Ar); 7.63 - 7.75 (m, 1H, H-Ar); 7.38 - 7.53 (m, 2H, H-Ar); 7.13 - 7.25 (m, 3H, H-Ar); 6.80 - 6.90 (m, 2H, H-Ar); 5.16 (s, 2H, C**H**$_2$Ph); 2.26 (s, 3H, $CH_3$); 2.11 (s, 3H, $CH_3$).

$^1$H NMR (300 MHz, [$D_6$]DMSO, 303K): δ = 8.69 (s, 1H, $H_{Ar}$-2); 8.09 - 8.17 (m, 1H, H-Ar); 7.81 - 7.90 (m, 1H, H-Ar); 7.65 - 7.72 (m, 1H, H-Ar); 7.18 - 7.30 (m, 3H, H-Ar); 7.00 - 7.08 (m, 2H, H-Ar); 5.13 (s, 2H, C**H**$_2$Ph); 2.10 (s, 6H, 2$CH_3$).

$^1$H NMR (300 MHz, $CF_3COOH$, 300K): δ = 8.40 (s, 1H, $H_{Ar}$-2); 8.17 - 8.36 (m, 1H, H-Ar); 7.87 - 7.98 (m, 1H, H-Ar); 7.57 - 7.70 (m, 2H, H-Ar); 7.21 - 7.30 (m, 3H, H-Ar); 6.90 - 7.00 (m, 2H, H-Ar); 5.29 (s, 2H, C**H**$_2$Ph); 2.38 (s, 3H, $CH_3$); 2.26 (s, 3H, $CH_3$) ppm.

$^1$H NMR (300 MHz, $CD_3CN$, 300K): δ = 8.41 (s, 1H, $H_{Ar}$-2); 8.10 - 8.18 (m, 1H, H-Ar); 7.76 - 7.84 (m, 1H, H-Ar); 7.48 - 7.62 (m, 2H, H-Ar); 7.19 - 7.31 (m, 3H, H-Ar); 6.97 - 7.05 (m, 2H, H-Ar); 5.11 (s, 2H, C**H**$_2$Ph); 2.13 (s, 3H, $CH_3$); 2.09 (s, 3H, $CH_3$) ppm.

$^1$H NMR (300 MHz, $CD_3CN$+$CF_3SO_3H$, 301K): δ = 8.82 (s, 1H, $H_{Ar}$-2); 8.32 - 8.39 (m, 1H, H-Ar); 8.12 - 8.21 (m, 1H, H-Ar); 7.77 - 7.96 (m, 2H, H-Ar); 7.26 - 7.38 (m, 3H, H-Ar); 7.08 - 7.17 (m, 2H, H-Ar); 5.31 (s, 2H, C**H**$_2$Ph); 2.36 (s, 3H, $CH_3$); 2.22 (s, 3H, $CH_3$) ppm.

$^1$H NMR (300 MHz, $CD_3OD$, 300K): δ = 8.40 (s, 1H, $H_{Ar}$-2); 8.16 - 8.21 (m, 1H, H-Ar); 7.80 - 7.89 (m, 1H, H-Ar); 7.51 - 7.68 (m, 2H, H-Ar); 7.20 - 7.31 (m, 3H, H-Ar); 7.01 - 7.08 (m, 2H, H-Ar); 5.18 (s, 2H, C**H**$_2$Ph); 2.25 (s, 3H, $CH_3$); 2.18 (s, 3H, $CH_3$) ppm.

$^{13}$C NMR (75.48 MHz, [$D_6$]DMSO): δ = 174.3, 160.9, 155.5, 136.4, 134.9, 128.6, 128.4, 127.5, 127.3, 126.4, 126.2, 125.6, 125.3, 123.6, 122.6, 121.9, 118.6, 110.5, 47.9, 8.7, 7.4 ppm.

MS (EI): m/z = 346 $[M]^+$.

Anal. $C_{21}H_{18}N_2O_3 \cdot 0{,}5H_2O$ (355): calcd. C 71.00; H 5.35; N 7.89; found C 71.45; H 5.13; N 7.84

IR $\nu_{max}$ (film) 3400-3100 (br), 2959, 2926, 2363, 1643, 1609, 1576, 1508, 1464, 1379, 1339, 1289, 1221, 1186, 1115, 1096, 849, 772, 748, 706, 669, 588 $cm^{-1}$.

*4.2.10. Ethyl 5-methyl-2(4-oxo-4H-chromen-3-yl)-1H-imidazole -4-carboxylate (**16**).*

A mixture of 1-hydroxyimidazole **4** (15.0 g, 0.0476 mol) and triphenylphosphine (20.0 g, 0.0762 mol) was refluxed with stirring in glacial acetic acid (64 mL) for 4 hours. The reaction mixture was cooled on an ice bath, the precipitate was filtered off and twice refluxed in ether (70 mL) yielding 8.1 g (57%) of chromatographically pure **16** as a white solid. M.p. 152-154°C.

$^1$H NMR (200 MHz, $CDCl_3$, 293K): δ = 11.73 (br. s, 0.5H, NH); 11.62 (br. s, 0.5 H, NH); 9.19 (s, 0.5H, $H_{Ar}$-2); 9.09 (s; 0.5H, $H_{Ar}$-2); 8.26 - 8.37 (m, 1H, H-Ar); 7.71 - 7.85 (m, 1H, H-Ar); 7.45 - 7.62 (m, 2H, H-Ar); 4.30 - 4.50 (m, 2H, OC**H**$_2$$CH_3$);

2.64 (s, 1.5H, $CH_3$); 2.56 (s, 1.5H, $CH_3$); 1.37 - 1.49 (m, 3H, $OCH_2C\underline{\mathbf{H}}_3$) ppm.

$^{13}$C NMR (75.48 MHz, [$D_6$]DMSO): δ = 174.5, 163.2, 157.2, 156.1, 155.5, 145.3, 137.8, 136.3, 134.9, 134.7, 127.4, 126.3, 126.1, 125.2, 123.3, 118.7, 114.5, 109.5, 60.1, 59.2, 14.4, 14.3, 11.1 ppm.

MS (EI): m/z = 298 $[M]^+$.

Anal. $C_{16}H_{14}N_2O_4$ (298): calcd. C 64.43; H 4.70; N 9.40; found C 64.10; H 4.58; N 9.37

IR $\nu_{max}$ (film) 3358, 2980, 1705, 1643, 1618, 1574, 1466, 1425, 1380, 1341, 1314, 1265, 1248, 1169, 1146, 1107, 1094, 1020, 991, 849, 760, 704, 636 $cm^{-1}$.

### 4.3. X-ray determination

*Compound **1**.* Crystals suitable for X-ray structure analysis were grown from an acetonitrile-benzene solution. A single crystal of dimensions 0.09 × 0.03 × 0.02 was subjected to X-ray measurements on a Bruker SMART-1K diffractometer using graphite monochromatized $MoK_\alpha$ radiation (0.71073 Å) and ω scan mode at 123K. Data reduction was performed using the SAINT program.[35] The structure was solved by direct methods and refined on $F^2$ by full-matrix least-squares in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were refined using the "riding" model.

*Compound **3**.* Crystals suitable for X-ray structure analysis were grown from methanol solution. A single crystal of dimensions 0.24 × 0.22 × 0.22 was subjected to X-ray measurements on a Bruker CCD SMART-APEX-II diffractometer using graphite monochromatized $MoK_\alpha$ radiation (0.71073 Å) and ω scan mode at room temperature. Data reduction was performed using the SAINT program.[35] The structure was solved by direct methods and refined on $F^2$ by full-matrix least-squares in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were refined using the "riding" model. In difference Fourier synthesis, several peaks of electron density corresponding to a methanol solvate molecule were located. The methanol molecule is disordered over four close positions with equal occupations. The refinement of solvent molecule was carried out in isotropic approximation.

All of the calculations were performed using SHELXLT-Plus software.[36] A summary of the crystallographic data and structure determination parameters is provided in Table 4.

**Table 4.** Crystal Data and Structure Refinement for compounds **1** and **3**.

| | compound **1** | compound **3** |
|---|---|---|
| empirical formula | $C_{14}H_{12}N_2O_3$ | $C_{19}H_{26}N_2O_5$ |
| formula weight | 256.26 | 362.42 |
| Color, habit | colourless, block | colourless, prism |
| Crystal system | orthorhombic | monoclinic |
| Space group | $Pca2_1$ | $P2_1/c$ |
| $a$ [Å] | 20.8148(15) | 6.862(3) |
| $b$ [Å] | 4.4300(4) | 18.604(8) |
| $c$ [Å] | 12.4420(10) | 13.772(6) |
| $\beta$ [°] | 90.0 | 91.468(7) |
| $V$ [Å$^3$] | 1147.27(16) | 1757.5(13) |
| $Z$ | 4 | 4 |
| $D_{calc}$ g $cm^{-3}$ | 1.484 | 1.370 |
| μ [$mm^{-1}$] | 0.106 | 0.099 |
| $F$(000) | 536 | 776 |
| $T$ [K] | 123(2) | 273(2) |
| $\theta$ range [sec] | 1.96 - 28.99 | 2.19 - 28.00 |
| Limiting indices | $-27 \le h \le 28$, $-6 \le k \le 5$, $-16 \le l \le 16$ | $-9 \le h \le 9$, $-24 \le k \le 24$, $-18 \le l \le 18$ |
| Reflections / collected / unique [$R_{int}$] | 8359/ 3012 [0.1387] | 17854/ 4221 [0.0356] |
| Completeness deg [%] | 99.9 | 99.7 |
| Reflections with $I > 2\sigma(I)$ | 1673 | 2777 |
| Data / parameters | 3012 / 172 | 4221 / 249 |
| GOF on $F^2$ | 1.019 | 1.043 |
| $R_1$ / $wR_2$ [$I > 2\sigma(I)$] | 0.0757 / 0.1267 | 0.0488 / 0.1397 |
| $R_1$ / $wR_2$ (all data) | 0.1615 / 0.1459 | 0.0769 / 0.1528 |
| Max/min residuals [e/A$^3$] | 0.262 and -0.255 | 0.307 and -0.175 |

CCDC-905069 contains the supplementary crystallographic data for compound **1**. CCDC-905068 contains the supplementary crystallographic data for compound **3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

### Supplementary Data

Copies of the $^1$H NMR and $^{13}$C NMR spectra of compounds **1-4**, **14**, **16**.

### 5. References


1. G.G. Allan, C.S. Chopra, T. Mattila, *Pestic. Sci*. **1972**, *3(2)*, 153–159 (*Chem. Abstr*. **1972**, *77*, 57559h).

2. DE 2254474, **1973** (*Chem. Abstr*. **1973**, *79*, 42507g).

3. M. Witschel, *Bioorg. Med. Chem.* **2009**, *17(12)*, 4221-4229.

4. US 3886180, **1975**.

5. US 4006160, **1977** (*Chem. Abstr*., **1977**, *86*, 189707).

6. M.R. Harnden, L.J. Jennings, C.M.D. Mckie, A. Parkin, *Synthesis* **1990**, *(10)*, 893-895.

7. WO 2005002002576, **2005**.

8. US 4232029, **1980** (*Chem. Abstr*. **1981**, *94*, 103377).

9. T.B. Stensbøl, P. Uhlmann, S. Morel, B.L. Eriksen, J. Felding, H. Kromann, M.B. Hermit, J.R. Greenwood, H. Bräuner-Osborne, U. Madsen, F. Junager, P. Krogsgaard-Larsen, M. Begtrup, P. Vedsø, *J. Med. Chem.* **2002**, *45*, 19-31.

10. G.V. Nikitina, M.S. Pevzner, *Chemistry of Heterocyclic Compounds* **1993**, *29*, 127-151.

11. M.R. Grimmett, *Science of Synthesis* **2002**, *(12)*, 325-528.

12. B.H. Lipshutz, M.C. Morey, *Tetrahedron Lett.* **1984**, *25*, 1319.

13. E.S. Kritschewskii, L.M. Alekseewa, O.S. Anisimova, W.G. Granik, *Khim.-farm. zh.* **1995**, *29(9)*, 50-53.

14. B.L. Eriksen, P. Vedsø, S. Morel, M. Begtrup, *J. Org. Chem.* **1998**, *63*, 12-16.

15. B.L. Eriksen, P. Vedsø, M. Begtrup, *J. Org. Chem.* **2001**, *66*, 8344-8349.

16. L.F.V. Pinto, G.C. Justino, A.J.S.C. Vieira, S. Prabhakar, A.M. Lobo, *ARKIVOC* **2010**, *(v)*, 17-23.

17. F.J. Allan, G.G. Allan, *Chem. Ind*. **1964**, 1837.

18. A.R. Katrizky, *Chem. Ind*. **1965**, 331.

19. K. Akagane, F.J. Allan, G.G. Allan, T. Friberg, S. Ó Muicheartaigh, J.B. Thomson, *Bull. Chem. Soc. Jpn*. **1969**, *42*, 3204-3207.

20. K. Volkamer, H.W. Zimmermann, *Chem. Ber*. **1969**, *102*, 4177-4187.

21. S.O. Chua, M.J. Cook, A.R. Katrizky, *J. Chem. Soc. B* **1971**, 2350-2355.

22. S. Takahashi, H. Kano, *Chem. and Pharm. Bull.* **1963**, *11*, 1375-1381.

23. D.J. Neadle, R.J. Pollitt, *J. Chem. Soc. C* **1967**, 1764-1766.

24. G.W. Stacy, T.E. Wollner, T.R. Oakes, *J. Heterocycl. Chem.* **1966**, *3*, 51-54.

25. M. Boiani, H. Cerecetto, M. González, O.E. Piro, E.E. Castellano, *J. Phys. Chem. A*, **2004**, *108*, 11241-11248.

26. S. Abuskhuna, M. McCann, J. Briody, M. Devereux, K. Kavanagh, N. Kayal, V. McKee, *Polyhedron* **2007**, *26*, 4573-4580.

27. A.K. Padhy, B. Chetia, S. Mishra, A. Pati, P.K. Iger, Tetrahedron Lett. **2010**, *51*, 2751-2753.

28. Y. Kamitori, *Heterocycles* **2000**, *53(1)*, 107-113.

29. R.B. Sparks, A.P. Combs, *Org. Lett.* **2004**, *6(14)*, 2473-2475.

30. A. Nohara, T. Umetani, Y. Sanno, *Tetrahedron* **1974**, *30(19)*, 3553-3561.

31. L. Wolff, *Justus Liebigs Ann. Chem.* **1902**, *325(2)*, 129-195.

32. J. Lifschitz, *Chem. Ber.* **1913**, *46*, 3233-3250.

33. M. Witanowski, L. Stefaniak, *Bull. Pol. Acad. Sci., Chem.* **1987**, *35*, 305-320.

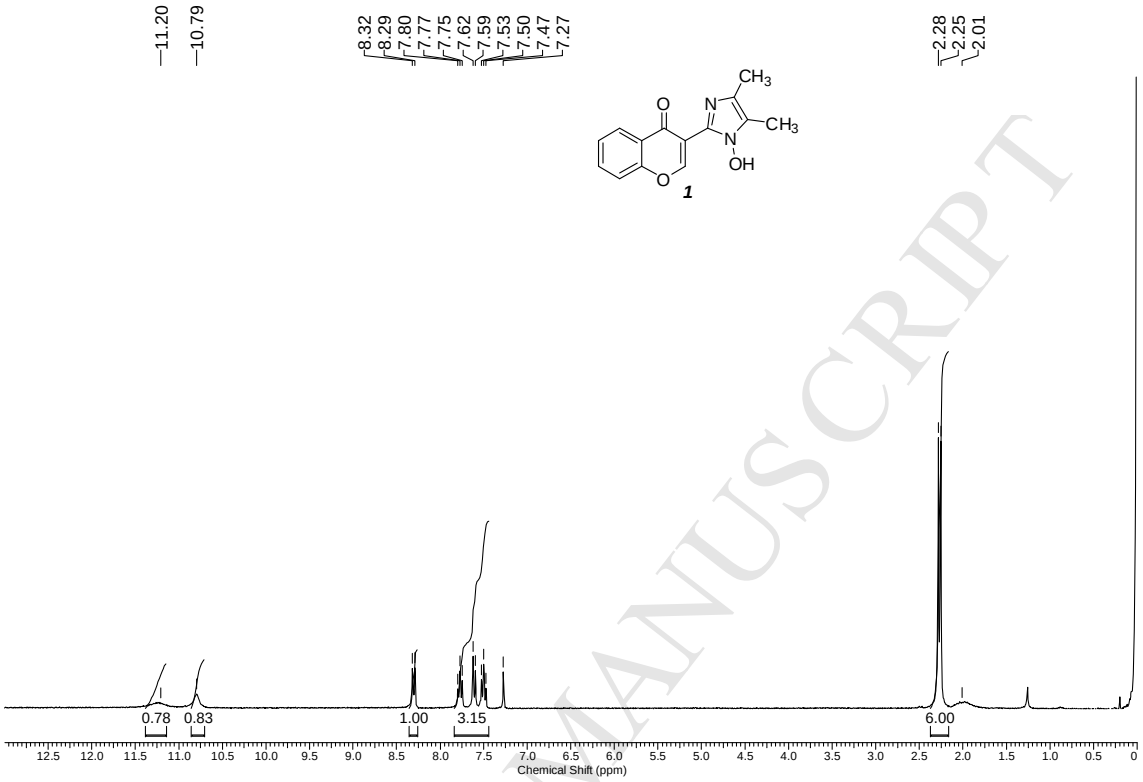
34. V.I. Minkin, A.D. Garnovskii, J. Elguero, A.R. Katrizky, O.V. Denisenko, *Adv. Heterocycl. Chem.* **2000**, *76*, 157-323.

35. *SAINT*. Version 6.02A. Bruker AXS Inc. Madison, Wisconsin, USA, 2001.

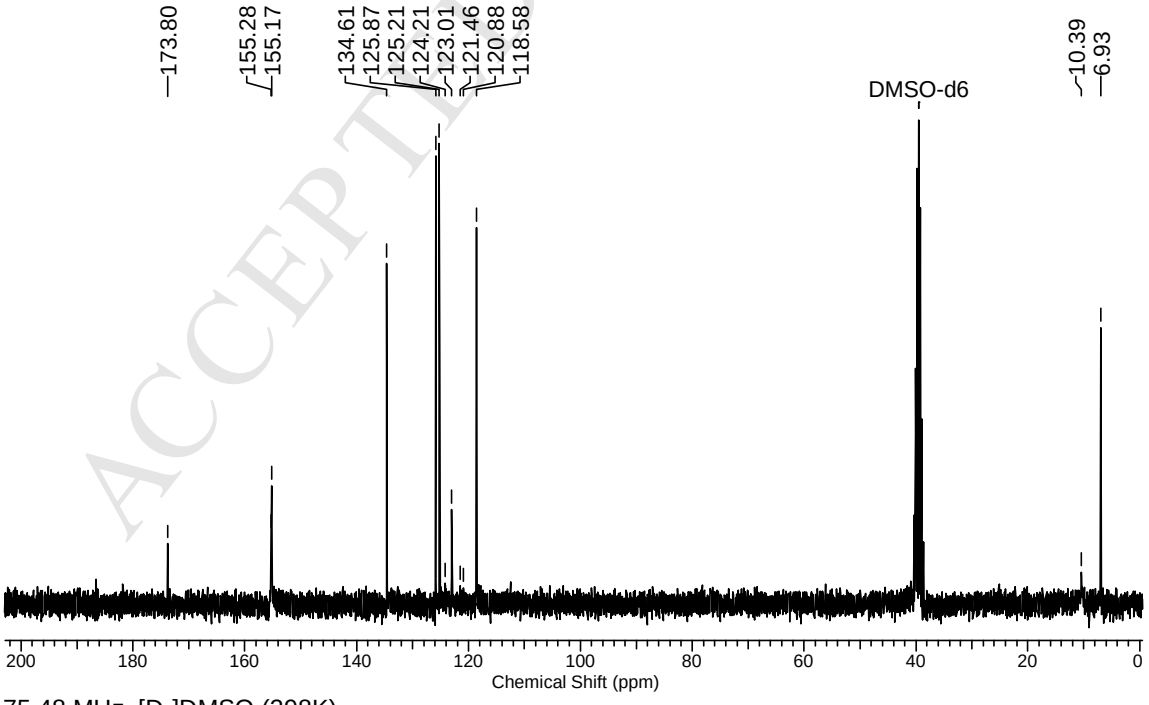
36. *SHELXTL-Plus*. Version 5.10. Bruker AXS Inc. Madison, Wisconsin, USA, 1997.

## Supplementary Data

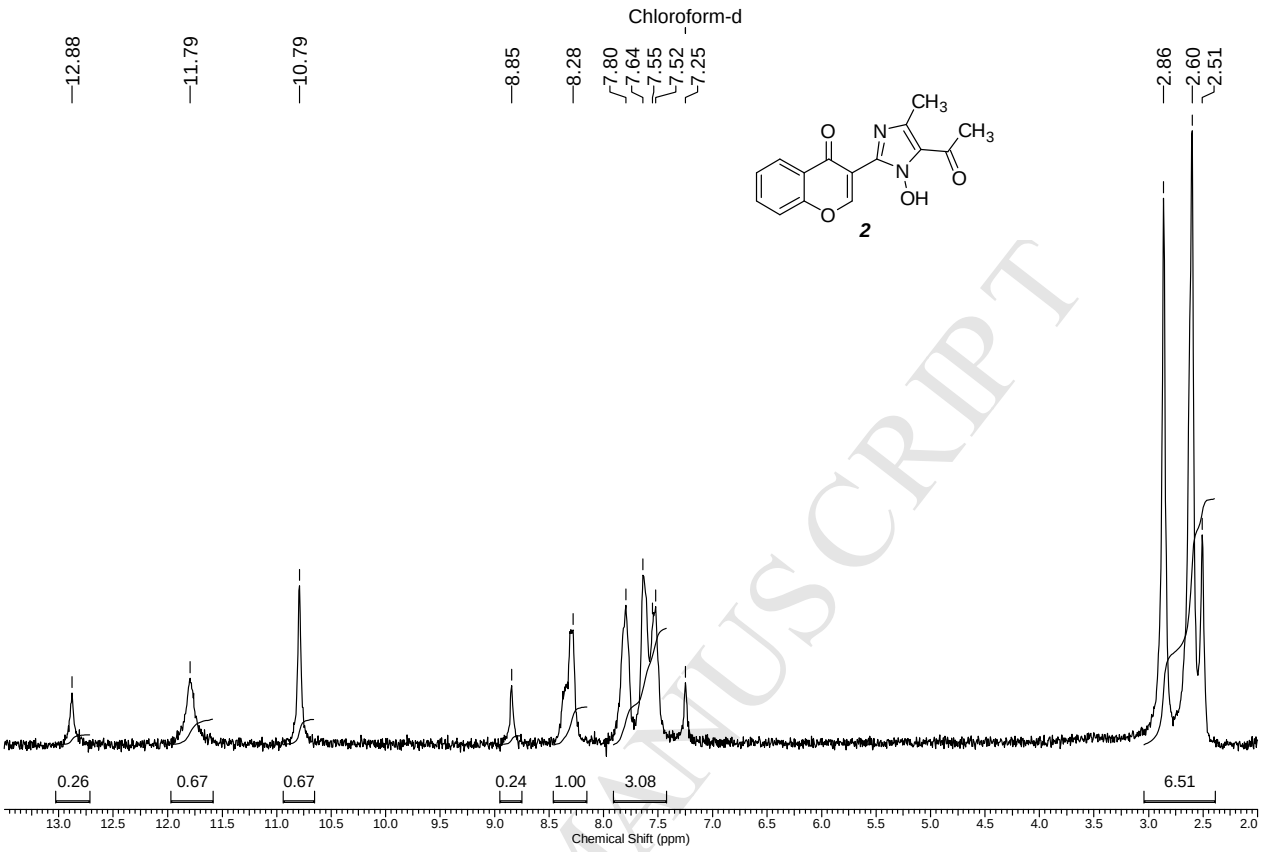
$^{1}H$ and $^{13}C$ NMR spectra



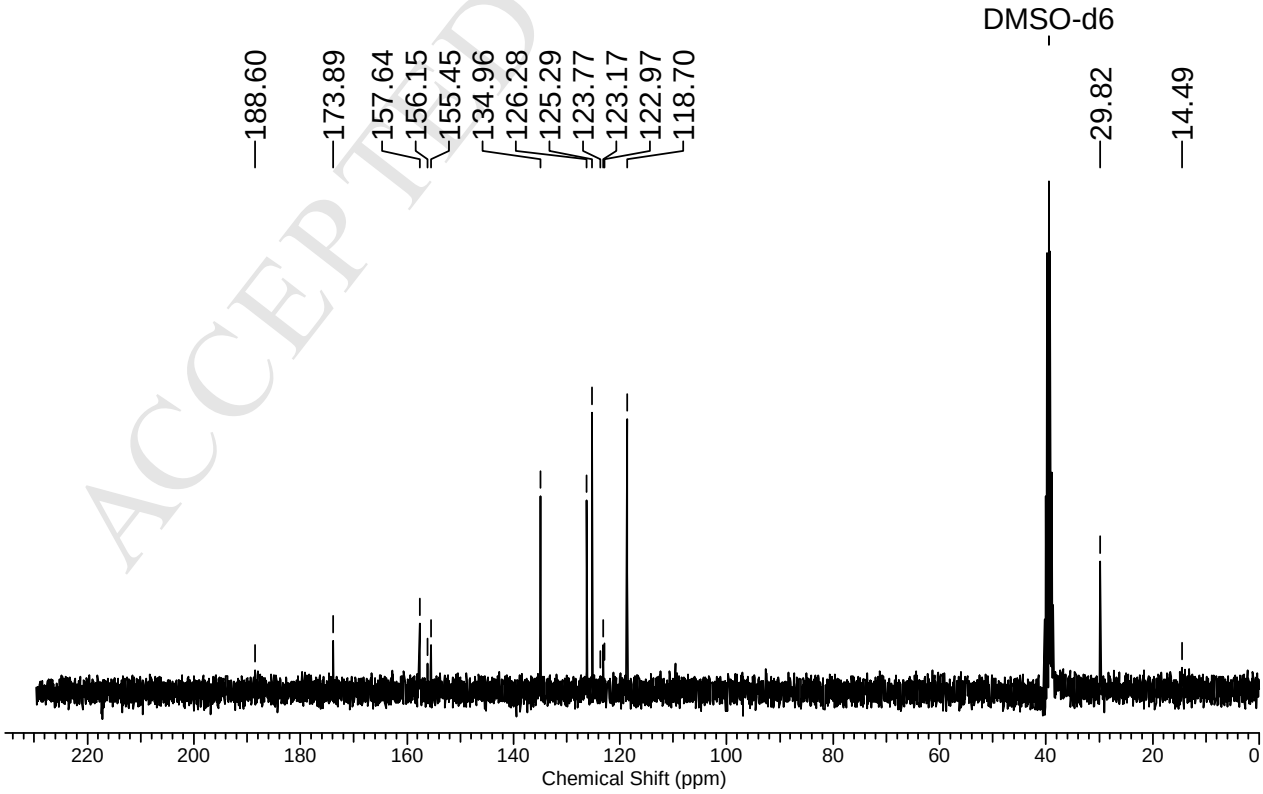

300.13 MHz, $CDCl_3$ (299K)



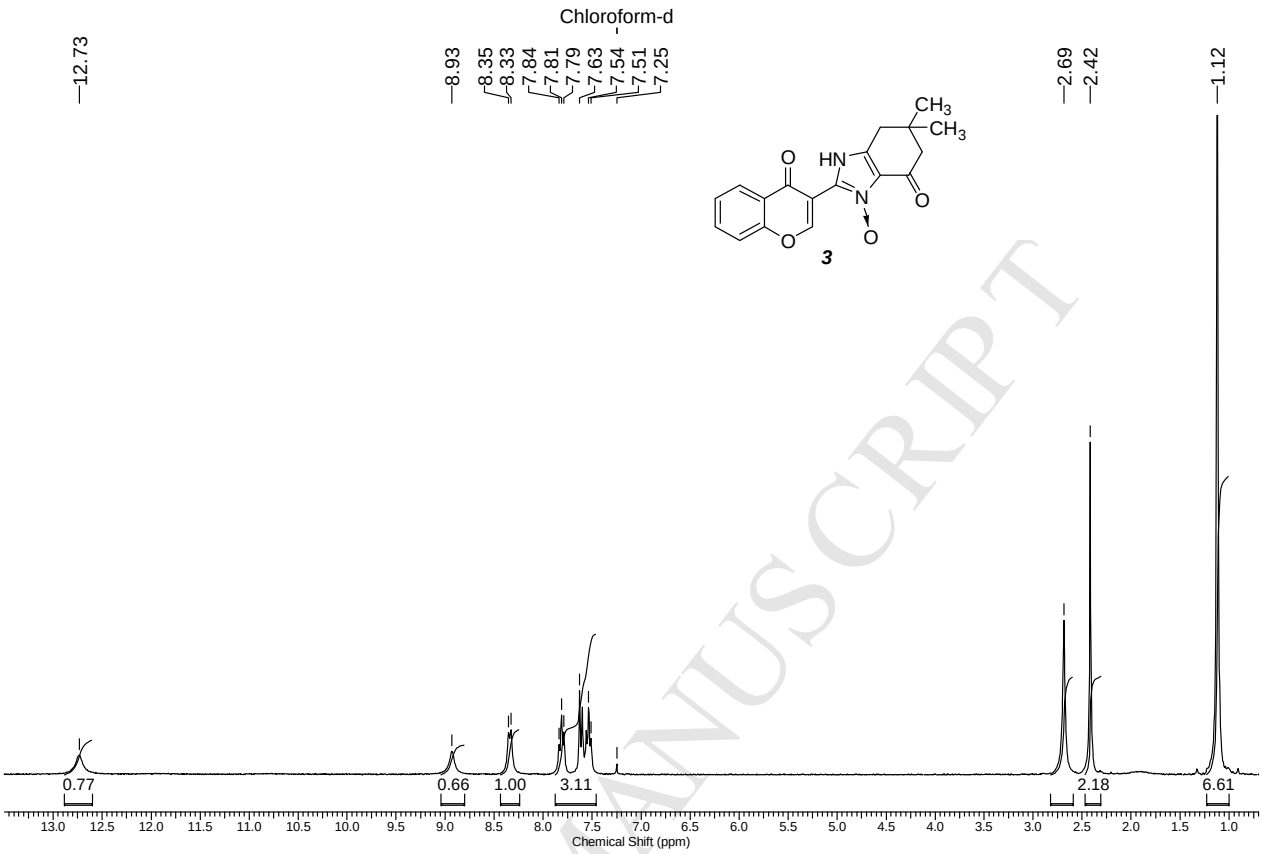

75.48 MHz, $[D_6]$DMSO (298K)



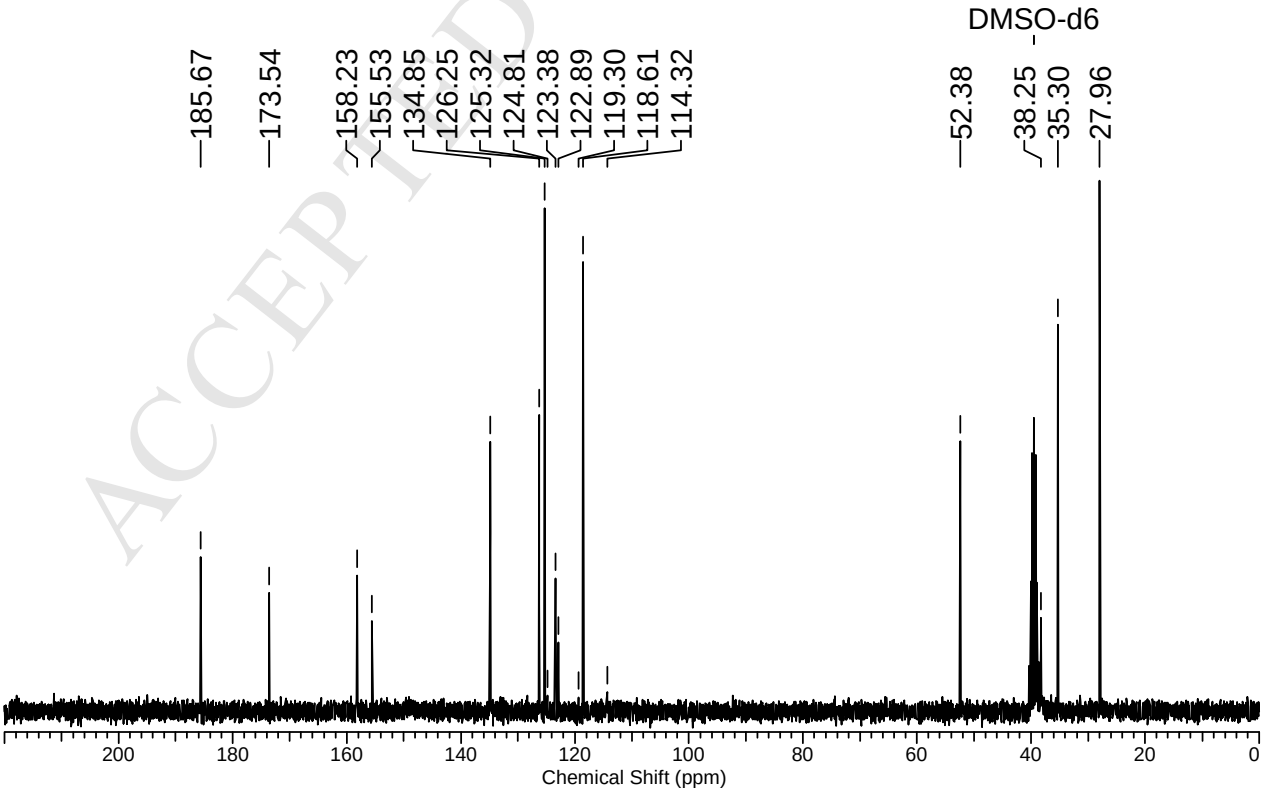

300.13 MHz, $CDCl_3$ (296K)



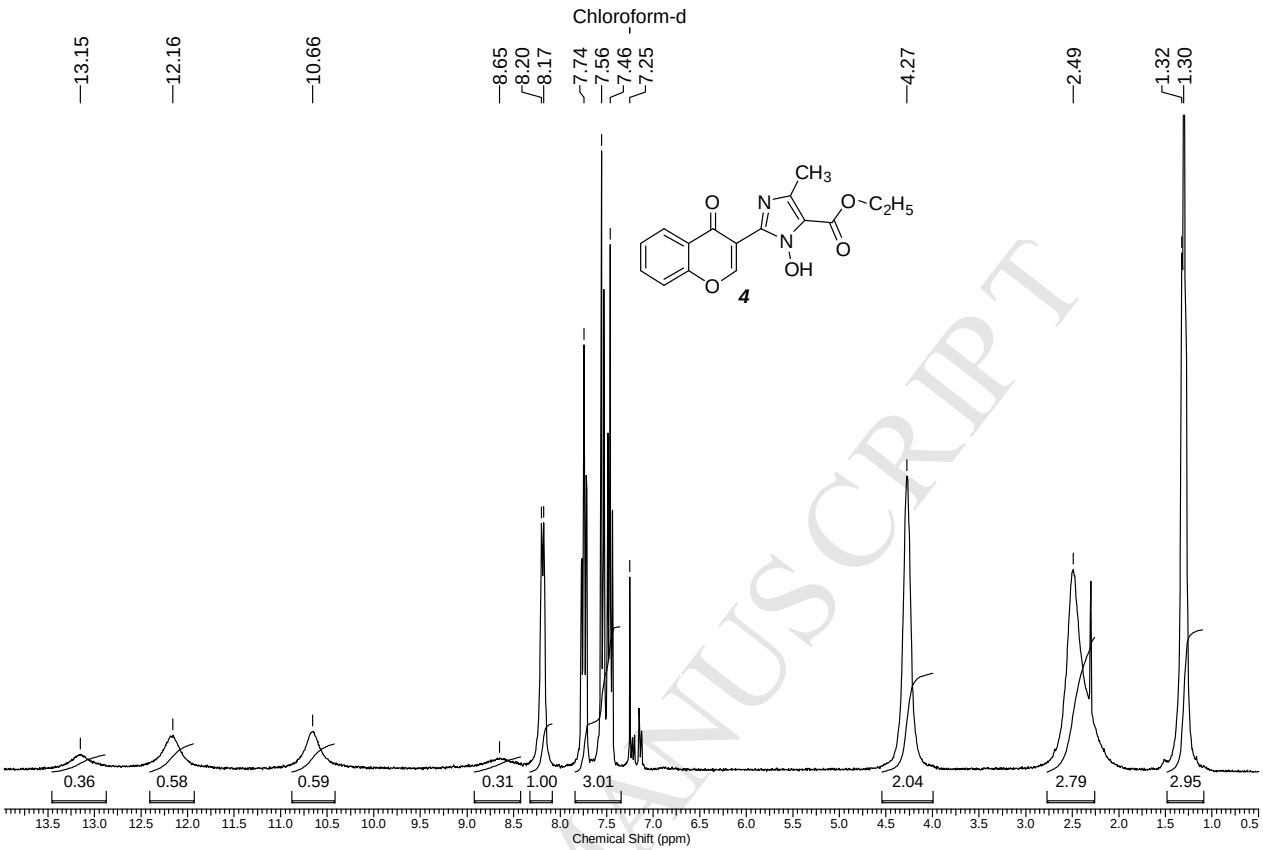

75.48 MHz, $[D_6]$DMSO (299K)



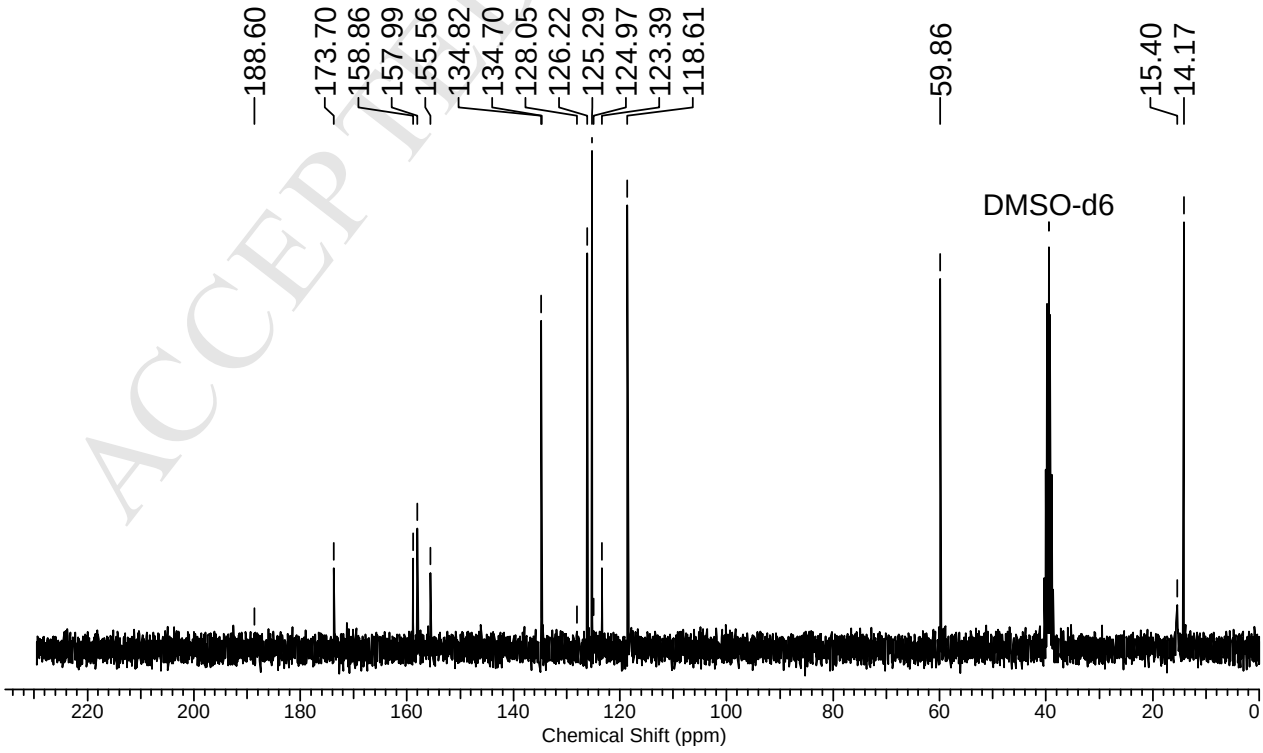

300.13 MHz, $CDCl_3$ (302K)



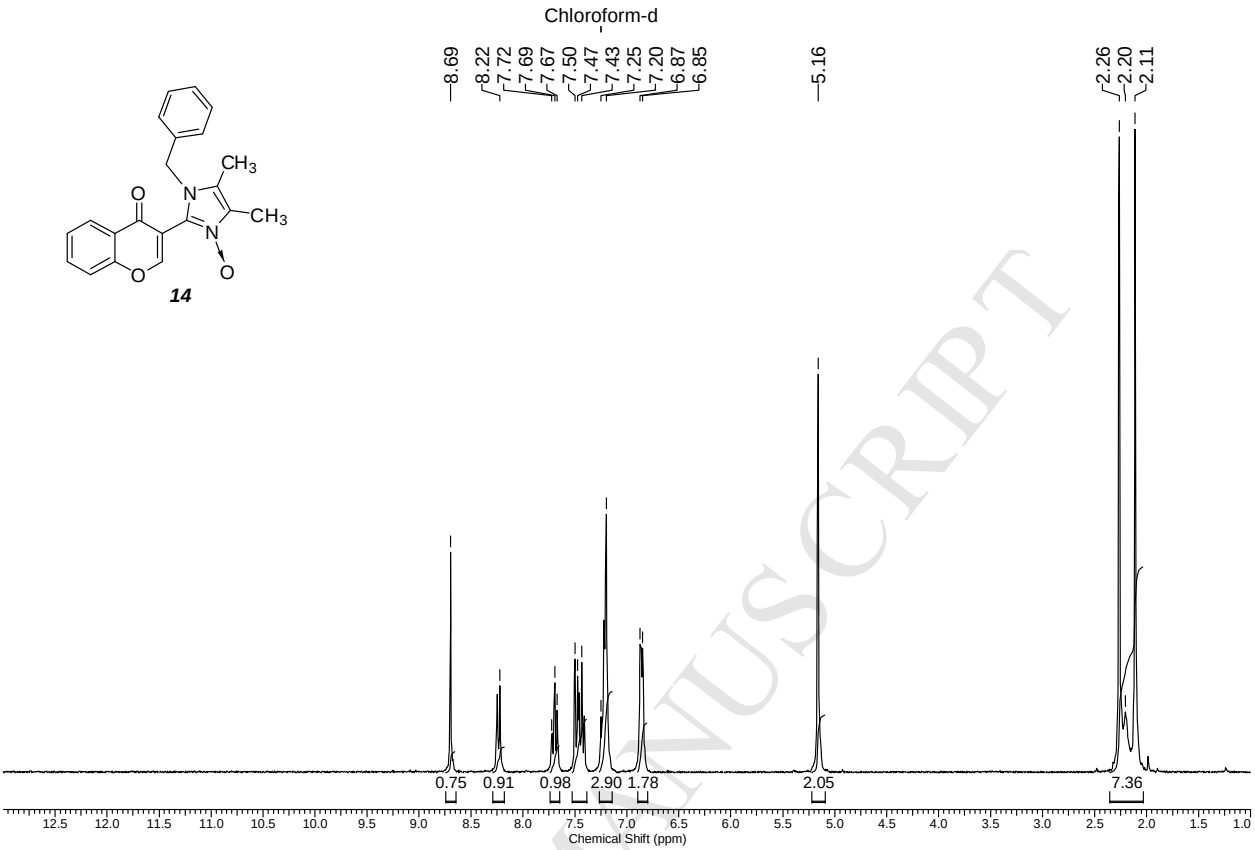

75.48 MHz, $[D_6]$DMSO (299K)



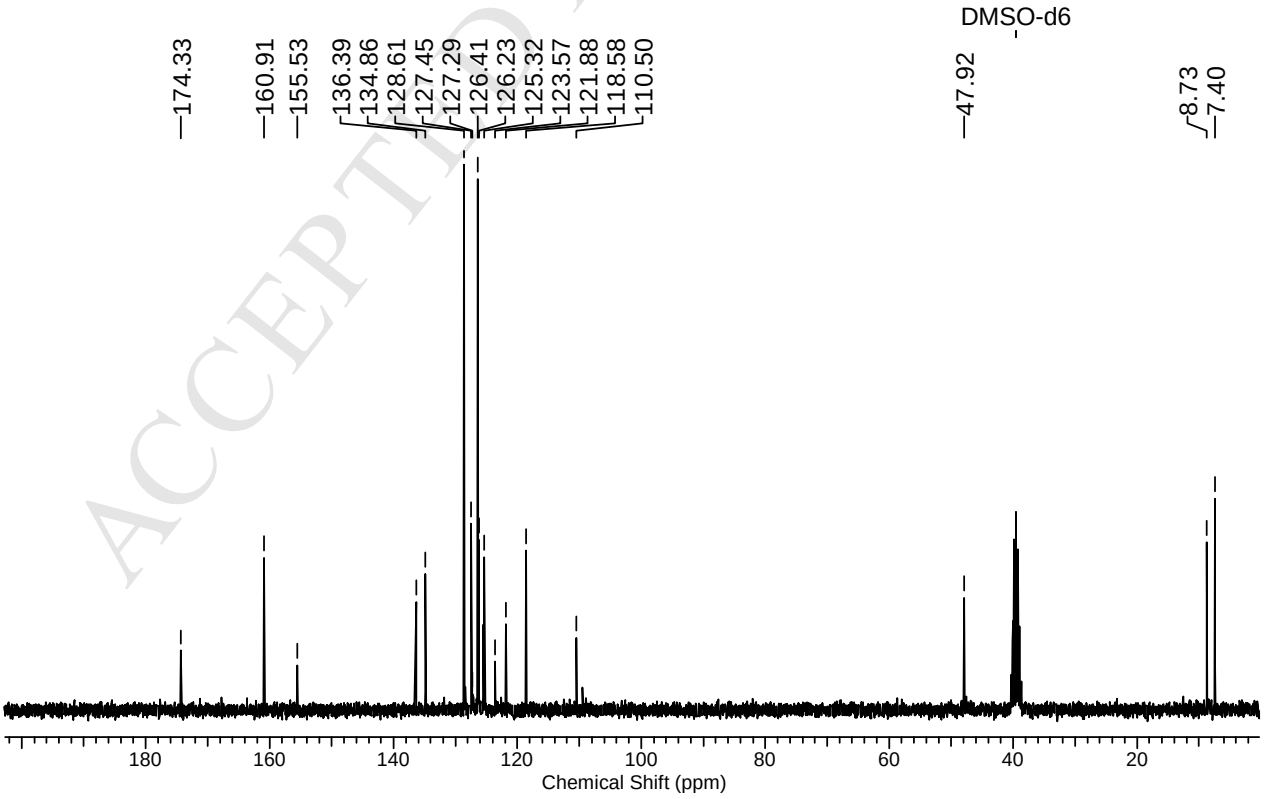

300.13 MHz, $CDCl_3$ (242K)



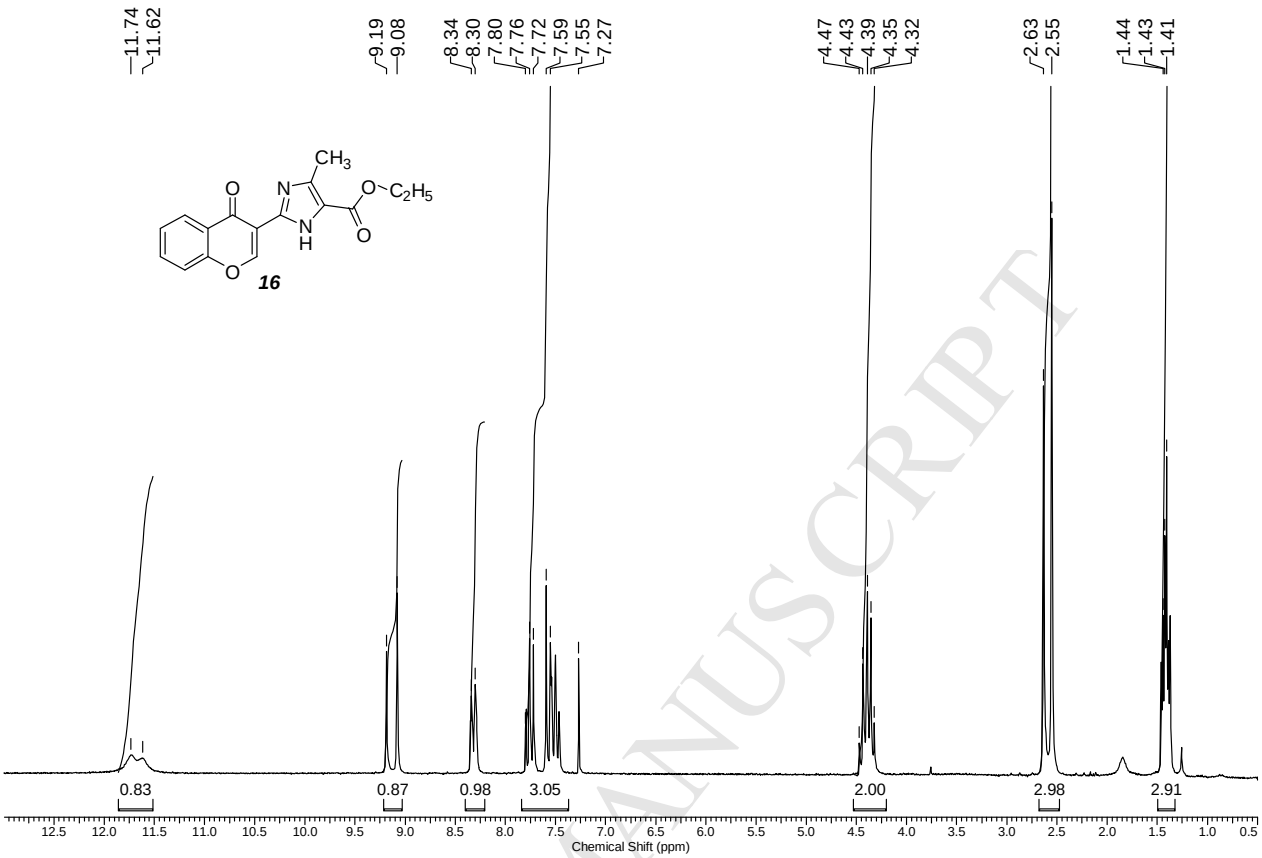

75.48 MHz; $[D_6]$DMSO (298K)



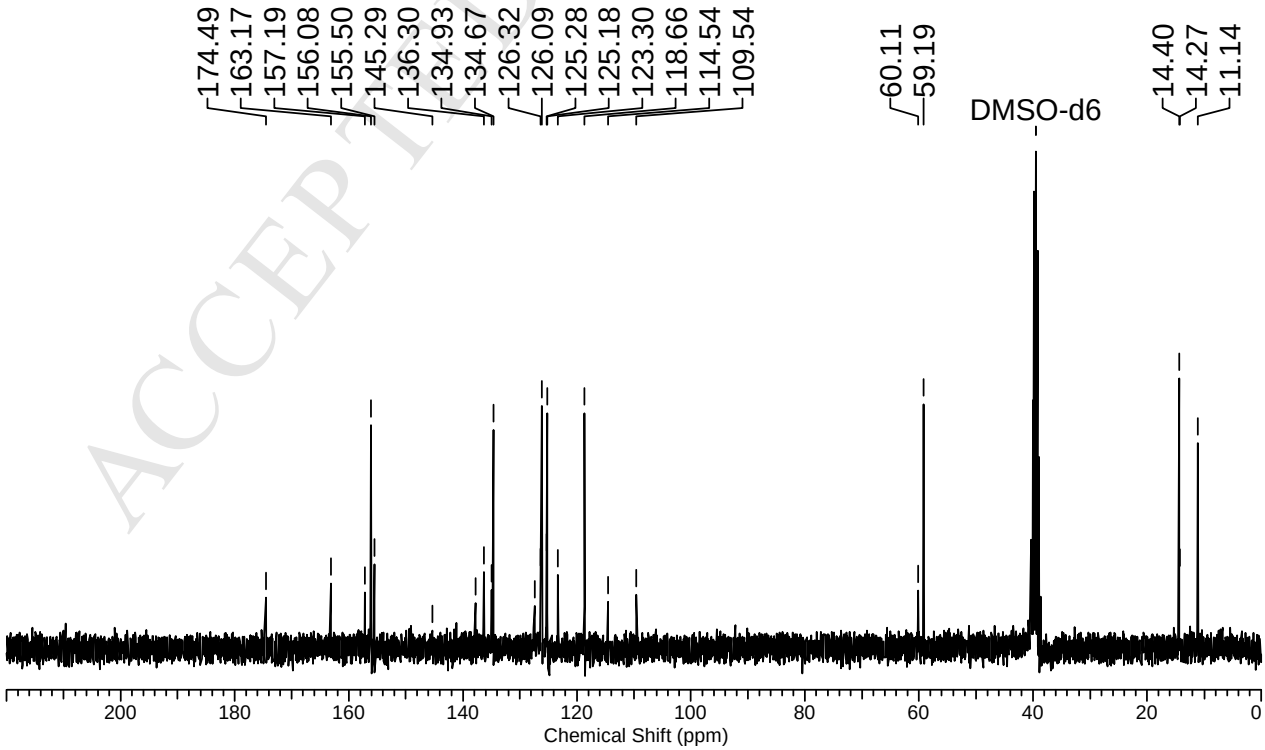

300.13 MHz, $CDCl_3$ (300K)




75.48 MHz, $[D_6]$DMSO (299K)




200.13 MHz, $CDCl_3$ (293K)




75.48 MHz, $[D_6]$DMSO (298K)