Original Research Article

Characterization of the Structure of 2-(4-Methyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl)-isoindole-1,3-dione by 1D, COSY AND HSQC 2D NMR Spectroscopy

ABSTRACT

The identity of the 2-(4-Methyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl)-isoindole-1,3-dione, previously synthesized in our laboratory, was proven without doubt by means of 1D and 2D NMR spectroscopy. Two-dimensional NMR spectroscopy played a major role. The analysis of the 2D-COSY spectrum of isoindoline-1,3-dione derivéative shows a perfect correlation between neighboring protons. Thus, a correlation was noted between the protons of the phthalimide, H(8) and H(9) on the one hand and H(8'), and H(9') on the other hand. The analysis of the 2D-HSQC spectrum of the studied compound indicates a faultless correlation between protons and adjacent carbons, and no correlation in the case of all quaternary carbons.

Keywords: Isoindoline,1,3-dione, 1D NMR, 2D COSY, 2D HSQC

1. INTRODUCTION

The synthesis of heterocyclic molecules has today become inevitable given its importance in human life. The biological interest [1-2-3] of these molecules is very broad and diversified. Several families of heterocyclic molecules are used as antiviral [4-5], anti tuberculosis [6-7], anti cancer [8-9-10], anti tuberculosis [11-12], anti malaria [13], anti fungus [14]. However, it is essential to have methods of analysis, which make it possible to elucidate the structure of these molecules.

Nuclear Magnetic Resonance Spectroscopy (NMR), which is a technique that exploits the magnetic properties of certain atomic nuclei, remains the most powerful spectroscopic technique in the study of the structural and dynamic aspects of organic molecules in solution. Its field of application is very broad. It is used to evaluate the pore size distribution [15], in food processing with dairy products [16]. Despite its advantages (being non-destructive and a highly reproducible form of analysis), it suffers from certain limitations, such as the problems of low sensitivity of the 13C core (resulting in a very long measurement time) and overlapping peaks [17]. However, there are new methods for perfecting it [18] at low field strength and low cost [19].

To obtain more accurate structural mapping, especially with complex molecules, the two-dimensional NMR. complements the 1D NMR. [20]. The 2D NMR. resides from the correlation of two 1D NMR. spectra. If two 1D NMR. spectra of the same nucleus are correlated; the resulting spectrum is called 2D homonuclear NMR. spectra and the most commonly used technique is the COSY experiment (homonuclear correlation Spectroscopy).

If it is two 1D NMR. spectra of two different nuclei, the spectrum obtained is called 2D hetero-nuclear NMR. spectra and the most common is the HSQC (Heteronuclear Single Quantum Correlation) technique [21]. There is also the HMBC (Heteronuclear Multiple Bond Connectivity) technique, which has a spectrum of lower couplings 2J, 3J and higher. It allows to establish connectivity without having to interpret the coupled spectrum. For example, HSQC, HMQC, and HMBC are among the most commonly used sequences for reverse detection. This sequence family allows to reach the same type of information provided by the HETCOR sequence. However, it is now a case of reverse detection, which ensures a much better sensitivity.

In view of these observations and in the continuity of our work corresponding to the synthesis and determination of the crystal structure of 2-(4-Methyl-2-phenyl-4,5-dihydro-oxazol-4-ylmethyl)-isoindole-1,3-dione by X-rays [22], we present in this paper the 2D NMR characterization of the isoindoline,1,3-dione derivative, we have chosen to use the COSY sequence and also HSQC rather than HMBC. Indeed, this heteronuclear 2D NMR experiment is the most sensitive, because it correlates the chemical displacements of the hydrogens to those of the carbons to which they are bound. However, it does not give any information on quaternary carbons.

2. MATERIAL AND METHODS

The melting points have been measured with an electrothermal device and are not corrected. The NMR spectra were recorded on a Bruker AC-300 MHz spectrometer in the CDCl3 with TMS as the internal standard. Chemical offsets (δ) and coupling constants (J) are given in parts per million (ppm) and Hertz (Hz), respectively. Multiplicities were recorded as s (singlet), br.s (wide signal), d (doublet), dd (double-doublet), t (triplet), q (quadruplet) or m (multiplet). Assignments given for the NMR spectra of the compound were carried out on the basis of COSY 1H/1H (standard procedures) and COSY 1H/13C (gHSQC) experiments.
All reactions were monitored by TLC performed on Merck's silica pre-coated aluminium-backed plates (0.2 mm, 60F254). For the column chromatography, Merck silica gel (70-230 mesh) was used.

2-(4-Methyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl)-isoindole-1,3-dione
The isoindoline-1,3-dione derivative was resynthesized according to the method described by Khadim et al. [22]. this compound crystallizes in the monoclinic system (P21/c, Z = 4) with the unit cell parameters: a = 14.3728 (13) Å, b = 9.6829 (10) Å, c = 11.8964 (12) Å and β = 107.384 (3). The refinement of the structure by the least-squares method with complete matrix leads to the following reliability factors R/Rw are 0.044/0.130.

Yield = 65% (white solid); m.p. = 148-150°C; Rf = 0.51 (Ethyl acetate/Hexane 1:4); 1H-NMR (CDCl3, δ ppm): 1.46 (s, 3H, CH_3); 3.85-4.01 (AB, 2H, J = 14.1 Hz, CH_2-phtalimide), 4.03-4.71 (AB, 2H, J = 9.0 Hz, CH_2-O (4,5-dihydro-oxazole)), 7.34-7.91 (m, 9Harom). 13C-NMR (CDCl3, δ ppm): 25.00 (CH_3), 46.08 (1C, CH2- phtalimide), 71.87 (1C, 4,5-dihydro-oxazole), 76.63 (1C, CH_2 (4,5-dihydro-oxazole)), 123.39, 127.53, 128.28, 128.42, 131.42, 131.86 and 134.07 (6C, phenyl ring + 6C, phtalimide), 163.70 (1C, C=N), 168.65(2CO).
MS–EI: $[M+1]^+$ = 321.

3. RESULTS AND DISCUSSION

The title compound (Figure 1) was obtained with a satisfactory yield, through N-alkylation reaction of the corresponding O-tosyl oxazoline derivative by heating in N,N-

dimethylformamide, and was recrystallized from ether and was obtained in the form of a single crystal [22]. Its structure was established based on (1H, 13C) NMR, IR spectroscopy, MS data and X-ray diffraction [22]. According the NMR spectra, the definite assignment of the chemical shifts of protons and carbons are shown in Table 1.

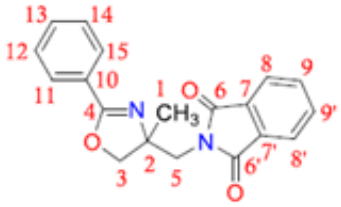

Fig. 1. Chemical structure of titled compound.

Table 1. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectral data for titled compound in $CDCl_3$, including results obtained by homonuclear 2D shift-correlated and heteronuclear 2D shift-correlated HSQC. Chemical shifts (δ in ppm) and coupling constants (*J* in Hz).

Position	δ_H	δ_C	Correlation H-H	Correlation C-H
1	1.46 (s)	25.00	$3H^1$-$3H^1$	C^1-$3H^1$
2	-	71.9	-	-
3	4.03-4.71 (AB, *J* = 9)	76.6	$2H^3$-$2H^3$	C^3-$2H^3$
4	-	163.7	-	-
5	3.85-4.01 (AB, *J* = 14.1)	46.1	$2H^5$-$2H^5$	C^5-$2H^5$
6; 6’	-	168.7	-	-
7; 7’	-	131.9	-	-
8; 8’	7.68-7.84 (AB, *J* = 3)	123.4	$1H^8$-$1H^8$; $1H^{8'}$-$1H^{8'}$ $1H^8$-$1H^9$; $1H^{8'}$-$1H^{9'}$	C^8-$1H^8$; $C^{8'}$-$1H^{8'}$
9; 9’	7.70-7.83 (AB, *J* = 3)	134.7	$1H^9$-$1H^9$; $1H^{9'}$-$1H^{9'}$ $1H^9$-$1H^8$; $1H^{9'}$-$1H^{8'}$	C^9-$1H^9$; $C^{9'}$-$1H^{9'}$
10	-	127.5	-	-
11; 15	7.34-7.38 (m)	128.3	$1H^{11}$-$1H^{11}$; $1H^{15}$-$1H^{15}$	C^{11}-$1H^{11}$; C^{15}-$1H^{15}$
12; 14	7.88-7.91 (m)	128.4	$1H^{12}$-$1H^{12}$; $1H^{14}$-$1H^{14}$	C^{12}-$1H^{12}$; C^{14}-$1H^{14}$
13	7.42-7.48 (m)	131.4	$1H^{13}$-$1H^{13}$	C^{13}-$1H^{13}$

The ^{1}H NMR spectrum (Figure 2 and Figure 3) of the titled compound shows the following signals:

- A singlet at 1.46 ppm corresponding to three protons of methyl radical.
- An AB system around 3.85-4.01 ppm corresponding to two protons of methylene groups -CH_2-(Phthalimide) with a coupling constant *J* = 14.1 Hz.
- An AB system around 4.03-4.71 ppm corresponding to two protons of methylene groups -CH_2-(Oxaz) with a coupling constant *J* = 9.0 Hz.
- Three multiplets around 7.34-7.42, 7.43-7.46 and 7.88-7.92 ppm corresponding respectively to $2H_{ar}^{(11+15)}$, $1H_{ar}^{(13)}$, and $2H_{ar}^{(12+14)}$.
- An AB system around 7.68-7.85 ppm corresponding to two protons of phthalimide ring $2H^{(8+8')}$ with a coupling constant *J* = 3.0 Hz.
- An AB system around 7.70-7.83 ppm corresponding to two protons of phthalimide ring $2H^{(9+9')}$ with a coupling constant *J* = 3.0 Hz.

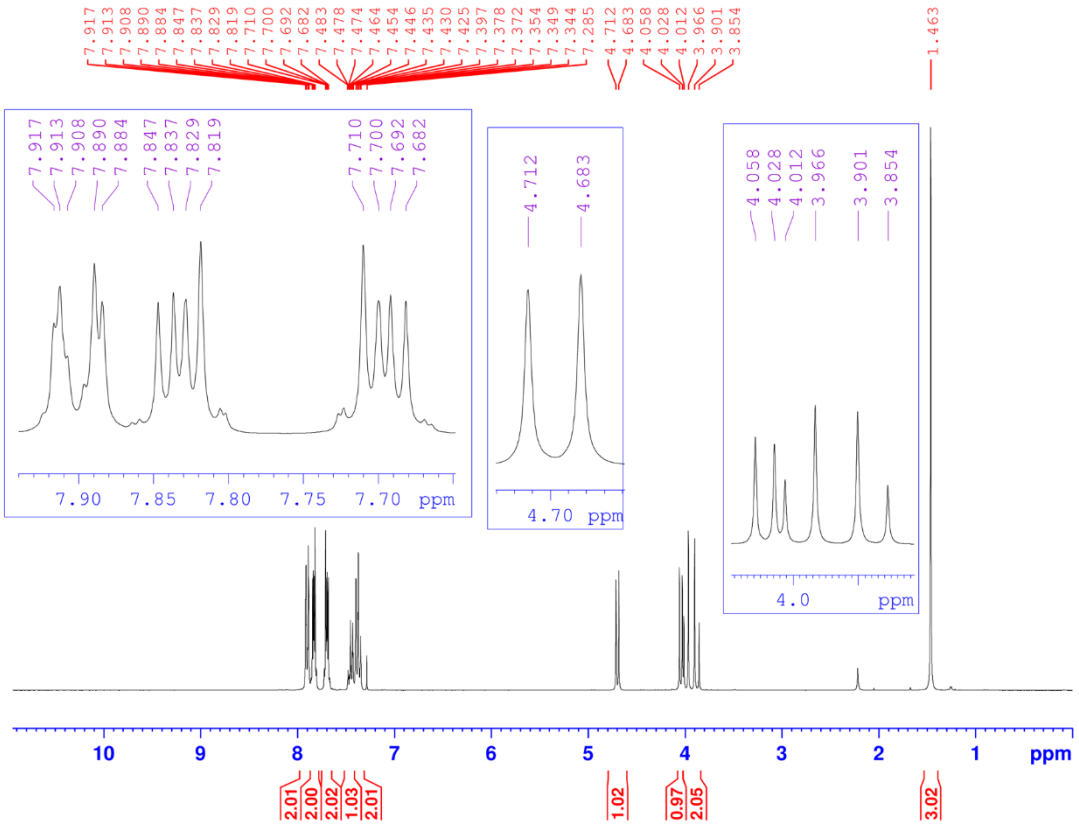

Fig. 2. ^{1}H NMR spectrum of titled compound.

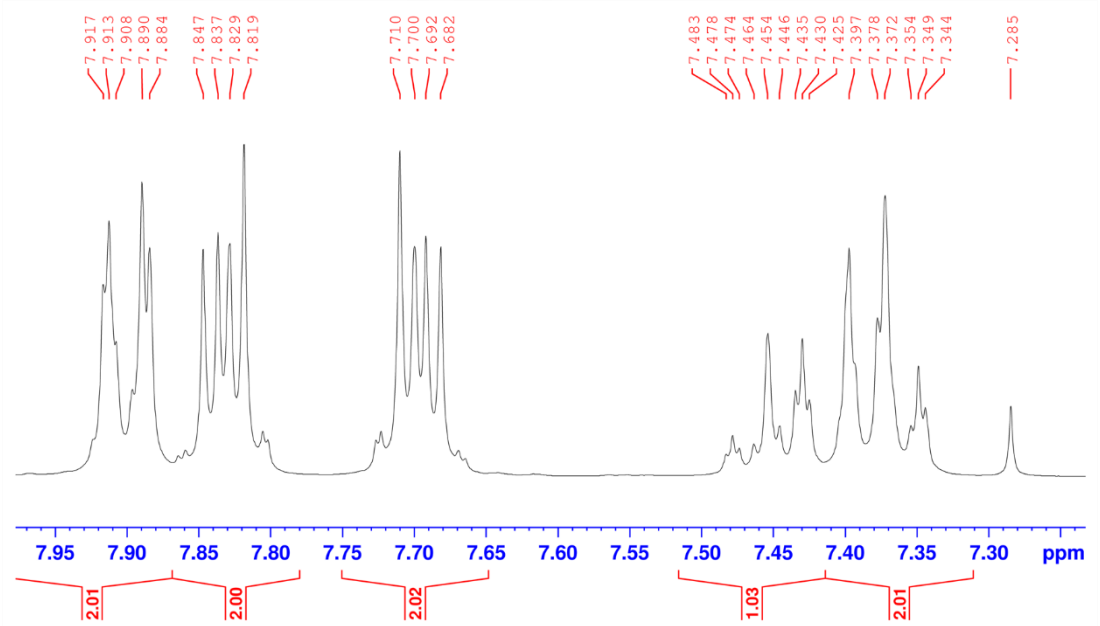

Fig. 3. 1H NMR spectrum (Aromatic Part) of titled compound

Whereas, its ^{13}C NMR spectrum (Figure 4) shows the following signals:

- A signal at 25.0 ppm corresponding to the carbon of methyl radical.
- A signal at 46.1 ppm corresponding to the carbon of methylene -CH_2-(Phthalimide).

- A signal at 71.9 ppm corresponding to the quaternary carbon of oxazoline ring.
- A signal at 76.6 ppm corresponding to the carbon of methylene of oxazoline ring.
- A signal at 123.4 ppm corresponding to two carbons of phthalimide ring $2C^{(8+8')}$.
- A signal at 127.5 ppm corresponding to the carbon of phenyl cycle $1C^{(10)}$.
- A signal at 128.3 ppm corresponding to two carbons of phenyl cycle $2C^{(11+15)}$.
- A signal at 128.4 ppm corresponding to two carbons of phenyl cycle $2C^{(12+14)}$.
- A signal at 131.4 ppm corresponding to the carbon of phenyl cycle $1C^{(13)}$.
- A signal at 131.9 ppm corresponding to two carbons of phthalimide ring $2C^{(7+7')}$.
- A signal at 134.7 ppm corresponding to two carbons of phthalimide ring $2C^{(9+9')}$.
- A signal at 163.7 ppm corresponding to the quaternary carbon C=N of oxazoline ring.
- A signal at 168.7 ppm corresponding to two quaternary carbons of carbonyl 2C=O.

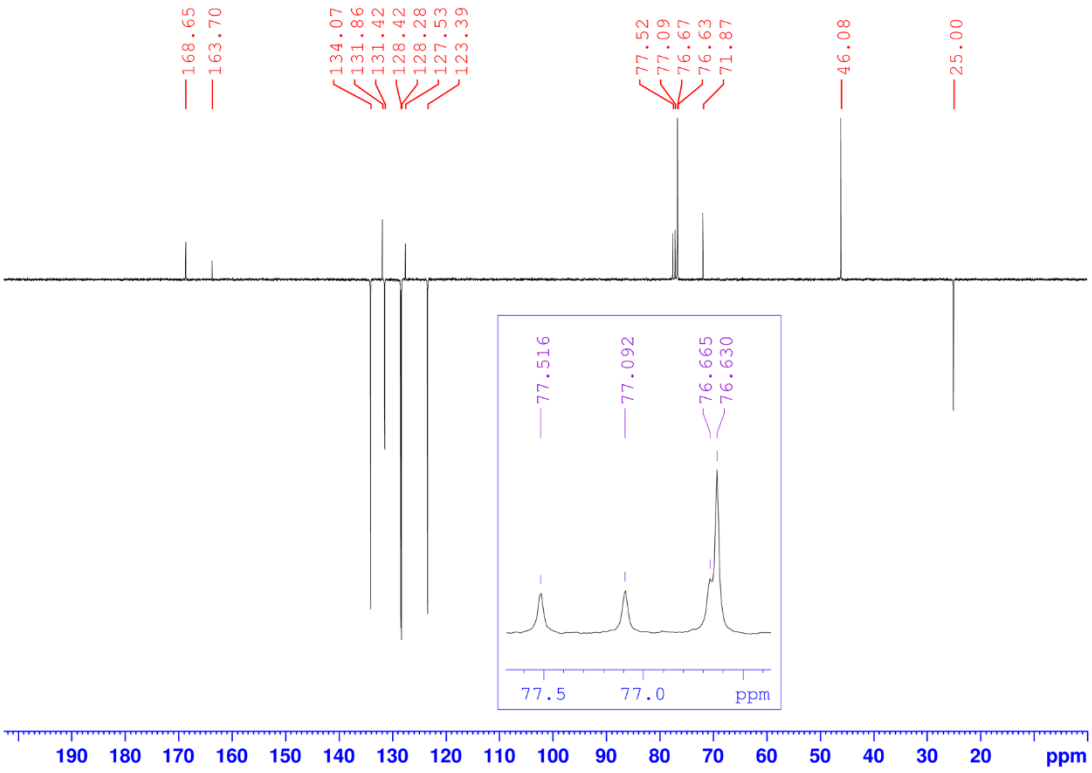

Fig. 4. ^{13}C NMR spectrum of titled compound.

Furthermore, the analysis of the 2D-COSY spectrum (Figures 5 and 6) also shows a perfect correlation between neighboring protons.

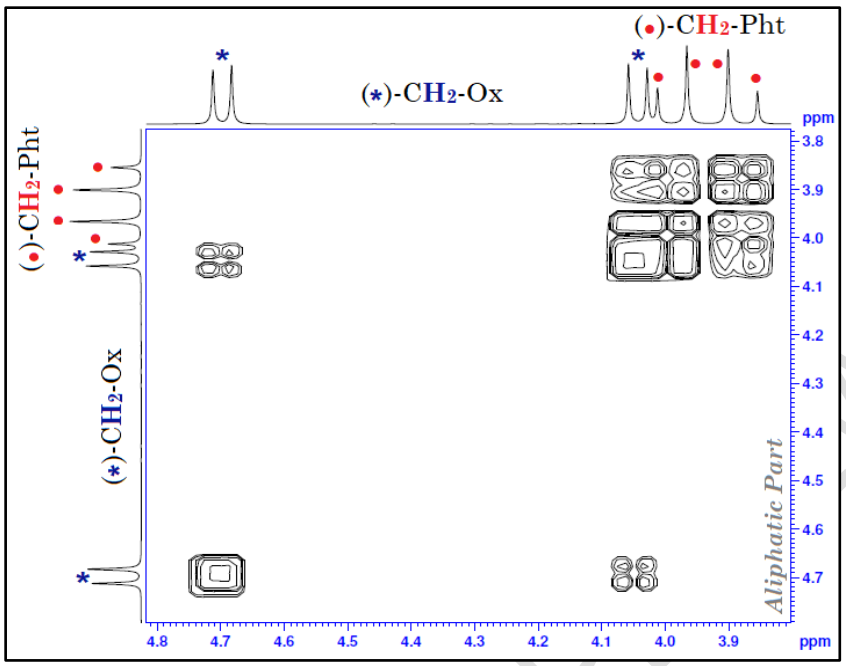

Fig. 5. 2D COSY spectrum (Aliphatic Part) of titled compound.

Thus, a correlation is noted between the protons of the phthalimide, H(8) and H(9) on the one hand and H(8'), and H(9') on the other hand.

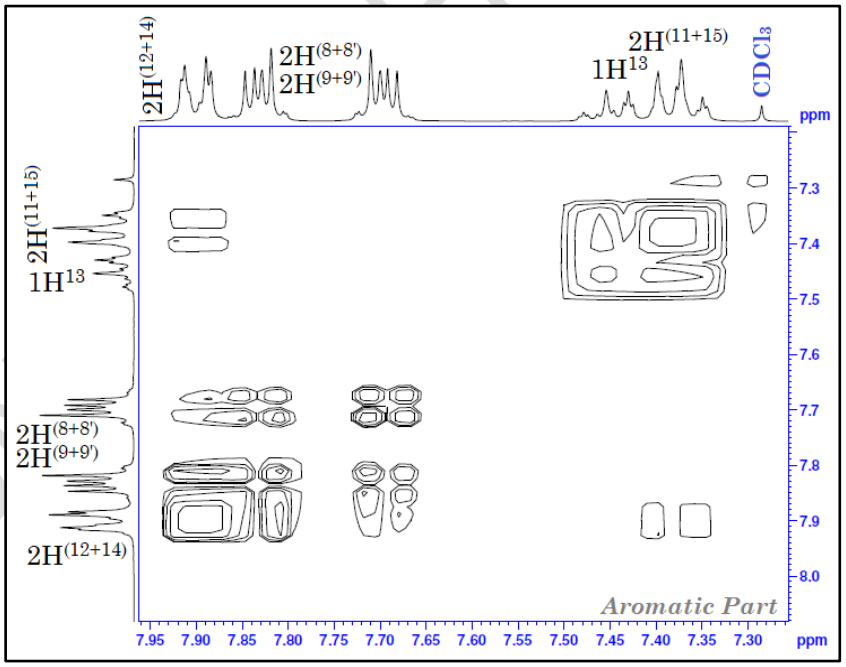

Fig. 6. 2D COSY spectrum (*Aromatic Part*) of titled compound.

The analysis of the 2D-HSQC spectrum (Figures 7 and 8) of the studied compound indicates a faultless correlation between protons and adjacent carbons, and no correlation in the case of all quaternary carbons.

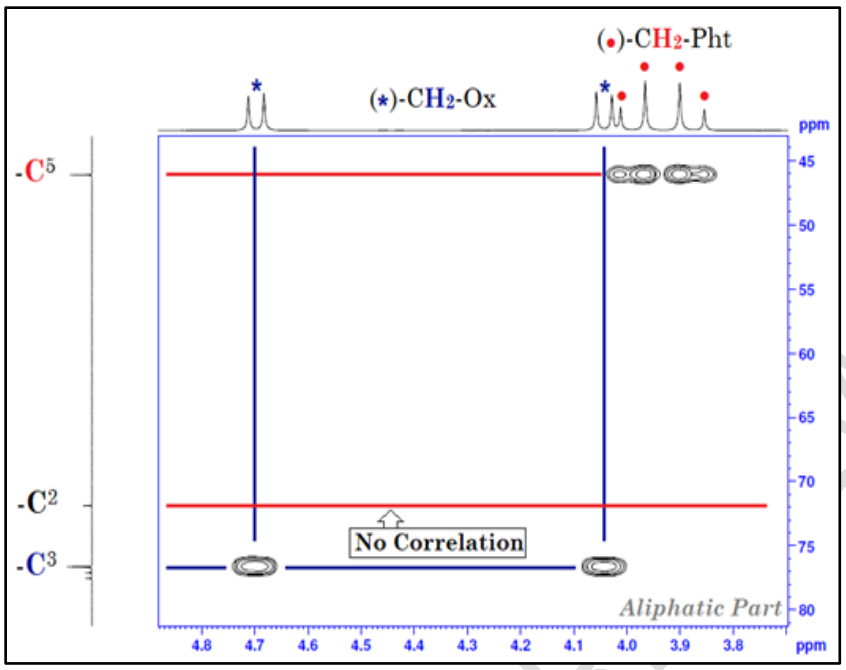

Fig. 7. 2D HSQC spectrum (*Aliphatic Part*) of titled compound.

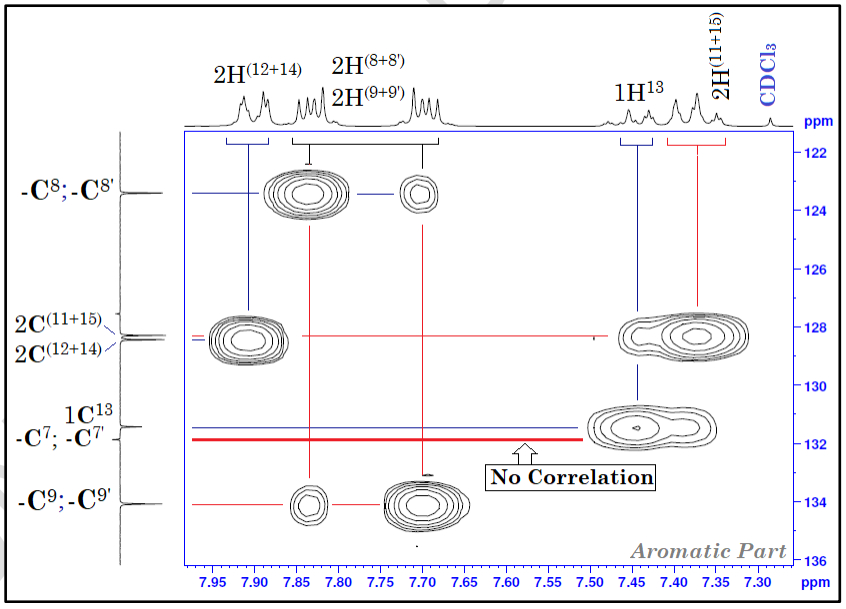

Fig. 8. 2D HSQC spectrum (*Aromatic Part*) of titled compound.

4. CONCLUSION

In summary, although the structure of -(4-Methyl-2-phenyl-4,5-dihydrooxazol-4-ylmethyl)-isoindole-1,3-dione was previously confirmed by us [22], by X-ray single crystal structure determination, its identity was also determined on the basis of a spectroscopic study using 1D NMR of the proton and carbon 13, as well as 2D NMR using COSY and HSQC

sequences. The evaluation of the corrosion and biological activities of this isoindoline derivative is the subject of ongoing work.

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