

Article

Efficient Consecutive Synthesis of Ethyl-2-(4-Aminophenoxy) Acetate, a Precursor for Dual GK and PPAR γ Activators, X-Ray Structure, Hirshfeld Analysis, and DFT Studies

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Materials and Equipments

The reaction was accomplished in dried glassware. CHN analyses were performed using a Thermo Fisher scientific, Flash 2000 Organic Elemental Analyzer, (MA, USA). NMR spectra were measured using a JEOLJNM ECA 500 (JOEL, Tokyo, Japan). The deuterated solvent was used as an internal deuterium lock. ¹³C NMR spectra were recorded using the UDEFT pulse sequence and broad band proton decoupling at 125 MHz. All chemical shifts (δ) are stated in units of parts per million (ppm) and presented using TMS as the standard reference point. Melting points were recorded using Thermo Scientific, Model NO: 1002D, 220–240v; 200 W; 50/60 Hz (IA, USA) and are uncorrected. Reaction time was monitored by TLC on Merck silica gel aluminum cards (0.2 mm thickness) with a fluorescent indicator at 254 nm. Visualization of the TLC during monitoring of the reaction was done by UV VILBER LOURMAT (Marne-la-Vallee-France), 4w-365 nm or 254 nm tube. X-Ray diffraction data were collected on a Rigaku Oxford Diffraction Supernova diffractometer and processed with CrysAlisPro software v. 1.171.41.93a (Rigaku Oxford Diffraction, Yarnton, UK, 2020) using Cu K α radiation.

X-Ray Structure Determinations

The crystal of **4** was immersed in cryo-oil, mounted in a loop, and measured at a temperature of 120 K. The X-ray diffraction data was collected on a Rigaku Oxford Diffraction Supernova diffractometer using Cu K α radiation. The CrysAlisPro [S1] software package was used for cell refinement and data reduction. A multi-scan absorption correction (CrysAlisPro [S1]) was applied to the intensities before structure solution. The structure was solved by intrinsic phasing (SHELXT [S2]) method. Structural refinement was carried out using SHELXL [S3] software with SHELXLE [S4] graphical user interface. Hydrogen atoms were positioned geometrically and constrained to ride on their parent atoms, with C–H = 0.95–0.98 Å and $U_{\text{iso}} = 1.2\text{--}1.5 \cdot U_{\text{eq}}(\text{parent atom})$.

Computational Methods

Hirshfeld Surface Analysis

The topology analyses were performed using Crystal Explorer 17.5 program [S5].

DFT Calculations

All DFT calculations were performed using Gaussian 09 software package [S6] utilizing B3LYP/6-31G(d,p) method. Natural bond orbital analyses were performed using NBO 3.1 program as implemented in the Gaussian 09W package [S7]. The self-consistent reaction field (SCRF) method [8,9] was used to model the solvent effects when calculating the optimized geometries in solution. Then, the UV-Vis electronic spectra of the compound were calculated using TD-DFT method.

H and C NMR spectra

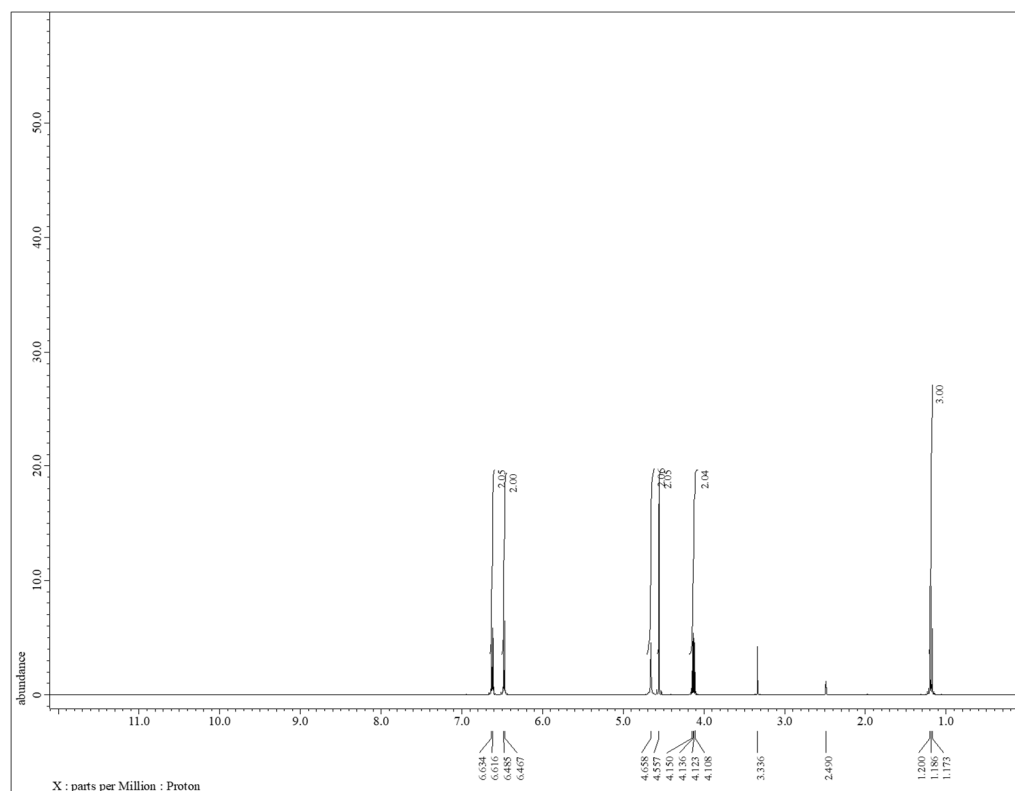


Figure S1. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) of 4.

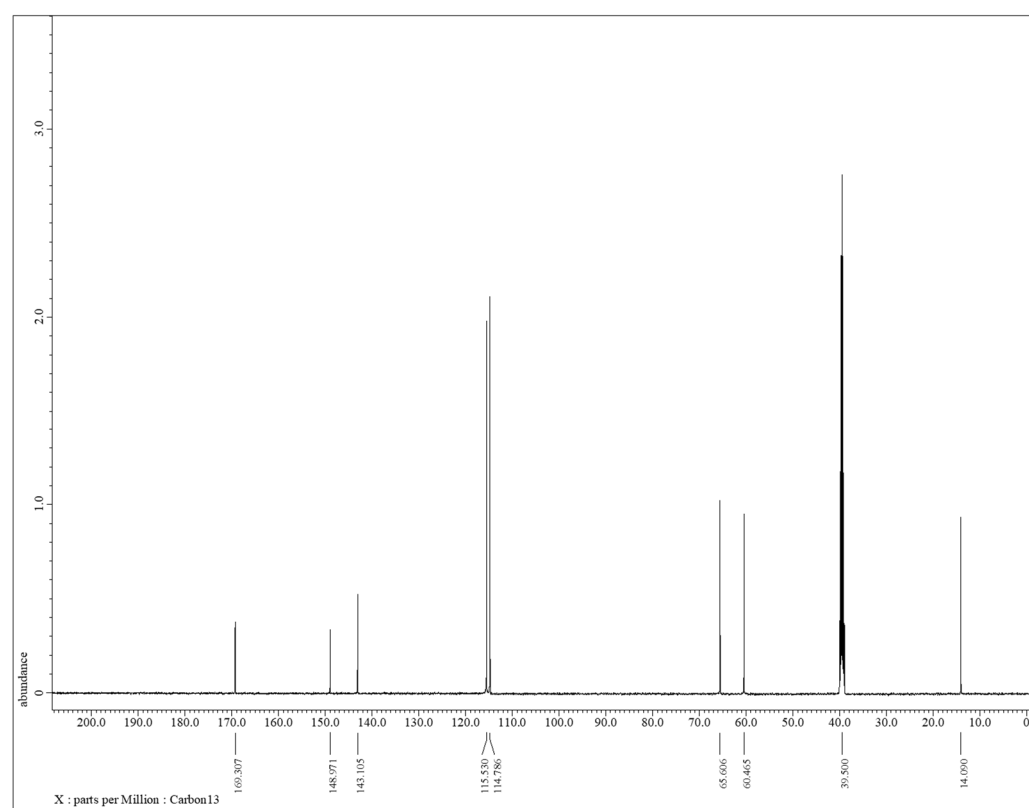
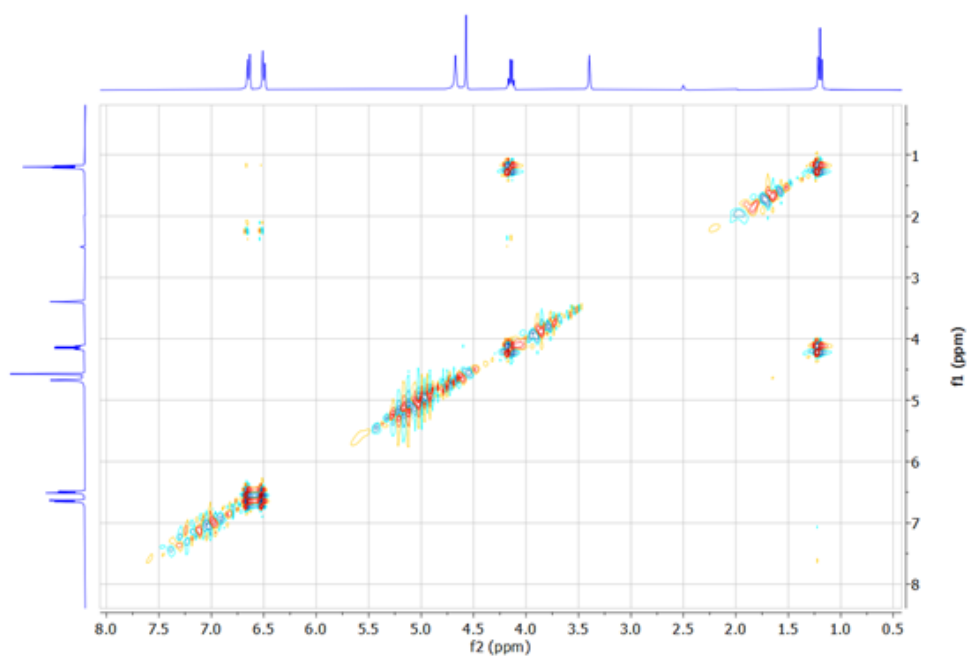
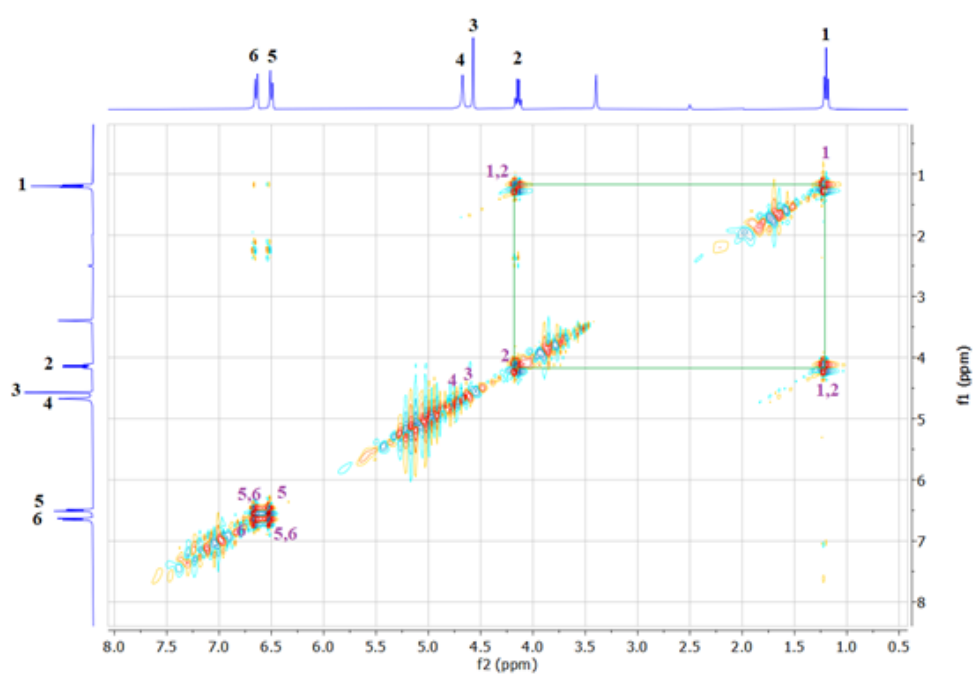


Figure S2. ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) of 4.

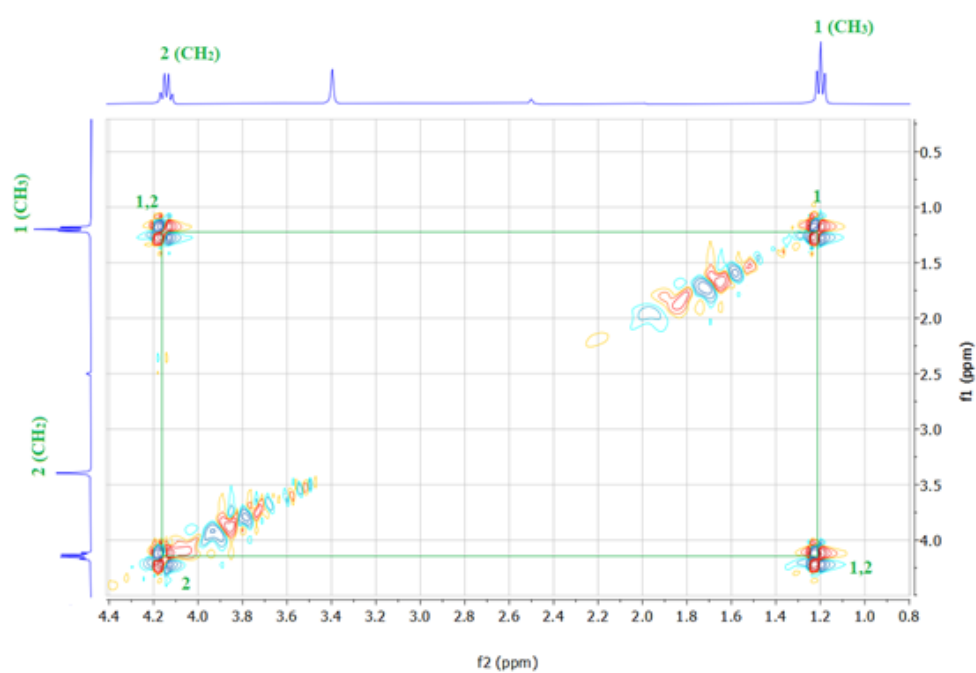
COSY Spectra



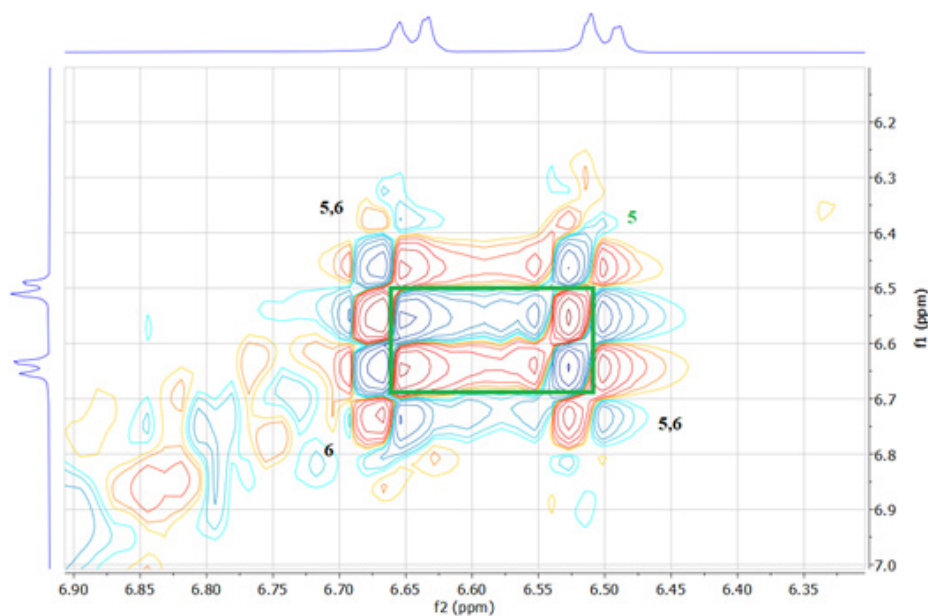
A.



B.



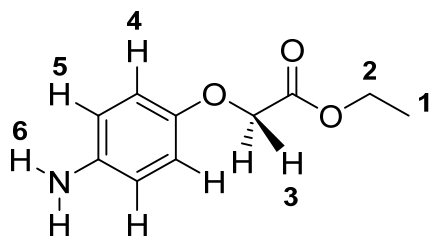
C



D

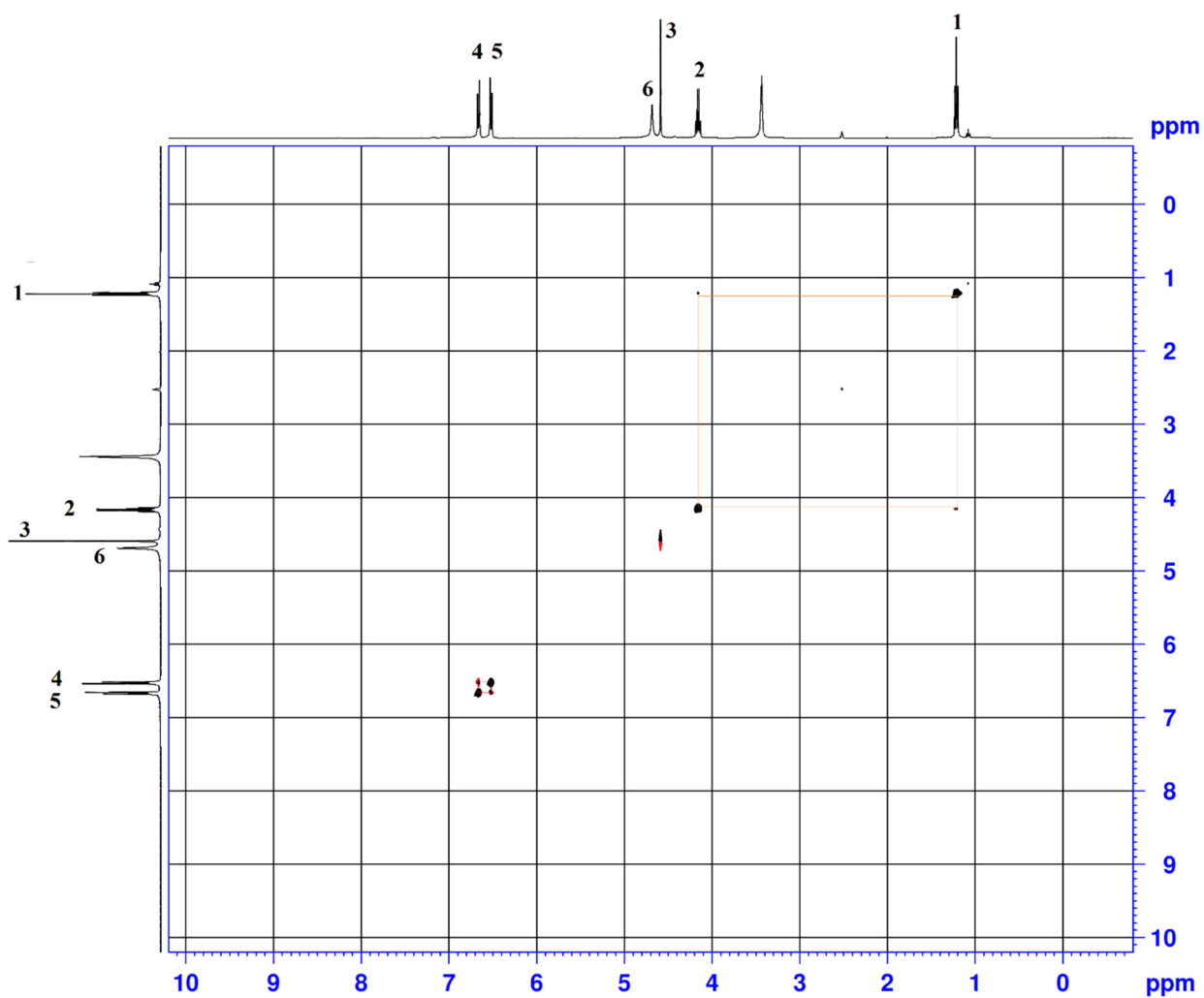
Figure S3. A–D. COSY NMR (125 MHz, DMSO- d_6) of **4**.

NOESY spectra

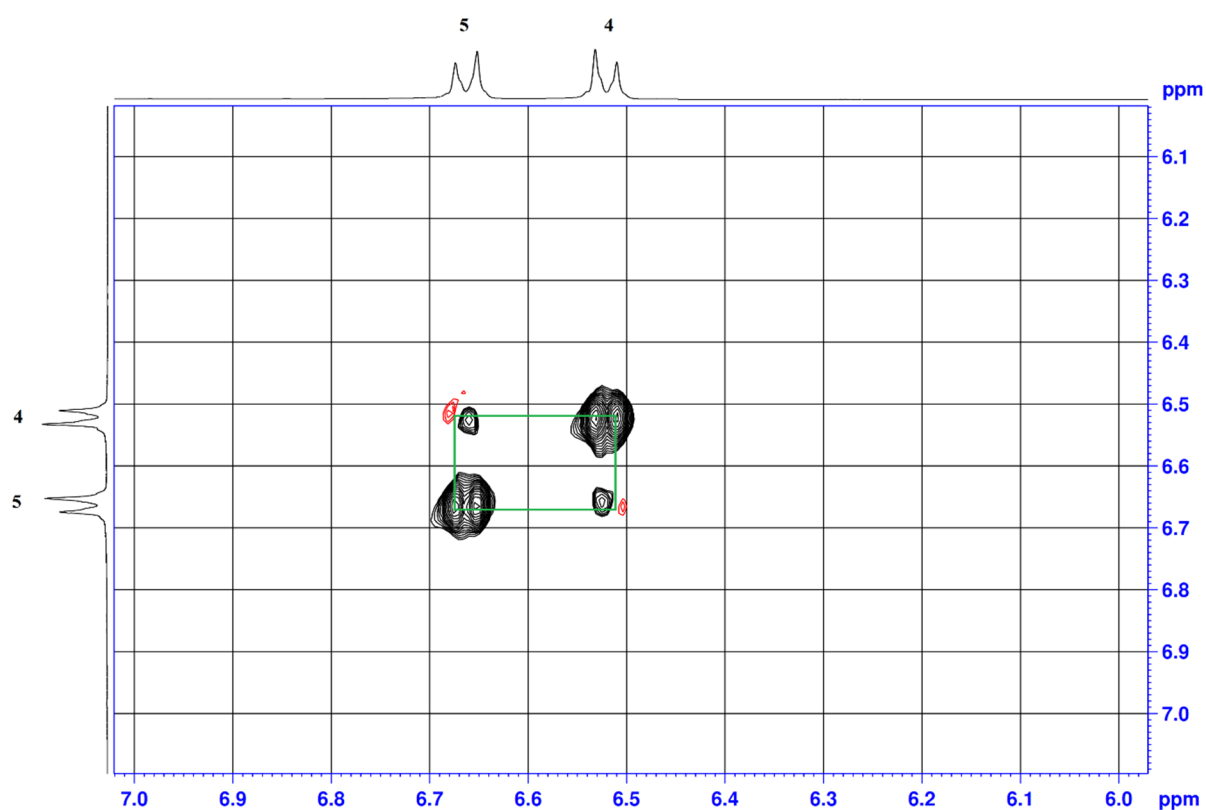


^1H NMR (400 MHz, DMSO- d_6) δ 6.68–6.61 (m, 2H, H), 6.53–6.47 (m, 2H), 4.66 (s, 2H), 4.57 (s, 2H), 4.14 (q, $J = 7.1$ Hz, 2H, CH_2CH_3), 1.20 (t, $J = 7.1$ Hz, 3H, CH_2CH_3).

The structure was drawn to explain the expected stereochemical interaction between protons; all homotopic protons take certain number.



A



B

Figure S4. A,B The NOESY spectrum as shown in Fig. 1 for the above molecules contains a diagonal and cross peaks. The diagonal consists of the 1D spectrum that is pure self-interaction spectra. The cross peaks signals arising from protons that are close in space. The above molecule does not show strong NOE correlations. The correlation between CH₃(1) and CH₃(2) at 1.20 and 4.14 ppm is mostly COSY type. A much weaker through-space correlation appears between them as very weak intensity cross peaks appeared. Similarly, very weak NOE correlations are appearing for aromatic protons H4 and H5. Other than those weak interaction, there is no such space interaction are found from this spectrum.

Table S1. Crystal data for **4**.

4	
CCDC	2130116
empirical formula	C ₁₀ H ₁₃ NO ₃
fw	195.21
temp (K)	120(2)
λ (Å)	1.54184
crystal system	Triclinic
space group	$P \bar{1}$
a (Å)	8.2104(6)
b (Å)	10.3625(9)
c (Å)	11.9562(9)
α (deg)	101.787(7)
β (deg)	91.849(6)
γ (deg)	102.755(7)
V (Å ³)	968.02(14)
Z	4
ρ_{calc} (Mg/m ³)	1.339
μ (Mo K α) (mm ⁻¹)	0.823
No. reflns.	7784
Unique reflns.	3954
Completeness to $\theta=67.684^\circ$	99.7%
GOOF (F ²)	1.023
R_{int}	0.0232
R_1^a ($I \geq 2\sigma$)	0.0358
wR_2^b ($I \geq 2\sigma$)	0.0913

$$^a R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|, ^b wR_2 = \{\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]\}^{1/2}$$

Table S2. The calculated geometric parameters of **4**^a.

Parameter	Calc	Exp	Parameter	Calc	Exp
R(1-9)	1.450	1.453	A(9-1-12)	116.2	115.6
R(1-12)	1.350	1.330	A(1-9-5)	107.4	107.5
R(2-12)	1.199	1.204	A(1-12-2)	124.8	124.8
R(3-13)	1.403	1.412	A(1-12-13)	108.5	109.9
R(3-16)	1.374	1.382	A(2-12-13)	126.6	125.3
R(4-21)	1.403	1.396	A(13-3-16)	118.0	117.1
R(5-9)	1.515	1.499	A(3-13-12)	108.7	107.0
R(12-13)	1.520	1.507	A(3-16-17)	125.2	125.3
R(16-17)	1.394	1.390	A(3-16-24)	115.7	115.3
R(16-24)	1.398	1.391	A(21-4-26)	114.3	116.3
R(17-19)	1.396	1.395	A(21-4-27)	114.3	113.4
R(19-21)	1.397	1.392	A(4-21-19)	121.3	121.3
R(21-22)	1.405	1.403	A(4-21-22)	120.7	120.4
R(22-24)	1.385	1.380	A(17-16-24)	119.1	119.3
R(1-9)	1.450	1.453	A(16-17-19)	120.0	119.8
			A(16-24-22)	120.6	120.8
			A(17-19-21)	121.4	121.2
			A(19-21-22)	117.9	118.2
			A(21-22-24)	121.0	120.7

^aAtom numbering refer to **Figure 7**

Table S3. The calculated natural charges of **4**^a.

Atom	Charge	Atom	Charge
O1	−0.5748	H15	0.1878
O2	−0.5697	C16	0.2921
O3	−0.5257	C17	−0.2748
N4	−0.7827	H18	0.2054
C5	−0.5847	C19	0.2388
H6	0.1991	H20	0.1963
H7	0.2032	C21	0.1639
H8	0.1990	C22	−0.2348
C9	−0.0191	H23	0.1982
H10	0.1782	C24	−0.2176
H11	0.1777	H25	0.2162
C12	0.8225	H26	0.3596
C13	−0.1229	H27	0.3592
H14	0.1871		

^aAtom numbering refer to **Figure 7**

References

- [S1] Rikagu Oxford Diffraction, *CrysAlisPro*, Agilent Technologies inc., **2018**, Yarnton, Oxfordshire, England.
- [S2] Sheldrick, G. M. SHELXT-Integrated Space-Group and Crystal-Structure Determination. *Acta Cryst. A* **2015**, *A71*, 3–8.
- [S3] Sheldrick, G. M. Crystal Structure Refinement with SHELXL. *Acta Cryst. C* **2015**, *C71*, 3–8.
- [S4] Hübschle, C. B.; Sheldrick, G. M.; Dittrich, B. *ShelXle*: a Qt graphical user interface for SHELXL. *J. Appl. Cryst.* **2011**, *44*, 1281–1284.
- [S5] M. J. Turner, J. J. McKinnon, S. K. Wolff, D. J. Grimwood, P. R. Spackman, D. Jayatilaka, M. A. Spackman, *Crystal Explorer17* (2017) University of Western Australia. <http://hirshfeldsurface.net>
- [S6] Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; *et al.* GAUSSIAN 09; Revision A02; Gaussian Inc.: Wallingford, CT, USA, 2009; *GaussView*; Version 4.1; Dennington II, R., Keith, T., Millam, J., Eds.; Semichem Inc.: Shawnee Mission, KS, USA, 2007.
- [S7] Reed, A.E.; Curtiss, L.A.; Weinhold, F. Intermolecular interactions from a natural bond orbital, donor-acceptor viewpoint. *Chem. Rev.* **1988**, *88*, 899–926.
- [S8] Marten, B.; Kim K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. New Model for Calculation of Solvation Free Energies: Correction of Self-Consistent Reaction Field Continuum Dielectric Theory for Short-Range Hydrogen-Bonding Effects, *J. Phys. Chem.* **1996** *100* 11775–11765.
- [S9] Tannor, D.J.; Marten, B.; Murphy, R.; Friesner, R.A.; Sitkoff, D.; Nicholls, A.; Ringnalda, M.; Goddard, W.A.; Honig, B. Accurate first principles calculation of molecular charge distributions and solvation energies from ab initio quantum mechanics and continuum dielectric theory. *J. Am. Chem. Soc.* **1994**, *116*, 11875–11882.