Supporting information for

Polymorphic and solvate structures of ethyl ester and carboxylic acid derivatives of WIN 61893 analogue and their stability in solution

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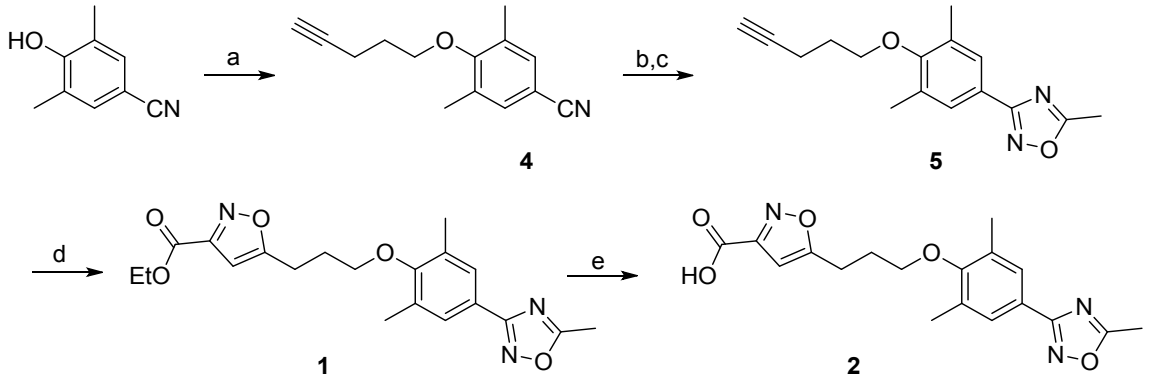
Synthesis of the WIN 61893 derivatives

Synthesis of the WIN 61893 derivatives **1** and **2** was accomplished by following a previously reported protocol (Scheme S1).[1] Shortly, nucleophilic substitution reaction of 3,5-dimethyl-4-hydroxybenzonitrile with 5-chloro-1-pentyne first produces the intermediate nitrile **4** in the presence of K_2CO_3/KI in DMF at 75°C with good yields. The subsequent treatment of nitrile **4** with hydroxylamine first gives amidoxime, which then upon acylation reaction with acetyl chloride affords the oxadiazole **5**. Noteworthy is the [3+2] cycloaddition reaction to produce the isoxazole **1**, which is accomplished by the reaction of the oxadiazole **5** with nitrile oxide obtained in situ from a reaction of chlorooximidoacetate[2] and triethylamine. Basic hydrolysis of the ester functionalized isoxazole **1** then finally affords the terminal carboxylic acid containing isoxazole **2**.



Scheme S1. Synthesis scheme for the preparation of pleconaril derivatives **1** and **2**: a) K_2CO_3/KI, DMF, 75°C, b) NH_2OH-HCl, K_2CO_3, EtOH, reflux, c) acetyl chloride, pyridine, reflux, d) chlorooximidoacetate, Et_3N, DMF, 90°C, e) aq NaOH, ethanol-H_2O 1:1, reflux, f) $NaNO_2$, conc HCl, H_2O, -5°C.

1 Y. Chen, W. Zhang, X. Chen, J. Wang and P. G. Wang, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1716

2 A. P. Kozikowski and M. Adamczyk*, J. Org. Chem.*, 1983, **48**, 366

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

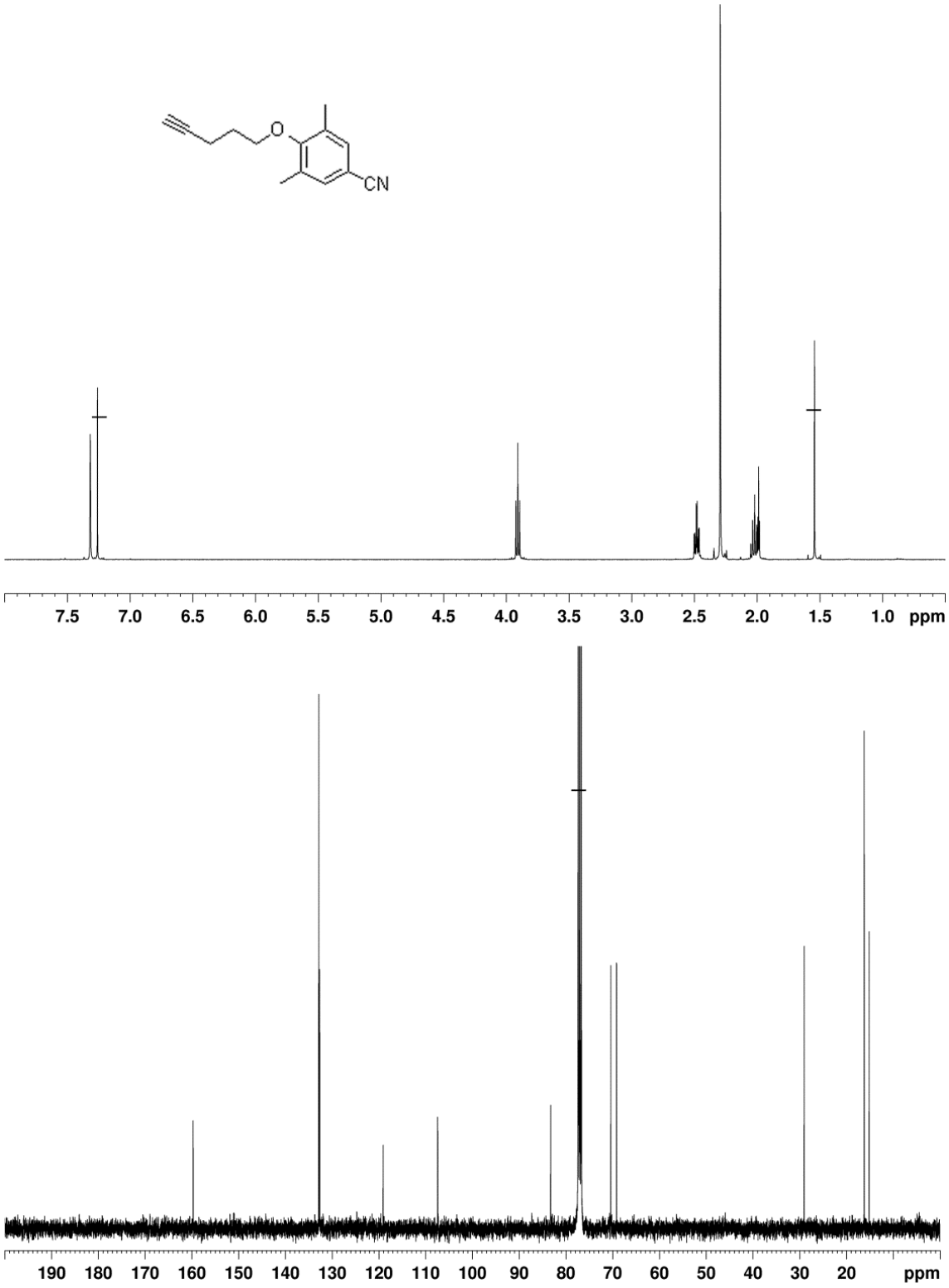


Figure S1. ^{1}H and ^{13}C NMR spectra of intermediate **4** in $CDCl_3$ at 30°C.

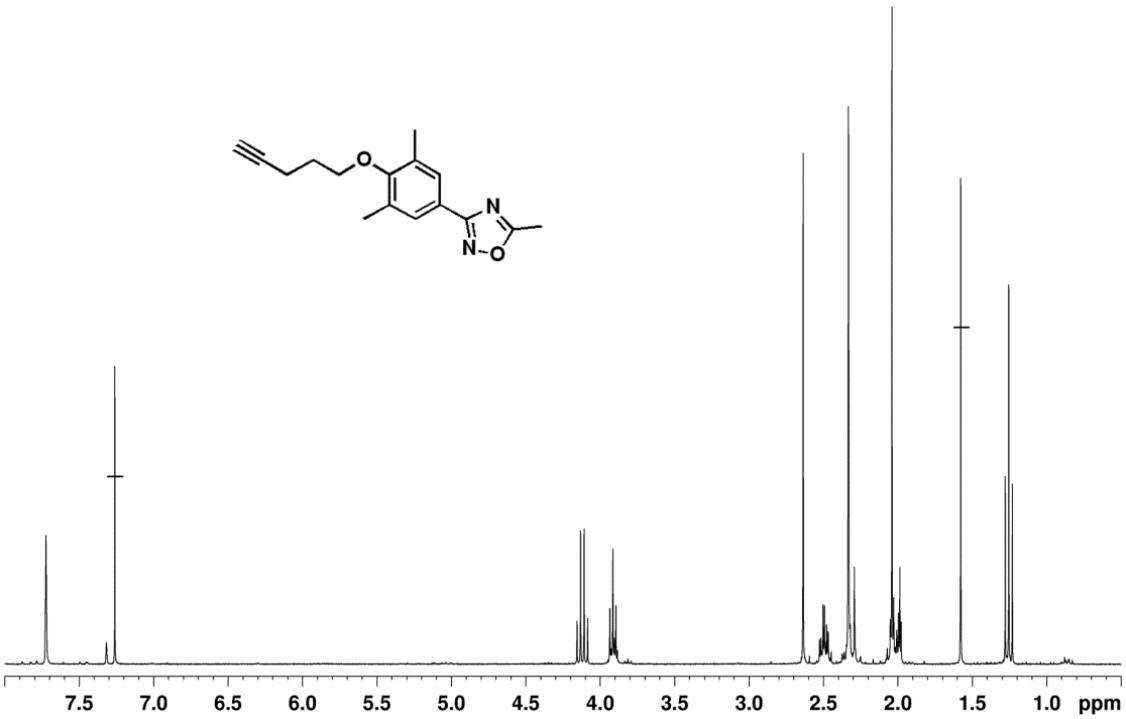


Figure S2. ^{1}H NMR spectrum of intermediate **5** in $CDCl_3$ at 30°C. Chemical shifts marked with (*) belong to residual ethyl acetate.

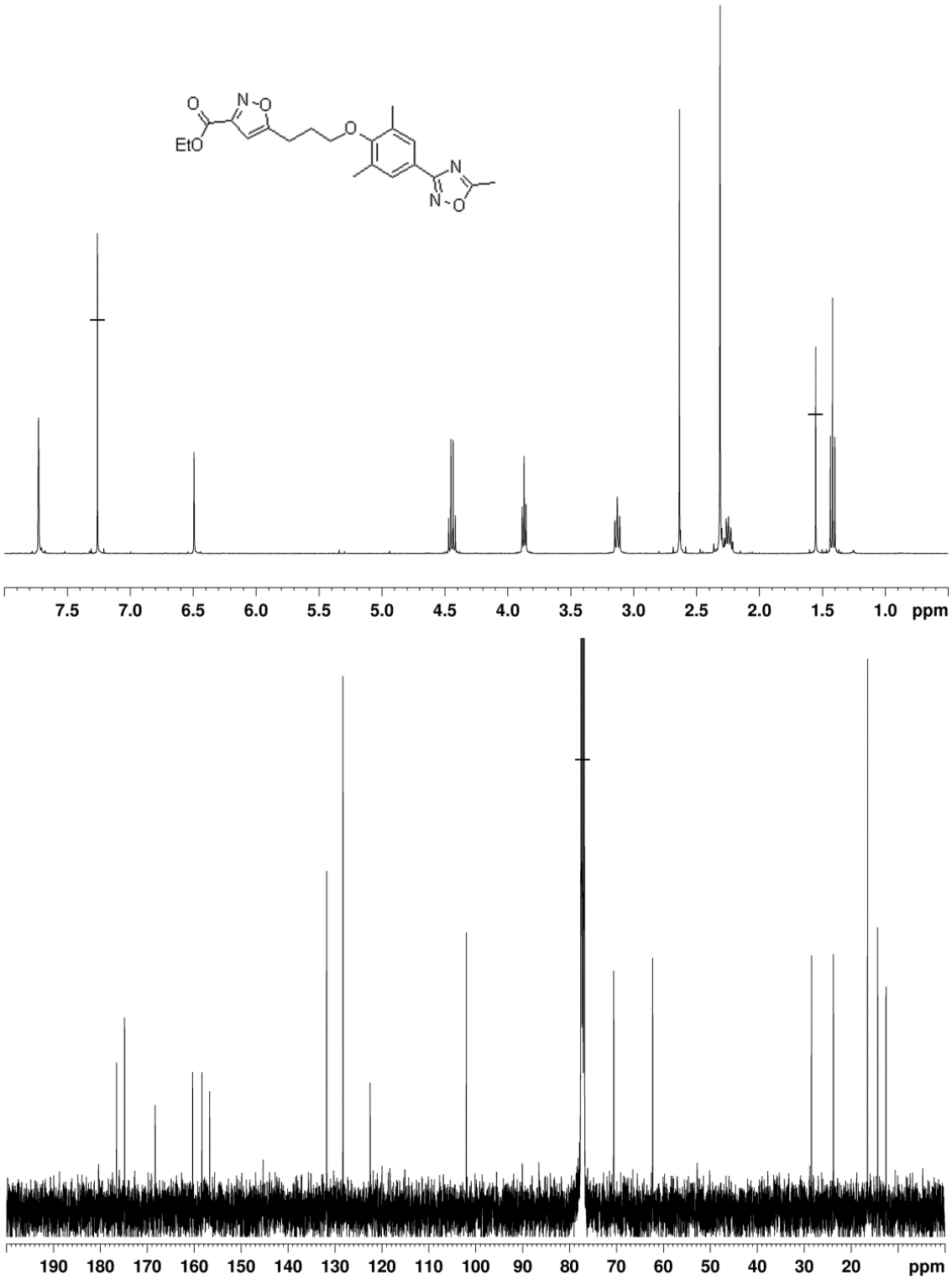


Figure S3. ^{1}H and ^{13}C NMR spectra of ethyl ester derivative **1** in $CDCl_3$ at 30°C.

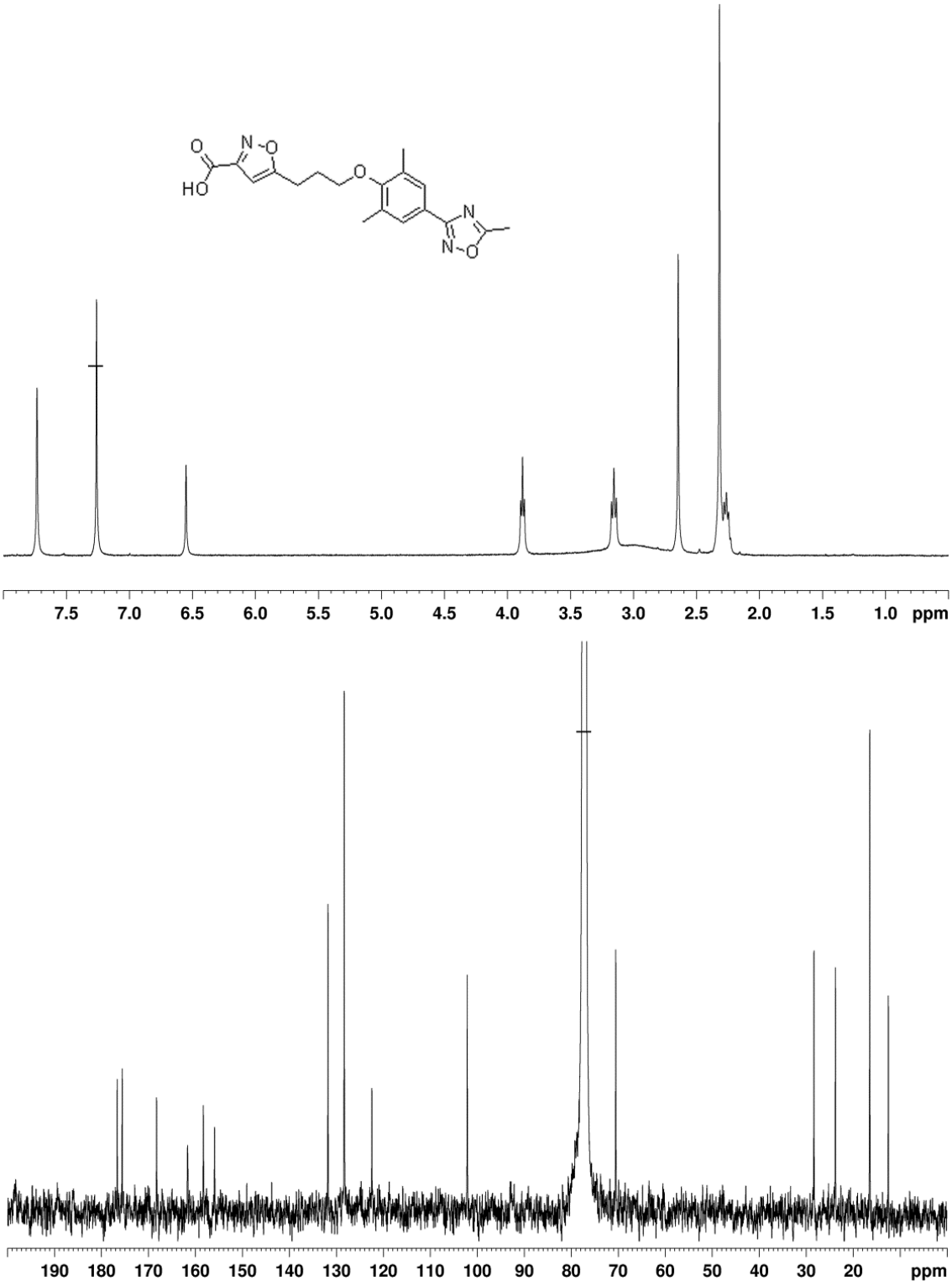


Figure S4. ^{1}H and ^{13}C NMR spectra of carboxylic acid derivative **2** in $CDCl_3$ at 30°C.

Crystallographic data and details

Table S1. Crystallographic details for derivatives **1** and **2** structures.

	1-form I	**1**-form II	**2**-EtOH	**2**-DMSO
Compound	**1**	**1**	**2**	**2**
Crystallization	CH_2Cl_2-Hexane (se)[a]	MeOH (sce)	EtOH (se)	DMSO (vd H_2O)
Crystal morphology	plate	block	plate (sheets)	long needles
Composition	$C_{20}H_{23}N_3O_5$	$C_{20}H_{23}N_3O_5$	2 ($C_{18}H_{19}N_3O_5 \cdot C_2H_5OH$)	$C_{18}H_{19}N_3O_5 \cdot C_2H_6SO$
Formula weight (g mol^{-1})	385.41	385.41	806.86	435.49
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P2_1/c$
a (Å)	7.8644(2)	18.6194(5)	8.3029(3)	13.7775(3)
b (Å)	23.7196(5)	8.3392(2)	45.516(2)	7.2131(1)
c (Å)	10.4242(2)	12.7669(3)	11.0152(4)	21.4071(3)
β (°)	96.213(3)	100.331(3)	103.692(4)	90.490(2)
V (Å^3)	1933.11(7)	1950.19(8)	4044.5(3)	2127.32(6)
Z	4	4	4	4
d_{calc} (g cm^{-3})	1.324	1.313	1.325	1.360
μ [Mo Kα] (mm^{-1})	0.096	0.096	0.099	0.194
F(000)	816	816	1712	920
Crystal size (mm^3)	0.11 × 0.12 × 0.17	0.13 × 0.19 × 0.24	0.05 × 0.12 × 0.25	0.08 × 0.12 × 0.22
θ range (°)	2.14 to 30.69	2.22 to 30.60	1.79 to 28.78	1.90 to 30.61
Reflections collected	11637	10497	18378	11563
Independent reflections	5318 (R_{int}=0.0202)	5164 (R_{int}=0.0420)	9215 (R_{int}=0.0267)	5806 (R_{int}=0.0182)
Restraints/parameters	0, 257	0, 257	0, 535	0, 277
GOF on F^2	1.053	1.025	1.063	1.048
Final R indices[$I>2\sigma(I)$], R1, wR2	0.0530, 0.1184	0.0596, 0.1498	0.0593, 0.1245	0.0446, 0.1137
R indices (all data), R1, wR2	0.0825, 0.1328	0.0840, 0.1674	0.0931, 0.1408	0.0607, 0.1245
Largest difference peak and hole (e Å^{-3})	0.202, -0.221	0.290, -0.275	0.295, -0.249	0.313, -0.350
CCDC number	999254	999255	999256	999257

vd = vapor diffusion, sce = slow cooling and evaporation, se = slow evaporation; [a] same unit cell was obtained from hot MeOH or EtOH (vd H_2O) solutions as well.

Stability of WIN 61893 derivatives 1 and 2 in solution

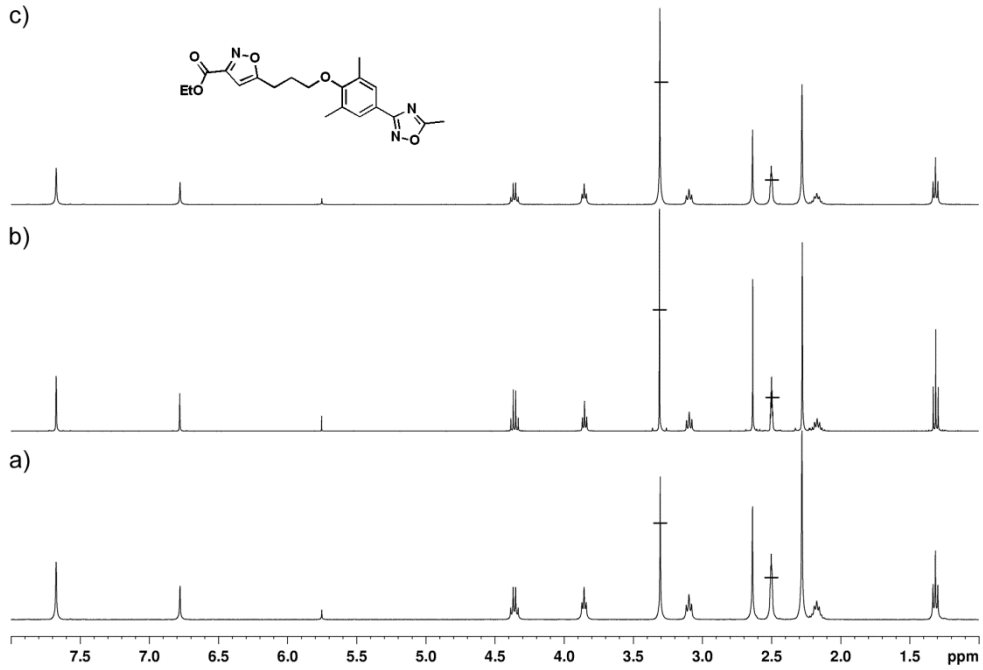
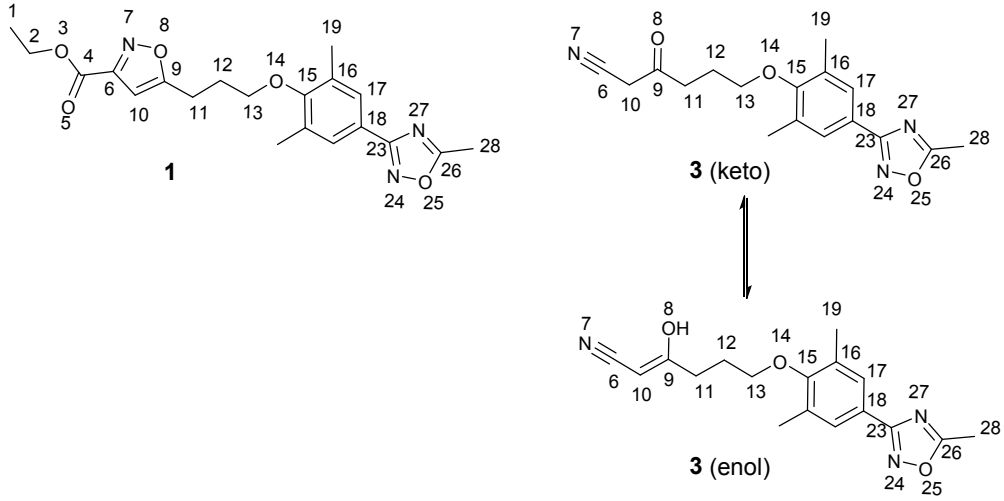


Figure S5. Time dependent ^{1}H NMR spectra of ethyl ester (**1**) derivative in DMSO-d_6 at 30°C measured over several days: a) freshly prepared sample, b) after 8 days and c) after 15 days showing no isoxazole ring opening.



Scheme S2. Numbering scheme used for the NMR chemical shift assignment of derivatives **1** – **3** (adopted from the crystallographic numbering scheme).

Table S2. ^{1}H and ^{13}C NMR chemical shift assignment of the WIN 61893 derivatives **1** – **2** and the ring opening product **3** in DMSO-d_6 at 30°C.[a]

	^{1}H chemical shift (ppm)			**^{13}C chemical shift (ppm)**		
atom #	**1**	**2**	**3**	**1**	**2**[b]	**3**
1	1.31	–	–	13.9	–	–
2	4.36	–	–	61.7	–	–
4	–	–	–	175.2	175.5	–
6	–	–	–	**157.9**	**158.3**	**115.5 (CN)**
9	–	–	–	**159.5**	**161.7**	**199.5 (C=O)** keto
10	**6.78**	**6.70**	**4.09**	**101.8**	**102.1**	**37.9 (CH_2-)** keto
11	3.09	3.08	2.76	22.8	23.8	23.7
12	2.17	2.17	1.97	27.6	28.4	31.9
13	3.85	3.85	3.78	70.4	70.5	70.7
15	–	–	–	156.1	155.9	158.0
16	–	–	–	131.5	131.7	131.5
17	7.67	7.67	7.67	127.5	128.3	127.4
18	–	–	–	121.6	122.4	121.5
19	2.28	2.28	2.28	15.9	16.5	15.9
23	–	–	–	167.3	168.2	167.3
26	–	–	–	177.1	176.6	177.1
28	2.64	2.64	2.64	11.9	12.5	11.9

[a] Most significant changes in the chemical shifts have been highlighted with blue color. [b] Measured in $CDCl_3$.

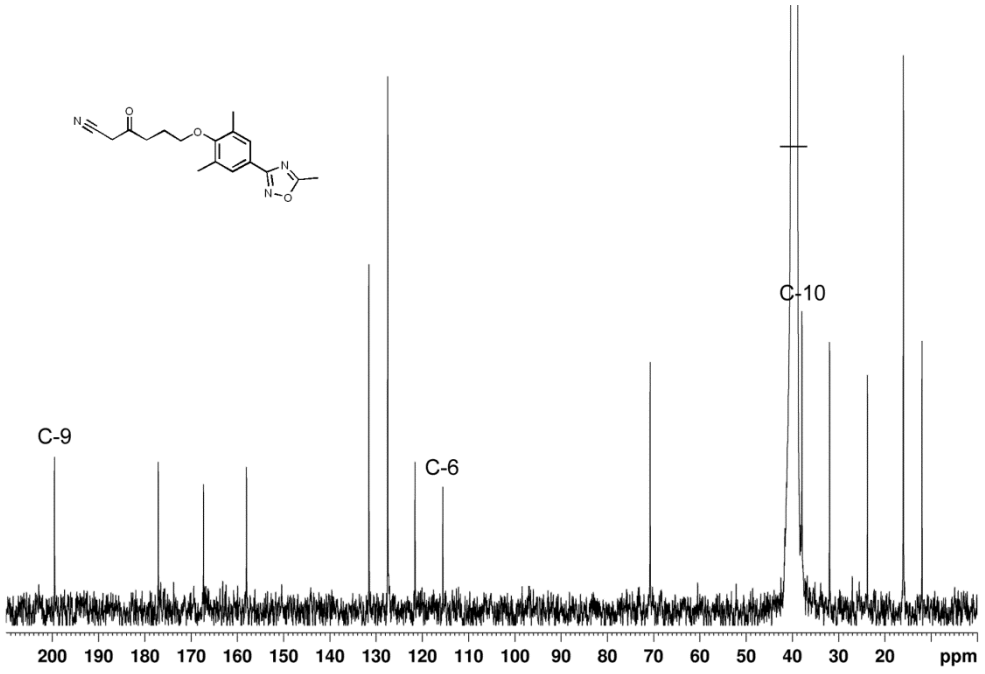


Figure S6. ^{13}C NMR spectrum of the ring-opening product β-keto nitrile derivative **3** in DMSO-d_6 at 30°C. Carbons C-6, C-9 and C-10 have been highlighted in the spectrum (see numbering in Scheme S2).