Supporting Information

Synthesis and Antimalarial Efficacy of Two-Carbon Linked Artemisinin-Derived Trioxane Dimers in Combination with Known Antimalarial Drugs

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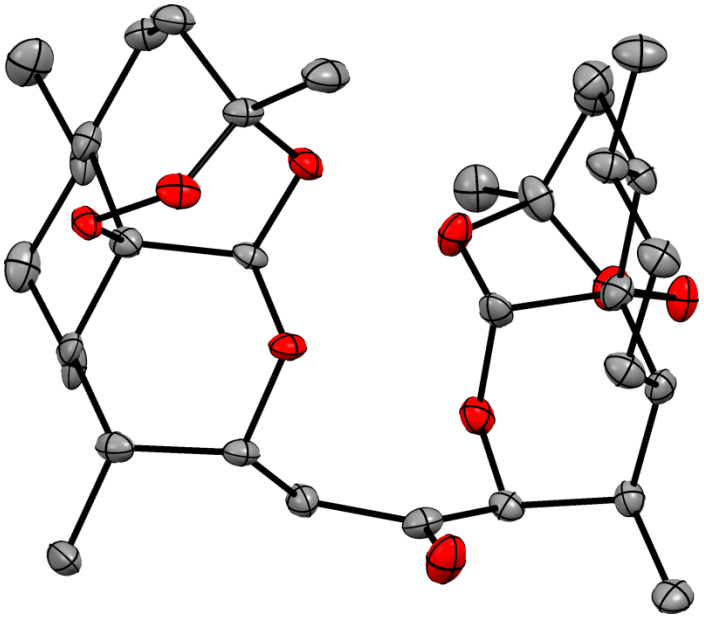
Figure S1 – Crystal structure of dimer ketone **24**



X-ray crystallography

All reflection intensities were measured at 110(2) K using a KM4/Xcalibur (detector: Sapphire3) with enhance graphite-monochromated Mo *K*α radiation (λ = 0.71073 Å) under the program CrysAlisPro (Version 1.171.35.11 Oxford Diffraction Ltd., 2011). The program CrysAlisPro (Version 1.171.35.11, Oxford Diffraction Ltd., 2011) was used to refine the cell dimensions. Data reduction was done using the program CrysAlisPro (Version 1.171.35.11, Oxford Diffraction Ltd., 2011). The structure was solved with the program SHELXS-97 (Sheldrick, 2008) and was refined on F^2 with SHELXL-97 (Sheldrick, 2008). Analytical numeric absorption corrections based on a multifaceted crystal model were applied using CrysAlisPro (Version 1.171.35.11, Oxford Diffraction Ltd., 2011). The temperature of the data collection was controlled using the system Cryojet (manufactured by Oxford Instruments). The H atoms (except when specified) were placed at calculated positions using the instructions AFIX 13, AFIX 23, or AFIX 137 with isotropic displacement parameters having values 1.2 or 1.5 times *U*eq of the attached C atoms.

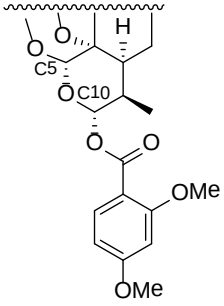
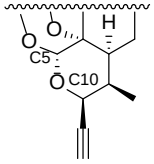
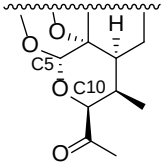
The structure is mostly ordered but the structure is built of channels along the *c* axis containing disordered solvent molecules; the contribution of the disordered species was then taken out using the program SQUEEZE for the final refinement. All details of the SQUEEZE refinement are

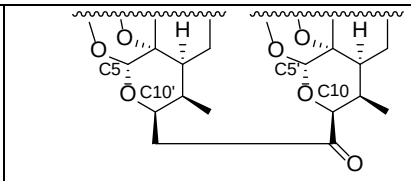
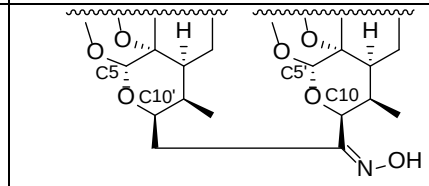
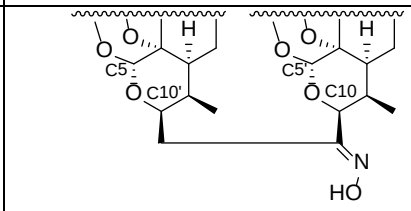
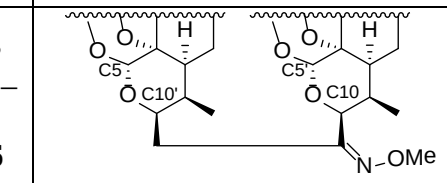
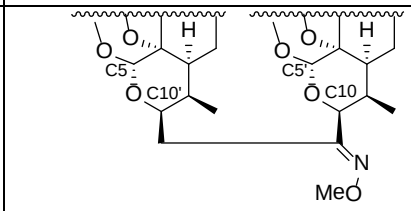
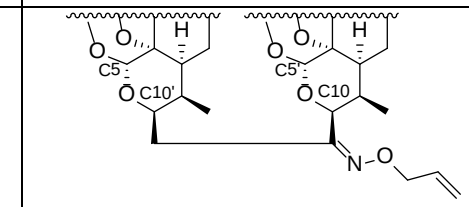
provided in the final CIF file. Because there were no significant anomalous scattering effects (data collection using Mo *K*α radiation and no element heavier than Si), the Flack parameter is indeterminate. Friedel pairs were merged. The absolute structure was assigned based on the known chirality of the target compound.

24, Fw = 576.70,* colorless lath, 0.77 × 0.15 × 0.14 mm^3, hexagonal, $P6_5$ (no. 170), a = 37.8319(8), c = 11.1225(2) Å, V = 13786(2) $Å^3$, Z = 18, D_x = 1.250 g cm^{-3},* μ = 0.090 mm^{-1},* abs. corr. range: 0.984–0.990. 49637 Reflections were measured up to a resolution of (sin $\theta/\lambda)_{max}$ = 0.59 $Å^{-1}$. 8525 Reflections were unique (R_{int} = 0.0587), of which 7406 were observed [$I > 2\sigma(I)$]. 1126 Parameters were refined with 1 restraint. $R1/wR2$ [$I > 2\sigma(I)$]: 0.0679/0.1636. $R1/wR2$ [all refl.]: 0.0762/0.1695. S = 1.077. Residual electron density found between −0.41 and 0.93 e $Å^{-3}$.

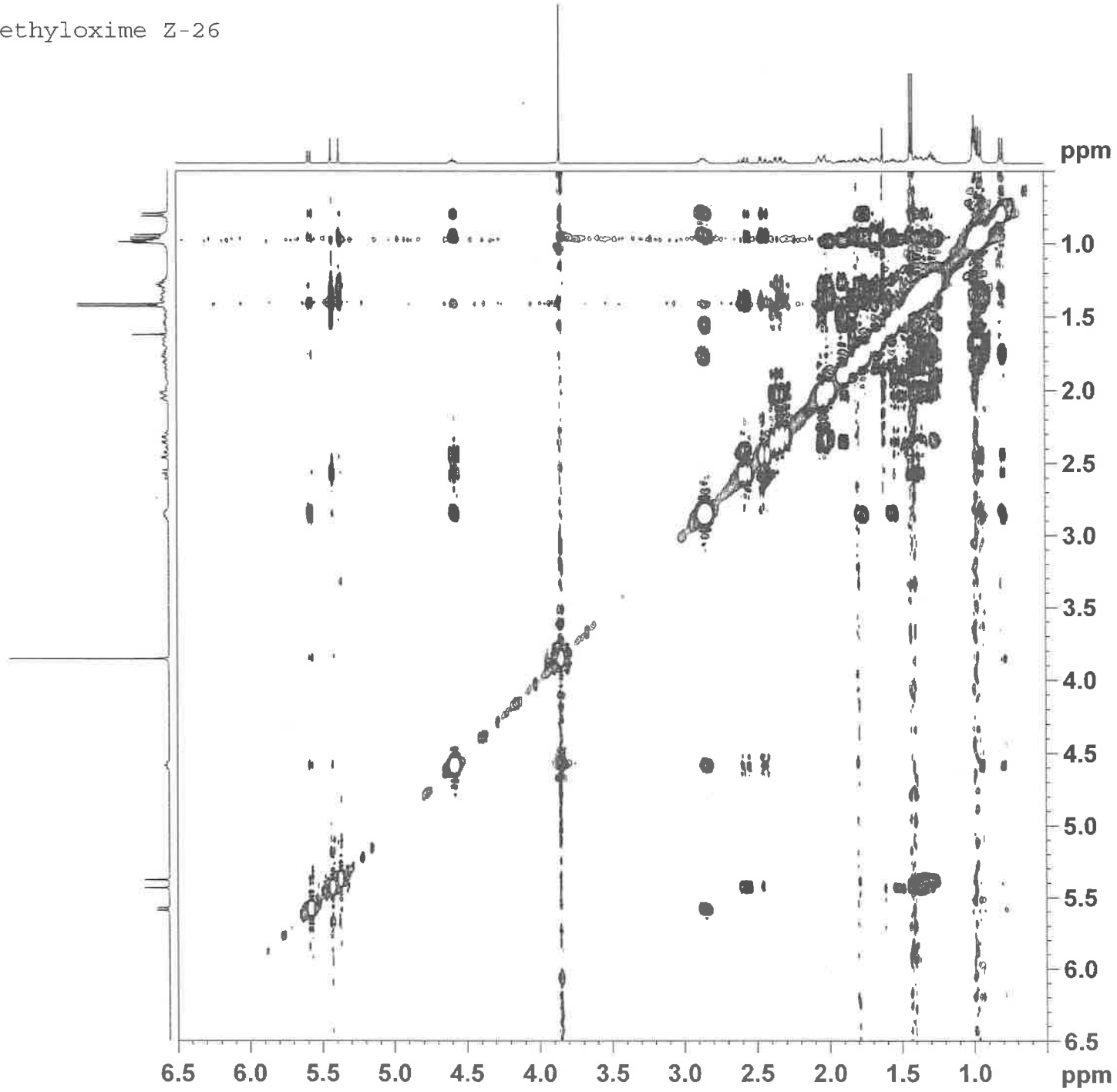
* excluding the contribution of the unresolved residual electron density

Table S1 – Relevant ^{1}H NMR chemical shifts and coupling constants for selected compounds:

Cmpd Info	Structure	C5 δ	C5' δ	C10 δ	J_{C10}	C10' δ	J_{C10}'
20		5.47	-	5.96	9.8 Hz	-	-
21		5.56	-	4.73	5.7 Hz	-	-
22		5.65	-	4.75	6.8 Hz	-	-

24		5.57	5.30	4.57	6.3 Hz	4.84	9.5 Hz 6.2 Hz 3.8 Hz
Less polar – ***Z*-25**		5.39	5.37	5.68	6.9 Hz	4.53	9.1 Hz 5.9 Hz 3.3 Hz
More polar – ***E*-25**		5.50	5.42	5.17	6.4 Hz	4.60	m
Less polar – ***Z*-26**		5.41	5.35	5.56	6.9 Hz	4.55	8.9 Hz 5.9 Hz 4.4 Hz
More polar – ***E*-26**		5.62	5.35	5.09	6.4 Hz	4.58	buried
27		5.40	5.36	5.63	6.9 Hz	4.56	buried

methyloxime Z-26



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RG	256
DW	122.400 usec
DE	6.50 usec
TE	298.8 K
D0	0.00010674 sec
D1	1.00000000 sec
D8	0.30000001 sec
IN0	0.00024480 sec
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ND0	1
TD	256
SFO1	400.1318 MHz
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GB	0
PC	1.00
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WDW	QSINE
SSB	2
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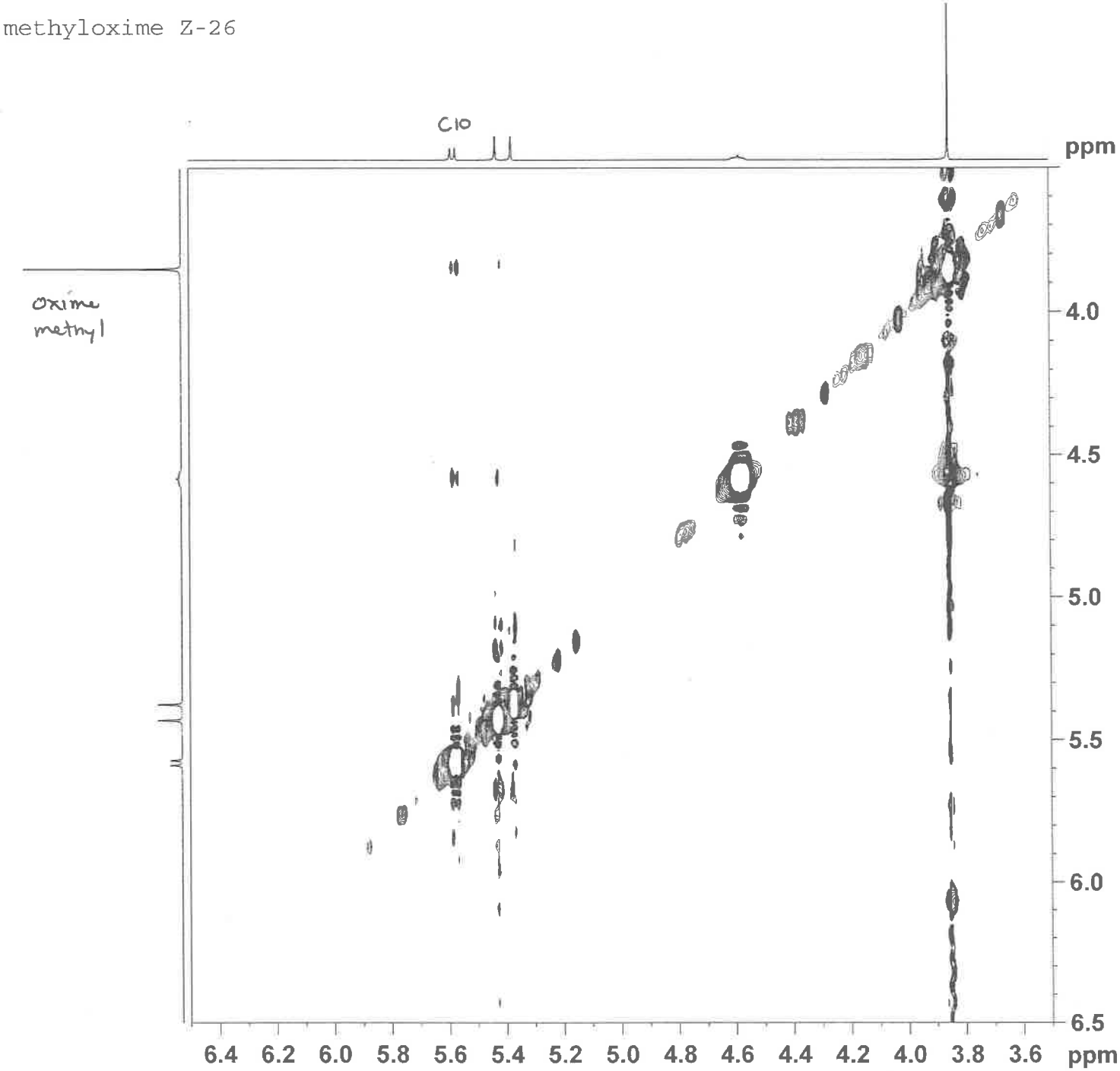
methyloxime Z-26



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TD	2048
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DS	4
SWH	4084.967 Hz
FIDRES	1.994613 Hz
AQ	0.2507252 sec
RG	256
DW	122.400 usec
DE	6.50 usec
TE	298.8 K
D0	0.00010674 sec
D1	1.00000000 sec
D8	0.30000001 sec
IN0	0.00024480 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	12.30 usec
PL1	-4.00 dB
PL1W	23.34542084 W
SFO1	400.1318419 MHz
ND0	1
TD	256
SFO1	400.1318 MHz
FIDRES	15.956903 Hz
SW	10.209 ppm
FnMODE	States-TPPI
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SSB	2
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GB	0
PC	1.00
SI	1024
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WDW	QSINE
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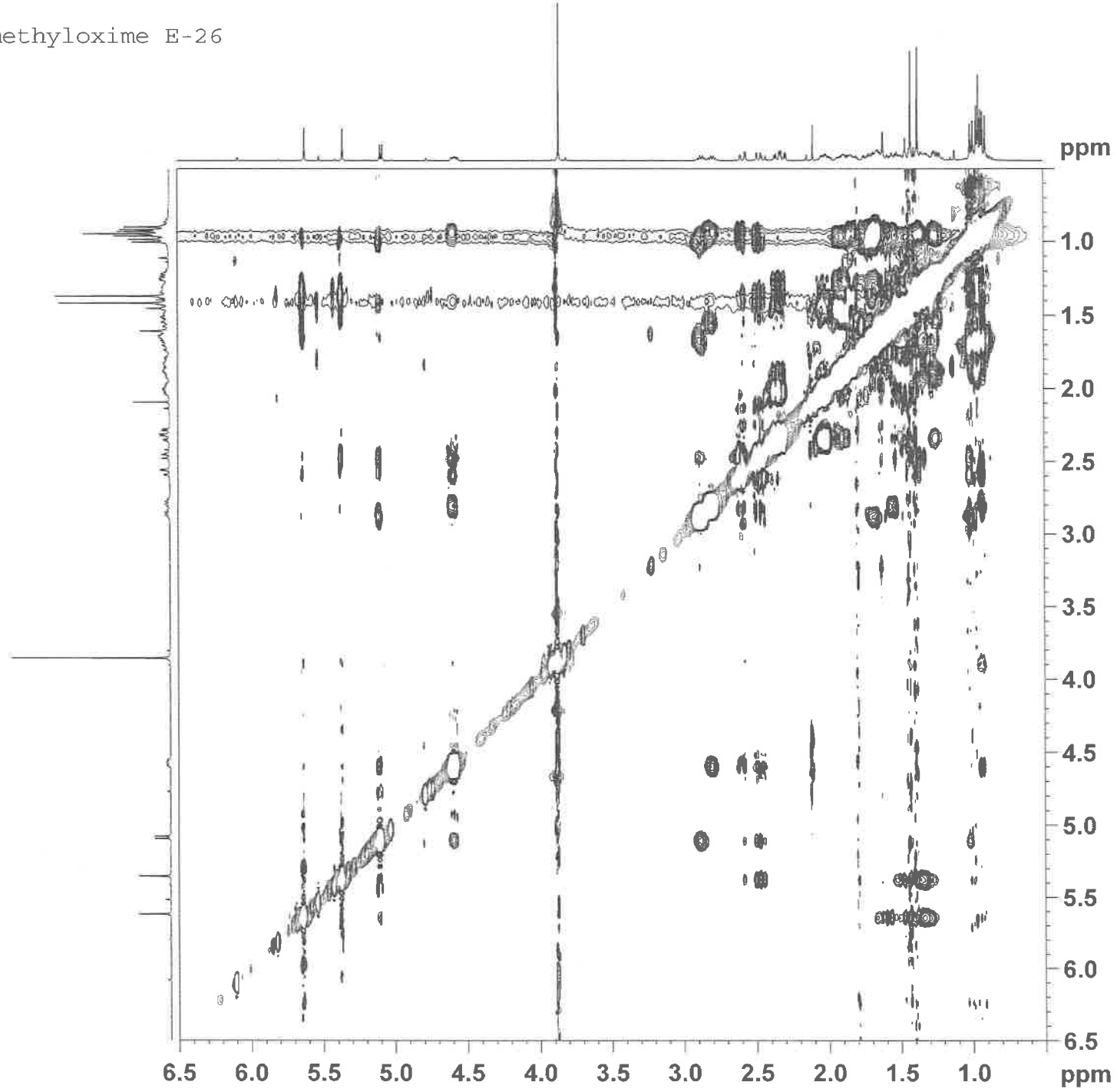
methyloxime E-26



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TD	2048	
SOLVENT	CDCl3	
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SWH	4084.967	Hz
FIDRES	1.994613	Hz
AQ	0.2507252	sec
RG	256	
DW	122.400	usec
DE	6.50	usec
TE	298.8	K
D0	0.00010674	sec
D1	1.00000000	sec
D8	0.30000001	sec
IN0	0.00024480	sec
======== CHANNEL f1 ========		
NUC1	1H	
P1	12.30	usec
PL1	-4.00	dB
PL1W	23.34542084	W
SFO1	400.1318419	MHz
ND0	1	
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SFO1	400.1318	MHz
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PC	1.00	
SI	1024	
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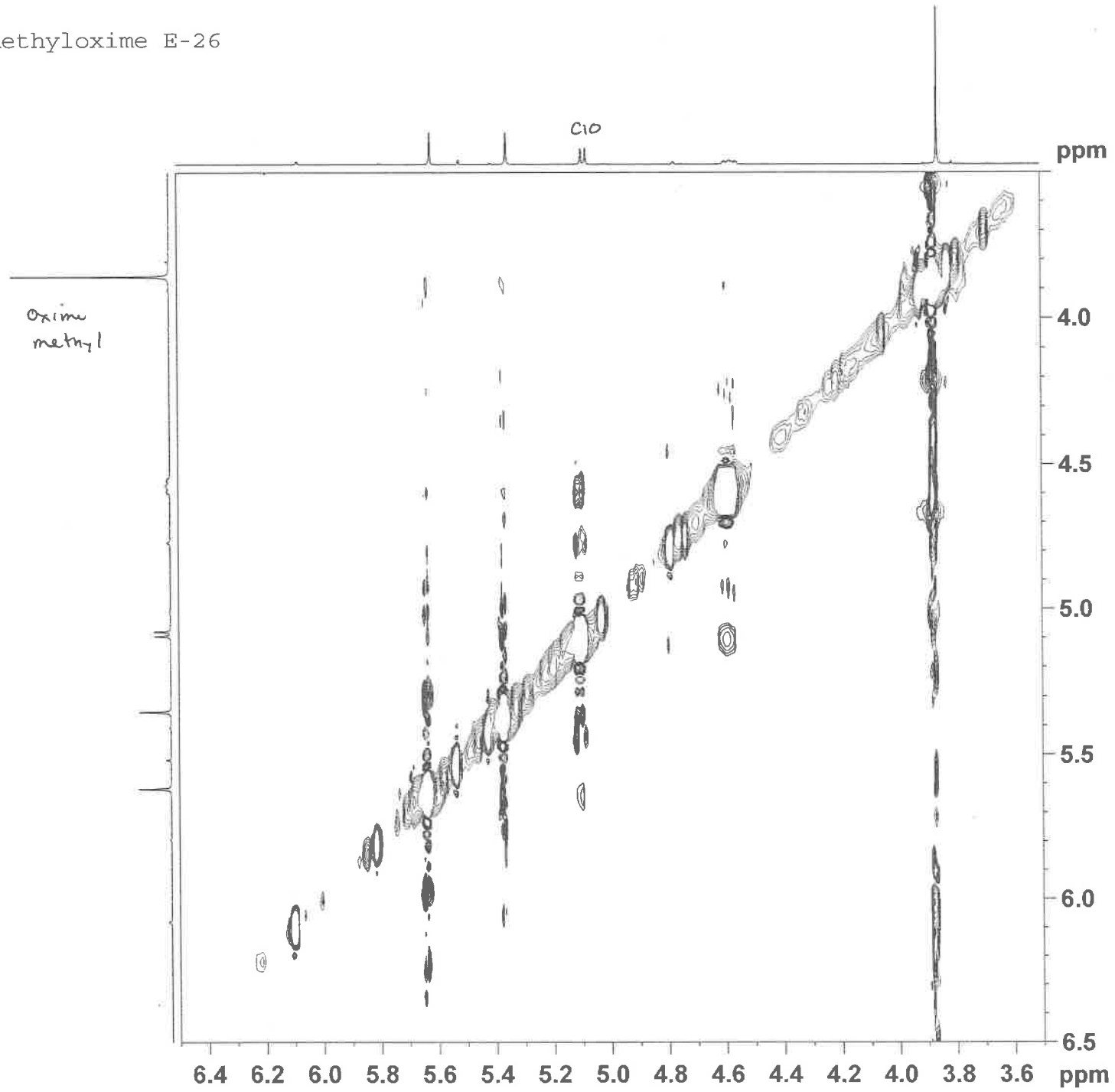
methyloxime E-26



BRUKER

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TD	2048	
SOLVENT	CDCl3	
NS	16	
DS	4	
SWH	4084.967	Hz
FIDRES	1.994613	Hz
AQ	0.2507252	sec
RG	256	
DW	122.400	usec
DE	6.50	usec
TE	298.8	K
D0	0.00010674	sec
D1	1.00000000	sec
D8	0.30000001	sec
IN0	0.00024480	sec
======== CHANNEL f1 ========		
NUC1	1H	
P1	12.30	usec
PL1	-4.00	dB
PL1W	23.34542084	W
SFO1	400.1318419	MHz
ND0	1	
TD	256	
SFO1	400.1318	MHz
FIDRES	15.956903	Hz
SW	10.209	ppm
FnMODE	States-TPPI	
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SF	400.1300000	MHz
WDW	QSINE	
SSB	2	
LB	0.00	Hz
GB	0	
PC	1.00	
SI	1024	
MC2	States-TPPI	
SF	400.1300000	MHz
WDW	QSINE	
SSB	2	
LB	0.00	Hz
GB	0	