Supporting Information for:

Synthetic Human Serum Albumin Sudlow I Binding Site Mimics

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STANDARD PROTON PARAMETERS

Fig. S1 Warfarin 34 mM in CDCl3+TMS

Unknown NMR (500 MHz,) δ 9.49 (s), 7.94 (d, *J* = 7.9 Hz), 7.89 (d, *J* = 7.9 Hz), 7.80 (d, *J* = 8.1 Hz), 7.61 – 7.52 (m), 7.49 (t, *J* = 7.8 Hz), 7.39 – 7.14 (m), 4.70 (dd, *J* = 10.1, 2.1 Hz), 4.28 (dd, *J* = 6.8, 3.3 Hz), 4.16 (dd, *J* = 11.4, 6.9 Hz), 3.85 (dd, *J* = 19.4, 10.1 Hz), 3.49 (d, *J* = 0.7 Hz), 2.29 (s), 2.16 (s), 2.07 – 1.95 (m), 1.70 (s), 1.67 (s), 1.61 (s).

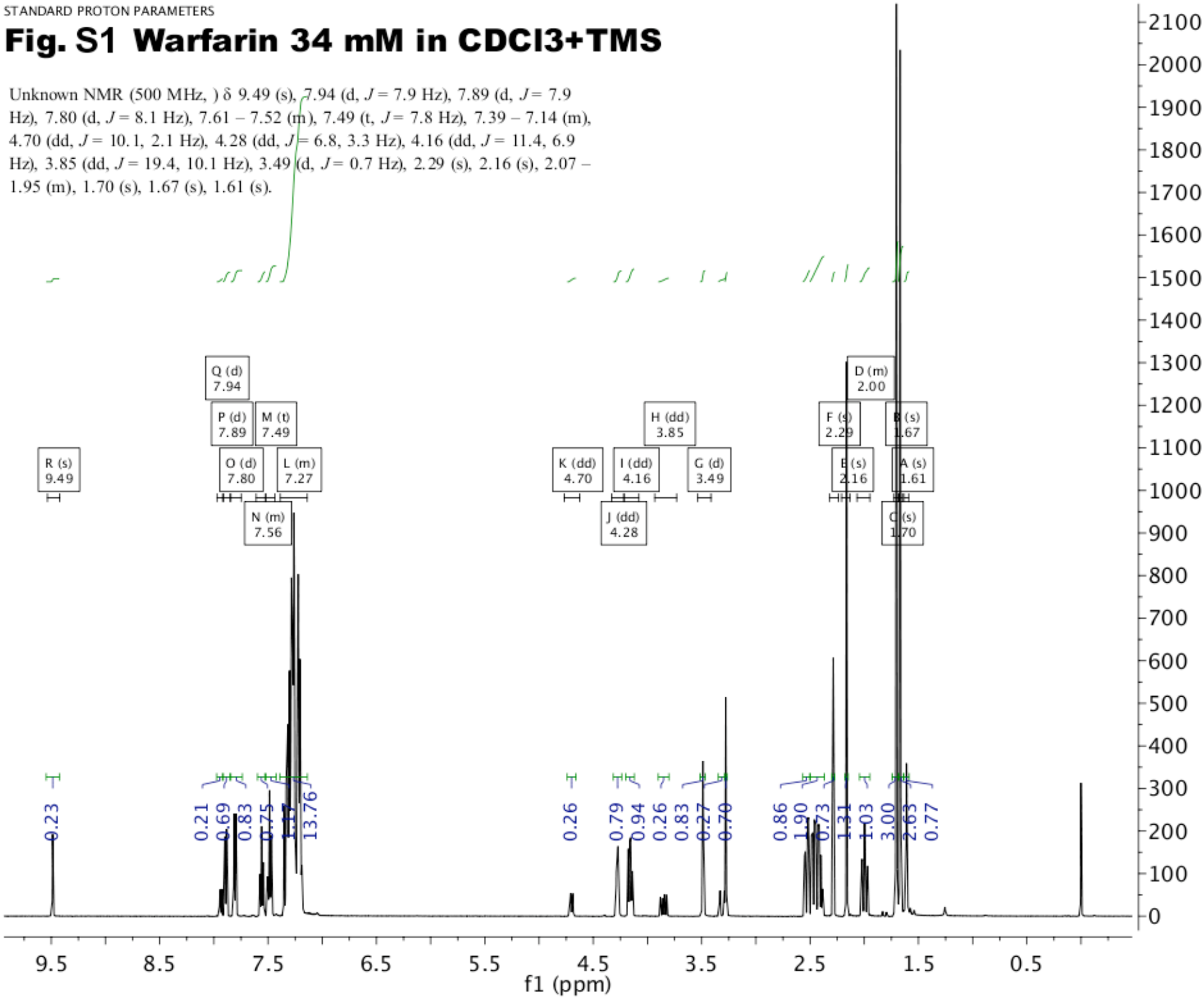


Fig. S2 Warfarin 34 mM in CDCl3+TMS, COSY

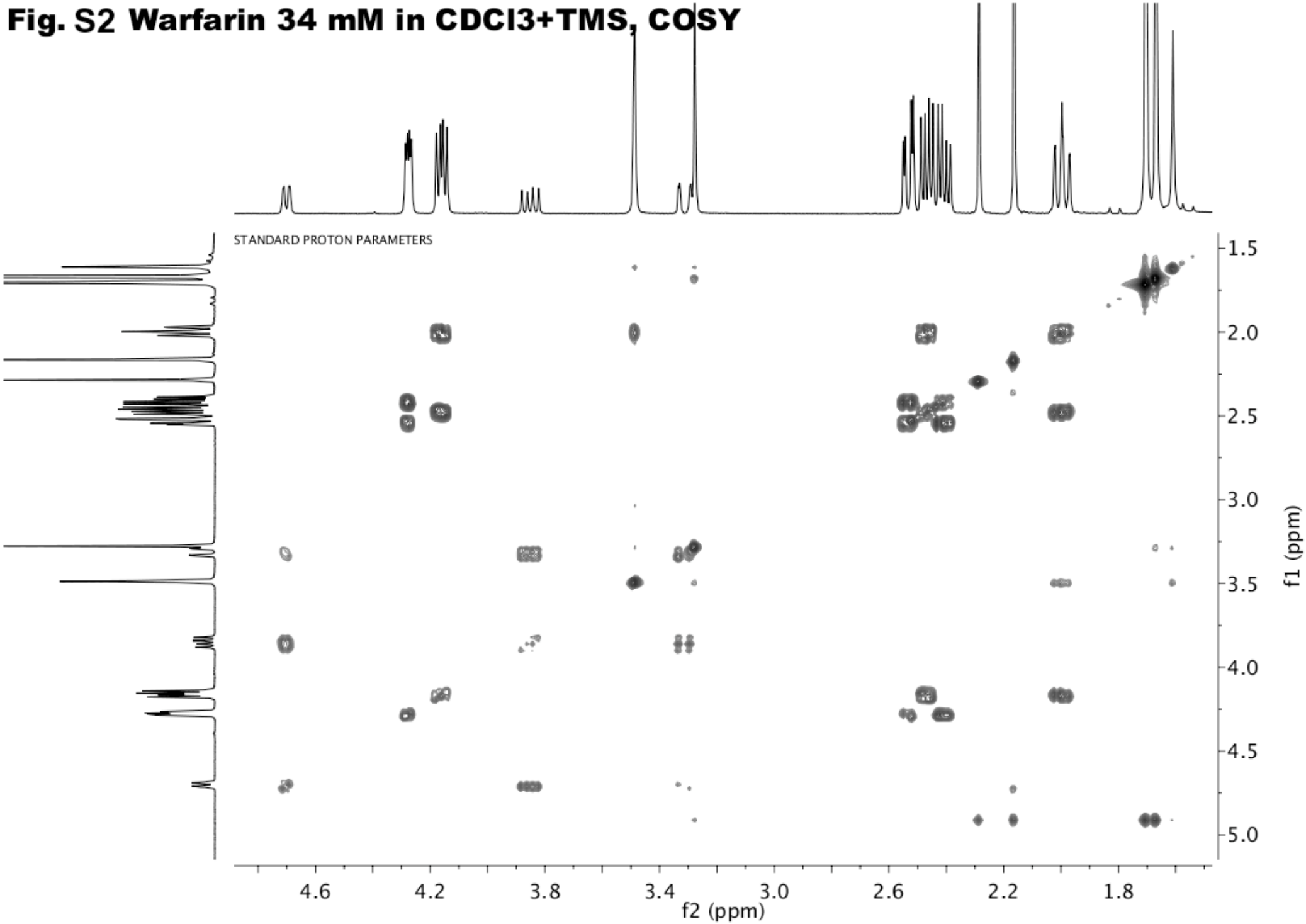
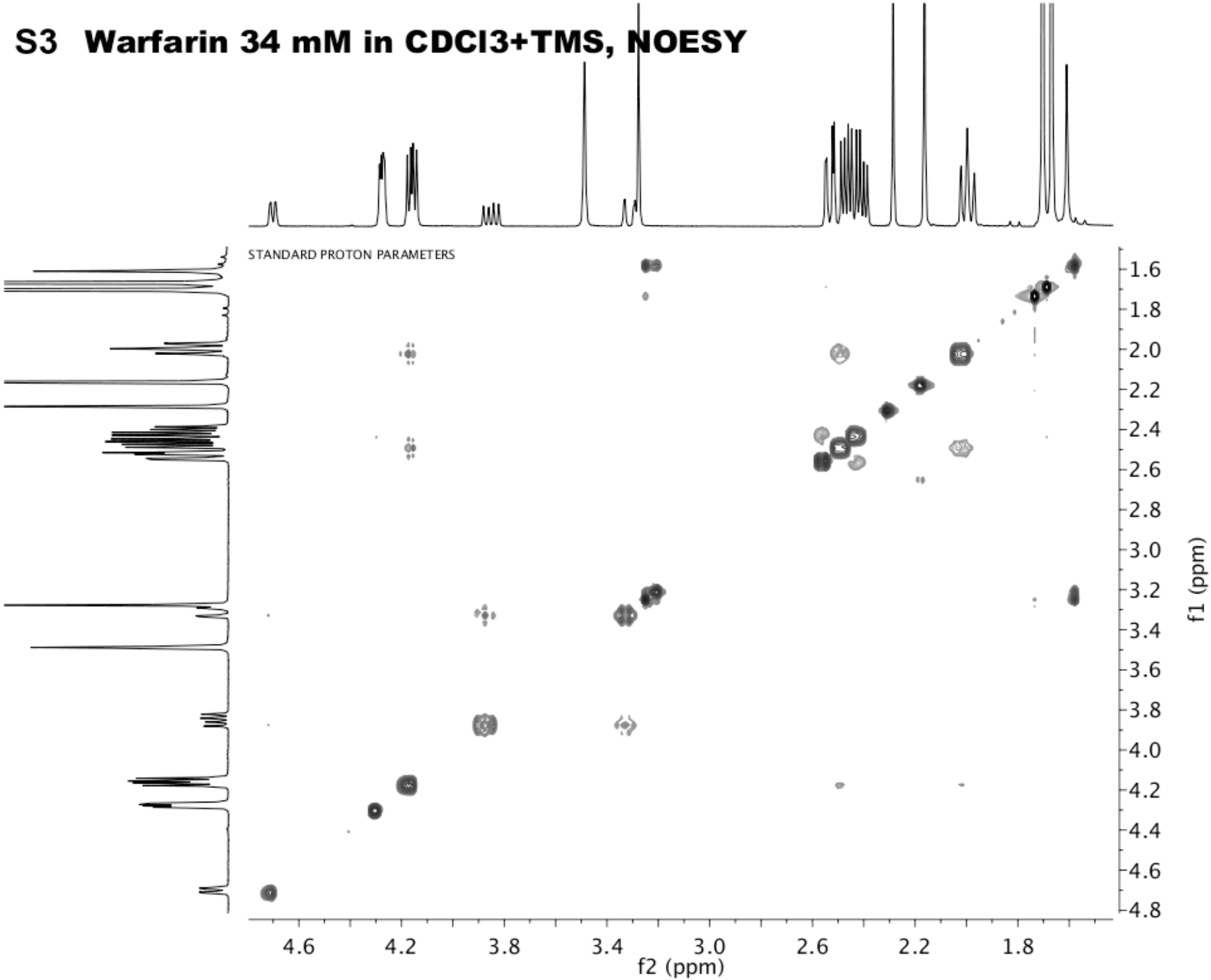


Fig. S3 Warfarin 34 mM in CDCl3+TMS, NOESY



NMR Titration Experiments

Warfarin Protons Studied by NMR

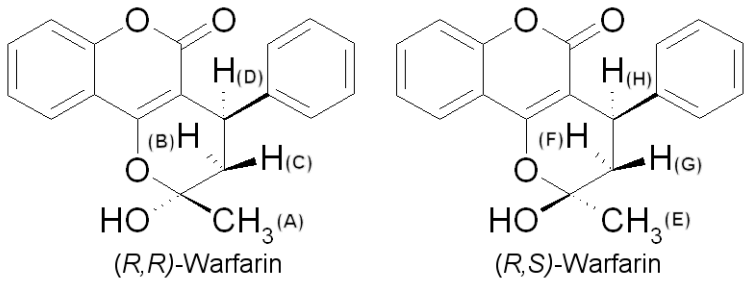


Fig. S4 Schematic representation of the major (here drawn as (*R,R*)-warfarin) and minor ((*R,S*)-warfarin) cyclic hemiketal isomers of warfarin studied by ^{1}H NMR spectroscopy in chloroform-d. For clarity, protons not included in the analysis have been omitted in this figure.

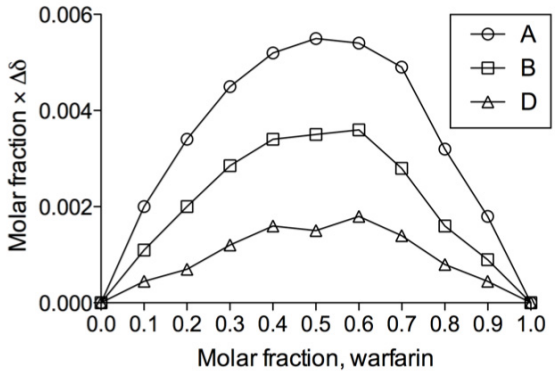


Fig. S5 Continuous variation study (Job plot) demonstrating complex optima for complex stoichiometries from changes in the chemical shifts, Δδ, of the protons A, B and D of the major cyclic hemiketal (*see* Fig. S4), of warfarin in $CDCl_3$

Titration Data

TABLE S1: ^{1}H NMR spectroscopic titrations performed at 298 K in chloroform-d. Protons studied have been named as presented in Fig. S4. Only changes in the chemical shifts, δ, following a non-linear one-site binding model are presented.

Isomer[a]	Monomer	^{1}H	K_D (M)	B_{max} (Δδ, ppm)	R^2
major	acetic-d_3-acid-d	A	0.434 ± 0.032	0.017 ± 0.000	0.99
major	pyridine-d_5	A	0.347 ± 0.034	0.059 ± 0.002	0.99
		C	0.176 ± 0.022	0.019 ± 0.001	0.98
		D	0.217 ± 0.018	0.139 ± 0.004	0.99
minor	pyridine-d_5	H	0.428 ± 0.028	0.178 ± 0.005	0.99

[a] The open side chain isomer of warfarin has been omitted from this table due to the low degree of warfarin-monomer complexation, upon additions of acetic-d_3-acid-d or pyridine-d_5.

Molecular Dynamics (MD)

System Design and Methodology

The isomeric distribution of warfarin chosen in the these mixtures was estimated from the results of ^{1}H NMR spectroscopic experiments (approximating an observed stoichiometry of 15, 40 and 45% of the WOP (open side chain), WMI (minor cyclic hemiketal) and WMA (major cyclic hemiketal) isomeric forms of warfarin), Table S2, and using the template-functional monomer stoichiometric concentrations approximating a typical MIP protocol.

A periodic boundary condition was imposed upon the system and the final equilibrated cubic boxes had volumes of 40.3^3 Å^3 in the case of the acetic acid system and 47.2^3 Å^3 in the case of 4-vinyl pyridine.

TABLE S2: System design and the molecular dynamics methodology applied.

	Number of molecules								
System	WOP	WMA	WMI	AcOH	4VP	$CHCl_3$	Eq. (ps)[a]	Prod. (ps)	Cut-off (Å)
AcOH	3	7	9	267	-	249	20 + 250	5000	9
4VP	3	7	8	-	218	444	20 + 280	5000	9

[a] The equilibration phase was divided into two parts of which the first involved a process of heating the system from 0 to 293 K (NVT) followed by a longer equilibration step at NPT (293 K, 1 bar) to assure stable value in density.

Thermodynamic Data for the System Studied

TABLE S3: Thermodynamic data for the different systems studied.

			Energies (kcal/mol)			
System	Temp. (K)	ρ (g/cm^3)	E_{POT}	E_{KIN}	E_{TOT}	Volume (Å^3)
AcOH	293.1 ± 4.0	1.32	-17766.8 ± 48.9	3200.9 ± 43.2	-14565.9 ± 66.0	40.3×40.3×40.1
4VP	293.1 ± 3.2	1.28	-9113.9 ± 56.2	4881.4 ± 52.9	-4232.5 ± 76.9	47.2×47.2×47.2

Grid Density Pictures
AcOH-warfarin

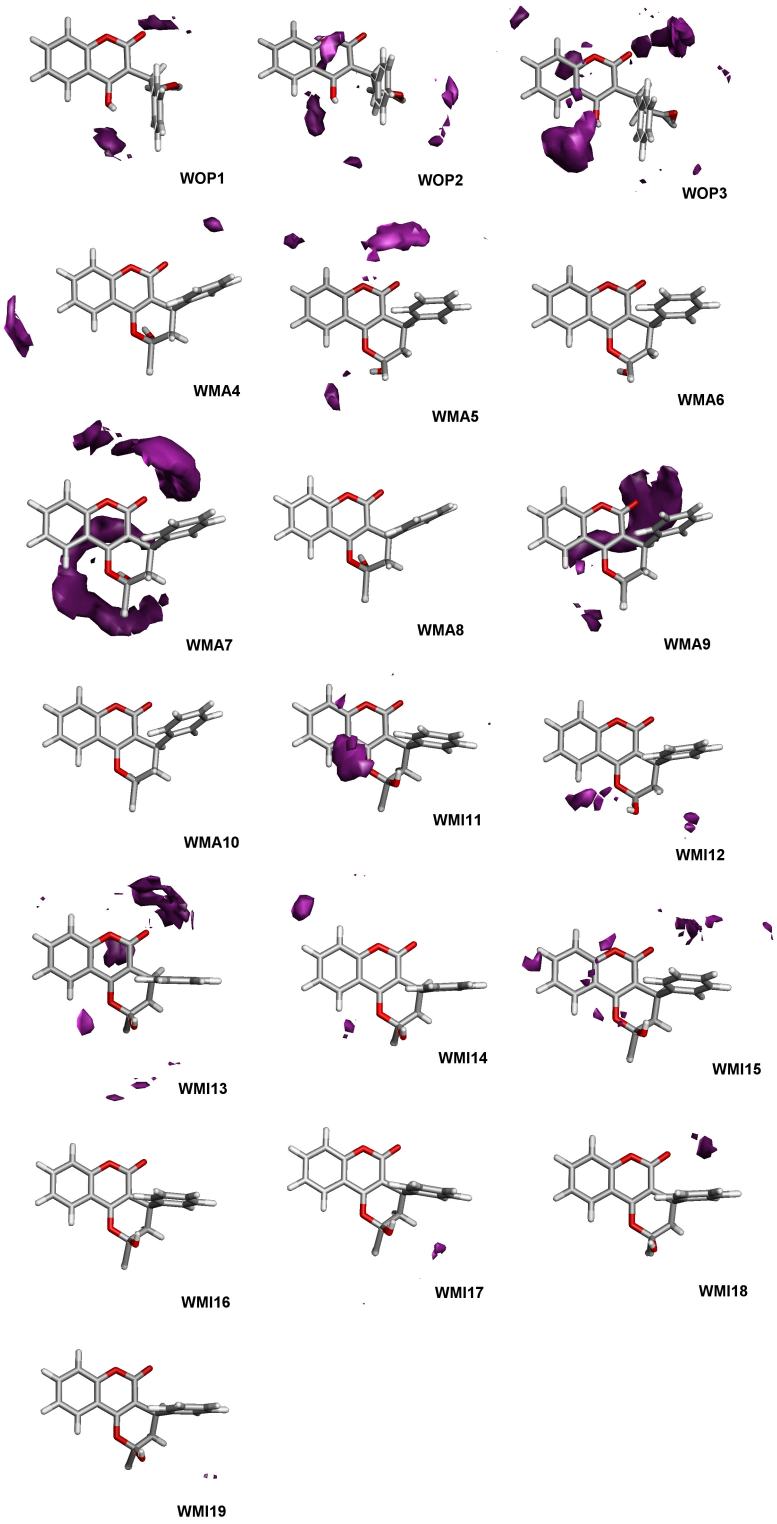


Fig. S6 The AcOH-warfarin 5 ns MD simulation at 293 K in chloroform. Contour grids representing the probability of finding the ***C1 atom*** of the carboxylic functionality in AcOH are plotted in solid surfaces (purple) at the contour level 30. See section *System design and methodology*, page S5, for explanation of the warfarin isomers studied.

4VP-warfarin

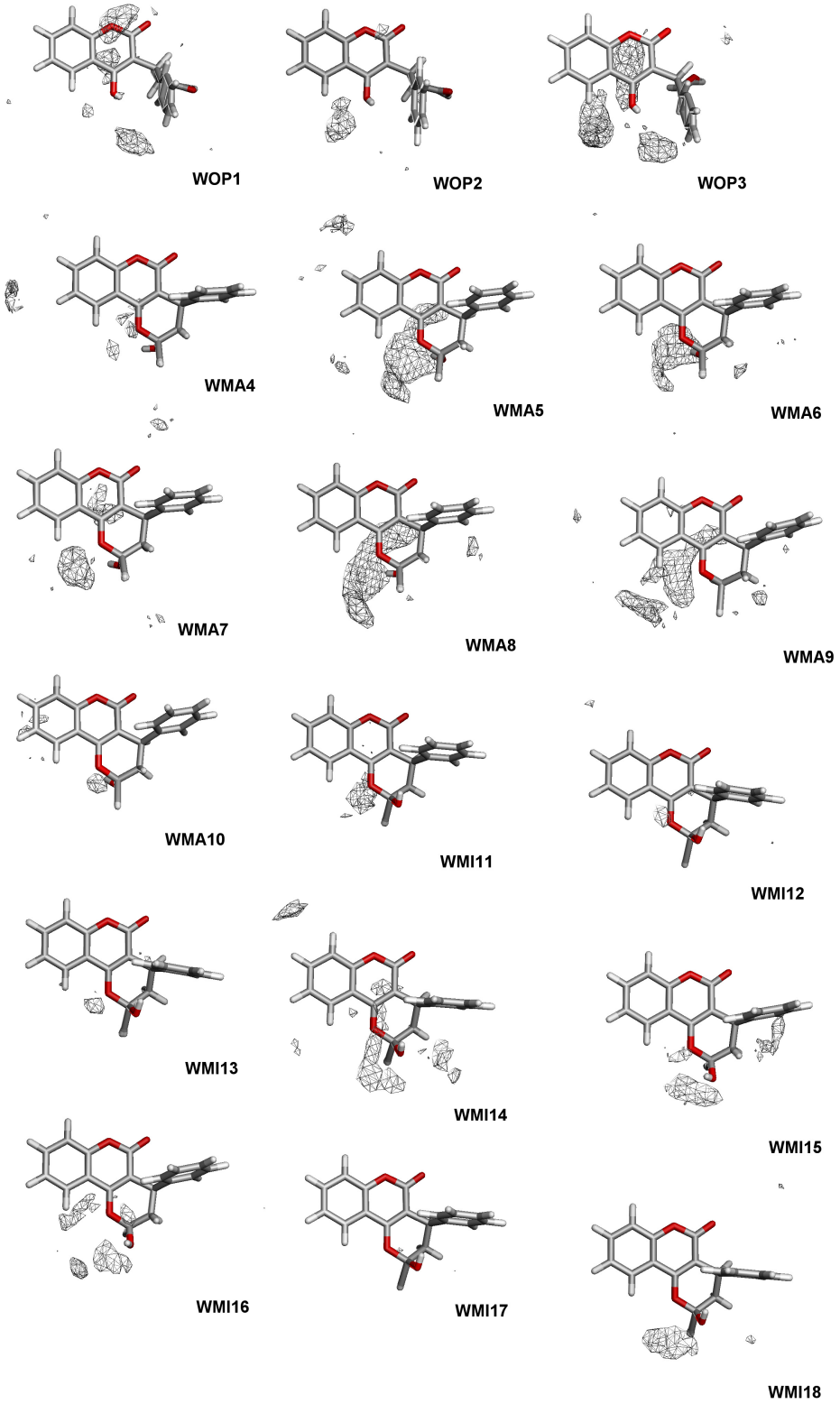


Fig. S7 The 4VP-warfarin 5 ns MD simulation at 293 K in chloroform. Contour grids for the probability of finding the ***N atom*** of the 4-vinylpyridine molecule around warfarin are plotted in mesh surfaces at the contour level 30. See section *System design and methodology*, page S5, for explanation of the warfarin isomers studied.

FT-IR – Diffuse Reflectance Polymer Spectra

MAA-Polymers

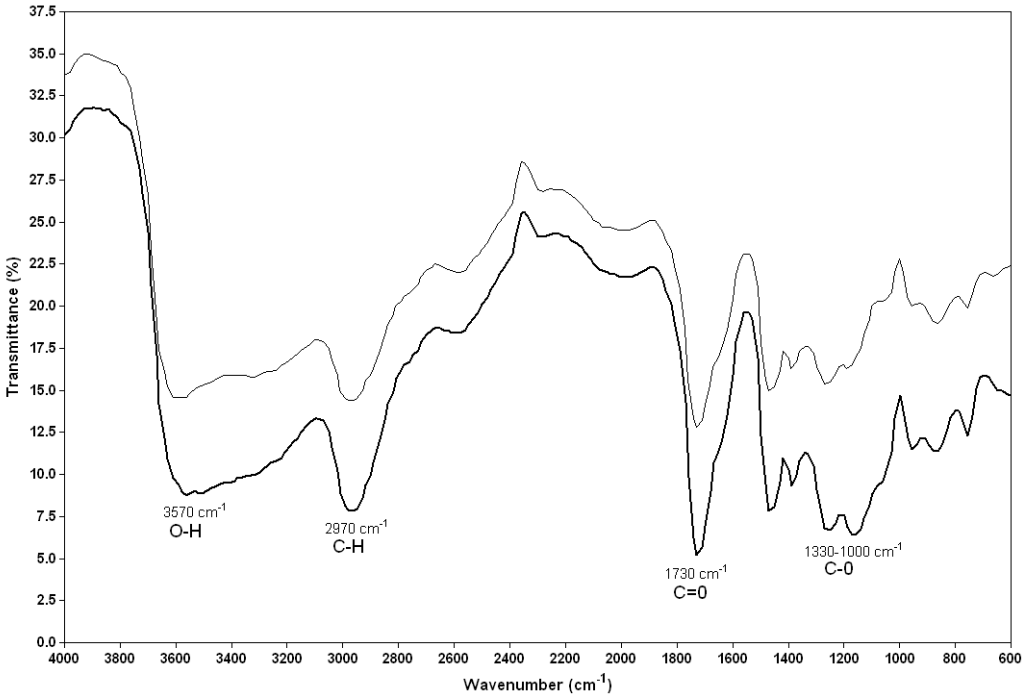


Fig. S8 FT-IR diffuse reflectance spectra of 50 mg of dry MAA-polymers in KBr. The MIP spectrum corresponds to the bold line (**—**) and the REF polymer spectrum is here represented by a thin line (—).

4VP-Polymers

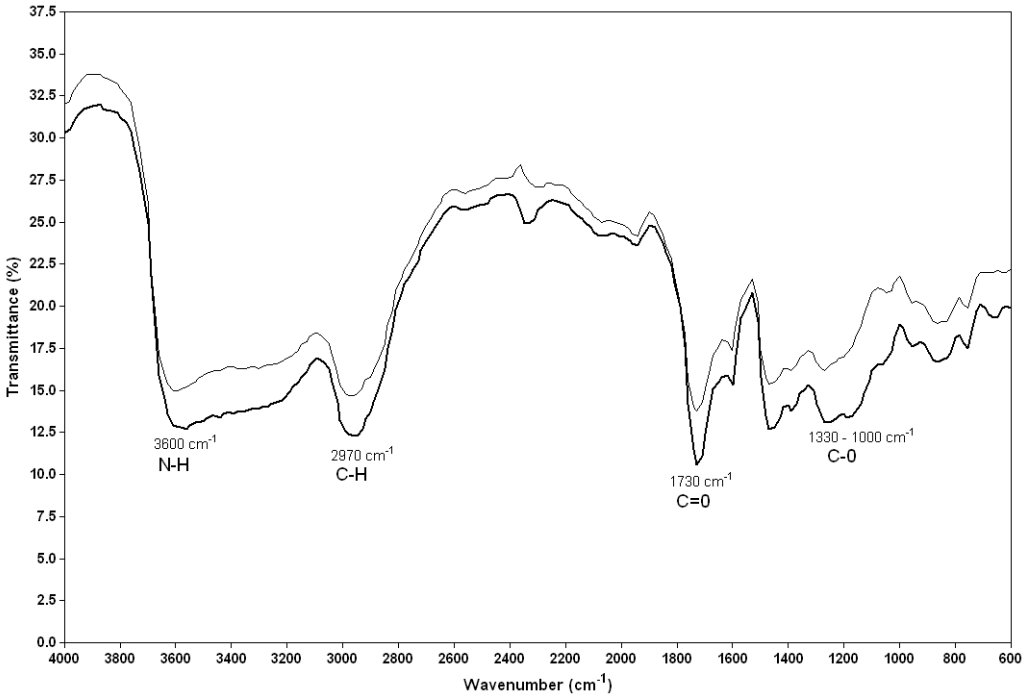


Fig. S9 FT-IR diffuse reflectance spectra of 50 mg of dry 4VP-polymers in KBr. The MIP spectrum corresponds to the bold line (**—**) and the REF polymer spectrum is here represented by a thin line (—).

Scanning Electron Microscopy (SEM)
MAA-polymers

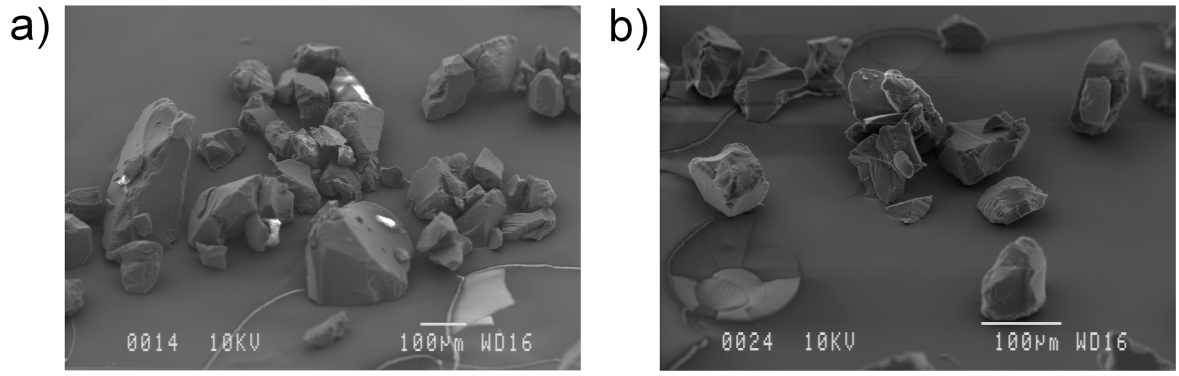


Fig. S10 SEM pictures of the MAA-polymers showing the a) MIP and b) the REF polymer particles.

Kinetic Studies
Raw data

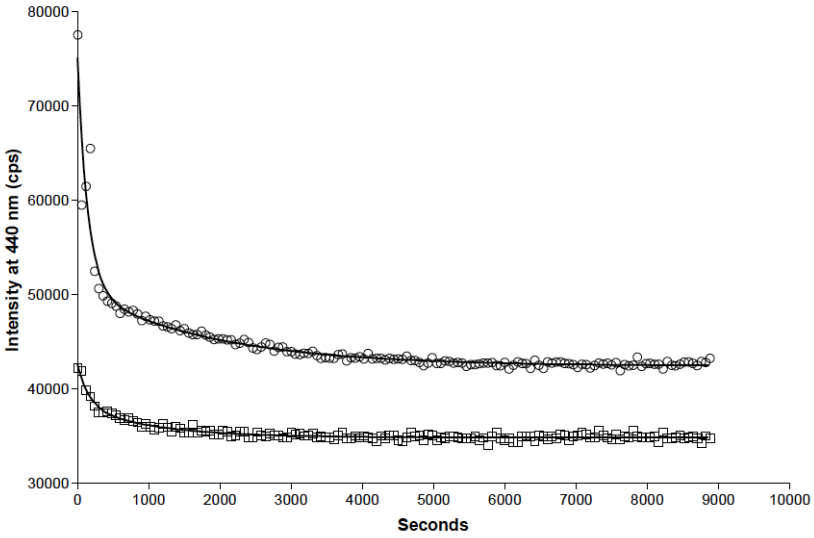


Fig. S11 Fluorescence spectroscopic time-based scans performed at 293 K. The sample signal is monitored as a function of time while both the excitation (295 nm) and emission (440 nm) wavelengths remain fixed. The scans were collected at 1-minute intervals immediately after addition of warfarin (0.5 µM) to the polymeric solutions (0.5 mg mL^{-1}) containing either MAA-MIP (□) or MAA-REF(○). Data analysis was performed using a two-site exponential decay model.

Fitted data

TABLE S4: Warfarin-MAA-polymer interaction rate constants, k_1 and k_2 ($\times 10^{-3}$ s^{-1}), calculated using a two phase exponential decay model (R^2>0.94). Rate constants are presented as mean ± standard error of the mean.

	k_1	k_2
MAA-REF	0.96 ± 0.12	6.2 ± 1.13
MAA-MIP	0.54 ± 0.076	7.0 ± 0.66