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Single-scan Ultra-selective 1D Total Correlation Spectroscopy

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1. Experimental details

NMR experiments were carried out using a 500 MHz Varian/Agilent VNMRS spectrometer with a triple resonance HCN probe. Example data including pulse programs and macros used are available from our website (https://nmr.chemistry.manchester.ac.uk). Raw experimental data are available at DOI: 10.17632/5tk4nx45cc.1. The GEMSTONE-TOCSY pulse program was derived from the standard zTOCSY pulse program and our recently developed code for the GEMSTONE experiment. The following typical parameters were used in the GEMSTONE-TOCSY experiments. Adiabatic swept frequency pulses were WURST-40 waveforms with τ_p = 100 ms, bw = 2.5 kHz, and G_1 = 0.25 G cm^{-1}. The duration of the adiabatic pulses (τ_p) was adjusted between 50 and 150 ms for the selectivity needed. Power levels of the WURST-40 pulses were calculated for an adiabaticity factor (Q) of 11. The experiment was automated using the VnmrJ software tools for on-the-fly waveform generation and parameter update. No additional phase cycling is needed for the GEMSTONE, the minimum number of scans is identical to that for the parent zTOCSY pulse program. The band-selective refocusing pulse in GEMSTONE was typically an 18.5 ms RSNOB, which corresponds to an effective bandwidth of 100 Hz, and was flanked by gradient pulses (1 ms, 8-12 G cm^{-1}) to enforce the desired coherence transfer pathway (CTP) without the need for additional phase cycling. The TOCSY mixing time was set to 50 or 100 ms, and DIPSI-2 mixing and zero-quantum suppression were employed as implemented in standard VnmrJ library experiments. User control was added to facilitate automated update of the pulses used for zero-quantum suppression.

The amikacin sample concentration was 17 mM in D_2O. The cinchona alkaloid mixture contained 100 mM each of quinine, quinidine and cinchonidine in DMSO-d_6. The mixture of

hesperidin and naringin contained 70 and 90 mM respectively in DMSO-d_6. All chemicals were used as supplied without any further purification.

2. Example: alkaloid mixture

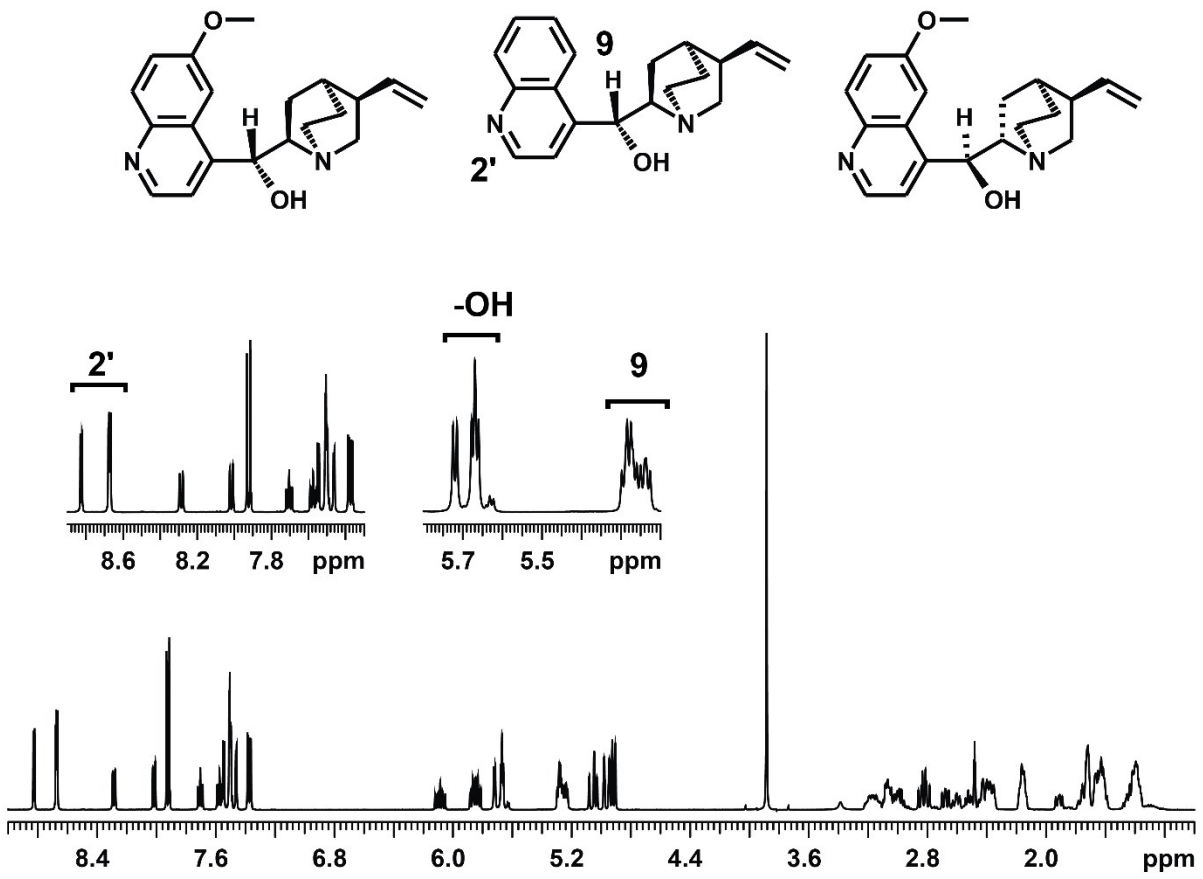

Fig. S1 ^{1}H NMR spectrum of a cinchona alkaloid mixture in DMSO-d_6. Severe signal overlap can be seen in all parts of the spectrum. The aromatic protons of quinine and quinidine are barely resolved, and similarly the aliphatic protons overlap severely for quinine and cinchonidine.

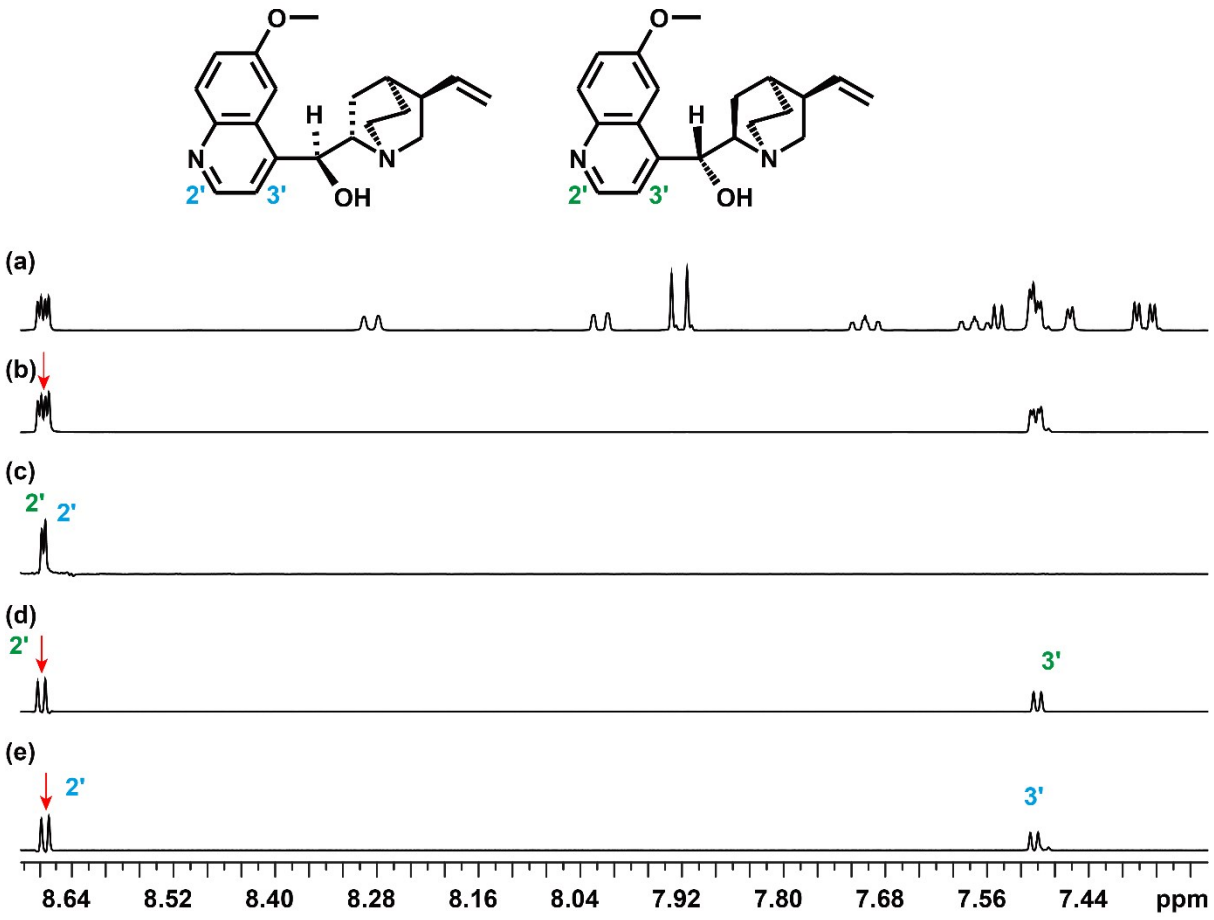

Fig. S2 (a) Aromatic region of the ^{1}H NMR spectrum of the cinchona alkaloid mixture in DMSO-d_6. (b) Conventional selective 1D TOCSY spectrum in which selective excitation (at the frequency indicated by the arrow) is not sufficient to separate the two overlapping doublets of quinine (green) and quinidine (blue) H-2' protons. (c) Semi-real-time pure shift NMR spectrum providing an accurate measurement of the chemical shifts of proton 2' in only 5 s. The chemical shift difference in this example is 2.1 Hz. (d-f) GEMSTONE-TOCSY spectra selectively observing the two TOCSY spectra corresponding to quinine and quinidine by setting the transmitter frequency (indicated by the arrow) on a signal of interest identified in the pure shift spectrum. The TOCSY mixing time was 60 ms in all experiments.

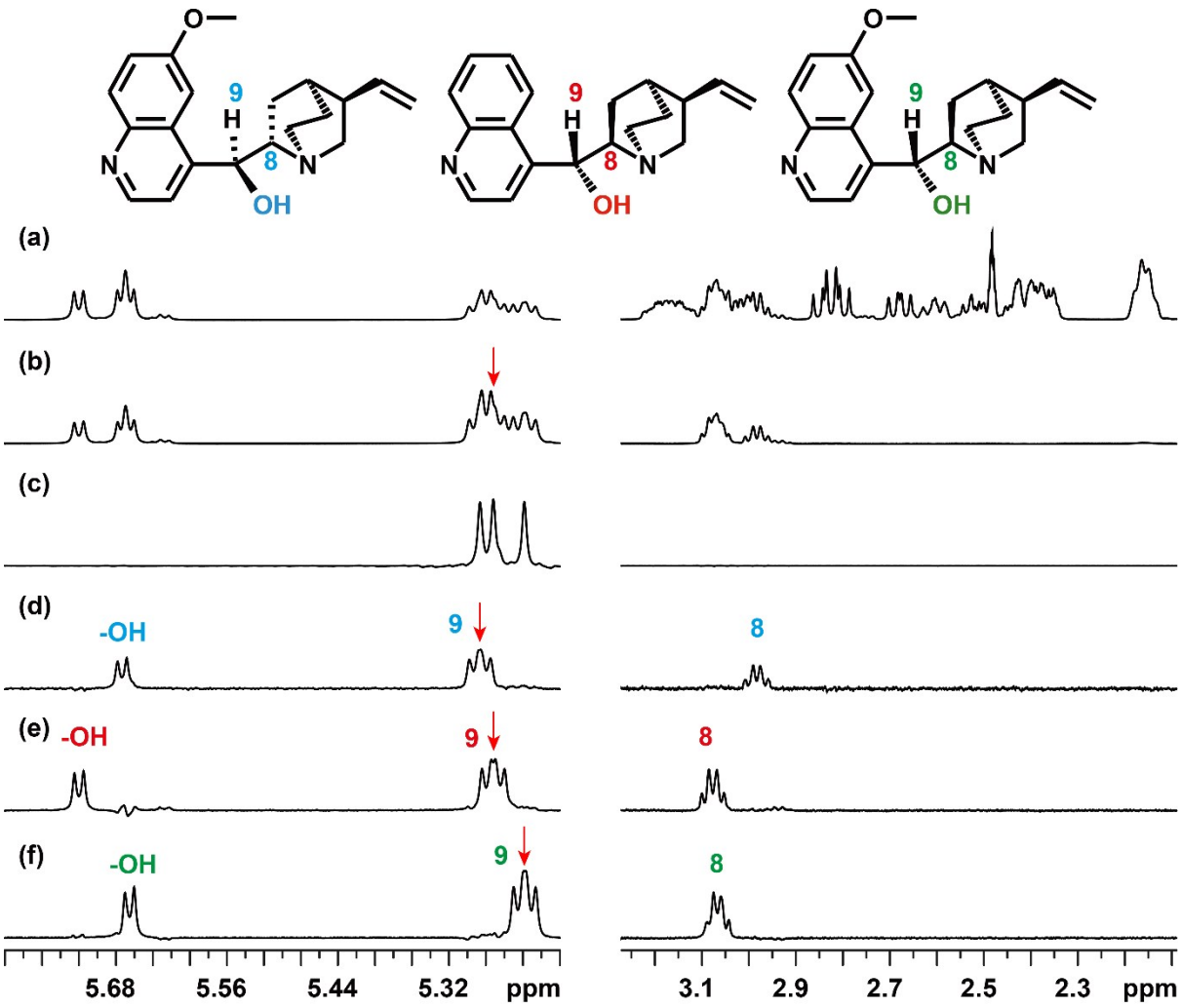

Fig. S3 (a) Selected regions of the ^{1}H NMR spectrum of the cinchona alkaloid mixture in DMSO-d_6. (b) Conventional selective 1D TOCSY spectrum in which selective excitation (at the frequency indicated by the arrow) is not sufficient. (c) Semi-real-time pure shift NMR spectrum providing an accurate measurement of the chemical shifts of proton H-9 for all the three components of the mixture in 5 s. The smallest chemical shift difference in this example is 7.1 Hz and corresponds to protons 9 from quinidine and cinchonidine. (d-f) GEMSTONE-TOCSY spectra selectively observing each of the three components, with the transmitter frequency set at the chemical shift (indicated by the arrow) of the signal of interest. The TOCSY mixing time was 40 ms in all experiments.

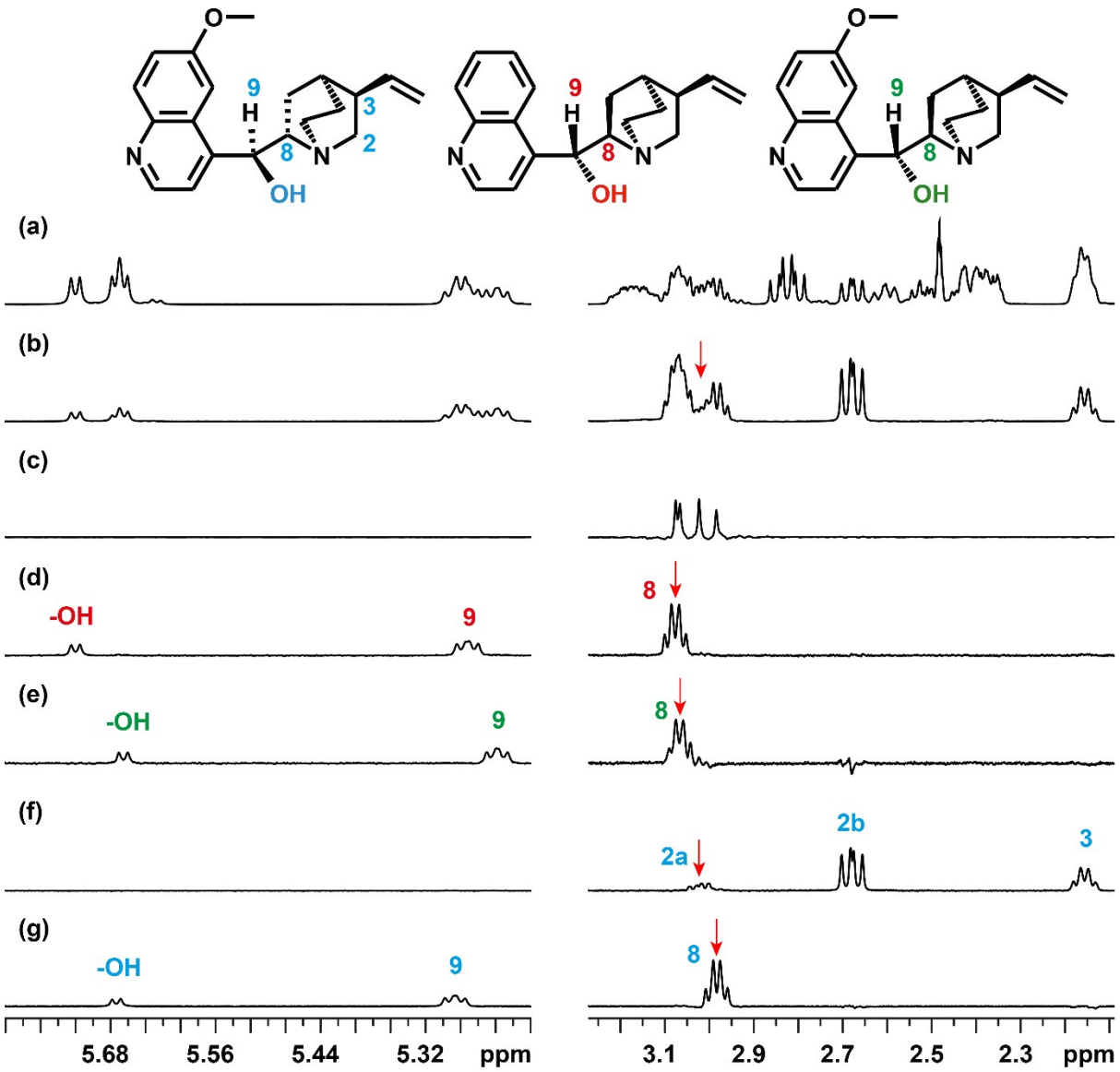

Fig. S4 (a) Selected regions of the ^{1}H NMR spectrum of the cinchona alkaloid mixture in DMSO-d_6. (b) Conventional selective 1D TOCSY spectrum in which selective excitation (at the frequency indicated by the arrow) is not sufficient. (c) Semi-real-time pure shift NMR spectrum providing an accurate measurement of the chemical shifts of proton H-8 for all of the three components and 2a from quinine in 5 s. The smallest chemical shift difference in this example is 4.7 Hz and corresponds to protons 8 from cinchonidine and quinine. (d-g) GEMSTONE-TOCSY spectra selectively observing each of the three components with the transmitter frequency set at the chemical shift (indicated by the arrow) of the signal of interest. The TOCSY mixing time was 60 ms in all experiments.

3. Example: amikacin

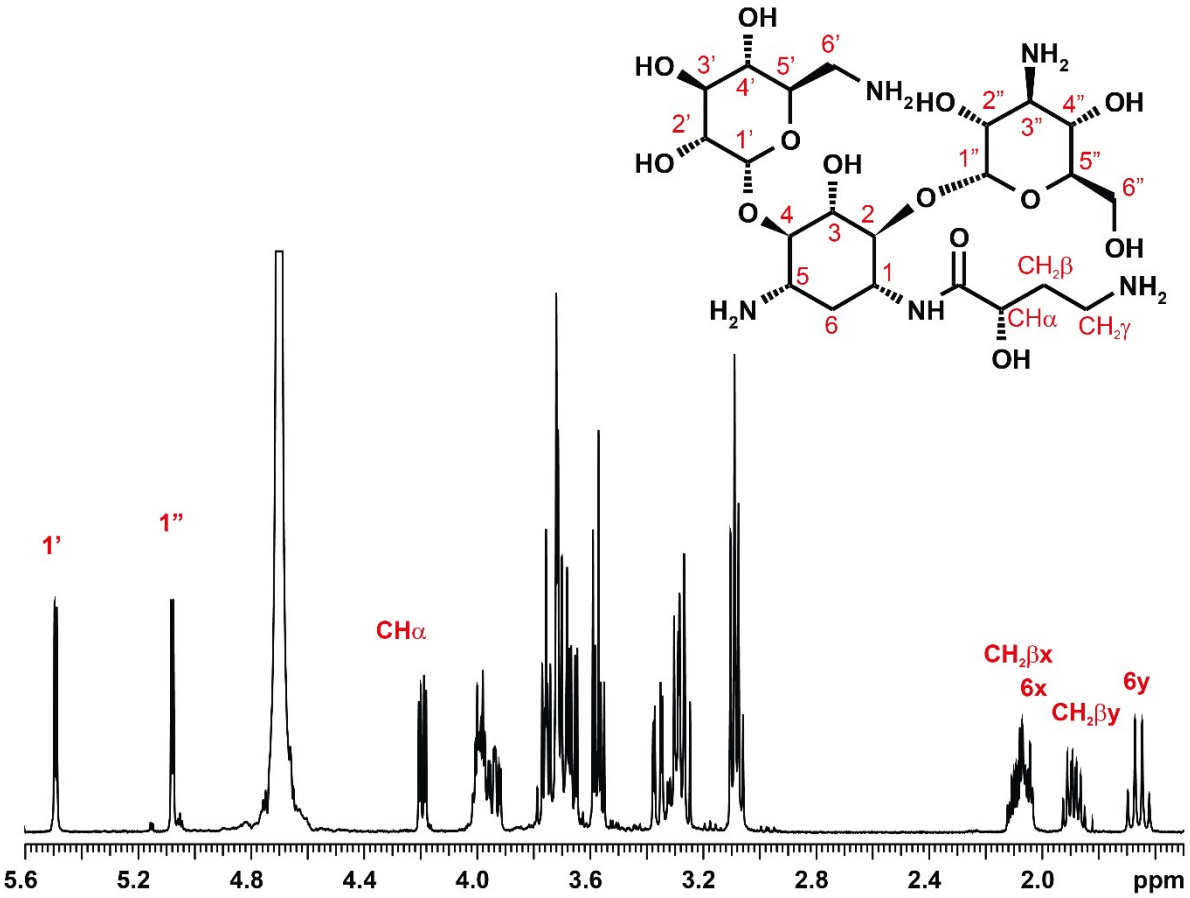

Fig. S5 ^{1}H NMR spectrum of amikacin in D_2O showing extensive signal overlap, particularly in the 1.8 – 2.2 ppm region.

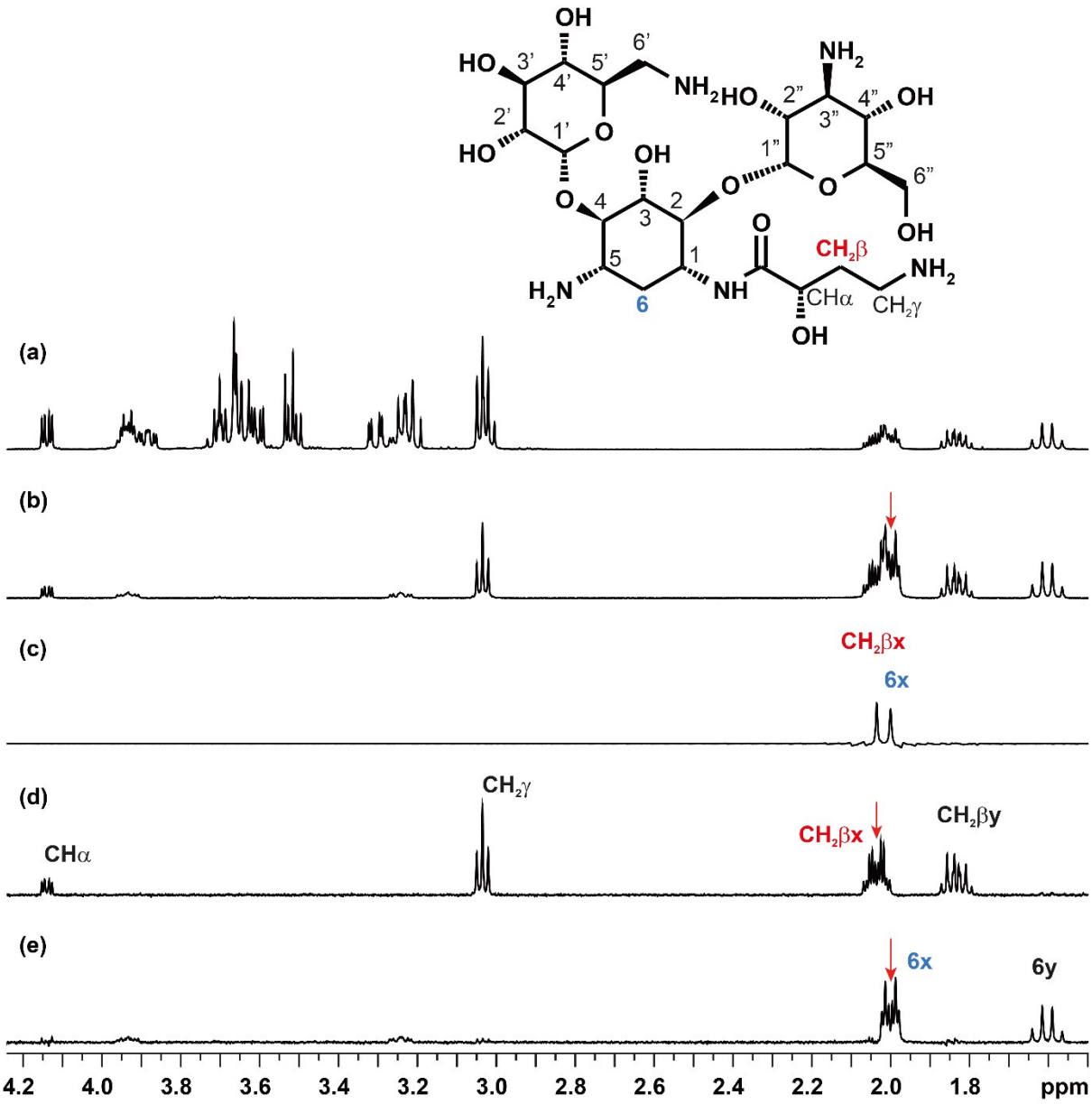

Fig. S6 (a) Selected region of the ^{1}H NMR spectrum of amikacin in D_2O. (b) Conventional selective 1D TOCSY spectrum in which selective excitation (at the frequency indicated by the arrow) is not sufficient. (c) Semi-real-time pure shift NMR spectrum providing an accurate measurement of the chemical shifts of overlapping protons $CH_2\beta x$ and 6x with experiment time of 5 s. The chemical shift difference in this example is 17.5 Hz. (d, e) GEMSTONE-TOCSY spectra selectively observing each of the two different spin systems. The selected protons are labelled with red. The TOCSY mixing time was 20 ms in this example. For the GEMSTONE-TOCSY spectra the transmitter frequency was set at the chemical shift (indicated by the arrow) of the signal of interest.

4. Example: mixture of hesperedin and naringin

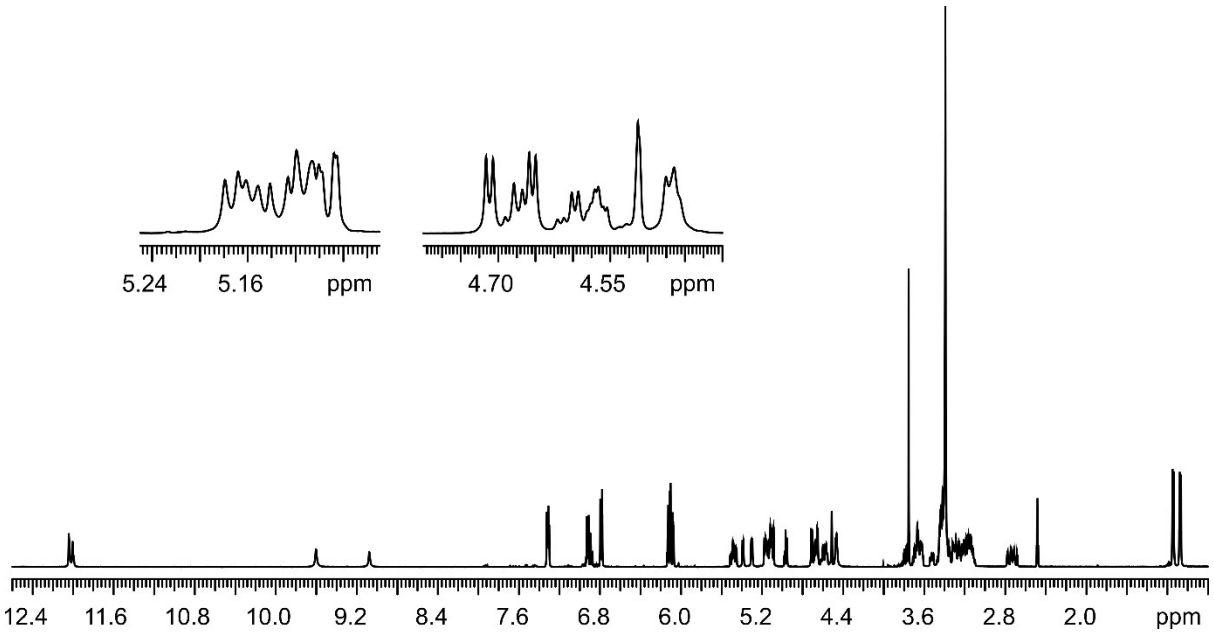

Fig. S7 ^{1}H NMR spectrum of a mixture of hesperidin and naringin in DMSO-d_6 showing extensive signal overlap throughout the spectrum.

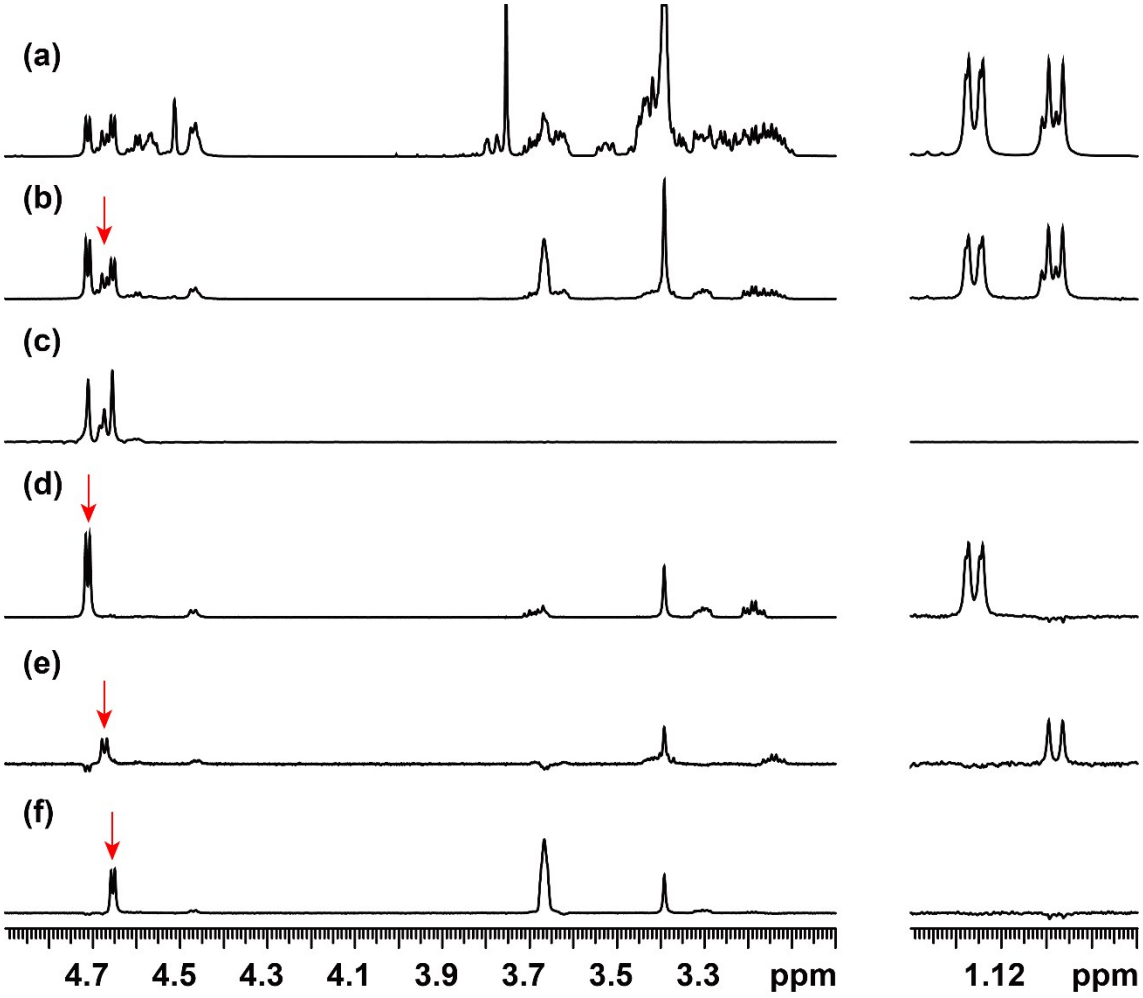

Fig. S8 (a) Selected region of the ^{1}H NMR spectrum of the mixture of hesperidin and naringin in DMSO-d_6. (b) Conventional selective 1D TOCSY spectrum in which selective excitation (at the frequency indicated by the arrow) is not sufficient. The methyl protons of all four components are observed on the right. (c) Semi-real-time pure shift NMR spectrum providing an accurate measurement of the chemical shifts of overlapping protons in the selected region. The smallest chemical shift difference in this example is 4.9 Hz. (d-f) GEMSTONE-TOCSY spectra selectively observing each spin system. The TOCSY mixing time was 80 ms in all experiments, GEMSTONE-TOCSY spectra were set up by setting the transmitter frequency to the chemical shift of the signal of interest (indicated by the arrow). The spectra (d) and (e) selectively provide TOCSY correlations to naringin and hesperidin methyl protons. The spectrum (d) is not selective for the naringin diastereomers, as there is no useful chemical shift difference between their selected hydroxyl protons. In (e) only one of the hesperidin methyl protons is observed, in line with selective excitation of one of the hydroxyl protons. The spectrum in (f) corresponds to another part of the structure, not the ring which contains the methyl protons, and accordingly no methyl protons are observed.

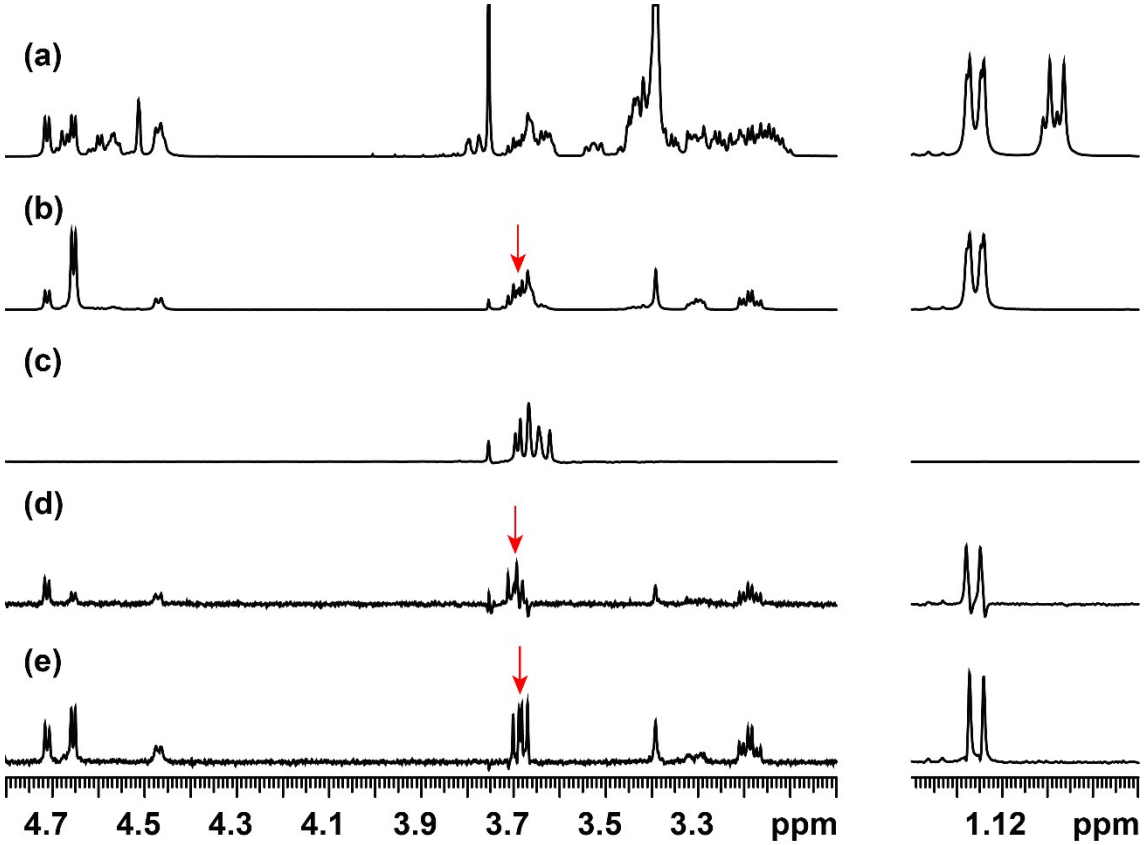

Fig. S9 (a) Selected region of the ^{1}H NMR spectrum of the mixture of hesperidin and naringin in DMSO-d_6. (b) Conventional selective 1D TOCSY spectrum in which selective excitation (at the frequency indicated by the arrow) is not sufficient. (c) Semi-real-time pure shift NMR spectrum providing an accurate measurement of the chemical shifts of overlapping protons in the selected region. The smallest chemical shift difference in this example is 5.4 Hz. (d-e) GEMSTONE-TOCSY spectra providing selective observation for the spin systems of the two naringin diastereomers, as seen on the right for their methyl protons. In GEMSTONE-TOCSY experiments the transmitter frequency was set at the chemical shift of the signal of interest (indicated by the arrow). The TOCSY mixing time was 100 ms in all experiments.

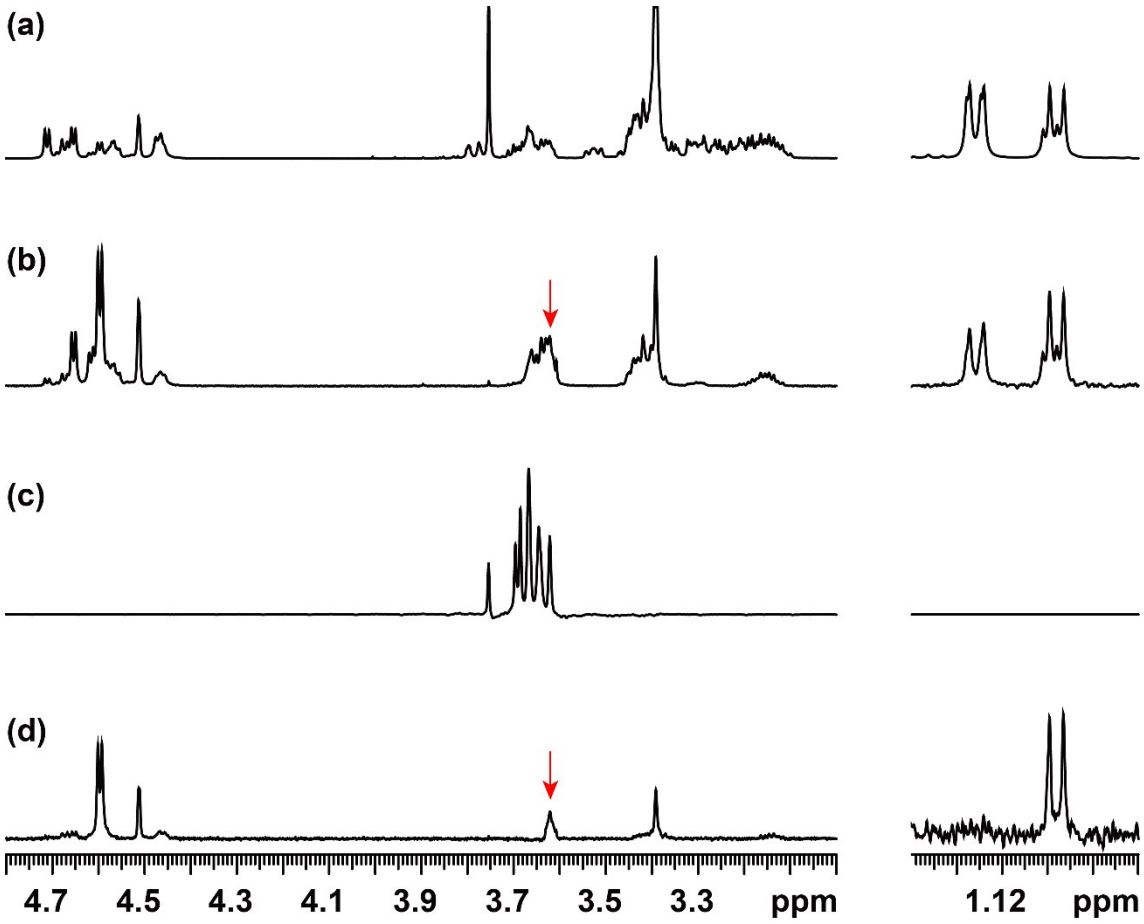

Fig. S10 (a) Selected region (same as in previous figure) of the ^{1}H NMR spectrum of the mixture of hesperidin and naringin in DMSO-d_6. (b) Conventional selective 1D TOCSY spectrum in which selective excitation (at the frequency indicated by the arrow) is not sufficient. (c) Semi-real-time pure shift NMR spectrum providing an accurate measurement of the chemical shifts of overlapping six protons in the selected region. The smallest chemical shift difference in this example is 5.4 Hz. (d) GEMSTONE-TOCSY spectra selectively observing another spin system, corresponding to 2*S*-hesperidin as revealed by setting the transmitter frequency to the chemical shift of the methyl proton on the right. The TOCSY mixing time was 100 ms in all experiments.