Electronic Supplementary Information

Improving solubility of fisetin by cocrystalization

Michał Sowa[a], Katarzyna Ślepokura[b], Ewa Matczak-Jon[a]

[a]Department of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland. Tel. (+4871) 320-41-34; Fax: (+4871) 320-43 60; E-mail: ewa.matczak-jon@pwr.wroc.pl

[b]Faculty of Chemistry, University of Wrocław, 14 F. Joliot-Curie Street, 50-383 Wrocław, Poland

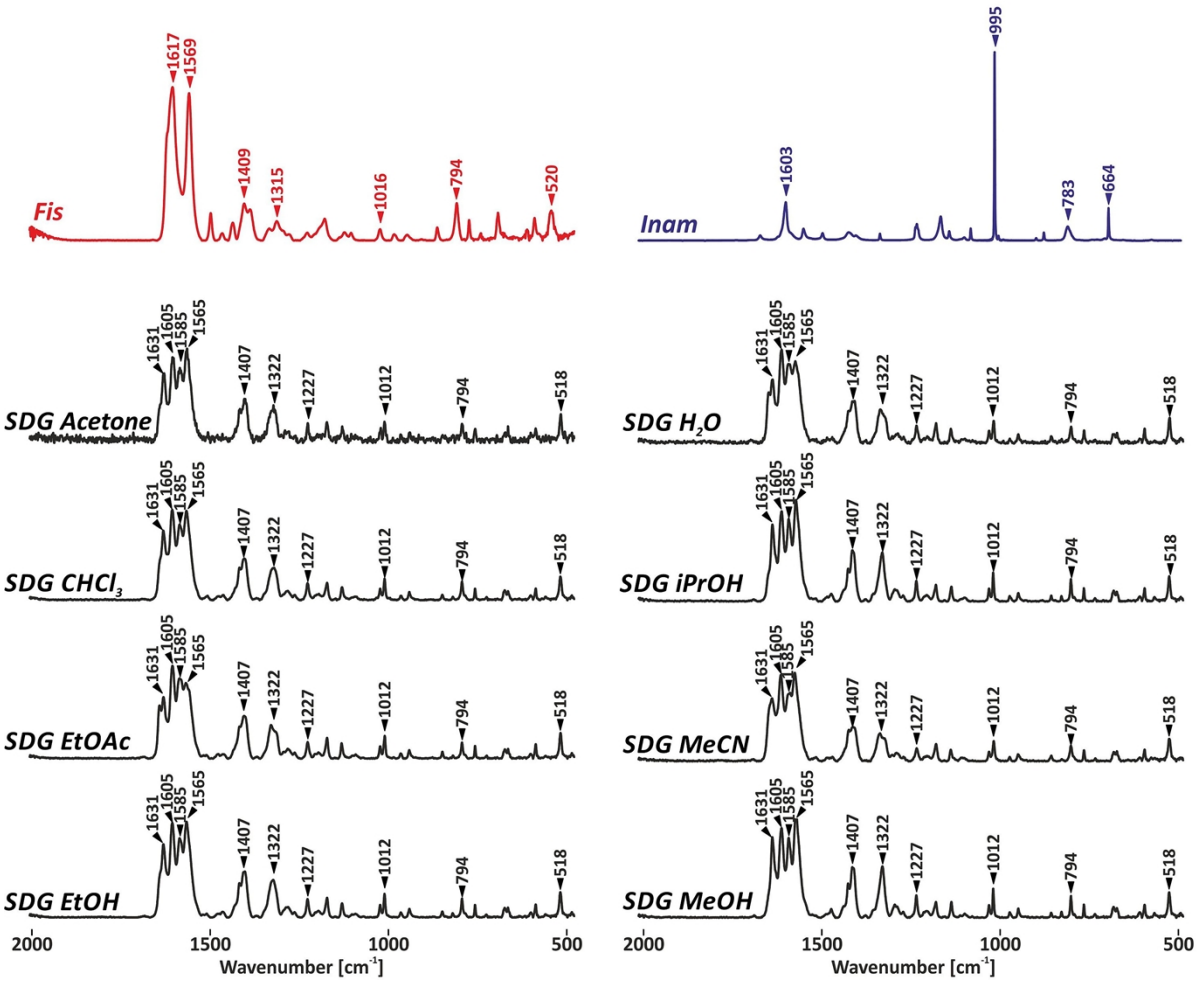


Fig. S1 FT-Raman spectra of fisetin (Fis), isonicotinamide (Inam) and products of their co-grinding with addition of a solvent (SDG). Selected vibrational bands are indicated.

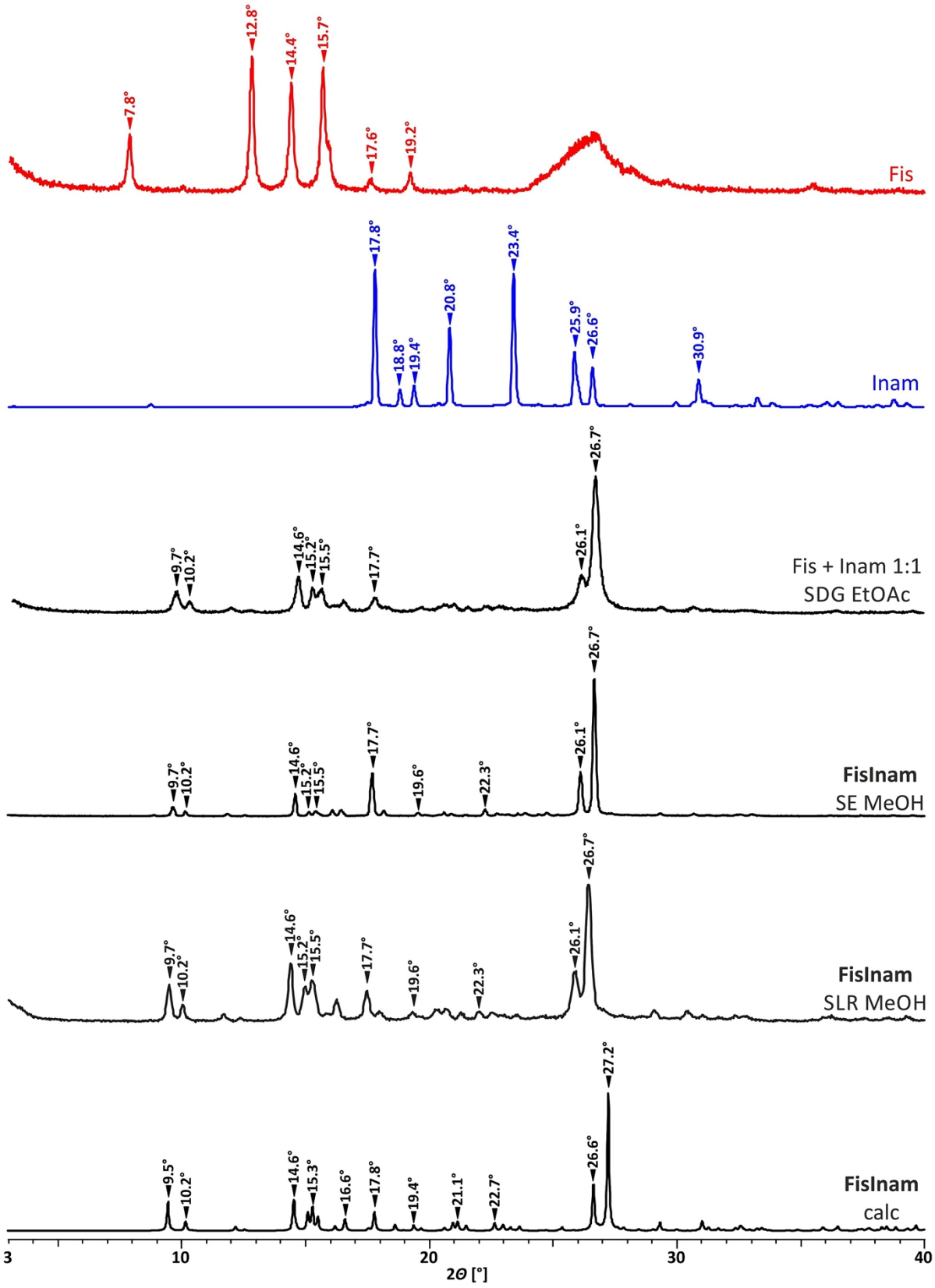


Fig. S2 XRPD plots of fisetin (Fis), isonicotinamide (Inam), product of their co-grinding with addition of ethyl acetate (Fis + Inam 1:1 SDG EtOAc), and corresponding **FisInam** cocrystal: obtained by slow evaporation of a methanolic solution (**FisInam** SE MeOH), by slurry technique (**FisInam** SLR MeOH) and diffractogram calculated from the low-temperature refinement of FisInam (**FisInam** calc). Positions of selected reflections are indicated.

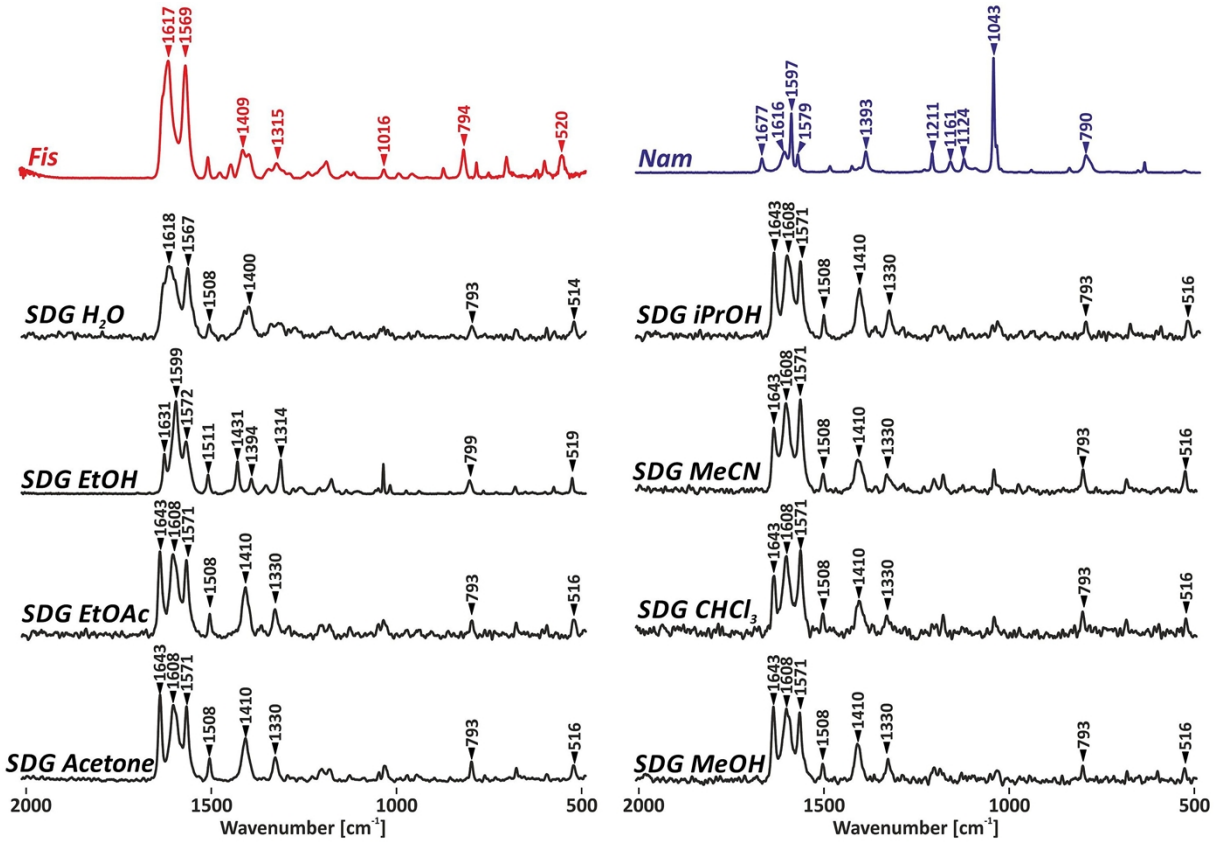


Fig. S3 FT-Raman spectra of fisetin (Fis), nicotinamide (Nam) and products of their co-grinding with addition of a solvent (SDG). Selected vibrational bands are indicated.

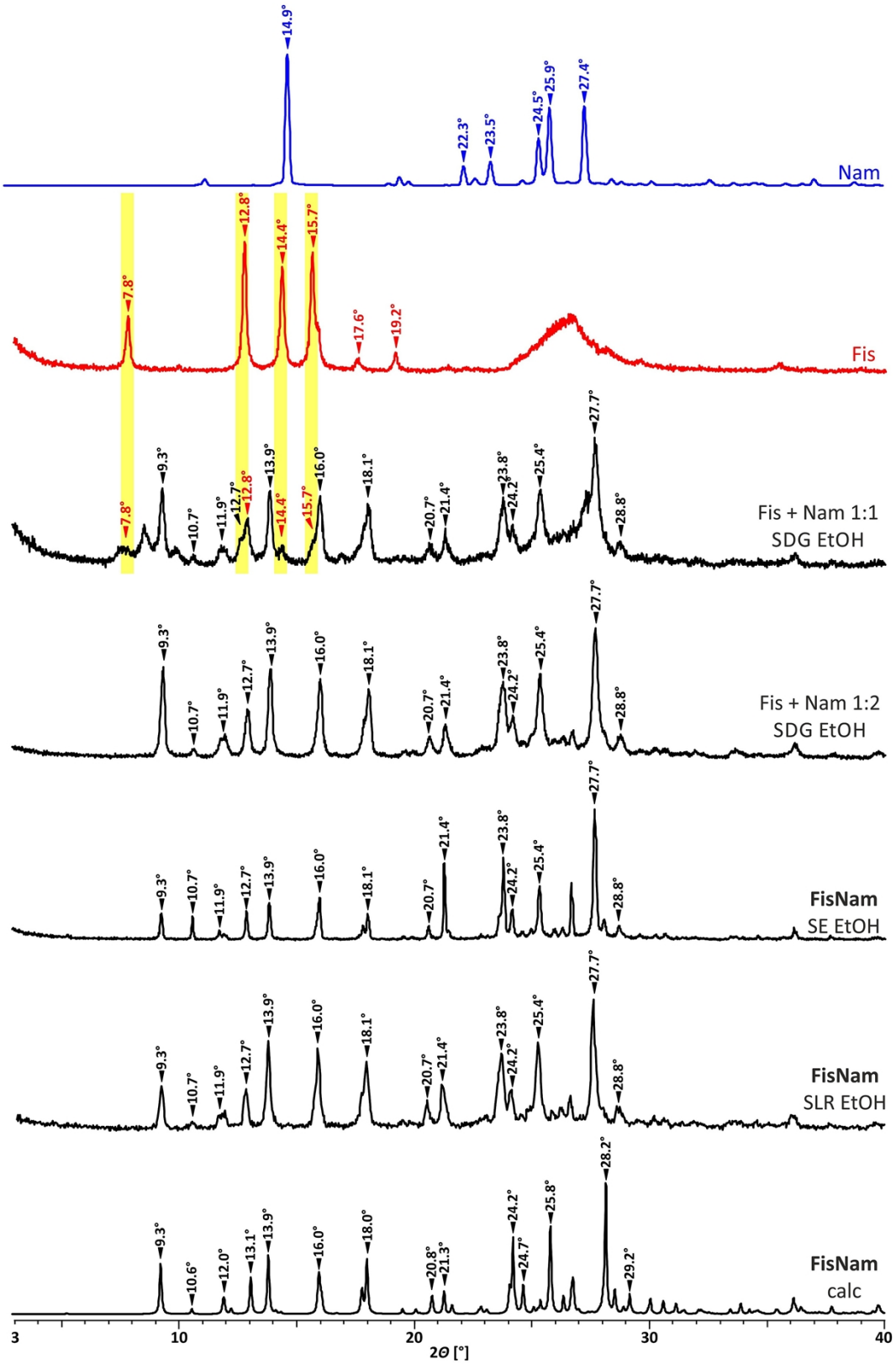


Fig. S4 XRPD plots of nicotinamide (Nam), fisetin (Fis), products of their co-grinding with addition of ethanol (Fis + Nam 1:1 SDG EtOH; Fis + Nam 1:2 SDG EtOH; note the reflections highlighted in yellow, which indicate presence of unreacted fisetin) and corresponding **FisNam** cocrystal: obtained by slow evaporation of a ethanolic solution (**FisNam** SE EtOH), by slurry technique (**FisNam** SLR Et_2O+EtOH) and diffractogram calculated from the low-temperature refinement of **FisNam** (**FisNam** calc). Positions of selected reflections are indicated.

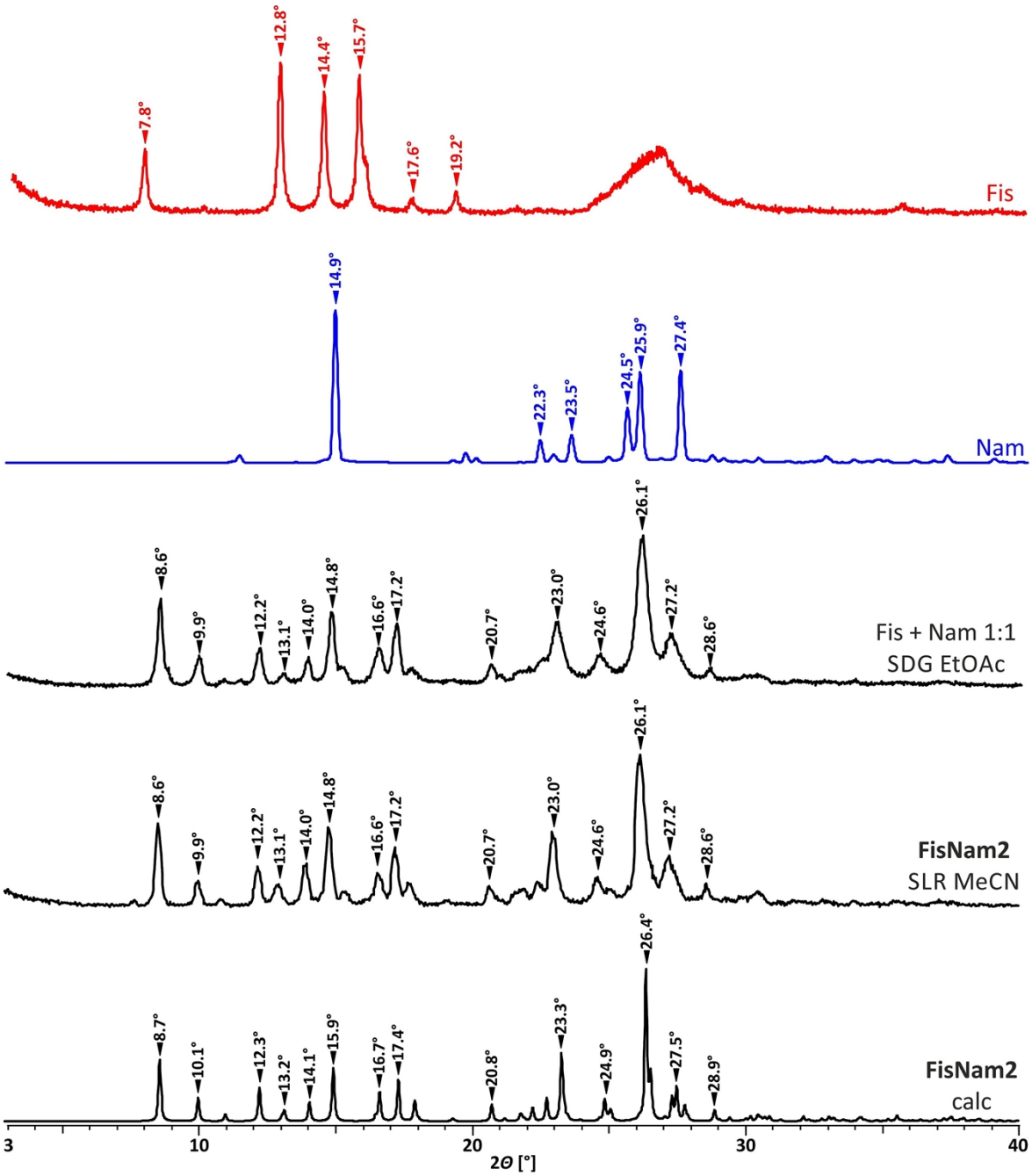


Fig. S5 XRPD plots of nicotinamide (Nam), fisetin (Fis), products of their co-grinding with addition of ethyl acetate (Fis + Nam 1:1 SDG EtOAc) and corresponding **FisNam2** cocrystal: obtained by slurry technique (**FisNam2** SLR MeCN) and diffractogram calculated from the low-temperature refinement of **FisNam2** (**FisNam2** calc). Positions of selected reflections are indicated.

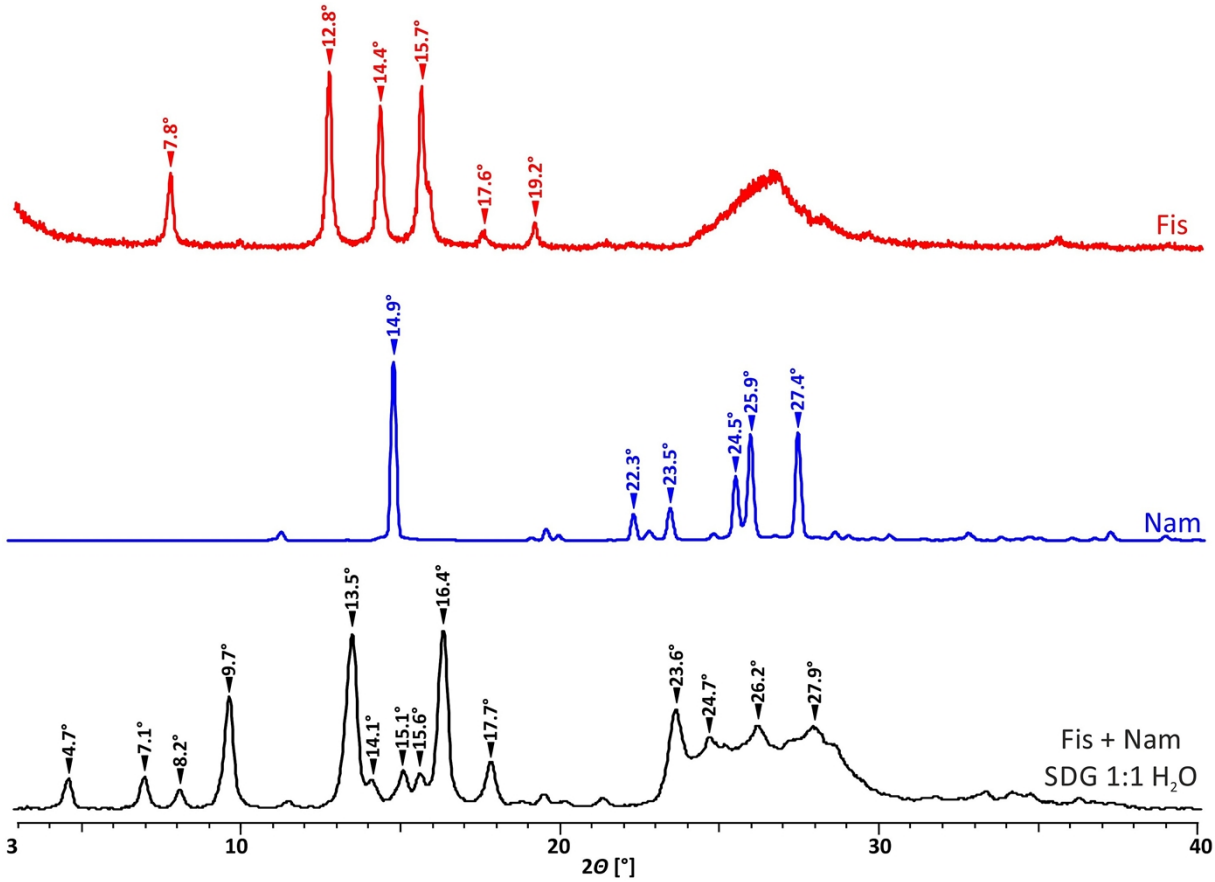


Fig. S6 XRPD plots of fisetin (Fis), nicotinamide (Nam) and product of their co-grinding with addition of water (Fis + Nam 1:1 SDG H_2O). Positions of selected reflections are indicated.

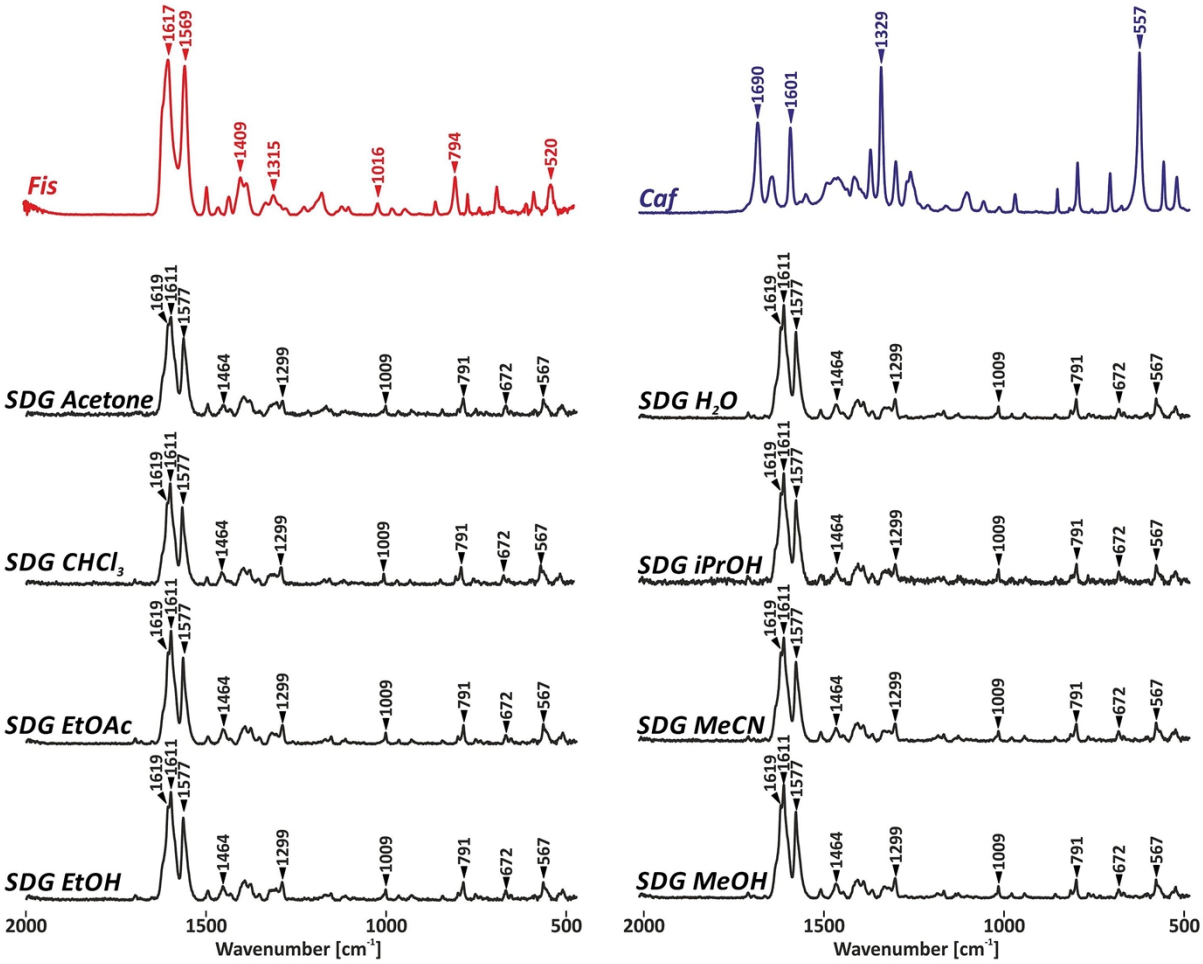


Fig. S7 FT-Raman spectra of fisetin (Fis), caffeine (Caf) and products of their co-grinding with addition of a solvent (SDG). Selected vibrational bands are indicated.

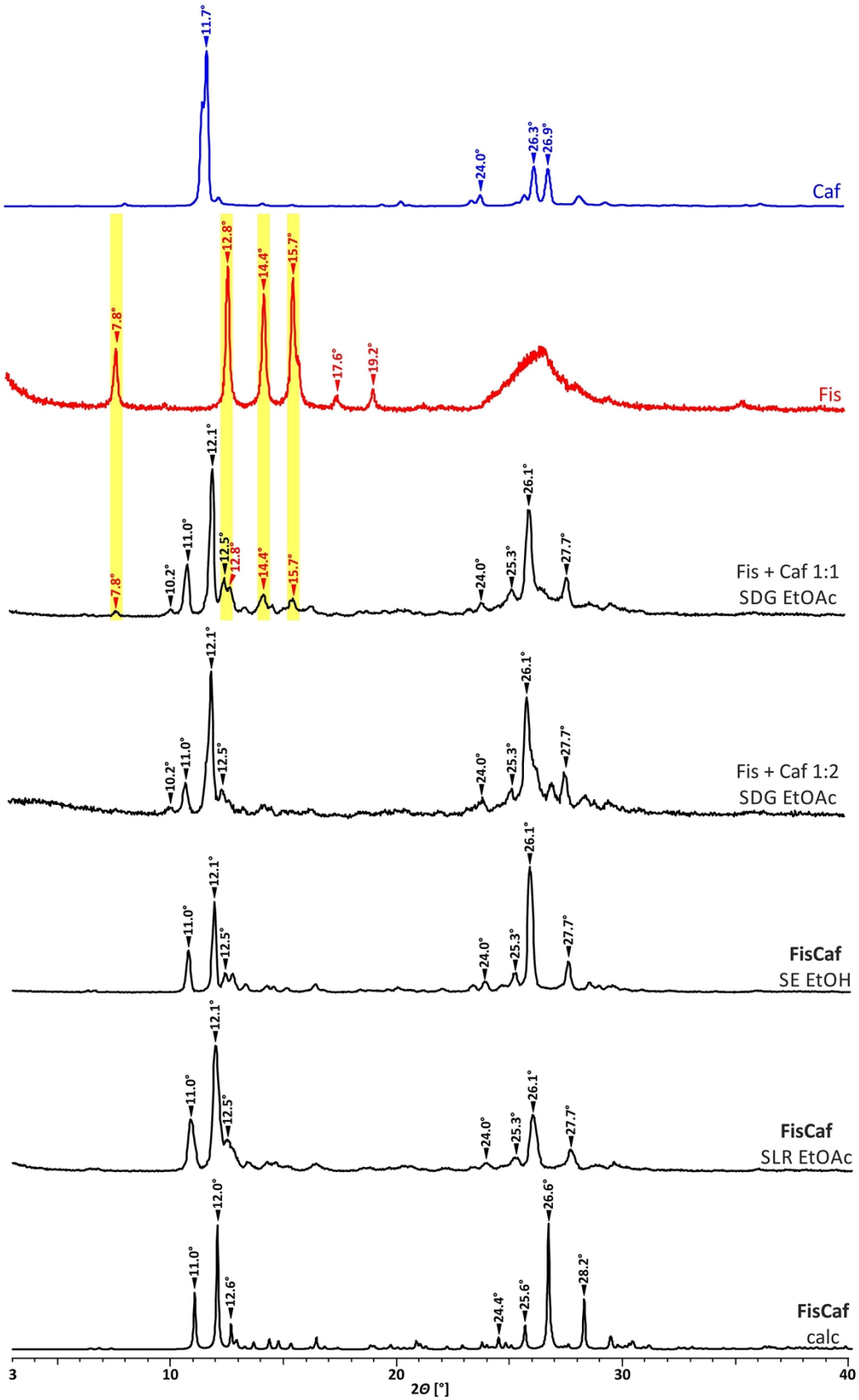
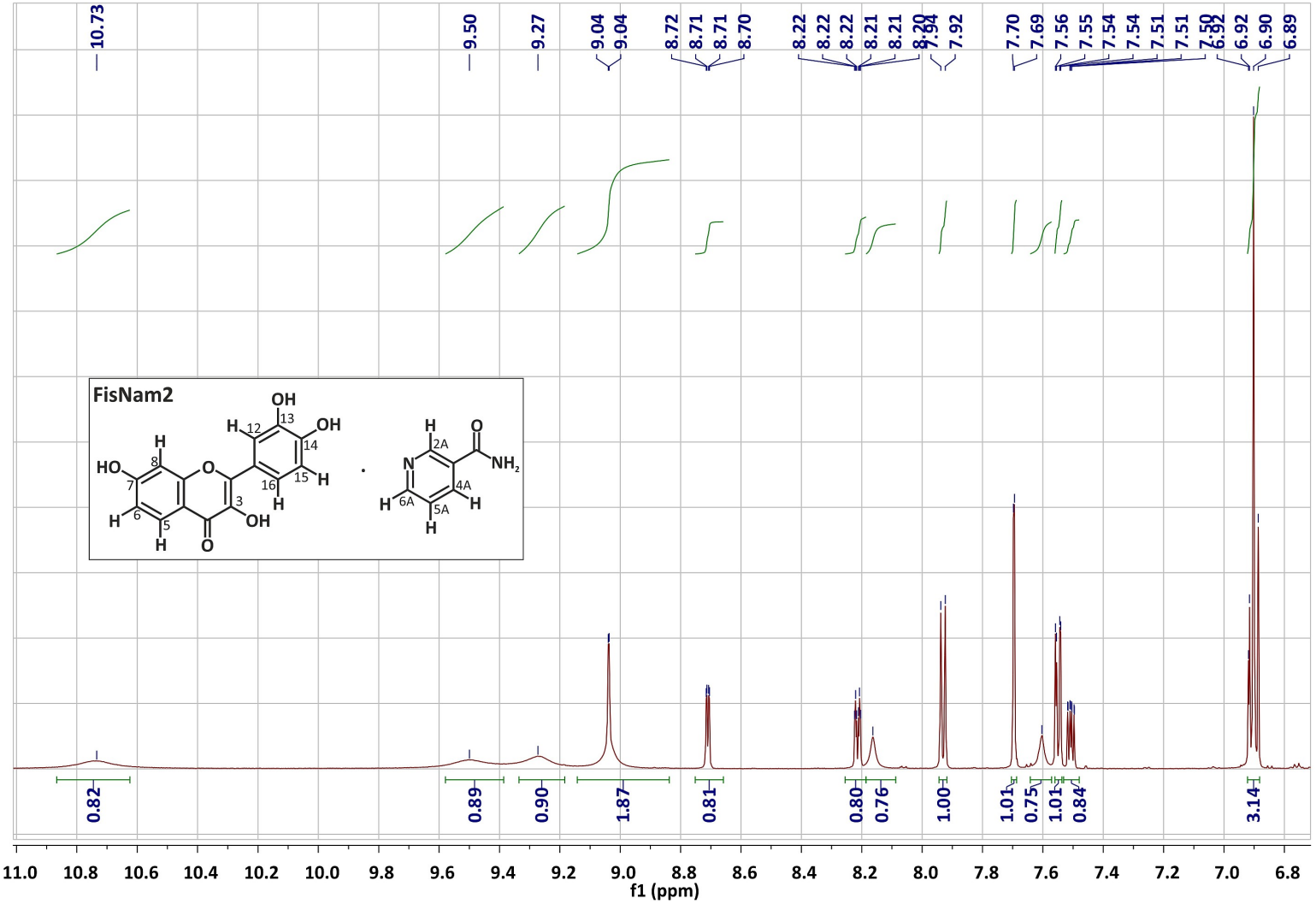
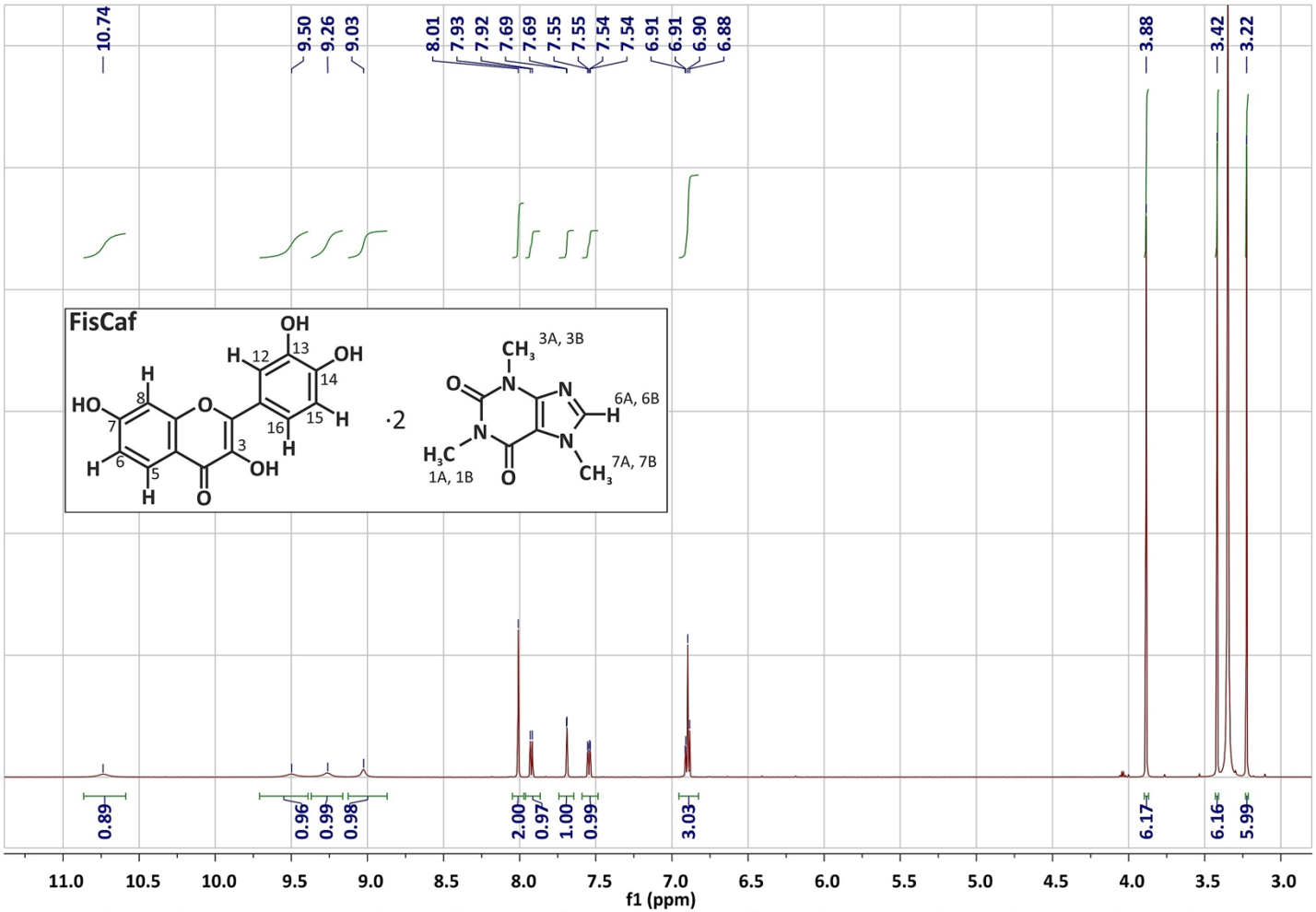


Fig. S8 XRPD plots of caffeine (Caf), fisetin (Fis), products of their co-grinding with addition of ethyl acetate (Fis + Caf 1:1 SDG EtOAc; Fis + Caf 1:2 SDG EtOAc; note the reflections highlighted in yellow, which indicate presence of unreacted fisetin) and corresponding **FisCaf** cocrystal: obtained by slow evaporation of a ethanolic solution (**FisCaf** SE EtOH), by slurry technique (**FisCaf** SLR EtOAc) and diffractogram calculated from the low-temperature refinement of **FisCaf** (**FisCaf** calc). Positions of selected reflections are indicated.



^{1}H NMR, ppm (DMSO-d_6, 600MHz, 25°C, TMS): 10.73 (s, 1H, OH-7), 9.50 (s, 1H, OH-14), 9.27 (s, 1H, OH-13), 9.04 (s, 1H, OH-3), 9.03 (d, J = 1.7 Hz, 1H, H-2A), 8.71 (dd, J = 4.8, 2.0 Hz, 1H, H-6A), 8.21 (ddd, J = 7.9, 2.0, 1.7 Hz, 1H, H-4A), 8.16 (s, 1H, NH_2), 7.93 (d, J = 9.1 Hz, 1H, H-5), 7.70 (d, J = 2.2 Hz, 1H, H-12), 7.60 (s, 1H, NH_2), 7.55 (dd, J = 8.4, 2.2 Hz, 1H, H-16), 7.51 (dd, J = 7.9, 4.8 Hz, 1H, H-5A), 6.90 (d, J = 9.1 Hz, 1H, H-6), 6.89 (d, J = 8.4 Hz, 1H, H-15), 6.89 (s, 1H, H-8).

Fig. S9 ^{1}H NMR spectrum and assignments for the **FisNam2** cocrystal dissolved in DMSO-d_6.



^{1}H NMR, ppm (DMSO-d_6, 600MHz, 25°C, TMS): 10.74 (s, 1H, OH-7), 9.50 (s, 1H, OH-14), 9.26 (s, 1H, OH-13), 9.03 (s, 1H, OH-3), 8.01 (s, 2H, H6A, H6B), 7.92 (d, *J* = 8.3 Hz, 1H, H-5), 7.69 (d, *J* = 2.1 Hz, 1H, H-12), 7.55 (dd, *J* = 8.5, 2.1 Hz, 1H, H-16), 6.90 (d, *J* = 8.3 Hz, 1H, H-6), 6.89 (d, *J* = 8.5 Hz, 1H, H-15), 6.89 (s, 1H, H-8), 3.88 (s, 6H, CH3-N7A, CH3-N7B), 3.42 (s, 6H, CH3-N1A, CH3-N1B), 3.22 (s, 6H, CH3-N3A, CH3-N3B).

Fig. S10 ^{1}H NMR spectrum and assignments for the **FisCaf** cocrystal dissolved in DMSO-d_6.

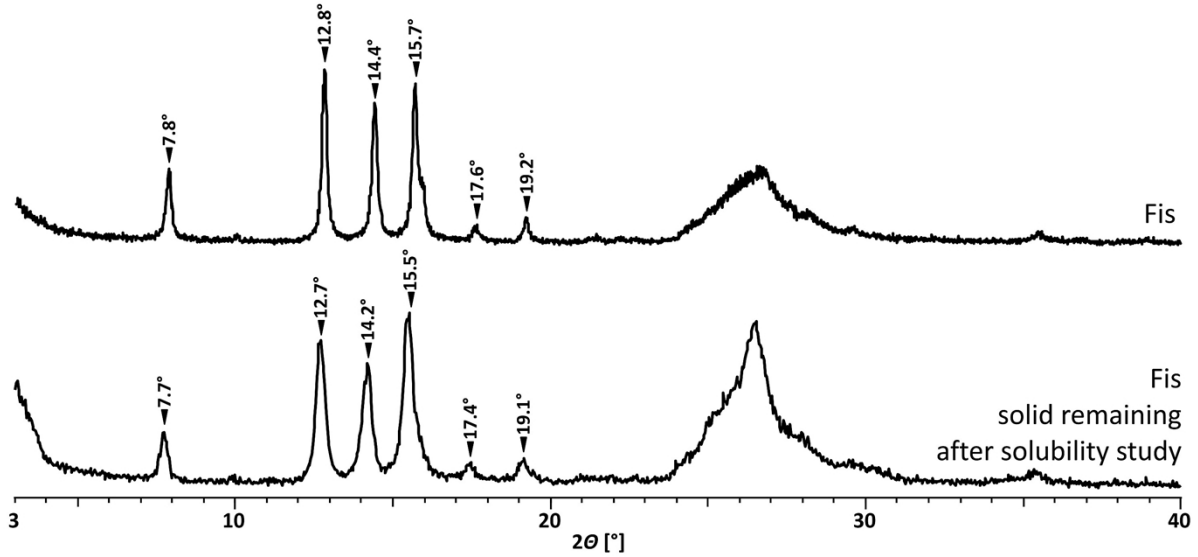


Fig. S11 XRPD plots of starting (anhydrous) fisetin and the solid phase remaining after its solubility study.

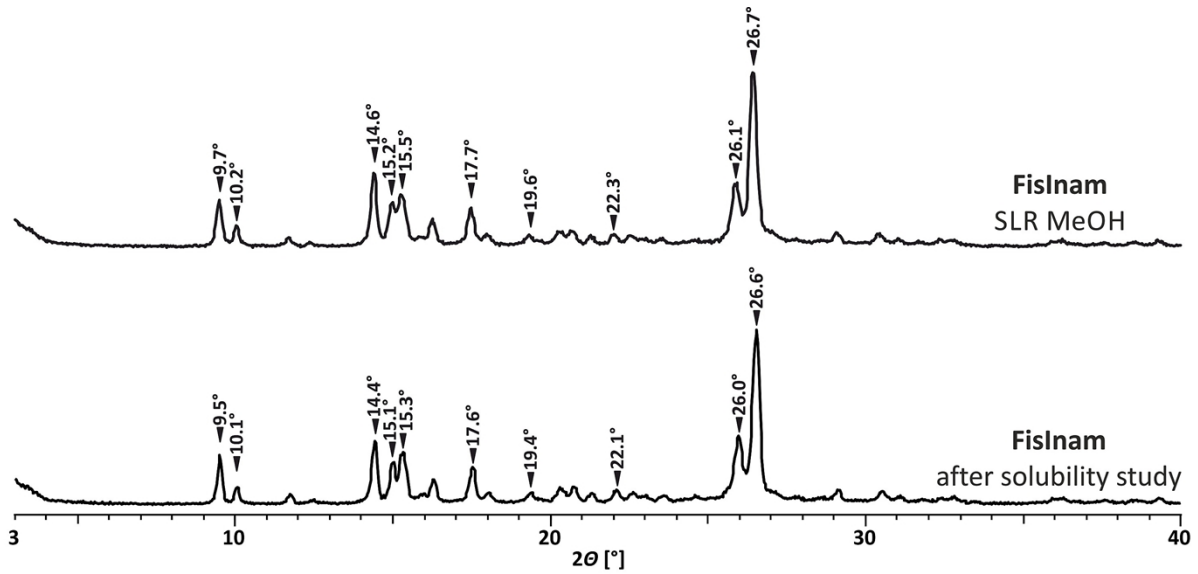


Fig. S12 XRPD plots of the **FisInam** cocrystal and the solid phase remaining after its solubility study.

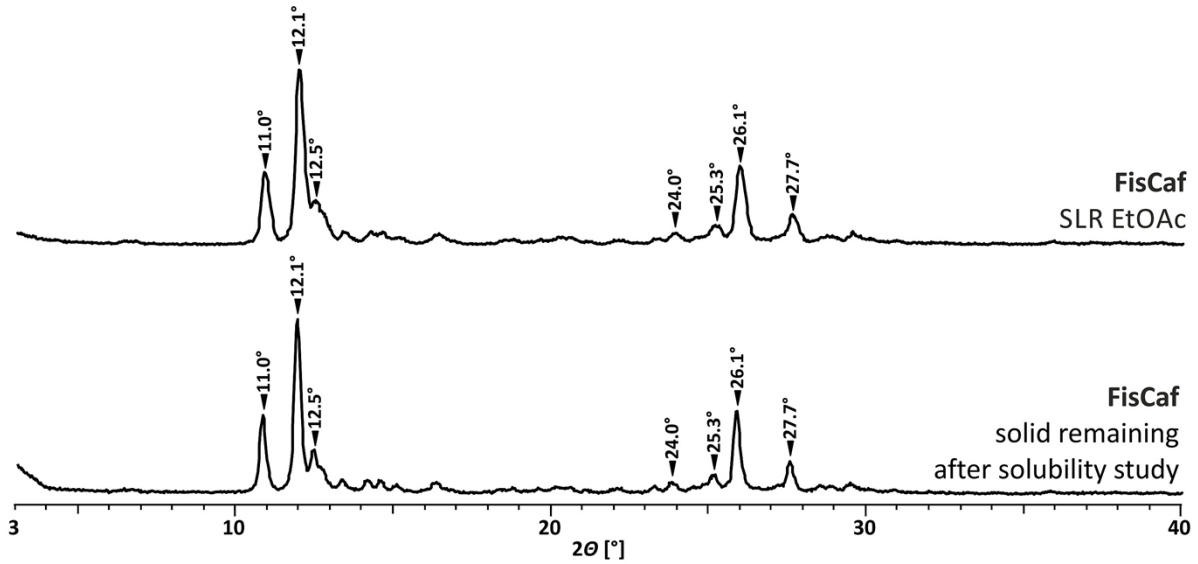


Fig. S13 XRPD plots of the **FisCaf** cocrystal and the solid phase remaining after its solubility study.

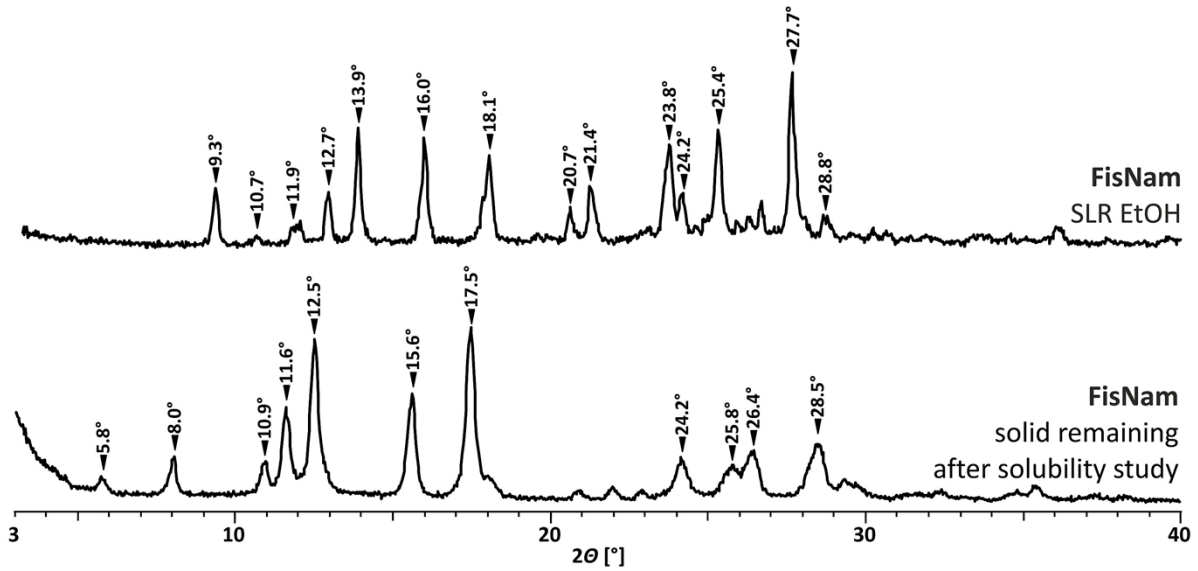


Fig. S14 XRPD plots of the **FisNam** cocrystal and the solid phase remaining after its solubility study (fisetin hydrate).

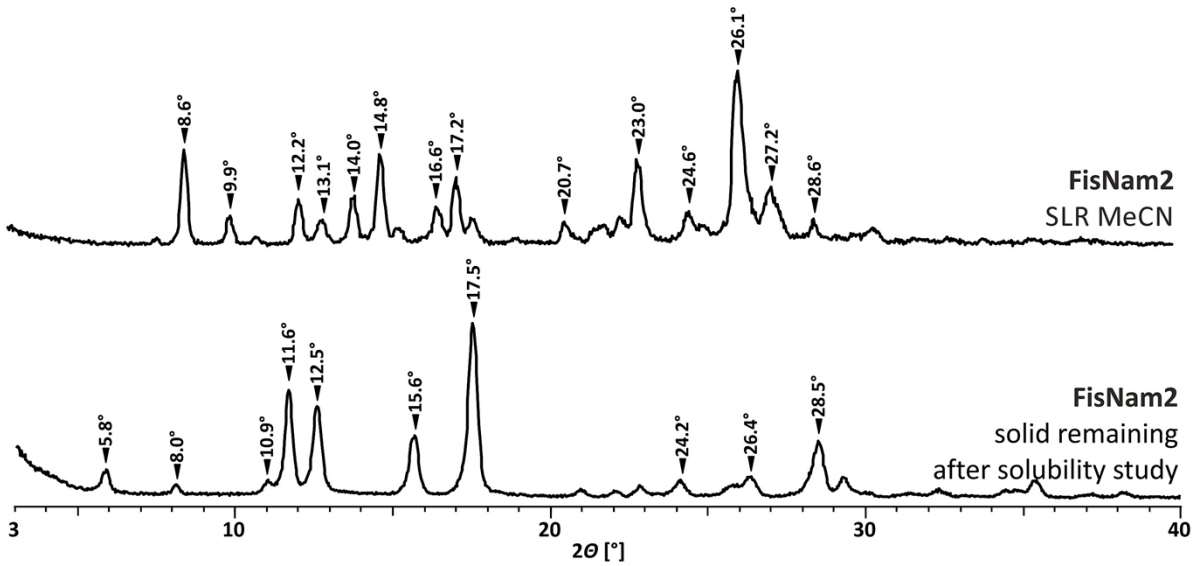


Fig. S15 XRPD plots of the **FisNam** cocrystal and the solid phase remaining after its solubility study (fisetin hydrate).

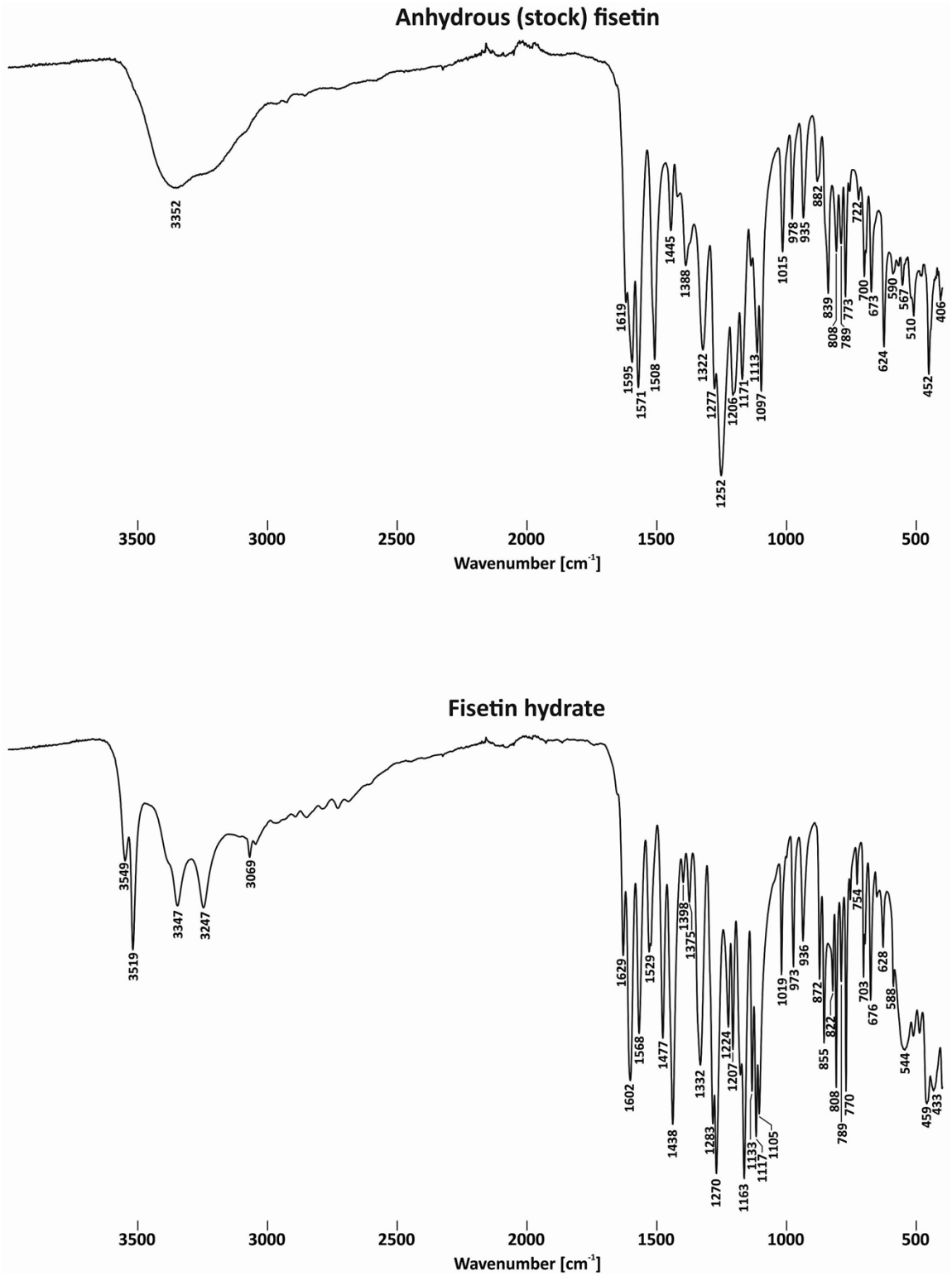
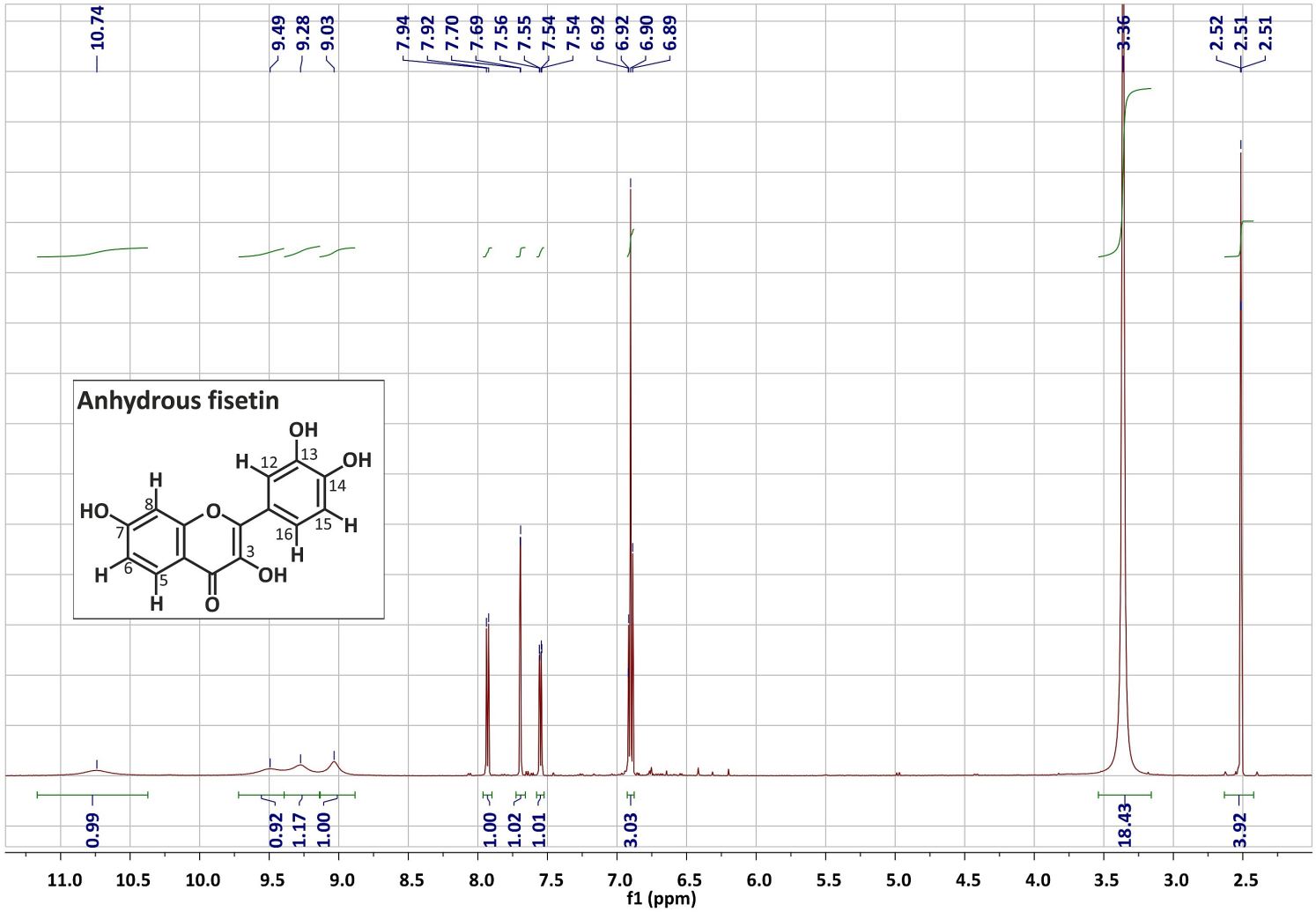
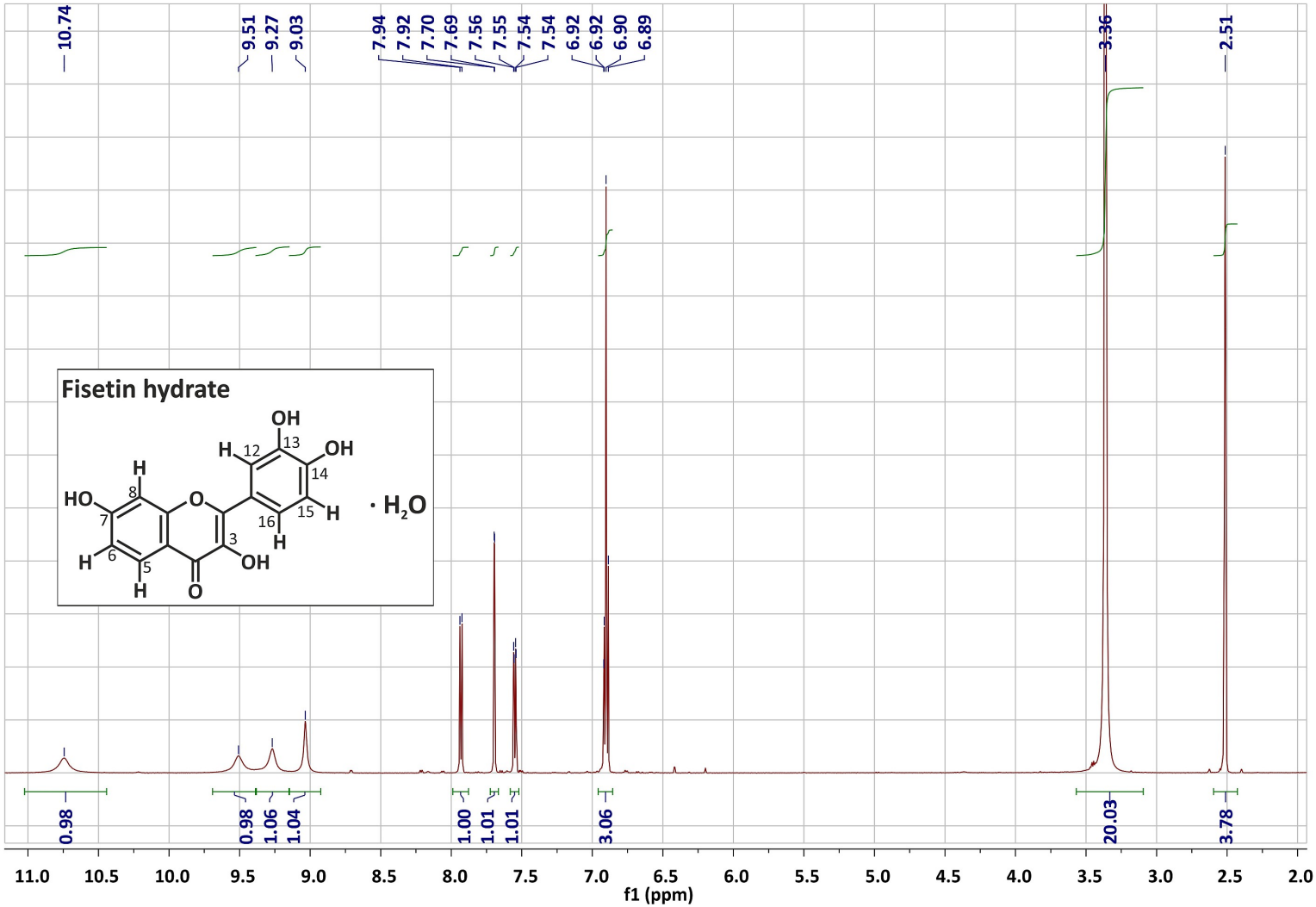


Fig. S16 FT-IR spectra of anhydrous (stock) fisetin (upper) and fisetin hydrate (lower). Selected vibrational bands are indicated.



^{1}H NMR, ppm (DMSO-d_6, 600MHz, 25°C, TMS): 10.74 (s, 1H, OH-7), 9.49 (s, 1H, OH-14), 9.28 (s, 1H, OH-13), 9.03 (s, 1H, OH-3), 7.93 (d, J = 9.3 Hz, 1H, H-5), 7.69 (d, J = 2.1 Hz, 1H, H-12), 7.55 (dd, J = 8.4, 2.1 Hz, 1H, H-16), 6.91 (d, J = 9.3 Hz, 1H, H-6), 6.90 (d, J = 8.4 Hz, 1H, H-15), 6.89 (s, 1H, H-8).

Fig. S17 ^{1}H NMR spectrum and assignments for anhydrous (stock) fisetin dissolved in DMSO-d_6.



^{1}H NMR, ppm (DMSO-d_6, 600MHz, 25°C, TMS): 10.74 (s, 1H, OH-7), 9.51 (s, 1H, OH-14), 9.27 (s, 1H, OH-13), 9.03 (s, 1H, OH-3), 7.93 (d, J = 9.2 Hz, 1H, H-5), 7.69 (d, J = 2.0 Hz, 1H, H-12), 7.55 (dd, J = 8.5, 2.0 Hz, 1H, H-16), 6.91 (d, J = 9.2 Hz, 1H, H-6), 6.90 (d, J = 8.5 Hz, 1H, H-15), 6.89 (s, 1H, H-8).

Fig. S18 ^{1}H NMR spectrum and assignments for fisetin hydrate dissolved in DMSO-d_6.

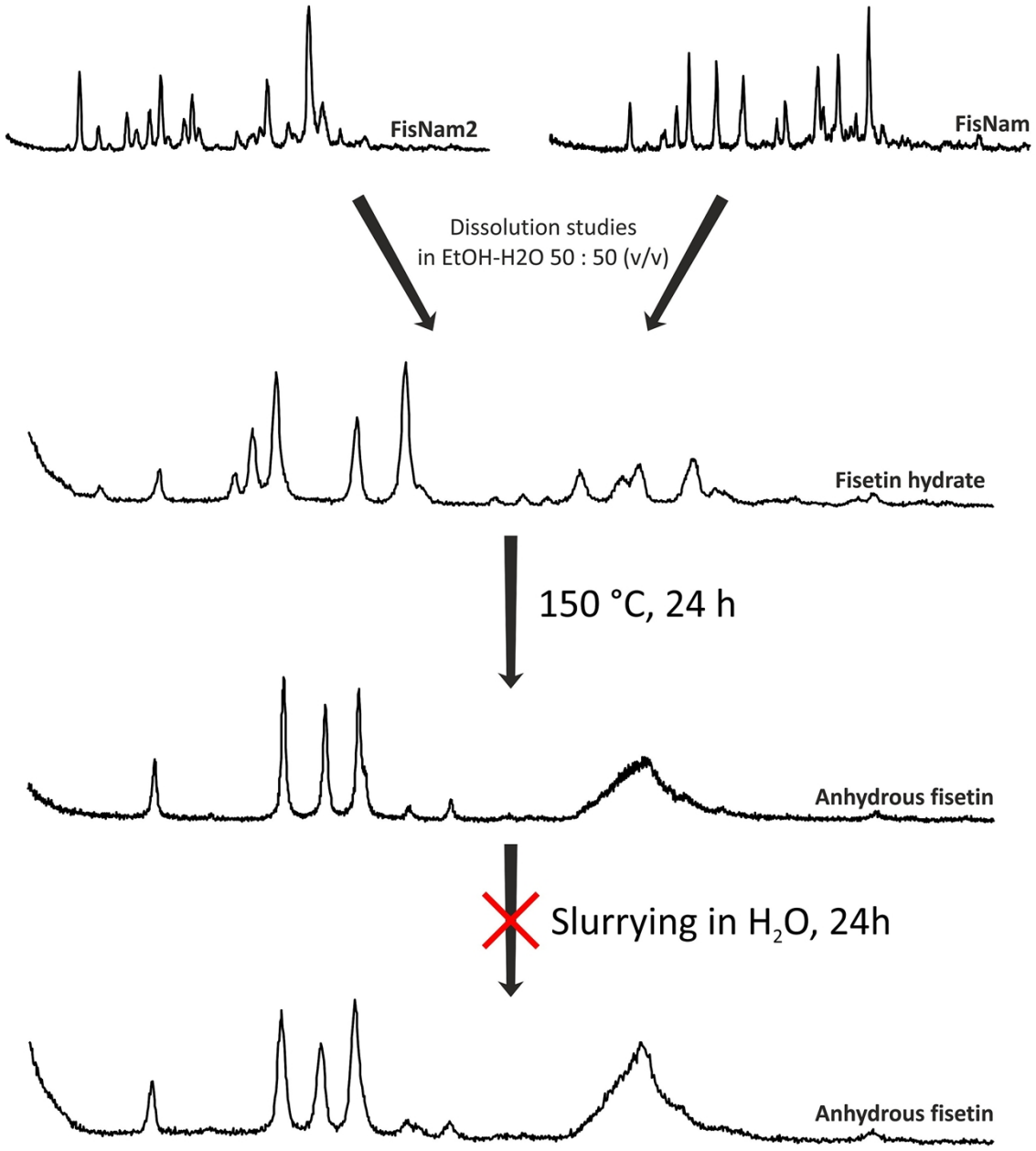


Fig. S19 Inter-conversion routes between anhydrous fisetin and fisetin hydrate.