Electronic Supplementary Material (ESI) for ChemComm.

Symmetry assisted tuning of bending and brittle multi-component forms of probenecid

Supporting Information

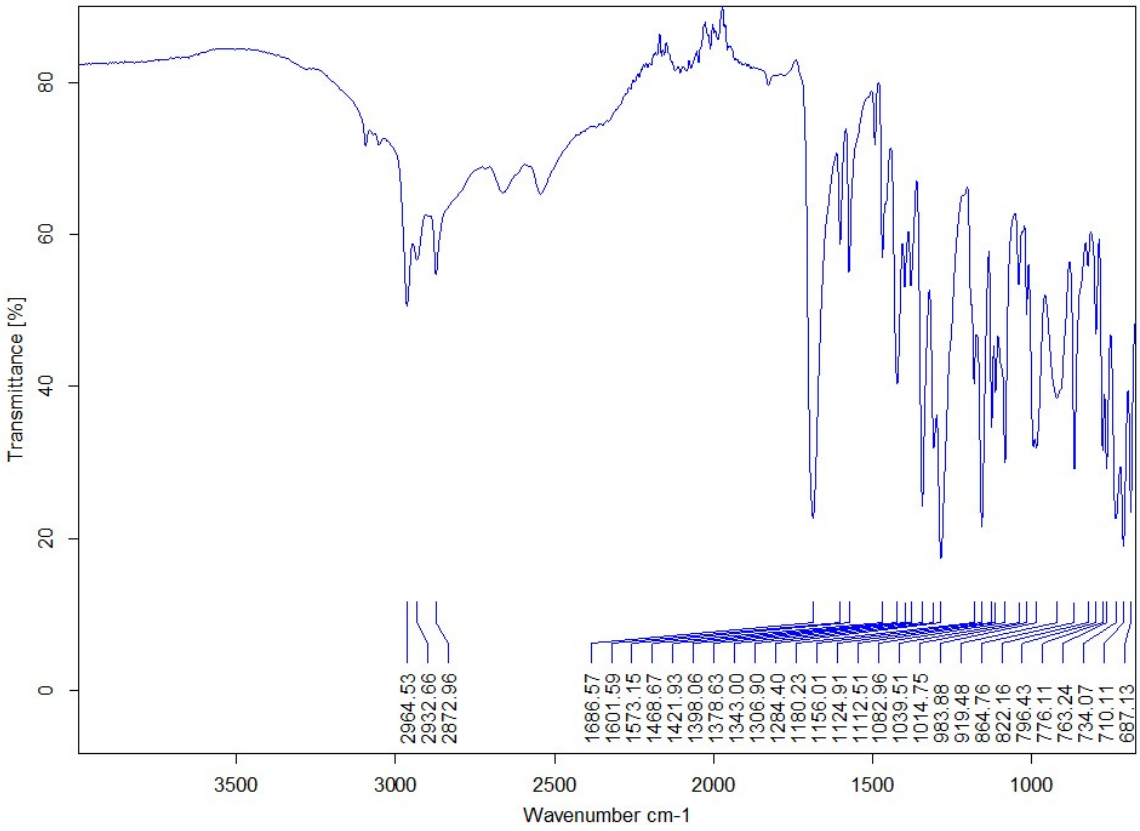

Figure 1. IR spectra for commercial probenecid.

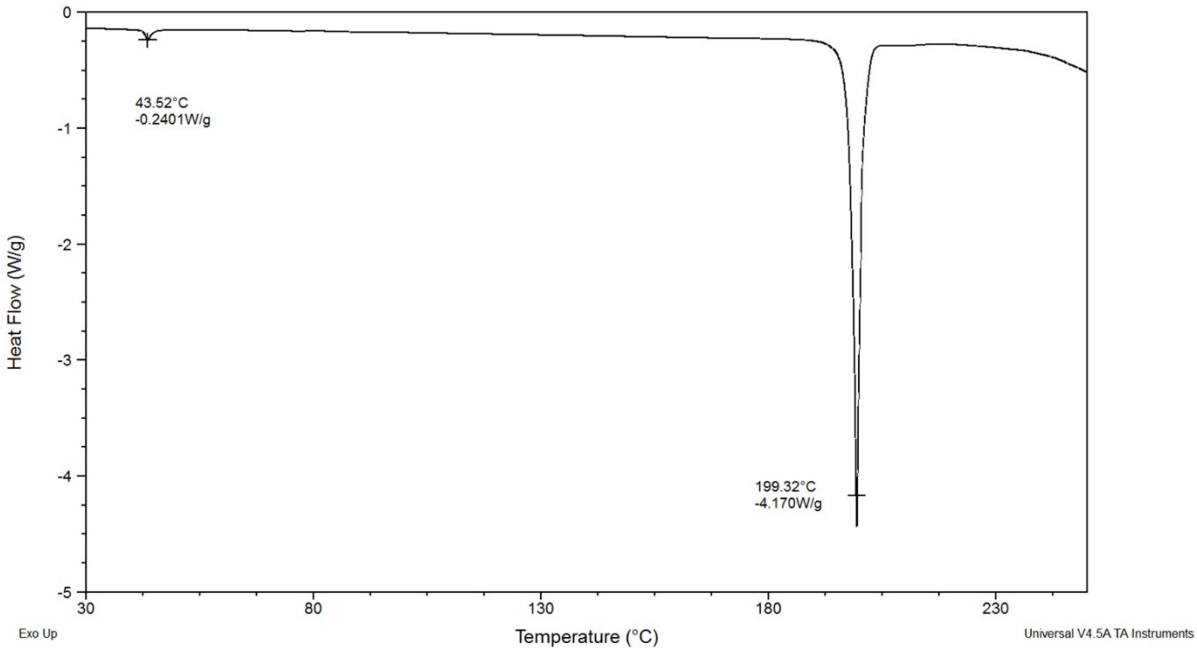

Figure 2. DSC data for commercial probenecid, matching the literature.[1]

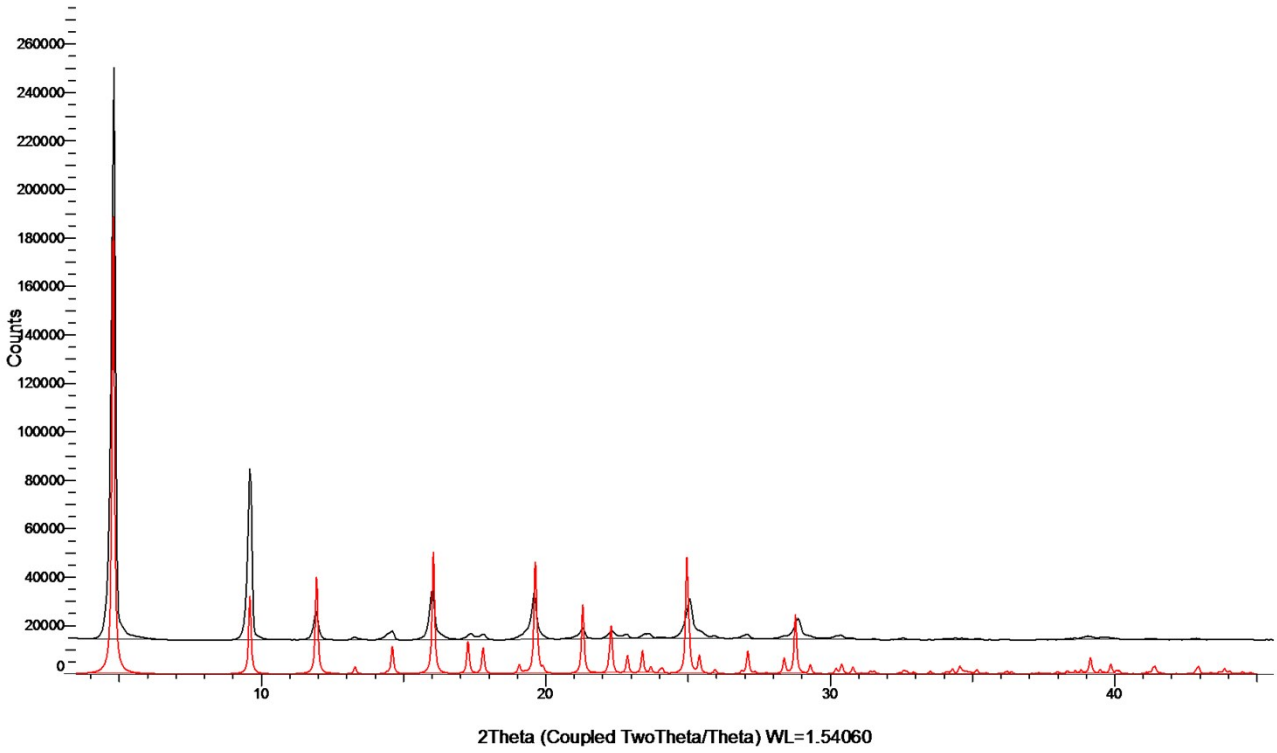

Figure 3. PXRD data for probenecid: commercial (black) and theoretical (red).

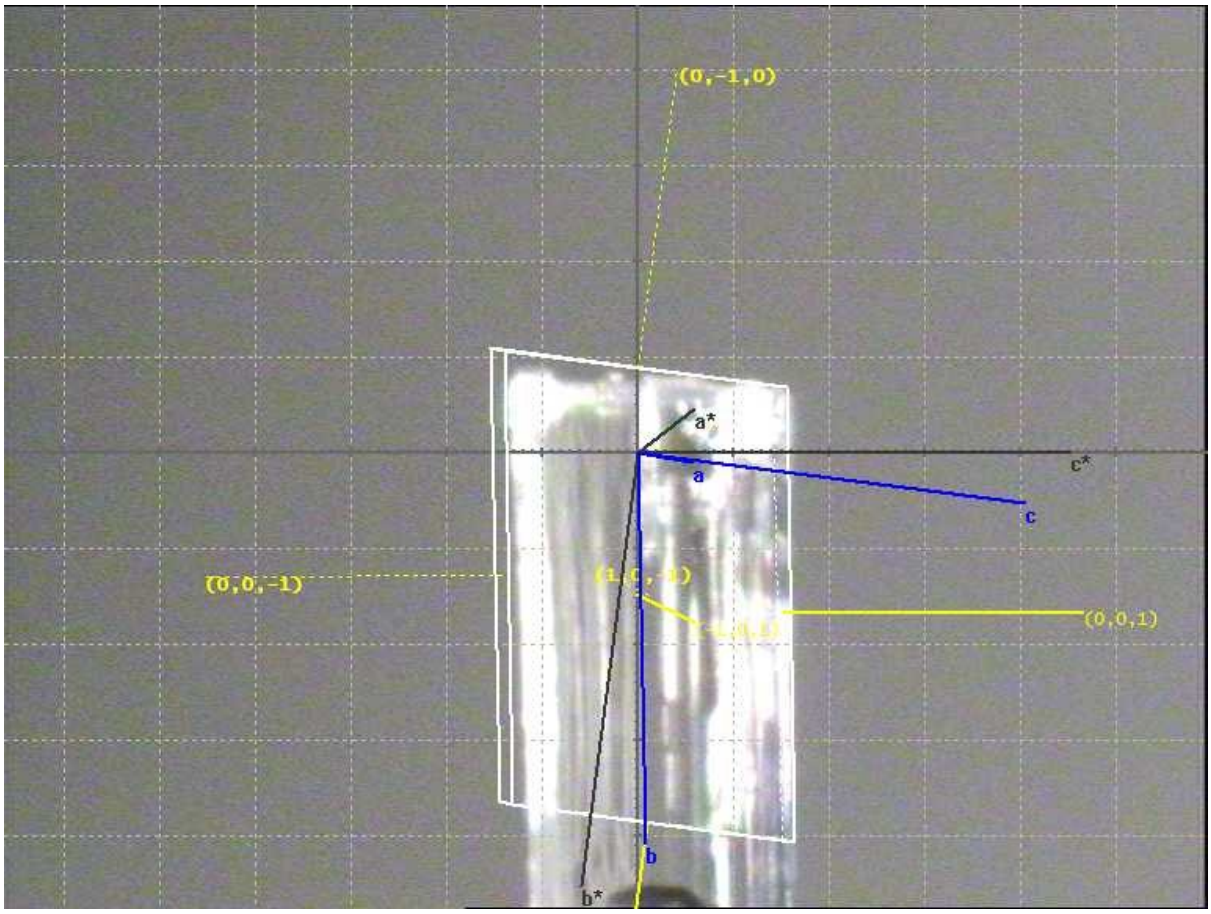

Figure 4 Face-indexed photograph of probenecid.

Table 1 The attachment energies for probenecid.

Face	Slice Attachment.Energy, kcal mol^{-1}
1 0 0	-21.27
0 1 0	-17.36
0 0 1	-7.04

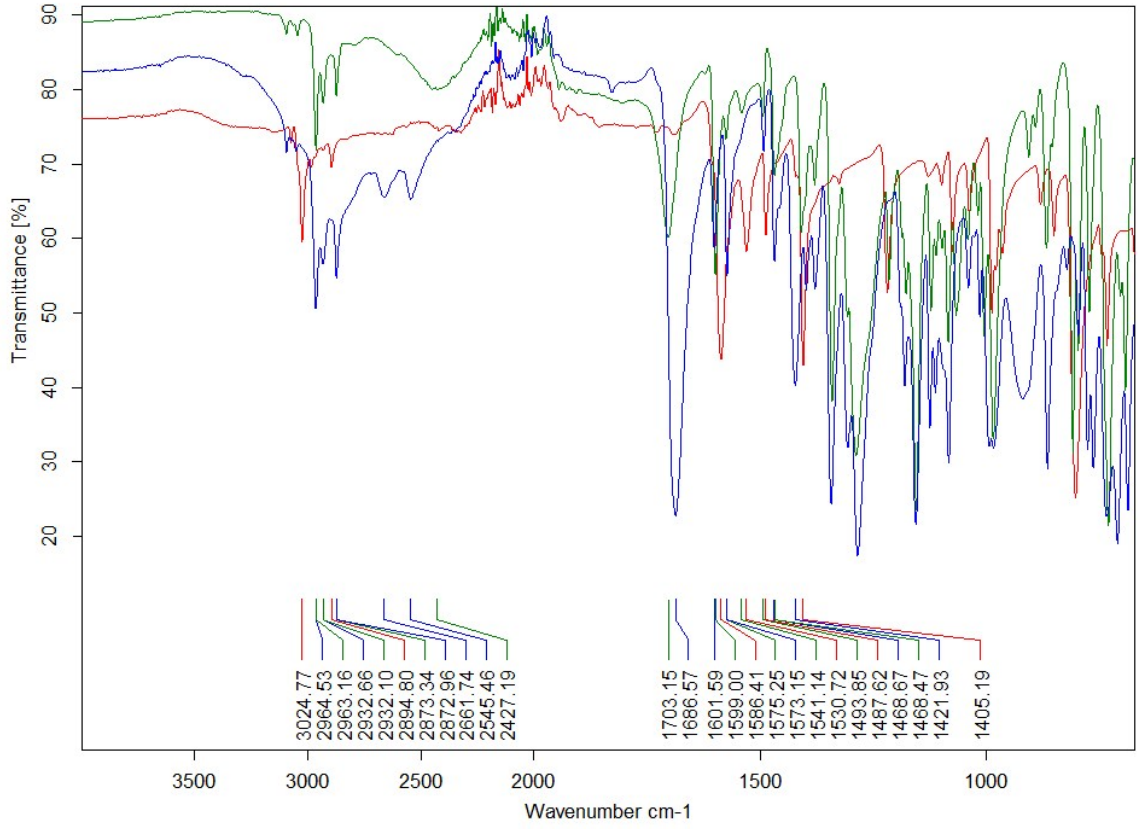

Figure 5. IR spectra comparison for probenecid (blue), 4,4′-bipyridine (red) and the co-crystal (green).

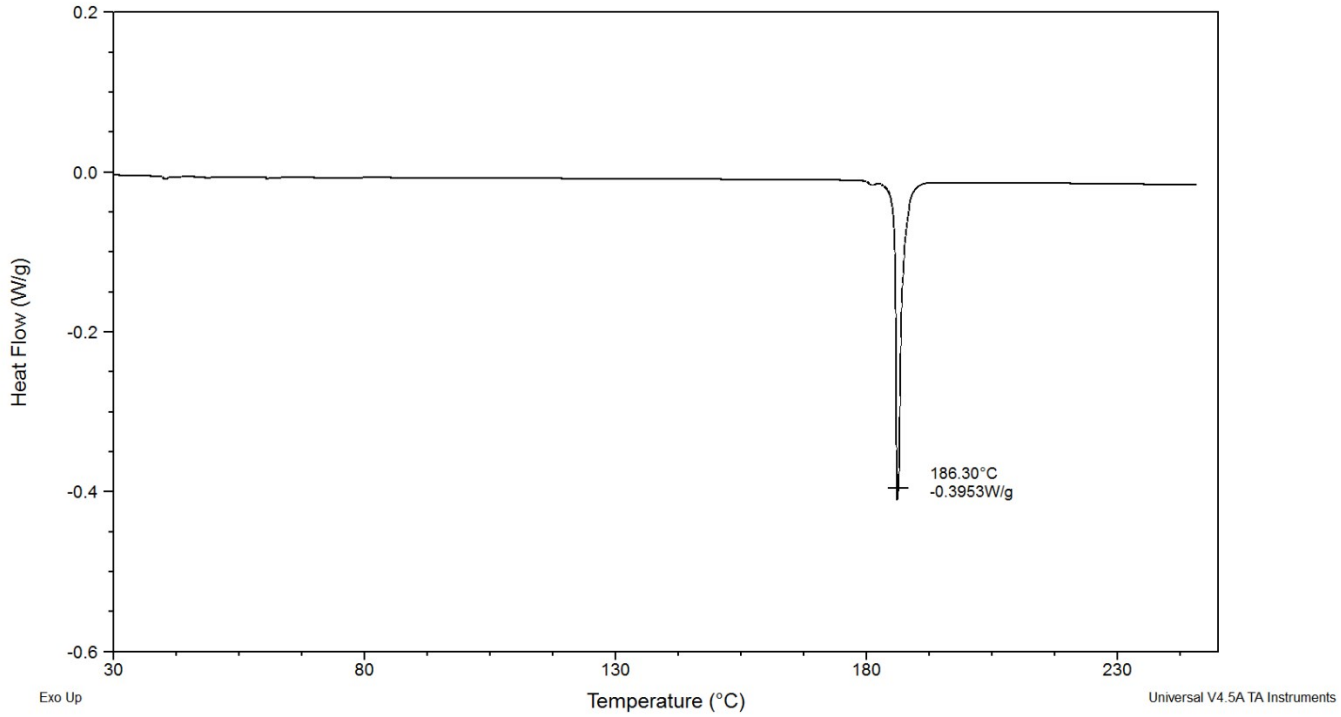

Figure 6. DSC data for the probenecid : 4,4′-bipyridine co-crystal.

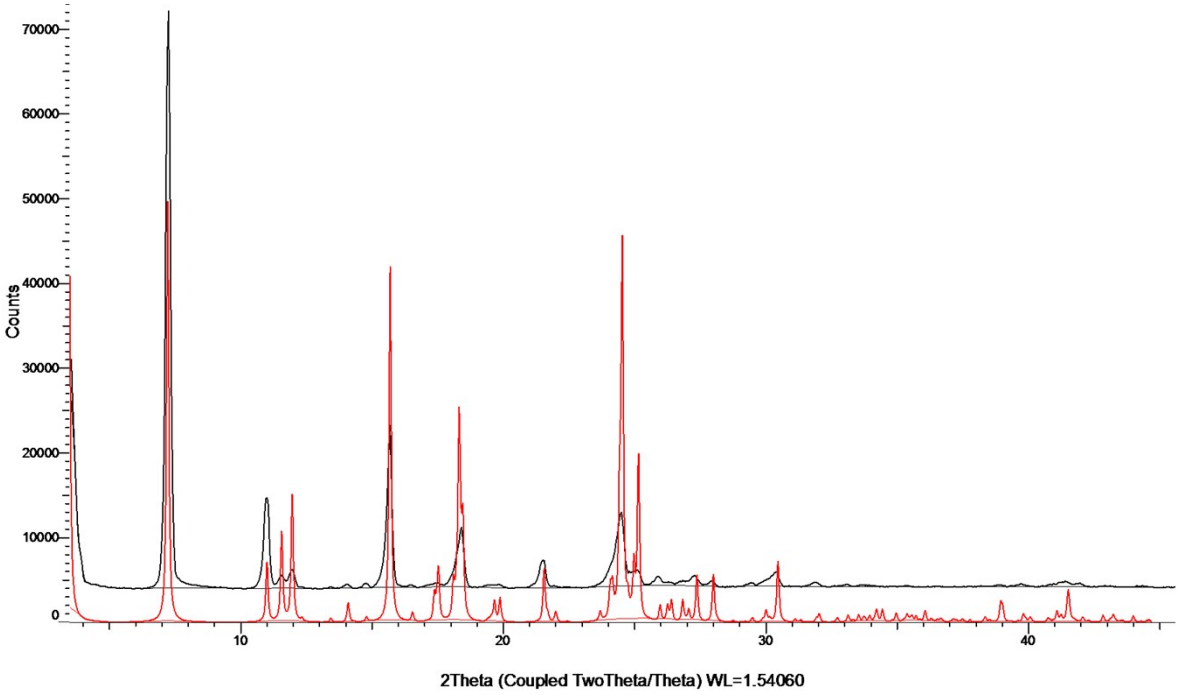

Figure 7. PXRD data for the probenecid : 4,4′-bipyridine co-crystal: experimental (black) and theoretical (red)

Crystallographic data for probenecid : bipyridine

$C_{36}H_{46}N_4O_8S_2$, M= 726.89, triclinic, *P*-1, a=5.3240(11) Å, b=7.8906(14) Å, c=23.599(5) Å, α=85.158(9) ˚, β=83.687(7) ˚, γ=70.746(6) ˚, V=929.0(3) Å, Z=2, D_c= 1.299 g cm^{-3}, F_{000}=386, Mo Kα radiation, λ=0.7107 Å, T=300(2) K, $2\theta_{max}$=26.4 ˚, μ=0.199 mm^{-1}, 10180 reflections collected, 3718 unique (R_{int}=0.0388), final GooF=0.882, R_1=0.0591, wR_2=0.1795, [2645 obs. Data: $I > 2\sigma(I)$]; R_1=0.0864, wR_2=0.1556, (all data).

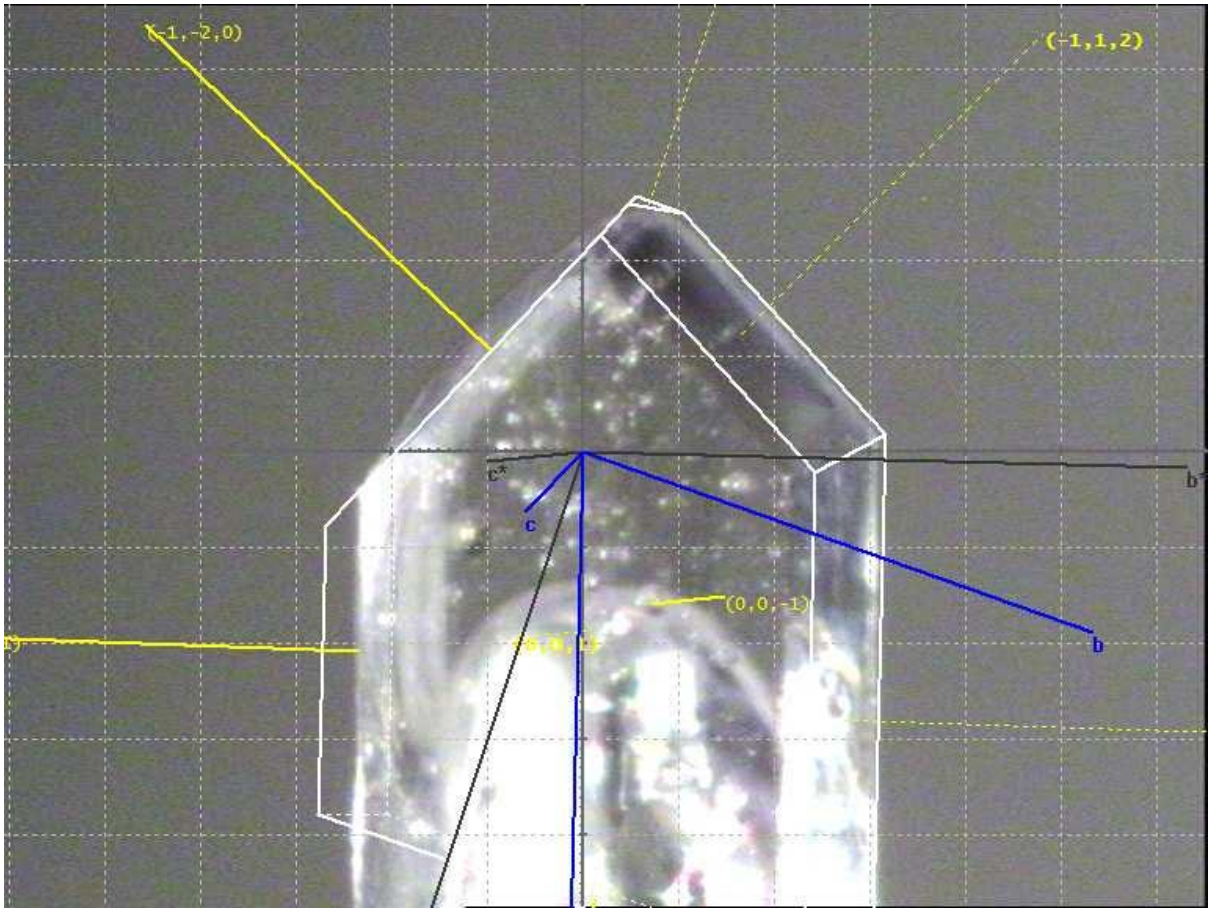

Figure 8 Face-indexed photograph of probenecid : bipyridine.

Table 2 The attachment energies for probenecid : bipyridine.

Face	Slice Attachment.Energy, kcal mol^{-1}
1 0 0	-22.97
0 1 0	-15.22
0 0 1	-5.65

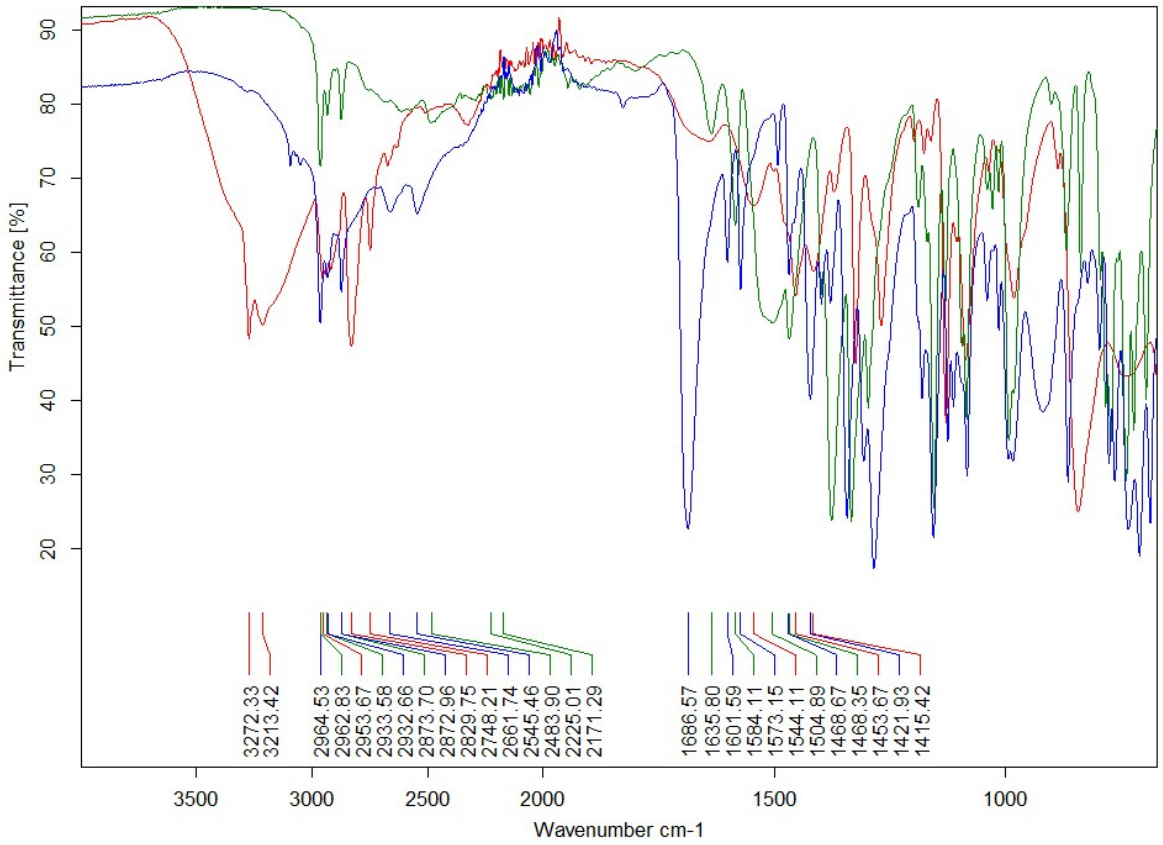

Figure 9. IR spectra comparison for probenecid (blue), piperazine (red) and salt (green).

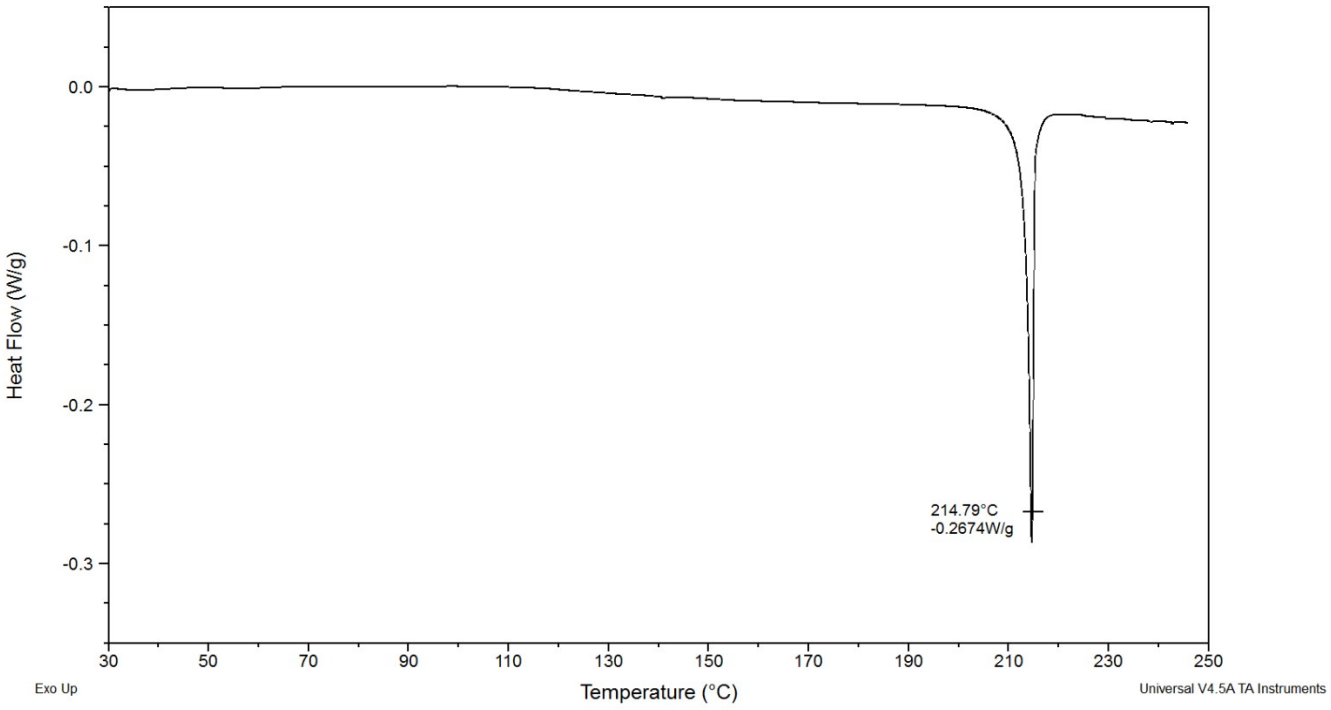

Figure 10. DSC data for probenecid : piperazine salt.

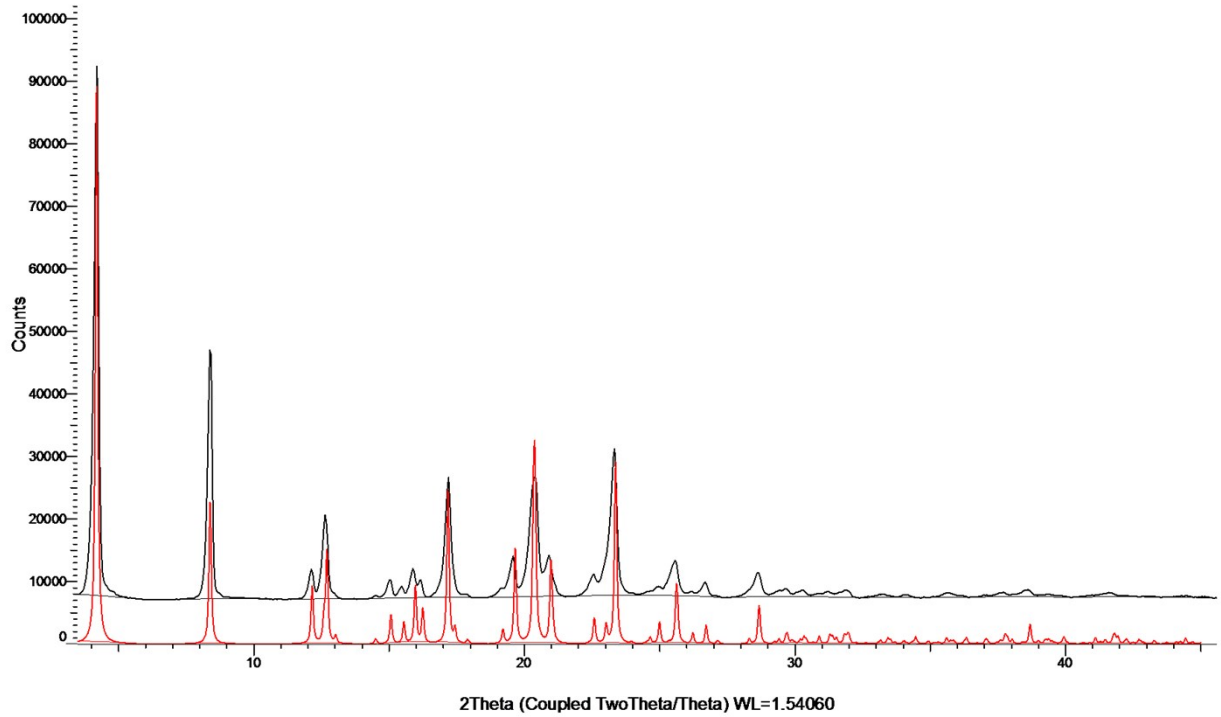

Figure 11. PXRD data for probenecid: piperazine salt: experimental (black) and theoretical (red).

Crystallographic data for probenecid : piperazine

$C_{15}H_{24}N_2O_4S_1$, M=328.42, triclinic, *P*-1, a=5.718(4) Å, b=7.307(4) Å, c=21.178(13) Å, α=92.355(17) °, β=91.732(16) °, γ=93.192(16) °, V=882.3(9)Å, Z=2, D_c= 1.236 g cm^{-3}, F_{000}=352, Mo Kα radiation, λ=0.7107 Å, T=300(2) K, $2\theta_{max}$=26.61 °, μ=0.201 mm^{-1}, 8654 reflections collected, 3550 unique (R_{int}=0.0627), final GooF=1.028, R_1=0.0708, wR_2= 0.2091, [2108 obs. Data: $I > 2\sigma(I)$]; R_1=0.1164, wR_2=0.1841, (all data).

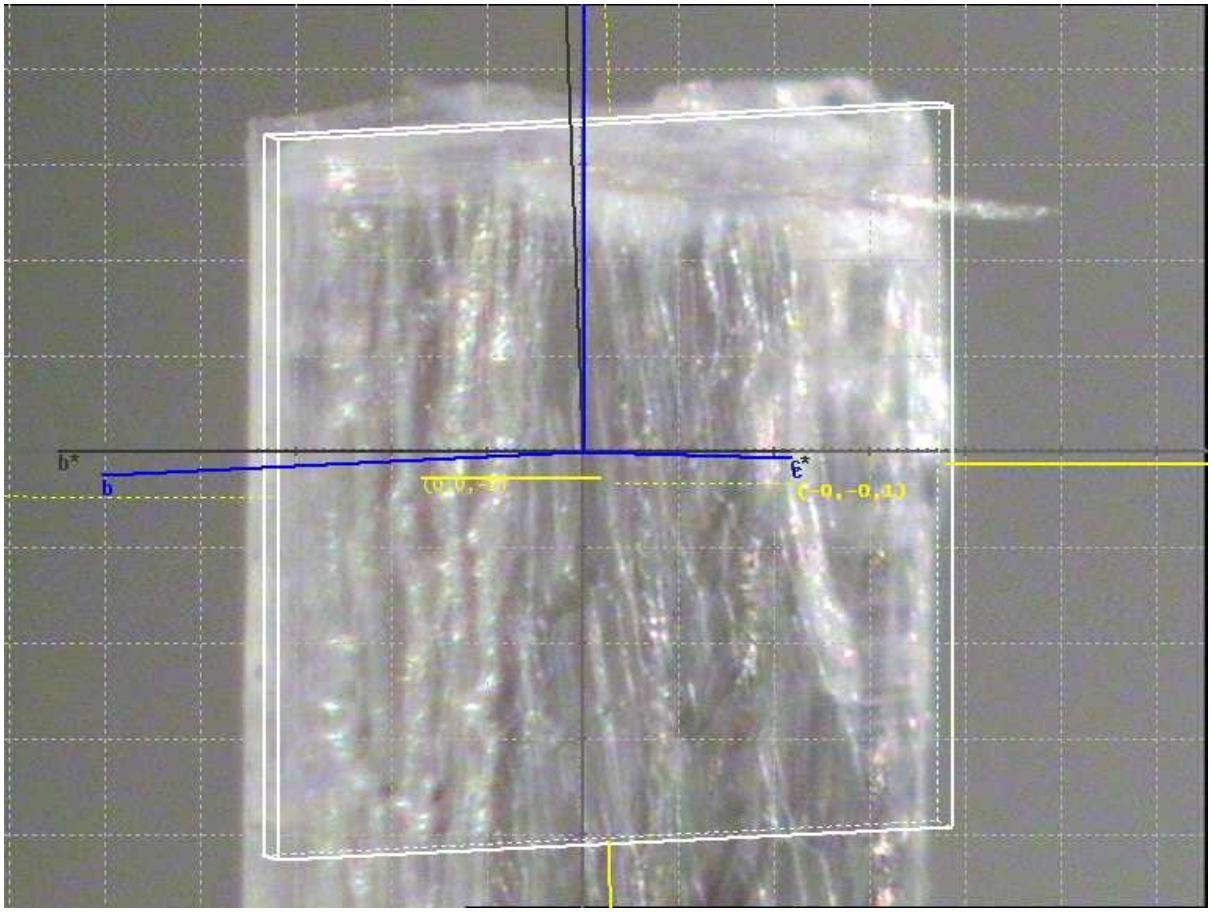

Figure 12 Face-indexed photograph of probenecid : piperazine.

Table 3 The attachment energies for probenecid : piperazine.

Face	Slice Attachment.Energy, kcal mol^{-1}
1 0 0	-79.06
0 1 0	-71.75
0 0 1	-61.32

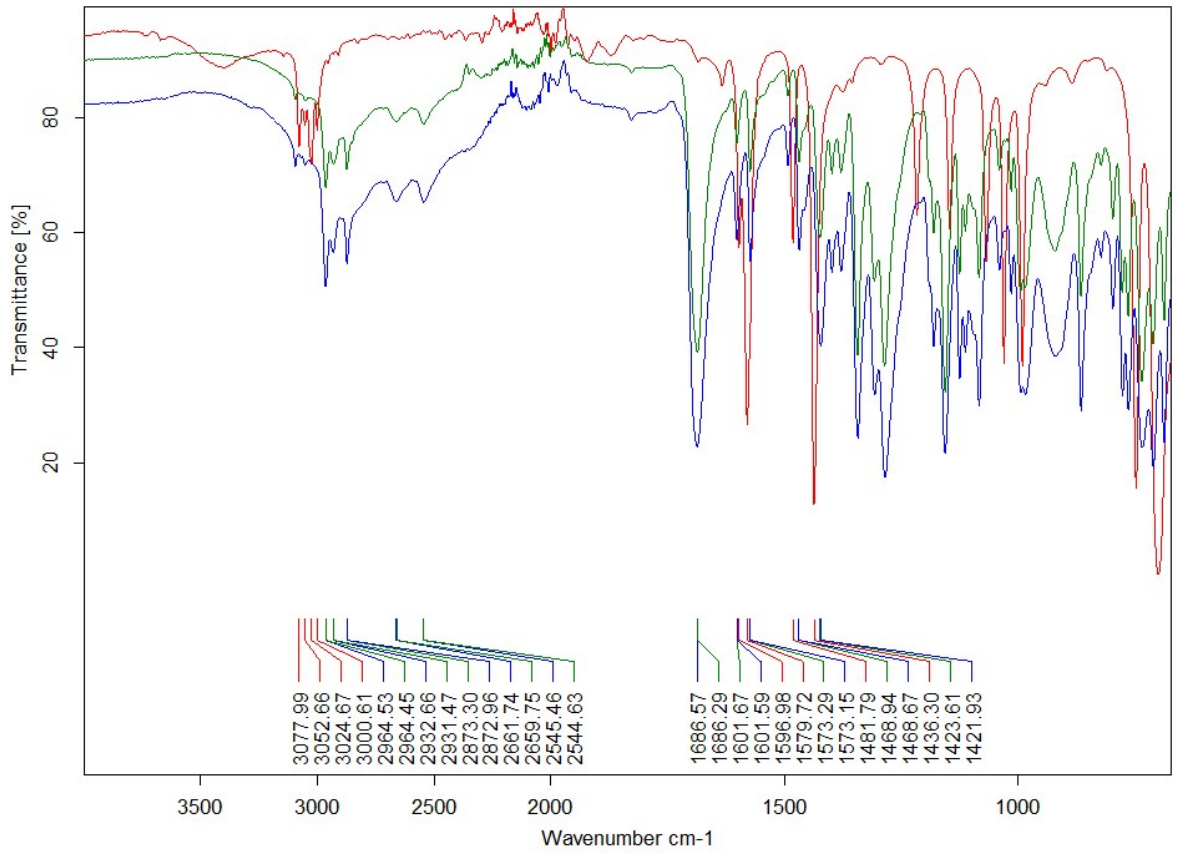

Figure 13. IR spectra comparison for probenecid (blue), pyridine (red) and co-crystal (green).

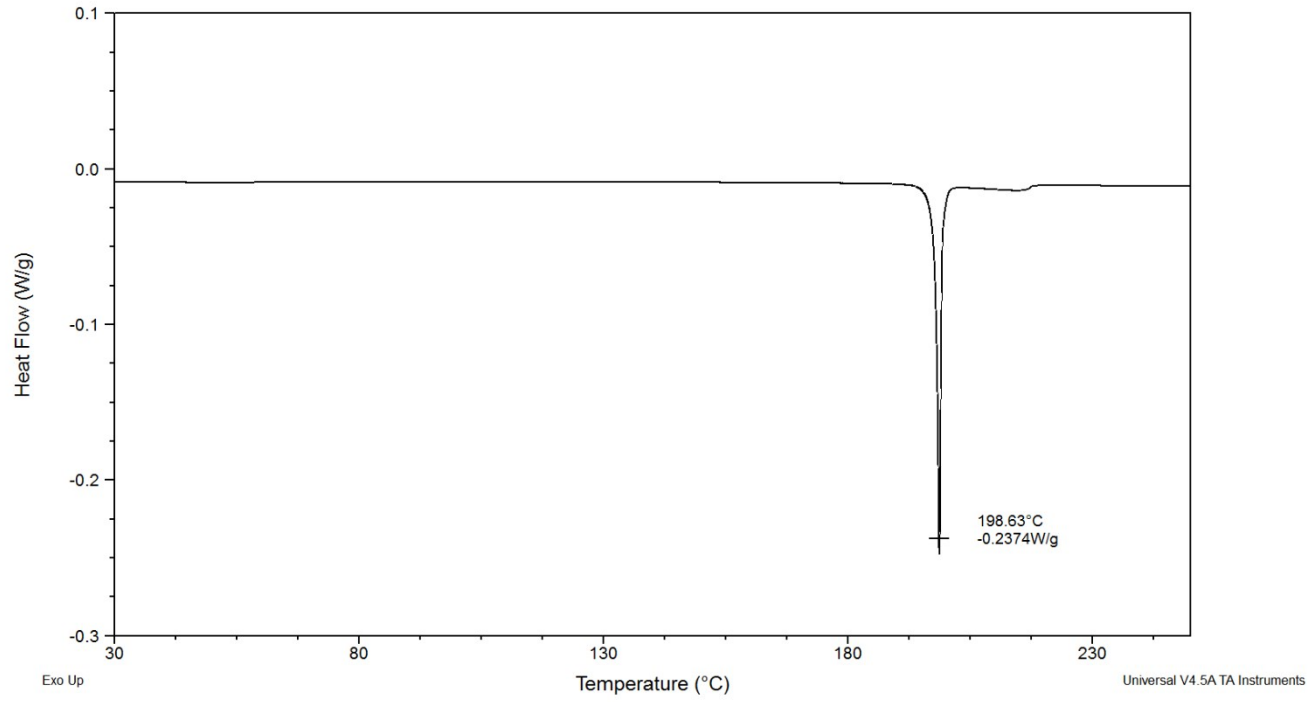

Figure 14. DSC data for probenecid : pyridine co-crystal.

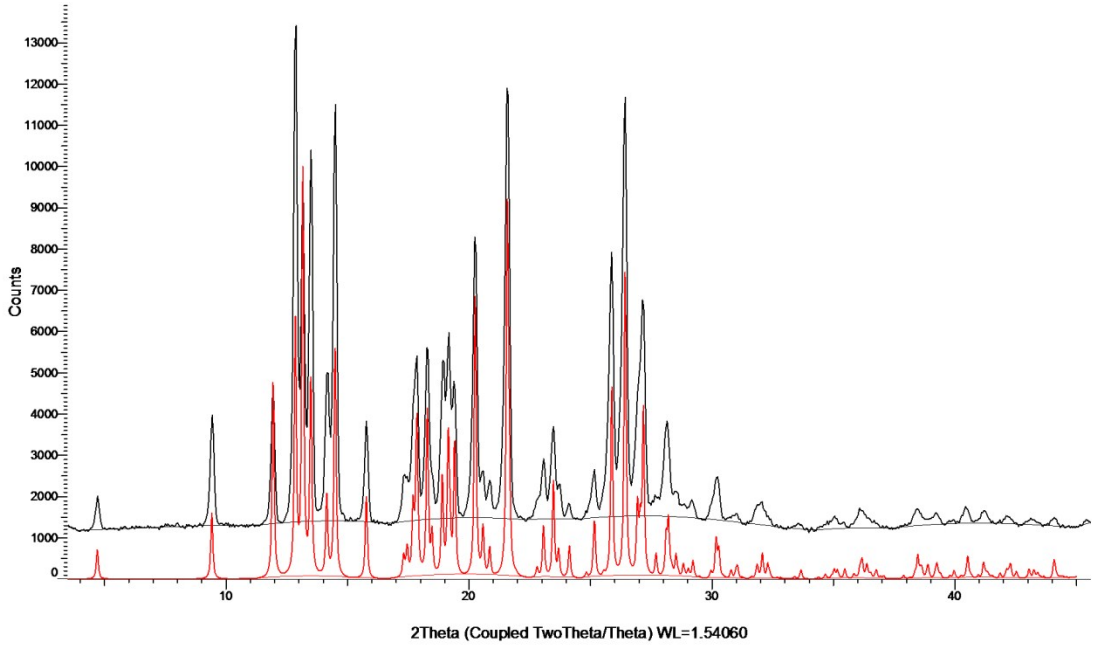

Figure 15. PXRD data for probenecid : pyridine co-crystal: experimental (black) and theoretical (red).

Crystallographic data for probenecid : pyridine

$C_{18}H_{24}N_2O_4S_1$, M=364.45, monoclinic, $P2_1/c$, a=7.4241(8) Å, b=6.9988(8) Å, c=37.621(4) Å, β=94.210(4) °, V=1949.5(4) Å, Z=4, D_c=1.242 g cm^{-3}, F_{000}=776, Mo Kα radiation, λ=0.7107 Å, T=300(2) K, $2\theta_{max}$=26.36 °, μ=0.189 mm^{-1}, 16381 reflections collected, 3897 unique (R_{int}=0.0441), final GooF=1.064, R_1=0.0876, wR_2=0.2756, [2773 obs. Data: $I > 2\sigma(I)$]; R_1=0.1138, wR_2=0.2460, (all data).

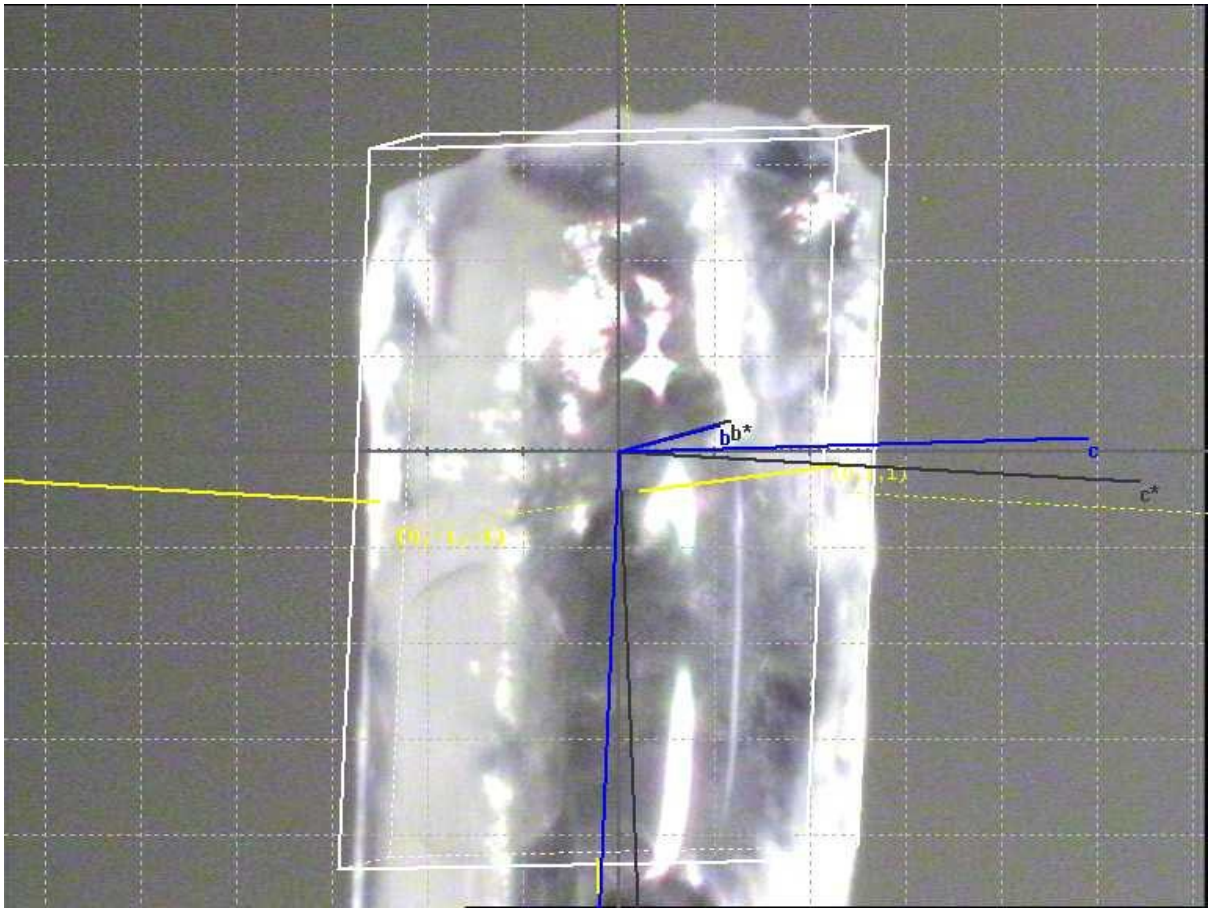

Figure 16 Face-indexed photograph of probenecid : pyridine.

Table 4 The attachment energies for probenecid : pyridine.

Face	Slice Attachment.Energy, kcal mol^{-1}
0 0 2	-13.58
1 0 0	-18.73
1 0 -2	-23.62
0 1 -1	-18.42
1 0 2	-24.31
0 1 -2	-18.78
1 -1 0	-23.59
1 -1 -1	-26.06

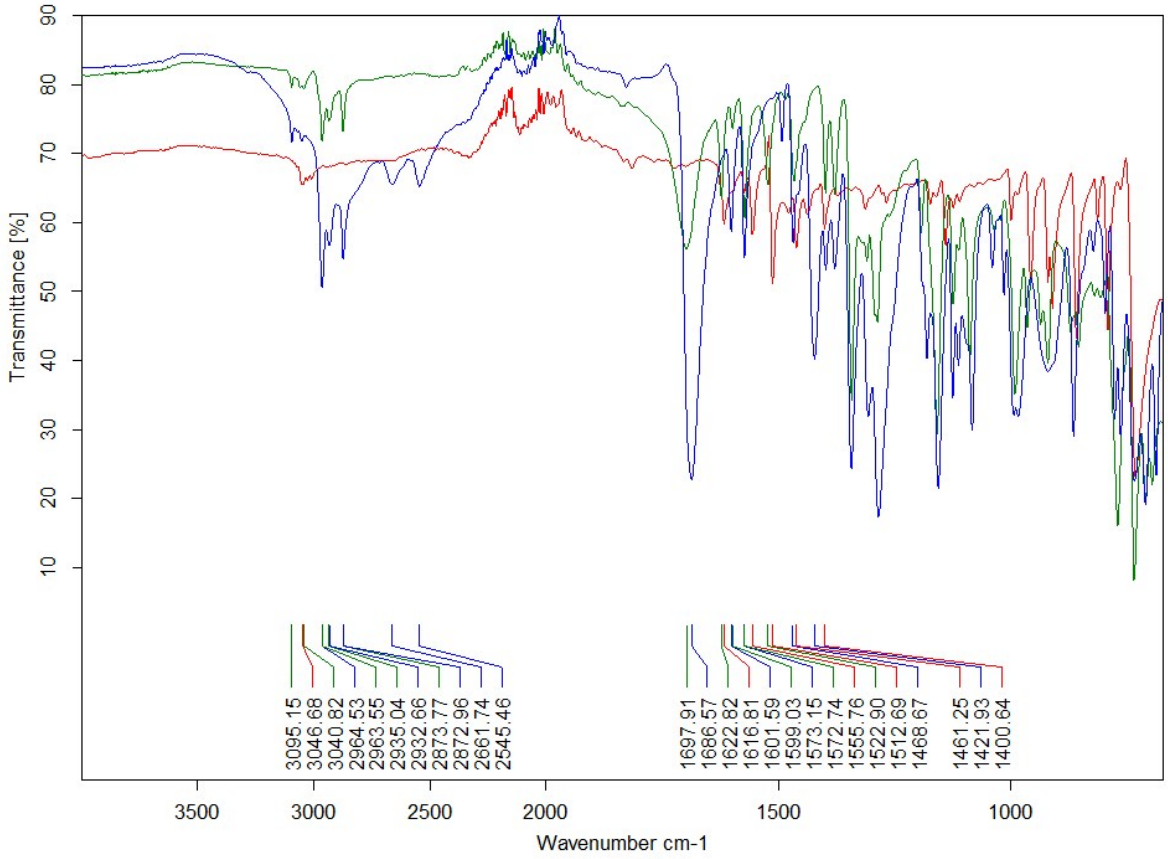

Figure 17. IR spectra comparison for probenecid (blue), acridine (red) and co-crystal (green).

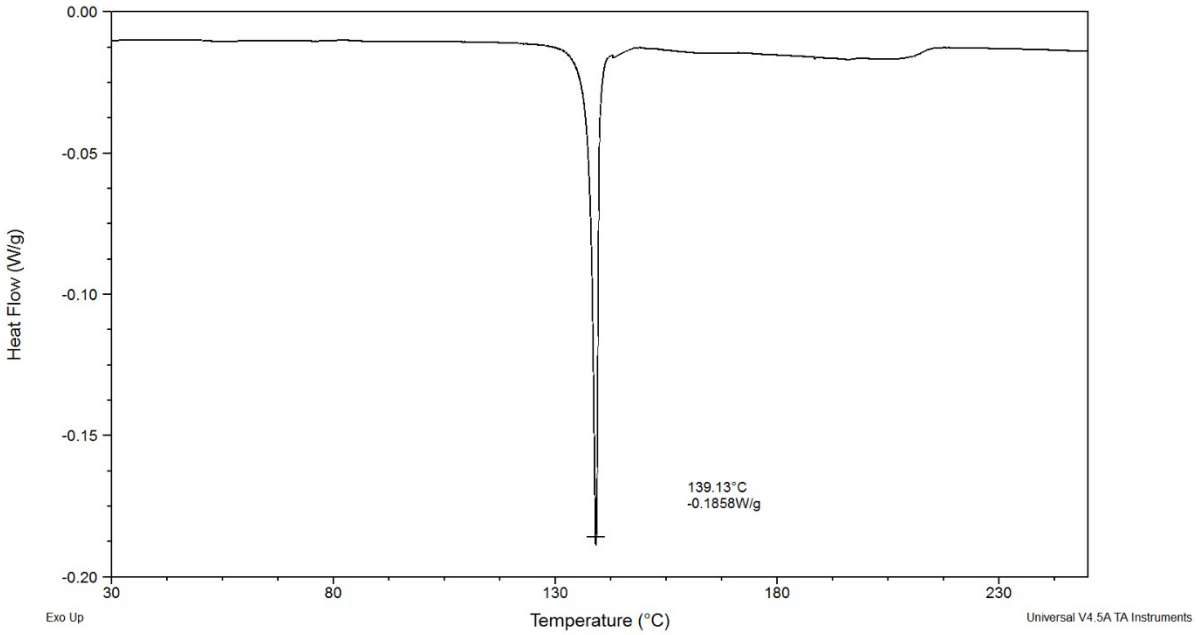

Figure 18. DSC data for probenecid : acridine co-crystal.

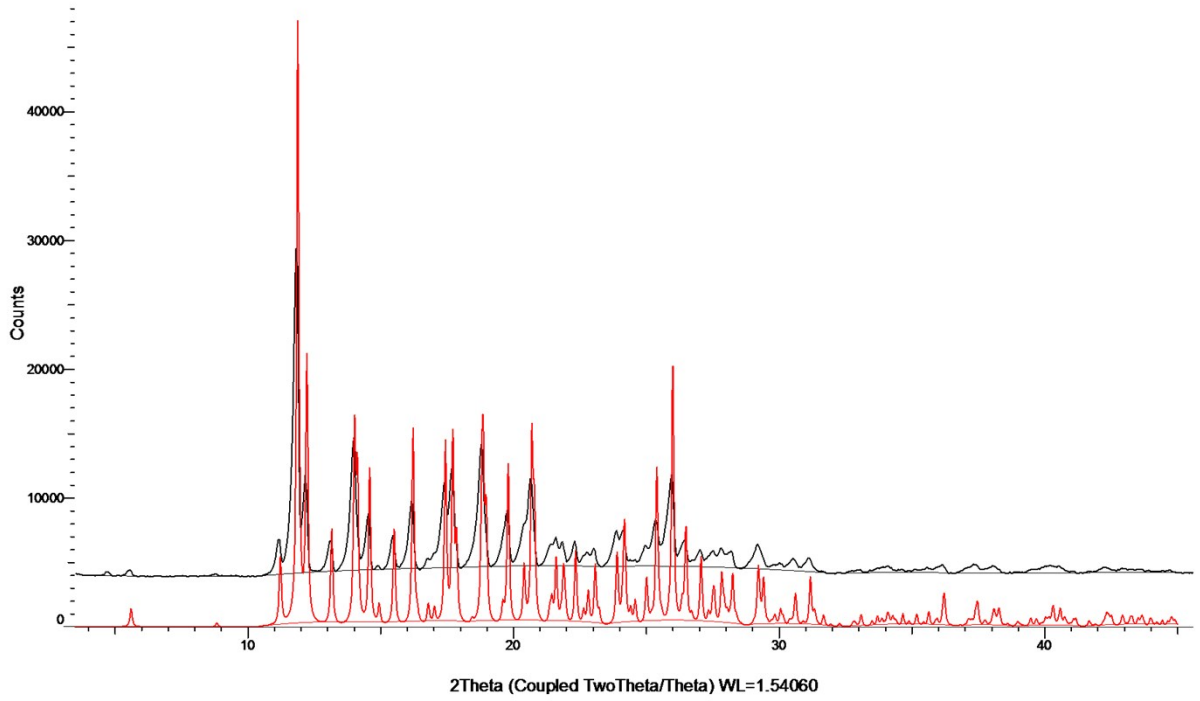

Figure 19. PXRD data for probenecid : acridine co-crystal: experimental (black) and theoretical (red)

Crystallographic data for probenecid : acridine

$C_{26}H_{28}N_2O_4S_1$, M=464.56, monoclinic, $P2_1/c$, a=7.4752(7) Å, b=31.526(3) Å, c=10.6100(9) Å, β=95.799(3) °, V=2487.6(4) Å, Z=4, D_c= 1.240 g cm^{-3}, F_{000}=984, Mo Kα radiation, λ=0.7107 Å, T=300(2) K, $2\theta_{max}$=26.47 °, μ=0.164 mm^{-1}, 27198 reflections collected, 5107 unique (R_{int}=0.0441), final GooF=0.988, R_1= 0.0419, wR_2= 0.988, [3788 obs. Data: $I > 2\sigma(I)$]; R_1= 0.0620, wR_2=0.1048, (all data).

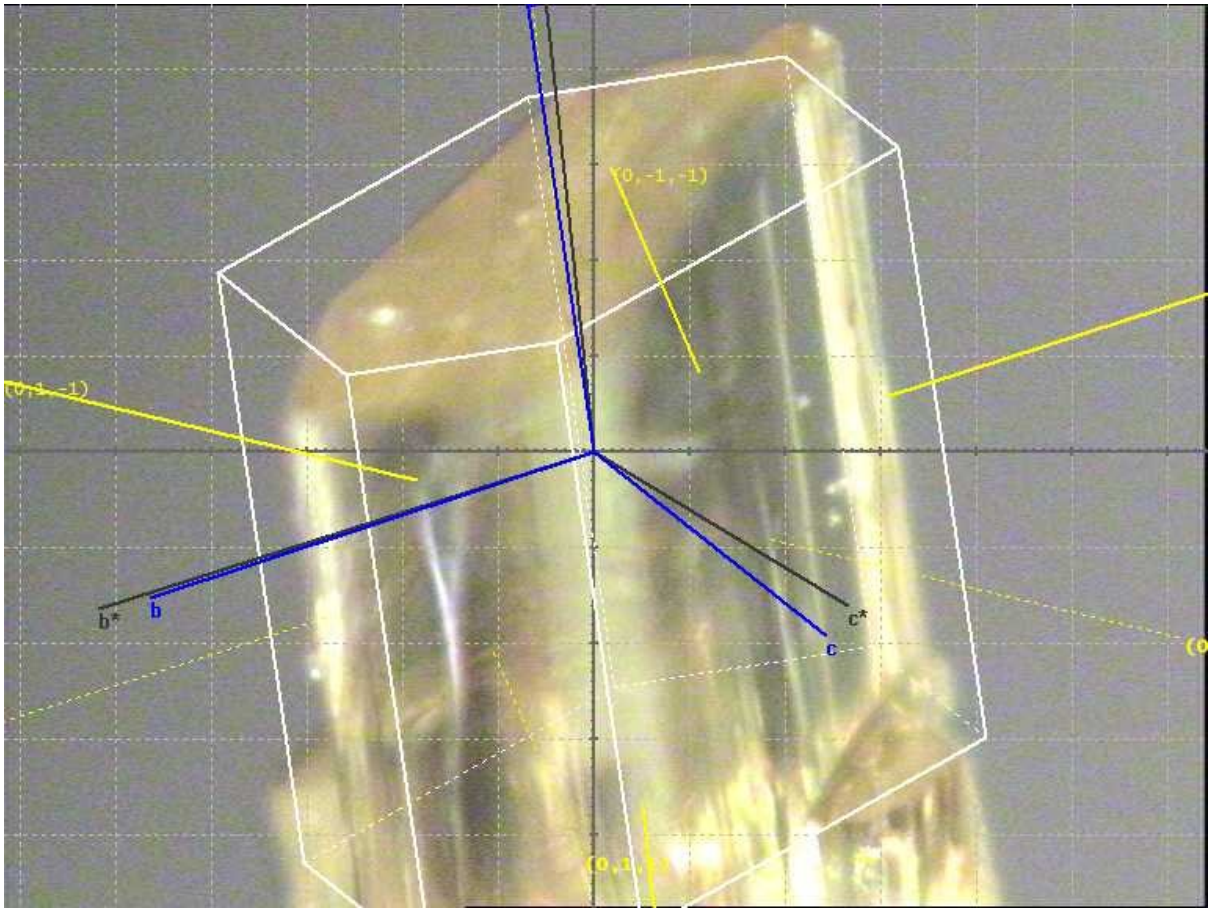

Figure 20 Face-indexed photograph of probenecid : acridine.

Table 5 The attachment energies for probenecid : acridine.

Face	Slice Attachment.Energy, kcal mol^{-1}
0 2 0	-17.37
0 1 -1	-12.00
0 2 -1	-15.22
1 0 0	-12.32
1 -1 0	-14.90
1 -2 0	-19.88
1 -1 -1	-15.98

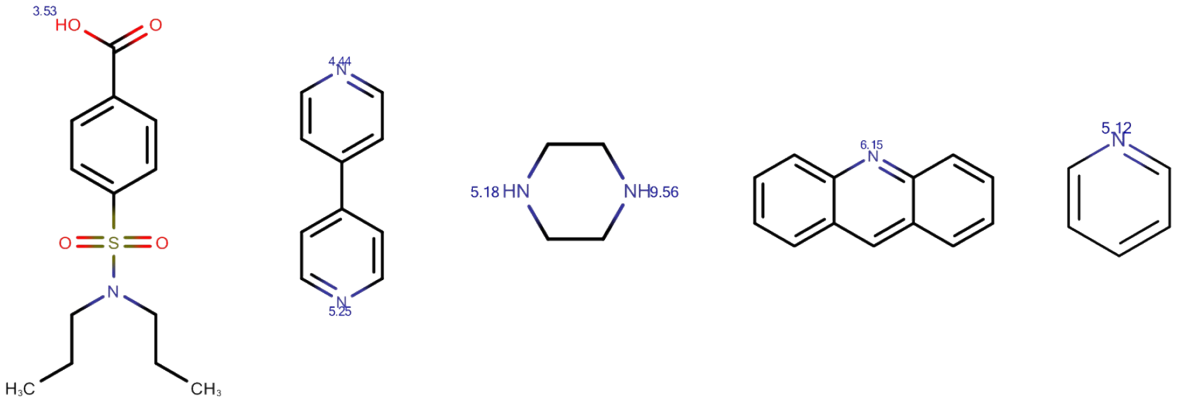

Figure 21 p*K*a values for probenecid and co-formers, calculated using MarvinSketch.[2]

Table 6 Reported and calculate p*K*a values for probenecid and co-formers.

Compound	**p*K*a reported**	**p*K*a from MarvinSketch.[2]**
Probenecid	3.40 [3]	3.53
Piperazine	9.73 [4]	9.56
Bipyridine	4.82 [5]	4.44
Acridine	5.62 [6]	6.15
Pyridine	5.25 [7]	5.12

References:

1. E. Nauha, and J. Bernstein, *J. Pharm. Sci.,* 2015, **104**, 2056-2061.
2. Marvin, 16.9.5.0, 2016, ChemAxon, http://www.chemaxon.com
3. Drug bank, https://www.drugbank.ca/drugs/DB01032
4. Drug bank, https://www.drugbank.ca/drugs/DB00592
5. C. Öğretir, İ. İ. Öztürk, and N. F. Tay, *ARKIVOC* 2009, xiv, 235– 254.
6. Y. Huh, J. -G. Lee, D. C. McPhail and K. Kim, *J. Solution Chem.*, 1993, **22**, 651-661.
7. I. -J. Chen and A. D. MacKerell Jr. *Theor. Chem. Acc.,* 2000, **103**, 483–494.