Electronic Supplementary Information (ESI)†

Single step synthesis of multi-component cocrystals and salts: the role of laboratory seeding

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Table S1. Ternary cocrystals and salts and their detailed experimental procedure

Sl. No.	Ternary system	Method and Sequence of addition	Figure number and Results
1	ACZ-NAM-2HP (1:1:1)	M1(a): ACZ + NAM, LAG for 30 min. Then add 2HP, and continue LAG for 30 min. M1(b): ACZ + 2HP, LAG for 30 min. Then add NAM, and continue LAG for 30 min. M2: Direct addition of ACZ + NAM + 2HP, LAG for 30 min. EtOAc for LAG	Figure S1 Match between M1(a), M1(b) and M2 PXRD lines Mismatch with calculated PXRD pattern 1H NMR is shown in Figure S12 (a)
2	SMBA-PAM-MeHP (1:1:1)	M1(a): SMBA + PAM, LAG for 30 min. Then add MeHP, and continue LAG for 30 min. M1(b): SMBA + MeHP, LAG for 30 min. Then add PAM, and continue LAG for 30 min. M2: Direct addition of SMBA + PAM + MeHP, LAG for 30 min. EtOAc for LAG	Figure S2 Match between M1(a), M1(b) and M2 PXRD lines Match with calculated PXRD pattern
3	SMBA-NAM-MeHP (1:1:1)	M1(a): SMBA + NAM, LAG for 30 min. Then add MeHP, and continue LAG for 30 min. M1(b): SMBA + MeHP, LAG for 30 min. Then add NAM, and continue LAG for 30 min. M2: Direct addition of SMBA + NAM + MeHP, LAG for 30 min.	Figure S3 Match between M1(a), M1(b) and M2 PXRD lines Match with calculated PXRD pattern

		EtOAc for LAG	
4	BUM-INA-PCA (1:1:1)	M1(a): BUM + INA, LAG for 30 min. Then add PCA, and continue LAG for 30 min. M1(b): BUM + PCA, LAG for 30 min. Then add INA, and continue LAG for 30 min. M2: BUM + INA + PCA, LAG for 30 min. EtOAc for LAG	Figure S4 Match between M1(a), M1(b) and M2 PXRD lines PXRD pattern matches with the reported line pattern in the original paper 1H NMR is shown in Figure S16
5	BUM-INA-VLA (1:1:1)	M1(a): BUM + INA, LAG for 30 min. Then add VLA, and continue LAG for 30 min. M1(b): BUM + VLA, LAG for 30 min. Then add INA, and continue LAG for 30 min. M2: BUM + INA + VLA, LAG for 30 min. EtOAc for LAG	Figure S5 Match between M1(a), M1(b) and M2 PXRD lines PXRD pattern matches with the reported line pattern in the original paper 1H NMR is shown in Figure S17
6	4NBA-OA-DIB (2:1:1)	M1(a): 4NBA + OA, LAG for 30 min. Then add DIB, and continue LAG for 30 min. M1(b): 4NBA + DIB, LAG for 30 min. Then add OA, and continue LAG for 30 min. M1(c): OA + DIB, LAG for 30 min. Then add 4NBA, and continue LAG for 30 min. M2: Direct addition of 4NBA + OA + DIB, LAG for 30 min. EtOH for LAG	Figure S6 Match between M1(a), M1(b), M1(c) and M2 PXRD lines Match with calculated PXRD pattern
7	4NBA-OA-BIB (2:1:1)	M1(a): 4NBA + OA, LAG for 30 min. Then add BIB, and continue LAG for 30 min. M1(b): 4NBA + BIB, LAG for 30 min. Then add OA, and continue LAG for 30 min. M1(c): OA + BIB, LAG for 30 min. Then add 4NBA, and continue LAG for 30 min.	Figure S7 Match between M1(a), M1(b), M1(c) and M2 PXRD lines Match with calculated PXRD pattern

		M2: Direct addition of 4NBA + OA + BIB, LAG for 30 min. EtOH for LAG	
8	PRZ-FLA-PRA (0.5:1:2)	M1(a): PRZ + FLA**,** LAG for 30 min. Then add PRA, and continue LAG for 30 min. M1(b): PRZ + PRA, LAG for 30 min. Then add FLA, and continue LAG for 30 min. M1(b): FLA + PRA, LAG for 30 min. Then add PRZ, and continue LAG for 30 min. M2: Direct addition of PRZ + FLA + PRA, LAG for 30 min. Acetone for LAG,	Figure S8 Match between M1(a), M1(b), M1(c) and M2 PXRD lines Mismatch with calculated PXRD pattern 1H NMR is shown in Figure S20
9	PRZ-FLA-PRA (1:2:2)	M1(a): PRZ + FLA**,** LAG for 30 min. Then add PRA, and continue LAG for 30 min. M1(b): PRZ + PRA, LAG for 30 min. Then add FLA, and continue LAG for 30 min. M1(b): FLA + PRA, LAG for 30 min. Then add PRZ, and continue LAG for 30 min. M2: Direct addition of PRZ + FLA + PRA, LAG for 30 min. Acetone for LAG,	Figure S9 Match between M1(a), M1(c) and M2 PXRD lines Mismatch of M1(a), M1(c) and M2 with M1(b) Mismatch of M1(a), M1(b), M1(c) and M2 with calculated PXRD pattern 1H NMR is shown in Figure S21
10	PRZ-FLA-PRA (0.5:1:2)	M2: Direct addition of PRZ + FLA + PRA, BMG for 90 min. Acetone for BMG, milling frequency 25 Hz	Figure S10 Match with manual grinding results but mismatch with calculated PXRD pattern 1H NMR is shown in Figure S22
11	PRZ-FLA-PRA (1:2:2)	M2: Direct addition of PRZ + FLA + PRA, BMG for 90 min. Acetone for BMG, milling frequency 25 Hz	Figure S11 Mismatch with manual grinding results and calculated PXRD pattern 1H NMR is shown in Figure S23

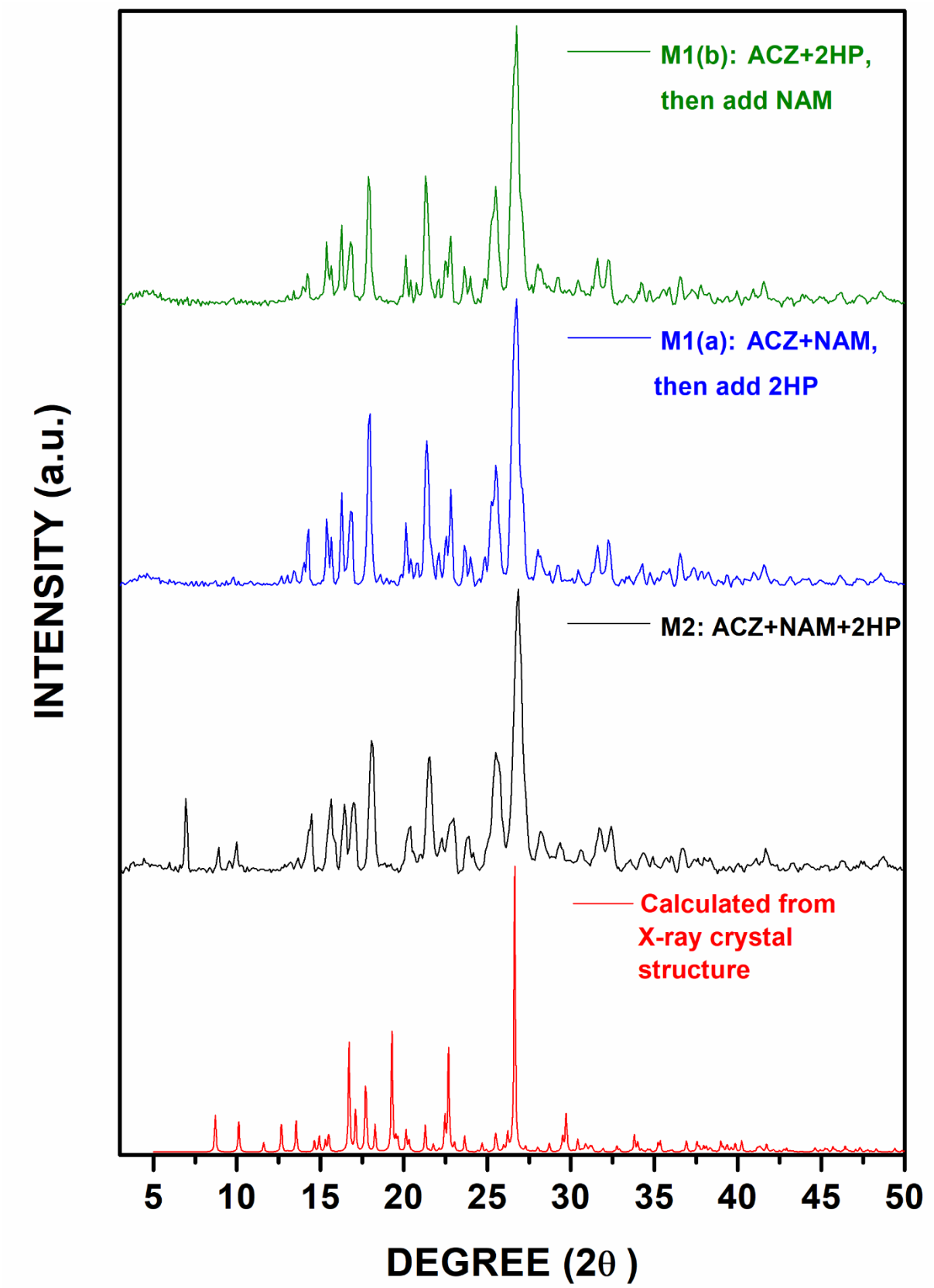


Figure S1. Overlay PXRD plots of ACZ-NAM-2HP (1:1:1) using different manual grinding conditions. M1(a): ACZ + NAM, then 2HP (blue); M1(b) SMBA + 2HP, then NAM (green); M2: ACZ + NAM + 2HP (black); calculated from the X-ray crystal structure (red). ^{1}H NMR of this cocrystal is shown in Figure S12 (a).

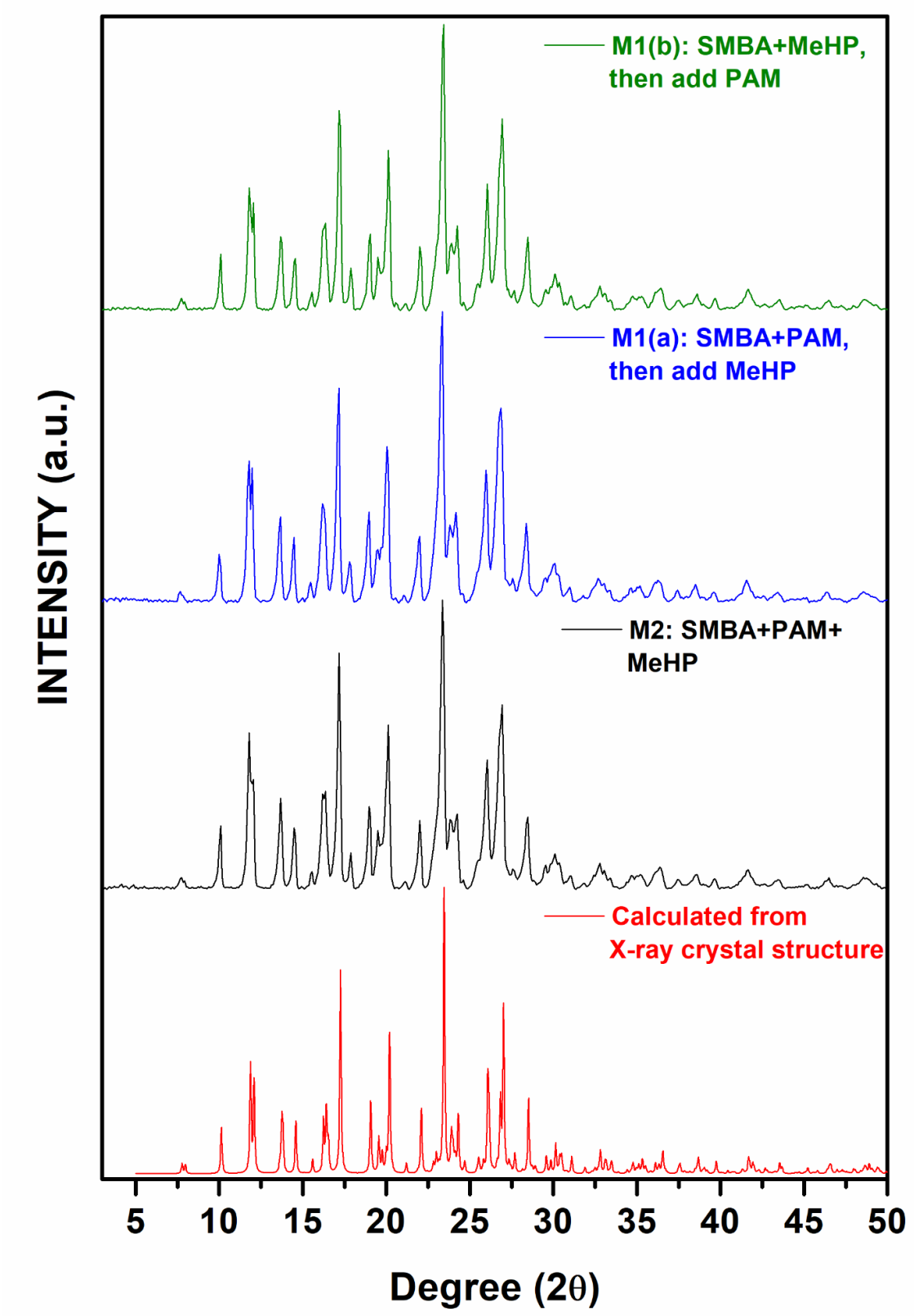


Figure S2. Overlay PXRD plots of SMBA-PAM-MeHP (1:1:1) using different manual grinding conditions. M1(a): SMBA + PAM, then MeHP (blue); M1(b) SMBA + MeHP, then PAM (green); M2: SMBA + PAM + MeHP (black); calculated from the X-ray crystal structure (red).

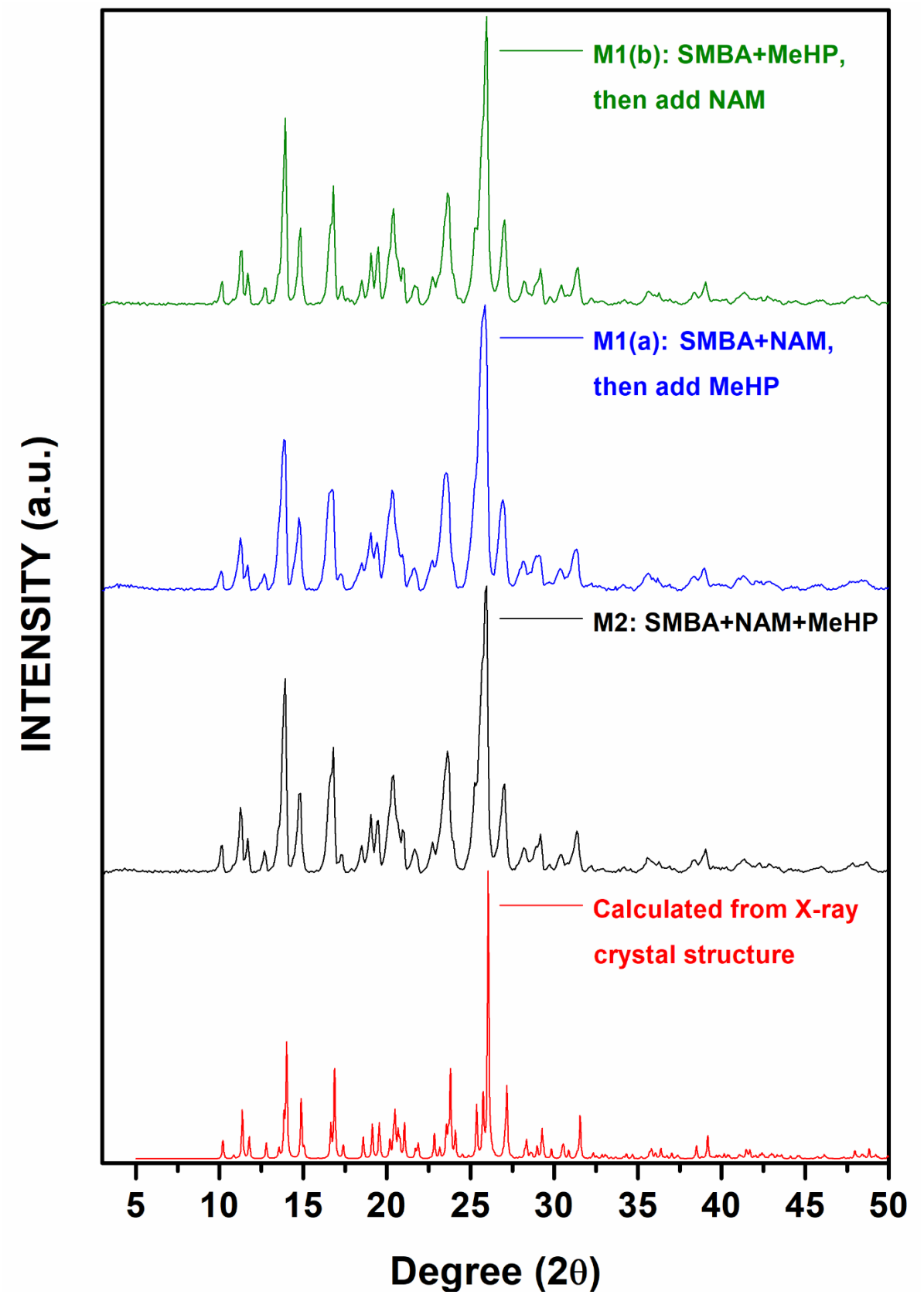


Figure S3. Overlay PXRD plots of SMBA-NAM-MeHP (1:1:1) using different manual grinding conditions. M1(a): SMBA + NAM, then MeHP (blue); M1(b) SMBA + MeHP, then NAM (green); M2: SMBA + NAM + MeHP (black); calculated from the X-ray crystal structure (red).

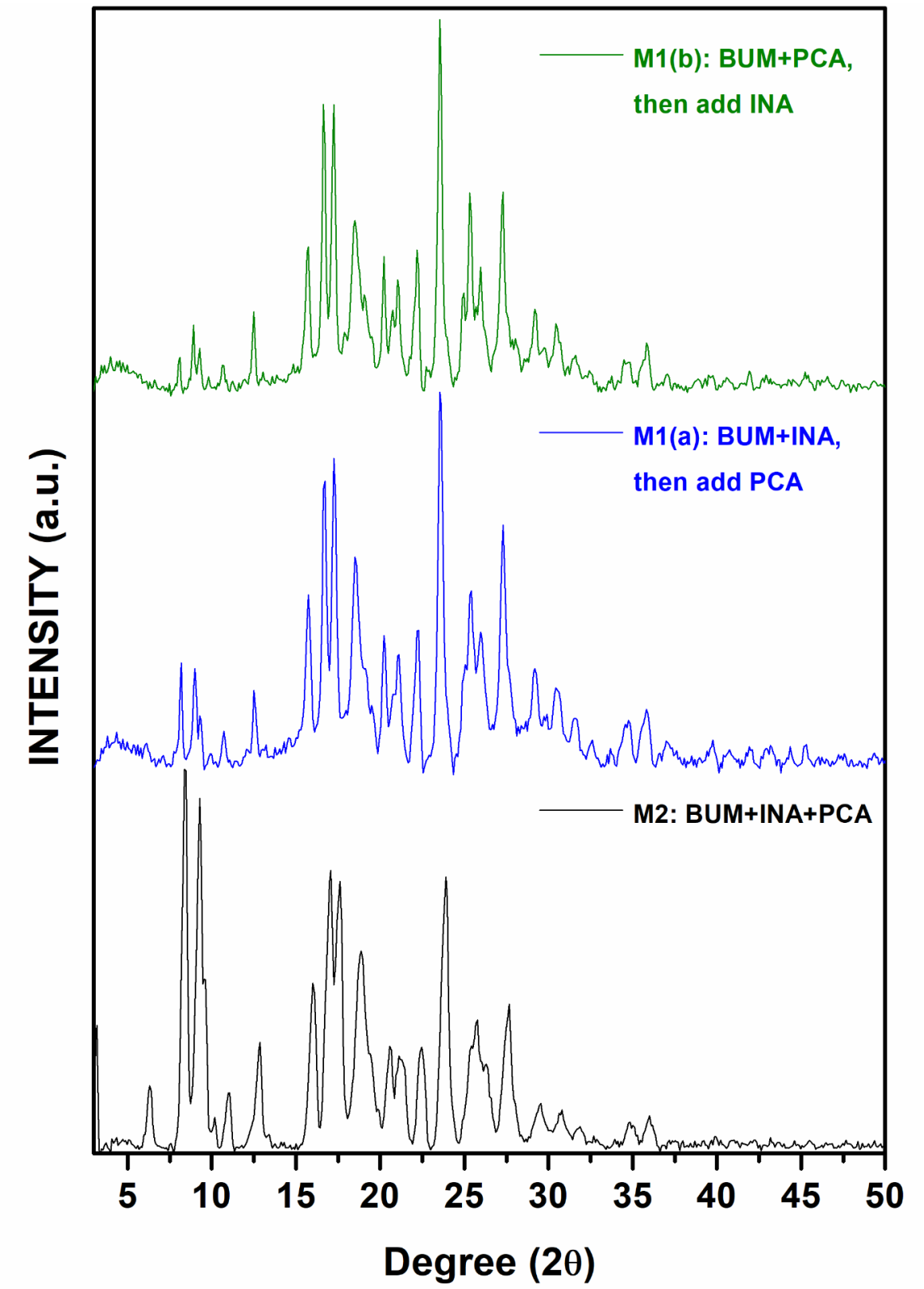


Figure S4. Overlay PXRD plots of BUM-INA-PCA (1:1:1) using different manual grinding conditions. M1(a): BUM + INA, then PCA (blue); M1(b): BUM + PCA, then INA (green); M2: BUM + INA + PCA (black). 1H NMR spectrum of the ternary cocrystal is shown in Figure S16.

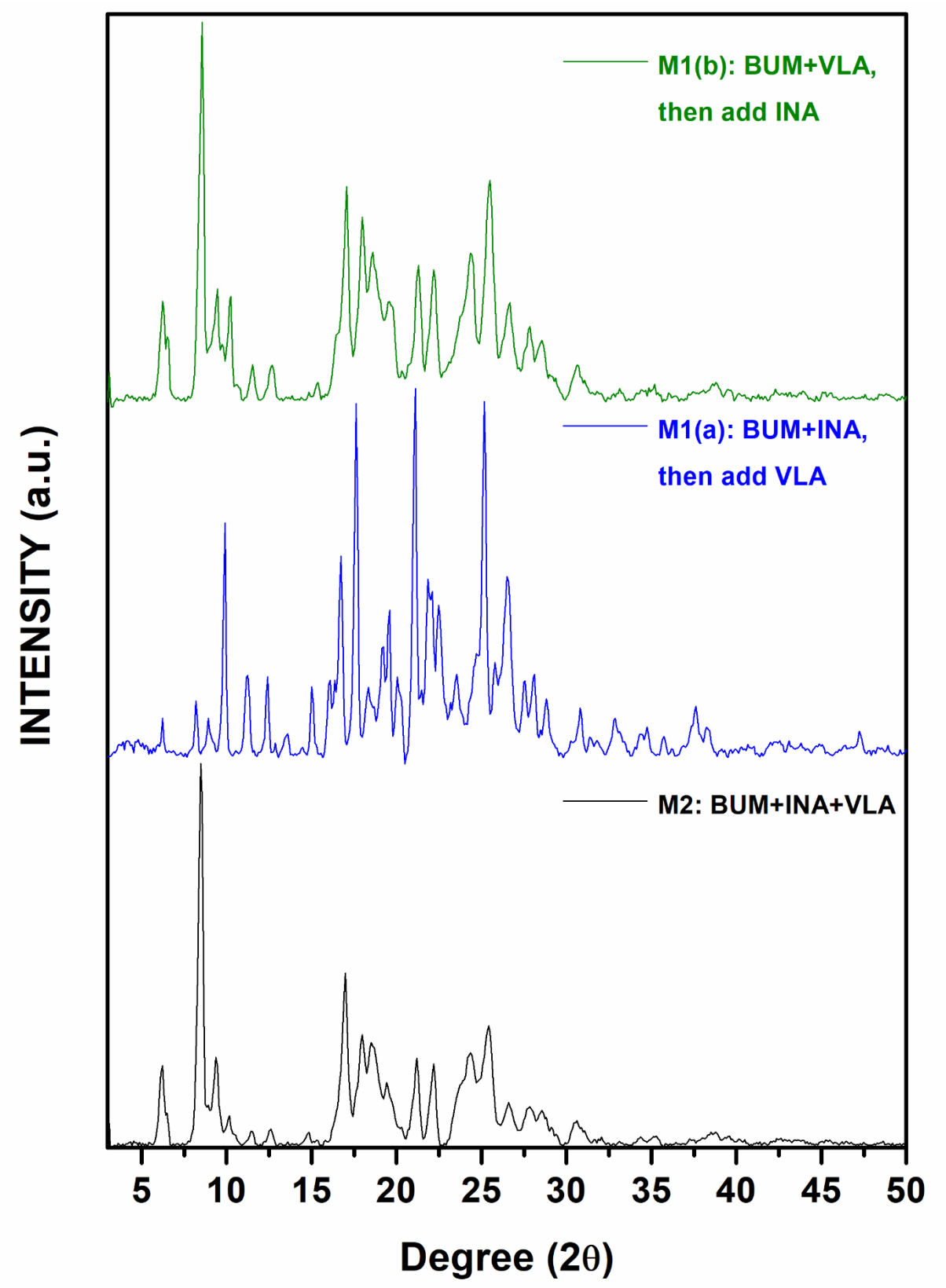


Figure S5. Overlay PXRD plots of BUM-INA-VLA (1:1:1) using different manual grinding conditions. M1(a): BUM + INA, then VLA (blue); M1(b): BUM + VLA, then INA (green); M2: BUM + INA + VLA (black). 1H NMR spectrum of the ternary cocrystal is shown in Figure S17.

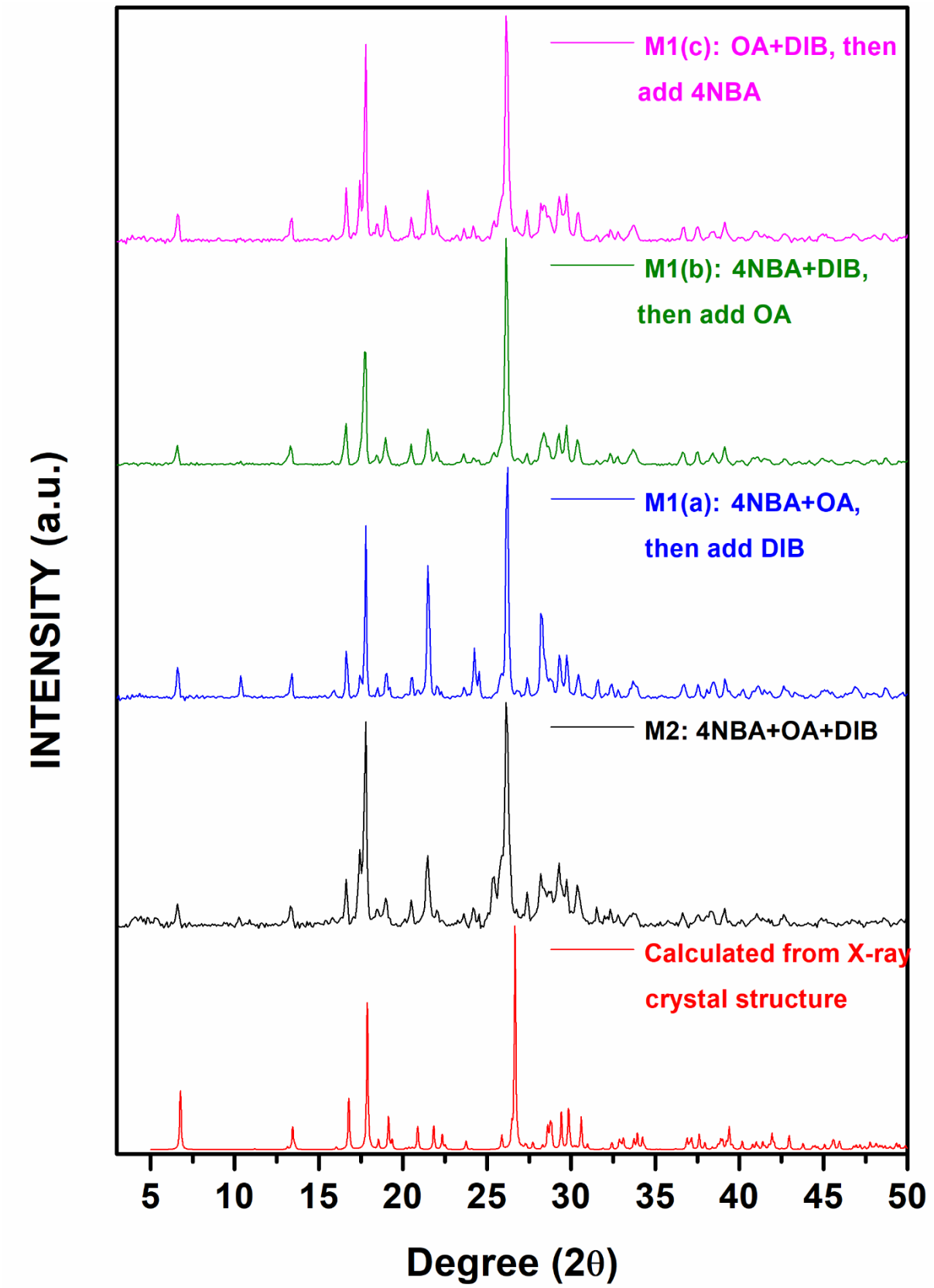


Figure S6. Overlay PXRD plots of 4NBA-OA-DIB (2:1:1) using different manual grinding conditions. M1(a): 4NBA + OA, then DIB (blue); M1(b): 4NBA + DIB, then OA (green); M1(c): OA + DIB, then 4NBA (magenta); M2: 4NBA + OA + DIB (black); calculated from the X-ray crystal structure (red).

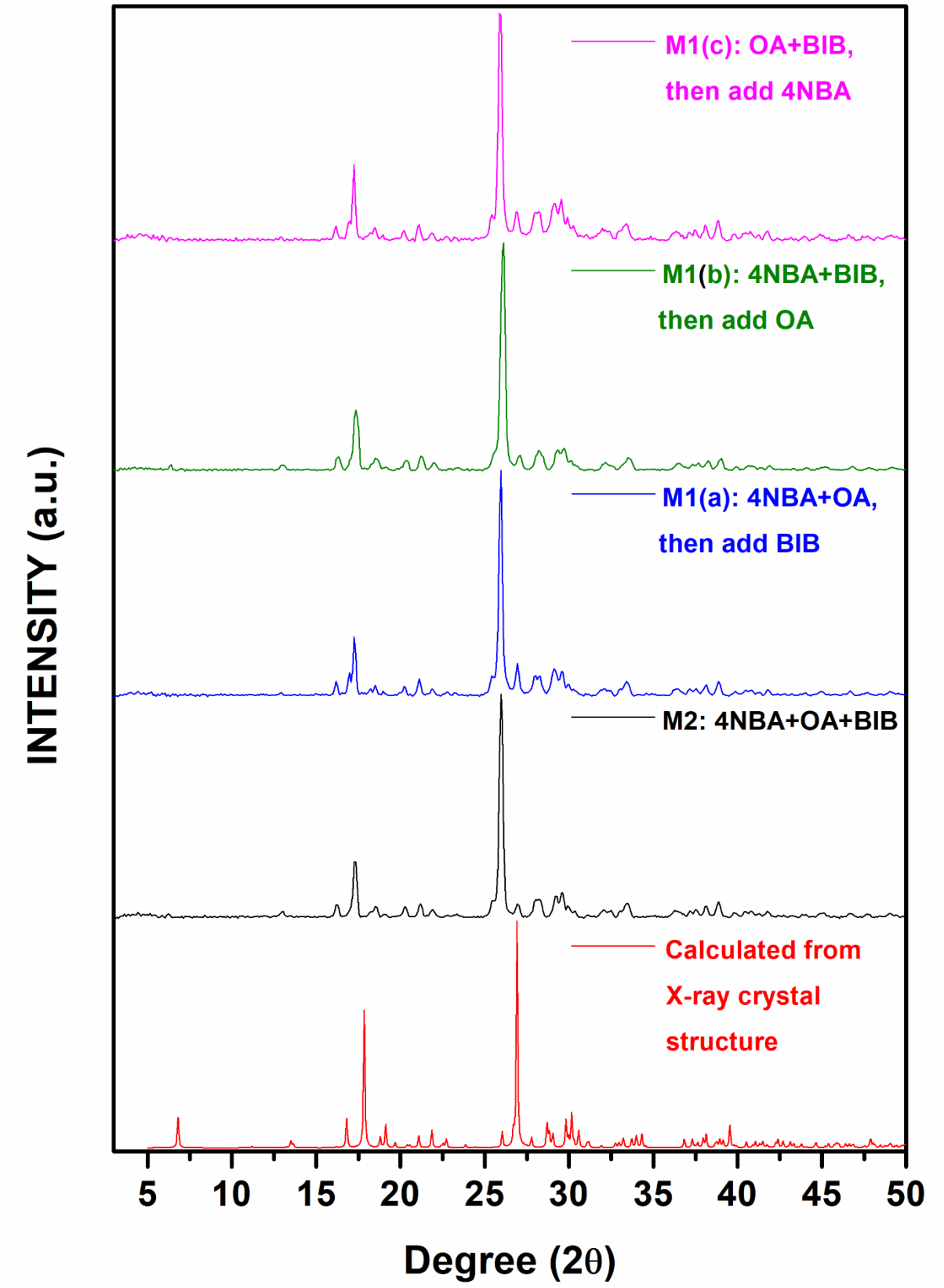


Figure S7. Overlay PXRD plots of 4NBA-OA-BIB (2:1:1) using different manual grinding conditions. M1(a): 4NBA + OA, then BIB (blue); M1(b): 4NBA + BIB, then OA (green); M1(c): OA + BIB, then 4NBA (magenta); M2: 4NBA + OA + BIB (black); calculated from the X-ray crystal structure (red).

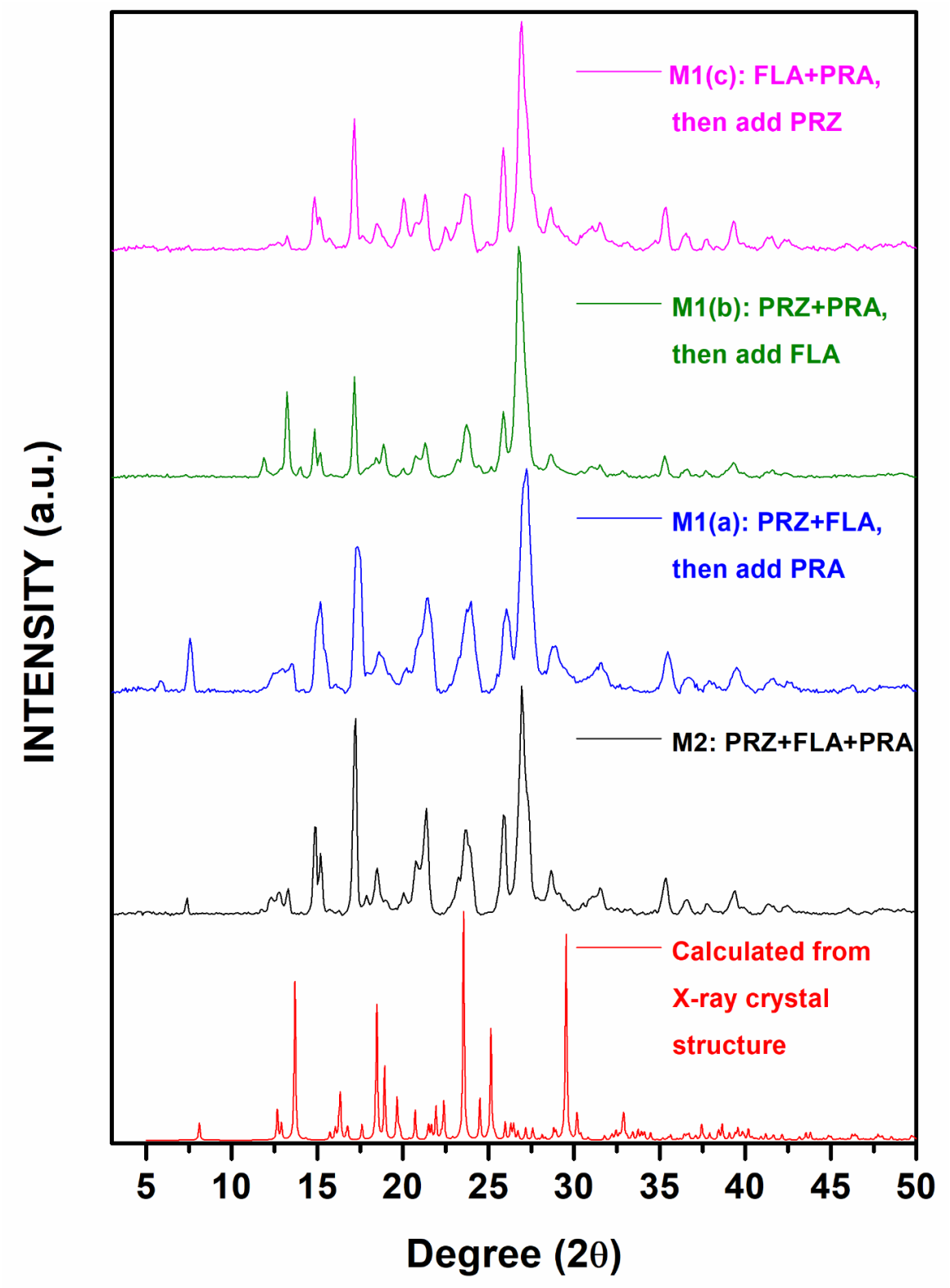


Figure S8. Overlay PXRD plots of PRZ-FLA-PRA (0.5:1:2) using different manual grinding conditions. M1(a): PRZ + FLA, then PRA (blue); M1(b) PRZ + PRA, then FLA (green); M1(c) FLA + PRA, then PRZ (magenta); M2: PRZ + FLA + PRA (black); calculated from the X-ray crystal structure (red). 1H NMR spectrum of the ternary cocrystal is shown in Figure S20. Note that M1(c) has a prominent peak at 2θ ~13°, which is not seen in M2, M1(a), M1(c) XRDs but matches with the calculated line profile.

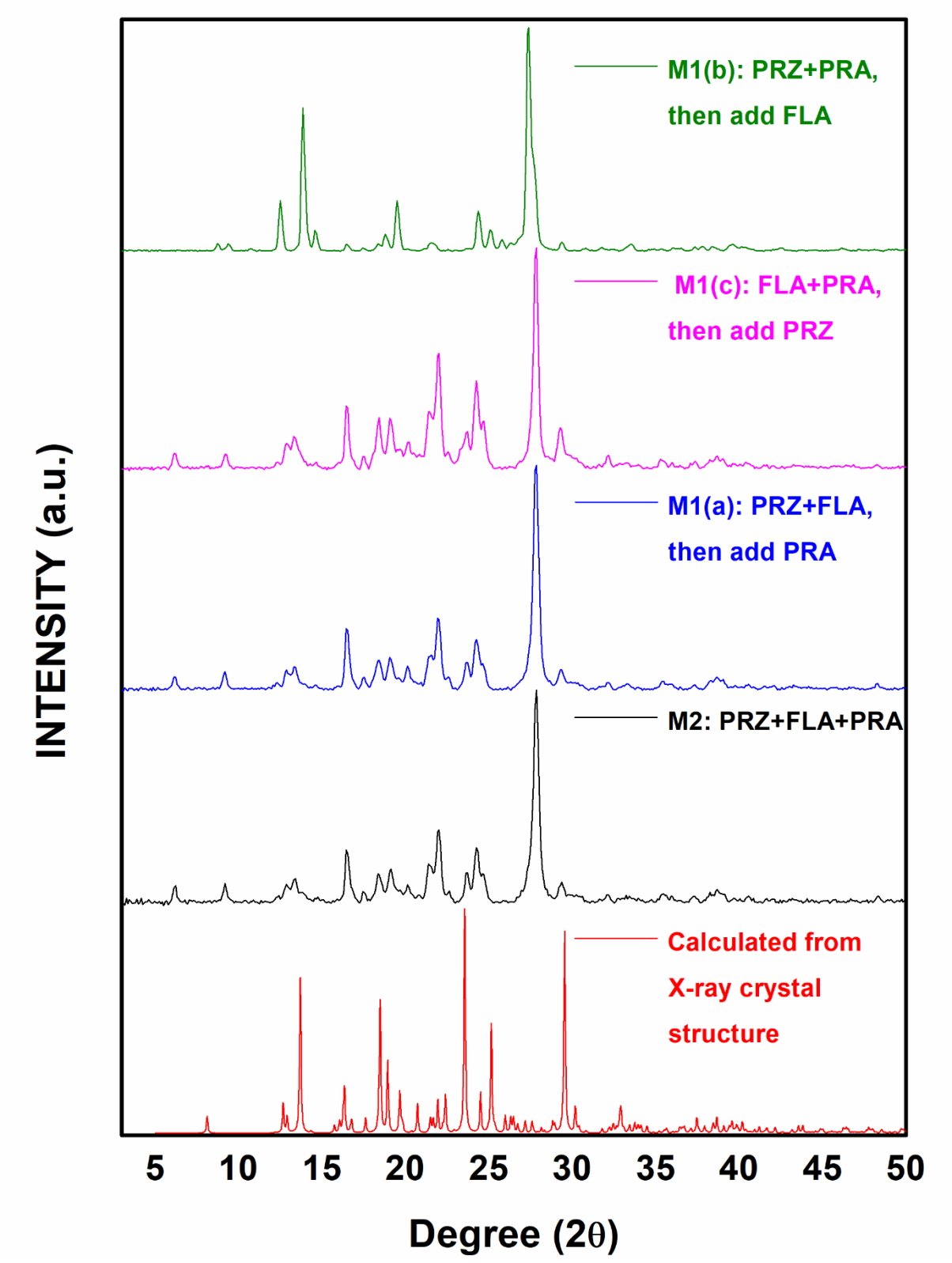


Figure S9. Overlay PXRD plots of PRZ-FLA-PRA (1:2:2) using different manual grinding conditions. M1(a): PRZ + FLA, then PRA (blue); M1(b) PRZ + PRA, then FLA (green); M1(c) FLA + PRA, then PRZ (magenta); M2: PRZ + FLA + PRA (black); calculated from the X-ray crystal structure (red). 1H NMR spectrum of the ternary cocrystal is shown in Figure S21.

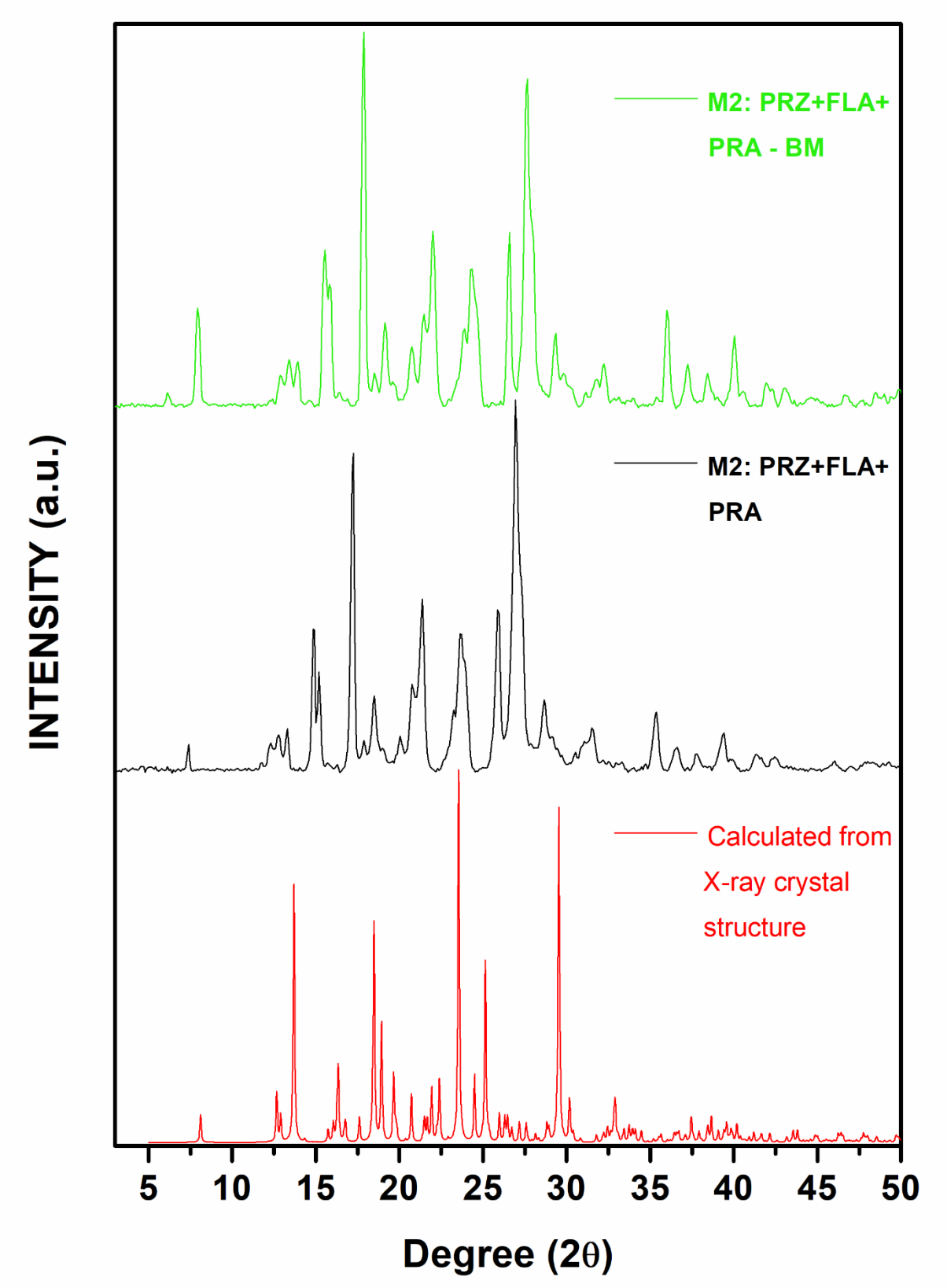


Figure S10. Overlay PXRD plot of PRZ-FLA-PRA -M2 (0.5:1:2) using ball-mill grinding conditions (light green); PXRD plot of PRZ-FLA-PRA -M2 (0.5:1:2) using manual grinding condition (black); calculated from the X-ray crystal structure (red). 1H NMR spectrum of the ternary cocrystal is shown in Figure S22.

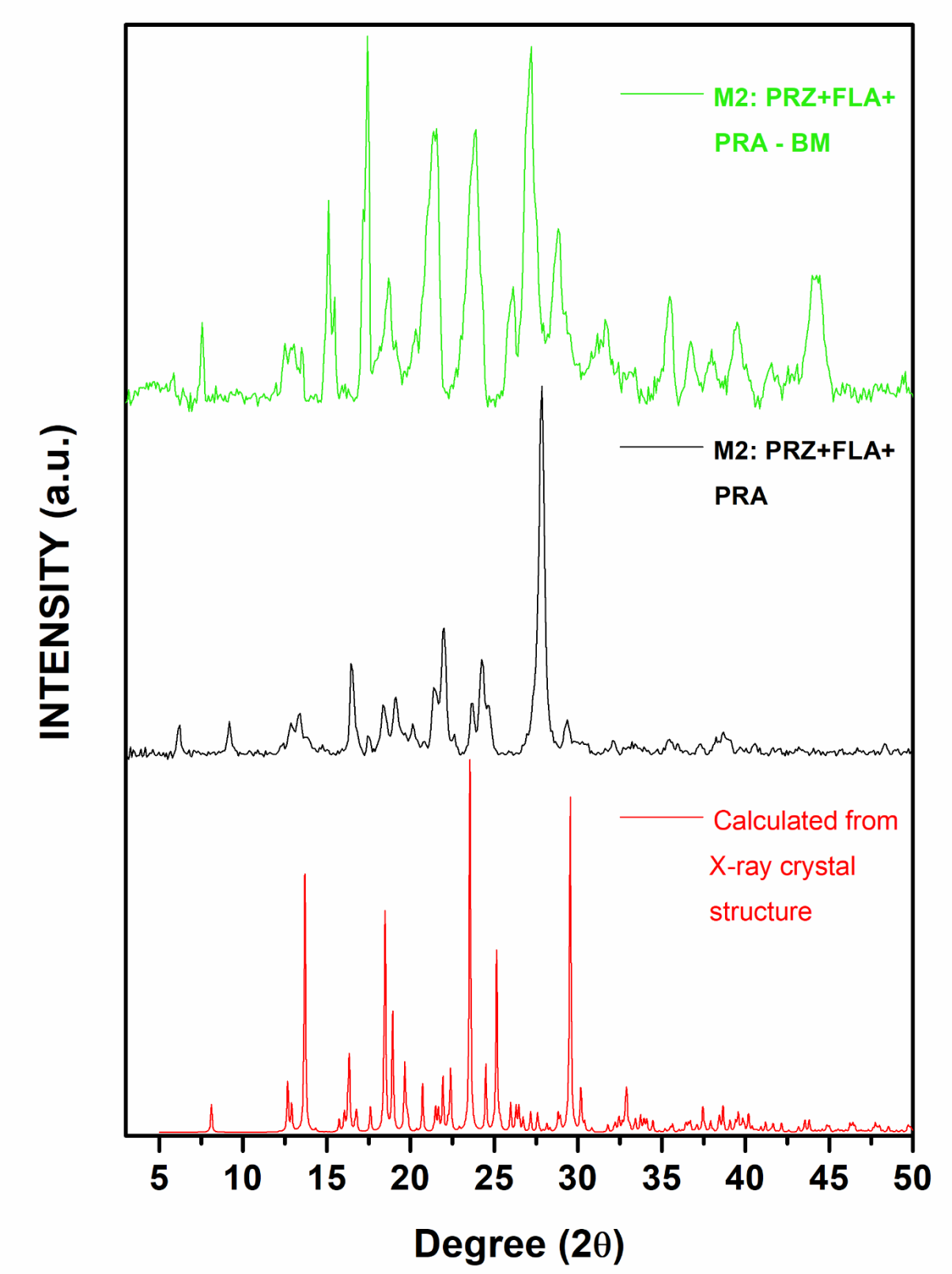
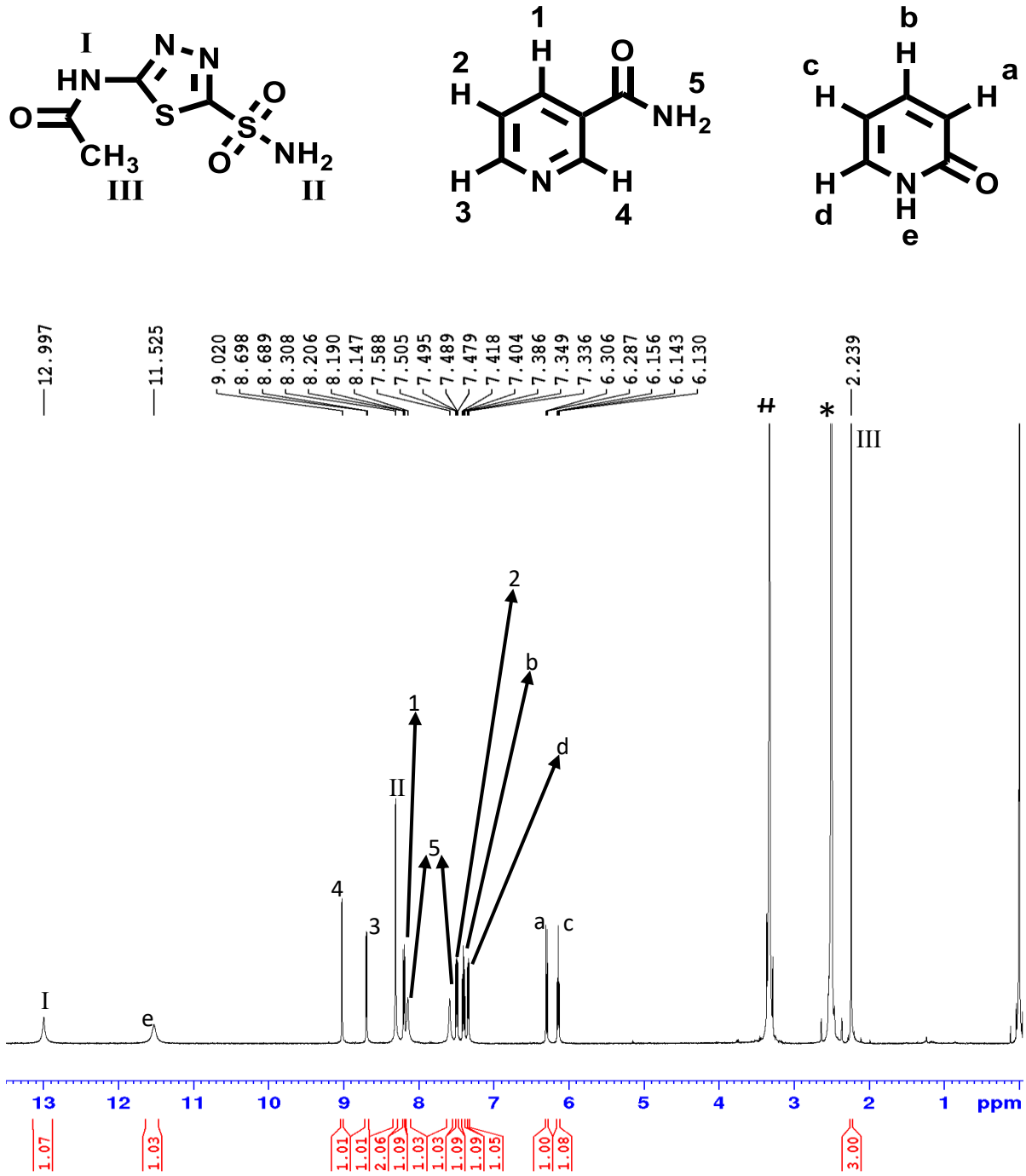


Figure S11. Overlay PXRD plot of PRZ-FLA-PRA -M2 (1:2:2) using ball-mill grinding conditions (light green); PXRD plot of PRZ-FLA-PRA -M2 (1:2:2) using manual grinding condition (black); calculated from the X-ray crystal structure (red). 1H NMR spectrum of the ternary cocrystal is shown in Figure S23.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NH2
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3
N
H
4
b
H
c
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a
H
H
d
N
H
e
O
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7.349
7.336
6.306
6.287
6.156
6.143
6.130
2.239
#
*
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2
b
1
d
II
5
4
3
a
c
I
e
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10
9
8
7
6
5
4
3
2
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ppm
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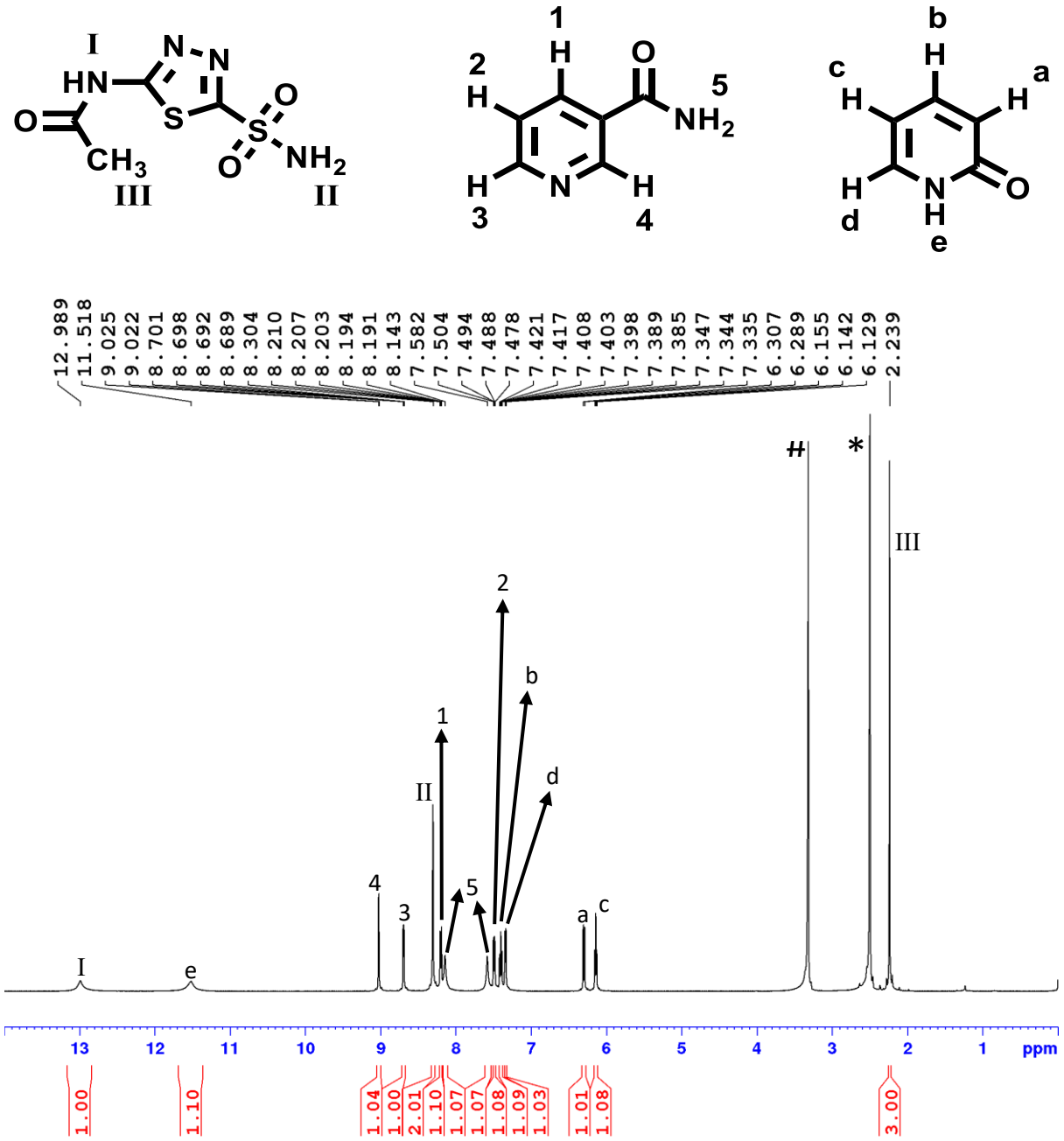
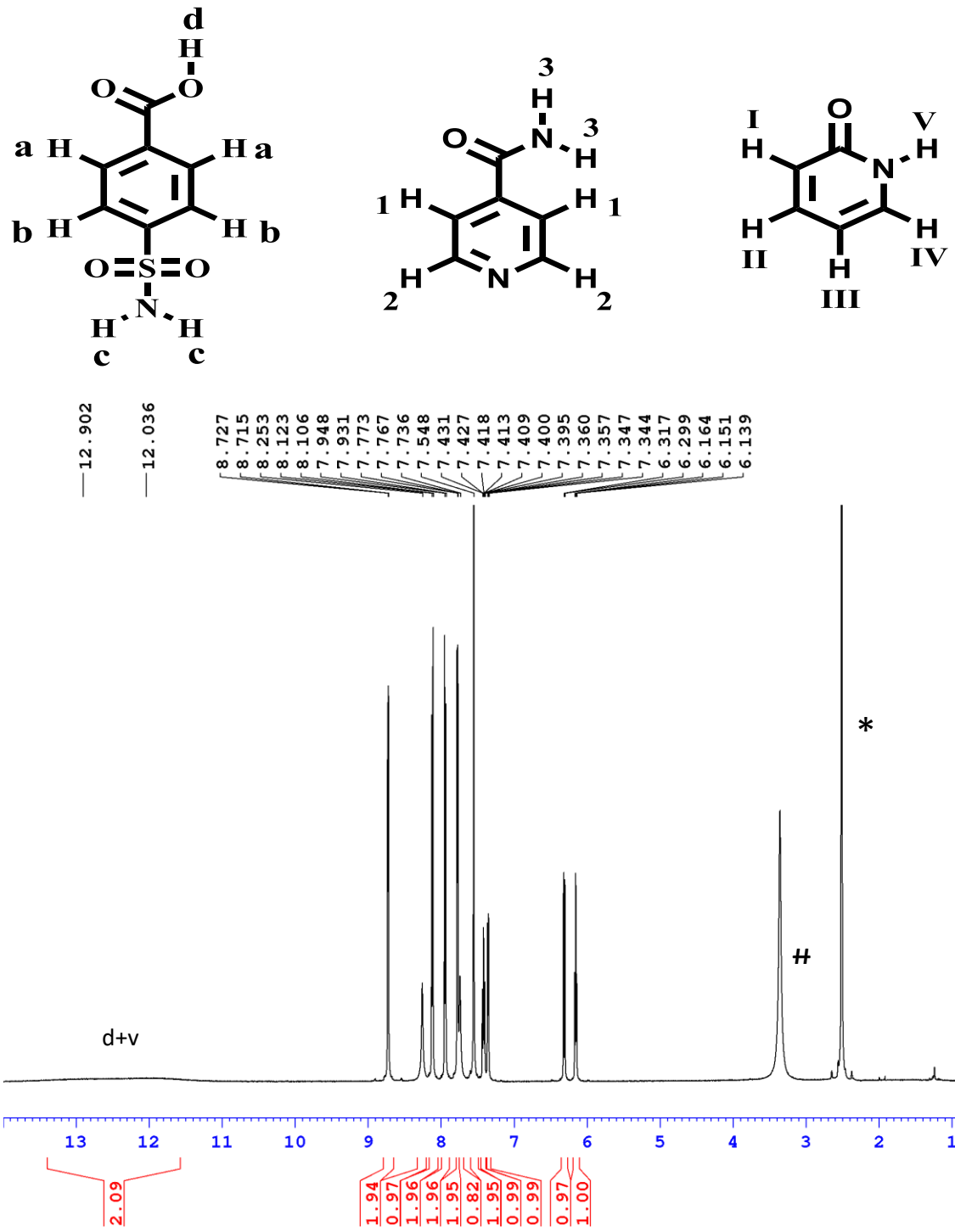
1.09
1.05
1.00
1.08
3.00

(a)



(b)

Figure S12. (a) 1H NMR of ACZ-NAM-2HP (M2) (full spectrum) prepared by manual grinding condition. Three components are present in the ratio 1:1:1. * is residual solvent peak and # is water peak in NMR. PXRD of the ternary cocrystal is shown in Figure S1. (b) 1H NMR of ACZ-NAM-2HP (M2) (full spectrum) prepared by ball mill grinding condition. Three components are present in the ratio 1:1:1. * is residual solvent peak and # is water peak in NMR. PXRD of the ternary cocrystal is shown in Figure 3.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b H
H b
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N
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c
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H
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V
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N
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8.253
8.123
8.106
7.948
7.931
7.773
7.767
7.736
7.548
7.431
7.427
7.418
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7.409
7.400
7.395
7.360
7.357
7.347
7.344
6.317
6.299
6.164
6.151
6.139
*
#
d+v
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12
11
10
9
8
7
6
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4
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ppm
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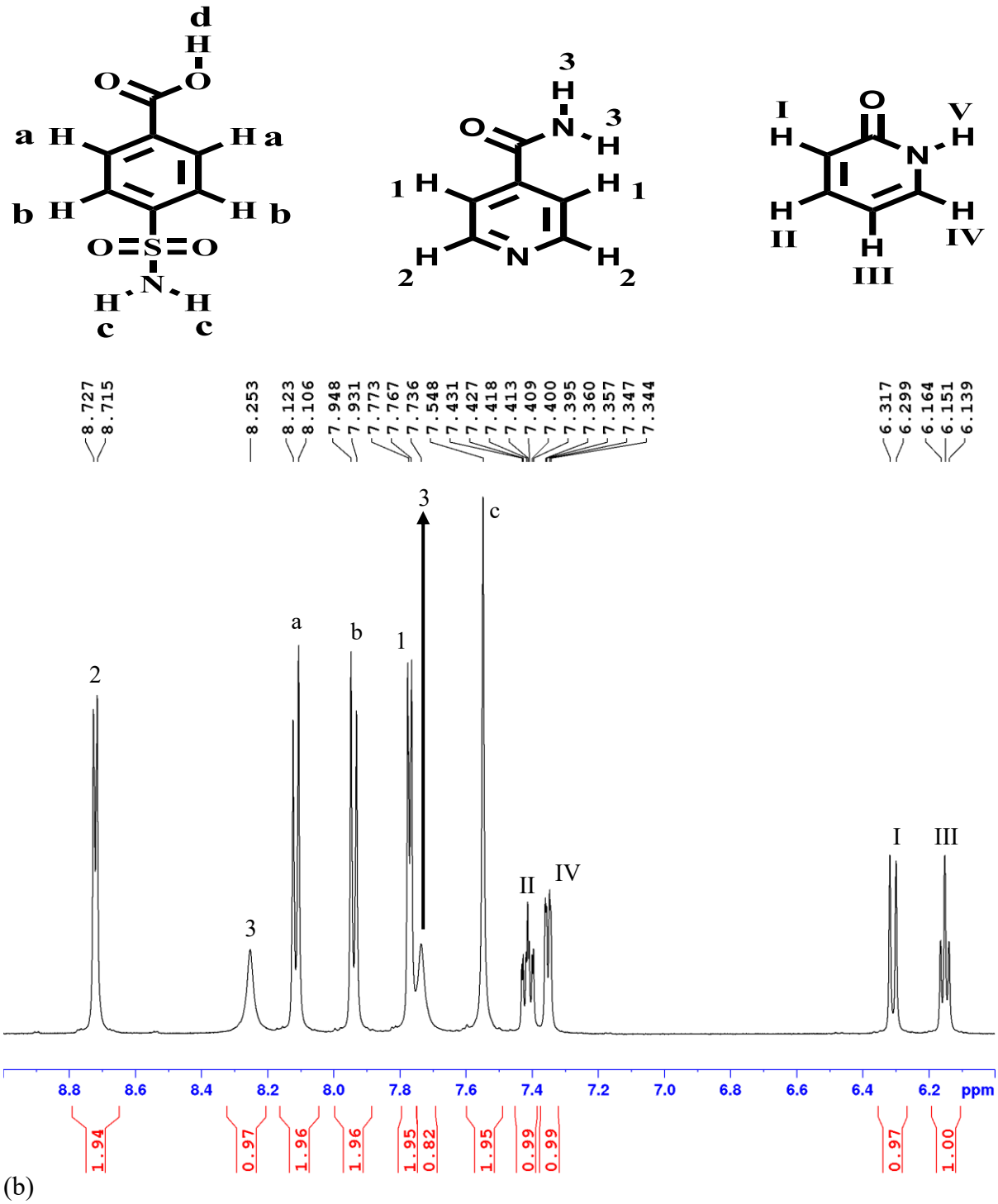
(a)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b H
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H
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c
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7.357
7.347
7.344
6.317
6.299
6.164
6.151
6.139
3
c
a
b
1
2
3
II
IV
I
III
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
ppm
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0.99
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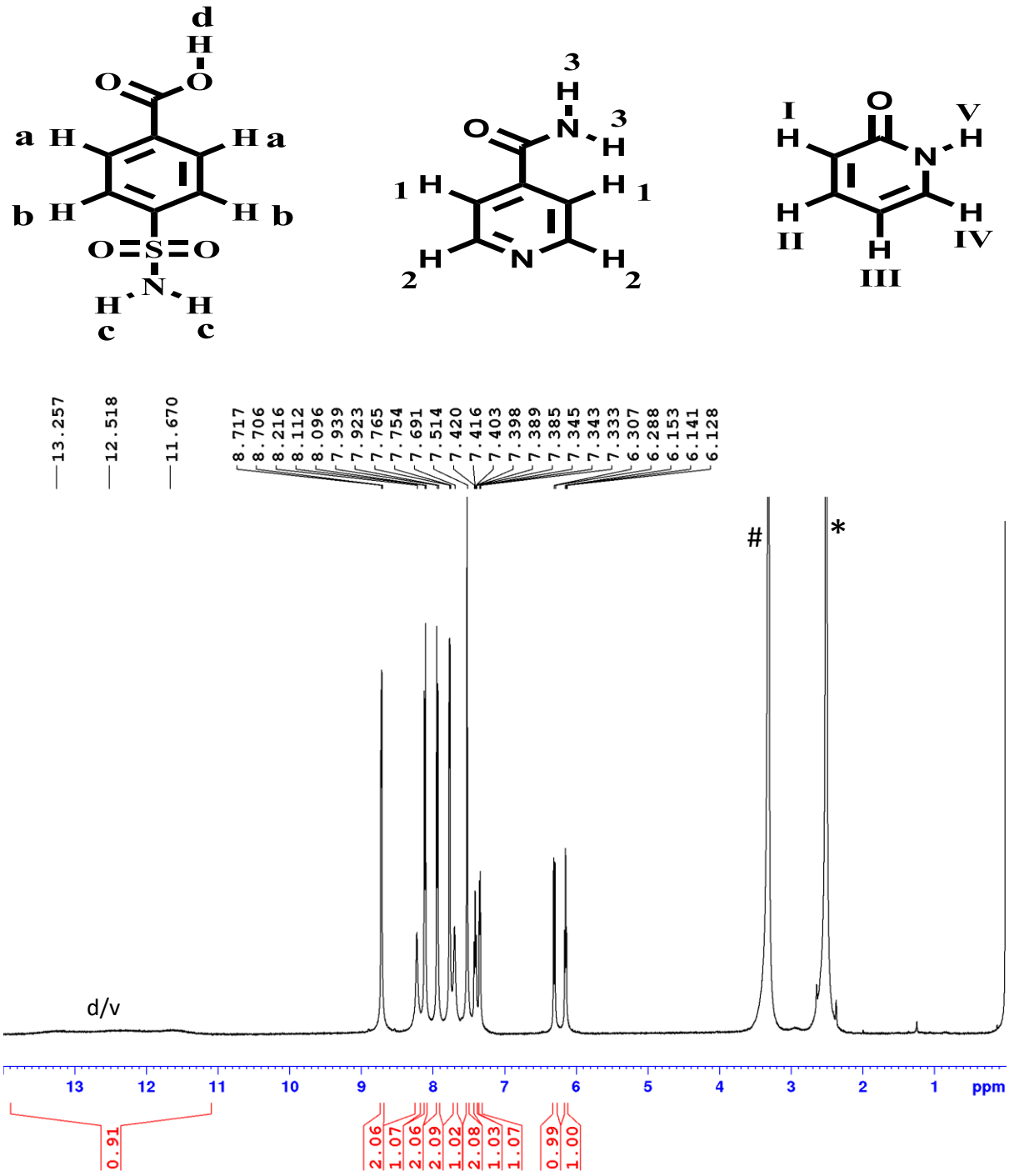
1.00

(b)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b H
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H
H
c
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H
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H
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2
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O
V
H
N
H
H
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II
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H
III
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7.939
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7.765
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7.398
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6.128
#
*
d/v
13
12
11
10
9
8
7
6
5
4
3
2
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1.03
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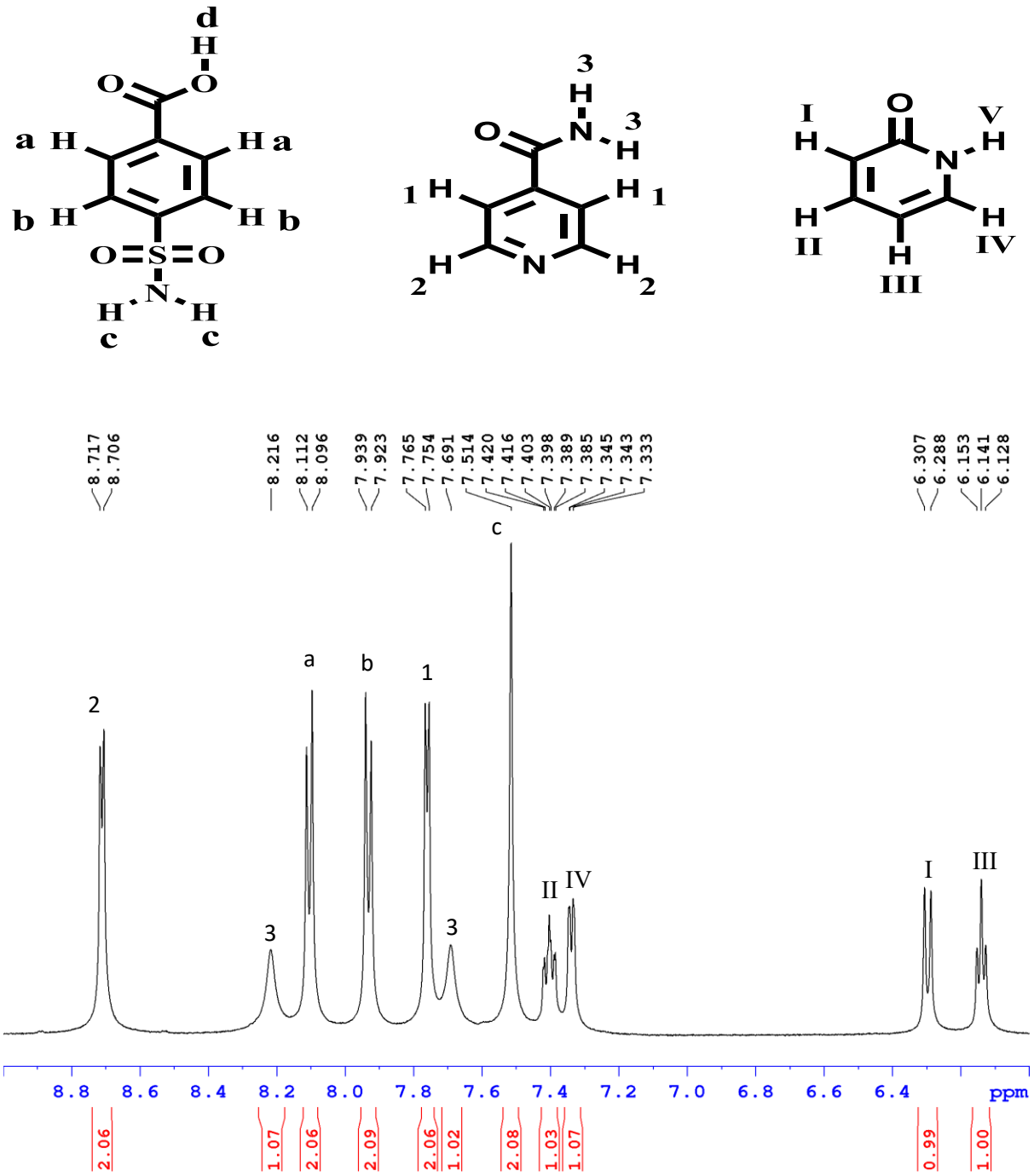
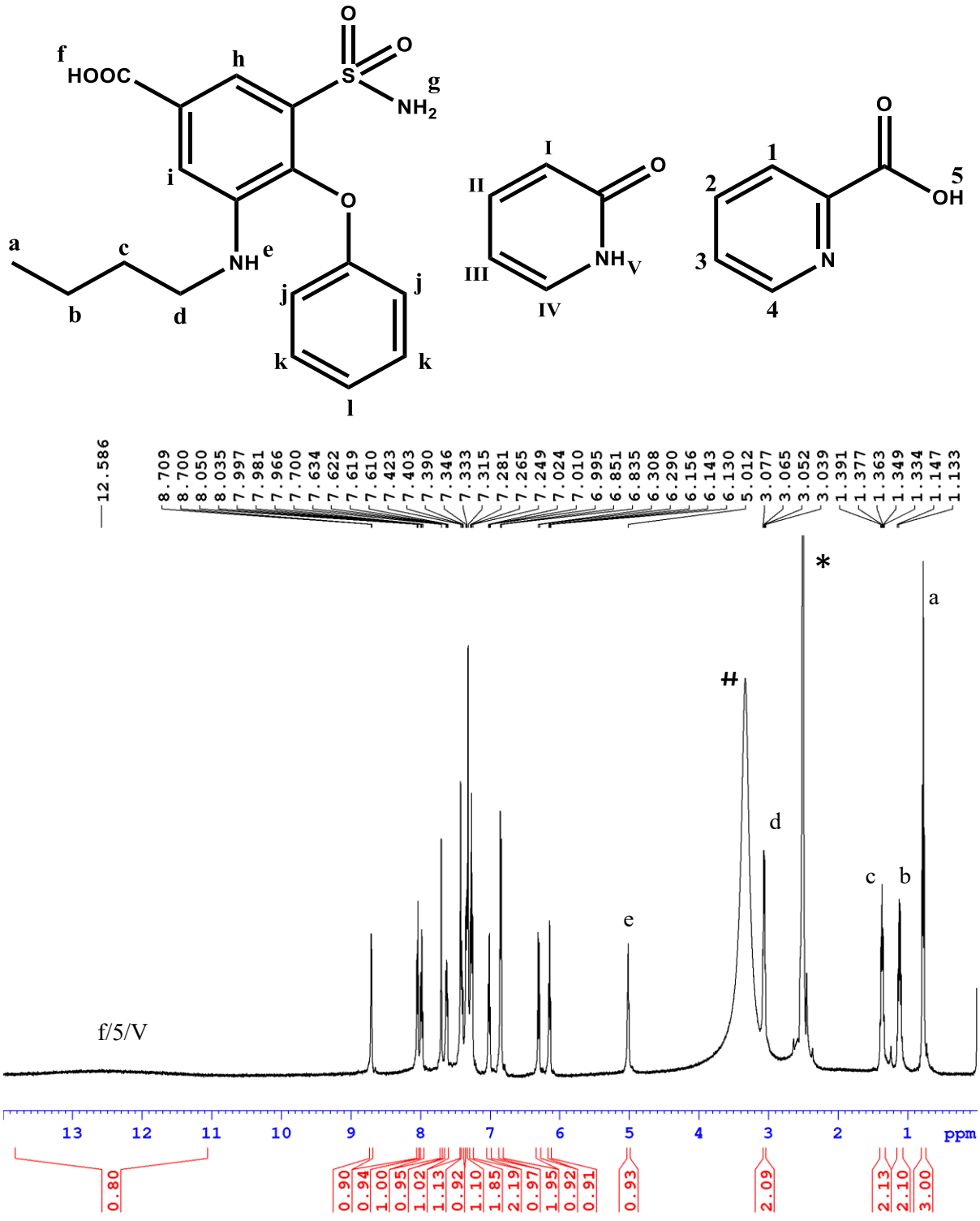
(c)



(d)

Figure S13. (a) 1H NMR of SMBA-INA-2HP (M2) (full spectrum) prepared by manual grinding. Three components are present in the ratio 1:1:1. * is residual solvent peak and # is water peak. The one COOH and one CONH protons (d/V) are not showing complete intergration (at 12-13 ppm) but they may have merged within the large water resonance (#) (b) Enlarged view of the same spectrum. PXRD of the ternary cocrystal is shown in Figure 5(a). (c) 1H NMR of SMBA-INA-2HP (M2) (full spectrum) prepared by ball-mill grinding. Three components are present in the ratio 1:1:1. * is residual solvent peak and # is water peak. The one COOH and one CONH protons (d/V) are not showing complete intergration (at 12-13 ppm) but they may have merged within the large water resonance (#) (d) Enlarged view of the same spectrum. PXRD of the ternary cocrystal is shown in Figure 5(c).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O
S
g
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NH
e
b
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j
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3.077
3.065
3.052
3.039
1.391
1.377
1.363
1.349
1.334
1.147
1.133
*
a
#
d
c
b
e
f/5/V
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.80
0.90
0.94
1.00
0.95
1.02
1.13
0.92
1.10
1.85
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1.95
0.92
0.91
0.93
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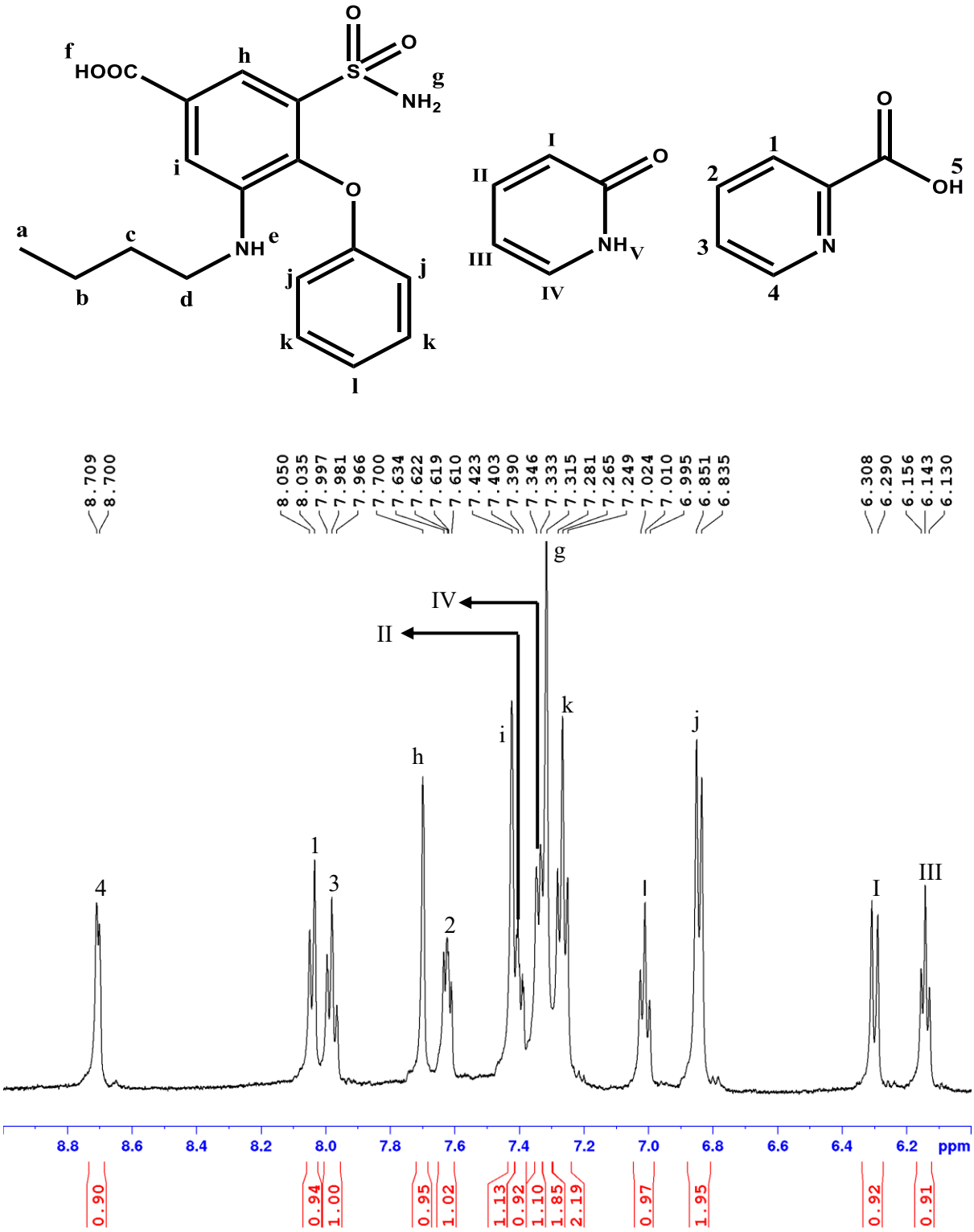
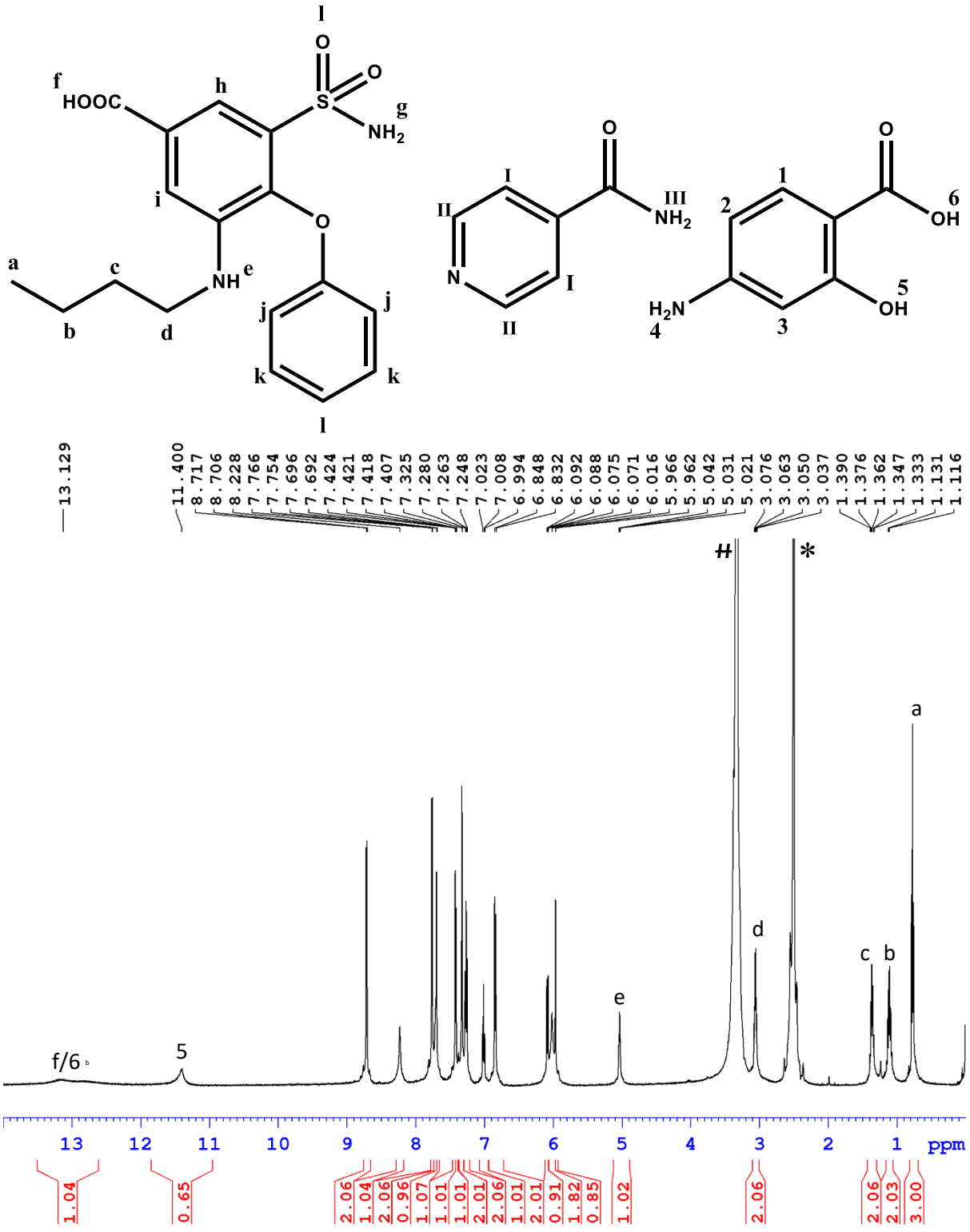
2.10
3.00

(a)

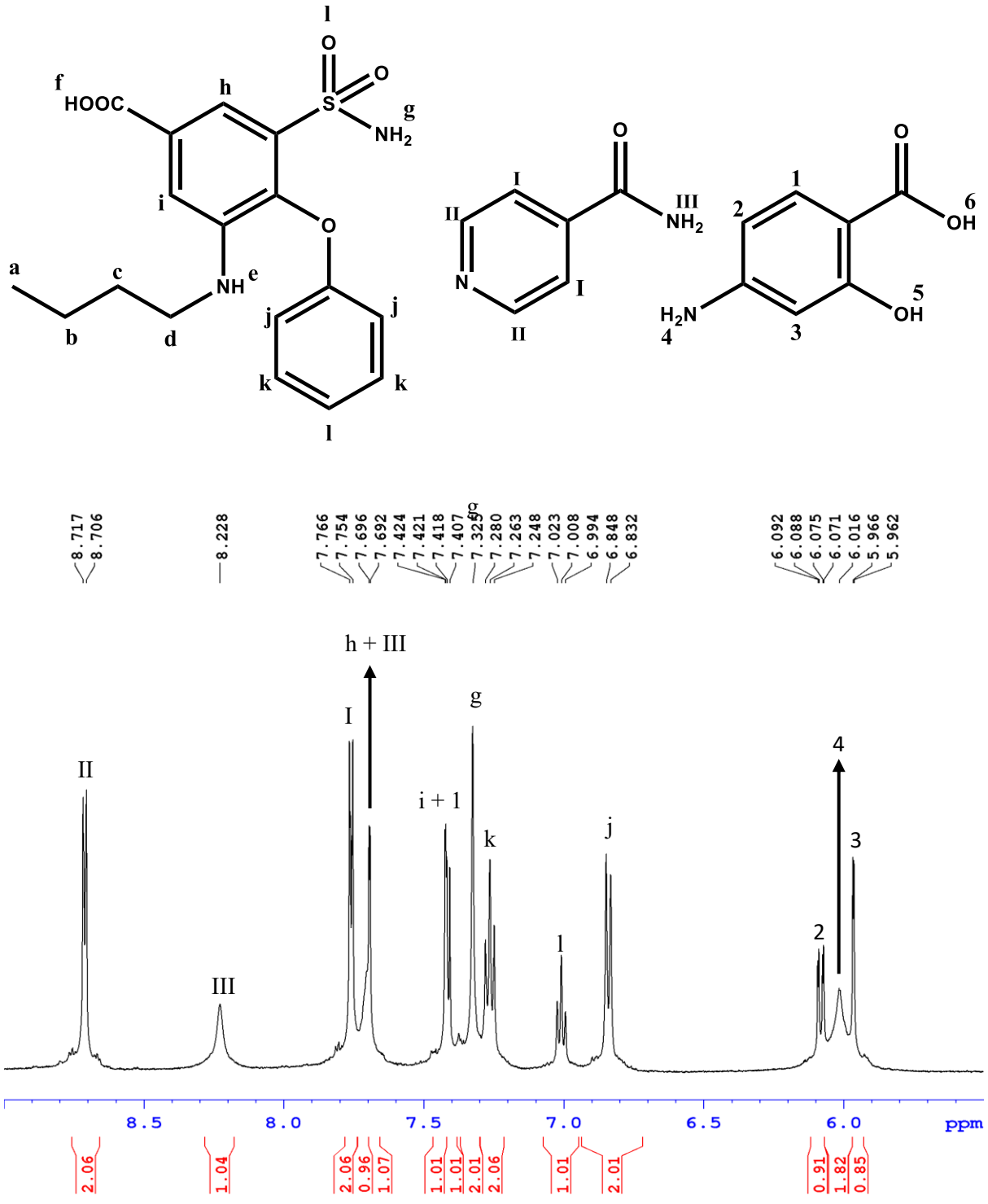


(b)

Figure S14. (a) 1H NMR of BUM-2HP-PCA (M2) (full spectrum) prepared by manual grinding. Three components are present in the ratio 1:1:1. * is residual solvent peak and # water peak. The two COOH and one CONH protons (f/5/V) are not showing complete intergration (at 12-13 ppm) but they may have merged within the large water resonance (#). (b) Enlarged view of the same spectrum. PXRD of the ternary product is shown in Figure 6.

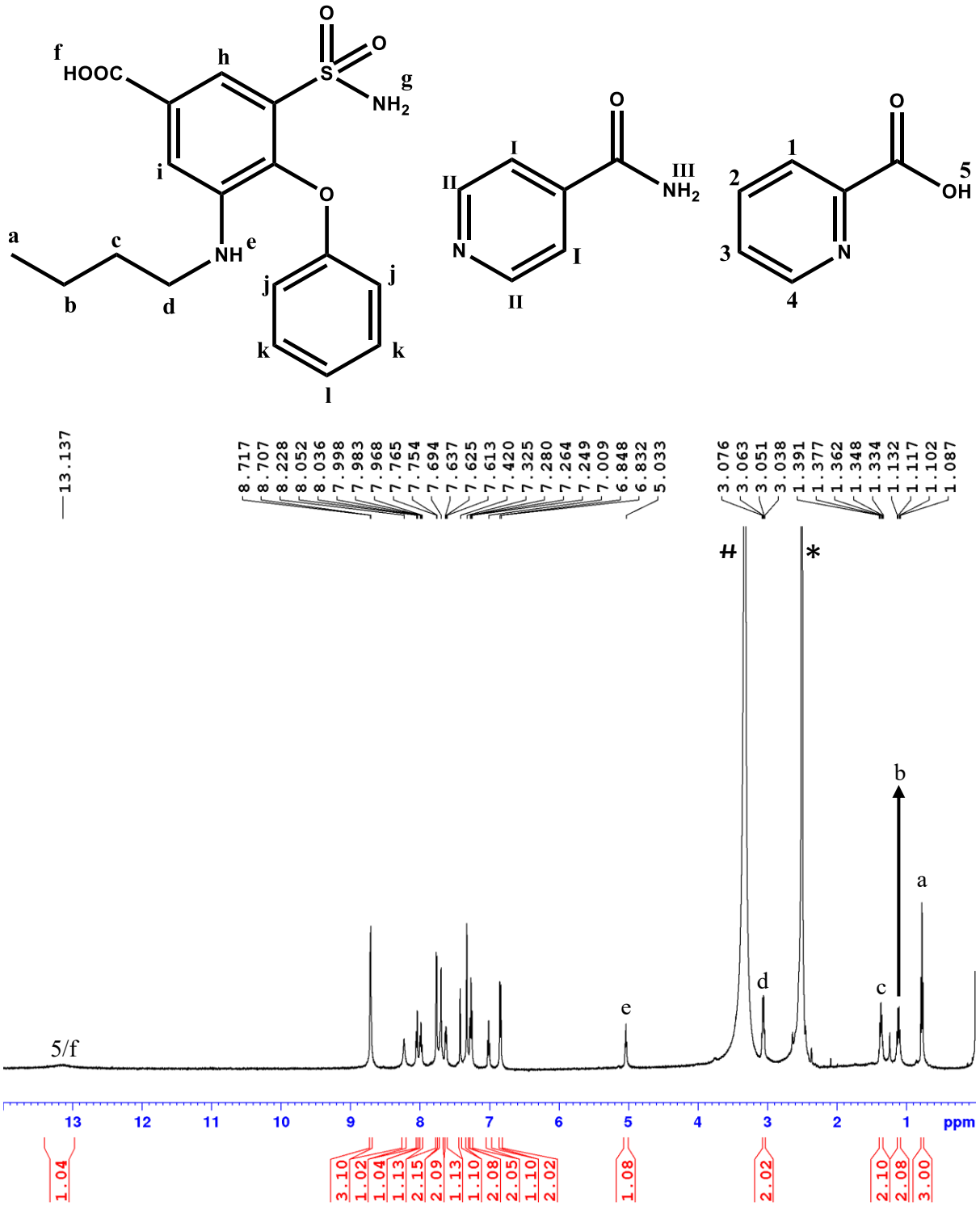

HOOC
NH2
NH
OH
H2N
OH
13.129
11.400
8.717
8.706
8.228
7.766
7.754
7.696
7.692
7.424
7.421
7.418
7.407
7.325
7.280
7.263
7.248
7.023
7.008
6.994
6.848
6.832
6.092
6.088
6.075
6.071
6.016
5.966
5.962
5.042
5.031
5.021
3.076
3.063
3.050
3.037
1.390
1.376
1.362
1.347
1.333
1.131
1.116
f/6
5
e
d
c
b
a
ppm
1.04
0.65
2.06
1.04
2.06
0.96
1.07
1.01
1.01
2.01
2.06
1.01
2.01
0.91
1.82
0.85
1.02
2.06
2.06
2.03
3.00

(a)

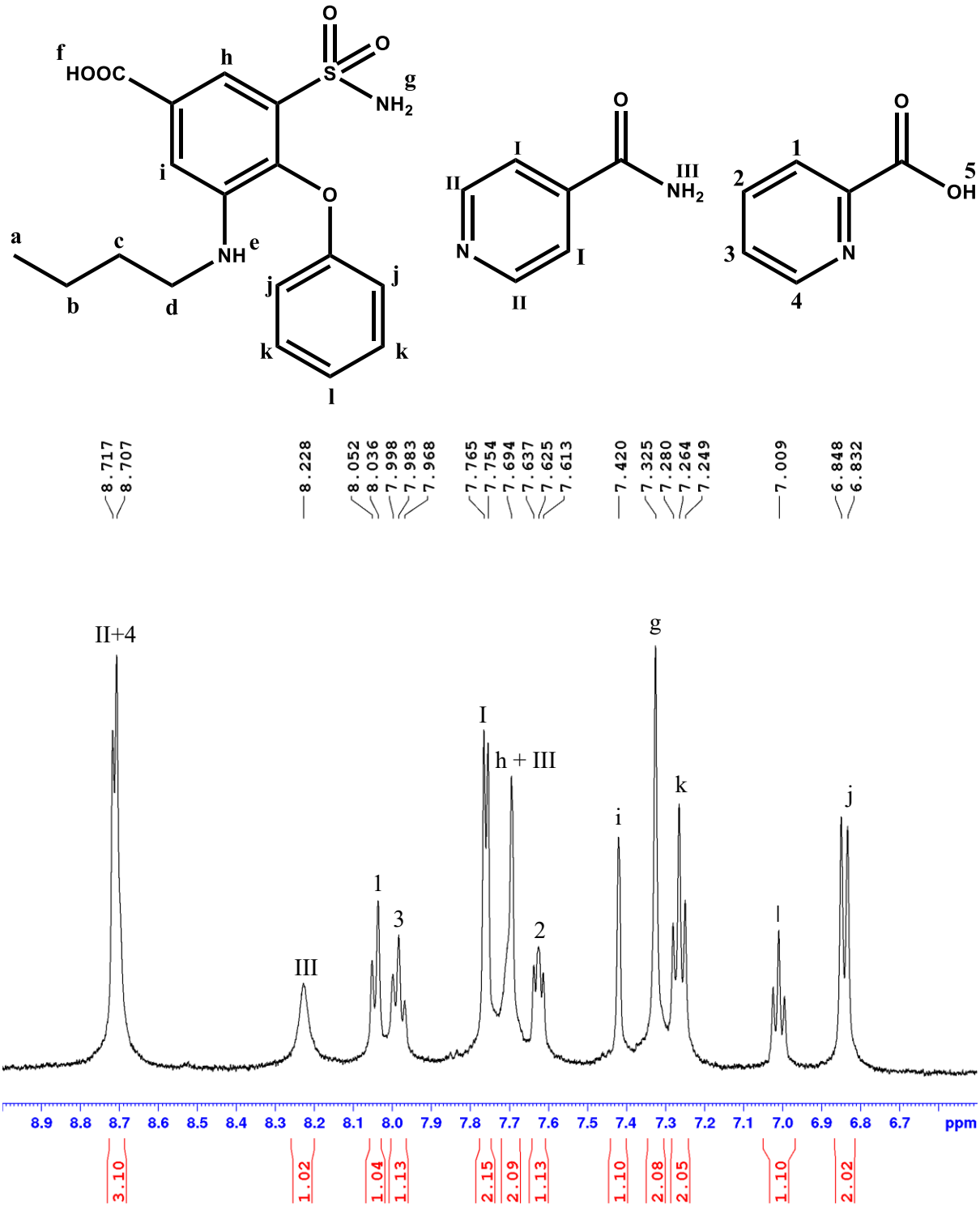


(b)

Figure S15. (a) 1H NMR of BUM-INA-PASA (M2) (full spectrum) prepared by manual grinding. Three components are present in the ratio 1:1:1 ratio. * is residual solvent peak and # water peak. The two COOH protons (f/6) are not showing complete intergration (at 13 ppm) but they may have merged within the large water resonance (#). (b) Enlarged view of the same spectrum. PXRD of the ternary product is shown in Figure 7.

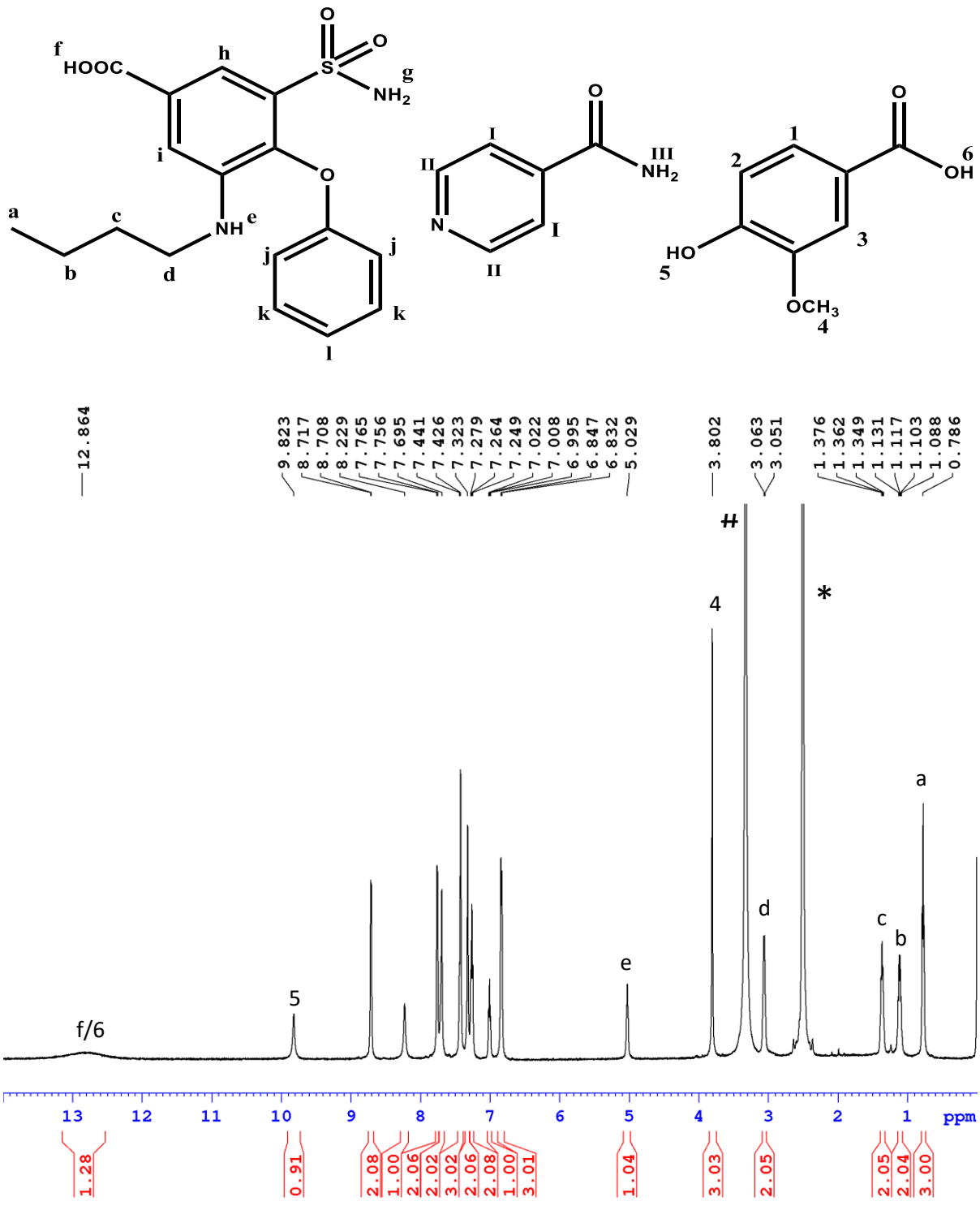

HOOC
NH2
NH
OH
13.137
8.717
8.707
8.228
8.052
8.036
7.998
7.983
7.968
7.765
7.754
7.694
7.637
7.625
7.613
7.420
7.325
7.280
7.264
7.249
7.009
6.848
6.832
5.033
3.076
3.063
3.051
3.038
1.391
1.377
1.362
1.348
1.334
1.132
1.117
1.102
1.087
#
*
a
b
c
d
e
5/f
ppm
1.04
3.10
1.02
1.04
1.13
2.15
2.09
1.13
1.10
2.08
2.05
1.10
2.02
1.08
2.02
2.10
2.08
3.00

(a)

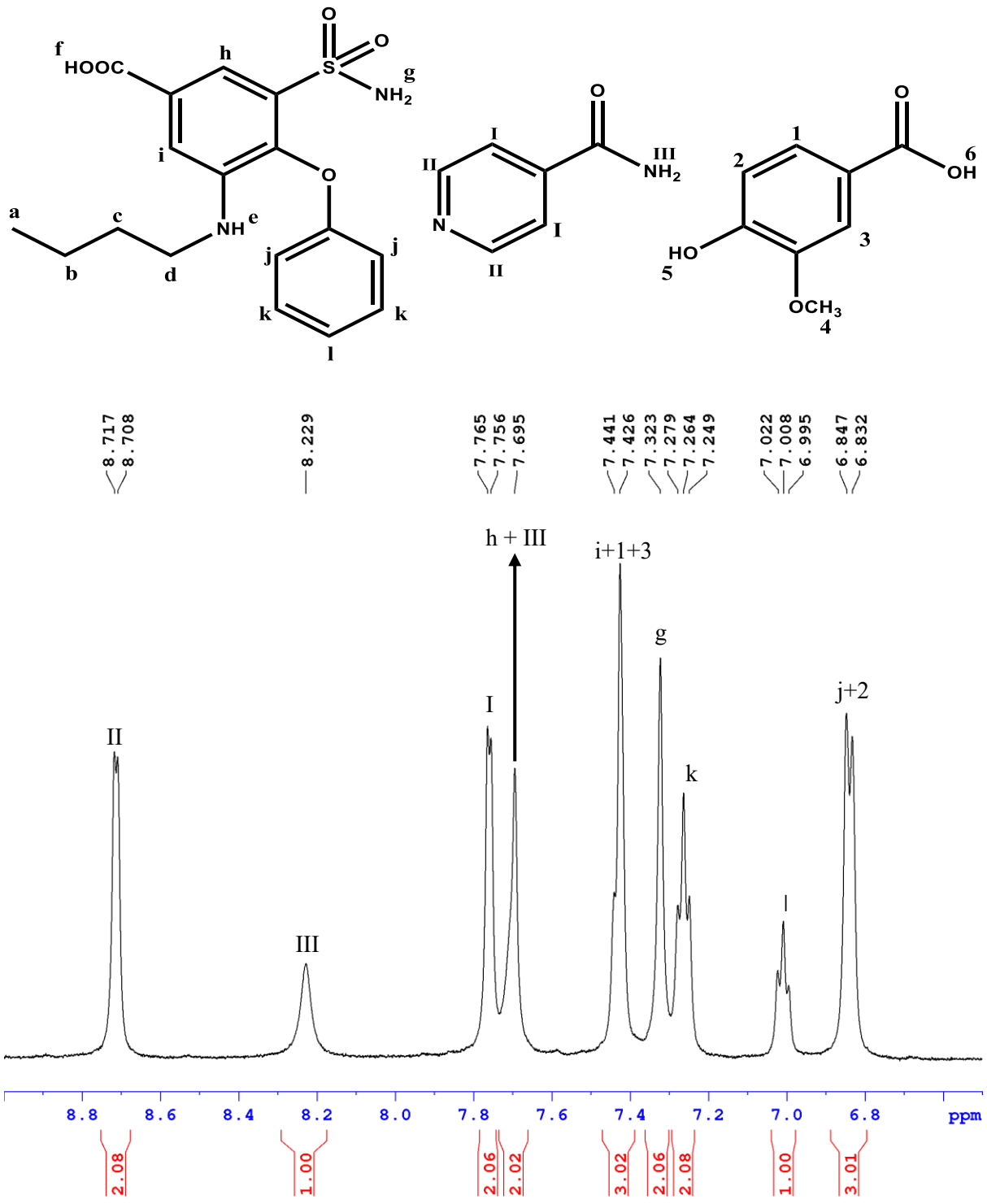


(b)

Figure S16. (a) 1H NMR of BUM-INA-PCA (M2) to show the presence of three components in 1:1:1 ratio. * is residual solvent peak and # water peak. The two COOH protons (f/5) are not showing complete intergration (at 13 ppm) but they may have merged within the large water resonance (#). (b) Enlarged view of the same spectrum. PXRD of the ternary product is shown in Figure S4.


f
HOOC
h
O
O
S
NH2
g
i
O
a
c
NH
e
b
d
j
j
k
k
l
I
II
III
NH2
N
II
I
O
1
2
6
OH
HO
5
3
OCH3
4
12.864
9.823
8.717
8.708
8.229
7.765
7.756
7.695
7.441
7.426
7.323
7.279
7.264
7.249
7.022
7.008
6.995
6.847
6.832
5.029
3.802
3.063
3.051
1.376
1.362
1.349
1.131
1.117
1.103
1.088
0.786
#
*
4
a
d
c
b
e
5
f/6
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.28
0.91
2.08
1.00
2.06
2.02
3.02
2.06
2.08
1.00
3.01
1.04
3.03
2.05
2.05
2.04
3.00

(a)



(b)

Figure S17. (a)1H NMR of BUM-INA-VLA (M2) to show the presence of three components in 1:1:1 ratio. * is residual solvent peak and # water peak. The two COOH protons (f/6) are not showing complete intergration (at 13 ppm) but they may have merged within the large water resonance (#). (b) Enlarged view of the same spectrum. PXRD of the ternary product is shown in Figure S5.

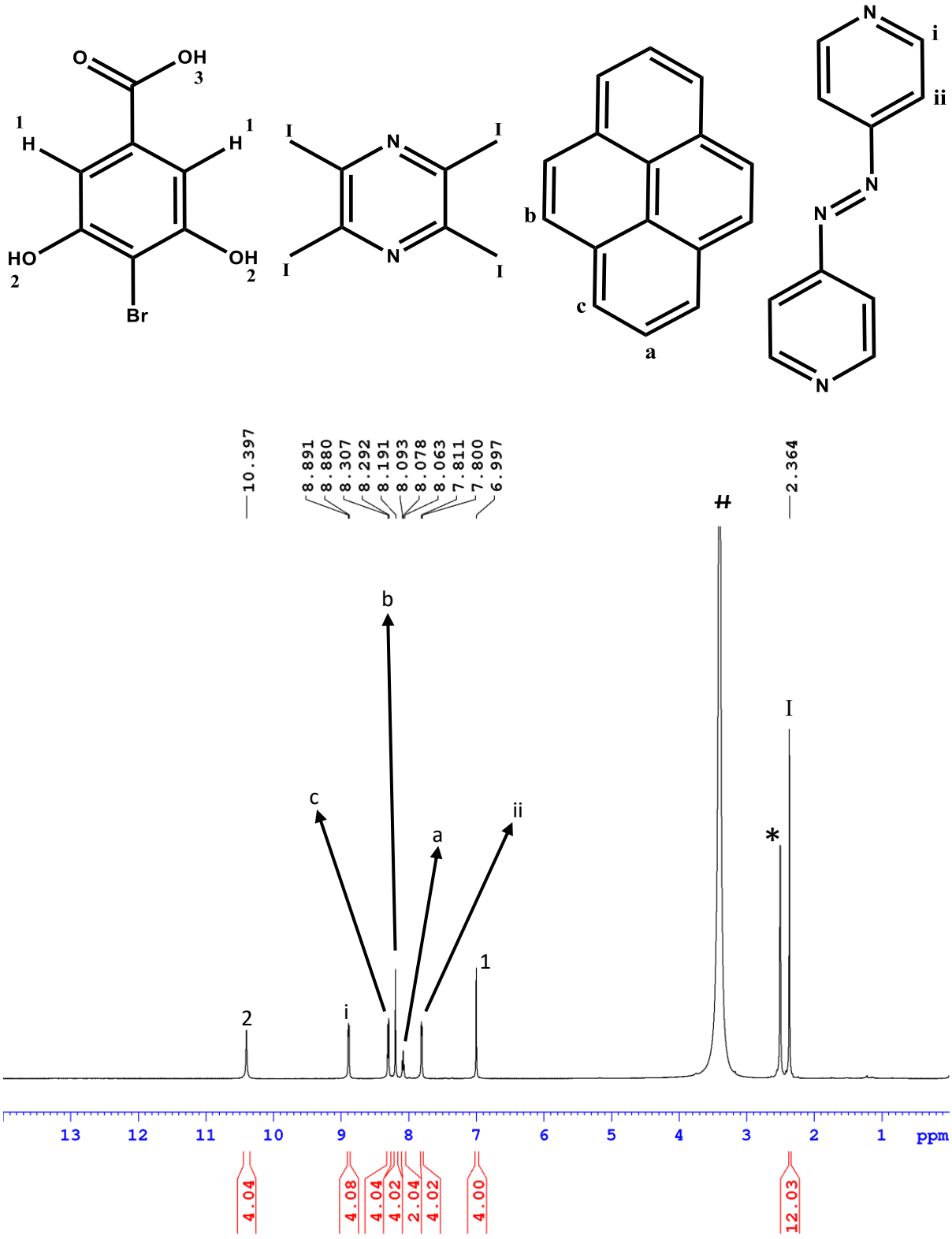


Figure S18. 1H NMR of BDHB-TMP-AZO-PYR (BMG) to confirm the components BDHB:TMP:PYR:AZO in ratio 2:1:1:1. * is residual solvent peak and # water peak. The COOH proton (3) is not coming, but it may have merged within the large water resonance (#). PXRD of the quaternary cocrystal is shown in Figure 13.

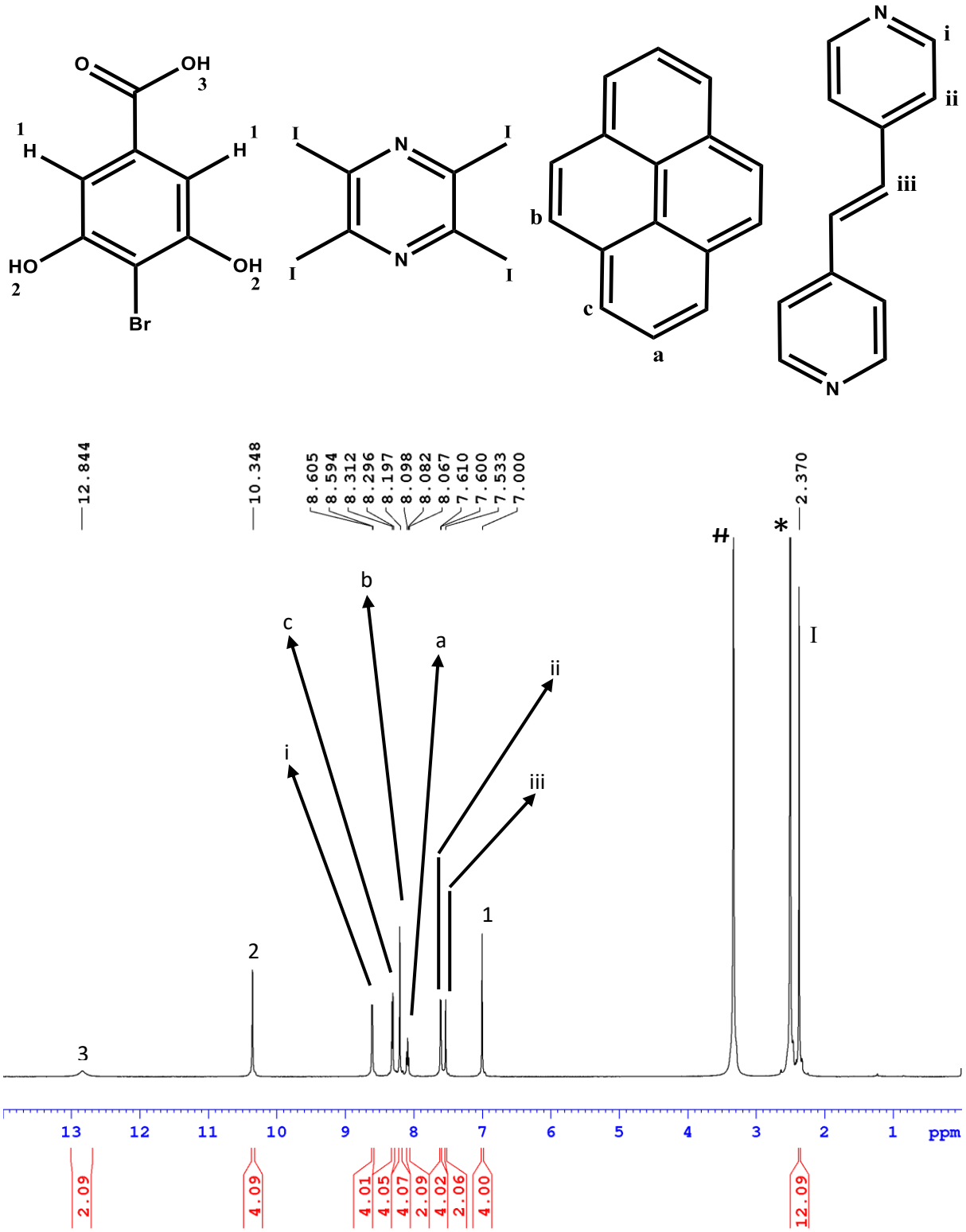


Figure S19. 1H NMR of TMP-PYR-BDHB-DPE-II (BMG) to confirm the components BDHB:TMP:PYR: DPE-II in ratio 2:1:1:1. * is residual solvent peak and # water peak. PXRD of the quaternary cocrystal is shown in Figure 16.

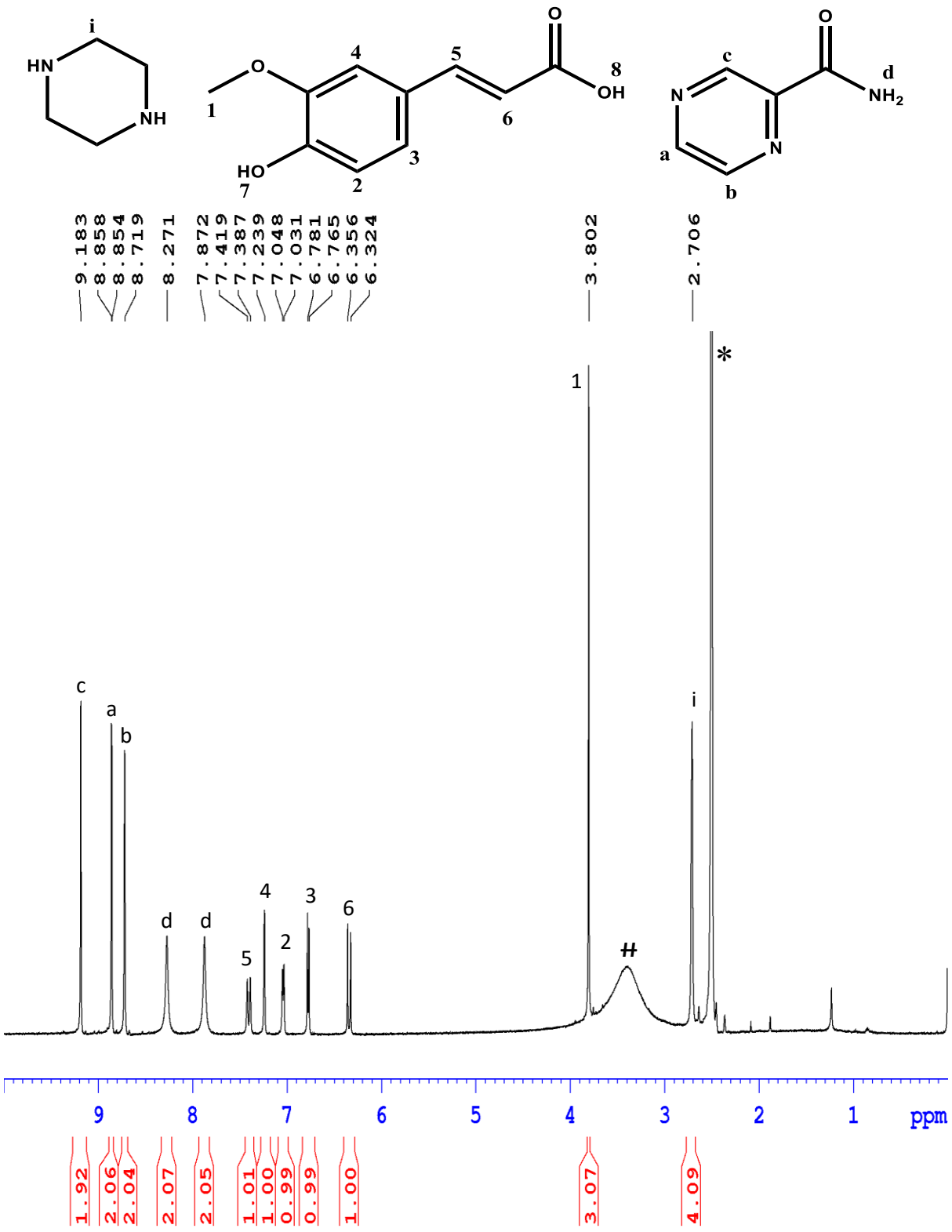


Figure S20. 1H NMR of PRZ-FLA-PRA-M2 prepared by manual grinding condition. Three components are present in the ratio 0.5:1:2. * is residual solvent peak and # water peak. The one OH and one COOH protons (7 & 8) are not showing, but it may have merged within the large water resonance (#). PXRD of the ternary product is shown in Figure S8.

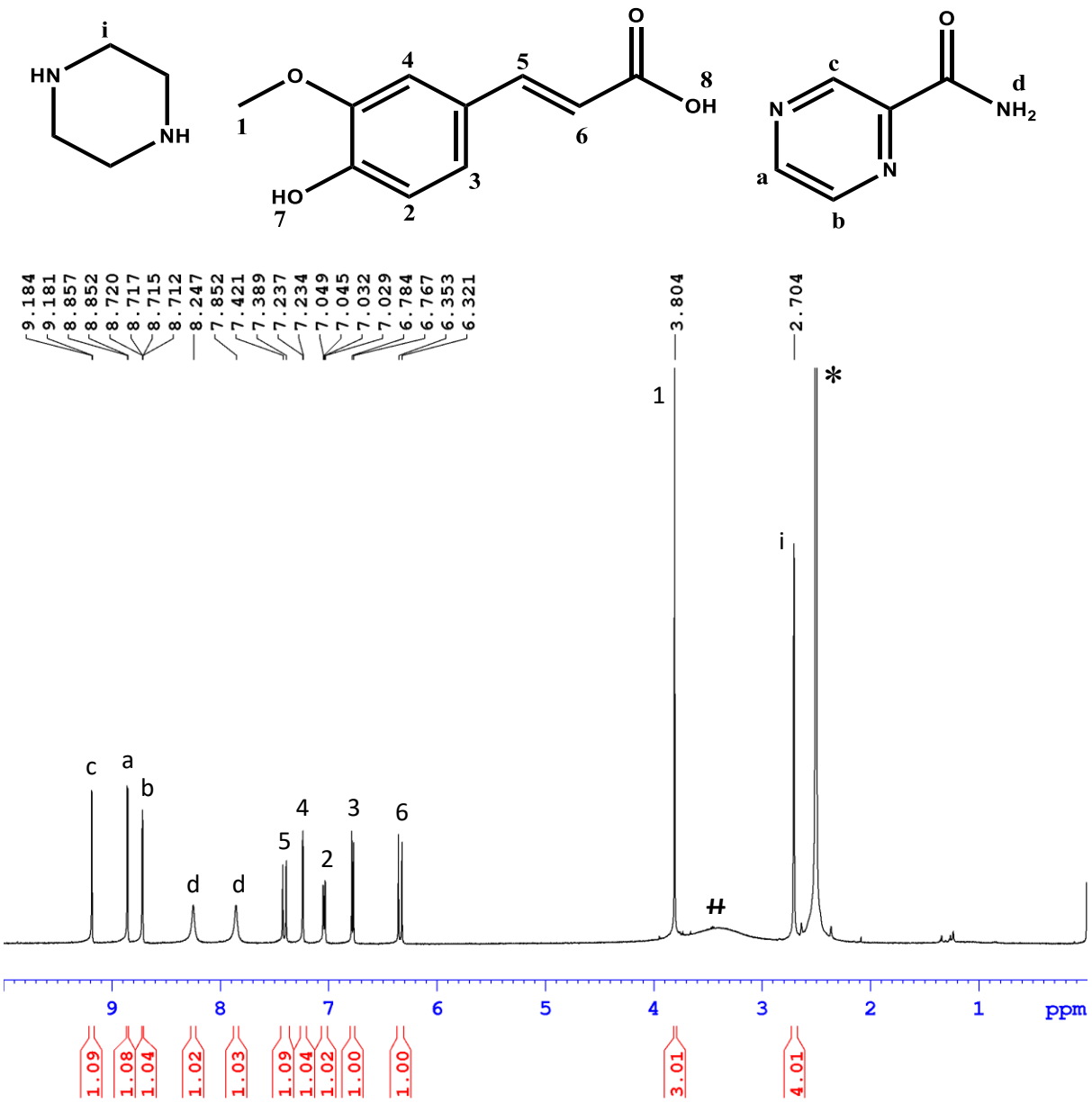
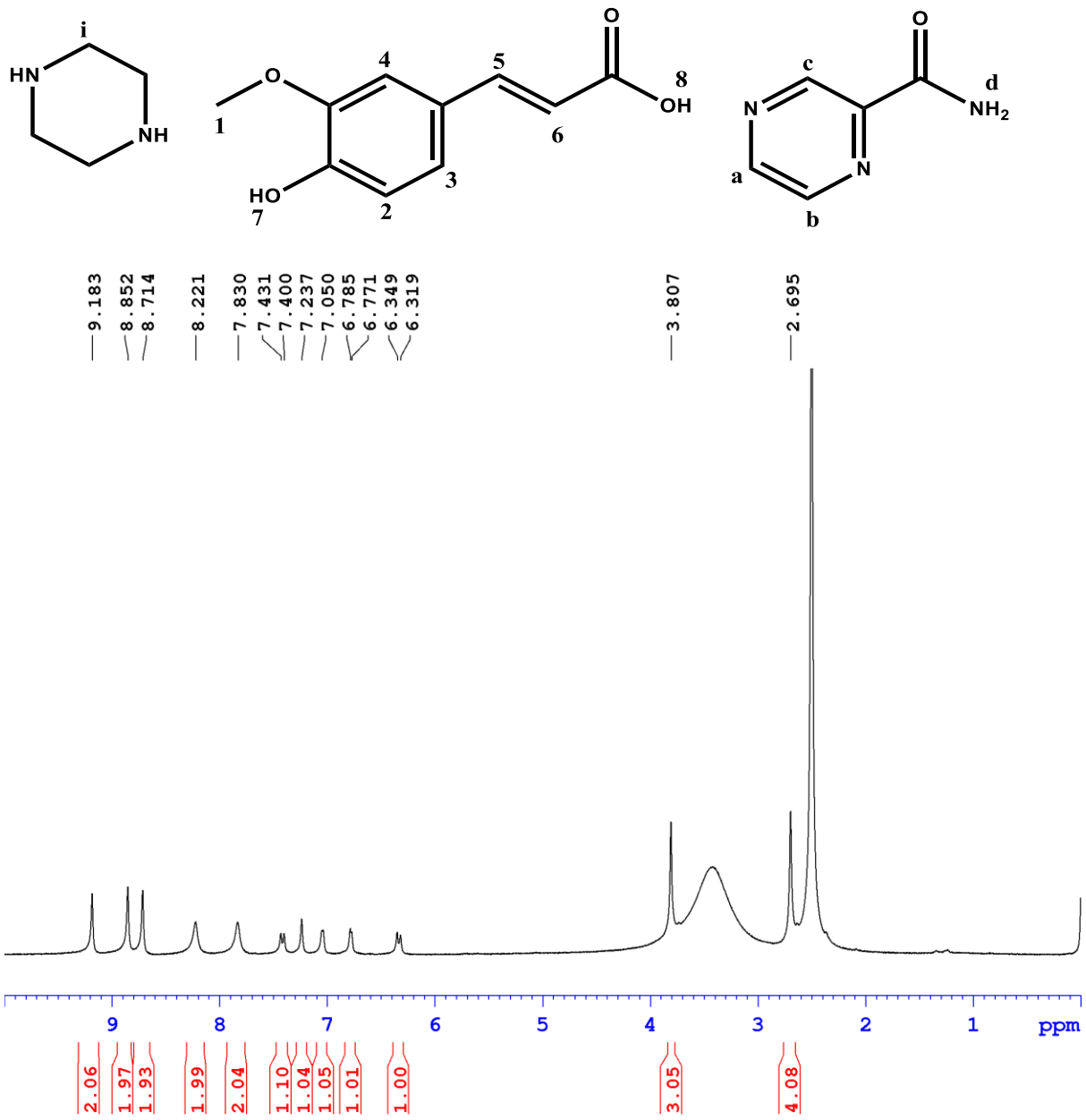


Figure S21. 1H NMR of PRZ-FLA-PRA-M2 prepared by manual grinding condition. Three components are present in the ratio 1:2:2. * is residual solvent peak and # water peak. The one OH protons and one COOH protons (7 & 8) are not showing, but it may have merged within the large water resonance (#). PXRD of the ternary product is shown in Figure S9.


i
HN
NH
O
1
4
5
O
8
OH
6
HO
7
2
3
c
d
N
NH2
a
N
b
9.183
8.852
8.714
8.221
7.830
7.431
7.400
7.237
7.050
6.785
6.771
6.349
6.319
3.807
2.695
9
8
7
6
5
4
3
2
1
ppm
2.06
1.97
1.93
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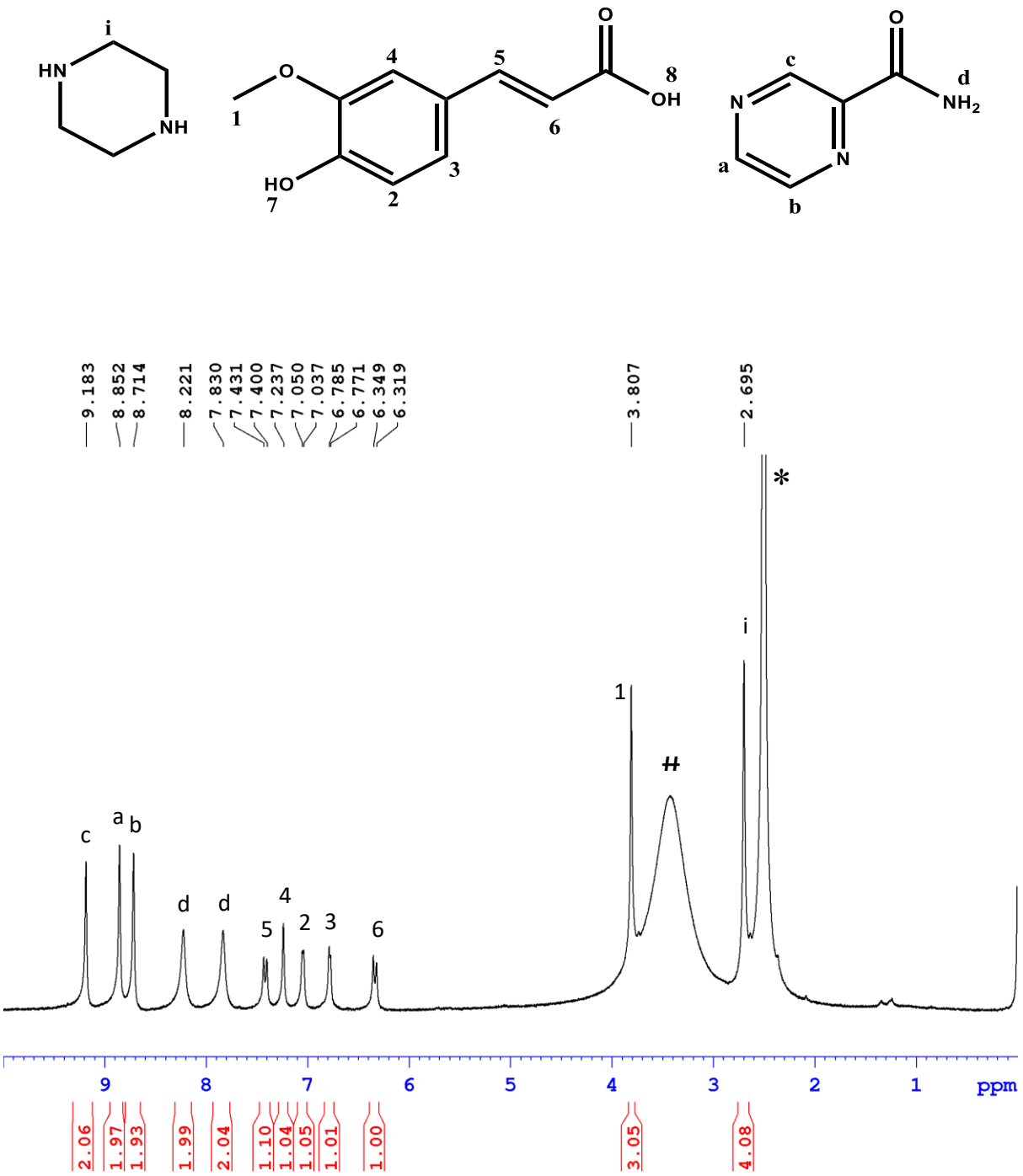
2.04
1.10
1.04
1.05
1.01
1.00
3.05
4.08

(a)



(b)

Figure S22. (a)1H NMR of PRZ-FLA-PRA-M2 prepared by ball-mill grinding condition (full spectrum). Three components are present in the ratio 0.5:1:2. * is residual solvent peak and # water peak. The one OH protons and one COOH protons (7 & 8) are not showing, but it may have merged within the large water resonance (#). (b) Enlarged view of the same spectrum. PXRD of the ternary product is shown in Figure S10.

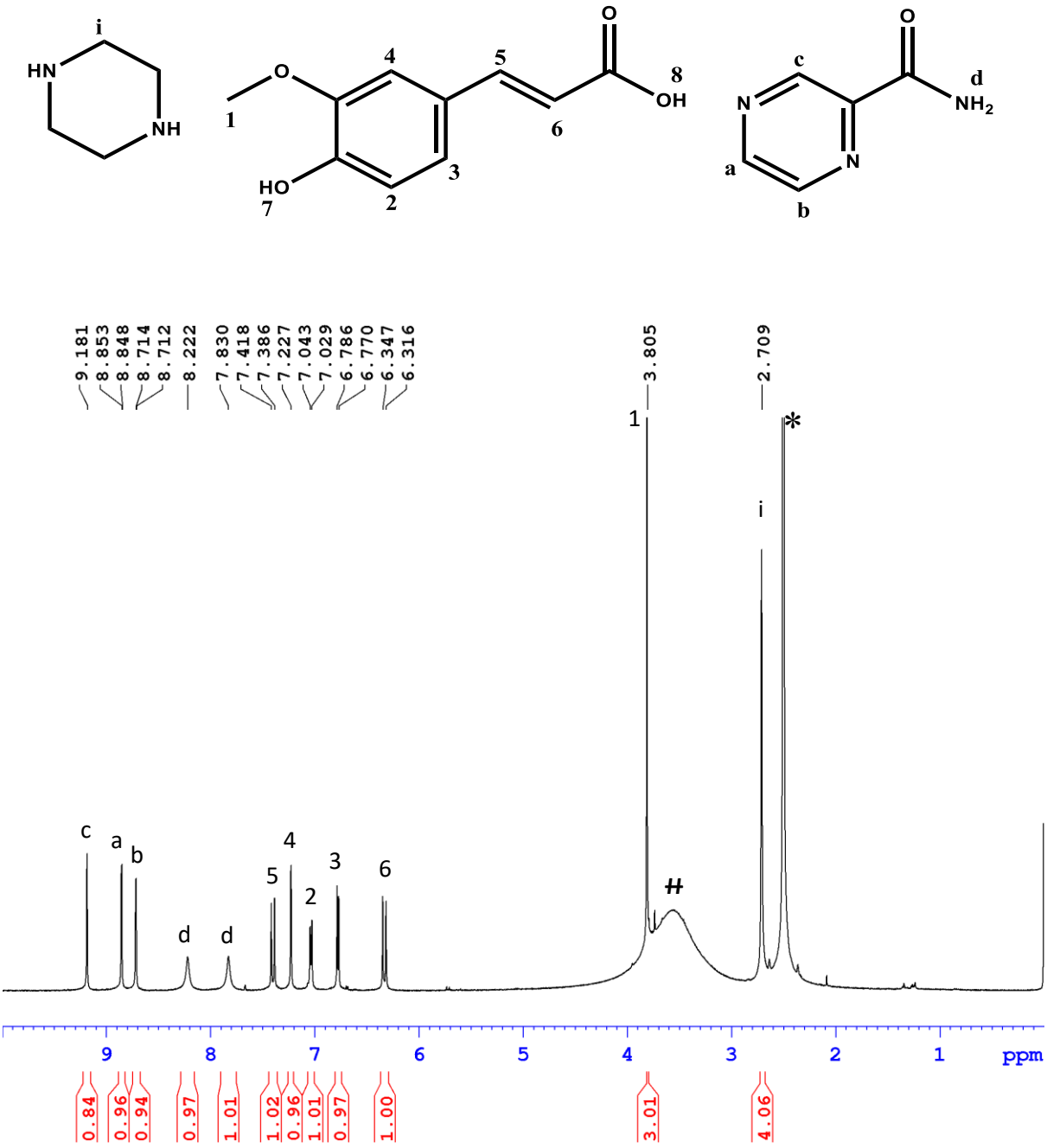


Figure S23. 1H NMR of PRZ-FLA-PRA-M2 prepared by ball-mill grinding condition. Three components are present in the ratio 1:2:2 ratio. * is residual solvent peak and # water peak. The one OH protons and one COOH protons (7 & 8) are not showing, but it may have merged within the large water resonance (#). PXRD of the ternary product is shown in Figure S11.

Experimental Section

Manual grinding of quaternary cocrystals

The ratio of the chemical components and solvent used for cocrystal formation was kept the same as in the original paper (given in Table 4) for all manual grinding conditions. One prototype procedure for quaternary cocrystal synthesis is detailed here.

BDHB-TMP-AZO-PYR: BDHB, TMP, PYR and AZO were taken in 2:1:1:1 ratio and MeOH was added as LAG to facilitate cocrystal formation. Except for the ratio of components and solvent, experimental procedure is similar for other systems.

M2 method: BDHB, TMP, AZO and PYR were taken along with few drops of MeOH added for LAG and the mixture was ground manually for 30 min. Solvent was added at periodic intervals whenever the solid mixture appeared to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(a) method: BDHB was taken with TMP and a few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, PYR was added with few drops of MeOH and again manual grinding was performed for 30 min. In the next step, AZO and a few drops of MeOH was added and further grinding was continued for 30 min. During grinding, the solvent was added at periodic intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(b) method: BDHB was taken with TMP and a few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, AZO was added with few drops of MeOH and again manual grinding was performed for 30 min. In the next step, PYR and a few drops of MeOH was added and further grinding was continued for 30 min. During grinding, the solvent was added at periodic intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(c) method: BDHB was taken with PYR and a few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, TMP was added with few drops of MeOH and again manual grinding was performed for 30 min. In the next step, AZO and a few drops of MeOH was added and further grinding was continued for 30 min. During grinding, the solvent was added at periodic intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(d) method: BDHB was taken with PYR and a few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, AZO was added with few drops of MeOH and again manual grinding was performed for 30 min. In the next step, TMP and a few drops of MeOH was added and further grinding was continued for 30 min. During grinding, the solvent was added at proper intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(e) method: BDHB was taken with AZO and a few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, TMP was added with a few drops of MeOH and again manual grinding was performed for 30 min. In the next step, PYR and a few drops of MeOH was added and further grinding was continued for 30 min. During grinding, the solvent was added at periodic intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(f) method: BDHB was taken with AZO with few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, PYR was added with a few drops of MeOH and again manual grinding was performed for 30 min. In the next step, TMP and few drops of MeOH was added and further grinding was continued for 30 min. During grinding, the solvent was added at periodic intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(g) method: TMP was taken with PYR with few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, BDHB was added with a few drops of MeOH and again manual grinding was performed for 30 min. In the next step, AZO and few drops of MeOH was added and further grinding was continued for 30 min. During grinding, the solvent was added at proper intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(h) method: TMP was taken with PYR with a few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, AZO was added with a few drops of MeOH and again manual grinding was performed for 30 min. In the next step, BDHB and a few drops of MeOH was added and further grinding was continued for 30 min. During grinding, the solvent was added at periodic intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(i) method: TMP was taken with AZO with few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, BDHB was added with a few drops of MeOH and again manual grinding was performed for 30 min. In the next step, PYR and few drops of MeOH was added and further grinding was continued for 30 min. During grinding, solvent was added at periodic intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(j) method: TMP was taken with AZO with few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, PYR was added with a few drops of MeOH and again manual grinding was performed for 30 min. In the next step, BDHB and a few drops of MeOH was added and further grinding was continued for 30 min. During grinding, solvent was added at periodic intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(k) method: PYR was taken with AZO with few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, BDHB was added with a few drops of MeOH and again manual grinding was done for 30 min. In the next step, TMP and a few drops of MeOH was added and further grinding was continued for 30 min. During grinding, solvent was added at periodic intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

M1(l) method: PYR was taken with AZO with few drops of MeOH were added, then the mixture was ground manually for 30 min. Then, TMP was added with few drops of MeOH and again manual grinding was performed for 30 min. In the next step, BDHB and a few drops of MeOH was added and further grinding was continued for 30 min. During grinding, solvent was added at periodic intervals whenever the solid mixture was appearing to be dried out due to rapid solvent evaporation from the open mortar and pestle jar.

Ball-mill grinding of quaternary cocrystals

The ratio of molecular components and solvent used for cocrystal formation was the kept same as in the original paper (given in Table 4) for all ball-mill grinding operations. One prototype procedure for quaternary cocrystal synthesis is elaborated here. Except for the ratio of components and solvent, experimental procedure is similar for other systems.

BDHB-TMP-AZO-PYR: BDHB, TMP, PYR and AZO were taken in 2:1:1:1 ratio and MeOH was the LAG solvent to facilitate cocrystal formation.

M1(g) method: Ball-mill grinding was conducted using Retsch MM400 ball mill, equipped with stainless steel 25 mL grinding jar and three 5-mm stainless steel grinding balls. TMP and PYR was taken in the jar with 2-3 drops of MeOH addition and grinding was performed at a rate of 25 Hz for 30 min. In next step, BDHB was added with 2-3 drops of MeOH in the same jar and again grinding was performed for 30 min at a rate of 25 Hz. In the last step, AZO and 2-3 drops of MeOH was added in the jar and grinding was continued for 30 min at 25 Hz.

M1(h) method: - Ball-mill grinding was conducted using Retsch MM400 ball mill, equipped with stainless steel 25 mL grinding jar and three 5-mm stainless steel grinding balls. TMP and PYR was taken in the jar with 2-3 drops of MeOH addition and grinding was performed at a rate of 25 Hz for 30 min. In next step, AZO was added with 2-3 drops of MeOH in the same jar and again grinding was performed for 30 min at a rate of 25 Hz. In the last step, BDHB and 2-3 drops of MeOH was added in the jar and grinding was continued for 30 min at 25 Hz.

M1(i) method: Ball-mill grinding was conducted using Retsch MM400 ball mill, equipped with stainless steel 25 mL grinding jar and three 5-mm stainless steel grinding balls. TMP and AZO was taken in the jar with 2-3 drops of MeOH addition and grinding was performed at a rate of 25 Hz for 30 min. In next step, BDHB was added with 2-3 drops of MeOH in the same jar and again grinding was performed for 30 min at a rate of 25 Hz. In the last step, PYR and 2-3 drops of MeOH was added in the jar and grinding was continued for 30 min at 25 Hz.

M1(j) method: Ball-mill grinding was conducted using Retsch MM400 ball mill, equipped with stainless steel 25 mL grinding jar and three 5-mm stainless steel grinding balls. TMP and AZO was taken in the jar with 2-3 drops of MeOH addition and grinding was performed at a rate of 25 Hz for 30 min. In next step, PYR was added with 2-3 drops of MeOH in the same jar and again grinding was performed for 30 min at a rate of 25 Hz. In the last step, BDHB and 2-3 drops of MeOH was added in the jar and grinding was continued for 30 min at 25 Hz.
