

Novel salts and cocrystals of antifolate drug, Trimethoprim and its role in enhancement of solubility and dissolution.

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Table S1: IR spectroscopy

	TMP	T7A	5FU	CAT	THY	TMP-T7A	TMP-5FU	TMP-CAT	TMP-THY-H2O
-N-H stretch	3467 (asymmetric) 3315 (symmetric)	-	3119	-	3746	3358 3293	3410 3143	3463 3358	3631 3437 3329
-N-H bend	1631 1591	-	1505	-	1555	1631 1586	1591 1507	1634 1591	1586 1565
-C=O stretch (carboxylate)	-	1732	-	-	-	1672	-	-	-
-C(=O)-N- (amide)	-	1707	1717 1651	-	1658	1705	1670 1646	-	1713 1648
-O-H (phenolic)	-	-	-	3444	-	-	-	3415	-
-O-H (water)	-	-	-	-	-	-	-	-	3520

Table S2:The ¹³C-NMR values of all four systems.

TMP-T7A	TMP-5FU	TMP-CAT	TMP-THY-H2O
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¹³ C-NMR TMP	¹³ C-NMR T7A	¹³ C-NMR TMP	¹³ C-NMR 5FU	¹³ C-NMR TMP	¹³ C-NMR CAT	¹³ C-NMR TMP	¹³ C-NMR THY
C1-33.47 to 32.88	C1- 27.95 to 27.89	C1-33.47 to 33.46	C1-126.63;126.88 to 126.70;127.02	C1-33.47 to 33.45	C1-116.5 to 116.14	C1-33.47 to 33.46	C1-12.28 to 12.28
C2-56.28 to 56.30 & 63.25	C2-29.96 to 29.87	C2-56.28 to 56.27	C2-139.39;141.20 to 139.19;141.44	C2-56.28 to 56.26	C2-119.75 to 119.74	C2-56.28 to 56.27	C2-108.16 to 108.18
C3-60.45 to 60.43	C3-47.68 to 49.08	C3-60.45 to 60.45	C3-150.55 to 150.60	C3-60.45 to 60.43	C3-145.73 to 145.73	C3-60.45 to 60.45	C3-138.19 to 138.23
C4;C5-106.28 to 106.47 & 106.96	C4-106.89 to 107.91	C4;C5-106.28 to 106.28	C4-158.35;158.55 to 158.31;158.56	C4;C5-106.28 to 106.27		C4;C5-106.28 to 106.28	C4-151.97 to 152.00
C6-136.18 to 134.63	C5-143.67 to 143.67	C6-136.18 to 136.18		C6-136.18 to 136.18		C6-136.18 to 136.18	C5-165.41 to 165.45
C7-136.38 to 136.43	C6-148.40 to 148.17	C7-136.38 to 136.36		C7-136.38 to 136.34		C7-136.38 to 136.37	
C8-153.16 to 153.26 & 145.79	C7-151.51 to 151.52	C8-153.16 to 153.16		C8-153.16 to 153.16		C8-153.16 to 153.16	
C9-156.17 to 158.04	C8-154.93 to 154.92	C9-156.17 to 156.09		C9-156.17 to 156.09		C9-156.17 to 156.14	
C10;C11-162.66;162.70 to 163.83	C9-169.48 to 171.24	C10;C11-162.66;162.70 to 162.67		C10;C11-162.66;162.70 to 162.67		C10;C11-162.66;162.70 to 162.68;162.71	

Table S3:The % cumulative drug release in 0.1N HCl media at specified intervals of time.

TIME INTERVAL (MINUTES)	% CUMULATIVE DRUG RELEASE OF TMP-API	% CUMULATIVE DRUG RELEASE OF TMP-THY-H2O	% CUMULATIVE DRUG RELEASE OF TMP-5FU
0	0	0	0
5	67.7	72.2	93.7
10	76.4	87.6	95.2
15	77.9	87.8	95.6
30	78.2	87.9	97.1
45	78.7	88.5	97.7

1	-	10.61	B3LYP/6-31G(d,p)	-79.6	-16.1	-14	122.7	-32.5
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Table S6: Interaction energies of heterosynthons and homosynthons present in TMP-5FU. R is the distance between molecular centroids (mean atomic position) in Å

N	Symp	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
1	-	9.03	B3LYP/6-31G(d,p)	-81.4	-17.8	-16.6	134.1	-30.9

Table S7: Interaction energies of homosynthons present in TMP-CAT. R is the distance between molecular centroids (mean atomic position) in Å

N	Symp	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
1	-	6.99	B3LYP/6-31G(d,p)	-82.8	-21.7	-17.8	102.8	-55.6
1	-	9.79	B3LYP/6-31G(d,p)	-18	-3.3	-8.2	18.7	-17.1

Table S8: Interaction energies of heterosynthons present in TMP A-THY B. R is the distance between molecular centroids (mean atomic position) in Å

N	Symp	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
1	-	7.31	B3LYP/6-31G(d,p)	-107.1	-22.4	-22.1	114.9	-78.1
1	-	8.69	B3LYP/6-31G(d,p)	-102	-6.2	-17.4	114.8	-56.7

Table S9: Interaction energies of heterosynthons present in TMP B-THY A. R is the distance between molecular centroids (mean atomic position) in Å.

N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
1	-	7.38	B3LYP/6-31G(d,p)	-109.9	-23.1	-22.4	120.5	-78.3
1	-	8.07	B3LYP/6-31G(d,p)	-102.5	-0.1	-17.5	112.8	-54

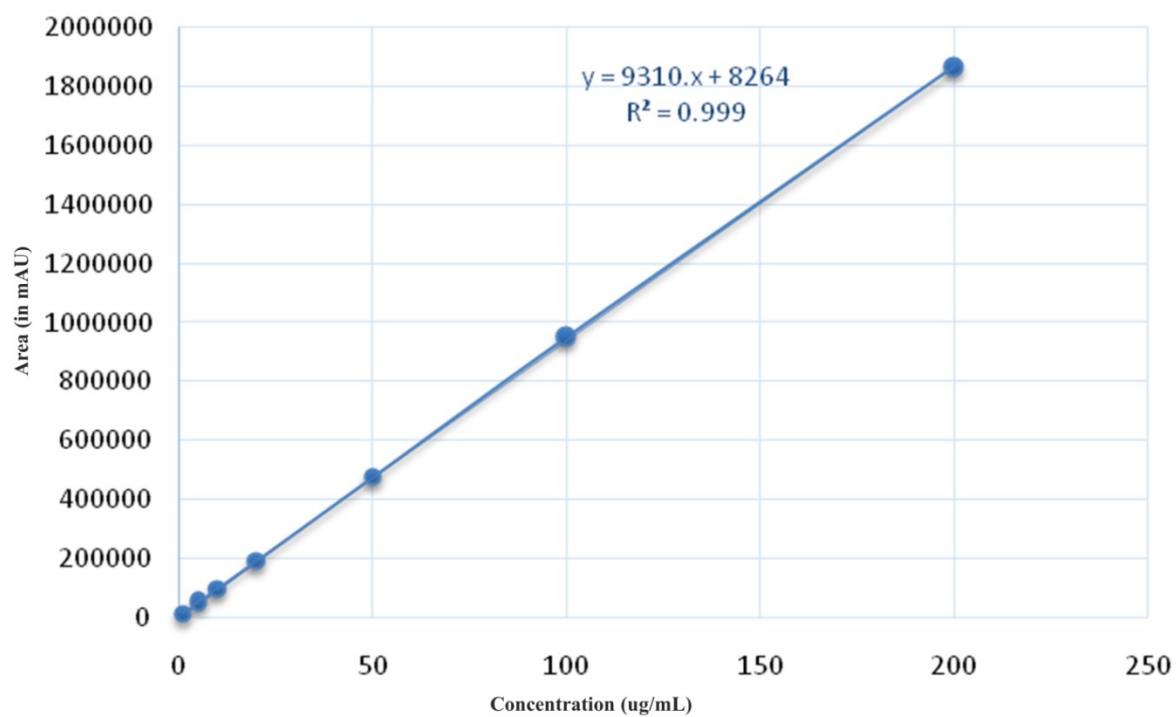


Fig.S1The linearity curve of TMP using HPLC for solubility studies

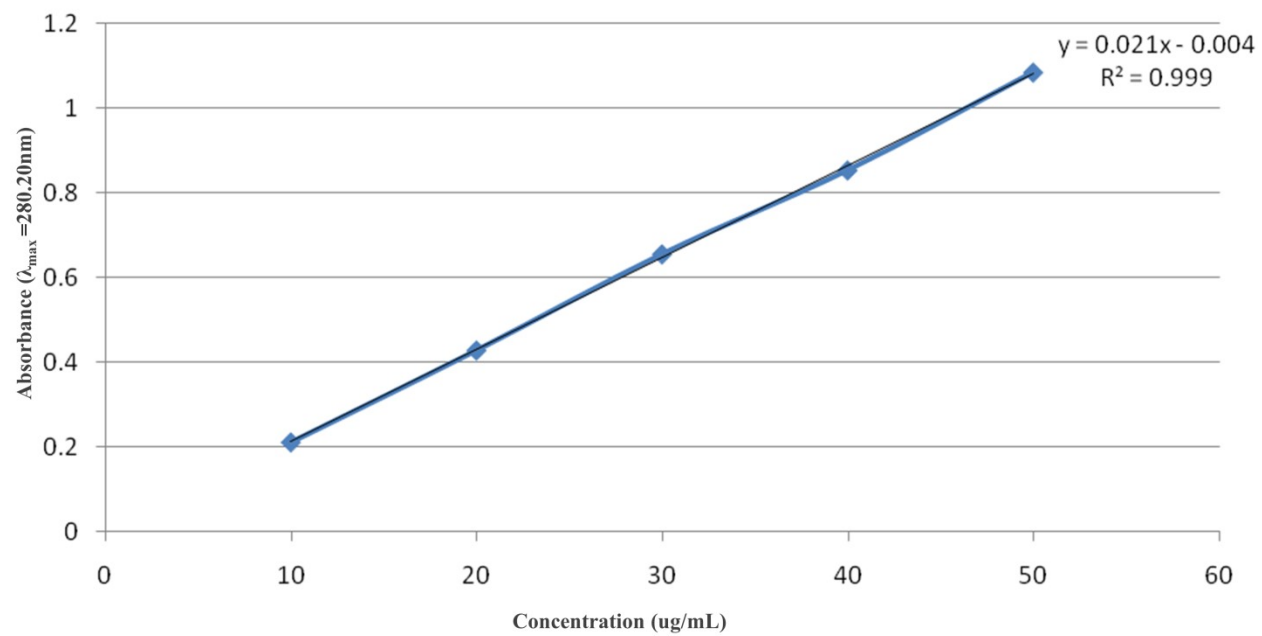
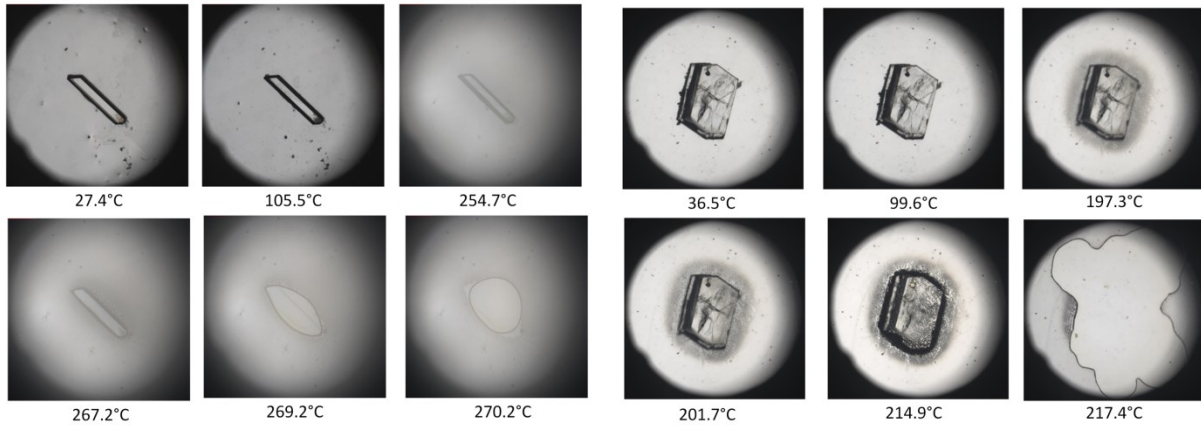
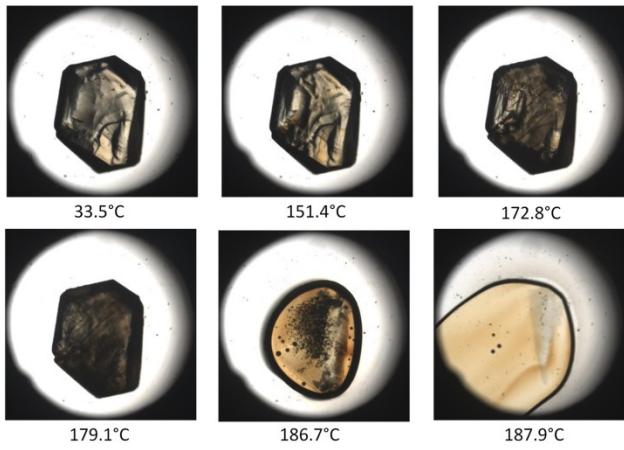


Fig.S2The linearity curve of TMP (in water) using UV-Visible spectroscopy for dissolution studies.

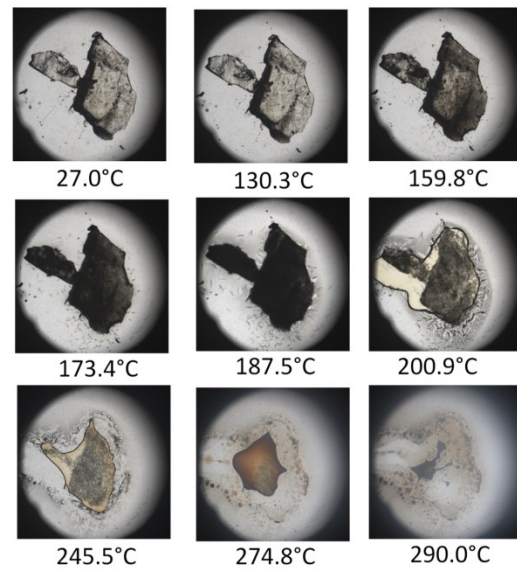


HSM OF TMP-T7A

HSM OF TMP-5FU



HSM OF TMP-CAT



HSM OF TMP-THY-H2O

Fig.S3HSM of TMP-T7A, TMP-5FU, TMP-CAT and TMP-THY-H₂O

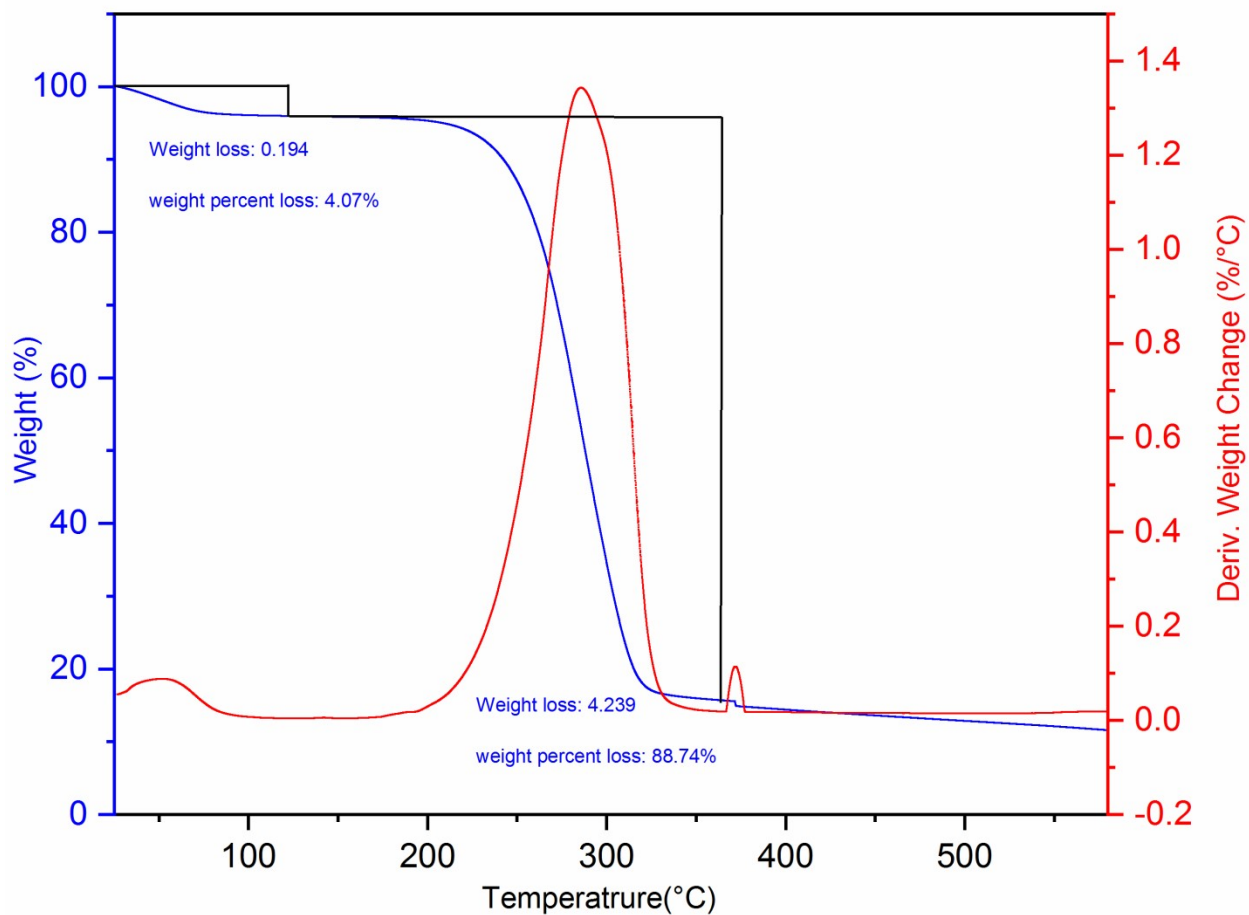


Fig.S4 The TGA plot of TMP-THY-H2O

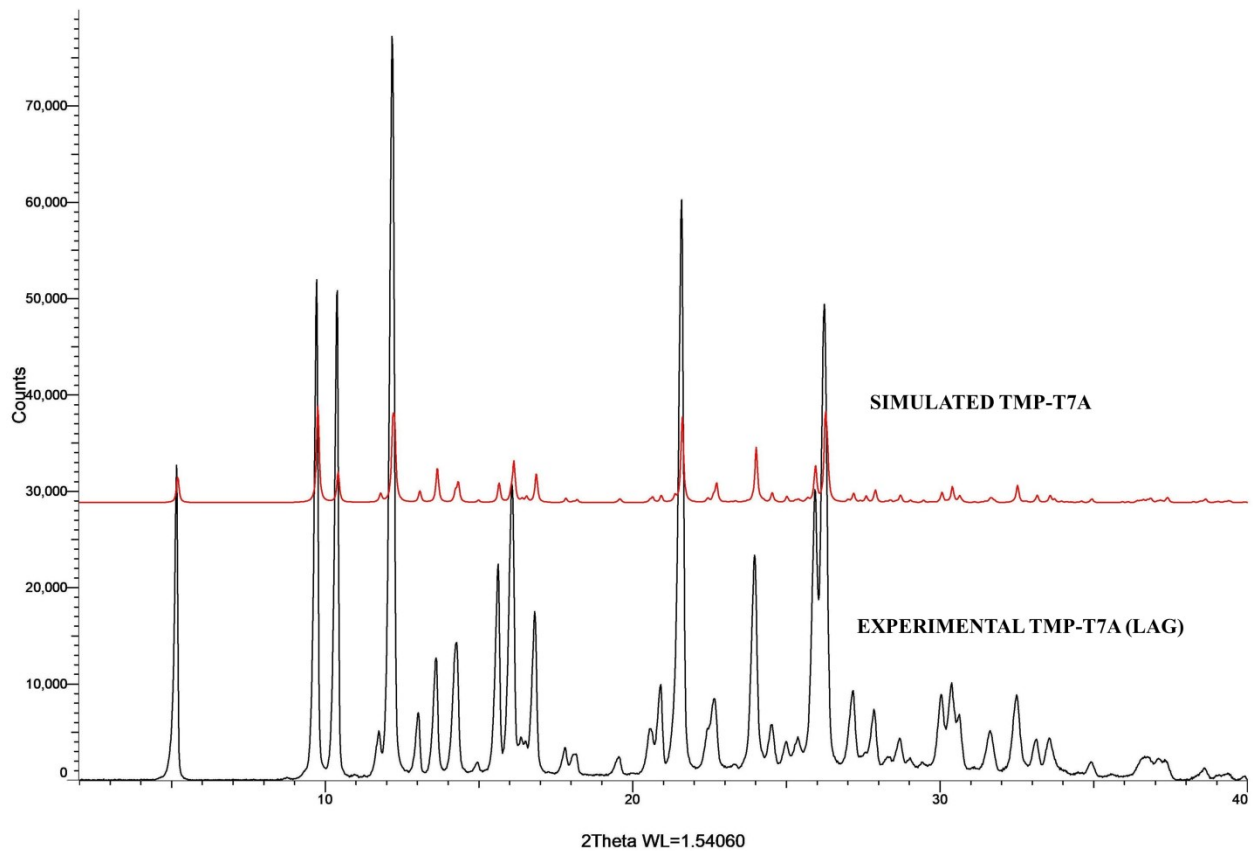


Fig.S5PXRD overlay of liquid assisted ground powder of TMP-T7A with its simulated pattern.

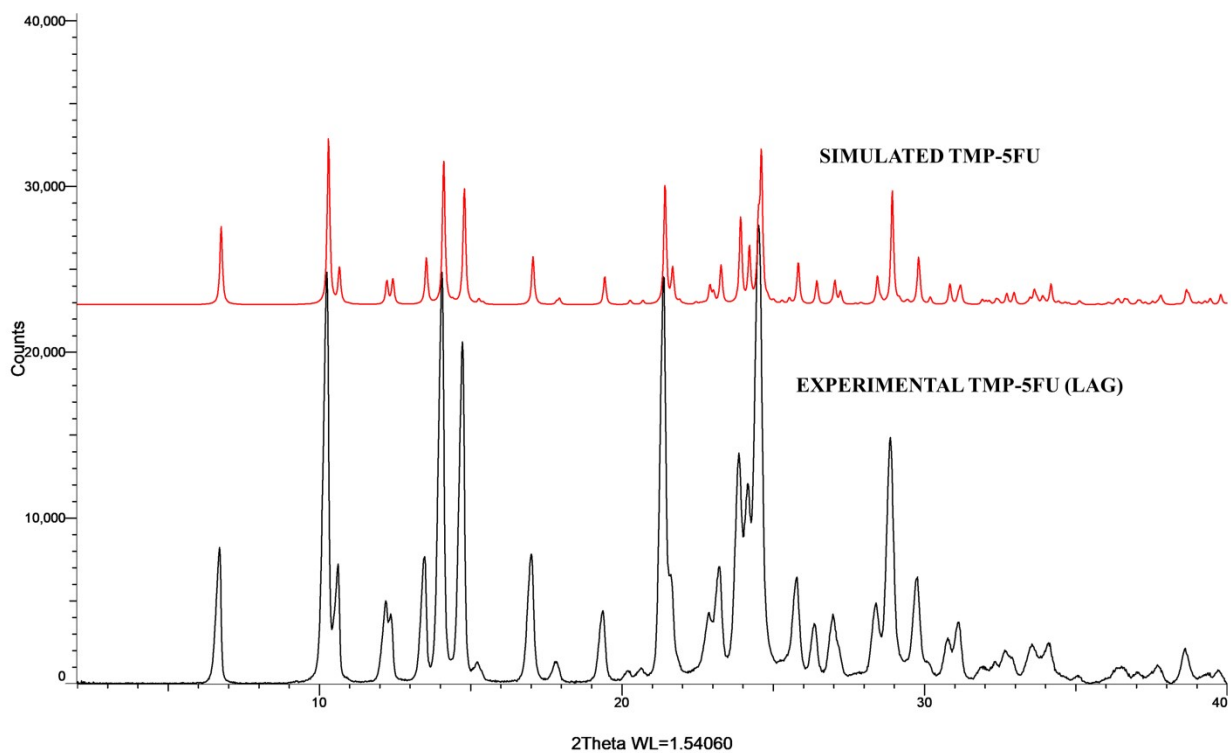


Fig.S6PXRD overlay of liquid assisted ground powder of TMP-5FU with its simulated pattern.

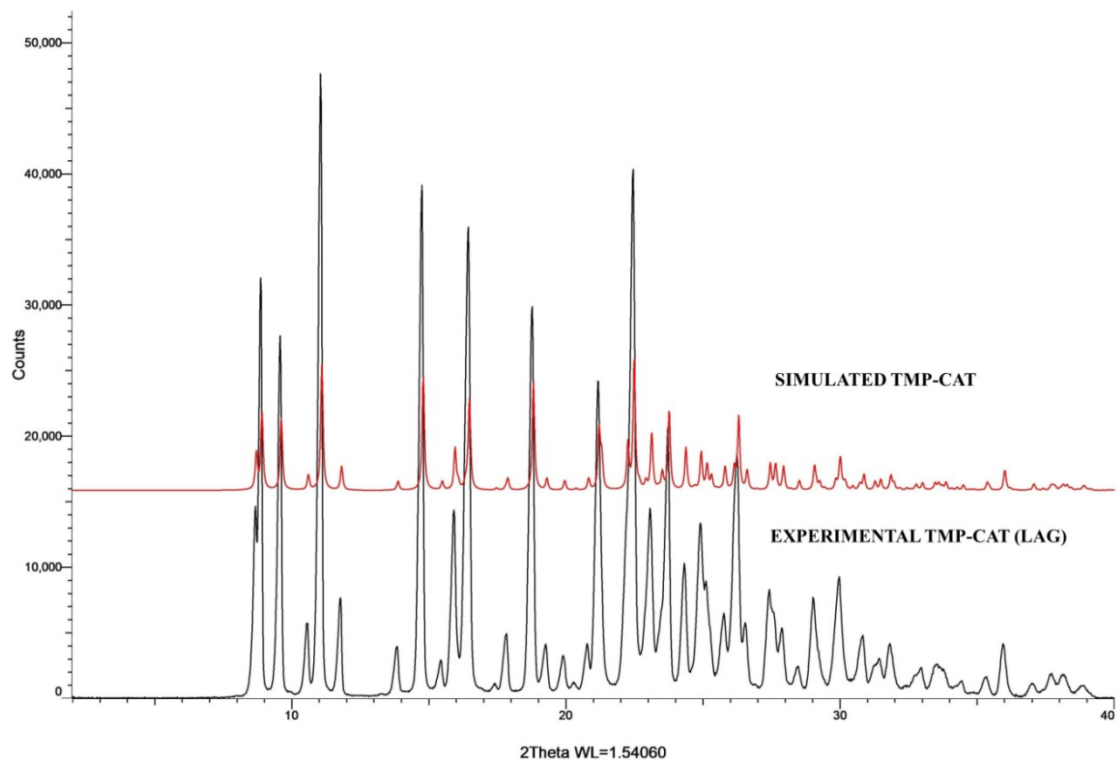


Fig.S7 XRD overlay of liquid assisted ground powder of TMP-CAT with its simulated pattern.

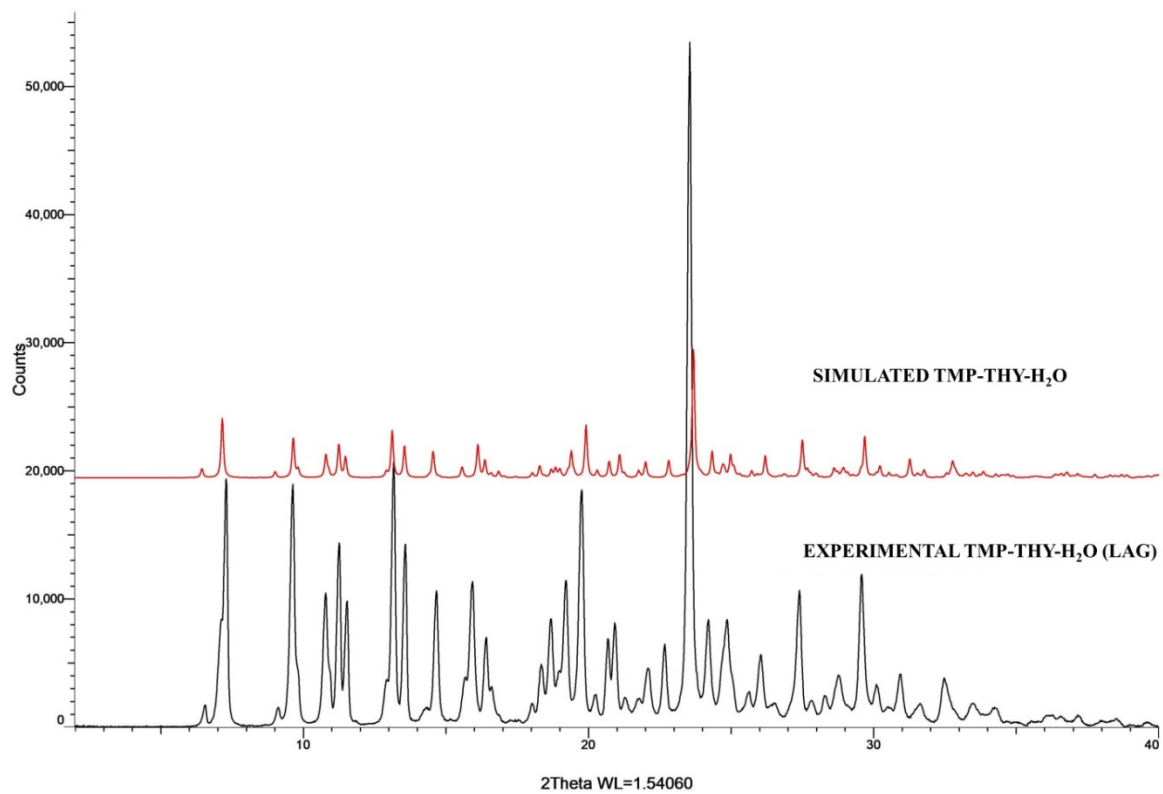


Fig.S8 XRD overlay of liquid assisted ground powder of TMP-THY-H₂O with its simulated pattern.

^1H NMR of TMP ($\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_3$)

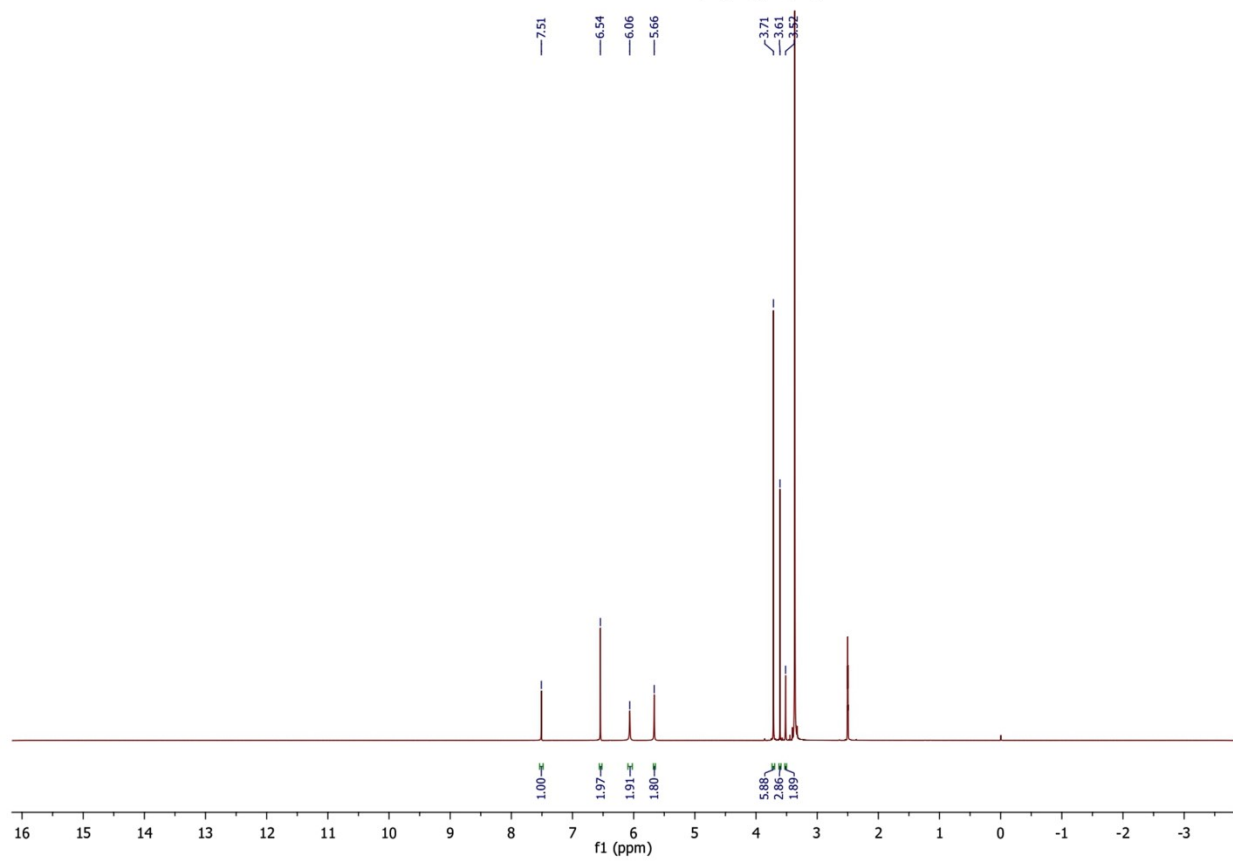


Fig.S9 ^1H NMR of TMP.

¹H NMR of T7A (C₉H₁₀N₄O₄)

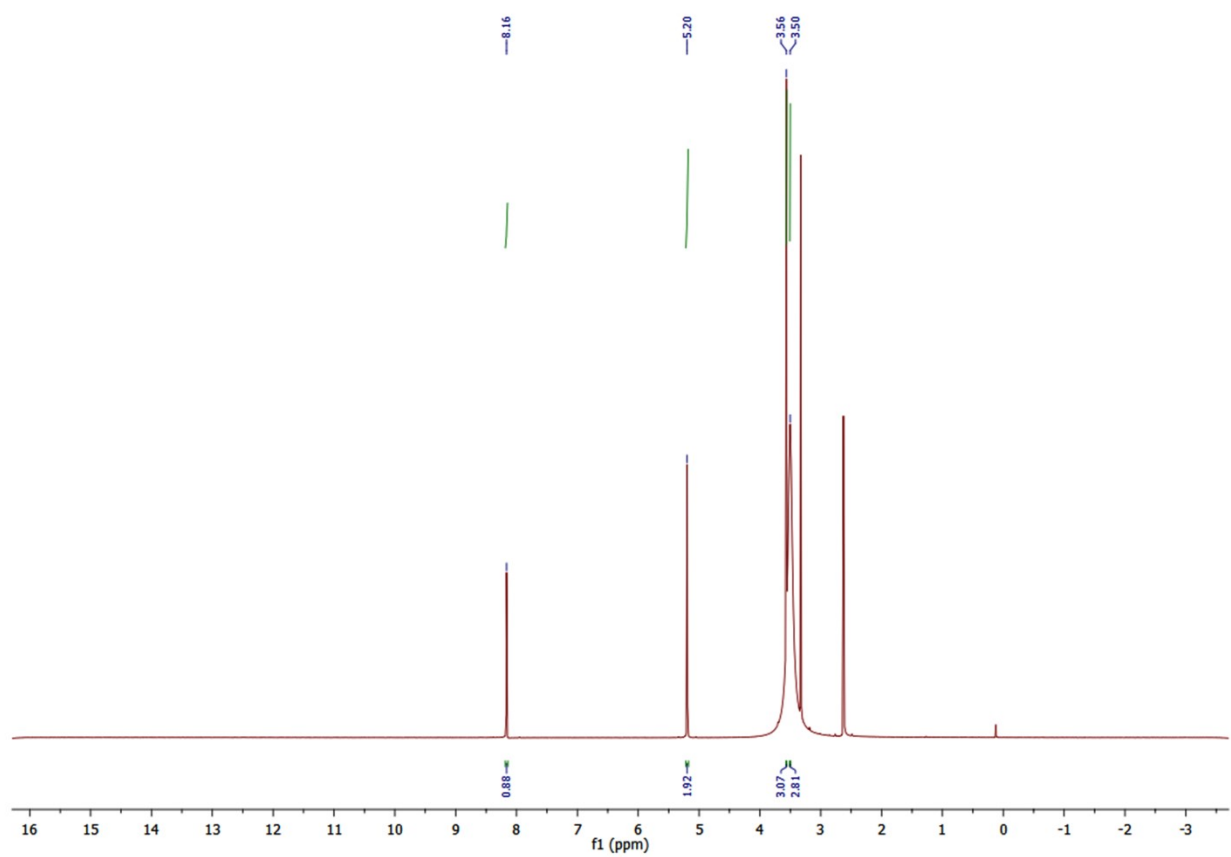


Fig.S10 ¹H NMR of T7A.

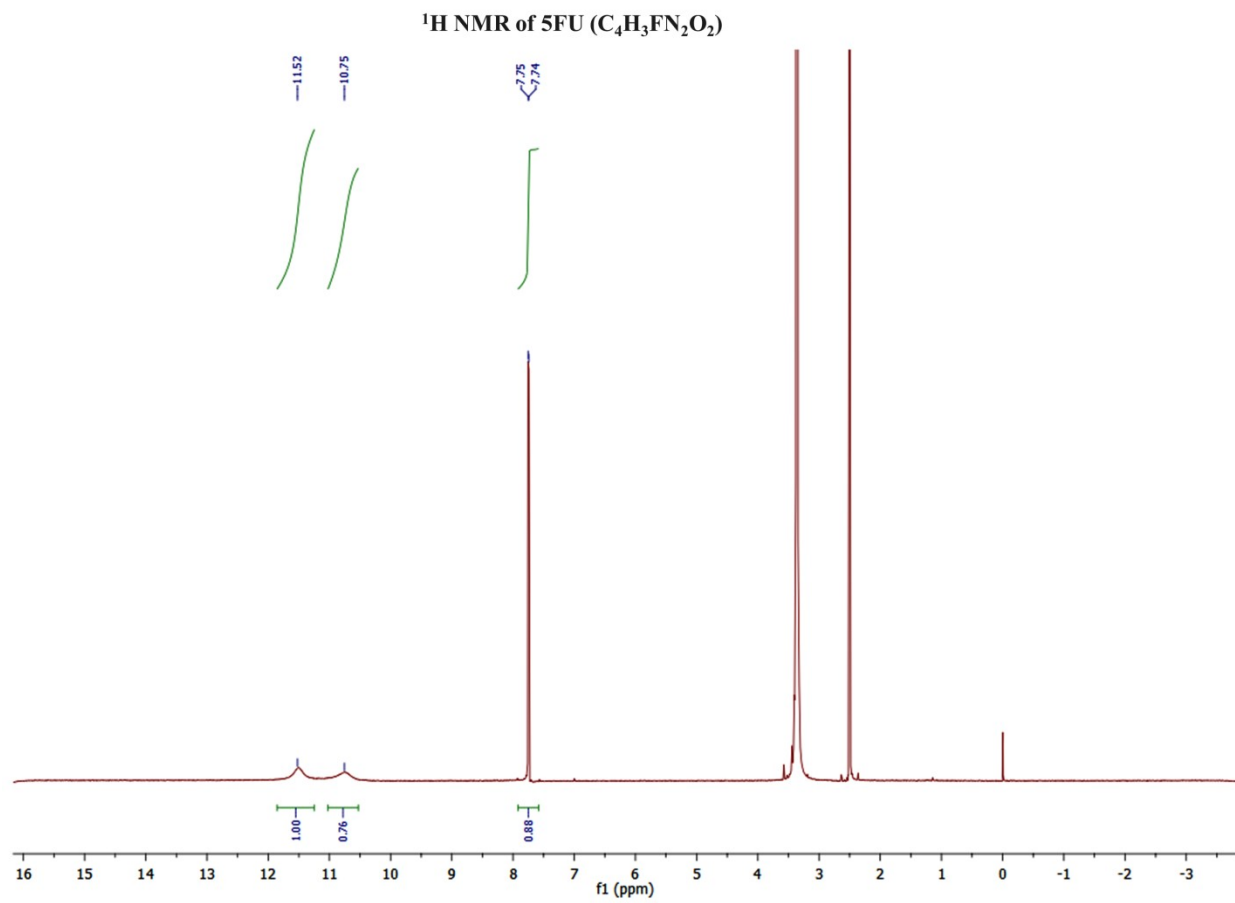


Fig.S11 ¹H NMR of 5FU.

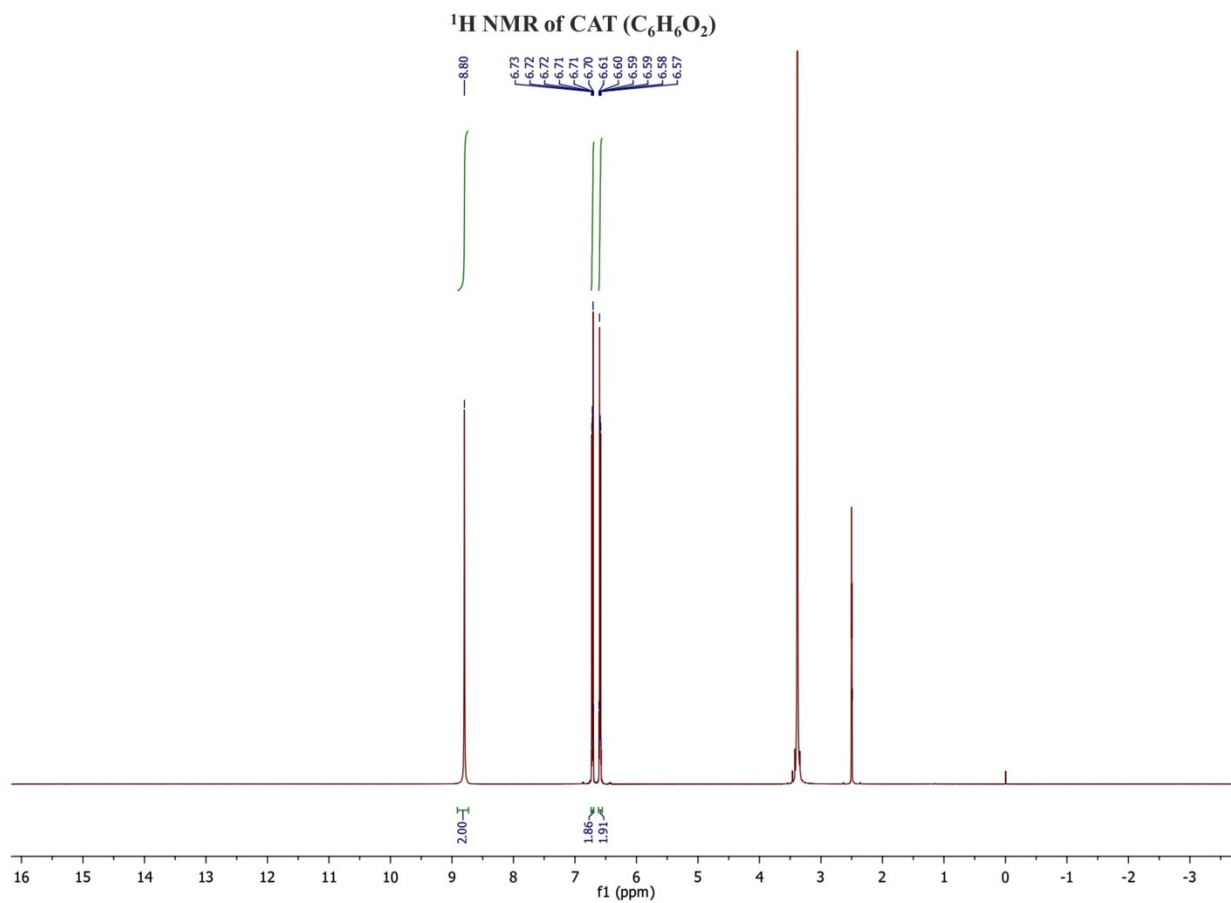


Fig.S12 ^1H NMR of CAT.

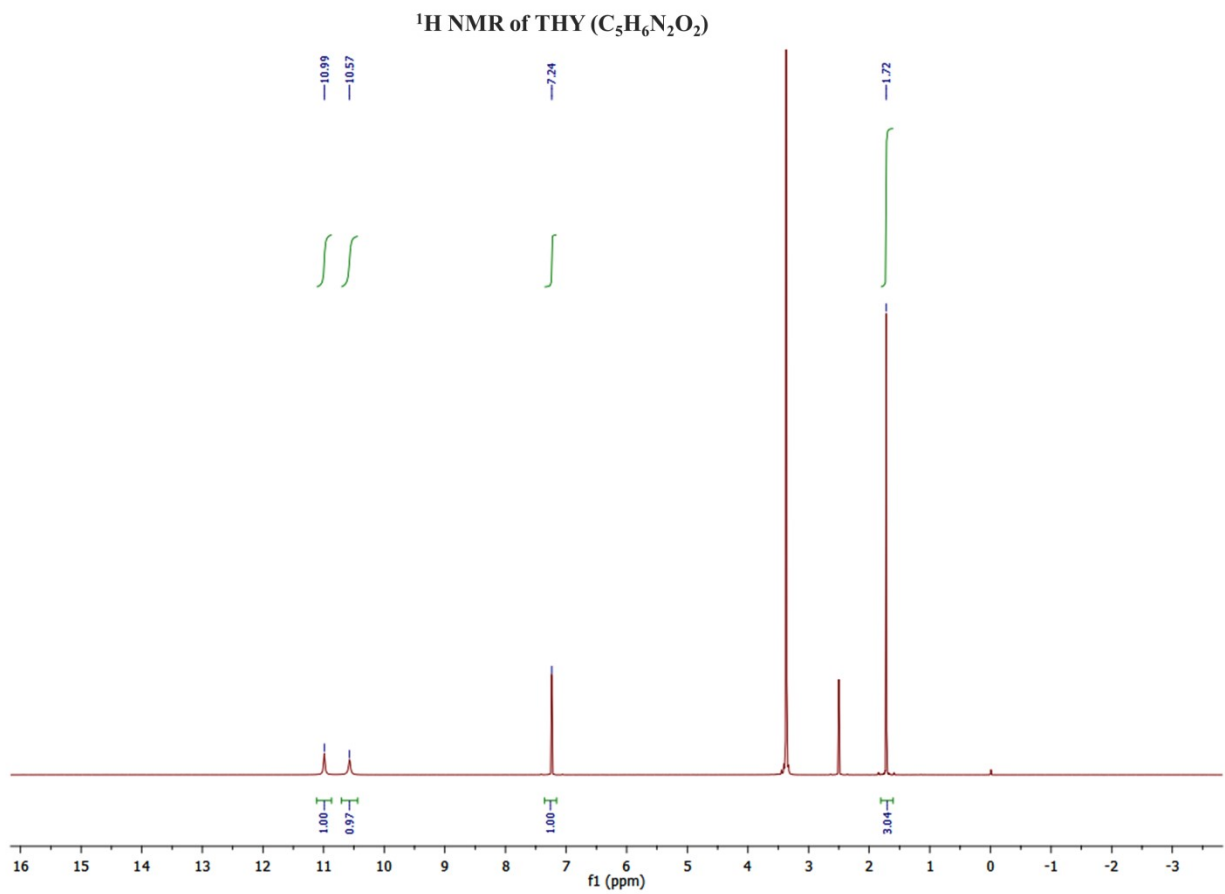


Fig.S13 ¹H NMR of THY.

¹H NMR of TMP-T7A (C₁₄H₁₉N₄O₃⁺ C₉H₉N₄O₄⁻)

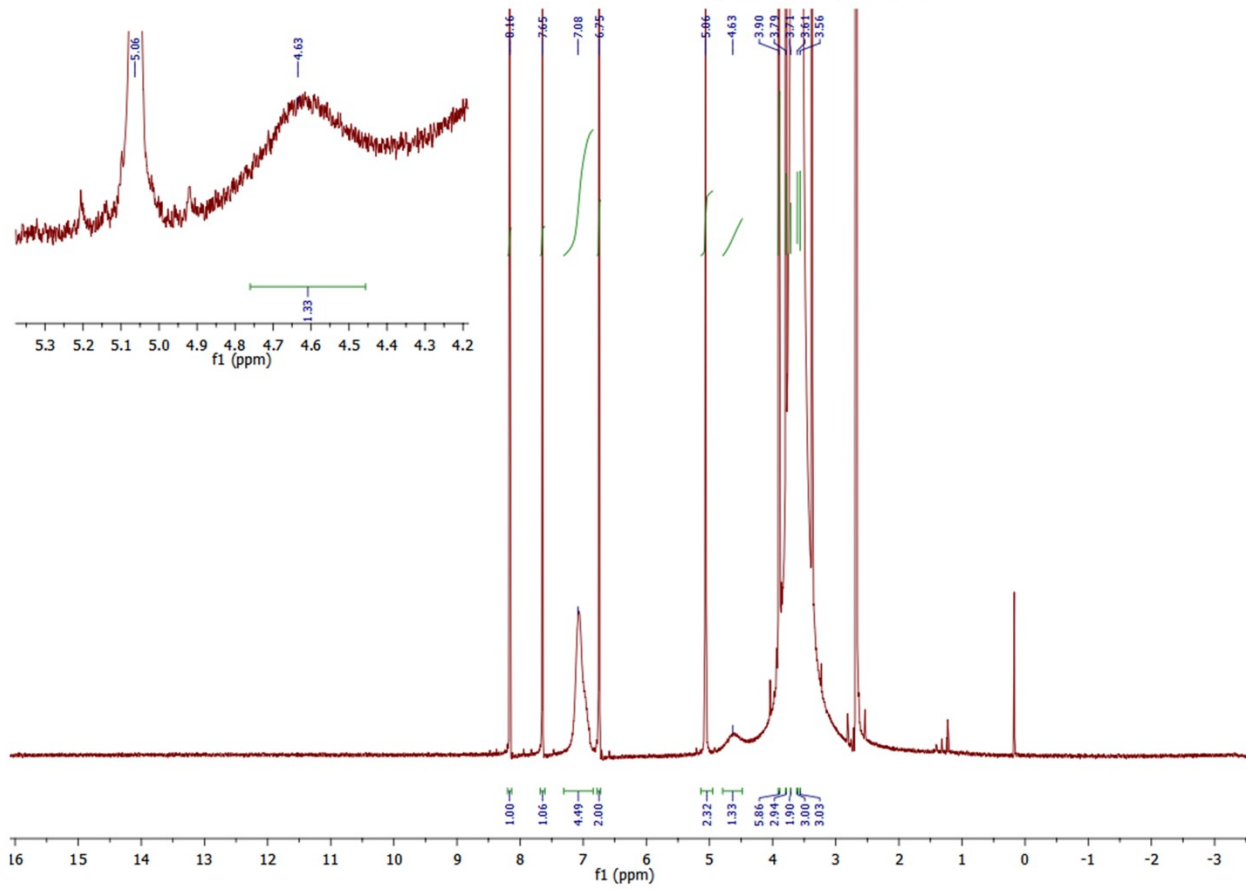


Fig.S14 ¹H NMR of TMP-T7A.

^1H NMR of TMP-5FU ($\text{C}_{14}\text{H}_{19}\text{N}_4\text{O}_3^+ \text{C}_4\text{H}_2\text{FN}_2\text{O}_2^-$)

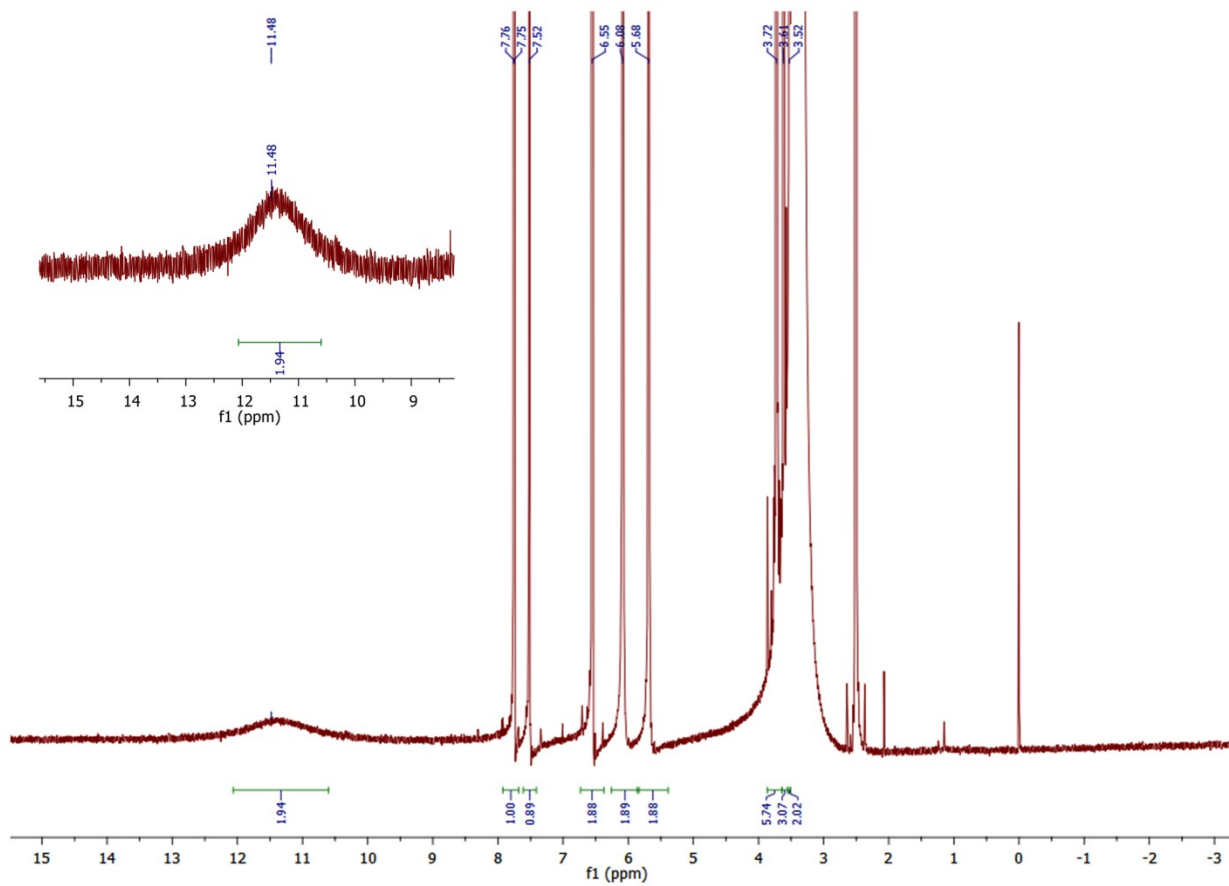


Fig.S15 ^1H NMR of TMP-5FU.

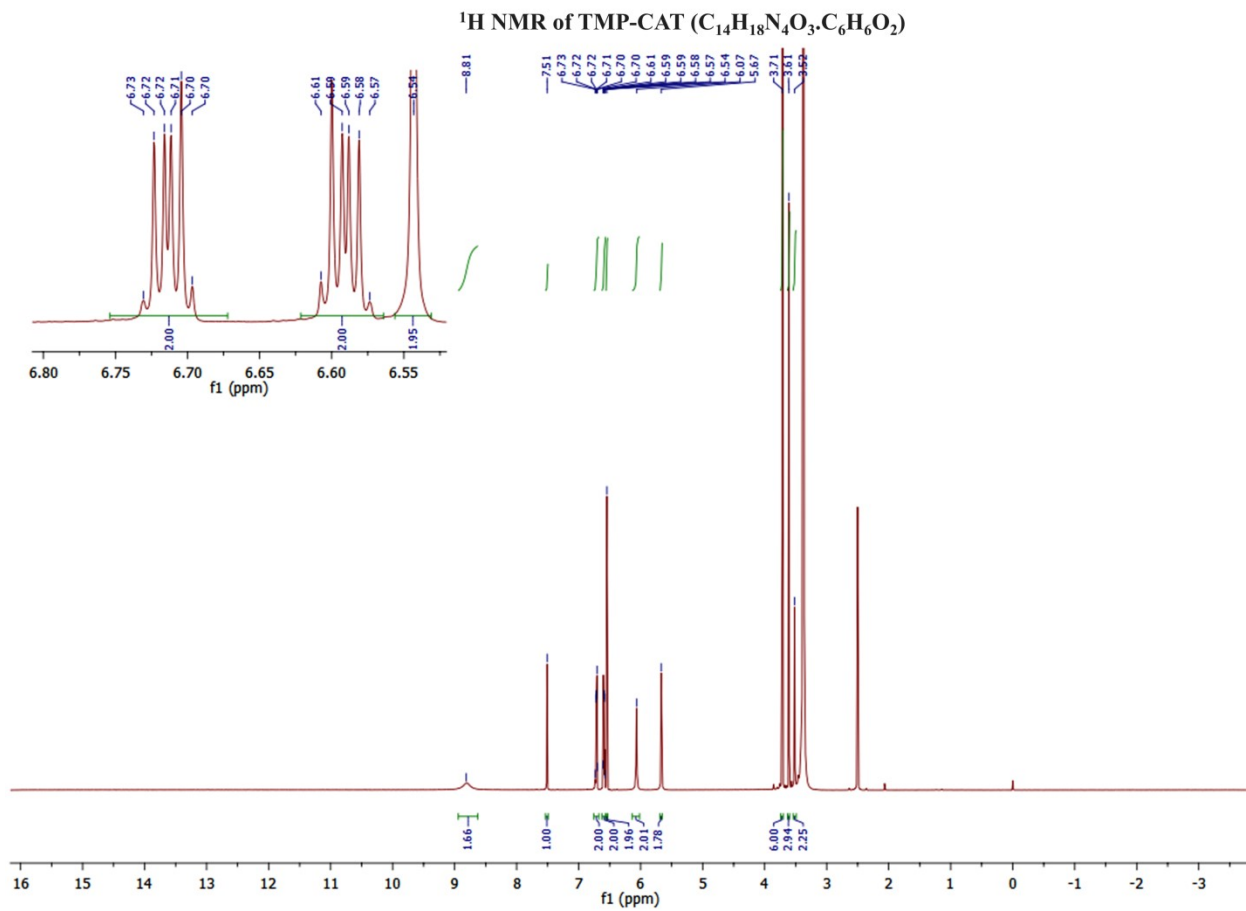


Fig.S16 ^1H NMR of TMP-CAT.

¹H NMR of TMP-THY-H₂O (C₁₄H₁₈N₄O₃·C₅H₆N₂O₂·H₂O)

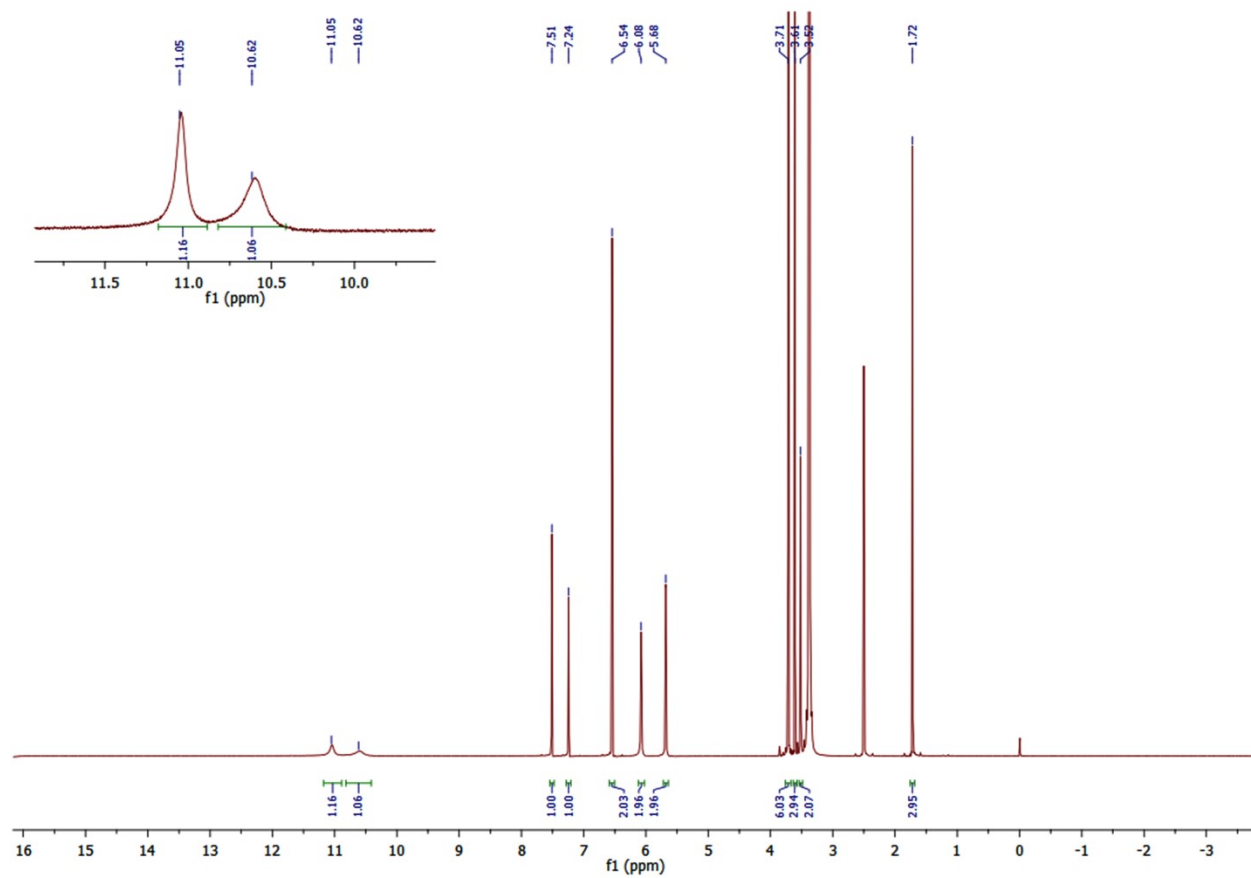


Fig.S17 ¹H NMR of TMP-THY-H₂O.

¹³C NMR OVERLAY of TMP-T7A (C₁₄H₁₉N₄O₃⁺ C₉H₉N₄O₄⁻)

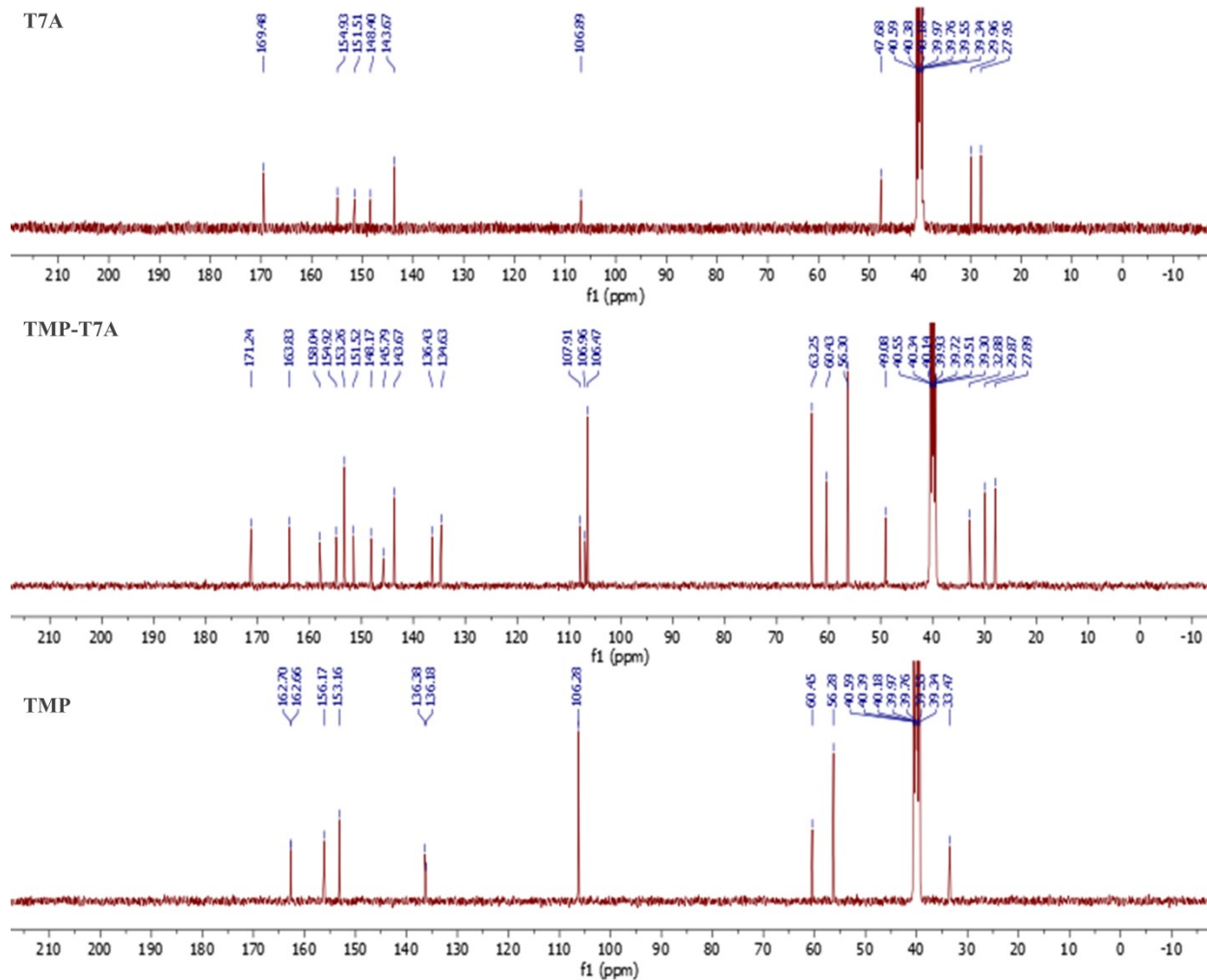


Fig.S18 ¹³C NMR of TMP-T7A.

¹³C NMR OVERLAY of TMP-5FU (C₁₄H₁₉N₄O₃⁺ C₄H₂FN₂O₂⁻)

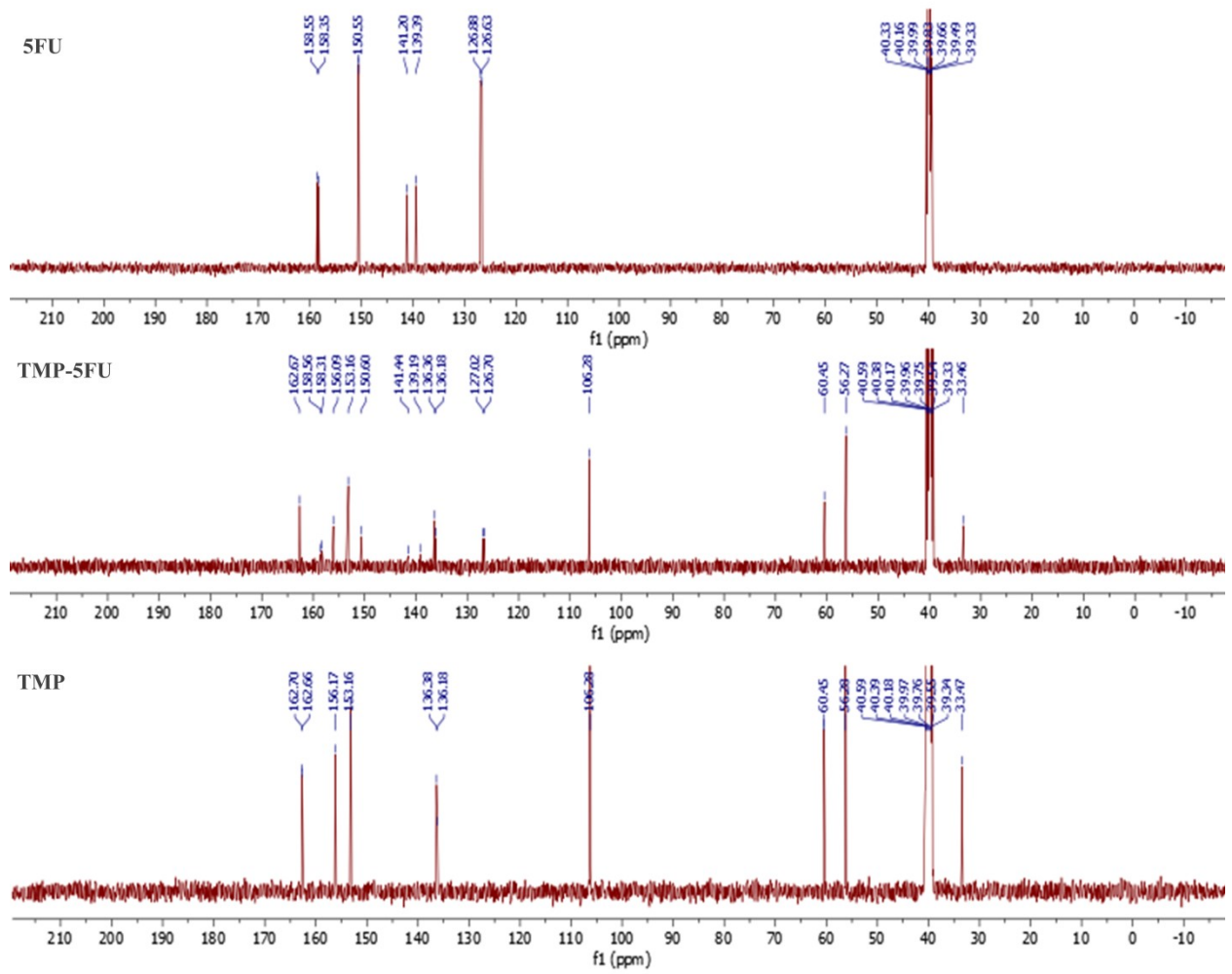


Fig.S19 ¹³C NMR of TMP-5FU.

¹³C NMR OVERLAY of TMP-CAT (C₁₄H₁₈N₄O₃·C₆H₆O₂)

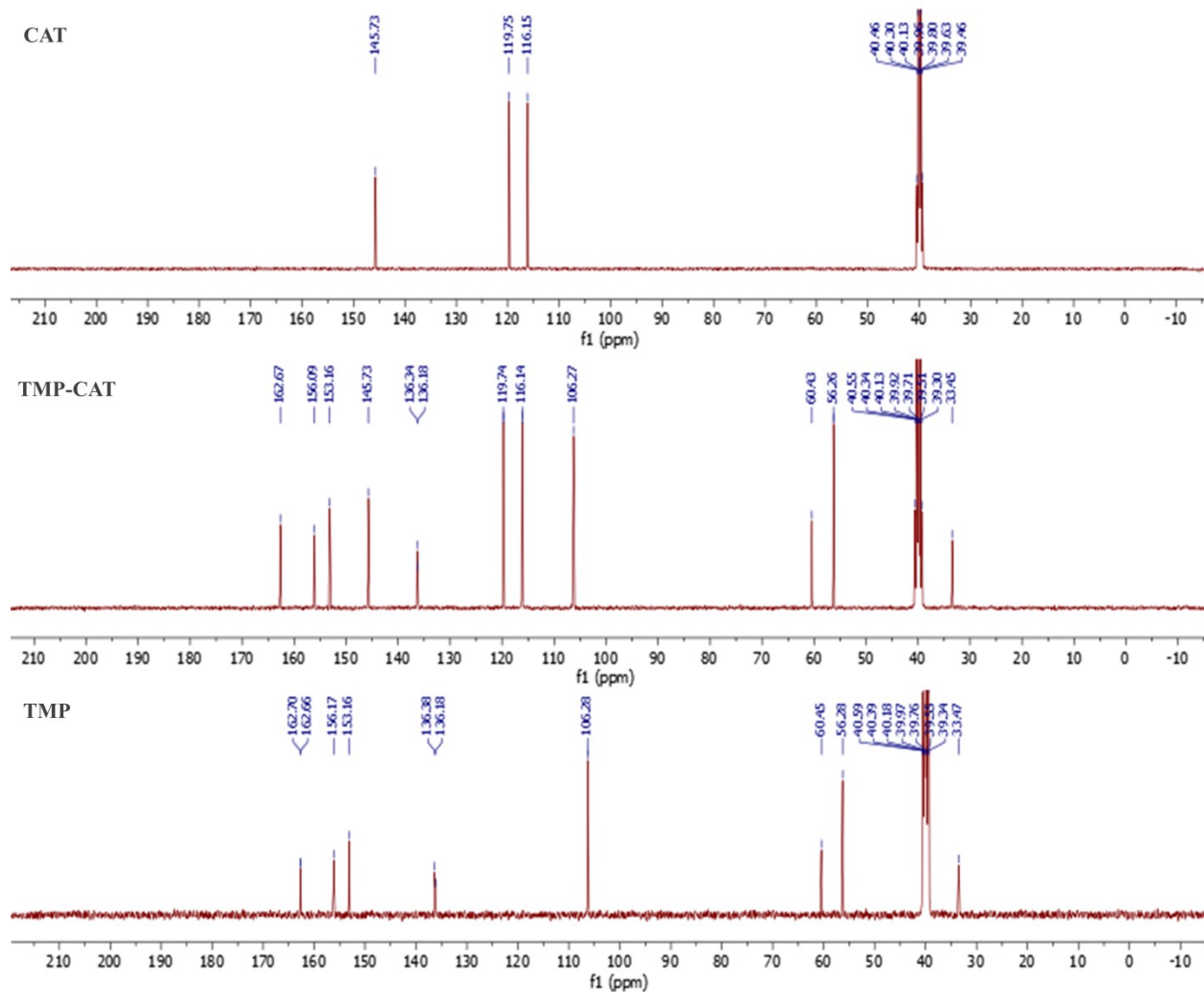


Fig.S20 ¹³C NMR of TMP-CAT.

¹³C NMR of OVERLAY TMP-THY-H2O (C₁₄H₁₈N₄O₃·C₅H₆N₂O₂·H₂O)

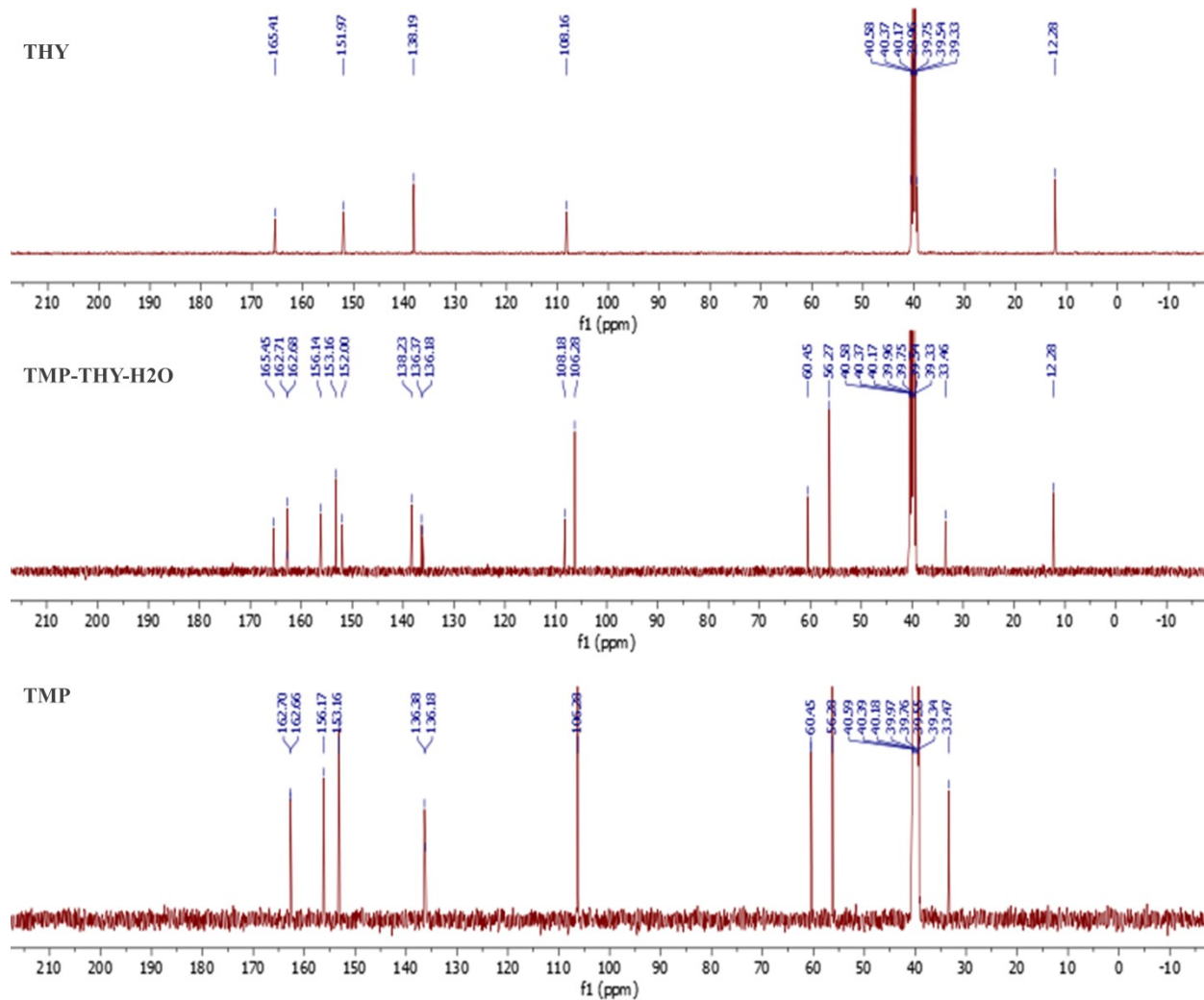


Fig.S21 ¹³C NMR of TMP-THY-H2O.

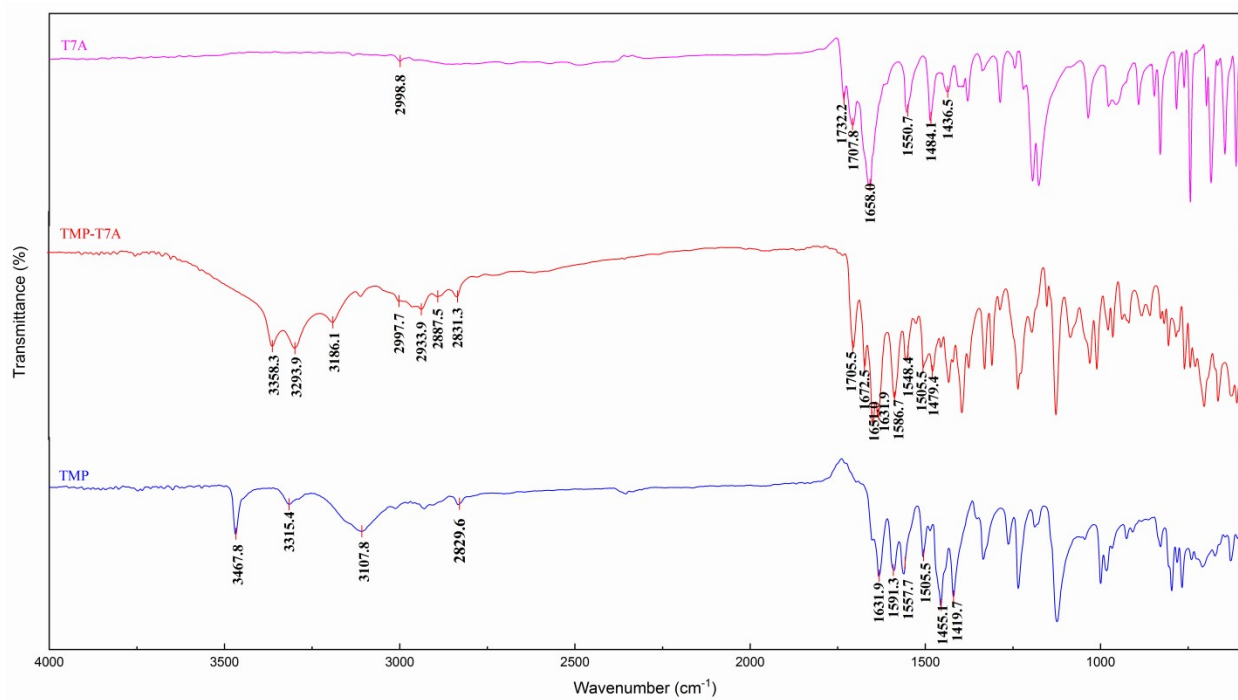


Fig.S22 Overlay of IR spectrum of TMP, TMP-T7A and T7A.

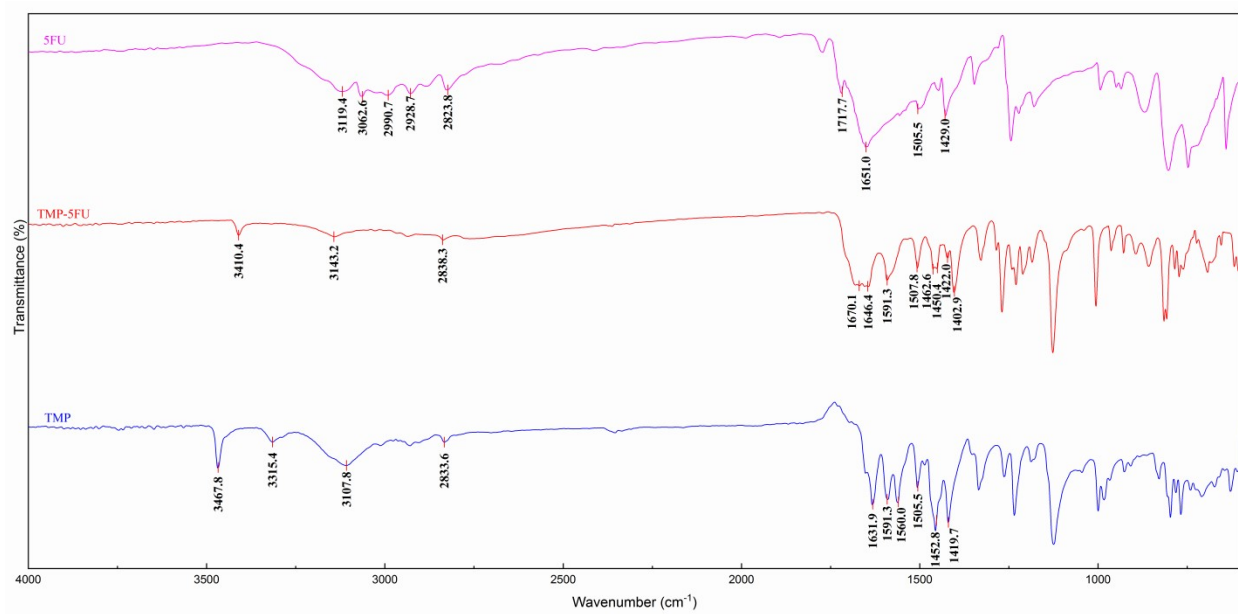


Fig.S23 Overlay of IR spectrum of TMP, TMP-5FU and 5FU.

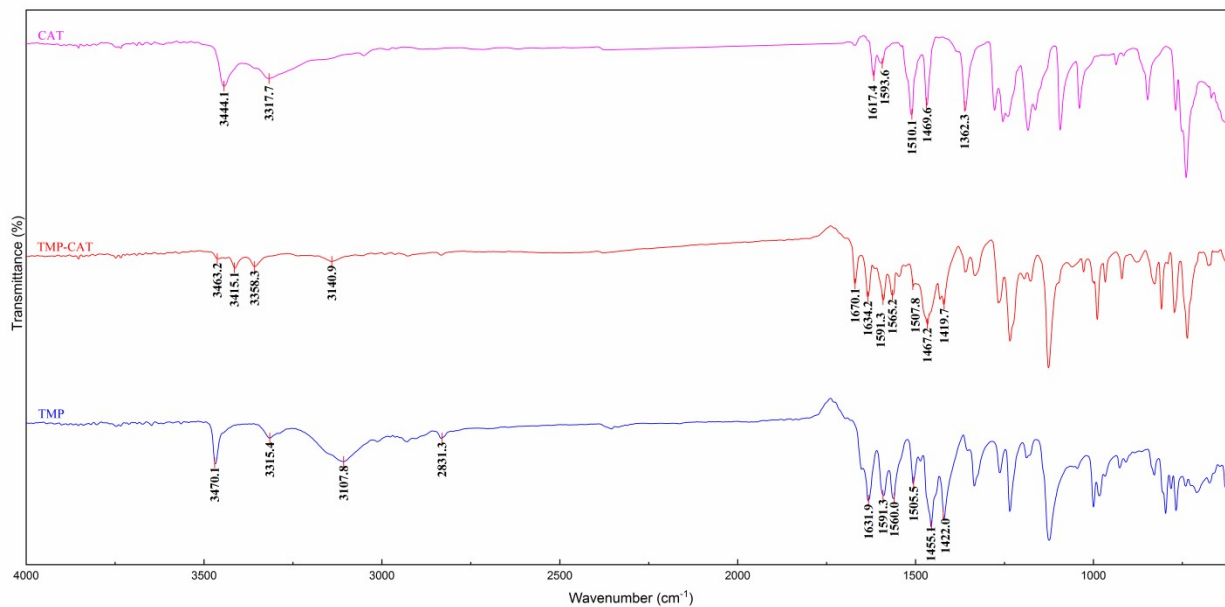


Fig.S24 Overlay of IR spectrum of TMP, TMP-CAT and CAT.

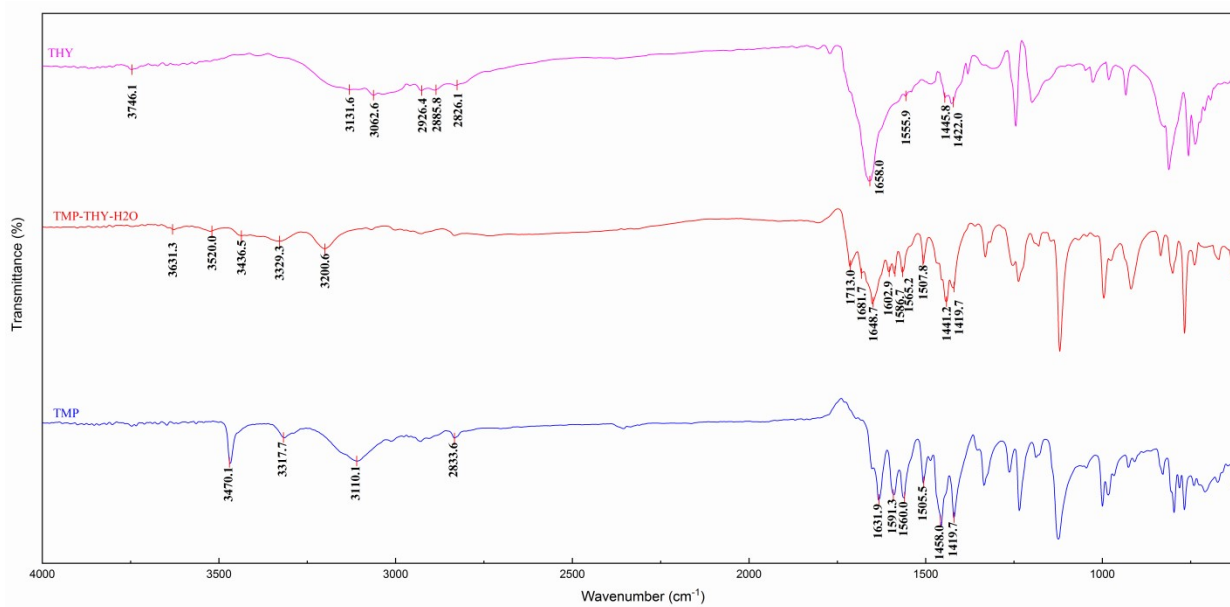


Fig.S25 Overlay of IR spectrum of TMP, TMP-THY-H2O and THY.

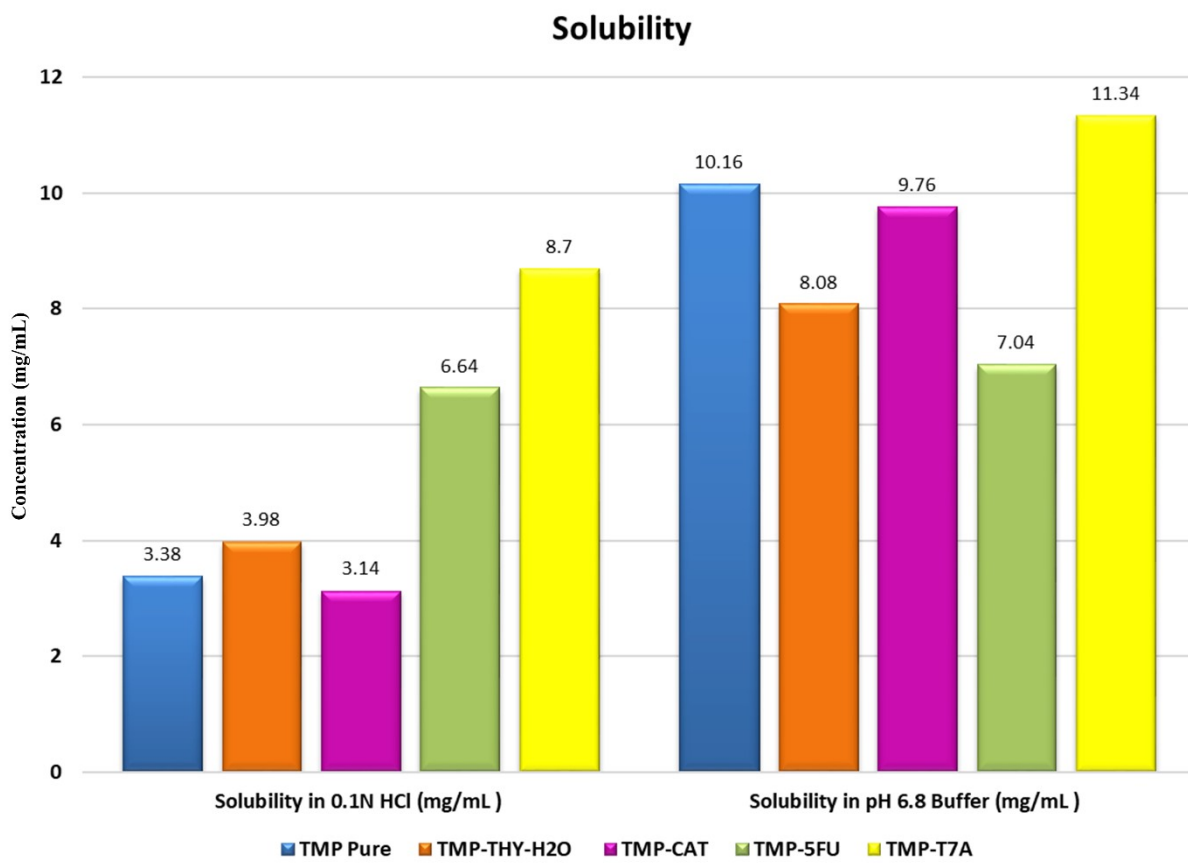


Fig.S26 The solubility data of TMP-API and four crystal systems performed in water, 0.1N HCl and pH 6.8 Buffer.

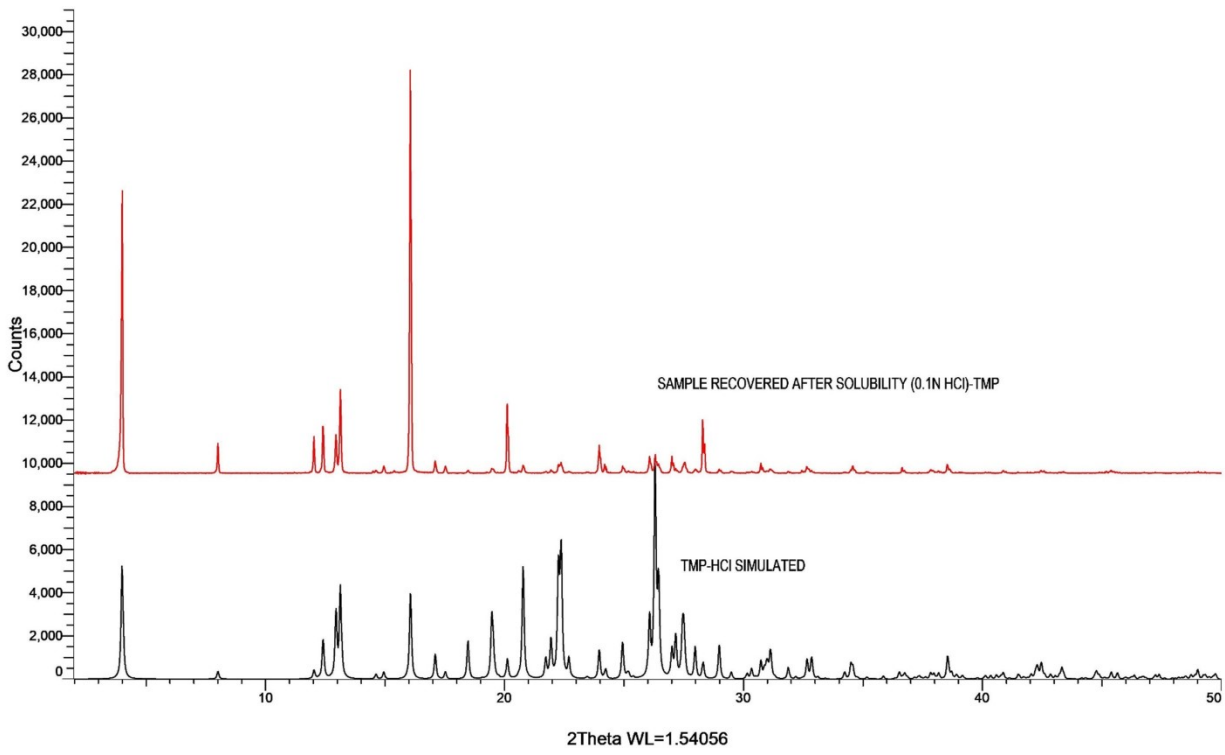


Fig.S27 PXRD overlay of TMP residue recovered from 0.1N HCl after 24hr.

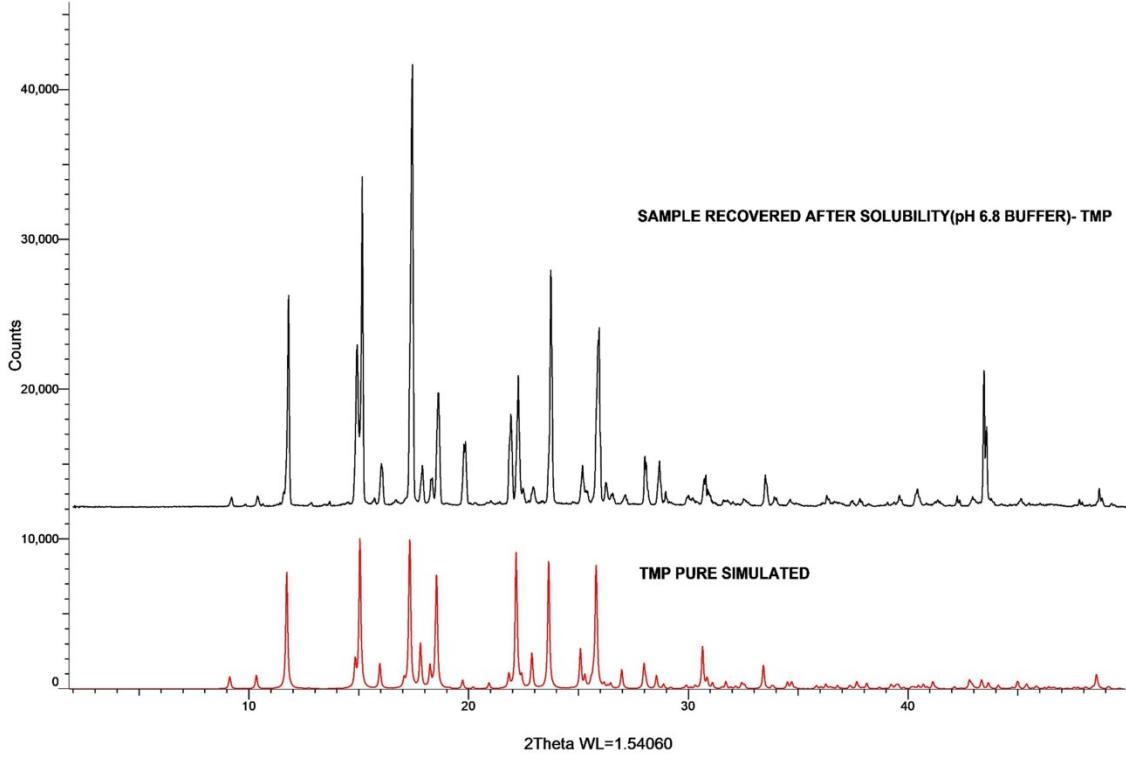


Fig.S28 PXRD overlay of TMP residue recovered from pH 6.8 buffer after 24hr.

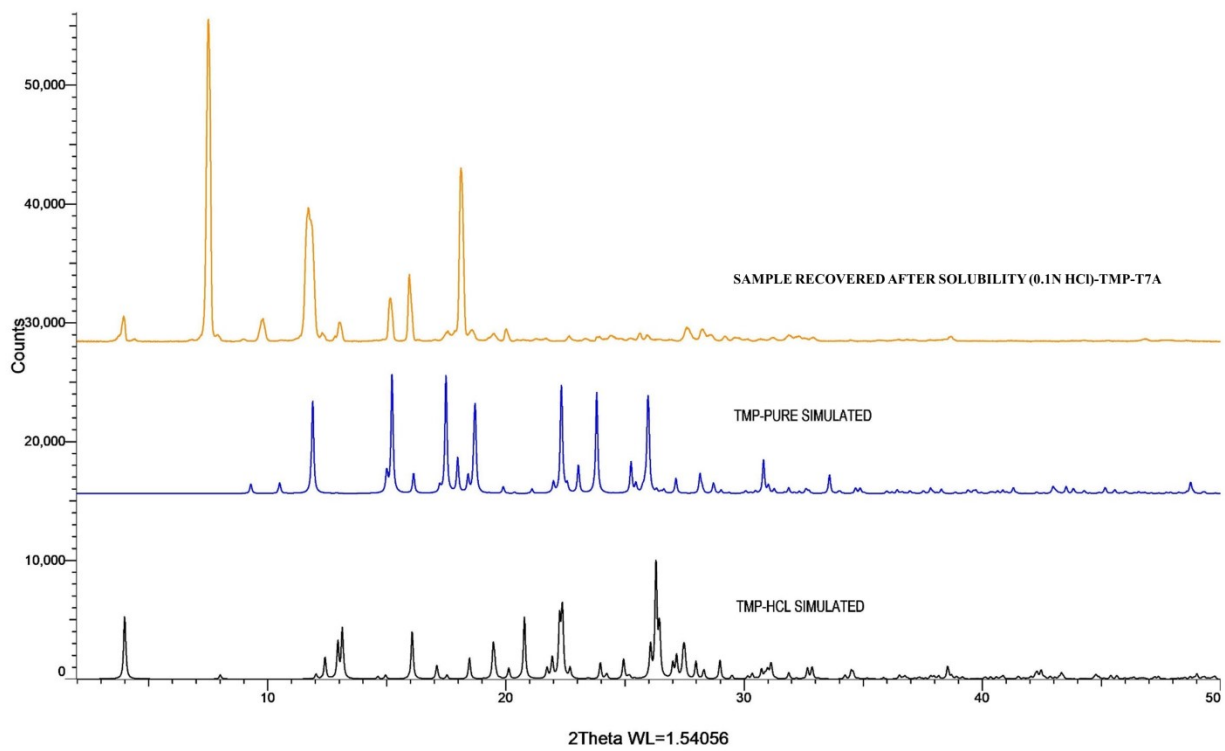


Fig.S29 PXR overlay of TMP-T7A residue recovered from 0.1N HCl after 24hr.

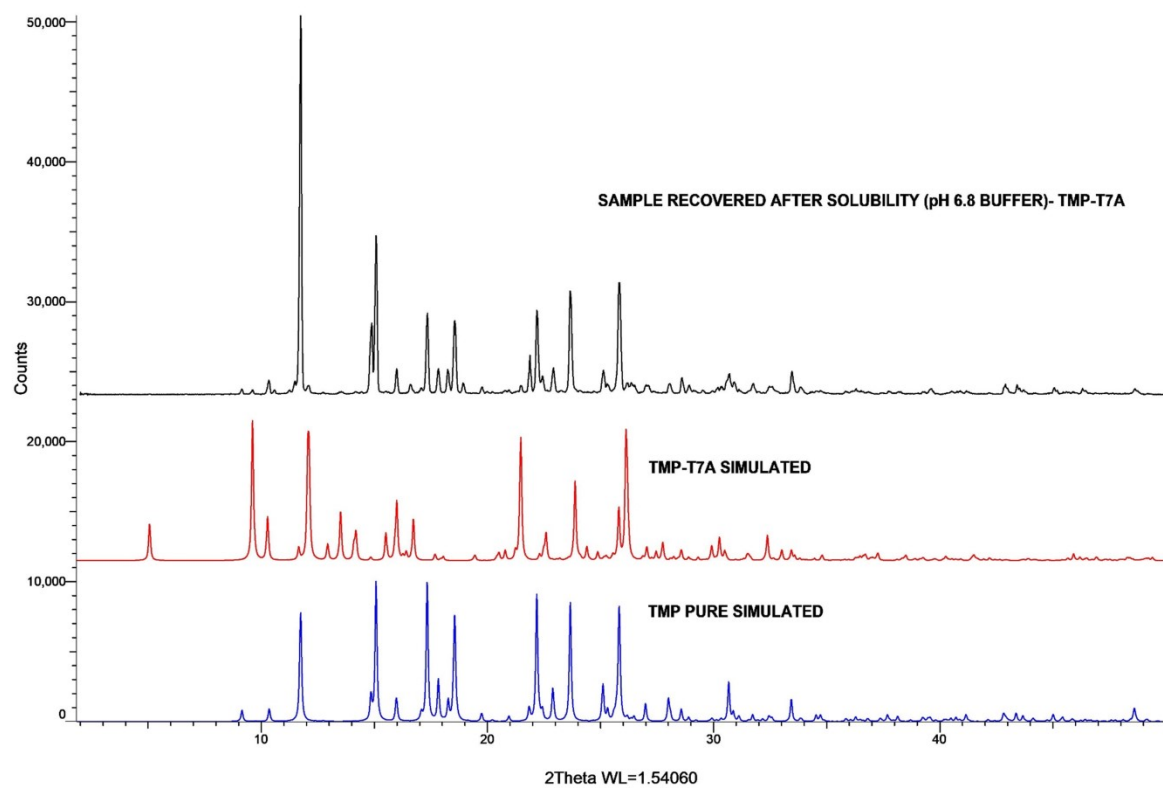


Fig.S30 PXRD overlay of TMP-T7A residue recovered from pH 6.8 buffer after 24hr.

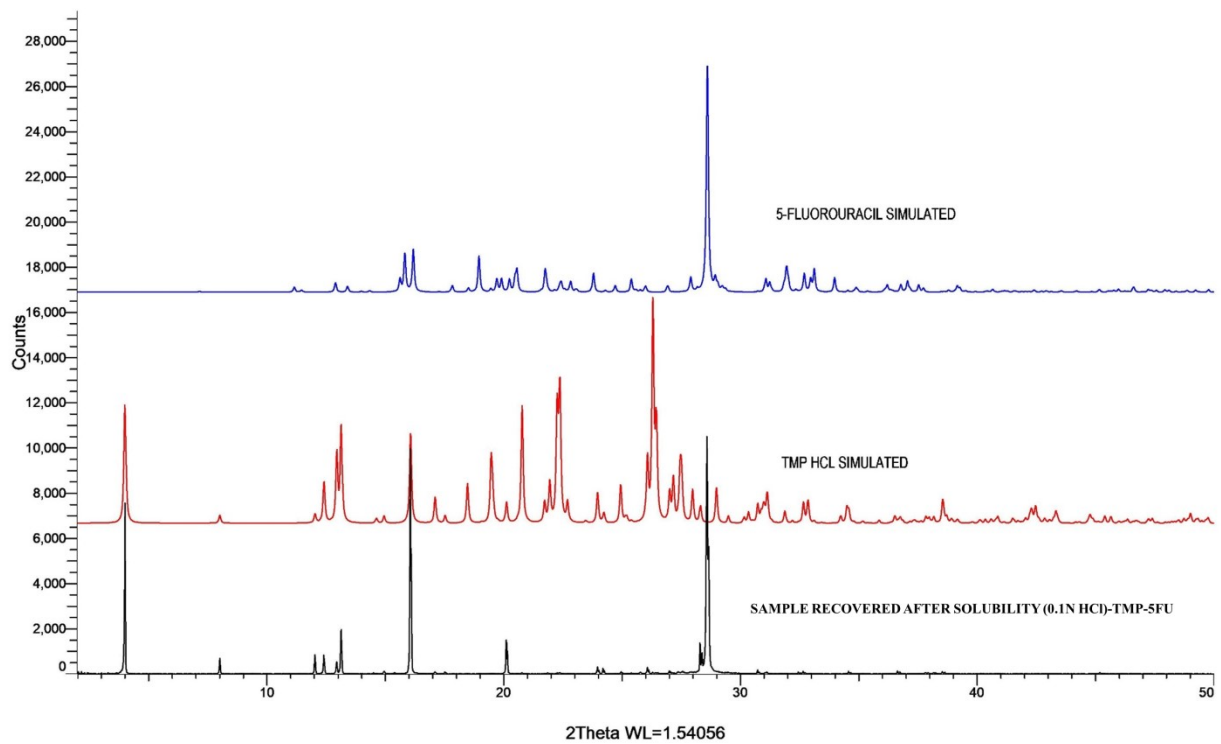


Fig.S31 PXR overlay of TMP-5FU residue recovered from 0.1N HCl after 24hr.

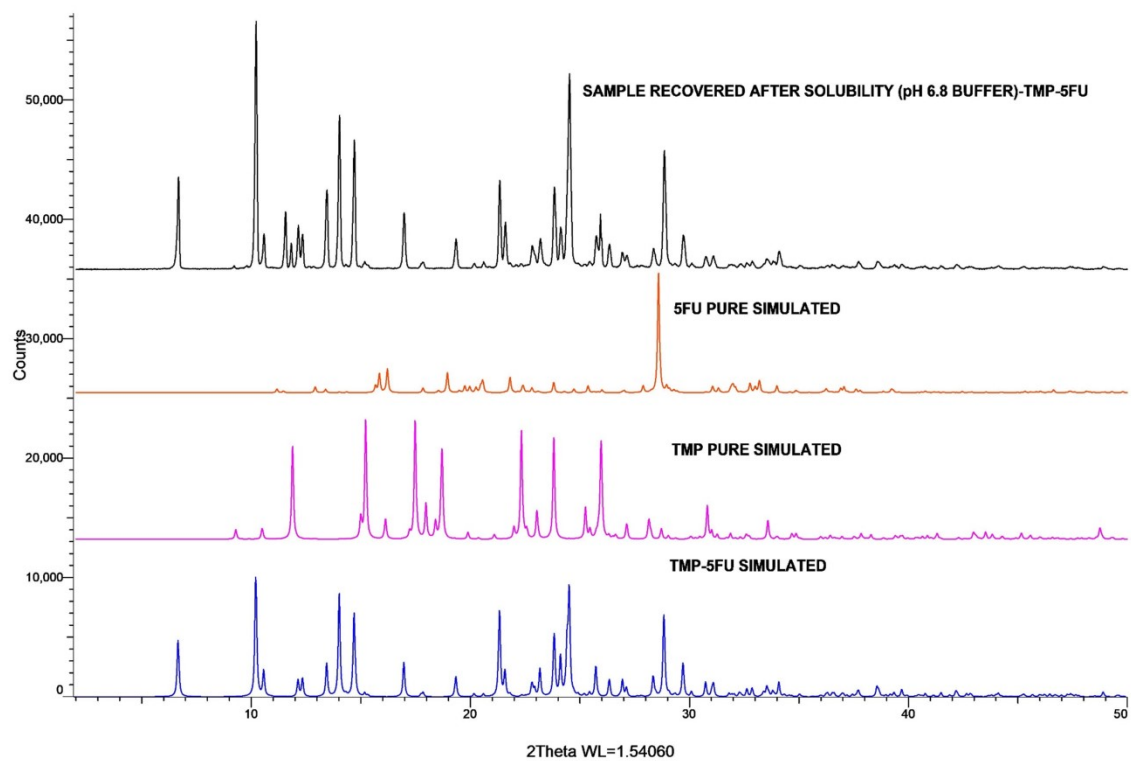


Fig.S32 PXRD overlay of TMP-5FU residue recovered from pH 6.8 buffer after 24hr.

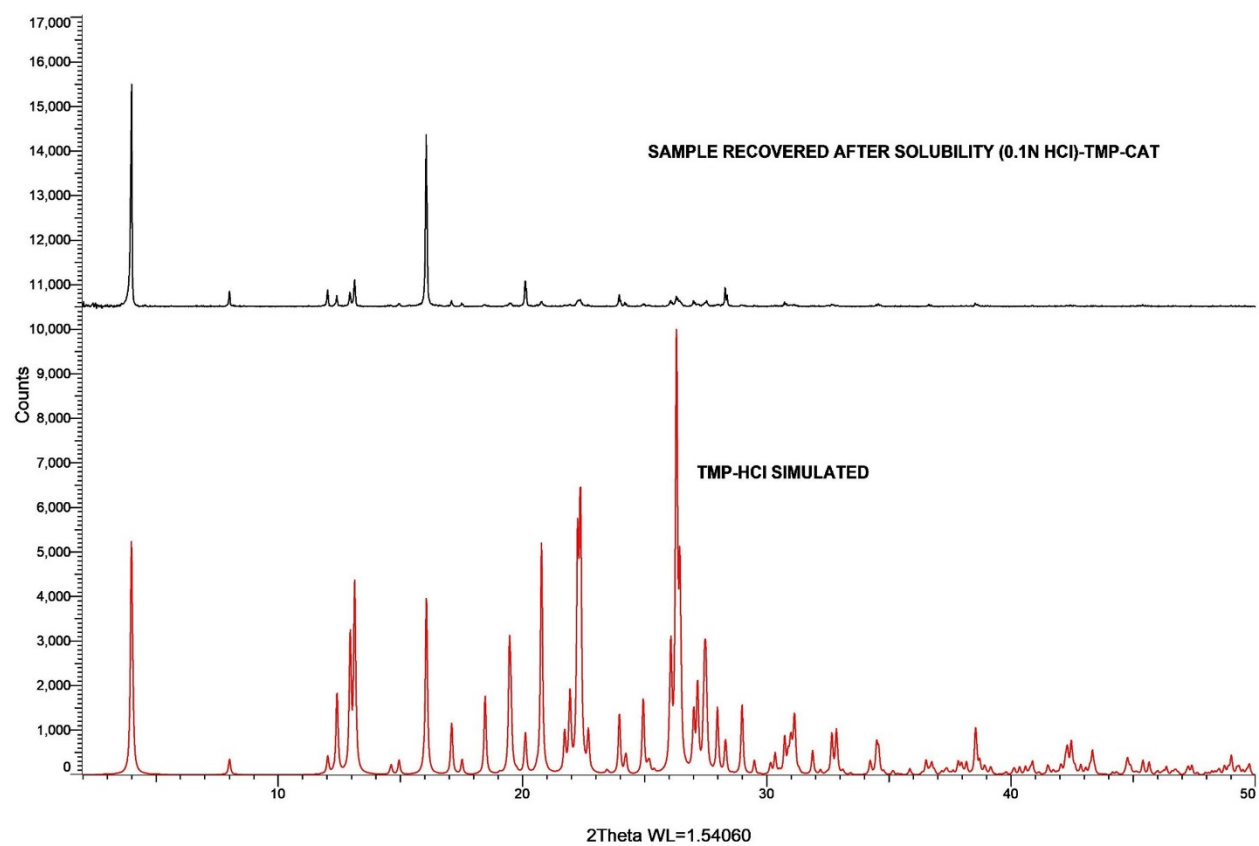


Fig.S33 PXRD overlay of TMP-CAT residue recovered from 0.1N HCl after 24hr.

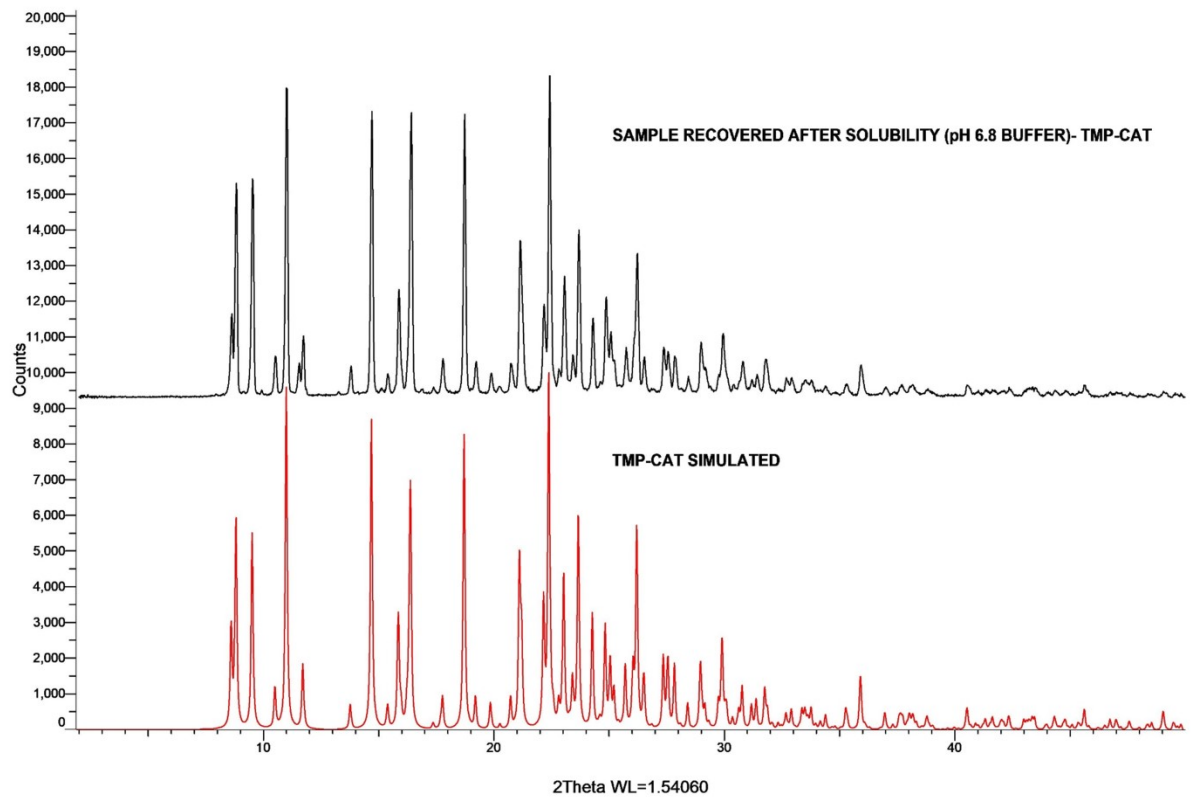


Fig.S34 PXRD overlay of TMP-CAT residue recovered from pH 6.8 buffer after 24hr.

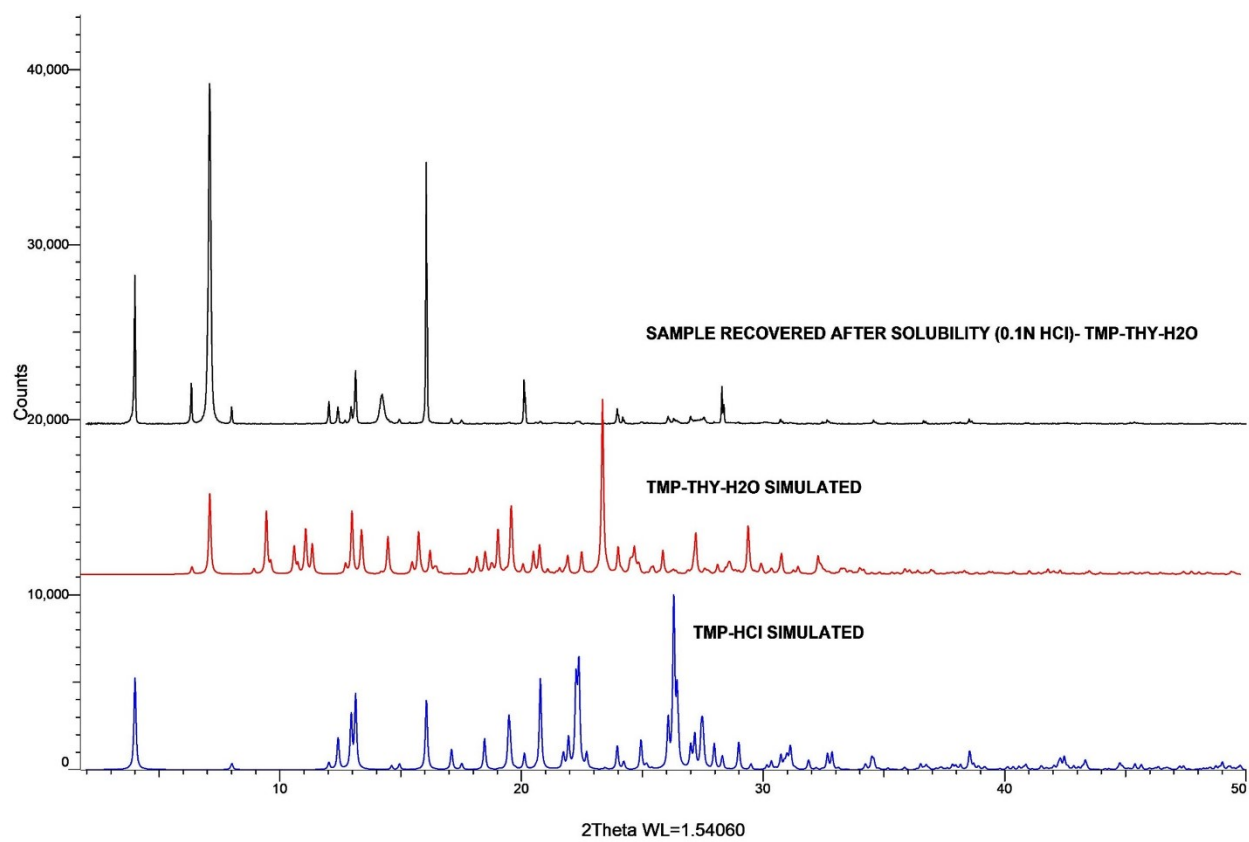


Fig.S35 PXRD overlay of TMP-THY-H₂O residue recovered from 0.1N HCl after 24hr.

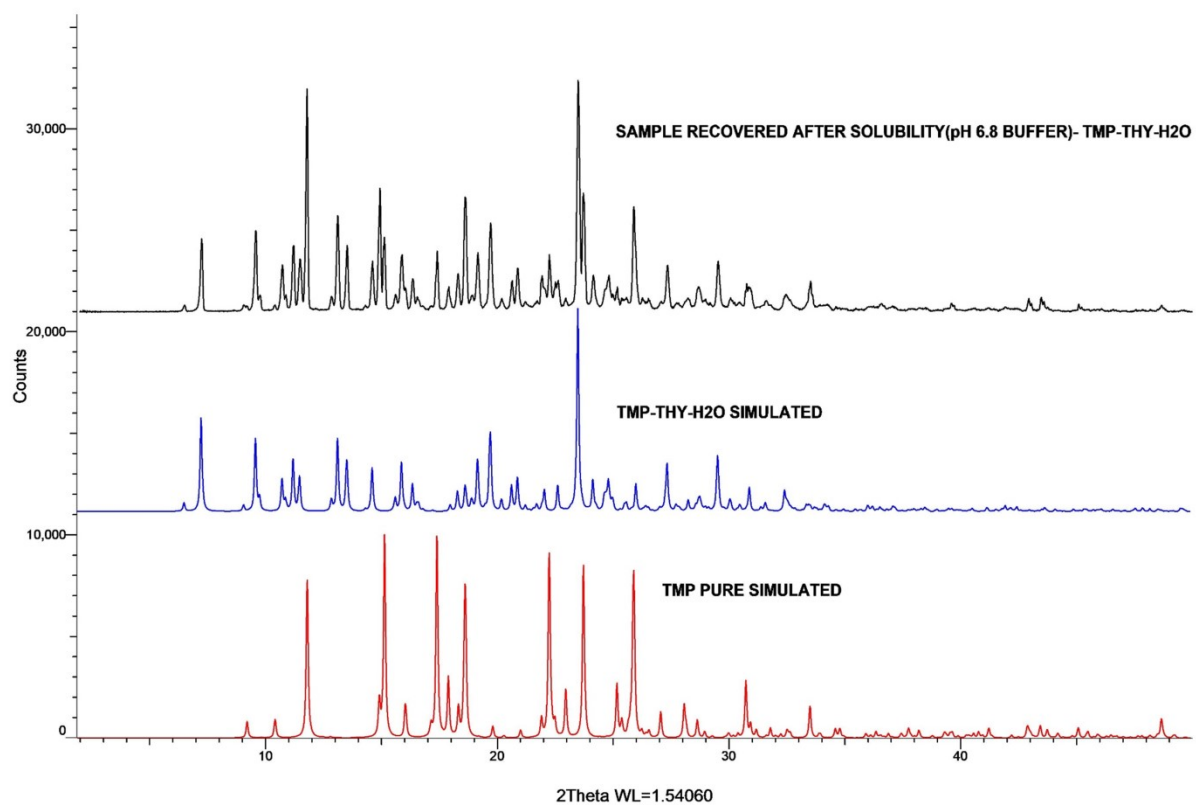


Fig.S36 PXRD overlay of TMP-THY-H₂O residue recovered from pH 6.8 buffer after 24hr.