Electronic Supporting Information

Hyphenation of lipophilic ruthenium(II)-diphosphine core with 5-fluorouracil: an effective metallodrug against glioblastoma brain cancer cells

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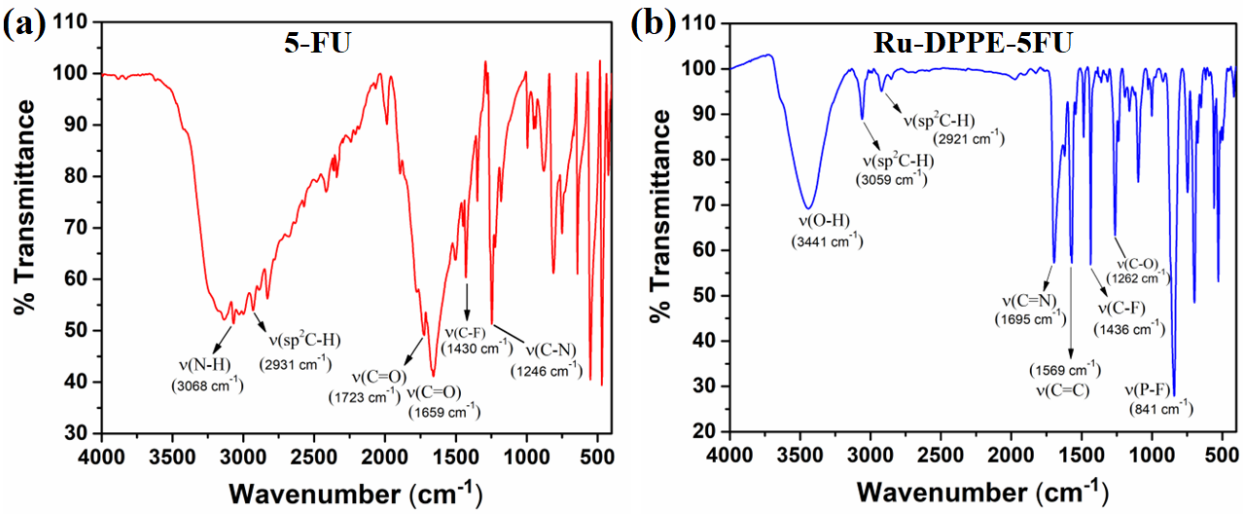

Fig. S1. The solid-state FT-IR spectrum of **5-FU** (a), and $[Ru(dppe)_2(5\text{-}FU)]PF_6$ (**Ru-DPPE-5FU**) (b) in KBr.

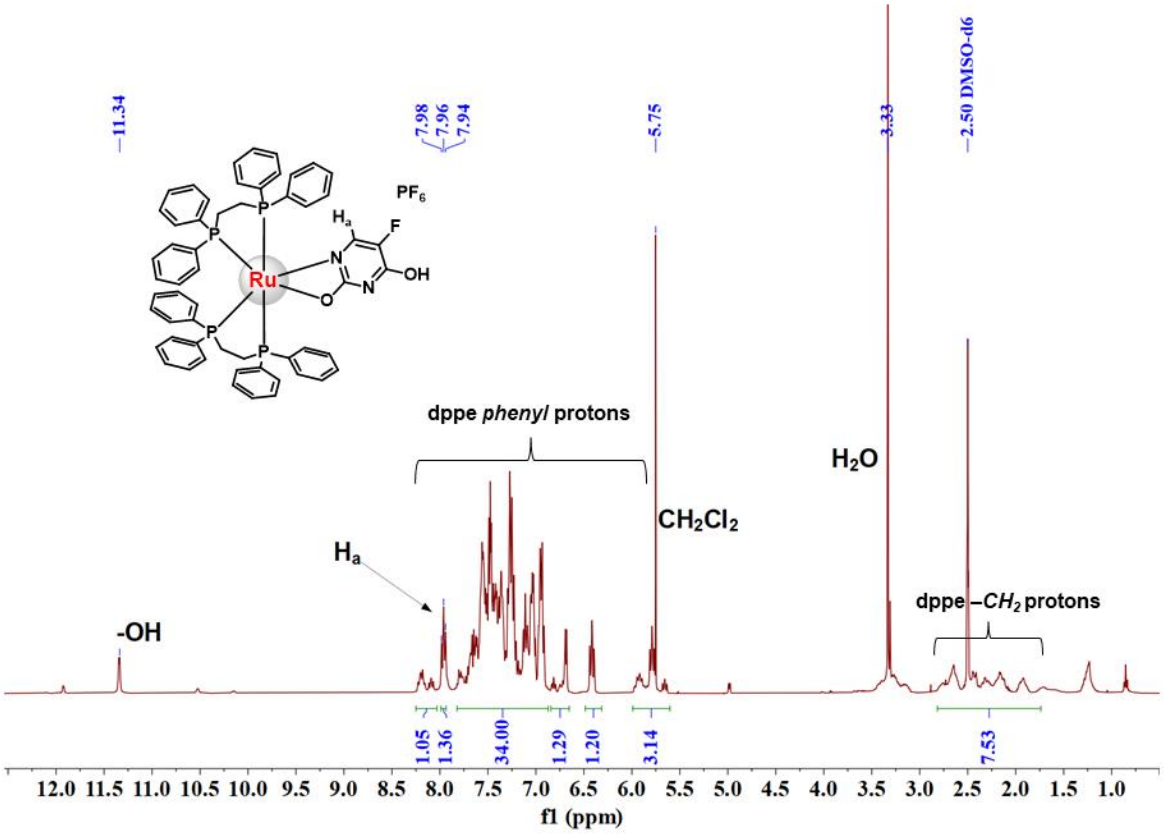

Fig. S2. ^{1}H-NMR (400 MHz) spectrum of **Ru-DPPE-5FU** in DMSO-d_6 at 298 K.

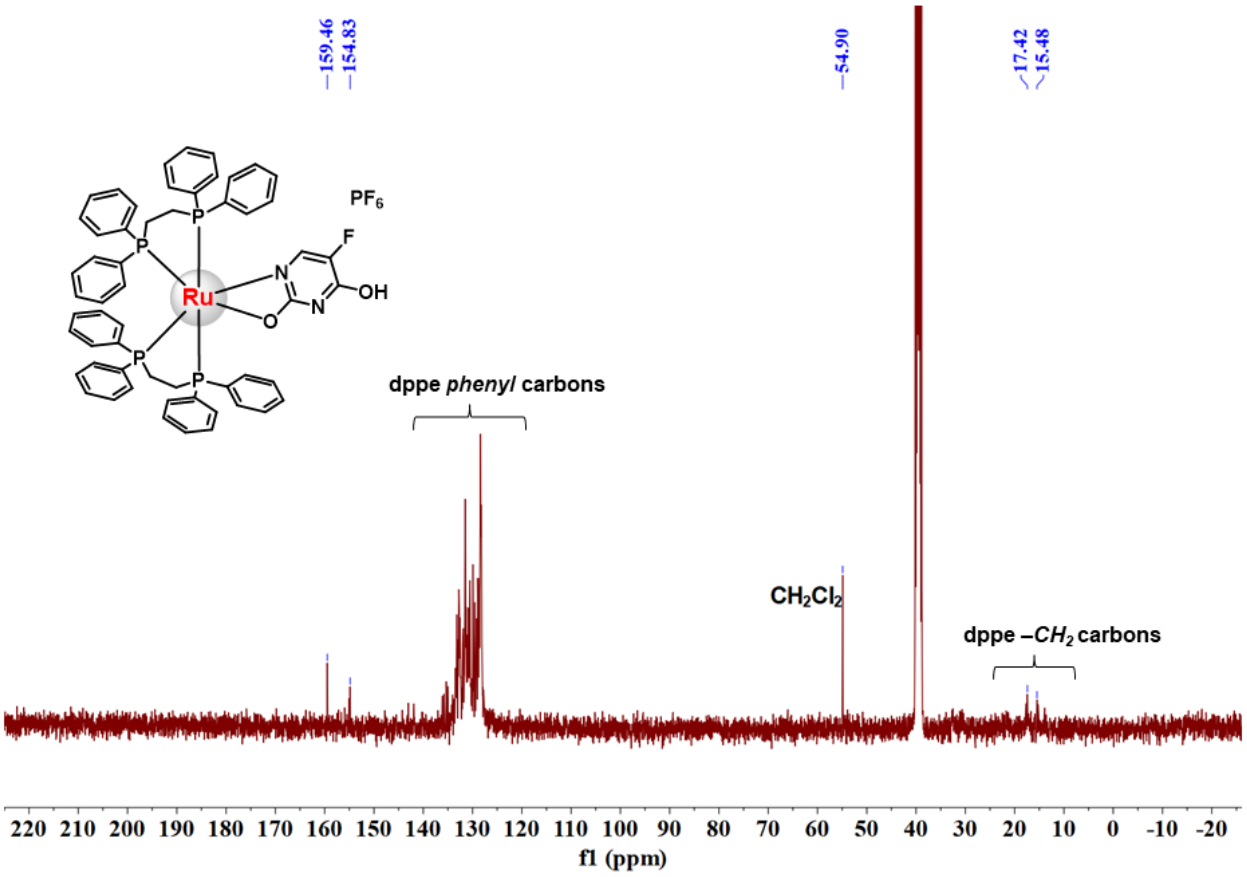

Fig. S3. $^{13}C\{^{1}H\}$-NMR (101 MHz) spectrum of $[Ru(dppe)_2(5\text{-FU})]PF_6$ (**Ru-DPPE-5FU**) in DMSO-d_6 at 298 K.

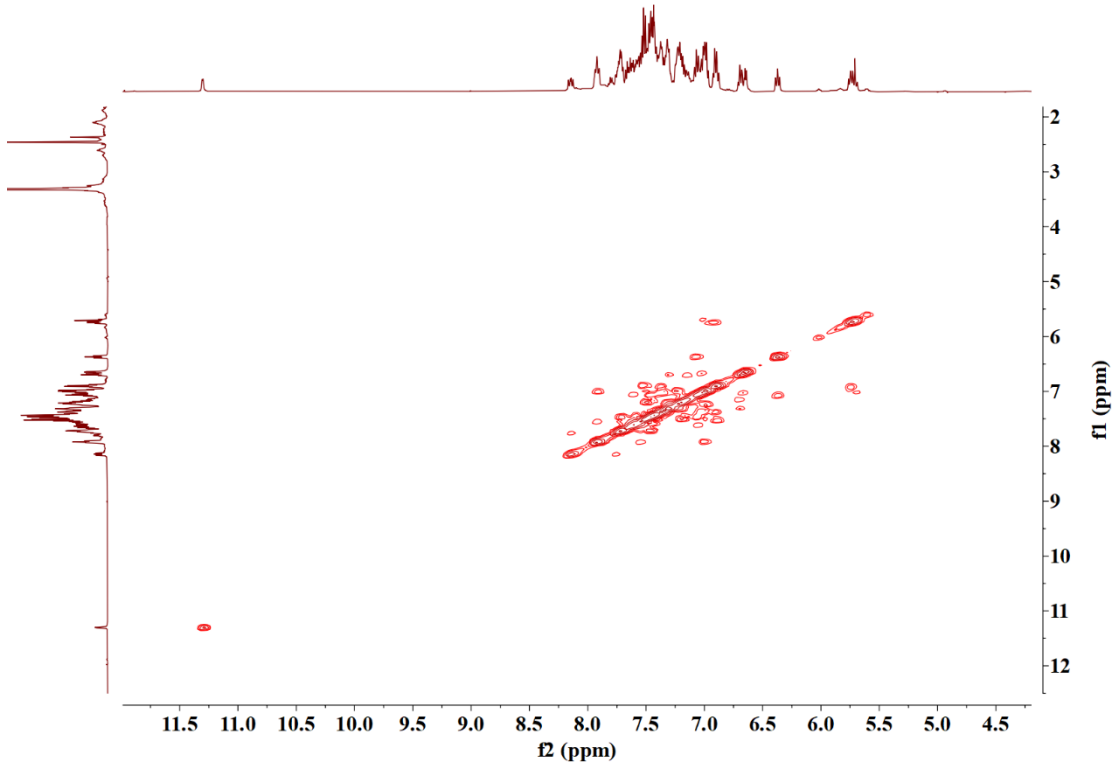

Fig. S4. (^{1}H-^{1}H) COSY NMR (500 MHz) spectrum of [Ru(dppe)$_2$(5-FU)]PF$_6$ (**Ru-DPPE-5FU**) in DMSO-d_6 .

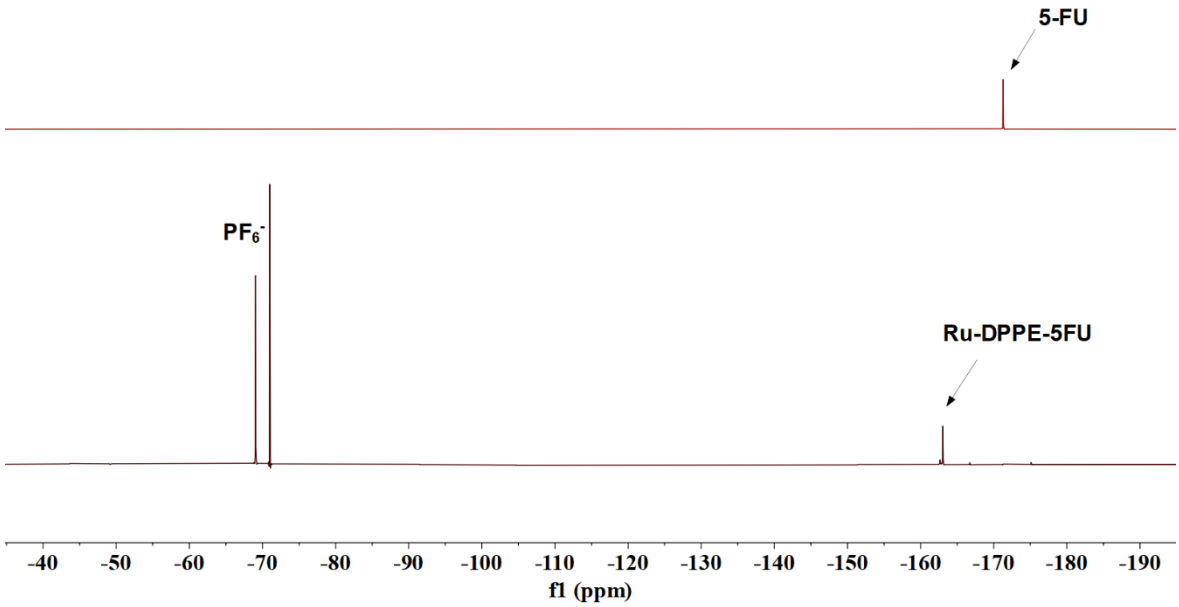

Fig. S5. ^{19}F{^{1}H}-NMR (373 MHz) spectrum of **5-FU** and [Ru(dppe)$_2$(5-FU)]PF$_6$ (**Ru-DPPE-5FU**) in DMSO-d_6 respectively at 298 K.

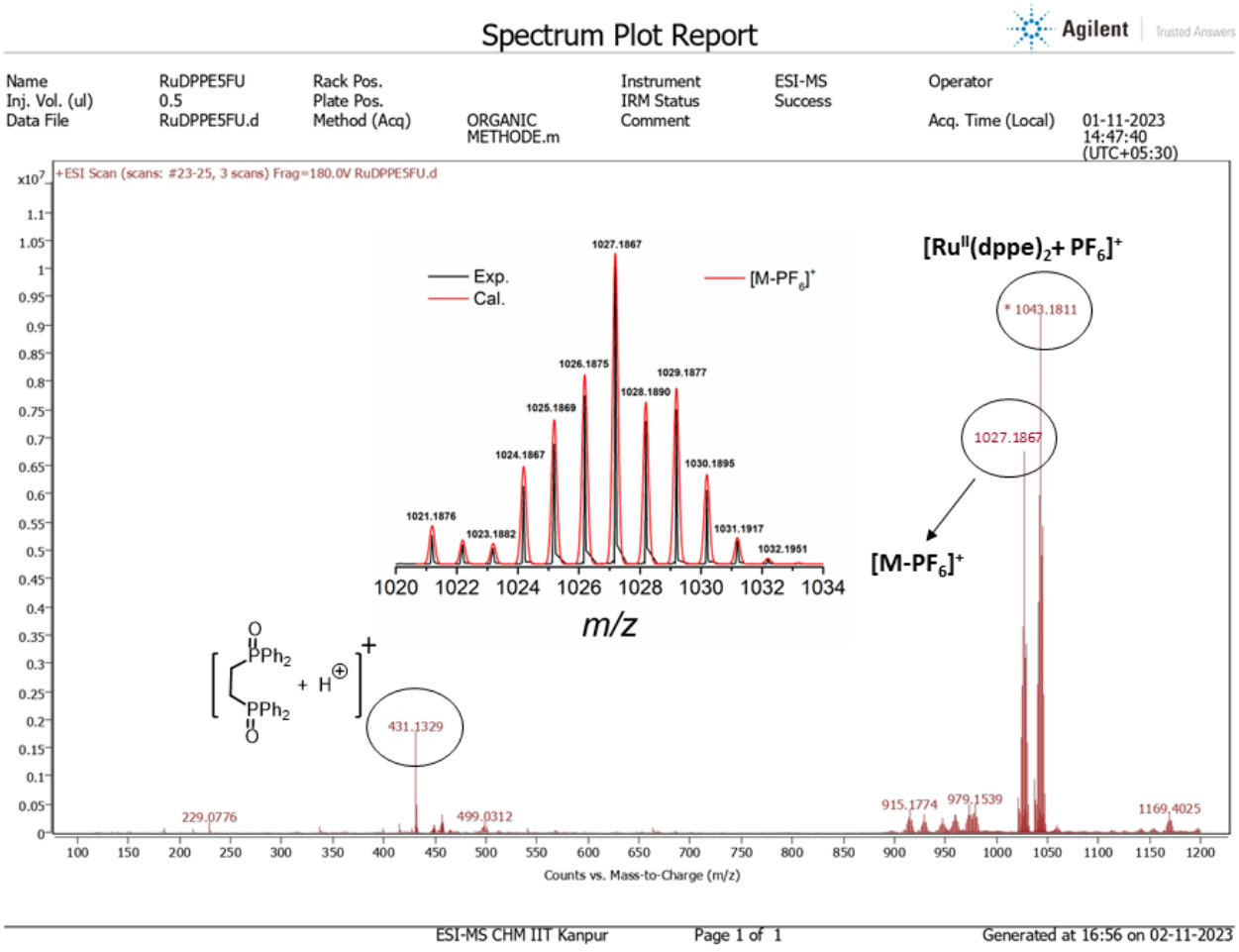

Fig. S6. ESI-MS(+) spectrum (full-range) of $[Ru(dppe)_2(5\text{-FU})]PF_6$ (**Ru-DPPE-5FU**) in methanol.

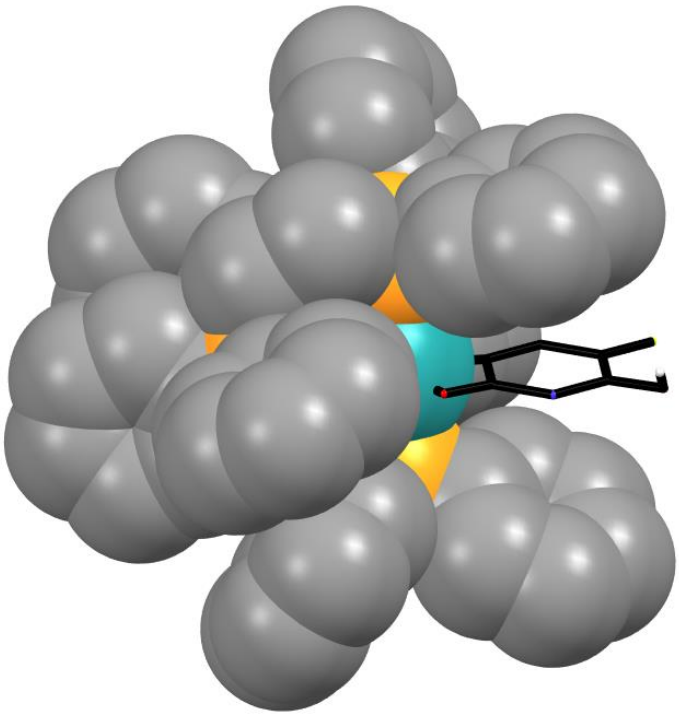

Fig. S7. 3-D perspective view indicative effective caging of hydrophilic **5-FU** within the hydrophobic pocket of lipophilic Ru(dppe)$_2$-core, generated from the SC-XRD structure.

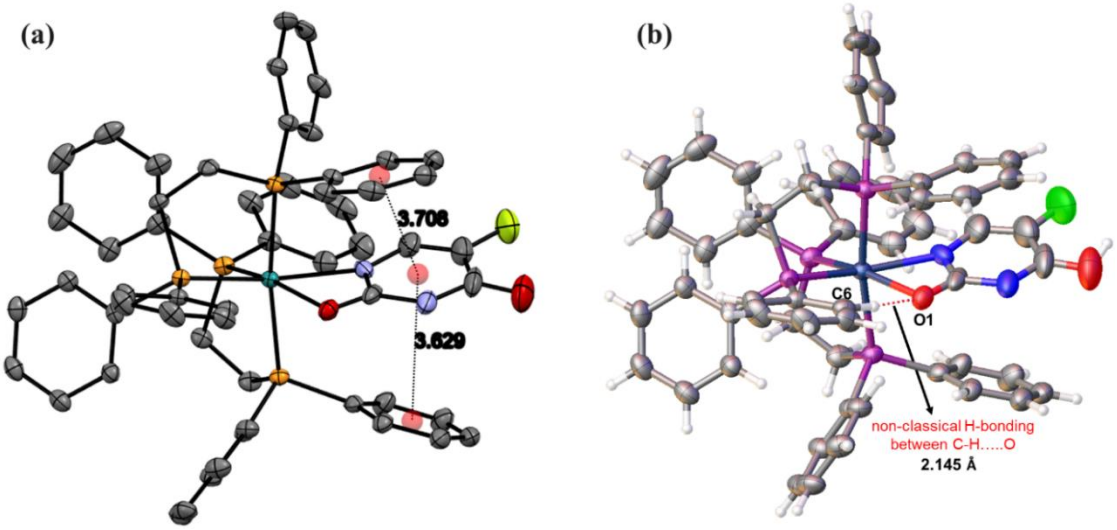

Fig. S8. ORTEP diagram of **Ru-DPPE-5FU** showing $\pi....\pi$ stacking interactions through centroid-centroid distance (a), and *OLEX2* view of intra-molecular non-classical H-bonding between C6-H…O1 (b).

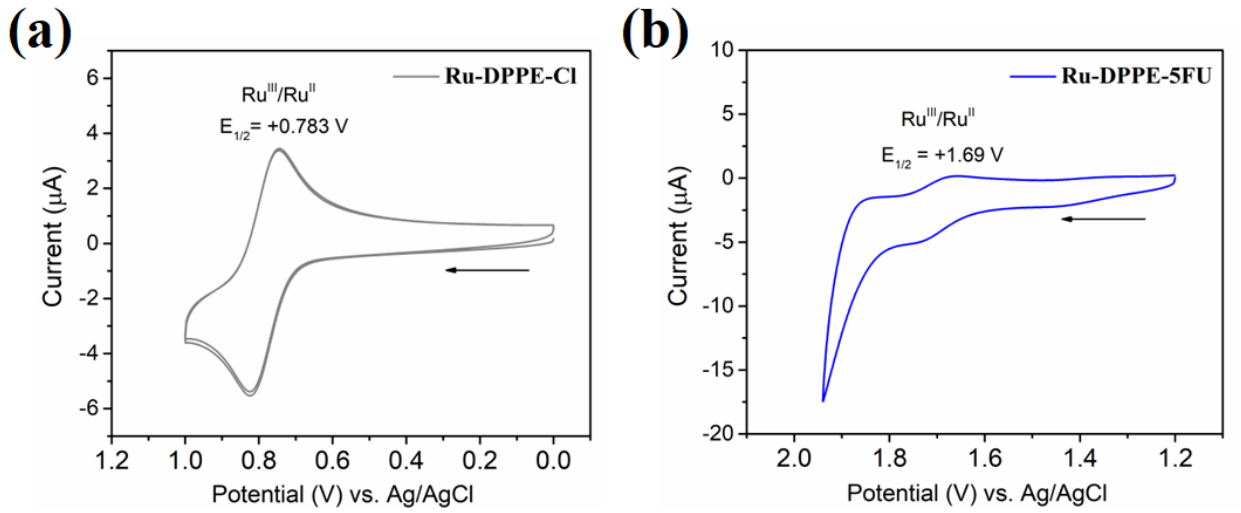

Fig. S9. Cyclic Voltammograms of (a) **Ru-DPPE-Cl** and (b) **Ru-DPPE-5FU** in dichloromethane (0.1M $TBAPF_6$) at 100 mV/sec scan rate.

Table S1. Electrochemical data of the ruthenium complexes.[a]

Compounds	Epa (V)	Epc (V)	ΔE (mV)	$E_{1/2}$ (V)
Ru-DPPE-Cl	0.823	0.744	79	0.783
Ru-DPPE-5FU	1.737	1.657	80	1.697

[a]Condition: Supporting electrolyte, $TBAPF_6$ (0.1 M); CH_2Cl_2; Ag/AgCl reference electrode, scan rate of 100 mV/sec.

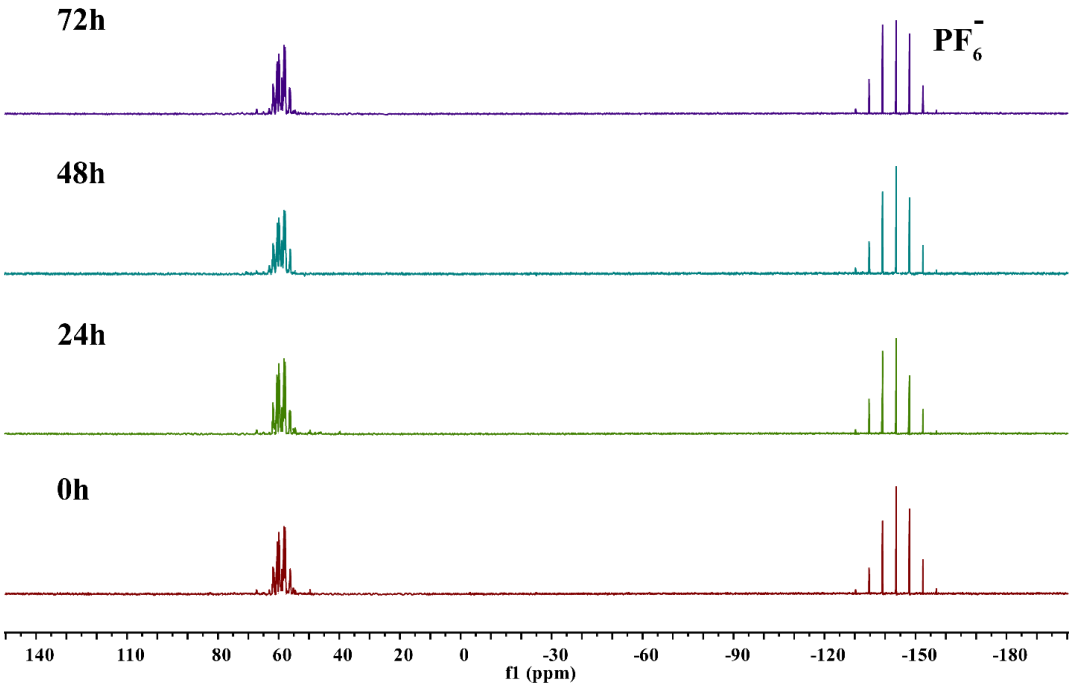

Fig. S10. $^{31}P\{^{1}H\}$-NMR (160 MHz) spectrum of $[Ru(dppe)_2(5\text{-FU})]PF_6$ (**Ru-DPPE-5FU**) in DMSO-d_6 at different time intervals: 0 h, 24 h, 48 h, and 72 h.

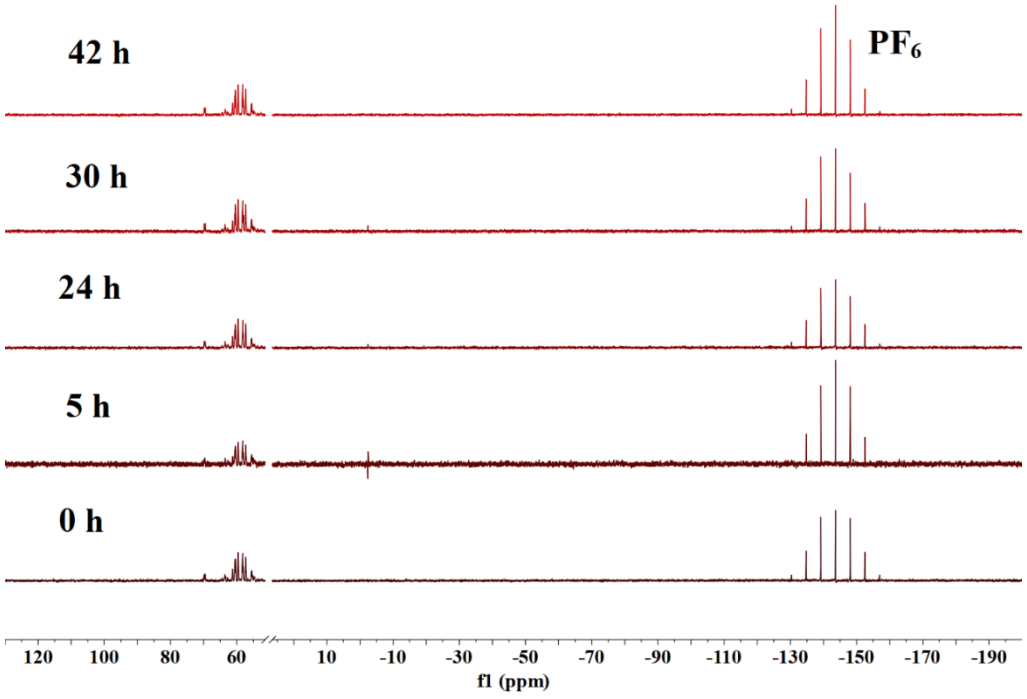

Fig. S11. $^{31}P\{^{1}H\}$-NMR (160 MHz) spectrum of **Ru-DPPE-5FU** in 20% D_2O/DMSO-d_6 at different time intervals: 0 h, 5 h, 24 h, 30 h, and 42 h.

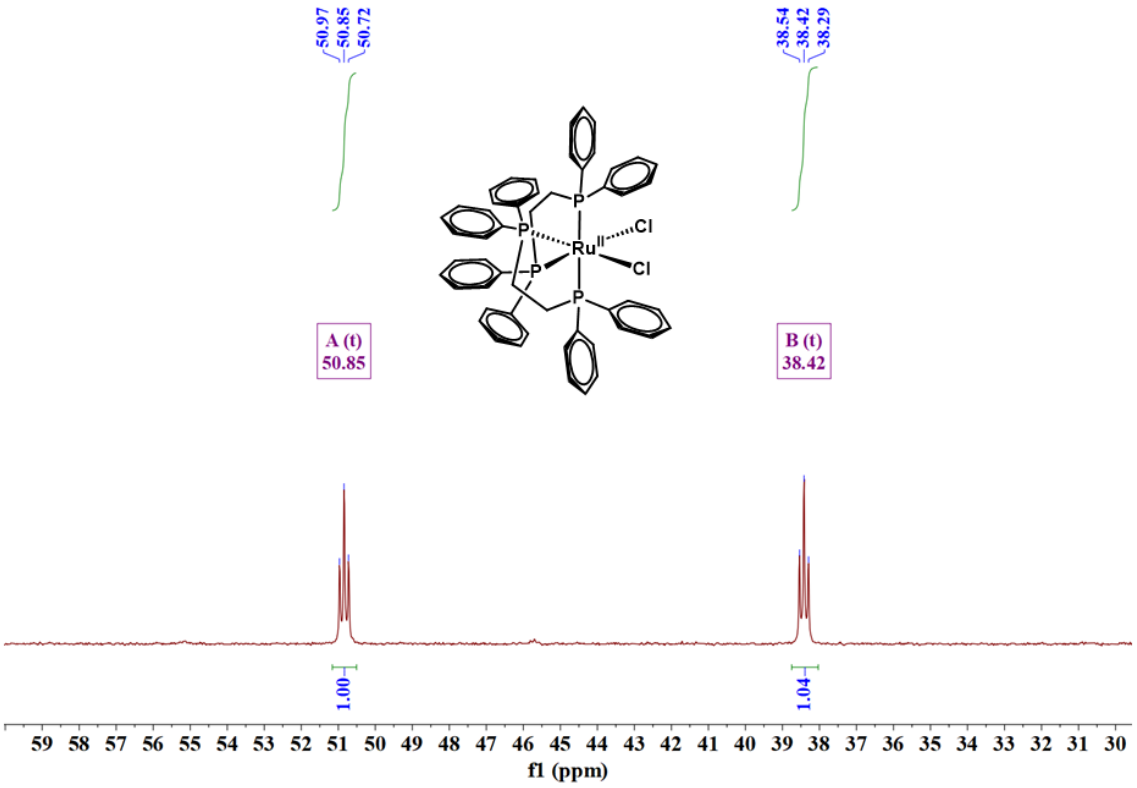

Fig. S12. $^{31}P\{^{1}H\}$-NMR (160 MHz) spectrum of **Ru-DPPE-Cl** i.e., *cis*-$[Ru(dppe)_2Cl_2]$ in DMSO-d_6 at 298 K.

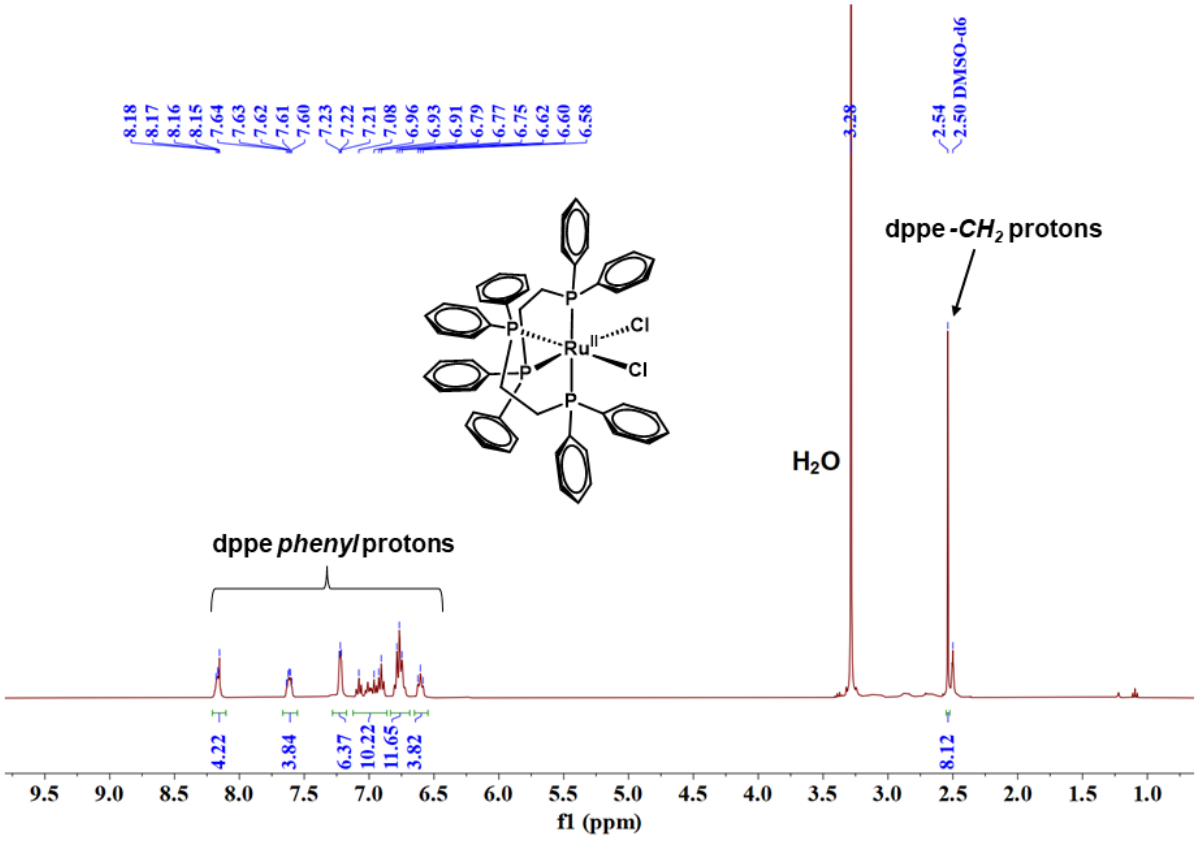

Fig. S13. ^{1}H-NMR (400 MHz) spectrum of **Ru-DPPE-Cl** i.e., *cis*-[Ru(dppe)$_2$Cl$_2$] in DMSO-d_6 at 298 K.

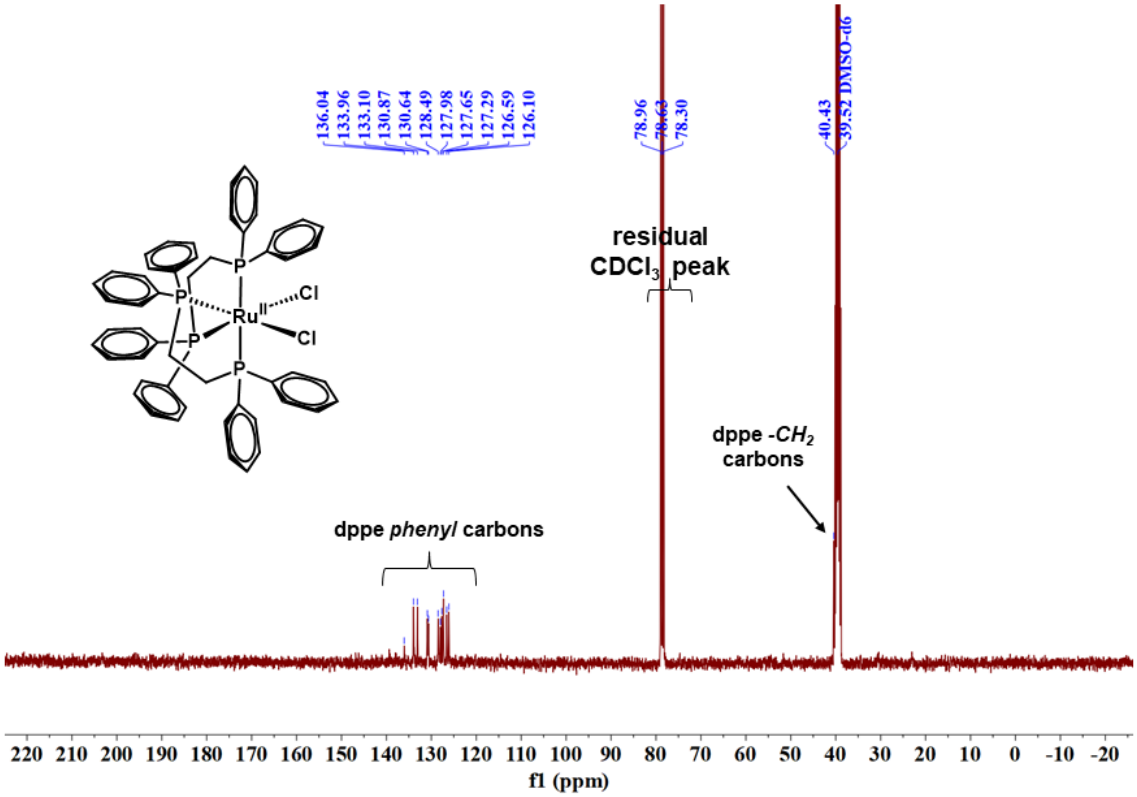

Fig. S14. $^{13}C\{^{1}H\}$-NMR (101MHz) spectrum of **Ru-DPPE-Cl** i.e., *cis*-[Ru(dppe)$_2$Cl$_2$] in DMSO-d_6 at 298 K.

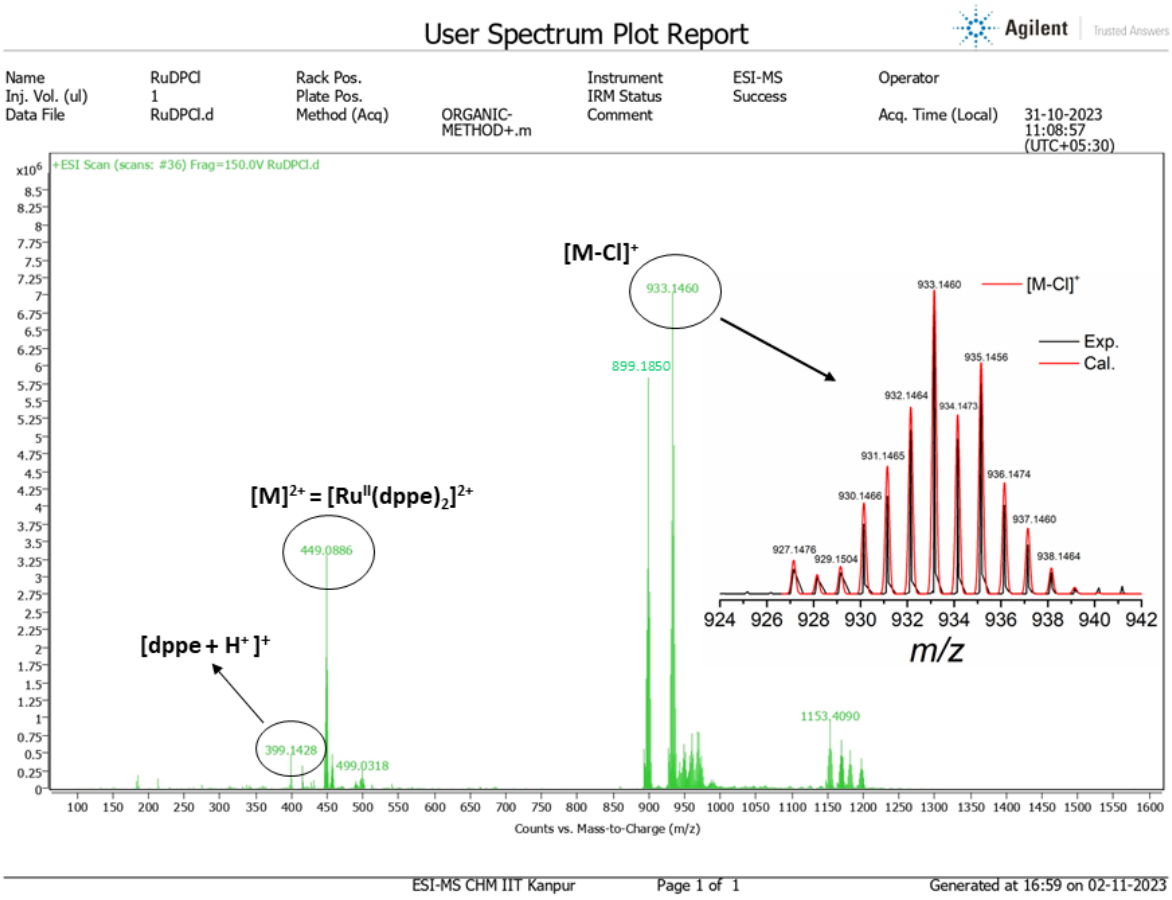

Fig. S15. ESI-MS(+) spectrum (full-range) of *cis*-[Ru(dppe)$_2$Cl$_2$] (**Ru-DPPE-Cl**) in dichloromethane.

Table S2. Selected crystallographic data and structure refinement parameters for the complex **Ru-DPPE-5FU** with co-crystallized solvent molecule i.e. $[Ru^{II}(dppe)_2(5\text{-FU})]PF_6 \cdot DMSO$

Identification code	CCDC No. 2294004
Empirical formula	$C_{58}H_{56}F_7N_2O_3P_5RuS$
Formula weight	1250.02
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	14.5354(4)
b/Å	20.8155(6)
c/Å	17.9751(5)
α/°	90
β/°	93.6410(10)
γ/°	90
Volume/Å^3	5427.6(3)
Z	4
ρ_{calc}g/cm^3	1.530
μ/mm^1	0.547
F(000)	2560.0
Crystal size/mm^3	0.2 × 0.18 × 0.16
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.544 to 52.098
Index ranges	$-17 \leq h \leq 17$, $-25 \leq k \leq 25$, $-22 \leq l \leq 22$
Reflections collected	72419
Independent reflections	10709 [R_{int} = 0.0548, R_{sigma} = 0.0344]
Data/restraints/parameters	10709/49/697
Goodness-of-fit on F^2	1.038
Final R indexes [I>=2σ (I)]	R_1 = 0.0581, wR_2 = 0.1537
Final R indexes [all data]	R_1 = 0.0740, wR_2 = 0.1692
Largest diff. peak/hole / e Å^{-3}	1.22/-1.61

[a]$R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$; [b]$wR_2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$. Goodness-of-fit (GOF) = $\{\Sigma[w(F_o^2-F_c^2)^2/(n-p)]\}^{1/2}$, where n = number of data and p = number of parameters refined.

Table S3. Selected bond lengths and bond angles obtained from the crystal structure of the complex **Ru-DPPE-5FU.**

Bond Lengths (Å)		**Bond Angles (degree)**	
Ru1-P1	2.3028(12)	P3-Ru1-P1	88.67(4)
Ru1-P2	2.3958(12)	P3-Ru1-P2	103.56(4)
Ru1-P3	2.3142(12)	P3-Ru1-P4	82.14(4)
Ru1-P4	2.3749(12)	P1-Ru1-P2	83.48(4)
Ru1-O1	2.203(3)	P1-Ru1-P4	103.64(4)
Ru1-N1	2.206(4)	O1-Ru1-N1	60.84(16)

Table S4. Comparative table of the specified bond length parameters in free **5-FU** ligand taken from the reference[S1] and in the **Ru-DPPE-5FU** complex obtained from SC-XRD data.

Bond Lengths (Å)	**5-FU**	**Ru-DPPE-5FU**
C1-N1	1.40(3)	1.364(8)
C1-N2	1.40(2)	1.381(7)
C2-N2	1.39(3)	1.352(9)
C2-O2	1.24(2)	1.256(8)
C3-C4	1.35(2)	1.330(10)
C1-O1	1.20(3)	1.245(7)
C4-N1	1.39(3)	1.363(8)
C3-F1	1.36(2)	1.361(8)

Table S5. Selected UV-vis absorption energy transitions at the TD-DFT/B3LYP level for **5-FU, Ru-DPPE-Cl** and **Ru-DPPE-5FU** in dichloromethane.

Excited state	**λ_{cal} (nm)/(eV)**	**Oscillator strength(f)**	**λ_{exp}(nm)**	**Key transitions**
5-FU				
S_2	249/4.9748	0.1567	229	H-2–L (3%), H–L (93%)
Ru-DPPE-Cl				
S_5	403/3.0725	0.0018	412	H-2–L (35%), H-1–L+1 (41%), H-1–L+2 (5%), H-1–L+3 (3%), H-1–L+17 (5%), H–L (4%)
S_7	328/3.7796	0.0018	350	H–L+1 (21%), H–L+2 (75%), H–L+3 (2%)
S_{53}	265/4.6768	0.0751	264	H-6–L+1 (3%), H-5–L (3%), H-4–L+1 (29%), H-3–L+3 (4%), H-2–L+12 (6%), H-1–L+13 (37%), H-1–L+16 (4%), H-1–L+17 (9%),
S_{71}	248/4.9840	0.0624	234	H-6–L+1 (7%), H-4–L+2 (33%), H-4–L+3 (48%), H-4–L+4 (3%)
Ru-DPPE-5FU				
S_9	311/3.9891	0.0751	310	H-2–L (87%), H-1–L(8%)
S_{38}	255/4.8501	0.1087	260	H-10–L(3%), H-3–L+1(15%), H-3–L+2(18%), H-2–L+7(40%), H-2–L+9(5%), H–L+13(4%)
S_{66}	243/5.0975	0.0720	229	H-11–L+1(5%), H-10–L+1(4%), H-9–L+1(10%), H-9–L+2(3%), H-8–L+1(4%), H-8–L+2(5%), H-7–L+2(9%), H-6–L+2(12%), H-4–L+2(8%), H-2–L+12(3%), H-1–L+12(8%)

Table S6. Atomic coordinates for all calculated species :

5-FU

C	-1.62730526	0.07776950	-0.00006683
C	0.75412571	0.87905251	0.00009301
C	1.13787376	-0.52781284	0.00007310
C	0.21871281	-1.51286325	0.00031892
H	0.48847625	-2.56097343	0.00036193
O	1.52549329	1.82797474	0.00011424
N	-0.63591103	1.05198368	0.00043139
H	-0.96747494	2.01000771	-0.00010034
O	-2.82120751	0.33415063	-0.00056574
N	-1.12489162	-1.21163137	0.00031080
H	-1.81159559	-1.95320457	0.00032283
F	2.45349828	-0.79690826	-0.00051967

Ru-DPPE-Cl

Ru	0.00001925	0.00027794	-0.62455404
P	1.04742207	1.41408321	1.13528703
P	-1.59932005	1.86705612	-0.76877277
C	2.35134173	2.78162120	0.82519906
C	-3.44102793	1.59475143	-0.44626076
C	1.72471917	0.75700848	2.77664826
C	-1.69514318	2.87899314	-2.36175216
C	-0.37904098	2.54497048	1.71562944
C	-1.07664276	3.18567962	0.50943558
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P	1.59930455	-1.86631111	-0.77028064
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C	3.44104193	-1.59423598	-0.44781314
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C	1.69492596	-2.87682825	-2.36416453
C	0.37913876	-2.54630648	1.71358728
C	1.07681130	-3.18600004	0.50689389
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C	-2.83269756	3.41835624	-4.46302635
H	-3.65832858	3.24695476	-5.14935357
C	-2.75754777	2.67590714	-3.26900998
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C	-4.27680272	2.64980943	-0.01664925
H	-3.87721505	3.64569008	0.15315031
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C	-5.39003266	0.11554046	-0.50725010

H	-5.81259165	-0.86568760	-0.70767278
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H	-6.28310944	3.25602251	0.51759566
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H	3.38384748	0.48146406	-1.05686396
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H	-3.32203433	0.35731585	1.81988487
C	-3.45857923	0.50363972	3.96312828
H	-4.34210678	1.13589607	3.92901527
C	-2.90821968	0.11774119	5.20216312
H	-3.36285470	0.45017148	6.13197113
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H	-1.33208135	-1.01204727	6.17207329
C	-1.17930765	-1.13987975	4.02016813
H	-0.30248137	-1.77521935	4.07531897
C	1.17929760	1.13640492	4.02111613
H	0.30255552	1.77181755	4.07683479
C	1.76699038	0.70072065	5.22487847

H	1.33203103	1.00667425	6.17290664
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C	2.87162669	-0.06825608	2.76166872
H	3.32186290	-0.35918220	1.81955462
C	2.99671933	3.38229263	1.93270315
H	2.81495656	3.02391418	2.94068130
C	3.89163147	4.45255268	1.74917135
H	4.37742726	4.89849980	2.61373398
C	4.15828868	4.94215364	0.45469847
H	4.85171180	5.76747056	0.31240076
C	3.51959068	4.34899040	-0.64951415
H	3.71741907	4.71132736	-1.65557378
C	2.62040549	3.27794116	-0.46716724
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C	-3.89129203	-4.45444993	1.74531080
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H	-0.15190864	-3.98127965	-2.02985204
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C	1.84515897	-4.37173785	-4.77012511
H	1.90365155	-4.94722389	-5.69077044
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H	0.00125221	-5.29899422	-4.10165234
Cl	1.30209787	1.01322972	-2.55344910
Cl	-1.30180091	-1.01104691	-2.55423299

Ru-DPPE-5FU

Ru	0.02742772	-0.13417449	0.04971964
P	-2.02636097	0.53338449	1.20580476
P	-0.22036660	1.73484524	-1.49779003
P	-0.93424776	-1.43400236	-1.82026015
P	1.10191506	0.96570262	1.96830354
O	0.40697690	-2.05296204	1.03587160
C	-3.94563829	-0.28592495	3.16226448
H	-4.50239991	0.59366642	2.85090882
C	-2.72565135	-0.62341987	2.53248892
N	1.95260909	-1.09924447	-0.27463717
C	-2.45946479	-2.50081426	-1.54276084
C	-4.45703910	0.18821841	-0.24229182
H	-4.19501684	-0.86432886	-0.24212203
C	-4.46151801	-1.09402178	4.19158624
H	-5.40191327	-0.82576846	4.66615492

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