Supplementary information

New dual inhibitors of SARS-CoV-2 based on metal complexes with schiff base 4-chloro-3-methyl phenyl hydrazine: synthesis, DFT, antibacterial properties and molecular docking studies

Ahmed S. M. Al-Janabi [1*], Amin O. Elzupir [2], Mortaga M. Abou-Krisha[3,4], T. A. Yousef [3,5*]

[1] Department of Chemistry, College of Science, Tikrit University, Tikrit, Iraq.
*[2]Deanship of Scientific Research, College of Science, Imam Mohammad Ibn Saud Islamic University, Riyadh, Riyadh, Saudi Arabia. * E. mail: aoalamalhuda@imamu.edu.sa*
[3] Chemistry department, Science College, Imam Mohammad Ibn Saud Islamic University, Riyadh, Riyadh, Saudi Arabia.
[4] Department of Chemistry, South Valley University, Qena, 83523, Egypt
[5]Toxic and Narcotic drug, Forensic Medicine Department, Mansoura Laboratory, Medicolegal organization, Ministry of Justice, Egypt

Figure SI 1: IR spectrum of complex Cmpy ligand

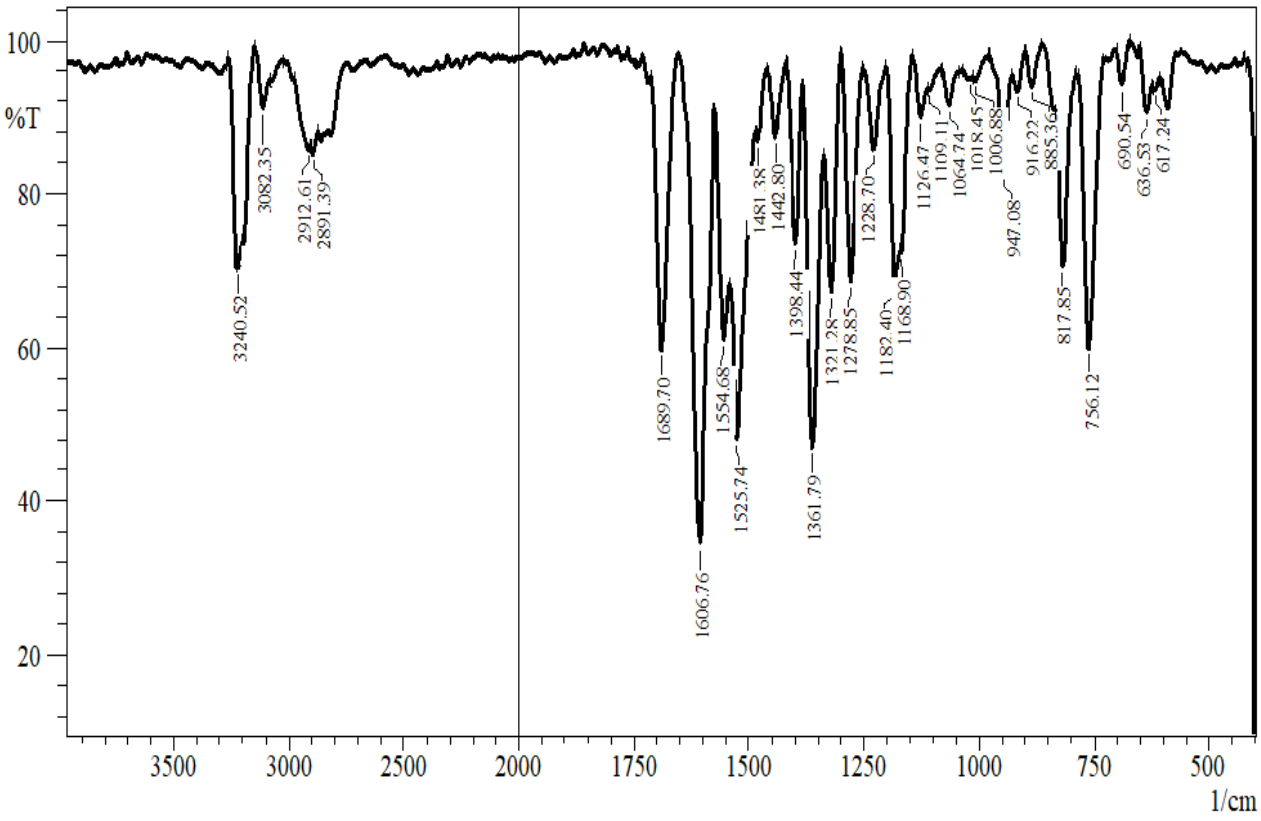

Figure SI2 : IR spectrum of complex 1

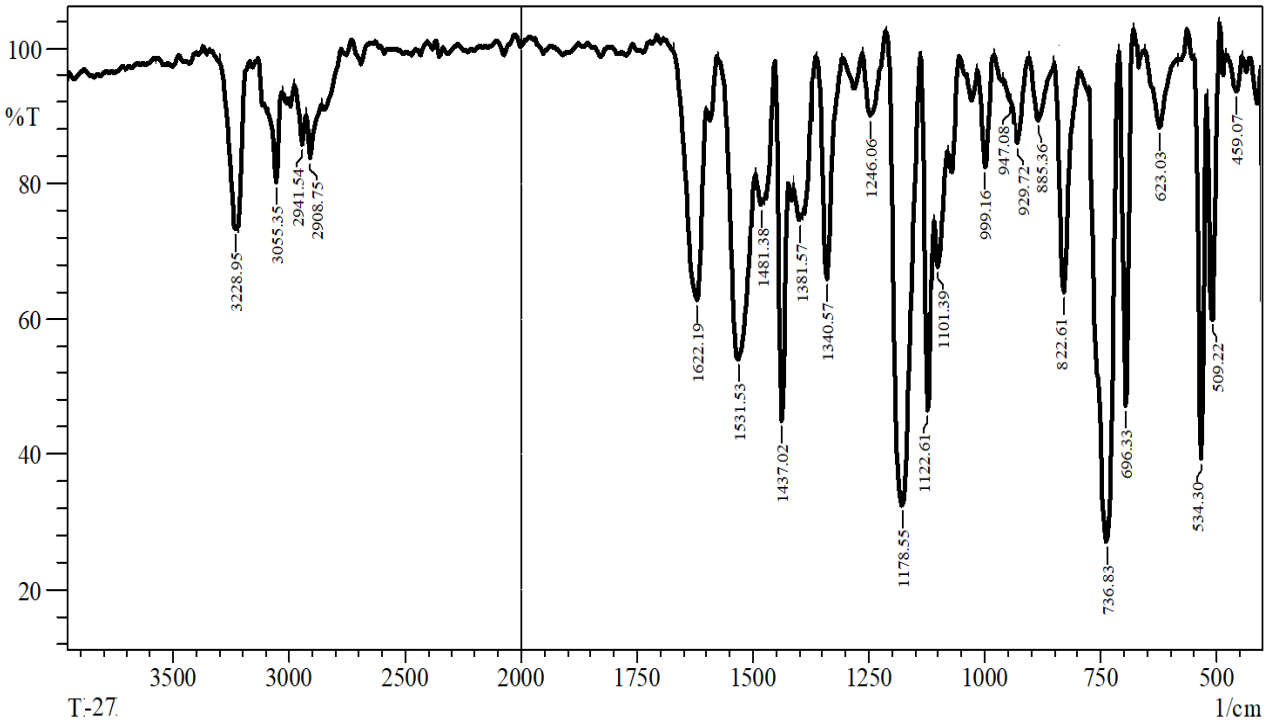

Figure SI3 : IR spectrum of complex 2

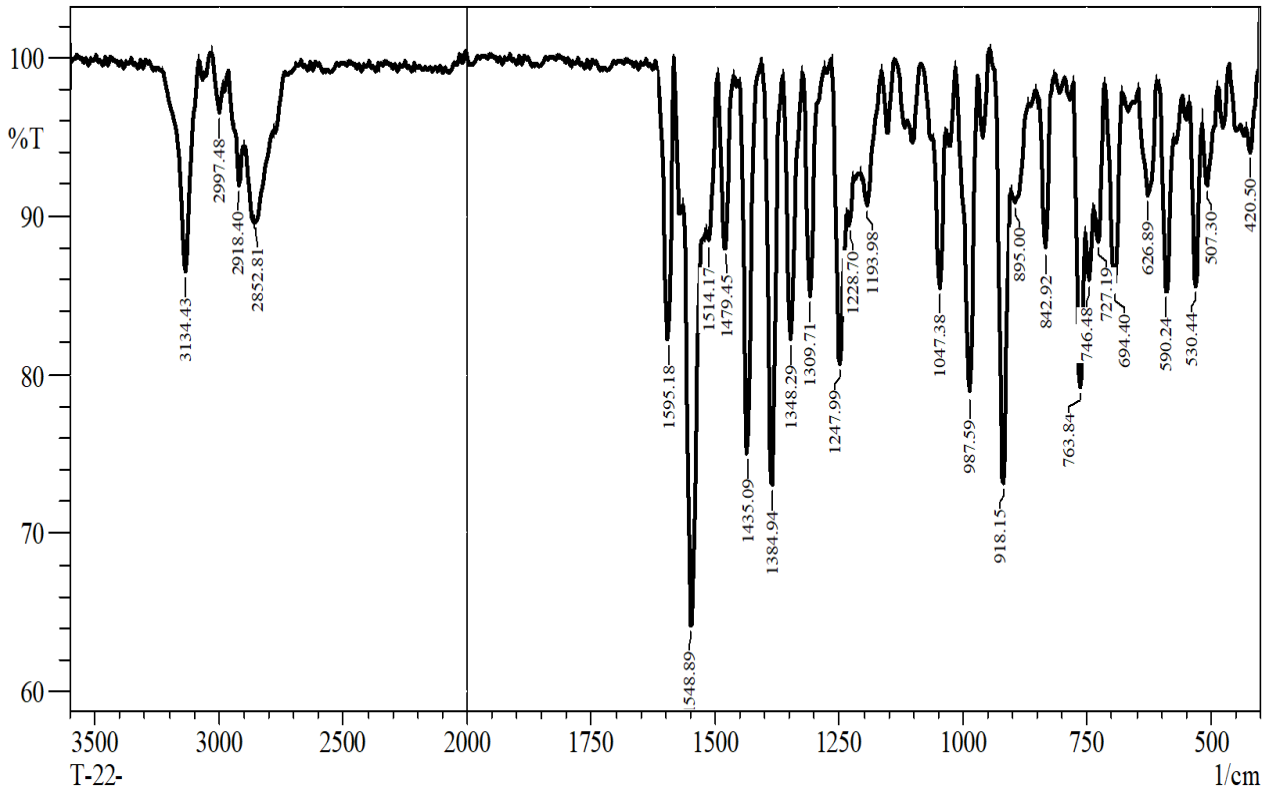

Figure SI4 : IR spectrum of complex 3

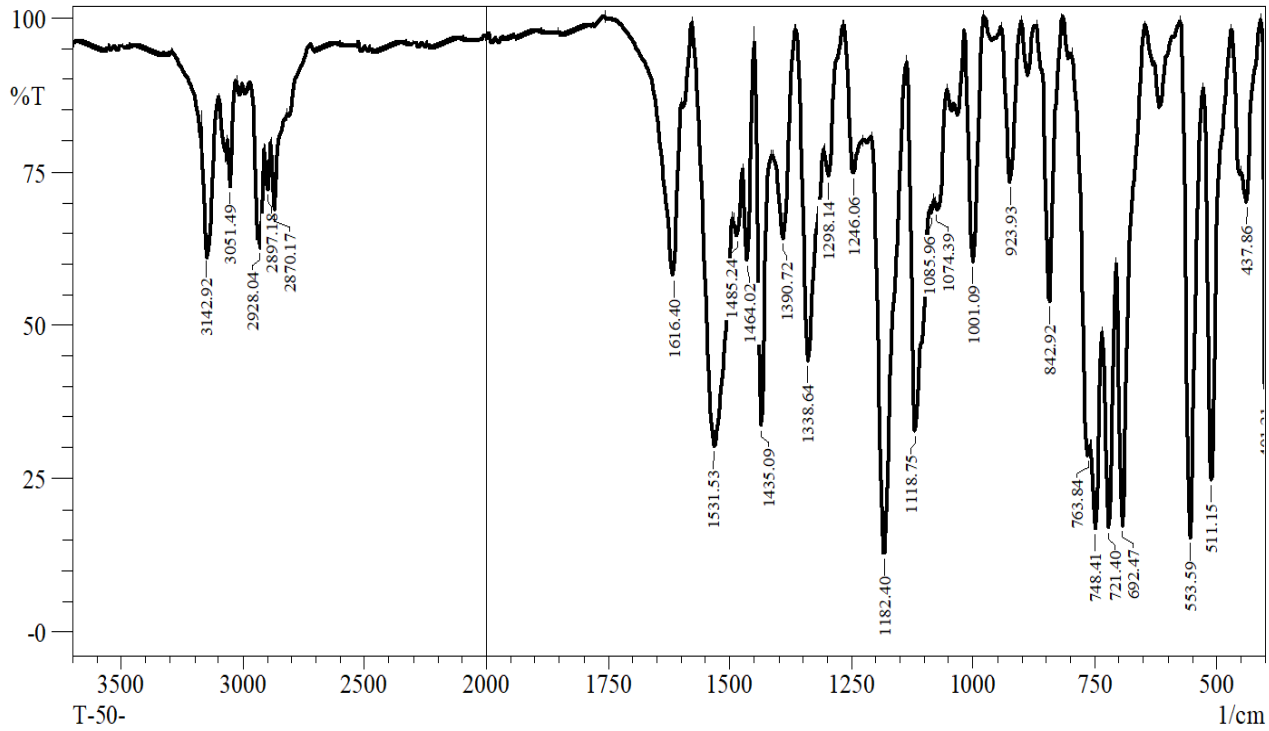

Figure SI5 : IR spectrum of complex 4

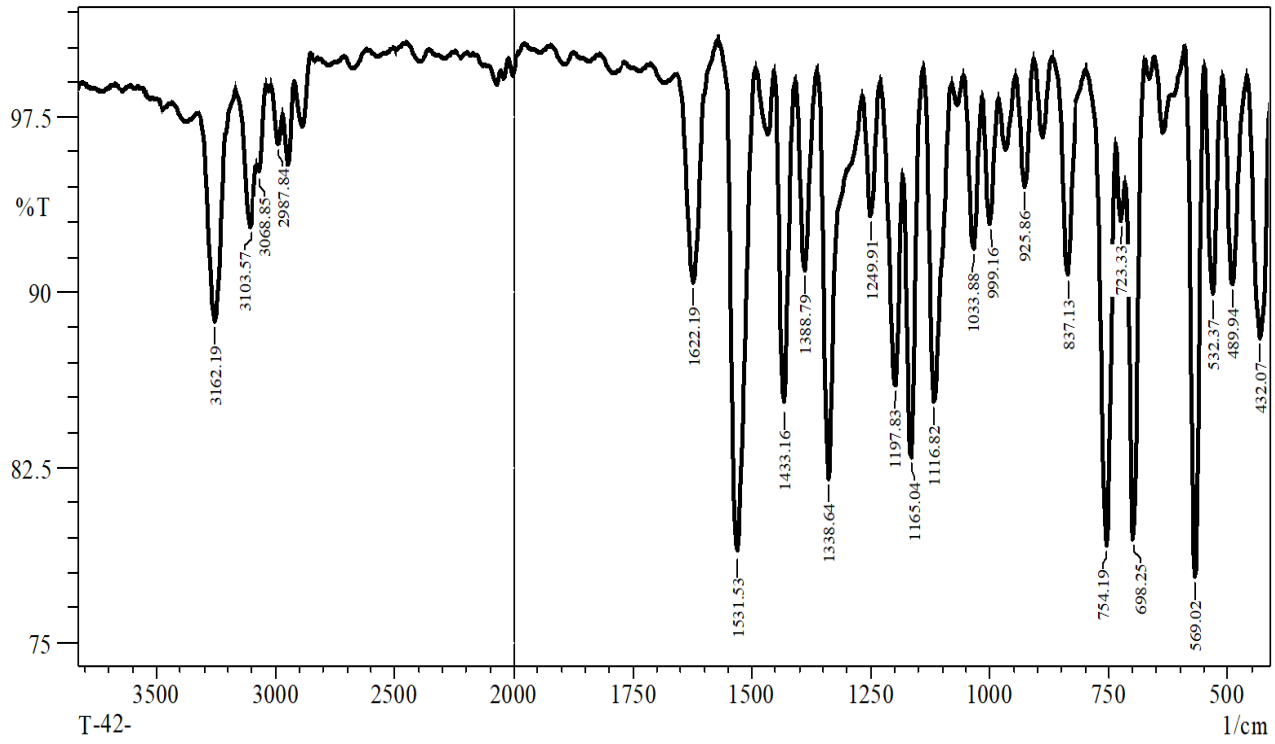

Figure SI 6 : IR spectrum of complex 5

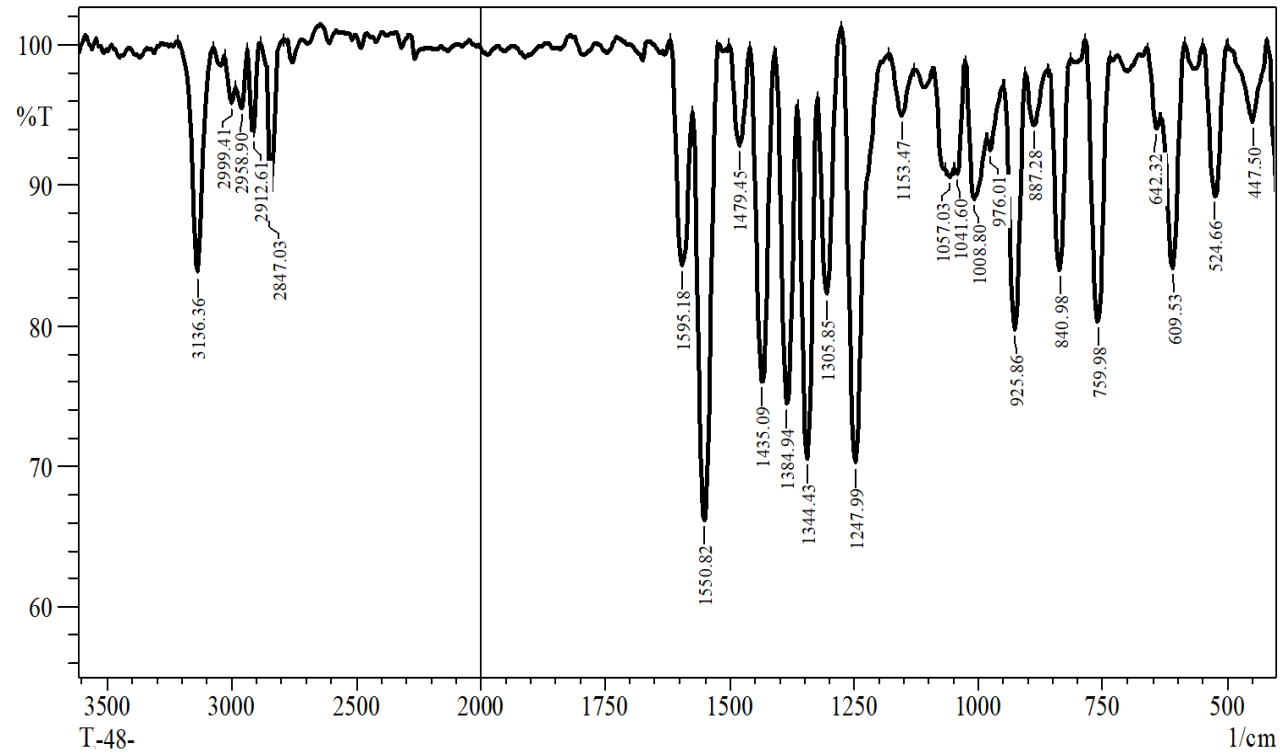

Figure SI 7 : ^{1}H NMR spectrum of Cmpy

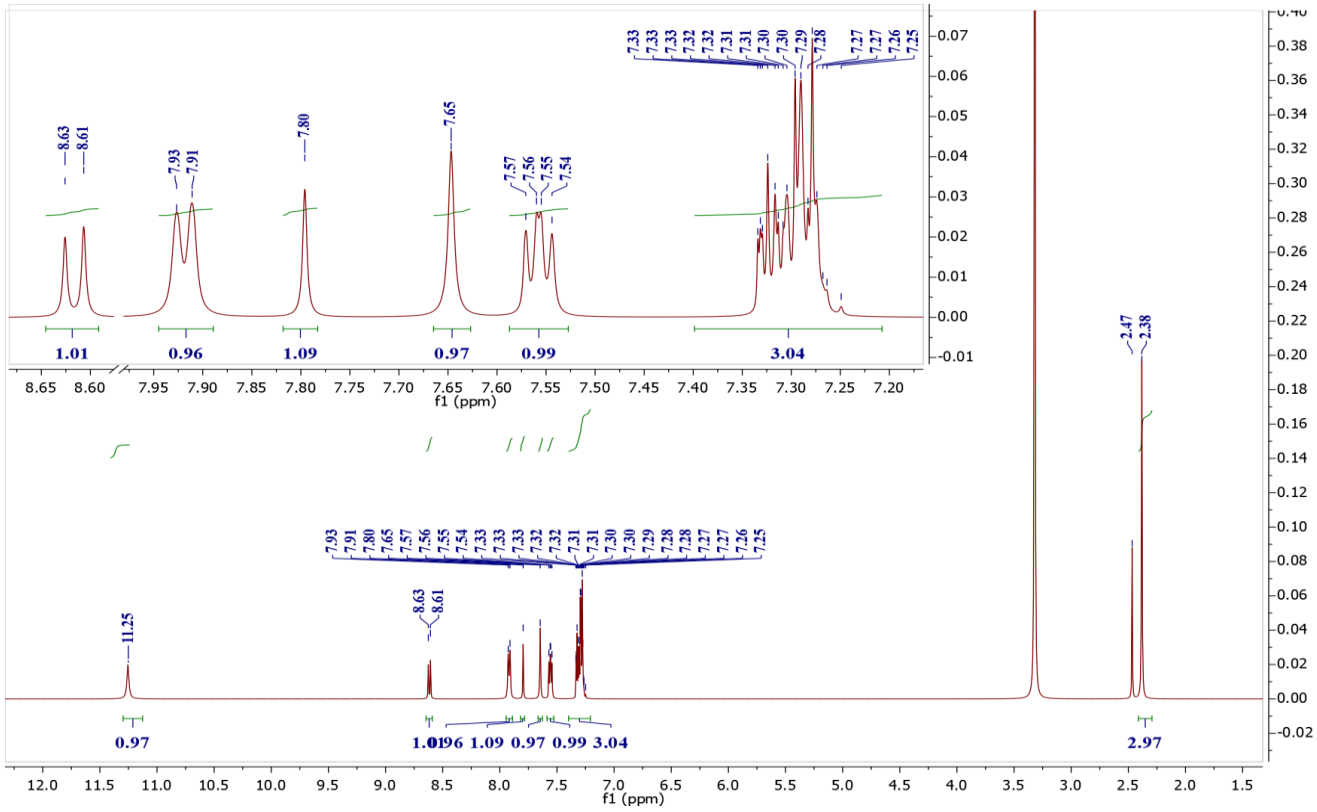

Figure SI 8 : ^{1}H NMR spectrum of complex 1

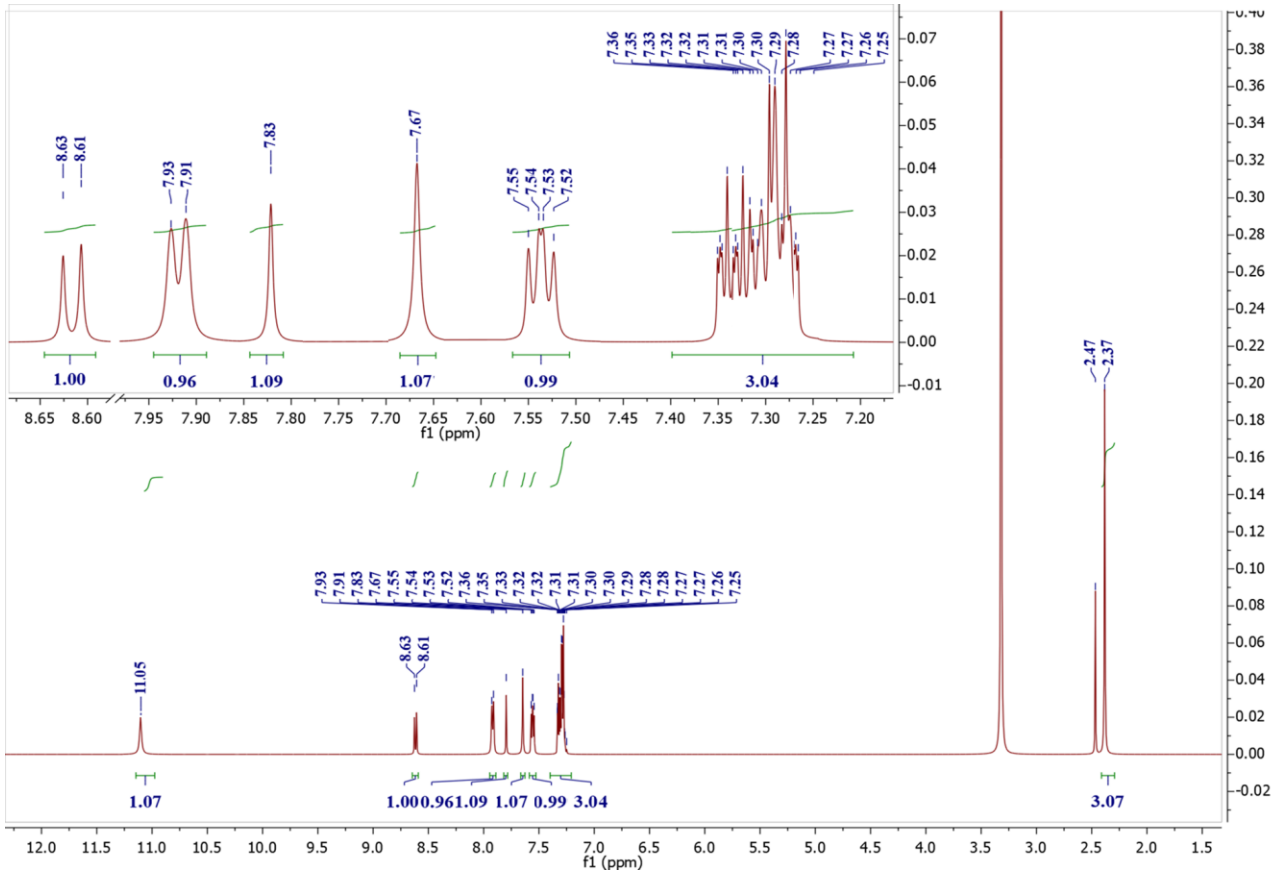

Figure SI 9 : ^{1}H NMR spectrum of complex 2

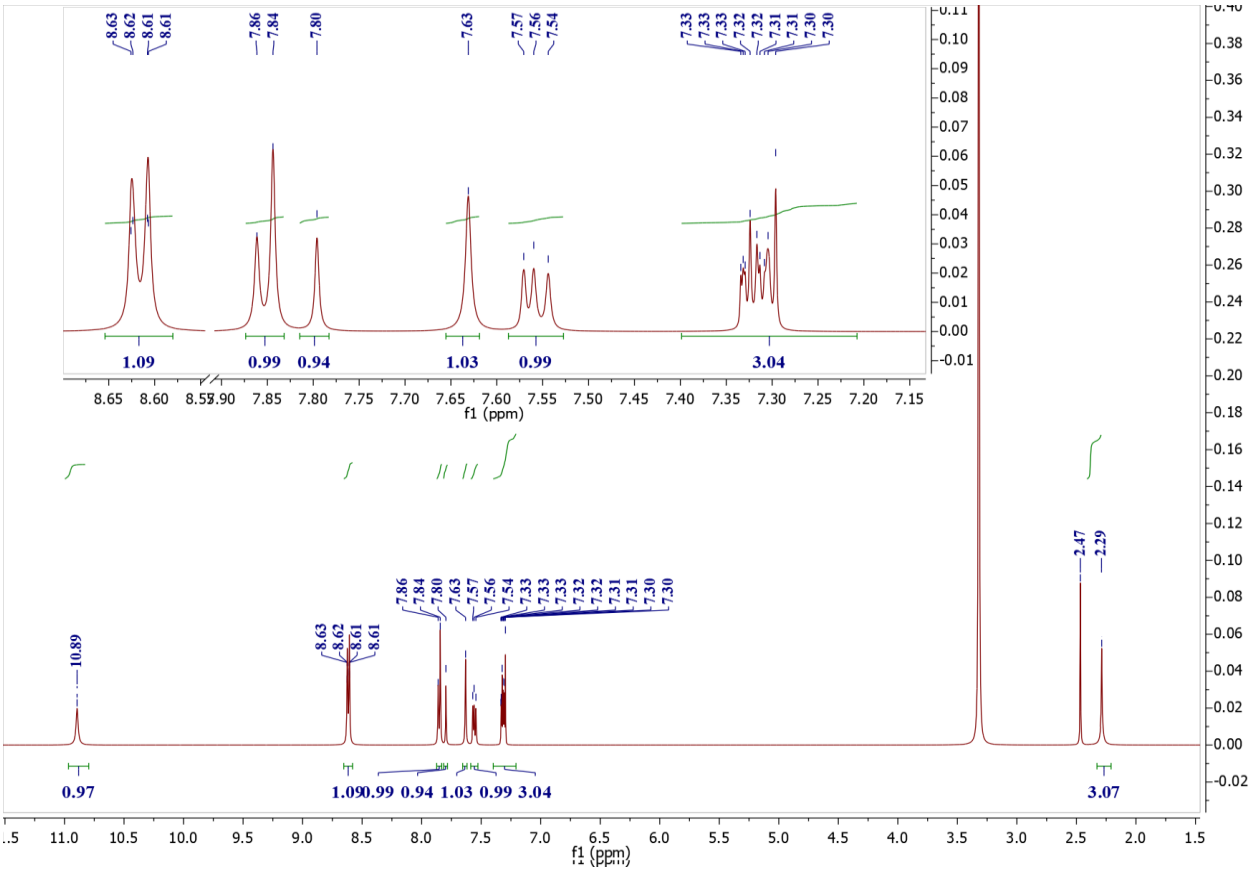

Figure SI 10 : ^{1}H NMR spectrum of complex 3

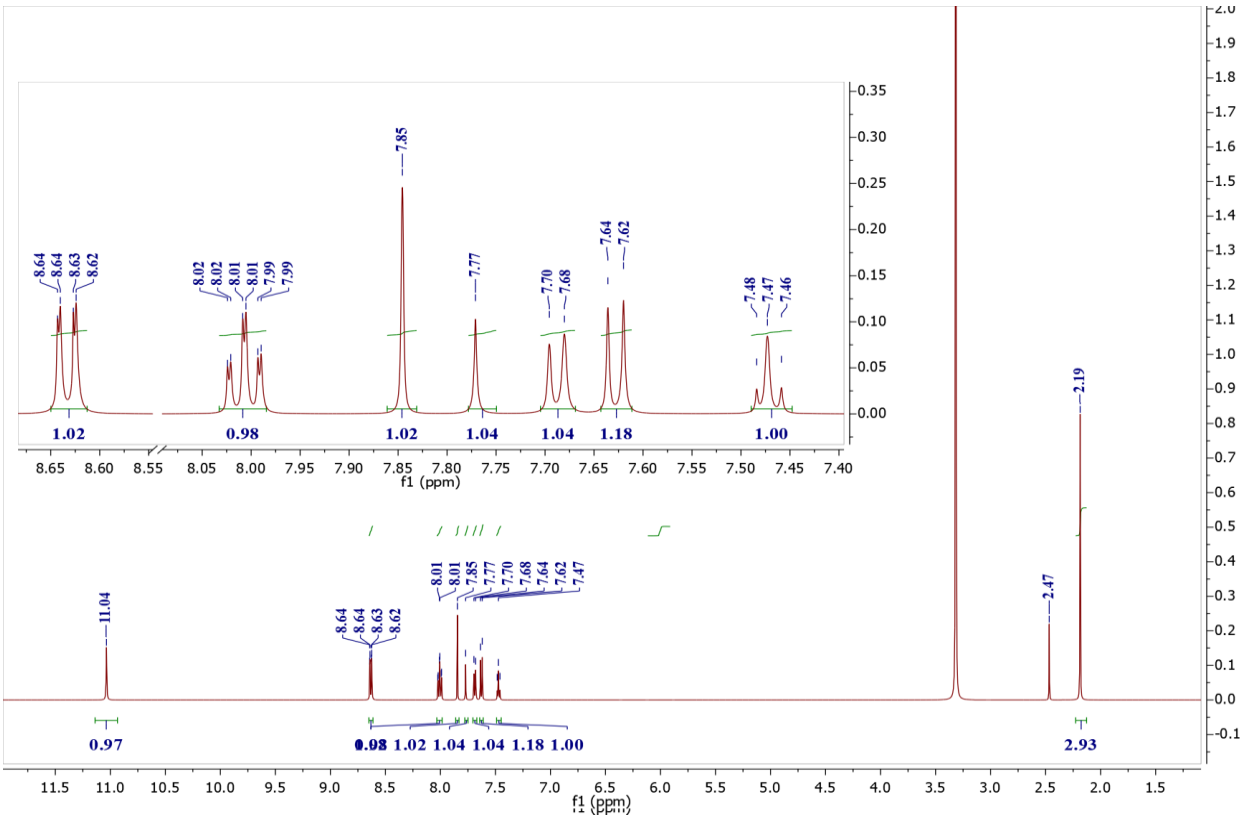

Figure SI 11 : ^{1}H NMR spectrum of complex 4

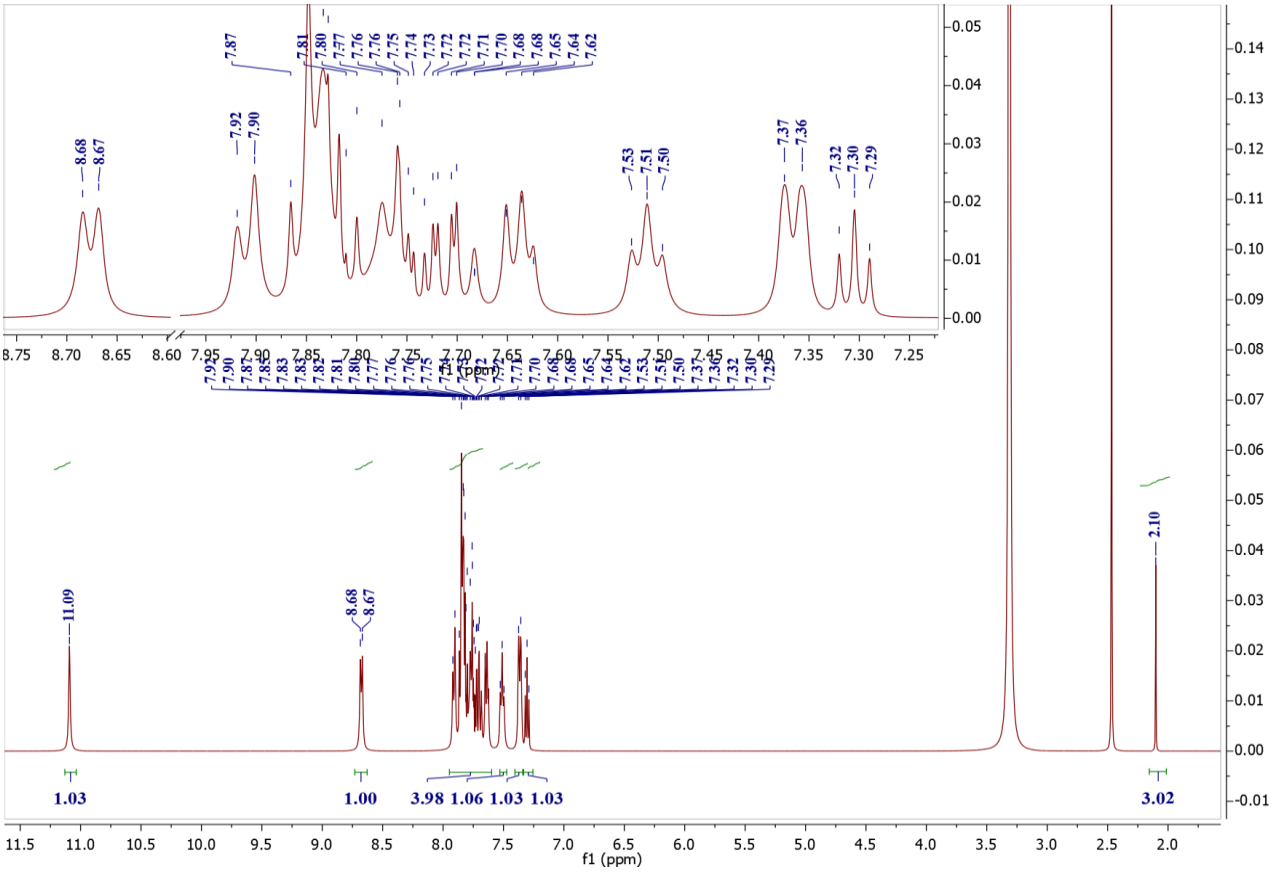

Figure SI 12 : ^{1}H NMR spectrum of complex 5

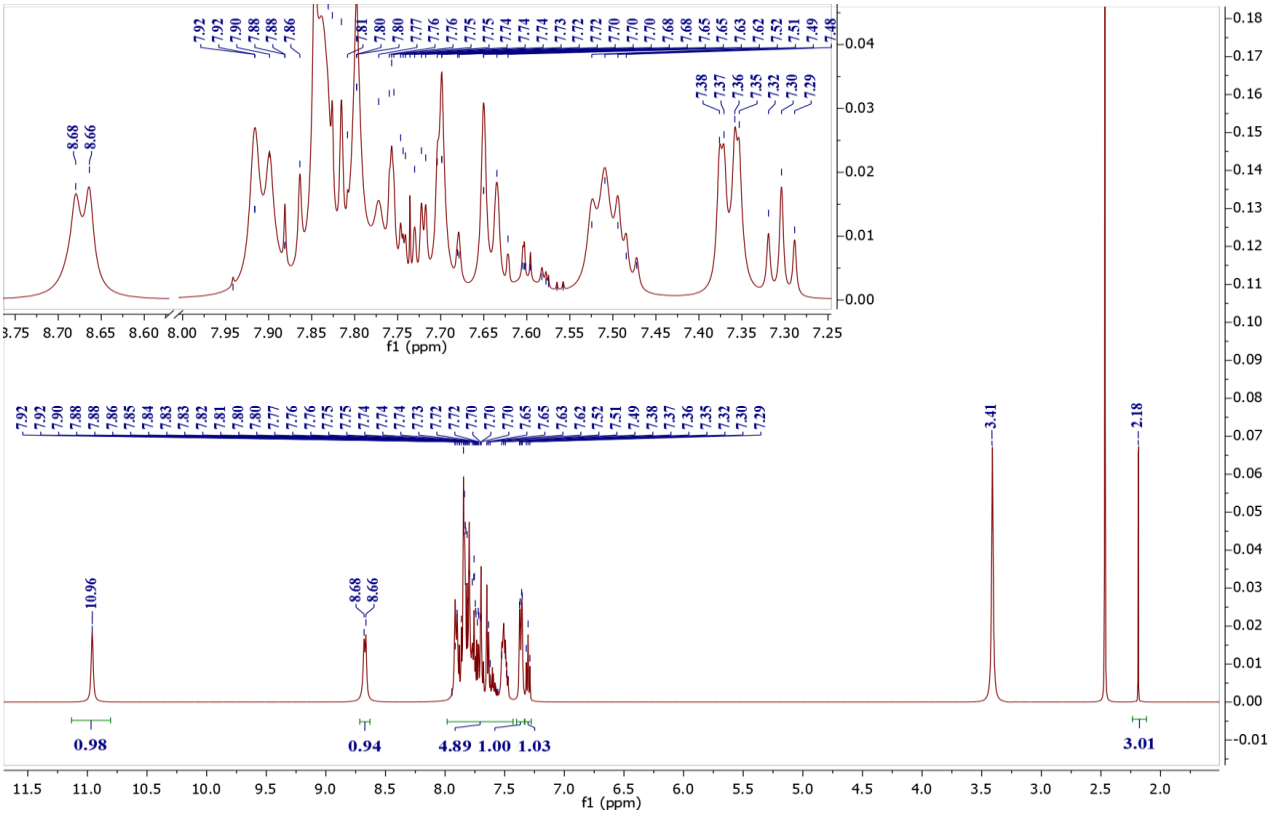

Figure SI 13 : ^{13}C NMR spectrum of Cmpy

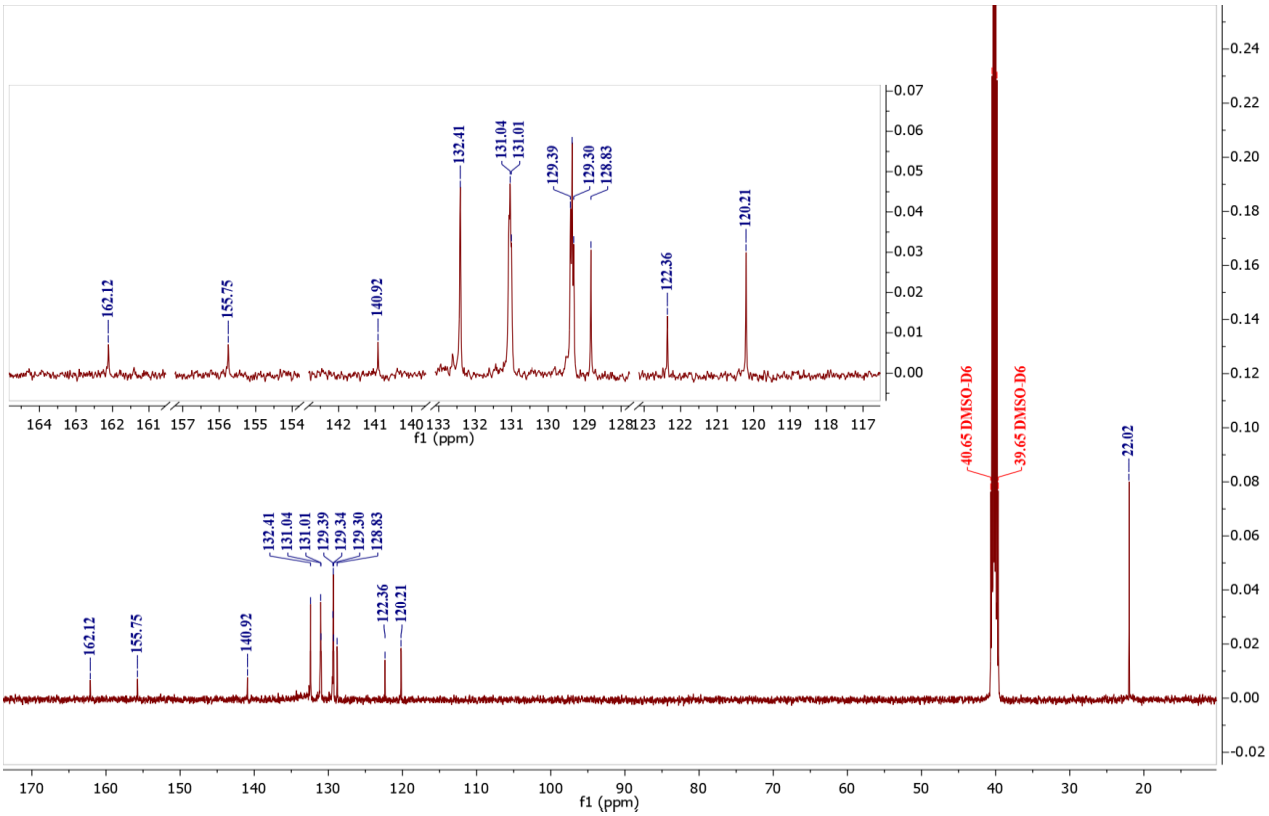

Figure SI 14 : ^{13}C NMR spectrum of complex 1

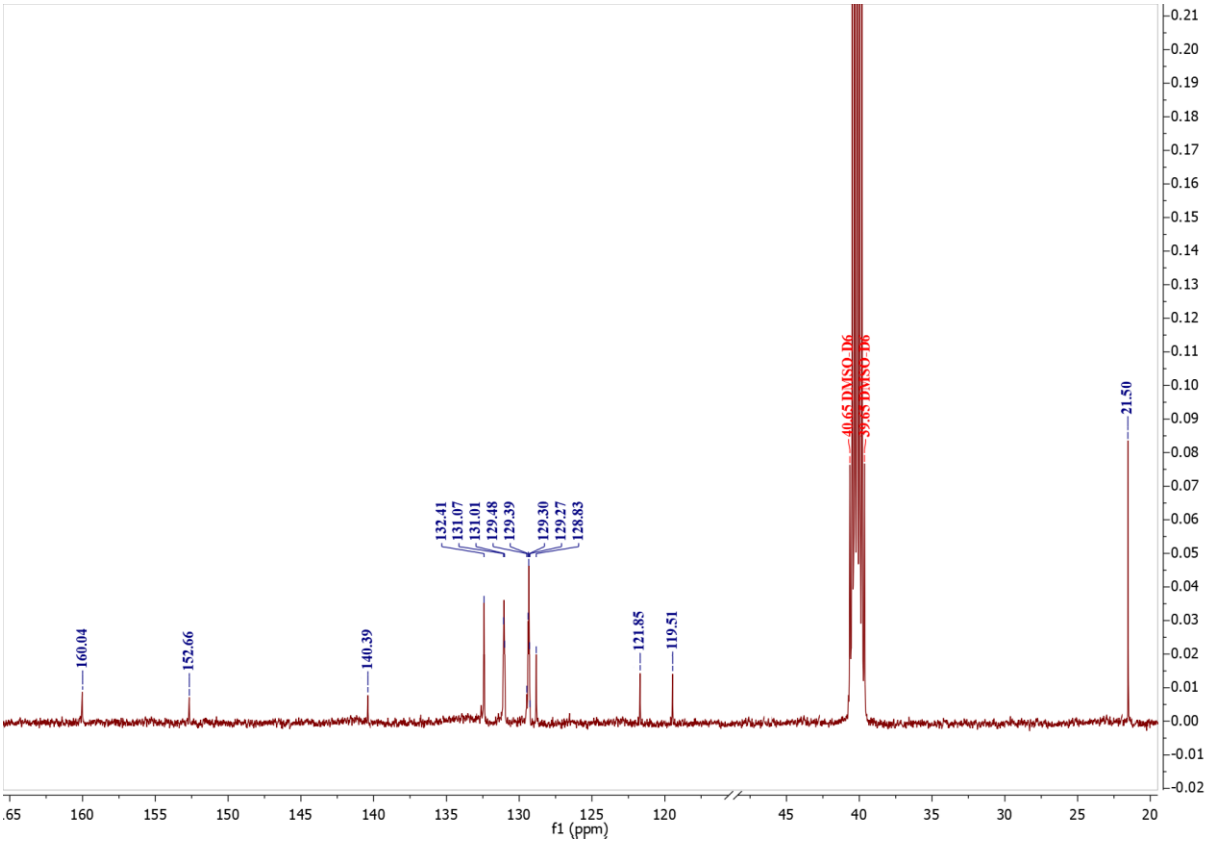

Figure SI 15 : ^{13}C NMR spectrum of complex 2

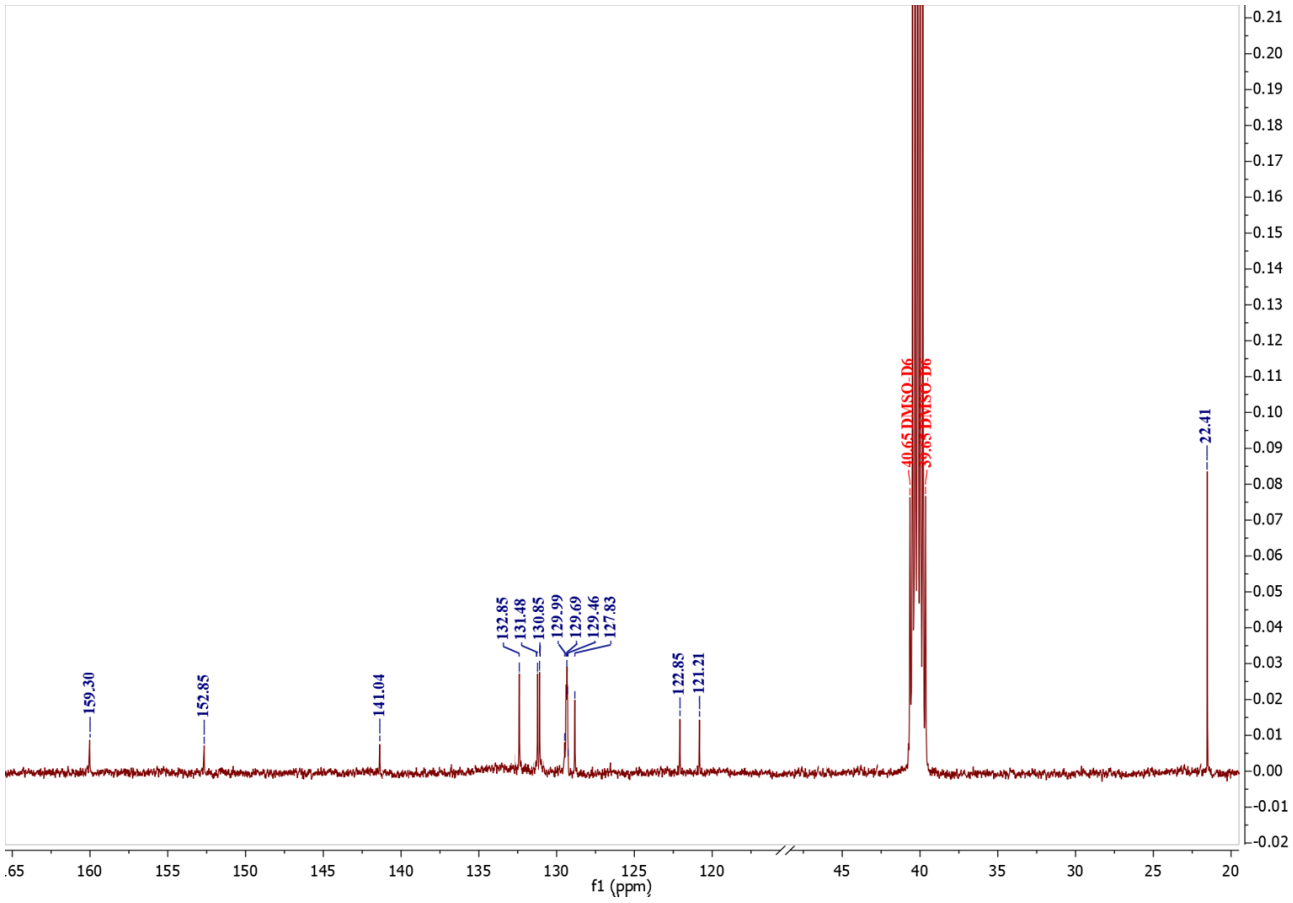

Table SI 1. Mulliken atomic charges of Cmpy and its complexes determined by DFT using 6-311G-based B3LYP (d, p).

Cmpy		Ni complex		Pd complex		Pt complex		Zn complex		Hg complex	
Atom	Charge	Atom	Charge	Atom	Charge	Atom	Charge	Atom	Charge	Atom	Charge
1 C	−0.46	1 C	0.08	1 C	0.04	1 C	0.09	1 C	0.08	1 C	−0.07
2 C	0.19	2 C	0.06	2 C	0.08	2 C	−0.18	2 C	0.07	2 C	−0.14
3 C	0.06	3 C	0.07	3 C	−0.08	3 C	0.23	3 C	0.06	3 C	0.33
4 N	−0.02	4 N	0.28	4 N	0.17	4 N	0.24	4 N	0.33	4 N	0.18
5 C	0.01	5 C	0.44	5 C	1.35	5 C	1.49	5 C	0.36	5 C	0.92
6 C	0.58	6 C	−0.09	6 C	−0.57	6 C	−0.47	6 C	−0.08	6 C	−0.32
7 C	−0.59	7 C	0.07	7 C	−1.79	7 C	−2.22	7 C	0.10	7 C	−1.37
8 N	−0.01	8 N	0.18	8 N	0.15	8 N	0.44	8 N	0.31	8 N	0.51
9 N	0.45	9 N	0.05	9 N	0.19	9 N	0.26	9 N	0.04	9 N	0.23
10 C	−0.83	10 C	0.25	10 C	1.52	10 C	1.24	10 C	0.35	10 C	1.42
11 C	0.41	11 C	−0.09	11 C	−0.33	11 C	−0.27	11 C	−0.09	11 C	−0.54
12 C	−0.32	12 C	0.04	12 C	−1.07	12 C	−1.14	12 C	0.01	12 C	−1.16
13 C	−0.15	13 C	−0.27	13 C	−0.20	13 C	−0.13	13 C	−0.26	13 C	−0.22
14 C	0.61	14 C	0.52	14 C	0.59	14 C	0.83	14 C	0.53	14 C	0.78
15 C	−0.14	15 C	−0.219	15 C	−0.96	15 C	−1.17	15 C	−0.25	15 C	−1.07
16 C	−0.33	16 C	−0.04	16 C	−0.12	16 C	0.00	16 C	−0.04	16 C	−0.06
17 C	0.49	17 C	0.03	17 C	0.82	17 C	0.99	17 C	−0.03	17 C	0.97
		18 Ni	0.19	18 Pd	0.04	18 Pt	−0.62	18 Zn	0.65	18 Hg	−1.06
		19 Cl	−0.28	19 Cl	−0.02	19 Cl	−0.02	19 Cl	−0.44	19 Cl	−0.41
		20 Cl	−0.28	20 Cl	−0.21	20 Cl	−0.34	20 Cl	−0.44	20 Cl	−0.61

Table SI2. Physiochemical properties of synthesized compounds.

	L	Ni	Pd	Pt	Zn	Hg
Molecular weight (g/mol)	245.71	375.31	423.03	511.69	381.99	517.20
Num. heavy atoms	17	20	20	20	20	20
Num. arom. heavy atoms	12	12	12	12	12	12
Fraction Csp3	0.08	0.08	0.08	0.08	0.08	0.08
Num. rotatable bonds	3	2	2	2	2	2
Num. H-bond acceptors	2	0	0	0	0	0
Num. H-bond donors	1	1	1	1	1	1
Molar Refractivity	71.69	86.72	86.72	86.72	86.72	86.72
TPSA	37.28 Å²	32.10 Å²	32.10 Å²	32.10 Å²	32.10 Å²	32.10 Å²

TPSA: Topological polar surface area.

Table SI3. Lipophilicity and water solubility of synthesized compounds.

	L	Ni	Pd	Pt	Zn	Hg
Log Po/w (iLOGP)	2.10	0.00	0.00	0.00	0.00	0.00
Log Po/w (XLOGP3)	3.79	5.41	5.41	5.41	5.41	5.41
Log Po/w (WLOGP)	3.30	2.98	2.98	2.98	2.98	2.98
Log Po/w (MLOGP)	2.41	2.91	2.91	2.91	2.91	2.91
Log Po/w (SILICOS-IT)	3.63	1.21	1.50	2.05	1.25	2.08
Consensus Log Po/w	3.05	2.50	2.56	2.67	2.51	2.68
Log S (ESOL)	−4.08	−5.89	−6.18	−6.73	−5.93	−6.77
Solubility	2.07x10⁻² mg/ml; 8.41x10⁻⁵ mol/l	4.87x10⁻⁴ mg/ml; 1.30x10⁻⁶ mol/l	2.78x10⁻⁴ mg/ml; 6.56x10⁻⁷ mol/l	9.47e−05 mg/ml; 1.85x10⁻⁷ mol/l	4.50e−04 mg/ml; 1.18x10⁻⁶ mol/l	8.85x10⁻⁵ mg/ml; 1.71x10⁻⁷ mol/l
Class	Moderately soluble	Moderately soluble	Poorly soluble	Poorly soluble	Moderately soluble	Poorly soluble
Log S (Ali)	−4.27	−5.84	−5.84	−5.84	−5.84	−5.84
Solubility	1.33e−02 mg/ml; 5.41e−05 mol/l	5.43e−04 mg/ml; 1.45e−06 mol/l	6.13e−04 mg/ml; 1.45e−06 mol/l	7.41e−04 mg/ml; 1.45e−06 mol/l	5.53e−04 mg/ml; 1.45e−06 mol/l	7.49e−04 mg/ml; 1.45e−06 mol/l
Class	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble
Log S (SILICOS-IT)	−5.70	−6.25	−6.37	−6.58	−6.27	−6.60
Solubility	4.95e−04 mg/ml; 2.01e−06 mol/l	2.12e−04 mg/ml; 5.65e−07 mol/l	1.80e−04 mg/ml; 4.25e−07 mol/l	1.33e−04 mg/ml; 2.60e−07 mol/l	2.07e−04 mg/ml; 5.42e−07 mol/l	1.31e−04 mg/ml; 2.52e−07 mol/l
Class	Moderately soluble	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble	Poorly soluble

Table SI4. Pharmacokinetics and druglikeness of synthesized compounds.

	L	Ni	Pd	Pt	Zn	Hg
GI absorption	**High**	**High**	**High**	**High**	**High**	**High**
BBB permeant	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
P-gp substrate	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
CYP1A2 inhibitor	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
CYP2C19 inhibitor	**Yes**	**Yes**	**Yes**	**No; 1 violation**	**Yes**	**Yes**
CYP2C9 inhibitor	**No**	**No**	**No**	**No**	**No**	**No**
CYP2D6 inhibitor	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 inhibitor	**No**	**Yes**	**Yes**	**Yes**	**No**	**No**
Log Kp (skin permeation)	**−5.11 cm/s**	**−4.75 cm/s**	**−5.04 cm/s**	**−5.58 cm/s**	**−4.79 cm/s**	**−5.61 cm/s**
Lipinski	**Yes; 0 violations**	**Yes; 0 violations**	**Yes; 0 violations**	**Yes; 1 violation**	**Yes; 0 violations**	**Yes; 1 violation**
Ghose	**Yes**	**Yes**	**Yes**	**No; 1 violation**	**Yes**	**No; 1 violation**
Veber	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Egan	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Muegge	**Yes**	**No; 1 violation**	**No; 1 violation**	**No; 1 violation**	**No; 1 violation**	**No; 1 violation**
Bioavailability Score	**0.55**	**0.55**	**0.55**	**0.55**	**0.55**	**0.55**