

# A Novel Ibuprofen Derivative and Its Complexes: Physicochemical Characterization, DFT Modeling, Docking, In Vitro Anti-Inflammatory Studies, and DNA Interaction

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**Table S1:** The <sup>1</sup>H NMR data of the HI and HL.

Comp.	$\delta$ (ppm)	
	9.13(1H, br, NH), 7.21-7.04 (4H, m, ArH), 4.18(2H, s, NH <sub>2</sub> ), 3.45(2H, s, CH <sub>2</sub> ), 2.39 (2H, s, CH <sub>2</sub> ), 1.80(1H, s, CH), 1.29 (3H, m, CH <sub>3</sub> ), 0.84-0.82(6H, m, (CH <sub>3</sub> ) <sub>2</sub> ).	
HI	$\Delta$ (ppm) map (experimental)	$\delta$ (ppm) map (computed)
	$\delta$ (ppm)	
	11.12(1H, s, OH), 10.03(1H, br, NH), 8.39(1H, s, CH), 7.27-6.63(8H, m, ArH), 3.69(2H, s, CH <sub>2</sub> ), 2.41(2H, s, CH <sub>2</sub> ), 1.83(H, s, CH), 1.39(3H, m, CH <sub>3</sub> ), 0.87-0.82(6H, m, (CH <sub>3</sub> ) <sub>2</sub> ).	
HL	$\Delta$ (ppm) map (experimental)	$\delta$ (ppm) map (computed)
	$\delta$ (ppm)	

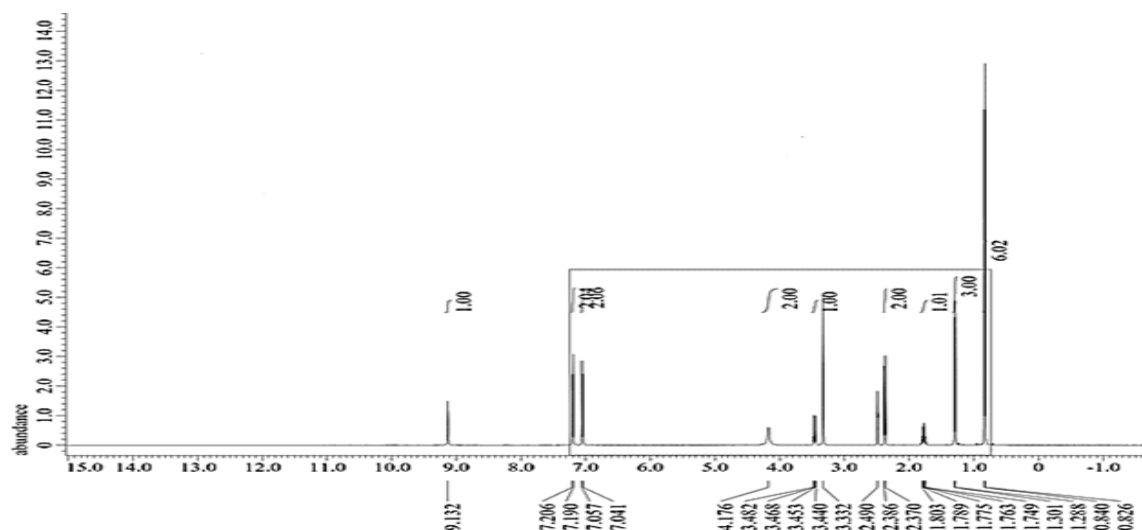
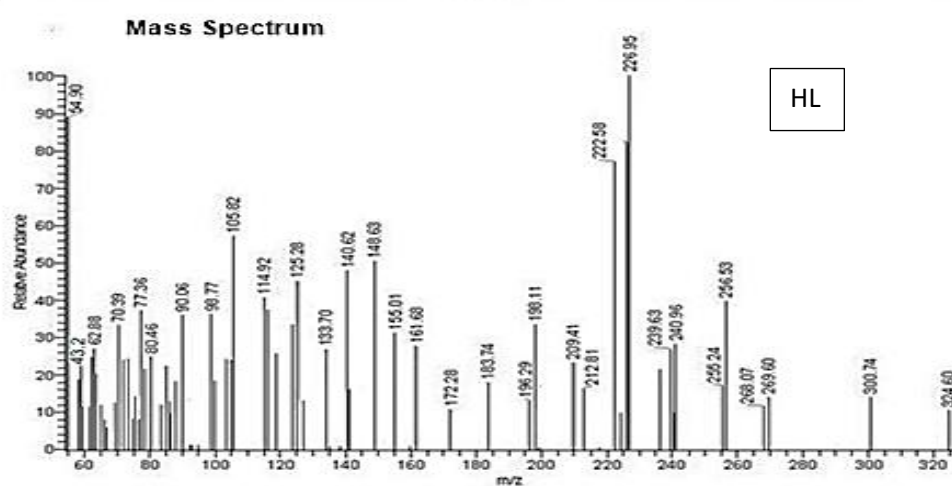
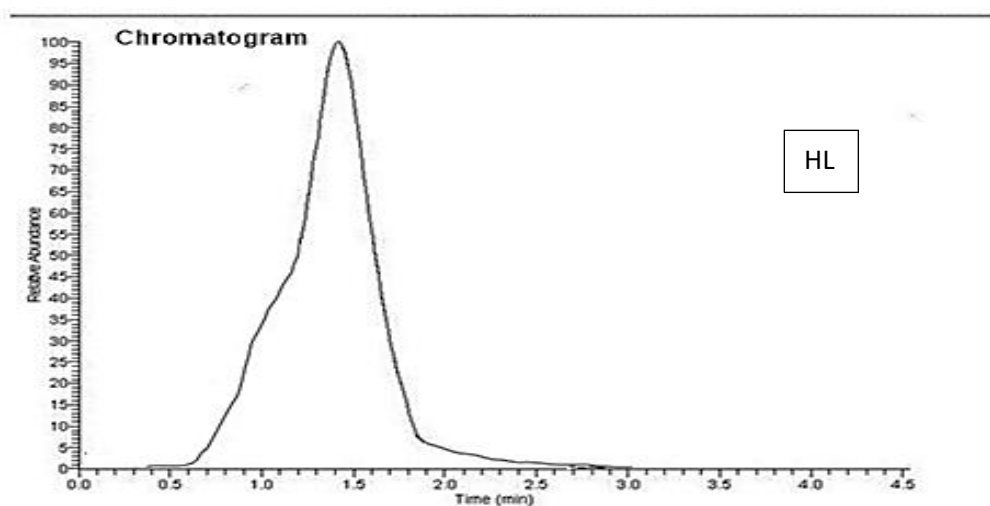
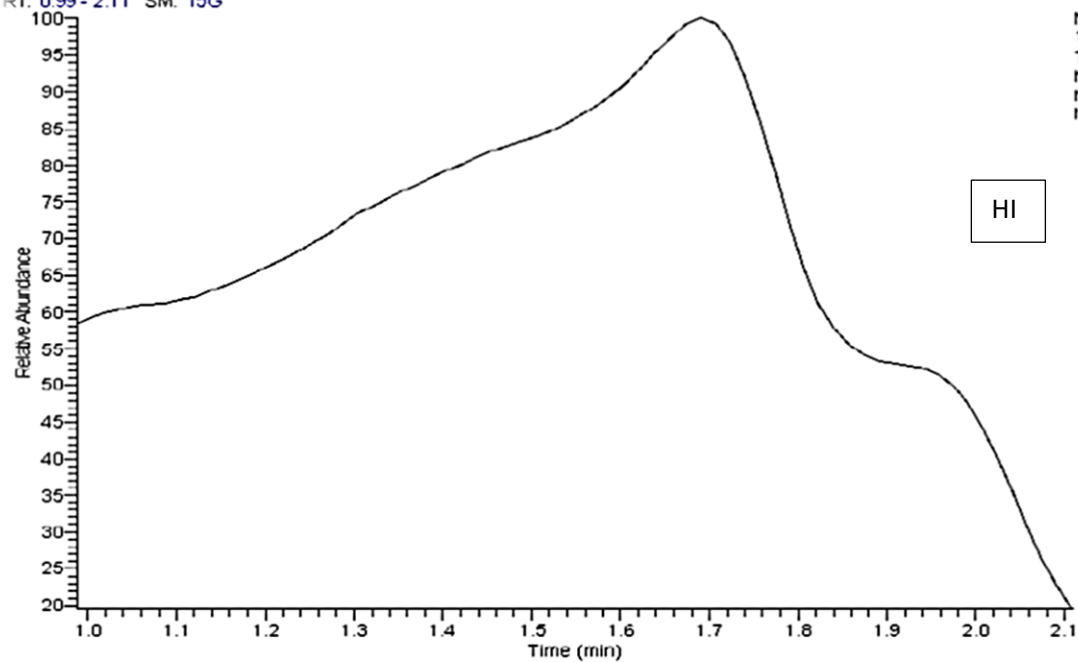
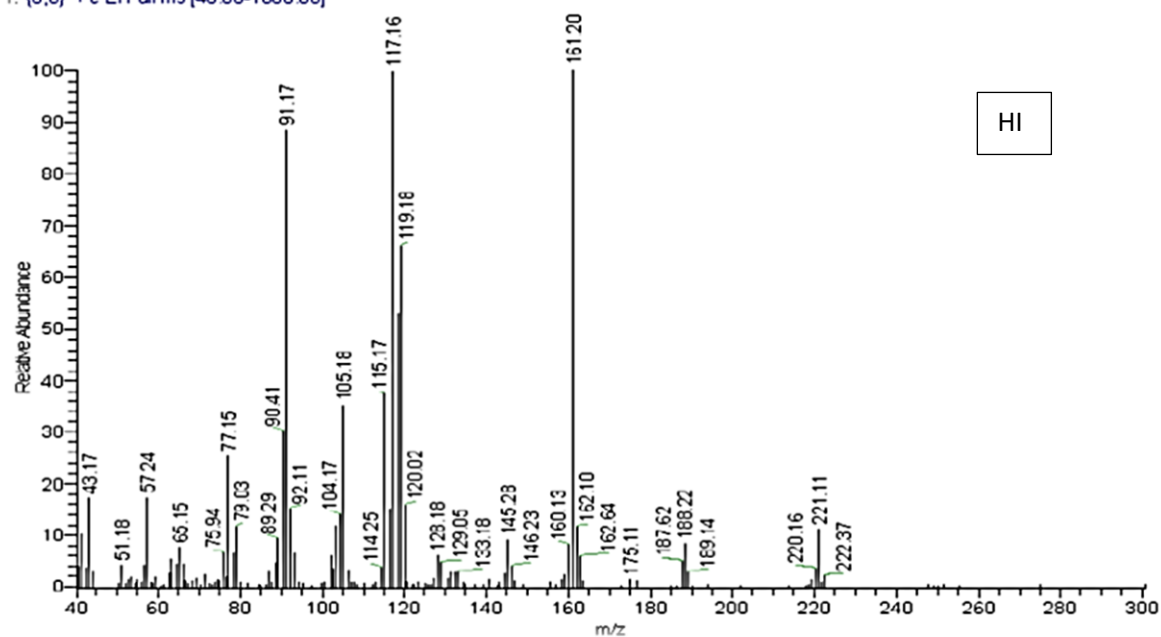


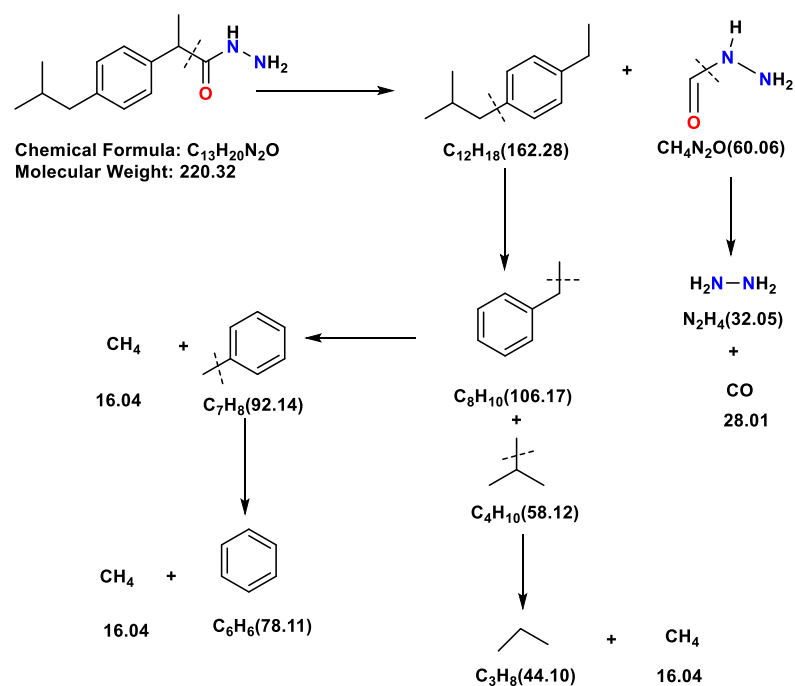
Figure S1: <sup>1</sup>H NMR spectrum of Hydrazide Ibuprofen (HI).



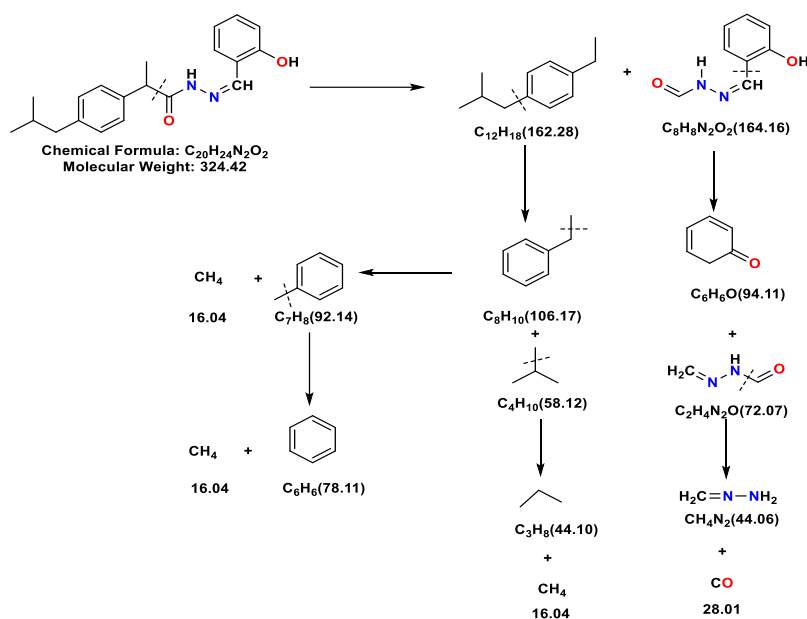
RT: 0.99 - 2.11 SM: 15G

NL:  
1.02E6  
TIC MS  
hossam-  
hamdy-N-  
hydrozide-1hossam-hamdy-N-hydrozide-1 #93 RT: 1.57 AV: 1 SB: 2 2.71, 2.71 NL: 7.10E4  
T: (0,0) + c EI Full ms [40.00-1000.00]

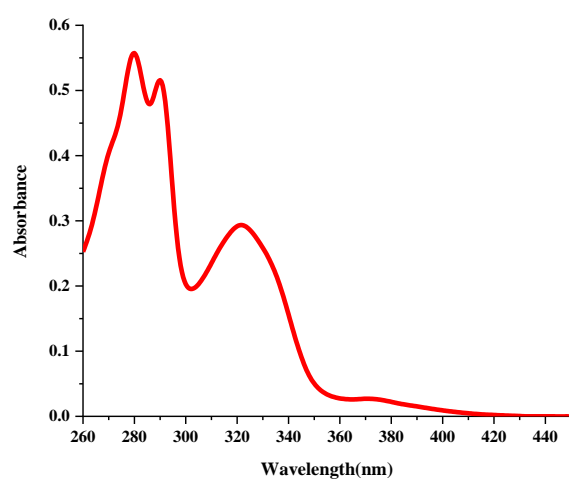
**Figure S2:** Chromatogram and mass spectrum of the Ibuprofen hydrazone (**HL**) and hydrazide (**HI**).



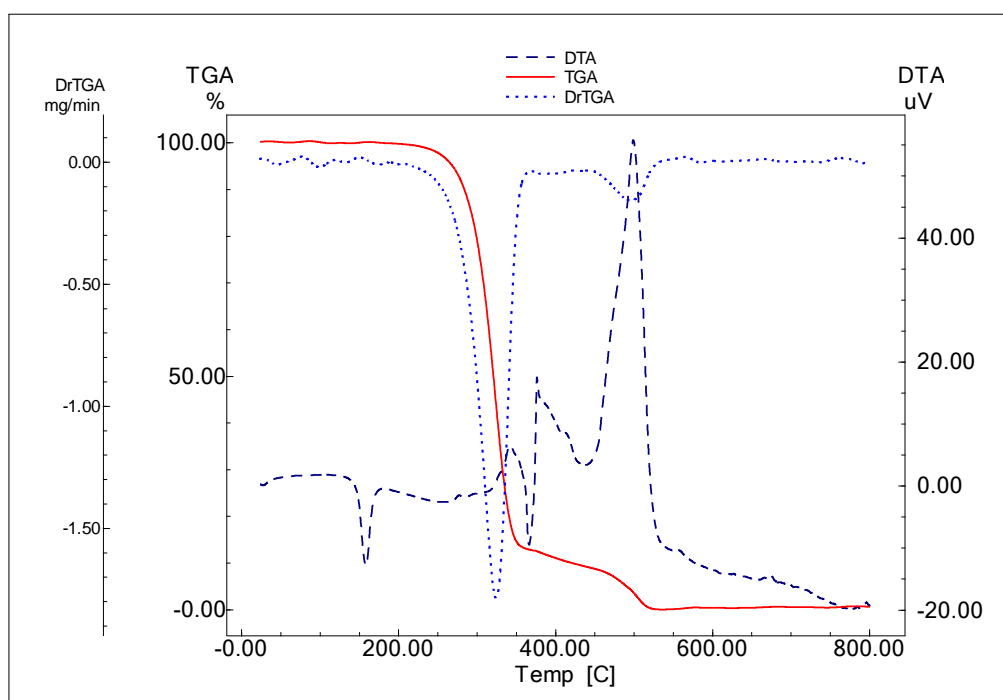
**Scheme S1:** The chromatogram of pathway fragmentation of Hydrazide Ibuprofen (**HI**).



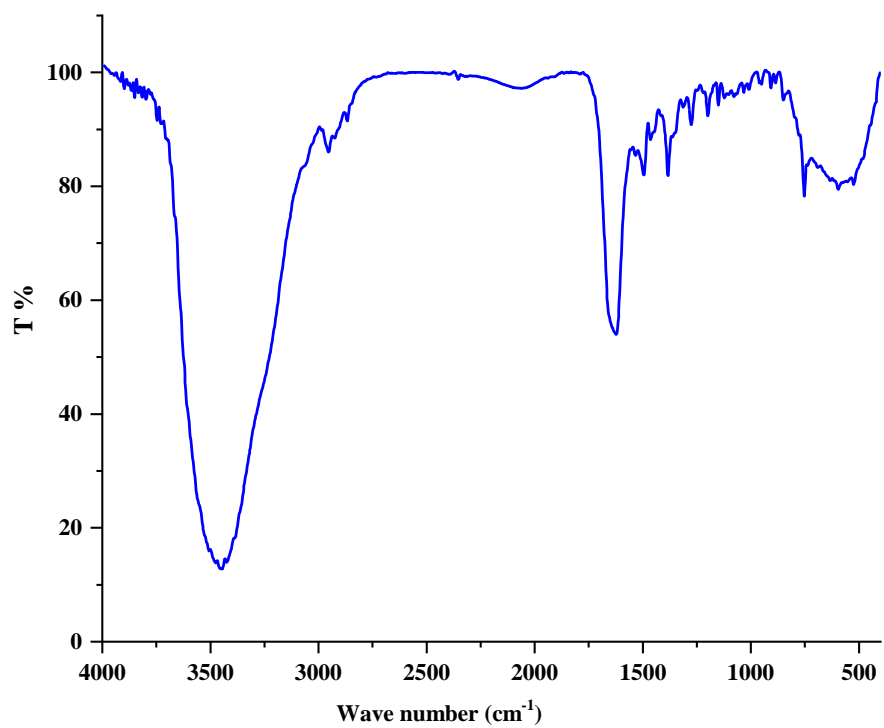
**Scheme S2:** The chromatogram of pathway fragmentation of **HL** ligand.



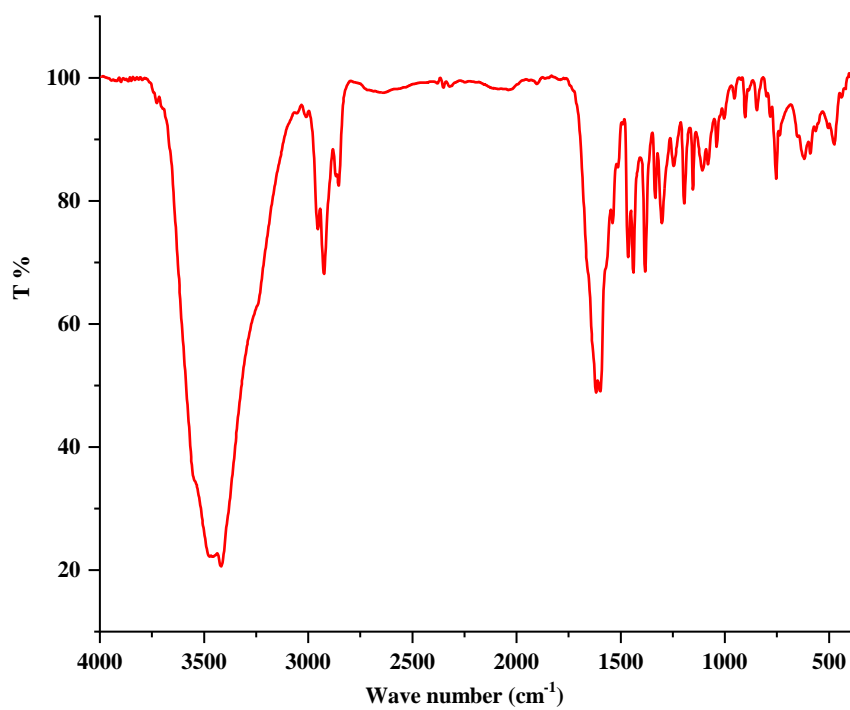
**Figure S3:** UV-Vis. Spectrum of the ligand **HL**.



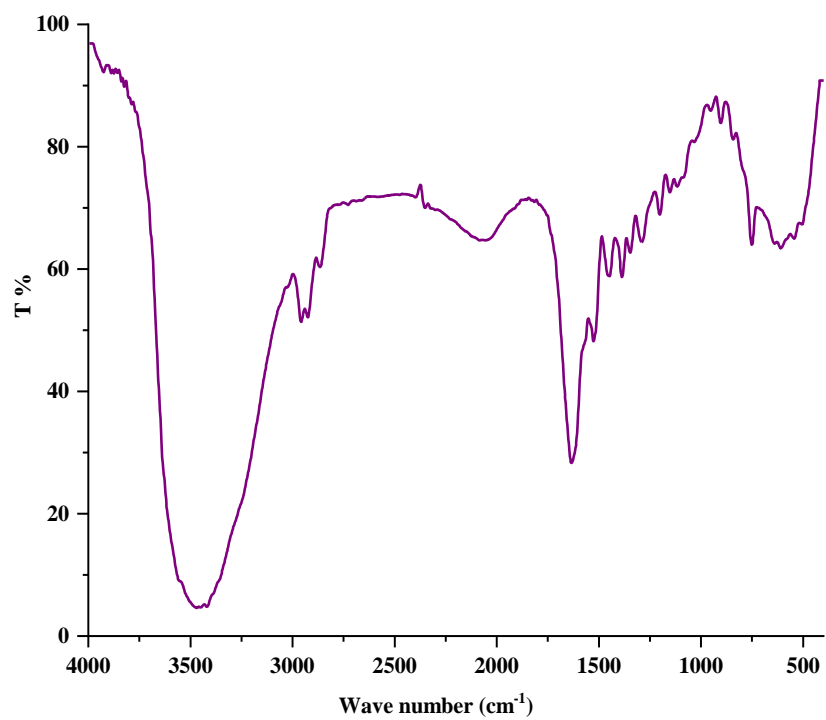
**Figure S4:** Thermal decomposition of Schiff base **HL**.



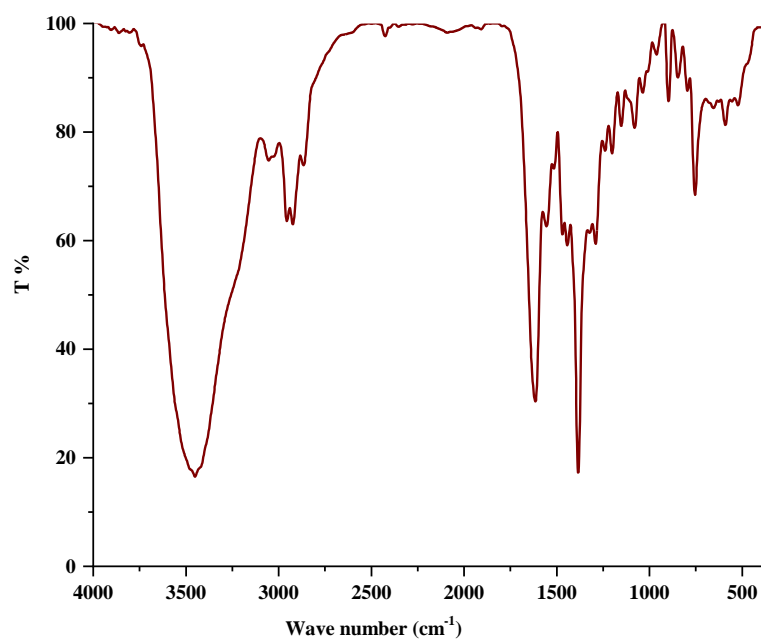
**Figure S5:** FTIR spectrum of [Cu(L)(H<sub>2</sub>O)]Cl.2H<sub>2</sub>O complex.



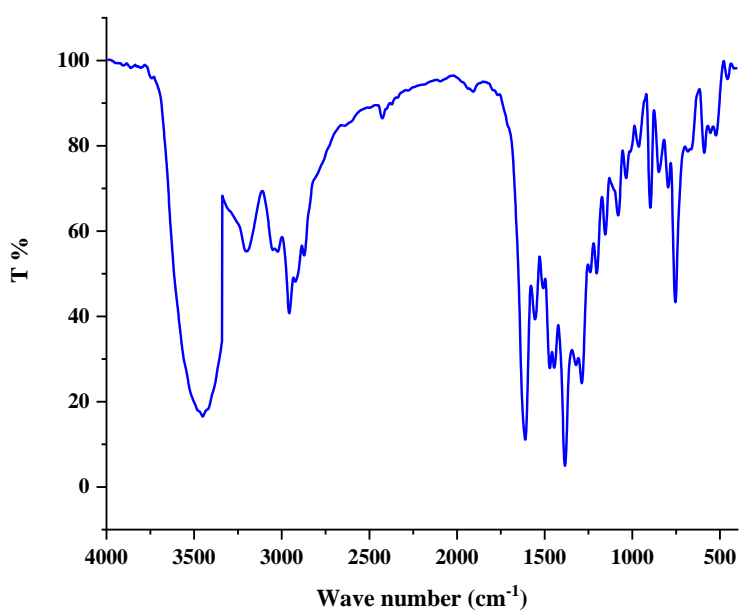
**Figure S6:** FTIR spectrum of [Ni(L)<sub>2</sub>] complex.



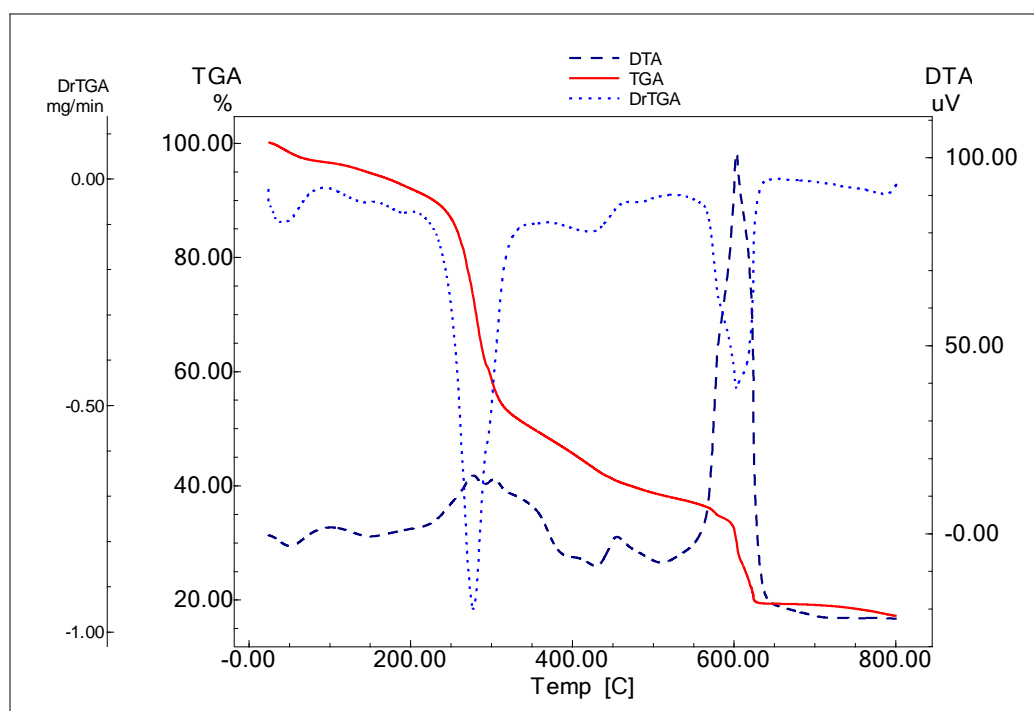
**Figure S7:** FTIR spectrum of [Co(L)<sub>2</sub>]H<sub>2</sub>O complex.



**Figure S8:** FTIR spectrum of [Gd(L)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] (NO<sub>3</sub>)<sub>3</sub>·3H<sub>2</sub>O complex.

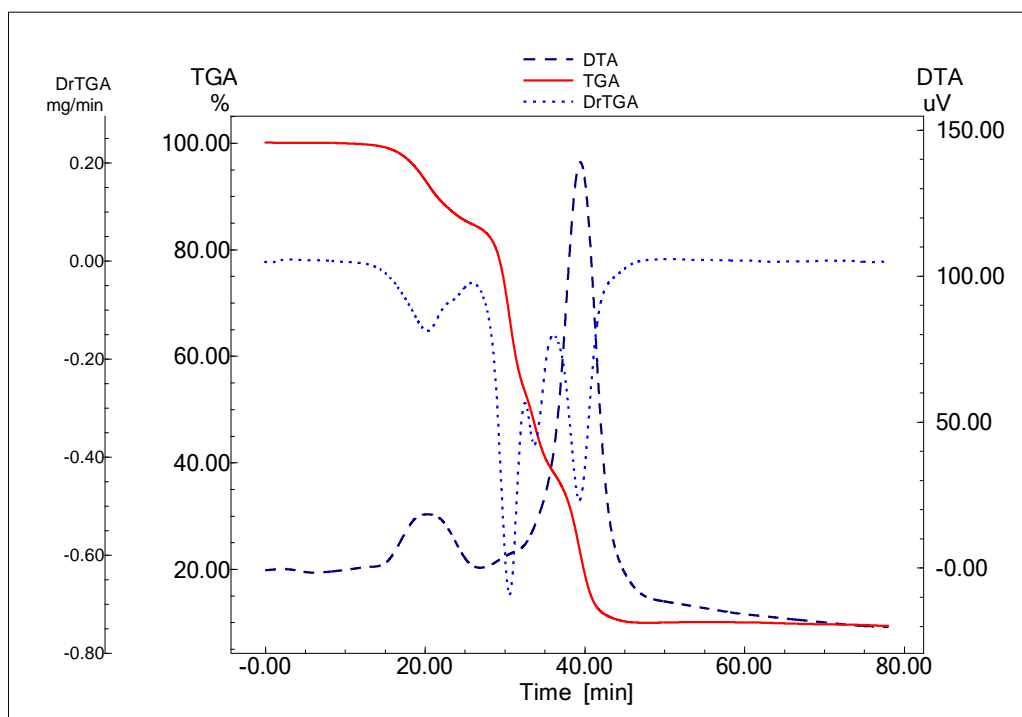


**Figure S9:** FTIR spectrum of  $[\text{Sm}(\text{L})_2(\text{H}_2\text{O})_2] (\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$  complex.

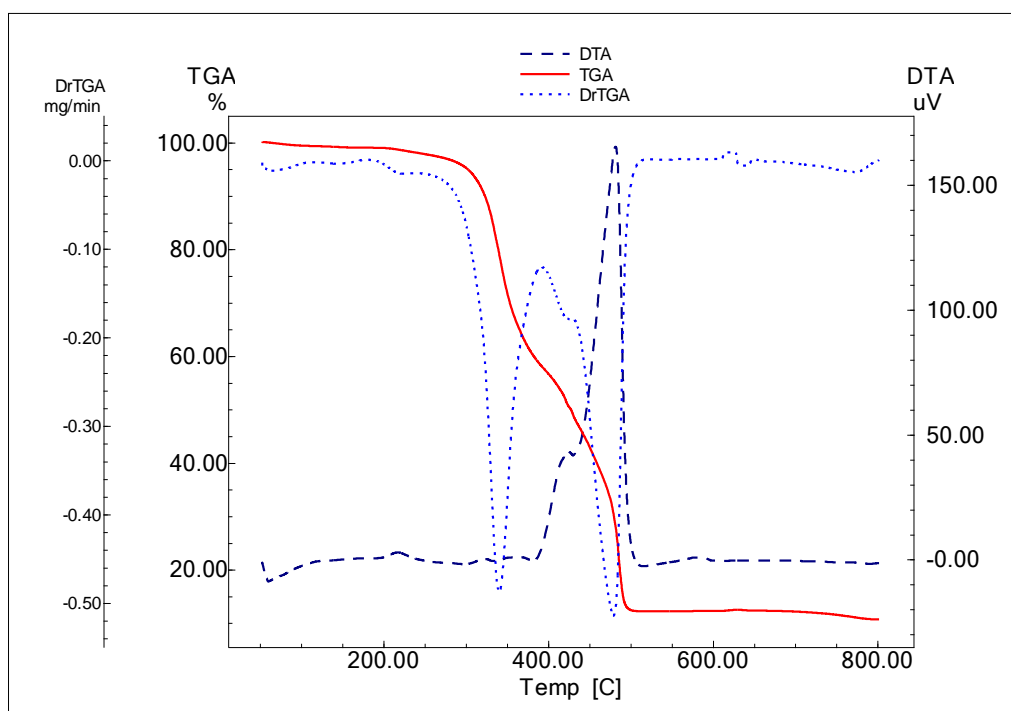


**Figure S10:** TGA/TG and DTA curves of  $[\text{Cu}(\text{L})(\text{H}_2\text{O})]\text{Cl} \cdot \text{H}_2\text{O}$  complex.

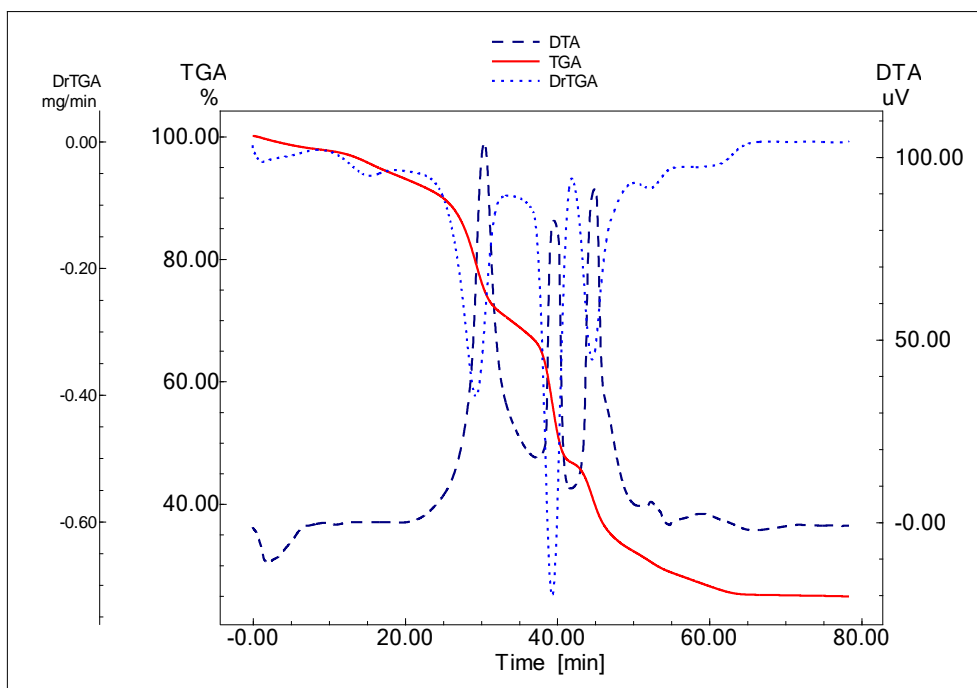




**Figure S11:** TGA/TG and DTA curves of  $[\text{Ni}(\text{L})_2]$  complex.



**Figure S12:** TGA/TG and DTA curves of  $[\text{Co}(\text{L})_2]1/2\text{H}_2\text{O}$  complex.



**Figure S13:** TGA/TG and DTA curves of  $[\text{Sm}(\text{L1})_2(\text{H}_2\text{O})_2](\text{NO}_3) \cdot 2\text{H}_2\text{O}$  complex.

**Table S2:** DTA of Complexes derived from HL Schiff base.

<i>Compound</i>	<i>Temp. range °C</i>	<i>DTA peak temp °C</i>	<i>Peak type</i>	<i><math>\Delta H</math> (KJ/g)</i>	<i>Process</i>
$[\text{Cu}(\text{L})(\text{H}_2\text{O})]\text{Cl} \cdot \text{H}_2\text{O}$	28-156	55	Endo	0.058	Dehydration+ Coordination sphere
	160-514	278	Exo	-0.997	ligand degradation + Coordination sphere
	520-800	603	Exo	-2.24	Final degradation
$[\text{Ni}(\text{L})_2]$	119-300	235	Exo	-1.21	Ligand degradation
	311-786	449	Exo	-6.17	End degradation
$[\text{Co}(\text{L})_2] \cdot 1/2\text{H}_2\text{O}$	55-150	60	Endo	0.311	Dehydration
	156-278	218	Exo	-0.109	ligand degradation
	435-495	481	Exo	-7.9	Final degradation
	24-210	116	Endo	0.231	Dehydration

[Gd(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> (NO <sub>3</sub> ) <sub>2</sub> · 3/2H <sub>2</sub> O]	307- 436	344, 412	Exo	-3.48	Coordination sphere+ Partial Ligand degradation
	436- 550	509	Exo	-0.698	Ligand degradation
	569- 727	627	Exo	-1.01	Final degradation
[Sm(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> (NO <sub>3</sub> ) <sub>2</sub> · (NO <sub>3</sub> ) <sub>2</sub> ·2H <sub>2</sub> O]	65-182	128	Endo	0.099	Dehydration + Coordination sphere
	320- 350	345	Exo	-2.21	Coordination sphere+ Ligand degradation
	440- 469	446	Exo	-0.545	Ligand degradation
	474- 486	492,554	Exo	-1.14	Final degradation

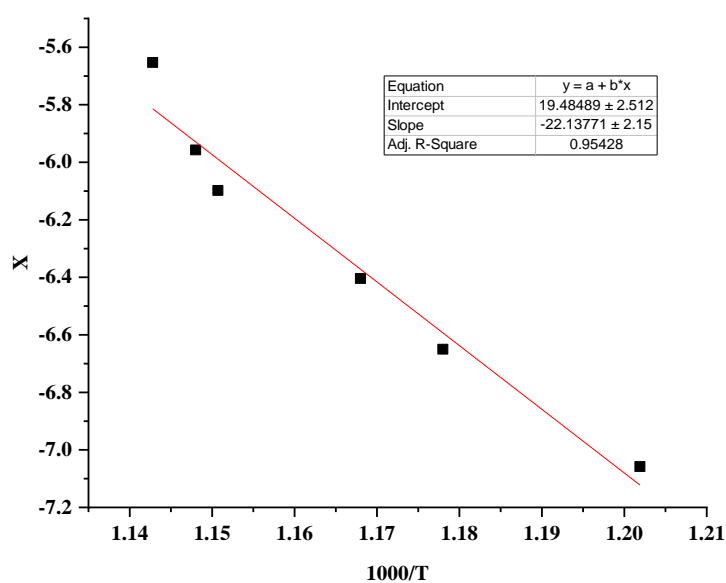
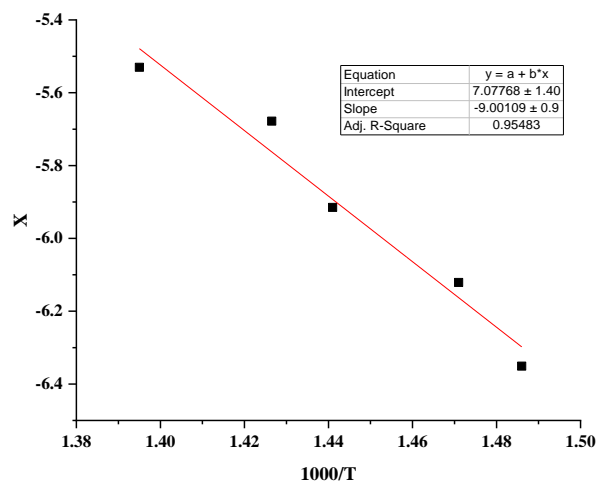
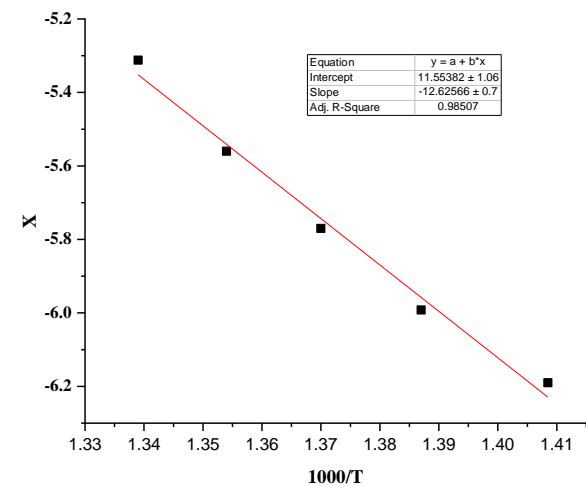


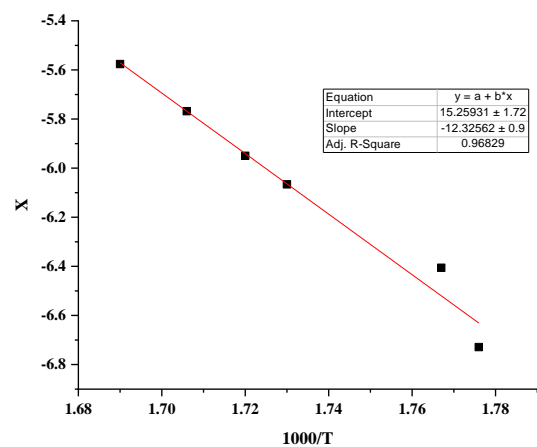
Figure S14: The fit-linear curve of the liberation of coordinate water step of **Cu-L1** complex.



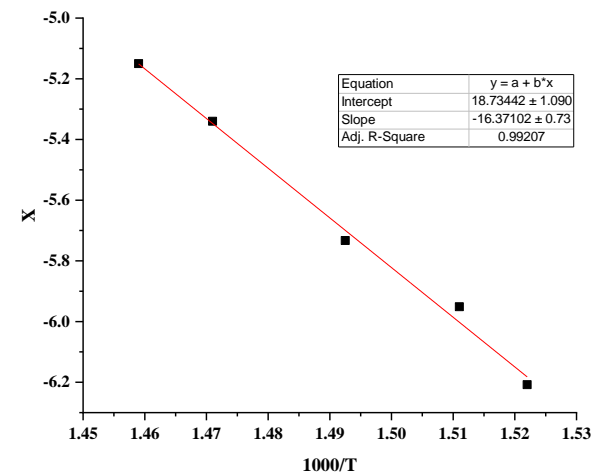
**Figure S15:** Fit-linear curve of liberation of coordinate water step of **Ni-L1** complex.



**Figure S16:** Fit-linear curve of liberation of coordinate water step of **Co-L1** complex.



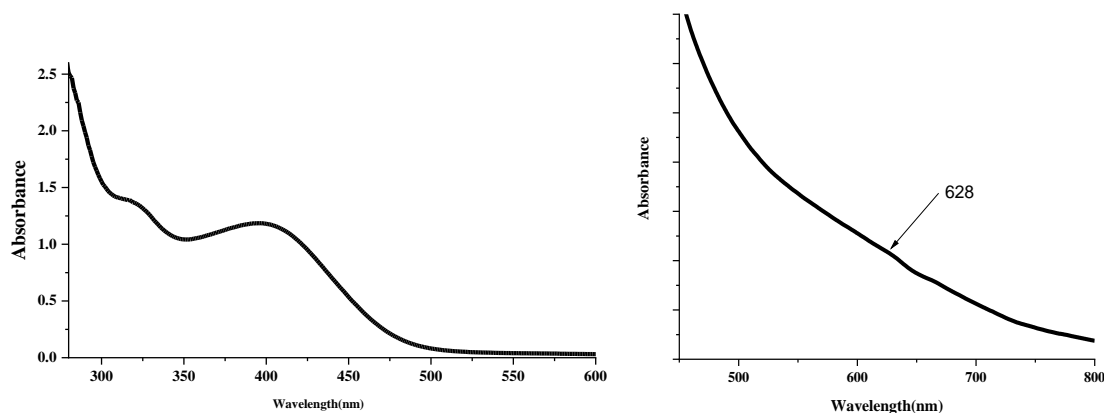
**Figure S17:** Fit-linear curve of liberation of coordinate water step of **Gd-L1** complex.

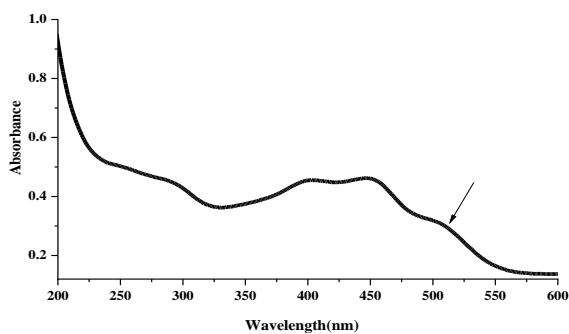


**Figure S18:** Fit-linear curve of liberation of coordinate water step of **Sm-L1** complex.

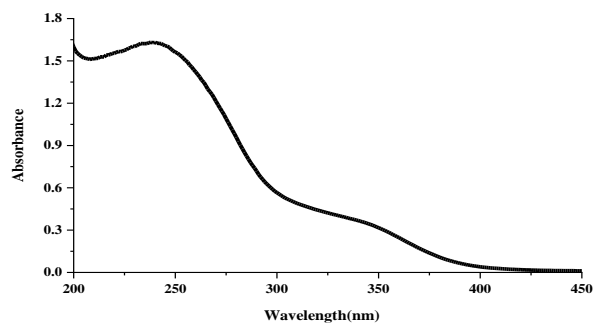
**Table S3:** The electronic spectra and magnetic features of the **HL** ligand and its complexes.

Compound	Peak		$\epsilon^*$ ( $M^{-1}cm^{-1}$ ) $\times 10^4$	Assignment	10Dq		$\mu_{eff}$ ( $\mu_B$ )	Postulated Structure
	nm	$cm^{-1}$			$cm^{-1}$	kJ/mol		
HL	280	35714	5.57	$\pi \rightarrow \pi^*$	---	---	---	---
	290	34482	5.12					
	322	31055	2.94	$n \rightarrow \pi^*$				
L-Cu	292	34246	2.27	$\pi \rightarrow \pi^*$	16556	201	1.49	Square planar
	363	27548	2.7	$n \rightarrow \pi^*$				
	404	24752	2.78	CT				
	451	22172	11.86					
	600	16556	0.05	d-d				
	L-Ni	317	31545	13.72				
400		25188	11.88	CT				
628		24875	9.25	${}^3A_{2g} \rightarrow {}^1E_g$				
L-Co	290	34482	4.43	$\pi \rightarrow \pi^*$	19762	240	5.00	Octahedral
	400	25000	4.58	$n \rightarrow \pi^*$				
	407	24570	4.56	$n \rightarrow \pi^*$				
	450	22222	3.13	CT				
	506	19762	15.87	${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$				
L-Gd	291	34364	3.21	$\pi \rightarrow \pi^*$	---	---	8.97	Bicapped trigonal prismatic / Square antiprismatic
	402	24875	3.25	$n \rightarrow \pi^*$				
	452	22123	4.018	CT				
	504	19841	2.99					
L-Sm	239	41841	16.32	$\pi \rightarrow \pi^*$	---	---	1.33	Bicapped trigonal prismatic / Square antiprismatic
	347	28818	3.41	$n \rightarrow \pi^*$				

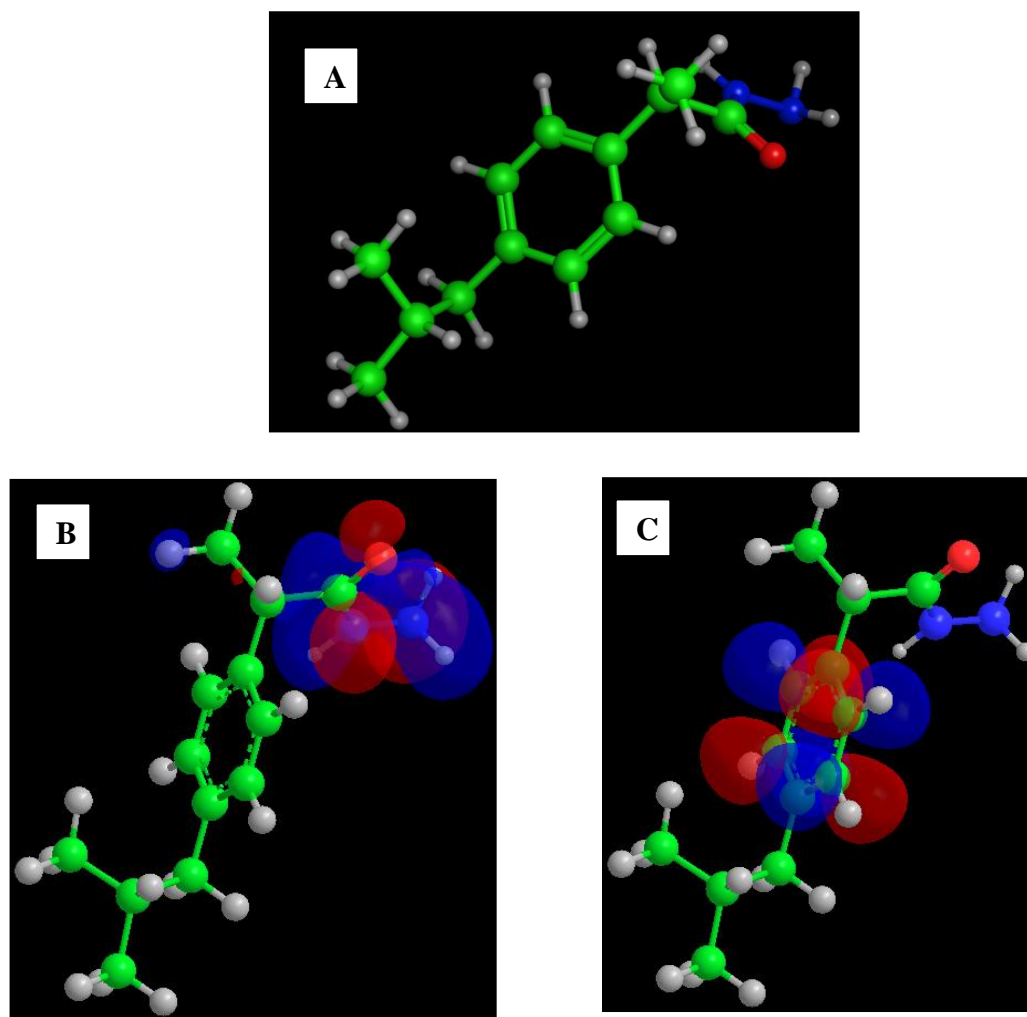
\*  $\epsilon$ = Absorptivity,  $10^{-5}$  M in DMSO,  $M^{-1}cm^{-1}$ .**Figure S19:** UV-Vis. spectrum of L1-Ni.



**Figure S20:** UV-Vis. spectrum of L1-Co.



**Figure S21:** UV-Vis. spectrum of L1-Sm.

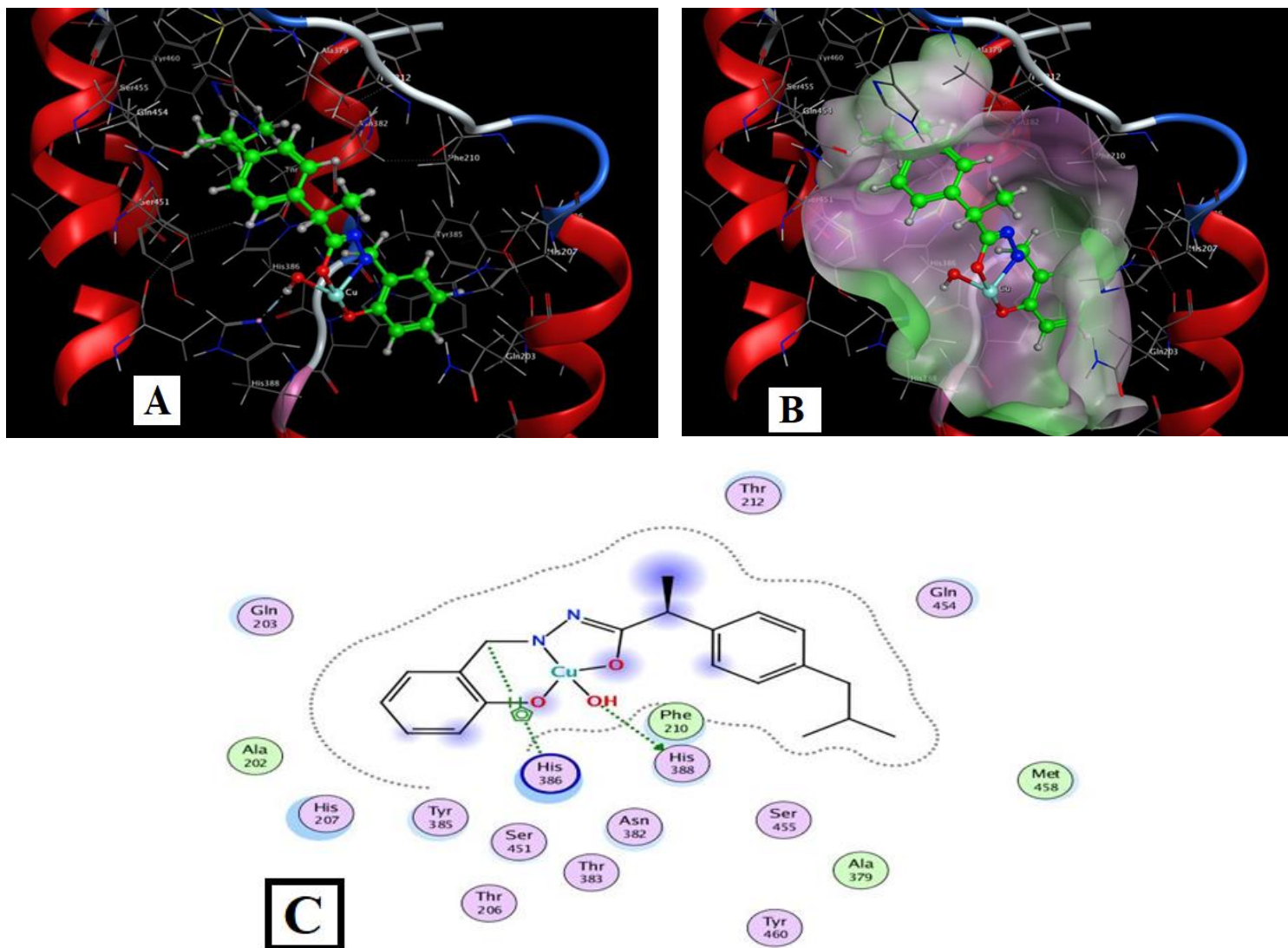


**Figure S22:** The DFT simulation for the Hydrazide Ibuprofen. (A) 3D view, (B) HOMO and (C) LUMO.

**Table S4:** The data from DFT calculations and the properties of synthesized compounds.

COMPOUND	IBUPROFEN	HI	HL
FORMULA	C <sub>13</sub> H <sub>18</sub> O <sub>2</sub>	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> O	C <sub>20</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub>
ATOMS	33	36	48
ORBITALS	78	84	120
ELECTRONS	82	88	126
SCF ENERGY	-93.85 au	-98.24 au	-144.94 AU
DIPOLE	1.94 d	3.37 d	6.20 D
E <sub>LUMO</sub>	0.007	0.0036	-0.012
E <sub>HOMO</sub>	-0.349	-0.351	-0.325
E <sub>LUMO-HOMO</sub>	127.81 nm	128.56 nm	145.36 NM
I (I.E)	0.348 au	0.351 au	0.325 AU
ELECTRON AFFINITY (A)	-0.007 au	-0.004 au	0.012 AU
ABSOLUTE			
ELECTRONEGATIVITY(X)	0.138	0.174	0.168
ABSOLUTE HARDNESS ( )	0.211	0.177	0.157
ABSOLUTE SOFTNESS ( )	4.739	5.640	6.382
GLOBAL SOFTNESS (S)	2.370	2.820	3.191
GLOBAL ELECTROPHILICITY ( )	0.045	0.085	0.090
CHEMICAL POTENTIAL (PI)	-0.138	-0.174	-0.168
ADDITIONAL			
ELECTRONEGATIVITY ( NMAX)	0.654	0.980	1.073
TOXIC.	No	Yes	NO
RSYNTH (%)	66.67	75	79.17
WEIGHT (G/MOL)	206.28	220.32	324.42
	37.30	55.12	61.69
TPSA	Hd Ha	Hd Ha	Hd HA
	1 2	2 2	2 3
LOG P	3.07	1.98	3.84
LOG S	-3.64	-3.90	-5.46

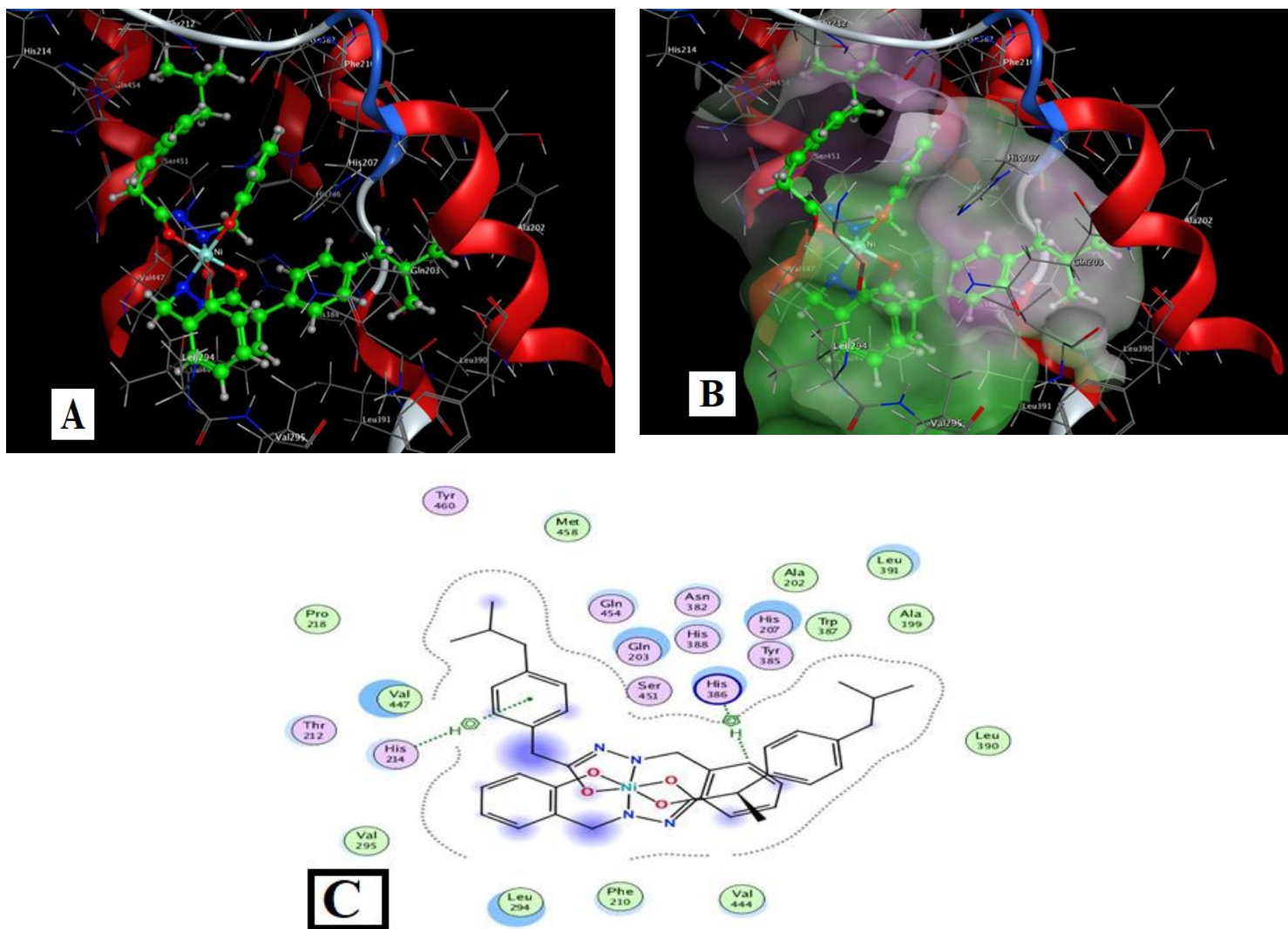
\* **SCF energy**: self-consistent field, **I**: Ionization potential, **Rsynth (%)**: Resynthesized %, **TPSA**: topological polar surface area, **HD**: Hydrogen donor, **HA**: Hydrogen acceptor, **Log p**: lipophilicity parameter and **Log S**: water solubility parameter.



**Figure S23:** Docking model of the interaction of **Cu-L1** with *Cox2* [PDB code: 5IKT] bonding sites:

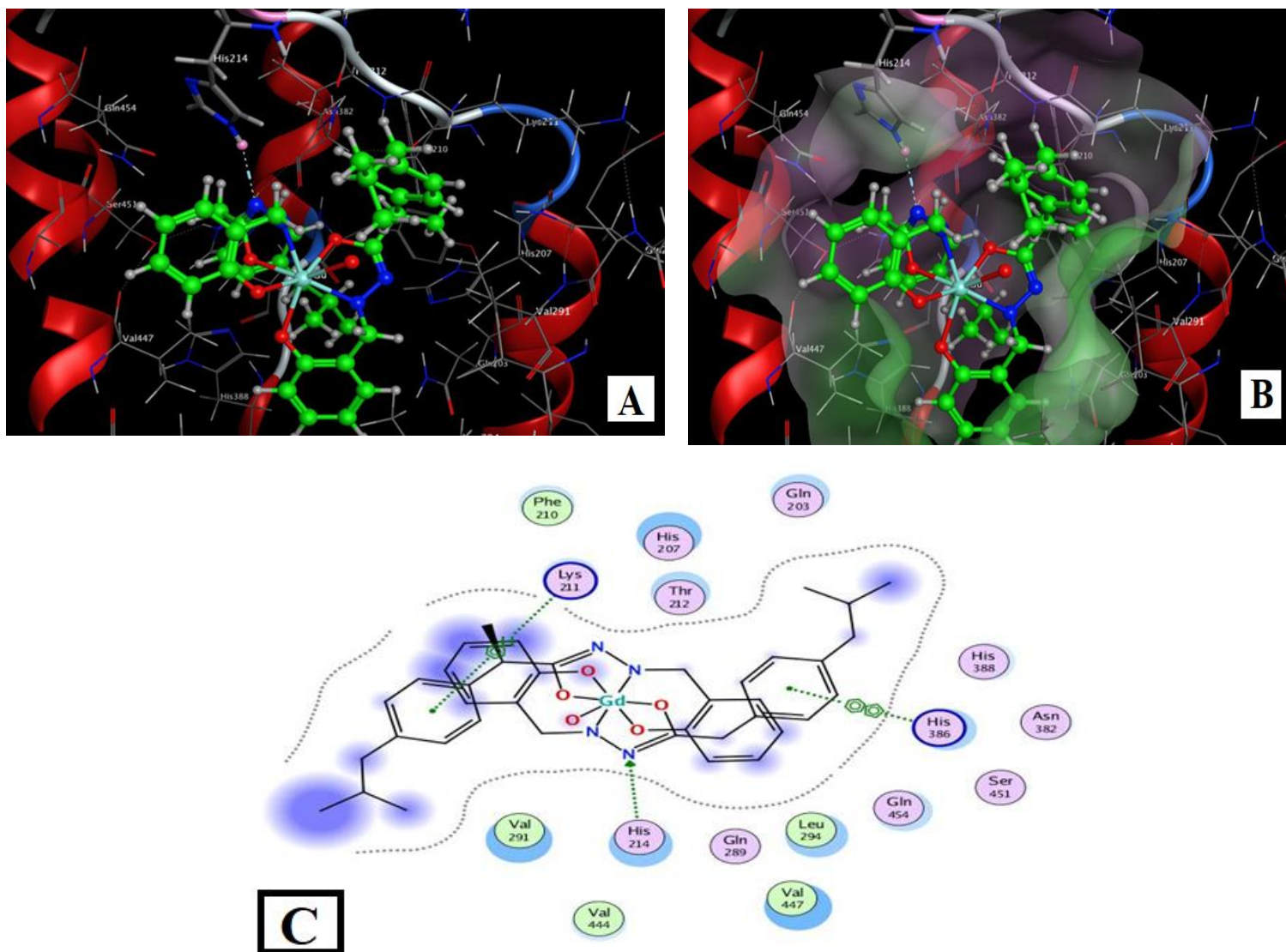
(A) 3D interaction diagram (B) The surface properties [Hydrophilic sites (violet color), neutral sites (white color) and lipophilic sites (green color)]. (C) 2D interaction diagram





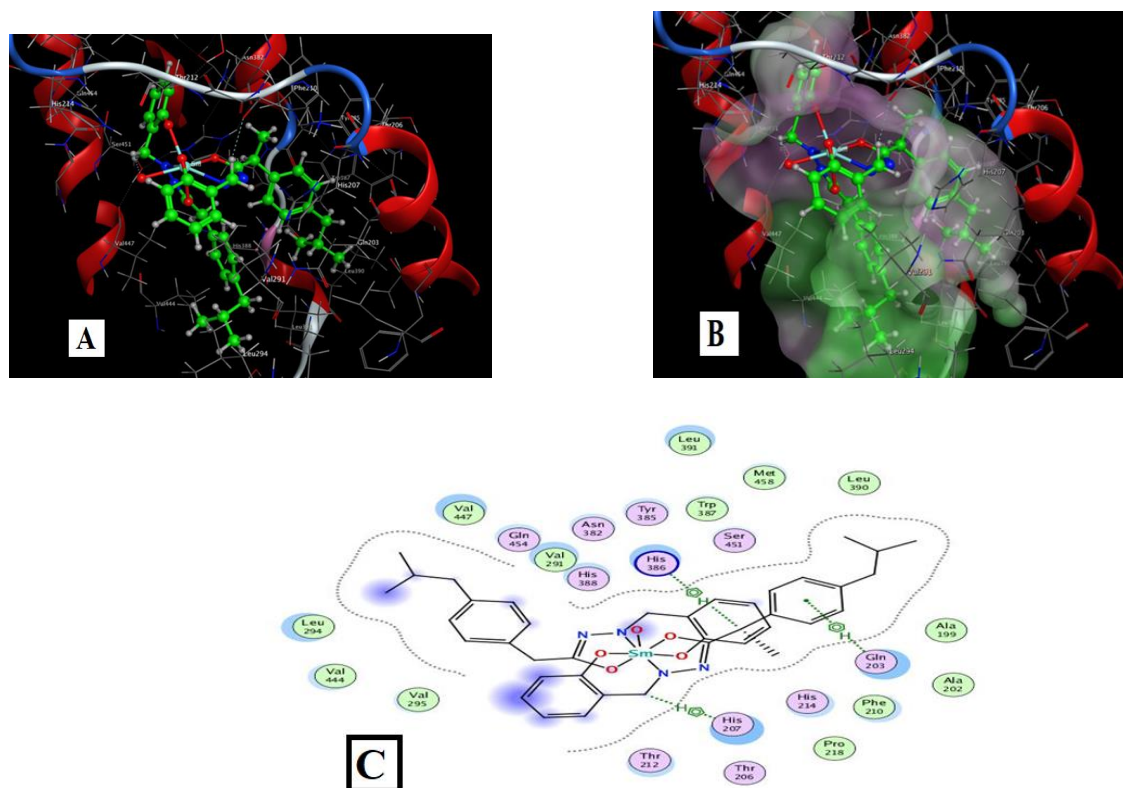
**Figure S24:** Docking model of the interaction of Ni-L1 with Cox2 [PDB code: 5IKT] bonding sites:

(A) 3D interaction diagram (B) The surface properties [Hydrophilic sites (violet color), neutral sites (white color) and lipophilic sites (green color)]. (C) 2D interaction diagram



**Figure S25:** Docking model of the interaction of **Gd-L1** with *Cox2* [PDB code: 5IKT] bonding sites:

(A) 3D interaction diagram (B) The surface properties [Hydrophilic sites (violet color), neutral sites (white color) and lipophilic sites (green color)]. (C) 2D interaction diagram



**Figure S26:** Docking model of the interaction of **Sm-L1** with *Cox2* [PDB code: 5IKT] bonding sites:

(A) 3D interaction diagram (B) The surface properties [Hydrophilic sites (violet color), neutral sites (white color) and lipophilic sites (green color)]. (C) 2D interaction diagram

**Table S5:** In vitro COX-1 and COX-2 inhibition of the synthesized derivatives.

Compound	COX-2 $IC_{50}$ ( $\mu M$ ) <sup>a</sup>
Hydrazide	4.3
Schiff base (L)	4.9
Cu-L	5.6
Ni-L	3.7
Co-L	1.7
Gd-L	2.3
Sm-L	2.9
Ibuprofen	31.4
Indomethacin	0.1
Diclofenac sodium	0.8