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Supplementary Material

Synthesis and Characterization of Novel Copper(II)-Sunitinib Complex: Molecular Docking, DFT Studies, Hirshfeld Analysis and Cytotoxicity Studies

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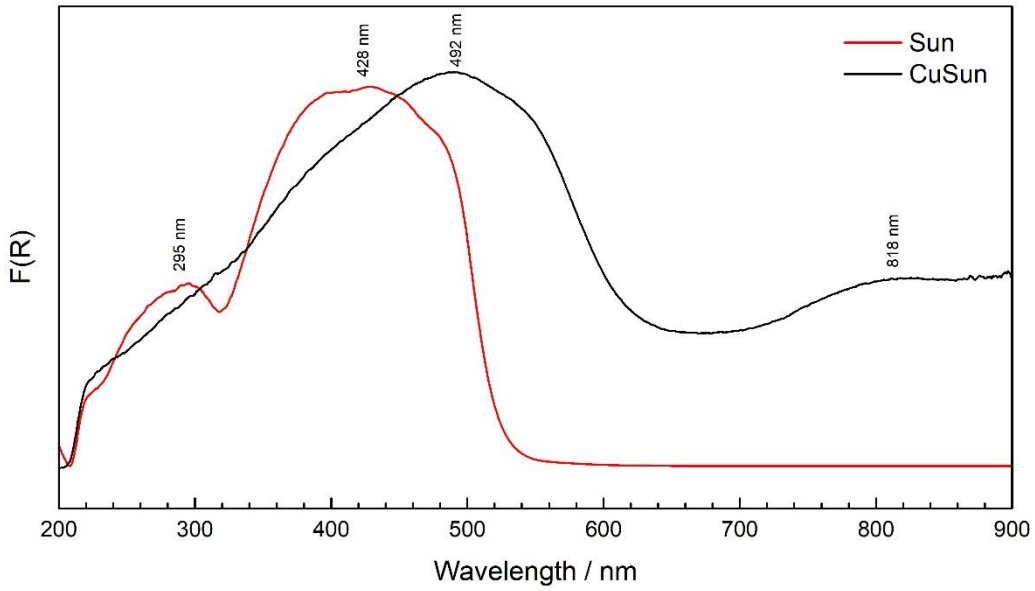

Figure S1. UV-visible reflectance diffuse spectra of solid sunitinib (Sun, in red), and copper(II) complex (CuSun, in black).

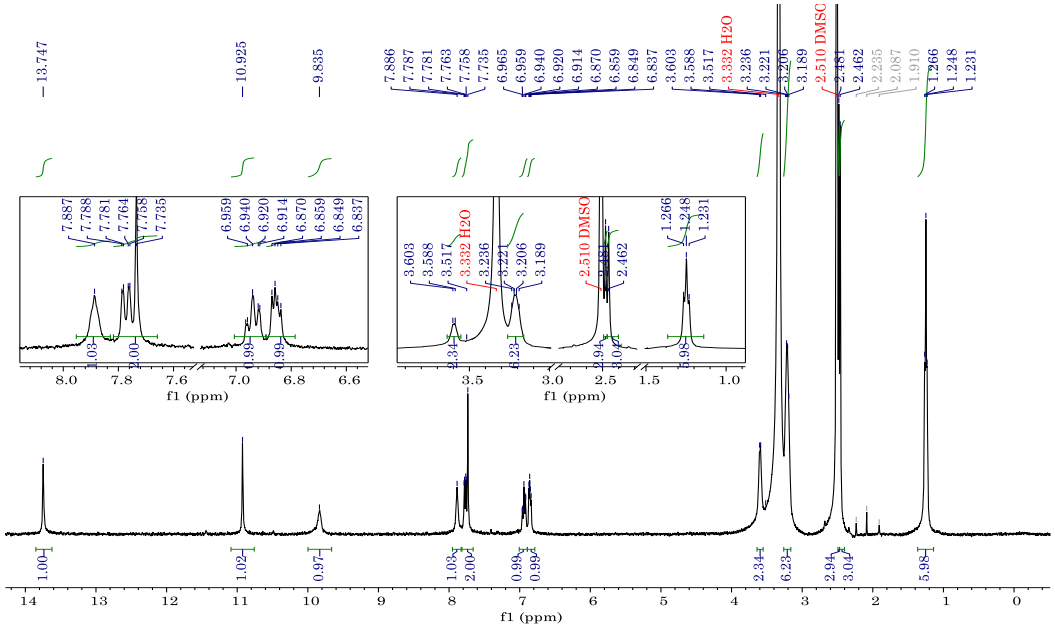

Figure S2. ^{1}H-NMR (400 MHz) spectrum of CuSun (in DMSO-d$_6$). Chemical shifts are marked in blue for complex and in red for solvent and impurities in the upper zone. Green curves show the integration area, values are in blue under each peak.

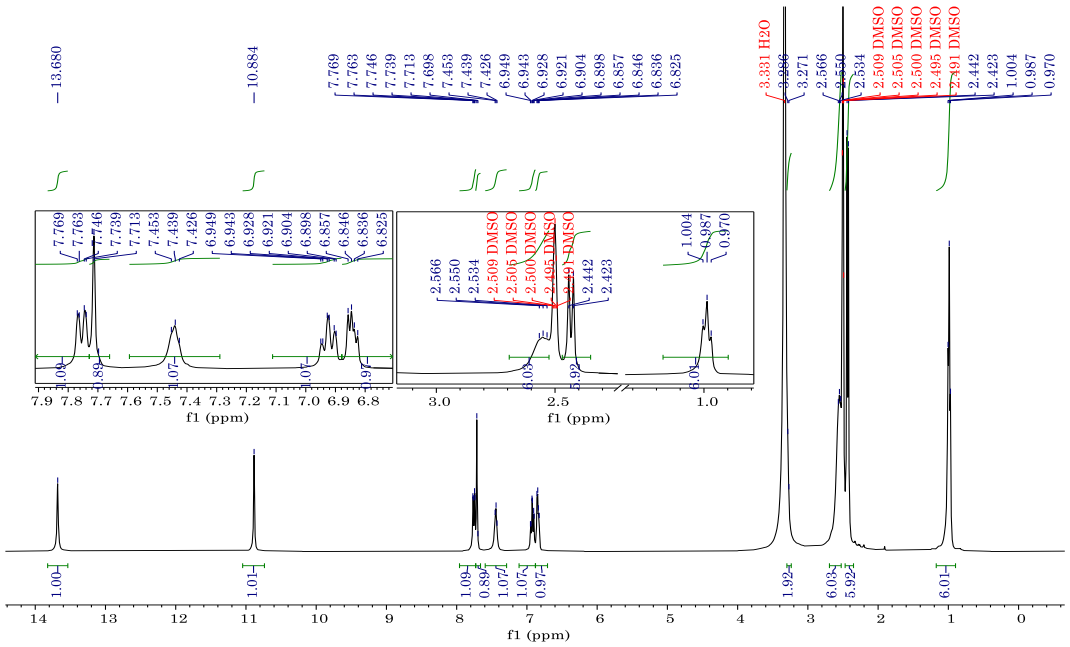

Figure S3. ^{1}H-NMR (400 MHz) spectrum of sunitinib (in DMSO-d$_6$). Chemical shifts are marked in blue for complex and in red for solvent and impurities in the upper zone. Green curves show the integration area, values are in blue under each peak.

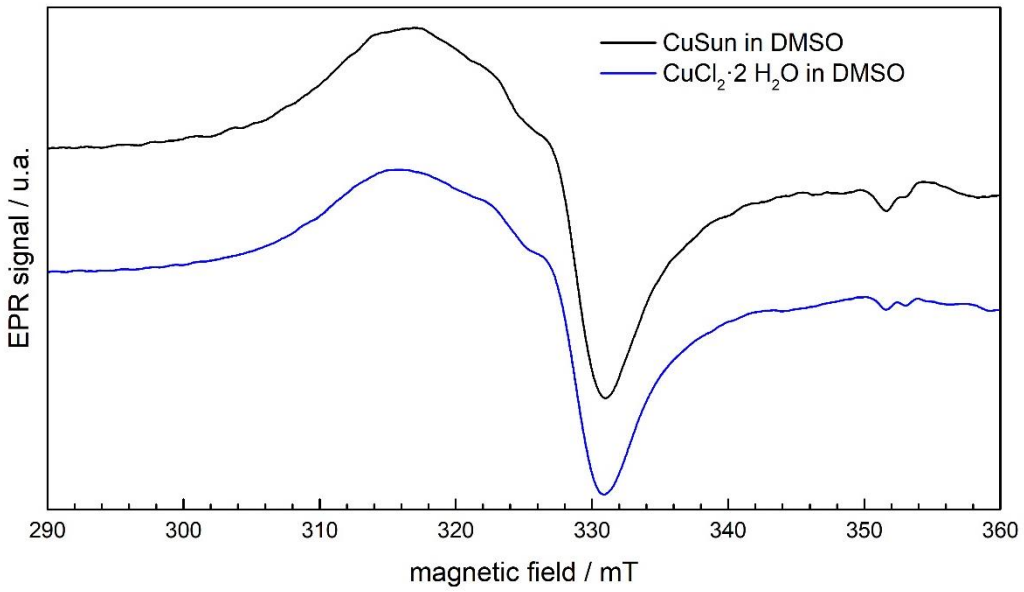

Figure S4. Band-X EPR spectra in DMSO solution of CuSun (in black) and $CuCl_2.2H_2O$ (in blue).

Table S1. Hydrogen bond distances and angles for trichlorosunitinibcopper(II) (CuSun) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(14)-H(14A)...Cl(1)	0.96	2.65	3.573(4)	160.7
N(1)-H(1N)...Cl(3)	0.78(4)	2.59(4)	3.240(3)	142(3)
N(2)-H(2N)...O(1)	0.85(1)	1.95(2)	2.728(3)	151(3)
N(3)-H(3N)...Cl(3)#1	0.85(1)	2.93(3)	3.580(3)	135(3)
C(4)-H(4)...Cl(2)#2	0.92(4)	2.98(4)	3.885(4)	167(3)
N(4)-H(4N)...O(2)	0.85(1)	1.87(2)	2.666(4)	157(3)
C(18)-H(18B)...Cl(2)#3	0.88(4)	2.86(4)	3.645(4)	149(3)
C(20)-H(20A)...Cl(1)#4	0.92(4)	2.95(4)	3.724(5)	143(3)
C(20)-H(20B)...Cl(2)#5	0.92(4)	2.96(4)	3.756(4)	146(3)

Symmetry transformations used to generate equivalent atoms: (#1) -x+1, -y+1, -z+1; (#2) -x+2, -y+1, -z+1; (#3) x-1, y+1, z; (#4) x, y+1, z; (#5) -x+1, -y+1, -z.

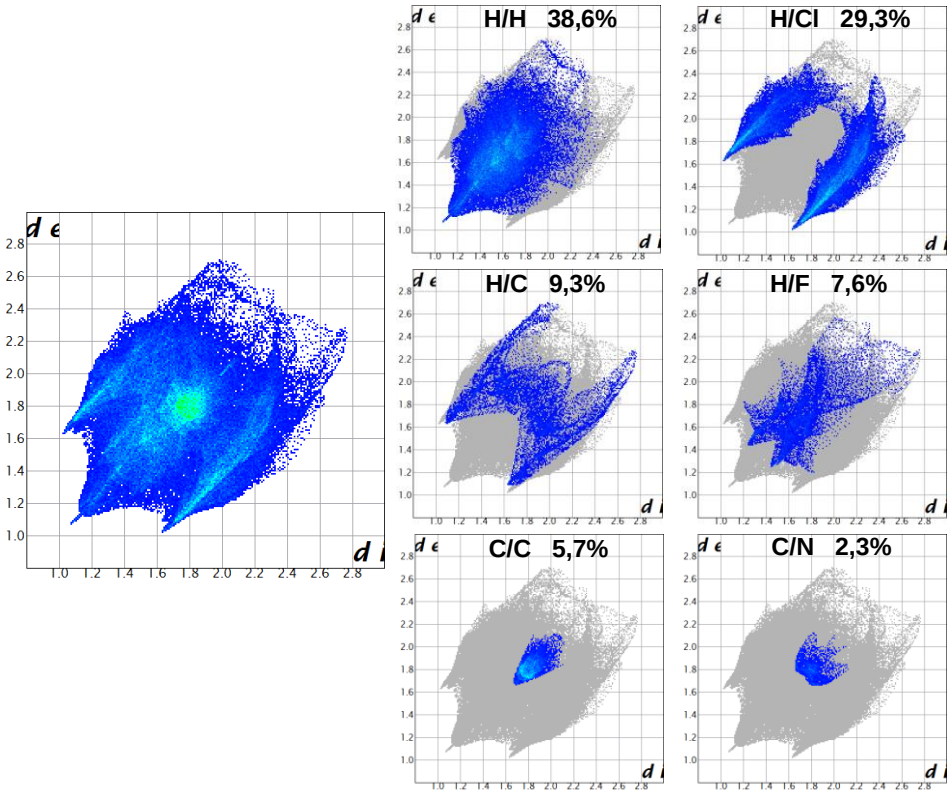

Figure S5. Fingerprint plots for CuSun, along with splitting for the specific contributions of each pair of elements for close contacts.

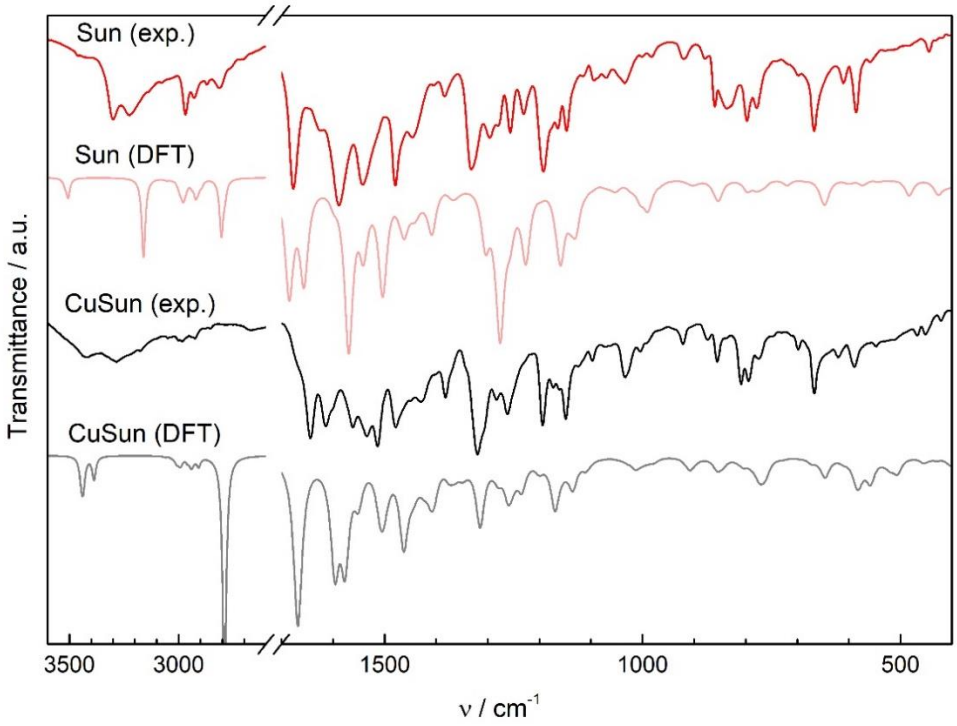

Figure S6. Experimental and calculated (by DFT) FTIR spectra of sunitinib (Sun, in red), and copper(II) complex (CuSun, in black). Theoretical spectra have been obtained using a scaling factor of 0.9530 according to [42].

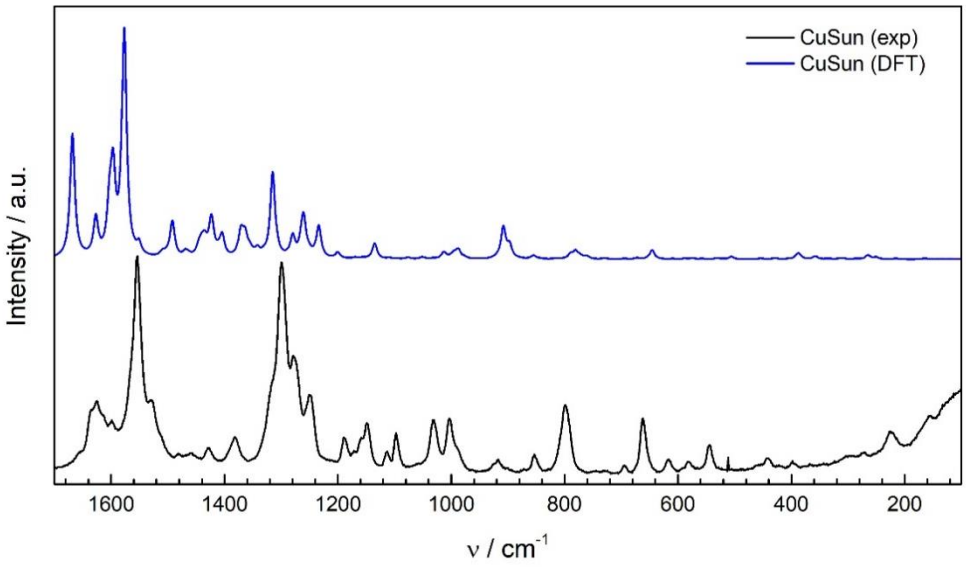

Figure S7. Experimental and calculated (by DFT) Raman specta of CuSun. The theoretical spectrum have been obtained using a scaling factor of 0.9530 according to [42].

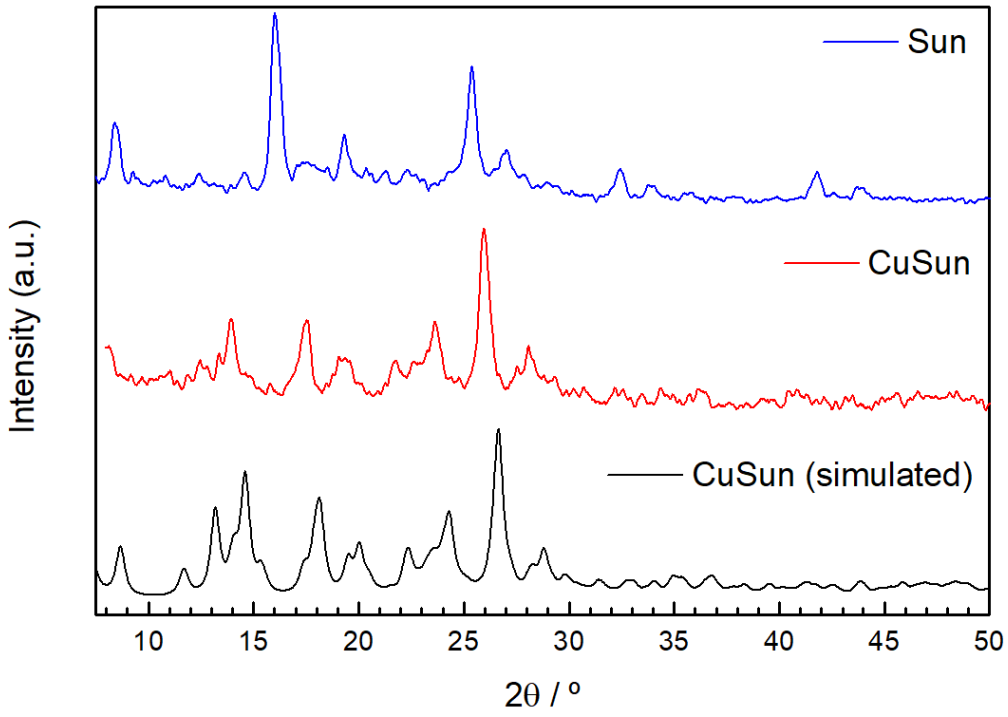

Figure S8. XRD pattern of sunitinib (Sun, blue), experimental (CuSun, red), and simulated (CuSun simulated, black) copper(II) complex.

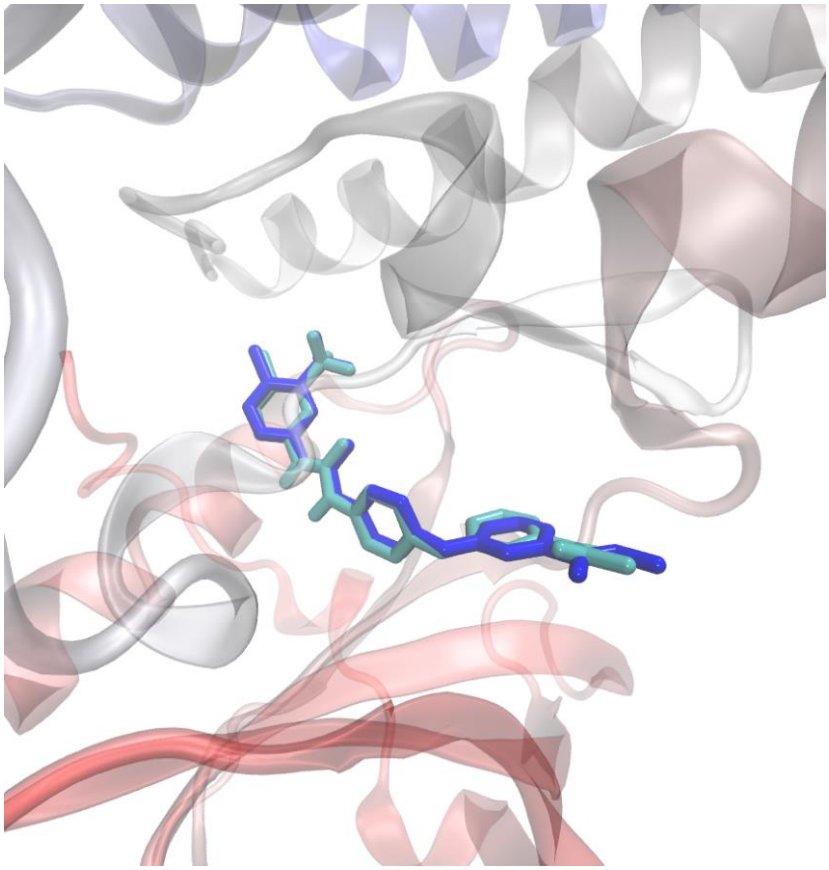

Figure S9. Superposition of the sorafenib structures obtained by X-ray diffraction (PDB ID: 3WZE, blue), and the lowest energy binding mode obtained by molecular docking (cyan). RMSD = 0,81 Å.

Table S2. Full bond lengths [Å] and angles [°] for trichlorosunitinibcopper(II).

C(1)-O(1)	1.258(4)	**C(8)-C(3)-C(2)**	107.6(3)
C(1)-N(1)	1.349(4)	**C(5)-C(4)-C(3)**	117.5(3)
C(1)-C(2)	1.462(4)	**F-C(5)-C(4)**	119.0(3)
C(2)-C(9)	1.366(4)	**F-C(5)-C(6)**	117.3(3)
C(2)-C(3)	1.469(4)	**C(4)-C(5)-C(6)**	123.6(3)
C(3)-C(4)	1.384(5)	**C(5)-C(6)-C(7)**	119.6(3)
C(3)-C(8)	1.400(5)	**C(8)-C(7)-C(6)**	116.9(4)
C(4)-C(5)	1.366(5)	**C(7)-C(8)-N(1)**	128.9(3)
C(5)-F	1.359(4)	**C(7)-C(8)-C(3)**	123.1(3)
C(5)-C(6)	1.388(5)	**N(1)-C(8)-C(3)**	108.0(3)
C(6)-C(7)	1.389(5)	**C(2)-C(9)-C(10)**	133.2(3)
C(7)-C(8)	1.382(5)	**N(2)-C(10)-C(9)**	125.5(3)
C(8)-N(1)	1.400(4)	**N(2)-C(10)-C(11)**	106.8(2)
C(9)-C(10)	1.406(4)	**C(9)-C(10)-C(11)**	127.7(3)
C(10)-N(2)	1.389(4)	**C(12)-C(11)-C(10)**	106.6(3)
C(10)-C(11)	1.411(4)	**C(12)-C(11)-C(15)**	128.2(3)
C(11)-C(12)	1.409(4)	**C(10)-C(11)-C(15)**	125.1(3)
C(11)-C(15)	1.482(4)	**C(13)-C(12)-C(11)**	107.8(3)

C(12)-C(13)	1.406(4)	**C(13)-C(12)-C(16)**	121.8(3)
C(12)-C(16)	1.472(4)	**C(11)-C(12)-C(16)**	130.3(3)
C(13)-N(2)	1.334(4)	**N(2)-C(13)-C(12)**	107.9(3)
C(13)-C(14)	1.490(4)	**N(2)-C(13)-C(14)**	121.8(3)
C(16)-O(2)	1.238(4)	**C(12)-C(13)-C(14)**	130.3(3)
C(16)-N(3)	1.333(4)	**O(2)-C(16)-N(3)**	120.3(3)
C(17)-N(3)	1.455(5)	**O(2)-C(16)-C(12)**	120.0(3)
C(17)-C(18)	1.510(5)	**N(3)-C(16)-C(12)**	119.7(3)
C(18)-N(4)	1.497(4)	**N(3)-C(17)-C(18)**	114.6(3)
C(19)-C(21)	1.480(6)	**N(4)-C(18)-C(17)**	113.0(3)
C(19)-N(4)	1.511(5)	**C(21)-C(19)-N(4)**	113.1(3)
C(20)-N(4)	1.500(5)	**N(4)-C(20)-C(22)**	112.7(3)
C(20)-C(22)	1.486(6)	**C(1)-N(1)-C(8)**	111.3(3)
O(1)-Cu	2.082(2)	**C(13)-N(2)-C(10)**	110.9(3)
Cu-Cl(1)	2.179(1)	**C(16)-N(3)-C(17)**	122.9(3)
Cu-Cl(2)	2.193(1)	**C(18)-N(4)-C(20)**	112.6(3)
Cu-Cl(3)	2.231(1)	**C(18)-N(4)-C(19)**	111.5(3)
		C(20)-N(4)-C(19)	111.8(3)
O(1)-C(1)-N(1)	123.6(3)	**C(1)-O(1)-Cu**	130.6(2)
O(1)-C(1)-C(2)	128.2(3)	**O(1)-Cu-Cl(1)**	93.48(7)
N(1)-C(1)-C(2)	108.1(3)	**O(1)-Cu-Cl(2)**	121.29(8)
C(9)-C(2)-C(1)	129.7(3)	**Cl(1)-Cu-Cl(2)**	104.24(4)
C(9)-C(2)-C(3)	125.3(3)	**O(1)-Cu-Cl(3)**	100.23(7)
C(1)-C(2)-C(3)	105.0(3)	**Cl(1)-Cu-Cl(3)**	133.95(5)
C(4)-C(3)-C(8)	119.2(3)	**Cl(2)-Cu-Cl(3)**	105.39(5)
C(4)-C(3)-C(2)	133.2(3)		

Table S3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for trichlorosunitinibcopper(II) (CuSun). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
C(1)	8527(4)	3540(3)	5121(2)	35(1)
C(2)	8811(4)	4695(3)	5798(2)	33(1)
C(3)	10174(4)	4684(3)	6784(2)	36(1)
C(4)	11023(5)	5506(3)	7717(3)	43(1)
C(5)	12222(5)	5187(3)	8501(3)	50(1)
C(6)	12641(5)	4095(4)	8406(3)	54(1)
C(7)	11831(5)	3264(3)	7466(3)	49(1)
C(8)	10603(4)	3581(3)	6675(2)	38(1)
C(9)	8028(4)	5615(3)	5601(2)	35(1)
C(10)	6703(4)	5778(3)	4732(2)	33(1)
C(11)	6007(4)	6789(3)	4624(2)	35(1)
C(12)	4738(4)	6533(3)	3610(2)	34(1)

C(13)	4686(4)	5382(3)	3118(2)	35(1)
C(14)	3560(5)	4670(3)	2060(3)	47(1)
C(15)	6589(5)	7896(3)	5427(3)	49(1)
C(16)	3652(4)	7268(3)	3061(2)	36(1)
C(17)	2224(5)	9000(3)	3156(3)	48(1)
C(18)	2779(5)	9472(3)	2370(3)	45(1)
C(19)	285(6)	8630(4)	717(4)	64(1)
C(20)	3362(6)	8924(4)	623(3)	59(1)
C(21)	-494(6)	7520(4)	-39(3)	70(1)
C(22)	5209(6)	8638(4)	984(3)	70(1)
N(1)	9597(4)	2925(3)	5662(2)	40(1)
N(2)	5843(3)	4953(2)	3796(2)	35(1)
N(3)	3440(4)	8280(2)	3617(2)	44(1)
N(4)	2248(4)	8678(2)	1276(2)	44(1)
O(1)	7479(3)	3141(2)	4196(2)	44(1)
O(2)	2949(4)	6948(2)	2087(2)	57(1)
F	13075(3)	5974(2)	9430(2)	74(1)
Cu	7362(1)	1631(1)	3061(1)	44(1)
Cl(1)	5006(1)	1950(1)	1922(1)	61(1)
Cl(2)	9327(1)	1357(1)	2198(1)	65(1)
Cl(3)	7856(2)	465(1)	4083(1)	69(1)

Table S4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for trichlorosunitinibcopper(II) (CuSun). The anisotropic displacement factor exponent takes the form: $-2p^2[h^2a^*2U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	37(2)	38(2)	31(2)	6(1)	13(1)	2(1)
C(2)	36(2)	37(2)	24(1)	5(1)	9(1)	1(1)
C(3)	36(2)	43(2)	28(2)	9(1)	12(1)	3(1)
C(4)	47(2)	45(2)	33(2)	5(2)	11(2)	6(2)
C(5)	46(2)	62(2)	28(2)	1(2)	1(2)	2(2)
C(6)	47(2)	64(3)	44(2)	19(2)	-1(2)	6(2)
C(7)	46(2)	47(2)	53(2)	20(2)	9(2)	5(2)
C(8)	36(2)	42(2)	31(2)	7(1)	8(1)	-1(1)
C(9)	40(2)	36(2)	27(2)	3(1)	13(1)	0(1)
C(10)	37(2)	32(2)	26(1)	4(1)	8(1)	0(1)
C(11)	38(2)	37(2)	27(2)	6(1)	10(1)	1(1)
C(12)	37(2)	33(2)	30(2)	7(1)	11(1)	1(1)
C(13)	36(2)	33(2)	30(2)	3(1)	8(1)	2(1)
C(14)	52(2)	35(2)	38(2)	-3(1)	0(2)	5(2)
C(15)	55(2)	41(2)	37(2)	1(2)	0(2)	6(2)
C(16)	39(2)	37(2)	30(2)	7(1)	7(1)	-1(1)
C(17)	53(2)	39(2)	47(2)	5(2)	14(2)	13(2)

C(18)	53(2)	32(2)	41(2)	6(2)	1(2)	4(2)
C(19)	53(2)	59(3)	56(3)	5(2)	-11(2)	16(2)
C(20)	78(3)	55(3)	38(2)	15(2)	10(2)	5(2)
C(21)	58(2)	70(3)	57(2)	-4(2)	-1(2)	-1(2)
C(22)	70(3)	82(3)	55(2)	11(2)	22(2)	4(2)
N(1)	44(2)	32(2)	40(2)	7(1)	8(1)	3(1)
N(2)	41(1)	28(1)	30(1)	3(1)	7(1)	2(1)
N(3)	59(2)	36(2)	31(2)	3(1)	12(1)	12(1)
N(4)	50(2)	34(2)	37(2)	8(1)	-2(1)	9(1)
O(1)	54(1)	36(1)	30(1)	0(1)	4(1)	8(1)
O(2)	84(2)	34(1)	36(1)	4(1)	-3(1)	13(1)
F	76(2)	75(2)	40(1)	-2(1)	-12(1)	8(1)
Cu	51(1)	43(1)	34(1)	9(1)	8(1)	11(1)
Cl(1)	63(1)	55(1)	49(1)	8(1)	-5(1)	16(1)
Cl(2)	61(1)	82(1)	48(1)	9(1)	18(1)	26(1)
Cl(3)	105(1)	46(1)	45(1)	17(1)	4(1)	9(1)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for trichlorosunitinibcopper(II) (CuSun).

Atom	x	y	z	U(eq)
H(14A)	3656	3892	2025	71
H(14B)	3955	4846	1514	71
H(14C)	2343	4811	1959	71
H(15A)	6813	8450	5090	74
H(15B)	7658	7851	5962	74
H(15C)	5674	8104	5749	74
H(21A)	82	7353	-581	105
H(21B)	-1742	7533	-360	105
H(21C)	-327	6954	332	105
H(22A)	5779	9076	1704	105
H(22B)	5860	8800	536	105
H(22C)	5181	7854	946	105
H(1N)	9640(50)	2280(30)	5470(30)	41(10)
H(2N)	6060(40)	4276(12)	3720(30)	43(10)
H(3N)	3760(50)	8450(30)	4294(9)	51(11)
H(4)	10810(50)	6250(30)	7800(30)	49(10)
H(4N)	2420(40)	8033(14)	1360(30)	36(9)
H(6)	13490(50)	3940(30)	8950(30)	55(11)
H(7)	12050(40)	2490(30)	7390(20)	37(9)
H(9)	8410(40)	6240(30)	6110(20)	32(8)
H(17A)	1040(50)	8610(30)	2810(30)	45(10)
H(17B)	2100(40)	9620(30)	3730(30)	48(10)
H(18A)	4050(50)	9670(30)	2600(30)	49(10)

H(18B)	2320(50)	10110(40)	2350(30)	61(12)
H(19A)	-360(60)	8710(40)	1210(40)	83(16)
H(19B)	160(70)	9150(50)	380(40)	91(18)
H(20A)	3290(50)	9680(40)	670(30)	63(12)
H(20B)	2780(50)	8530(30)	-70(30)	50(10)

Table S6. Binding energy (kcal mol^{-1}) and inhibition constant (Ki, mM) for the CuSun complex at the ATP binding site of VEGFR2, obtained by performing docking simulations. Each X-Sun entry (where X = Cu, Zn or Mn) shows the results obtained by using the standard parameters in Autodock 4.2.6. of the metal X for the Cu atom of the complex. In addition, the RMSD for each conformation is shown, taking as a reference the most favorable pose for the ligand calculated with the parameters proposed for Cu [52].

Ligand	Binding Energy / kcal mol^{-1}	Ki / mM	RMSD / Å
CuSun	-3,67	2,03	0
ZnSun	-3,80	1,64	0,88
MnSun	-3,55	2,51	1,03