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Synthesis, Spectroscopic Characterization, and Biological Applications of Sulfamethoxazole Metal Complexes: Bioinorganic and Molecular Docking Studies

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Abstract
Sulfamethoxazole complexes of [Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and Hg(II)] were characterized using IR, UV-Vis, ESR, magnetic susceptibility, IR measurements revealed that sulfamethoxazole coordinates with metal ions as a bidentate ligand with stochiometries 1:2 (M:L). Electronic absorption spectra obtained using magnetic moment values revealed that all sulfamethoxazole compounds have octahedral geometry. The estimated room temperature powdered ESR data for the copper sulfamethoxazole complex with the formula is revealed to anisotropic spectra. Antimicrobial activities were screened for some metal complexes of sulfamethoxazole. Molecular docking studies of complexes against 3s7s protein as anti-breast cancer.

Keywords
Sulfamethoxazole, Complexes, Biological Activity, Breast Cancer, Molecular Docking

1. Introduction
Sulfamethoxazole Fig 1. is an antibiotic which it's used to treat bacterial illnesses such as urinary tract infections, asthma, and prostatitis, and it works against both gram-negative and gram-positive bacteria like E. coli and Listeria monocytogenes.[1] Sulfamethoxazole is known for creating complexes with Cr (III), Mn (II), Fe (III), Ni (II), Cu (II), and Zn (II). The isolated solid complexes were characterized using conductivity measurements, elemental analysis, magnetic, spectral (UV-Visible, IR, and H NMR), and thermal studies. Sulfamethoxazole is a monobasic bidentate ligand that binds metal ions via deprotonated sulfonamide nitrogen and sulfonyl oxygen or isoxazole ring nitrogen. The following data regarding the ligational behavior of sulfamethoxazole is derived from several spectroscopic, magnetic, and thermal experiments on Sulfamethoxazole metal complexes. Sulfamethoxazole acts as a monoanionic ligand in alkaline reaction conditions. The sulfonamide NH proton was extracted from the ligand during metal coordination. [2] The aim of the present work is studying and suggesting the chemical structure, molecular docking studies, antibacterial and antifungal evaluation of Sulfamethoxazole and its metal complexes.

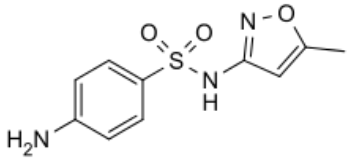


Fig. 1 structure of Sulfamethoxazole

2. Experimental

Sulfamethoxazole and metal chlorides of [Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and Hg(II)] were dissolved in distilled water. The molar amount of the metal chloride salt was combined with the predicted amount of the ligand at molar ratios (M:L) of 1:1 and 1:2. The reaction mixture was refluxed for around 50 minutes before being left overnight to filter the generated complexes, which were then washed multiple times with an EtOH-H_2O mixture and dried in a vacuum desiccator. The analytical data are shown in Table 1. All of these compounds have melting points above 300^{o}C.The metal contents were determined using the atomic absorption technique using a Shimadzu model 6650 atomic absorption spectrophotometer and complexometric titration with standard EDTA solution using the appropriate indicator, as previously reported [3]. The analysis of chloride contents of the complexes were examined by Volhard method.

3. Measurements

The infrared spectra of the Sulfamethoxazole and their metal complexes were detected by Perkin Elmer spectrophotometer, Model 1430, the instrument was located at central lab of Alexandria University. The electronic spectra for the solid complexes were measured in Nujol mull spectra; the instrument was located at central lab of Alexandria University. Molar magnetic susceptibilities, constants were analyzed using Faraday's method at room temperature 25 °C. The electron spin resonance spectra were tested by spectrometer operating at (9.1–9.8) GHz in a cylindrical resonance cavity with 100 KHz modulation, the instrument was located at central lab of Alexandria University. The g values were calculated by comparison with DPPH signal. The antimicrobial activity was performed by agar well diffusion assay [4] for all samples. Five microbial species known to be pathogenic including Gram negative Bacteria (*klebsila pneumonia ATCC700603*, E.coli ATCC25922), Gram positive Bacteria (*Staphylococcus aureus* ATCC25923 and *Streptococcus pyogenes EMCC1772*) and one fungal strain *Aspergillus niger EMCC 72*.The bacteria strains were grown in nutrient broth at 37°C for 24h while fungal strains were grown in potato dextrose broth at 28°C for 24h. A set of 3 concentrations of reconstituted tested material were examined to determine the minimum inhibitory concentration (MIC) of each against a specific pathogenic strain. Hundred µL of the inoculums (1×10^8 cfu/mL) were inculcated on agar media and poured into the Petri plate. A well was prepared on the plates with the help of a cork-borer (0.5 cm) and100 µL of the tested compound were applied into the well. All the tested bacteria were incubated at 37°C for 24 hr, all the tested fungal strains were incubated at 28°C for 3-5 days. The zone of inhibition was calculated by measuring the diameter of the inhibition zone around the well (mm), including the well diameter. The readings were taken in three different fixed directions in all triplicates and the average values were tabulated.

Table 1 Elemental analysis, melting points and colors of sulfamethoxazole complexes

Complexes	colour	*m.p. /°C	Found %						
			C	H	N	S	M	Cl	O
[Cr(Sulfamethoxazole)$_2$Cl(H$_2$O]	Dark green	**294**	39.250	3.953	13.732	10.477	8.496	5.792	18.299
[Mn(Sulfamethoxazole)$_2$Cl$_2$]	Buff	**280**	37.986	3.507	13.289	10.139	8.687	11.211	15.179
[Fe(Sulfamethoxazole)$_2$Cl(H$_2$O]	Dark brown	**227**	39.005	3.928	13.646	10.411	9.068	5.756	18.185
[Co(Sulfamethoxazole)$_2$Cl$_2$]	Pink	**258**	37.747	3.485	13.206	10.076	9.260	11.141	15.084
[Ni(Sulfamethoxazole)$_2$Cl$_2$]	Pale green	**273**	37.761	3.486	13.211	10.079	9.226	11.145	15.090
[Cu(Sulfamethoxazole)$_2$Cl$_2$]	Green	**282**	37.475	3.460	13.111	10.003	9.913	11.061	14.976
[Zn(Sulfamethoxazole)$_2$Cl$_2$]	White	**264**	37.369	3.450	13.074	9.974	10.170	11.029	14.933
[Cd(Sulfamethoxazole)$_2$Cl$_2$]	Off white	**244**	34.821	3.215	12.182	9.295	16.294	10.277	13.915
[Hg(Sulfamethoxazole)$_2$Cl$_2$]	Off white	**230**	30.875	2.850	10.802	8.241	25.781	9.113	12.338

4. Results and Discussion

4.1 IR Spectra of Sulfamethoxazole and their Metal Complexes

From IR spectra of sulfamethoxazole simple complexes, Table (2), showed broad band at 3449-3470 due to ν_{N-H} of NH_2 group, this band disappeared in all complexes due to covering by ν_{OH} of the water or OH group which appeared at a range of 3391-3567 cm^{-1}. We can extract the following points from the IR spectra The sharp band of O←S→O stretching vibration of sulfamethoxazole appears at 1319 cm^{-1} and shifted within the range of 1366-1434 cm^{-1} in the complexes, Table (2), that mean the group is involved in complexation. The band at 1662 cm^{-1}, Table (2), corresponding to stretching vibration of C=N group of sulfamethoxazole is affected by complexation and this band appears in the range of 1621-1650 cm^{-1} in the complexes. The C-N stretching vibration this is appeared at 1310 cm^{-1} of spectrum of sulfamethoxazole, Table (2), while for the Cr-, Fe- and Hg-complexes it appeared within the range of 1346-1399 cm^{-1}. This band doesn't appear in the rest complexes. In complexes ν_{OH} appear in the range of 3231 – 3567 cm^{-1} indicating that water or OH group share in coordination of the complexes. This band is not observed in the free sulfamethoxazole. The ν_{N-O} appeared at a range of 1315-1321 cm^{-1}. ν_{M-O} and ν_{M-N} bands are observed in the ranges of 477-477 cm^{-1} and 405-459 cm^{-1}, respectively.

Table 2 Fundamental infrared bands (cm^{-1}) of sulfamethoxazole and its metal complexes

Cpd	ν_{NH2}	ν_{O-H}	ν_{SO2}	ν_{N-H}	ν_{C-C}	$\nu_{C=C}$	ν_{C-N}	$\nu_{C=N}$	ν_{C-H}	ν_{S-N}	ν_{O-N}	$\nu_{O=N}$	ν_{M-O}	ν_{M-N}
Sulfamethoxazole	3449 3470	-----	1319	3075	1079	1452	1310	1662	2919	998	1319	1690	----	---
[Cr(Sulfamethoxazole)$_2$Cl(H_2O)]	----	3395	1366	----	1089	-----	1366	1640	----	842	1320	----	497	412
[Mn(Sulfamethoxazole)$_2Cl_2$]	----	3414	1407	----	1079	1450	----	1650	3000	864	1320	1692	510	414
[Fe(Sulfamethoxazole)$_2$Cl(H_2O)]	----	3395	1434	3231	1068	1452	1346	1632	3000	896	1321	1689	471	411
[Co(Sulfamethoxazole)$_2Cl_2$]	----	3495	---	----	1070	1453	----	1630	3000	947	----	1690	515	417
[Ni(Sulfamethoxazole)$_2Cl_2$]	----	3434	1412	----	1071	1455	----	1635	2995	840	----	1635	452	422
[Cu(Sulfamethoxazole)$_2Cl_2$]	----	3407 3325	1398	----	1100	1499	----	1630	2995	880	----	1700	522	428
[Zn(Sulfamethoxazole)$_2Cl_2$]	----	3391	1386	----	1047	1505	----	1632	3000	954	----	1690	472	410
[Cd(Sulfamethoxazole)$_2Cl_2$]	----	3500	1415	----	1075	----	----	1635	3000	----	1315	1690	570	406
[Hg(Sulfamethoxazole)$_2Cl_2$]	----	3567	1399	----	1062	----	1393	1621	2904	886	----	1690	577	459

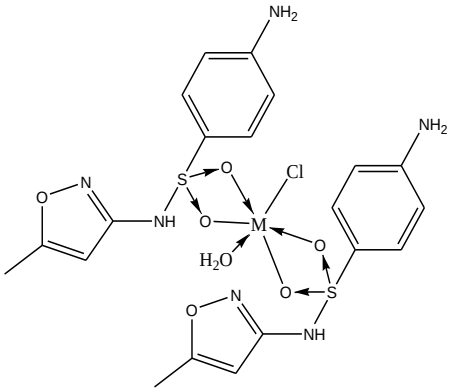
4.2 Electronic Absorption Spectra and Magnetic Susceptibility Studies

The electronic absorption spectra and effective magnetic moment values, give us the information to suggest structure geometry as listed in Table (3) and Fig. (2) ,However, Zn,Hg and Cd complexes exhibited only a high intensity band at 200-255 nm, which are assigned to ligand →metal charge transfer. Owing to the d10- configuration of Zn(II), Cd(II) and Hg(II), no d-d transition could be observed and therefore the strerochemistry around these metals in its complexes can be hardly determined [5-15].

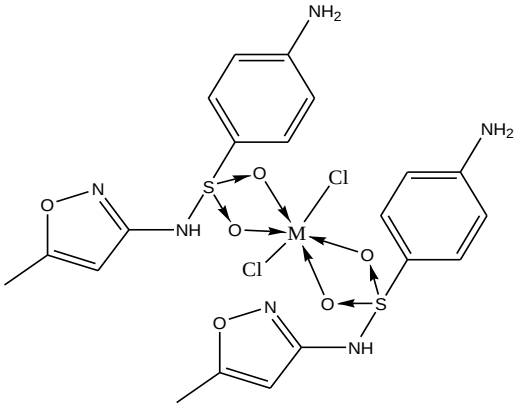
Table 3 Nujol mull electronic absorption spectra λ_{max} (nm), room temperature effective magnetic moment values (μ_{eff} 298 K) and geometries of (sulfamethoxazole) and its metal complexes.

Complex	Color	Absorption region (nm) (λ_m)	Band assignment	Magnetic moment μ_{eff} (B.M)	Geometry
Sulfamethoxazole	White	224 350	n→ π* n→ π*	----	------
[Cr(Sulfamethoxazole)$_2$Cl(H_2O)]	Green	350 420 570	$^4A_{2g}$→$^4T_{1g}$(p) $^4A_{2g}$→$^4T_{1g}$(F) $^4A_{2g}$→$^4T_{2g}$(F)	3.40	O_h
[Mn(Sulfamethoxazole)$_2Cl_2$]	Buff	300 350 540	$^6A_{1g}$→$^4A_{1g}$ $^6A_{1g}$ → $^4T_{2g}$ $^6A_{1g}$→$^4T_{1g}$	4.92	O_h
[Fe(Sulfamethoxazole)$_2$Cl(H_2O)]	Dark Brown	350 385 500	CT CT (t_{2g} → π^*) CT (π → e_g)	5.7	O_h
[Co(Sulfamethoxazole)$_2Cl_2$]	Green	350 420 579	CT $^4T_{1g}$(F) → $^4T_{1g}$(P) $^4A_{2g}$→$^4T_{1g}$(F)	5.85	O_h
[Ni(Sulfamethoxazole)$_2Cl_2$]	Green	350 472 650	CT $^3A_{2g}$(F)→$^3T_{1g}$(P) $^3A_{2g}$(F) → $^3T_{1g}$(F)	2.78	O_h
[Cu(Sulfamethoxazole)$_2Cl_2$]	Green	350 504	CT ^2E_g → $^2T_{2g(D)}$	1.72	O_h

[Zn(Sulfamethoxazole)$_2$Cl$_2$]	White	245	CT	Zero	O_h
[Cd(Sulfamethoxazole)$_2$Cl$_2$]	White	220	CT	Zero	O_h
[Hg(Sulfamethoxazole)$_2$Cl$_2$]	White	255	CT	Zero	O_h



M= Cr, Fe



M= Mn,Co, Ni, Cu, Zn, Cd, Hg

Fig. 2 The proposed structure of Sulfamethoxazole complexes

4.3 Electron spin resonance of copper complex

The room temperature polycrystalline X-band ESR spectral pattern of copper sulfamethoxazole complex, Figure (3) is anisotropic in nature. The spectral analysis of this complex gave two g values g_{11}= 2.0263 and g_1= 2.263. where <g>=2.18, f^2 =0.81 and α^2 =0.80 . The calculated <g> value=2.185 where $< g >= \frac{(g_{11}+2g_1)}{3}$ .The low value of f^2 shows strong axial field.

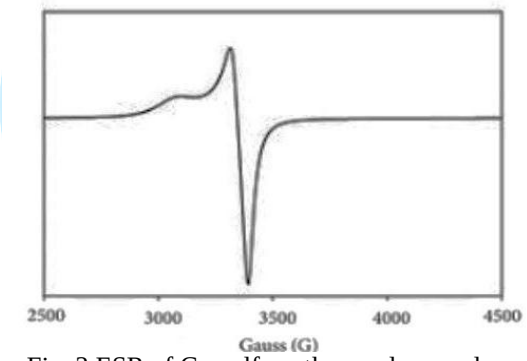
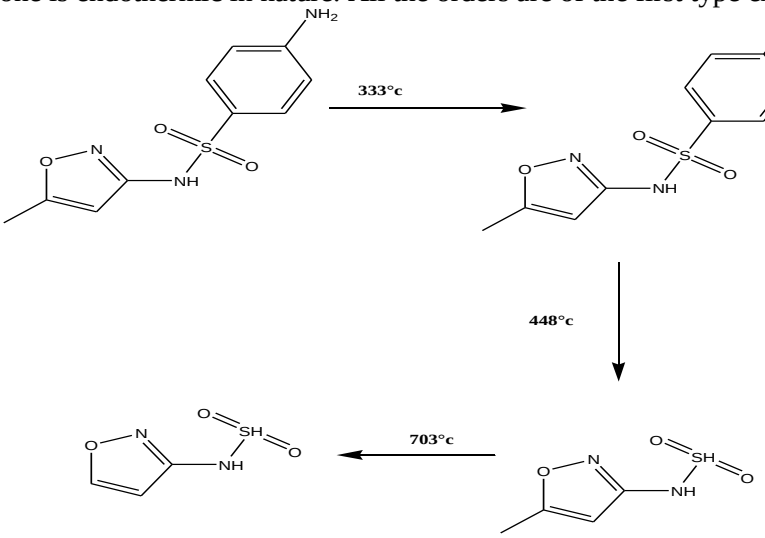


Fig. 3 ESR of Cu-sulfamethoxazole complex

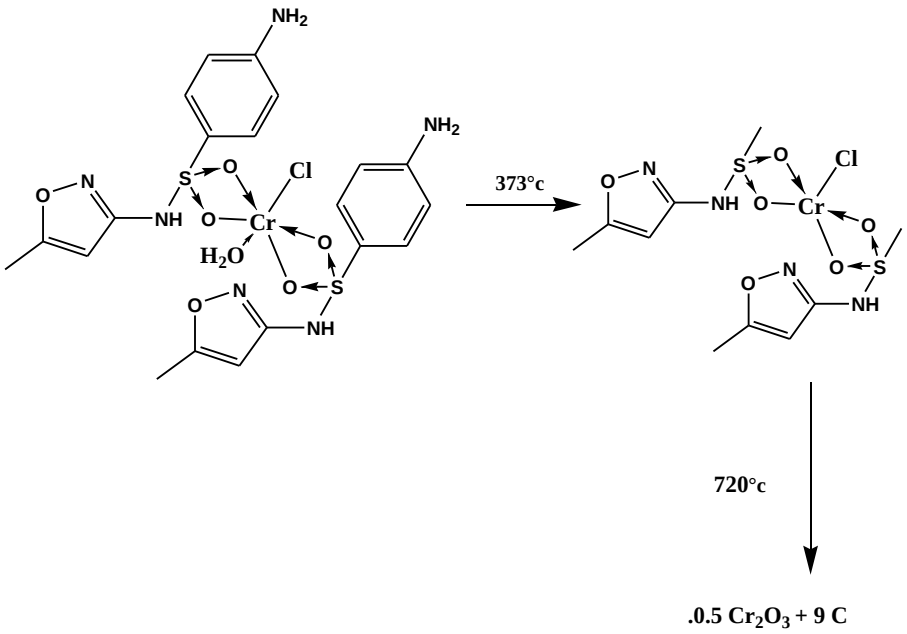
5. Thermal Analysis

The DTA data of ligand " Sulfamethoxazole ", Figure (4) and Table (4), gave three peaks at 333, 448 and 703 °K with activation energies of 0.399,74.75 and 20.60 kJ/mole and their orders are 1.61,1. 30 and 1.44, respectively. All peaks are exothermic except the first one is endothermic in nature. All the orders are of the first type except first one, scheme (1):



Scheme 1 Sulfamethoxazole reaction

For example the DTA data of [Cr -Sulfamethoxazole]complex as an example , Figure (5) and Table (4), gave two peaks at 373, and 320 °K with activation energies of 9.59 and 15.22 kJ/mole and their orders are 1.92 and 1.77, respectively. All peaks are exothermic except the first one is endothermic in nature. All the orders are of the second type, scheme (2),



Scheme 2 Cr- Sulfamethoxazole complex reaction

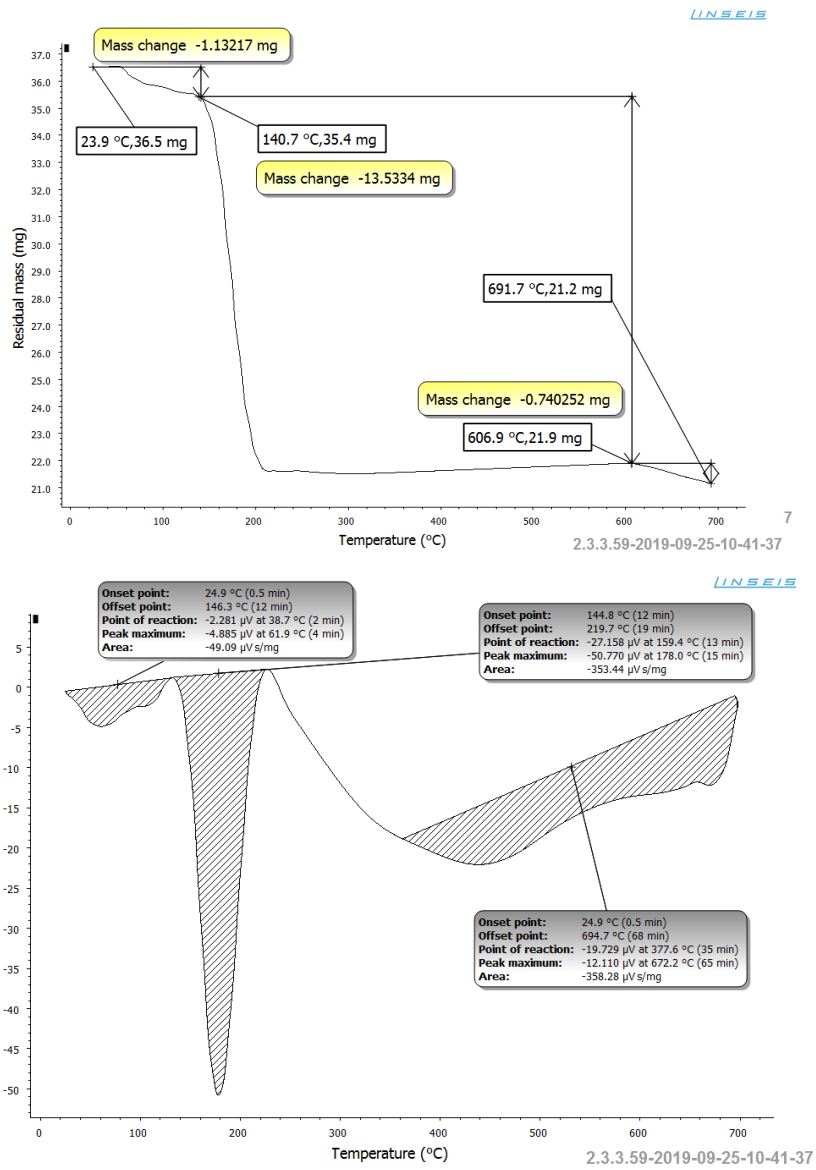


Fig. 4 TG and DTA of Sulfamethoxazole

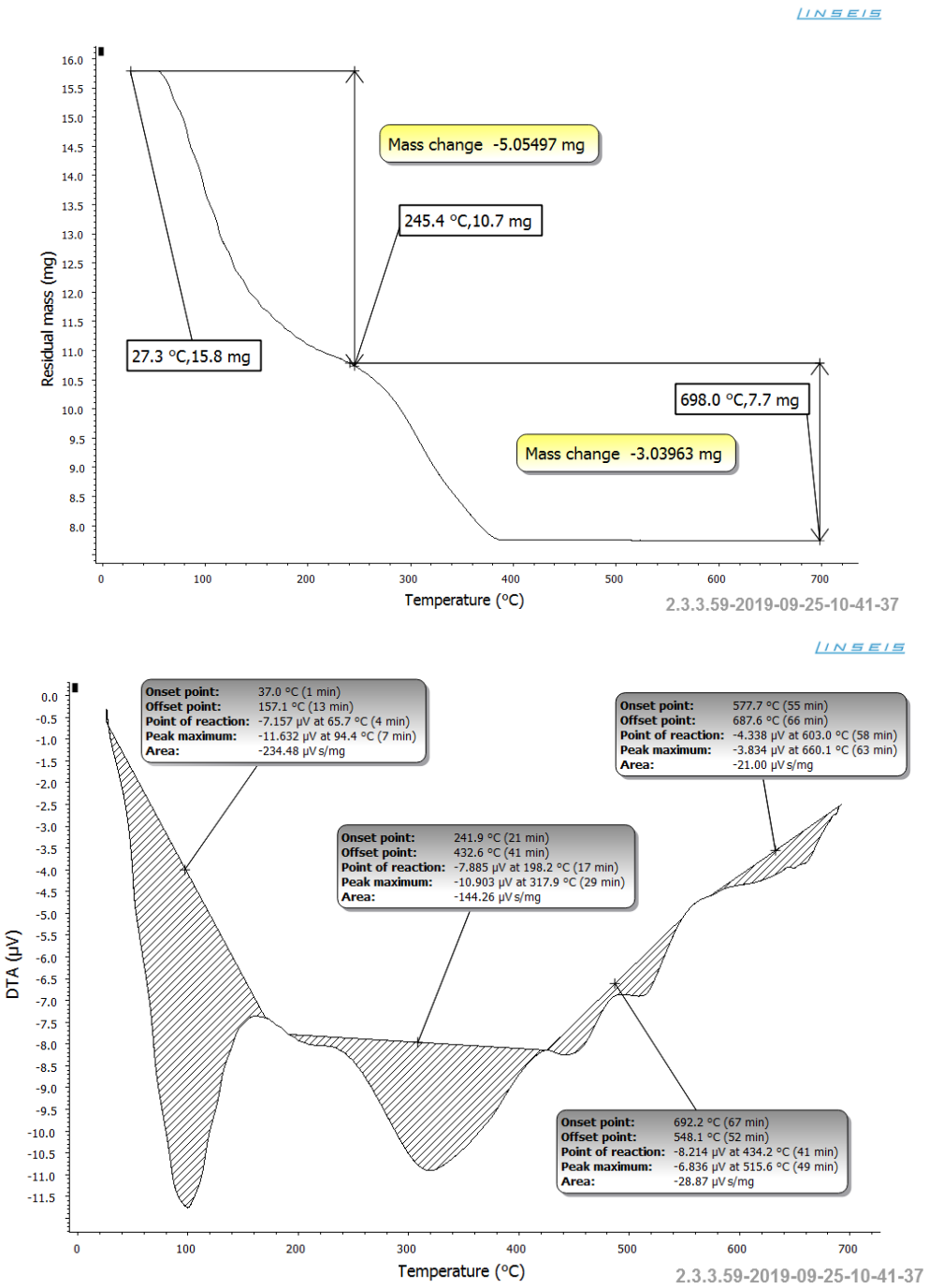


Fig. 5 TG and DTA of Cr-Sulfamethoxazole complex

Table 4 kinetic parameters of the thermal dissociation steps of sulfamethoxazole and its complexes

a	b	N	S	α	slope	Tm,K	E	Z	□S	□□□	remain %	
1.8	1.1	1.6118	0.61	0.5417	-0.0480	333.0	0.399	0.00014	-0.33851	-112.725	96.99	sulfamethoxazole
1.4	1.3	1.3076	0.93	0.5818	-8.9919	448.0	74.759	0.02007	-0.29994	-134.374	60.00	
7.5	5.7	1.4453	0.76	0.5627	-2.4778	703.0	20.600	0.00352	-0.31815	-223.659	58.08	
5.1	2.2	1.9184	0.43	0.5080	-1.1535	373.0	9.590	0.00309	-0.31397	-117.110	67.72	Cr-sulfamethoxazole
11.9	6.0	1.7745	0.50	0.5231	-1.8315	320.3	15.227	0.00572	-0.30759	-98.513	48.73	
0.3	0.6	0.8910	2.00	0.6531	-0.5536	373.0	4.603	0.00148	-0.32007	-119.387	93.40	Co-sulfamethoxazole
3.2	1.6	1.7819	0.50	0.5223	-0.3039	773.0	2.527	0.00039	-0.33717	-260.636	78.00	
0.4	1.0	0.7969	2.50	0.6730	-1.6930	823.0	14.076	0.00206	-	-	30.00	

									0.32394	266.600	
2.0	1.9	1.2927	0.95	0.5840	-0.0950	314.0	0.790	0.00030	-0.33186	-104.204	75.60
3.2	7.8	0.8070	2.44	0.6708	-5.2462	693.0	43.617	0.00757	-0.31167	-215.991	57.36
0.4	0.6	1.0288	1.50	0.6269	-0.2552	323.0	2.122	0.00079	-0.32412	-104.690	92.00
2.3	3.0	1.1032	1.30	0.6139	-0.4193	435.0	3.486	0.00096	-0.32494	-141.348	85.00
1.4	1.5	1.2173	1.07	0.5954	-14.5170	568.0	120.694	0.02556	-0.29991	-170.346	79.00
6.3	3.8	1.6224	0.60	0.5404	-3.0652	693.0	25.484	0.00442	-0.31614	-219.087	66.00
1.5	4.0	0.7716	2.67	0.6787	-5.1956	963.0	43.196	0.00540	-0.31723	-305.489	59.12
3.2	1.0	2.2540	0.31	0.4770	-0.1362	328.0	1.132	0.00042	-0.32959	-108.106	88.60
1.9	2.9	1.0199	1.53	0.6285	-3.7218	538.0	30.943	0.00692	-0.31032	-166.952	81.00
2.0	1.4	1.5060	0.70	0.5548	-4.7574	593.0	39.553	0.00802	-0.30990	-183.769	73.00
2.6	1.4	1.7171	0.54	0.5295	-3.0707	713.0	25.530	0.00431	-0.31660	-225.736	62.69
1.6	4.4	0.7598	2.75	0.6813	-17.0190	953.0	141.496	0.01786	-0.30719	-292.750	56.99
1.2	0.9	1.4549	0.75	0.5614	-0.0474	303.0	0.394	0.00016	-0.33705	-102.126	98.00
1.4	3.6	0.7857	2.57	0.6755	-0.3325	458.0	2.764	0.00073	-0.32772	-150.097	92.26
3.2	3.7	1.1718	1.16	0.6026	-9.0806	638.0	75.496	0.01423	-0.30574	-195.061	83.00
4.5	3.5	1.4287	0.78	0.5649	-7.3197	713.0	60.856	0.01027	-0.30938	-220.587	77.00
3.7	4.8	1.1062	1.30	0.6134	-5.2391	873.0	43.558	0.00600	-0.31553	-275.454	66.07

			Ni-sulfamethoxazole
			Cu-sulfamethoxazole
			Zn-sulfamethoxazole
			Cd-sulfamethoxazole

6. Biological Activity

Table (5) shows that compounds B, C and D had anti- *Klebsila pneumonia, Staphylococcus aureus, Streptococcus pyogenes and Aspergillus niger* while the tested compounds showed anti- *E.coli.* Compared to reference antibiotic (Amoxicillin).

Table 5 Antimicrobial effect of compounds

Pathogenic strain	**Tested material**	**Inhibition zone diameter (mm)**/**	**Sample concentration %**	
	100 µg/mL	**50 µg/mL**	**25 µg/mL**	**MIC**
Gram negative Bacteria				
Klebsila pneumonia ATCC700603				
$[Zn(Sulfamethoxazole)_2Cl_2]$	ND	ND	ND	ND
Sulfamethoxazole	18	11	ND	50
Amoxicillin 100 µg/mL	35			
E.coli ATCC25922				
$[Zn(Sulfamethoxazole)_2Cl_2]$	17	ND	ND	50
Sulfamethoxazole	25	20	15	25
Amoxicillin 0.01%	31			
Gram positive Bacteria				
Staphylococcus aureus ATCC25923				
$[Zn(Sulfamethoxazole)_2Cl_2]$	ND	ND	ND	ND
Sulfamethoxazole	11	10	ND	50
Amoxicillin 0.01%	23			
Streptococcus pyogenes EMCC1772				
$[Zn(Sulfamethoxazole)_2Cl_2]$	ND	ND	ND	ND
Sulfamethoxazole	21	11	ND	50
Amoxicillin 0.01%	28			

Fungal strains				
Aspergillus niger EMCC 72				
[Zn(Sulfamethoxazole)$_2$Cl$_2$]	ND	ND	ND	ND
Sulfamethoxazole	11	ND	ND	50
Amoxicillin 0.01%	ND			

7. Molecular Docking Study

The selected protein 3s7s represents the crystal structure of the human placentalany proposed biologically active compound. This approach elucidates the ligand-receptor site and type of interactions. It also givesan estimation of the distance between the ligand and the receptor inside the interaction grid. The scoring energy of each pose simulated by the docking calculations reflects the degree of inhibition effect of the corresponding ligand. In the present study, the selected protein 3s7s represents the crystal structure of the human placental aromatase enzyme that catalyzes the synthesis of estrogen hormone and contributes to estrogen-dependent breast cancer 50. All ligands possess an appreciable extent of interactions with the receptor protein based on the scoring energy . The result show the abibilty of ligand to inhibt 3s7s protien[16-20].

[Mn(Sulfamethoxazole)$_2$Cl$_2$]

The docked (Mn-sulfa) Fig. (6) have effective ligand-receptor interaction distances were ≤ 3.3 A in most cases, which indicates the presence of typical real bonds and hence high binding affinity. For example, the nearest interaction is observed *via* H-donors with 3S7S (2.69A) and (Mn-sulfa) With plant score- 1182.39 and Moldock score -38336 Furthermore, four binding sites were observed of different amino acids(Ser 310, Thr 314, Val 370 and Met 364) with 3a demonstrating their high inhibition.

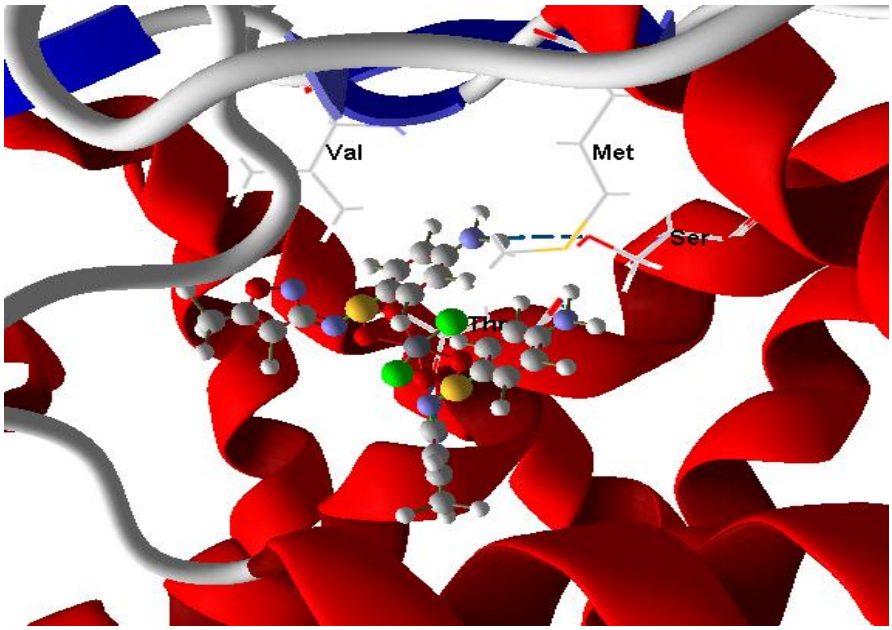


Fig. 6 Virtual Molecular docking of the best docked (Mn-sulfa) with 3s7s protein

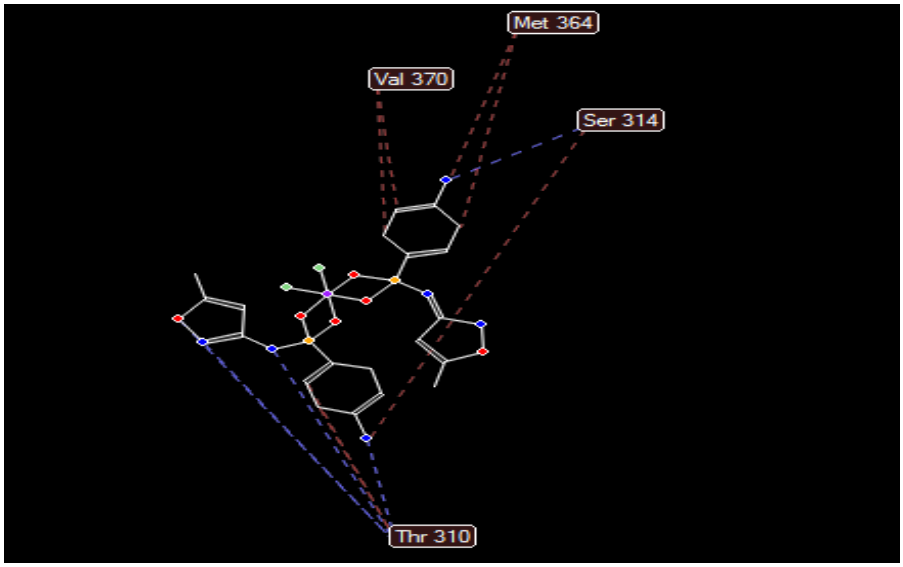


Fig. 7 2D structure of Molecular docking of (Mn-sulfa) with 3s7s protein

[Co(Sulfamethoxazole)$_2$Cl$_2$]

While the docked (Co-sulfa) Fig. (8) have effective ligand-receptor interaction distances were ≤ 3.17 A in most cases, which indicates the presence of typical real bonds and hence high binding affinity . For example, the nearest interaction is observed *via* H-donors with 3S7S (3.07A) and (Co-sulfa) With plant score -1189.31 and Moldock score -38341 Furthermore, four binding sites were observed of different amino acids(Leu 152, Thr 310, Met 446 and Met 311) with 3a demonstrating their high inhibition.

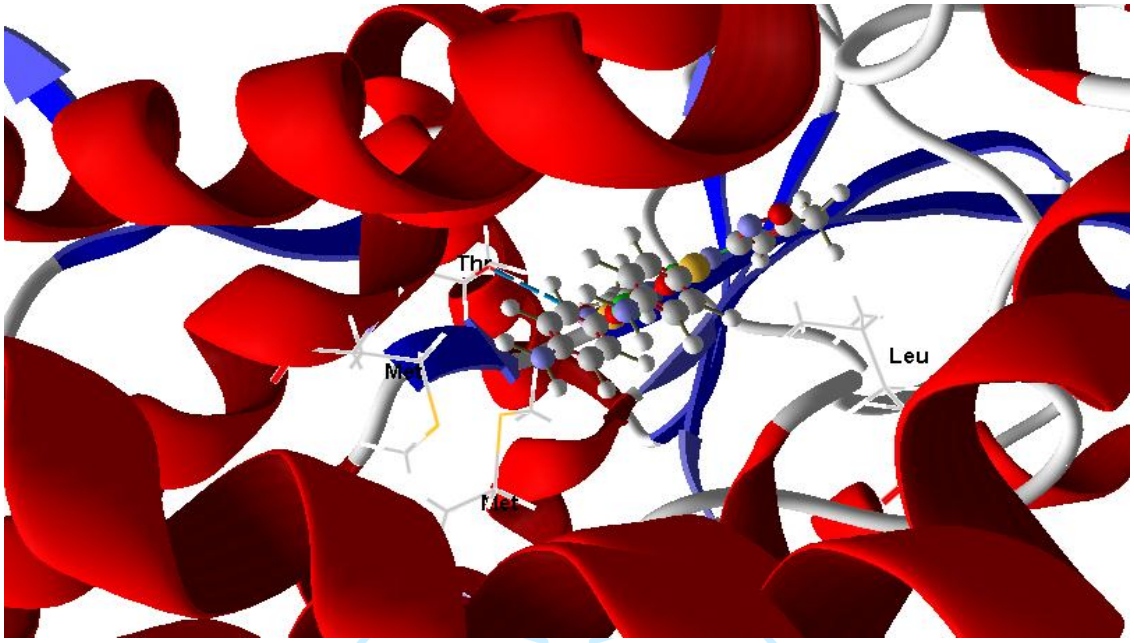


Fig. 8 Virtual Molecular docking of the best docked (Co-sulfa) with 3s7s protein

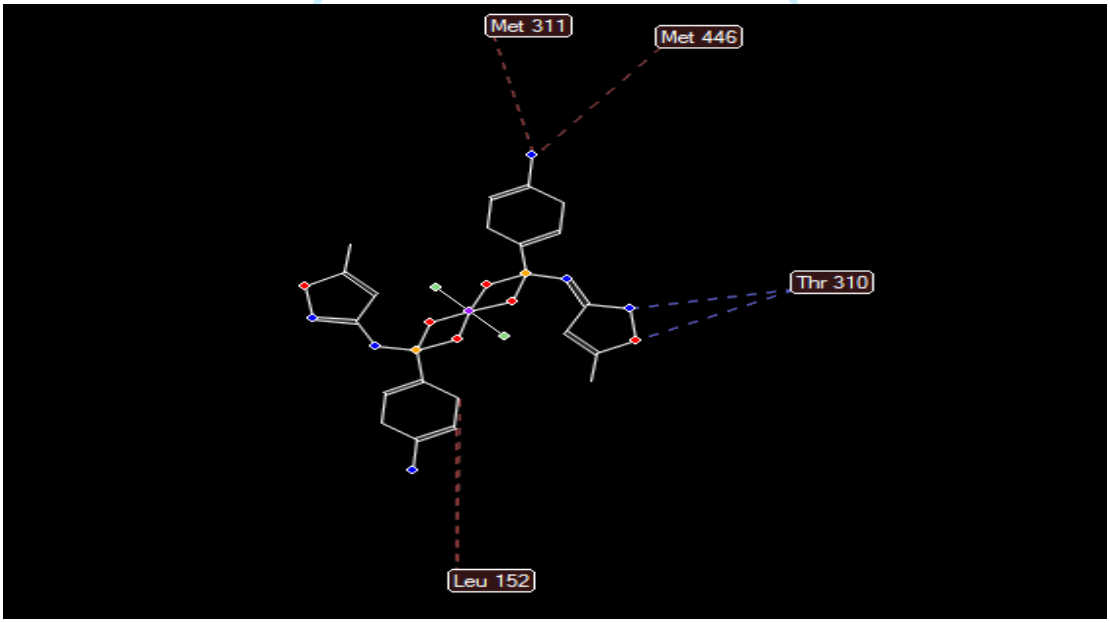


Fig. 9 2D structure of Molecular docking of (Co-sulfa) with 3s7s protein

[Zn(Sulfamethoxazole)$_2$Cl$_2$]

However the docked (Zn-sulfa) Fig. (10) have effective ligand-receptor interaction distances were ≤ 3.3 A in most cases, which indicates the presence of typical real bonds and hence high binding affinity . For example, the nearest interaction is observed *via* H-donors with 3S7S (2.87A) and (Zn-sulfa) With plant score -1191.97 and Moldock score -38349 Furthermore, four binding sites were observed of different amino acids(Ser 314, Thr 310, Val 370 and Met 364) with 3a demonstrating their high inhibition.

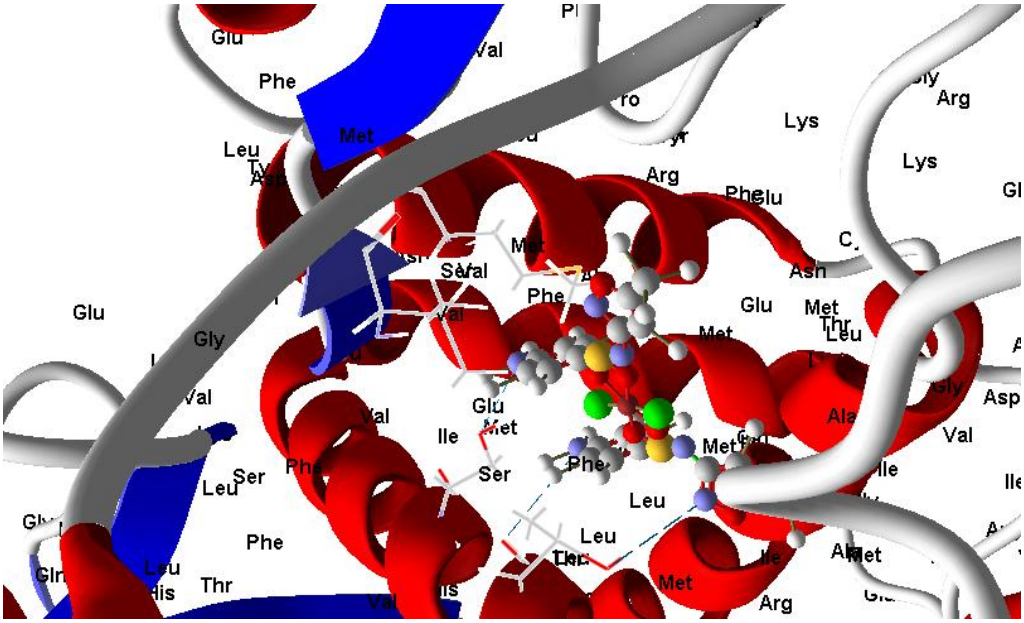


Fig. 10 Virtual Molecular docking of the best docked (Zn-sulfa) with 3s7s protein

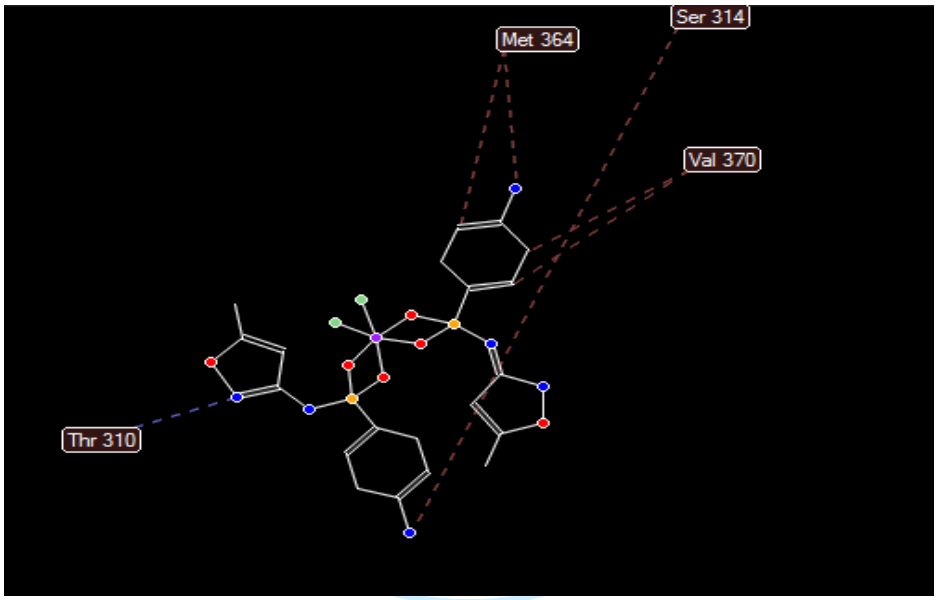


Fig. 11 2D structure of Molecular docking of (Zn-sulfa) with 3s7s protein

Hence Zn-sulfa> Mn-sulfa>Co-sulfa towards inhibition of 3S7S breast cancer protein

Author's Contributions

Alaa E. Ali and Gehan S. Elasala designed the study and performed the complexes synthesis. Rana M. Atta, Ismail A. Ismail, and Sherif A. kolkaila performed most of the experiments analyzed and interpreted the data. Sherif A. kolkaila performed and interpreted the molecular docking studies. Rana M. Atta, Ismail A. Ismail, and Sherif A. kolkaila wrote the first version of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflict of Interest

The authors have declared no conflict of interest.

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