Chemistry Research Journal, 2024, 9(3):202-209
Available online www.chemrj.org

Research Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

Synthesis, Characterization, Biological Activity of Sulfaquinoxaline metal Complexes and Molecular Docking Study as Anti-Colorectal Cancer

Sherif A. Kolkaila[1,*], Alaa E. Ali[1], Elsayed M. Elmanooh[2] and Gehan S. Elasala[1]

[1]Department of Chemistry, Faculty of Science, Damanhour University, Egypt
[2]Department of Chemistry, Institute of Graduate Studies and Environmental Research, Damanhour University, Egypt
*Corresponding author, Email address: sherifkolkaela@yahoo.com

Abstract Sulfaquinoxaline metal complexes with transition metals (Cr(III), Mn(II), Co(II), Fe(III),Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)) have been synthesized. IR spectra demonstrated that the sulfaquinoxaline ligand works as a tetradentate ligand. All sulfaquinoxaline compounds have octahedral geometry, as evidenced by magnetic and spectroscopic data. For some bacteria, sulfaquinoxaline complexes outperform industrial sulfaquinoxaline. Molecular docking study is done for some metal complexes as anti-Colorectal cancer.

Keywords Sulfaquinoxaline; Complexes; Molecular docking study; Spectroscopic analysis: Colorectal cancer

Introduction

Sulfaquinoxaline (Figure 1) is an antiprotozoal and antimicrobial antibiotic used to treat several coccidial infections [1-2] (coccidiosis) in pigs, cattle, poultry, and other animals. Sulfa drugs used to treat poultry typhoid were caused by sensitive organisms, as opposed to fowl cholera, which was caused by Pasteurella multocida [3-4]. Previous work in sulfaquinoxaline metal complexes focused on synthesizing sulfaquinoxaline complexes with (Ni, Co, Cu, Sn, Cd) [5-7]. Previous investigations demonstrated that Cu and Co sulfaquinoxaline have a very high cytotoxic effect on a colon carcinoma cell line at low concentrations, reducing lifespan to 50% [8-9]. The complexation characteristics, and biological activities were investigated. Molecular docking study is done for some metal complexes as anti-Colorectal cancer**.**

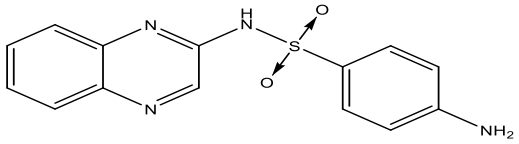

Figure 1: Structure of sulfaquinoxaline (HL)

Experimental Section

Similarly, all metal sulfaquinoxaline complexes were produced. This was accomplished by dissolving the chlorides inorganic salts of transition metal ions in 40 mL of bidistilled water, while the ligand was dissolved in ethanol. The ethanolic ligand solution was combined with a metal chloride solution in a variable ratio (M:L). In each case, the reaction mixture was refluxed for around 5 minutes before being allowed overnight, after which the precipitated complexes were filtered, washed several times with an EtOH-H_2O combination, and dried in a vacuum desiccator over anhydrous $CaCl_2$. The metal contents were determined using two methods: first, using the atomic absorption technique with a model 6650 Shimadzu-atomic absorption spectrophotometer, and second, complexometrically with

a standard EDTA solution and the suitable indicator as described [9]. The chloride content of complexes was measured using the classic Volhard method **Table 1** [10].

Table 1: Elemental analysis, m.p, formula, stoichiometries and color of simple sulfaquinoxaline complexes

Complexes	Color	Calculated/(Found)%					
		C	H	N	S	M	Cl
$[Cr_2(HL)\,Cl_6(H_2O)_2]$	Dark Green	25.75 (25.60)	2.47 (2.57)	8.58 (8.80)	4.91 (4.95)	15.92 (15.90)	32.57 (32.50)
$[Mn_3(HL)_2\,(H_2O)_6(OH)_4]$	Pale Brown	35.72 (35.70)	4.28 (4.32)	11.90 (11.95)	6.81 (6.84)	17.50 (17.61)	- -
$[Fe_2(HL)\,Cl_6(H_2O)_2]$	Dark Brown	25.45 (25.47)	2.44 (2.42)	8.48 (8.55)	4.85 (5.10)	16.90 (16.82)	32.19 (32.17)
$[Co_2(HL)_3\,Cl_4(H_2O)_2]$	Pale Pink	42.15 (42.71)	3.37 (3.32)	14.05 (14.11)	8.04 (8.09)	9.85 (9.77)	11.85 (11.99)
$[Ni_2\,(HL)_2(OH)_4\,(H_2O)_2]$	Green	40.03 (40.09)	4.08 (4.11)	13.34 (13.30)	7.63 (7.60)	13.97 (13.90)	- -
$[Cu_2(HL)_3\,Cl_2(H_2O)_2]$	Green	44.44 (44.66)	3.55 (3.41)	14.81 (14.70)	8.47 (8.50)	11.20 (11.09)	6.25 (6.38)
$[Zn_2\,(HL)_3Cl_4(H_2O)_2]$	Yellow	42.21 (42.32)	3.46 (3.38)	13.74 (13.68)	7.86 (7.82)	10.69 (10.73)	11.59 (11.68)
$[Cd_2(HL)_2Cl_4(H_2O)_2]$	Yellow	32.93 (32.85)	2.96 (2.88)	10.97 (10.82)	6.28 (6.32)	22.01 (22.11)	13.88 (13.77)
$[Hg_2(HL)_3Cl_4(H_2O)]$	Orange	34.50 (34.39)	2.62 (2.55)	11.50 (11.42)	6.58 6.52)	27.44 (27.42)	9.70 (9.73)

Physical Measurements

The IR spectra of sulfaquinoxaline and their metal complexes were determined using a Perkin Elmer spectrophotometer, Model 1430, with a range of 200-4000 cm-1, as well as a Unicam UV/Vis spectrometer [11]. The spectra of sulfaquinoxaline and solid complexes were measured in Nujol mull spectra. The magnetic measurements were taken at room temperature (298 K) using Faraday's method Sulfaquinoxaline and its metal complexes were tested against five microorganisms: two Gram-positive (Staphylococcus Aureas ATCC6538P and Bacillus subtilis ATCC19659), two Gram-negative (Escherichia coli ATCC8739 strain and Pseudomonas aeruginosa ATCC9027), and candida albicans as a fungus. For ligand, A molecular docking study was conducted by the Molegro virtual docker 6.0.

Result and Discussion

Table 2 summarizes the allocations for sulfaquinoxaline bonding sites and metal complexes. The elemental analysis of the complexes revealed that all of them contain water molecules in their structures. Sulfaquinoxaline complexes produce broad bands in the 3400–3580 cm^{-1} area, indicating coordination with water. Metal-oxygen bands in the 422-450 cm^{-1} area imply coordinated water in these complexes [12]. The O=S=O stretching vibration of sulfaquinoxaline is assigned a sharp band at 1350 cm^{-1}; however, for metal complexes, this band is moved to the (1384-1416 cm^{-1}) region, indicating that the oxygen of the sulfonyl group facilitates ligand interaction with these metal ions. The N-H stretching vibration of the secondary NH group of sulfaquinoxaline exhibits a sharp band around 3192 cm^{-1}, whereas simple complexes exhibit a wide shift in the range of 3240-3361 cm^{-1}. This indicates that metal ligand coordination is occurring through the nitrogen of the secondary amino group. In the sulfaquinoxaline spectrum, the sharp band at 3318 cm^{-1} corresponds to symmetrical stretching vibration, while the band at 3356 cm^{-1} corresponds to asymmetrical stretching vibration of N-H of hydrogen bonded NH_2. Metal complexes are assigned at ranges of (3360-3437 cm^{-1}) and (3420-3576 cm^{-1}) for symmetrical and asymmetrical stretching vibrations, respectively. This change indicates that the terminal amino group's nitrogen is facilitating ligand coordination with metal ions. The complexes exhibit this band in the (1637–1642) cm^{-1} range, indicating that there is no metal ligand

coordination because the band at 1637 cm^{-1} corresponds to the stretching vibration of the C=N of sulfaquinoxaline. Nevertheless, the shifting is not significant. The sulfaquinoxaline spectrum shows a narrow band of C-N stretching vibration at 1308 cm^{-1}, whereas the band for simple complexes corresponds to (1307-1315 cm^{-1}), indicating that no shift in the band happened and hence no metal ligand coordination occurred. The sulfaquinoxaline spectrum has a distinct band of CH stretching vibration at 2942 cm^{-1}; however, for simple complexes, this band occurs in the range of 2920–2955 cm^{-1}. The C=C aromatic bending vibration of sulfaquinoxaline is responsible for the absorption band at 1598 cm^{-1}, whereas complexes emerge in the range of (1592–1594) cm^{-1}.

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

Compound	**νNH 2^{o}amine**	**ν (O=S=O)**	**ν(NH) 1^{o}amine sym**	**ν(NH) 1^{o}amine asym**	**ν (C=N)**	**ν (C-N)**	**ν (CH) stretch**	**ν(NH) 1^{o}amine bend**
Sulfaquinoxaline	3192	1350	3318	3356	1637	1308	2942	1598
$[Cr_2(HL)\,Cl_6(H_2O)_2]$	3075	1416	3361	3438	1640	1311	2927	1592
$[Mn_3(HL)_2\,(H_2O)_6(OH)_4]$	3255	1414	3360	3437	1640	1310	2927	1592
$[Fe_2(HL)\,Cl_6(H_2O)_2]$	3075	1416	3360	3442	1639	1314	2944	1592
$[Co_2(HL)_3\,Cl_4(H_2O)_2]$	3075	1415	3360	3400	1640	1311	2940	1594
$[Ni_2(HL)_2(OH)_4(H_2O)_2]$	3075	1415	3360	3438	1639	1311	2940	1593
$[Cu_2(HL)_3\,Cl_2(H_2O)_2]$	3075	1416	3360	3437	1642	1314	2942	1592
$[Zn_2\,(HL)_3Cl_4(H_2O)_2]$	3375	1414	3360	3438	1639	1311	2920	1593
$[Cd_2(HL)_2Cl_4(H_2O)_2]$	3075	1415	3360	3437	1638	1310	2940	1593
$[Hg_2(HL)_3Cl_2(H_2O)]$	3074	1415	3360	3437	1640	1311	2940	1593

Electronic Spectral and Magnetic Studies

The electronic absorption spectra and effective magnetic moment values, give us the information to suggest structure geometry as listed in **Table 3, Figure 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 [13-14].

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

Complex	**λ_{max} (nm)**	**Transitions**	**μ_{eff}**	**Geometry**
$[Cr_2(L)\,Cl_3(H_2O)_3]$	288,320, 354	$^4A_{2g}\rightarrow{}^4T_{2g}$ (F), $^4A_{2g}\rightarrow{}^4T_{1g}$(F) $^4A_{2g}\rightarrow{}^4T_{1g}$(p)	6.61	O_h
$[Mn_3(HL)_2\quad(H_2O)_6]$	300, 337, 366	π - π* $^6A_{1g}\rightarrow{}^4A_{1g}$ $^6A_{1g}\rightarrow{}^4T_{2g}$	5.62	O_h
$[Fe_2(L)\,Cl_6(H_2O)_2]$	305, 334, 367	CT ($t_{2g}\rightarrow\pi^*$) CT ($\pi\rightarrow e_g$)	4.66	O_h
$[Co_2(L)_3\,Cl_6(H_2O)_6]$	285, 314, 338	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(P)$	3.69	O_h
$[Ni_2\,(L)_2\,(H_2O)_4]$	287, 318, 373	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(P)$	2.64	O_h
$[Cu_2(L)_3\,Cl_4(H_2O)_2]$	304, 343,362	$^2E_g\rightarrow{}^2T_{2g}$	1.62	O_h
$[Zn_2\,(L)_3Cl_4(H_2O)_2]$	314,364	ligand →metal charge transfer	diamagnetic	O_h
$[Cd_2(HL_2)Cl_2(H_2O)_2]$	327,371	ligand →metal charge transfer	diamagnetic	O_h
$[Hg_2(L)_3Cl(H_2O)]$	308,348	ligand →metal charge transfer	diamagnetic	O_h

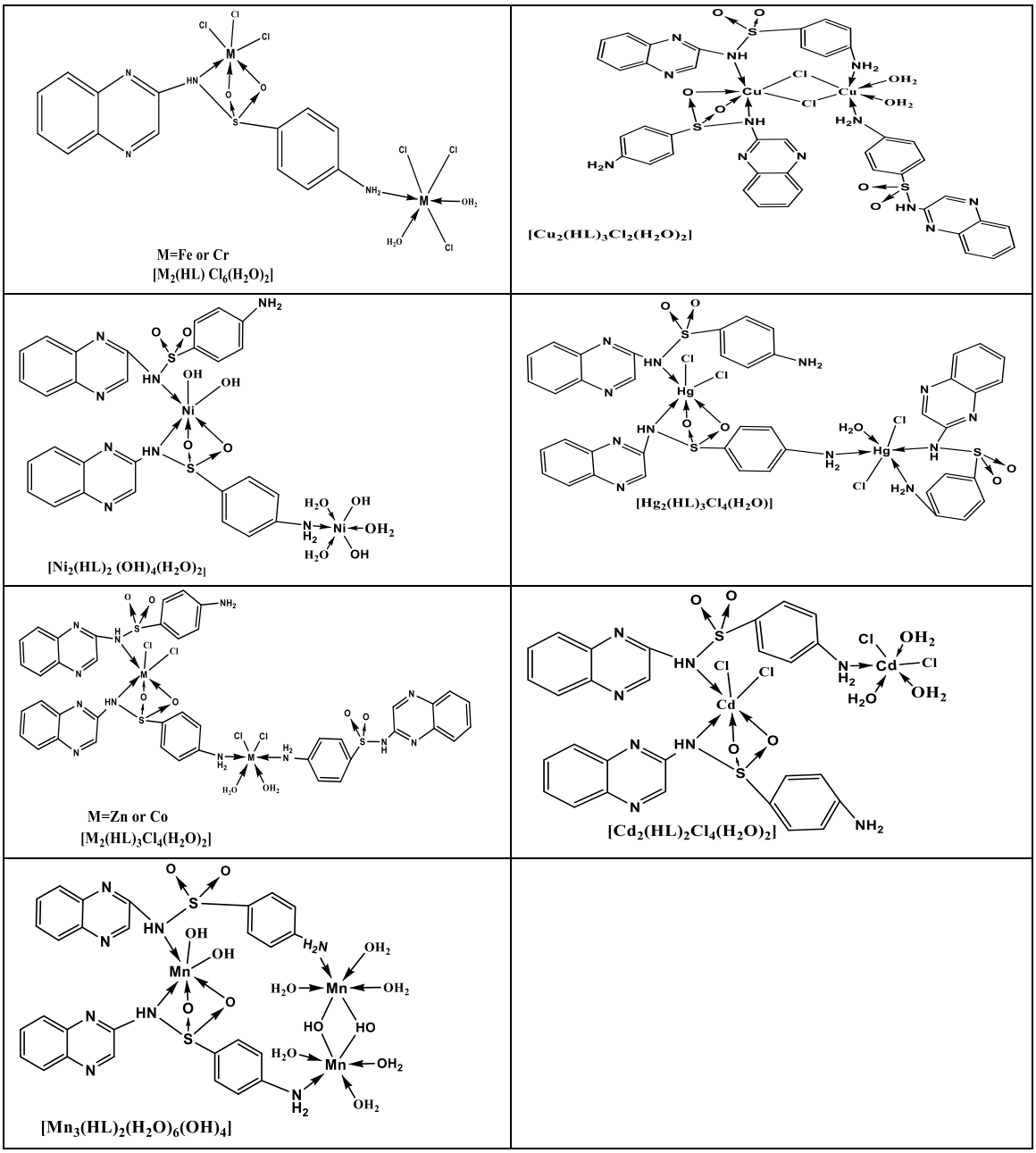

Figure 2: Proposed structures of sulfaquinoxaline complexes

Biological Activity

In order to examine the biological activity of sulfaquinoxaline and its compounds, we focus on five distinct microorganisms that belong to various microbial species. Five organisms were used in this study: two Gram-positive (Bacillus subtilis ATCC19659 and Staphylococcus aureas ATCC6538P), two Gram-negative (Escherichia coli ATCC8739 strain and Pseudomonas aeruginosa ATCC9027) bacteria, and Candida albicans as fungus. Four complexes of different metal ions (Zn, Cu, Co, and Fe) and two different broad antibiotics (Ciprofloxacin and Clotrimazole) are used as references in this study (Table 4).

From the data we conclude that: Sulfaquinoxaline ligand showed similar activities for all five micro organisms. All investigated compounds showed higher activity for Staphyllococcus aureus except $[Fe_2(HL)\ Cl_6(H_2O)_2]$ which showed similar activity for it. All chemicals have similar actions to Candida albicans, Escherichia coli, Pseudomonas aeruginosa, and Bacillus subtilis. The favorable antibacterial activity of all investigated compounds is more than the antifungal activity; however, the activity of compounds is lower than the references. Free ligands have reduced activity compared to metal complexes [16]. Metal chelates have higher activity, which can be explained by overtone theory and chelation theory [17]. Chelation reduces the polarity of metal ions to a greater extent due to ligand orbital overlap and partial sharing of the metal ion's positive charge with the donor groups, which leads to increased delocalization of p- and d-electrons throughout the chelate and increases the complex's lipophilicity. The cell permeability of the lipid membrane that surrounds the cell favors the passage of only lipid-soluble molecules, as liposolubility is a key element in antibacterial action. The increased lipophilicity improves the complexes' penetration into lipid membranes and the blockage of metal binding sites on the microorganism's enzymes.

Table 4: The antibacterial activity of the free ligands and its complexes against some reference strains expressed in absolute activity (AU)

Complexes	***Candida albicans***		***Escherischia coli***		***Pseudomonas aeruginosa***		***Staphyllococcus aureus***		***Bacillus subtilis***	
	Blank	**Cpd**	**Blank**	**Cpd**	**Blank**	**Cpd**	**Blank**	**Cpd**	**Blank**	**Cpd**
Sulfaquinoxaline	9	9	9	9	9	9	9	9	9	9
$[Fe_2(HL)\ Cl_6(H_2O)_2]$	9	9	9	9	9	9	9	9	9	9
$[Co_2(HL)_3\ Cl_4(H_2O)_2]$	9	9	9	9	9	9	9	26	9	9
$[Cu_2(HL)_3\ Cl_2(H_2O)_2]$	9	9	9	9	9	9	9	22	9	9
$[Zn_2\ (HL)_3Cl_4(H_2O)_2]$	9	9	9	9	9	9	9	21	9	9
Ciprofloxacin(as reference)	-	-	9	30	9	30	9	30	10	30
Clotrimazole (as reference)	9	18	-	-	-	-	-	-	-	-

Ligand

The docked ligand **Figure 3** have effective ligand-receptor interaction distances were ≤ 3.0 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 2x7x (2.62A) With Mol dock score 18100 kcal Furthermore, two binding sites were observed of different amino acids(Asp 171 ,Glu 69) with ligand demonstrating their good inhibition [18-22].

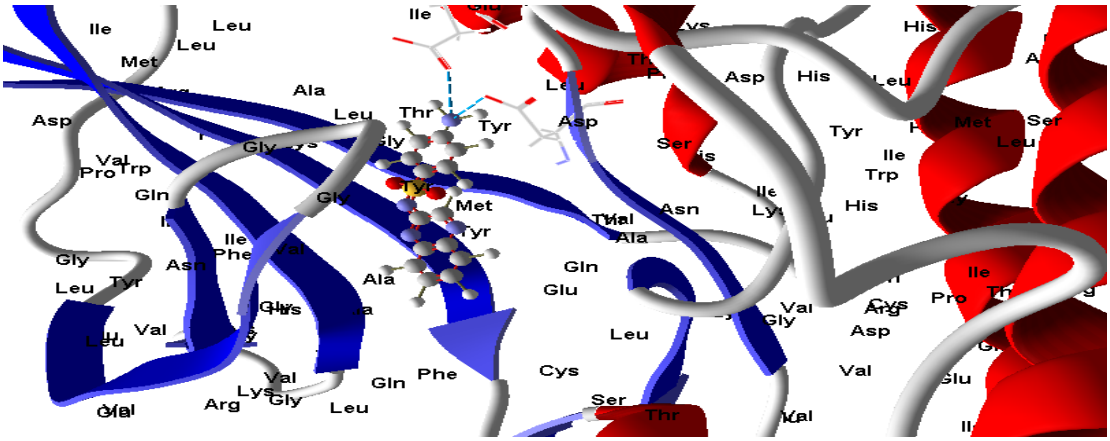

Figure 3: Virtual Molecular docking of the best docked ligand with 2x7x

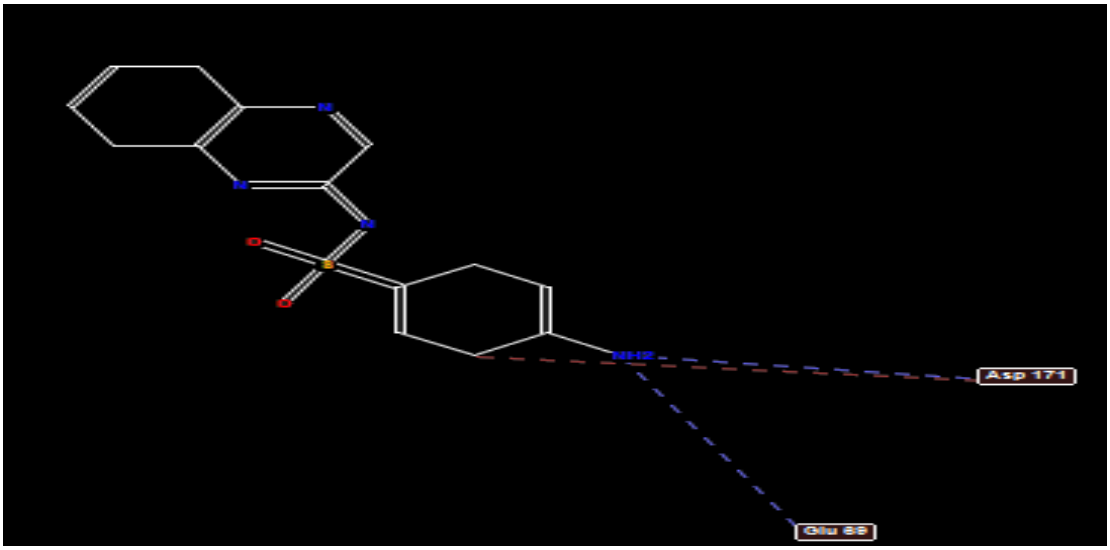

Figure 4: 2D structure of Molecular docking of ligand with 2x7x protein

$[Co_2(HL)_3\ Cl_4(H_2O)_2]$

The docked $[Co_2(HL)_3\ Cl_4(H_2O)_2]$ (**Figure 5)** is the only complex have effective ligand-receptor interaction distances were ≤ 3.5 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 2x7x (3.23A) $[Co_2(HL)_3\ Cl_4(H_2O)_2]$ With Mol dock score 302305 kcal Furthermore, eighteen binding sites were observed of different amino acids(Asp 116(A) ,Asn 118(A), Ala 110(A), , lle 308(A), Leu 118(A) and Thr 308(A)) with $[Co_2(HL)_3\ Cl_4(H_2O)_2]$complex demonstrating their excellent inhibition than ligand [23-25].

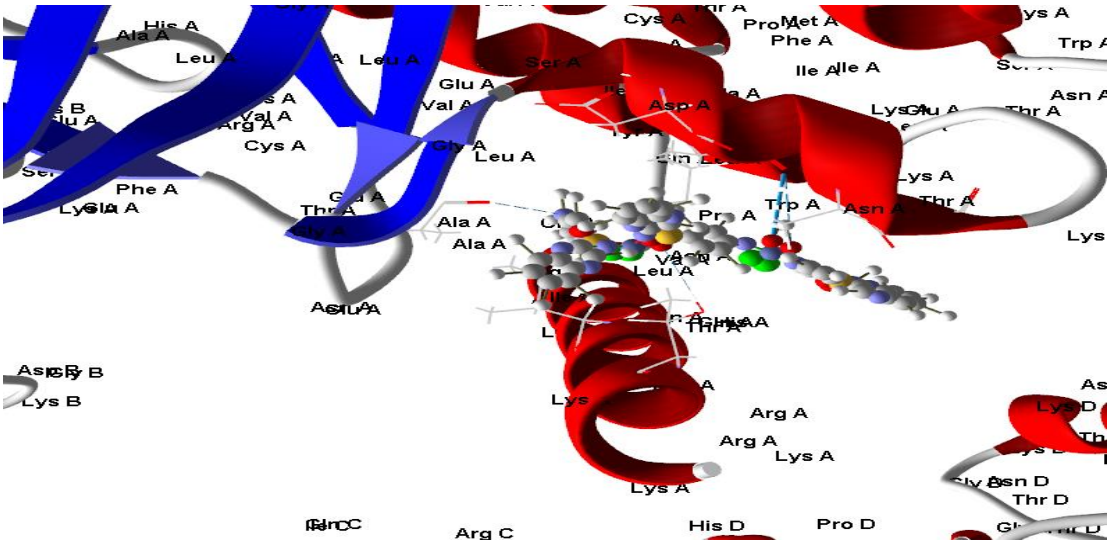

Figure 5: Virtual Molecular docking of the best docked $[Co_2(HL)_3\ Cl_4(H_2O)_2]$ with 2x7x

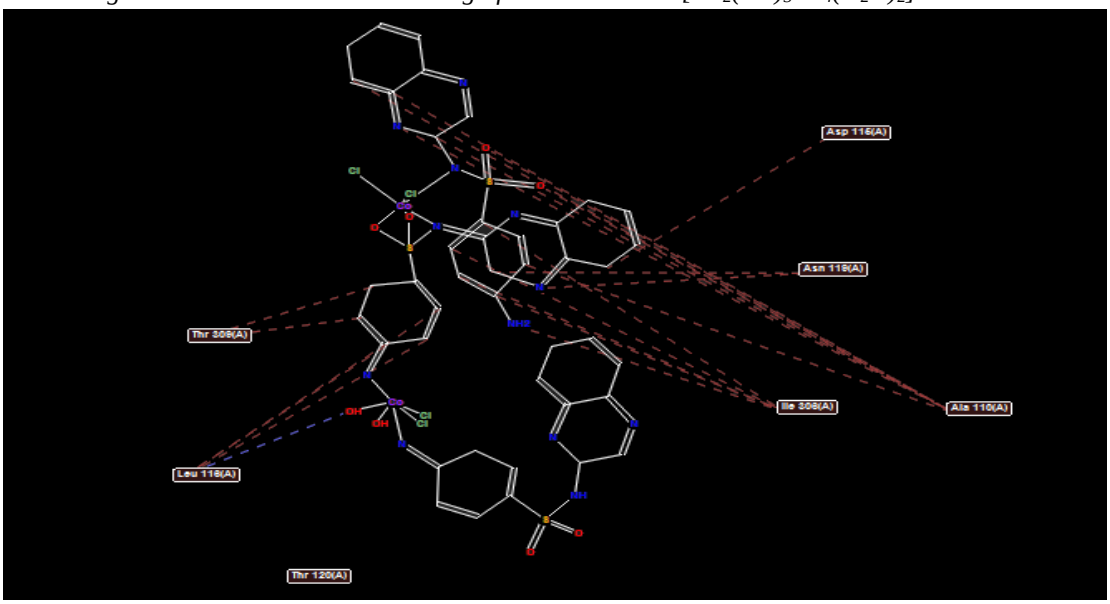

Figure 6: 2D structure of Molecular docking of $[Co_2(HL)_3\ Cl_4(H_2O)_2]$ with 2x7x protein

Conclusion

Sulfaquinoxaline metal complexes with transition metals (Cr(III), Mn(II), Co(II), Fe(III),Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)) have been synthesized. IR spectra demonstrated that the sulfaquinoxaline ligand works as a tetradentate ligand. All sulfaquinoxaline compounds have octahedral geometry, as evidenced by magnetic and spectroscopic data. For some bacteria, sulfaquinoxaline complexes outperform industrial sulfaquinoxaline. Molecular docking study is done for some metal complexes as anti-Colorectal cancer

Reference

[1]. Rodrigo, H. Tarso, B.K., Analysis of sulfanomides by capillary electrophoresis, J of separation science, (2009), 32(5-6), 854-66.

[2]. Lide, David R. Handbook of Chemistry and Physics (87 ed., Boca Raton, Florida: CRC Press, (1998), pp. 3–26.
[3]. Kahn, C.M. Ed.,The Merck Veterinary Manual 9th ed, Merck & Co. Whitehouse Station, NJ. (2005), p. 2261.
[4]. Ullmann's Encyclopedia of Industrial Chemistry. 6th ed. Vol 1: Federal Republic of Germany: Wiley-VCH Verlag GmbH & Co. 2003 to Present, p. V. 38 24 (2003).
[5]. Cook D. S. and Turner M. F. J. Chem. Soc. Perkin Trans., (1975), 2, 1021.
[6]. Yakuphanoglu, F. Gorgulu, A.O. Cukurovali, A. Physica B, (2004), 353, 223.
[7]. Xiu, H.Z., Ya-Yun, Z. Jie, Z. Jian-Guo, P. Xing, L., Synthesis, crystal structure and fluorescence spectrum of a cadmium(II) sulfaquinoxaline complex, J. of metal-organic compounds, (2013), 69(11), 1332-1335.
[8]. Saleh N., Khowdiary M., Badawi A.F., Synthesis and Antitumor and Surface Activity of Novel Tetrachloro Metallate Complexes of Sulfaquinoxaline with Co(II), Cu(II), or Sn(II) Chlorides, J. of hanser elibrary, 2014, 318-324.
[9]. Schwarzenbach G. Complexometric Titration, Translated by H, Methuen Co., London, Irving, (1957).
[10]. Lee R.H, Griswold E, Kleinberg J. Inorg. Chem., (1964), 3, 1278-1283. http://doi.org/10.1021/ic50019a018.
[11]. Kolkaila S.A. , Ali A.E. and Elasala G.S., Synthesis, Spectral Characterization of Azithromycin with Transition Metals and a Molecular Approach for Azithromycin with Zinc for COVID-19. Int J Cur Res Rev. (2021)13, 23, 53-59.
[12]. Masoud M.S., Ali A.E., Elasala G.S. and Kolkaila S.A., Synthesis, spectroscopic, biological activity and thermal characterization of ceftazidime with transition metals. Spectrochim. Acta. (2018) 193, 458-466.
[13]. Ali A. E., Elasala G. S., Mohamed E. A. and Kolkaila S.A., Spectral, thermal studies and biological activity of pyrazinamide complexes heliyon, (2019) 5(11).
[14]. Ali A.E., Elasala G.S., Mohamed E. A. and Kolkaila S.A., Structural and thermal analysis of some imipramine complexes. J. Materials Today Proceeding.
[15]. Masoud M.S., Ali A.E., Elasala G.S. and Kolkaila S.A., Synthesis, Spectroscopic Studies and Thermal Analysis on Cefoperazone Metal Complexes. J. Chem. Pharm. Res. (2017)9(4), 171-179.
[16]. Masoud M.S., Ali A.E., Elasala S. G., S.F Sakr, Kolkaila S.A., Structural, Physicochemical Studies of Some Biologically Active Metal Complexes of Cefazolin Antibiotics. J. Chem. Pharm. Res. (2020) 12, 42-52.
[17]. Kolkaila S.A. , Ali A.E., Doha Beltagy and Elasala G.S., Spectral and Biological Studies of Some Selected Thiouracil, Barbital and Thiobarbituric Acid Complexes. J Drug Des. Res. (2018) 5, 2, 1071-1079.
[18]. Ali A. E. Elmelegy E., Kolkaila S. A., Mustafa A. A., Eledkawy A. M. and Alnaggar G. A. Removal of Cadmium (II) from Water by Adsorption on Natural Compound. Journal of Environmental Treatment Techniques, (2022), 10(2), 164-169.
[19]. Kolkaila S.A. , Ali A.E. , Mustafa Ahmed A. Removal of Aluminum (III) from Water by Adsorption on the Surface of Natural Compound. J. of Environmental Treatment Techniques, 2023, 11(2), 10-105.
[20]. Ali A.E., Elasala G.S., Rana M. Atta. and Kolkaila S.A., Synthesis, Thermal Analysis and Characterization of Doxycycline Metal Complexes chemistry research journal. (2022) 7, 2, 90-91.
[21]. Ali A. E., Elasala G. S., Eldeeb M. H., kolkaila S. A. Synthesis and Biological Activity and Thermal Analysis of Sulfaquinoxaline Mixed Metal Complexes. Journal of Chemistry & its Applications. (2022) SRC/JCIA-119.DOI: doi.org/10.47363/JCIA/2023(2)119.
[22]. El-Tabl, A. S., El-Wahed, M. M. A., El Kadi, N. M., Kolkaila, S. A., & Samy, M. Novel Metal Complexes of Bioactive Amide Ligands as New Potential Antibreast Cancer Agents. TWIST, (2023)18(4), 151-169.
[23]. El-Tabl, A. S., Kolkaila, S. A., Abdullah, S. M., & Ashour, A. M. Nano-Organometallic Compounds as Prospective Metal Based Anti-Lung Cancer Drugs: Biochemical and Molecular Docking Studies. TWIST, (2023) 18(4), 141-150.

[24]. El-Tabl, A. S., Dawood, A. A. E. R., Kolkaila, S.A., Mohamed, E. H., & Ashour, A. The Cytotoxicity of Some Biologically Active Nano Compounds against Colon Cancer: Advanced Biochemical Analyses. TWIST, (2023) 18(4), 360-371.

[25]. El-Tabl, A. S., Abd El-Wahed, M. M., Kolkaila, S. A., Abd El-Nasser, A. G., & Ashour, A. M. Biochemical Studies on Some Novel Organometallic Complexes as Anti-Human Prostate Cancer. TWIST, (2024) 19(1), 16-26.