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Evaluation of the Binding Affinities of Mixed Ligands Metal (II) Complexes of Quercetin Sulphonic Acids on Breast Cancer Cells Using Molecular Docking

Idongesit Nathaniel Ufot*, Nzikakyel Simon, Atim Sunday Johnson, Ekarika Clement Johnson, Idongesit Bassey Anweting and Victor Mkpenie

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Abstract: This study investigated the binding affinities of mixed-ligands metal (II) complexes of quercetin sulphonic acids on a protein macromolecule from Breast Cancer cells using molecular docking. The protein macromolecule with code: 1OQA, was downloaded from the protein data bank and prepared using the Discovery Studio software, the mixed-ligands metal (II) complexes of quercetin-5-sulphonic and quercetin-8-sulphonic acids were drawn using Chemsketch software and afterwards converted to a structure data format (sdf) with the help of Open Babel software. The co-ligands used in this study included Benzoic, Citric, Isophthalic, Oxalic, Salicylic, Succinic, Terephthalic acids and Imidazole. The docking was performed with PyRx software, and visualized with Discovery Studio. The results indicate that apart from the nature of the binding sites of the breast cancer cell protein 1OQA, the position of the sulphonic substituent on the quercetin ring, the type of metal ion used in the coordination, and the nature of the co-ligand all affected the binding affinities of the complexes. Generally, the observed enhanced binding affinities of the complexes seem to be more pronounced when Benzoic, Isophthalic acids and Fe^{2+}, Mn^{2+} ions are involved in the structures. Also, the co-ligand with aromatic ring shows enhanced affinity compared to aliphatic co-ligands with several variations.

***Keywords**: Molecular docking, Quercetin derivatives, Metal coordination, Breast cancer*

Idongesit Nathaniel Ufot
Department of Chemistry, Faculty of Physical Sciences, University of Uyo, Akwa Ibom, Nigeria.
Email: idongesitufot@ymail.com
Orcid id: 0000-0002-2990-499X

Nzikahyel Simon
Department of Chemistry, Faculty of Physical Sciences, University of Uyo, Akwa Ibom, Nigeria.
Email: nzikahyelsimon@uniuyo.edu.ng
Orcid id: 0000-0002-6753-7633

Atim Sunday Johnson
Department of Chemistry, Faculty of Physical Sciences, University of Uyo, Akwa Ibom, Nigeria.
Email: atimjohnson@uniuyo.edu.ng
Orcid id: 0000-0001-8732-2704

Ekarika Clement Johnson
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Uyo, Akwa Ibom, Nigeria.
Email: ekarikajohnson@uniuyo.edu.ng
Orcid id: 0000-0002-0932-5254

Idongesit Bassey Anweting
Department of Chemistry, Faculty of Physical Sciences, University of Uyo, Akwa Ibom, Nigeria.
Email: idongesitanweting@uniuyo.edu.ng
Orcid id: 0000-0002-9251-3991

Victor Mkpenie
Department of Chemistry, Faculty of Physical Sciences, University of Uyo, Akwa Ibom, Nigeria.
Email: victormkpenie@uniuyo.edu.ng
Orcid id: 0000-0002-3264-5474

1.0 Introduction

Cancer is a complex and heterogeneous group of diseases characterized by uncontrolled cell growth and the potential to invade other tissues. It remains a major global health challenge, with conventional treatments such as surgery, chemotherapy, and radiation therapy often accompanied by significant side effects and limited effectiveness in some cases. The search for alternative therapeutic strategies has led to extensive research into metal-based drugs, which have shown promising anticancer properties. The field of medicinal inorganic chemistry, which gained significant attention following the discovery of the cytotoxic activity of Cisplatin, has continued to evolve, leading to the development of metal complexes with enhanced anticancer potential. Various metal-based compounds, including platinum and ruthenium complexes, have demonstrated their ability to interact with cellular components, induce apoptosis, and inhibit tumor growth. However, challenges such as drug resistance, toxicity, and selectivity remain significant concerns, necessitating further research into novel metal-based therapeutics with improved pharmacological properties.

Quercetin, a naturally occurring flavonoid, has attracted considerable interest due to its diverse biological activities, including anticancer, anti-inflammatory, antioxidant, and cardioprotective effects. Despite its promising pharmacological properties, its application in drug development has been limited by its poor solubility and instability in physiological conditions. To overcome these limitations, researchers have explored chemical modifications of quercetin, including the introduction of sulphonic acid groups, to enhance its water solubility and bioavailability. Studies have demonstrated that quercetin sulphonic acid derivatives exhibit improved physicochemical properties and enhanced biological activity. However, while individual quercetin derivatives have been extensively studied, little is known about the potential of mixed-ligand metal complexes of quercetin sulphonic acids in anticancer therapy.

Molecular docking, a widely used computational technique in drug discovery, provides valuable insights into the binding interactions between small molecules and biological macromolecules. It enables the prediction of ligand-receptor interactions, helping to identify potential drug candidates with strong binding affinities. Recent studies have applied molecular docking approaches to investigate the anticancer properties of flavonoid-metal complexes, but research specifically targeting the interactions of mixed-ligand metal complexes of quercetin sulphonic acids with breast cancer protein macromolecules remains scarce. Understanding these interactions could provide crucial information for the design of novel metal-based anticancer drugs with enhanced efficacy.

Despite the progress in metal-based drug research, there remains a gap in knowledge regarding the molecular docking interactions of mixed-ligand metal complexes of quercetin sulphonic acids with breast cancer-associated proteins. Most studies have focused on individual flavonoid-metal complexes, without exploring the impact of incorporating co-ligands in coordination with metal ions. Additionally, the influence of different metal ions and ligand substitutions on binding affinities has not been systematically analyzed. Addressing this knowledge gap is essential for the rational design of metal-based therapeutics with improved anticancer potential.

This study aims to evaluate the binding affinities and interactions of mixed-ligand metal (II) complexes of quercetin sulphonic acids with the breast cancer protein 1OQA using molecular docking. The study investigates how variations in the position of sulphonic substituents on the quercetin ring, the nature of co-ligands, and the type of metal

ions affect the binding affinity of the complexes. The results are expected to provide valuable insights into the structure-activity relationships governing the interaction of these metal complexes with breast cancer protein targets.

The significance of this study lies in its potential to contribute to the development of novel metal-based anticancer drugs with improved selectivity and therapeutic efficacy. By exploring the interactions between quercetin sulphonic acid metal complexes and breast cancer proteins, the study could offer new perspectives for designing drug candidates with enhanced binding properties. Additionally, the findings may serve as a foundation for further computational and experimental studies aimed at optimizing metal-flavonoid complexes for cancer therapy. Understanding these molecular interactions could ultimately facilitate the development of targeted treatments with fewer side effects and greater therapeutic potential.

2.0 Materials and Methods

2.1 Hardware and Software

The computational tools used in this study included PyRx – Python Prescription 0.8, Discovery Studio 2021, Open Babel version 2.4.1, and ChemSketch (Freeware 2023.1.1). These software programs facilitated ligand preparation, molecular docking, and result visualization.

Ligands A total of ninety-six (96) mixed-ligand metal (II) complexes of quercetin-5-sulphonic acid (Q5SA) and quercetin-8-sulphonic acid (Q8SA) were designed using ChemSketch and converted to Structure Data Format (SDF) using Open Babel. The co-ligands incorporated in these complexes included benzoic acid (BA), citric acid (CA), isophthalic acid (Iso), oxalic acid (Oxa), salicylic acid (SA), succinic acid (SU), terephthalic acid (TA), and imidazole (Imi). Representative structures of these metal-ligand complexes are provided in Fig. 1–10.

Receptor The macromolecular target used in this study was the breast cancer gene-regulatory protein with Protein Data Bank (PDB) code 1OQA. This protein was obtained from the Protein Data Bank (PDB) and was originally characterized by Gaiser et al. (2004). The prepared protein structure is shown in Fig. 11.

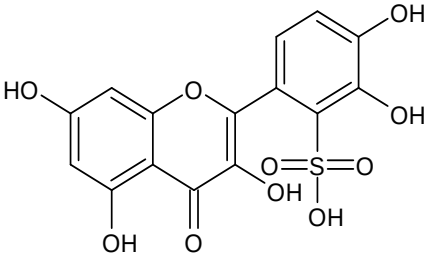


Fig. 1: Quercetin-5-sulphonic acid

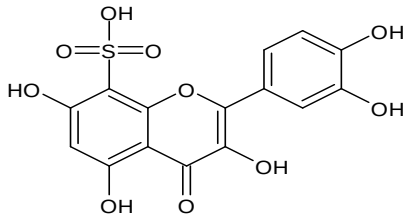
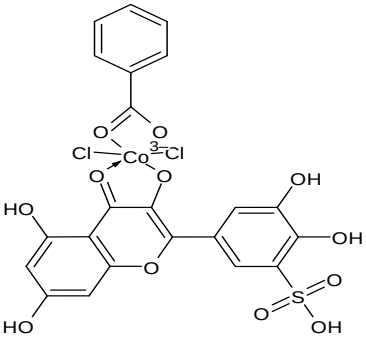


Fig. 2: Quercetin-8-sulphonic acid



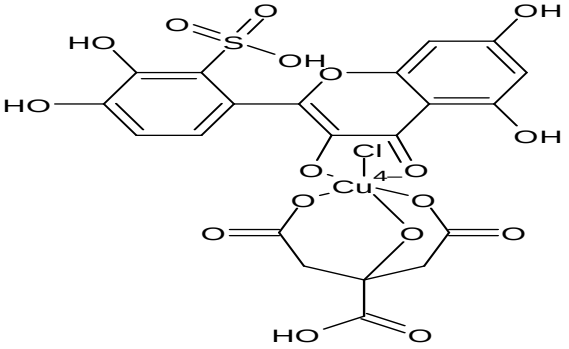


Fig. 3: Co[Q5SA][BA]Cl_2

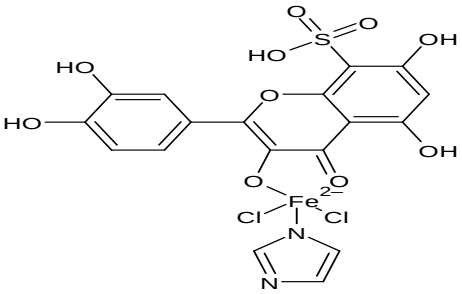


Fig. 4: Cu[Q5SA][CA]Cl

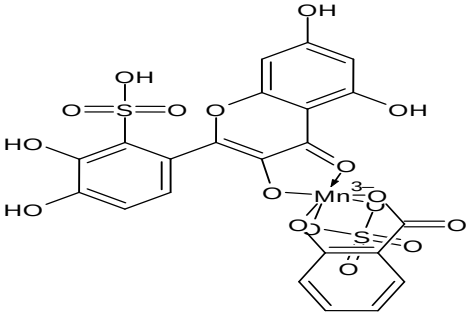


Fig. 5: Fe[Q8SA] [Imi]Cl_2

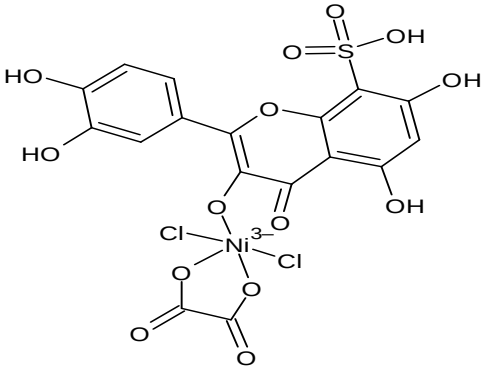


Fig. 6: Mn[Q5SA] [SA]SO_4

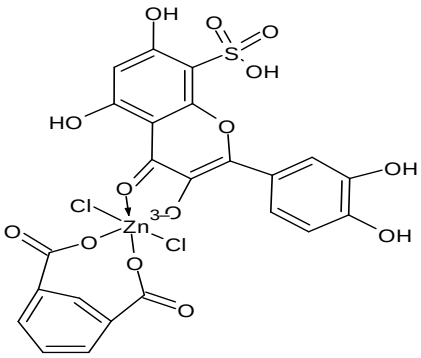


Fig. 7: Ni[Q8SA] [Oxa]Cl_2

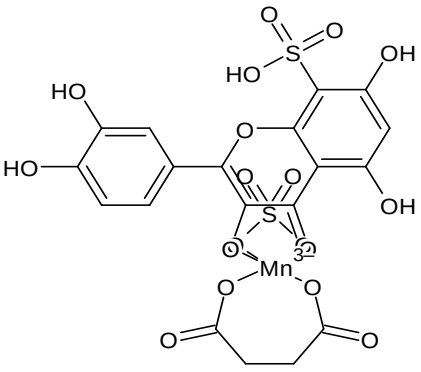


Fig. 8: Zn[Q8SA] [Iso]Cl_2

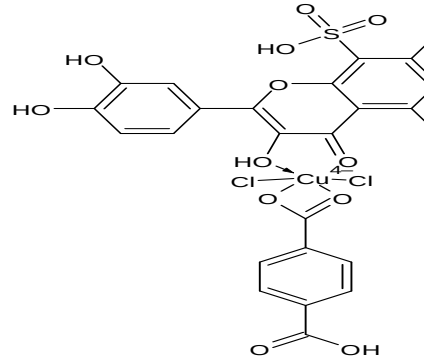


Fig. 9: Mn[Q8SA] [SU]SO_4

iii. Receptor

The macromolecule used in this study has a Protein Data Bank (PDB) code; 1OQA (Fig 11). It is classified as a gene-regulation breast cancer protein molecule (Gaiser *et al*., 2004). This was downloaded from the Protein Data Bank

Fig.10: Cu[Q8SA] [TA]Cl_2

2.1 Docking Protocol

Preparation of Ligands All ligands were drawn using ChemSketch software and converted to SDF format using Open Babel. This ensured compatibility with the molecular docking software.

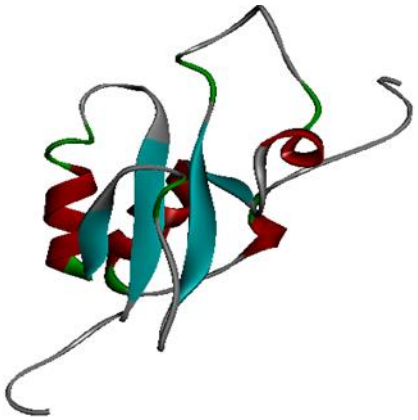


Fig 11: Prepared Protein Molecule (1OQA)

Preparation of the Protein The downloaded protein structure was processed using Discovery Studio Visualizer. To ensure accurate docking, all conformations except conformation A, along with other chains, water molecules, and heteroatoms, were deleted. Polar hydrogen atoms were then added to optimize interactions between the protein and ligands.

Molecular Docking and Visualization Molecular docking simulations were conducted using AutoDock Vina, embedded within PyRx software. The docking grid was defined using the following parameters:

- **Exhaustiveness:** 8 (indicating the number of search attempts to optimize ligand binding)
- **Grid Center Coordinates:** X: -2.2575, Y: -2.1629, Z: -3.5605
- **Grid Box Dimensions (Å):** X: 47.5700, Y: 45.7999, Z: 33.9740

After docking, the binding interactions were analyzed and visualized using Discovery Studio software to assess ligand-protein interactions and binding affinities.

3.0 Results and Discussion

Table 1 presents the molecular docking results of Q5SA metal complexes, showing their binding affinities (kcal/mol) with different co-ligands. The binding affinity values provide insights into the interaction strength between the complexes and the target protein (1OQA). More negative energy values indicate stronger binding, suggesting higher stability and potential bioactivity.

Table 1: Results of Molecular Docking of Complexes of Q5SA Showing Binding Affinities

DERIVATIVE	COMPLEX	BINDING AFFINITY(kcal/mol)							
Q5SA		[BA]	[CA]	[Imi]	[Iso]	[Oxa]	[SA]	[SU]	[TA]
	Mn[Q5SA]	-7.6	-7.5	-7	-8.5	-7.9	-7.7	-7.6	-7.3
	Fe[Q5SA]	-8.7	-7.7	-6.8	-7.7	-7	-7.4	-7.1	-7.7
	Co[Q5SA]	-8.1	-7.6	-7.2	-7.7	-7.3	-8	-7.2	-7.9
	Ni[Q5SA]	-8.1	-7.7	-7.3	-7.8	-7.3	-7.6	-6.9	-7.7
	Cu[Q5SA]	-7.8	-7	-7	-7.7	-7.1	-7.3	-7.8	-7.7

**** The complexes in the second column are coordinated with the ligands in the first row**

The Fe[Q5SA] complex coordinated with benzoic acid (BA) exhibits the strongest binding affinity with lowest energy (-8.7 kcal/mol), indicating a highly stable interaction with the receptor. This suggests that Fe[Q5SA]-BA may be particularly effective in potential applications requiring strong metal-ligand interactions.

The Mn[Q5SA] complex with isophthalic acid (Iso) also shows a strong binding affinity (-8.5 kcal/mol), indicating that Iso plays a crucial role in stabilizing this interaction. The Co[Q5SA] and Ni[Q5SA] complexes exhibit relatively consistent binding affinities across different co-ligands, with values ranging between -7.2 and -8.1 kcal/mol.

Among all the metal complexes, Cu[Q5SA] consistently demonstrates weaker binding affinities with high binding energies, with values ranging from -7.0 to -7.8 kcal/mol. This suggests that copper-based coordination may not enhance receptor binding as effectively as iron or manganese.

Fig. 12 and Fig. 13 provide a graphical comparison of the binding affinities of Q5SA complexes with respect to different metal ions and co-ligands. While **Fig. 12** illustrates how different metal ions influence binding affinity when coordinated with various co-ligands. The trend confirms that Fe[Q5SA] and Mn[Q5SA] demonstrate stronger binding, especially when coordinated with BA and Iso. Furthermore, **Fig. 13** presents the effect of different co-ligands on metal complex stability. The data suggests that Iso and BA enhance binding across different metal ions, while CA and Imi result in relatively weaker interactions.

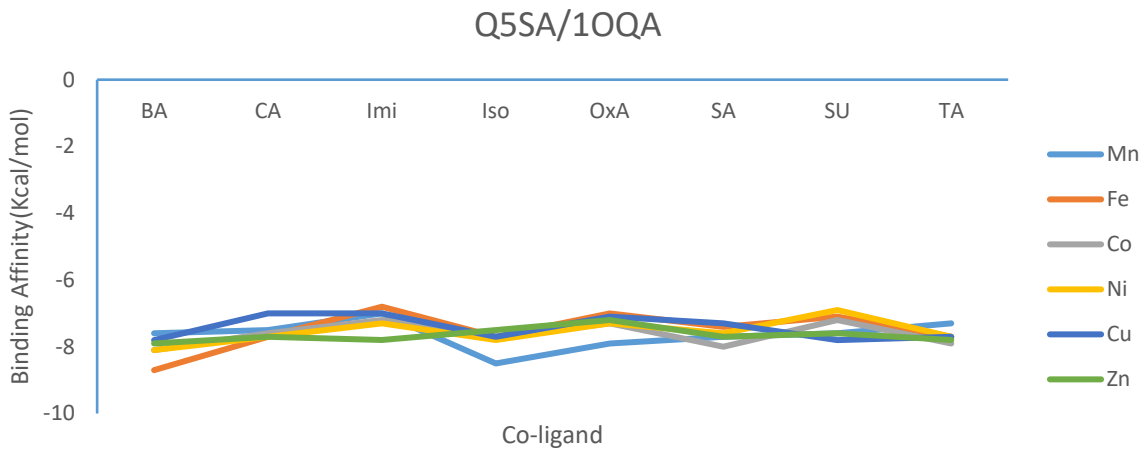


Fig. 12: Graphical comparison of the co-ligands effects on binding affinities of the Q5SA complexes to the coordinating metal ions.

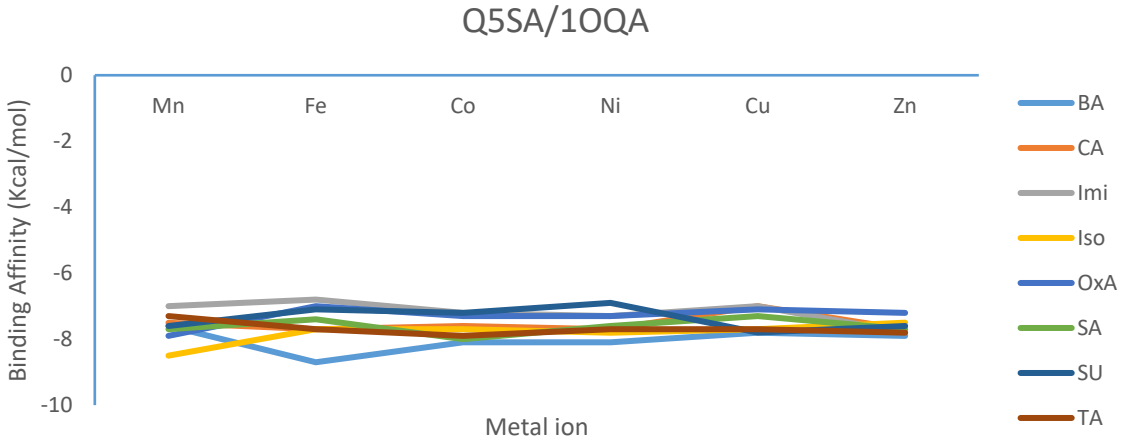


Fig. 13: Graphical comparison of the metal ions effects on binding affinities of the Q5SA complexes with respect to their co-ligands.

The results suggest that the nature of both the metal ion and co-ligand significantly impacts binding affinity. The lowest binding energy observed for Fe[Q5SA]-BA and Mn[Q5SA]-Iso may be attributed to favorable electronic interactions, steric compatibility, and hydrogen

bonding. The weaker binding affinities for Cu[Q5SA] complexes may indicate suboptimal coordination geometry, reducing its ability to form stable interactions. These findings highlight the potential of Fe and Mn-based Q5SA complexes for further bioactivity studies.

Table 2 presents the molecular docking results for Q8SA complexes, displaying the binding affinities of different metal ions coordinated with co-ligands.

Table2: Results of Molecular Docking of Complexes of Q8SA Showing Binding Affinities

DERIVATIVE	COMPLEX	BINDING AFFINITY(kcal/mol)							
Q8SA		[BA]	[CA]	[Imi]	[Iso]	[OxA]	[SA]	[SU]	[TA]
	Mn[Q8SA]	-8.1	-7.6	-6.6	-8.4	-8.3	-8.3	-8.3	-8.3
	Fe[Q8SA]	-7.8	-7.6	-7.2	-8.4	-6.9	-7.6	-7	-7.8
	Co[Q8SA]	-8.2	-7.9	-7.2	-8.6	-7.3	-7.8	-7.3	-7.6
	Ni[Q8SA]	-8.2	-7.4	-7.2	-8.6	-7.5	-7.7	-7.4	-7.7
	Cu[Q8SA]	-7.8	-7.7	-7.3	-7.8	-7.1	-7.8	-7.2	-7.4
	Zn[Q8SA]	-7.5	-7.6	-7	-7.8	-7.3	-7.5	-7.4	-7.4

Note: The complexes in the second column are coordinated with the ligands in the first row and so on.

The Co[Q8SA] and Ni[Q8SA] complexes with isophthalic acid (Iso) exhibit the strongest binding affinities with lowest binding energy (-8.6 kcal/mol), suggesting that Iso contributes significantly to stabilizing these complexes. Similarly, Mn[Q8SA] coordinated with oxalic acid (OxA) shows a strong binding affinity (-8.3 kcal/mol), comparable to its binding with Iso.

Unlike Q5SA, where Fe[Q5SA] had the highest affinity with lowest energies, Q8SA complexes exhibit more uniform binding behavior across different metal ions, with Co[Q8SA], Ni[Q8SA], and Mn[Q8SA] showing consistently low binding values. The Zn[Q8SA] complexes demonstrate the weakest binding affinities having highest binding energies, particularly when coordinated with BA and CA, suggesting that zinc may not favorably interact with the receptor.

Fig.14 compares binding affinities across different metal ions in Q8SA complexes, highlighting that Co and Ni exhibit the strongest interactions with the receptor, particularly when coordinated with Iso, whereas Fig. 15 illustrates how different co-ligands influence binding in complexes of Q8SA. Iso consistently enhances binding affinity across metal ions, while Imi results in relatively weaker interactions.

The results suggest that the Q8SA ligand system demonstrates strong and consistent binding across different metal ions, with Co[Q8SA] and Ni[Q8SA] showing the highest stability. The presence of Iso and OxA as co-ligands significantly enhances binding interactions, likely due to their ability to facilitate hydrogen bonding and electron delocalization.

The lower binding affinities observed for Zn[Q8SA] suggest that zinc does not coordinate effectively with the receptor, making it a less favorable candidate for further applications. The relatively uniform binding affinities for Q8SA complexes suggest that this ligand system may offer more predictable and stable interactions across different metal ions compared to Q5SA.

The docking results for Q5SA and Q8SA highlight the importance of metal-co-ligand interactions in determining binding affinity.

While Fe[Q5SA] and Mn[Q5SA] exhibited the strongest binding in Q5SA complexes, Co[Q8SA] and Ni[Q8SA] were the most stable in Q8SA complexes. The choice of co-ligand, particularly Iso and OxA, plays a significant role in enhancing stability. These findings provide valuable insights for designing metal-based bioactive complexes.

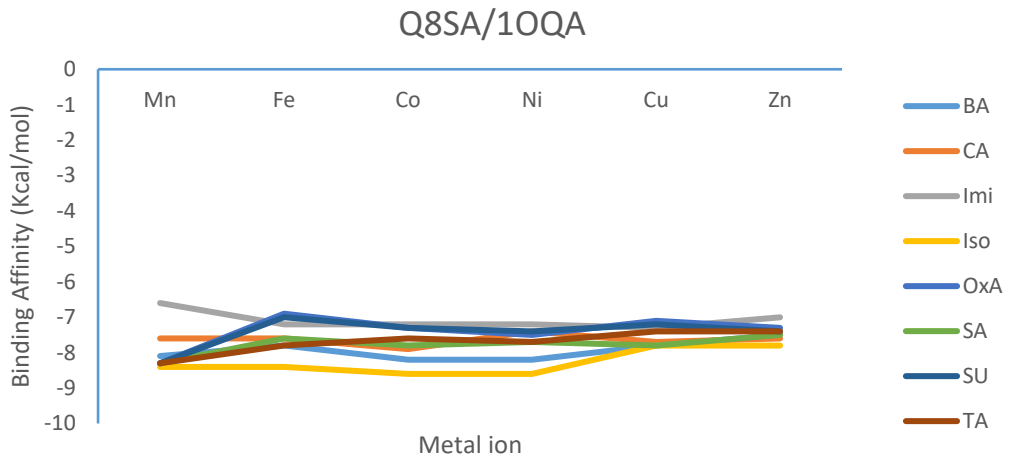


Fig. 14: Graphical comparison of the effects of metal ions on binding affinities of the Q8SA complexes with respect to their co-ligands.

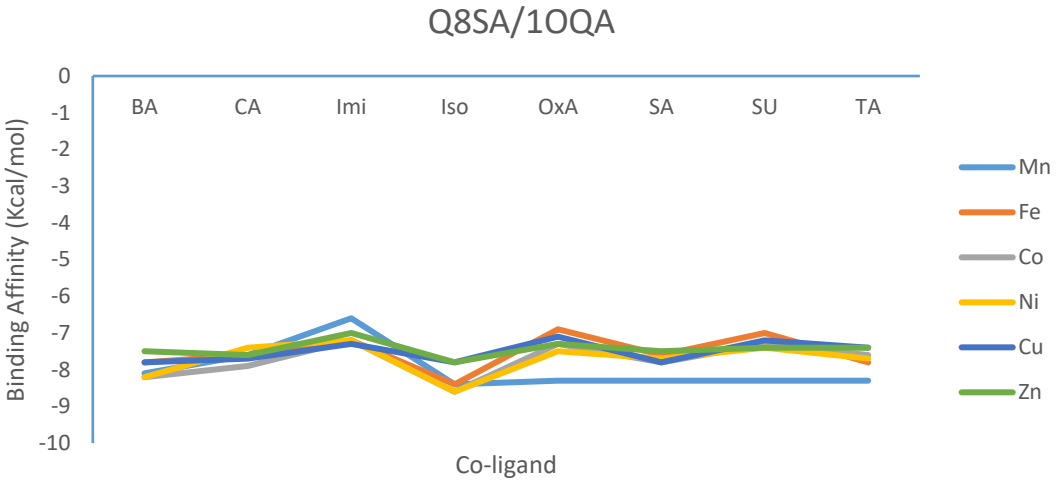


Fig. 15: Graphical comparison of the co-ligands effects on binding affinities of the Q8SA complexes with respect to the coordinating metal ions.

Some of the interactions between the mixed-ligand metal complexes of quercetin sulphonic acids in the binding site of the 1OQA macromolecule are presented in Figures 16 -19. These interactions are affected by: the position of the sulphonic functional group on the main quercetin ring, the type of co-ligand, the metal ion and the type of solvent used. It has been observed that the $–SO_4$ attached to position 8 on the main quercetin ring is far from the site of the metal coordination and hence faces less constraint, whereas this same functional group at position 5 should be expected to face several constraints due to steric hindrances. However, more interactions are observed with ligands having the $–SO_4$ at position 8 as seen in Figures

21 and 22. Most of these interactions occur at the Quercetin C ring where interactive co-ligands are used in the coordination. Meanwhile, the $–SO_4$ at position 8 rarely interact unlike at position 5. Nevertheless, stable interactions were expected with Quercetin derivatives due to variability in oxidation states of transition metals compared to pure Quercetin and the co-ligands (Kumar and Ameta, 2018; Xu *et al*., 2019). The specific interactions exhibited by the metal ions seem to depend on the electronic and steric properties of the metal and the ligands involved in the coordination (Haas and Franz, 2009). Also, the strength of a bond is affected by the bond length, hence, the shorter the bond length the stronger the binding ability and therefore the stronger the binding affinity. It is noted that in molecular docking the lesser the binding energy, the stronger the binding ability. This summation is confirmed by the number of interactions of Q8SA complexes with binding affinities less than -8 kcal/mol compared to number for Q5SA complexes. Also, co-ligands with aromatic rings bind more easily in most cases compare to those without aromatic rings. This on one part is due to the ability of the pi electrons in the aromatic rings to form different types of interactions with the amino acids present at the binding sites of the macromolecule as listed in Table 3.

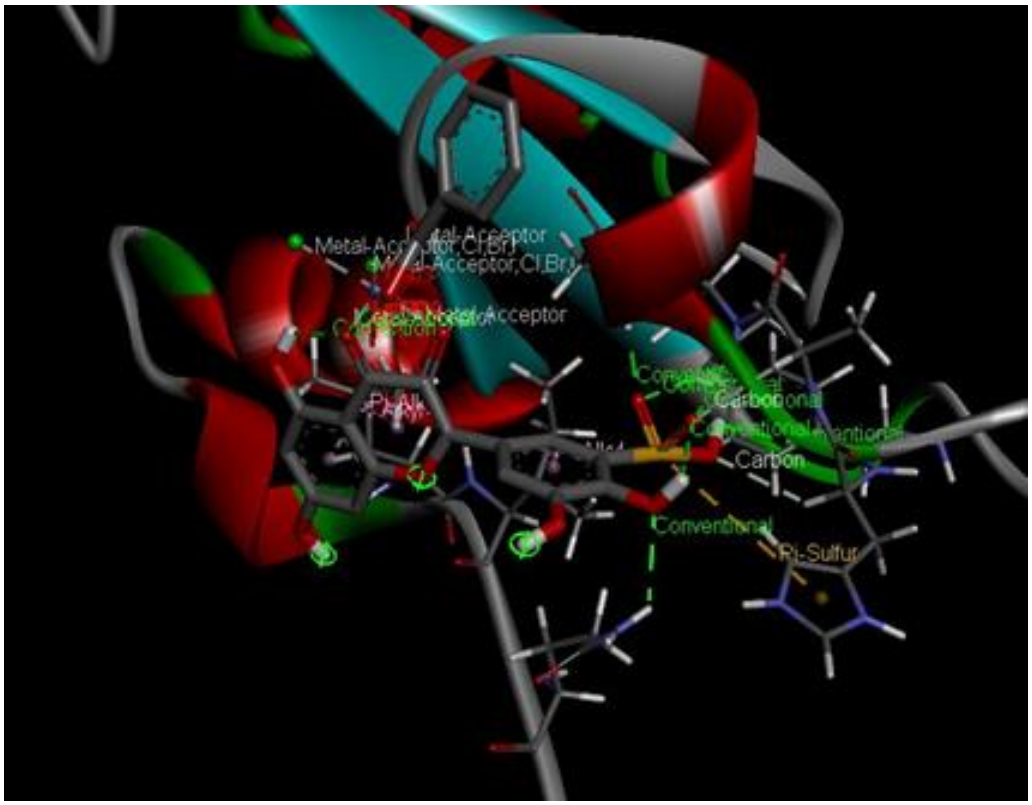


Fig. 16: Labelled Interactions of Fe[Q5SA] [BA] with 1OQA

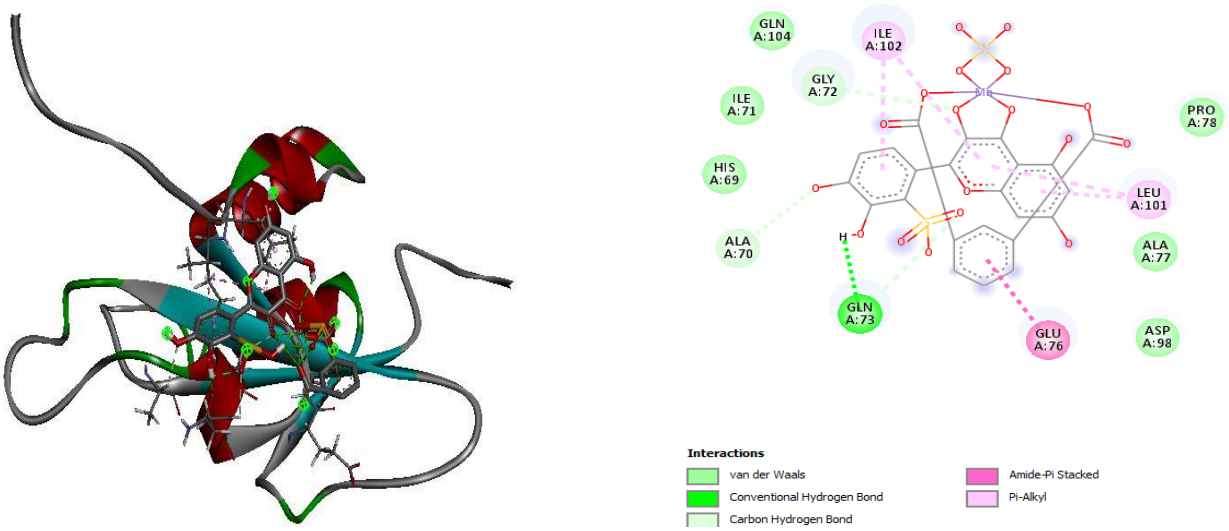


Fig. 17: 3D and 2D Interactions of Mn[Q5SA] [Iso] with 1OQA

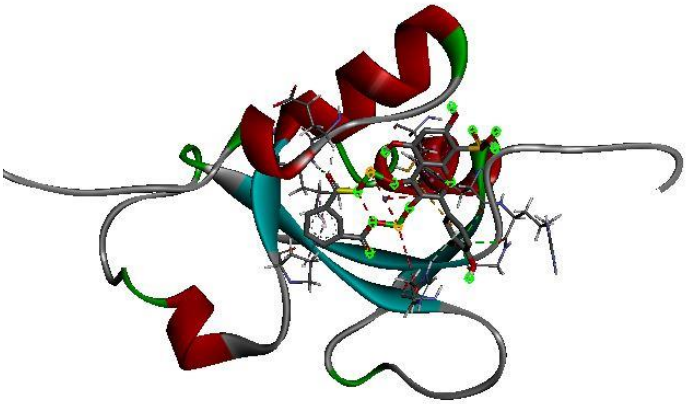


Fig. 18: Interactions of Co[Q8SA] [Iso] with 1OQA.

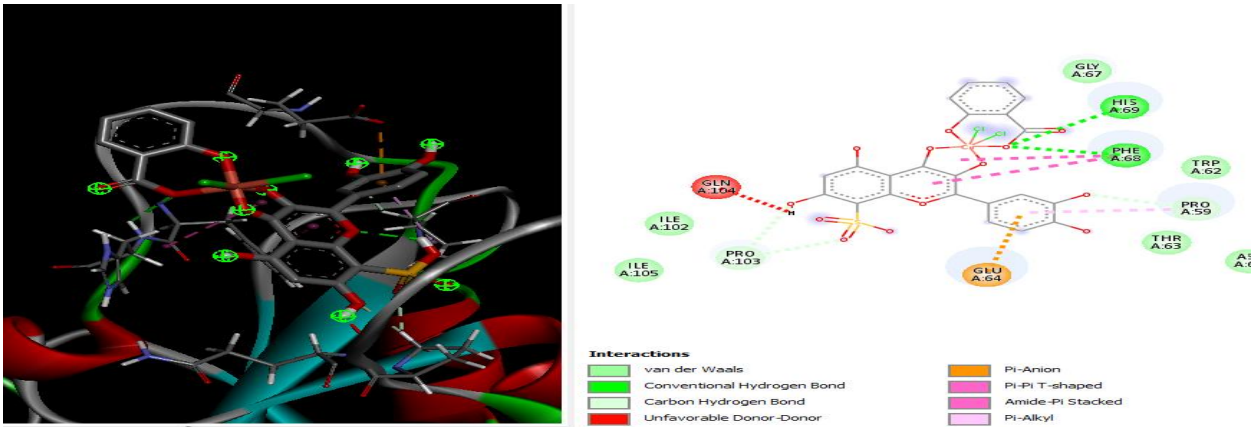


Fig. 19: Labelled 3Dand 2D Interactions of Cu[Q8SA][SA] with 1OQA.

Table 3: Molecular Docking Results for Best Ligands Showing Interactions with the Amino acids in the Macromolecule (1OQA)

Complex	B. aff (kcal/mol)	C-C	H-bond	π - alkyl	π - donor	π - sulphur	π – amide stacked	π - anion	π - π T shaped	+ve-+ve	Acceptor-acceptor	Donor-donor	Charge-charge
Q8CoSA	-7.8	Glu96	Gly10 Arg9 Phe8 Leu97	Pro78 Leu97 Cys94	His52	Cys94	-	-	-	His52		-	-
Q5CoBA	-8.1	His69	Gly72 Ala70	Leu101	-	His69	Gly72	-	-	-	-	-	-
Q5NiBA	-8.1	His69	His69 Gly72 Phe68	Leu101	-	His69	Gly72	-	-	-	-	Ile71	-
Q8NiIso	-8.6	Glu96	Phe8 Arg9 Gly10 Gly50 His52 Cyc94	Pro78 Leu97 Cyc94	His52	Cys94	-	-	-	-	-	-	-
Q5FeBA	-8.7	Ala70 His69 Ile71	Gln104 Gly72 Phe68	Leu101 Ile102	-	His69	-	-	-	-	-	-	-
Q5ZnBA	-7.9	-	Pro59	Pro59 Ile102 Pro103	-	-	-	Glu64	-	-	-	-	His69
Q8FeIso	-8.4	Glu96	Gly50 Gly10 Arg9	Cys94 Lue97 Pro78	His52	Cys94	-	-	His52	His52	-	-	-
Q8ZnIso	-7.8	-	Ile105 His69	Pro105 Pro59	-	-	-	Glu64	-	-	-	His69	-

			Thr63 Gly67 Phe68										
Q5CuSu	-7.8	Ser108	Thr63 Ile105 Gln104	Pro59 Pro103 Ile102	-	-	-	-	-	-	-	-	His69
Q5MnIso	-8.5	Gly72 Ala70 Gln73	Gln73	Ile102 Leu101	-	-	Ala77	-	-	-	-	-	-

Note: (-) means no interaction. B. aff means binding affinity.

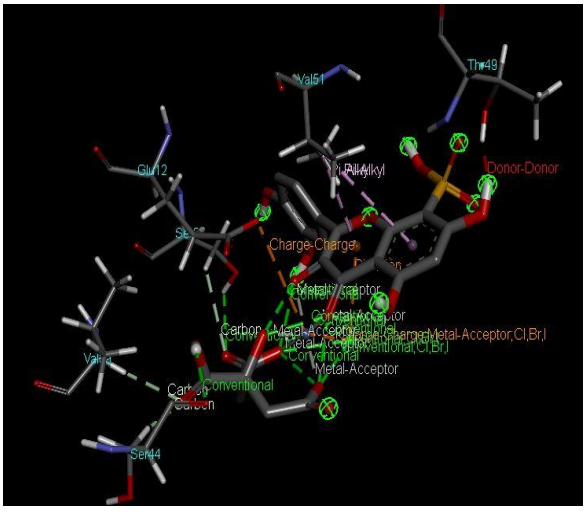


Fig.20: Labelled interactions of CuQ8SACA

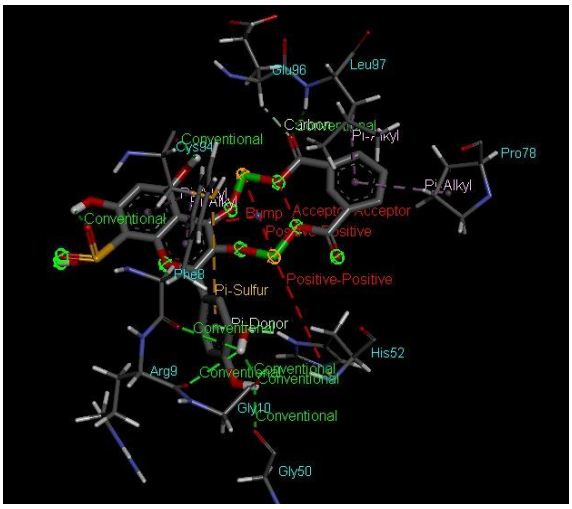


Fig.21: Labelled interactions of NiQ8SAIso

4.0 Conclusion

Quercetin mixed-ligand metal (II) complexes bind more easily to the gene-regulation breast cancer protein (1OQA) compared to quercetin and the sulphonic derivatives. The interactions between the macromolecule and the complexes are affected by the type of derivative, the nature of the co-ligand, and the metal ion which in turn determines the number and types of interactions possible at the most preferred poses of the macromolecule. It is therefore recommended that an effective anticancer drugs could be synthesised from an appropriate combination of quercetin sulphonic derivatives and aromatic co-ligands in a mixed-ligand coordination reaction. However, more investigations are required specifically to study the amino acid residues that are involved in the interactions at the binding sites of the macromolecule in order to gain more insights for specificity.

5.0 References

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Declaration

Ethical Approval

Not Applicable

Competing interests

The authors declare no known competing financial interests

Data Availability

Data shall be made available on request

Conflict of Interest

The authors declare no conflict of interest

Ethical Considerations

Not applicable

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Authors' Contributions

I. N. Ufot: conceptualization, methodology, software analysis, writing and development of original draft. N. Simon: supervision. A. S. Johnson: review and project administration, E. C. Johnson. molecular docking review. I. B. Anweting; review and editing, V. Mkpenie; review and editing of final copy.