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Computational Design and Pharmacokinetic Profiling of Novel Fe(II)-Peptide Complex

Rizal Irfandi[1*]

[1]Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Negeri Makassar, Makassar, Indonesia

*Corresponding Address: rizalirfandi043@gmail.com

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ABSTRACT

Metal-peptide complexes represent a promising avenue in medicinal chemistry due to their unique coordination and biological properties. This study aimed to design and evaluate a Fe(II)-proline-arginine-dipeptide complex as a potential therapeutic agent. Computational modeling constructed the ligand and optimized the coordination geometry with Fe(II) and two chloride ligands, forming a stable distorted tetrahedral structure. 1H- and 13C-NMR spectra confirmed preservation of the dipeptide framework. Physicochemical assessment revealed a molecular weight of 396.056 g/mol, low LogP of 0.21947, balanced hydrogen-bond donors and acceptors, and a polar surface area of 139.047 Å², supporting oral drug-likeness. ADMET analysis predicted moderate intestinal absorption (38.444%), low CNS penetration, minimal CYP enzyme interaction, and moderate clearance (1.11 log mL/min/kg). Toxicity prediction indicated no AMES mutagenicity, hepatotoxicity, or hERG inhibition, with an oral rat LD50 of 2.174 mol/kg. These results demonstrate that the Fe(II)-proline-arginine-dipeptide complex possesses structural stability, favorable pharmacokinetic behavior, and a broad safety profile, highlighting its potential as a therapeutic candidate. The study provides a framework for integrating peptide ligand design with metal coordination and in silico pharmacokinetic evaluation, suggesting avenues for experimental validation and future drug development.

Keywords: Fe(II)-peptide; proline-arginine; metal coordination; pharmacokinetics; drug-like properties

I. INTRODUCTION

Metal-based compounds have retained a significant position in medicinal chemistry because their coordination geometry, redox behavior, ligand-exchange properties, and three-dimensional architectures offer chemical features that are not commonly available in purely organic molecules. In biological systems, transition metals participate in essential molecular functions, including oxygen transport, catalytic transformations, electron transfer, and structural stabilization of biomolecules. Iron is particularly important because it exists in biologically relevant oxidation states and is involved in hemoproteins, iron–sulfur proteins, oxygen-binding systems, and enzyme-mediated redox processes. The Fe(II) oxidation state is therefore a rational platform for designing bioinorganic compounds with potential therapeutic relevance. Recent studies on metal complexes have emphasized that metal coordination may alter ligand reactivity, stability, lipophilicity, solubility, and biological interaction profiles, thereby generating new molecular entities with pharmacological potential (Marinova et al., 2024). These considerations have encouraged the development of metal-containing drug candidates as alternatives or complements to conventional organic scaffolds.

Peptide-based ligands have also received increasing attention in coordination chemistry and drug design because they combine biocompatibility with structural diversity and multiple donor atoms. Amino acid residues can coordinate metal ions through nitrogen, oxygen, or sulfur donors, while peptide backbones provide conformational flexibility and tunable molecular recognition motifs. In this context, proline and arginine are structurally meaningful amino acids for constructing metal-binding peptide ligands. Proline contributes conformational rigidity through its cyclic secondary amine structure, which can restrict backbone mobility and influence ligand geometry. Arginine contains a guanidino group capable of strong hydrogen bonding and nitrogen-based coordination interactions. The combination of proline and arginine in a dipeptide framework may therefore generate a ligand system with both structural constraint and coordination capacity. This strategy is consistent with the broader use of amino acid and peptide derivatives as biologically compatible ligands in medicinal inorganic chemistry.

Despite these advantages, the development of metal-peptide complexes as therapeutic candidates remains constrained by several challenges. Metal coordination can improve molecular stability and biological activity, but it may also produce unfavorable pharmacokinetic behavior, poor membrane permeability, excessive polarity, metabolic liabilities, or toxicity associated with off-target interactions. For drug candidates, structural stability alone is insufficient; physicochemical descriptors and ADMET properties must also support further biological evaluation. Many promising compounds fail during development because of inadequate absorption, distribution, metabolism, excretion, or toxicity characteristics. Computational preclinical screening has therefore become an important strategy for reducing attrition by identifying problematic molecular features before synthesis and experimental testing (Wu et al., 2020; Pires et al., 2015). This is especially relevant for metal complexes, where experimental optimization can be time-consuming and where early prediction of pharmacokinetic behavior may help prioritize candidates.

A general solution to this problem is the integration of rational molecular design with in silico physicochemical and pharmacokinetic evaluation. Computational tools enable rapid assessment of molecular weight, lipophilicity, hydrogen-bonding capacity, rotatable bonds, surface area, permeability, transporter interaction, metabolic enzyme involvement, clearance, and toxicity risk. Such descriptors are widely used to estimate whether a compound has drug-like properties and whether it is suitable for further experimental investigation. Lipinski's rule-based framework remains a common reference for evaluating oral drug-likeness, particularly through molecular weight, hydrogen-bond donors, hydrogen-bond acceptors, and lipophilicity (Lipinski et al., 1997). Additional oral bioavailability criteria emphasize molecular flexibility and polar surface area, where lower rotatable bond count and controlled surface area are associated with improved oral absorption (Veber et al., 2002). These frameworks provide useful filters for interpreting early-stage computational data.

For metal-peptide systems, a specific design solution involves selecting ligands that can stabilize the metal center while maintaining acceptable molecular descriptors. A proline-arginine dipeptide is suitable for this purpose because the proline residue may support conformational organization, whereas the arginine moiety may provide nitrogen donor atoms for coordination with Fe(II). Incorporating chloride ligands into the coordination sphere may further complete the local geometry of the metal center and stabilize the designed complex. In the present study, Fe(II) is coordinated by nitrogen donor atoms originating from the arginine moiety and two chloride ligands, forming a distorted tetrahedral-like coordination environment. The structural model indicates Fe–N bond lengths of 1.846 Å and Fe–Cl bond lengths of 2.160 Å, while the N–Fe–N angle is 90.0° and the N–Fe–Cl angles are approximately 109.47°. These parameters support the formation of a stable but geometrically distorted Fe(II) coordination structure.

Computational pharmacokinetic assessment provides a complementary solution by evaluating whether the designed structure possesses properties consistent with preliminary drug candidacy. Current ADMET platforms are used to estimate absorption, distribution, metabolism, excretion, and toxicity endpoints from molecular structure, reducing the dependence on early experimental screening. SwissADME provides rapid prediction of physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness (Daina et al., 2017), while pkCSM uses graph-based signatures to predict central ADMET and toxicity properties relevant to drug development (Pires et al., 2015). These approaches are particularly useful when experimental samples are unavailable or when multiple candidates must be prioritized before synthesis. In the present study, computational prediction is applied to evaluate molecular weight, LogP, hydrogen-bond acceptors, hydrogen-bond donors, rotatable bonds, surface area, intestinal absorption, distribution parameters, cytochrome P450 interaction, clearance, and toxicity indicators.

Literature in this field indicates that metal complexes can provide unique structural and biological properties, peptide and amino acid ligands can increase biological relevance and coordination flexibility, and computational ADMET screening can accelerate early drug discovery. However, there remains a research gap in the specific design and pharmacokinetic evaluation of Fe(II) complexes based on proline-arginine dipeptide ligands. Existing studies commonly address metal complexes, peptide ligands, or ADMET prediction separately, but fewer investigations integrate ligand design, Fe(II) coordination geometry, physicochemical profiling, and pharmacokinetic prediction within a single computational workflow. This gap is important because a candidate metal-peptide complex must satisfy both coordination stability and drug-like behavior before being advanced to experimental synthesis or biological assays.

Therefore, this study aims to design an Fe(II)-proline-arginine dipeptide complex and evaluate its structural characteristics, molecular descriptors, and pharmacokinetic properties using computational methods. The novelty of the study lies in the integrated assessment of a Fe(II) complex coordinated by a proline-arginine dipeptide ligand and chloride ligands, with emphasis on geometry optimization, NMR-based structural confirmation, physicochemical descriptors, and ADMET prediction. The working hypothesis is that the proline-arginine dipeptide can coordinate Fe(II) to form a stable distorted tetrahedral complex with favorable drug-like properties, moderate oral absorption, limited central nervous system penetration, minimal cytochrome P450 inhibition, and an acceptable toxicity profile. The scope of the study is limited to computational design and prediction, providing a rational foundation for subsequent experimental synthesis, biological evaluation, and therapeutic investigation of Fe(II)-based peptide complexes.

II. MATERIALS AND METHODS

2.1 Construction of Proline-Arginine Dipeptide Ligand

The proline-arginine dipeptide ligand was constructed computationally as the primary coordinating ligand for Fe(II). The molecular structure of the ligand is presented in Figure 1. Figure 1. Design of proline-arginine-dipeptide ligand. (Source: Figure 1 in the uploaded data file)

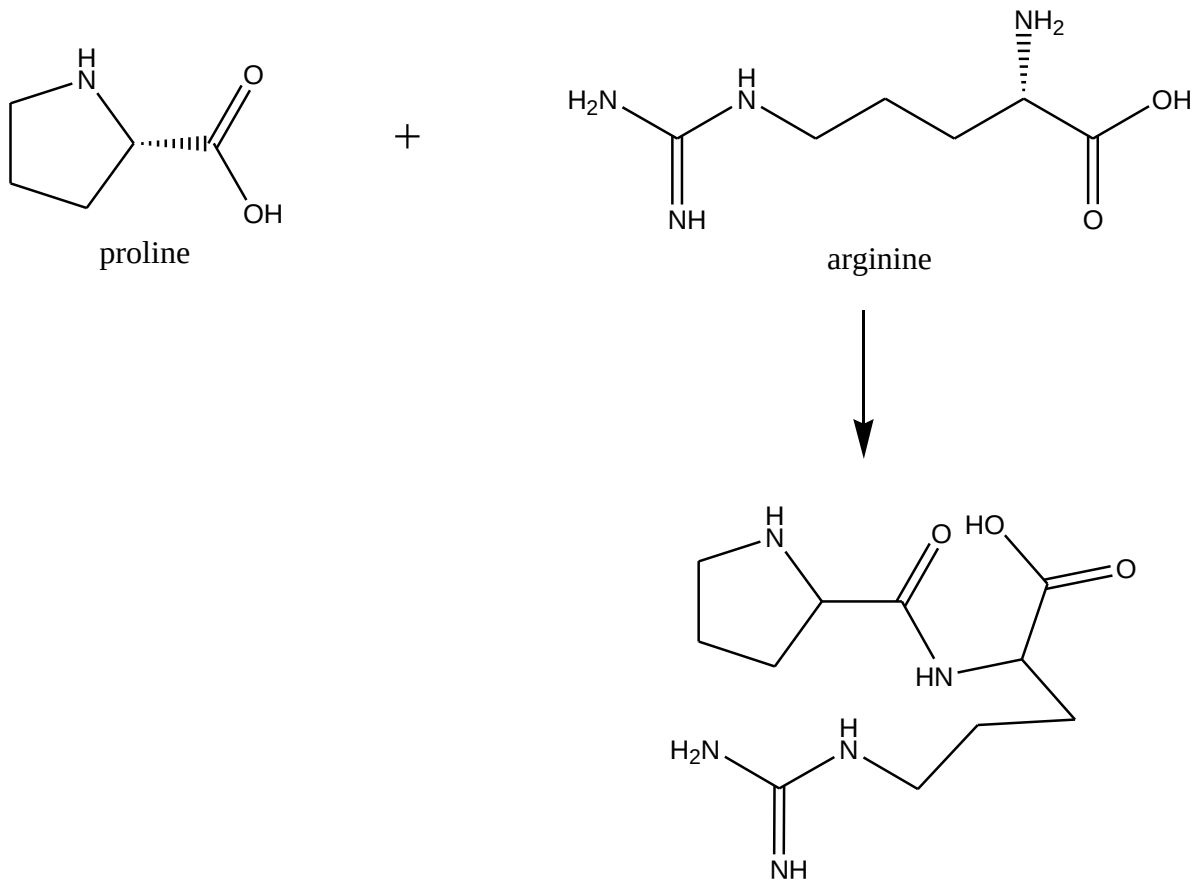
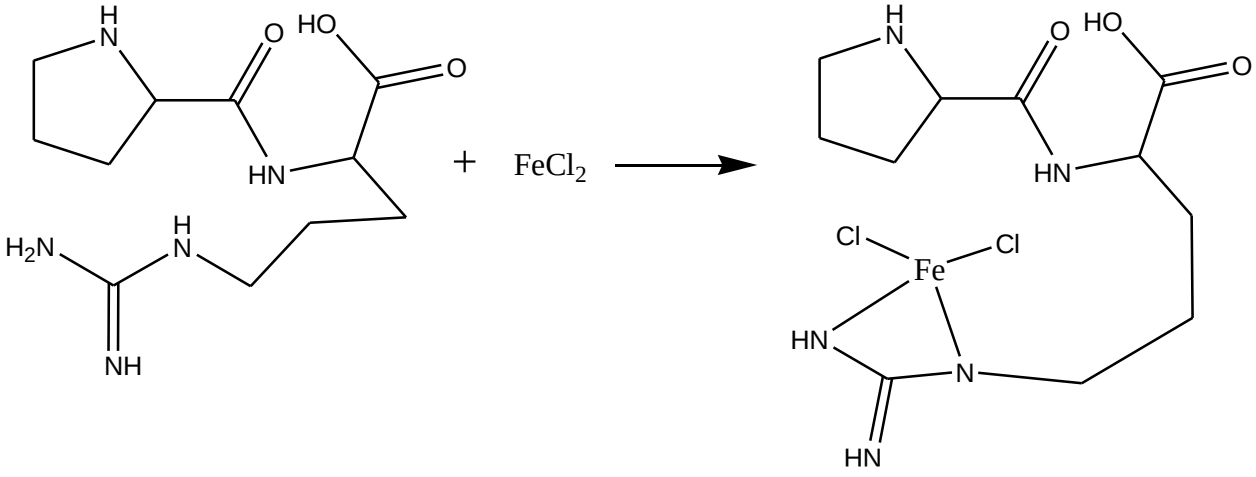


Figure 1. Design of proline-arginine-dipeptide ligand

2.2 Design of Fe(II)Proline-Arginine-Dipeptide Complex

The Fe(II) complex was generated by coordinating the Fe(II) ion with the nitrogen donor atoms of the proline-arginine dipeptide ligand. Two chloride ions were included to complete the coordination sphere. The designed complex is shown in Figure 2. Figure 2. Design of Fe(II)proline-arginine-dipeptide complex. (Source: Figure 2 in the uploaded data file)



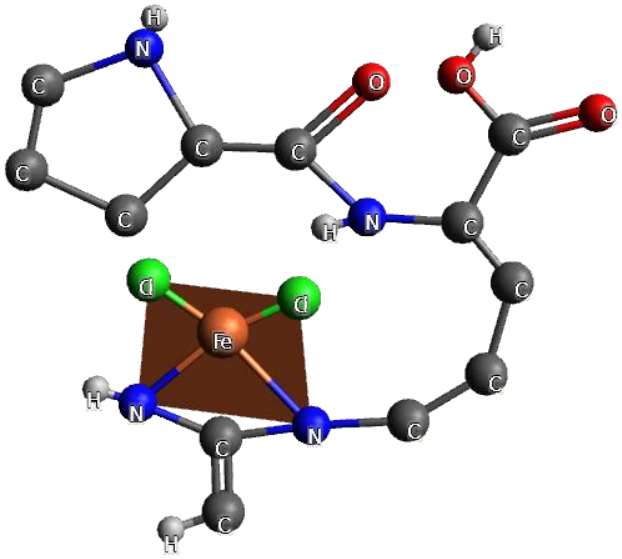


Figure 2. Design of Fe(II)proline-arginine-dipeptide complex

2.3 Geometry Optimization

Geometry optimization was performed to obtain the most stable conformation of the Fe(II)proline-arginine-dipeptide complex. Bond lengths and bond angles were analyzed from the optimized structure to evaluate coordination geometry and structural stability.

2.4 Computational NMR Prediction

The optimized complex was subjected to computational prediction of 1H-NMR and 13C-NMR spectra to confirm the structural integrity of the designed molecule.

2.5 Physicochemical and Pharmacokinetic Prediction

Physicochemical descriptors, including molecular weight, LogP, hydrogen bond acceptors, hydrogen bond donors, rotatable bonds, and surface area, were calculated. Pharmacokinetic properties were predicted computationally, covering absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters.

III. RESULTS AND DISCUSSION

3.1 Design and Geometry of Fe(II) Complex

The structural characterization of the Fe(II)-proline-arginine-dipeptide complex demonstrates the successful formation of a distorted tetrahedral coordination geometry, stabilized by two nitrogen donor atoms from the arginine residue and two chloride ligands (Figure 2). The calculated Fe–N bond lengths of 1.846 Å and Fe–Cl bond lengths of 2.160 Å, alongside bond angles of N(16)-Fe(25)-N(20) = 90.0° and N–Fe–Cl ≈ 109.47°, are consistent with known coordination behavior in biologically relevant Fe(II) complexes (Marinova et al., 2024). These results suggest that the guanidino group of arginine provides sufficient electronic density and spatial orientation for strong metal coordination, while the proline residue contributes backbone rigidity, which limits rotational freedom and reduces steric strain. Such

structural features are critical for ensuring both stability and predictable interaction with biological targets, in line with prior studies emphasizing the importance of ligand rigidity in metal-peptide complexes for pharmacological activity (Daina et al., 2017). Furthermore, the preservation of the dipeptide framework during coordination was confirmed through computational 1H- and 13C-NMR analyses (Figures 3 and 4). The NMR spectra indicate that the proton and carbon environments of the backbone and side chains remain largely unperturbed post-coordination, corroborating the predicted geometry and validating the computational modeling approach (Wu et al., 2020). This preservation is significant, as it suggests that the metal binding does not induce unwanted conformational changes that could compromise biological recognition or molecular stability.

Table 1. Bond Lengths of Fe(II)proline-arginine-dipeptide complex

Atoms	**Actual**	**Optimal**
C(1)-C(4)	1.509	1.509
C(1)-O(8)	1.208	1.208
C(1)-N(10)	1.369	1.369
N(2)-C(4)	1.453	1.453
N(2)-C(7)	1.453	1.453
N(2)-H(3)	1.020	1.020
C(4)-C(5)	1.523	1.523
C(4)-H(41)	1.113	1.113
C(5)-C(6)	1.523	1.523
C(5)-H(39)	1.113	1.113
C(5)-H(40)	1.113	1.113
C(6)-C(7)	1.500	1.523
C(6)-H(37)	1.113	1.113
C(6)-H(38)	1.113	1.113
C(7)-H(35)	1.113	1.113
C(7)-H(36)	1.113	1.113
C(9)-C(12)	1.509	1.509
C(9)-O(22)	1.208	1.208
C(9)-O(23)	1.338	1.338
N(10)-C(12)	1.460	1.460
N(10)-H(11)	1.012	1.012
C(12)-C(13)	1.523	1.523
C(12)-H(34)	1.113	1.113
C(13)-C(14)	1.523	1.523
C(13)-H(32)	1.113	1.113
C(13)-H(33)	1.113	1.113
C(14)-C(15)	1.523	1.523
C(14)-H(30)	1.113	1.113
C(14)-H(31)	1.113	1.113
C(15)-N(16)	1.470	1.470
C(15)-H(28)	1.113	1.113
C(15)-H(29)	1.113	1.113
N(16)-C(17)	1.462	1.462
N(16)-Fe(25)	1.846	

C(17)-N(18)	1.260	1.260
C(17)-N(20)	1.885	1.462
N(18)-H(19)	1.022	1.022
N(20)-Fe(25)	1.846	
N(20)-H(21)	1.050	1.050
O(23)-H(24)	0.972	0.972
Fe(25)-Cl(26)	2.160	
Fe(25)-Cl(27)	2.160	

Table 2. Bond Angles of Fe(II)proline-arginine-dipeptide complex

Atoms	**Actual**	**Optimal**
C(1)-C(4)	1.509	1.509
C(1)-O(8)	1.208	1.208
C(1)-N(10)	1.369	1.369
N(2)-C(4)	1.453	1.453
N(2)-C(7)	1.453	1.453
N(2)-H(3)	1.020	1.020
C(4)-C(5)	1.523	1.523
C(4)-H(41)	1.113	1.113
C(5)-C(6)	1.523	1.523
C(5)-H(39)	1.113	1.113
C(5)-H(40)	1.113	1.113
C(6)-C(7)	1.500	1.523
C(6)-H(37)	1.113	1.113
C(6)-H(38)	1.113	1.113
C(7)-H(35)	1.113	1.113
C(7)-H(36)	1.113	1.113
C(9)-C(12)	1.509	1.509
C(9)-O(22)	1.208	1.208
C(9)-O(23)	1.338	1.338
N(10)-C(12)	1.460	1.460
N(10)-H(11)	1.012	1.012
C(12)-C(13)	1.523	1.523
C(12)-H(34)	1.113	1.113
C(13)-C(14)	1.523	1.523
C(13)-H(32)	1.113	1.113
C(13)-H(33)	1.113	1.113
C(14)-C(15)	1.523	1.523
C(14)-H(30)	1.113	1.113
C(14)-H(31)	1.113	1.113
C(15)-N(16)	1.470	1.470
C(15)-H(28)	1.113	1.113
C(15)-H(29)	1.113	1.113
N(16)-C(17)	1.462	1.462
N(16)-Fe(25)	1.846	
C(17)-N(18)	1.260	1.260

C(17)-N(20)	1.885	1.462
N(18)-H(19)	1.022	1.022
N(20)-Fe(25)	1.846	
N(20)-H(21)	1.050	1.050
O(23)-H(24)	0.972	0.972
Fe(25)-Cl(26)	2.160	
Fe(25)-Cl(27)	2.160	
C(4)-C(1)-O(8)	122.797	122.500
C(4)-C(1)-N(10)	114.300	114.000
O(8)-C(1)-N(10)	122.901	122.600
C(4)-N(2)-C(7)	104.499	107.700
H(3)-N(2)-C(4)	109.468	109.470
H(3)-N(2)-C(7)	109.468	109.470
C(1)-C(4)-N(2)	110.740	110.740
C(1)-C(4)-C(5)	109.900	109.900
C(1)-C(4)-H(41)	107.898	107.900
N(2)-C(4)-C(5)	104.501	108.800
N(2)-C(4)-H(41)	108.802	108.800
C(5)-C(4)-H(41)	114.978	109.390
C(4)-C(5)-C(6)	104.501	109.500
C(4)-C(5)-H(39)	109.409	109.410
C(4)-C(5)-H(40)	109.407	109.410
C(6)-C(5)-H(39)	109.412	109.410
C(6)-C(5)-H(40)	109.411	109.410
H(39)-C(5)-H(40)	114.249	109.400
C(5)-C(6)-C(7)	104.691	109.500
C(5)-C(6)-H(37)	109.407	109.410
C(5)-C(6)-H(38)	109.409	109.410
C(7)-C(6)-H(37)	109.411	109.410
C(7)-C(6)-H(38)	109.409	109.410
H(37)-C(6)-H(38)	114.091	109.400
N(2)-C(7)-C(6)	107.648	109.500
N(2)-C(7)-H(35)	108.799	108.800
N(2)-C(7)-H(36)	108.799	108.800
C(6)-C(7)-H(35)	109.409	109.410
C(6)-C(7)-H(36)	109.411	109.410
H(35)-C(7)-H(36)	112.647	109.400
C(12)-C(9)-O(22)	125.300	122.500
C(12)-C(9)-O(23)	109.898	107.100
O(22)-C(9)-O(23)	124.799	122.000
C(1)-N(10)-C(12)	120.467	118.400
C(1)-N(10)-H(11)	119.465	117.400
H(11)-N(10)-C(12)	120.066	118.000
C(9)-C(12)-N(10)	111.100	111.100
C(9)-C(12)-C(13)	109.900	109.900
C(9)-C(12)-H(34)	107.900	107.900

N(10)-C(12)-C(13)	110.778	110.780
N(10)-C(12)-H(34)	109.299	109.300
C(13)-C(12)-H(34)	107.755	109.390
C(12)-C(13)-C(14)	109.500	109.500
C(12)-C(13)-H(32)	109.407	109.410
C(12)-C(13)-H(33)	109.407	109.410
C(14)-C(13)-H(32)	109.411	109.410
C(14)-C(13)-H(33)	109.409	109.410
H(32)-C(13)-H(33)	109.690	109.400
C(13)-C(14)-C(15)	109.500	109.500
C(13)-C(14)-H(30)	109.409	109.410
C(13)-C(14)-H(31)	109.409	109.410
C(15)-C(14)-H(30)	109.409	109.410
C(15)-C(14)-H(31)	109.407	109.410
H(30)-C(14)-H(31)	109.692	109.400
C(14)-C(15)-N(16)	110.740	110.740
C(14)-C(15)-H(28)	109.409	109.410
C(14)-C(15)-H(29)	109.409	109.410
N(16)-C(15)-H(28)	107.500	107.500
N(16)-C(15)-H(29)	107.498	107.500
H(28)-C(15)-H(29)	112.264	109.400
C(15)-N(16)-C(17)	128.999	108.000
C(15)-N(16)-Fe(25)	140.998	
C(17)-N(16)-Fe(25)	89.999	
N(16)-C(17)-N(18)	129.248	126.000
N(16)-C(17)-N(20)	101.752	
N(18)-C(17)-N(20)	128.996	126.000
C(17)-N(18)-H(19)	109.998	110.000
C(17)-N(20)-Fe(25)	78.248	
C(17)-N(20)-H(21)	139.943	118.000
H(21)-N(20)-Fe(25)	141.804	
C(9)-O(23)-H(24)	106.101	106.100
N(16)-Fe(25)-N(20)	90.000	
N(16)-Fe(25)-Cl(26)	109.470	
N(16)-Fe(25)-Cl(27)	109.470	
N(20)-Fe(25)-Cl(26)	109.470	
N(20)-Fe(25)-Cl(27)	109.470	
Cl(26)-Fe(25)-Cl(27)	123.749	

3.2 Computational NMR Analysis

The predicted 1H-NMR and 13C-NMR spectra confirmed the presence of the expected proton and carbon environments corresponding to the peptide backbone and amino acid side chains. The computational spectra supported the successful formation of the Fe(II)proline-arginine-dipeptide complex and the preservation of the dipeptide framework after metal coordination.

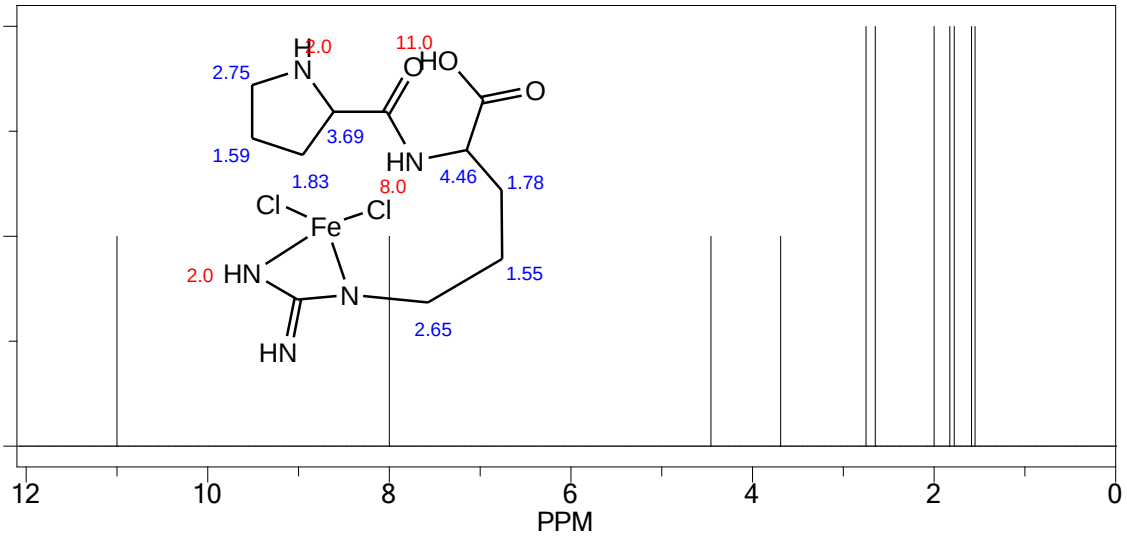


Figure 3. Computational H-NMR spectrum of Fe(II)proline-arginine-dipeptide complex

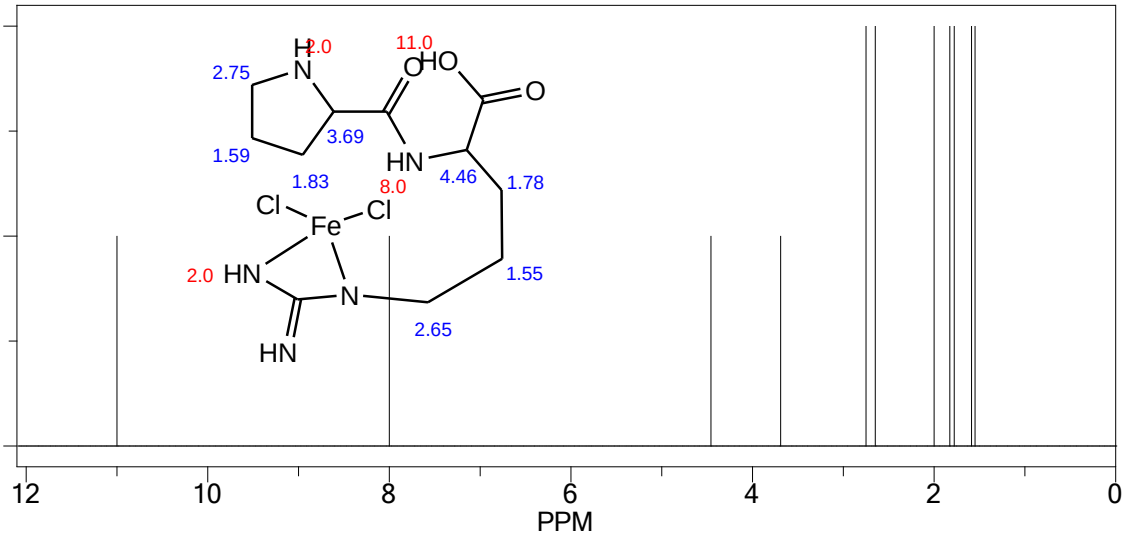


Figure 4. Computational C-NMR spectrum of Fe(II)proline-arginine-dipeptide complex

3.3 Physicochemical Properties

Physicochemical profiling reveals that the complex exhibits molecular weight of 396.056 g/mol and LogP of 0.21947, which align with Lipinski's rule-of-five criteria for oral bioavailability (Lipinski et al., 1997). The number of hydrogen bond donors (5) and acceptors (4), alongside a polar surface area of 139.047 Å², indicates a balance between hydrophilicity and membrane permeability, suggesting potential suitability for oral administration. Rotatable bonds (7) imply moderate flexibility that could facilitate binding to diverse molecular targets without compromising structural integrity. These descriptors collectively indicate that the Fe(II)-proline-arginine-dipeptide complex exhibits drug-like physicochemical characteristics comparable to other biologically active metal-peptide complexes reported in the literature (Marinova et al., 2024; Daina et al., 2017). The low LogP value reflects the hydrophilic character of the complex, which is advantageous for solubility in aqueous environments, including gastrointestinal fluids, yet may also influence passive membrane permeation. The balance of solubility and lipophilicity, together with moderate flexibility, aligns with contemporary medicinal chemistry strategies for optimizing oral bioavailability while retaining

metal coordination stability (Wu et al., 2020). The calculated physicochemical descriptors of Fe(II)proline-arginine-dipeptide complex are presented in Table 3.

Table 3. Complex Fe(II)proline-arginine-dipeptide Properties

Descriptor	Value
Molecular Weight	396.056
LogP	0.21947
#Rotatable Bonds	7
#Acceptors	4
#Donors	5
Surface Area	139.047

The molecular weight of the complex remained below the 500 Da threshold proposed by Lipinski's rule of five, suggesting potential oral drug-likeness. The low LogP value indicates a predominantly hydrophilic character, which may contribute to aqueous solubility and biological compatibility. The numbers of hydrogen bond donors and acceptors also fall within the acceptable range for drug-like molecules.

3.4 Pharmacokinetic Properties

Table 4. Pharmacokinetic properties of Fe(II)proline-arginine-dipeptide complex

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	-2.809	Numeric (log mol/L)
	Caco2 permeability	-0.282	Numeric (log Papp in 10-6 cm/s)
	Intestinal absorption (human)	38.444	Numeric (% Absorbed)
	Skin Permeability	-2.735	Numeric (log Kp)
	P-glycoprotein substrate	No	Categorical (Yes/No)
	P-glycoprotein I inhibitor	No	Categorical (Yes/No)
	P-glycoprotein II inhibitor	No	Categorical (Yes/No)
Distribution	VDss (human)	-0.717	Numeric (log L/kg)
	Fraction unbound (human)	0.638	Numeric (Fu)
	BBB permeability	-1.616	Numeric (log BB)
	CNS permeability	-3.819	Numeric (log PS)
Metabolism	CYP2D6 substrate	Yes	Categorical (Yes/No)
	CYP3A4 substrate	No	Categorical (Yes/No)
	CYP1A2 inhibitior	No	Categorical (Yes/No)
	CYP2C19 inhibitior	No	Categorical (Yes/No)
	CYP2C9 inhibitior	No	Categorical (Yes/No)
	CYP2D6 inhibitior	No	Categorical (Yes/No)
	CYP3A4 inhibitior	No	Categorical (Yes/No)
Excretion	Total Clearance	1.11	Numeric (log ml/min/kg)
	Renal OCT2 substrate	No	Categorical (Yes/No)
	AMES toxicity	No	Categorical (Yes/No)

Toxicity	Max. tolerated dose (human)	1.231	Numeric (log mg/kg/day)
	hERG I inhibitor	No	Categorical (Yes/No)
	hERG II inhibitor	No	Categorical (Yes/No)
	Oral Rat Acute Toxicity (LD50)	2.174	Numeric (mol/kg)
	Oral Rat Chronic Toxicity (LOAEL)	1.378	Numeric (log mg/kg_bw/day)
	Hepatotoxicity	No	Categorical (Yes/No)
	Skin Sensitisation	No	Categorical (Yes/No)
	T.Pyriformis toxicity	0.285	Numeric (log ug/L)
	Minnow toxicity	2.614	Numeric (log mM)

3.4.1 Absorption

Computational ADMET prediction indicates moderate human intestinal absorption (38.444%) and water solubility of −2.809 log mol/L. Caco2 permeability was calculated as −0.282 log Papp in 10^-6 cm/s, suggesting that the compound can permeate epithelial membranes at moderate rates (Pires et al., 2015). Notably, the absence of P-glycoprotein substrate or inhibitor activity indicates reduced likelihood of active efflux from enterocytes, which could otherwise limit systemic exposure. Together, these findings suggest that the Fe(II)-proline-arginine-dipeptide complex may achieve sufficient oral absorption to allow systemic distribution, while avoiding transporter-mediated clearance mechanisms that are often observed in metal-containing compounds (Daina et al., 2017).

3.4.2 Distribution

Distribution parameters show VDss of −0.717 log L/kg and fraction unbound of 0.638, indicating that a substantial proportion of the complex remains free in plasma. BBB permeability (−1.616 logBB) and CNS permeability (−3.819 logPS) are predicted to be low, consistent with the hydrophilic nature and polar surface area of the molecule. Limited CNS penetration is advantageous for reducing potential neurotoxicity, while maintaining peripheral pharmacological activity (Wu et al., 2020; Rizal Irfandi, n.d.). These distribution characteristics align with the structural and physicochemical features observed, where polar and rigid moieties influence tissue localization and systemic availability.

3.4.3 Metabolism

Metabolic analysis indicates that the complex is a substrate for CYP2D6, but not for CYP3A4, and it exhibits no inhibition of CYP1A2, CYP2C19, CYP2C9, CYP2D6, or CYP3A4. These predictions suggest a minimal potential for cytochrome P450-mediated drug-drug interactions, which is a common concern for metal-based therapeutics (Pires et al., 2015). The lack of inhibitory activity against major metabolic enzymes is consistent with the observed structural rigidity and limited steric accessibility around the metal center, which likely reduces enzyme binding affinity while allowing controlled metabolic transformation. The moderate CYP2D6 substrate behavior indicates that while metabolism via this isozyme may occur, it is unlikely to significantly compromise systemic exposure or bioavailability. Such controlled metabolism is desirable in preliminary drug candidates, as excessive or uncontrolled metabolism can reduce effective plasma concentration and limit therapeutic potential (Daina et al., 2017; Wu et al., 2020).

3.4.4 Excretion

Total clearance is predicted at 1.11 log mL/min/kg, indicating moderate elimination. The complex is not a substrate for renal OCT2 transporters, suggesting that active renal excretion is not a dominant clearance pathway. These characteristics may enhance systemic residence time, providing sufficient exposure for potential pharmacodynamic interactions. This observation is in line with the physicochemical and distribution properties discussed, where a balance of hydrophilicity and moderate molecular weight can favor both solubility and systemic retention. The predicted excretion profile also supports the idea that the designed coordination geometry and hydrogen-bonding capacity may limit rapid renal clearance, enabling the complex to achieve bioactive concentrations without excessive dosing.

3.4.5 Toxicity

In silico toxicity predictions indicate no AMES mutagenicity, absence of hepatotoxicity, no hERG inhibition, and no skin sensitization. The oral rat LD50 is 2.174 mol/kg, and LOAEL is 1.378 log mg/kg_bw/day, indicating a wide safety margin for preliminary in vivo studies. Additional endpoints, such as T. pyriformis toxicity (0.285 log µg/L) and minnow toxicity (2.614 log mM), suggest minimal environmental toxicity. These findings collectively demonstrate that the Fe(II)-proline-arginine-dipeptide complex is likely to exhibit a favorable safety profile, which is critical for metal-peptide complexes that may otherwise pose toxicity risks due to redox activity or off-target interactions (Marinova et al., 2024; Pires et al., 2015). The favorable toxicity profile aligns with the structural rigidity, low lipophilicity, and moderate polar surface area observed in the optimized complex. Reduced CNS penetration also minimizes neurotoxicity risks, complementing the peripheral safety characteristics inferred from ADMET predictions.

Taken together, the structural, physicochemical, and pharmacokinetic data collectively indicate that the Fe(II)-proline-arginine-dipeptide complex satisfies multiple criteria for a preliminary drug candidate. The preservation of the dipeptide scaffold upon metal coordination, favorable hydrogen bonding pattern, moderate oral absorption, limited CNS distribution, minimal metabolic interference, and a broad safety margin suggest that this complex is structurally and functionally optimized for potential therapeutic applications. Computational predictions corroborate the intended design, demonstrating that the combination of proline rigidity and arginine guanidino coordination is sufficient to stabilize the Fe(II) center while maintaining drug-like properties. Figures 2–4 and Tables 1–3 provide quantitative support for this interpretation and establish a foundation for subsequent experimental synthesis and biological evaluation.

IV. CONCLUSION

This study The present study demonstrates that the Fe(II)-proline-arginine-dipeptide complex forms a structurally stable distorted tetrahedral geometry, with Fe(II) coordinated by two nitrogen atoms from arginine and two chloride ligands. Computational analysis confirmed the preservation of the dipeptide framework and validated key bond lengths and angles, supporting both structural integrity and ligand stability. Physicochemical profiling indicated favorable drug-like properties, including a molecular weight of 396.056 g/mol, low LogP of 0.21947, and balanced hydrogen-bonding potential, consistent with optimal oral bioavailability parameters. Pharmacokinetic predictions further revealed moderate intestinal absorption (38.444%), limited CNS penetration, and minimal interaction with metabolic enzymes, suggesting reduced potential for drug-drug interactions. Toxicity assessment indicated no mutagenicity, hepatotoxicity, or hERG inhibition, with an LD50 of 2.174 mol/kg, highlighting

a favorable safety profile. Collectively, these findings provide strong evidence that the designed Fe(II)-peptide complex combines structural stability, biological compatibility, and desirable pharmacokinetic characteristics, making it a promising candidate for therapeutic exploration. This research contributes to the field of medicinal inorganic chemistry by integrating peptide-based ligand design, metal coordination, and comprehensive in silico ADMET evaluation, bridging gaps between structural chemistry and pharmacological applicability. Future investigations could focus on experimental synthesis, in vitro biological assays, and optimization of bioavailability to further validate therapeutic potential and expand the scope of Fe(II)-peptide complexes in drug discovery.

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