Theoretical Chemistry Accounts

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RESEARCH

New Au(III)‑ and Fe(III)‑based complexes of bio‑pharmacological

interest: DFT and in silico studies

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Abstract

Many researchers have tried to overcome the limitations of clinical Cis-platin, which has led to several generations of

platinum-based drugs that are derived from the Cis-platin matrix with a large number of molecules, but only f ve complexes

have been approved. These include f ve cornerstone drugs in modern platinum-based chemotherapy, namely carboplatin,

oxaliplatin, nedaplatin, heptaplatin and albaloplatin. These latest generations of platinum-based drugs are rather important

in chemotherapy, as they are often involved in the treatment of dif erent types of cancer. Their use remains hampered by

their severe toxicity, resistance to tumor cells, poor oral bioavailability as well as the repair of the resulting adducts, and the

failure of the apoptotic pathways. It is obvious that dif erent strategies are needed. To understand the structural, electronic,

and spectroscopic properties of new Au(III)-based complexes, a theoretical study at the density functional theory is under-

taken in this work using dif erent functional and basis sets. If a correlation is found between the various descriptors and the

anti-cancer activity, it would probably indicate a better solution to substitute Au(III) with Fe(III), which is commonly used

in the manufacturing of drugs, for its attractive cost.

Keywords New Au(III) and Fe(III) complexes · DFT and ADMET studies · Spectroscopic properties · anti-cancer activity

1 Introduction

by Rosenberg in 1965, meanwhile a simple experiment in

bacteriology, which was to study the ef ect of an electric

f eld using platinum electrodes on cell division of E.coli

(Escherichia coli); the unexpected results of this experi-

ment have been ground-breaking for modern-day cancer

treatment. Rosenberg noticed that the bacterial cell division

had st[opped although bacter](#br13)ial cell growth continued into

long strands [[14](#br13)]. These results were the starting point for

other researc[h.](#br13)

Modern medicinal c[hemistry in](#br13)volves the development of

new metal-based drugs [[1](#br13)–[10](#br13)]; these latter complexes have

several applicati[ons,](#br13) and [they a](#br13)re mainly used in the treat-

ment of cancers [[11](#br13)]. Complex platinum compounds [(II](#br13))

[repr](#br13)esent a cr[itical class of dr](#br13)ugs for cancer control [[12](#br13),

[13](#br13)]. Among them, we f nd that Cis-platin is regarded [as](#br13)

[the benc](#br13)hmark in its class of organometallic complexes.

Its discovery as an anti-cancer agent was made by chance

Cis-platin was [pr](#br13)oduced for the f rst time in 1845 by

Michele Peyrone [[15](#br13)]; hence, its f rs[t name w](#br13)as "Peyrone's

chloride"; it w[as tested on r](#br13)ats in 1969 [[16](#br13)]. Clinical tests

carried out in 1971, on Cis-platin, show[ed t](#br13)hat it had sig-

nif cant anti-cancer activity[. In 1978, it w](#br14)as approved as a

treatment for several types of cancer [[17](#br14)], mainl[y cancers](#br14)

[inv](#br14)olving the testicles, ovar[ies, lungs, head, and nec](#br14)k [[18](#br14),

[19](#br14)].

This work is dedicated to the memory of Mohamed Lamine

Abdelatif.

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This anti-cancer activity is dose-dependent because of

the adverse gastrointes[tinal, o](#br14)tological, neurological, and

nephr[ological side ef ects [20](#br14)]. The main target of plati-

num (II) salts is DNA [[21](#br14), [22]. Thus, once in t](#br14)he organism,

they hydrolyze to giv[e hydroxide der](#br14)ivatives in an aqueous

medium. This allows them to bind to DNA by the formation

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of cross-link[ed covalent bonds be](#br14)tween complementary

strands of DNA [[23](#br14), [25](#br14)] by a stereoselective mechanism of

[purine bases in](#br14)v[olving t](#br14)he donor site (nitrog[en) of guanine](#br14)

[[25](#br14)–[28](#br14)]. The pr[oduct is s](#br14)tabilized by hydrogen bonding [[29](#br14)]

[with pr](#br14)oton release [[30](#br14)], which leads to the reaction pr[od](#br14)-

ucts t[hat induce cell deat](#br14)h processes, hence the cytotoxic

ef ect of the drug [[31](#br14)]. Unfortunately, the ef ectiveness of

t[he Cis-platin is limited because of its t](#br14)oxicity, which is due

to the ability of platinum ions to bind with proteins, and to

the resistance of tumor cells to treatment; t[hese tumor cells](#br14)

may have intrinsic resistance or acquired resistance [[32](#br14)–[36](#br14)].

Many researchers have devoted their ef orts to over[coming](#br14)

the limitations of clinical Cis-platin, which has led to sev-

eral generations of drugs derived from t[he Cis-platin matr](#br14)ix

with a signif cant number of molecules [[37](#br14)–[39](#br14)]; however,

only f ve of them have been approved as a[nti](#br14)-[can](#br14)cer agents,

namely carbo[pla](#br14)ti[n,](#br14) oxaliplatin, nedaplatin, heptaplatin and

albaloplatin [[40](#br14)–[43](#br14)]. These derivatives, remaining indis-

[pensable in modern-da](#br14)y cancer treatment, are used to treat

several types of cancer. Nevertheless, they possess severe

toxicity with tumor cell resist[ance, low or](#br14)al bioavailability,

and failure of apoptotic pathways [[44](#br14), [45](#br14)]. Dif erent path-

ways employing new approaches t[o the synt](#br14)hesis of new

[organome](#br14)tallic complexes, similar to platinum complexes

[[46](#br14)–[53](#br14)], involving transition atoms as com[plexing ag](#br14)ents

[such as gold, copper](#br14), cobalt, iron, and others [[54](#br14)–[57](#br14)] have

been developed over the past few decades. A[u (I/III) coor](#br14)-

dination complexes have known a great development due to

the fact that gold has a s[trong capacity t](#br14)o complex with many

ligands, like platinum [[58](#br14)–[66](#br14)]. The gold atom has several

possible oxidation st[ates ranging fr](#br14)om (I to V), but only the

s[tates (I) and (III) ar](#br14)e used in the pharmaceutical industry

[[67](#br14)]. The choice of ligands inf uences the stability, overall

[phar](#br14)macodynamic pr[of le, and biophar](#br14)maceutical activity

of the resulting complexes [[68](#br14)].

To better understand the structural, electronic, and

spectroscopic proper[ties of ne](#br15)w Au(III)-based complexes,

synthesized in 2017 [[82](#br15)], a theoretical study at the density

functional theor[y (DFT) le](#br15)vel was performed using dif-

ferent functional with various basis sets. Moreover, iron

is a much less toxic element and is involved in several

living mechanisms, so if the theoretical study of gold com-

plexes leads to a good understanding and correlation of

the various descriptors and their anticancer activity, we

may also extrapolate this concordance for the suggestion

of creating newer, safer anti-cancer solutions with Fe(III)

instead of Au(III), as Fe(III) is commonly used in drug

manufacturing.

2 Computational strategies

DFT [[83](#br15)] calculations of these complexes of Au(III) and

F[e(III) ha](#br15)ve been carried out with the hybrid density func-

tional B3LYP with the 6–311 + G\*\* basis sets for the H, N,

O, S, Cl, and Fe atoms and a LANL2DZ pseudo-potential

for Pt, A[u. All calculations ar](#br15)e performed with the Gauss-

ian09 programs [[84](#br15)]. To build the complex, geometries of

the org[anic molecules ar](#br15)e optimized separately. Harmonic

frequencies are calculated to ensure that stable complexes

are obtained in absolute minima energy without imagi-

nary frequency and the IR and NMR (1H and 13C) spectra

are obtained at the same theoretical levels. All values are

[scaled b](#br15)y a constant factor of 0.98, for the IR frequencies

[[85](#br15)]. Energy gaps, OM frontiers, and electronic density

[are](#br15) obtained at the same level of theory.

For each complex, we have modeled at the DFT, NMR

proton spectrum (1H NMR), and the carbon ones (13C

[NMR). The solv](#br15)ents were chosen in agreement with the

experiment [[82](#br15)] for the se[rie](#br15)s of Au(III) complexes by

applying t[he CPCM model [86](#br15)]. For comparison purposes,

the same solvents ar[e used in t](#br15)he Fe(III) complexes stud-

ies. The 1H-NMR spectra of the M1 and M2 complexes

(M = Au and Fe) were obtained, respectively, in dichlo-

romethane (CH Cl ) and chloroform (CHCl ) whereas the

Several organomet[allic com](#br14)plexes, synthesized recently,

have shown promise in vitro activity. The passage to perform

in vivo tests is often very expensive, and in addition to this,

the majority of new complexes lose their activity, which

does not allow them to reach clinical trials. Modeling is, in

this context, of paramount importance to better understand

t[heir activity and t](#br14)o be able to choose the most relevant ones

[[69](#br14)–[71](#br14)] before carrying out in vivo tests.

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other spectra are obtained in the DMSO solvent. It is the

same for the 13C-NMR spectra, which are obtained with

tetra methyl silane (TMS) as the internal standard. The

absolute chemical isotropic shielding was calculated using

t[he GIA](#br15)O (gauge-independent atomic orbital) method

[[87](#br15)].

[Au(I/III) com](#br14)[ple](#br15)xes have better cytotoxic properties than

cis-platin [[72](#br14)–[77](#br15)] whereby Au(I) selectively targets tumor

cells mor[e than healt](#br14)hy cells thanks to its af nity to thiol and

[selenol g](#br14)roups of cysteine and selenocysteine, respectively

[[69](#br14), [70](#br14)]. On the other hand, Au (III) has a d8 conf guration,

[which giv](#br14)[es it an iso-structur](#br15)al and iso-electronic character

rather than Pt (II) [[78](#br15), [79](#br15)]. However, the Au (III) complexes

have more activ[e anticancer activity t](#br15)han those based on Au

[(I), which can be e](#br14)xplained by the reduction of Au (III) in

Au (I) [[71](#br14), [80](#br15), [81](#br15)].

[The in silico ADME/T](#br15)ox study is very useful for pre-

dicting the pharmacological proper[ties of candidate mol](#br15)-

[ecules to be a drug. The pkCSM-phar](http://biosig.unimelb.edu.au/pkcsm/)macokinetics tool [[88](#br15)]

(<http://biosig.unimelb.edu.au/pkcsm/>) is used to describe [the](#br15)

[absorption, distribution, metabolism, e](http://biosig.unimelb.edu.au/pkcsm/)xcretion, and toxicity

of our complexes.

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3 Results and discussion

3.1 Cis‑Platin studies

smaller than that obtained by X-ray dif raction and there is

an increase of the N–Pt–N and Cl–Pt–Cl angle.

3.1.2 IR spectrum

3.1.1 Geometrical parameters

The IR (scaled by 0.98 [[85](#br15)]) and Raman spectra were car-

ried out at the DFT lev[els wit](#br15)h t[he 6–311](#br3)+G \*\* basis sets

for H, Cl, and N as depicted [in F](#br15)ig. [1](#br3) where the calcu-

lated and experimental results [[91](#br15)] ar[e plo](#br3)tted. The same

trend is obtained with the sq[uared cor](#br15)relation coef cient

This work will f rst focus on a theoretical study of Cis-

platin at the DFT level using the functional B3LYP with

the 6-311G \*\* basis sets for the H, N, and Cl atoms and

the pseudo-potential LANL2DZ basis for the platinum atom

(Pt). This step is performed to validate the choice of the

appropriate method. The optimized geometrical parameters

[(bond lengt](#br3)hs, valence, and dihedral angles) are depicted

in Table [1](#br3). The square planar geometry, of lower energy, is

ther[modynamicall](#br3)y the most stable. In this conformation,

the Pt–N and Pt–Cl bonds are equal to 2.120 Ǻ and 2.350

Ǻ, respectively, whic[h i](#br15)s in agreement with the theoretical

data of the literature [[89](#br15)]. Theoretical calculations overesti-

mate t[he Pt–N and Pt–Cl bond lengt](#br15)hs by 0.12 and 0.019 Å,

respectively, compared to the exper[iment](#br15)al results obtained

by X[-ra](#br3)y diffraction on Cis-platin [[90](#br15)]. The results, in

Table [1](#br3), show that the theoretical ang[les N–Pt–N](#br15), Cl–Pt–Cl

are o[ver](#br3)estimated by 11.3 and 3.3 degrees, respectively,

[wher](#br15)eas the N–Pt–Cl angle is underestimated by 7.0 degrees

[[90](#br15)]. This dif erence can be explained by the formation of

i[nte](#br15)r and/or intramolecular hydrogen bonds of the NH …

Cl type and by the steric ef ects between dif erent groups of

the same molecule or between interacting Cis-platin mol-

ecules. In isolated Cis-platin molecules, the intramolecu-

lar hydrogen bond NH … Cl would bring the NH3 and Cl

groups together; hence, the calculated angle (N-Pt-Cl) is

(R

2 = 0.998) for the Raman spectrum. Consequently, it is

Fig. 1 Theoretical IR frequencies vs. experimental ones

Table 1 Geometrical parameters of Cis-platin optimized at B3LYP/Gen, with LANL2DZ as the basis for Pt and 6-311G\*\* for all other atoms

Parameters

Cis-Platin

Bond lengths in Ǻ

Theoretical

Experi-

[ment](#br15)al

[[90](#br15)]

Pt-Cl

Pt–N

2.350

2.120

2.331

2.000

Valence angles in degrees

Cl–Pt–Cl

N-Pt–N

N-Pt-Cl

95.2

98.3

83.3

91.9

87.0

90.3

Dihedral angles in degrees

Theoretical

H -N -Pt-Cl

0.002

0.055

0.033

0.002

10

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2

3

2

3

H -N -Pt-Cl

10

4

H -N -Pt-Cl

11

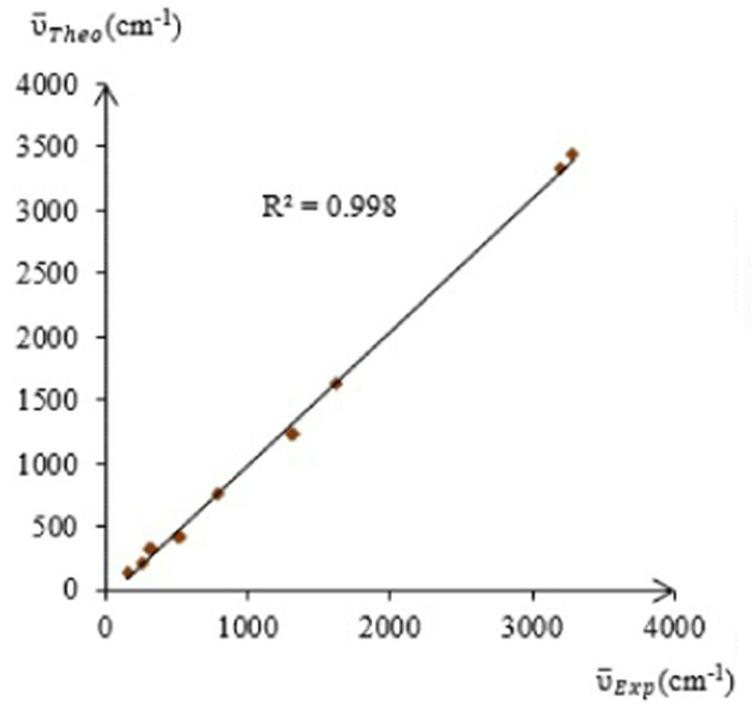
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H -N -Pt-Cl

11

5

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possible to validate the calculation method for the dif er-

ent Au complexes, especially since t[hese results ar](#br15)e in good

agreement with those of the literature [[89](#br15)–[91](#br15)].

square planar geometry with dihedral angles close to zero

in the Au1, Au2, and Au4 complexes and a slight f atness

deviation to the order of 10 degrees in the Au3a and Au3b

complexes, which is due to the steric ef ects of the sub-

stitution at the 8-quinoline group. The results are in good

agreement with the experimental ones.

3.2 Au(III) and Fe(III) complexes

3.2.1 Geometrical parameters

On the other hand, in the Fe(III) series complexes, we

notice, according to Table S2-b, that the two bonds Fe-Cl

1

Figure [2](#br4) shows the complexes to be studied in this work. We

[will f rst e](#br4)xplain the ef ect of the substitution in position 8

of the quinoline fragment on the stability and the reactivity

of the complexes. We will then examine the substitution of

Au by Fe. The results obtained will be compared with those

obtained for Cis-platin at the same theoretical level.

Fe(III) complexes can adopt two dif erent geometries

according to their spin and multiplicity state, namely a tetra-

hedral geometry with high spin (S= 5/2) conf guration, and

a square-planar geometry with low spin (S= 1/2) state. Both

possibilities have been investigated and their thermodynamic

stability has been compared. The complexes with the tet-

rahedral geometry are the most thermodynamically stable.

The geometric parameters of the Au(III) and Fe(III) com-

plexes, as obtained at the B3LYP/Gen (with LANL2DZas

the basis for Pt and Au and 6-311G\*\* for all other atoms),

are shown in supplementary materials (Tables S1-a and b),

respectively.

and Fe–Cl have the same exact lengths: 2.189, 2.145, and

2

2.196 Å, respectively, in the Fe1, Fe2, and Fe4 complexes.

Unlike the Fe3a complex, whose Fe–Cl bond increased

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slightly (2.204 Å) with the Fe–Cl bond having recorded

2

a length of 2.193 Å, for the Fe3b complex, the Fe–Cl

1

bond was recorded at 2.197 Å, and the Fe–Cl bond was

2

of the order of 2.210 Å. The variation of the M–Cl length

could be justif ed by the steric ef ects. Another peculiarity

that has been noticed in the Fe3a and Fe3b complexes is

the position of the substitution of the sulfonyl groups; the

mesyl (methylsulfonyl) group in the 8-quinoline position

in the Fe3a complex is located in the upper part of the

complex as well as the tosyl group in the Fe3b complex,

which is located below the coordination plane of the com-

plex. Unlike their Au(III)-based analogs, the set of valence

and torsion angles around the Fe(III) metallic center indi-

cate that all of the complexes have a tetrahedral geometry

where the valence angles are close to 109.5 degrees (sp3

hybridization). The torsion angles are zero for the angles

involving the quinoline bonds with the exception of the

Fe3a and Fe3b complexes, which show a slight deforma-

tion that can be considered negligible. This indicates that

the two bonds (Fe-N ) and (Fe–X) with 8-quinoline are

The Au-Cl bond length is more elongated than the

2

Au-Cl lengths (see table S1-a). For the Au1 complex, the

1

shortest Au-Cl (Au-Cl ) bond length is equal to 2.328

1

2

(2.352 Å); the longest bond length is found in the Au4

complex with a value of 2.347 (2.416 Å). The Au–O bond

length, equal to 2.062 Å in the Au1 complex, is shorter

than the Au–N bond equal to 2.091 Å and 2.086 Å in the

Au3a and Au3b complexes, respectively. In the Au2, it is

2.135 Å whereas the Au–S bond is equal to 2.376 Å in the

Au4 complex. The latter is the most elongated, because

of the atomic radius of sulfur. The f ve complexes have a

1

in the same plane, on the other hand, the two chlorines

are outside of the plane with the quinoline group, which

corresponds to tetrahedral geometry. The shortest M–Cl,

MO, MN, and MS lengths are observed for the Fe(III)

complexes. These results are due to the dif erence in the

atomic and V[an der W](#br15)aals radii of Au (1.79; 2.13) and Fe

(1.72; 1.89) [[92](#br15)].

Fig. 2 MX complexes with

(M=Au(III) and Fe(III) and

X=O (1), NH (2), N–SO Me

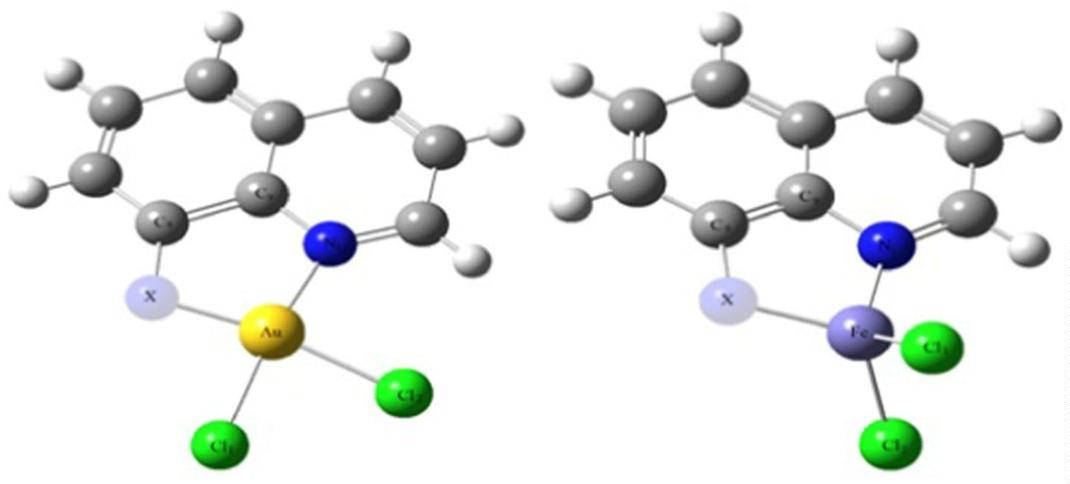
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(3a), N–SO Tol (3b), and S (4)

2

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3.2.2 NMR spectrum

1H-NMR chemical shifts are reported in Table S2-a and

13C-NMR shifts in Table S2-b. The theoretical and experi-

mental values are in the same regions for the Au(III)-based

complexes. This allows us to assume that it will be the same

for the complexes based on Fe(III), for which we have no

experimental data.

The experimental (δ ) and theoretical (δ ) chemical

exp

theo

shifts are summarized in Tables S2-a and S2-b for 1H-NMR

and 13C-NMR, respectively.

The experimental chemical shifts of the proton (see

Table S2-a) indicate the presence of six characteristic sig-

nals of the protons carried by quinoline, which are located

in the intervals of: [7.31–9.14], [6.50–9.37], and [7.76–9.90]

[ppm](#br15), respectively, for the Au1, Au2, and Au4 complexes

[[82](#br15)]. The calculated chemical shifts are in the intervals

[[6.93–9.21], [5.58–9.58], and [7.65–9.98] ppm. The pr](#br15)oton

chemical shifts for the Fe(III) complexes are found in the

ranges [6.60–8.99], [5.45–9.27], and [7.59–9.22], respec-

tively, in the Fe1, Fe2, and Fe4 complexes. These displace-

ments are due to the resonance of chemically non-equivalent

nuclei. The experimental spectrum of the Au3a complex is

characterized by the presence of a triplet at approximately

3.52 ppm, which corresponds to the CH protons of the mesyl

3.2.3 Electrochemistry

The molecular structures of the neutral complexes (oxi-

dized forms) and their reduced forms are optimized with

a frequency calculation to conf rm the energy minima. The

reduction potential was calculated from the solvation-free

energies. The latter w[as obt](#br15)ained by implicitly using the

CPCM solvation model [[86](#br15)] with dichloromethane as a sol-

vent in accordance wit[h the e](#br15)xperiment. The free energies

in the gas state and the solvated state of each species were

evaluated at 298.15 K and under a pressure of 1 atm. We

calculated the absolute reduction potential for each com[plex](#br5)

using the Born-Haber thermodynamic cycle, given in Fig. [3](#br5),

which links the dif erent electron transfer processes in t[he](#br5)

gas and solvated phases.

3

group. The electronic cloud of the last mesyl group is denser

because of its electro-attractive character compared to the

quinoline nucleus. Consequently, a strongly shielded ef ect

is observed. The corresponding theoretical mean value is

3.24 ppm for the Au3a complex, and it is 3.37 ppm for the

Fe3a complex. On the experimental spectrum of the Au3b

complex, three types of aromatic protons appear. They cor-

respond to those of toluene in the tosyl group in the 8-qui-

noline position with a chemical shift of 7.67 ppm for the

protons in the ortho position, 7.27 ppm for the protons in the

met[a position, and a shif](#br15)t of 2.29 ppm for the protons of the

CH group [[82](#br15)]. The calculated values are not very far from

According to Nernst's relation:

0∕abs

= −ΔG0sol(RedOx)∕nF

(1)

(2)

E

Ox∕Red

0

Ox∕Red

0∕abs

E

= E

− EAg∕AgCl

Ox∕Red

with:

E

0∕abs : is the absolute standard redox potential of the

3

Ox∕Red

the exper[iment](#br15)al values, but they are overestimated by shift

dif erences of 0.86, 0.40, and 0.25 ppm, respectively. For

the Fe3b complex, the same shifts are observed around 7.67,

8.30, and 2.48 ppm. A doublet at 6.50 ppm, corresponding

to the protons of the –NH group in the 8-quinoline position

couple Ox/Red

ΔG0sol(Ox): the standard solvation energy of the oxidized

species

ΔG0sol(Red): the standard solvation energy of the reduced

species

2

appears on the experimental spectrum of the Au2 complex,

and the calculated value is underestimated by 0.72 ppm. The

same calculation on the Fe2 complex leads to a chemical

shift of the order of 5.45 ppm. Experimental and theoretical

ΔG (RedOx): the standard free energy of the gas phase

0

g

reduction

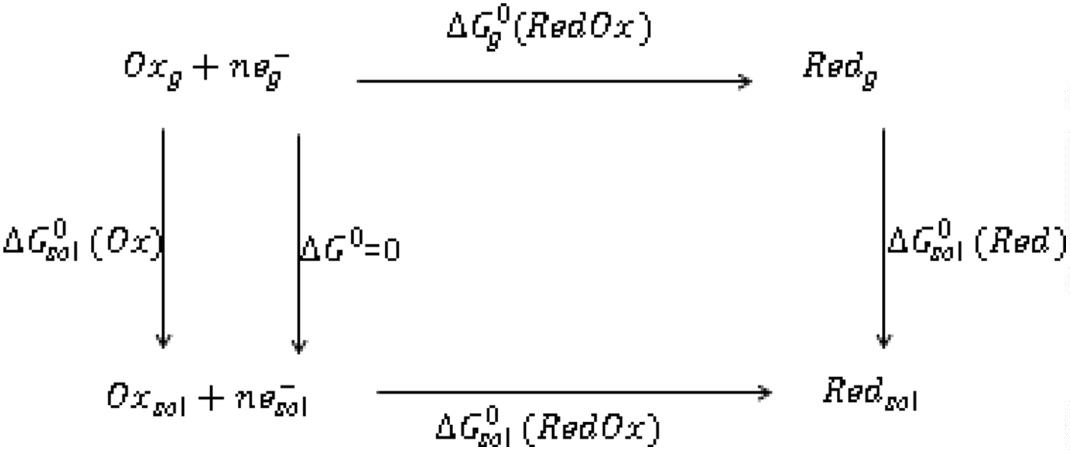
ΔG0 (RedOx): the Gibbs free energy associated with the

sol

reduction of complexes in solution

Fig. 3 Born-Haber cycle

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Table 2 The Gibbs free energies associated with the reduction (in

kcal.mol−1); the absolute reduction potential ((abs) in V) obtained

at the DFT/B3LYP/GEN level (6–311+g\*\* for all atoms and

LANL2DZ for Au) as well as the experimental

reduction potentials (in V).Eexp

ΔG0 (RedOx)E0∕abs

sol

Ox∕Red

Complexes

ΔG0sol(RedOx)(kcal.mol−1)

Eexp(V)

E0∕abs

(V)

Ox∕Red

Au1

Protonated Au2

Deprotonated Au2

Au3a

Au3b

Au4

Fe1

Protonated Fe2

Deprotonated Fe2

Fe3a

Fe3b

Fe4

−221.4

−248.5

−214.7

−220.4

−220.1

−215.5

−627.7

−627.8

−627.7

−627.7

−627.7

−627.7

4.801

+0.175

−0.170

−0.170

+0.125

0.095

−0.115

–

–

–

–

–

–

5.388

4.656

4.781

4.773

4.674

3.495

4.340

3.296

3.716

3.705

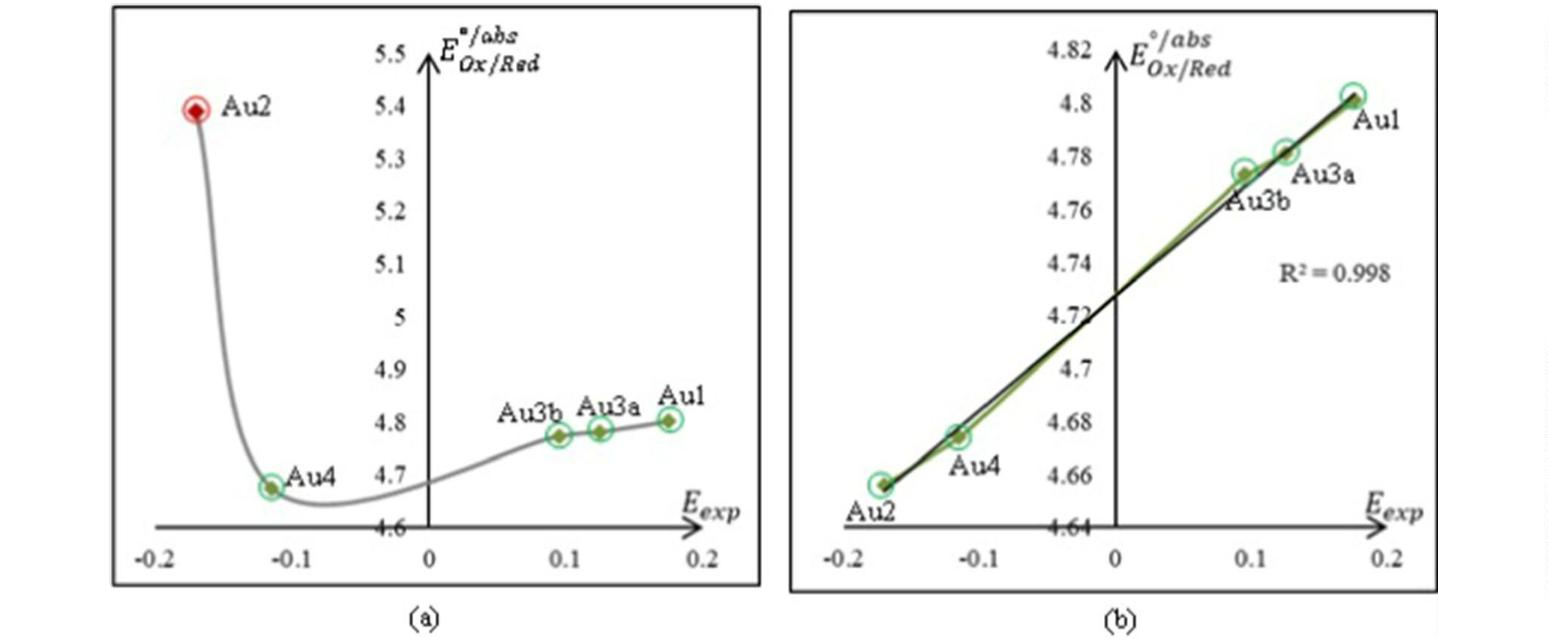
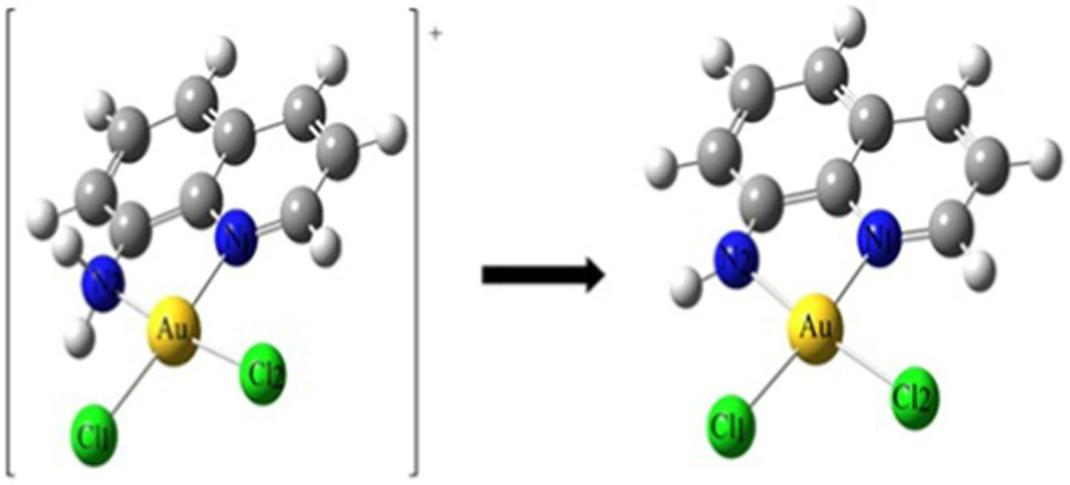
3.598

Fig. 4 Charged, and deproto-

nated Au2 complexes

Fig. 5 Theoretical absolute potential vs. experimental ones

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n: is the number of electrons involved during the reduc-

tion process

[using density functional t](#br15)heory-based molecular dynamics

[[93](#br15)] and standard hydrogen electr[ode (SHE) dev](#br15)eloped by

[Cheng, Sulpizi, and Spr](#br15)ik in water solution [[94](#br15)]. If this is

considered, the two Au2 and Au4 complexe[s w](#br15)ill have a

negative redox potential, and the rest of the complexes will

have a positive redox potential.

F: is Faraday's constant where F[=](#br6)23.06 kcal mol−1 V−1.

The results are reported in Table [2](#br6).

To calculate the re[du](#br5)ction pote[n](#br6)[t](#br5)ials, we use, respec-

tively, the Nernst Eq. ([1](#br5)), then Eq. ([2](#br5)) giving the theoreti-

cal standard potential, [w](#br5)hich must [b](#br5)e compared with the

experimental values. As the absolute potential of the refer-

These results, in agreement with the experiment [[82](#br15)], are

due to the stabilization of the metal center by t[he natur](#br15)e of

the ligand in position 8 of the quinoline. Donating power

of the –NH group decreases due to the substitution of the

hydrogen atom by attractor groups in the M3a and M3b com-

plexes (M= Au and Fe). This leads to instability (decrease

in the quantity of M(III) in favor of M(I)) of the metal

center, which results in increasing the calculated absolute

redox potential (4.781 V for Au3a) and (4.773 V for Au3b)

whereas, for the Au2 complex, we have 4.659 V. Due to

the aforementioned proposed potential value of the refer-

ence electrode (Ag/AgCl) in dichloromethane (4.727 V),

the oxidation–reduction potentials of the three respective

complexes Au3a, Au3b, and Au2 calculated (experimental)

are + 0.054 (0.125) V, + 0.046 (0.095) V and – 0.068 (−0.17)

V. These results lead to a good corr[elation be](#br6)tween t[he cal](#br7)-

culated and experimental v[al](#br6)ues (see Fig. [4](#br6)a and Fig. [6](#br7)).

The results given in Table [2](#br6) for the com[ple](#br6)x[es based on](#br7)

Fe(III)show that the v[alues in t](#br6)his series are more stable

than those based on Au(III), as they have a more accentuated

stability for the complexes Fe2 and Fe1.The latter are more

resistant to redox reactions with theoretical absolute poten-

tials of 3.296 V and 3.495 V, respectively, unlike the other

complexes in the same series. The substitution of the amino

group by sulfonamide in the Fe3a and Fe3b complexes gives

the highest theoretical absolute potential values of the series

(3.716, and 3.705 V, respectively) due to the decreasing of

the donating power of the amino group. The metal centers

of both series gain maximum stability with an amino group

at the 8-position of the quinoline.

ence electrode,E

is not available in the literature, to

Ag∕AgCl

evaluate it, we plot the curv[e giving t](#br6)he calculated values vs.

Experimental ones (see Fig. [5](#br6)a).

In this step, we f nd that t[he v](#br6)alue of the absolute poten-

tial of the Au2 complex (with a –NH group in position 8

2

of t[he q](#br6)uinoline) proposed by Antonio Sanchez et al. (see

Fig. [4](#br6)) is 5.388 V. The dif erence between t[his](#br6) value and

t[hose](#br6) of the other complexes is high (see Fig. [5](#br6)a).

If, instead, the Au2 complex is consider[ed t](#br6)o be depro-

tonated (–NH in the 8 position of the quinoline instead of

–NH ), the theoretical potential becomes 4.656 V. This

2

result leads to a good correlation between the calculated and

experimental values wit[h a sq](#br6)[uar](#br7)ed correlation coef cient

equal to 0.998 (see Fig. [5](#br6)b and [6](#br7)).

The regression eq[uation](#br6) giv[en](#br7) in Fig. [5](#br6)b is:

0∕abs

(3)

E

= 0.433Eexp + 4.727 (V)

Ox∕Red

where the y-intercept (4.727 V) represents the absolute

potential of the reference electr[ode](#br6) E

.

Ag∕AgCl

The results analysis of Table [2](#br6) shows that the type of

ligand and its arrang[ement af ect t](#br6)he energy levels of the

valence electrons and therefore the redox potential of the

complex.

This allows us to propose, for the f rst time, a value of

4.727 V for the potential of the reference electrode (Ag/

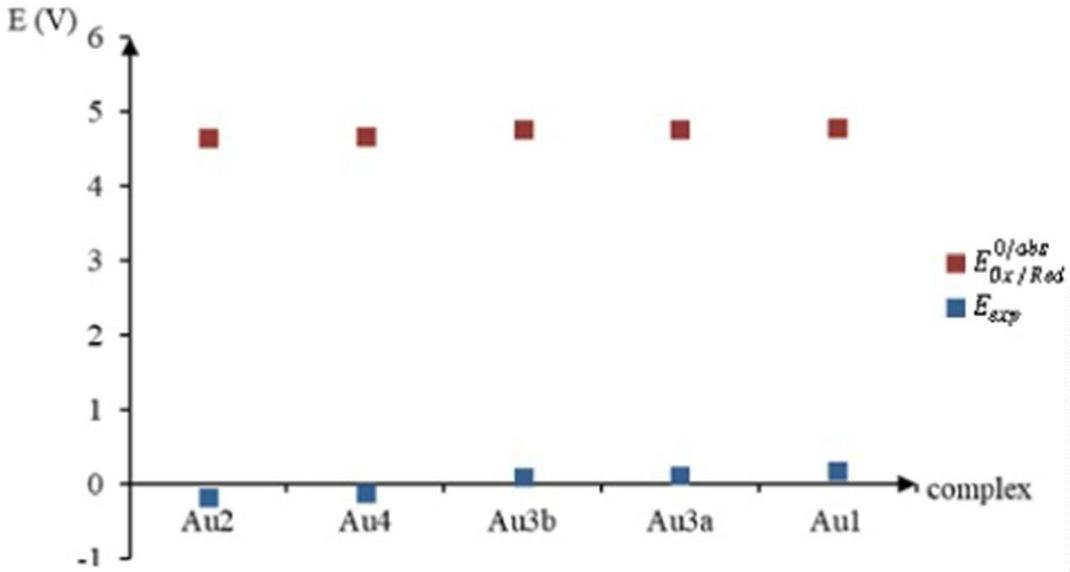
AgCl) in dichloromethane. A dif erence of 0.28 V was found

compared to the value given by a computational scheme

Fig. 6 Experimental and calcu-

lated Reduction potentials

1 3



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Table 3 The complexation

energies (kcal.mol−1) of the

complexes obtained at the DFT

level

Table 4 The intramolecular

Complexes

Ecomp(kcal.mol−1)

Complexes

Edisp(kcal.mol−1)

dispersion energies (kcal.mol−1)

of the complexes obtained at the

DFT/ωB97XD level

Cis-Platin

Au1

Au2

Au3a

Au3b

Au4

Fe1

Fe2

Fe3a

Fe3b

Fe4

−724.7

−1429.3

−1490.6

1420.6

−1419.5

−1445.4

−1300.1

−1313.1

−1288.6

−1291.1

−1298.1

Cis-Platin

Au1

Au2

Au3a

Au3b

Au4

Fe1

Fe2

Fe3a

Fe3b

Fe4

− 3.1

− 9.5

−10.4

−15.5

−20.6

− 9.7

− 8.5

− 9.3

−14.1

−19.7

− 8.9

3.2.4 Complexation energy

stability to the M(III)-based complexes. A slight variation

of this is observed for the Fe(III) complexes when the sub-

stituents at the 8-position of the quinoline are changed. This

dif erence does not exceed 25 kcal mol−1, whereas in the

case of the complexes based on Au(III), it is of the order of

71 kcal mol−1.

The complexation energies of the studied compounds were

calculated from the optimized geometries using the follow-

ing equation:

n

i=1

(4)

Ecomp = ET −

Ei

3.2.5 Dispersion energy

where E

: The electronic energy of complexation; E :

T

[DFT-D me](#br15)thods [[95](#br15)–[98](#br15)] take into account the dispersion

[[99](#br15), [100]. These me](#br15)t[hods ar](#br15)e widely used in the study of

[non-covalent inter](#br15)actions. In this part of the work, we have

considered a corrected hybrid dens[ity functional based on](#br8)

the GGA and Becke exchange functions. Table [4](#br8) demon-

strates that the dispersion energies are higher[, in absolute](#br8)

value, for the complexes of the two series compared to that

comp

The total electronic energy of the system; E : The electron

i

energy of ligand (i) is optimized in the isolated state at the

same t[heor](#br8)etical level. The r[esults (kcal](#br8) mol−1) are reported

in Table [3](#br8) and schematized in Fig. [7](#br8):

[The com](#br8)plexation energy of the two M(III) series

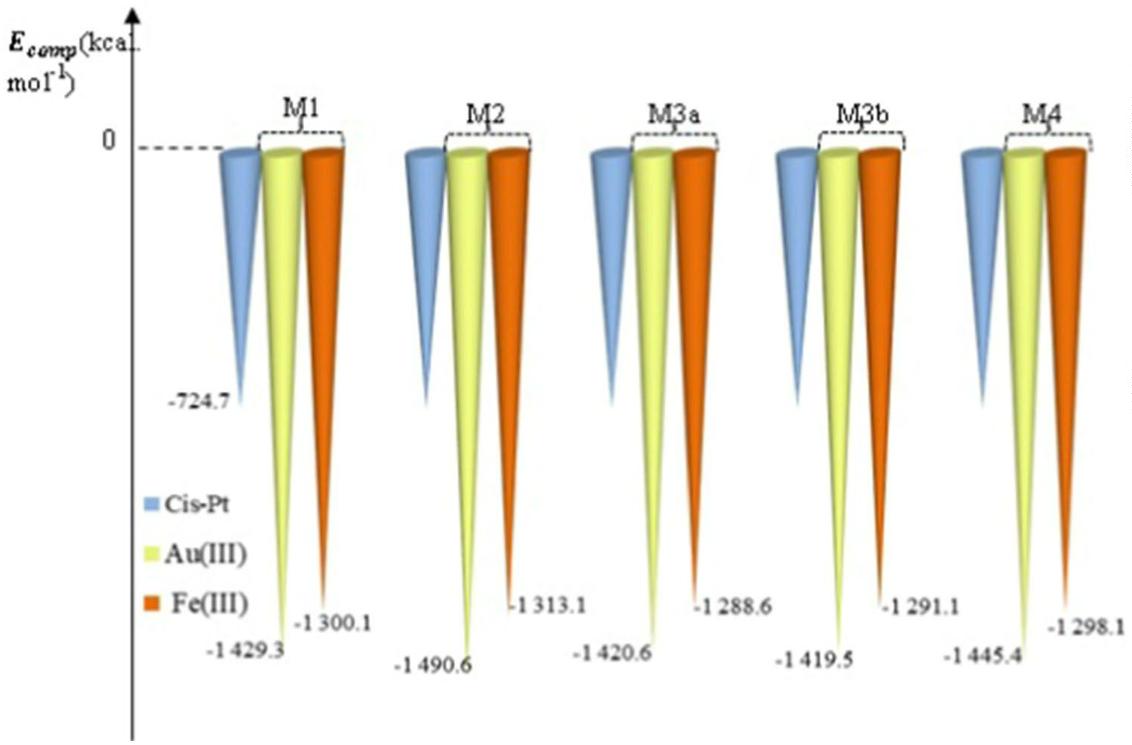
(M = Au, and Fe) is two times lower than that of Cis-platin at

the same theoretical level. This gives greater thermodynamic

Fig. 7 Complexation energy

obtained at DFT level

1 3



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Table 5

HOMO, LUMO, and Gap (|EHOMO-ELUMO|) energies (in eV)

reactions might be more dif cult on the Fe(III) complexes.

These results conf rm the conclusions of the electrochem-

istry section (see paragraph 3.2.3).

Complexes

EHOMO

ELUMO

Gap

Cis-Platin

Au1

Au2

Au3a

Au3b

Au4

Fe1

Fe2

Fe3a

Fe3b

Fe4

−6.364

−6.599

−6.144

−6.780

−6.631

−6.532

−6.560

−6.101

−6.621

−6.456

−6.406

−2.006

−4.331

−3.834

−4.192

−4.120

−4.112

−2.875

−2.737

−2.814

−2.690

−3.033

4.358

2.268

2.310

2.588

2.511

2.420

3.703

3.364

3.807

3.766

3.373

3.2.7 Global reactivity descriptors within the conceptual

DFT framework

Global reactivity descriptors [[103](#br15)–[109](#br15)] are calculated

within the framework of t[he density functional t](#br15)heory.

Among these descriptors are the chemical potential (μ),

which quantif es the electron-withdrawing power of a mol-

ecule, the chemical hardness (η), which tells us about the

resistance of a molecular system to electron transfer, and

whether it is a gain or a loss, and the electrophilicity index

(ω), which measures the ability of a molecule to receive

electrons, and the f exibility (). These quantities of the

global reactivity descriptors are def ned, respectively, by

the relations given below:

of Cis-platin. We note that the dispersion energies of the

Au(III)-based complexes are slightly higher.

Among all the complexes, those containing the amino

group have the highest dispersion energies. Furthermore, the

more the amino group is branched, the greater the dispersion

energy (in absolute value), which results in greater stability.

2

1

1; = −;

; =

= − (EI + AE); = (EI − AE); =

2

2

(5)

where EI is the ionization energies, and AE is the electron

af nity[. These ar](#br15)e calculated without Koopmans’ approxi-

mation [[110](#br15)]. EI is calculated as the energy difference

betw[een the neutr](#br15)al and ionized complexes, and AE is the

energy dif erence between the neutral and ionized complexes

with (N+ 1) electrons. A good electrophile is characterized

by a low value of chemical potential (μ) and a high value of

electr[ophilicity inde](#br11)x (ω). All the calculated descriptors are

gathered in Table [6](#br11).

3.2.6 The frontier molecular orbitals (FMO)

The highest occupied molecular orbital (HOMO) describes

the molecule's ability to donate an electron, and the low-

est empty molecular orbital (L[UMO) def nes t](#br15)he molecule's

ability to accept an electron [[101](#br15), [102](#br15)]. The optimized

geometries without symmetr[y constraints conduce t](#br15)[o t](#br9)he

HOMO, L[UMO, and Gap ener](#br10)gies are given in Table [5](#br9) and

schematized in Fig. [8](#br10)a, and b.

The M3a com[ple](#br10)xes (M = Au, Fe) have the lowest

HOMO with an energy of −6.78 eV for the Au(III)-based

complex and an energy of −6.62 eV for the Fe(III)-based

complex. On the other hand, the highest LUMO was

obtained in the Au2 complex with energy of −3.83 eV

and in the Fe3b complex with energy of −2.69 eV. Overall,

Cis-platin has the highest energy gap (4.36 eV). There-

fore, our new complexes are more r[eactiv](#br10)e compared to

the Cis–platin. The FMOs (see Fig. [8](#br10)a, and b) show that

the LUMO in Cis-platin and in the A[u(III) com](#br10)plexes are

localized to the metal site and to the ligands. Whereas in

Fe(III) complexes, The LUMO is localized on the qui-

noline level without involving the metal ion and the two

Cl atoms. In the Au(III) and Fe(III) series, the HOMO is

mainly localized throughout the structure. In Cis-platin,

the HOMO is localized on its metallic center as well as

on the two Cl atoms. Complexes based on Fe(III) have

the largest energy gaps compared to complexes based on

Au(III), and since the LUMO is partially localized on the

metallic center, this explains the instability of the Au(III)

complexes in the biological medium. Therefore, reduction

According to t[he calculated descr](#br11)iptors (see Table [6](#br11)), the

complexes of both series are more reactive t[han Cis-platin.](#br11)

This latter has the highest gap and chemical hardness (η)

of 4.358 eV, which ref ects a more remarkable resistance

to electron transfer compared to the other complexes. The

molecules studied are both nucleophiles (Nu =−EI) and

good electrophiles (ω). As nucleic bases are nucleophilic

molecules, the studied complexes can be good candidates

to replace Cis-platin, namely the M3a and M3b complexes

(M = Au, Fe) due to their electrophilic character.

3.2.8 Molecular electrostatic potential (MEP)

The reaction pr[of le of a molecule can be predicted b](#br15)y ana-

lyzing its molecular electrostatic potential [[111](#br15)]. One of the

pieces of information that we can extract fr[om a molecule](#br15)’s

surface is the type of attack site (electrophilic or nucleo-

[philic). Indeed, t](#br15)here are essentially two types of regions

[[112](#br15)], the blue-colored region represents the sites likely to

[under](#br15)go a nucleophilic attack (sites def cient in electrons),

1 3



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Fig. 8 Frontier molecular orbital (FMO). a Cis-Platin and Au(III) complexes. b Cis-Platin and Fe(III) complexes

and the red colored region represents the sites likely to be

attacked by electrophiles (sites rich in electrons). Using

Gaussian 09, we generated t[he molecular electr](#br11)ostatic poten-

tial (MEP). The results are depicted in Fig. [9](#br11)a, and b.

In all of the complexes, the negative r[egions ar](#br11)e mainly

located on the two Cl atoms and extend to cover the 8-qui-

noline oxygen atom in the M1 complexes, the sulfur in M4,

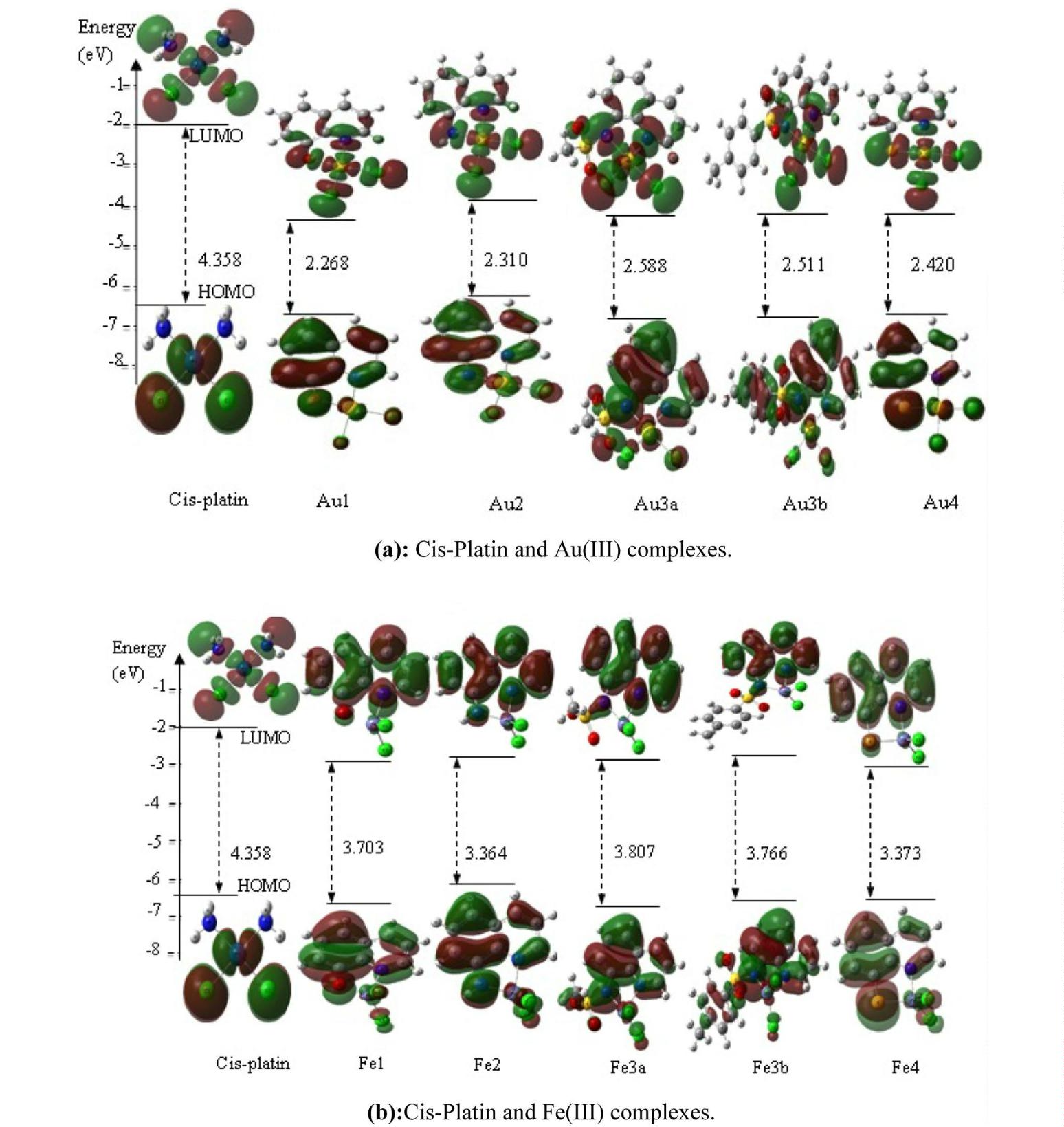
and the sulfonyl groups in M3a and M3b (M= Au and Fe).

These last two complexes, namely M3a and M3b, represent

more electron-rich regions. The two -NH3 groups of Cis-

platin are more electrophilic than quinoline.

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Table 6 Global reactivity

Complexes

Descriptors

μ

descriptors in eV

η

ω

χ

Nu

Cis-Platinum

−4.898

4.358

2.752

0.229

4.898

−8.378

Au1

−5.663

2.268

7.070

0.441

5.663

−7.963

Fe1

−5.533

3.703

4.134

0.270

5.533

−7.882

Au2

Fe2

−5.222

−5.191

2.310

3.364

5.902

4.005

0.433

0.297

5.222

5.191

−7.491

−7.380

Au3a

−5.600

2.588

6.059

0.386

5,600

−7.825

Fe3a

−5.595

3.807

4.111

0.263

5.595

−7.792

Au3b

Fe3b

−5.470

−5.424

2.511

3.766

5.958

3.906

0.398

0.266

5.470

5.424

−7.560

−7.524

Au4

−5.520

2.420

6.296

0.413

5.520

−8.002

Be4

−5.502

3.373

4.487

0.296

5.502

−7.781

Fig. 9 Molecular electrostatic

potential (MEP). a Cis-Platin

and Au(III) complexes. b Cis-

Platin and Fe(III) complexes

3.3 ADME/Tox properties

with very high intestinal absorption percentages of 95.24%

for Au3b and 95.20% for Fe3b, respectively. Lower intestinal

absorption (90.65%) for Au2 and (90.62%) for Fe2 were also

obtained. Finally, the intes[tinal absor](#br12)ption of Cis-platin was

estimated to be 92.60% (Scheme [2](#br12)).

The in silico study of the ADME proper[ties led t](#br12)o t[he results](#br12)

shown in Tables S3-a, b, and c and Schemes [1](#br12) and [2](#br12). The

absorption of the compounds studied w[as predicted b](#br12)y

[human intestinal absor](#br15)ption (%HIA) and Caco-2 perme-

ability [[113](#br15), [114](#br15)]. All the studied complexes presented a

high per[meability t](#br15)o CaCo-2, whic[h is manif](#br12)ested by log

(Papp) values greater than 1 (Scheme [1](#br12)). The M3b com-

plexes (M = Au, Fe) have a value less t[han 0.8 (T](#br12)able S3-a)

Table S3-a shows that only [C](#br12)is-platin, Au1, and Fe1

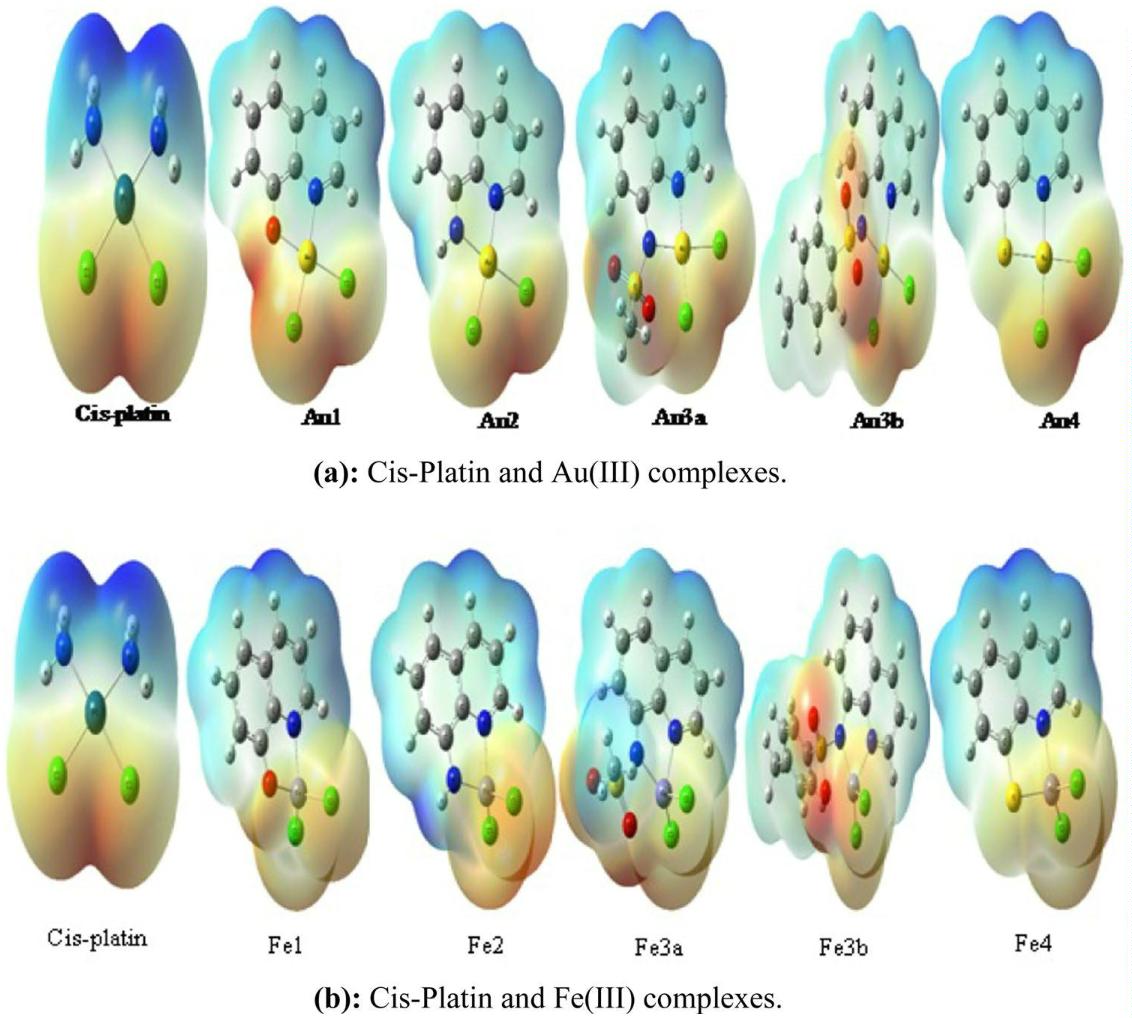
can be substrates for P-glycoprotein ( +) without any

inhibitory ef ect on the two P-glycoprotein I/II(−) vari-

ants. One of the most remarkable results is that the Au3b

and Fe3b complexes are the only ones with an ability to

1 3



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Scheme 1 Histogram of perme-

ability (Caco-2)

Scheme 2 Histogram of intesti-

nal absorption (%HIA)

inhibit P-glycoprotein I and II ( +) without being at the

same time a substrate for P-glycoprotein (−), which could

have the ef ect of increasing their bioavailability, hence a

more ef ectiv[e anti-cancer activity](#br15). Analysis of the volume

of distribution (log VDss) [[115](#br15)] (see Table S3-a) shows

that all of the complexes e[xhibit a lar](#br15)ger distribution

(0.413–0.631) in relation to that of Cis-platin’s (0.302)

except for the Au3a (0.011) and Fe3a (0.010) complexes.

A value of log(VDss) greater than 0.45 is considered rela-

tively high; therefore, a molecule with a high log(VDss)

will have a longer half-life. The study of permeability

at the blood–brain barrier (BBBP) is described by the

log(BB) and t[hat of the](#br15) Central Nervous System (CNS)

by the log(PS) [[116](#br15), [117](#br15)]. According to their values (see

Table [S3-a), all of the com](#br15)plexes should be able to eas-

ily cross the BBB and to even be able to enter the CNS

(with a value of log(BB) > 0.3, the drug can easily cross

the blood–brain barrier and with a value of log(PS) > −2,

the drug can penetrate the CNS). According to the results

obtained in Table S3-b, we f nd that all of the complexes

in both series inhibit the CYP1A2 ( +) isoform except for

Cis-platin (−). CYP2D6 is only inhibited by the M3a com-

plexes (M= Au, Fe) (−). On the other hand, the CYP2C19

iso-form is inhibited only by the M4( +) complexes.

CYP2C9 and CYP3A4 are not inhibited by any complex

(−). Complexes with a nitrogen moiety at the 8-quino-

line position (M2, M3a, and M3b) are the only candidates

that have been predicted as a substrate for CYP3A4 ( +);

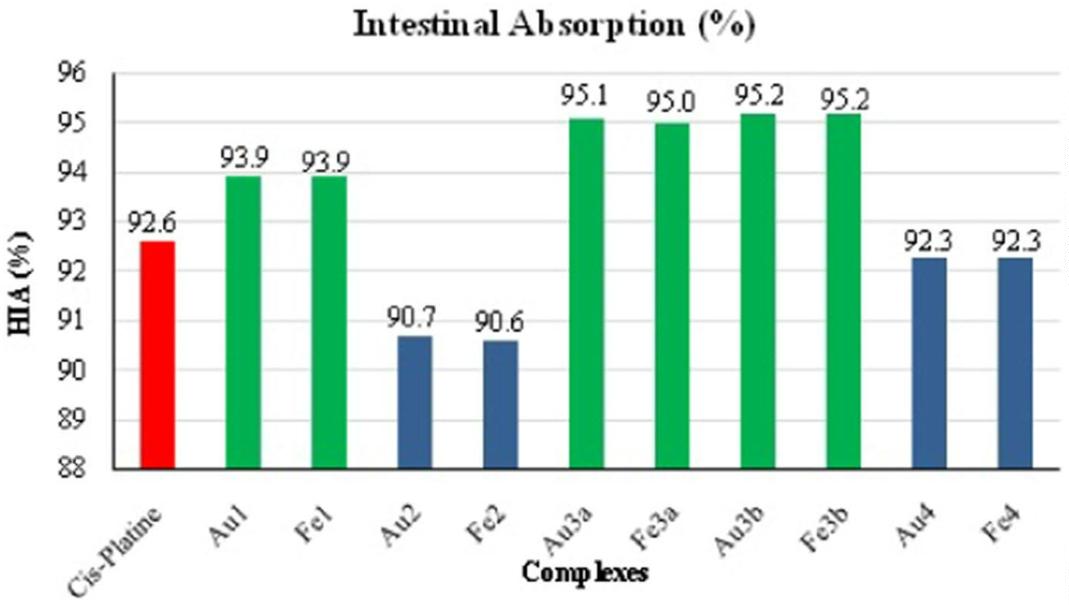
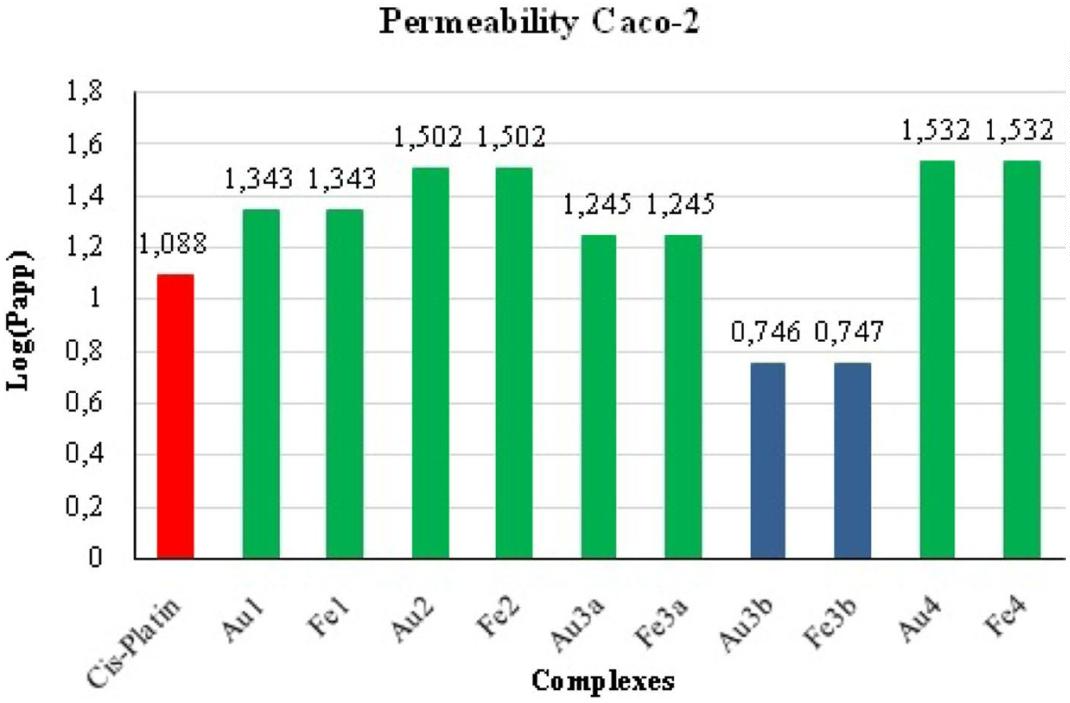
therefore, they can be metabolized in the liver with little

or no hepatotoxicity. Cis-platin was not predicted to be

either an inhibitor or a substrate of CYP450. Excretion

was predicted and are reported in Table S3-b, using the

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total clearance (log(CL )) resulting from a combination

of 4.727 V for the potential of the reference electrode (Ag/

AgCl) in dichloromethane. Finally, the new complexes are

less toxic and appear to be better anti-cancer drug candidates

than Cis-platin.

tot

of hepatic and renal clearance. Only the M3a and M3b

complexes seem to be eliminated via the kidneys where

they were predicted to be substrates for the OCT2 protein

( +). While the other complexes are eliminated by other

means, namely sweat, bile, or other (−). Predicted val-

ues for total clearance, log(CL ), range from −0.099 to

Supplementary Information [The online version contains supplemen](https://doi.org/10.1007/s00214-022-02940-3)-

tary material available at <https://doi.org/10.1007/s00214-022-02940-3>.

tot

1.187 ml.min−1.kg−1, which are lower than the predicted

values of Cis-platin (see Table S3-b). According to the

toxicological properties obtained at the pkCSM level

(see Table S3-c), all the molecules treated in this analysis

showed no ability to cause allergic contact dermatitis. It

was also observed that none of the complexes presented a

mutagenic potential, except for the M2 complexes (Ames

toxicity positive). Only the M3a complexes are predicted

to be hepatotoxic ( +). Inhibition of hERG (human ether

a gogo-reelated g[ene) po](#br15)tassium channels leads to heart

rhythm disturbances [[118](#br15)]. None of the complexes exhib-

ited an inhibitory ef[fect t](#br15)oward hERG (I/II) (−). The

predicted LD50 lethal doses are 2.876 mol kg−1 for Cis-

platin and are included in the interval [3.103–3.513] mol

kg−1 (Fe3a) for all of the complexes studied. Similarly,

the oral rat chronic toxicity (LOAEL) of the complexes

[0.657–1.239] is greater than that of Cis-platin (0.428).

It appears from this that the new complexes are less toxic

than Cis-platin.

Author contributions "AY carried out all theoretical calculations with

Gaussian09.AY, SA and MB wrote the main manuscript text and MD

prepared the spectrocopique discussions. All authors reviewed the

manuscript."

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Declarations

Conflict of interest The authors declare no conf ict of interests.

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[2174/156802611794785226](https://doi.org/10.2174/156802611794785226)

4 Conclusion

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[002](https://doi.org/10.1016/j.ccr.2014.08.002)

From the results, particularly those presented in the elec-

trochemistry section, we can f nally explain the instability

of Au(III)-based complexes in the biological environment

because they tend to undergo reduction reactions. The Au1

complex has the highest electrophilic character followed by

the Au3a complex and lastly the Au2 complex. Similarly,

the highest reduction potential was obtained for the Au1

complex, and the lowest potential was obtained for the Au2

complex.

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FMO theory and the global reactivity descriptors show

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character compared to quinoline. On the other hand, the

complexes which contain the amino group have the high-

est dispersion energies. This is true even more so when the

amino group is branched, which results in even greater sta-

bility. This work allows us to propose theoretically a value

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