N,N-bis (1*H*-pyrazol-1-yl) derivatives : Synthesis, Liquid-liquid extraction of metals and electronic DFT calculations

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Abstract
Liquid-liquid extraction of metals using new synthetic N,N-bis(1*H*-pyrazolyl-1-yl) derivatives as new extractants was studied. The extractability for Fe^{2+}, Zn^{2+}, Cu^{2+}, Co^{2+}, Cd^{2+} and Pb^{2+} from the aqueous phase was determined by atomic absorption. The competitive extraction and the effect of pH were also investigated. We found high selectivity towards Fe^{2+} (68.03 %),Cu^{2+} (44.15%), Pb^{2+} (32.12%) and Cd^{2+} (26.22%) respectively. In addition, the geometry and the electronic structure were carried out by DFT calculations.

Keywords: Pyrazole; Synthesis; Liquid-Liquid extraction; metal cations; DFT calculations.

1. Introduction
For their pharmacological and medicinal properties, pyrazole moiety attracts considerable attention especially as anticonvulsant [1], antimicrobial [2], antihypertensive [3], analgesic [4], antiviral [5],antioxidant [6], anti-inflammatory [7] and anticancer [8]. Moreover, pyrazole is an important active compound in biology and coordination chemistry [9]. Otherwise, liquid–liquid extraction of metals is considered one of the most important techniques for separation and recovery of metal ions [10]. However, the success of this recovery process is still limited by the extraction selectivity for the targeted metal using a specific extractant. The design and the preparation of selective extractants for the separation of heavy metals remained a great challenge for researches. In this context, we have previously investigated the liquid-liquid extraction of metals using nitrogen-donor pyrazole ligands and studied their ability to extract metals from aqueous solutions [11]. In continuation of our investigations in this topic, herein we report the synthesis of new N,N-bis(1*H*-pyrazol-1-yl) derivative ligands**L₁-L₇**(**Figure 1**), the study of their liquid-liquid extraction of metals and theoretical DFT calculations.

2. Experimental section
2.1. Apparatus
NMR spectra were recorded by use of a Bruker 300 instrument operating at 300.14 MHz for ^{1}H spectra and 75.47 MHz for ^{13}C spectra (Pz: pyrazole) (Ph: Phenyl). Mass spectra were recorded using a Shimadzu GC-MS 2014 Shimadzu Gas Chromatograph-Mass Spectrometer.
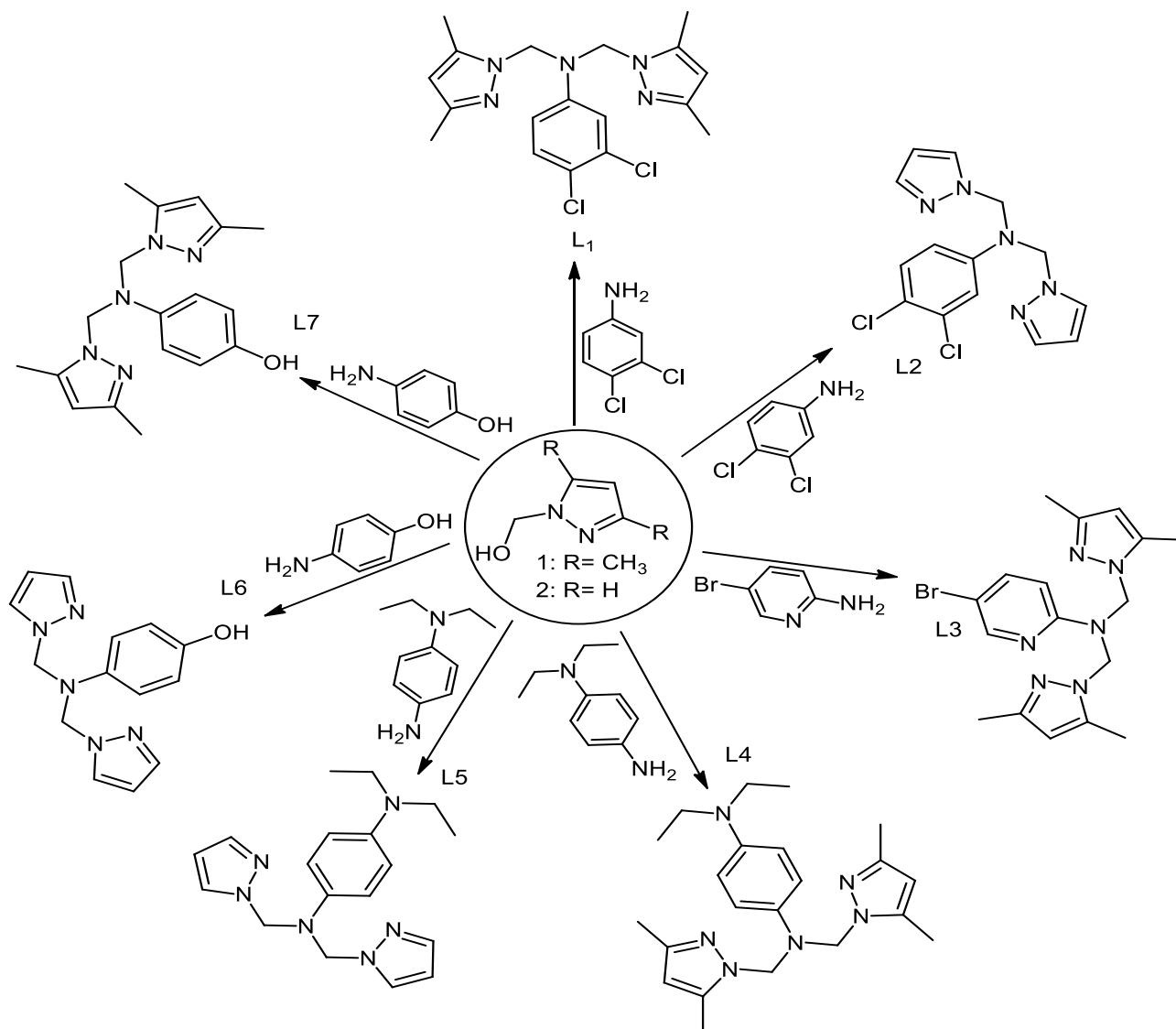
Fig. 1. Chemical structures of N,N-bispyrazolyl ligands **L₁-L₇**

2.2. General method for synthesis of ligands L₁-L₆

The appropriate amine (10mmol) was added to a suspension of (3,5-dimethyl-1H-pyrazol-1-yl)methanol (20 mmol) in anhydrous CH_3CN (25mL) . The mixture was refluxed and stirred for4 hours. Then the mixture was dried over Na_2SO_4filtered and concentrated to yield the corresponding compound. The compound 4-(bis((3,5-dimethyl-1*H*-pyrazol-1-yl)methyl)amino)phenol(**L₆**)known product previously reported in the literature [12].

2.3. Characteristic data of new compounds L₁-L₆

3,4-dichloro-N,N-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)aniline (L₁) :

Yield: 89%; ^{1}HNMR (300 MHz, CDCl₃, d (ppm)): 7.21-6.33 (m, 3H, HPh); 5.77 (s, 2H, HPz); 5.47 (s, 4H, N-CH₂-N); 2.19 (s, 6H, CH₃Pz); 2.13 (s, 6H, CH₃Pz); ^{13}C NMR (75 MHz, CDCl₃, d (ppm)): 148.58(CPh); 130.73(CPz); 130.56(CPz); 115.64-113.81 (CPh) ;106.06 (CPz) ;62.58 (N-CH₂-N) ;11.14 (CPz) ; 11.06 (CPz); ESI-SM m/z: 2M+Na = 767.

N,N-bis((1H-pyrazol-1-yl)methyl)-3,4-dichloroaniline (L₂) :

Yield: 84%; ^{1}HNMR (300 MHz, CDCl₃, d (ppm)): 7.45 (dd, 2H, HPz, J=3Hz); 7.28 (d, 1H, HPh, J=3Hz); 7.20 (d, 1H, HPh, J=9Hz); 7.04 (dd, 2H, HPz, J=3Hz); 6.58(dd, 1H, HPh, J=3Hz); 6.29 (t, 2H, HPz); 5.79 (s, 4H, N-

CH$_2$-N); ^{13}C NMR (75 MHz, CDCl$_3$, d (ppm)): 145.49(CPh); 140.33(CPz); 133.26(CPh) 130.93(CPh) 129.00 (CPz) 124.46 (CPh) 115.46 (CPh) 113.31 (CPh) 106.59 (CPz);66.03 (N-CH$_2$-N) ; ESI-SM m/z: M= 322.

5-bromo-N,N-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)pyridin-2-amine (L$_3$) :
Yield: 78%; ^{1}HNMR (300 MHz, CDCl$_3$, d (ppm)): 8.10 (s, 1H, HPh); 7.73 (dd, 1H, HPh, J=3Hz); 7.26 (dd, 1H, HPh, J=3Hz); 5.62 (s, 2H, HPz); 5.42 (s, 4H, N-CH$_2$-N); 2.21 (s, 6H, CH$_3$Pz); 2.19(s, 6H, CH$_3$Pz).^{13}C NMR (75MHz, CDCl$_3$, d (ppm)): 151.85 (C14Ph); 148.20(CPh); 146.67 (CPh); 140.15 (CPz); 115.64-107.64 (CPh);105.40 (CPz) ;54.57 (N-CH$_2$-N) ; 11.53 (CPz); ESI-SM m/z: M= 388.

N,N-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-N4,N4-diethylbenzene-1,4-diamine (L$_4$) :
Yield: 88%; ^{1}HNMR (300 MHz, CDCl$_3$, d (ppm)): 7.69 (d, 2H, HPh, J=6Hz); 7.34 (d, 2H, HPh, J=6Hz); 5.71 (s, 2H, HPz); 5.53 (s, 4H, N-CH$_2$-N); 4.30 (q, 4H; CH$_2$, J=6Hz); 2.09 (s, 6H, CH$_3$Pz); 1.93(s, 6H, CH$_3$Pz); 1.30 (t, 6H, CH$_3$,J=6Hz); 13C NMR (75 MHz, CDCl$_3$, d (ppm)): 144.45 (CPh); 140.06 (CPh); 137.27(CPz); 126.49 (CPh); 117.63 (CPh); 105.82 (CPz); 66.51 (N-CH$_2$-N) ; 44.30 (C); 13.25 (CH$_3$); 12.15 (CPz); 10.70 (CPz).

N,N-bis((1H-pyrazol-1-yl)methyl)-N4,N4-diethylbenzene-1,4-diamine (L$_5$) :
Yield: 85%; ^{1}HNMR (300 MHz, CDCl$_3$, d (ppm)): 7.75 (dd, 2H, HPzJ=6Hz); 7.43 (dd, 2H, HPz, J=6Hz); 7.36 (m, 2H, HPh); 7.12(m, 2H, HPh); 6.64(t, 2H, J=6Hz); 5.43 (s, 4H, N-CH$_2$-N); 4.41 (q, 4H; J=6Hz); 1.10 (t, 6H, J=6Hz); ^{13}C NMR (75 MHz, CDCl$_3$, d (ppm)): 144.07 (CPh); 141.14 (CPz); 140.12 (CPh); 125.11 (CPz); 124.35 (CPh); 106.36 (CPz); 57.77 (N-CH$_2$-N) ; 44.75 (C); 12.74 (CH$_3$).

4-(bis((1H-pyrazol-1-yl)methyl)amino)phenol (L$_7$)
Yield: 89%; ^{1}HNMR (300 MHz, CDCl$_3$, d (ppm)): 6.59 (dd, 2H, J=6Hz); 6.34 (dd, 2H, J=3Hz); 6.83 (d, 2H, J=6Hz); 6.73 (t, 2H, J=6Hz); 6.54(d, 2H, J=6Hz); 5.30 (s, 4H, N-CH$_2$-N); ^{13}C NMR (75 MHz, CDCl$_3$, d (ppm)): 155.05 (CPh); 147.42 (CPh); 140.06 (CPz); 126.49 (CPz); 117.63 (CPh); 116.15 (CPh); 105.82 (CPz); 66.51 (N-CH$_2$-N).

2.4. Liquid-liquid extraction tests

A solution of 7.10^{-5}M of ligand in CH$_2$Cl$_2$ (20 mL) was stirred for 2h with 20 mL of an aqueous solution of metal salt (7.10^{-5}M). Liquid-liquid extraction experiments were carried out at room temperature and pH neutral [13]. The aqueous phase was separated and analysed by atomic absorption spectrometry with an air-acetylene flame. Single element standards were prepared for these metals from Fluka 1000 mg/L stock solutions. The measurements are carried out using standard conditions for calibration. All standards were made acidic to avoid metal hydrolysis and to match content in the sample using nitric acid 2%.The organic phase was back-extracted with HCl, H$_2$SO$_4$ and HNO$_3$ solution (1M).The metal ion concentrations in the organic phases were calculated from the mass balance between the aqueous and organic phases. The extractability or the extraction efficiency (E%) was calculated from Equation (1)

$$E\,(\%) = ([M]_{org,eq}/\,[M]_{aq,init})\,x100 = ([M]_{aq,init} - [M]_{aq,eq}/\,[M]_{aq,init})\,x\,100 \qquad (1)$$

Where $[M]_{aq,init}$ represents the initial concentration of metal ion in the aqueous phase. $[M]_{aq,eq}$ and $[M]_{org,eq}$ are the total concentrations of metal ion in the aqueous and organic phases, respectively, at equilibrium.

2.5. Theoretical calculations

Density functional theory has developed the concept of chemical potential (μ) and absolute electronegativity (χ) [14]:

$$\mu = (\delta E\,/\,\delta N)v(r) = -\chi \qquad (2)$$

where, E is the total energy, N is the number of electrons, and v(r) is the external potential of the system. Hardness (η) is defined [19] as the corresponding second derivative.

$$\eta = (\delta 2 E / \delta N2)v(r) = (\delta\mu / \delta N)v(r) \quad (3)$$

Ionization potential (I) and electron affinity (A), the electronegativity (χ), global hardness (η) and softness (S), may be defined in terms of the energy of the HOMO (highest occupied molecular orbital) and the LUMO (lowest unoccupied molecular orbital) according to Koopman's theorem [15].
Softness (σ) is the inverse of hardness and is given as follows:

$$\sigma = 1/\eta \quad (4)$$

Ionization potential (I) is defined as the amount of energy required to remove an electron from a molecule [16].

It is related to the energy of the E_{HOMO} through Eq. (5):

$$I = -E_{HOMO} \quad (5)$$

Electron affinity (A) is defined as the energy released when a proton is added to a system [17]. It is related to E_{LUMO} through Eq. (6):

$$A = -E_{LUMO} \quad (6)$$

Using a finite difference method working equations for the calculations of χ and η may be given as:

$$\chi = (I + A) / 2 \quad (7)$$
$$\eta = I - A \quad (8)$$

where, I is the ionization potential and A is the electron affinity. If ε_{HOMO} and ε_{LUMO} are the energies of the HOMO and LUMO, respectively, the Eqs. (7) and (8) can rewritten using Koopman's theorem [16]:

$$\chi = (\varepsilon_{LUMO} - \varepsilon_{HOMO}) / 2 \quad (9)$$

$$\eta = \varepsilon_{LUMO} - \varepsilon_{HOMO} \quad (10)$$

3. Results and discussions
3.1. Individual extraction of metal ions with the ligands L_{1-7}
To examine the coordination capacity of these ligands against each metal,we proceeded to extract the metals individually from aqueous media. Obtained extractabilities are presented in (**Table 1**).

Table. 1. Extraction efficiencies of metal cations using L_1-L_7.

	Fe^{2+}	Cu^{2+}	Zn^{2+}	Pb^{2+}	Co^{2+}	Ni^{2+}	Cd^{2+}
L_1	**95.90**	26.14	0.68	**78.17**	7.59	7.51	23.69
L_2	**93.91**	34.69	0.66	**77.63**	5.49	11.02	13.98
L_3	**89.25**	31.89	1.31	**90.56**	7.42	13.33	25.11
L_4	42.47	2.77	3.44	53.52	11.49	12.77	4.07
L_5	**67.05**	3.09	1.84	32.42	11.40	8.23	20.25
L_6	**84.31**	57.11	27.76	10.94	7.11	2.76	29.72
L_7	**73.72**	44.06	6.55	10.73	10.97	2.90	12.95

The **Table1** display a remarkable and high extraction efficiency for both Fe^{2+} and Pb^{2+}, while this ligands L_1-L_7 shown a medium and low efficiencies with Cu^{2+}, Cd^{2+}, Zn^{2+} and Co^{2+}.The extractabilities of Fe^{2+} by these

ligands vary between 42.47% (**L₄**) and 95.90% (**L₁**). In fact, the presence of a chlorure group in *para* position of the phenyl gives a high value of extraction efficiency for Fe^{2+}; 95.9% (**L₁**) and 93.91% (**L₂**) respectively. Interestingly, the presence brome group in the o*rtho* position (**L₃**)has allowed higher extractability for Pb^{2+} to be reached; 90.56%, whilst 78.17% can be attained when the substitution in the *para* position (**L₁**) is Cl.In general, the liquid-liquid extraction of Cu^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+} and Cd^{2+} remains low. For Zn^{2+} and Co^{2+}these ligands show an identical behavior but the extraction efficiencies remain very low and do not exceed 57.11% in the best case for Cu^{2+}. The ligands do not show an important efficiency toward Cd^{2+} and the maximum value is 29.72% for **L₆**.According to the results obtained by these ligands, it seems that some molecules have trend to coordinate with Fe^{2+}, other with Pb^{2+} and most of cases with both of metals. This can be attributed to the different nature of each ligand as well asits capacity to complex the various metals, the nature of metal may also be an important factor. The phenyl ring which is directly attached to the amine function which involve a sp^3 nitrogen and which forms with the azote a coordination site to receive metals is strongly influenced by the nature of the substituent group and its position. For these ligands, there are various substituents into different positions(halogen or hydroxyl group). Therefore, each substituent group has a specific effect on the coordination site in way that may increase or decrease the coordination capacity of the ligands.

3.2. Selective extraction of divalent metal cations

To understand the behavior of these ligands toward metal cations, we proceeded to investigate the selectivity of these ligands through a competitive extraction. For this purpose, we have extracted metal cations from a solution containing the four metals that have previously shown certain affinity vis-a-vis these ligands (Fe^{2+}, Pb^{2+}, Cu^{2+} and Cd^{2+}). The obtained results of this study are displayed in **Figure2**.
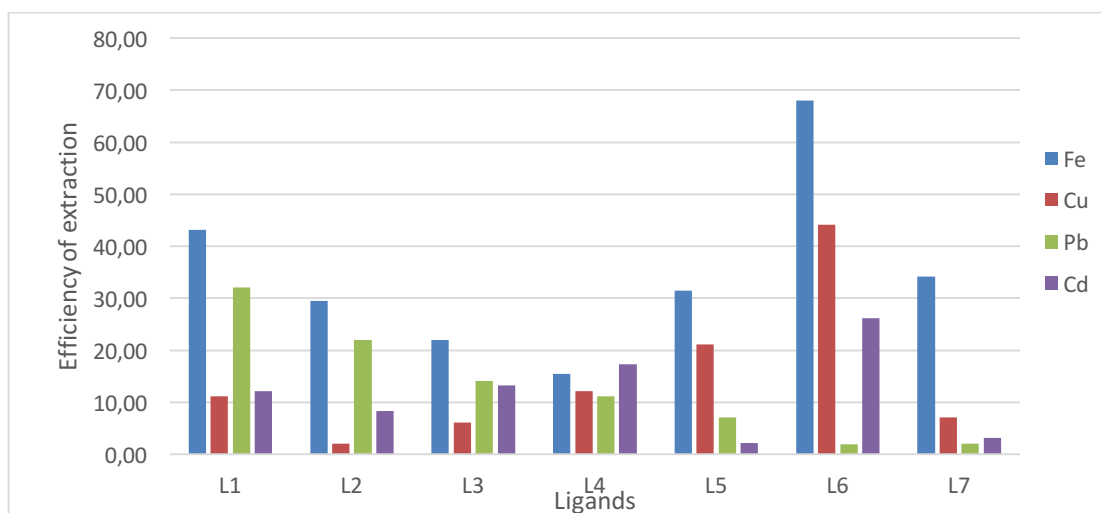

Fig. 2. Competitive extraction E(%) of metal ions using **L₁-L₇**

From the obtained results of the competitive extraction, the ligands unveil good efficiencies to extract selectively Fe^{2+} and Cu^{2+}. The ligand**L₆** shows an excellent selectivity towards Fe^{2+} while other ligands **L₁ - L₅** and **L₇** display a similar efficiency but some interference was shown with Fe^{2+} and Pb^{2+}. The substitution on the phenyl by a halogen or hydroxyl group and the changing of the position do not improve sufficiently the selectivity.

3.3. Effect of the pH medium on metal extraction

The aqueous phase pH is one of the determining factors for metals extraction by ligands. To examine the behavior of these ligands in different pH values and to determine the optimum pH, we have carried out a competitive liquid-liquid extraction of Fe^{2+} at different pH using **L₁-L₃**.The extraction properties of $Fe^{2+}$by these three ligands were investigated over the pH range 2 to 8 (**Figure 3**). For the ligands **L₁– L₃**with Fe^{2+}, an

identical behavior has been shown. In 4-8 pH range, the efficiency decreased slowly with pH decreasing, which can be explained by a stable coordination. Under pH = 4 the efficiencies decreases seriously and become neglected when the pH attained a value of pH= 2, this can be explained by a rapid and total protonation of coordination sites. Above pH = 8 and because of hydrolysis of Fe^{2+} we cannot distinguish between hydrolyzed or extracted cation. It seems that these ligands resist to the protonation and remain effective in acidic medium.
This can be attributed to different form of protonation or deprotonation. It can be said that there is two structural conformations when forming metal complex at different pH.
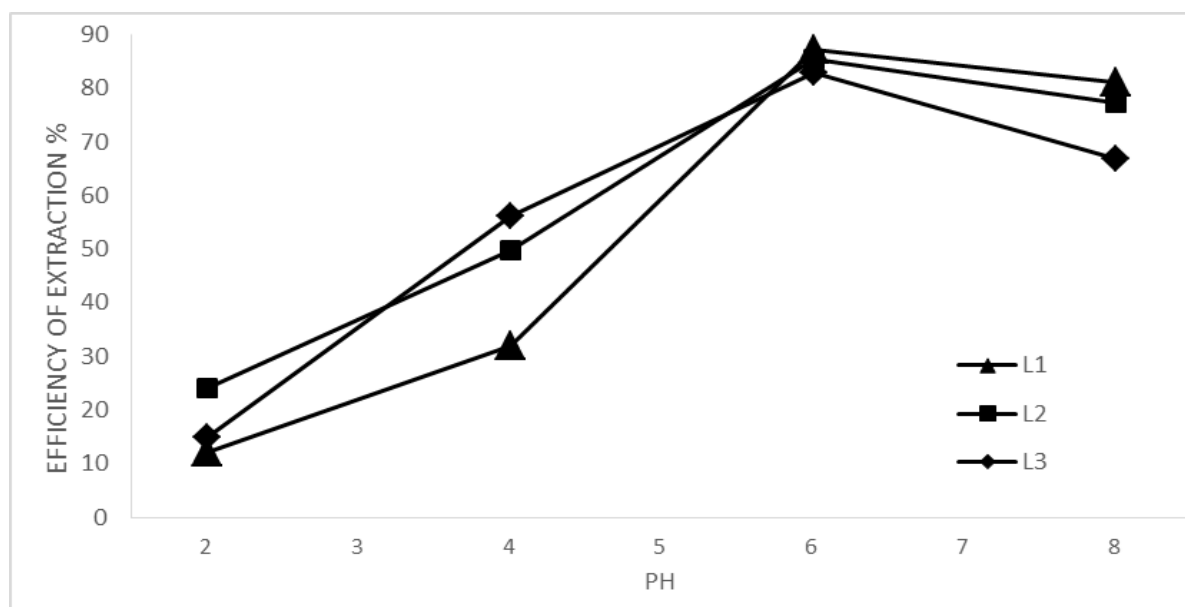

Fig. 3. Competitive extraction E(%) of Fe^{2+} ions using L_1-L_3 function of the pH

3.5. Back extraction of metal ions extracted with L_1 and L_7

In back-extraction, metal ions are extracted from the metal ligand complex using a stripping liquid immiscible with the organic solvent used. As the extraction of Fe^{2+} and Pb^{2+} by L_1–L_3 respectively decreases at acidic pH, we chose aqueous acid as stripping solution for the back-extraction. All back-extraction tests were carried out in 10 minutes; the results are summarized in **Table 2**.

Table. 2. Back-extraction of metal ions extracted with L_1, L_2 and L_3.

	Fe^{2+}			Pb^{2+}		
	HCl	HNO_3	H_2SO_4	HCl	HNO_3	H_2SO_4
L_1	45.12	**81.27**	60.23	54.18	42.18	**89.38**
L_2	51.17	**94.90**	72.44	**82.70**	66.20	**95.86**
L_3	72.35	**83.10**	31.77	**93.47**	39.52	77.52

3.6. DFT analysis
3.6.1-Geometry optimization
All calculations were performed using the Gaussian 03W series of program [17]. The geometry optimization of the four ligands (**Figure 4**) was optimized by the density functional theory DFT [18] with the Becke's three parameter exchange functional and the Lee Yang Parr correlation functional (B_3LYP) [19]. The electronic populations as well as the Fukui indices and local nucleophilicities are computed using different populations analysis MPA (Mulliken population analysis) and NPA (natural population analysis) [20-23].

3.6.2- Frontier Molecular Orbital Energies

The frontier molecular orbital such as HOMO and LUMO of the chemical species are very important in defining organic compounds reactivity [24-26], transition of electron is due to interaction between HOMO and LUMO of reacting species [27]. The 3D of the frontier orbitals HOMO and LUMO for four ligands are shown in Fig. 5. The most important orbitals in a molecules are the frontier molecular orbitals, called highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) [28]. HOMO-LUMO gap is an important stability index, a molecule with a small frontier orbital gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule [29]. The high stability in turn indicates low chemical reactivity and large band gap. In other words, the smaller band gap between HOMO and LUMO, which indicates a less stability of the compound, the easier the electron transition and lesser the stability of the compound. The HOMO LUMO energy gap values increases in the order:**L$_5$<L$_6$<L$_4$<L$_1$<L$_3$<L$_2$<L$_7$**.

L1   *L2*   *L3*

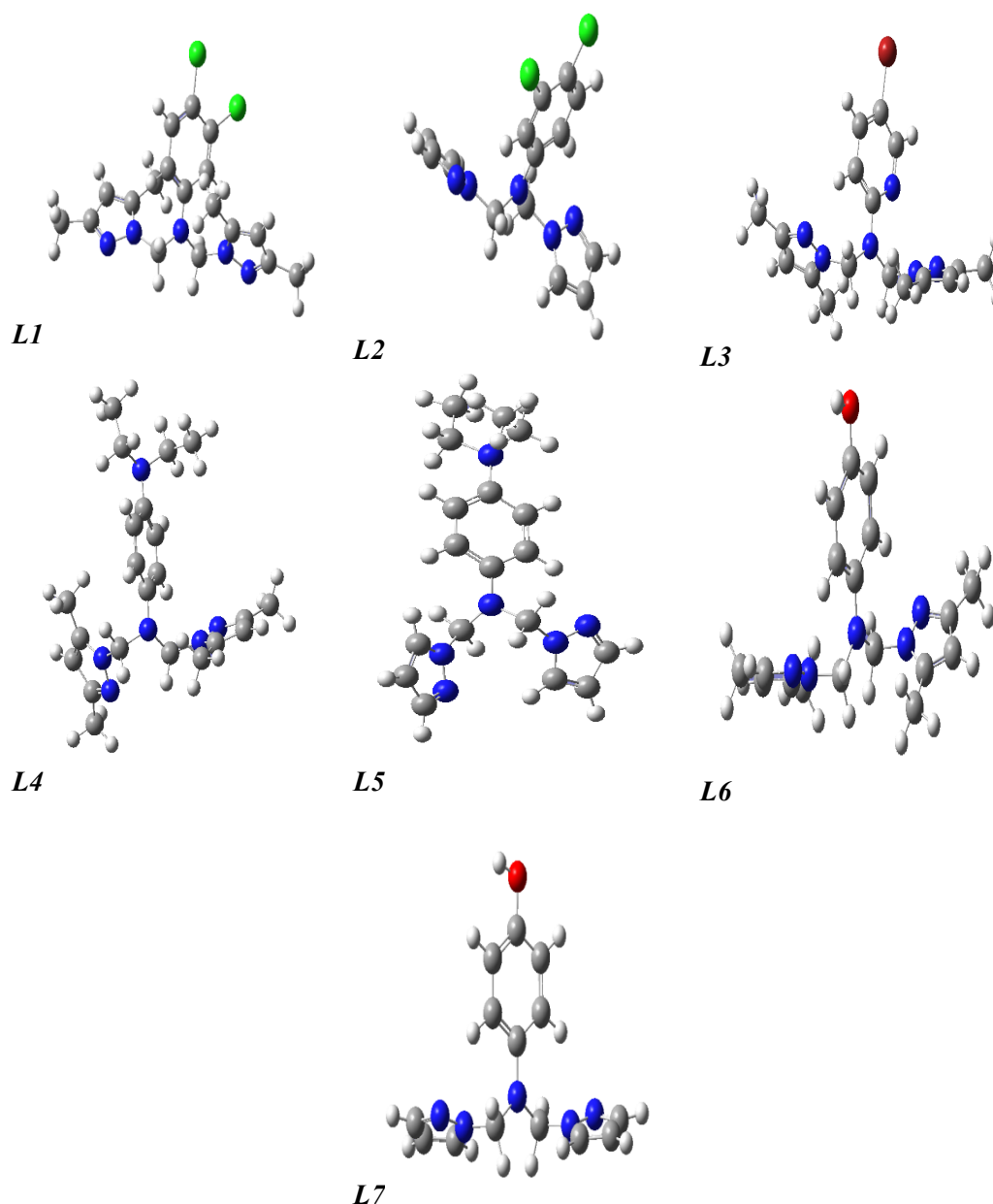*L4*   *L5*   *L6*

L7

Fig.4   Optimized structures of ligands **L$_1$-L$_7$** calculated by B3LYP/6-31G(d).
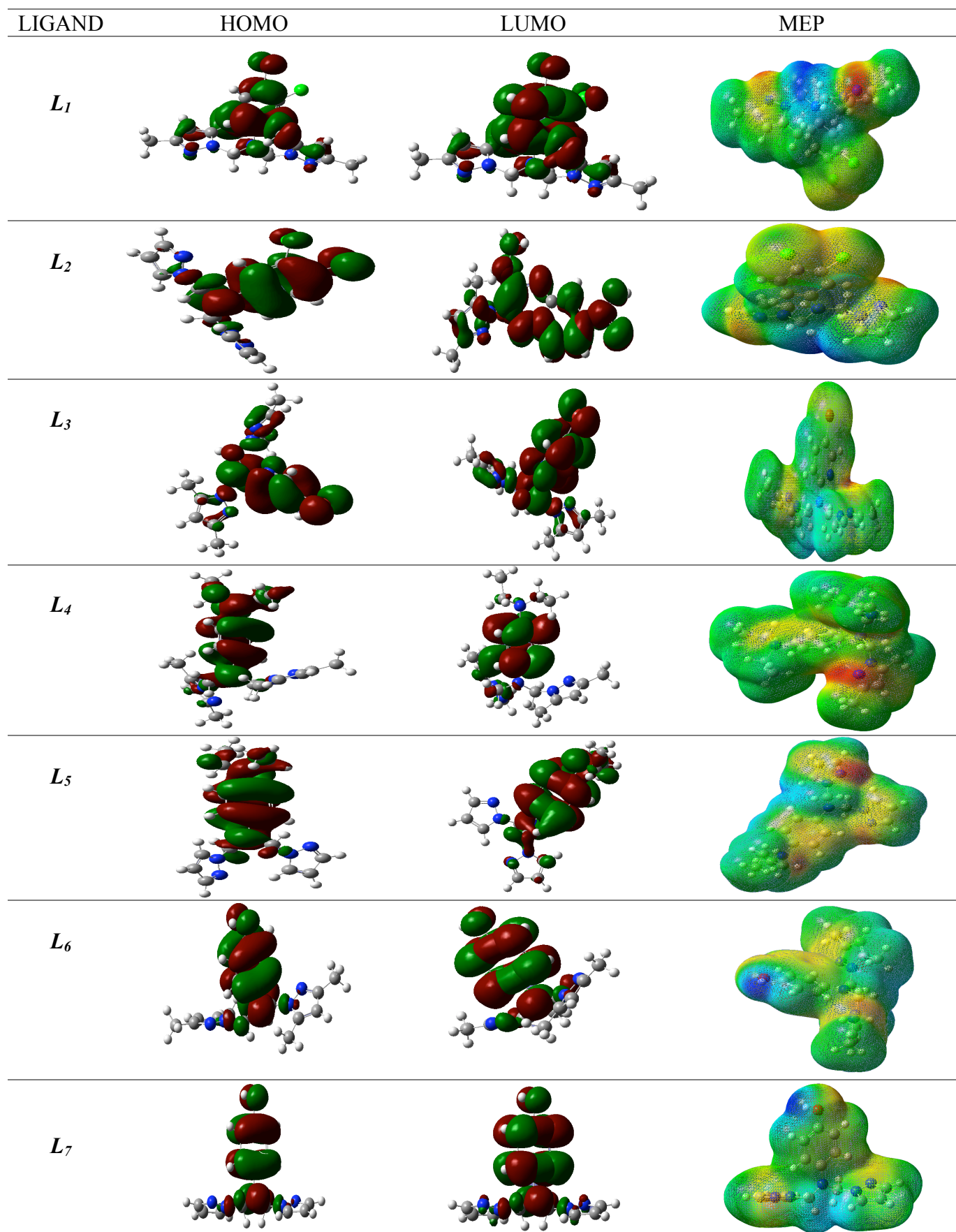
Fig. 5. The highest occupied (HOMO), lowest unoccupied (LUMO) molecular orbitals and MEP surfaces of ligands **L₁-L₇**.

This demonstrate that the lower value for frontier orbital gap in case of L5 than other ligands makes its lightly more reactive and less stable (**Table 3**). The HOMO is the orbital that primarily acts as an electron donor and the LUMO is the orbital that largely acts as the electron acceptor. The 3D plots of the frontier orbitals HOMO and LUMO and the molecular electrostatic potential map (MEP) figures for four molecules are shown in **Figure 5**. The MEP (molecular electrostatic potential) is related to the electronic density and a very useful descriptor for determining sites for electrophilic attack and nucleophilic reactions as well as hydrogen-bonding interactions (**Fig.5**), whereas electrophilic reactivity has been presented by negative (red) regions, nucleophilic reactivity has been shown by the positive (blue) regions of MEP. As seen from the **Figure 5**, the red region has been localized on the vicinity of nitrogen atoms. On the other hand, nucleophilic reactivity of the molecule has been localized on the hydrogen atoms.

Table 3: HOMO and LUMO energies, dipole moment (M), potential ionization (I), electron affinities (A), energy gap and energy (HF).

Ligands	HOMO	LUMO	M (D)	I	A	Energy gap	Energy (HF) (u.a)
L1	- 0.25297	- 0.03593	2.2217	0.25297	0.03593	- 0.21704	-1892.3379
L2	- 0.24087	- 0.03173	2.1467	0.24087	0.03173	- 0.20914	-1735.4059
L3	- 0.24160	- 0.02703	3.9499	0.24160	0.02703	- 0.21457	-3560.6476
L4	-0.22349	0.00270	3.5122	0.22349	-0.00270	-0.22619	-1186.09421
L5	-0.33218	0.14074	2.5892	0.33218	-0.14074	-0.47292	-1022.208427
L6	-0.23181	0.00746	2.7505	0.23181	-0.00746	-0.23927	-1048.713894
L7	-0.19401	0.00024	2.0188	0.19401	-0.00024	-0.19425	-891.433312

Conclusion

The studied ligands were found to be efficient for the liquid-liquid extraction of metal cations. Fe^{2+} and Pb^{2+} were selectively extracted with these pyrazole derivatives and the studies of pH effect confirm the performance of such type of ligands in selective extraction as well as in protonation resistance. These results have conclusively shown that the formation of coordination complexes for these ligands is highly dependent on the substituent nature; high selectivity towards Fe^{2+} is provided by electron withdrawing group whilst high selectivity against Pb^{2+} is ensured by the presence of electron donor group. Interestingly, it was found that the back-extraction was extremely effective by using acidic solutions. The present work has also investigated the ground and excited state geometries using DFT calculations, It was also shown that these calculations are in an acceptable agreement with experimental data.

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