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Biomimetic catecholase activities by prepared *in-situ* complexes: development of a quantitative structure–properties relationship (QSPR)

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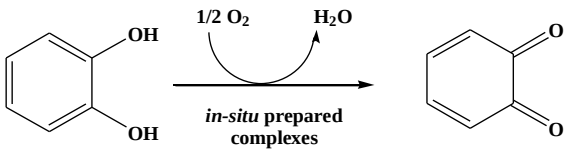
Abstract
In this study we worked on a series of the *in-situ* prepared complexes with ligand and copper metal salts regarding the catecholase reaction activities. The objective is to find a correlation between the structure and the catalytic properties. These were determined by combining DFT and QSAR results. This study was conducted using the principal component analysis (PCA) method, the multiple linear regression method (MLR), the non-linear regression (RNLM) and the artificial neural network (ANN). We accordingly propose a quantitative model, and we interpret the activity of the compounds relying on the multivariate statistical analysis. This study shows that the prediction results were in excellent agreement with the experimental value.

Keywords: catecholase, oxidation, nitrogen ligands, metal salts, 3D-QSAR model, DFT study.

1. Introduction
Catecholase and tyrosinase are very important and interesting metalloproteins, and many of these are enzymes that contain one or more metal ions and catalyze crucial biological process, such as photosynthesis and respiration, among others[1-3].In the active sites of numerous metalloenzymes, two adjacent metal centers act cooperatively in the transformation of substrate molecules. This is particularly true for biological oxidase or oxygenase activity involving molecular oxygen (O_2), in which the metal ions serve to activate the kinetically inert O_2 and the combined redox power of the two metal ions is used to mediate and to control the multielectron redox reactions. In view of the great importance of oxidation reactions in industrial and synthetic processes and of the ongoing search for new and efficient oxidation catalysts, it is of paramount interest to elucidate the basic functional principles that govern such bimetallic reactivity of natural enzymes [4-10]. Copper (II) complexes coordinated to polydentate pyrazole-based ligands have been proposed as models for the type-3 active-site of the copper proteins hemocyanin and tyrosinase [11–13]. The role of these proteins [14, 15] is to bind and transport dioxygen. In addition, tyrosinase has both catecholase and cresolase activity [16]. Enzymatic syntheses often proceed under mild conditions and are very selective. It is therefore interesting to study and to model these bio-catalysts in order to use them as effective chemical tools for common reactions. The reaction model which was used in this study is the oxidation of catechol to *o*-quinone using ambient oxygen air (**Scheme 1**) [17-26].



Scheme 1: Reaction model for catecholase activities

2. Experimental data

To determine a quantitative structure propriety relationship QSPR, we achieved our study on a series of 32 selected ligands derivatives (**Figure 1**) that have been synthesized and evaluated for their reaction rate propriety, the experimental reaction rate propriety of the studied compounds were been collected from [27-31] (**Table 1**).

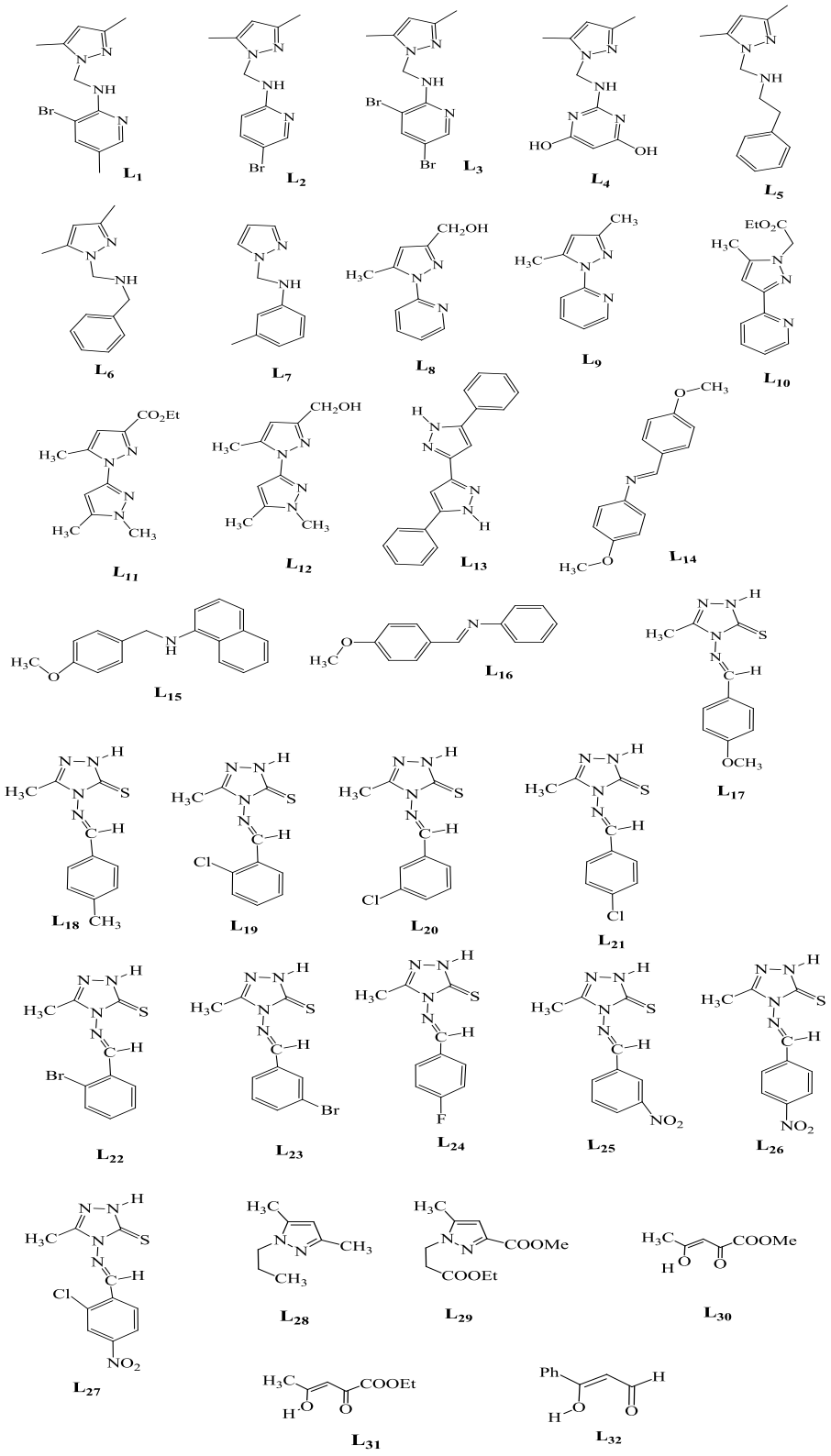


Figure 1: Chemical structure of the studied compounds

Table 1: Rate oxidation reaction of catechol in Methanol (µmol.L^{-1}.min^{-1})

N°	$Cu(CH_3COO)_2$	$CuSO_4$	$Cu(NO_3)_2$	$NiCl_2$	$ZnCl_2$	N°	$Cu(CH_3COO)_2$	$CuSO_4$	$Cu(NO_3)_2$	$NiCl_2$	$ZnCl_2$
L_1	**1.926**	**1.799**	**0.528**	**0.258**	**0.434**	**L_{17}**	**2.027**	**-**	**3.953**	**2.483**	**0.215**
L_2	**1.752**	**0.143**	**0.454**	**0.332**	**0.243**	**L_{18}**	**0.929**	**-**	**1.659**	**4.116**	**0.913**
L_3	**1.400**	**1.200**	**0.203**	**0.542**	**0.064**	**L_{19}**	**2.819**	**-**	**2.071**	**2.618**	**0.264**
L_4	**-**	**0.159**	**0.570**	**0.219**	**0.756**	**L_{20}**	**2.130**	**-**	**2.025**	**3.684**	**0. 729**
L_5	**13.380**	**12.543**	**0.559**	**0.240**	**0.792**	**L_{21}**	**2.185**	**-**	**2.015**	**3.469**	**0.766**
L_6	**7.143**	**14.365**	**3.293**	**1.110**	**4.598**	**L_{22}**	**2.265**	**-**	**1.584**	**3.281**	**0.036**
L_7	**6.170**	**5.547**	**5.524**	**0.431**	**0.351**	**L_{23}**	**1.982**	**-**	**1.930**	**3. 524**	**0.461**
L_8	**0.006**	**0.005**	**0.002**	**-**	**-**	**L_{24}**	**2.947**	**-**	**1.914**	**1.994**	**0.101**
L_9	**0.020**	**0.005**	**0.001**	**-**	**-**	**L_{25}**	**2.106**	**-**	**2.319**	**1.790**	**0.129**
L_{10}	**0.039**	**0.003**	**0.002**	**-**	**-**	**L_{26}**	**11.528**	**-**	**2.285**	**2.209**	**0.096**
L_{11}	**0.023**	**0.002**	**0.002**	**-**	**-**	**L_{27}**	**2.066**	**-**	**1. 924**	**5.717**	**0.197**
L_{12}	**0.022**	**0.002**	**0.006**	**-**	**-**	**L_{28}**	**1.853**	**3.606**	**-**	**0.573**	**0.552**
L_{13}	**1.060**	**1.610**	**3.104**	**-**	**-**	**L_{29}**	**1.131**	**3.605**	**-**	**0.243**	**1.791**
L_{14}	**1.071**	**1.680**	**5.992**	**-**	**-**	**L_{30}**	**0.888**	**2.736**	**-**	**0.264**	**1.459**
L_{15}	**2.740**	**0.609**	**8.473**	**-**	**-**	**L_{31}**	**0.534**	**1.980**	**-**	**0.756**	**0.797**
L_{16}	**3.567**	**5.062**	**6.200**	**-**	**-**	**L_{32}**	**1.749**	**1.544**	**4.100**	**0.230**	**1.717**

Computational methods:

An attempt was been made to correlate the study propriety of these compounds with various physicochemical parameters. DFT (Density Functional Theory) methods have used in this study. The 3D structures of the molecules was generated using the Gauss View 5.0, and then, all calculations were performed using Gaussian 09 program series, Geometry optimization of 32 compounds was carried out by B_3LYP functional employing $LanL_2DZ$ basis set [32].

Calculation of molecular descriptors:

From the results of the DFT calculations:
The quantum chemistry descriptors were obtained for the model building as follows:

- The total energy E (eV),
- The highest occupied molecular orbital energy E_{HOMO}(eV),
- The lowest unoccupied molecular orbital energy E_{LUMO} (eV)
- The absolute hardness η(eV), $\eta = (E_{HOMO} - E_{LUMO})/2$
- The Softness S(eV), it is the reactivity index and defined reciprocal of handress $S = 1/\eta$
- The electrophilicity index ω (eV), $\omega = \chi^2/2\eta$
- The Gap energetic Gap (eV), (the difference between E_{HOMO} and E_{LUMO})
- The dipole moment µ (Debye),
- The absolute electronegativity χ (eV), $\chi = (E_{HOMO} + E_{LUMO})/2$

In this work, we will show only the values of E, LUMO, HOMO,ω and S that are involved in the equations of QSAR models proposed.The thermodynamic chemistry descriptors have obtained for the model building as follows:

- E_{elec}: the electronic energy of the system.
- ZPC (Zero-point correction): corresponds to the term to add to the electronic energy E_{elec} to get the energy of the system to 0 K.
- TCE (Thermal correction to Energy): the sum of ZPC and internal energy U. It should add this energy to the energy of the system to have the energy at the study temperature (generally 298.15 K) and study pressure (generally 1 atm).
- TCEnth: Thermal correction to Enthalpy: the term must add the electronic energy for obtained the enthalpy H of the system. TCEnth = ZPC + U + RT. R is the gas constant and T the temperature in Kelvin
- TCG (Thermal correction to Gibbs free energy): the term to add to the electronic energy for obtained the Gibbs free energy G of the system. This term involves the entropy S of the system. TCG = ZPC+ U +RT – TS. R is the gas constant and T the temperature in Kelvin.
- E0: the electronic energy of the system at 0°K, it is the sum of electronic and zero point Energy.
- H (Sum of electronic and thermal enthalpy): the enthalpy of the system in the conditions of pressure and temperature study.
- G (Sum of electronic and thermal Free Energies): the free energy de Gibbs G in the conditions of pressure and temperature study.
- S (the entropy S of the system): S= (H - G)/T

In this work, we will show only the values of ZPC, TCE and TCGthat are involved in the equations of QSAR models proposed.

Statistical analysis

To explain the structure-propriety relationship, these descriptors are calculated for the 32 molecules using the Gaussian 09W and Gauss View 5.0software (**Table 2**). The study we conducted consists of the multiple linear regressions (MLR) and the nonlinear regression (MNLR) available in the XLSTAT software. The multiple linear regression statistic technique used to study the relation between one dependent variable and several independent variables; it is a mathematic technique that minimizes differences between observed (experimental) and predicted values. It has served also to select the descriptors used as the input parameters in the multiples nonlinear regression (MNLR).The MLR and the MNLR were generated to predict the reaction rate propriety.

Equations were justified by the correlation coefficient (R), the Mean Squared Error (MSE), the Fishers F-statistic (F), and the significance level (F value).85% of the molecules (27 molecules) are selected to propose the quantitative model (training set), and 15% (5 molecules) compounds which were not used in training set and have been selected randomly, have served to test the performance of the proposed model (test set).In this the study (RLM and RNLM),85% of the molecules are selected to propose the quantitative model (training set), and 15% of the molecules which were not used in training set and have been selected randomly, have served to test the performance of the proposed model (test set) (**Table 2**).

V= V (reaction rate) = reaction oxidation of catechol in presence of combinations (Ligand/Metal) in MeOH ($\mu mol.L^{-1}.min^{-1}$)

Table 2: The electronic and the thermodynamic chemistry descriptors calculated by the Gaussian 09 software.

N°	E	E_{HOMO}	E_{LUMO}	S	ω	ZPC	TCE	TCG
L_1	-19001.912	-6/009	-1.155	0.412	2.643	7.069	7.544	5.734
L_2	-17932.449	-6/063	-1.216	0.413	2.732	6.325	6.744	5.067
L_3	-18273.794	-6/269	-1.544	0.423	3.230	6.032	6.499	4.670
L_4	-22120.602	-6/243	-0.841	0.370	2.322	6.494	6.928	5.281
L_5	-19293.366	-6.081	-0.303	0.346	1.763	8.485	8.945	7.174
L_6	-18227.607	-6.022	-0.193	0.343	1.657	7.707	8.126	6.472
L_7	-16521.144	-5.875	-0.464	0.370	1.857	5.841	6.177	4.683
L_8	-17061.586	-6.321	-1.126	0.385	2.669	5.469	5.804	4.381
L_9	-15015.442	-6.276	-1.080	0.385	2.604	5.351	5.655	4.327
L_{10}	-22284.462	-6.170	-1.028	0.389	2.519	7.290	7.754	5.976
L_{11}	-22753.208	-6.268	-1.238	0.398	2.800	7.539	8.020	6.249
L_{12}	-18603.638	-5.560	-0.154	0.370	1.510	6.497	6.916	5.292
L_{13}	-24847.663	-5.972	-1.146	0.414	2.624	7.808	8.263	6.516
L_{14}	-21378.209	-5.459	-1.558	0.513	3.156	7.312	7.754	6.081
L_{15}	-22475.564	-5.002	-0.861	0.483	2.075	8.382	8.839	7.122
L_{16}	-18262.460	-5.795	-1.660	0.484	3.360	6.436	6.805	5.302
L_{17}	-19878.464	-5.779	-1.951	0.523	3.903	6.132	6.558	4.914
L_{18}	-17832.366	-5.853	-2.017	0.521	4.037	6.005	6.410	4.793
L_{19}	-17152.538	-5.998	-2.308	0.542	4.673	4.982	5.371	3.799
L_{20}	-17152.776	-6.103	-2.422	0.543	4.935	4.985	5.373	3.808
L_{21}	-17152.779	-6.080	-2.379	0.540	4.833	4.985	5.374	3.804
L_{22}	-17104.035	-5.992	-2.293	0.541	4.638	4.966	5.363	3.752
L_{23}	-17104.295	-6.086	-2.396	0.542	4.873	4.971	5.365	3.764
L_{24}	-19463.108	-6.065	-2.315	0.533	4.682	5.022	5.400	3.867
L_{25}	-22326.311	-6.283	-3.427	0.700	8.251	5.295	5.719	4.064
L_{26}	-22326.309	-6.384	-3.603	0.719	8.969	5.295	5.719	4.063
L_{27}	-22716.079	-6.424	-3.824	0.769	10.099	5.016	5.478	3.719
L_{28}	-11501.934	-6.237	-0.562	0.352	2.036	5.783	6.091	4.756
L_{29}	-22831.368	-6.893	-1.194	0.351	2.869	7.329	7.837	5.940
L_{30}	-14536.896	-7.063	-2.180	0.410	4.374	3.726	4.033	2.679
L_{31}	-15606.611	-6.990	-2.149	0.413	4.314	4.505	4.846	3.403
L_{32}	-13553.959	-6.725	-2.146	0.437	4.297	4.047	4.301	3.092

For $Cu(CH_3COO)_2$:

RLM:

$V(Cu(CH_3COO)_2) = -38.779+6.167\ 10^{-04}E+ 2.002\ \omega+193.417ZPC-130.676\ TCE-58.090TCG$

$R^2=0.527$, R= 0.726 ; F=0.007 ; RMCE=2.483 ; R_{Test}= 0.631

RNLM:

$V(Cu(CH_3COO)_2) = -9.576+34.718\ TCG+79.595TCE-124.265ZPC+2.380\ \omega-2.821\ 10^{-03}E-8.302\ (TCG)^2-15.695\ (TCE)^2+24.641\ (ZPC)^2-2.310\ 10^{-02}\ (\omega)^2-9.161\ 10^{-08}\ (E)^2$

$R^2=0.701$; R=0.837; RMCE = 2.280; R_{Test} =0.755

Table 3: Experimental, predicted activities and residues values according to MLR and MNLR methods

N°	$V(Cu(CH_3COO)_2)_{Obs}$	Pred $(V(Cu(CH_3COO)_2)_{RLM}$	Residue	Pred $(V(Cu(CH_3COO)_2)_{RNLM}$	Residue
L_1	1.926	3.155	-1.229	3.326	-1.400
L_2	1.752	3.377	-1.625	3.406	-1.654
L_3	1.400	2.570	-1.170	1.277	0.123
L_5	13.380	8.366	5.014	12.494	0.886
L_7	6.170	5.281	0.889	4.544	1.626
L_8	0.006	0.908	-0.902	1.497	-1.491
L_9	0.020	1.824	-1.804	1.761	-1.741
L_{10}	0.039	2.128	-2.089	1.790	-1.751
L_{11}	0.023	-0.056	0.079	-1.055	1.078
L_{12}	0.022	-1.762	1.784	-1.490	1.512
L_{13}	1.060	3.065	-2.005	1.837	-0.777
L_{14}	1.071	2.118	-1.047	2.609	-1.538
L_{17}	2.027	0.386	1.641	0.895	1.132
L_{20}	2.130	1.382	0.748	2.293	-0.163
L_{21}	2.185	1.279	0.906	2.098	0.087
L_{22}	2.265	1.702	0.563	1.829	0.436
L_{23}	1.982	2.181	-0.199	2.429	-0.447
L_{24}	2.947	-0.349	3.296	0.912	2.035
L_{25}	2.106	4.705	-2.599	4.521	-2.415
L_{26}	11.528	6.201	5.327	5.977	5.551
L_{27}	2.066	5.736	-3.670	4.894	-2.828
L_{28}	1.853	4.514	-2.661	0.805	1.048
L_{29}	1.131	1.280	-0.149	-0.328	1.459
L_{30}	0.888	-0.952	1.840	0.269	0.619
L_{31}	0.534	0.644	-0.110	1.390	-0.856
L_{32}	1.749	2.575	-0.826	2.280	-0.531
L_6	7.143	6.135	1.008	8.573	-1.430
L_{15}	2.740	3.979	-1.239	5.514	-2.774
L_{16}	3.567	4.278	-0.711	5.571	-2.004
L_{18}	0.929	3.721	-2.792	4.180	-3.251
L_{19}	2.819	1.061	1.758	1.797	1.022

The last five lines containing the compounds used for the test (**Table 3 and Figure 2**).

For $CuSO_4$:

RLM:

$$V(CuSO_4)= -66.494 +32.380\ E_{LUMO} +25.098\ \omega +175.342\ ZPC -124.479\ TCE - 45.859 TCG$$

$R^2=0.778$; $R= 0.882$; $F=0.002$; $RMCE=2.044$; $R_{Test}= 0.982$

RNLM:

$$V(CuSO_4) = -204.036 + 53.681\ E_{LUMO} + 57.755\ \omega + 378.600\ ZPC -183.041\ TCE- 179.393\ TCG+ 6.613 (E_{LUMO})^2 - 4.838\ (\omega)^2 -16.125\ (ZPC)^2 + 4.375\ (TCE)^2 + 12.999\ (TCG)^2$$

$R^2=0.896$; $R=0.946$; $RMCE = 1.895$; $R_{Test}=0.989$

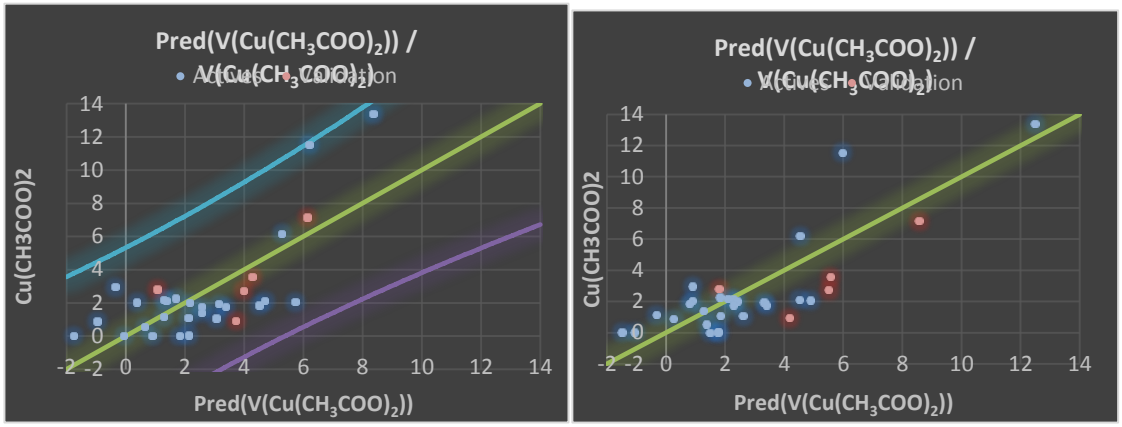


Figure 2: Correlations of observed and predicted activities calculated using MLR and MNLR methods

Table 4: Experimental, predicted activities and residues values according to MLR and MNLR methods

N°	$V(CuSO_4)_{Obs}$	Pred $(V(CuSO_4)_{RLM}$	Residue	Pred $(V(CuSO_4)_{RNLM}$	Residue
L_1	1.799	-0.093	1.892	-0.957	2.756
L_2	0.143	-0.118	0.261	0.995	-0.852
L_4	0.159	-1.351	1.510	-0.859	1.018
L_6	14.365	11.887	2.478	13.279	1.086
L_7	5.547	5.595	-0.048	5.559	-0.012
L_8	0.005	-0.408	0.413	0.423	-0.418
L_9	0.005	-0.216	0.221	-0.583	0.588
L_{10}	0.003	2.419	-2.416	1.501	-1.498
L_{11}	0.002	0.701	-0.699	1.180	-1.178
L_{12}	0.002	2.030	-2.028	1.172	-1.170
L_{13}	1.610	3.936	-2.326	3.632	-2.022
L_{14}	0.609	0.542	0.067	-0.230	0.839
L_{15}	5.062	2.360	2.702	4.518	0.544
L_{28}	3.606	4.102	-0.496	3.830	-0.224
L_{29}	3.605	3.985	-0.380	3.043	0.562
L_{30}	2.736	1.139	1.597	2.879	-0.143
L_{32}	1.544	4.292	-2.748	1.420	0.124
L_3	1.200	-0.912	2.112	2.846	-1.646
L_5	12.543	13.260	-0.717	13.363	-0.820
L_{13}	1.680	0.287	1.393	2.185	-0.505
L_{31}	1.980	2.825	-0.845	4.375	-2.395

The last four lines containing the compounds used for the test (**Table 4 and Figure 3**).

***For Cu $(NO_3)_2$*:**

RLM:

$V(Cu(NO_3)_2) = 28.593+4.295E_{HOMO}-2.148E_{LUMO}+41.038\ ZPC-39.076\ TCE$

$R^2=0.699$; $R= 0.836$; $F<0.0001$; $RMCE=1.450$; $R_{Test}= 0.857$

RNLM:

$V(Cu(NO_3)_2) = 117.242 +376.99\ E_{HOMO}-1.727\ E_{LUMO}+4.489\ ZPC-2.092TCE^2+2.876\ (E_{HOMO})^2-5.084\ 10^{-03}\ (E_{LUMO})^2+2.687\ (ZPC)^2-2.576\ (TCE)$

$R^2=0.733$; $R=0.856$; $RMCE = 1.548$; $R_{Test} = 0.705$

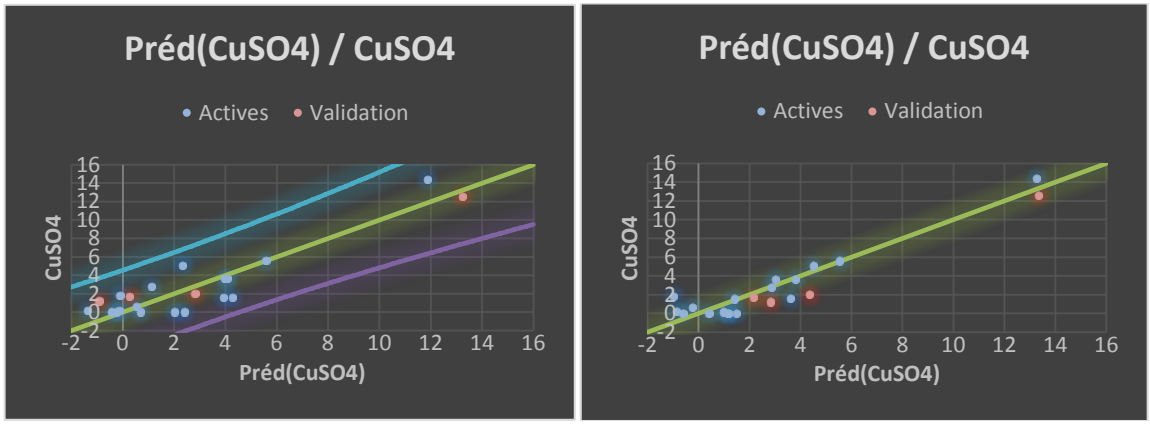


Figure 3: Correlations of observed and predicted activities calculated using MLR and MNLR methods

Table 5: Experimental, predicted activities and residues values according to MLR and MNLR methods

N°	$V(Cu(NO_3)_2)_{Obs}$	Pred $(V(Cu(NO_3)_2)_{RLM}$	Residue	Pred $(VCu(NO_3)_2)_{RNLM}$	Residue
L_1	0.528	0.570	-0.042	0.141	0.387
L_2	0.454	1.198	-0.744	1.088	-0.634
L_3	0.203	-1.433	1.636	-0.984	1.187
L_4	0.570	-0.635	1.205	-0.257	0.827
L_5	0.559	1.795	-1.236	1.559	-1.000
L_6	3.293	1.888	1.405	1.929	1.364
L_7	5.524	2.684	2.840	2.494	3.030
L_8	0.002	1.499	-1.497	1.778	-1.776
L_9	0.001	2.574	-2.573	2.515	-2.514
L_{10}	0.002	0.469	-0.467	0.296	-0.294
L_{11}	0.002	0.324	-0.322	0.140	-0.138
L_{12}	0.006	1.415	-1.409	1.698	-1.692
L_{14}	5.992	5.565	0.427	5.193	0.799
L_{15}	8.473	7.544	0 .929	8.755	-0.282
L_{16}	6.200	5.475	0.725	4.860	1.340
L_{18}	1.659	3.740	-2.081	3.157	-1.498
L_{19}	2.071	2.361	-0.290	2.042	0.029
L_{20}	2.025	2.199	-0.174	1.966	0.059
L_{21}	2.015	2.167	-0.152	1.924	0.091
L_{22}	1.584	2.010	-0.426	1.774	-0.190
L_{26}	2.285	2.731	-0.446	2.809	-0.524
L_{27}	1.924	1.002	0.922	1.622	0.302
L_{28}	4.100	2.331	1.769	2.975	1.125
L_{13}	3.104	2.941	0.163	2.322	0.782
L_{17}	3.953	3.345	0.608	2.817	1.136
L_{23}	1.930	1.955	-0.025	1.767	0.163
L_{24}	1.914	2.596	-0.682	2.241	-0.327
L_{25}	2.319	2.787	-0.468	2.640	-0.321

The last five lines containing the compounds used for the test (**Table 5 and Figure 4**).

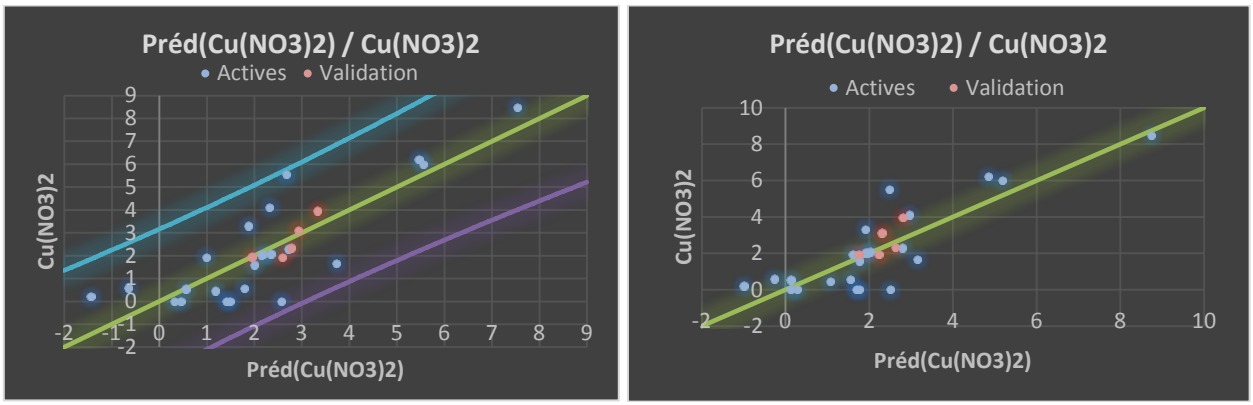


Figure 4: Correlations of observed and predicted activities calculated using MLR and MNLR methods

***For $NiCl_2$*:**

RLM:

$V(NiCl_2) = -3.480+3.358\ 10^{-04}E+11.424\ S-15.874ZPC+15.784\ TCE$

$R^2=0.722$; $R= 0.850$; $F=0.001$; $RMCE=0.969$; $R_{Test}= 0.786$

RNLM:

$$V(NiCl_2) = -13.412+3.003\ 10^{-04}E+14.815\ S-74.314\ ZPC+73.706\ TCE+2.601\ 10^{-09}\ (E)^2-6.953(S)^2+5.214\ (ZPC)^2-4.869\ (TCE)^2$$

$R^2=0.773$; $R=0.879$; $RMCE = 1.036$; $R_{Test} = 0.954$

Table 6: Experimental, predicted activities and residues values according to MLR and MNLR method

N°	$V(NiCl_2)_{Obs}$	Pred $(V(NiCl_2))_{RLM}$	Residue	Pred $(V(NiCl_2))_{RNLM}$	Residue
L_2	0.332	1.260	-0.928	1.149	-0.817
L_3	0.542	2.043	-1.501	1.805	-1.263
L_4	0.219	-0.416	0.635	-0.025	0.244
L_5	0.240	0.490	-0.250	0.602	-0.362
L_6	1.110	0.236	0.874	0.630	0.480
L_7	0.431	-0.024	0.455	0.189	0.242
L_{15}	2.618	2.643	-0.025	2.786	-0.168
L_{16}	3.684	2.638	1.046	2.769	0.915
L_{17}	3.469	2.620	0.849	2.769	0.700
L_{18}	3.281	2.775	0.506	2.977	0.304
L_{19}	3.524	2.739	0.785	2.914	0.610
L_{20}	1.994	1.587	0.407	1.977	0.017
L_{21}	1.790	3.235	-1.445	3.111	-1.321
L_{22}	2.209	3.452	-1.243	3.205	-0.996
L_{23}	5.717	4.517	1.200	4.467	1.250
L_{24}	0.573	1.019	-0.446	0.747	-0.174
L_{25}	0.243	0.221	0.022	-0.562	0.805
L_{26}	0.264	0.832	-0.568	1.231	-0.967
L_{28}	0.230	0.605	-0.375	-0.271	0.501
L_1	0.258	1.706	-1.448	0.901	-0.643
L_{13}	2.483	1.991	0.492	1.815	0.668
L_{14}	4.116	2.335	1.781	2.050	2.066
L_{27}	0.756	0.974	-0.218	1.338	-0.582

The last four lines containing the compounds used for the test (**Table 6 and Figure 5**).

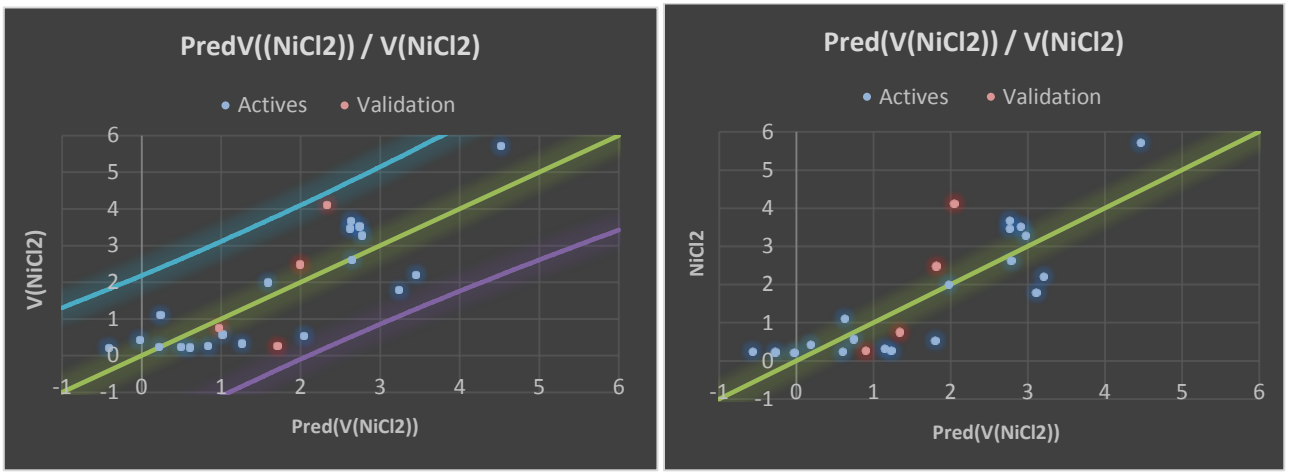


Figure 5: Correlations of observed and predicted activities calculated using MLR and MNLR methods

The obtained results confirm in most of the cases, that the multiple non-linear regression (MNLR) was best to build the models of the relation quantitative activity-structure, because with MLNR we obtained from the best values of coefficient of correlation R, and we established a satisfactory relation between several sizes (greatnesses) (E_{HOMO}, E_{LUMO}) and the catalytic activity (the speed of the reaction of oxidation of the catechol).

Proposed mechanism of the catecholase:

Generally, four various approaches were used to study the mechanism of catecholase activity. The first approach is based on the binding of substratum with the metallic center, by studying the spectroscopic structure of the compound containing substrate bounded to the complex of metallic ion, and the type of interaction of complex with the substrat in the ambient conditions [33-34]. The second approach is based on the relationship activity - structure, by studying the correlation of the catecholase activity of different chemical system and different physico-chemical properties of this system, like the distance metal - metal in the coordination site, their potential redox, the properties of ligand (The electronics properties, the basicity, …) and the nature of the bridge hydroxylates between both metallic centers. [35-36].The third approach includes the kinetic studies on the catalytic reaction, for example the influence of various factors (the nature of substrat, the catalyst and the concentration of dioxygen, etc.) on the reaction rate, to propose the mechanism of the reaction. Finally, the fourth group includes the examples of stoichiometric oxidation of catechol substrates by peroxo- or oxo-dicopper complexes, which are almost always proposed as intermediate species in the catalytic oxidation of catechol by copper (II) compounds [37-40]. We also tried to propose a mechanism of our best catalysts action on kinetic reaction of catechol oxidation; after the determination of the kinetic parameters[27-31], we noticed that Michaelis conditions are respected for all combinations; our results show that just after time 0, the slope of the curve increases very quickly, which amounts to saying that the reaction rate increases quickly, this phase corresponds to equilibrium in bone formation and the disappearance of the complex catalyst-substrat. The curve becomes linear, which means that the reaction rate becomes constant; it's the steady state during this period, and the formation of product *o*-quinones till in significant; we also observed that the catecholase activity involves the oxidation of two *o*-diphenols in two quinones with the reduction of $4e^-$of oxygen, producing two water molecules. This activity is introduced by the fixation of an *o*-diphenol to the form puts of the enzyme which is followed by the reduction of the dicopper leading to the training of the deoxytyrosinase and to the production of *o*-quinone. Finally, interaction of $[(L/M)_2O_2]$ complex with catechol leads to regeneration of the catalyst in its original active form and formation of *o*-quinone in addition to two molecules of water as a by-product (**Figure 6**).

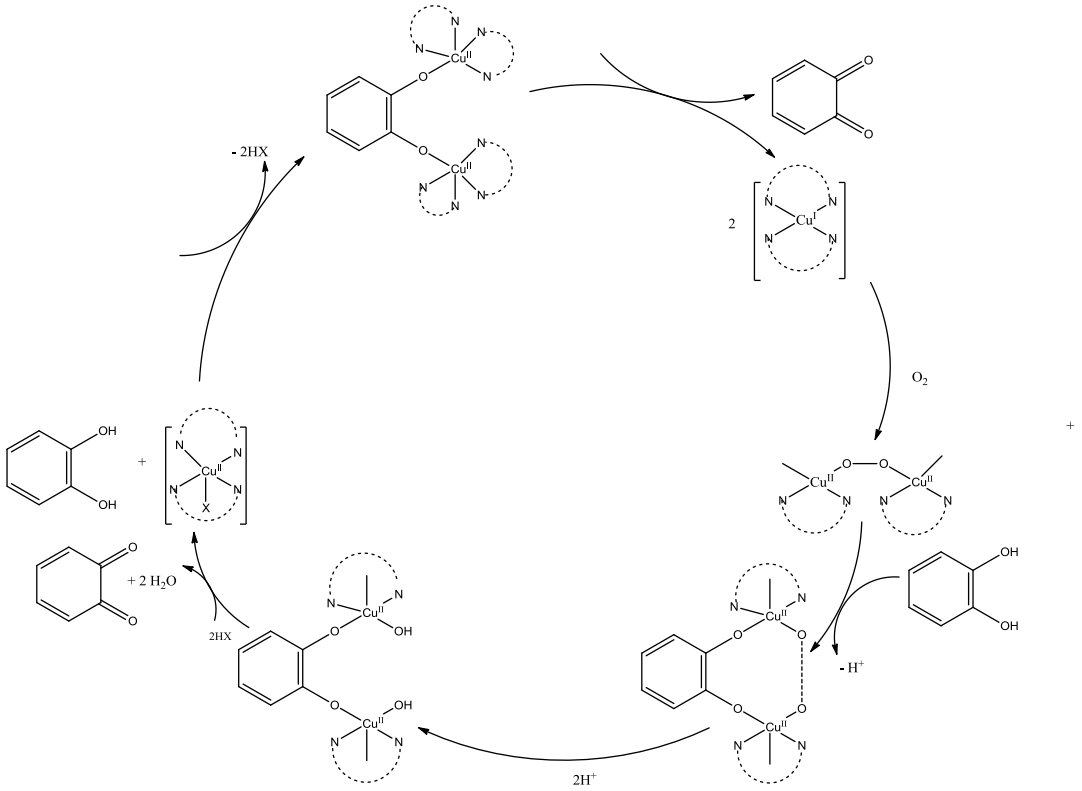


Figure 6: Proposed mechanism of catecholase activity

Conclusion

In this paper, we have studied the QSAR regression to predict the catalytic activities of chemical model to reproduce the catecholase activity, and to establish a relationship activity - structure, The obtained results confirm in most of the cases, that the multiple non-linear regression (MNLR) was best to established a relationship between several descriptors of 32 organic compounds, and catecholase activity. On the other hand, we tried to propose a mechanism of action of our best catalysts, basing on kinetic studies of the studied catalytic reaction.

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