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Computational Chemistry studies of some cyano(3-phenoxyphenyl) methyl isobutyrate derived insecticides and molecular design of novel ones

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Abstract *This work was designed to study some isobutyrate derived insecticides (using computational chemistry) and to designed novels ones using quantitative structure activity relationship (QSAR) model. PM 7 quantum chemical descriptors were calculated for cyhalothrin (CYH), fenpropathrin (FEP), cypermethrin (CYP), deltamethrin (DEL), permethrin (PEM) and cyfluthrin (CYF). Calculated descriptors were frontier molecular energies (including the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the lowest unoccupied molecular orbital (E_{LUMO}) and the energy gap (ΔE)), the binding energy (E_{Bind}), the electronic energy (E_{Elect}), the hydration energy (E_{Hyd}) and logP. Those descriptors that exhibited excellent correlations with the experimental LD_{50} values (of the studied insecticides) were used to derive quantitative structure activity relationship (QSAR). Correlation between the theoretical and experimental LD_{50} values was excellent (R^2 = 0.9500). The active sites of reactivity for the insecticides were identified through Fukui function analysis and were supported by their HOMO and LUMO diagrams. Based on the derived quantitative structure activity relationship, eleven (11) novel insecticides were designed and their theoretical activities (which ranged from 1319 to 5630 mg/kg) were comparable and better (in some cases) to the known insecticides. Therefore, quantitative structure activity approached can be effective in molecular design and modelling of insecticides.*

Key Words: *Insecticides; toxicity, design of isobutyrate derived insecticides*

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1.0 Introduction

Insecticides are known for their role in terminating or reducing the unwanted impact of some insects, which may exhibit deleterious environmental and health consequences. The potential toxicity of insecticides can be measured through their LD_{50} values. LD_{50} value defines the concentration of insecticides that will kill 50 % of the targeted experimental animals (Hodgston, 2004). Therefore, investigation of the activity and environmental consequences of insecticide is significant in understanding their potential usefulness and toxicity. It is also significant to search for novel insecticides, some of which may have better or lesser toxic impact on the target organisms. This can be achieved through molecular design, which involves the prediction of activity or viability of proposed molecules through established molecular descriptors. Quantitative structure activity/property relationship provides a significant tool for

understanding the effect of molecular structure on the activity or property of chemical compounds including insecticides (Eddy *et al.,* 2011; Eddy and Ita, 2011; Netzeva *et al*.,2005). It has been found that the property of most chemical compounds and their reactivity depend on the electronic properties. Therefore, the use of quantum chemical indices can effectively provide information on the probably and expected activity of a compound.

Some studies have been carried on the use of QSAR to investigate the behavior of some insecticides. However, most of these studies are based on topological descriptors. For example, Naik *et al*. (2009) adopted QSAR to investigate organophosphate and carbamates insecticides using topological, spatial, thermodynamic, information content, lead likeness and energy-state descriptors. The descriptors provided good predictive models with linear correlation coefficients of 0.871 and 0.788 for organophosphate and carbamates respectively. Results obtained from QSAR study provided a model for predicting novel potent insecticides. Can (2014) implemented QSAR study on some organophosphate insecticides using descriptors such as lipophilicity, polarity and molecular geometry. The results of his study were useful in deriving a relationship between the chemical structures of the insecticides and their toxicity. Naik *et al*. (2016) also employed QSAR approach to investigate cytoxic activity and structural properties of 119 podophyllotoxin analogs, based on 2D and 3D structural descriptors. Overall root-mean square error between experimental and predicted value was 0.265 while R^2 value (0.824) was satisfactory in confirming good predictability of the model. Iwamura *et al*. (Iwamura *et al*.,1985) used QSAR to investigate effect of structure/properties on the activities of some insecticides and plant growth regulators (including neurotoxic carbamates, phosphates, pyrethroids (and DDT analogs), insect juvenile hormone mimics, and cytokinin agonistic compounds. They were able to establish a relationship between activities and structures of these compounds and adopted QSAR approach to predict new compounds that exhibited closely related potent activities. Jian *et al*. (2014) used QSAR principle to study some synthesized rosin-based diamides insecticides and found that those with electron withdrawing groups on the benzene ring exhibited better insecticidal activity than those with electron donating groups

In most of these reported studies, quantum chemical descriptors are rarely used, even though they have been documented to be unique descriptors in structural studies (due to their dependence on electronic parameters of molecules) compared to other descriptors. However, Vikas (2015) recently used quantum chemical descriptor to develop active relationship (QSAR) for the acute toxicity of 252 diverse organic chemicals toward Daphnia magna. Eddy *et.al*., (2015) also employed quantum chemical descriptors to derive theoretical relationship between activities and quantum chemical indices of some m-tolyl acetate derived insecticides. R^2 values obtained in their study were excellent. The success of using quantum chemical descriptors over other descriptors and the non-availability of adequate literature on the adoption of QSAR for design of new molecules with better activities encourage the present study. The work shall be achieved through the application of experimental data in QSAR modelling (Bendjeddou *et al*., 2016; Devillers *et al*., Karelson and Lobanov, 1996; Kikuchi, 1987; Eddy, 2011; Ameh and Eddy, 2018)

2.0 Computational methods

All chemical structures were drawn using ChemBio software. Full structure optimization was achieved by successive application of molecular mechanics, semiempirical, ab initio and DFT models in structure optimization package of the HyperChem software. All semiempirical calculations were performed using PM7 Hamiltonian in the MOPAC software. Although range separated functionals have been recently reported to be comparatively adequate, double hybrid functionals were used for all DFT calculations because they have been proven to be very successful in modelling insecticides. Fukui functions were calculated using B2LYP method in the Perturbative corrected double hybrid functional (which combine DFT and MP2) in the ORCA software. In order to accelerate convergence, Scfcov 6*energy convergence check Etol =10-6) was selected in the program icon. Pople basis set (6-311G** 6-311G plus one polarisation function all atoms) was also used to modify the atomic orbitals.

3.0 Results and discussions

3.1 Quantum chemical study and QSAR

The chemical structures of the studied compounds and their IUPAC names are presented in Fig. 1.

In Table 1, calculated quantum chemical parameters for the studied insecticides are presented. Calculated quantum chemical parameters included, the frontier molecular orbital energies (i.e. $E_{HOMO,}$ the energy of the highest occupied molecular orbital, $E_{LUMO,}$ the energy of the lowest unoccupied molecular orbital and the energy gap ($\Delta E = E_{LUMO} - E_{HOMO}$). The electronic energy of the molecule (E_{Elect}), the binding energy (E_{Bind}), the hydration energy (E_{Hyd}) and logP were also computed. Correlations between calculated quantum chemical parameters and experimentally derived LD_{50} values indicated that only E_{HOMO}, ΔE, E_{Elect} and E_{Bind} exhibited excellent R^2 values as shown in Fig. 2. Consequently, they were used to establish QSAR with the experimental LD_{50} values. The established linear model gave the following relationship,

$$LD_{50}(Exp) = 1346.08E_{HOMO} - 115.285\Delta E + 2.2379E_{Elect} + 0.0021E_{Hyd} + 30125.78 \quad (1)$$

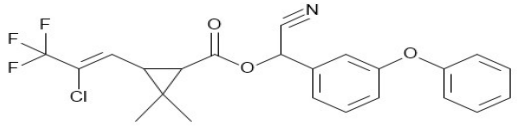
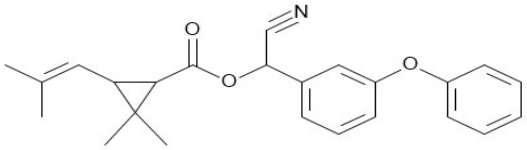
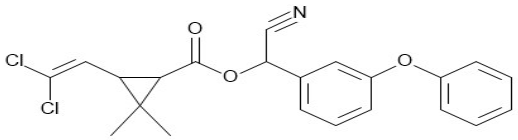
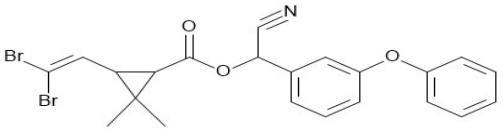
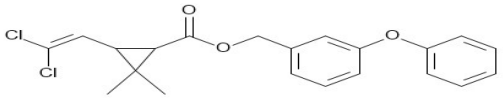
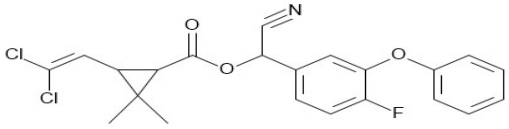
Chemical structure	IUPAC name (generic name in bracket)
	(Z)-cyano(3-phenoxyphenyl)methyl 3-(2chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethyl cyclopropanecarboxylate (cyhalothrin-CYH)
	cyano(3-phenoxyphenyl)methyl-2,2-dimethyl3-(2-methylprop-1-enyl) cyclopropane carboxylate (Fenpropathrin-FEP
	cyano(3-phenoxyphenyl)methyl 3-(2,2dichlorovinyl)-2,2-dimethyl cyclopropane carboxylate (Cypermethrin-CYP)
	cyano(3-phenoxyphenyl)methyl3-(2,2dibromovinyl)-2,2-dimethylcyclopropane carboxylate (deltamethrin-DEL)
	3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2dimethylcyclopropanecarboxylate (Permethrin-PEM)
	cyano(4-fluoro-3-phenoxyphenyl)methyl 3(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate (Cyfluthrin-CYF)

Fig. 1: Chemical structure and identity (generic name in bracket) of the studied insecticides

Table 1: Quantum chemical parameters and LD_{50} values of the studied insecticides

Molecule	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE(eV)	E_{Bind} (eV)	E_{Elect} (eV)	E_{Hyd} (ev)	logP	LD_{50} (exp)	LD_{50} (theor)
CYH	-10.3607	-0.6580	-9.7027	-5398.68	-1097675.00	-8.39	3.08	632	708.06
FEP	-9.7560	-0.2818	9.4742	-5654.96	-888563.50	-7.67	3.04	2000	1407.51
CYP	-9,3275	-0.4464	8.8811	-5048.66	-870658.10	-8.50	3.23	2000	3446.58
DEL	-10/1893	-1.1568	9.0325	-5013.3	-891194.09	-8.55	3.84	2000	2305.62
PEM	-9.6744	-0.0005	9.6739	-4866.65	-747286.03	-5.53	3.04	4000	3550.34
CYF	-9.2421	-1.1213	8.1208	-4716.56	-957615.98	-8.86	2.63	5000	4212.47

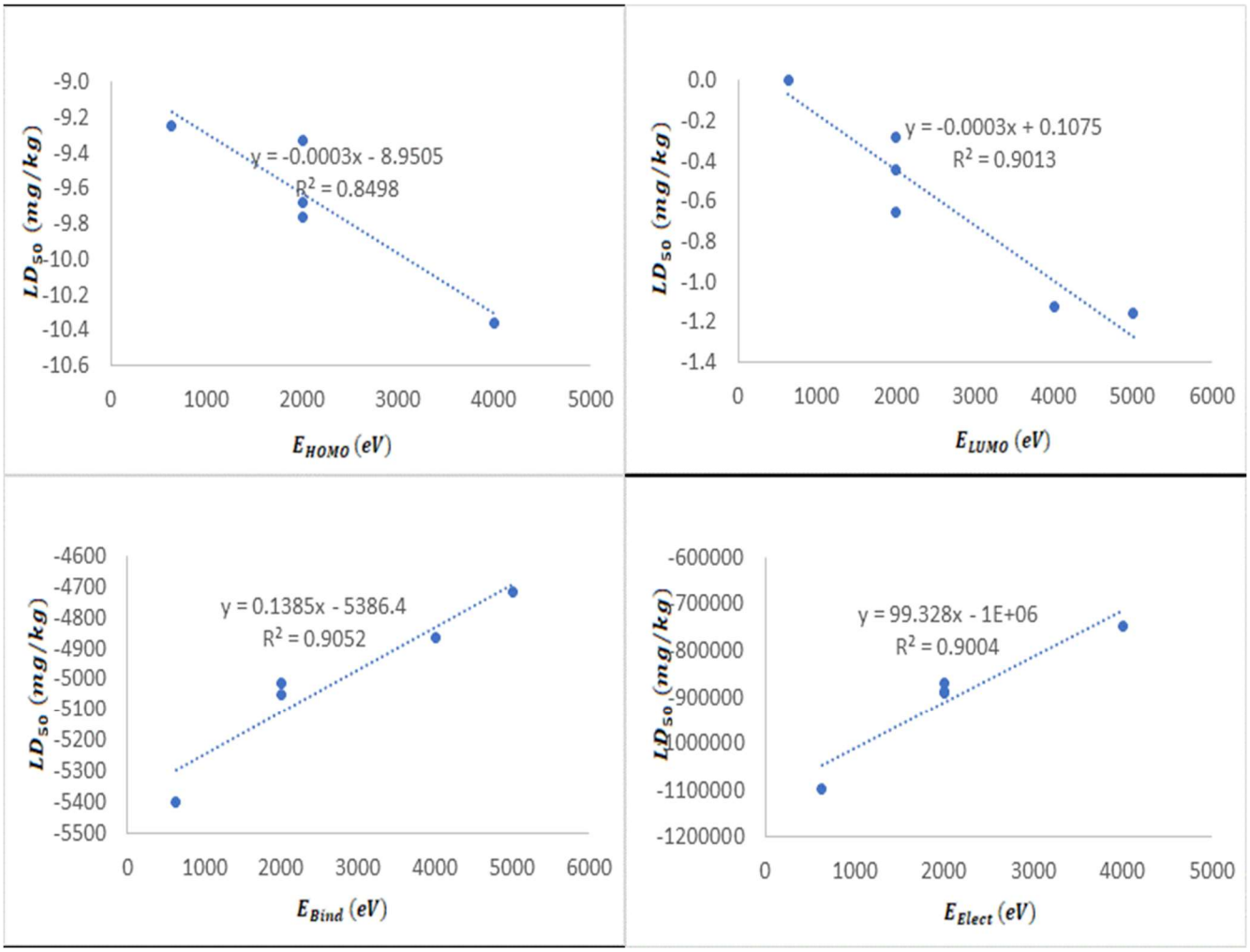


Fig. 2: Variation of LD_{50} with some quantum chemical parameters

Based on equation, 1 calculated theoretical LD_{50} (Theor) were 708.06, 1407.51, 3446.58, 2305.62, 3550.34 and 4212.47 mg/kg for CYH. FEB. CYP, DEL, PEM and CYF respectively. These values correlated excellently with experimental values (R^2 = 0.950), indicating 95 % agreement as shown in Fig. 3. The model also reveals that the LD_{50} values of these insecticides tend to decrease with increase in the value of the energy gap but increase with increasing values of E_{HOMO}, E_{Elect} and E_{Bind} respectively.

E_{HOMO} is a quantum chemical index that denotes the tendency of a molecule to give out electron implying that better adsorption or reactivity is facilitated by increasing value of E_{HOMO} (Eddy and Ita, 2011b). Insecticidal action becomes effective when the molecules of the insecticide is absorbed on the surface of the target insect, hence, lower LD_{50} value is expected for high E_{HOMO} values. The energy gap of a molecule is an index that point toward the hardness or softness of a molecule (Eddy *et al*., 2015).

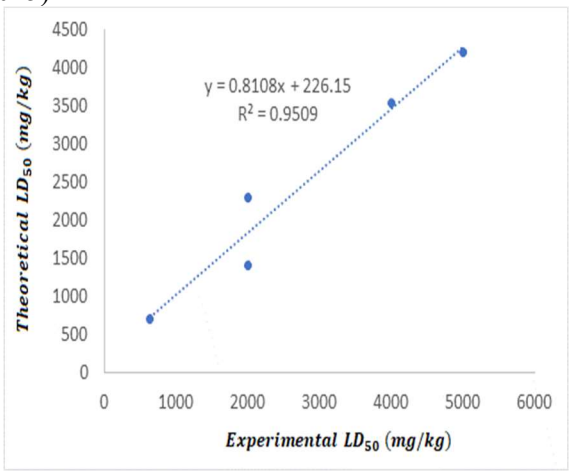


Fig. 3: Variation of theoretical LD_{50} with experimental LD_{50}

Hard molecules are less reactive than soft molecules because in soft molecules, the gap requires for transition between the HOMO and the LUMO levels is much smaller indicating that electron or charge can easily undergo transition compared to hard molecules, whose energy gap is relatively larger. Our findings reveal that the activities of the studied insecticides increase with decreasing energy gap, indicating that increasing softness favours better LD_{50} value. An active insecticide is expected to be relatively soft in order to be more reactive. The electronic and binding energies of the molecules were all negative and they play significant role toward the activity of the studied insecticides.

Institution of molecular models probe for the studied insecticidal molecules requires that each of them should have a potent active site, which may reside in one of its atom or bonds. In Tables 3 to 7, calculated values of the Fukui functions are recorded. These include the Fukui function for electrophilic (f_X^+), nucleophilic (f_X^-) and radical attacks (f_X^0). These functions were calculated from Mulliken and Lowdin charges according to equations 2 to 3 respectively (Eddy and Essien, 2018).

$$f_x^+ = q_{N+1} - q_N \quad (2)$$

$$f_x^- = q_N - q_{N-1} \quad (3)$$

$$f_x^0 = \left(\frac{q_{N+1} - q_{N-1}}{2}\right) \quad (4)$$

where q_N, q_{N+1} and q_{N-1} are the charges of the molecule with N, N+1 and N-1 electrons respectively. Fukui function is related to the Frontier molecular orbital theory, which is also called Fukui theory of reactivity and selection. The theory conceives that in a nucleophile attacks the HOMO places its surplus electrons in the LUMO. Toxicity increases with decrease in LD_{50} values. Prior to exhibition of toxic effect, some surface and internal processes including adsorption, absorption, solubilization and desorption are likely to be observed. Therefore, the overall process can be analysed through the Frontier molecular orbital theory. In analyzing Fukui function, it is necessary to identify the most favourable substitution that will favours each atom on the molecule. The difference between nucleophile and electrophilic Fukui functions provide an index that allows the prediction of the favourable sites for nucleophilic and electrophilic Fukui functions. This index was calculated using equation 5

$$\Delta fx = fx+ - fx- \quad (5)$$

When $\Delta f > 0$, the site favours nucleophilic attack but when $\Delta f < 0$, electrophilic attack is favoured (Eddy *et.al*., 2015). . Values of calculated Δf are also presented in Tables 2 to 7. The results reveal that in CHY, the sites for nucleophilic and electrophilic attacks are in C (2) and O (4) atoms respectively. In FEB, the corresponding sites are C (22) and O (1) respectively. CYP presented O (13) and C (5) as the favourable sites for nucleophilic and electrophilic attacks (respectively) while in DEL the sites are C (1) and C (5) respectively. In PEM, the site for electrophilic attack resides in Cl (24) while the site for nucleophilic attack is in C (10). Finally, in CYF, the sites are in C (13) and O (3) respectively.

Fig. 4 presents the optimized structures, the HOMO and LUMO diagrams of the studied molecules. In CYH, although the atoms of fluorine are bonded to C (28), the HOMO lobes are concentrated around the C (24)-Cl (25) bond, whose bond length is 1.9685 Å compare to C-F bonds (bond length = 1.580 Å). Generally, the longer the bond, the lesser is the force of attraction between the bonding atoms and vice versa. Therefore, C-Cl bond will preferentially be more reactive than the C-F bond, which has a shorter bond length. In FEP, the HOMO lobes are preferentially found at the enol oxygen that connects the two benzene rings whereas in CYP, the lobes extend between the two benzene rings. In CYF, the HOMO lobes reside between the enol oxygen and one of the benzene rings. In PEM, the HOMO lobes reside between the two alkene bonds connected to the electronegative chlorine atoms, as in PEM. The similarity in the location of HOMO electron density in DEL and PEM reveals that the present of -CN bond in DEL might not contribute significantly toward the reactivity of the molecule due to overshadowing or shielding effect of the more electronegative halogens. It is interesting to note that the LUMO electron density in all the molecules resides basically at the carbonyl bond while the HOMO electron density differs for each of the molecules. Indeed, the studied molecules do not have the same value of activity function (i.e. LD_{50}) and their reactivity is significantly influence by the E_{HOMO} and not the E_{LUMO}.

3.2 Molecular design

Based on the derived QSAR between values of LD_{50} and some quantum chemical descriptors, eleven (11) molecules were designed. The chemical structures

and IUPAC names of the proposed molecules are shown in Table 8. Table 9 presents calculated quantum chemical parameters and the predicted values of LD_{50} for the proposed molecules. The predicted values ranged from 1317.559 to 5630.35 mg/kg, which gave an improvement over the LD_{50} values of the existing insecticides (that ranged from 632 to 5000 mg/kg and 708.06 to 4312.46 mg/kg for experimental and theoretical values respectively).

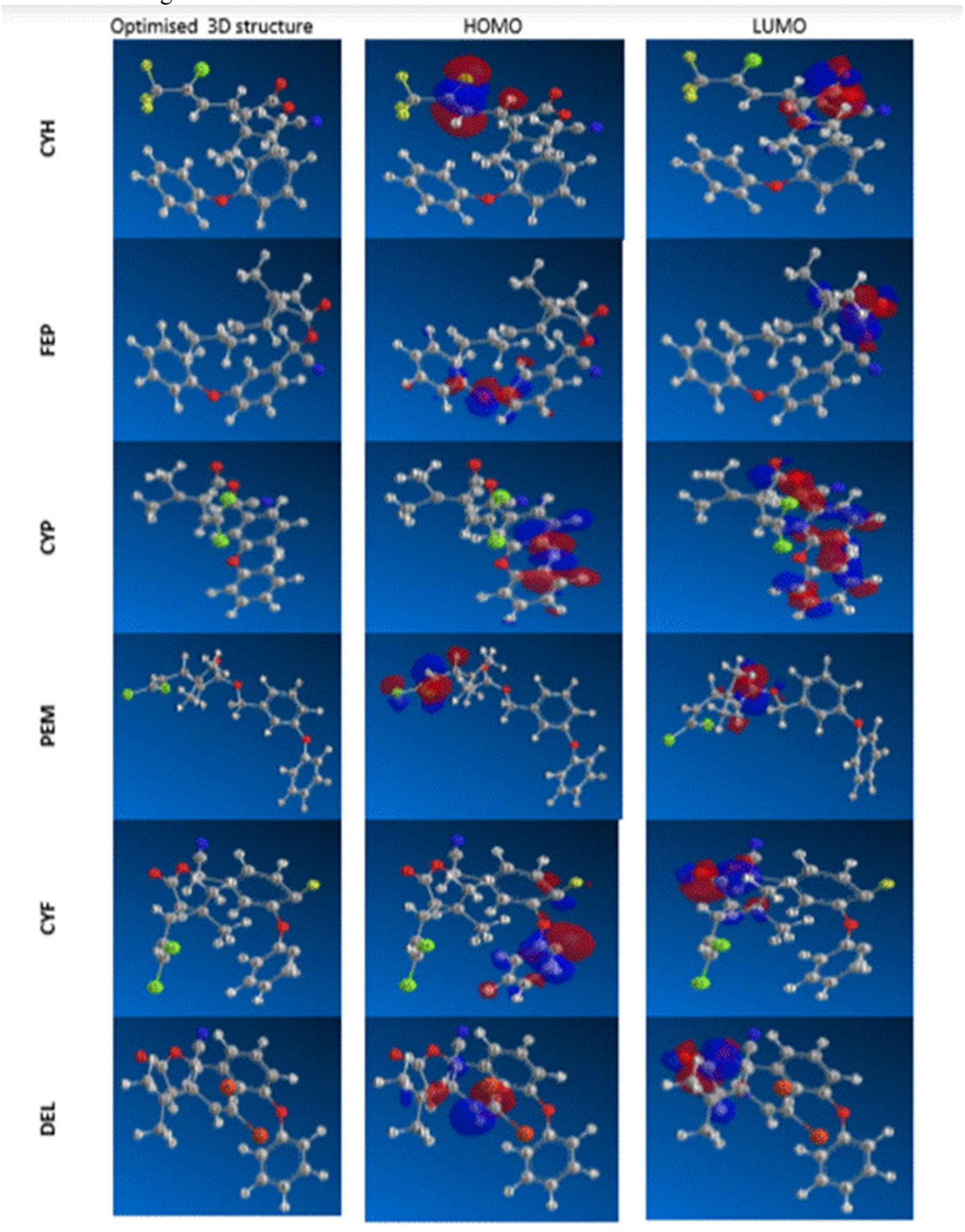


Fig. 4: HOMO and LUMO diagrams of the studied insecticides

Table 2: Mulliken and Lowdin Fukui parameters for CHY

Atom/No	Muliken		Lowdin		Mulliken	Lowdin	Mulliken	Lowdin
	f_X^+	f_X^-	f_X^+	f_X^-	f_X^0	f_X^0	Δf	Δf
1 C	-0.1132	0.8628	-0.1147	0.4139	-0.9760	-0.5286	-0.4880	-0.2643
2 C	-0.0120	-1.5646	0.0474	-0.6227	1.5526	0.6701	0.7763	0.3351
3 O	0.0600	0.2600	0.0582	0.0296	-0.2000	0.0286	-0.1000	0.0143
4 O	-0.0505	1.2523	-0.0632	0.3503	-1.3028	-0.4136	-0.6514	-0.2068
5 C	0.1035	-1.1980	0.1173	-0.4039	1.3016	0.5212	0.6508	0.2606
6 C	-0.0429	0.4438	-0.0411	0.1780	-0.4867	-0.2190	-0.2433	-0.1095
7 C	-0.0293	-0.1229	0.0015	-0.0652	0.0936	0.0667	0.0468	0.0334
8 C	-0.0257	-0.0114	-0.0874	0.0054	-0.0143	-0.0928	-0.0072	-0.0464
9 C	0.0352	0.2424	0.0825	0.0189	-0.2073	0.0636	-0.1036	0.0318
10 C	-0.0562	-0.1478	0.0203	-0.0697	0.0916	0.0900	0.0458	0.0450
11C	-0.0794	-0.9025	-0.2440	-0.1369	0.8232	-0.1071	0.4116	-0.0536
12 O	0.0264	1.0717	0.0154	0.3320	-1.0453	-0.3166	-0.5226	-0.1583
13 C	-0.0363	-0.3359	0.0191	-0.2126	0.2997	0.2316	0.1498	0.1158
14 C	-0.1231	0.0177	-0.1307	0.0989	-0.1407	-0.2297	-0.0704	-0.1148
15 C	-0.0616	-0.0540	-0.1108	-0.0281	-0.0076	-0.0827	-0.0038	-0.0414
16 C	-0.0576	-0.0615	0.0068	-0.1232	0.0039	0.1300	0.0020	0.0650
17 C	-0.0548	-0.0453	-0.0308	-0.0276	-0.0095	-0.0031	-0.0048	-0.0016
18 C	-0.0558	-0.2138	-0.1364	-0.1298	0.1581	-0.0066	0.0790	-0.0033
19 C	0.0761	0.3779	0.1335	0.0595	-0.3018	0.0741	-0.1509	0.0370
20 C	-0.1057	-0.2228	-0.1093	-0.0619	0.1171	-0.0474	0.0586	-0.0237
21 C	-0.1719	-0.6634	-0.3373	-0.2288	0.4915	-0.1085	0.2457	-0.0542
22 C	-0.1022	0.1552	-0.0925	0.0930	-0.2574	-0.1855	-0.1287	-0.0927
23 N	0.2466	1.1434	0.3188	0.3557	-0.8968	-0.0369	-0.4484	-0.0185
24 C	-0.0162	-0.7475	-0.0139	-0.5001	0.7313	0.4862	0.3657	0.2431
25 Cl	-0.2045	-0.8218	-0.1698	-0.5179	0.6173	0.3481	0.3086	0.1741
26 F	-0.0563	0.0811	-0.0549	0.1207	-0.1373	-0.1756	-0.0687	-0.0878
27 F	-0.0420	-0.0720	-0.0364	-0.0961	0.0300	0.0597	0.0150	0.0299
28 F	-0.0506	0.3645	-0.0475	0.2417	-0.4151	-0.2893	-0.2075	-0.1446

Table 3: Mulliken and Lowdin Fukui parameters for FEB

Atom/No	Muliken		Lowdin		Mulliken	Lowdin	Mulliken	Lowdin
	f_X^+	f_X^-	f_X^+	f_X^-	f_X^0	f_X^0	Δf	Δf
1 C	0.0142	-0.1205	0.0340	-0.1477	0.0673	0.0908	-0.1347	-0.1817
2 C	0.0095	-0.0230	-0.0020	-0.0207	0.0163	0.0093	-0.0325	-0.0187
3 O	0.0124	-0.0431	0.0111	-0.0458	0.0278	0.0284	-0.0555	-0.0569
4 O	-0.0863	-0.0238	-0.1038	-0.0180	-0.0312	-0.0429	0.0625	0.0858
5 C	-0.0852	-0.0678	-0.0318	-0.0928	-0.0087	0.0305	0.0174	-0.0610

6 C	-0.0453	-0.0259	0.0033	0.0378	-0.0097	-0.0172	0.0194	0.0344
7 C	-0.0695	0.0693	-0.0089	0.0806	-0.0694	-0.0448	0.1388	0.0895
8 C	-0.0688	0.0577	-0.1322	0.0454	-0.0633	-0.0888	0.1265	0.1777
9 C	0.0482	-0.0294	0.1001	-0.0275	0.0388	0.0638	-0.0776	-0.1276
10 C	-0.0336	0.0489	0.0365	-0.0026	-0.0413	0.0196	0.0825	-0.0391
11 C	-0.0195	0.0857	-0.1718	0.1563	-0.0526	-0.1641	0.1052	0.3281
12 O	0.0344	-0.0254	0.0262	-0.0176	0.0299	0.0219	-0.0598	-0.0438
13 C	-0.0703	-0.0043	-0.0043	-0.0416	-0.0330	0.0186	0.0660	-0.0373
14 C	-0.1551	0.0795	-0.1802	0.0621	-0.1173	-0.1212	0.2346	0.2423
15 C	-0.1124	0.0029	-0.1388	0.0796	-0.0576	-0.1092	0.1153	0.2184
16 C	-0.0946	0.0088	-0.0353	-0.0616	-0.0517	0.0132	0.1034	-0.0263
17 C	-0.1062	-0.0105	-0.0699	-0.0154	-0.0479	-0.0272	0.0957	0.0545
18 C	-0.0850	0.0178	-0.1927	0.0670	-0.0514	-0.1299	0.1028	0.2597
19 C	-0.1074	0.1271	-0.0842	0.0776	-0.1173	-0.0809	0.2345	0.1618
20 C	-0.0877	-0.0532	-0.0733	-0.0331	-0.0172	-0.0201	0.0344	0.0401
21 C	-0.0206	-0.1947	-0.1394	-0.0477	0.0870	-0.0458	-0.1740	0.0916
22 C	-0.1868	0.2763	-0.0976	0.1673	-0.2315	-0.1325	0.4631	0.2649
23 N	-0.0802	-0.1698	-0.1350	-0.2268	0.0448	0.0459	-0.0896	-0.0918
24 C	0.1614	-0.5126	0.1622	-0.5164	0.3370	0.3393	-0.6740	-0.6786
25 C	0.2345	-0.4698	0.2276	-0.4585	0.3521	0.3431	-0.7043	-0.6861

Table 4: Mulliken and Lowdin Fukui parameters for CYP

Atom/No	**Muliken**		**Lowdin**		**Mulliken**	**Lowdin**	**Mulliken**	**Lowdin**
	f_X^+	f_X^-	f_X^+	f_X^-	f_X^0	f_X^0	Δf	Δf
1 C	0.2320	-0.1683	0.2327	-0.0007	0.2002	0.1167	0.4004	0.2334
2 C	-0.2000	-0.0725	-0.7379	0.5379	-0.0638	-0.6379	-0.1275	-1.2758
3 O	0.1734	0.0195	0.7347	-0.5613	0.0770	0.6480	0.1539	1.2960
4 O	0.1336	-0.0616	0.5301	-0.3965	0.0976	0.4633	0.1953	0.9267
5 C	-0.2178	0.0291	-0.7349	0.5170	-0.1235	-0.6259	-0.2470	-1.2519
6 C	0.1575	-0.0310	0.3806	-0.2231	0.0943	0.3018	0.1885	0.6037
7 C	0.0029	0.0112	-0.3832	0.3861	-0.0041	-0.3846	-0.0082	-0.7692
8 C	-0.0723	0.0386	-0.1073	0.0350	-0.0555	-0.0711	-0.1109	-0.1423
9 C	-0.0166	-0.0197	0.0231	-0.0397	0.0015	0.0314	0.0031	0.0628
10 C	-0.0241	0.0029	-0.0722	0.0481	-0.0135	-0.0601	-0.0271	-0.1202
11 C	-0.0719	0.0207	-0.2779	0.2060	-0.0463	-0.2419	-0.0926	-0.4838
12 C	-0.0571	-0.0305	-0.1334	0.0763	-0.0133	-0.1048	-0.0267	-0.2097
13 O	0.1558	-0.0005	0.7410	-0.5852	0.0781	0.6631	0.1563	1.3262
14 C	-0.0668	-0.0538	-0.2989	0.2321	-0.0065	-0.2655	-0.0130	-0.5310
15 C	0.0727	-0.0576	0.0909	-0.0183	0.0651	0.0546	0.1302	0.1092
16 C	0.0231	-0.0814	0.0592	-0.0360	0.0523	0.0476	0.1046	0.0952

17 C	0.0359	-0.0734	0.0528	-0.0169	0.0546	0.0348	0.1093	0.0697
18 C	0.0271	-0.0930	0.0496	-0.0225	0.0601	0.0361	0.1201	0.0721
19 C	0.0232	-0.0612	0.0135	0.0096	0.0422	0.0020	0.0844	0.0039
20 N	0.0031	-0.0286	0.3968	-0.3937	0.0158	0.3953	0.0317	0.7905
21 C	0.0138	0.0057	0.0383	-0.0246	0.0040	0.0314	0.0080	0.0629
22 C	0.0159	-0.2698	-0.1633	0.1792	0.1428	-0.1713	0.2856	-0.3425
23 C	0.1457	-0.2798	0.0691	0.0766	0.2127	-0.0038	0.4255	-0.0075
24 C	0.0093	-0.1038	0.7021	-0.6928	0.0565	0.6974	0.1130	1.3949
25 Br	0.2272	-0.2866	-0.1153	0.3425	0.2569	-0.2289	0.5138	-0.4578
26 Br	0.2747	-0.3545	-0.0902	0.3650	0.3146	-0.2276	0.6293	-0.4552

Table 5: Mulliken and Lowdin Fukui parameters for DEL

Atom/No	f_X^+	f_X^-	f_X^+	f_X^-	f_X^0		Δf	
	Mulliken		**Lowdin**		**Mulliken**	**Lowdin**	**Mulliken**	**Lowdin**
1 C	0.0142	-0.0215	0.0313	-0.0214	0.0179	0.0264	0.0358	0.0527
2 C	-0.0237	-0.0180	-0.0448	-0.0058	-0.0029	-0.0195	-0.0057	-0.0389
3 O	-0.0160	-0.0030	-0.0128	-0.0068	-0.0065	-0.0030	-0.0130	-0.0061
4 O	-0.0533	-0.0268	-0.0569	-0.0272	-0.0133	-0.0149	-0.0265	-0.0297
5 C	-0.1008	-0.0292	-0.1404	-0.0287	-0.0358	-0.0558	-0.0716	-0.1116
6 C	0.0063	0.0009	-0.0292	0.0073	0.0027	-0.0182	0.0054	-0.0365
7 C	-0.0510	-0.0080	-0.0102	0.0053	-0.0215	-0.0077	-0.0430	-0.0155
8 C	-0.0359	-0.0457	-0.0202	-0.0513	0.0049	0.0156	0.0098	0.0311
9 C	-0.0430	-0.0549	-0.0168	-0.0515	0.0060	0.0173	0.0119	0.0347
10 C	-0.0585	-0.0324	-0.0858	-0.0374	-0.0130	-0.0242	-0.0260	-0.0484
11 C	-0.0005	-0.0247	0.0003	-0.0170	0.0121	0.0086	0.0242	0.0172
12 C	-0.0551	-0.0481	-0.0218	-0.0587	-0.0035	0.0185	-0.0070	0.0370
13 O	-0.0183	-0.0074	-0.0168	-0.0093	-0.0055	-0.0038	-0.0109	-0.0075
14 C	-0.0150	-0.0232	-0.0157	-0.0143	0.0041	-0.0007	0.0082	-0.0014
15 C	-0.0190	-0.0412	-0.0334	-0.0311	0.0111	-0.0012	0.0222	-0.0023
16 C	-0.0454	-0.0617	-0.0217	-0.0771	0.0082	0.0277	0.0164	0.0554
17 C	-0.0636	-0.0685	-0.0846	-0.0616	0.0025	-0.0115	0.0049	-0.0230
18 C	-0.0603	-0.0692	-0.0473	-0.0558	0.0044	0.0042	0.0089	0.0085
19 C	-0.0516	-0.0606	-0.0503	-0.0844	0.0045	0.0171	0.0090	0.0341
20 N	-0.0892	-0.0409	-0.1141	-0.0479	-0.0242	-0.0331	-0.0483	-0.0663
21 C	-0.0368	-0.0294	-0.0396	-0.0316	-0.0037	-0.0040	-0.0074	-0.0081
22 C	-0.0429	-0.0686	-0.0374	-0.0800	0.0128	0.0213	0.0257	0.0426
23 C	-0.0112	-0.0323	-0.0026	-0.0380	0.0106	0.0177	0.0211	0.0354
24 C	-0.0052	-0.0046	-0.0254	-0.0180	-0.0003	-0.0037	-0.0006	-0.0074
25 Br	-0.0707	-0.0952	-0.0589	-0.0822	0.0123	0.0116	0.0246	0.0233
26 Br	-0.0537	-0.0859	-0.0447	-0.0755	0.0161	0.0154	0.0322	0.0307

Table 6: Mulliken and Lowdin Fukui parameters for PEM

Atom/No	Muliken		Lowdin		Mulliken	Lowdin	Mulliken	Lowdin
	f_X^+	f_X^-	f_X^+	f_X^-	f_X^0	f_X^0	Δf	Δf
1 C	-0.0180	-0.0621	0.1327	0.0163	0.0221	0.0582	0.0441	0.1164
2 C	0.0022	-0.1375	0.1108	0.0856	0.0698	0.0126	0.1396	0.0252
3 O	-0.0240	0.0159	-0.3170	0.0112	-0.0199	-0.1641	-0.0399	-0.3282
4 O	-0.1417	0.0043	-0.1549	0.1988	-0.0730	-0.1768	-0.1460	-0.3537
5 C	-0.0206	-0.2613	-0.2611	0.3586	0.1204	-0.3098	0.2407	-0.6196
6 C	0.0559	0.1096	0.2667	-0.0630	-0.0269	0.1648	-0.0537	0.3296
7 C	-0.0387	-0.1257	-0.0113	0.0136	0.0435	-0.0125	0.0870	-0.0249
8 C	0.0360	0.0344	-0.0773	0.0544	0.0008	-0.0658	0.0015	-0.1317
9 C	-0.0615	-0.0622	-0.0297	0.0995	0.0003	-0.0646	0.0007	-0.1292
10 C	0.0106	-0.1013	0.1002	0.0012	0.0560	0.0495	0.1119	0.0990
11 C	-0.1021	-0.0200	-0.1287	0.1286	-0.0411	-0.1287	-0.0821	-0.2573
12 O	-0.0043	0.0142	-0.2439	0.0111	-0.0092	-0.1275	-0.0185	-0.2550
13 C	-0.0343	-0.0501	0.0930	-0.0078	0.0079	0.0504	0.0158	0.1007
14 C	-0.0043	-0.0280	0.0344	0.0453	0.0119	-0.0055	0.0238	-0.0109
15 C	-0.0373	-0.0494	-0.0237	0.0734	0.0061	-0.0485	0.0121	-0.0971
16 C	-0.0344	-0.0406	-0.0667	0.1072	0.0031	-0.0869	0.0062	-0.1738
17 C	-0.0517	-0.0612	-0.0749	0.0845	0.0048	-0.0797	0.0095	-0.1594
18 C	-0.0249	-0.0182	-0.0059	0.0920	-0.0033	-0.0489	-0.0067	-0.0979
19 C	-0.1797	0.0428	0.0630	0.1062	-0.1113	-0.0216	-0.2225	-0.0432
20 C	-0.0324	0.0139	-0.0253	0.1223	-0.0232	-0.0738	-0.0463	-0.1476
21 C	-0.0137	-0.0335	0.1175	0.0285	0.0099	0.0445	0.0198	0.0890
22 C	0.0139	-0.0034	0.7268	0.0956	0.0087	0.3156	0.0173	0.6312
23 Cl	-0.1599	-0.0988	-0.6278	0.1926	-0.0306	-0.4102	-0.0611	-0.8203
24 Cl	-0.1350	-0.0817	-0.5970	0.1444	-0.0267	-0.3707	-0.0534	-0.7414

Table 7: Mulliken and Lowdin Fukui parameters for CYF

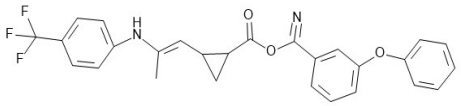
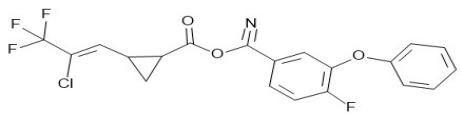
Atom/No	Muliken		Lowdin		M[ulliken	Lowdin	Mulliken	Lowdin
	f_X^+	f_X^-	f_X^+	f_X^-	f_X^0	f_X^0	Δf	Δf
1 C	0.0122	0.0167	0.1128	-0.0404	-0.0045	0.1532	-0.0045	0.1532
2 C	0.0019	0.0039	-0.2902	0.0077	-0.0020	-0.2979	-0.0020	-0.2979
3 O	0.0027	0.0018	0.2002	-0.0083	0.0008	0.2085	0.0008	0.2085
4 O	-0.0071	-0.0124	0.1743	0.0178	0.0053	0.1565	0.0053	0.1565
5 C	-0.0170	-0.0297	-0.1205	-0.0026	0.0127	-0.1180	0.0127	-0.1180
6 C	-0.0009	0.0107	0.0696	0.0428	-0.0116	0.0268	-0.0116	0.0268
7 C	-0.0586	-0.1188	-0.1577	0.1872	0.0602	-0.3449	0.0602	-0.3449
8 C	-0.0384	-0.0691	-0.0492	0.0688	0.0307	-0.1180	0.0307	-0.1180

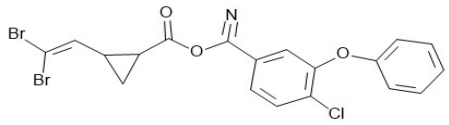
9 C	-0.0038	-0.0557	-0.1669	0.0716	0.0519	-0.2385	0.0519	-0.2385
10 C	0.0134	0.0074	-0.1099	0.0013	0.0060	-0.1112	0.0060	-0.1112
11 C	-0.0266	-0.0856	-0.1432	0.0681	0.0589	-0.2114	0.0589	-0.2114
12 O	0.0139	-0.1264	0.0058	0.1660	0.1403	-0.1602	0.1403	-0.1602
13 C	-0.1388	0.0370	-0.0866	0.0424	-0.1758	-0.1290	-0.1758	-0.1290
14 C	-0.1325	-0.0609	-0.0131	0.2081	-0.0716	-0.2212	-0.0716	-0.2212
15 C	-0.1397	-0.0705	-0.0587	0.1926	-0.0692	-0.2513	-0.0692	-0.2513
16 C	-0.1216	-0.1159	-0.1254	0.2376	-0.0058	-0.3630	-0.0058	-0.3630
17 C	-0.1420	-0.0637	-0.0396	0.1534	-0.0783	-0.1931	-0.0783	-0.1931
18 C	-0.1626	-0.1261	-0.1388	0.3905	-0.0365	-0.5293	-0.0365	-0.5293
19 C	-0.0136	-0.0192	-0.0149	0.0303	0.0056	-0.0452	0.0056	-0.0452
20 C	-0.0001	-0.0005	-0.0196	0.0014	0.0004	-0.0211	0.0004	-0.0211
21 C	0.0006	-0.0004	0.0131	-0.0063	0.0010	0.0193	0.0010	0.0193
22 C	-0.0025	-0.0034	0.1684	0.0193	0.0008	0.1491	0.0008	0.1491
23 Cl	-0.0185	-0.0259	-0.1423	0.0351	0.0074	-0.1774	0.0074	-0.1774
24 Cl	-0.0110	-0.0155	-0.1470	0.0211	0.0045	-0.1681	0.0045	-0.1681
25 N	-0.0170	-0.0355	-0.0015	0.0564	0.0185	-0.0579	0.0185	-0.0579
26 F	0.0078	-0.0423	0.0810	0.0379	0.0500	0.0431	0.0500	0.0431

Table 8: Some quantum chemical parameters and theoretical LD_{50} for the predicted insecticides

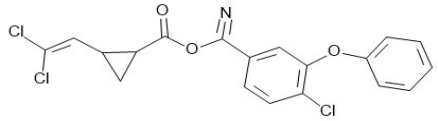
Label	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	E_{Bind}	E_{Elect}	Predicted LD_{50} (mg/kg)
I	-9.2253	-0.3747	8.8506	-5639.5934	-997001.7766	2003.77
II	-9.5807	-0.9483	8.6324	-5664.3660	-1150853.1906	1848.17
III	-10.0902	-1.2001	8.8901	-4999.4812	-962198.8865	2339.54
IV	-9.7801	-0.6327	9.1474	-5031.0592	-961875.3966	2657.29
V	-9.2437	-1.2878	7.9559	-4678.9134	-970352.0399	4287.22
VI	-9.6879	-0.4987	9.1892	-4742.9040	-820603.3837	3713.74
VII	-8.7508	-0.7665	7.9843	-4527.8876	-803633.3470	5630.35
VIII	-9.6726	-0.2530	9.4196	-4848.1032	-803051.0441	3508.66
IX	-9.9093	-0.9490	8.9603	-4705.3480	-828888.9596	3509.01
X	-8.7792	-0.7870	7.9922	-4587.6402	-807148.9457	5450.22
XI	-9.0650	-0.4920	8.5730	-6073.4474	-979159.8113	1317.56

Table 9: Chemical identity of the predicted insecticides

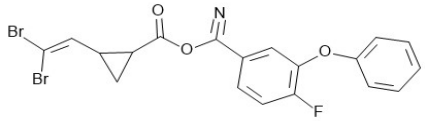
Label	Chemical structure	IUPAC name
I		cyano(3-phenoxyphenyl)methyl 2-(4(trifluoromethyl)phenylamino)propanoate
II		(Z)-cyano(4-fluoro-3-phenoxyphenyl) methyl- 3-(2-chloro-3,3,3-trifluoroprop-1enyl)-2,2-dimethylcyclopropane carboxylate

III 

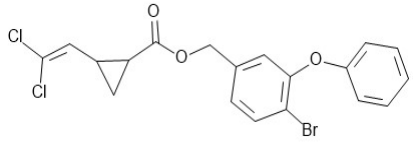
(4-chloro-3-phenoxyphenyl)(cyano) methyl 3-(2,2-dibromovinyl)-2,2dimethylcyclopropane carboxylate

IV 

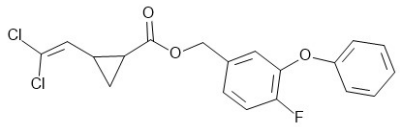
(4-chloro-3-phenoxyphenyl)(cyano) methyl 3-(2,2-dichlorovinyl)-2,2dimethylcyclopropanecarboxylate

V 

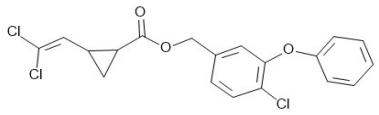
cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dibromovinyl)-2,2-dimethylcyclo propane carboxylate

VI 

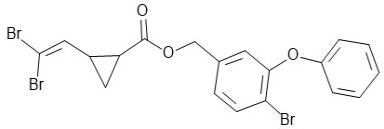
4-bromo-3-phenoxybenzyl 3-(2,2dichlorovinyl)-2,2-dimethylcyclopropane carboxylate

VII 

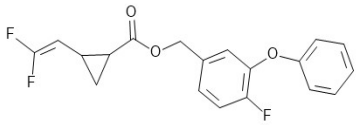
4-fluoro-3-phenoxybenzyl 3-(2,2dichlorovinyl)-2,2-dimethylcyclopropane carboxylate

VIII 

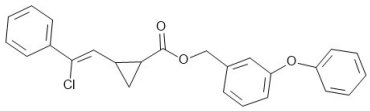
4-chloro-3-phenoxybenzyl 3-(2,2dichlorovinyl)-2,2-dimethylcyclopropane carboxylat

IX 

4-bromo-3-phenoxybenzyl 3-(2,2dibromovinyl)-2,2-dimethylcyclopropane carboxylate

X 

4-fluoro-3-phenoxybenzyl 3-(2,2difluorovinyl)-2,2-dimethylcyclopropane carboxylate

XI 

(Z)-3-phenoxybenzyl 3-(2-chloro-2phenylvinyl)-2,2-dimethylcyclopropane carboxylate

Molecule I can be viewed as a structure designed by replacing 1,1-dimethyl-2-(2methylprop-1-enyl) cyclopropane group in FEB by N-ethyl-4-(trifluoromethyl)aniline. This is seen to improve the HOMO energy from -9.7560 to -9.2253 eV, the energy gap is decreased from 9.4742 to 8.8506 eV, the binding energy was decreased while the electronic energy decreased. The overall effect of these changes is a slight increase in the activity of the insecticide. Molecule II can be viewed as a structure developed from FEP by replacing the propane tail of the molecule with 2-chloro-1,1,1-trifluoroethane, which is a more electronegative group than propane and the addition of fluorine bond to one of the benzene rings. Consequently, the HOMO energy, was decreased, the energy gap decreases, the binding energy increases while electronic energy decreased. Compound III replaces the tail end propane with dibromo propane and dichloropropane respectively. In addition, chlorine substituent is introduced into the second benzene ring. These halogens have the tendency of increasing the electron density of the aromatic ring and thus decreases the HOMO energy as seen in Table 8. However, their activity was not significantly affected. Compounds IV to XI (except, compound IX) have HOMO energy values than that of FEP, which seems to be the parent compounds.

The position, nature and type of substituent are important factors that influences the magnitude of the quantum chemical descriptors and hence the LD50 values of the studied molecules. Fig. 5 shows the HOMO and LUMO diagrams of the eleven predicted molecules.

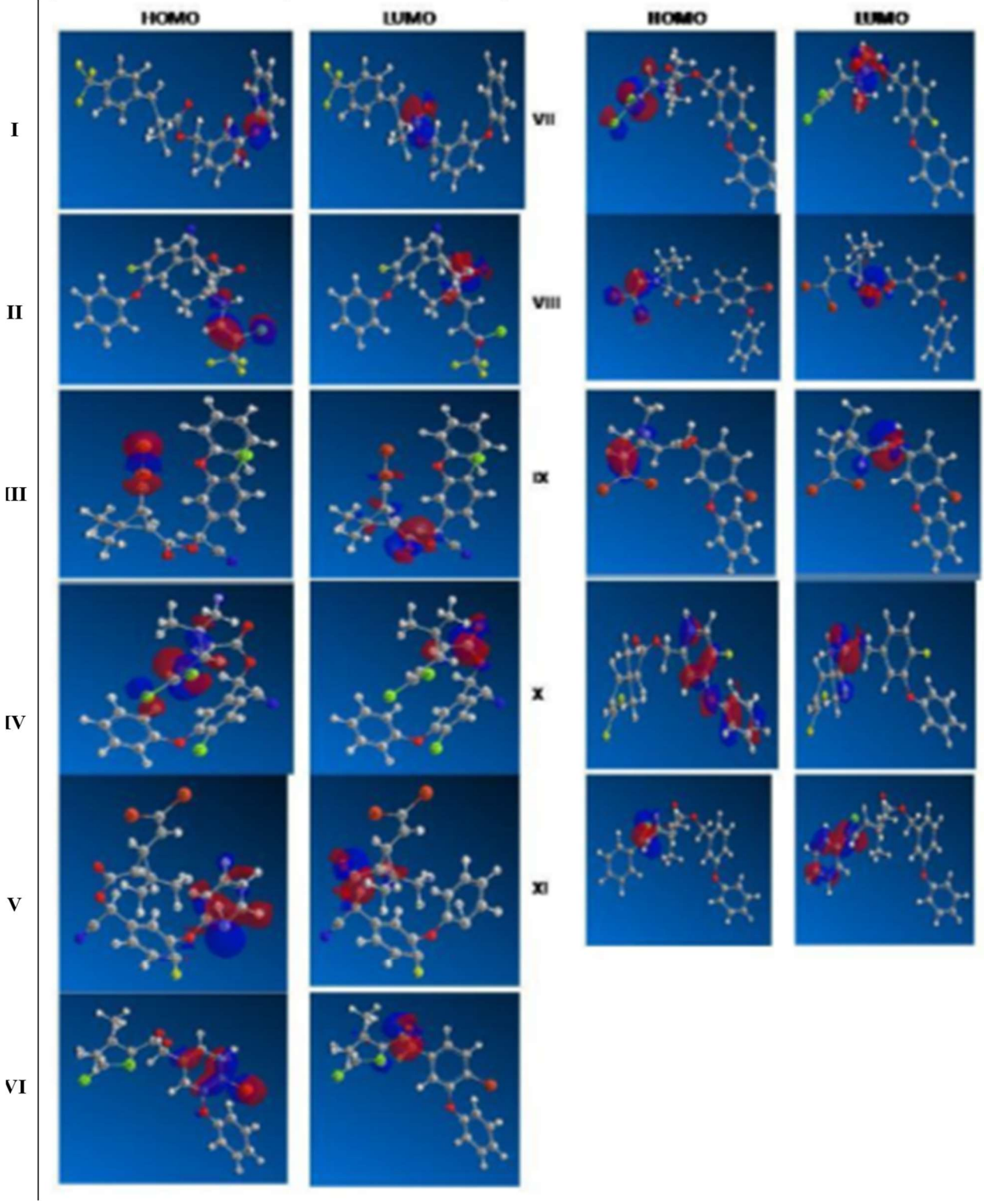


Fig. 5: HOMO and LUMO diagrams of the predicted insecticides

In all the molecules, the LUMO electron density is found to reside in the carbonyl functional group indicating that their behaviours with respect to the LUMO orbital may not have any significant difference. This also explains why the LUMO energy of these molecules does not appear as a descriptor for estimating their activities.

In Molecule I, the HOMO electron density resides around the enol oxygen, O(7) but in Molecule II, the HOMO electron density runs around C(19), C(23) and Cl(25) In Molecule III and IX, the HOMO electron density resides around the halopropane bonds (i.e atoms 23, 35 and 26).

In Molecule IV, VII and VIII, the HOMO electron density concentrates on the halopropene bonds and in the cyclopropane ring. In Molecules 5 and 6, the HOMO electron density are concentrated in the benzene rings, that is C(1) to C(6) and C(8) to C(13) indicating that the introduction of bromine substituent into the C(8) to C(13) ring, enrich this ring with preference to C(1) to C(6). In Molecule IX, the HOMO electron density resides in the alkene bond, C (23). In Molecule, the HOMO electron density is concentrated in the two benzene rings. This compound exhibited the second to the highest value of LD_{50} (5450.216 mg/kg) among all the predicted compound. The highest value was obtained for molecule VII (5630.35 mg/kg). Their high activity values maybe attributed to the respective effect of the electronegative fluorine and chlorine atoms on the ring. These atoms, been electronegative, might have enriched the rings and provoke them to be more reactive. These compounds had the highest values of EHOMO and least value of ΔE, indicating that they have the best tendency to donate electron, hence best reactive tendency. In Molecule XI, the HOMO electron density is concentrated in chlor-alkene bond (C (23), C (24) and Cl (26)) while the LUMO is in the third benzene ring (extending from C (25) to C (30)).

Interestingly, among all the predicted molecules, Molecule XI is the only molecule, whose LUMO electron density is not resided in the carbonyl bond.

4.0 Conclusion

Toxicological activities of some cyano(3-phenoxyphenyl) methyl isobutyrate related insecticides especially, cyhalothrin (CYH), fenpropathrin (FEP), cypermethrin (CYP), deltamethrin (DEL), permethrin (PEM) and cyfluthrin (CYF) are functions of some quantum chemical descriptors. QSAR is a useful tool in modeling the activities of these insecticides and has been used to developed novel potential insecticides with activities that are very close to the known ones

5.0 References

Ameh, P. O. & Eddy, N. O. (2018). Theoretical and Experimental Investigations of the Corrosion Inhibition Action of Piliostigma Thonningii Extract on Mild Steel in Acidic Medium. Communication in Physical Sciences, 3, 1, pp. 27-42.

Bendjeddou, A., Abbaz, T., Maache, S., Rehamnia, R., Gouasmia, A. K. & Villemin, D. (2016). Quantum chemical descriptors of some paminophenyl tetrathiafulvalenes through density functional theory (dft). *Rasayan Journal*, 9, 1, pp. 18-26

Can A.(2014). Quantitative structure-toxicity relationship (QSTR) studies on the organophosphate insecticides. Toxological Letters,

Devillers, J. & Devillers, H. (2009). Prediction of acute mammalian toxicity from QSARs and interspecies correlations. SAR QSAR. *Environmental Research*, 20, 5-6, 467–500.

Eddy NO & Ita BI (2011a) Theoretical and experimental studies on the inhibition potentials of aromatic oxaldehydes for the corrosion of mild steel in 0.1 M HCl. *Journal of Molecular Modelling* 17, 4, pp. 633-647.

Eddy, N. O. & Ita, , B. I. (2011b). Experimental and theoretical studies on the inhibition potentials of some derivatives of cyclopenta-1,3-diene. *International Journal of Quantum Chemistry,* 111, 14, pp. 3456-3473.

Eddy, N. O. & Ita, B. I. (2011). QSAR, DFT and quantum chemical studies on the inhibition potentials of some carbozones for the corrosion of mild steel in HCl. *Journal of Molecular Modelling*, 17, 2, pp. 359–376.

Eddy, N. O. & Essien, N. B. (2017). Computational chemistry study of toxicity of some m-tolyl acetate derivatives insecticides and molecular design of structurally related products. In Silico Pharmacology, 5, 1, pp. 14, doi:10.1007/s40203-017-0036-y.

Eddy, N. O. (2011). Experimental and theoretical studies on some amino acids and their potential activity as inhibitors for the corrosion of mild steel, Part 2. Journal of Advanced Research, 2, pp. 2:35–47. Doi: 10.1016/j.jare.2010.08.005.

Eddy, N. O., Ameh, P. O. & Essien N B. (2015). Experimental and computational chemistry studies on the inhibition of aluminium and mild steel in 0.1 M HCl by 3-nitrobenzoic acid. *Journal of Taibah University for Science*, DOI: 10.1080/16583655.2018.1500514

Eddy, N. O., Ita, B. I., Ibisi, N. E. & Ebenso, E. E. (2011). Experimental and quantum chemical studies on the corrosion inhibition potentials of 2-(2-oxoindolin-3-ylideneamino) acetic acid and indoline-2,3-dione. *International Journal of Electrochemistry*, 6, pp.1027-1044

Eddy, N. O., Momoh-Yahaya, H. & Oguzie, E. E.(2015). Theoretical and experimental studies on the corrosion inhibition potentials of some purines for aluminum in 0.1 M HCl. *Journal of Advanced Research,* 6, pp. 203–216. doi: 10.1016/j.jare.2014.01.004.

Hodgston E (2004) *A textbook of modern toxicology*. Wiley-interscience. 3rd edition. New York

Iwamura, H., Nishimura, K. & Fujita T. (1985) Quantitative structure-activity relationships of insecticides and plant growth regulators: comparative studies toward understanding the molecular mechanism of action. *Environmental Health Perspective*, 61, pp. 61:307–320. doi: 10.1289/ehp.8561307.

Jian, L., Yanging, G., Shibin, S., Xiaoping, R., Jie, S. & Zongde, W. (2014). Synthesis and quantitative structure-activity relationship (QSAR) studies of novel rosin-based diamide insecticides. RSC Advances, 4, pp. 58190-58199. doi: 10.1039/c3ra45801f.

Karelson, M. & Lobanov, V. S. (1996). Quantum-chemical descriptors in QSAP/QSPR studies. Chem. Rev. 96(3): 1027-1044.

Kikuchi, O. (1987) Systematic QSAR procedures with quantum chemical descriptors

Molecular Informatics, 6, 4, pp. 179-184.

Naik, P. K., Alam, A., Malhotra, A. & Rizvi O. (2010). Molecular modeling and structure-activity relationship of podophyllotoxin and its congeners. *Journal of Biomedical Screening*, 15, 5, pp. 528–540.

Naik, P. K., Singh, T. & Singh, H. (2009). Quantitative structure-activity relationship (QSAR) for insecticides: development of predictive in vivo insecticide activity models. SAR/QSAR *Environmental Research*, 20, 5-6, pp. 551–556.

Netzeva, T. I., Worth, A., Aldenberg, T., Benigni, R., Cronin, M.T.D., Gramatica, P., Jaworska, J.S., Scott, Kahn, S., Klopman, G., Carol, A., Marchant, C.A., Myatt, G., Nikolova-Jeliazkova, N., Patlewicz, G.Y., Perkins, R., Roberts, D.W., Schultz, T.W., Stanton, D.T., van de Sandt, J.J. M., Tong, W., Veith, G., &Yang, C. (2005) Current status of methods for defining the applicability domain of (quantitative) structure–activity relationships: the report and recommendations of ECVAM workshop 52. Altern Lab Anim, 33, 2, pp. 155–173

Vikas, R. (2015) Exploring the role of quantum chemical descriptors in modeling acute toxicity of diverse chemicals to *Daphnia magna*. *Journal of Molecular Graphics and Modelling*, 61, pp. 61:89–101. doi: 10.1016/j.jmgm.2015.06.009.