Computational chemistry study of toxicity of some *m*-tolyl acetate derivatives insecticides and molecular design of structurally related products

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Abstract

Molecular descriptors (including quantum chemical, topological and physicochemical descriptors) were calculated for five *m*-tolyl derivatives insecticides [namely, carbosulfan (CBS), carbofuran (CBF), isoprocab (IFP), methiocarb (MTC) and isocarbophos (ICP)]. Calculated quantum chemical parameters included the total energy, the electronic energy, the binding energy, the core–core repulsion energy, the heat of formation, the dipole moment and the frontier molecular orbital energies. All the calculated quantum chemical parameters (except dipole moment) exhibited strong correlation with the experimental LD₅₀ values of the studied insecticides (at various Hamiltonians). Calculated topological parameters included the molecular topological index (MTI), polar surface area (PSA), total connectivity (TC), total valence connectivity (TVC), Wiener index (WI), topological diameter (TD) and Balaban index (BI). However, only MTI, PSA, WI and BI exhibited excellent correlation with the toxicological activity of the insecticides. Also among all the calculated physicochemical parameters [logP, surface area (SA), surface volume (SV), hydration energy (E_{Hydr}), polarizability (PLZ) and refractivity (RFT)], only SV, E_{Hydr}, PLZ and RFT were useful in establishing quantitative structure activity relationship (QSAR). Application of QSAR indicated that the calculated theoretical LD₅₀ values for the studied insecticides displayed excellent correlation with experimentally derived LD₅₀ values. However, best results were obtained from quantum chemical descriptors under modified neglect of atomic overlap (MNDO). The toxicity profile of the insecticides also correlated strongly with ionization energy, electron affinity, global softness and global hardness. Reactive sites of each of the insecticides were established using Fukui function, Huckel charges and HOMO/LUMO diagrams. Six new molecules were proposed and their theoretical activities were estimated. The proposed molecules included 2-methyl-2-(methylthio)-2,3-dihydrobenzofuran-7-yl methylcarbamate, *O*-methyl *O*-2-((methylaminoxy)carbonyl)phenyl phosphoramidothioate, 2-((methylaminoxy)carbonyl)phenyl methylcarbamate, 2-(1-(methylthio)ethyl)phenyl methylcarbamate, *N*-methyl-*O*-(2-(methylthiooxy) benzoyl) hydroxyl amine and 4-methyl naphthalen-2-yl methylcarbamate. Some of the proposed molecules exhibited negative values of LD₅₀ (indicating extreme toxicity) while two of them exhibited values that are comparable to existing insecticides.

Keywords *m*-Tolyl acetate insecticides · Molecular modeling · Quantum, topological and physicochemical descriptors

Introduction

Organic insecticides are widely use in homes, offices and other environment to reduce the health impact of insects by suppressing or terminating their life. All insecticides are

toxic to some extent and their toxicity is measure by LD₅₀ values, which refers to the concentration that will terminate 50% of the target organism (Husarova and Ostatnikova 2013). The general mode of action of insecticide is it suppressing effect on target organs when it comes in contact with it (Barbosa and Hastings 2012).

Prior to contact with the target organism and after the contact, it is certain that there exist some molecular properties that will enhance or retard their action. Theoretical chemistry provides a framework through which the properties of molecules can be correlated with its activity through the use of suitable molecular descriptors. Some of the

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commonly used descriptors are quantum chemical descriptors (which include the frontier molecular energies, total and electronic energy of the molecule, core–core repulsion energy, heat of formation, binding energy, etc.), physicochemical descriptors (such as polarizability, logP, surface area, surface volume, hydration energy, refractivity, etc.) and topological descriptors (including total and valence connectivity indices, Wiener index, Balaban index, polar surface area and others). Quantitative structure activity relationship (QSAR) is useful in establishing the relationship between correlated molecular descriptors and the activity of the molecule. Several works on QSAR of some pesticides (including some insecticides) have been reported (Iwamura et al. 1985; Jian et al. 2014; Naik et al. 2009, 2010). However, most of the reported research works are centered on the use of single molecular descriptors and to the best of the knowledge of the author, literature is scanty on the use of quantum chemical, topological and physicochemical descriptors for QSAR study of *m*-tolyl acetate insecticides. Therefore, the present study is aimed at carrying out theoretical study in *m*-tolyl acetate insecticides through QSAR and related molecular descriptors. The work shall also propose new molecules (that are structurally related to the studied molecules) and their theoretical activities shall be estimated in order to assess the feasibility of their synthesis.

Materials and methods

The experimental LD₅₀ (dermal toxicity in rabbit) of the studied insecticides were obtained from insecticidal activity data base (Kard et al. 2014; Lorenz 2006). All chemical structures were drawn using ChemBio office software. Full structure optimization was carried out using molecular mechanics and semiempirical packages in the HyperChem software. The optimization process was achieved through successive applications of molecular mechanics, semiempirical (PM6), Ab initio and DFT until the final gradient of the molecule was zero.

In calculating the semi-empirical parameters for the respective molecules, the charge of the molecule was set to zero while the spin multiplicity was unity. The convergence and iteration limits were set at 0.001 and 50 respectively. Topological parameters were calculated using the Chem Pro (a package in the ChemBio software) included molecular topological index (MTI), polar surface area (PSA), total connectivity (TC), total valence connectivity (TVC), Wiener index (WI), topological diameter (TD) and Balaban index (BI).

Muliken charges on the atoms were calculated using Ab initio and DFT levels of theory in the HyperChem software. The calculation were done using UHF spin pairing, STO3G* basic set, iteration limit of 50, converging limit of

1×10^{-5} and spin multiplicity of 1 and 2 for 0 and + 1/– 1 charges respectively. All statistical analysis were performed using Excel package in the Microsoft office.

Results and discussions

Molecular descriptors

Tables 1, 2 and 3 show calculated quantum chemical, topological and physicochemical descriptors for CBS, CBF, IFP, MTC and ICP insecticides respectively.

Molecular quantum chemical descriptors

Calculated quantum chemical parameters included the total energy (E_T), the electronic energy (E_{Elec}), the binding energy (E_{Bind}), the core–core repulsion energy (E_{CCR}), the heat of formation (H_f) the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the lowest unoccupied molecular orbital (E_{LUMO}), the energy gap (ΔE) and the dipole moment (μ). These parameters were calculated for PM3 (parameterized model 3), RM1 (Recife model 1), AM1 (Austin model 1), MNDO (Modified neglect of diatomic overlap) and CNDO (complete neglect of diatomic overlap) Hamiltonians. The use of quantum chemical parameters in predicting the reactivity or activity of a molecular species has been extensively documented with respect to corrosion inhibition, drugs activity, molecular reactivity, adsorption and other response properties (Musa et al. 2012; Usha et al. 2013; Borget et al. 2001). The total molecular energy, electronic energy, core–core repulsion and binding energies of a molecule are indices that often correlate with molecular properties/activities. They express the readiness of a molecule to be subjected to chemical or physical changes based on its structure. In most cases, the reactivity of a molecules or envisaging activity increases with increase in these parameters. The frontier molecular energies of a molecule (which include the E_{HOMO} , the E_{LUMO} and the ΔE) are perhaps the most widely use and significant quantum chemical parameters that have shown promises in bridging the gap between experiment and theory (Table 4). The E_{HOMO} of a molecule indicates its tendency toward reactivity or adsorption. Therefore, the higher its value, the better is the extent of reactivity or adsorption. It is an index that represents the tendency of a molecule to donate electron while the E_{LUMO} represent the tendency towards acceptance of electron (Ameh and Eddy 2016). The ΔE is associated with the level of hardness or softness of molecular specie (Eddy and Ita 2011a). Soft molecules are characterized by low energy gap and are more reactive than hard molecules which are characterized by large energy gap (Eddy et al. 2015). The dipole moment, though a quantum chemical parameter, has not been fully

Table 1 IUPAC/generic name, chemical structure and dermal LD₅₀ values of the studied insecticides

Insecticide	Chemical structure	LD ₅₀ (mg/kg)
2,2-Dimethyl-2,3-dihydrobenzofuran-7-yl dibutylaminothiocarbamate (carbosulfan)—CBS		2000
2,2-Dimethyl-2,3-dihydrobenzofuran-7-yl methylcarbamate (carbofuran)—CBF		46.4
2-Isopropylphenyl methylcarbamate (isoprocarb) isofenphos—IFP		4100
3,5-Dimethyl-4-(methylthio)phenyl methylcarbamate (methiocarb)—MTC		2000
Propan-2-yl 2-[amino(methoxy)phosphinothioyl]oxybenzoate (isocarbophos)—ICP		224

Table 2 Calculated quantum chemical descriptors for the studied insecticides

	Hamiltonian	E _T (kcal)	E _{EL} (kcal)	E _b (kcal)	E _{CCR} (kcal)	H _F (kcal)	E _{HOMO} (eV)	E _{LUMO} (eV)	ΔE (eV)	μ (Debye)
CBS	PM3	-87,882.1952	-765,428.0011	-5256.3387	677,545.8058	-34.8507	-8.720929	-0.704338	8.016591	5.684
	RM1	-93,436.4370	-775,838.6410	-4279.5670	682,402.2039	941.9210	-8.590023	-0.119205	8.470818	5.561
	AM1	-94,381.3285	-777,119.8372	-5224.4584	682,738.5087	-2.9704	-8.402936	-0.249184	8.153752	5.628
	MNDO	-95,471.7743	-779,073.3020	-5220.6829	683,601.5277	0.8051	-8.811419	-0.213510	8.597909	4.832
CBF	CNDO	-144,065.4914	-880,808.2452	-15,186.3733	736,742.7538	-9964.8853	-10.760163	2.985323	13.74549	7.368
	PM3	-62,181.1353	-395,521.9522	-3225.8041	333,340.8169	-101.9171	-9.021661	0.098313	13.74549	1.831
	RM1	-66,403.7445	-402,299.3439	-2491.5667	335,895.5993	632.3203	-8.887171	0.171882	9.119974	1.770
	AM1	-67,115.4621	-403,224.6438	-3203.2843	336,109.1817	-79.3973	-8.956043	0.125546	9.059053	1.827
IFP	MNDO	-67,345.5387	-403,839.2971	-3218.0865	336,493.7584	-94.1995	-9.075384	-0.096061	9.081589	1.902
	CNDO	-102,868.1894	-471,781.1359	-9441.4744	368,912.9466	-6317.5874	-11.511815	3.518590	8.979323	1.683
	PM3	-52,679.3599	-321,213.9914	-2961.6196	268,534.6315	-68.1816	-9.266334	0.227611	9.493945	2.661
	RM1	-56,204.4680	-326,884.9759	-2368.0100	270,680.5079	525.4280	-9.111288	0.355505	9.466793	2.625
MTC	AM1	-56,782.6239	-327,644.5977	-2946.1659	270,861.9738	-52.7279	-9.212922	0.325316	9.538238	2.613
	MNDO	-56,954.1886	-328,200.2737	-2935.9869	271,246.0852	-42.5489	-9.252501	0.065282	9.317783	2.077
	CNDO	-86,755.0929	-385,639.4165	-8543.7308	298,884.3236	-5650.2928	-12.009649	3.800140	15.80979	2.069
	PM3	-56,975.5956	-3027.2226	-347,608.5087	290,632.9130	-67.3846	-8.813284	-0.342996	8.470288	1.822
ICP	RM1	-60,561.2850	-354,217.1584	-2303.2955	293,655.8734	656.5425	-8.928601	-0.080980	8.847621	1.555
	AM1	-61,265.9865	-355,122.9187	-3007.9969	293,856.9322	-48.1589	-8.519956	-0.202056	8.317900	1.578
	MNDO	-62,245.8703	-356,687.3633	-3015.6058	294,441.4930	-55.7678	-9.356261	-0.345669	9.010592	1.679
	CNDO	-93,426.4881	-416,257.2938	-8459.4028	322,830.8057	-5499.5648	-11.450028	3.368808	14.81884	2.483
ICP	PM3	-73,697.2872	-489,031.2770	-3382.1535	415,333.9898	-175.5255	-9.381167	-1.821023	7.560144	4.493
	RM1	-78,436.6764	-498,410.1213	-2467.0778	419,973.4449	739.5502	-9.732583	-2.078462	7.654121	6.728
	AM1	-793.24.3680	-499,509.8420	-3354.7694	420,185.4740	-148.14142	-9.755600	-2.170310	7.58529	7.126
	MNDO	-81,016.2731	-501,783.2629	-3323.27979	420,766.9898	20.4845	-9.289090	-1.719348	7.569742	3.991
CNDO		-121,073.9902	-577,180.8153	-8747.6719	456,106.8250	-5541.0439	-11.163250	-0.207070	10.95618	6.076

Table 3 Calculated molecular topological descriptors for the studied insecticides

Hamiltonian	MTI	PSA	TC	TVC	WI	TD	BI
CBS	11,125	33.13	0.0003844	2.4263	1469	12	581,662
CBF	3150	47.56	0.004915	0.0001447	425	8	76,283
IFP	2346	38.33	0.01389	0.0006682	308	7	59,754
MTC	2770	38.33	0.01134	0.001063	360	9	84,549
ICP	4177	74.92	0.004710	0.0002315	615	9	197,212

MTI molecular topological index, *PSA* polar surface area, *TC* total connectivity, *TVC* total valence connectivity, *WI* Wiener index, *TD* topological diameter, *BI* Balaban index

Table 4 Calculated physicochemical descriptors for the studied insecticides

Molecule	logP	SA (Å ²)	SV (Å ³)	PLZ (Å ³)	E _{Hydr} (kcal/mol)	RFT (Å ³)
CBS	2.76	568.50	1064.62	40.74	− 2.07	107.49
CBF	− 0.50	397.56	703.61	23.38	− 4.53	65.55
IFP	1.21	377.65	638.27	21.68	− 3.20	59.00
MTC	− 0.01	439.51	704.70	24.68	− 3.85	66.95
ICP	1.34	456.13	815.27	78.85	− 8.67	78.85

SA surface area, *SV* surface volume, *PLZ* polarizability, *E_{Hydr}* hydration energy and *RFT* = refractivity

explored in analyzing theoretical or experimental molecular data. This is because in some cases, activity increases with increasing value of μ and in others, it decreases with decreasing value of μ (Eddy and Ita 2011b).

Plots showing the variation of the calculated quantum chemical parameters with activity of the studied insecticides are presented in Fig. 1. Correlation coefficients deduced from the plots are recorded in Table 5. From the results presented, all the molecular quantum chemical parameters displayed positive correlation with the LD₅₀ values of the studied insecticides. Hence, the activity of these insecticides increases with increase in the molecular quantum chemical properties (also see Fig. 1). However, correlation between LD₅₀ values and dipole moment were extremely low (< 0.2) and is not presented in the Table. This confirms the uncertainty of using dipole moment in explaining the relationship between theory and experiment.

Molecular topological and physicochemical descriptors

Calculated molecular topological indices for the studied insecticides are presented in Table 3. These include molecular topological index (MTI), polar surface area (PSA), total connectivity (TC), total valence connectivity (TVC), Wiener index (WI), topological diameter (TD) and Balaban index (BI). Molecular topological index (MTI) has been found to be strongly related to Wiener and connectivity indices and some physicochemical properties of molecules (Nikolić et al. 1993). On the other hand, polar surface area (PSA) is the surface sum over all polar atoms (which primarily include oxygen and nitrogen atoms and their attached

nitrogen). This index, PSA, often shows excellent correlation with the adsorption of drugs (which operate through physical interaction of surface through electrostatic potential) in humans and some animals, (Prasanna and Doerksen 2009; Schaftenaa and de Vilieg 2012). According to Kier and Hall (2002), connectivity indices are related to the relative possibility of each bond in a molecule to have an encounter with other bond in the same molecule or in another neighbouring molecule during bimolecular collision. Connectivity indices (including total and valence connectivity) have been found to correlate excellently with properties of some molecules. For example, Wiener index (WI) has been reported to exhibit excellent correlation with the binding energy or absorption ability of most molecules (Garcia et al. 2005). However, the Balaban index (BI), also called distance connectivity index is a topological indices, which is highly discriminatory because its value does not increase with the size of the molecule or number of ring (Todeschini and Consonni 2000). Topological diameter (TD) is known to have a significant relationship with some molecular properties. For example, Gao et al. (2016), reported that some molecular properties of anti cancer drugs correlate strongly with TD values, indicating their significant in QSAR. Table 6 present correlation coefficients between the calculated molecular topological parameters and LD₅₀ values of the studied insecticides. The results obtained revealed that LD₅₀ values of the insecticides increase as the topological indices increase. Best negative correlation was obtained for TC which suggests that the activity of the insecticidal molecules has some dependency on the tendency of the molecules to experience an encounter and impart on the target organism.

Fig. 1 Variation of molecular quantum chemical parameters with LD₅₀ values of the studied insecticides

Calculated physicochemical descriptors were logP, surface area (SA), surface volume (SV), hydration energy (E_{Hydr}), polarizability (PLZ) and refractivity (RFT). These parameters also correlated positively with LD₅₀ values of the insecticides as shown in Table 6.

QSAR study

Quantitative structure activity relationship (QSAR) or quantitative property relationship (QSPR) is a powerful mathematical chemistry tool that can be applied to establish a relationship

between suitable molecular descriptors and response molecular parameters. QSAR relies on the fact that the observed or expected activity of a molecule depends on its structure (Tani 1994). In this study, QSAR was carried out between LD₅₀ values of the insecticides and descriptors that exhibited best correlation coefficients. Examination of correlations between quantum chemical parameters and LD₅₀ values reveals that strong correlations existed for E_{LUMO} and ΔE . Consequently, regression analysis between these correlated quantum chemical parameters and LD₅₀ values gave Eqs. 1–5 for PM3, RM1, AM1, MNDO and CNDO Hamiltonians,

Table 5 Correlation coefficient between quantum chemical descriptors and LD₅₀ values of the studied insecticides

Quantum descriptor	PM3	RM1	AM1	MNDO	CNDO
E _T (kcal)	0.6605	0.6601	0.6605	0.6397	0.6695
E _{EI} (kcal)	0.6337	0.6335	0.6337	0.6312	0.6426
E _b (kcal)	0.7745	0.5048	0.7745	0.8506	0.4534
E _{CCR} (kcal)	0.6296	0.6295	0.6296	0.6296	0.6367
H _F (kcal)	0.6432	0.6549	0.6432	0.4911	0.2296
E _{HOMO} (eV)	0.648	0.3612	0.648	0.4949	0.7265
E _{LUMO} (eV)	0.822	0.7902	0.822	0.7926	0.754
ΔE (eV)	0.964	0.9412	0.964	0.8437	0.915

Table 6 Correlation coefficient between physicochemical/topological descriptors and LD₅₀ values of the studied insecticides

Descriptor	Correlation coefficient
MTI	0.8488
PSA	0.7617
TC	0.9386
TVC	0.4243
WI	0.7811
TD	0.4638
BI	0.828
LogP	0.1465
SA	0.398
SV	0.7768
PLZ	0.7464
E _{Hydr}	0.7349
REF	0.8275

MTI molecular topological index, *PSA* polar surface area, *TC* total connectivity, *TVC* total valence connectivity, *WI* Wiener index, *TD* topological diameter, *BI* Balaban index, *SA* surface area, *SV* surface volume, *PLZ* polarizability, *E_{Hydr}* hydration energy, *RFT* refractivity

$$LD_{50} = 808E_{LUMO} + 1065.51\Delta E - 6319.54 \quad (1)$$

$$LD_{50} = -97.29E_{LUMO} + 2158\Delta E - 16545.80 \quad (2)$$

$$LD_{50} = 449.75E_{LUMO} + 1402.29\Delta E - 9438.36 \quad (3)$$

$$LD_{50} = 356.359E_{LUMO} + 1556.50\Delta E - 11145.36 \quad (4)$$

$$LD_{50} = -602.54E_{LUMO} + 1214.90\Delta E - 13225.80 \quad (5)$$

Correlation coefficients between experimental and theoretical LD₅₀ values for PM3, RM1, AM1, MNDO and CNDO Hamiltonians (0.9576, 0.9418, 0.9957, 0.8468 and 0.8897, respectively) were excellent. Calculated theoretical LD₅₀ values are presented in Table 7 while Fig. 2 presents

plots for the variation of experimental LD₅₀ with theoretical values according to Eqs. 1–5. The excellent correlation obtained at this levels indicates that values of E_{LUMO} and ΔE are useful in exploring the relationship between theoretical and experimental toxicity values of the studied insecticides. However, when all the calculated quantum chemical parameters were regressed against LD₅₀ values of the studied insecticides, perfect correlations (R² = 1 and standard error = 0) were found to be associated with regression Eqs. 6–10 (for PM3, RM1, AM1, MNDO and CNDO Hamiltonians respectively).

$$LD_{50} = -23.72E_T + 25.31E_{Elec} + 25.31E_{Bind} + 25.59E_{CCR} + 89300.41 \quad (6)$$

$$LD_{50} = 1.6800E_T - 0.2260E_{Elec} + 17.89E_{Bind} + 15.99H_F + 75636.79 \quad (7)$$

$$LD_{50} = 1.6169E_T - 0.2341E_{Elec} + 20.28E_{Bind} - 6.532H_F + 78615.60 \quad (8)$$

$$LD_{50} = 0.5281E_{Elec} + 2.0621E_{Bind} + 0.5808E_{CCR} + 27.6217H_F + 27095.61 \quad (9)$$

$$LD_{50} = 0.8609E_{Elec} + 15.9149E_{Bind} + 1.0558E_{CCR} + 15.6807H_F + 67935.62 \quad (10)$$

Theoretical LD₅₀ values obtained from Eqs. 6–10 are also recorded in Table 6. There is no significant difference between these values and those obtained from experiments (P > 0.5).

Regression of topological descriptors with LD₅₀ values yielded Eq. 11 while Eq. 12 was obtained for physicochemical descriptors.

$$LD_{50} = -59.10MTI - 850.76PSA + 437.3WI + 0.008689BI + 40130.51 \quad (11)$$

$$LD_{50} = -37.21SV + 208.20PLZ + 2225.44E_{Hydr} + 150.15RFT + 21597.71 \quad (12)$$

Both regression equations gave perfect relation characterized with standard error of zero and R² values of 1 (Figs. 3, 4). Calculated or predicted LD₅₀ values obtained from these equations are presented in Table 7.

In statistical analysis, positive outcome becomes more reliable as the number of data or parameters increases. Therefore, all the perfectly regressed descriptors can be combined to derived single equation that relates the toxicological activity of the insecticides with the descriptors. The results of the combination yielded Eqs. 13–17 for PM3, RM1, AM1, MNDO and CNDO Hamiltonians,

$$LD_{50} = -0.00348E_T + 0.0665E_{Elec} + 0.0713E_{Bind} + 0.0526BI + 2237.37 \quad (13)$$

$$LD_{50} = 1.088E_T - 0.1420E_{Elec} - 5455MTI + 0.0431PLZ + 29019.69 \quad (14)$$

Table 7 Experimental and theoretical LD₅₀ values of the studied insecticides, calculated from different models

Molecule	Experimental LD ₅₀ (mg/kg)	Theoretical LD ₅₀ (mg/kg) [Eqs. 6–10]				
		PM3	RM1	AM1	MNDO	CNDO
CBS	2000.00	2004.20	2000.68	2002.00	1999.84	1997.31
CBF	46.40	48.68	46.75	47.43	46.37	45.048
IFP	4100.00	4101.87	4100.28	4100.83	4099.95	4098.92
MTC	2000.00	2001.79	2000.31	2000.90	1999.95	1998.82
ICP	224.00	226.80	224.43	225.27	223.88	222.34
Molecule	Experimental LD ₅₀ (mg/kg)	Theoretical LD ₅₀ (mg/kg) [Eqs. 13–17]				
		PM3	RM1	AM1	MNDO	CNDO
CBS	2000.00	2001.87	1964.78	1998.16	1994.23	1997.73
CBF	46.40	47.32	36.09	45.53	43.52	46.16
IFP	4100.00	4100.75	4092.26	4099.29	4097.66	4099.82
MTC	2000.00	2000.17	1990.92	1999.22	1997.47	1999.72
ICP	224.00	225.17	210.36	222.88	220.42	223.28
Molecule	Experimental LD ₅₀ (mg/kg)	Topological (mg/kg) [Eq. 11]			Physicochemical (mg/kg) [Eq. 12]	
CBS	2000.00	1905.09			2000.04	
CBF	46.40	18.69			46.43	
IFP	4100.00	4079.88			4100.02	
MTC	2000.00	1976.53			2000.02	
ICP	224.00	183.95			224.03	

$$LD_{50} = 1.0332E_T - 0.1343E_{Elec} - 5.2958MTI + 0.04377PLZ + 28546.16 \quad (15)$$

$$LD_{50} = 0.6591E_T + 0.7464E_{Bind} - 4.7420MTI + 0.05547PLZ + 25790.89 \quad (16)$$

$$LD_{50} = 1.2846E_T + 5.1709E_{Elec} + 1.6039E_{Bind} - 0.06506BI + 68166.59 \quad (17)$$

Also, correlation between the experimental and theoretical LD₅₀ were perfect as shown in Fig. 5. Calculated theoretical or predicted toxicological indices (i.e. LD₅₀) are also presented in Table 7. The results of the analysis reveal that at 95% level of probability, there is no significant difference between the experimental and predicted LD₅₀ values.

Global reactivity

Global reactivity considers the activity of a molecule as a consequence of the contribution of its entire component. Chemical descriptors are often used to analyze global reactivity of a molecule. LD₅₀ values are indices that measure the toxicity of a chemical compound such as insecticides. The lower the LD₅₀ value, the more

toxic is the insecticide. From Table 1, it can be seen that CBF has the least value of LD₅₀ (46.4 mg/kg) while IFP has the highest value (4100 mg/kg). Therefore, CBF is the most toxic while IFP is the least toxic. Toxicity has strong correlation with reactivity. Therefore, that indices that measures reactivity are relevant in the estimation of degree of toxicity. From the calculated quantum chemical parameters (Table 2), it can be seen that highest values of E_T , E_{Elec} , E_{Bind} , E_{CCR} and E_{HOMO} were obtained for CBF (which is the most toxic insecticides), while least values were obtained for IFP (which is the least toxic). Similar trends were observed for some topological and physicochemical descriptors (Tables 3, 4). Consequently, value of MTI, TVC, WI, TD and BI are highest for CBF but least for IFP. Also CBF had the highest values of SA, SV, PLZ and RFT while IFP had least values for the listed physicochemical parameters.

Ionization is the process involving loss of electron and the energy associated with the process is called ionization energy (IE). On the other hand, electron affinity (EA) is the opposite of ionization energy and refers to the energy required for a molecule to accept electron. Table 8 presents IE and EA of the studied insecticides. These values were

Fig. 2 Variation of experimental LD₅₀ values of the studied insecticides with theoretical values calculated from E_{LUMO} and ΔE according to Eqs. 1–5

calculated by substituting the DFT energies of the molecules into the finite difference approximation equations (Eqs. 18, 19) (Eddy 2011),

$$IE = E_{(N-1)} - E_N \quad (18)$$

$$EA = E_N - E_{(N+1)} \quad (19)$$

where E_N , $E_{(N-1)}$ and $E_{(N+1)}$ are the ground state energy of the N , $N - 1$ and $N + 1$ electron systems of the molecule. From the results obtained are not out of expected range and magnitude. i.e. values of IE are negative while those of EA are positive. Correlation between IE and LD₅₀ values are excellent ($R^2 = 0.9719$). The most toxic insecticide had the highest value of EA while the least toxic insecticide had the

Fig. 3 Variation of experimental LD₅₀ values of the studied insecticides with theoretical values calculated from quantum chemical parameters according to Eqs. 6–10

least. Consequently, the toxicity of the studied insecticides increases with increase in EA values, indicating that the reactivity of the studied insecticides is influenced by tendency towards donation and acceptance of electron between the insecticide and the target organism. Evidence abounds in using global softness and hardness in predicting the reactivity

of a molecule such as insecticide. Generally, global hardness is an inverse of global softness (S) and can be calculated from the following equations (Eddy 2011),

$$S = \frac{1}{(E_{(N-1)} - E_N) - (E_N - E_{(N+1)})}, \quad (20)$$

Fig. 4 Variation of experimental LD₅₀ values of the studied insecticides with theoretical values calculated from topological and physicochemical descriptors according to Eqs. 11 and 12, respectively

$$\eta = (E_{(N-1)} - E_N) - (E_N - E_{(N+1)}). \quad (21)$$

Correlation between S and LD₅₀ ($R^2 = 0.9945$) and between η and LD₅₀ ($R^2 = 0.9347$) were excellent. Therefore, the toxicity of the studied insecticides increases with increase in the values of S and η .

Local reactivity

Local reactivity approaches the reactivity of a molecule as a function of its constituent atoms or chemical bond. Local selectivity analysis can be achieved through the use of Fukui function. The Fukui function approaches reactivity through the transfer or donation of charge/electron. For an N -electron system, losing or gaining electron changes the system to $N - 1$ or $N + 1$ electron system. Therefore, there are three types of Fukui function corresponding to the nucleophilic Fukui function, f^- , when it loses electron, the electrophilic Fukui function, f^+ when it gains electron and the average of the two, f^0 for radical attack. The finite difference approximation method, defines Fukui functions as follow (Eddy 2010),

$$f_x^- = q_N - q_{(N-1)} \quad (22)$$

$$f_x^+ = q_{(N+1)} - q_N \quad (23)$$

where q_N , $q_{(N-1)}$ and $q_{(N+1)}$ are the Muliken charges for N , $N - 1$ and $N + 1$ electron systems respectively. Huckel charges and condensed Fukui function (calculated for both DFT and Ab initio levels of theory) for CBS, CBF, IFP, MTC and ICP are presented in Tables 9, 10, 11, 12 and 13.

In CBS, the site for electrophilic and nucleophilic attacks deduced from Ab initio and DFT Fukui functions are in the enol-thiocarbonyl bond, i.e. O(3)–C(1)–S(4) bond. Similar finding is revealed by the trend in values of the calculated Huckel charges for the atoms in the CBS molecule (Table 14). It is also evident from the Huckel charges on atoms in CBS that the atom with the highest positive charge is C(1). Hence, the reaction center of CBS molecule is in C(1)–O(3) and C(1)–S(4) bonds. The HOMO of the molecule rest on the thiocarbonyl sulphur bond while the LUMO loop is concentrated around the benzene ring (Fig. 6). The HOMO corresponds to anion while the LUMO correspond to cation. Although the Huckel charge on the enol oxygen atom, O(3) is more negative (-0.481636) than that in the thiocarbonyl sulphur (-0.346769), the presence of double bond between C(1) and S(4) preferentially places the HOMO loops on the sulphur atom. Also, the bond length between C(1) and S(4) is $2.212 \text{ \AA}$ while that of C(1)–O(3) is $1.904 \text{ \AA}$. Therefore, the thiocarbonyl bond (which is unsaturated) is more prone to reaction than the enol bond. As a rule, shorter bond are less prone to chemical reaction than longer bond because the Columbic interaction increases with decrease in bond length. The total positive Huckel charge on the benzene carbon atoms is 0.512385 while the total negative charge is -0.11949 . This renders the benzene ring as a strong provider of carbo-cation due to excess of positive charge, explaining why the LUMO is preferentially attracted to the benzene ring. In CBF, both Ab initio and DFT levels of theory (Table 10) reveal that the nucleophilic Fukui function resides around the alkanes carbon 15 and 16 while the electrophilic Fukui function is domicile in the tetra hydrofuran ring [i.e. C(8) and C(9)]. The HOMO and LUMO diagrams of CBF (Fig. 6) also reveal that their respective negative and positive loops are concentrated on the benzene and tetra hydrofuran rings. The total positive Huckel charge on the benzene ring (0.38841) exceeded the total negative charge (-0.15015) in the same ring. In the tetra hydrofuran ring, the corresponding sums of Huckel charges are 0.49858 and -0.40359 , respectively. Since these two rings are joined together, the pulled effect move the reactive site from the C(1) atom (which has the highest Huckel charge of 0.63959 ,

Fig. 5 Variation of experimental LD₅₀ values of the studied insecticides with theoretical values calculated from quantum chemical, topological and physicochemical descriptors according to Eqs. 13–17

Table 8 Ionization energy, electron affinity and softness parameters of the studied insecticides, calculated from DFT energy of the molecules

	E_N (kcal/mol)	$E_{(N-1)}$ (kcal/mol)	$E_{(N+1)}$ (kcal/mol)	IE (kcal/mol)	EA (kcal/mol)	$S \times 10^{-5}$	η
CBA	− 580,112	− 586,289	− 563,400	− 6176.94	22,889.36	− 3.44041	− 29,066.3
CBF	− 398,020	− 398,282	− 295,738	− 261.879	102,543.7	− 0.97271	− 102,806
IFP	− 336,604	− 336,840	− 336,132	− 235.706	707.1533	− 0.001060	− 942.859
MTC	− 518,730	− 528,365	− 507,047	− 9635.11	21,317.66	− 3.23073	− 30,952.8
ICP	− 724,883	− 819,616	− 741,494	− 94,732.9	78,122.12	− 0.578519	− 172,855

Table 9 Huckel charges and Fukui function for CBS, calculated from Ab Initio and DFT level of theories

Atom	DFT		Ab initio		Huckel charge
	f_x^-	f_x^+	f_x^-	f_x^+	
1 6	0.15777	0.18110	-0.54414	2.75444	0.48791
2 7	0.02064	-0.04993	0.01413	-0.05111	0.00173
3 8	1.58596	1.18450	1.18759	-4.47271	-0.48164
4 16	-0.89506	-1.33830	-2.74002	4.03293	-0.34677
5 7	0.00016	-0.00024	-0.00014	0.00019	-0.23498
6 6	0.00001	-0.00001	-0.00001	0.00001	0.13435
7 6	0.00000	0.00000	0.00000	0.00000	-0.01004
8 6	0.00000	0.00000	0.00000	0.00000	0.00853
9 6	0.00000	0.00000	0.00000	0.00000	-0.00744
10 6	0.00002	-0.00004	-0.00001	0.00002	0.13331
11 6	0.00011	-0.00016	-0.00001	0.00001	-0.00759
12 6	0.00968	-0.01376	-0.00058	0.00054	0.00874
13 6	0.11297	-0.22566	-0.00277	0.00116	-0.00759
14 8	-0.00055	-0.18397	0.02940	-1.05578	-0.53279
15 6	-0.05904	0.07086	0.01767	-0.05581	0.31478
16 6	-0.00430	0.00404	-0.00004	-0.00018	0.01521
17 6	-0.00182	0.00317	-0.00012	-0.00091	-0.02172
18 6	-0.04130	0.12371	0.00588	-0.07813	0.24797
19 6	-0.00298	0.00281	-0.00010	0.00009	-0.02827
20 6	-0.04014	0.03852	-0.00016	0.00009	-0.03487
21 6	-0.19588	0.19631	0.00111	-0.00611	-0.03463
22 6	-0.08754	0.34159	0.06718	-0.21135	0.24920
23 6	-0.22303	-0.02074	0.16837	-0.42779	-0.01017
24 6	-0.15535	0.13479	0.29751	-0.27100	-0.01009

Table 10 Huckel charges and Fukui function for CBF, calculated from Ab Initio and DFT level of theories

Atom	DFT		Ab initio		Huckel charge
	f_x^-	f_x^+	f_x^-	f_x^+	
1 6	-0.06453	-3.87521	0.00064	-0.01391	0.63959
2 7	-0.05109	-3.02550	-0.00475	-0.01009	0.05661
3 8	-0.19384	-2.06748	-0.01389	-0.02468	-0.80401
4 8	-0.08346	-1.50522	-0.01725	-0.02061	-0.20305
5 6	-0.00438	-4.08016	0.00250	0.00299	0.01154
6 8	-0.02709	1.90602	-0.26771	-0.03052	-0.32965
7 6	-0.00661	-1.63462	-0.00224	-0.00525	0.30898
8 6	-0.00525	3.73557	0.00090	0.00868	-0.06951
9 6	-0.03866	3.99450	-0.04815	-0.11205	-0.00443
10 6	-0.02836	3.76439	-0.02858	-0.01226	0.18960
11 6	-0.03637	3.98179	-0.02099	-0.09250	-0.08105
12 6	-0.03929	3.96069	-0.04425	-0.00650	-0.06467
13 6	-0.02396	3.80669	-0.01989	-0.08961	-0.09212
14 6	-0.02212	3.39387	-0.06013	-0.12086	0.19881
15 6	0.00118	-4.02405	0.00706	0.00421	-0.10978
16 6	0.00114	-3.94437	0.00748	0.00411	-0.10985

Table 11 Huckel charges and Fukui function for IFP, calculated from Ab Initio and DFT level of theories

Atom	DFT		Ab initio		Huckel charge
	f_x^-	f_x^+	f_x^-	f_x^+	
1 6	-0.06934	-0.10443	-0.00012	-0.01266	0.89025
2 7	-0.00246	-0.03509	-0.01376	-0.00882	-0.06731
3 8	-0.28696	-0.18193	-0.05918	-0.00898	-0.90349
4 8	-0.11143	-0.03367	-0.06683	-0.01708	-0.37301
5 6	-0.00843	-0.00575	0.00407	0.00177	0.13347
6 6	0.00168	-0.17259	-0.12951	-0.01863	0.26311
7 6	-0.02128	0.12153	-0.08517	-0.11666	-0.02552
8 6	-0.03701	-0.04303	-0.01465	-0.09269	-0.02177
9 6	-0.02773	-0.17108	-0.07742	-0.00873	-0.03395
10 6	-0.01942	0.11517	-0.08632	-0.10144	-0.01124
11 6	-0.05145	-0.07344	-0.01241	-0.09711	-0.03796
12 6	-0.00199	-0.00212	0.00428	0.00729	0.03416
13 6	0.00128	0.01437	0.00395	0.00439	-0.00725
14 6	0.00208	0.00536	0.00242	0.00394	-0.01046

Table 12 Huckel charges and Fukui function for MTC, calculated from Ab Initio and DFT level of theories

Atom	DFT		Ab initio		Huckel charge
	f_x^-	f_x^+	f_x^-	f_x^+	
1 6	0.06602	-0.18455	-0.84937	-0.00556	0.76056
2 7	0.21825	-0.34793	-1.37475	-0.00744	0.00123
3 8	-1.40586	1.97874	-1.25800	-0.01398	-0.84945
4 8	-1.56773	2.35072	-1.23397	-0.01658	-0.30429
5 6	1.97887	-1.98623	-0.68259	0.00250	0.07863
6 6	-0.41199	0.72002	-1.77337	-0.01681	0.24356
7 6	-0.46482	0.62370	-2.09721	-0.09765	-0.07885
8 6	-0.22935	0.18701	0.79967	-0.10047	0.01058
9 6	0.05962	-0.15035	1.78338	0.00721	-0.03001
10 6	-0.03284	0.54220	1.27616	-0.09474	0.00970
11 6	-0.35976	0.52827	-1.36511	-0.09997	-0.08246
12 16	-0.00356	-0.05340	2.10353	-0.05936	0.06076
13 6	-0.14243	-0.24891	0.92814	0.00029	-0.02937
14 6	-0.63950	2.08314	1.90980	0.01108	-0.04014
15 6	0.22915	-1.86962	0.72262	0.01134	-0.03893

among all the atoms) to the joined ring. In IFP, DFT and Ab initio models positioned the nucleophilic Fukui function at the alkane carbon atoms [C(12), C(13) and C(14)]. However, the DFT model proposed the site for electrophilic attack to be in the benzene ring, the Ab initio model relies on the same alkane atoms. In the context of comparative advantage, the DFT model is better than the Ab initio model because it incorporate electron–electron correlation. Therefore, the site propose by the DFT is upheld. Fortunately,

Table 13 Huckel charges and Fukui function for ICP, calculated from Ab Initio and DFT level of theories

Atom	DFT		Ab initio		Huckel charge
	f_x^-	f_x^+	f_x^-	f_x^+	
1 6	- 3.16891	0.00109	0.00529	- 0.01227	0.64410
2 6	- 6.05923	0.64162	- 0.01613	- 0.04542	- 0.06596
3 6	1.36704	- 1.07447	0.01374	- 0.16804	0.26102
4 6	0.76581	- 0.15553	- 0.01170	- 0.02877	- 0.09985
5 6	5.27233	- 0.09032	- 0.00686	- 0.04714	- 0.01686
6 6	5.06626	- 0.49175	- 0.02239	- 0.06208	- 0.07024
7 6	- 4.40784	0.15214	- 0.00719	- 0.03345	- 0.00834
8 8	- 0.97040	0.00008	- 0.00327	- 0.03521	- 0.67857
9 8	- 0.04334	0.00001	- 0.00304	- 0.00376	- 0.19551
10 8	4.31936	- 3.17427	- 0.03829	0.01375	- 0.44601
11 15	0.11151	- 0.46229	- 0.00593	- 0.05817	1.88058
12 16	- 5.37752	4.02402	- 0.54826	- 0.10321	- 0.00865
13 8	- 0.59646	- 0.14689	- 0.08085	- 0.01219	- 0.55330
14 6	1.70669	- 0.14672	0.00323	0.00077	0.13802
15 7	1.22941	- 0.68505	- 0.02669	- 0.01537	- 0.40303
16 6	- 0.00039	0.00000	0.00007	0.00218	- 0.10027
17 6	- 0.00173	0.00000	0.00042	- 0.00349	0.24997
18 6	- 0.00039	0.00000	0.00135	0.00238	- 0.09958

the HOMO loops in IFP lies in the benzene ring for reasons explained for CBF while the LUMO loops are positioned in the benzene ring, the carbonyl and amide bonds. In MTC, the DFT model proposes the nucleophilic site to be between the alkane C(5) and the amide nitrogen, N(2) while the Ab initio model proposes the site to be in the thioether bond, C(9)–S(12). The Huckel charge on C(5) is greater than that on S(12). However, the HOMO loops rest on S(12) (Fig. 6). The C(9)–S(12) bond length is 2.225 Å while the C(5)–N(2) bond length is 1.841 Å. Therefore, C(9)–S(12) is the most likely site for nucleophilic attack. On the other hand, DFT model proposed the carboxyl functional group as the site for electrophilic attack with possibility for C(14), even as Ab initio support same. In ICP both DFT and Ab initio models propose the site for nucleophilic attack to be in

the benzene ring while the site for electrophilic attack is the enolate oxygen, O(10) for DFT and the sulphur atom, S(12). The HOMO and LUMO of ICP (Fig. 6) resides in the benzene ring and in the carboxyl functional group.

The results obtained in this study does not contradict evidences obtained and reported by other researchers for some insecticides, which confirm that the behavior of insecticides is strongly related to molecular descriptors, their chemical structures and electronic parameters (Vikas 2015; Can 2014; Karabunarliev et al. 1996; Pandith et al. 2010; Gomez-Jeria et al. 1995).

Prediction of new molecules

Figure 7 presents the chemical structures and IUPAC names of the predicted insecticides. From the forgone derived models, the descriptors that gave best approximated values of LD₅₀ were those associated with quantum chemical parameters as expressed by Eq. 7. Therefore, parameters of interest in estimating the LD₅₀ values of the proposed molecules are the MNDO total energy, the electronic energy, the binding energy and the heat of formation. The calculated parameters and the theoretical levels of toxicity are presented in Table 14. From the results obtained, the predicted LD₅₀ values of 22MDM, 2MCPM, NMBH and 4MNMC are negative indicating that attempts to synthesize insecticides of these nature may not be feasible. However, the predicted toxicity of OMCP and 2MPMC are positive and relatively comparable to existing insecticides. OMCP in particular suggest a new product, that is less toxic than the existing ones.

Conclusion

The toxicity of *m*-tolyl acetate derived insecticides can be adequately modeled using molecular quantum chemical, molecular topological and physicochemical descriptors. Predicted results obtained from the various descriptors are closely comparable to the experimental values and displayed

Table 14 Some quantum chemical parameters and predicted LD₅₀ values of the proposed insecticides

	E _T (kcal)	E _{Elec} (kcal)	E _{Bind} (kcal)	H _F (kcal)	Predicted LD ₅₀ (mg/kg)
22MDM	- 72,601.52	- 450,111.52	- 3262.01	- 71.72	- 4112.72
OMCP	- 78,560.20	- 475,147.92	- 2577.27	244.27	8837.601
2MCPM	- 72,567.59	- 416,811.80	- 2819.83	- 21.47	- 2867.36
2MPMC	- 62,212.10	- 370,985.80	- 2981.84	- 22.00	1266.355
NMBH	- 62,423.40	- 326,333.00	- 2518.76	- 49.55	- 1336.18
4MNMC	- 62,130.13	- 364,813.87	- 3103.31	27.71	- 1369.03

Fig. 6 HOMO and LUMO diagram of the studied insecticides

strong correlation. However, exact approximation is obtained from some quantum chemical parameters (namely, total energy, electronic energy, binding energy and heat of formation) under MNDO Hamiltonian. Toxicity of the studied insecticides is closely related to other molecular parameters

such as ionization energy, electron affinity and global softness/hardness. The sites for electrophilic and nucleophilic attacks is expressly revealed through condensed Fukui function analysis and through the Huckel charges on the atom as well as in the HOMO/LUMO diagrams.

Fig. 7 Chemical structures of the newly proposed molecules

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