التقييم والتنبؤ بسمية بعض المبيدات البيرثرويدية العضوية باستخدام نموذج جديد من فهارس كيمياء الكم والطوبوغرافية

مجدى دياب؛ وسمير سنيور

تم فى هذا البحث حساب فهارس كيمياء الكم والطبوغرافية لبعض المبيدات البيرثرويدية العضوية التى تعتمد على العزم متعدد الأقطاب والتى تم ربطها مع سمية هذه المواد على فئران التجارب LD_{50}، حيث تم حساب متغيرات كيمياء الكم من الشكل الفراغى المستقر للمركبات المحسوبة بطريقة (B3LYP/LANL2DZdp-ECP)، وعن طريق استخدام تحليل الارتباط الخطى تم تطوير نموذج متعدد جديد للتنبؤ بسمية الصيغ الكيميائية العديدة لهذه المبيدات. ومن خلال هذه الدراسة تم استنباط 50 صيغة كيميائية لمبيد الفينوثرين، السيبرميثرين، السيفلوثرين، السيهالوثرين، الدلتاميثرين والفينبروباثرين. وقد كان معامل التحليل الخطى (R^2) مساوياً للقيمة واحد، والتغير فى الجرعة نصف المميتة أقل من $1x10^{-3}$ وقيمة F أكبر من $1x10^{16}$. وقد أشارت الدراسة إلى أن الجرعة نصف المميتة لهذه المبيدات تعتمد فى الأساس على التركيب الكلى للمبيد، وليس على الصيغ المختلفة للمبيد نفسه. وبالتالى لا يمكن التحكم فى سمية المبيد إلا من خلال المركب الكلى لهذا المبيد.

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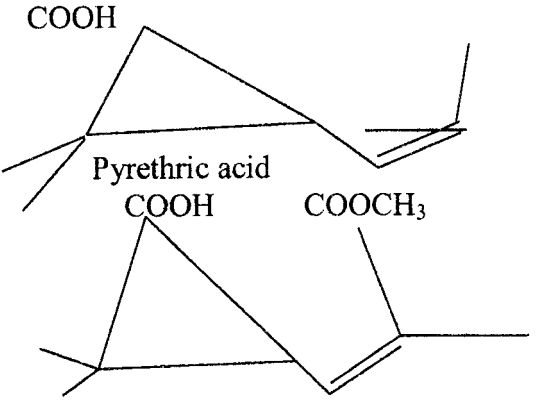
Figure captions

Fig. 1: The Structures of the studied pyrethroids **A-G**.

Fig. 2: Essential features of pyrethroid structure–activity relationships, general structure of pyrethroid insecticides calculated and their configurational nomenclature

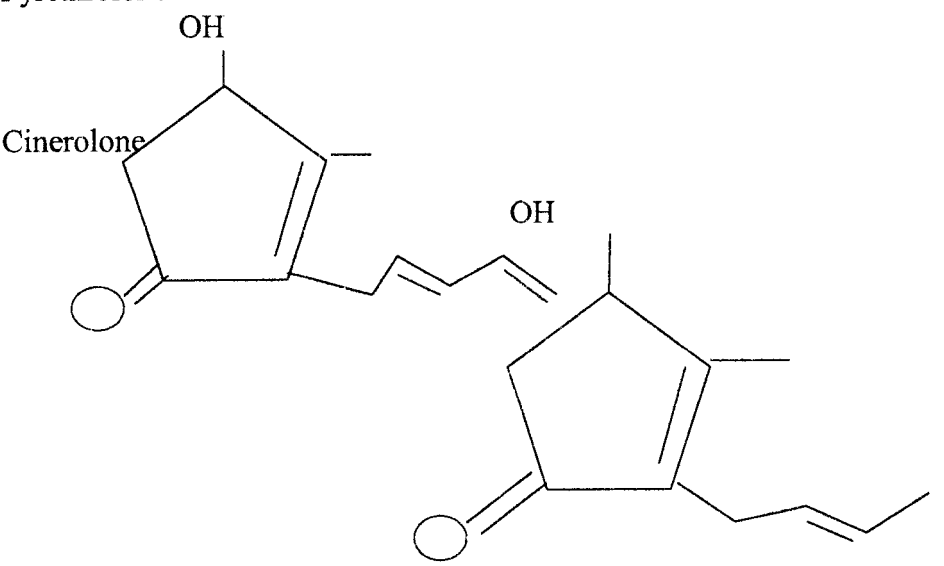
Fig. 3. Stereochemical determinants of insecticidal activity in pyrethroid acid moieties.

Chrysanthemic acid



Pyrethric acid

Pyrethrolone



Cinerolone

Fig3

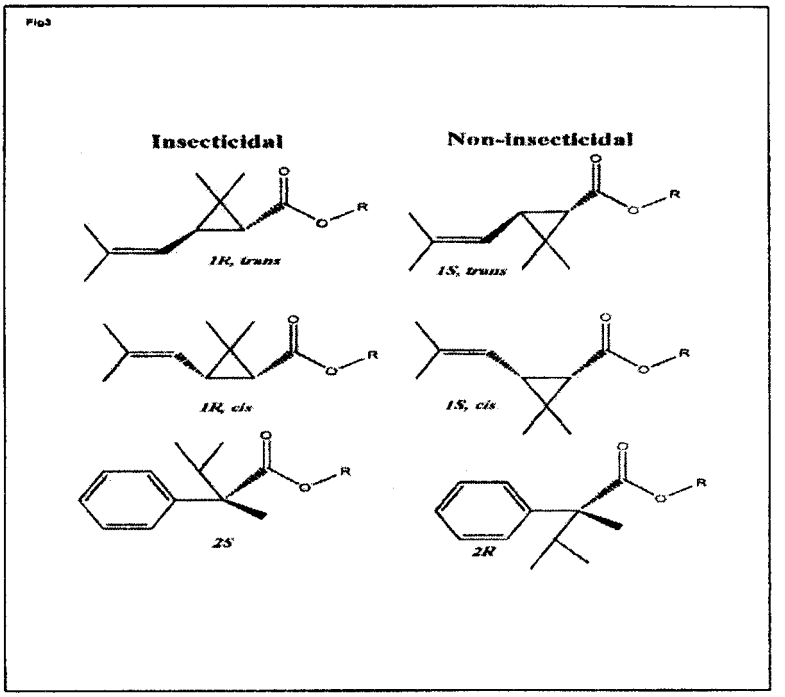
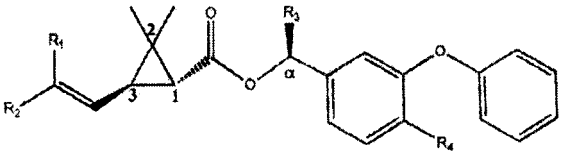
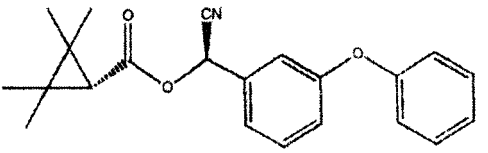

Insecticidal
Non-insecticidal
1R, trans
1S, trans
1R, cis
1S, cis
2S
2R
R
O

Fig1

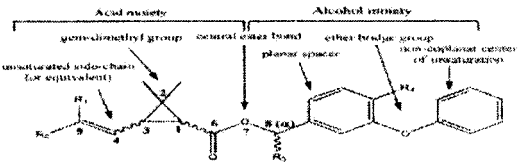


A-Phenothrin: R_1=R_2=CH_3, R_3=R_4=H (*1R,trans*)
B-Permethrin: R_1=R_2=Cl, R_3=R_4=H (*1R,trans*)
C-Cypermethrin: R_1=R_2=Cl, R_3=CN, R_4=H (*1R,trans,αS*)
D-Cyfluthrin: R_1=R_2=Cl, R_3=CN, R_4=F (*1R,trans,αS*)
E-Cyhalothrin: R_1=CF_3, R_2=Cl, R_3=CN, R_4=H (*1R,trans,αS,I:*)
F-Deltamethrin: R_1=R_2=Br, R_3=CN, R_4=H (*1R,trans,αS*)



G-Fenpropathrin: (*αS*)

Fig2



A.1	*1R,cis*	C.6	*1S,trans,αR*	E.5	*1R,cis,α S,Z*	E.14	*1S,trans,α S,E*
A.2	*1S,cis*	C.7	*1S,trans,α S*	E.6	*1R,cis,α S,Z*	E.15	*1S,trans,αS,Z*
A.3	*1S,trans*	D.1	*1R,cis,αR*	E.9	*1S,trans,α R,E*	F.1	*1R,cis,αR*
B.1	*1R,cis*	D.2	*1R,cis,αS*	E.6	*1R,trans,α S,Z*	F.2	*1R,cis,αS*
B.2	*1S,cis*	D.3	*1R,trans,αR*	E.7	*1R,trans,α S,Z*	F.3	*1R,trans,αR*
B.3	*1S,trans*	D.4	*1S,cis,αR*	E.8	*1S,cis,α R,E*	F.4	*1S,cis,αR*
C.1	*1R,cis,αR*	D.5	*1S,cis,αS*	E.9	*1S,cis,α R,E*	F.5	*1S,cis,αS*
C.2	*1R,cis,αS*	D.6	*1S,trans,αR*	E.10	*1S,cis,α S,E*	F.6	*1S,trans,αR*
C.3	*1R,trans,αR*	D.7	*1S,trans,αS*	E.11	*1S,cis,α S,Z*	F.7	*1S,trans,αS*
C.4	*1S,cis,αR*	E.1	*1R,cis,α R,E*	E.12	*1S,trans,α R,E*	G.1	*αR*
C.5	*1S,cis,αS*	E.2	*1R,cis,α R,Z*	E.13	*1S,trans,α R,Z*		

Table (2): The LD_{50} (cal) obtained from Eqs. (9)–(14) of compounds **A.1-G.1**

Comp.	LD_{50} (cal)						Average	SD
	Eq. (9)	Eq. (10)	Eq. (11)	Eq. (12)	Eq. (13)	Eq. (14)		
A.1	4897.4	4971.2	4785.5	4838.0	4705.0	4767.6	4827.4	95.9
A.2	4207.0	4292.4	4389.2	4206.5	4382.4	4324.2	4300.3	81.0
A.3	4674.9	4845.1	4612.6	4692.3	4652.9	4641.5	4686.5	82.4
B.1	2119.7	2274.7	2195.6	2085.8	2297.3	2274.8	2208.0	89.2
B.2	1828.5	1826.4	1728.9	1669.4	1826.9	1711.9	1765.3	70.6
B.3	2140.6	2134.6	2124.1	2190.4	2232.6	2172.9	2165.9	41.2
C.1	481.8	293.3	551.3	433.3	351.2	371.5	413.7	94.0
C.2	1757.1	1963.2	1986.6	1837.3	1902.3	1857.3	1884.0	85.0
C.3	1234.7	1253.3	1263.4	1210.3	1304.0	1112.1	1229.6	65.5
C.4	1195.7	1189.1	1030.8	1130.5	1061.1	1023.3	1105.1	77.5
C.5	660.0	695.1	558.2	520.3	676.6	621.6	622.0	69.5
C.6	658.4	766.4	762.9	839.8	742.1	671.2	740.1	67.2
C.7	161.9	185.0	258.0	161.0	201.4	285.4	208.8	51.8
D.1	402.6	331.9	353.7	357.6	363.4	390.6	366.6	25.8
D.2	1984.0	1845.9	1885.1	1795.5	1705.3	1837.4	1842.2	92.6
D.3	74.1	86.7	90.3	96.0	66.6	80.2	82.3	10.9
D.4	2.3	0.1	1.2	4.9	25.1	0.1	5.6	9.7
D.5	567.7	665.5	573.2	594.5	718.1	776.8	649.3	85.7
D.6	1909.3	1977.1	1966.4	1896.0	1774.4	1917.2	1906.7	72.5
D.7	1161.1	1040.1	1206.2	1045.1	1096.4	1234.1	1130.5	82.5
E.1	1526.1	1576.8	1453.9	1560.9	1403.8	1414.8	1489.4	75.2
E.2	1228.4	1353.6	1390.1	1359.7	1280.7	1276.1	1314.8	62.2
E.3	1769.8	1942.7	1793.5	1701.5	1845.3	1747.3	1800.0	84.7
E.4	1542.3	1508.9	1300.6	1478.6	1491.6	1503.2	1470.9	86.1
E.5	193.3	247.9	201.6	364.2	111.7	290.6	234.9	87.2
E.6	1595.2	1517.3	1448.8	1518.1	1670.1	1636.4	1564.3	83.7
E.7	1961.3	2019.3	1834.5	1988.4	1928.0	1867.6	1933.2	71.2
E.8	378.5	399.1	375.4	421.7	447.1	361.3	397.2	32.3
E.9	1596.3	1670.5	1664.8	1653.7	1718.7	1781.3	1680.9	62.9
E.10	579.9	527.2	647.8	575.9	617.2	595.7	590.6	40.9
E.11	2281.0	2228.3	2205.1	2175.9	2216.8	2151.1	2209.7	44.9
E.12	1386.8	1284.8	1377.8	1515.7	1274.3	1398.2	1372.9	88.0
E.13	188.1	405.2	271.7	270.4	291.1	201.0	271.2	77.7
E.14	638.1	613.5	426.9	522.1	589.3	433.4	537.2	91.5
E.15	1830.5	1952.4	1979.1	1855.3	2010.0	1835.5	1910.5	79.3
F.1	3173.8	3323.5	3362.2	3251.9	3133.3	3282.0	3254.4	87.6
F.2	2107.0	2141.1	2112.1	2024.0	2304.8	2058.1	2124.5	97.8
F.3	147.8	162.7	252.8	217.2	210.3	180.9	195.3	38.8
F.4	355.0	266.1	306.9	369.5	331.8	460.7	348.3	66.1
F.5	3413.4	3475.4	3610.1	3639.2	3506.4	3523.4	3528.0	84.3
F.6	1353.7	1411.2	1337.3	1162.8	1361.6	1217.2	1307.3	95.7
F.7	1850.3	2002.2	2084.6	1882.0	1951.4	1944.6	1952.5	84.1
G.1	382.2	408.6	393.3	316.5	410.7	427.0	389.7	39.0

Table (1): The LD_{50} (exp) and LD_{50} (cal) obtained from Linear Eqs. (3)–(8) for compounds **A–G**

Comp.	LD_{50}* (exp)	LD_{50} (cal)					
		Eq. (3)	Eq. (4)	Eq. (5)	Eq. (6)	Eq. (7)	Eq. (8)
A	4300.0	4299.999	4300.001	4300.000	4300.002	4300.002	4299.998
B	1200.0	1200.003	1199.995	1199.996	1199.989	1199.996	1200.004
C	297.0	297.002	297.002	297.011	297.022	296.975	297.007
D	155.0	155.000	154.996	154.998	154.989	155.014	155.004
E	79.0	79.002	78.998	78.997	78.997	79.000	78.993
F	95.0	94.994	95.008	94.997	95.000	95.006	95.017
G	70.6	70.600	70.599	70.600	70.601	70.607	70.576
R^2		1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
F		5.33×10^{10}	2.50×10^{10}	1.77×10^{10}	3.97×10^{9}	3.14×10^{9}	2.89×10^{9}
$\Delta LD_{50(av)}$		0.002	0.003	0.003	0.007	0.008	0.009

*Ref [18].

4. Conclusions

The acute oral toxicities to rats $LD_{50}(exp)$ of seven pyrethroid compounds were used and a QSTR have been performed using B3LYP/6-31G(d,p) results at ambient temperature.

Good correlations are shown between $LD_{50}(exp)$ and $LD_{50}(cal)$ with correlation coefficient R^2 equal to 1.0000 and the F value was found to have values higher than $1x10^9$, that gives an indication of the high correlation obtained between these variables and the experimental toxicity values for the studied pyrethroid compounds.

New quantum chemical descriptors were proposed based on calculated multipole moments of molecular structure and used to obtain the toxicity of the enantiomers and isomers of pyrethroid compounds. A new method called the SCF-QSTR method was proposed to predict the toxicity of isomers and enantiomers with good results. The equations used in this method include twelve variables, seven of which were the newly proposed multipole moment indices.

The *1S,cis* isomer of phenothrin or permethrin has a significant insecticidal activity relative to the main active structure (*1R,trans*). In case of racemic cypermethrin isomers, it was found that the *1R,cis,R*, *1S,cis,S* and *1S,trans,S* isomers have high insecticidal activity which contradicted with the data shown by Gray and Soderland. This high insecticidal activity can be attributed to the isomeric structure of pyrethroid compounds which depends only on the configuration of the overall isomers of the compound. For cyfluthrin, the data show that the main active isomer is D.4 isomer not D.1 (1*R*,trans,*S*) isomer (calculated LD_{50} for D.4=5.6 mg/kg). It was found that the presence of F atom in position R4 (Fig 3) increases the insecticidal activity of cyfluthrin compared to cypermethrin and this explains the higher effect of the overall configuration (*1S,cis,R*) not of (*1R,cis,trans,S*) configuration. Fenpropathrin shows only one isomer with low insecticidal activity as expected from the *R* configuration of the cyano substituent.

permethrin, the experimental LD_{50}= 1200 mg/kg, while for *1R,cis* and *1S,trans* isomers, the average calculated LD_{50} were found to be 2208.0 and 2165.9 mg/kg which is the least active isomers, also the calculations show that the isomer *1S,cis* are relatively insecticidal more than the two other isomers with average calculated LD_{50}=1765.3. These findings conclude that the *1S,cis* isomer of phenothrin or permethrin has a significant insecticidal activity relative to the main active structure (*1R,trans*).

For the racemic cypermethrin isomers, it was found that isomers C.1 (*1R,cis,R*), C.5 (*1S,cis,S*) and C.7 (*1S,trans,S*) have low calculated LD_{50} i.e. high insecticidal activity which contradicted with the data shown by Gray and Soderland[28] who reported that the four inactive isomers of cypermethrin are α-cyano substituent in *R* configuration. This indicates that the insecticidal activity of the isomeric pyrathroid compounds depends not only on configuration of one substituent but also on the configuration of the overall isomer, and this explains, as described before, the difficulty to measure accurately the insecticidal activity of the isomeric mixtures of four or eight optical and geometrical isomers of a pyrethroid compound containing only one or two active isomers[29]. In case of cyfluthrin, the calculation shows that the D.1 (*1R,cis,R*), D.3 (*1R,trans,R*) and D.4 (*1S,cis,R*) have high insecticidal activity and the main active isomer is D.4 isomer not D.1 (1*R*,trans,*S*) isomer (calculated LD_{50} for D.4=5.6 mg/kg), and this explained by the presence of F atom which increases the insecticidal activity of the cyfluthrin over the cypermethren and gives the higher effect of the overall configuration (*1S,cis,R*).

For cyhalothrin, the isomers E.5 (*1R,trans,R,E*) E.13 (*1S,trans,R,Z*) with calculated LD_{50} =234.9 and 271.2 mg/kg respectively are more active than the other isomers. Also, Table 2 revealed that the insecticidal activity of the isomer F.3 (*1R,trans,R*) still high (the average LD_{50} calculated) compared to the other isomers. Fenpropathrin shows only one isomer that has calculated LD_{50}= 389.7 mg/kg with low insecticidal activity as expected from *R* configuration of the cyano substituent.

The structure and three-dimensional configuration of pyrethroids are critical determinants of both insecticidal activity and acute toxicity to rats and mammals. In particular, pyrethroid action is highly stereospecific: typically, mixtures of four or eight optical and geometrical isomers of a pyrethroid contain only one or two active isomers, and the remaining isomers have very low toxicities so that they are difficult to be measured accurately[25]. So all the pyrethroid pesticides act as a racemic mixture.

Also, the neurotoxicity of pyrethroids depends on the stereochemical configuration at cyclopropane C1 or the homologous position in compounds lacking the cyclopropanecarboxylate moiety (Fig.3). Only esters of *1R* cyclopropanecarboxylates and isosteric 2*S* isomers of non-cyclopropane acids are neurotoxic, whereas the corresponding 1*S* cyclopropanecarboxylates and their sterically equivalent 2*R* acyclic analogs are without measurable toxicity even when administered at high doses[26]. This relationship parallels the stereospecificity of insecticidal action of pyrethroid compounds. Moreover, the presence of an α-cyano substituent in *S* configuration in the 3-phenoxybenzyl alcohol moiety also greatly enhances the acute neurotoxicity of cypermethrin, cyfluthrin, cyhalothrin, deltamethrin and fenpropathrin. The α-cyano substituent also indirectly alters structure–toxicity relationships in the acid moiety. The most dramatic effects were seen with the 1*R*,*trans* cyclopropanecarboxylates of 3-phenoxybenzyl alcohol (e.g.[1*R*,*trans*]-permethrin), which exhibit extremely low toxicity to mammals; addition of an α-cyano substituent in the *S* configuration to these esters produces compounds (e.g.[1*R*,*trans*,α*S*]-cypermethrin, Table 1) with significant neurotoxicity to rodents. Both the 1*R*, *trans*, α*RS* and 1*R*, *cis*, α*RS* isomers of cypermethrin were identified as producing the neurotoxicity to rats and mice[27].

Table (2) revealed that the least insecticidal active isomers for phenothrin were *1R,cis* and *1S,trans* isomers (the average calculated LD_{50} are 4827.4 and 4686.5 mg/kg, respectively), while the *1S,cis* isomer shows insecticidal activity similar to the main active isomer (*1R,trans*) which contradicted with the above discussion (Fig 3). For

$$LD_{50}(cal) = -1176.1^{1}X_{mod} + 621.3f_{H/L} + 1218.9D - 11.6^{0}E^{T} + 15229.9^{1}X_{MDen} - 375.4QM + 68586.7TQM - 12.1QM + 6.8HM - 45499.8QM2 - 42.6QM2 - 10.9HM2 - 1569.5 \quad (9)$$

$$LD_{50}(cal) = 561.9f_{H/L} - 1057.7^{1}X_{Den} - 45449.1P + 76.9^{C}T^{E} + 10591.6^{1}X_{MDen} - 309.7QM + 63598.5TQM - 8.5QM + 5.9HM - 42214.7QM2 - 47.3QM2 - 9.2HM2 + 1918.7 \quad (10)$$

$$LD_{50}(cal) = -53655.1^{1}X_{MV} - 1547.6^{1}X_{EN} + 46869.9^{1}X_{MDen} + 179.6^{0}E^{T} - 27.2^{1}E^{T} - 203.9QM + 89866.0TQM - 8.2QM + 1.2HM - 59776.4QM2 - 41.3QM2 - 2.3HM2 - 24253.0 \quad (11)$$

$$LD_{50}(cal) = -4597.9^{1}X_{V} + 40651.9^{1}X_{HDEC} - 37633.2^{1}X_{DDEC} - 7939.7Q^{-} - 10546.7^{1}X_{MDen} - 123.6QM + 35507.1TQM - 31.1QM + 1.0HM - 23600.8QM2 - 14.0QM2 - 3.6HM2 - 6202.6 \quad (12)$$

$$LD_{50}(cal) = -24039.8^{1}X_{MV} - 1844.4ECI + 518.5f_{H/L} + 314.2Q^{+}_{max} + 26542.1^{1}X_{MDen} - 186.0QM + 96364.3TQM - 1.9QM + 4.7HM - 64124.6QM2 - 54.8QM2 - 8.0HM2 - 12566.1 \quad (13)$$

$$LD_{50}(cal) = 12232.2^{1}X^{r} + 512.4f_{H/L} + 6654.9^{1}X_{DDEC} - 25.1^{0}E^{T} - 13319.7^{1}X_{MDen} - 164.2QM + 114606.8TQM + 17.2QM + 2.1HM - 76285.0QM2 - 73.9QM2 - 5.3HM2 - 30712.2 \quad (14)$$

Very good correlations are obtained between $LD_{50}(exp)$ and $LD_{50}(cal)$indicated from the very low values of the standard deviation of the coefficients in equations 9-14, their values are smaller than 10^{-4} so it is not described in equations.

Fig (3) identifies the principle elements of the pyrethroids structure-activity relationship and illustrated these elements with four structurally divergent pyrethroid insecticides. As a result, there is no specific substructure, reactive entity, or molecular moiety that can be identified as the toxophore conferring pyrethroid like insecticidal activity. The stringent stereospecifity of the insecticidal activity of pyrethroid comes from the presence of two chiral centers at C1 and C3 of the acid moeity that produces two pairs of *trans* and *cis* isomers based on the orientation of C1 and C3 substituents in relation to the plane of the cyclopropane ring. Elliott et al[24] showed that the acid moiety of natural pyrethrins are exclusively in *1R,trans* configuration when esters were prepared from the four resolved chrysanthemic acid isomers, those with the *R* configuration at C1 possess insecticidal activity whereas the enantiomeric *1S* compounds were insecticidal inactive.

$$LD_{50}(cal) = 6273.264 \pm 0.498\,{}^{1}X^{T} + 490.313 \pm 0.009 f_{HIL} - 3312.667 \pm 0.416\,{}^{1}X_{DOC} + 11.321 \pm 0.001\,{}^{0}E^{T} - 22.309 \pm 0.004 QM2 - 21968.882 \pm 0.770 \quad (8)$$

The point which noted in these equations is that the standard deviation of the coefficients is very small indicating the very good correlations obtained between experimental and calculated LD_{50} for the pyrethroid.

The isomers of the pyrethroid compounds are shown in Fig 2. Using these equations to detect the $LD_{50}(cal)$ for these 43 isomers and enantiomers, it is noted that this method has two draw backs; first, the equation reflects the same toxicity for the two enantiomers if the equation has no any multipole moment variables e.g. Eq. (5), second, the obtained values from the six's equations have a large standard deviation between the average values and the calculated values for all compounds, it is found that the standard deviation range from 102.9 to 4134.3, so it can be concluded that this method while it has very high correlation it is not suitable for predicting the toxicity of the isomers and enantiomers.

To get the toxicity of isomers and enantiomers with good results, another method are newly suggested in this work, it is called the SCF-QSTR method, using this method and using an equations including twelve variables, those are the 5 variables of equations 3-8 and the new proposed 7 multipole moment variables. In case of equations including one of the multipole moments the ${}^{1}X_{MDen}$ index is used to complete the 12 variables equations. Running the SCF procedure using the 6 equations 9-14, the SCF obtained before maximum iteration reached with ΔLD_{50av} is smaller than 1×10^{-3}, R^2 value equal to 1.0000 and F value is larger than 1×10^{16}. The $LD_{50}(cal)$ for the 43 compounds obtained at the final iteration of these equations are collected in Table 2. According to the values obtained it is noted that the standard deviation between the average values and the calculated values for all compounds is small, it is found that the standard deviation range from ±0.0 to ±97.8, so it is can be concluded that this method is suitable for predicting the toxicity of the isomers and enantiomers.

A regression analysis was performed for each available combination for two, three and four variables of used indices, as a statistical fact, increasing the number of variables will give higher correlations with R^2 above 0.9 and reaches to unity. In this work, to reach the most suitable equations which reflect good results of toxicity for the studied compounds, the correlations of five variables are used.

The six linear equations with the highest F value, and the lowest ΔLD_{50av} are considered. Linear equations were obtained by the indices ${}^{1}X_{mod}, f_{H/L}, D, {}^{0}E^{T}, OM2$, for Eq. (3); $f_{H/L}, {}^{1}X_{Den}, P, {}^{C}T^{E}, QM$ for Eq. (4); ${}^{1}X_{MV}, {}^{1}X_{EN}, {}^{1}X_{MDen}, {}^{0}E^{T}, {}^{1}E^{T}$ for Eq. (5); ${}^{1}X_{V}, {}^{1}X_{HCEC}, {}^{1}X_{DCEC}, Q^{-}, OM$ for Eq. (6); ${}^{1}X_{MV}, ECI, f_{H/L}, Q^{+}_{\max}, OM$ for Eq. (7) and ${}^{1}X^{*}, f_{H/L}, {}^{1}X_{DCEC}, {}^{0}E^{T}, QM2$ for Eq. (8). $LD_{50}(cal)$ from Eqs. (3)–(8) for compounds **1**–**7**are tabulated in Table 1. Good correlations are shown between $LD_{50}(exp)$ and $LD_{50}(cal)$with correlation coefficient R^2 equal to 1.0000. The F value was found to have the higher value in case of Eq. (3) and subsequently the lower value of the LD_{50av}. According to values described in Table 1, in which the F values are higher than $1x10^9$, that gives an indication of the high correlation obtained between these variables and the experimental toxicity values for the pyrethroid.

$$LD_{50}(cal) = 67.135 \pm 0.001\,{}^{1}X_{mod} + 567.588 \pm 0.002 f_{H/L} + 13026.653 \pm 0.143 D + 84.395 \pm 0.001\,{}^{0}E^{T} + 142.097 \pm 0.002 OM2 - 27763.489 \pm 0.183 \quad (3)$$

$$LD_{50}(cal) = 513.417 \pm 0.003 f_{H/L} + 253.085 \pm 0.017\,{}^{1}X_{Den} - 79145.700 \pm 3.631 P + 535.523 \pm 0.011\,{}^{C}T^{E} + 23.530 \pm 0.010 QM - 5289.217 \pm 0.390 \quad (4)$$

$$LD_{50}(cal) = -28411.159 \pm 0.696\,{}^{1}X_{MV} + 2926.176 \pm 0.173\,{}^{1}X_{EN} + 21865.044 \pm 0.530\,{}^{1}X_{MDen} + 194.781 \pm 0.001\,{}^{0}E^{T} - 28.193 \pm 0.001\,{}^{1}E^{T} - 3961.979 \pm 0.145 \quad (5)$$

$$LD_{50}(cal) = -4610.910 \pm 0.143\,{}^{1}X_{V} + 40620.735 \pm 0.720\,{}^{1}X_{HCEC} - 47515.798 \pm 0.835\,{}^{1}X_{DCEC} - 7362.572 \pm 0.101 Q^{-} - 84.263 \pm 0.007 OM - 6425.810 \pm 0.720 \quad (6)$$

$$LD_{50}(cal) = 9594.656 \pm 0.433\,{}^{1}X_{MV} - 2323.232 \pm 0.157 ECI + 610.183 \pm 0.007 f_{H/L} - 2481.257 \pm 0.220 Q^{+}_{\max} + 4.963 \pm 0.005 OM - 17689.529 \pm 0.395 \quad (7)$$

and finally tabulating them in an Excel sheet for subsequent regression analysis[22].

Correlation analysis of LD_{50} values with each index of the topological indices W, $H, \sqrt[3]{G_1^{Top}}, {}^1X_{\text{mod}}, {}^1X_V, {}^1X_{MV}, {}^1X^r, {}^1X_{EN}$, ${}^1X_{HCEA}$, and ECI gives poor correlations. All topological indices give very poor correlations with correlation coefficient (R^2) values (ranging from 0.046 to 0.241) except the Harary Index (H) and the cubic root of the topological gravitational index ($\sqrt[3]{G_1^{Top}}$) give correlations with correlation coefficient (R^2) values 0.320 and 0.323, respectively. All correlations are with negative slope, which indicates the enhancement of the toxicity of pyrethroid by increasing the values of these indices in molecule.

By correlating LD_{50} with the quantum-chemical indices, almost, all indices give very poor correlations with correlation coefficient (R^2) values (ranging from 0.000 to 0.282) except the cubic root of the geometrical gravitational index ($\sqrt[3]{G_1^{Geom}}$) and the octapole moment index OM give correlations with correlation coefficient (R^2) values 0.332 and 0.448, respectively. While the dipole moment index DM and HOMO/LUMO energy fraction ($f_{H/L}$) give good correlations with correlation coefficient (R^2) values 0.665 and 0.863, respectively.

Linear regression analysis was used to correlate the topological indices, quantum chemical indices with the experimental toxicity ($LD_{50}(exp)$). The linear model approximates toxicity, ($LD_{50}(cal)$), shown in the Eq. (2):

$$LD_{50}(cal) = Ax_j + B \qquad (2)$$

where A and B are constants obtained by regression analysis, x_j is the topological or quantum chemical index characteristic for the molecule j[23]. Such linear approach was found to be satisfactory for correlating the results obtained for compounds **1–7** using B3LYP/6-31G(d,p) optimized geometrical calculations. The standard deviations were calculated between the average $LD_{50}(cal)$ obtained by using different equations and the $LD_{50}(exp)$.

moment (*TQM*), the mean of octapole moment (*OM*), the mean of hexadecapole moment (*HM*),and 2nd the mean of the diagonal-less matrix of the multipole moments, namely *QM2*, *OM2* and *HM2*.

The average magnitude of deviation (ΔLD_{50av}) is used as a simple indicator of goodness of fit between calculated and observed toxicity: Thus

$$\Delta LD_{50}=LD_{50}(cal)-LD_{50}(exp), \text{ and } \Delta LD_{50av}=\frac{1}{n}\sum_{i=1}^{n}|\Delta LD_{50}(i)| \qquad (1)$$

Also, in this work the *F*-value and the multiple correlation coefficient R^2 are used as indicators of goodness of fit. As expected the large value of *F* corresponds to relatively small values of ΔLD_{50av} and values of R^2 approaches unity.

The new model proposed is the SCF-QSTR method (self-consistent field), depends on the QSTR method in which at the beginning the unknown values are approximated, and the QSTR calculations are done getting new values, then these values are recalculated until the self-consistent field obtained meaning that the calculated values of two successive calculations are different by very small values. In these work the unknown values are approximated at zero values in the 1st trial and the SCF reached when ΔLD_{50av} are smaller than or equal to$1x10^{-5}$ and R^2 value above than or equal to 0.9999, with maximum iteration value reaches to 2000 iteration.

3. Results and discussion

The acute oral toxicities to rats $LD_{50}(exp)$ of seven pyrethroid compounds, Fig. (1), namely, Phenothrin (A), permethrin (B), Cypermethrin (C), Cyfluthrin (D), Cyhalothrin(E), Deltamethrin (F) and Fenpropathrin (G) were used[21] and a quantitative structure toxicity relationships (QSTR) have been performed using B3LYP/6-31G(d,p) results at ambient temperature. Supplementary Tables 1-6 represent the results of all described indices. These indices were calculated using a software written using the Visual Basic of Application within the Microsoft Excel, which operates by reading the outputs of the Gaussian calculations, calculating all described indices,

and the heteroatom corrected extended connectivity Randic index ($^1X_{HCEC}$) are also used.

The quantum-chemical indices which are obtained by using the optimum geometry of the molecules under investigation can be described as follows. The cubic root of the Wiener-3DH Index ($\sqrt[3]{W_H^{3D}}$),The cubic root of the geometrical gravitational index ($\sqrt[3]{G_1^{Geom}}$), The HOMO/LUMO energy fraction ($f_{H/L}$)[19].

The charge indices or the electronic indices defined in terms of atomic charges are obtained from quantum chemical calculations. The natural population atomic charges (NPA) are used to describe electronic aspects of the whole molecule and of particular regions, such as atoms, bonds, and molecular fragments. They can be described as the maximum positive charge (Q^+_{max}), total negative charge (Q^-), charge polarization (P), topological electronic indices (T^E, $^CT^E$), local dipole index (D), corrected electron charge density connectivity index ($\bar{\Omega}$), and electronic-topological indices ($^0E^T$, $^1E^T$). Another two quantum chemical electronic indices were supposed[20] based on the Randic index while using the quantum chemical calculated charge density matrix, which are the density Randic index ($^1X_{Den}$) and the modified density Randic index ($^1X_{MDen}$). Another index of these types is newly supposed in this work which is the density corrected extended connectivity Randic index ($^1X_{DCEC}$).

These indices show high sensitivity to geometric isomers, conformations and heteroatoms. However these indices are identical for the enantiomers, so to predict the toxicity of enantiomers we must define other indices. The enantiomers are deferent only on the multipole moment components signs, e.g. the sign of calculated quadrupole moment xy component, while the magnitude of the calculated multipole moments are similar, so the new indices defined here can be summarized as two groups, 1st the mean values of all multipole moments calculated at defined level of theory, namely the mean of quadrupole moment (QM), the mean of traceless quadrupole

subsequent quantitative structure activity relationship (QSAR) has been found, the design of compounds, including those not yet synthesized, can be targeted. For toxic compounds, the effect is found to depend mainly on some physicochemical and electronic properties, which relate to its functional groups, steric effects, electronic density of donor atoms, and orbital character of donating electrons[12].

The task of this work is assessing and predicting the toxicity of the studied pyrethroid pesticides by modeling a relationship between toxicity endpoints and expected measurable characteristics of the toxic pyrethroids molecules done by performing detailed calculations of the molecular structure of these molecules and a number of quantum molecular properties and topological descriptors. The Experimental LD_{50} as acute oral toxicities of pyrethroids to rats were used[13]. Considering that the increasing use of this category of organic pesticides. Development of QSTR models to fill in data gap for environmental toxicology and risk assessment is necessary and useful. These relations were used to determine the toxicities of pyrethroids isomeric compounds with theoretically improved LD_{50} by determining the most suitable indices that describe the behavior of the isomeric compounds acting to LD_{50}.

2. Method of Calculations

All computational studies were performed at the DFT-B3LYP[14]/6-31G(d,p)[15] level of theory using the Gaussian 03 package, 2003[16]. All quantum chemical calculations were performed in gas phase without geometrical constraints to full geometrical optimizations.

The calculated topological indices used are the Wiener index (W), the Harary index (H), the cubic root of the topological gravitational index ($\sqrt[3]{G_i^{Top}}$), and some Randic connectivity indices such as the modified Randic index ($^1X_{\text{mod}}$), the valence Randic index (^1X_V) as well as the modified valence Randic index ($^1X_{MV}$),the Kupchik modified connectivity index ($^1X^r$) in addition edge connectivity index(ECI) are used[17]. The two newly supposed[18] types of Randic indices, that are the electronegative Randic index ($^1X_{EN}$)

there are two crucially important centers of asymmetry (Fig. 1), that can modify insecticidal activity, viz. C1 of the cyclopropane ring (only the (*R*) configuration is active) and the-carbon (C8) of the alcohol moiety (only the (*S*) configuration is active in Type II compounds that subtend a cyano-substitutent at this atom). A third asymmetric center can also modify insecticidal activity slightly, viz. the C3 of the cyclopropane ring for which the (*R*) and (*S*) configurations (*cis*- and *trans*-, respectively) show small changes in activity, usually differing by a factor<2.These stereochemical requirements are strongly suggestive that the compounds act at a chiral receptor, or at least need to be able to adopt a defined shape. In addition the large range of biological activities (five orders of magnitude) within similar series suggests that molecular properties are also of crucial significance. Since some of these are likely to be highly dependent on stereochemistry, the conformational behavior of these compounds is extremely important. Given that the structural, conformational and physicochemical properties of these compounds are likely to affect their biological activities[9].

Available structure–toxicity data show that acute toxicity of pyrethroids to mammals depends on the shape and three-dimensional configuration of the entire molecule. The absence of any single structural feature or reactive moiety that is required to produce pyrethroid-like toxicity implies that there is no common toxophore that mediates the acute toxicity of pyrethroids to mammals. As an example Zeta-cypermethrin, the *1RS,cis,trans,αS* isomer of cypermethrin, contains four of the eight isomers present in fully racemic cypermethrin including both of the isomers (e.g. the *1R,trans,αS* and*1R,cis,αS* isomers) expected to exhibit high mammalian toxicity[10]. The ecotoxicological end-points selected to model the toxicity of pyrethroids were LD_{50} (lethal dose to 50% of the organisms in mg/kg) of rats[11].

Quantum chemical characterization methods have already proven useful in determining molecular structure as well as in elucidating electronic structure and reactivity. Assessing toxicity with the aid of computational chemistry has attracted attention. Once the

insecticides, pet sprays and shampoos. Some pyrethroids also are used as lice treatments applied directly to the head and as mosquito repellents that can be applied to clothes.

Pyrethroids are eventually broken down in the soil. They are not easily taken up by the roots of plants because they bind to the soil[3]. Because of this, pyrethroids usually do not get into ground water and do not contaminate drinking water supplies[4]. Pyrethroids do not cause cancer in people, their mode of action is interference with transmission of nerve impulses, they are axonic poisons and cause paralysis of an organism[5]. Even though pyrethroids are nerve poisons, they are not chlorinastrase inhibitors like organophosphorous and carbamate pesticides and they are one of the least acutely toxic insecticides to mammals because they are quickly deactivated by metabolic processes[6]. Symptoms are more common with exposure to the pyrethroids whose structures include cyano-groups. Pyrethroids are highly toxic to fish and tadpoles, they affect their skin touch receptors and balance organs[7].

The account of the elucidation of the chemical composition of pyrethrin is complex. O' Brin showed that pyrethrin contains esters of two alcohols which called L_1 and L_2, with two different acids which called C_1 and C_2. So there are four esters L_1C_1, L_1C_2, L_2C_1 and L_2C_2. The two acids are quite similar to each other, both containing a triangular ring (cyclopropane). One acid contains a free carboxyl group, and the other has one free and one esterified carboxyl group. Also the two alcohols are similar to each other, both contain a five-membered ring to which is attached ketone oxygen as well as the alcoholic OH, so that their chemical names contain"-one" as well as "-OL-". Because all four esters are *cis* and *trans* esters we can call them pyrethric acid and pyrethrolone, respectively. The esters containing pyrethrolones are called pyrethrin I if the acid is chrysanthemic acid and pyrethrin II if the acid is pyrethric acid[8]. These acids are lipophilic and rapidly penetrate many insects and paralyze their nervous system.

Although the standard classification of pyrethroids ignores the isomer situation, the chemical structure of pyrethroids indicates that

ASSESSMENT AND PREDICTION OF TOXICITY OF SOME PYRETHROID PESTICIDES BY QSTR METHOD USING TOPOLOGICAL DESCRIPTORS, NEW QUANTUM CHEMICAL DESCRIPTORS AND NEW SCF-QSTR METHOD.

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In this work a new quantum chemical indices were proposed based on multipol moments of the insecticide molecule structure. Based on these indices a new SCF-QSTR multiple linear regression model was developed to predict the toxicity of enantiomers and isomers of pyrethroid insecticides. The toxicity of 50 pyrethriod isomer, which are based on Phenothrin (A), Permethrin (B), Cypermethrin (C), Cyfluthrin (D), Cyhalothrin (E), Deltamethrin (F) and Fenpropathrin (G) were calculated by the model. The regression coefficient R^2 was found to be 1.0000, the ΔLD_{50av} is smaller than$1x10^{-3}$ and the F value was found to have values higher than $1x10^{16}$. It is found that the LD_{50} of the studied pyrethroids are mainly depending on the overall structure and not only on the S or R configuration.

1 - Introduction

The plant extract of East African chrysanthemum flowers known as pyrethrum contains pyrethrin I and pyrethrin II collectively, called pyrethrins(1). Pyrethrins are widely used for control of various insect-pests. Pyrethroids, the ester of chrysanthate or pyrethrate, are a group of man-made pesticides similar to the natural pesticide pyrethrum. There are two types of pyrethroid compounds that differ in their chemical structures and symptoms of exposure. Type I pyrethroids include allethrin, tetramethrin, resmethrin, d-phenothrin, bioresmethrin, and permethrin. Some examples of type II pyrethroids are cypermethrin, cyfluthrin, deltamethrin, cyphenothrin, fenvalerate, α-fenvalerate and fluvalinate(2). Pyrethroids are found in many commercial products used to control insects, including household

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