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Journal of Chemical and Pharmaceutical Research, 2012, 4(12):5076-5080

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

A theoretical investigation of cytotoxic activity of halogenated monoterpenoids from plocamium cartilagineum

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ABSTRACT

The molecular geometry of nine halogenated monoterpenoids from the red alga plocamium cartilagineum in the ground state has been calculated by B3LYP/6-31G. Furoplocamioid C (1), pre furoplocamioid (2), pirene (3) and compound 5 had selective effect against cancer cells versus CHO cells. The gap energy of compounds 1, 2, 3, and 5 ranges from 5.6 to 6.1 and is lower than that of the compounds 4, 6, 7 and 8.Thus the gap energy plays an important role towards selective activity. The stereochemical features of the compounds also play an important role to activity.*

Key words: Cytotoxicity, Density functional theory, Halogenated monoterpenoids

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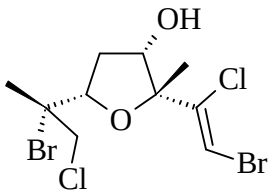
INTRODUCTION

Marin algae reported to have wide applications, such as antibacterial, antiviral, insecticidal and antitumor activities [1-3]. Nine halogenated monoterpenoids furoplocamioid C (1), pre furoplocamioid (2), pirene (3), and the cyclohexanes (4-9), including mertensene (7) and violacene (8), (Figure 1) were isolated from the red alga plocamium cartilagineum have shown notable cytotoxic activity [4]. The cytotoxic effects of these compounds have been evaluated on the tumor cell lines CT26 (murin colon adenocarcinoma), SW480 (human colon adenocarcinoma), HeLa (human cervical adenocarcinoma) and SkMel28 (human malignant melanoma) with several multidrug resistance mechanism against the mammalian non tumor cell line CHO (Chinese hamster ovary cells) [5].In this work, we have provided an explanation of the cytotoxic activity of the studied molecules using electronic properties such as the highest occupied molecular orbital (HOMO) energies, lowest unoccupied molecular orbital (LUMO) energies, LUMO-HOMO energy gap, dipole moment and stereo chemical structure.



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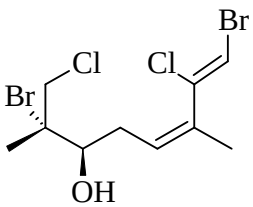

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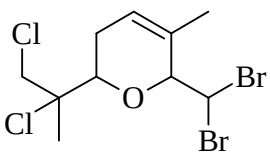

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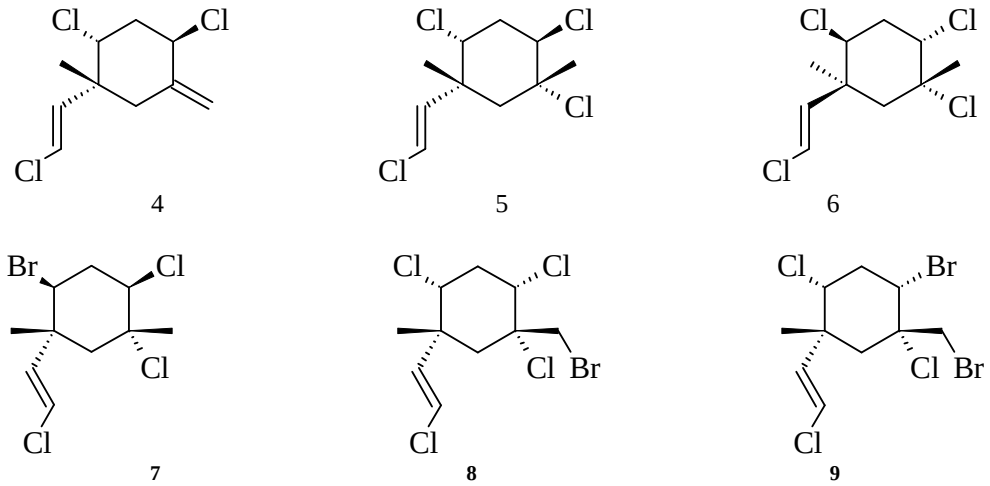


Figure 1: Chemical structures of furoplocamioid C (1), prefuroplocamioid (2), pirene (3), cyclohexanes (4-9), including mertensene (7), and violacene (8).

EXPERIMENTAL SECTION

The structures of the molecules (Fig. 1) under investigation were constructed using ACD/ChemSketch, version 12.01 [6]. All quantum chemical calculations were performed with the PC Gamess (Firefly) [7]. As Density functional theory (DFT) is a cost-effective general procedure for studying physical properties of the molecules [8, 9], the ground-state geometries and electronic properties of the studied molecules have been determined by DFT/B3LYP calculation and the basis set 6-31G* was used.

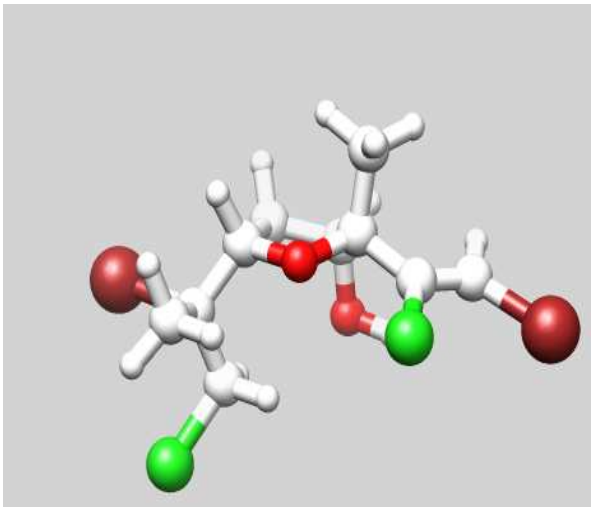
RESULTS AND DISCUSSION

The minimal inhibitory concentration (MIC) of the studied compounds which produce a cytotoxic effect on the different cell lines along with their molecular electronic properties are summarized in table 1 and their optimized geometry structures are illustrated in Figure 2.

Table 1: Minimal inhibitory concentration (MIC) and selected molecular electronic properties of the studied compounds

Number	$MIC_{(CHO)}$ µM	$MIC_{(CT26)}$ µM	$MIC_{(SW480)}$ µM	$E_{(HOMO)}$ eV	$E_{(LUMO)}$ eV	ΔE_{gap} eV	Dipole (D)	Total energies (hartree)
1	126	63	126	-7.0668	-0.9415	6.1253	4.89	-6603.7885
2	132	66	66	-6.479	-0.8626	5.6164	3.99	-6528.5601
3	262	262	131	-6.9307	-0.9225	6.0082	4.94	-6528.583
4	3.3	6.52	3.3	-6.9389	-0.283	6.6559	2.19	-1769.4516
5	23	181	5.7	-6.7321	-0.6585	6.0736	2.98	-2230.2748
6	362	362	362	-7.0341	-0.2503	6.7838	0.8	-2230.2751
7	39	78	78	-7.1158	-0.7293	6.3865	1.54	-4341.8244
8	141	141	141	-6.9961	-0.6694	6.3267	4.95	-4801.4049
9	63	125	125	-6.9743	-0.8735	6.1008	4.83	-6912.9557

Compounds 1, 2, 3 and 5 had selective activity against cancer cells versus CHO cells. Compounds 1 and 3 exhibited selective cytotoxicity to CT26 and SW480 cell lines respectively, with MIC values of 63 µM and 131 µM. Compound 2 produced a selective cytotoxic effect on CT26 and SW480 cells with MIC value of 66 µM. Interestingly, compound 5 was the most active and exhibited cytotoxicity against SW480 cell lines with MIC value of 5.70 µM [5].



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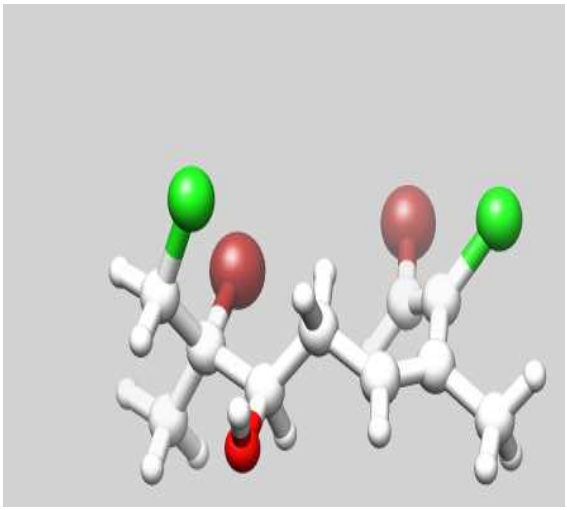

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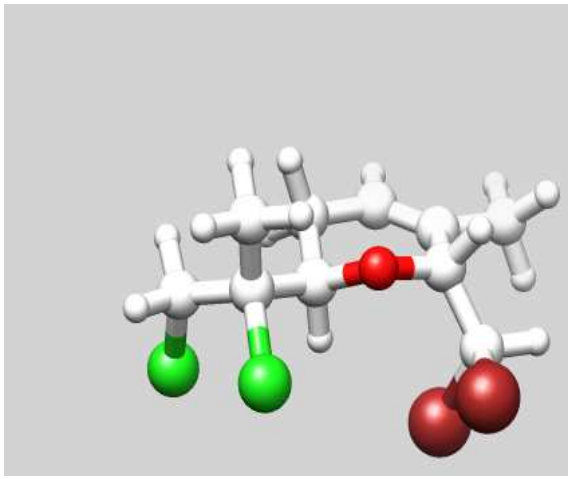

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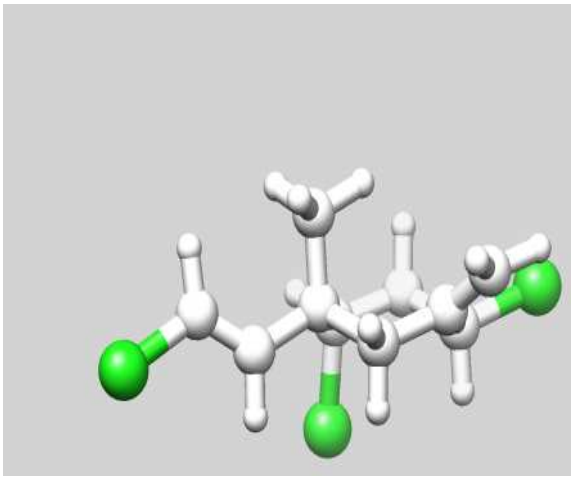

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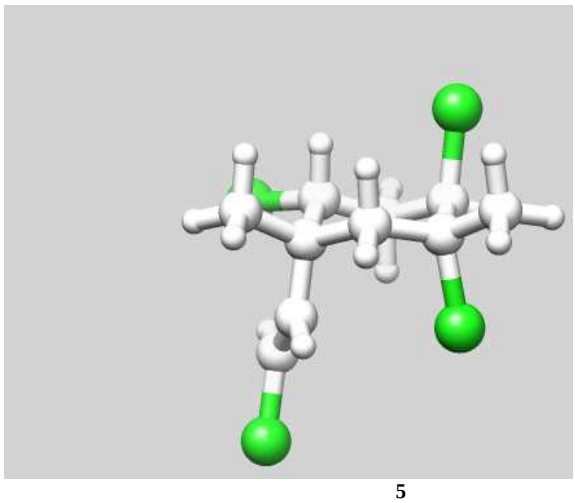

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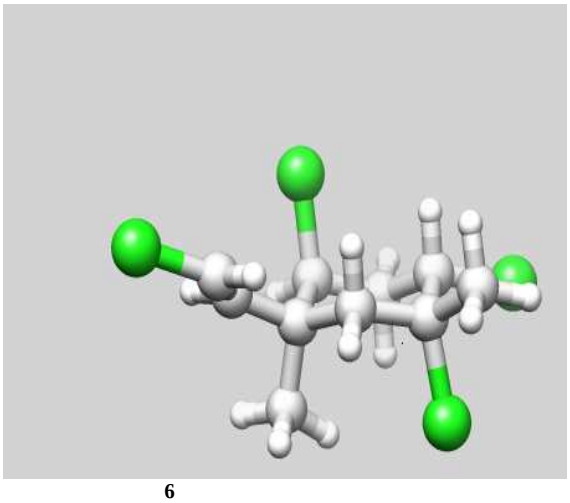

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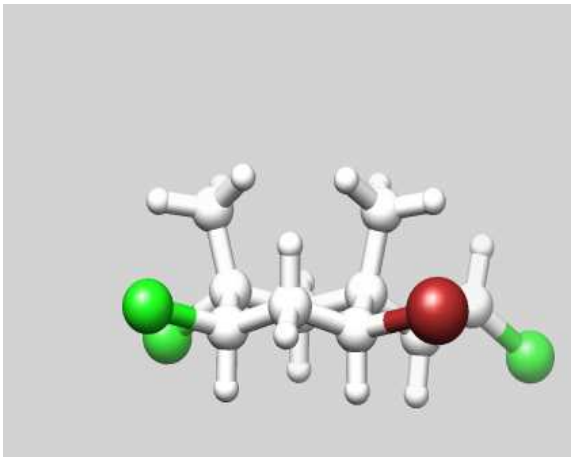

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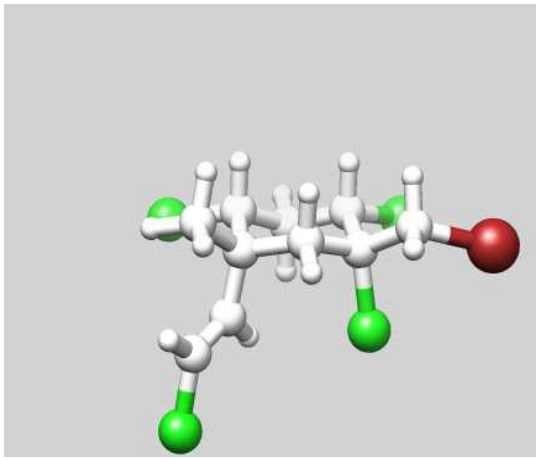

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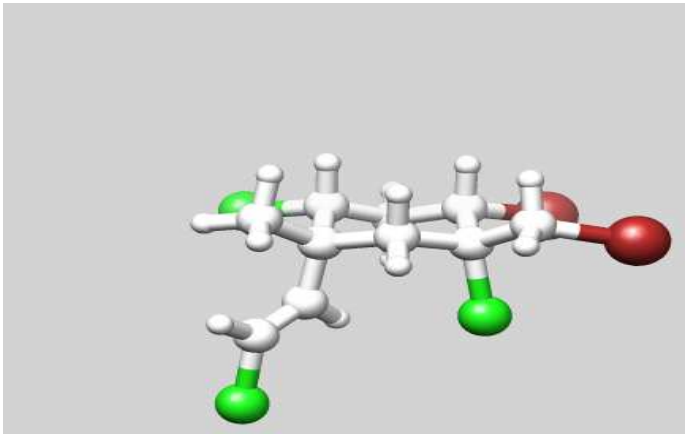

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Figure 2: Optimized structures of studied molecules obtained by B3LYP/6-31G* level.

The energies of HOMO and LUMO of the inhibitor molecule are important. A high energy HOMO means weakly held electrons while a low energy LUMO indicates a more stable orbital for electrons. A molecule with a high HOMO may act as a donor while with a low LUMO may act as an acceptor. The ΔE_{gap} provides a measure for the stability of the formed complex on the metal surface. Thus the complex stability increases with decreasing the value of ΔEgap. Compounds 1, 2, 3, and 5 have lower value of ΔE_{gap} (ranges from 5.6 to 6.1) compared to the compounds 4, 6, 7 and 8. A cross correlation matrix (Table 2) between electronic descriptors and the MIC (SW480) values demonstrates ΔE_{gap} is positively correlated with $MIC_{(SW480)}$. But $E_{(HOMO)}$, $E_{(LUMO)}$, and dipole moment are weakly correlated with $MIC_{(SW480)}$. Thus the stereo chemical features of these compounds also play an important role towards activity.

Table 2: Correlation matrix of $MIC_{(SW480)}$ and the electronic descriptors for the studied compounds

	$MIC_{(SW480)}$	$E_{(HOMO)}$	$E_{(LUMO)}$	ΔE_{gap}	dipole(D)
$MIC_{(SW480)}$	1.000	-0.389	0.279	0.423	-0.235
$E_{(HOMO)}$	-0.389	1.000	-0.176	-0.689	0.168
$E_{(LUMO)}$	0.279	-0.176	1.000	0.835	-0.779
ΔE_{gap}	0.423	-0.689	0.835	1.000	-0.668
dipole(D)	-0.235	0.168	-0.779	-0.668	1.000

Compound 6 is a diastereomer of 5 though the cytotoxicity of 6 is lower than 5. This is due to high gap energy (6.78 eV) and low dipole moment (0.80 D) of the molecule. In compound 6, the resultant bond moment of the –Cl and -CH=CHCl groups at one side of the molecule is in the opposite direction to the resultant moment of the two –Cl groups on the other side. Hence, the bond moment is nearly cancelled out. Again the LUMO energy of the

compound 6 is high compared to the other. These result suggest that 6 should be a lesser charge acceptor and hence less potent than other studied compounds. This is also an agreement with the experimental results.

Compounds 1, 2, 3 and 5 had selective activity against cancer cells versus CHO cells. Their selective cytotoxic activity depends mainly on the gap energy and the stereo chemical features of these compounds.

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