CHAPTER 6

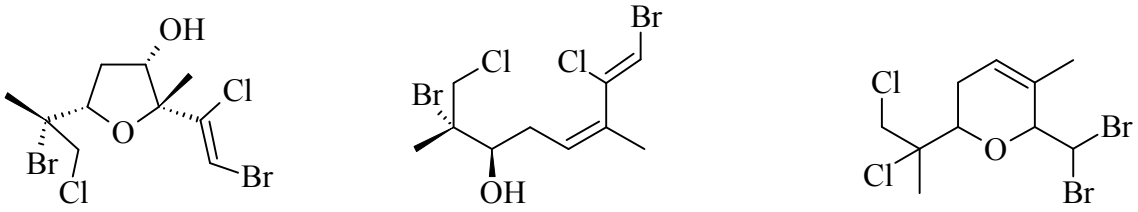
A theoretical investigation of cytotoxic activity of halogenated monoterpenoids from plocamium cartilagineum

6.1. Introduction

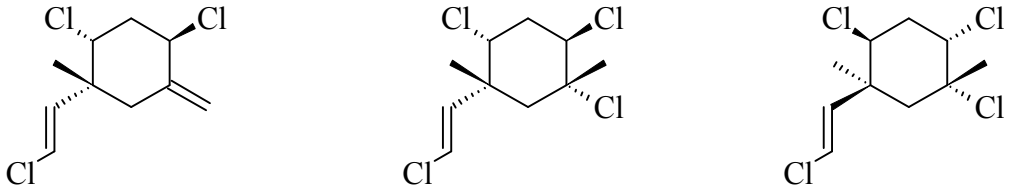
Marin algae considered to have wide applications, such as antibacterial, antiviral, insecticidal and antitumor activities [1-3]. Nine halogenated monoterpenoids furoplocamioid C (1a), pre furoplocamioid (1b), pirene (1c), and the cyclohexanes (1d-1i), including mertensene (1g) and violacene (1h) were isolated from the red alga plocamium cartilagineum have exhibited notable cytotoxic activity [4]. The cytotoxic effects of these compounds have been tested 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 tried to give an explanation about 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.

6.2. Computational studies

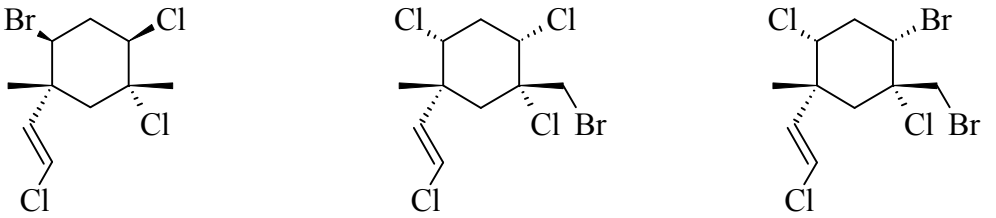
The structures of the molecules (Figure 6.1) under investigation were constructed using ACD/ChemSketch, version 12.01 [6]. All quantum chemical calculations were performed with the Firefly [7]. The ground-state geometries and electronic properties of the studied molecules have been determined at the B3LYP/6-31G*.



1a 1b 1c



1d 1e 1f



1g 1h 1i

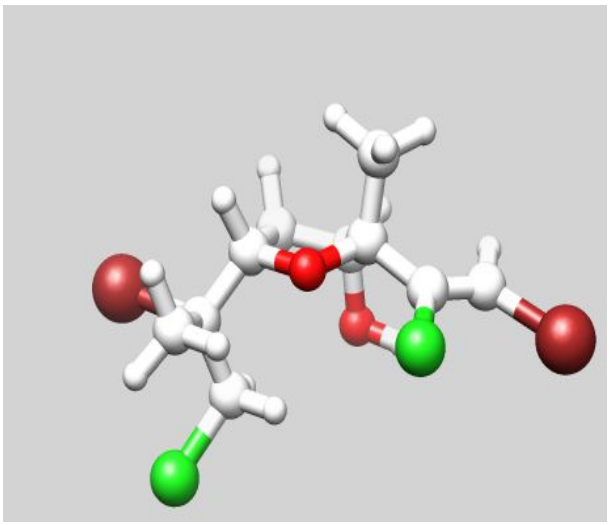
Figure 6.1. Chemical structures of furoplocamioid C (1a), prefuroplocamioid (1b), pirene (1c), cyclohexanes (1d-1i), including mertensene (1g), and violacene (1h).

6.3. Results and discussion

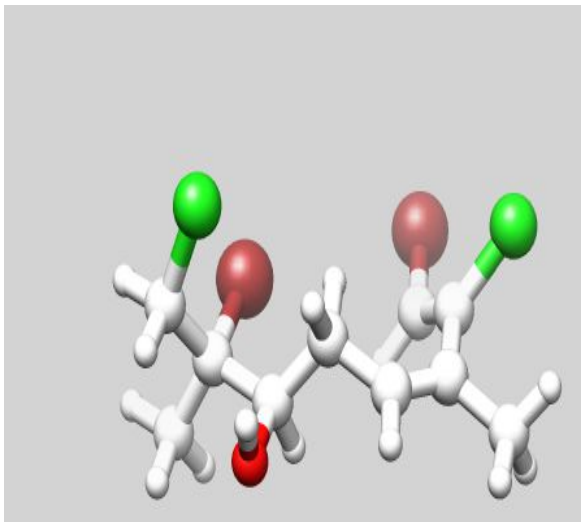
The minimal inhibitory concentration (MIC) of the studied compounds which produce a cytotoxic effect on the different cell lines along with their molecular electronic properties are summarized in Table 6.1 and their optimized geometry structures are illustrated in Figure 6.2.

Table 6.1. Minimal inhibitory concentration (MIC) and selected molecular electronic properties of the studied compounds

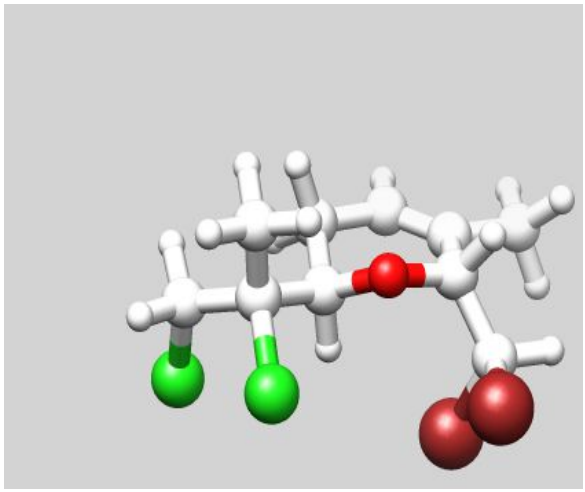
Comp. No.	$MIC_{(CHO)}$ µM	$MIC_{(CT26)}$ µM	$MIC_{(SW480)}$ µM	$E_{(HOMO)}$ eV	$E_{(LUMO)}$ eV	ΔE_{gap} eV	Dipole (D)	Total energies (hartree)
1a	126	63	126	-7.0668	-0.9415	6.1253	4.89	-6603.7885
1b	132	66	66	-6.479	-0.8626	5.6164	3.99	-6528.5601
1c	262	262	131	-6.9307	-0.9225	6.0082	4.94	-6528.583
1d	3.3	6.52	3.3	-6.9389	-0.283	6.6559	2.19	-1769.4516
1e	23	181	5.7	-6.7321	-0.6585	6.0736	2.98	-2230.2748
1f	362	362	362	-7.0341	-0.2503	6.7838	0.8	-2230.2751
1g	39	78	78	-7.1158	-0.7293	6.3865	1.54	-4341.8244
1h	141	141	141	-6.9961	-0.6694	6.3267	4.95	-4801.4049
1i	63	125	125	-6.9743	-0.8735	6.1008	4.83	-6912.9557



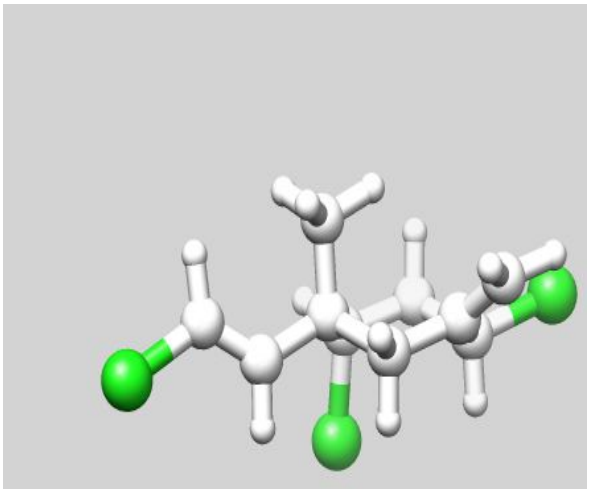
1a



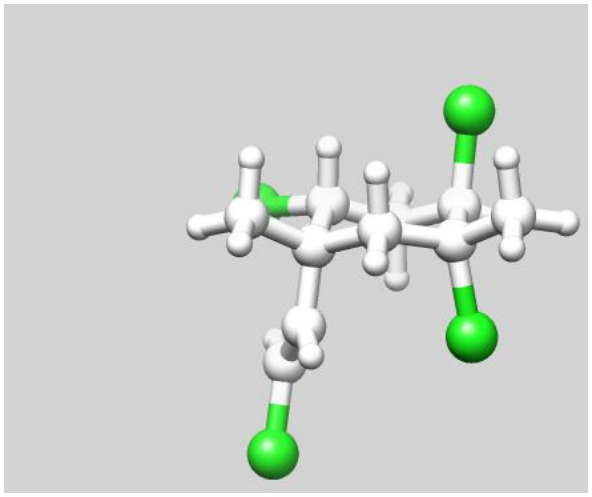
1b



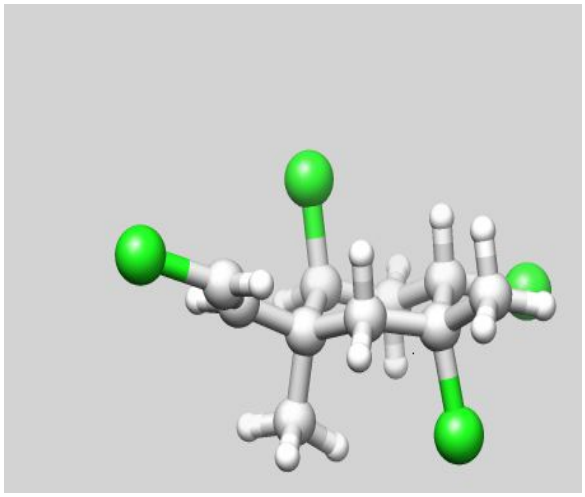
1c



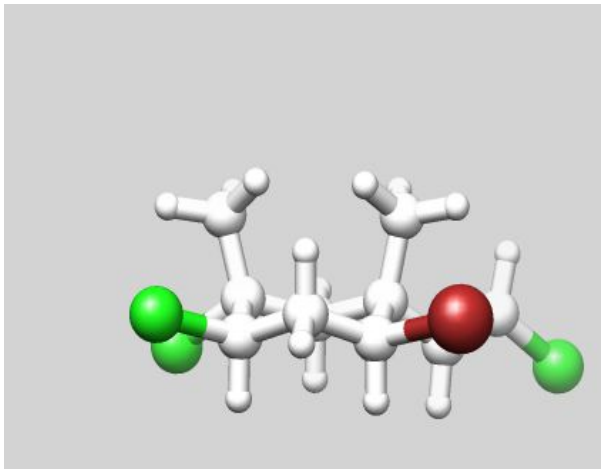
1d



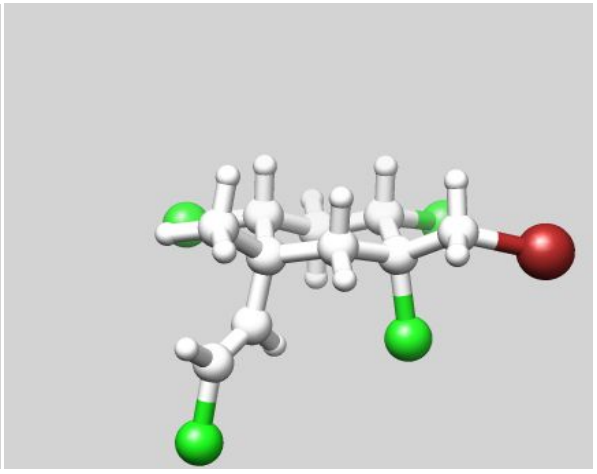
1e



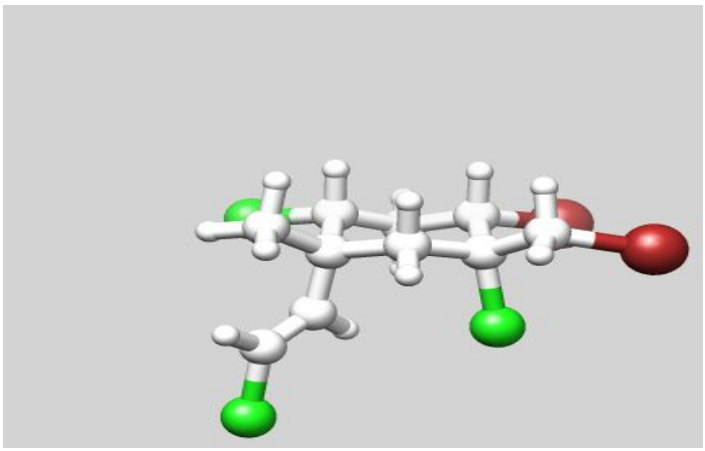
1f



1g



1h



1i

Figure 6.2. Optimized structures of studied molecules obtained by B3LYP/6-31G* level.

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

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 1a, 1b, 1c, and 1e have lower value of ΔE_{gap} (ranges from 5.6 to 6.1) compared to the compounds 1d, 1f, 1g and 1h. A cross correlation matrix (Table 6.2) 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 6.2. 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 1f is a diastereomer of 1e though the cytotoxic activity of 1f is lower than 1e. This is due to high gap energy (6.78 eV) and low dipole moment (0.80 D) of the molecule. In compound 1f, 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 1f is high compared to the other. These result suggest that 1f should be a lesser charge acceptor and hence less potent than other studied compounds. This is also an agreement with the experimental results.

6.4. Conclusion

Compounds 1a, 1b, 1c and 1e 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.

6.5. References

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