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Electronic Structure and Physical-Chemistry Properties Relationship for Citral Derived Amides by Quantum Chemical Calculations.

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ABSTRACT

The citral derived amides on bioevaluation as efflux pump inhibitors (EPIs) against Staphylococcus aureus1199 and NorAoverexpressing S. aureus 1199B bacteria resulted in the identification of several of these as potent EPIs.Many of these amides have been shown to possess potency higher or equivalent to known EPIs such as reserpine, verapamil, carsonic acid, and piperine. In this communication, we report the electronic structure and physical-chemistry properties relationship for citral derived amides by quantum chemical calculations.

Keywords: Citral derived amides, Efflux pump inhibitors, HF, DFT, QSAR, MPO, Lipinski rule

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INTRODUCTION

Bacterial multidrug efflux pumps are the major contributors of microbial resistance to several classes of antibiotics [1] [2]. Efflux of an antibiotic confers an environment of greater selection of resistant mutants having mutations in drug targets [3] [4]. By interfering with the development of resistance, clinical use of some antibiotics can be enhanced. the inhibition of an efflux pump can potentially improve the clinical efficacy of an antibiotic and simultaneously decrease the selection of resistant mutants, pharmaceutical companies and research institutes are therefore focusing on identifying novel efflux pump inhibitors (EPIs), which may be clinically useful[4] [5]. Staphylococcus aureus is a common cause of nosocomial infections and is less susceptible to hydrophilic quinolones due to their active expulsion from the cells by the NorA multidrug resistant (MDR) efflux pump [6]. There has been a continuous search for EPIs that can restore the activity of hydrophilic quinolones by inhibiting the NorA MDR efflux pump [7] [8].

Among several MDR transporters, NorA transporter [9] (member of the major facilitator family-MF family [10]), considered to be one of the major contributors toward drug effluxing, contribute to the resistance of Staphylococcus aureus to antibiotics such as ciprofloxacin by promoting their active extrusion from the cell [11].Development of clinically useful inhibitors that decrease the effectiveness of efflux pumps would represent a significant advance to provide successfultreatment of multi-drug resistant conditions. Efforts to develop potent and clinically competent EPIs are being explored both from natural sources and through bioevaluation of synthetic chemical libraries [12] [13] and some interesting molecules have come up whichare in the process of being developed as EPI's [14] [15] such as citral derived amides, a potent efflux pump inhibitors against S. aureus 1199 and Nor Aoverexpressing S. aureus 1199B, it was prepared from synthesis of alkenyl amides.

Contrary to aromatic amides, alkenyl amides have not been explored as EPIs, but are reported to have several other biological properties, which include insecticidal, larvicidal, sialogogue, and antitumor activities [16] [17]. It was, therefore, thought worthwhile to explore the possibility of preparing compounds and subject them to bioevaluation as efflux pump inhibitors.In this direction, we chose citral (E/Z ratio 77:23) as starting material, it was subjected to three-step reaction sequence to give 5,9-dimethyldeca-2,4,8-trienamide.
The present paper reports molecular properties of 5,9-dimethyldeca-2,4,8-trienamide, by using PM3, HF and density functional theory (DFT) methods, next some of its derivatives are reported by using DFT method and determined their QSAR proprieties.

MATERIALS AND METHODS

All calculations were performed by using HyperChem 8.0.6 software [18] and Gaussian 09 program package [19]. The optimization geometries of 5,9-dimethyl-deca-2,4,8-trienamide (citral derived) and its derivatives are optimized by PM3, HF and DFT/B3LYP with 6-311++G(d,p) basis set with Gaussian 09 program package. The calculation of propertiesQSAR is performed by the module (QSAR Properties, version 8.0). QSAR Properties is a module that, together with HyperChem, allows several properties commonly used in QSAR studies to be calculated. The calculated results have been reported in the present work.

RESULTS AND DISCUSSION

Synthesis of 5,9-dimethyl-deca-2,4,8-trienamide and their oxidized derivatives

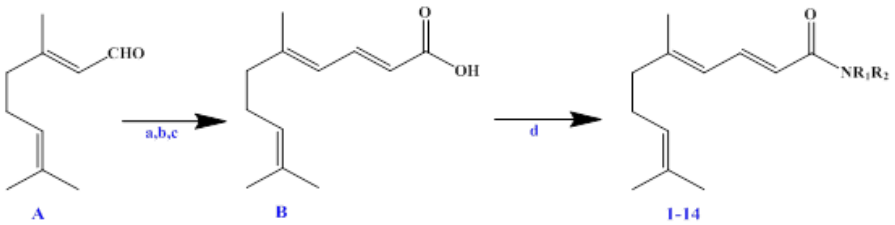

Figure 1: Reagents and conditions: (a) P(Ph)3/BrCH2COOEt/NaH/benzene0 °C to room temp; (b) NaOH/MeOH; (c)HCl; (d) SOCl2/DCM; NHR1R2/C6H6. NR_1R_2 (figure5)

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The aliphatic acid amides were synthesized through a reaction sequence as depicted in figure 1 [20].Firstly,citral**(A)** was subjected to Wittig reaction followed by saponification of the products to afford 5,9-dimethyl-deca-2,4,8-trienoic acid **(B)**. This acid was then converted to its acid chlorides and then treated with appropriate amines to get corresponding amides, 5,9-dimethyl-deca-2,4,8-trienamides **(1-14)** (fig 1).

Geometric Structure of 5,9-dimethyl-deca-2,4,8-trienamide

The optimized geometrical parameters of5,9-dimethyl-deca-2,4,8-trienamide(A_0)(Fig2) are obtained using PM3, HF and DFT/B3LYP methods, listed in Table 1. We can note a good correlation between the three methods for bond lengths, valence angles and dihedral angles but we note that these parameters calculated by HF are more similar to those calculated by DFT method (table I, II, III). We note also that some of the Dihedral angles are different to 0.0 and 180.0degree (table III), sothe geometry of 5,9-dimethyl-deca-2,4,8-trienamide is not planar (fig 3).

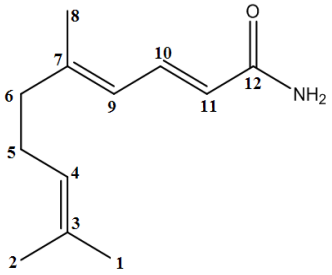

Figure 2: 5,9-dimethyl-deca-2,4,8-trienamide

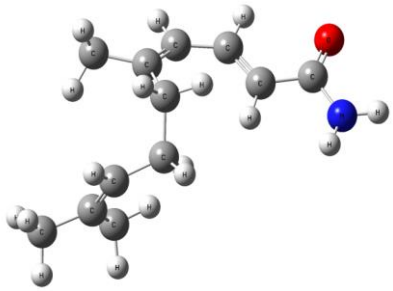

Figure 3:3D Conformation of 5,9-dimethyl-deca-2,4,8- Trienamide (Gauss View 5.0)

Table I: Bond length in Angstrom

Bond length	PM3	HF	DFT/B3LYP
C1-C3	1.485	1.509	1.507
C2-C3	1.487	1.510	1.509
C3-C4	1.340	1.325	1.340
C4-C5	1.486	1.507	1.504
C5-C6	1.526	1.546	1.556
C6-C7	1.493	1.514	1.509
C7-C8	1.490	1.509	1.506
C7-C9	1.345	1.332	1.352
C9-C10	1.448	1.472	1.454
C10-C11	1.340	1.326	1.345
C11-C12	1.478	1.490	1.487
C12-N	1.422	1.359	1.373
C12-O	1.225	1.197	1.222

Table II: Valence angle in degree

Valence angle	PM3	HF	DFT/B3LYP
C1-C3-C2	115.2	113.8	114.3
C1-C3-C4	123.7	125.5	125.0
C2-C3-C4	121.1	120.7	120.7
C3-C4-C5	124.5	129.1	128.7
C4-C5-C6	112.9	114.9	114.6
C5-C6-C7	112.2	115.7	114.9
C6-C7-C8	114.8	116.1	115.9
C6-C7-C9	125.8	124.4	124.3
C8-C7-C9	119.4	119.5	119.7
C7-C9-C10	130.0	129.8	130.6
C9-C10-C11	126.9	129.1	130.8
C10-C11-C12	121.6	120.2	120.0
C11-C12-N	117.2	114.6	117.2
C11-C12-O	125.6	123.6	124.0
O-C12-N	117.2	121.8	121.5

Table III: Dihedral angles in degree.

Dihedral angle	PM3	HF	DFT/B3LYP
C1-C3-C2-C4	179.9	179.9	180.0
C2-C3-C4-C5	178.7	178.2	178.6
C3-C4-C5-C6	134.9	126.1	122.8
C3-C4-C5-C7	101.1	94.5	91.8
C9-C7-C6-C8	178.3	176.4	177.5
C6-C7-C8-C10	176.9	173.2	174.9
C7-C9-C10-C11	19.4	40.7	25.6
C9-C10-C11-C12	178.8	179.3	179.8
C10-C11-C12-N	175.0	178.4	178.8
C11-C12-N-O	176.3	179.2	179.3

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The Substitution Effect on 5,9-dimethyl-deca-2,4,8-trienamide

The Frontier orbitals, highest occupied molecular orbital (**HOMO**) and lowest unoccupied molecular orbital (**LUMO**) are important factors in quantum chemistry [21] as these determine the way the molecule interacts with other species. The frontier orbital gap helps to characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbital gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule [22].

For understanding various aspects of pharmacological sciences including drug design and the possible eco-toxicological characteristics of the drug molecules, several new chemical reactivity descriptors have been proposed. Conceptual DFT based descriptors have helped in many ways to understand the structure of the molecules and their reactivity by calculating the chemical potential**μ**, global hardness **η**,electrophilicity**ω**,global softness **S**,energy band gap **ΔE**,ionization energy**I** and electron affinity**A** using **HOMO** and **LUMO** orbital energies according the formula done below:

$$\Delta E = (E_{LUMO} - E_{HOMO})$$

$$I = -E_{HOMO},\ A = -E_{LUMO},\ \eta = (E_{LUMO} - E_{HOMO})/2;\ \mu = (E_{HOMO} + E_{LUMO})/2,\ S = 1/\eta$$ [23].

Parr et al, [24] proposed the global electrophilicity power of a ligand as $\omega = \mu^2/2\eta$.

This index measures the stabilization in energy when the system acquired an additional electronic charge from the environment. Electrophilicity encompasses both the ability of an electrophile to acquire additional electronic charge and the resistance of the system to exchange electronic charge with the environment. It contains information about both electron transfer (chemical potential) and stability (hardness) and is a better descriptor of global chemical reactivity. The hardness **η** and chemical potential **μ** are given by the following relations: $\eta = (I-A)/2$ and $\mu = -(I+A)/2$, where **I** and **A** are the first ionization potential and electron affinity of the chemical species [25].

The calculated values of substituted 5,9-dimethyl-deca-2,4,8-trienamide (Fig. 4) are gathered in [Table IV].
These values indicate the effect of the donor substituent (Methyl: CH_3) and the acceptor substituent (Atom of chlorine: Cl).

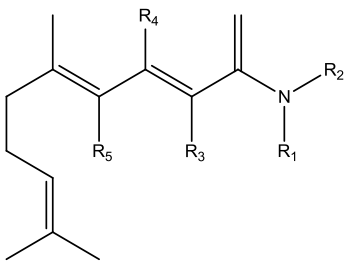

Figure 4: 5,9-dimethyl-deca-2,4,8-trienamide systems

SERIE 1:
A1:R1=CH_3R2=R3=R4=R5=H
A2 :R2=CH_3R1=R3=R4=R5=H
A3 :R3=CH_3R1=R2=R4=R5=H
A4 :R4=CH_3R1=R2=R3=R4=H
A5 :R5=CH_3R1=R2=R3=R4=H
A6 :R1=R2=CH_3 R3=R4=R5=H
A7 :R1=R3=CH_3 R2=R4=R5=H
A8 : R1=R4=CH_3 R2=R3=R5=H
A9 :R1=R5=CH_3 R2=R3=R4=H
A10 : R2=R3=CH_3 R1=R4=R5=H
A11 : R2=R4=CH_3 R1=R3=R5=H
A12 : R2=R5=CH_3 R1=R3=R4=H
A13 : R3=R4=CH_3 R1=R2=R5=H
A14 : R3=R5=CH_3 R1=R2=R4=H
A15 : R4=R5=CH_3 R1=R2=R3=H

SERIE 2:
B1:R1=ClR2=R3=R4=R5=H
B2 : R2=ClR1=R3=R4=R5=H
B3 : R3=ClR1l=R2=R4=R5=H
B4 : R4=ClR1=R2=R3=R4=H
B5 : R5=ClR1=R2=R3=R4=H
B6 : R1=R2=Cl R3=R4=R5=H
B7 : R1=R3=Cl R2=R4=R5=H
B8 : R1=R4=Cl R2=R3=R5=H
B9 : R1=R5=Cl R2=R3=R4=H
B10 : R2=R3=Cl R1=R4=R5=H
B11 : R2=R4=Cl R1=R3=R5=H
B12 : R2=R5=Cl R1=R3=R4=H
B13 : R3=R4=Cl R1=R2=R5=H
B14 : R3=R5=Cl R1=R2=R4=H
B15 : R4=R5=Cl R1=R2=R3=H

As it is known, for lesser HOMO-LUMO gap there is easy flow of electrons to the higher energy state making it reactive and softer (HSAB principle: hard and soft acids and bases). Hard bases have highest occupied molecular orbitals (HOMO) of low energy; and hard acids have lowest unoccupied molecular orbitals (LUMO) of high energy [26].

So for the effect of the donor substituent (CH_3), we note from the Table IV, that the compound A6and A9 have smaller HOMO - LUMO energy gap (0.167 a.u), these compounds are the most reactive. In the same way, the high value of chemical potential (-0.126 a.u) and low value of electrophilicity index (0.083 a.u) for compound A7 favor its nucleophilicitybehavior.

For the effect of theacceptor substituent (Cl), we can note that compound B6 hassmaller HOMO - LUMO energy gap (0.141a.u), higherionization energy (I) (2.41 a.u), higher electron affinity (A) (0.100 a.u), smaller global hardness (η) (0.070 a.u), higher global softness (S) (14.285 $u.a^{-1}$), and higher global electrophilicity index (Ω) (0.204 u.a) thus, compound B6 is a strong electrophile than others compounds.

We can see that all values of chemical potential of all compounds arenegative and it meansthat the compounds are stable.

Table IV: Proprieties of substituted 5,9-dimethyl-deca-2,4,8-trienamide

COMP	E_{HOMO} (a.u)	E_{LUMO} (a.u)	ΔE (a.u)	μ (a.u)	I (a.u)	A (a.u)	S ($a.u^{-1}$)	η (a.u)	ω (a.u)
A0	-0.231	-0.063	0.168	-0.147	0.231	0.063	11.904	0.084	0.128
A1	-0.230	-0.062	0.168	-0.146	0.230	0.062	11.904	0.084	0.162
A2	-0.229	-0.058	0.171	-0.143	0.229	0.058	11.764	0.085	0.119
A3	-0.230	-0.045	0.185	-0.137	0.230	0.045	10.869	0.092	0.101
A4	-0.232	-0.053	0.179	-0.142	0.232	0.053	11.235	0.089	0.112
A5	-0.226	-0.057	0.169	-0.141	0.226	0.057	11.904	0.084	0.117
A6	-0.227	-0.060	0.167	-0.143	0.227	0.060	12.048	0.083	0.122
A7	-0.229	-0.030	0.199	-0.129	0.229	0.030	10.101	0.099	0.083
A8	-0.230	-0.052	0.178	-0.141	0.230	0.052	11.235	0.089	0.111
A9	-0.224	-0.057	0.167	-0.140	0.224	0.057	12.048	0.083	0.117
A10	-0.228	-0.041	0.187	-0.134	0.228	0.041	10.752	0.093	0.096
A11	-0.229	-0.049	0.180	-0.139	0.229	0.049	11.111	0.090	0.107
A12	-0.223	-0.053	0.170	-0.138	0.223	0.053	11.764	0.085	0.112
A13	-0.226	-0.032	0.194	-0.129	0.226	0.032	10.309	0.097	0.085
A14	-0.224	-0.036	0.188	-0.130	0.224	0.036	10.638	0.094	0.089
A15	-0.228	-0.035	0.193	-0.131	0.228	0.035	10.416	0.096	0.088
B1	-0.237	-0.080	0.157	-0.158	0.237	0.080	12.820	0.078	0.159
B2	-0.238	-0.074	0.164	-0.156	0.238	0.074	12.195	0.082	0.148
B3	-0.234	-0.060	0.174	-0.147	0.234	0.060	11.949	0.087	0.124
B4	-0.241	-0.066	0.175	-0.153	0.241	0.066	11.494	0.087	0.133
B5	-0.237	-0.069	0.168	-0.153	0.237	0.069	11.904	0.084	0.139
B6	-0.241	-0.100	0.141	-0.170	0.241	0.100	14.285	0.070	0.204
B7	-0.238	-0.082	0.156	-0.160	0.238	0.082	12.820	0.078	0.164
B8	-0.244	-0.084	0.160	-0.164	0.244	0.084	12.500	0.080	0.168
B9	-0.241	-0.087	0.154	-0.164	0.241	0.087	12.987	0.077	0.174
B10	-0.238	-0.069	0.169	-0.153	0.238	0.069	11.904	0.084	0.138
B11	-0.246	-0.077	0.169	0.161	0.246	0.077	11.904	0.084	0.153
B12	-0.242	-0.080	0.162	-0.161	0.242	0.080	12.345	0.081	0.160
B13	-0.242	-0.069	0.173	-0.155	0.242	0.069	11.627	0.086	0.138
B14	-0.241	-0.079	0.162	-0.160	0.241	0.079	12.345	0.081	0.158
B15	-0.246	-0.079	0.167	-0.162	0.246	0.079	12.048	0.083	0.157

Study of Structure-Activity/Property Relationships for citral derived amides

An important objective for this project was to evaluate the physicochemical domain of the citral derived amides (Figure 5) reported in literature has a biological activity [20].Some of physicochemical properties were calculated using HyperChem 8.03 software like (Surface Area, Volume, Polazability, Refractivity and Hydratation Energy). We will continue this work in the future by a quantitative calculation.

QSAR proprieties are, van der Waals-surface-bounded molecular volume, the log of the octanol-water partition coefficient (logP), polarizability, solvent-accessible surface bounded molecular volume and molecular mass (M). Calculation of logP is carried out using atomic parameters derived by Viswanadhan and coworkers [27]. Computation of molar refractivity was made via the same method as logP. Ghose and Crippen presented atomic contributions to the refractivity [28].

The polarizability was estimated from an additivity scheme given by Miller [29] with a precision on the calculation of 3%, where different increments are associated with different atom types. The hydration energy is a key factor determining the stability of different molecular conformation [30]. The calculation is based on exposed surface area, and employs the surface area as computed by the approximate method (above), weighted by atom type.

Molecular volume determines transport characteristics of molecules, such as intestinal absorption or blood-brain barrier penetration. Volume is therefore often used in QSAR studies to model molecular properties and biological activity.

The molar refractivity is a steric parameter that is dependent on the spatial array of the aromatic ring in the synthesized compounds. The spatial arrangement also is necessary to study the interaction of the ligand with the receptor [31].

Molar refractivity is related, not only to the volume of the molecules but also to the London dispersive forces that act in the drugreceptor interaction.

Molecular Polarizability of a molecule characterizes the capability of its electronic system to be distorted by the external field, and it plays an important role in modeling many molecular properties and biological activities [32]. Solvent-accessible surface bounded molecular volume and van der Waals surface bounded molecular volume calculations are based on a grid method derived by Bodor et al [33],using the atomic radii of Gavezotti[34].

Hydration energy is a key factor determining the stability of different molecular conformations in water solutions [35]. The calculation is based on exposed surface area as computed by the approximate method (above), weighted by atom type.

compounds	NR_1R_2
1	Piperidine
2	Benzylamine
3	n-octylamine
4	D-2-aminobutanol
5	L-2-aminobutanol
6	o-anisidine
7	p-anisidine
8	aniline
9	pyrrolidine
10	isopropylamine
11	o-toluidine
12	morpholine
13	isobutylamine
14	diisopropylamine

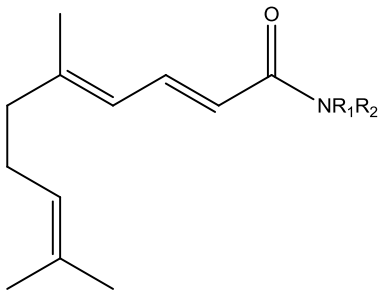

Table V: QSAR proprieties forcitral derived amides

Polarizability values are generally proportional to the values of surfaces and of volumes, the decreasing order of polarizability for these studied citral derivatives is:

3 >6>7 >2>11> 14 > 8 > 1 > 12> 5 >4> 13> 9> 10

The order of polarizability is approximately the same one for volume and surface. This also is explained by the relation between polarizability and volume, for the relativity non polar molecules. They are directly linked, for the centers of gravity of negative and positive charges in the absence of external fields to coincide, and the dipole moment of the molecule is zero. For these citralderivatives, surfaces vary from 509.36Å^2 to 694.33 Å^2 and they have a great variation of distribution volume, in particular compound **3**, **6** and **7** which have respective volumes: 1150.69, 1003.26 and 1006.52 Å^3. The most important hydration energy in the absolute value, is that of the compound**7** (3.98 kcal/mol) and the weakest is that of compound **9** (0.40 kcal/mol). Indeed, in the biological environments the polar molecules are surrounded by water molecules. They are established hydrogen bonds between a water

molecule and these molecules. The donor sites of the proton interact with the oxygen atom of water and the acceptor sites of the proton interact with the hydrogen atom.

The first correspond to the complex with the strongest hydrogen bond. These hydrated molecules are dehydrated at least partially before and at the time of their interaction. These interactions of weak energy, which we observe in particular between messengers and receivers, are generally reversible [36].

Compound **7**does not possess any donor site of proton, but it has three acceptor sites of proton (O on the groups R_1R_2 and 1N, 1O on the core base). On the other hand, compound **9**does not possess any donor site, but it possesses two acceptor sites of proton (1N and 1O on the core base). The first having higher value, it has one more donor site of protons. This property supports the first compound, not only by fixing on the receiver, but in more activates it. It is thus about an agonist. It has as a consequence a better distribution in fabrics.

The coefficient of division (LogP) are widely used to make estimation for membranepenetration and permeability, includinggastrointestinal absorption [37] [38], blood–brain barrier (BBB) crossing [39] [40], and correlations to pharmacokinetic properties [41].Log P values of citralderivatives were found to be in the range of (2.54) – (5.25).

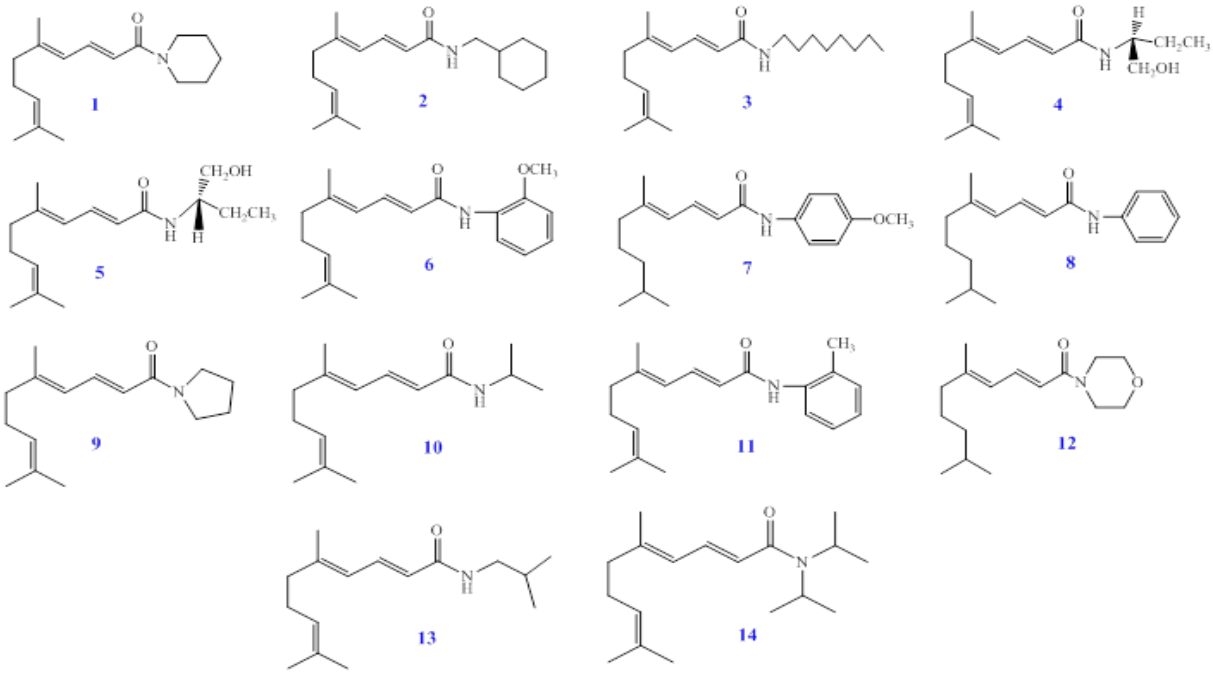

Figure 5: structure of citral derived amides

CONCLUSION

The present work is interested to the theoretical study of the molecular proprieties of 5,9-dimethyl-deca-2,4,8-trienamide. The PM3, HF and DFT methods can be used quite satisfactorily in predicting the chemical reactivity of the molecules and the effect of substitution of either donor or acceptor electron.

In the substituted methyl group, A6 and A9 are predicted to be the most reactive with its least HOMO- LUMO energy gap and A7 havenucleophilicitybehaviorbecause of its low value of electrophilicity.

In the substituted chlorine atom, B6 has the smallest valueHOMO - LUMO energy gap and the highest global electrophilicity, it is a strong electrophile.We have determinate, at the last, the properties QSAR of citral derived amides.

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