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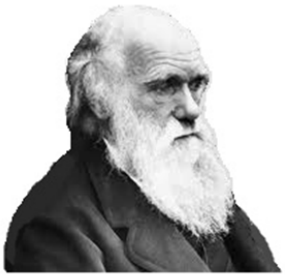

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Elucidation of Potential Inhibitor Compounds from *Zingiber officinale* against Migraine Headache

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ABSTRACT

Migraine is a type of headache that generates a pulsing sensation oftentimes on one side of the head. *Zingiber officinale* (ginger) is a plant material that is used as spice in foods; it has proven to have many health benefits such as reducing nausea and vomiting, inflammation and migraine headache. Herein, we investigate the migraine headache inhibiting ability of the ethanol extract of *Zingiber officinale*. Molecular docking approach was used to study the ligand-target interactions to identify the compounds with low docking scores, density functional theory calculations was used to estimate the electronic properties of some of the molecules and absorption distribution metabolism elimination and toxicity (ADMET) screening was performed to identify compounds with good pharmacokinetics, and pharmacodynamics properties. Estra-1,3,5(10)-trien-17.beta.-ol showed the best binding scores of -6.8 and -8.8 $1Kcalmol^{-1}$ in calcitonin gene-related peptide (CGRP) receptor (PDB:3n7r) and human NK1 tachykinin receptor (PDB:6e59) respectively, very close to the control drug Telcagepant which gave the lowest binding scores for the two migraine headache proteins studied $-10.4\ and\ -9.1Kcalmol^{-1}$ in 3n7r and 6e59 respectively. All the other compounds also showed low binding scores indicating that the plant may be a drug lead candidate for the control of migraine headache. The density functional theory results revealed that the plant would be biologically stable. The results obtained from this research validate the local claim that Zingiber *officinale* is effective in the treatment of migraine headache.

Keywords: *zingiber officinale*, migraine, molecular docking, calcitonin gene-related peptide (CGRP), human NK1 tachykinin

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1. INTRODUCTION

Migraine headache is a neurovascular disorder with known intricate mechanisms [1-2], it is the third most prevalent and obviously the second most disabling neurological disorder characterized with a throbbing pain on one side of the head [3-4]. The main cause of migraine headache is unknown although several hypothesis and approaches have been proposed by various researchers to investigate the possible course of this disorder. In the cause of the pains it has been shown that calcitonin gene-related peptide (CGRP) hormone content increases [5-6]. CGRP is a member of the calcitonin family of peptides that is prepared in peripheral and also central neurons, after production it is absorbed by the CGRP receptor and a complex is formed which helps in the transmission of pain signals [7-10]. As a result of the role played by CGRP in migraine trauma, many researchers have investigated the role of CGRP receptor antagonists in the management of migraine headache [11-12],

Zingiber officinale is a flowering plant whose root or rhizome is used as a spice for food as well as a folk medicine [13-14] *Zingiber officinale* is used in traditional medicine for the control of indigestion, stomach upset, diarrhea, nausea and headache [15-16]. *Zingiber officinale* extracts may likely increase serotonin in the body, a chemical messenger linked to migraine attacks [17]. The Increase in the level of serotonin in the brain may likely stop migraine attack by restricting blood vessels and reducing inflammation [18]. A class of prescription medications used in the treatment of migraine headache work in similar mechanism. Ginger taken in forms of capsules and gels have been investigated for their migraine reducing properties and they have shown to be very effective [19]. The present research investigates the bioactive components of *Zingiber officinale* using gas chromatography mass spectrophotometry method and their applications in the control of migraine headache using molecular docking approach. The chemical reactivities of the investigated compounds were evaluated using density functional theory.

2. MATERIALS AND METHODS

2. 1. Preparation of *Zingiber officinale* extract

The plant material used for this project was harvested from the botanical garden of The Imo State university Owerri, peeled, washed, dried and pulverized. The powdered plant was dipped in 98% ethanol and left for 72-h [20], filtered concentrated and sent for GC-MS experiment.

2. 2. Gas chromatography-mas spectrophotometry (GC-MS) Experiment

The prepared plant material was subjected to GC-MS experiment using an Agilent GC-MS instrument with model number 19091S-433UI USA and parameter 0 °C - 325 °C (350 °C): 30 m x 250 μm x 0.25 μm. The initial temperature was 50℃ and pressure 7.3614 psi and flow rate of 0.97414 mL/min, the carrier gas was helium, the maximum temperature and pressure were 325 °C and 0 psi respectively.

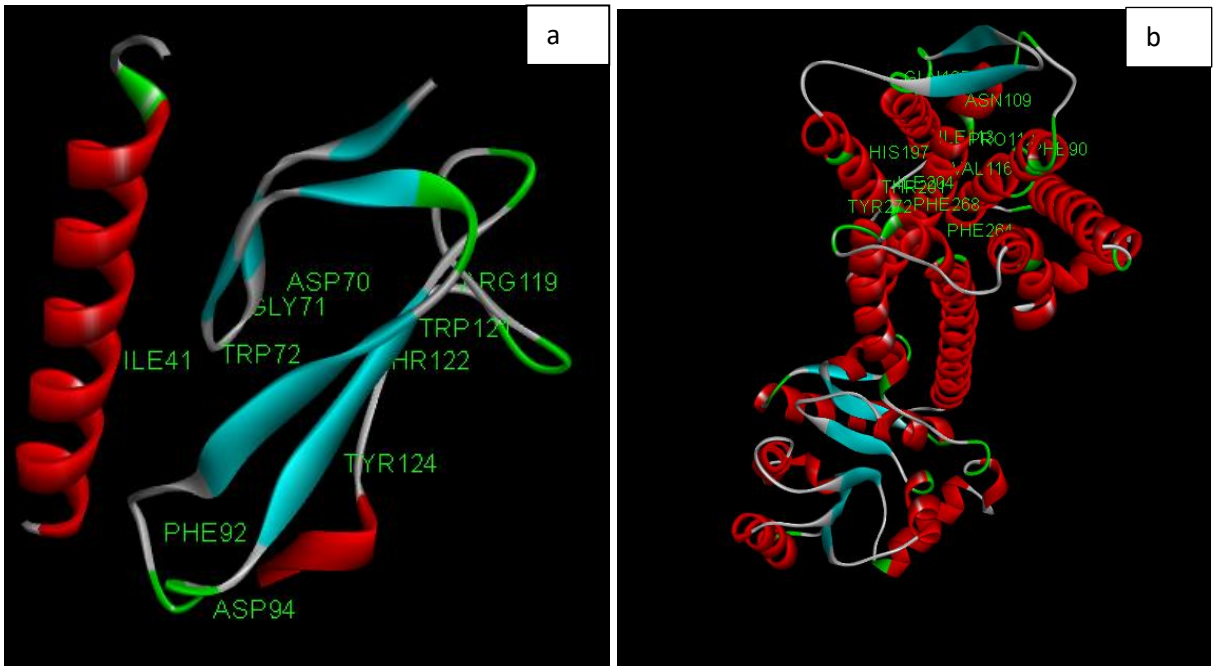
2. 3. Ligand preparation

The compounds identified from the GC-MS experiment were used as the ligands, the 3-dimensional structure data files (SDF) were sourced and downloaded from pubchem online

database, minimized at a universal force field of 200 steps using the famous PYRX visual screening and molecular docking software [21].

2. 4. Protein Preparation

Two migraine headache targets Scheme. 1(a) calcitonin gene-related peptide (CGRP) receptor (PDB:3n7r) [22] and (Scheme. 1b) the human NK_1 tachykinin receptor (PDB:6e59) [23] were sourced from literature and downloaded from protein data bank (PDB). Protein preparation was achieved in Biovia discovery studio software where the crystallographic water molecules and interfering co-crystallized ligands were removed, the proteins were saved as PDB files and used as macromolecules for the molecular docking interactions.



Scheme 1. Migraine headache proteins with the amino acids residues of the active site (a) 3n7r and (b) 6e59

2. 5. molecular docking

Molecular docking to study the protein-ligand interactions between the identified compounds and the prepared proteins was achieved using Autodock Vina found in PYRX [24] molecular docking software 08 version. Post docking visualization was achieved with the Biovia discovery studio software.

2. 6. Absorption, Distribution, Metabolism, Elimination and Toxicity (ADMET) Screening

Six of the compounds with the lowest binding scores for each of the studied proteins were selected and submitted to ADMETSA2 server for pharmacokinetics, drug-like and pharmacodynamics properties [25]. Their canonical smiles were obtained from pubchem software and employed in the ADMET drug properties screening.

2. 7. Density functional theory (DFT)calculations

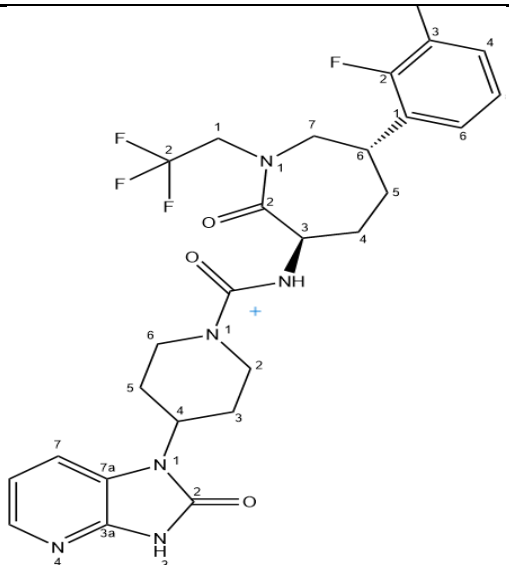
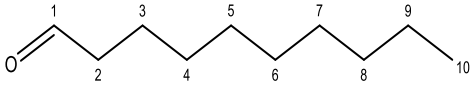
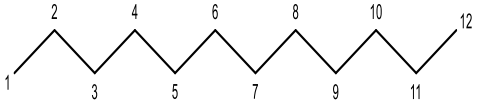
All the density functional theory calculations done in this project were achieved with the material studio 7.0 modeling and simulation software by accerryl. Inc with DMol [26]

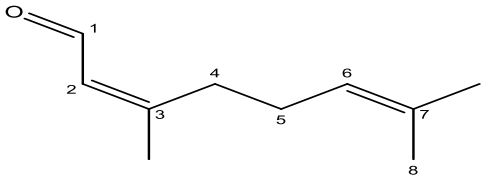
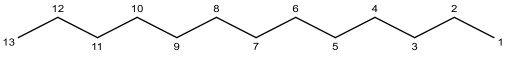
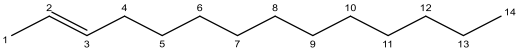
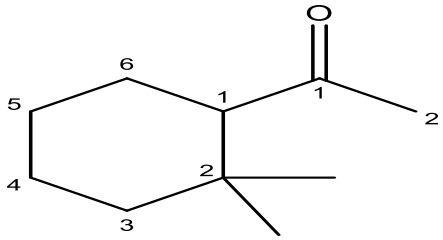
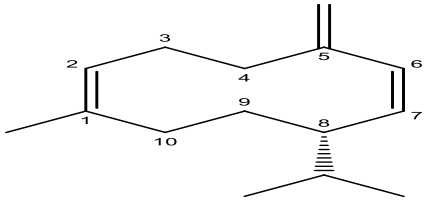
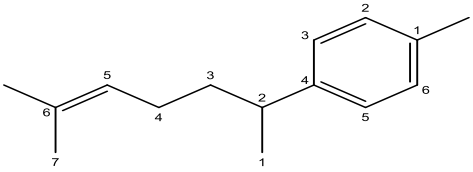
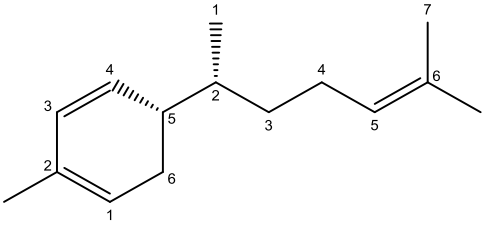
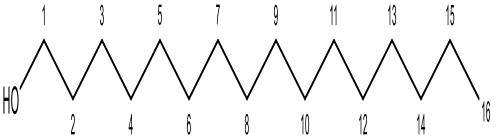
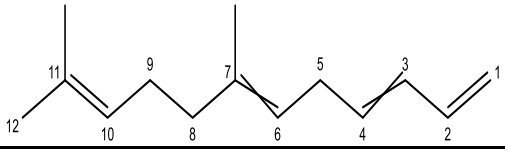
3. RESULTS

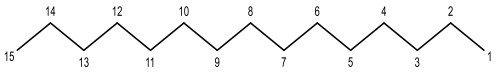
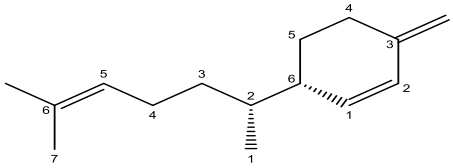
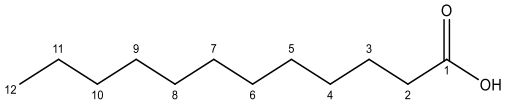
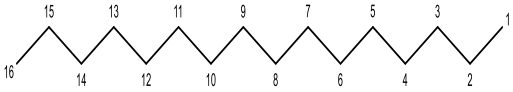
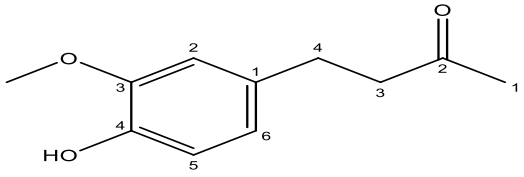
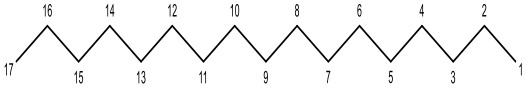
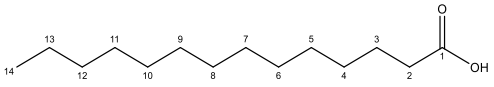
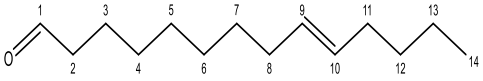
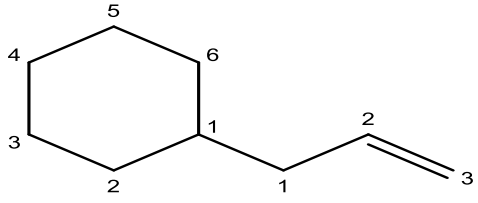
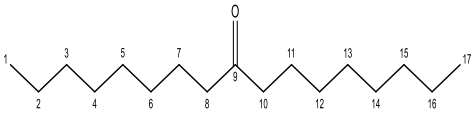
3. 1. gas-chromatography mass-spectrophotometry Result (GC-MS)

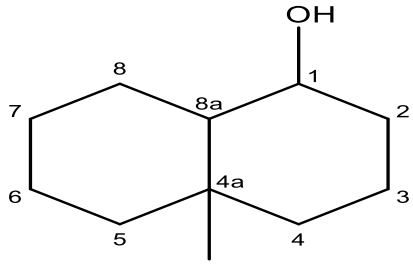
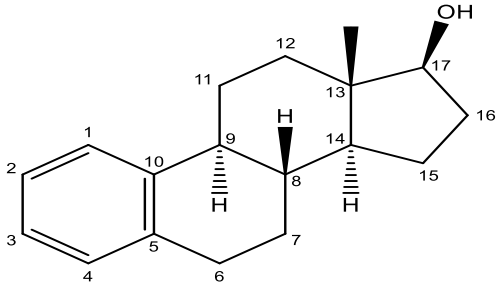
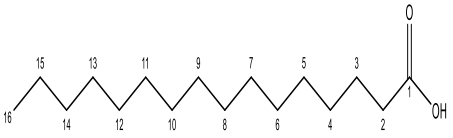
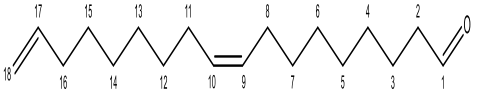
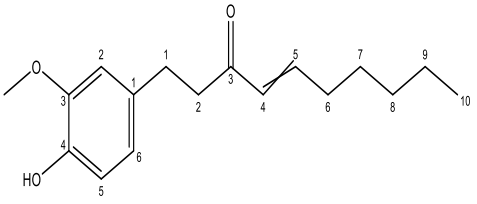
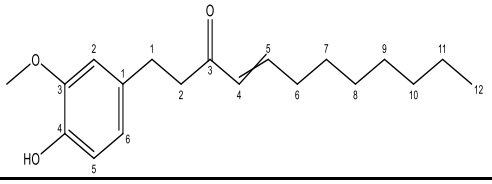
CG-MS analysis was performed on the *Zingiber officinale* powder to ascertain the chemical compounds therein, 28 of the bioactive chemical compounds identified in the plant material are listed in Table 1 while the mass spectra of 5 of the compounds identified in the GC-MS analysis are presented in Figures 1-5. All the identified compounds have previously shown good pharmacological effects [27].

Table 1. Chemical compounds present in *Zingiber officinale* powder and Telcagepant (control)

S.no	Compound	Area peak	Pubchem cid	Molecular Structure
1	Telcagepant		11319053	
2	Decanal	0.9671	8175	
3	Dodecane	0.3202	8182	

4	2,6-Octadienal, 3,7-dimethyl-, (Z)-	1.8929	643779	
5	Tridecane	0.1722	12388	
6	2-Tetradecene, (E)-	3.9620	5352912	
7.	Ketone, 2,2-dimethylcyclohexyl methyl	0.1818	549806	
8	(S,1Z,6Z)-8-Isopropyl-1-methyl-5-methylenecyclodeca-1,6-diene	1.194	91723653	
9	Benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl-	4.1746	92139	
10	1,3-Cyclohexadiene, 5-(1,5-dimethyl-4-hexenyl)-2-methyl-, [S-(R*,S*)]-	4.6564	101708	
11	1-Hexadecanol	0.3891	2682	
12	.alpha.-Farnesene	1.1025	5281516	

13	Pentadecane	0.2529	12391	
14	Cyclohexene, 3-(1,5-dimethyl-4-hexenyl)-6-methylene-, [S-(R*,S*)]-	0.9007	519764	
15	Dodecanoic acid	5.414	3893	
16	Hexadecane	0.5692	11006	
17	2-Butanone, 4-(4-hydroxy-3-methoxyphenyl)-	1.8841	31211	
18	Heptadecane	0.5036	12398	
19	Tetradecanoic acid	5.2783	11005	
20	E-9-Tetradecenal	0.1278	5283368	
21	Cyclohexane, 2-propenyl-	0.2593	75027	
22	9-Heptadecanone	0.3497	10887	

23	1-Naphthalenol, decahydro-4a-methyl-	0.494	543753	
24	Cetene	1.9257	12395	
25	Estra-1,3,5(10)-trien-17.beta.-ol	0.1882	537293	
26	n-Hexadecanoic acid	4.6996	985	
27	9,17-Octadecadienal, (Z)-	5.0745	5365667	
28	1-(4-Hydroxy-3-methoxyphenyl)dec-4-en-3-one	0.7183	5281794	
29	1-(4-Hydroxy-3-methoxyphenyl)dodec-4-en-3-one	0.5144	6442560	

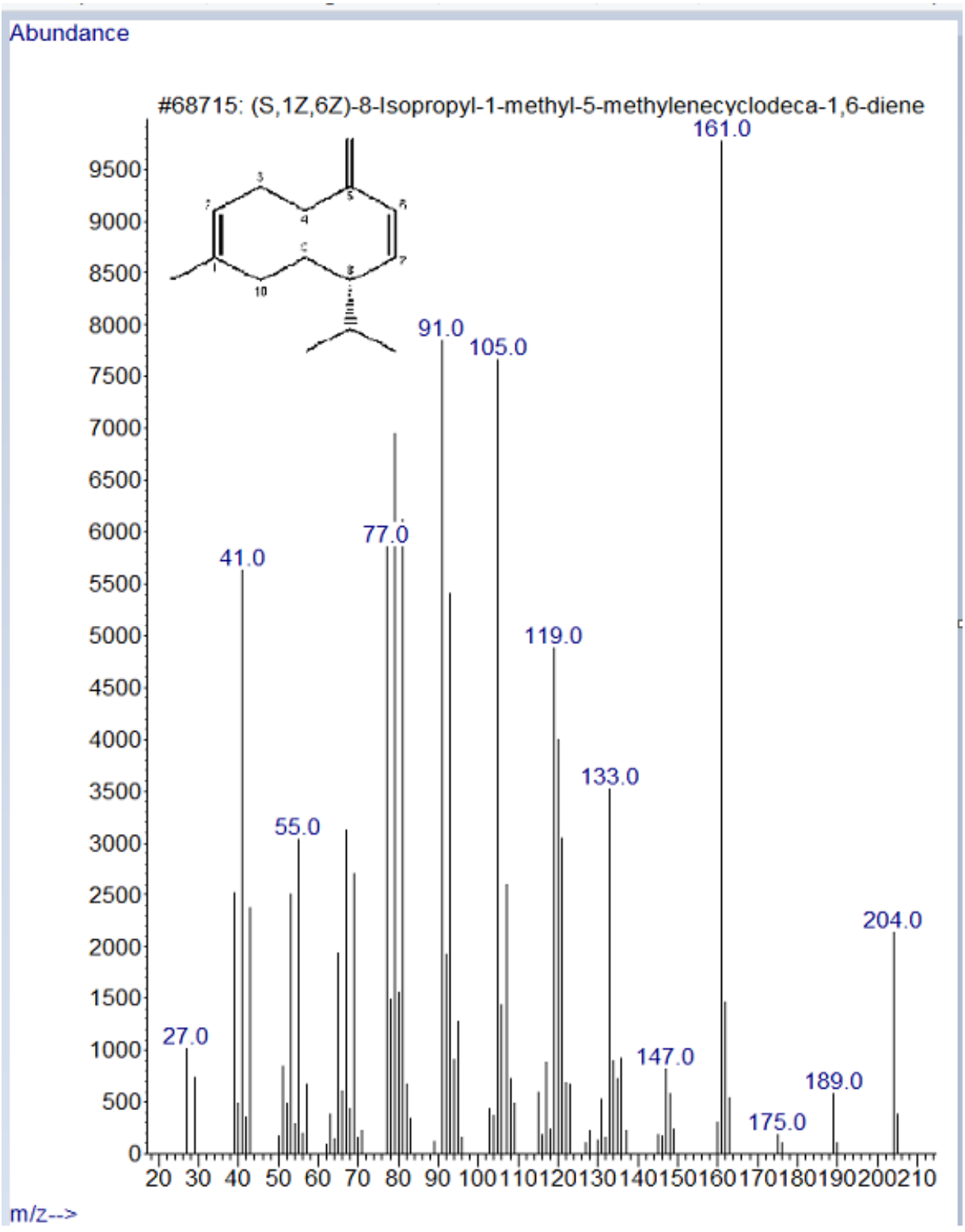


Figure 1. Mass spectrum of (S,1Z,6Z)-8-Isopropyl-1-methyl-5-methylenecyclodeca-1,6-diene

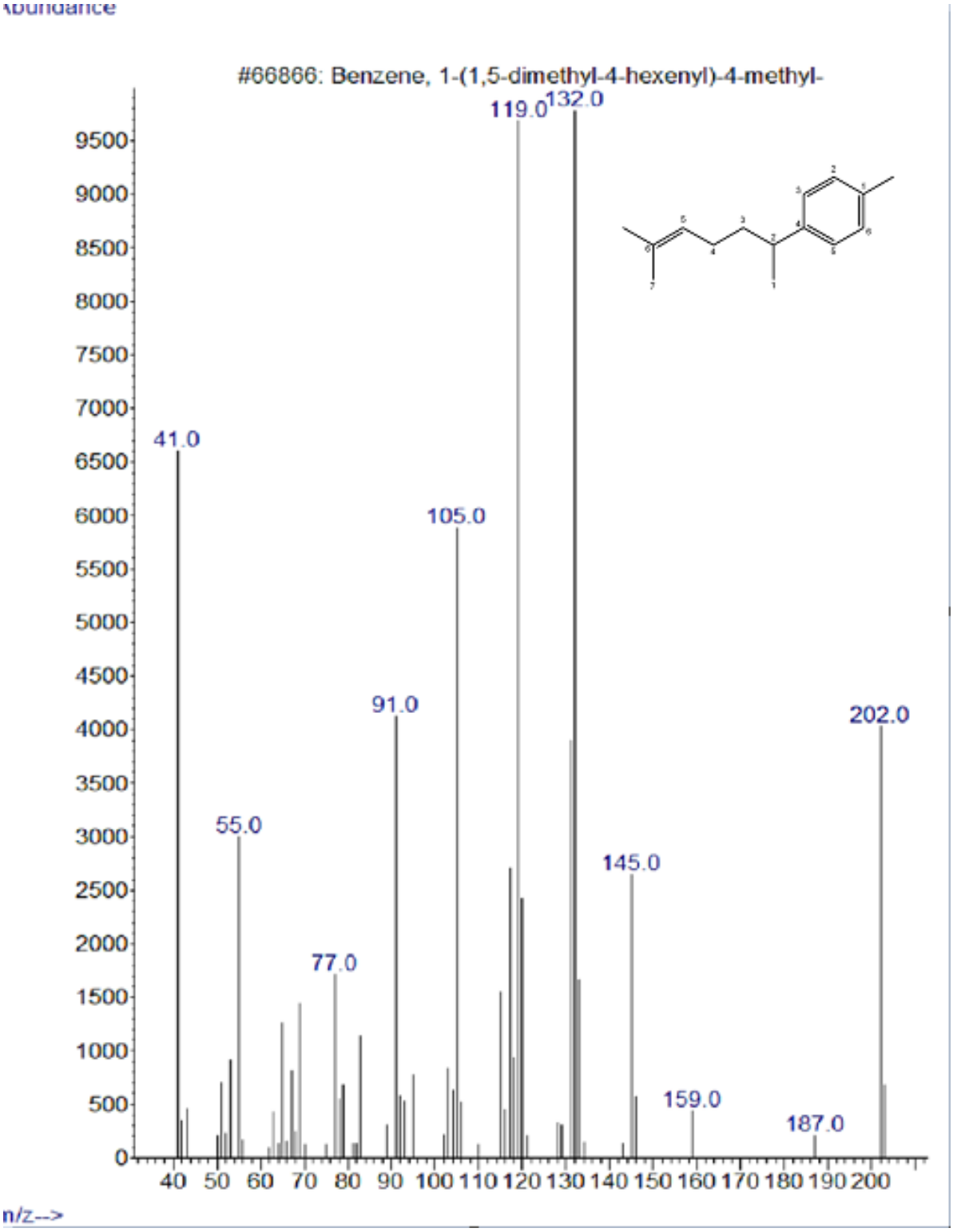


Figure 2. Mass spectrum of Benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl-

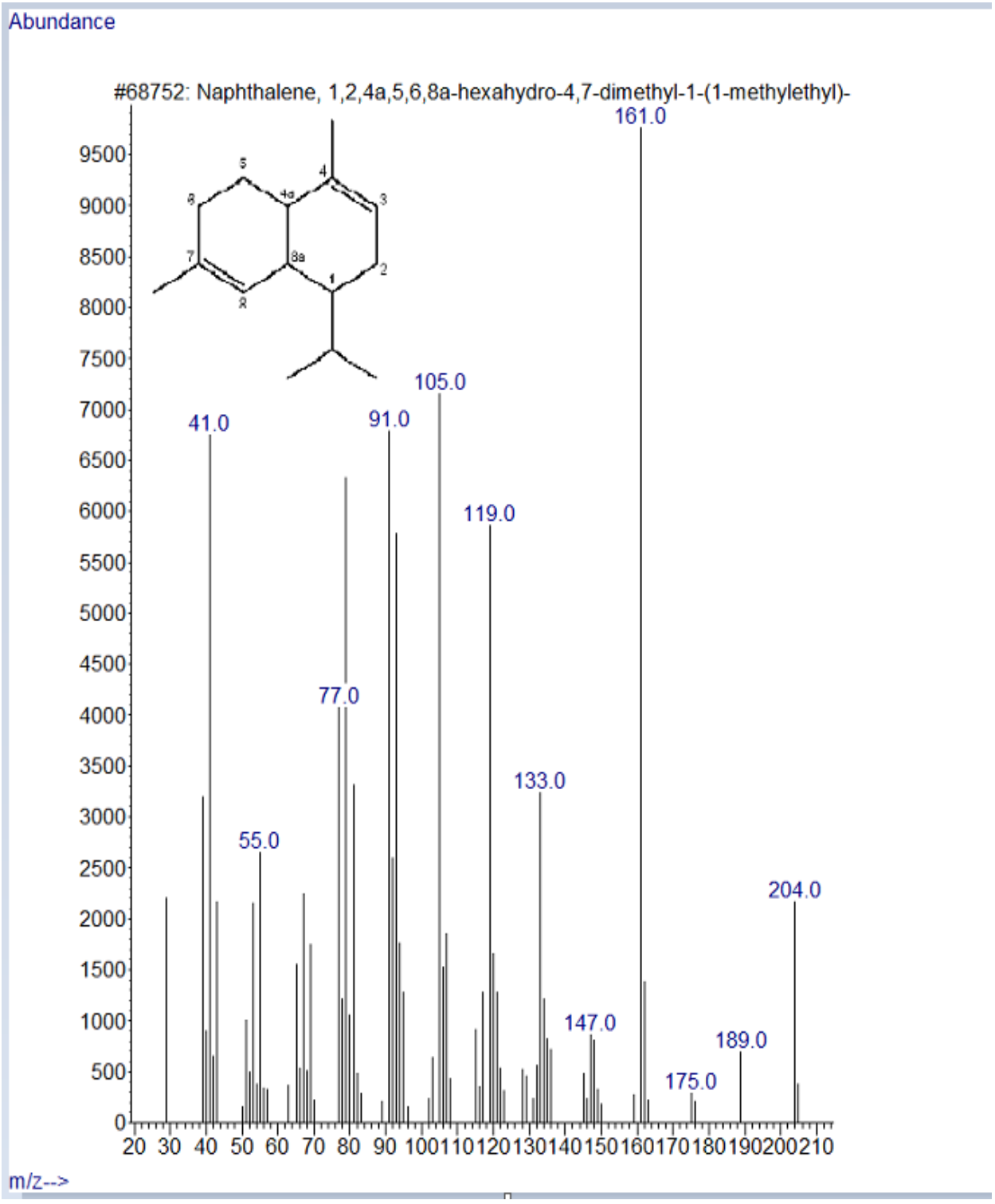


Figure 3. Mass spectrum of Naphthalene, 1,2,4a,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-

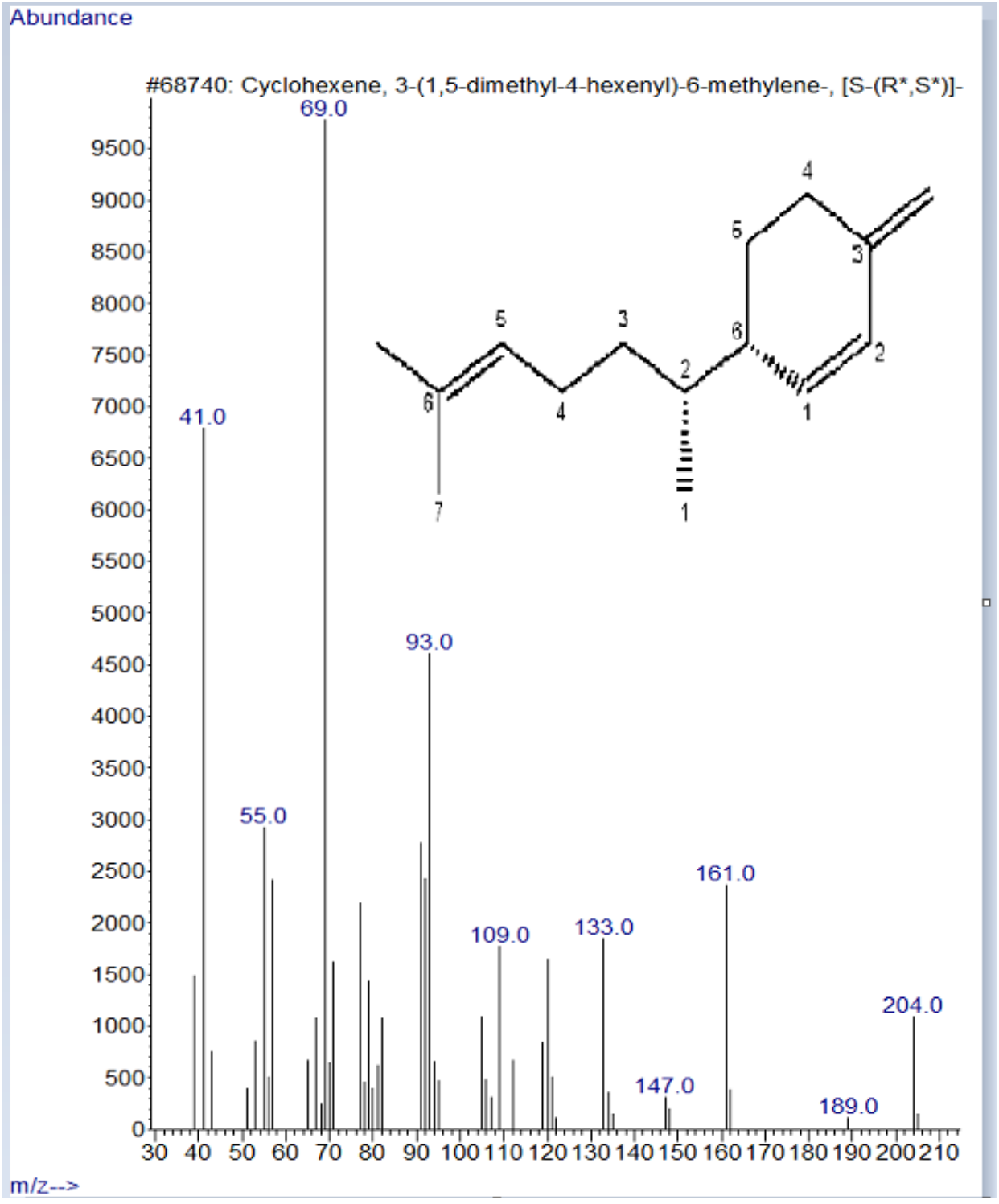


Figure 4. Mass spectrum of Cyclohexene, 3-(1,5-dimethyl-4-hexenyl)-6-methylene-, [S-(R*,S*)]-

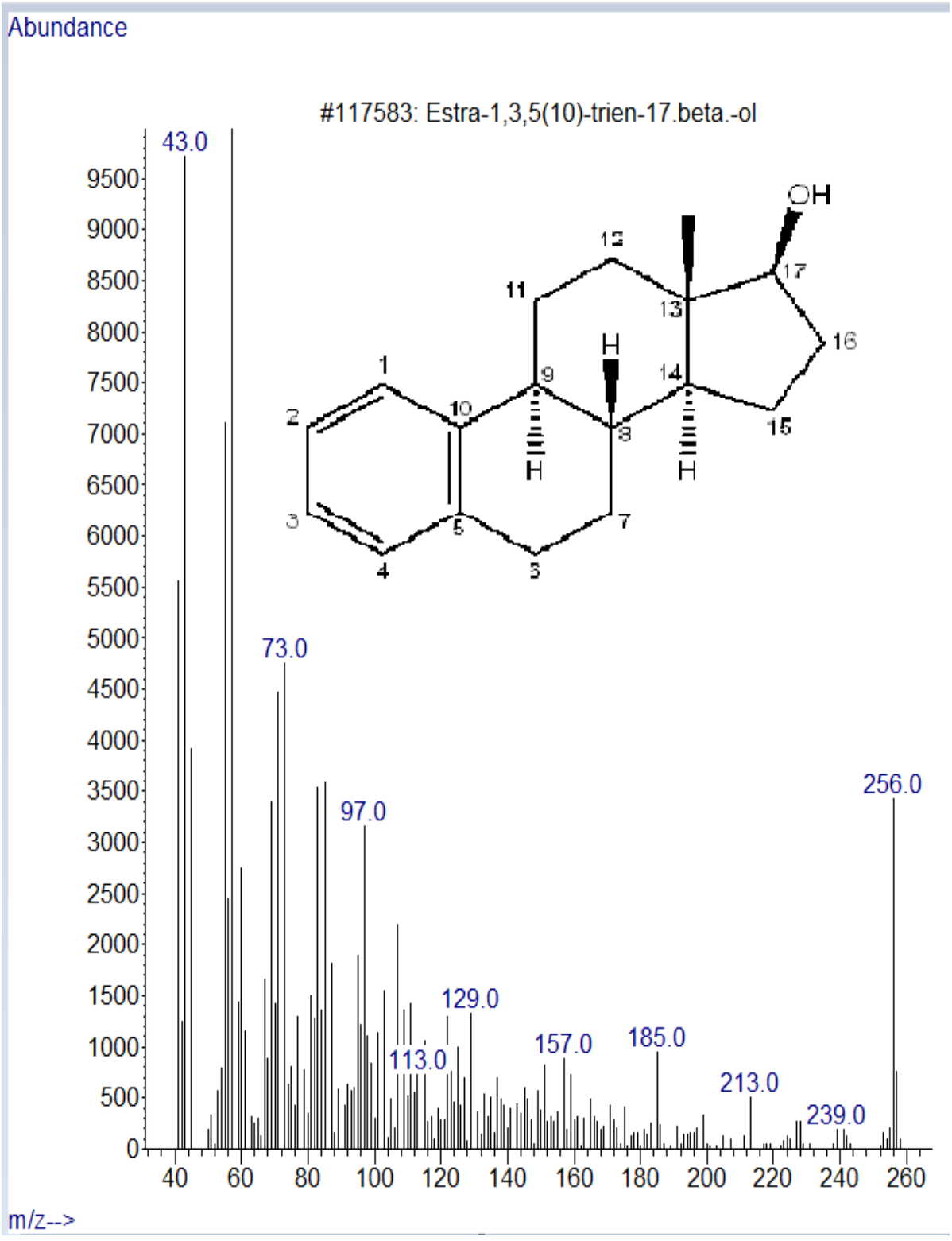


Figure 5. Mass spectrum of Estra-1,3,5(10)-trien-17.beta.-ol

3. 2. Molecular Docking Result

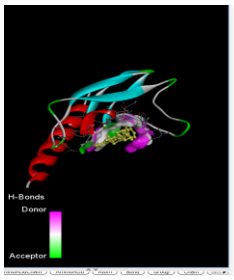
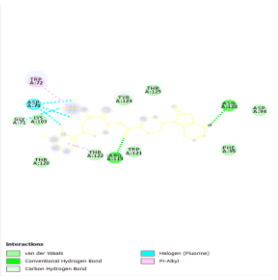
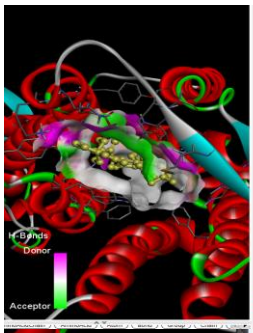
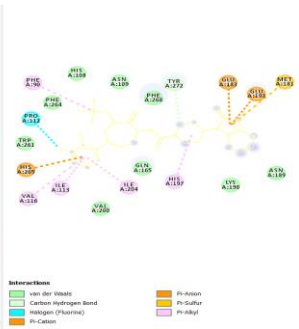
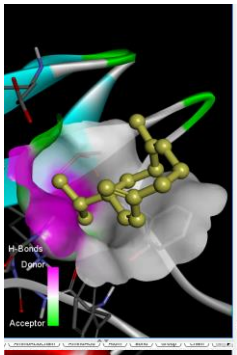
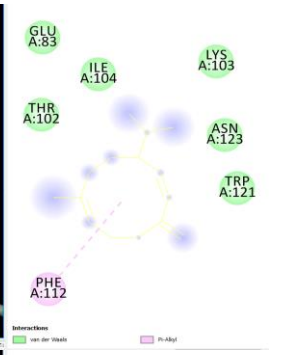
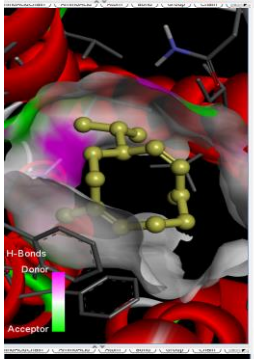
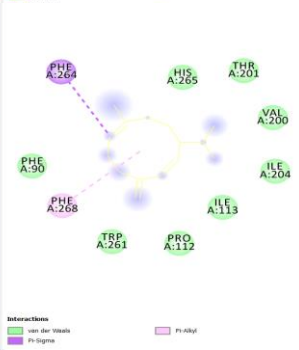
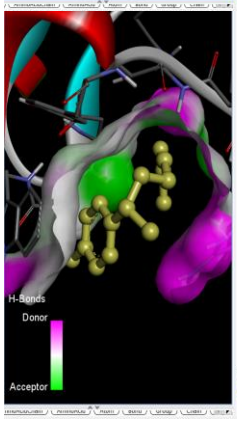
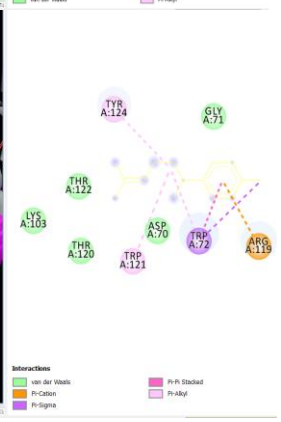
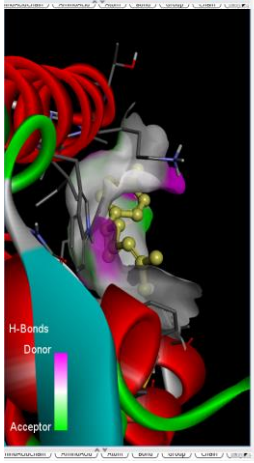
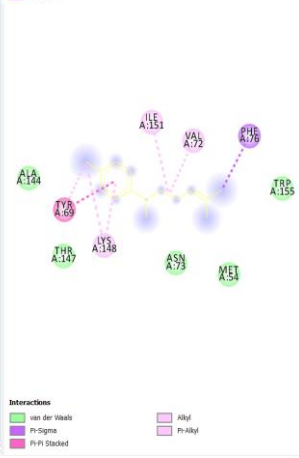
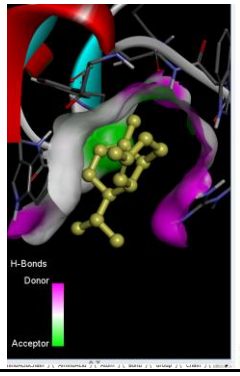
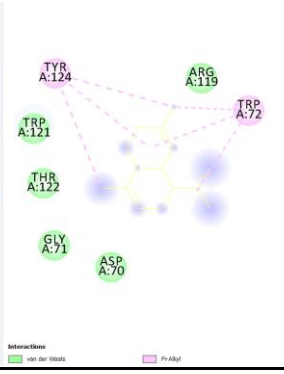
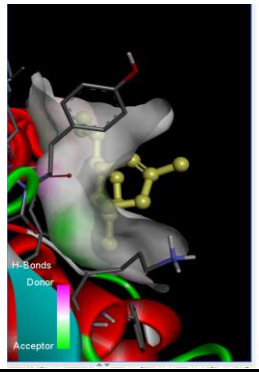
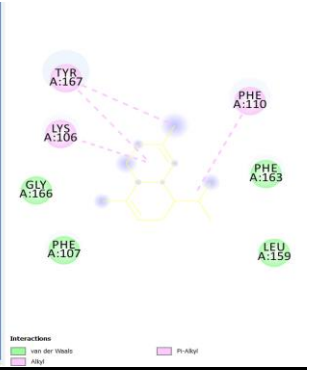
Molecular docking to ascertain the protein-ligand interaction between the identified compounds and the migraine headache proteins was performed using telcagepant a calcitonin gene-related peptide receptor antagonist used for the management of acute migraine headache as the drug control [28]. The compounds exhibited varying degrees of binding on the migraine headache proteins studied.

Binding affinities of compounds in the *Zingiber officinale* leaves for migraine headache proteins are shown in Table 2. The three dimensional (3D) and two dimensional (2D) interactions are presented in Figure 6. The control drug Telcagepant gave the lowest binding score for the two migraine headache proteins studied -10.4 and $-9.1 Kcalmol^{-1}$ in 3n7r and 6e59 respectively, followed by Estra-1,3,5(10)-trien-17.beta.-ol which showed binding scores of -6.8 and -8.8 $1 Kcalmol^{-1}$ in 3n7r and 6e59 respectively. All the other ligands studied also showed good binding scores showing that *Zingiber officinale* may be a good drug lead candidate for the management of migraine headache.

Table 2. Docking scores of compounds in the *Zingiber officinale* powder for migraine headache proteins

S.no	Compound	Pubchem id	ΔG $(Kcalmol^{-1})$	
			3n7r	6e59
1.	Telcagepant	11319053	-9.1	-10.4
2	Decanal	8175	-4.4	-4.9
3	Dodecane	8182	-4.6	-4.9
4	2,6-Octadienal, 3,7-dimethyl-, (Z)-	643779	-4.9	-5.8
5	Tridecane	12388	-4.1	-5.1
6	2-Tetradecene, (E)-	5352912	-4.6	-5.6
7.	Ketone, 2,2-dimethylcyclohexyl methyl (S,1Z,6Z)-8-	549806	-5.0	-5.9
8	Isopropyl-1-methyl-5-methylenecyclodeca-1,6-diene	91723653	-5.2	-8.5
9	Benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl-	92139	-5.8	-7.6

10	Naphthalene, 1,2,4a,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-	101708	-6.1	-7.1
11	1-Hexadecanol	2682	-4.8	-5.4
12	alpha.-Farnesene	5281516	-5.9	-6.5
13	Pentadecane	12391	-4.0	-5.3
14	Cyclohexene, 3-(1,5-dimethyl-4-hexenyl)-6-methylene-, [S-(R*,S*)]-	519764	-5.9	-7.1
15	Dodecanoic acid	3893	-4.7	-4.9
16	Hexadecane	11006	-4.7	-5.0
17	2-Butanone, 4-(4-hydroxy-3-methoxyphenyl)-	31211	-5.6	-6.3
18	Heptadecane	12398	-4.5	-5.0
19	Tetradecanoic acid	11005	-4.6	-5.8
20	E-9-Tetradecenal	5283368	-4.3	-5.8
21	Cyclohexane, 2-propenyl-	75027	-4.7	-5.5
22	9-Heptadecanone	10887	-4.7	-5.2
23	1-Naphthalenol, decahydro-4a-methyl-	543753	-5.3	-6.7
24	Cetene	12395	-4.5	-5.1
25	Estra-1,3,5(10)-trien-17.beta.-ol	537293	-6.8	-8.8
26	n-Hexadecanoic acid	985	-4.9	-5.5
27	9,17-Octadecadienal, (Z)-	5365667	-4.5	-6.1
28	1-(4-Hydroxy-3-methoxyphenyl)dec-4-en-3-one	5281794	-5.9	-5.4
29	1-(4-Hydroxy-3-methoxyphenyl)dodec-4-en-3-one	6442560	-5.7	-6.2

COMPOUND	3D and 2D interaction			
	3n7r		6e59 (**human NK1 tachykinin receptor)**	
Telcagepant				
(S,1Z,6Z)-8-Isopropyl-1-methyl-5-methylenecyclodeca-1,6-diene				
Benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl-				
Naphthalene, 1,2,4a,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-				

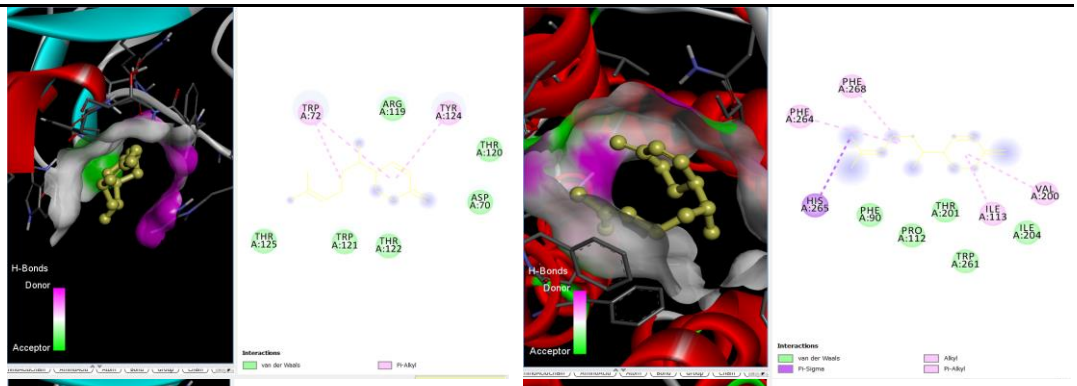
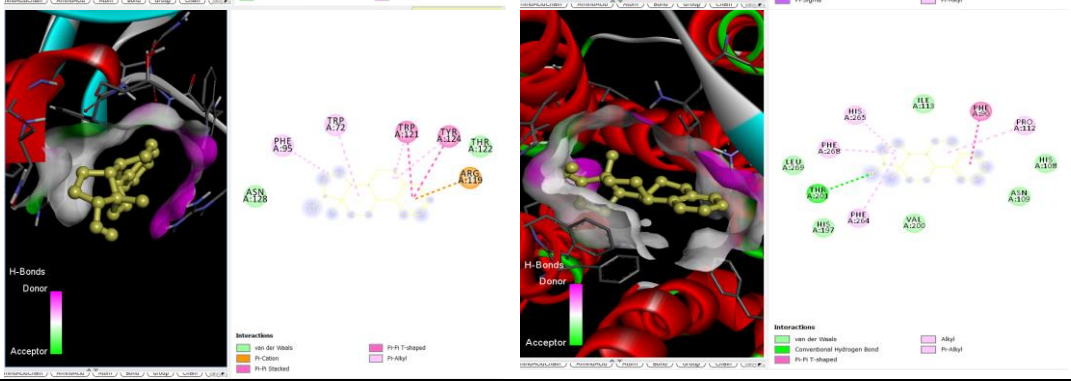
Cyclohexene, 3-(1,5-dimethyl-4-hexenyl)-6-methylene-, [S-(R*,S*)]-	
Estra-1,3,5(10)-trien-17.beta.-ol	

Figure 6. 3D and 2D protein-ligand interactions of the compounds with good values of ΔG

3. 3. Absorption, Distribution, Metabolism, Elimination and Toxicity (ADMET) Result

ADMET properties of the identified compounds were predicted to ascertain their pharmacokinetics and pharmacodynamics behaviors. The results are presented in Table 3. The results show that all the selected compounds obeyed the Lipinski's rule of five which says that a chemical compound which will serve as an oral drug specimen should have molecular mass of less than 500 daltons, not more than 5 hydrogen bond donor, and that the hydrogen bond acceptors should not be more than 10, its calculated octan-water partition coefficient (Clog *P*) should not be more 5. Interestingly none of the studied compounds violated more than one of the rules. None of the compounds showed positive carcinogenicity and they all showed positive human intestine absorptivity meaning that they would be easily absorbed by the human intestine.

Table 3. ADMET properties of the selected compounds

No	Compound	MW	HIA	C	BBB	WS	Alog P	HBA	HBD	NRB
1.	Telcagepant	566.50	+	-	+	-3.9923	3.131	9	2	4
2.	(S,1Z,6Z)-8-Isopropyl-1-	204.35	+	-	+	-5.0233	5.601	0	0	1

	methyl-5-methylenecyclodeca-1,6-diene									
3.	Benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl-	202.17	+	-	-	- 4.6061	5.9	0	0	4
4.	Naphthalene, 1,2,4a,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-	204.19	+	-	+	-5.3459	5.562	0	0	1
5.	Cyclohexene, 3-(1,5-dimethyl-4-hexenyl)-6-methylene-, [S-(R*,S*)]-	204.35	+	-	-	-5.0153	5.608	0	0	4
6.	Estra-1,3,5(10)-trien-17.beta.-ol	256.4	+	-	+	-4.9452	4.186	1	1	0

MW=molecular weight, HIA=human intestine absorptivity, AOT=acute oral toxicity, C=cacinogeneity, BBB=blood brain barrier. HBA-Number of hydrogen bond acceptor, HBD-Number of hydrogen bond donor, NRB-Number of rotatable bond, logp=n-octanol/water distribution coefficient.

3. 4. Density Functional Theory Calculations Results

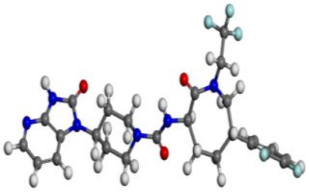
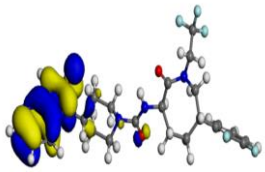
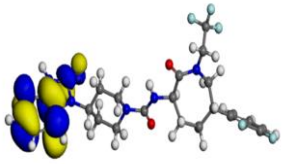
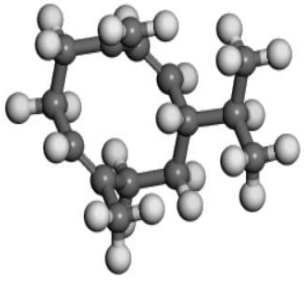
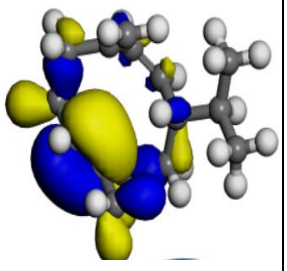
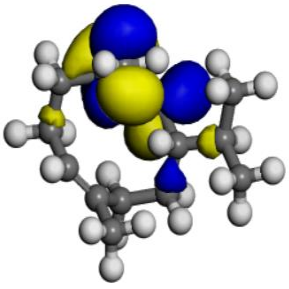
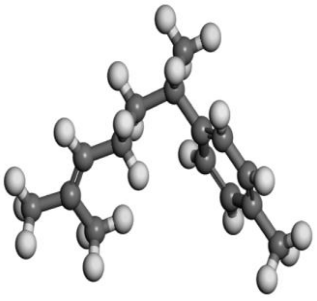
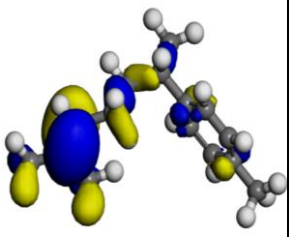
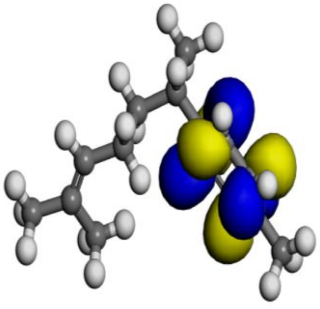
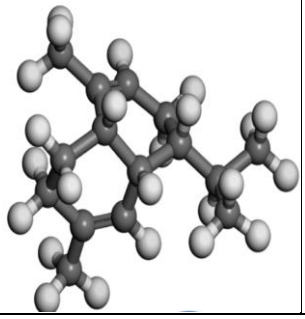
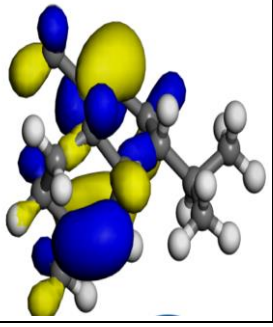
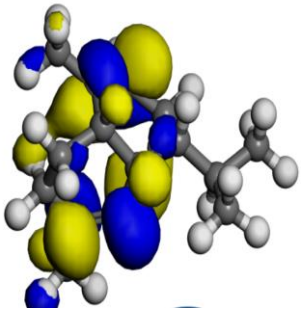
Density functional theory calculations were undertaken on the identified compounds. Calculations were performed with the electronic structure program DMol^3 in the frame work of Mulliken population analysis, the Perdew-Wang (PW) local correlation density functional and the DND basis set [29]. The optimized structures, highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbitals (LUMO) are presented in Figure 7 while the calculated quantum chemical descriptors which include absolute hardness (η), the absolute electronegativity (χ), and softness (δ) are shown in Table 4. The HOMO orbital represent the electron donating nature of a molecule whereas the LUMO orbital shows its electron accepting nature, low energy gap ($\boldsymbol{E_{LUMO} - E_{HOMO}}$) shows the ease of electron transfer between the ligand to the target [30]. The low values of energy gaps observed for the studied compounds indicate that the compounds would be biologically stable. The quantum chemical descriptors presented in Table 4 were estimated as follows

$$\chi = \frac{I+A}{2} \quad (1)$$

$$\eta = \frac{I-A}{2} \quad (2)$$

$$\delta = \frac{1}{\eta} \quad (3)$$

where I is the ionization potential and A is the electron affinity. *The* absolute hardness represents the compounds' tendency to resist electron transfer and it reflects good chemical reactivity, the softness is a property that shows the ability of the compound to accept electron to itself while the absolute electronegativity describes the compound's tendency to attracts electron to itself in a covalent bond.

Compound	Optimized structure	HOMO orbital	LUMO orbital
Telcagepant			
(S,1Z,6Z)-8-Isopropyl-1-methyl-5-methylenecyclodeca-1,6-diene			
Benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl-			
Naphthalene, 1,2,4a,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-			

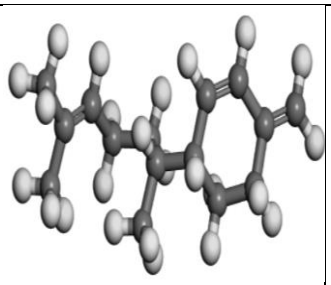
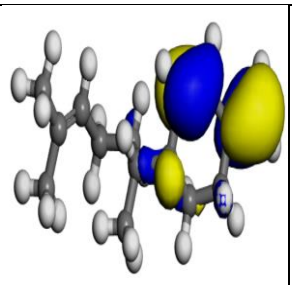
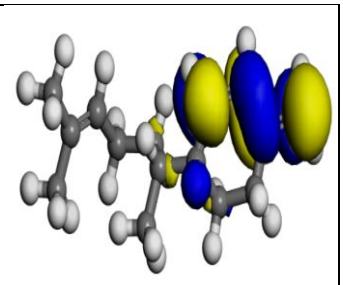
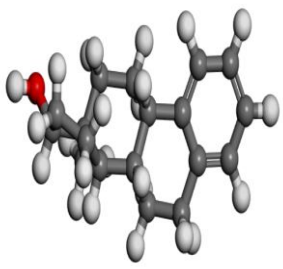
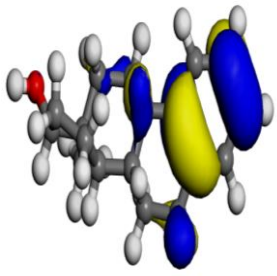
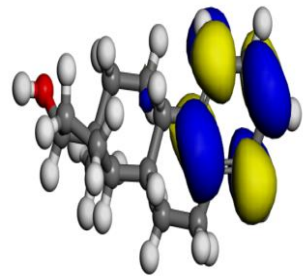
Cyclohexene, 3-(1,5-dimethyl-4-hexenyl)-6-methylene-, [S-(R*,S*)]-			
Estra-1,3,5(10)-trien-17.beta.-ol			

Figure 7. DFT properties of the compounds optimized structures, HOMO and LUMO orbitals

Table 4. Calculated quantum chemical descriptors of the compounds

Compound	E_{HOMO}	E_{LUMO}	I= - E_{HOMO}	A= - E_{LUMO}	Energy gap ($E_{LUMO} - E_{HOMO}$)	χ	η	δ
Telcagepant	-0.199	-0.063	0.199	0.063	0.136	0.131	0.068	14.705
(S,1Z,6Z)-8-Isopropyl-1-methyl-5-methylenecyclodeca-1,6-diene	-0.197	-0.038	0.197	0.038	0.159	0.118	0.080	12.500
Benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl-	-0.191	-0.033	0.191	0.033	0.158	0.112	0.079	12.658
Naphthalene, 1,2,4a,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-	-0.191	-0.009	0.191	0.009	0.182	0.100	0.091	10.989
Cyclohexene, 3-(1,5-dimethyl-4-hexenyl)-6-methylene-, [S-(R*,S*)]-	-0.189	-0.048	0.189	0.048	0.141	0.119	0.071	14.085
Estra-1,3,5(10)-trien-17.beta.-ol	-0.206	-0.029	0.206	0.029	0.177	0.118	0.089	11.236

4. CONCLUSION

In the current research, we explored migraine headache inhibiting potentials of the active chemical components of *Zingiber officinale* using molecular docking and density functional theory methods, Telcagepant, an anti-migraine drug was used as a control to compares the results. Our result revealed that among all the studied compounds Estra-1,3,5(10)-trien-17.beta.-ol bound tightly to the receptors and can interfere with its migraine attacking potential, all the other compounds studied also showed some degrees of interaction with the receptors. The density functional theory results showed that all the studied compounds show low energy gap which is an indication of their reactivity towards the receptors. ADMET results showed that none of the compounds violated more than one of the Lipinski's rule of five, none was carcinogenic or toxic. The results proved that *Zingiber officinale* may be a good drug candidate for the management of migraine headache.

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