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Research Article

In silico calculations of Binding energy, Dipole moment by DFT and Drug Activity Predictions for the bioactive constituent present in Tabernaemontana divaricata leaves.

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ABSTRACT

Knowing the importance of Tabernaemontana divaricata leaves for the treatment of fever, pain,dysentry and as rejuvenator for eyes as revealed by various literature resources, the bioactive constituents isolated from the Tabernaemontana divaricata leaves like 19-epivoacristine, 11-Methoxy-N-methyldihydropericyclivine, Mehranine, Lahoricine, Voaharine, Voafinidine were taken for our studies. DFT calculations for the determination of binding energy and dipole moment were carried out by using the Gaussian software. DFT were performed at B3LYP and HF methods using the basis set STO-3G, 3-21G, 6-31G. Insilico drug activities of the above constituents were also predicted using the PASS prediction method. The DFT calculations of binding energy and dipole moment showed that 19-epivoacristine was found to be more stable among the above six compounds. PASS prediction result revealed that these six compounds were found to exhibit various pharmacological activities like antineoplastic, anti- inflammatory, analgesic activities in the range of 60 -85% and can also be useful for the treatment of Alzheimer's disease.

Keywords: Tabernaemontana divaricata, DFT, HF , B3LYP and STO-3G.

INTRODUCTION

Tabernaemontana divaricata belongs to the family of Apocyanceae[1]. It has been used in conventional rejuvenation remedies in Thailand[2] and these remedies are thought to improve the memory Power. Local people in America, Africa and continental Asia have used this plant as a central nervous system stimulant[3]. Leaves are evergreen, with milky sap and the milky juice of the leaves have anti-inflammatory, anti-hypertensive and diuretic actions and also used to cure wounds. The milky juice of the leaves along with oil is applied over the forehead for pain present in the eyes. The flower juice can be mixed with oil are used as eye drops and also used for skin diseases[4]. The roots are used to relieve tooth-ache and to remove intestinal worms[5]. It has been used in the folk medicine as anti-infection, , analgesic, anti-tumor, anti-oxidative and neuronal activity agents[6]. In our present work, relative energies and dipole moment have been calculated, using the B3LYP and HF methods[7]. The drug likeness Properties for the compounds of *T. divaricata* leaves, were determined by Prediction Activity Spectra for Substances (PASS)[8].

EXPERIMENTAL METHODS

i) Materials:

Six bioactive compounds reported in the Tabern aemontana divaricata leaves extract like 19-epiv oacristine, 11-Methoxy-N-methyl dihydro peri cyclivine, Mehranine, Lahoricine, Voaharine and Voafinidine were taken from the reported resources[9] as given in **Figures 1 to 6.**

ii) Methods:

A) DFT Calculation:

DFT calculation were carried out using Gaussian software 05.Binding energies and dipole moment of the 19 - epivoacristine, 11- Methoxy – N - methyl dihydropericyclivine, Mehranine, Lahoricine, Voaharine and Voafinidine compounds were

calculated by B3LYP and HF methods using STO-3G, 3-21G, 6-31G basis sets[10]. For drawing the structure of these compounds Gauss View 5.0 was used.

The drawn chemical structure appeared as given in **Figure7**.

The binding energy and the dipole moment of the above six compounds predicted by by B3LYP and HF methods were given in **Tables I** to **IV**

B) PASS Prediction:

Generally the chemical compounds different types of biological activity was evaluated using PASS software, which estimates the probabilities of 900 types of biological activity on the basis of structural formulae of the compound with an accuracy of 85%[11]. The structures of the above six compounds were drawn in **chemdraw ultra10.0** as given in **Figure 8** and saved as mol files **(*.mol)** .

PASS prediction window for prediction of bioactivity appear as given in **Figure 9**.

Various Pharmacological activities predicted for 19 - epivoacristine,11- Methoxy- N- methyldihydroperi cyclivine, Mehranine, Voaharine, Lahoricine, and Voafinidine compounds using PASS were given in **Table – Va & Vb.**

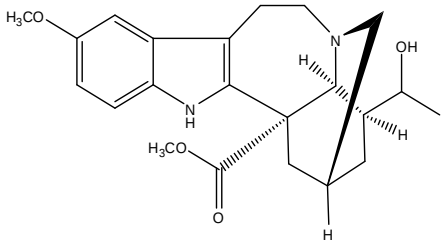


Figure 1: 19-epivoacristine

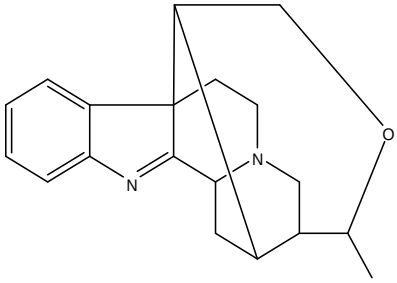


Figure 2: Lahoricine

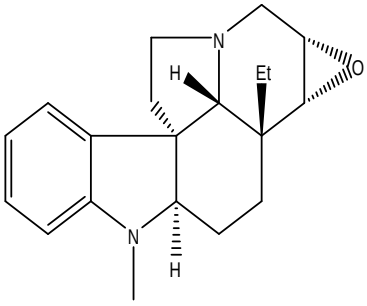
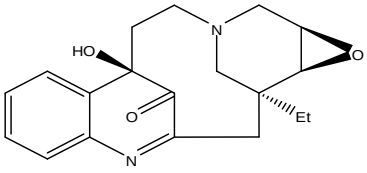


Figure 3: Mehranine



Figrue 4: Voaharine

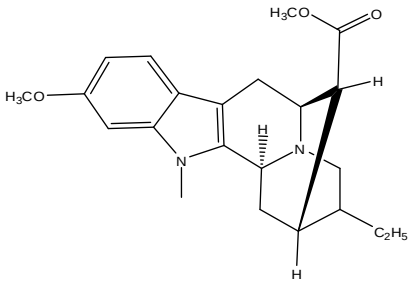


Figure 5: 11-Methoxy-N-methyldihydropericyclivine

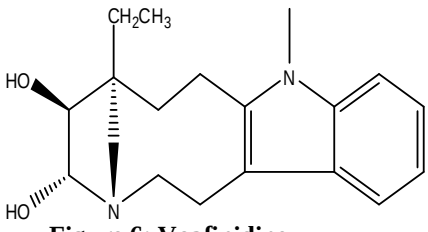


Figure 6: Voafinidine

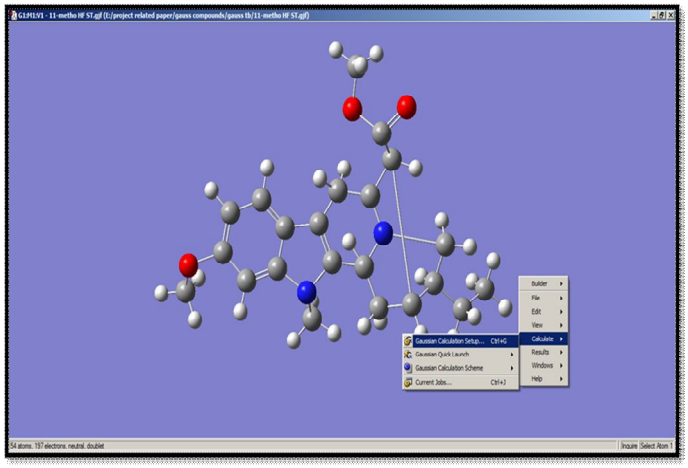


Figure 7: Structure of 19-Epivoacristine

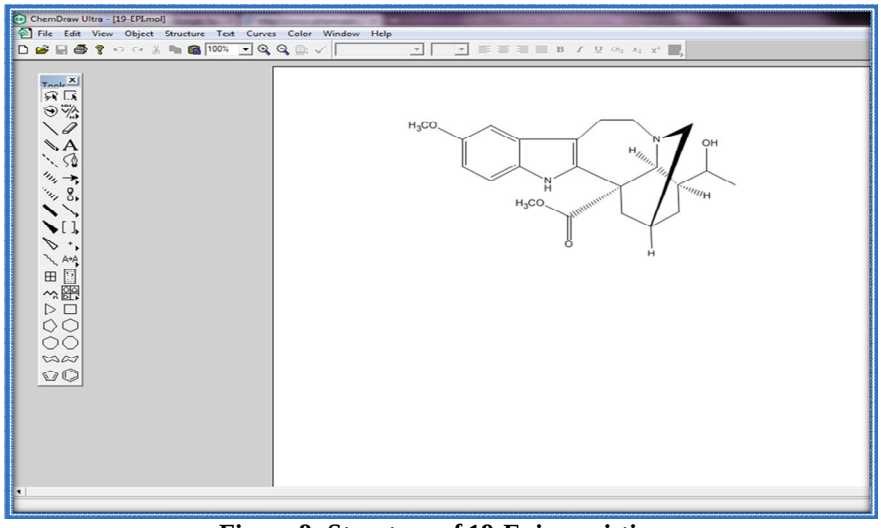


Figure 8: Structure of 19-Epivoacristine

Figure 9: Pass Prediction Window

Table – I Binding Energy (a.u.) of compounds in B3LYP

S.No	Compounds	Compounds Name	Basis sets		
			STO-3G	3-21G	6-31G
1	A	19-epivoacristine	-1248.719	-1257.848	-1246.406
2	B	11-Methoxy-N-methyldihydropericylivine	-1174.003	-1182.471	-1188.663
3	C	Voaharine	-1058.472	-1066.304	-1071.860
4	D	Voafinidine	-987.210	-994.240	-999.386
5	E	Lachoricine	-994.943	-952.318	-
6	F	Mehranine	-866.891	-873.742	-878.353

Table – II Dipole moment (Debye) of compounds in (B3LYP) method.

S.No	Compounds	Compounds Name	Basis sets		
			STO-3G	3-21G	6-31G
1	A	19-epivoacristine	2.5148	2.7710	2.5521
2	B	11-Methoxy-N-methyldihydropericylivine	5.2483	10.0359	10.9445
3	C	Voaharine	8.4480	8.9351	8.8874
4	D	Voafinidine	5.4194	6.1499	-
5	E	Lachoricine	7.0294	5.5836	-
6	F	Mehranine	5.3805	5.6581	5.7977

Table- III Binding energy (a.u.) of compounds in HF method

S.No	Compounds	Compounds Name	Basis sets		
			STO-3G	3-21G	6-31G
1	A	19-epivoacristine	-1240.948	-1249.729	-1256.164
2	B	11-Methoxy-N-methyldihydropericylivine	-1166.745	-1174.886	-1180.965
3	C	Voaharine	-1051.779	-1059.340	-1064.790
4	D	Voafinidine	-981.081	-987.776	-992.770
5	E	Lachoricine	-938.697	-945.591	-950.592
6	F	Mehranine	-861.046	-867.673	-872.198

Table – IV Total Dipole moment (Debye) of compounds in (HF) method.

S.No	Compounds	Compounds Name	Basis sets		
			STO-3G	3-21G	6-31G
1	A	19-epivoacristine	2.9545	3.7142	3.7214
2	B	11-Methoxy-N-methyldihydropericylivine	10.8845	13.3403	14.2575
3	C	Voaharine	16.2864	21.3888	21.6160
4	D	Voafinidine	5.7914	6.9262	7.3614
5	E	Lachoricine	9.3442	-	29.8524
6	F	Mehranine	4.3699	5.4582	5.6732

Table – V(a) Biological activities of the compounds predicted using PASS

S.NO	Name of the compound	Name of activity	Pa	Pi
1	19- Epivoacristime	CYP2D6 substrate	0.789	0.005
		5- Hydroxy tryptamine uptake inhibitor	0.690	0.027
		Muramoyltetrapeptide carboxy peptidase inhibitor	0.676	0.017
2	11-Methoxy-N-methyldihydropericyclivine	CYP2H substrate	0.840	0.012
		Gluconate 2-dehydrogenase (acceptor) inhibitor	0.723	0.044
		Respiratory analeptic	0.656	0.018
		5 Hydroxytryptamine uptake inhibitor	0.609	0.004
		Antinociceptive	0.529	0.022
3	Mehranine	Antineoplastic	0.814	0.010
		Respiratory analeptic	0.704	0.014
		Analeptic	0.629	0.016
		CYP2D2 inhibitor	0.497	0.020
		Prostate cancer treatment	0.487	0.011
		Phosphatase inhibitor	0.548	0.076
		TP53 expression enhancer	0.537	0.073

Table – V(b) Biological activities of the compounds predicted using PASS

S.NO	Name of the compound	Name of activity	Pa	Pi
4	Voaharine	Antineoplastic	0.732	0.021
		Gluconate 2-dehydrogenase inhibitor	0.745	0.034
		Anti-inflammatory	0.636	0.025
		Antidyskinetic	0.607	0.037
		Phosphatase inhibitor	0.611	0.042
5	Lahoricine	Antineoplastic	0.851	0.007
		General pump inhibitor	0.573	0.032
		Anesthetic general	0.512	0.020
		Alzheimer's disease treatment	0.479	0.015
		CYP2H substrate	0.529	0.105
6	Voafinidine	Alzheimer's disease treatment	0.747	0.005
		Neurodegenerative disease treatment	0.747	0.005
		Analgesic	0.713	0.009
		Coginition disorder treatment	0.677	0.005

RESULT AND DISCUSSION

A) DFT Calculation:

DFT calculation for binding energy and dipole moments by B3LYP and HF methods using three basis sets (STO-3G, 3-21G, 6-31G) were given in **Table – I & II** revealed the following observations:

a)Energy Calculations by:

i) B3LYP method:

The binding energy values by STO-3G basis sets were found to be -1248.716,-1174.003,-1058.472,-987.210, -944.943 ,-866.891, and by 3-21G basis sets, -1257.848,-1182.471, -1066.304,-994.240.- 952.318, - 873.742 for the above six compounds. Using 6-31G basis sets -1246.406, -118.663, -1071.806, -999.386 and 878.353 a.us. were predicted respectively for the above six compounds

From the above results, it was observed that 19-epivoacristine was found to be more stable than others.

ii) HF method:

The binding energy values for the above six compounds were found to be -1240.948,- 1167.745, -1051.779, -981.081, -938.697, -861.046 a.u by STO-3G basis sets, and -1249.729, -1174.886, -1059.340, -987.776, -945.591, -867.673a.u by3-21G basis sets. & -1256.164, -1180.965, -1064.790, -992.770, -950.592, -872.198 a.u. by 6-31G basis sets respectively.

From the above results, it was also observed that 19-epivoacristine was found to be more stable.

b)Dipole moment Calculation:

i) B3LYP method:

The Dipole moment values for the above six compounds by STO-3G basis sets were found to be 2.5148, 5.2483, 8.4480, 5.4194, 7.0294 and 5.3805 Debye .Using 3-21G basis sets, the Dipole moment were 2.7710, 10.0359, 8.9351, 6.1499, 5.5836 and 5.6581 Debye and by 6-31G basis sets 2.5521, 10.9445, 8.8874, 5.7977 Debye units were found respectively for the above six compounds.

From the above results, it was observed that 19-epivoacristine was found to have lowest Dipole moment values (2.5148, 2.7710 and 2.5521) and hence it was found to be more stable.

ii) HF method:

The Dipole moment values for the above six compounds by STO-3G basis sets were found to be 2.9545, 108845, 16.2864, 5.7914, 9.3442, 4.3699 Debye and by3-21G basis sets, 3.7142, 13.3403, 21.3888, 6.9262 and 5.4582 Debye were observed for

these compounds. The Dipole moment values were found to be 3.7214, 14.2575, 21.6160, 7.3614, 29.8524 and 5.6732 Debye by 6-31G basis sets for the above compounds

From the above results, it was also observed that 19-epivoacristine was found to have lowest Dipole moment values (2.9545, 3.7142 and 3.7214) among other compounds and hence it was found to be more stable.

B) PASS Prediction:

All the six compounds isolated from T.divaricata plant were found to exhibit various pharmacological activities in the range (70-85%) as given in **Table – Va&Vb.**

Lahoricine was found to exhibit antineoplastic activity (85.1%) and can be used for the treatment of Alzheimer's disease (47.9%). 11-Methoxy-N-methyldihydropericyclivine was found to have Gluconate 2-dehydrogenase inhibitor (72.3%) and respiratory analeptic (65.6%) activities. Mehranine exhibited respiratory analeptic (70.4%) and analeptic(62.9%) activities. Antineoplastic and Anti-inflammatory activities for Voaharine was found to 73.2% & 63.6% respectively. 19-epivoacristine was found to exhibit 5-hydroxy tryptamine release stimulant (69%) and muramoyltetrapeptide carboxypeptidase inhibitor (67.6%) activities. Voafinidine can be used for the treatment of alzheimer's disease (74.7%) and also exhibited analgesic activities(71.3%).

CONCLUSION

Binding energy calculation for Lahoricine, Mehranine, Voafinidine, Voaharine, 11-Methoxy-N-methyldihydropericyclivine and 19-epivoacristine compounds byB3LYP & HF methods with STO-3G,3-21G,6-31G basis sets using Gaussian software, indicated that 19-epivoacristine was found to be more stable compared to other compounds as revealed by the binding energy values. The stability of these compounds were also confirmed by dipole moment measurement. The lowest dipole moment values of 19-epivoacristine by B3LYP and HF methods showed that19-epivoacristine was found to be more stable.

The PASS prediction pharmacological activities showed that among the six compounds, Lahoricine, Mehranine and Voaharine exhibited antineoplastic activity as 85% , 81.4% &73.2% respectively . Voafinidine can be used for treatment of Alzheimer's disease (74.7%). 11-Methoxy-N-methyldihydropericyclivine exhibited gluconate 2-dehydrogenase inhibitor activity 72.3% and 19-epivoacristine can be used as 5-hydroxytryptamine release stimulant (69%).

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