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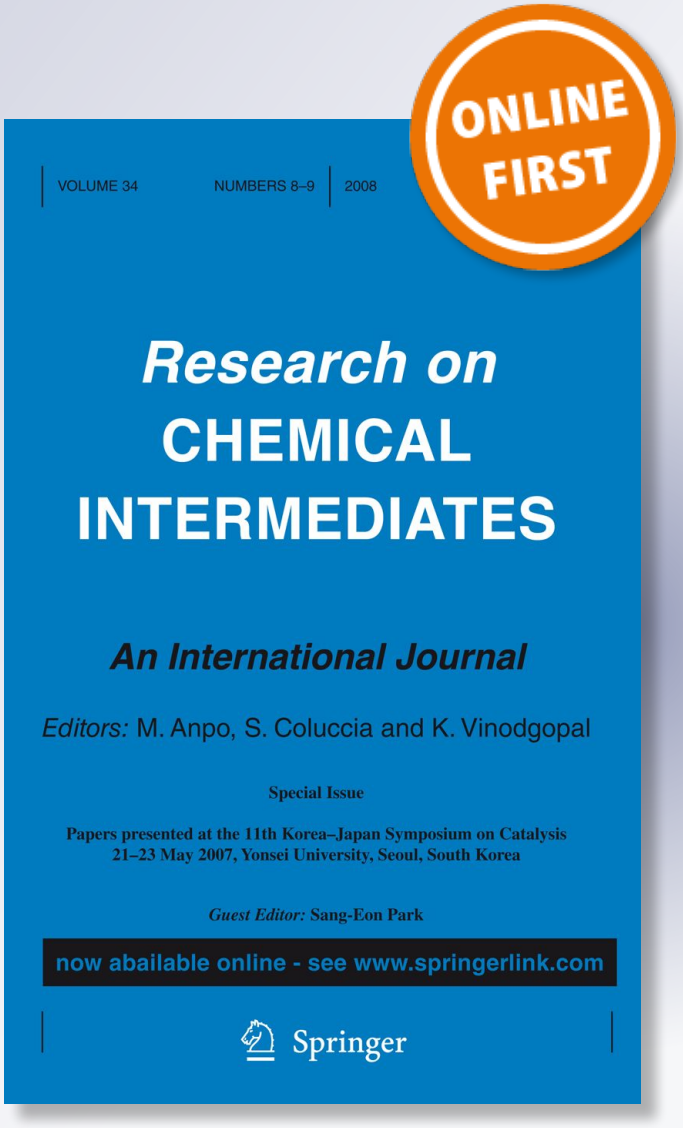

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Quantitative structure–activity relationship of antitumor and neurotoxic β-carbolines alkaloids: nine harmine derivatives

F. Lamchouri · H. Toufik · Z. Elmalki · S. M. Bouzzine · H. Ait Malek · M. Hamidi · M. Bouachrine

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Abstract Cancer is the worldwide health problem and the most frightening disease of humans. Modification of natural product lead is an important way to find promising anticancer agents. The β-carboline alkaloids present in medicinal plants have recently drawn attention due to their antitumor properties. Nine harmine derivatives (including harmine) were investigated for their antitumor effects and acute toxicities in mice, and the structure–activity relationship (SAR) was also analyzed by Qi Chen et al. In the present study, density functional theory calculations have been carried out in order to get insight into the structure and property information for this series of molecules. Descriptors such as total energy, gap energy, HOMO and LUMO energies, dipole moment (μ), electronegativity (χ), electron affinity (A), global hardness (η), softness (σ), and ionization potential (I), provide vital information about the activity of nine harmine derivatives. Further, we utilized our recently proposed model descriptor defined based on such calculated parameters to predict the antitumor activity/neurotoxicity of β-carboline alkaloids. Furthermore, satisfactory quantitative SAR models were derived to calculate the activities values from the DFT-computed electronic parameters.

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Keywords β-carbolines · Harmine derivatives · Quantitative structure–property relationship · DFT calculations · Descriptors

Introduction

Over 21,000 alkaloids have been identified, which thus constitute the largest group among the nitrogen-containing secondary metabolites. β-carboline alkaloids are important constituents of *Peganum harmala* (Linn Zygophylaceae). The seeds of *P. harmala* contain about 2–6 % pharmacologically active alkaloids [1], which are mostly β-carbolines such as harman, harmine, harmaline, and harmalol [2, 3]. In traditional medicine, *P. harmala* has been used to treat coughs, hypertension, diabetes, asthma, jaundice, lumbago, and many other human ailments [4, 5].

Those alkaloids identified from the plants of the genus *Peganum* showed extensive pharmacological actions, such as antitumor effects [6], analgesic effects [7], vasorelaxant activities [8], antimicrobial activity [9, 10], strong reversible inhibition of monoamine oxidase [11, 12], and inhibitive activity against acetylcholinesterase [13]. In the past decades, more attention has been drawn on their anticancer potencies [14–16]. A number of alkaloids have been used as anticancer drug over 40 years. It is well known that the β-carboline alkaloids are a widely used antitumor agent. However, due to anticancer drug limitations, such as toxicity, resistance, and its poor aqueous solubility, many other derivative alkaloids with anticancer activity have been tested and received attention in the past few years [17, 18].

Therefore, great efforts have been made to look for new alkaloids with better activity and lower resistance. The β-carboline alkaloids present in medicinal plants such as *P. harmala* have recently drawn attention due to their antitumor properties. Our previous studies show that the alkaloidal extract of *P. harmala* seeds is cytotoxic to several murine cell lines in vitro and has an antitumor effect in a tumor model in vivo [19–22]. The antiproliferative activity of four alkaloids harmalacidine (**1**), harmine (**2**), peganine (**3**), and vasicinone (**4**) isolated from *P. harmala* seeds and theirs computational study was investigated. Compounds (**1**–**4**) were assayed in vitro for their effect on thymidine incorporation using Jurkat leukemia cell line at concentration of 5, 10, 25, 50, and 100 μg/ml. Their cytotoxicity was also evaluated at the concentrations indicated above on Sp2/O-Ag14 myeloma cells, Med-mek carcinoma, UCP-med Carcinoma, and UCP-med sarcoma. Results showed that vasicinone, harmine, and harmalacidine inhibited the proliferation of Jurkat, clone E6-1 cell line with significant cytotoxic effect. No noticeable effect of peganine (compound **3**) on thymidine incorporation was observed. These in vitro studies have shown that harmine, β-carbolines alkaloid have more activity [23] and was highly cytotoxic and significantly inhibited tumor cell growth with apoptotic effect according to Hamsa et al. [24].

Recently, in an attempt to discover novel β-carboline alkaloids with potent antitumor activity and low neurotoxicity, nine harmine derivatives were investigated for their antitumor effects and acute toxicities in mice, and structure–activity relationship (SAR) analysis was then conducted by Qi et al. [25]. In their study, nine harmine derivatives (including harmine) were investigated for their potential

cytotoxicities against human HepG2 cells using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays. The harmine and its derivatives resulted in in vitro cytotoxicity (IC50) values of 0.011–0.021 μmol/ml HepG2 cells, with compounds **8** being the most potent among all agents tested. Compounds **6**, **7**, and **9** were more active than compound **1**. The compounds with both methyl substitution at R1 of the β-carboline skeleton and methoxyl substitution at R7 (compounds **1**, **6**, **7**, **8**, and **9**) were more potent than the compounds with formate at R3 (compounds **2**, **3**, **4**, and **5**). This suggests that a short alkyl or aryl substitution at R9 might increase cytotoxicity, while a long alkyl at R9 or formate substitution at R3 (such as compounds **2**, **3**, **4**, and **5**) might reduce antitumor activity.

Our recent paper [23] has shown that the study of cytotoxic and antiproliferative activities of *P. harmala* on experimental models of cancer allowed us to show that harmalacidine (**1**), harmine (**2**) vasicinone (**4**), compounds (**1**, **2**, **4**), isolated from the alcaloidic fraction have an in vitro cytotoxic activity on carcinogenic cellular lines and an inhibitory activity of the synthesis of DNA. The obtained results showed that the activity may depend on the product tested and the cellular line considered. The three pure alkaloids of *P. harmala* contrary to the peganine (compound **3**) seem to act on the Jurkat line, E6-1 clone by inhibiting the synthesis of the DNA and also the cellular division. From the theoretical calculations carried out for the studied molecules **1**, **2**, **3**, and **4**, it can be concluded that the electronic properties are well correlated with their experimental results.

On the other hand, several quantum chemical methods and quantum-chemistry calculations have been performed in order to study the molecular structure and the reaction mechanisms in order to interpret the experimental results as well as to solve chemical ambiguities and to correlate the biological activities to the molecular properties [26–28]. The structure and electronic parameters can be obtained by means of theoretical calculations using the computational methodologies of quantum chemistry. The geometry of the studied molecules in its ground state, as well as the nature of their molecular orbitals, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are involved in the properties of activity of inhibitors. The relationships between the structural parameters and the antitumor activity of those compounds have not yet been studied. The antitumor activities effects of harmine and derivatives depend on their physical and chemical properties, and it is therefore important to recognize the structure–property relationships that allow a complete understanding of their environmental consequences. Hence, in the present study, the molecular structures of the series of nine harmine derivatives (including harmine) have been studied with the density functional theory (DFT). Quantitative structure–activity relationships are generally used to evaluate and predict the "activity" and other properties [29–32]. The structures of the studied compounds are shown in Table 1.

The more relevant molecular properties are the highest occupied molecular orbital energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}), energy gap (ΔE), dipole moment (μ), electronegativity (χ), electron affinity (A), global hardness (η), softness (σ), ionization potential (I), the fraction of electrons transferred (ΔN), and the total energy (TE).

Table 1 Structures of the studied compounds (**1**–**9**): nine harmines derivatives (β-carbolines alkaloids)

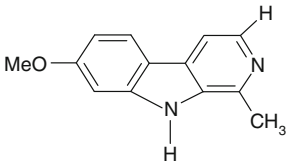
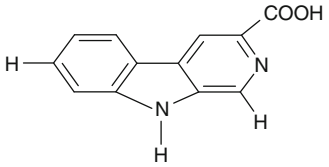
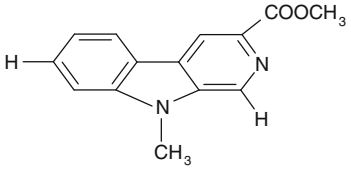
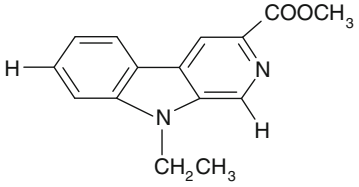
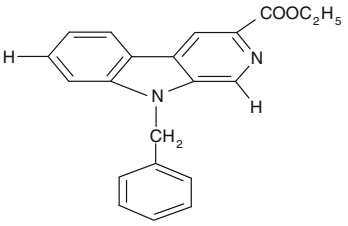
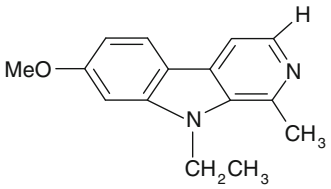
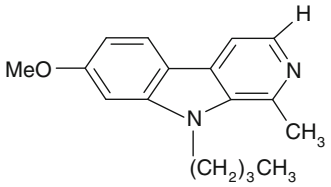
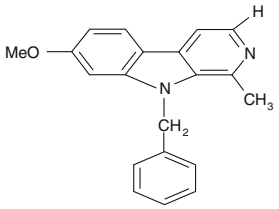
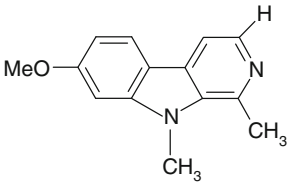
Compounds	Chemical structure
1 = Harmine	
2	
3	
4	
5	

Table 1 continued

Compounds	Chemical structure
6	
7	
8	
9	

Computational details

DFT methods were used in this study. These methods have become very popular in recent years because they can reach exactitude similar to other methods in less time and less expensive from the computational point of view. In agreement with the DFT results, energy of the fundamental state of a polyelectronic system can be expressed through the total electronic density, and in fact, the use of electronic

density instead of wave function for calculating the energy constitutes the fundamental base of DFT [33, 34]. All calculations were done by GAUSSIAN 03 W software [35] using the B3LYP functional [36] and a 6-31G* basis set [37–39]. The B3LYP, a version of DFT method, uses Becke's three-parameter functional (B3) and includes a mixture of HF with DFT exchange terms associated with the gradient corrected correlation functional of Lee, Yang, and Parr (LYP). The geometry of all species under investigation was determined by optimizing all geometrical variables without any symmetry constraints. Frontier molecular orbital's (HOMO and LUMO), the ionization potential, $I = -E_{\mathrm{HOMO}}$, and the electron affinity, $A = -E_{\mathrm{LUMO}}$, the absolute electronegativity, $\chi = \frac{I+A}{2}$, and absolute hardness, $\eta = \frac{I-A}{2}$ and the softness $\sigma = \frac{1}{\eta}$ were calculated from the DFT-optimized structures for each molecule.

Results and discussion

Experimental results

The results reported by Qi et al. [25] of the antitumor effects and acute toxicities in mice, and the structure–activity relationship (SAR) of nine harmine derivatives (including harmine) are summarized in Table 2.

The tumor inhibition rates of harmine derivatives in mice bearing Lewis lung cancer, sarcoma180, or HepA tumor shows that harmine (compound **1**) has only moderate antitumor effect, yet its derivatives **5**, **6**, and **8** showed inhibition rates of more than 40 %. Compounds **5**, **6**, and **8** exhibited the highest antitumor effect among these compounds. Moreover, compound **6** showed the highest inhibition rate (49.5 %) against mouse hepatoma. It appears that short alkyl or aryl substitution at R9 is favorable for antitumor activity, and perhaps aryl substitution is more favorable.

The study of acute neurotoxicity of harmine derivatives in mice shows that all the compounds resulted in acute toxic manifestations. For compounds **1**, **3**, **4**, **6**, **7**, **8**, and **9**, the acute toxic effects included tremble, twitch, jumping, tetanus, and supination. Death occurred mostly in the high-dosage group within 1 min after injection and reached a peak 1 h later. In surviving animals, the tremble lasted for about 20 min then relieved gradually. All surviving animals returned to normal in the next day. For compounds **2** and **5**, neurotoxic effects were much more fateful. Animals were drowsy and lacked activity after injection of compound **2**, but did not tremble or twitch. Death occurred in the high-dosage group 10 min after drug injection and reached a peak 1 h later. Compound **5** caused no obvious neurotoxic reaction or death at tested dosages, except for partial contortion at the injection point at the highest dosage used. All the animals were found to have no obvious organic changes in the heart, kidneys, and liver. The lower toxicities of compounds **2**, **3**, **4**, and **5** than other compounds suggest that formate substitution at R3 might lower the neurotoxicity. The compounds with both substitutions at R3 and R9 might be of high antitumor activity and low neurotoxicity. Compound **5** with both a benzyl at R9 and an ethyl formate at R3 exhibited high antitumor activity and low neurotoxicity.

Table 2 Acute neurotoxicity, antitumor, and cytotoxic activities of nine harmines derivatives: compounds **1**–**9** (β-carbolines alkaloids)

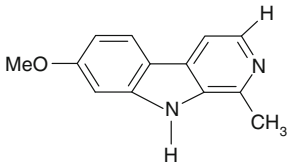
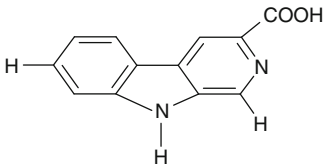
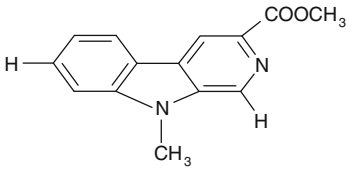
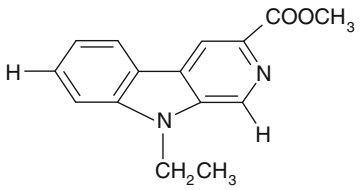
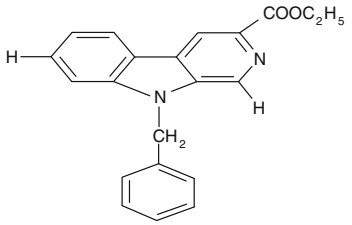
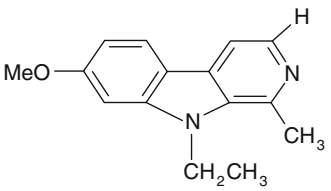
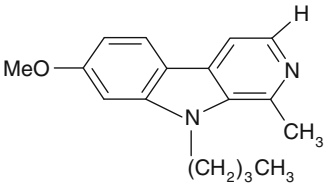
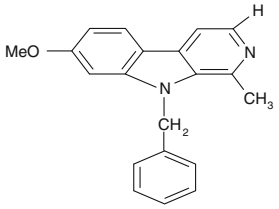
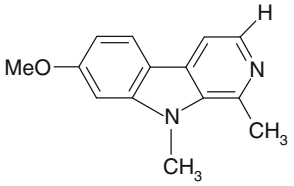
Compounds	Chemical structure	I Acute neurotoxicity	II Antitumor activity (%)	III Cytotoxic activity
1 = Harmine		++	24	
2		−	33	
3		+	33	
4		+	30	
5		−	42	
6		++	43 (49.5 % on the HepA hepatoma)	

Table 2 continued

Compounds	Chemical structure	I Acute neurotoxicity	II Antitumor activity (%)	III Cytotoxic activity
7		++	31	
8		++	45	The most active
9		++	35	

I: Neurotoxicity of harmine and its derivatives, − No such reactions, score = 0; + Score of severity of acute neurotoxicity = 5; ++ Score of severity of acute neurotoxicity = 10

II: Antitumor activity of harmine and its derivatives. The tumor inhibition rate is the mean of the tested tumors by each compound. The percentages given are an average of action on 3 types of cancer: Lewis lung cancer, S180, and HepA hepatoma

III: Cytotoxic activity of harmine and its derivatives. The in vitro activity was not given in detail for all products. The study reported that compound **8** is the most active product. Products **6**, **7**, and **9** are more active than a product **1**

In vitro cytotoxicity of harmine derivatives to HepG2 cells shows that compound **8** is the most potent among all agents tested. Compounds **6**, **7** and **9** were more active than compound **1**. The compounds with both methyl substitution at R1 of the β-carboline skeleton and methoxyl substitution at R7 (compounds **1**, **6**, **7**, **8**, and **9**) were more potent than the compounds with formate at R3 (compounds **2**, **3**, **4**, and **5**). This suggests that a short alkyl or aryl substitution at R9 might increase cytotoxicity, while a long alkyl at R9 or formate substitution at R3 (such as compounds **2**, **3**, **4**, and **5**) might reduce antitumor activity. SAR analysis indicated that the formate substitution at R3 of the tricyclic skeleton reduced their neurotoxicity, while the short alkyl or aryl substitution at R9 increased the antitumor activity.

All these findings indicate that compounds with both substitutions at R3 and R9 (such as compound **5**) have high antitumor activity and low toxicity.

Theoretical results

On the other hand, quantum chemical calculations were performed to investigate the structural parameters affect the activities of the studied compounds. Geometric and electronic structures of these molecules were calculated by the optimization of their structures. The theoretical results are reported in Tables 3 and 4. The obtained molecular structures by DFT/B3LYP/6-31G*(d) obtained from the DFT calculations are given in Figs. 1 and 2 and the obtained HOMO and LUMO orbitals of are also given in Fig. 3.

To study the different correlations, we have proposed two groups (group 1: Series of compounds **1**, **6**, **7**, **8**, and **9**) and group 2: Series of compounds **2**, **3**, **4**, and **5**). Each group represents a set of molecules with similar structures and properties.

When analyzing the different results, interesting findings were observed:

- The experimental study reported that molecule **8**, containing a benzyl substituent on the nitrogen, is the most active product. When comparing the different parameters obtained from structures of molecules **1**, **6**, **7**, **8**, and **9** obtained after optimization by the DFT method, we note that molecule **8** has the lowest total energy, the highest affinity, and the lowest value of HOMO energy.
- The most active molecule and the less toxic is the product 5. The structure of this molecule is characterized by the benzyl group on the nitrogen atom and the $COOC_2H_5$ group on R3. Theoretical calculations show that this product has a lower total energy, a higher affinity, and lower HOMO energies than those obtained in the case of molecule **8**. It also notes that the dipole moment is higher. We believe that the substitution R3 is the main cause.
- The difference of electronic parameters and experimental properties obtained in the case of molecules **5** and **8** and molecules of **2** and **5** comes from chemical structures: in the molecule **8** differs from the molecule by a donor group methoxy (OMe), while the latter (molecule **5**) differs from the molecule **2** by the benzyl group on the nitrogen atom. This shows that the structure is directly related to the biological properties determined experimentally on the one hand and the electronic properties determined theoretically.

On the other hand, and with the aim to find a mathematical model that can collect the parameters influencing the desired biological activity, quantum chemical parameters are obtained from the calculations which are responsible for the "activity" of our molecules such as the energies of highest occupied molecular orbital (E_{HOMO}), energy of lowest unoccupied molecular orbital (E_{LUMO}), energy gap (ΔE), dipole moment (μ), electronegativity (χ), electron affinity (A), global hardness (η), softness (σ), ionization potential (I), and the total energy (TE) are collected in (Table 5).

We have set up a model for calculating the "activity" of the studied molecules. This model has been suggested including descriptors as many as possible to increase the probability of a good characterization of the studied compounds. Among the descriptors selected in the study, nine descriptors reflected the overall characters of our molecules. They are gap energy (E_g), absorption length (λ_{max}), active energy (E_a), oscillator strength (f), ionic affinity (A), potential of ionization (I), electronegativity

Table 3 The calculated quantum chemical parameters of the studied molecules **1**, **6**, **7**, **8**, and **9**

Compounds **1**, **6**, **7**, **8**, and **9**	I Acute neurotoxicity	II Antitumor activity (%)	Egap	λ	E	f	A	I	χ	η	σ	Dipole Moment (Debye)	Total energy (u.a)
1 = Harmine	++	24	4.8172	306.85	4.0405	0.2752	0.7616	5.5789	3.1703	2.4086	0.4152	4.0501	−687.3502
6	++	43 (49.5 % sur mous hepatoma)	4.3565	349.37	3.5488	0.0876	0.3064	4.6629	2.4847	2.1783	0.4591	1.7519	−766.5134
7	++	31	4.3549	349.60	3.5464	0.0882	0.2969	4.6518	2.4743	2.1775	0.4593	1.8529	−805.8273
8	++	45	4.6338	307.88	4.0270	0.2026	0.8131	5.4469	3.1300	2.3169	0.4316	3.5102	−957.7073
9	++	35	4.7122	307.72	4.0291	0.2345	0.7380	5.4502	3.0941	2.3561	0.4244	4.1059	−726.6571

Table 4 The calculated quantum chemical parameters of the studied molecules **2**, **3**, **4**, and **5**

Compounds 2, 3, 4, and 5	I Acute neurotoxicity	II Antitumor activity (%)	Egap	λ	E	f	A	I	χ	η	σ	Dipole Moment (Debye)	Total energy (u.a)
2	−	33	4.6937	323.56	3.8318	0.1421	1.3263	6.0200	3.6731	2.3468	0.4261	4.857	−722.0776
3	+	33	4.5321	329.18	3.7665	0.1280	1.3793	5.9114	3.6454	2.2660	0.4413	7.2465	−800.6834
4	+	30	4.5130	330.29	3.7538	0.1296	1.3712	5.8842	3.6277	2.2565	0.4432	7.3959	−839.9999
5	−	42	4.5851	330.06	3.7564	0.1694	1.2115	5.7966	3.5040	2.2926	0.4362	4.2428	−1071.0646

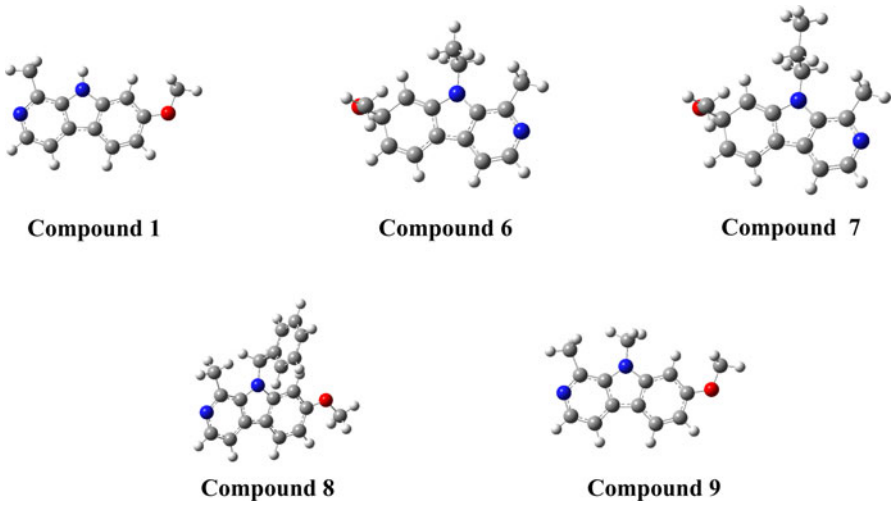


Fig. 1 The obtained molecular structures of molecules **1**, **6**, **7**, **8**, and **9**

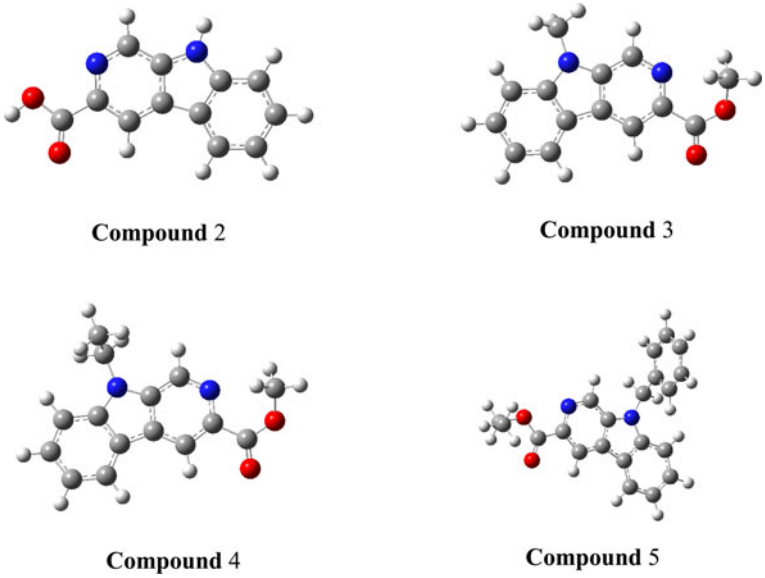


Fig. 2 The obtained molecular structures of molecules **2**, **3**, **4**, and **5**

(χ), hardness (η), and softness (σ). The calculated antitumor activity model was developed using the linear combination of the descriptors:

$$\begin{aligned}\text{Activ(calc)} = {} & a \times E_g + b * log(\lambda_{\max}) + c * E_a + d \times \exp^{(f)} + e \times A \\ & + f \times I + g \times \chi + h \times \eta + k \times \sigma\end{aligned}$$

where a, b, c, d, e, f, g, h, and k are the coefficients of determination.

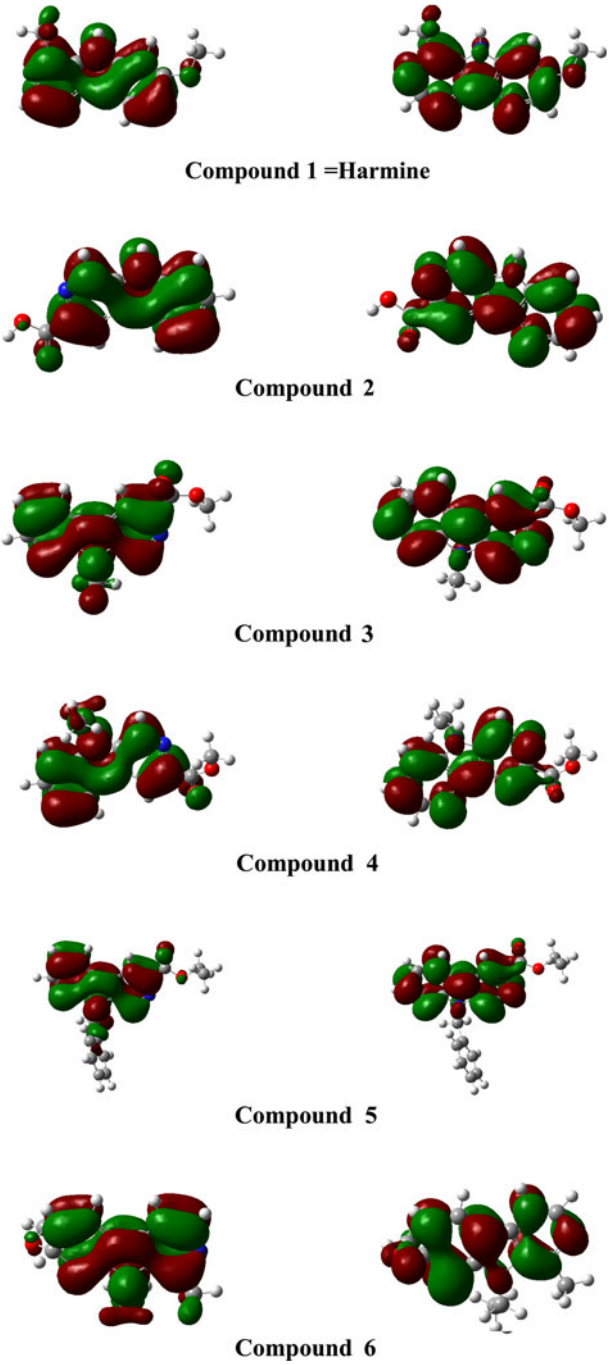


Fig. 3 The obtained HOMO and LUMO orbitals of the studied molecules by DFT/B3LYP/6-31G*(d)

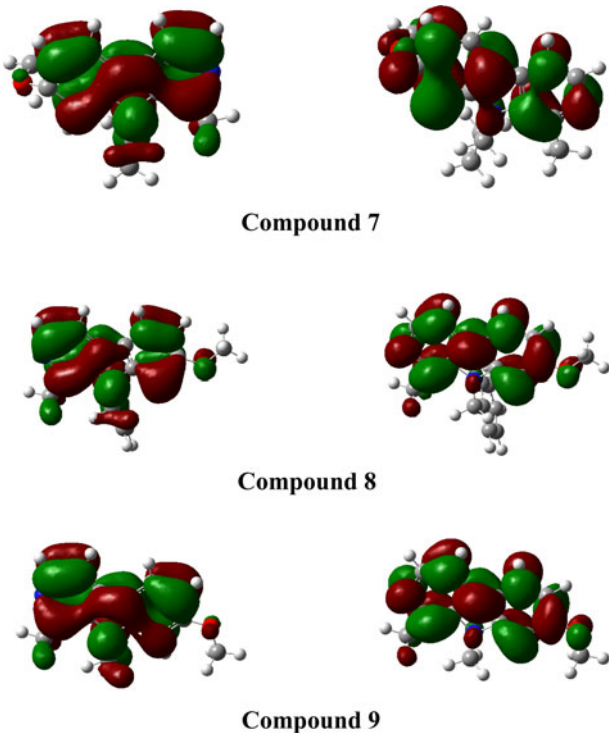


Fig. 3 continued

The proposed model of the calculated antitumor activity is described by a linear relationship with the gap energy (E_g), active energy (E_a), ionic affinity (A), ionic potential (I), electronegativity (χ), hardness (η), and softness (σ). On the other hand, calculated activity varies with the logarithm values of the absorption length (λ_{max}) and exponential values of the oscillator strength (f).

The values of the coefficients of all the nine descriptors and the calculated and experimental values of the antitumor activity are listed in Table 6.

For the all compounds contained in the training set, the correlation between calculated and experimental antitumor activity values is very significant (Fig. 4), as indicated by the R value. A plot between the experimental and calculated property values provides a correlation coefficient (r) value of 0.998, which reveals the fact that this model can be effectively used as a descriptor in the property prediction.

As shown in Fig. 4, the calculated antitumor activity values are in good agreement with the experimental values. From the positive and negative symbols of the coefficients of the variables, we can evaluate the effects of each variable on activity. The antitumor activity values of the studied molecules increases with increasing (A), (I), (χ), (η) and (σ). As indicated by the coefficients for the calculated variables, decreasing (λ_{max}) and increasing (fosc) values of the studied compounds results in the decrease of antitumor activity values. Decreasing (E_g) and (E_a) leads to decreasing antitumor activity values (see Table 2). The activity of the studied

Table 5 The calculated quantum chemical parameters of the studied molecules

β-carbolines alkaloids (compounds **1–9**)	I Acute neurotoxicity	II Antitumor activity (%)	III Cytotoxic activity	Egap	λ	E	f	A	I	χ	η	σ
1 = Harmine	++	24		4.8172	306.85	4.0405	0.2752	0.7616	5.5789	3.1703	2.4086	0.4152
2	–	33		4.6937	323.56	3.8318	0.1421	1.3263	6.0200	3.6731	2.3468	0.4261
3	+	33		4.5321	329.18	3.7665	0.1280	1.3793	5.9114	3.6454	2.2660	0.4413
4	+	30		4.5130	330.29	3.7538	0.1296	1.3712	5.8842	3.6277	2.2565	0.4432
5	–	42		4.5851	330.06	3.7564	0.1694	1.2115	5.7966	3.5040	2.2926	0.4362
6	++	43 (49.5 % sur mous hepatoma)		4.3565	349.37	3.5488	0.0876	0.3064	4.6629	2.4847	2.1783	0.4591
7	++	31		4.3549	349.60	3.5464	0.0882	0.2969	4.6518	2.4743	2.1775	0.4593
8	++	45	The most active	4.6338	307.88	4.0270	0.2026	0.8131	5.4469	3.1300	2.3169	0.4316
9	++	35		4.7122	307.72	4.0291	0.2345	0.7380	5.4502	3.0941	2.3561	0.4244

Table 6 Calculated and experimental values of antitumor activity and coefficients of descriptors

No.	*a*	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*k*	Activ (calc) (%)	Activ (exp) (%)
1	−5.00	−5.00	−5.00	−5.00	−4.80	3.20	−0.30	5.00	29.76	24.01	24
2	−5.00	−5.00	−5.00	−5.00	−5.00	2.90	−0.90	2.90	40.62	32.99	33
3	−5.00	−5.00	−5.00	−5.00	−4.90	2.40	5.00	−3.40	34.93	33.01	33
4	−5.00	−5.00	−5.00	−5.00	−4.90	1.10	5.00	4.10	11.27	30.01	30
5	−5.00	−5.00	−5.00	−5.00	−4.60	4.40	2.40	5.00	−9.48	42.01	42
6	−5.00	−5.00	−5.00	−5.00	−5.00	1.00	5.00	0.10	43.35	43.01	43
7	−5.00	−5.00	−5.00	−5.00	−5.00	1.20	5.00	4.00	29.93	31.01	31
8	−5.00	−5.00	−5.00	−5.00	−5.00	3.10	5.00	1.40	11.71	44.99	45
9	−5.00	−5.00	−5.00	−5.00	−4.90	3.50	3.40	5.00	−0.95	35.01	35

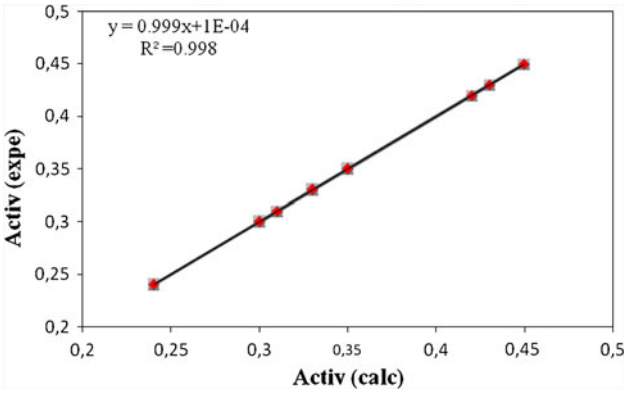


Fig. 4 Plot of calculated and experimental antitumor activity of the studied compounds

molecules is also influenced by their inherent physico-chemical properties such as (E_g) and (E_a). The β-carbolines alkaloids compounds (**6**) and (**8**) with the smaller E_a (3.5488–4.0270 eV) are the most active.

Conclusions

The study reported by Qi Chen et al. shows that harmine derivatives have considerable antitumor activity but also cause remarkable acute neurotoxicity. The R3 and R9 positions played an important role for both antitumor effects and neurotoxicity of these compounds.

SAR analysis indicated that the short alkyl or aryl substitution at R9 might increase cytotoxicity, while the long alkyl at R9 or the formate substitution at R3 (such as compounds **2**, **3**, **4**, and **5**) might reduce antitumor activity. However, the formate substitution at R3 also lowers the neurotoxicity. It appears that compounds

such as compound **5** with both substitutions at R3 and R9 would produce high antitumor activity and low neurotoxicity.

Theoretical calculations have been carried out on the same series of β-carboline alkaloids (harmine derivatives) in order to assess the stable structures and their geometric and electronic properties. The nature, number, and position of the substituents play a vital role in deciding the structural stability/activity of the studied molecules based on β-carboline alkaloids. Global descriptors such as total energy, gap energy, HOMO and LUMO energies, dipole moment (μ), electronegativity (χ), electron affinity (A), global hardness (η), softness (σ), and ionization potential (I), provide necessary information about the "activity" of the studied compounds. The activity of the studied molecules is also influenced by their inherent physico-chemical properties such as HOMO, LUMO, (E_g) energies, and (E_a). The β-carbolines alkaloids compounds (**6**) and (**8**) with the smaller E_a (3.5488–4.0270 eV) are the most active, which is in agreement with the experimental result reported by Qi Chen et al.

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