Insight into the antiviral activity of synthesized schizonepetin derivatives: A theoretical investigation

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The antiviral activity of schizonepetin derivatives 1A-1C were investigated via theoretical methods and results are compared with experimental results. The derivatives 1A and 1C have the highest and the lowest antiviral activity, respectively. The interactions of derivatives 1A-1C and BN-nanotube are examined. Results show that, derivatives 1A-1C can effectively interact with BN-nanotube (9, 9) and their adsorptions are favorable. The energy of derivative 1A is higher than derivatives 1B and 1C. The derivative 1A has highest absolute $\mu$, $\omega$ and $\Delta N$ values and it has lowest absolute $\eta$ value. Results show that, theoretical and experimental trends of antiviral activity of derivatives 1A-1C were similar, successfully.

The schizonepetin structures (1A-1C) were synthesized and their antiviral activities are studied. The antiviral potential of schizonepetin structures (1A-1C) against HSV-1 and influenza H3N2 were investigated in Table 11–6.

The derivative 1A is the most active drug against HSV-1 virus and influenza virus H3N2. Derivative 1C has higher TAC50 values and so has lowest activity HSV-1 and influenza. The structure analysis of derivative 1A-1C shown that the F, Br and CF3 substituents have high important role in antiviral activity of synthesized schizonepetin. The F and Br atoms of derivatives 1A and 1B can share their electrons pairs to resonate with unsaturated ring and they have high potential to stable the schizonepetin and these structures can have high potential to adsorb the electrons. About derivative 1C the CF3 group is reduced he stability of schizonepetin and it cannot share electrons with unsaturated ring, therefore derivative 1C has lower activity than derivatives 1A and 1B. Results indicate that antiviral activity of schizonepetin derivatives 1A-1C in according to TAC50 scale decreased in the following order: 1C < 1B < 1 A12–12.

In the present work, the antiviral potential of synthesized schizonepetin derivatives 1A-1C (structures were shown in Table 1) are studied. In this study the $\mu$, $\eta$, $\omega$ and $\Delta N$ related to schizonepetin derivatives 1A-1C and BN-nanotube (9, 9) were investigated. The energies of derivatives 1A-1C and nanotubes were examined (Fig. 1). These results can be useful to predication the potential of nanotube to derivatives 1A-1C based on calculated quantum molecular descriptors2,13–16.

The aims are: (1) to calculate the antiviral potential of schizonepetin derivatives 1A-1C; (2); to find derivatives 1A-1C with higher antiviral activity; (3) to compare the $\Delta E_{ad}$ and $\Delta G_{ad}$ of derivatives 1A-1C on BN-nanotube surface; (4) to investigate the quantum molecular descriptors of derivatives 1A-1C; (5) to compare the theoretical and experimental trends of antiviral activity of derivatives 1A-1C.

Computational details

The structures of schizonepetin derivatives 1A-1C are optimized by DFT/B3LYP and 6–31G (d, p). The adsorption energy of schizonepetin derivatives 1A-1C on BN-nanotube (9, 9) surface is $\Delta E_{ad} = E_{BSSE}(BN-nanotube (9, 9)/drug) - E_{BSSE}(BN-nanotube (9, 9)) + E_{BSSE}(drug)$. The negative $\Delta E_{ad}$ and $\Delta G_{ad}$ shown that the adsorption of derivatives 1A-1C on BN-nanotube (9, 9) are favorable reaction$^{4,13,17–19}$.
Results and discussion

**Calculated ΔE_d and ΔG_d of schizonepetin derivatives 1A-1C on nanotube.** The F, Br and CF$_3$ synthesized derivatives of schizonepetin have high antiviral activity than other derivatives. The experimental researchers confirmed that F, Br and CF$_3$ synthesized derivatives of schizonepetin can be synthesized more
comfortable than other derivatives. The experimental researchers shown that F, Br and CF3 synthesized derivatives of schizonepetin have most antiviral active against HSV-1 virus and influenza virus H3N2.

The ∆E_{ad} and ∆G_{ad} of schizonepetin derivatives 1A-1C on nanotubes are stated in Table 2. The ∆E_{ad} and ∆G_{ad} are negative and the adsorption of derivatives 1A-1C on studied BN-nanotube (9, 9) are favorable processes. The ∆E_{ad} of derivatives 1A and 1B are higher than derivative 1C. The ∆G_{ad} of derivatives 1A on BN-nanotube (9, 9) are higher than derivatives 1B and 1C. ca 0.10 and 0.17 eV. The ∆G_{ad} value of derivative 1B on BN-nanotube (9, 9) are more negative than derivative 1C ca 0.07 eV. The derivative 1A has the best ability to nanotube adsorption. These results can be interpret based on this fact that the electrons of orbitals of F and Br groups have higher interactions with unoccupied orbitals of BN-nanotube (9, 9). The electrons of C atoms of CF3 group have lower potential to interaction with orbitals of BN-nanotube (9, 9). Therefore, the ∆E_{ad} and ∆G_{ad} of derivatives 1A and 1B are more negative than derivative 1C and the most interactions are obtained for derivatives 1A and BN-nanotube (9, 9).

| Structures | ∆E_{ad} (eV) | ∆G_{ad} (eV) |
|------------|--------------|--------------|
| 1A         | −0.54        | −0.45        |
| 1B         | −0.42        | −0.35        |
| 1C         | −0.36        | −0.28        |

Table 2. Calculated ∆E_{ad} and ∆G_{ad} (in eV) of schizonepetin derivatives 1A-1C on BN-nanotube (9, 9) surface.

| Structures | µ (eV) | η (eV) | ω (eV) | ∆N (eV) |
|------------|--------|--------|--------|---------|
| BN-nanotube (9, 9) | −0.56 | 0.69   | 1.81   | —       |
| 1A         | −0.47  | 0.08   | 1.44   | −0.281  |
| 1B         | −0.46  | 0.12   | 0.88   | −0.232  |
| 1C         | −0.45  | 0.17   | 0.66   | −0.220  |

Table 3. Calculated µ, η, ω and ∆N (in eV) of schizonepetin derivatives 1A-1C and BN-nanotube (9, 9).

Calculated quantum molecular descriptors of schizonepetin derivatives 1A-1C and BN-nanotube (9, 9). The calculated energy parameters for schizonepetin derivatives 1A-1C and BN-nanotube (9, 9) are reported in Table 3. The calculated µ value of BN-nanotube (9, 9) is −0.56 eV. The calculated µ value of derivatives 1A-1C ranges from −0.45 to −0.47 eV and absolute µ values of them decreases in the order: 1A > 1B > 1C. Therefore, obtained absolute µ values show that derivative 1A has highest electron and derivative 1C has lowest electron.

In Table 3, the η of BN-nanotube (9, 9) is 0.09 eV. The obtained η values of derivatives 1A-1C decrease in the order: 1A < 1B < 1C. As the minimum of the η value within the derivatives 1A-1C is for derivative 1A. Therefore, η values show that 1A has lowest stability and high reactivity and 1C has lowest reactivity. These results can be interpret based on this fact that the F and Br atoms of derivatives 1A and 1B are shared electrons to unsaturated ring and they have high potential to stable the schizonepetin. In the derivative 1C the CF3 substituent can decrease the stability of schizonepetin and C atoms of CF3 do not transfer the electrons to ring of schizonepetin. Therefore, it can be concluded the derivative 1C has lower activity than derivatives 1A and 1B.

Calculated ω value of BN-nanotube (9, 9) is 1.81 eV. The calculated ω value of derivatives 1A-1C ranges from 0.60 to 1.44 eV. Among the derivatives 1A-1C the ω value decreases in the order: 1A > 1B > 1C. Therefore, obtained ω values show that derivative 1A has highest capacity to accept electrons and derivative 1C has lowest capacity to accept electrons.

The calculated ∆N value of complexes of derivatives 1A-1C with BN-nanotube (9, 9) are reported in Table 3. The all of the calculated ∆N values are negative and derivatives 1A-1C can act as electron donors and BN-nanotube (9, 9) can act as electron acceptors. Results show that derivative 1A has highest absolute ∆N value and it has highest interaction with BN-nanotube (9, 9). The derivative 1C has lowest absolute ∆N value and it has lowest interaction with BN-nanotube (9, 9).

Comparison of experimental and theoretical trends of antiviral activity of schizonepetin derivatives 1A-1C. The antiviral activity of derivatives is decreased as follow: 1C < 1B < 1A. The adsorption ability of derivatives 1A-1C via adsorption parameters (∆E_{ad} and ∆G_{ad}) is: 1A > 1B > 1C. The obtained µ, η and ω values show that derivative 1A has highest absolute µ and ω values and it has lowest absolute η values. Also derivative 1C has lowest absolute µ and ω values and it has highest η value. This can be concluded the calculated µ, η, ω values of derivatives 1A-1C in section 3.3 and energies is same. The highest absolute ∆E_{ad}, ∆G_{ad}, µ and ω values and lowest η value for derivative 1A are appropriate benchmark to approval the adsorption ability on BN-nanotube (9, 9) surface. The ∆E_{ad}, ∆G_{ad}, µ, η, ω values of schizonepetin derivatives 1A-1C can consider as important parameters to predicate the adsorption ability on BN-nanotube (9, 9) surface.
Conclusion
In this study, the antiviral activity of schizonepetin derivatives 1A-1C are investigated via theoretical methods. The derivatives 1A and 1C have the highest and the lowest of antiviral activity, respectively. The interactions of derivatives 1A-1C with BN-nanotube (9,9) are investigated and quantum molecular descriptors of derivatives 1A-1C are calculated. The energies of derivatives 1A-1C on BN-nanotube (9,9) surface are studied. The adsorption ability of derivatives 1A-1C in according to adsorption parameters is: 1A > 1B > 1C. The derivative 1A has the highest absolute μ and ω values and it has the lowest absolute η value. Results show that, quantum molecular descriptors and adsorption parameters of derivatives 1A-1C is same on BN-nanotube (9,9) surface. Results show that, theoretical and experimental trends of antiviral activity of derivatives 1A-1C were similar.

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Author contributions
Alireza Baghban worked on conceptualization, methodology, results and first draft. Amir Mosavi collaborated in revision, validation, proof and final draft.

Competing interests
The authors declare no competing interests.
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