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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 μ, ω and ΔN values and it has lowest absolute η 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 1[1–6].

The derivative 1 A is the most active drug against HSV-1 virus and influenza virus H3N2. Derivative 1 C has higher TAC_{50} values and so has lowest activity HSV-1 and influenza. The structure analysis of derivative 1A-1C shown that the F, Br and CF_3 substituents have high important role in antiviral activity of synthesized schizonepetin. The F and Br atoms of derivatives 1 A 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 1 C the CF_3 group is reduced he stability of schizonepetin and it cannot share electrons with unsaturated ring, therefore derivative 1 C has lower activity than derivatives 1 A and 1B. Results indicate that antiviral activity of schizonepetin derivatives 1A-1C in according to TAC_{50} scale decreased in the following order: 1 C < 1B < 1 A[1,7–12].

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 μ, η, ω and ΔN 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 descriptors[2,13–16].

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 ΔE_{ad} and ΔG_{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 6–31 G (d, p). The adsorption energy of schizonepetin derivatives 1A-1C on BN-nanotube (9, 9) surface is ΔE_{ad} = E (BN-nanotube (9, 9)/drug) – E (drug) – E (BN-nanotube (9, 9)) + E_{BSSE}. The negative ΔE_{ad} and ΔG_{ad} shown that the adsorption of derivatives 1A-1C on BN-nanotube (9, 9) are favorable reaction[14,15,17–19].

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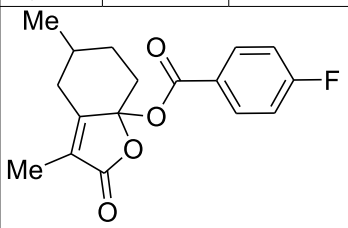
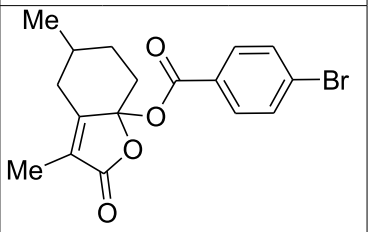
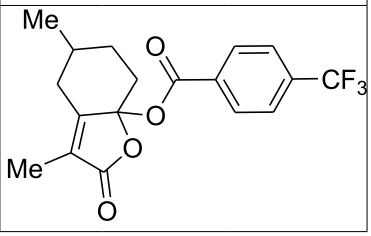
Derivatives	Group	HSV-1 virus	H_3N_2 virus
1A	F	77.8	60.5
1B	Br	80.3	71.0
1C	CF_3	82.8	75.4
1A			
1B			
1C			

Table 1. Structure of schizonepetin derivatives 1A-1C.

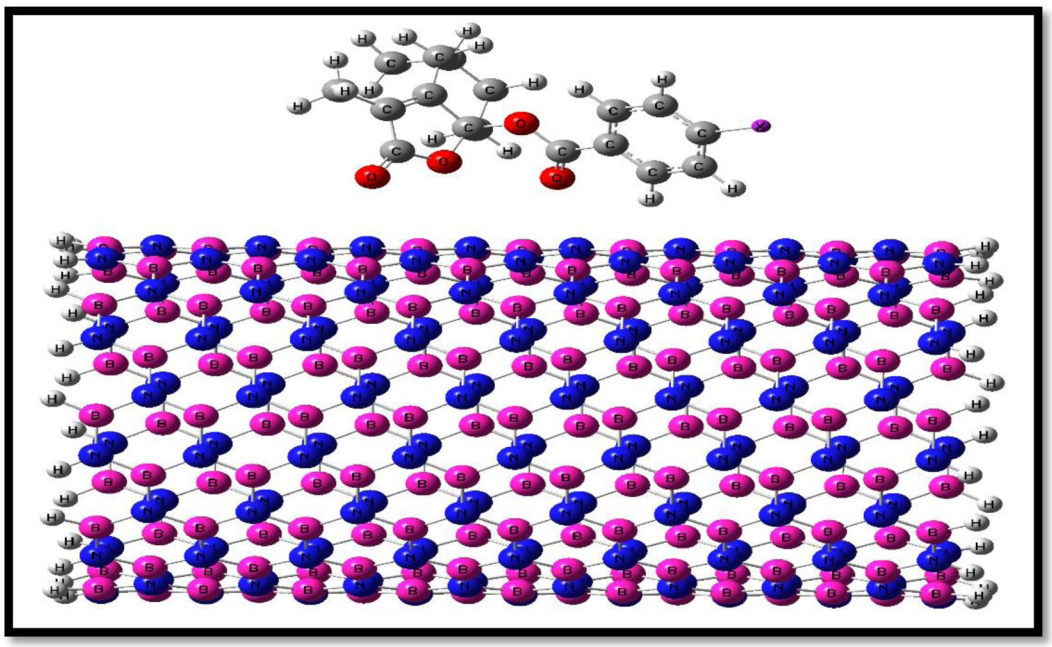


Figure 1. Structure of complexes of schizonepetin derivatives 1A-1C with BN-nanotube (9, 9).

Results and discussion

Calculated ΔE_{ad} and ΔG_{ad} 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

Structures	ΔE_{ad}	ΔG_{ad}
1A	−0.54	−0.45
1B	−0.42	−0.35
1C	−0.36	−0.28

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

Structures	μ	η	ω	ΔN
BN-nanotube (9, 9)	−0.56	0.09	1.81	—
1 A	−0.47	0.08	1.44	−0.281
1B	−0.46	0.12	0.88	−0.232
1 C	−0.45	0.17	0.60	−0.220

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

comfortable than other derivatives. The experimental researchers shown that F, Br and CF_3 synthesized derivatives of schizonepetin have most antiviral active against HSV-1 virus and influenza virus H3N2 [20–25].

The ΔE_{ad} and ΔG_{ad} of schizonepetin derivatives 1A-1C on nanotubes are stated in Table 2. The ΔE_{ad} and ΔG_{ad} are negative and the adsorption of derivatives 1A-1C on studied BN-nanotube (9, 9) are favorable processes. The ΔE_{ad} of derivatives 1 A and 1B are higher than derivative 1 C. The ΔG_{ad} of derivatives 1 A on BN-nanotube (9, 9) are higher than derivatives 1B and 1 C ca 0.10 and 0.17 eV. The ΔG_{ad} value of derivative 1B on BN-nanotube (9, 9) are more negative than derivative 1 C ca 0.07 eV. The derivative 1 A 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 CF_3 group have lower potential to interaction with orbitals of BN-nanotube (9, 9). Therefore, the ΔE_{ad} and ΔG_{ad} of derivatives 1 A and 1B are more negative than derivative 1 C and the most interactions are obtained for derivatives 1 A 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: 1 A > 1B > 1 C. Therefore, obtained absolute μ values show that derivative 1 A has highest electron and derivative 1 C 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: 1 A < 1B < 1 C. As the minimum of the η value within the derivatives 1A-1C is for derivative 1 A. Therefore, η values show that 1 A has lowest stability and high reactivity and 1 C has lowest reactivity. These results can be interpret based on this fact that the F and Br atoms of derivatives 1 A and 1B are shared electrons to unsaturated ring and they have high potential to stable the schizonepetin. In the derivative 1 C the CF_3 substituent can decrease the stability of schizonepetin and C atoms of CF_3 do not transfer the electrons to ring of schizonepetin. Therefore, it can be concluded the derivative 1 C has lower activity than derivatives 1 A 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: 1 A > 1B > 1 C. Therefore, obtained ω values show that derivative 1 A has highest capacity to accept electrons and derivative 1 C has lowest capacity to accept electrons.

The calculated ΔN value of complexes of derivatives 1A-1C with BN-nanotube (9, 9) are reported in Table 3. The all of the calculated ΔN 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 1 A has highest absolute ΔN value and it has highest interaction with BN-nanotube (9, 9). The derivative 1 C has lowest absolute ΔN 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: 1 C < 1B < 1 A. The adsorption ability of derivatives 1A-1C via adsorption parameters (ΔE_{ad} and ΔG_{ad}) is: 1 A > 1B > 1 C. The obtained μ, η and ω values show that derivative 1 A has highest absolute μ and ω values and it has lowest absolute η values. Also derivative 1 C 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 ΔE_{ad}, ΔG_{ad}, μ and ω values and lowest η value for derivative 1 A are appropriate benchmark to approval the adsorption ability on BN-nanotube (9, 9) surface. The ΔE_{ad}, ΔG_{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 1 A and 1 C have the highest and the lowest of antiviral activity, respectively. The interactions of derivatives 1A-1C with BN-nanotube (9, 9) are investigated and also 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: 1 A > 1B > 1 C. The derivative 1 A 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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References

1. Esrafili, M. D., Nematollahi, P. & Abdollahpour, H. Applied Surface Science A comparative DFT study on the CO oxidation reaction over Al- and Ge-embedded graphene as efficient metal-free catalysts. *Appl. Surf. Sci.* **378**, 418–425 (2016).
2. Duan, H. & Xu, C. Nanoporous PdZr surface alloy as highly active non-platinum electrocatalyst toward oxygen reduction reaction with unique structure stability and methanol-tolerance. *J. Power Sources* **316**, 106–113 (2016).
3. Chen, R., Li, H., Chu, D. & Wang, G. Unraveling oxygen reduction reaction mechanisms on carbon-supported fe-phthalocyanine and co-phthalocyanine catalysts in alkaline solutions. *J. Phys. Chem. C* **113**, 20689–20697 (2009).
4. Exner, K. S. & Over, H. Kinetics of Electrocatalytic Reactions from First-Principles: A Critical Comparison with the Ab Initio Thermodynamics Approach. *Acc. Chem. Res.* **50**, 1240–1247 (2017).
5. Soliman, N. K. Factors affecting CO oxidation reaction over nanosized materials: A review. *J. Mater. Res. Technol.* **8**, 2395–2407 (2019).
6. Nigam, R., Habeeb, S., Priyadarshi, A. & Jaggi, N. Electrical conductivity of metal-carbon nanotube structures: Effect of length and doping. *Bull. Mater. Sci.* **37**, 1047–1051 (2014).
7. Jin, J. *et al*. Insight into Room-Temperature Catalytic Oxidation of Nitric oxide by Cr_2O_3: A DFT Study. *ACS Catal.* **8**, 5415–5424 (2018).
8. Hou, H. *et al*. The effect of carbonization temperature of waste cigarette butts on Na - storage capacity of N - doped hard carbon anode. *Chem. Pap*., https://doi.org/10.1007/s11696-018-00674-w (2019).
9. Seyyedin, S. T., Sovizi, M. R. & Yaftian, M. R. Enhancing lithium – sulphur battery performance by copper oxide @ graphene oxide nanocomposite-modified cathode. **70**, 1590–1599 (2016).
10. Esra, M. D. & Nurazar, R. Surface Science Methylamine adsorption and decomposition on $B_{12}N_{12}$ nanocage: A density functional theory study. **626**, 44–48 (2014).
11. Baei, M. T., Ahmadi, A. & Bagheri, Z. B-doping makes the carbon nanocones sensitive towards NO molecules. *Phys. Lett. A* **377**, 107–111 (2012).
12. Exner, K. S. & Over, H. Beyond the Rate-Determining Step in the Oxygen Evolution Reaction over a Single-Crystalline IrO_2(110) Model Electrode: Kinetic Scaling Relations. *ACS Catal.* **9**, 6755–6765 (2019).
13. Hwang, J. *et al*. Mesoporous Ge/GeO_2/Carbon Lithium-Ion Battery Anodes with High Capacity and High Reversibility (2015).
14. Martins, J., Thsayane, C., Morais, C. D, Ambrósio, N. & Almeida, F. D. Influence of current density and W concentration on Co – W alloys used as catalysts in electrodes for Li – O_2 batteries. Chem. Pap., https://doi.org/10.1007/s11696-018-0661-x (2018).
15. Qiang, Z., Zhi, H., Yang, G. & Ping, Y. Synthesis of vanadium oxides nanosheets as anode material for asymmetric supercapacitor. *Chem. Pap*. **4** (2018).
16. Zhou, S., Yang, X., Pei, W., Zhao, J. & Du, A. Silicon Nanocages for Selective Carbon Dioxide Conversion under Visible Light Silicon Nanocages for Selective Carbon Dioxide Conversion under Visible Light., https://doi.org/10.1021/acs.jpcc.9b01784 (2019).
17. Natalia, V., Rahmawati, F., Wulandari, A. & Purwanto, A. Graphite/Li_2 ZrO_3 anode for a $LiFePO_4$ battery., https://doi.org/10.1007/s11696-018-0626-0 (2018).
18. Zhang, J., Gu, P., Xu, J., Xue, H. & Pang, H. High performance of electrochemical lithium storage batteries: ZnO-based nanomaterials for. 18578–18595, https://doi.org/10.1039/c6nr07207k (2016).
19. Exner, K. S. Is Thermodynamics a Good Descriptor for the Activity? Re-Investigation of Sabatier's Principle by the Free Energy Diagram in Electrocatalysis. *ACS Catal.* **9**, 5320–5329 (2019).
20. Xu, L., Zhu, X., Feng, Y. & Ding, A. Study on antiviral activity of the alcohol extract of schizonepeta tenuifolia. *Res. Tradit. Chin. Med.* **16**, 45–46 (2000).
21. Lu, J. *et al*. Effect of herba chizonepetae tenuifoliae lipids on acute inflammation of mice (in Chinese). *J. Nanjing Univ. Tradit. Chin. Med.* **6**, 350–351 (2003).
22. Zhang, L., Zhang, M., Sun, E. & Ding, A. Anti-inflammatory, analgesic and antipyretic effects of schizonepetolide poly-lactic-co-glycolic acid nanoparticles (in Chinese). *J. China Pharm. Univ.* **39**, 433–436 (2008).
23. Liu, D. *et al*. Acute and subacute toxicity and genotoxicity of schizonepetin, a naturally occurring monoterpene with antiviral activity. *Food Chem. Toxicol.* **50**, 2256–2262 (2012).
24. Bao, B. *et al*. Effects of schizonepetin on activity and mRNA expression of cytochrome p450 enzymes in rats. *Int. J. Mol. Sci.* **13**, 17006–17018 (2012).
25. Geng, T. *et al*. Pharmacokinetics and tissue distribution of schizonepetin in rats. *Fitoterapia* **82**, 1110–1117 (2011).

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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.

Additional information

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