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### ► **To cite this version:**

Thi Chinh Ngo, Duy Quang Dao, Tam V.-T. Mai, Dinh Hieu Truong, Thi Le Anh Nguyen, et al.. A DFT study on radical scavenging activity and chemical repair of damaged DNA by natural diterpenoids. 2022 #RSCPoster Twitter Conference, Mar 2022, London, United Kingdom. <hal-03596844>

**HAL Id: hal-03596844**

**<https://hal.science/hal-03596844v1>**

Submitted on 4 Mar 2022

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# A DFT study on radical scavenging activity and chemical repair of damaged DNA by natural diterpenoids

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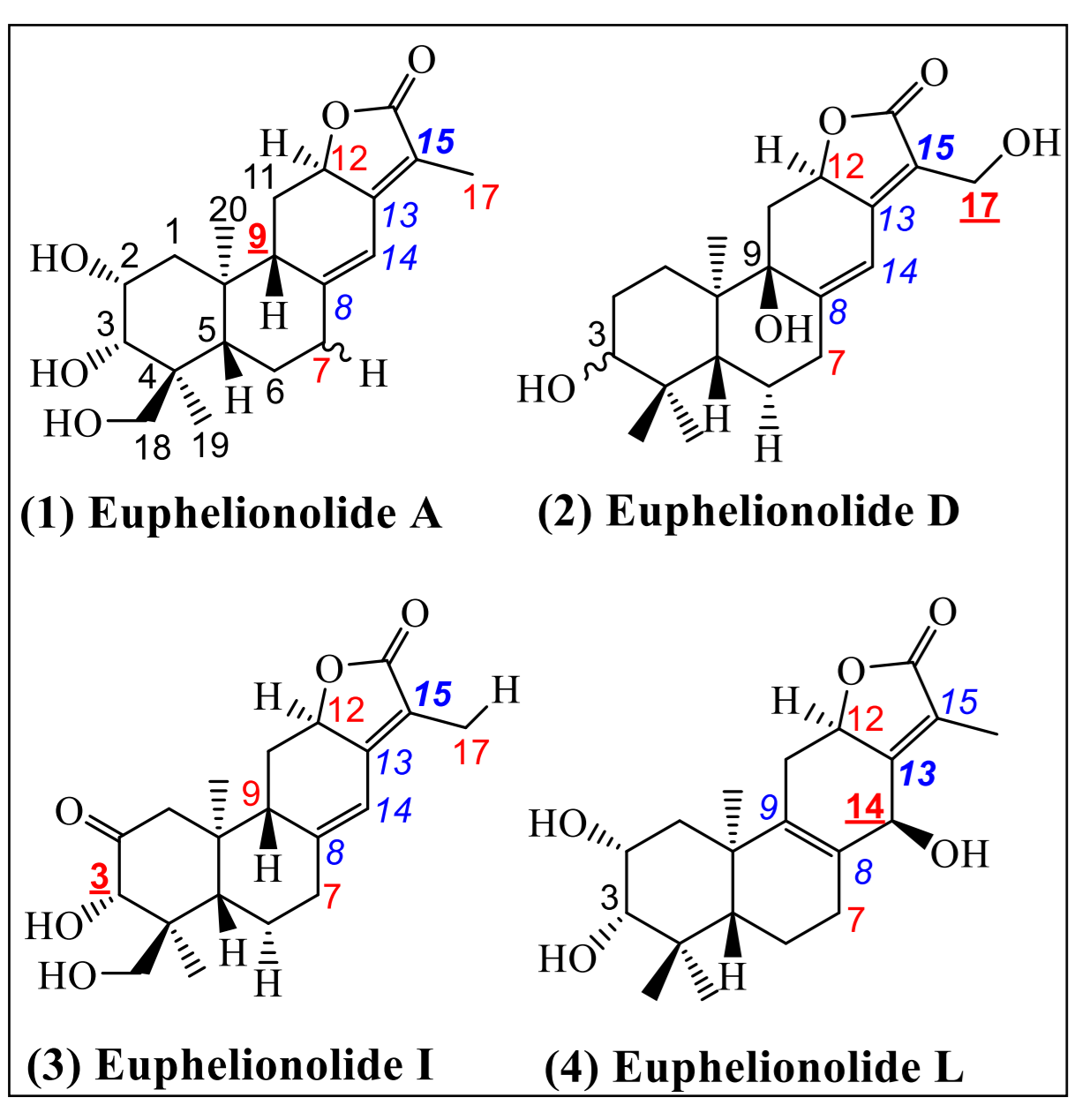
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## INTRODUCTION

Reactive oxygen species (ROS) at high concentration has resulted in severe damages to cellular activity and subsequent generation of many diseases.<sup>(1)</sup> In modern conception, a good antioxidant not only has high free-radical scavenging activity to minimize the harmful impact of ROS but also can repair damaged biomolecules resulting from oxidation



Diterpenoids are abundant and important compounds in Euphorbia species owing to their structural diversity. In this study, we investigate the modern-concept antioxidant activities, including free-radical scavenging and oxidative DNA damage repairing, of highly oxygenated diterpenoids originating from the aerial part of *Euphorbia helioscopia*.<sup>(2)</sup>



### Cytotoxicity

- ✓ human breast cancer cell line MCF-7
- ✓ human pancreatic cell line PANC-1s

Fig. 1: Chemical structures of Euphelinolide (A, D, E, L)

## COMPUTATIONAL METHOD

M05-2X(SMD)<sup>(3,4)</sup>/6-311++G(d,p)// M05-2X/6-31+G(d,p)  
Solvent: water and pentyl ethanoate (PEA)

- **Hydrogen transfer (HT)** <sup>(5,6)</sup>  
R-H + HOO•/HO•/2dG• → R• + HOOH/HOH/2dG (R1)
- **Radical adduct formation (RAF)**  
R-H + HOO•/HO• → [R-HOOH]•/[R-HOH]• (R2)
- **Single-electron transfer (SET)**  
R-H + HOO•/HO•/2dG•+ → R-H•+ + HOO-/HO-/2dG (R3)

### Conventional transition state theory (TST)

$$k = \sigma \kappa \frac{k_B T}{h} e^{-(\Delta G^\ddagger)/RT}$$

$k_B$ : Boltzmann constant  
 $h$ : Planck constant  
 $\sigma$ : reaction symmetry number  
 $\kappa$ : tunneling corrections

Multi-Species and Multi-Channels (MSMC) <sup>(7)</sup>



## RESULTS AND DISCUSSION

### Radical scavenging activity

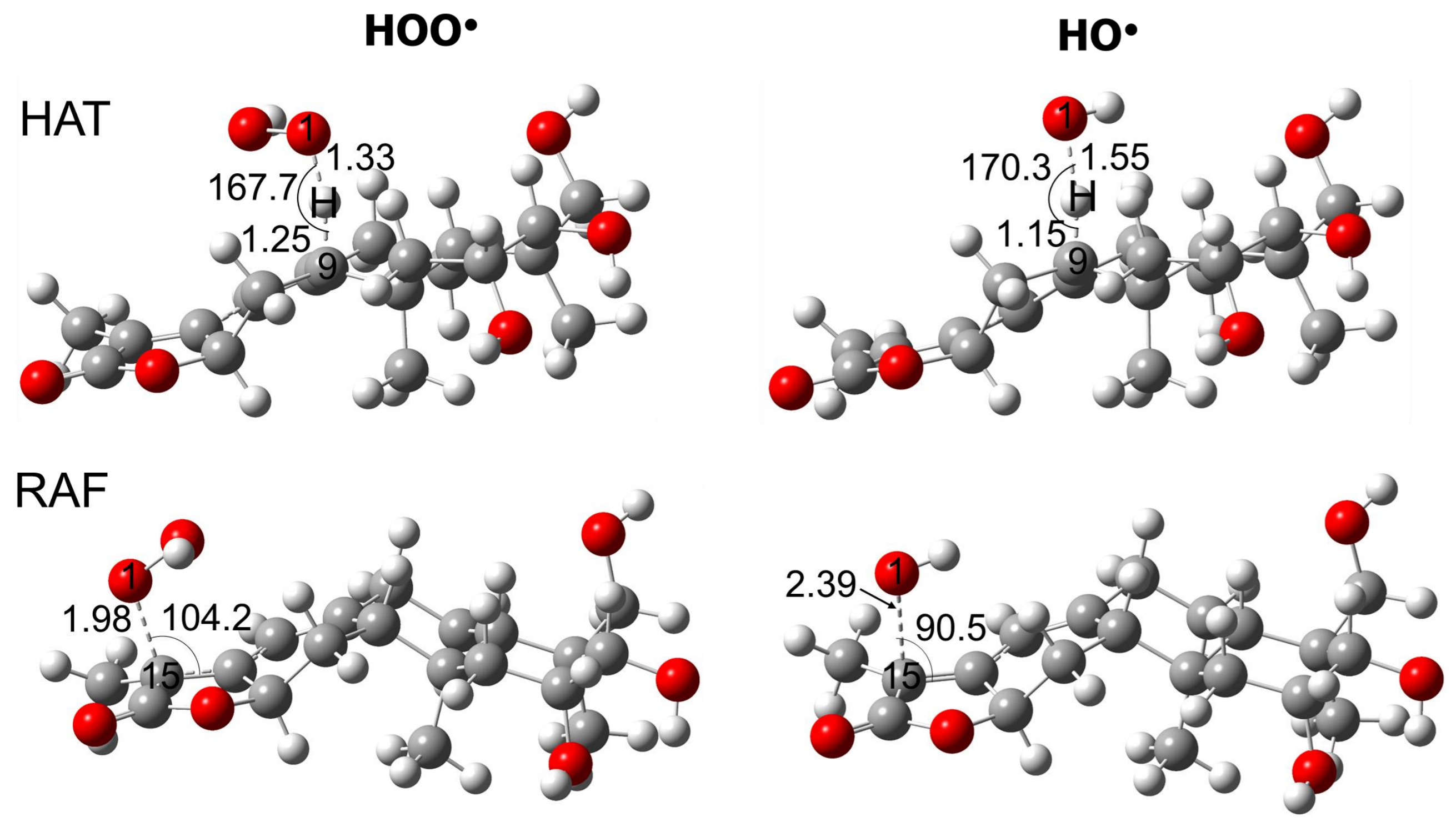


Fig. 2: Optimized structures of transition state of HAT and RAF reactions between Euphelinolide A and HOO•/HO• radicals

Table 1. Overall apparent rate constant ( $k_{overall}$ , M<sup>-1</sup>s<sup>-1</sup>) and reaction branching ratios for each channel ( $\Gamma_i$ , %) for reactions with HOO• and HO• radicals

Radi	Cp	$k_{total}^{HAT}$	$k_{total}^{RAF}$	$k^{SET}$	$k_{overall}$	$\Gamma_{HAT}$	$\Gamma_{RAF}$	$\Gamma_{SET}$	
HOO•	In water								
	1	$2.5 \times 10^3$	$3.6 \times 10^0$	$4.6 \times 10^{-12}$	$2.5 \times 10^3$	99.9	0.1	0.0	
	2	$1.2 \times 10^1$	$7.6 \times 10^{-1}$	$3.4 \times 10^{-20}$	$1.3 \times 10^1$	93.9	6.1	0.0	
	3	$2.5 \times 10^1$	$3.3 \times 10^0$	$1.8 \times 10^{-12}$	$2.8 \times 10^1$	88.3	11.7	0.0	
	4	$9.5 \times 10^1$	$2.2 \times 10^{-1}$	$1.1 \times 10^{-13}$	$9.5 \times 10^1$	99.8	0.2	0.0	
	In PEA								
	1	$1.5 \times 10^3$	$2.6 \times 10^{-1}$	$7.4 \times 10^{-72}$	$1.5 \times 10^3$	100	0.0	0.0	
	2	$1.2 \times 10^1$	$2.4 \times 10^{-1}$	$4.6 \times 10^{-84}$	$1.2 \times 10^1$	98.1	1.9	0.0	
3	$4.4 \times 10^0$	$4.6 \times 10^{-2}$	$8.9 \times 10^{-72}$	$4.5 \times 10^0$	99.0	1.0	0.0		
4	$1.3 \times 10^1$	$2.3 \times 10^{-2}$	$4.0 \times 10^{-71}$	$1.3 \times 10^1$	98.8	0.2	0.0		
HO•	In water								
	1	$1.1 \times 10^9$	$8.9 \times 10^8$	$1.8 \times 10^7$	$2.0 \times 10^9$	54.2	44.9	0.9	
	2	$1.8 \times 10^8$	$3.3 \times 10^8$	$4.2 \times 10^{-1}$	$5.2 \times 10^8$	35.4	64.6	0.0	
	3	$3.7 \times 10^8$	$4.3 \times 10^8$	$7.6 \times 10^6$	$8.1 \times 10^8$	45.9	53.1	0.9	
	4	$1.9 \times 10^8$	$1.5 \times 10^8$	$6.1 \times 10^5$	$3.5 \times 10^8$	55.3	44.6	0.2	
	In PEA								
	1	$8.0 \times 10^8$	$8.7 \times 10^8$	$3.9 \times 10^{-77}$	$1.7 \times 10^9$	48.1	51.9	0.0	
	2	$3.6 \times 10^8$	$1.1 \times 10^9$	$3.1 \times 10^{-93}$	$1.5 \times 10^9$	24.9	75.1	0.0	
3	$3.4 \times 10^8$	$3.9 \times 10^8$	$2.1 \times 10^{-75}$	$7.3 \times 10^8$	46.8	53.2	0.0		
4	$2.6 \times 10^8$	$5.6 \times 10^8$	$1.1 \times 10^{-68}$	$8.2 \times 10^8$	31.9	68.1	0.0		

### Chemical repair of damaged DNA

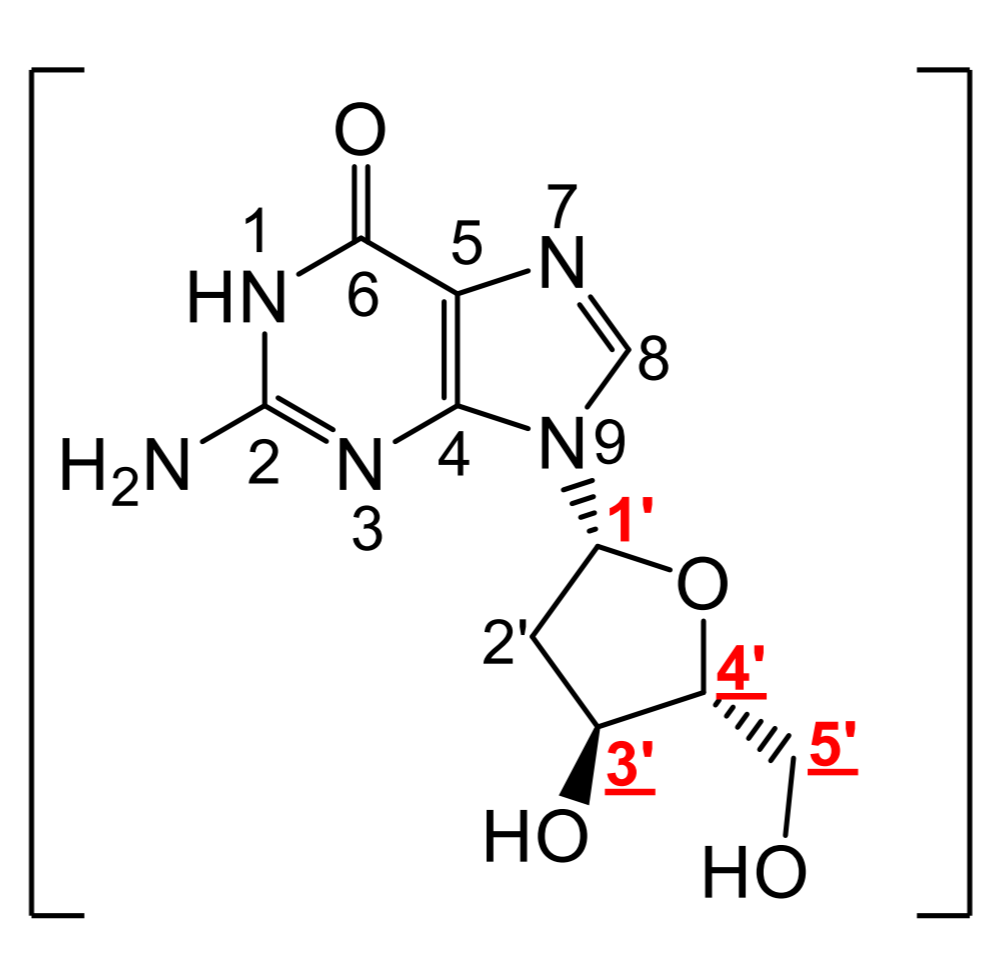


Fig. 3: Chemical structure of 2'-deoxyguanosine radical (2dG•)/radical cation (2dG•+), a damaged DNA model <sup>(8)</sup>

Table 2. Total rate constant of HAT ( $k_{total}^{HAT}$ , M<sup>-1</sup>s<sup>-1</sup>) and SET ( $k^{SET}$ , M<sup>-1</sup>s<sup>-1</sup>) reactions with 2dG• and 2dG•+

Cp	Water		PEA	
	$k_{total}^{HAT}$	$k^{SET}$	$k_{total}^{HAT}$	$k^{SET}$
1	$6.7 \times 10^3$	$4.2 \times 10^9$	$7.8 \times 10^3$	$8.9 \times 10^8$
2	$3.8 \times 10^3$	$5.0 \times 10^5$	$4.3 \times 10^3$	$1.5 \times 10^4$
3	$4.5 \times 10^3$	$3.1 \times 10^9$	$1.4 \times 10^3$	$4.2 \times 10^8$
4	$8.5 \times 10^3$	$8.6 \times 10^8$	$1.3 \times 10^3$	$1.4 \times 10^7$

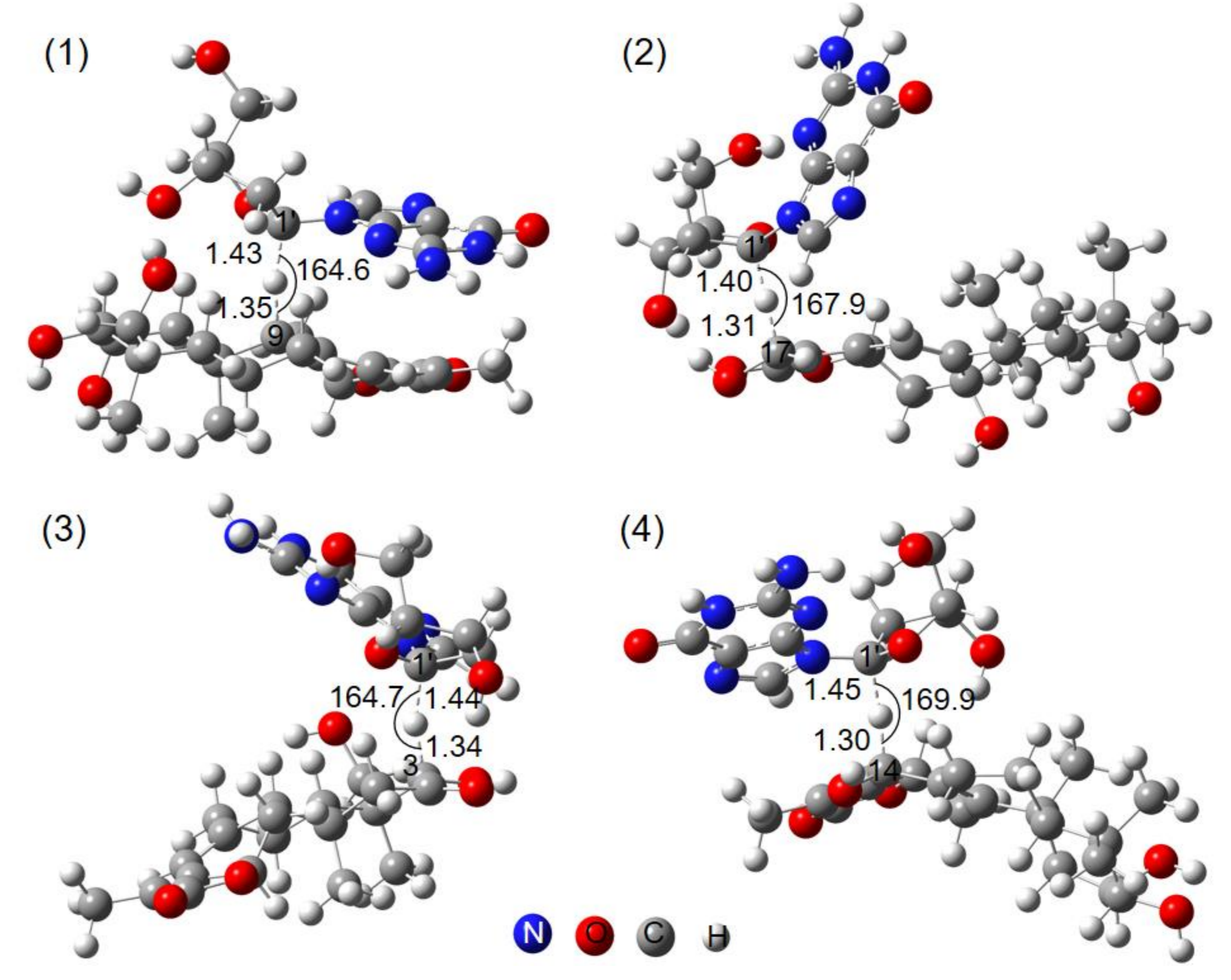


Fig. 4: Optimized structures of transition state of HAT reactions between Euphelinolide (A, D, E, L) and 2dG• radicals

## CONCLUSIONS

- Euphelinolide (A, D, E, L) are demonstrated as effective free-radical scavengers in trapping HOO•/HO• at multiple reactive sites *via* various reaction pathways.
- The studied compounds show better scavenging activity toward HO• ( $k_{overall} \sim 10^7-10^8$  M<sup>-1</sup>s<sup>-1</sup>) than toward HOO• ( $k_{overall} \sim 10^3$  M<sup>-1</sup>s<sup>-1</sup>).
- Euphelinolide (A, D, E, L) show chemical repairing activity for 2dG-damaged species (*i.e.*, 2dG•-formed radical and 2dG•+-formed radical cation), a DNA model, with  $k_{total}^{HAT}$  of 2dG• reactions  $\sim 10^3$  M<sup>-1</sup>s<sup>-1</sup>,  $k_{app}^{SET}$  of 2dG•+ reactions  $\sim 10^4-10^9$  M<sup>-1</sup>s<sup>-1</sup>.
- Compound 1 is expected as the most promising molecule to prevent the propagation of the DNA damage.

## ACKNOWLEDGMENTS

This research is funded by the Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 103.01-2019.380. This work used the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number OCI-1053575.

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