

Supporting Information

Theoretical study of radical and neutral intermediates of artemisinin decomposition

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CONTENTS with simple item descriptions

Figure A. Oxygen-oxygen bond length-bond order relationship	S2
Table A. Data for experimental O-O bond length-bond order relationships	S3
Table B. Data for <i>ab initio</i> O-O bond length-bond order relationships	S10
CSD REFCODEs with formula and references for crystal structures of artemisinins	S11
Table C. Selected structural data for artemisinins from the CSD Database	S16
Figure B. Correlations between internal coordinates in artemisinin derivatives	S17

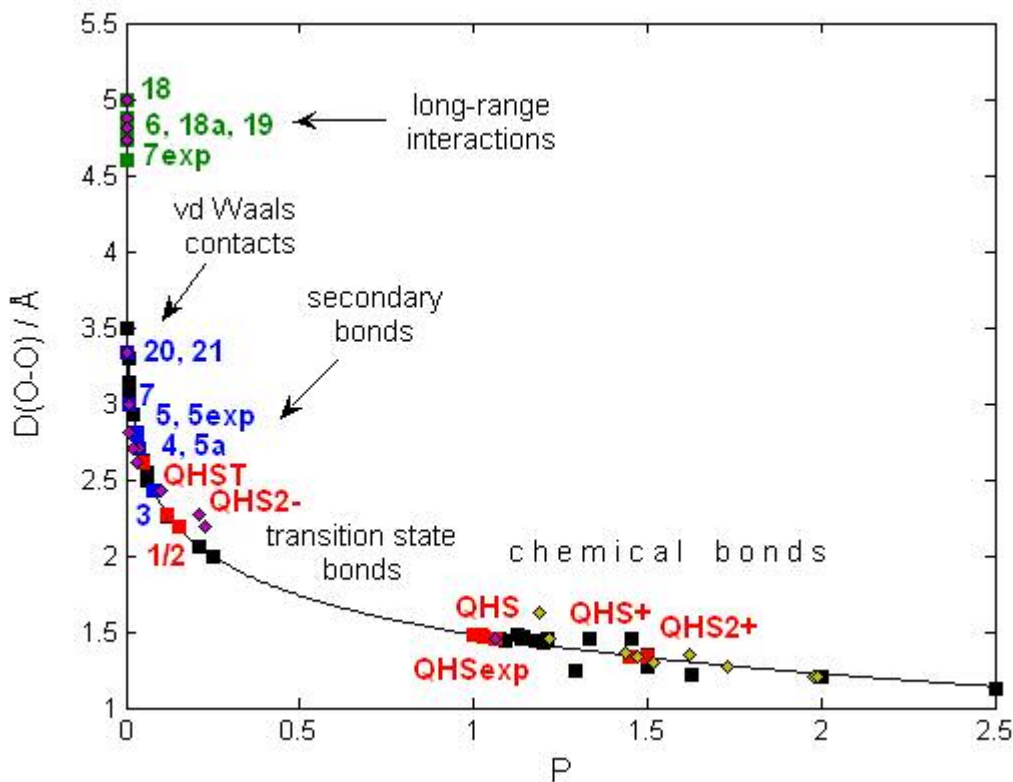
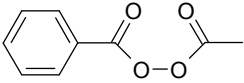
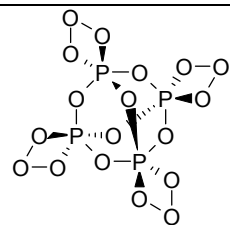


Figure A. Oxygen-oxygen bond length-bond order relationship over a broad range of valence bond order values P . The curve was constructed based on the O'Keeffe-Brese equation $D(\text{O-O})/\text{\AA} = 1.48 - 0.37 \ln P$ [O'Keeffe, M.; Brese, E. N. Bond-Valence Parameters for Anion-Anion Bonds in Solids. *Acta Cryst. B* **1992**, *48*, 152-154.]. Black squares present chemical systems for which the values of valence bond order P were determined by resonance structure counts when $P > 1$ or calculated from the equation when $P < 0.25$. Data for these systems are in Table A. The O'Keeffe-Brese equation was also used to calculate P for DFT geometries of artemisinin and its ions (red squares: **QHS**, **QHST**, **1/2**, **QHS2-**, **QHS+**, **QHS2+**) and experimental geometries of artemisinin and epiartemisinin (also red squares). **QHSexp** stands for the cluster of two crystal structures of artemisinin EXP-Q1 (CSD: QNGHSU03) and EXP-Q2 (CSD: QNGHSU10) and of epiartemisinin EXP-EA (CSD: WIMMEK). Five distinct regions of P are illustrated by adding artemisinin in various oxidation states (red squares) and its decomposition intermediates and products (green and blue squares) and using the O'Keeffe-Brese equation for DFT and experimental O1-O2 bond lengths. Diamonds represent Löwdin bond orders from Table B for artemisin, its ions and decomposition species (pink), and also for simple systems with O-O bond (yellow). Correlation between the two bond orders is high (correlation coefficient is 0.995).

Table A. Collected literature data for experimental oxygen-oxygen bond length-bond order relationships.^a

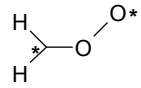
No. ^b	Species ^c	Structure description ^d	D(O-O)/Å ^e	P ^f	References and Notes ^g
1	O ²⁻ ... O ²⁻	O ²⁻ ... O ²⁻ , weak anion-anion interaction	2.5	0.06	Using equation $D(\text{O-O})/\text{Å} = 1.48 - 0.37 \ln P$, reported value 2.5 Å for weak interactions, and $P = 0.25$ as the cut-off for weak interactions, all from Ref.:
2	O ²⁻ ... O ²⁻	O ²⁻ ... O ²⁻ , weak anion-anion interaction	1.99	0.25	O'Keeffe, M.; Brese, E. N. Bond-Valence Parameters for Anion-Anion Bonds in Solids. <i>Acta Cryst. B</i> 1992 , <i>48</i> , 152-154.
3	2O	O ... O, two O atoms in van der Waals contact	3.04	0.01	The O'Keeffe-Brese equation was used, and double van der Waals radius for O was taken from Ref.: Bondi, A. Van der Waals Volumes and Radii. <i>J. Phys. Chem.</i> 1964 , <i>68</i> , 441-451.
4	ABP	Ph-C(O)-O-O-C(O)-Me, acetyl benzoyl peroxide 	acetyl 1.445(3)	1.176	The bond order P was determined from resonance structures. Crystal structure data were from Ref.: Karch, N. J.; Kohn, E. T.; Whitsel, B. L.; McBride, J. M. An X-Ray and Electron Paramagnetic Resonance Structural Investigation of Oxygen Discrimination during the Collapse of Methyl-Benzoyloxy Radical Pairs in Crystalline Acetyl Benzoyl Peroxide. <i>J. Amer. Chem. Soc.</i> 1975 , <i>97</i> , 6729-6743.
5	P ₄ O ₁₈	P ₄ O ₁₈ , phosphorous oxide tetraozonide	1.457(6)	1.333	The bond order P was determined from resonance structures. Crystal structure data were from Ref.: Dimitrov, A.; Ziemer, B.; Hunnius, W.-D.; Meisel, M. The First Ozonide of a Phosphorous Oxide - Preparation and

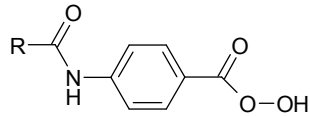
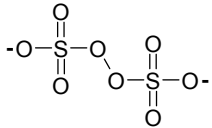
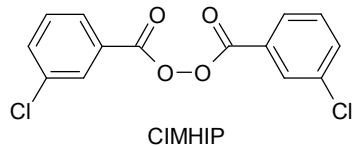
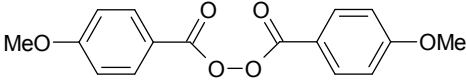


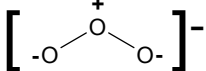
Characterization, and Structure of P₄O₁₈.
Angew. Chem. Int. Ed. **2003**, *42*, 2484-2486.

6	O ₂	¹⁶ O ₂ (g), oxygen molecule, gas-phase	1.20748(2)	2.000	Considered formal bond order P = 2. Microwave structure was from Ref.: Tiemann, E. Isotope Shifts of the Molecular Parameters in the X ³ Σ ⁻ State of Sulfur Monoxide. <i>J. Mol. Spectrosc.</i> 1982 , <i>91</i> , 60-71.
7	CF ₃ OOOCF ₃	F ₃ C-O-O-O-CF ₃ , <i>bis</i> (trifluoromethyl)trioxide	1.452(5)	1.136	The bond order P for the trioxide was determined from resonance structures. Formal bond order P = 1.5 was considered for ozone. Original and cited spectroscopical data were from Ref.: Gobbato, K. I.; Klapdor, M. F.; Mootz, D.; Poll, W.; Ulic, S. E.; Willner, H.; Oberhammer, H. <i>Bis</i> (trifluoromethyl)trioxide: First Structure of a Straight-Chain Trioxide. <i>Angew. Chem. Int. Ed.</i> 1995 , <i>34</i> , 2244-2245.
8	O ₃	O ₃ (g), ozone molecule, gas-phase	1.2716(2)	1.500	
9	FC(O)OOOC(O)F	F-C(O)-O-O-O-C(O)-F, <i>trans,syn,syn-bis</i> (fluoroformyl)trioxide	1.440(1)	1.091	The bond order P was determined from resonance structures. Crystal structure was from Ref.: Pernice, H.; Berkei, M.; Henkel, G.; Willner, H.; Argüello, G. A.; McKee, M. L.; Webb, T. R. <i>Bis</i> (fluoroformyl)trioxide, FC(O)OOOC(O)F. <i>Angew. Chem. Int. Ed.</i> 2004 , <i>43</i> , 2843-2846.
10	FOO*	FOO*, F-O-O* radical	1.200(13)	2.000	The bond order P was determined from resonance structures. Crystal structure data were those cited in Ref.:
11	F ₂ O ₂	FOOF, F-O-O-F,	1.217(3)	1.625	Jursic, B. .S. The density functional theory

		perfluoroperoxide			investigation of the equilibrium structures of OOF, FOOF, OOF ₂ and FOOOF. <i>J. Mol. Struct.</i> 1996 , 366, 97-101.
12	O ₂ ⁺	O ₂ ⁺ , dioxygenyl cation [O≡O] ⁺	1.123	2.500	Considered formal bond order P = 2.5. Calculated structure was from Ref.: Wikipedia - the free encyclopedia, in English. http://www.wikipedia.org (accessed 21 June, 2007)
13	O ²⁻ ... O ²⁻	O ²⁻ ... O ²⁻ , weak anion-anion interaction	2.054	0.21	Bond orders P were determined from the above equation. The minimum and mean O ²⁻ ... O ²⁻ distances were reported from statistics of inorganic crystal data in Ref.: Prince, E., Ed. International Tables for Crystallography, Vol. C: Mathematical, Physical and Chemical Tables, 3 rd ed.; International Union of Crystallography by Kluwer Academic Publishers: Dordrecht, The Netherlands, 2004, p. 789.
14	O ²⁻ ... O ²⁻	O ²⁻ ... O ²⁻ , weak anion-anion interaction	2.545	0.06	The bond order P was determined from resonance structures. Spectroscopic data were from Ref.: Birk, M.; Friedl, R. R.; Cohen, E. A.; Pickett, H. M.; Sander, S. P. The rotational spectrum and structure of chlorine peroxide. <i>J. Chem. Phys.</i> 1989 , 91, 6588-6596.
15	Cl ₂ O ₂	ClOOCl, Cl-O-O-Cl, chlorine peroxide	1.5259(21)	1.200	The bond order P for carbonyl oxide was determined from resonance structures. Calculated (MP2 6-31G*) structure of carbonyl oxide biradical was from Ref.: Bach, R. D.; Andrés, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W. Electronic Structure and Reactivity of Dioxirane and Carbonyl oxide. <i>J. Amer. Chem. Soc.</i> 1992 ,
16	O ... O	O ... O long range interactions H ₂ COO, H ₂ C*-O-O*,	3.500	0.000	

17	H ₂ COO	carbonyl oxide biradical 	1.296	1.250	114, 7207-7217. The limit of 3.5 Å for O - O steric interactions (P = 0) was considered according to the computational results in this Ref. The double value of the oxygen van der Waals (1.52 Å, see Bondi's work) with tolerance (0.2 Å, as used in the PLATON program) roughly corresponds to 3.5 Å.
18	O ... O	O ... O, interactions between oxygen atoms adsorbed on Rh(110) surface	3.3(4)	0.01	Bond orders P were calculated using the O'Keeffe-Brese formula. Various reported and cited structural data are from crystal structures in Ref.:
19	O ... O	O ... O, interactions between oxygen atoms adsorbed on Rh(110) surface	2.93	0.02	Hla, S. W.; Lacovig, P.; Comelli, G.; Baraldi, A.; Kiskinova, M.; Rosei, R. Orientational anisotropy in oxygen dissociation on Rh(110). <i>Phys. Rev. B</i> 1999 , <i>60</i> , 7800-7803.
20	O ... O	O ... O, interactions between oxygen atoms adsorbed on Rh(110) surface	2.5	0.06	
21	O ... O	O ... O, interactions between oxygen atoms adsorbed on Rh(110) surface	2.62	0.05	
22	O ²⁻ ... O ²⁻	O ²⁻ ... O ²⁻ in Rh ₂ O ₃ , weak anion-anion interaction	3.14	0.01	
23	O ²⁻ ... O ²⁻	O ²⁻ ... O ²⁻ in high-pressure Fe ₂ O ₃ , weak anion-anion interaction	2.26	0.12	The bond order P was calculated using the O'Keeffe-Brese formula. Crystal structure data were from Ref.: Rozenberg, G. Kh.; Dubrovinsky, L. S.; Pasternak, M. P.; Naaman, O.; Le Bihan, T.; Ahuja, R. High-pressure structural studies of hematite Fe ₂ O ₃ . <i>Phys. Rev. B</i> 2002 , <i>65</i> ,

064112, 1-8.					
24	PAA	<i>p</i> -alkyl-aminobenzoic acids, RC(O)NH-C ₆ H ₄ -C(O)-O-OH	1.455(5)	1.214	The bond order P was determined from resonance structures. The crystal structure data is the average of the data for two structures with CSD (Cambridge Structural Database) REFCODES: ZUHHOC (R = Et) and ZUHHUF (R = Pr). The structures are from Ref.: Feder, N.; Jones, W. Structures of Four <i>p</i> -Aminoperbenzoic Acids. <i>Acta Cryst. C</i> 1996 , <i>52</i> , 919-923.
					
25	O ₃ SOOSO ₃ ²⁻	[O ₃ S-O-O-SO ₃] ²⁻ , peroxodisulfate(VI) anion	1.462	1.143	The bond order P was determined from resonance structures. Crystal structure data were from Ref.: Skogareva, L. S.; Minacheva, L. Kh.; Sergienko, V. S.; Minaeva, N. A.; Filippova, T. V. Magnesium, calcium, and zinc phenanthroline peroxodisulfates: Crystal structure of the complex [Mg(Phen) ₂ (OH) ₂] ₂ S ₂ O ₈ ·2Phen. <i>Russ. J. Inorg. Chem.</i> 2004 , <i>49</i> , 855-862.
					
26	PhC(O)OOC(O)Ph	PhC(O)OOC(O)Ph, substituted	1.455(5)	1.459	The bond order P was determined from resonance structures. The crystal structure data is the average of the data for two structures with CSD REFCODES: a) CIMHIP, with Ref.: Syed, A.; Umrigar, P.; Stevens, E. D.; Griffin, G. W.; Majeste, R. J. Structure of 3,3'-Dichlorodibenzoyl Peroxide, C ₁₄ H ₈ Cl ₂ O ₄ . <i>Acta Cryst. C</i> 1984 , <i>40</i> , 1458-1460. b) DISJEU, with Ref.: Kosnikov, S. Y.; Antonovskii, V. L.; Lindeman, S. V.; Struchkov, Y. T.; Zyatkov, I.
		 CIMHIP			
		 DISJEU			

					P.; Pitsevich, G. A.; Gogolinskii, V. I. Molecular structure of 4,4'-dimethoxybenzoyl peroxide. <i>Bull. Acad. Sci. USSR Chem. Sci.</i> 1985 , <i>34</i> , 853-857.
27	O_3^-	O_3^- , ozonide ion in organic compounds	1.313(3)	1.500	Considered formal bond order $P = 1.5$. The inorganic data is the average of inorganic crystal data cited in Ref.: Seyeda, H.; Armbruster, K.; Jansen, M. Synthesis and Characterization of Ionic Ozonides with Bisquaternary Ammonium Counterions. <i>Chem. Ber.</i> 1996 , <i>129</i> , 997-1001. The organic data is the average of organic crystal data cited in the above Ref. (CSD REFCODEs: TIBRIF and TIBROF) and the following Ref. (CSD REFCODE: JOGWOR): Hesse, W.; Jansen, M. New Ionic Ozonides: Syntheses, Structures, and Properties of $N(CH_3)_4O_3$ and $N(C_2H_5)_4O_3$. <i>Inorg. Chem.</i> 1991 , <i>30</i> , 4380-4385.
28		O_3^- , ozonide ion in inorganic compounds 	1.344(6)	1.500	
29	H_2O_2	H_2O_2 , H-O-O-H, hydrogen peroxide	1.475	1.125	The bond order P was determined from resonance structures. Spectroscopic data were from Ref.: Lide, D., Ed. CRC Handbook of Chemistry and Physics, 87 th ed. (2006-2007 ed.). CRC Press: Boca Raton, FL, 2006, Section 9, p 9-22.
30	O_2^{2-}	O_2^{2-} , $[O-O]^{2-}$, peroxide anion from BaO_2	1.482(10)	1.000	Considered formal bond order $P = 1$. Crystal structure data were from Ref.: VerNooy, P. D. Redetermination of the Structure of Barium Peroxide by Single-Crystal X-ray Diffraction. <i>Acta Cryst.</i> 1993 , <i>C49</i> , 433-434.
31	O_2^-	O_2^- , $[O-O]^-$, superoxide anion from β - NaO_2	1.28(2)	1.500	Considered formal bond order $P = 1.5$. Crystal structure data were from Ref.:

^aThese are literature data, mostly experimental and all related to real structures, used to construct the O-O bond length-bond order relationship plot in this work.

^bOrdinal number of the sample.

^cAtomic or ionic systems, ions and molecules for which O ... O bonding or non-bonding distance is reported in this table.

^dDescription, formula or other identifying information.

^eOxygen-oxygen bond length or non-bonding distance, with experimental estimated standard deviation in brackets whenever possible.

^fValence bond order assigned to reported O ... O distance by using the formula $D(\text{O-O})/\text{\AA} = 1.48 \ln P$, considered as formal bond order according to the literature, or assigned based on counts of resonance structures. The method of resonance structures included determination of all chemically significant resonance structures with at most two formal ion pairs. For an O-O bond under study, the P value was obtained as the ratio $P = B / N$, where B is the sum of formal bond orders for this bond in all resonance structures, and N is the number of resonance structures. Therefore, P may be considered as the average bond order for the O-O chemical bond.

^gDetailed description of the literature sources and methods for determination of the values of P.

OTHER NOTES.

The O-O bond length-bond order curve was constructed differently for distinct regions of the O-O distance: a) up to 2.5 Å the equation $D(\text{O-O})/\text{\AA} = 1.48 - 0.37 \ln P$ was used; b) from 2.5 to 3.04 Å a linear relationship was used, considering that $P = 0$ for 3.04 Å and $P = 0.06$ for $P = 2.5$ Å; c) for any O-O distance greater than 3.04 Å the bond order P was assigned zero.

Bond orders were assigned for all non-bonding O-O distances by using the equation. However, bond order for all chemical bond lengths were either determined from resonance structures or assigned as in the literature (also confirmed by the resonance structures method).

PLATON program is software used for analysis of crystallographic structures of small molecules. References:

Spek, T. PLATON – A Multipurpose Crystallographic Tool. *Acta Cryst. A* **1990**, *46*, C34.

Farrugia, L. J. *Platon for Windows Taskbar*, v. 1.10 (27/09/2006); University of Glasgow: Glasgow, UK, 2006.

Table B. Data for *ab initio* O-O bond length-bond order relationships

Species ^a	D(O-O) / Å ^b	Lw ^c	P ^c
QHS	1.460	1.056	1.056
QHST	2.614	0.031	0.047
1/2	2.186	0.232	0.148
QHS2-	2.267	0.206	0.119
QHS+	1.342	N SCF	1.452
QHS2+	1.330	N SCF	1.500
3	2.434	0.096	0.076
4	2.700	0.035	0.037
5	2.806	0.006	0.028
5a	2.713	0.019	0.036
6	4.720	0.003	0.000
7	2.999	0.006	0.017
18	5.000	0.001	0.000
18a	4.872	0.002	0.000
19	4.812	0.002	0.000
20	3.328	0.005	0.007
21	3.328	0.005	0.007
O ₂ (triplet)	1.214	1.975	2.000
O ₂ ⁻	1.353	1.616	1.500
O ₂ ²⁻	1.618	1.185	1.000
H ₂ O ₂	1.456	1.217	1.125
O ₃ (triplet)	1.302	1.524	1.500
O ₃ ⁻	1.360	1.436	1.500
F ₂ O ₂	1.266	1.726	1.625
FOO	1.212	1.988	2.000
H ₂ COO	1.357	1.437	1.250
Cl ₂ O ₂	1.331	1.471	1.200

^aArtemisinin in singlet (**QHS**) and triplet (**QHST**) states, artemisinin ions and decomposition intermediates and product, all typed in bold. Other species are small neutral molecules or ions with O-O bond, already presented in Table A.

^bLength of the peroxide bond from were geometry optimized at the B3LYP 6-31G** level. The small oxygen and peroxide species were optimized with Gaussian, previously modeled by the Titan program.

^cLöwdin bond order were obtained from single-point calculations by Titan, using the previously optimized geometries by Gaussian. Löwdin bond orders could not be calculated for artemisinin radical cations **QHS+** and **QHS2+** because no SCF convergence was achieved (N SCF).

^dValence bond order was calculated for artemisinin species by using the O’Keeffe-Brese equation, whilst for other small species it was from Table A. The valence and Lowdin bond orders for the 25 samples are mutually highly correlated, with correlation coefficient 0.995.

CSD REFCODEs with formula and references for crystal structures of artemisinins used in this work

ADAHAP:

9,10-Dehydrodeoxyartemisinin C₁₅H₂₂O₄ antimalarial activity

Li, S.-H.; Yue, Z.-Y.; Gae, P.; Yan, P.-F. 9,10-Dehydrodeoxyartemisinin. *Acta Cryst. E* **2006**, *62*, o1898-o1900.

DIJDAB01:

10-Acetoxy-4,7-dimethyl-8-oxo-tetrahydrofuran(2,3-i)-2-oxa-perhydronaphthalene C₁₅H₂₂O₅

Luo, X.-D.; Yeh, H. J. C.; Brossi, A.; Flippen-Anderson, J. L.; Gilardi, R. The Chemistry of Drugs. 6. Thermal Decomposition of Qinghaosu. *Heterocycles* **1985**, *23*, 881-887.

DIJDEF:

12,14-Epoxy-11-hydroxy-4,8,12-trimethyl-2,13-dioxatricyclo(7.4.1.0^{5,14})tetradecan-3-one C₁₅H₂₂O₅

Lin, A. J.; Klayman, D. L.; Hoch, J. M.; Silverton, J. V.; George, C. F. Thermal Rearrangement and Decomposition Products of Artemisinin (Qinghaosu). *J. Org. Chem.* **1985**, *50*, 4504-4508.

FAHFV01:

10- α -Artesunate C₁₉H₂₈O₈ antimalarial activity

R.K.Haynes, Ho-Wai Chan, Man-Ki Cheung, Wai-Lun Lam, May-Kei Soo, Hing-Wo Tsang, A.Voerste, I.D.Williams. C-10 Ester and Ether Derivatives of Dihydroartemisinin 10- α -Artesunate, Preparation of Authentic 10- β -Artesunate, and of Other Ester and Ether Derivatives Bearing Potential Aromatic Intercalating Groups at C-10. *Eur. J. Org. Chem.* **2002**, 113-132.

IDOYUV:

9,9',16,16'-Tetrahydro-9,16'-biartemisitenone C₃₀H₄₂O₁₀ antimalarial activity

Ekthawatchai, S.; Kamchonwongpaisan, S.; Kongsaree, P.; Tarnchompoo, B.; Thebtaranonth, Y.; Yuthavong, Y. C-16 Artemisinin Derivatives and Their Antimalarial and Cytotoxic Activities: Syntheses of Artemisinin Monomers, Dimers, Trimers, and Tetramers by Nucleophilic Additions to Artemisitenone. *J. Med. Chem.* **2001**, *44*, 4688-4695.

JUDRAB:

9-epi-Arteether $C_{17}H_{28}O_5$

El-Ferally, F. S.; Al-Yahya, M. A.; Orabi, K. Y.; McPhail, D. R.; McPhail, A. T. A New Method for the Preparation of Arteether and Its C-9 Epimer. *J. Nat. Prod.* **1992**, *55*, 878-883.

JUXGOY:

3-(Octahydro-3,6,9-trimethyl-3,12:9,10-diepoxyprano(4,3-j))-1,2-benzodioxepine (Artemisinin epoxide)
 $C_{15}H_{22}O_5$

Hufford, C. D.; Khalifa, S. I.; McPhail, A. T.; El-Ferally, F. S.; Ahmad, M. S. Preparation and Characterization of New C-11 Oxygenated Artemisinin Derivatives. *J. Nat. Prod.* **1993**, *56*, 62-66.

PEXKIM:

Epoxyartemisitenone $C_{15}H_{20}O_6$

Acton, N.; Karle, J. M.; Miller, R. E. Synthesis and antimalarial activity of some 9-substituted artemisinin derivatives. *J. Med. Chem.* **1993**, *36*, 2552-2557.

QEYCEC:

(R)-2-(4-Bromophenyl)-2-(dihydroartemisinyloxy)acetonitrile $C_{23}H_{28}BrNO_5$ antitumor activity

Li, Y.; Shan, F.; Wu, J.-M.; Wu, G.-S.; Ding, J.; Xiao, D.; Yang, W.-Y.; Atassi, G.; Leonce, S.; Caignard, D.-H.; Renard, P.. Novel antitumor artemisinin derivatives targeting G1 phase of the cell cycle. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 5-8.

QNGHSU03:

Octahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano(4,3-j)-1,2-benzodioxepin-10(3H)-one (Artemisinin, Qinghaosu) $C_{15}H_{22}O_5$ antimalarial drug

Lisgarten, J. N.; Potter, B. S.; Bantuzeko, C.; Palmer, R. A. Structure, Absolute Configuration, and Conformation of the Antimalarial Compound, Artemisinin. *J. Chem. Cryst.* **1998**, *28*, 539-543.

QNHGSU10:

Octahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano(4,3-j)-1,2-benzodioxepin-10(3H)-one (Artemisinin, Qinghaosu) $C_{15}H_{22}O_5$ antimalarial drug

Leban, I.; Golič, L.; Japelj, M. Crystal And Molecular Structure of Qinghaosu – A Redetermination. *Acta Pharm. Jugosl.* **1988**, *38*, 71-77.

SIHHEW:

Dihydroartemisitenone $C_{15}H_{22}O_5$

El-Feraly, F. S.; Ayalp, A.; Al-Yahya, M. A.; McPhail, D. R.; McPhail, A. T. Conversion of Artemisinin to Artemisitenone. *J. Nat. Prod.* **1990**, *53*, 66-71.

SIKLAZ:

9-Bromo-10-deoxy-10-(2-pyridylamino)-artemisinin $C_{20}H_{27}BrN_2O_4$ antimalarial activity

Lin, A. J.; Li, L.-Q.; Klayman, D. L.; George, C. F.; Flippen-Anderson, J. L.. Antimalarial activity of new water-soluble dihydroartemisinin derivatives. 3. Aromatic amine analogs. *J. Med. Chem.* **1990**, *33*, 2610-2614.

TAFWUT:

10 β -(4'-Fluorophenyl)-10-deoxy-10-dihydroartemisinin $C_{21}H_{27}FO_4$

Haynes, R. K.; Chan, H.-W.; Cheung, M.-K.; Chung, S. T.; Lam, W.-L.; Tsang, H.-W.; Voerste, A.; Williams, I. D.. Stereoselective Preparation of 10- α - and 10- β -Aryl Derivatives of Dihydroartemisinin. *Eur. J. Org. Chem.* **2003**, 2098-2114.

TAFXAA:

10 β -(9'-Phenanthryl)-10-deoxy-10-dihydroartemisinin $C_{29}H_{32}O_4$

Haynes, R. K.; Chan, H.-W.; Cheung, M.-K.; Chung, S. T.; Lam, W.-L.; Tsang, H.-W.; Voerste, A.; Williams, I. D.. Stereoselective Preparation of 10- α - and 10- β -Aryl Derivatives of Dihydroartemisinin. *Eur. J. Org. Chem.* **2003**, 2098-2114.

TAFXII:

10 β -(4'-N,N-Dimethylaminophenyl)-10-deoxy-10-dihydroartemisinin $C_{23}H_{33}NO_4$

Haynes, R. K.; Chan, H.-W.; Cheung, M.-K.; Chung, S. T.; Lam, W.-L.; Tsang, H.-W.; Voerste, A.; Williams, I. D.. Stereoselective Preparation of 10- α - and 10- β -Aryl Derivatives of Dihydroartemisinin. *Eur. J. Org. Chem.* **2003**, 2098-2114.

UCIMID:

Artemisone $C_{19}H_{31}NO_6S$ antimalarial drug

Haynes, R. K.; Fugmann, B.; Stetter, J.; Rieckmann, K.; Heilmann, H.-D.; Chan, H.-W.; Cheung, M.-K.; Lam, W.-L.; Wong, H.-N.; Croft, S. L.; Vivas, L.; Rattray, L.; Stewart, L.; Peters, W.; Robinson, B. L.; Edstein, M. D.; Kotecka, B.; Kyle, D. E.; Beckermann, B.; Gerisch, M.; Radtke, M.; Schmuck, G.; Steinke, W.; Wollborn, U.; Schmeer, K.; Romer, A.. Artemisone - A Highly Active Antimalarial Drug of the Artemisinin Class. *Angew. Chem. Int. Ed.* **2006**, *45*, 2082-2088.

VENPUZ:

10-Deoxo-10-hydroperoxo-artemisitenone $C_{15}H_{22}O_6$

El-Ferally, F. S.; Ayalp, A.; Al-Yahya, M. A.; McPhail, D. R.; McPhail, A. T. Conversion of Artemisinin to Artemisitenone. *J. Nat. Prod.* **1990**, *53*, 66-71.

WIMMEK:

Octahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano(4,3-j)-1,2-benzodioxepin-10(3H)-one

Epiartemisinin $C_{15}H_{22}O_5$ poor antimalarial activity

Jefford, C. W.; Burger, U.; Millasson-Schmidt, P.; Bernardinelli, G.; Robinson, B. L.; Peters, W. Epiartemisinin, a Remarkably Poor Antimalarial: Implications for the Mode of Action. *Helv. Chim. Acta* **2000**, *83*, 1234-1246.

ZILMUC

3(R)-(p-Nitrophenyl)-3-(10 β -dihydroartemisininoxy)propionic acid $C_{24}H_{31}NO_9$ acid form of synthetic analogue of antimalarial agent

Karle, J. M.; Lin, A. J. Correlation of the crystal structures of diastereomeric artemisinin derivatives with their proton NMR spectra in $CDCl_3$. *Acta Cryst. B* **1996**, *51*, 1063-1068.

ZULNAV

1- α -Hydroxyarteether $C_{17}H_{28}O_6$

Hufford, C. D.; Khalifa, S. I.; Orabi, K. Y.; Wiggers, F. T.; Kumar, R.; Rogers, R. D.; Campana, C. F.. 1 α -Hydroxyarteether, a New Microbial Transformation Product. *J. Nat. Prod.* **1995**, *58*, 751-755.

Table C. Selected structural^a data for artemisinins from the Cambridge Structural Database

REFCODE ^b	O1-O2	O11-O13	O13-O2	O13-O1	O11-O2	O11-O1	O2-C3	O1-C14	TOR1	ANG1	ANG2	H4 α -O1	H4 α -O2
ADAHAP	1.467	2.248	2.318	2.867	2.822	2.973	1.424	1.453	44.96	108.63	111.61	2.565	2.466
FAHFAV01	1.474	2.244	2.318	2.860	2.788	2.942	1.412	1.457	45.86	108.27	111.56	2.572	2.473
IDOYUV	1.467	2.248	2.298	2.827	2.851	3.024	1.421	1.452	49.78	107.30	112.25	2.471	2.428
	1.467	2.264	2.301	2.857	2.908	3.02	1.400	1.463	44.59	109.10	111.38	2.524	2.432
JUDRAB	1.474	2.239	2.310	2.857	2.782	2.933	1.413	1.458	45.08	108.36	111.41	2.617	2.421
JUXGOY	1.473	2.242	2.320	2.867	2.807	2.949	1.430	1.448	42.12	109.38	111.61	2.648	2.505
PEXKIM	1.480	2.278	2.314	2.867	2.847	2.995	1.417	1.467	45.33	108.53	110.89	2.549	2.450
	1.480	2.280	2.307	2.862	2.912	3.036	1.405	1.461	45.63	108.28	110.97	2.544	2.457
QEYCEC	1.481	2.247	2.307	2.852	2.771	2.937	1.431	1.434	46.07	108.24	111.43	2.532	2.447
QINGHSU10 ^c	1.474	2.270	2.307	2.859	2.935	3.072	1.418	1.450	47.73	107.72	111.55	No H	No H
SIHHEW	1.473	2.260	2.304	2.847	2.786	2.918	1.414	1.456	43.76	108.86	112.00	2.532	2.378
SIKLAZ	1.482	2.323	2.296	2.868	3.211	3.185	1.429	1.468	44.05	109.15	112.75	2.585	2.433
TAFWUT	1.468	2.322	2.304	2.853	3.249	3.203	1.418	1.471	42.58	108.31	113.04	2.594	2.457
TAFXAA	1.471	2.314	2.294	2.856	3.233	3.181	1.415	1.469	39.98	109.73	113.15	2.649	2.457
TAFXII	1.466	2.319	2.302	2.853	3.259	3.202	1.422	1.474	41.35	108.80	113.15	2.605	2.452
UCIMID	1.478	2.261	2.305	2.862	2.819	2.956	1.417	1.463	44.62	109.10	111.18	2.585	2.463
	1.470	2.247	2.318	2.866	2.739	2.889	1.406	1.467	44.75	108.94	111.74	2.610	2.474
	1.466	2.256	2.323	2.858	2.773	2.918	1.439	1.468	45.10	108.50	111.53	2.521	2.431
	1.460	2.254	2.322	2.854	2.746	2.894	1.408	1.468	44.83	108.61	112.94	2.591	2.458
VENPUZ	1.478	2.243	2.319	2.858	2.756	2.917	1.419	1.448	45.43	107.80	111.49	2.529	2.463
	1.472	2.243	2.319	2.856	2.753	2.891	1.417	1.456	43.91	108.64	111.68	2.590	2.462
WIMMEK	1.481	2.277	2.303	2.857	2.824	2.964	1.411	1.466	45.23	109.00	110.92	2.591	2.460
ZILMUC	1.448	2.225	2.317	2.835	2.805	2.941	1.388	1.446	45.01	108.21	112.76	2.562	2.451

ZULNAV ^c	1.471	2.242	2.322	2.867	2.799	2.934	1.413	1.477	44.09	108.77	112.06	No H	No H
	1.478	2.246	2.315	2.862	2.795	2.933	1.411	1.463	43.84	108.96	111.81	No H	No H
	1.475	2.250	2.307	2.860	2.850	2.968	1.397	1.461	43.82	109.91	111.87	No H	No H
	1.465	2.243	2.311	2.859	2.797	2.927	1.405	1.464	43.48	109.74	112.15	No H	No H
Minimum ^d	1.448	2.225	2.294	2.827	2.739	2.889	1.388	1.434	39.98	107.30	110.89	2.471	2.378
Maximum ^d	1.482	2.323	2.323	2.868	3.259	3.203	1.439	1.477	49.78	109.91	113.15	2.649	2.505
Mean ^d	1.472	2.262	2.310	2.857	2.875	2.989	1.515	1.460	44.55	108.70	111.88	2.571	2.451
Range ^d	0.034	0.098	0.029	0.041	0.520	0.314	0.051	0.043	9.80	2.61	2.60	0.178	0.127

^aGeometry parameters: O-O and O-C bond lengths, O-O and H-O non-bonding distances in Å; bond angles C3-O2-O1 (ANG1) and O2-O1-C12a (ANG2) in °; torsion angle C3-C2-O1-C12a (TOR1) in °.

^bReference codes for crystal structures of artemisinin retrieved from the Cambridge Structural Database (CSD). Some structures contain two or more artemisinin fragments because there is more than one molecule in the asymmetric unit or the molecule contains of two artemisinin fragments.

^cStructures without determined positions of hydrogen atoms.

^dMinimum, maximum and mean values and the range (maximum – minimum) for a particular parameter.

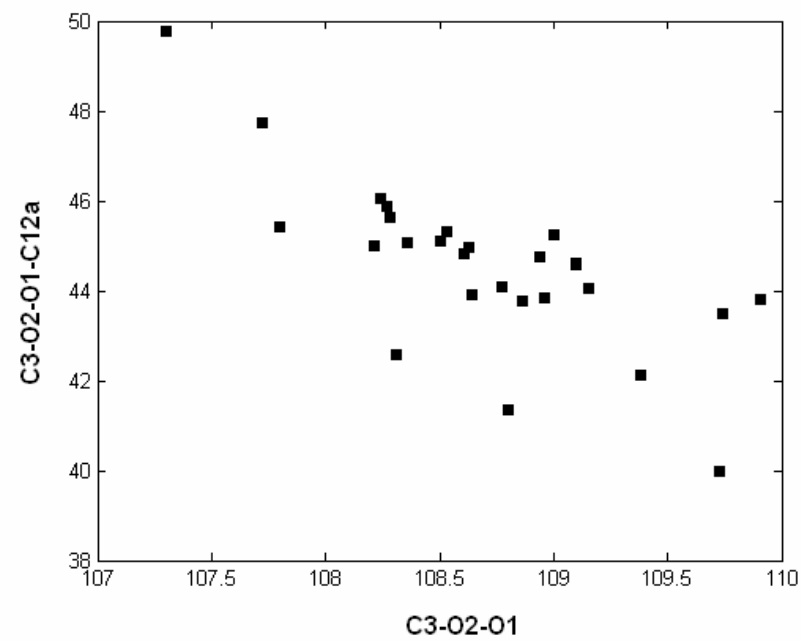
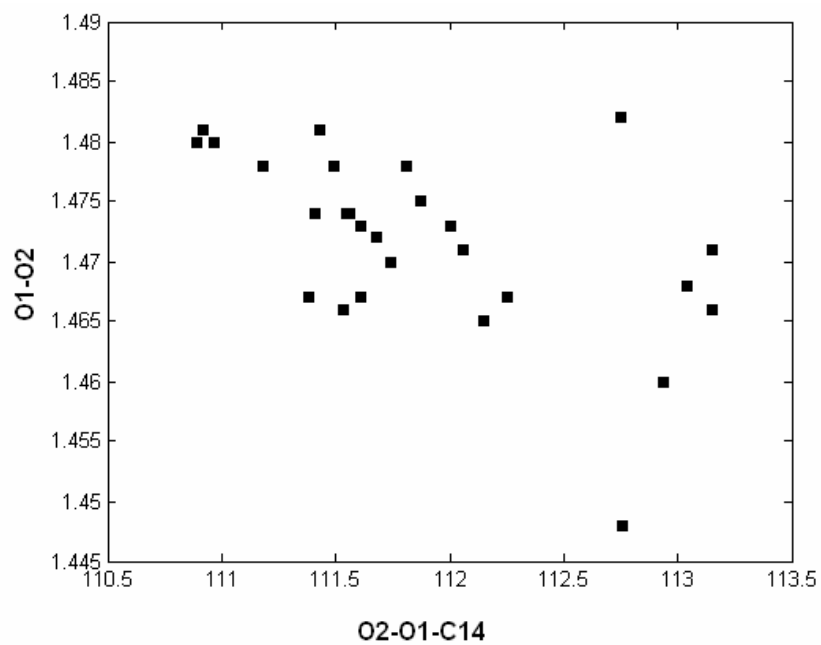


Figure B. Correlations between internal coordinates in artemisinin derivatives. Data are from Table B. Units: bond length in Å, bond and torsion angles in degrees (°).