**1,4,9,9-tetramethyloctahydro-4,7-(epoxymethano)azulen-5(1*H*)-one, a natural product as a potential inhibitor of COVID-19: Extraction, crystal structure, and virtual screening approach**

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**Supporting material**

**Table S1:** Experimental details of the title compound

|  |  |
| --- | --- |
| Chemical formula | [C15H24O2](skm262_4_a_a%20_chemical_formula_moiety) |
| CCDC Deposition Number | 2164481 |
| *M*r | [236.34](skm262_4_a_a%20_chemical_formula_weight) |
| Crystal system, space group | [Orthorhombic](skm262_4_a_a%20_space_group_crystal_system), [*P*212121](skm262_4_a_a%20_space_group_name_H-M_alt) |
| Temperature (K) | [150](skm262_4_a_a%20_cell_measurement_temperature) |
| *a, b, c* (Å) | [9.1153 (5)](skm262_4_a_a%20_cell_length_a), [11.7023 (6)](skm262_4_a_a%20_cell_length_b), [12.5848 (7)](skm262_4_a_a%20_cell_length_c) |
| *V* (Å3) | [1342.42 (13)](skm262_4_a_a%20_cell_volume) |
| *Z* | [4](skm262_4_a_a%20_cell_formula_units_Z) |
| Radiation type | [Cu *K*α](skm262_4_a_a%20_diffrn_radiation_type) |
| µ (mm−1) | [0.59](skm262_4_a_a%20_exptl_absorpt_coefficient_mu) |
| Crystal size (mm) | [0.29](skm262_4_a_a%20_exptl_crystal_size_max) × [0.23](skm262_4_a_a%20_exptl_crystal_size_mid) × [0.16](skm262_4_a_a%20_exptl_crystal_size_min) |
| **Data collection** | |
| Diffractometer | [Bruker D8 VENTURE PHOTON 100 CMOS](skm262_4_a_a%20_diffrn_measurement_device_type) |
| Absorption correction | [Multi-scan](skm262_4_a_a%20_exptl_absorpt_correction_type) [*TWINABS* (Sheldrick, 2009)](skm262_4_a_a%20_exptl_absorpt_process_details) |
| *T*min, *T*max | [0.85](skm262_4_a_a%20_exptl_absorpt_correction_T_min), [0.91](skm262_4_a_a%20_exptl_absorpt_correction_T_max) |
| No. of measured, independent and observed [[*I*> 2σ(*I*)](skm262_4_a_a%20_reflns_threshold_expression)]reflections | [25898](skm262_4_a_a%20_diffrn_reflns_number), [2630](skm262_4_a_a%20_reflns_number_total), [2482](skm262_4_a_a%20_reflns_number_gt) |
| *R*int | [0.078](skm262_4_a_a%20_diffrn_reflns_av_R_equivalents) |
| (sin θ/λ)max (Å−1) | 0.618 |
| **Refinement** | |
| *R[F*2>2σ(*F*2)]*, wR*(*F*2)*, S* | [0.045](skm262_4_a_a%20_refine_ls_R_factor_gt), [0.114](skm262_4_a_a%20_refine_ls_wR_factor_ref), [1.10](skm262_4_a_a%20_refine_ls_goodness_of_fit_ref) (IAM)  0.041, 0.097, 1.15 (HAR) |
| No. of reflections | [2630](skm262_4_a_a%20_refine_ls_number_reflns) |
| No. of parameters | [239](skm262_4_a_a%20_refine_ls_number_parameters) (IAM); 370 (HAR) |
| H-atom treatment | [H atoms are treated by a mixture of independent and constrained refinement](skm262_4_a_a%20_refine_ls_hydrogen_treatment) |
| Δ*ρ*max, Δ*ρ*min (e Å−3) | [0.31](skm262_4_a_a%20_refine_diff_density_max), [−0.30](skm262_4_a_a%20_refine_diff_density_min) (IAM)  0.21, -0.32 (HAR) |
| Absolute structure | [Flack x determined using 983 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons *et al*., 2013).](skm262_4_a_a%20_refine_ls_abs_structure_details) |
| Absolute structure parameter | [0.12 (13)](skm262_4_a_a%20_refine_ls_abs_structure_Flack) |

**Table 1.** Hydrogen-bond geometry (Å, °)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
| C15—H15C···O1i | 0.97(4) | 2.56(4) | 3.454(3) | 154(3) |

Symmetry code: (i) −x+1/2, −y+1, z−1/2.

**Table S3.** Anisotropic Displacement Parameters (Å2×103) for skm262\_4\_a\_a. The Anisotropic displacement factor exponent takes the form: -2π2[h2a\*2U11+2hka\*b\*U12+…]. Atom

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **U11** | **U22** | **U33** | **U12** | **U13** | **U23** |
| O1 | 47.9(7) | 50.9(7) | 33.7(6) | -11.2(6) | 11.7(5) | 9.5(5) |
| O2 | 33.2(6) | 28.0(5) | 17.8(4) | 1.5(4) | -0.9(4) | -1.3(3) |
| C1 | 29.2(8) | 31.2(7) | 22.9(6) | -1.6(5) | -0.6(5) | 0.8(5) |
| H1 | 34(9) | 29(4) | 66(15) | -5(2) | -15(6) | 5(3) |
| C2 | 27.6(8) | 41.9(8) | 36.5(8) | -3.9(6) | -2.3(6) | 6.7(7) |
| H2 | 27(8) | 94(16) | 75(11) | 3(5) | 4(4) | 51(7) |
| C3 | 38.6(10) | 67.4(12) | 46.8(10) | -7.1(9) | -13.5(8) | -4.7(9) |
| H3A | 80(15) | 85(12) | 56(15) | 11(5) | -23(8) | -9(7) |
| H3B | 67(16) | 80(7) | 120(20) | -21(5) | -28(11) | 10(6) |
| C4 | 42.4(9) | 37.2(8) | 25.9(7) | 0.1(7) | -10.7(6) | -0.1(6) |
| H4A | 64(18) | 67(10) | 36(5) | 21(8) | -1(4) | 14(3) |
| H4B | 84(18) | 44(3) | 29(9) | 13(3) | -23(7) | -4(3) |
| C5 | 31.6(8) | 27.6(7) | 20.6(6) | 0.1(6) | -2.2(5) | 1.2(5) |
| H5 | 75(17) | 23(10) | 47(13) | -13(10) | 24(12) | -1(9) |
| C6 | 34.2(8) | 30.6(7) | 16.2(6) | 1.0(5) | 2.5(5) | 0.5(5) |
| C7 | 32.4(8) | 32.6(7) | 23.7(7) | -1.9(6) | 6.1(5) | 3.1(6) |
| C8 | 33.2(8) | 28.7(7) | 28.1(7) | -3.8(6) | 1.4(6) | -3.2(6) |
| H8A | 34(8) | 36(7) | 23(10) | 0(3) | 4(5) | -3(5) |
| H8B | 33(5) | 44(9) | 41(11) | -9(3) | -1(3) | 4(7) |
| C9 | 29.4(8) | 31.0(7) | 20.3(6) | -2.1(5) | 0.5(5) | -5.0(5) |
| H9 | 81(19) | 66(15) | 18(6) | -39(13) | -4(4) | -4(4) |
| C10 | 30.6(8) | 37.5(7) | 23.1(6) | -0.3(6) | 4.1(6) | -6.2(6) |
| H10A | 52(14) | 43(5) | 43(11) | 4(3) | 16(8) | -3(3) |
| H10B | 79(18) | 63(10) | 38(8) | -4(7) | 18(6) | 7(4) |
| C11 | 33.1(10) | 48.5(10) | 68.7(13) | 5.6(8) | -0.4(9) | 6.3(9) |
| H11A | 43(9) | 64(11) | 87(8) | 0(4) | 6(4) | 7(4) |
| H11B | 36(5) | 76(14) | 75(10) | 6(3) | 3(3) | 0(6) |
| H11C | 66(12) | 104(16) | 81(6) | -9(6) | 2(3) | -11(4) |
| C12 | 50.9(11) | 44.5(9) | 19.1(6) | 4.4(8) | 5.8(7) | -4.1(6) |
| H12A | 56(10) | 58(8) | 34(8) | 5(4) | 7(4) | 6(4) |
| H12B | 72(10) | 52(5) | 42(12) | -4(3) | -3(6) | 0(3) |
| H12C | 55(5) | 60(10) | 53(13) | 6(2) | 3(2) | -3(6) |
| C13 | 29.0(7) | 31.2(6) | 17.1(6) | -0.8(6) | -2.4(5) | -1.5(5) |
| C14 | 44.1(10) | 39.4(8) | 22.7(7) | -4.8(7) | -1.0(6) | 5.1(6) |
| H14A | 58(9) | 49(6) | 27(9) | 3(4) | -2(5) | 3(4) |
| H14B | 51(10) | 65(12) | 30(5) | -4(5) | -1(3) | -6(3) |
| H14C | 47(4) | 46(10) | 45(10) | -5(2) | -2(2) | -3(5) |
| C15 | 30.5(8) | 38.8(8) | 30.4(7) | 1.5(6) | -4.8(6) | -1.0(6) |
| H15A | 53(12) | 46(5) | 41(9) | 6(3) | -13(5) | -3(3) |
| H15B | 35(11) | 54(8) | 43(6) | 0(5) | -8(4) | 7(3) |
| H15C | 89(17) | 50(9) | 37(5) | -1(6) | -16(3) | -3(3) |

**Table S4.** Bond lengths (Å) and Bond angles (°)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **IAM** | **HAR** | **DFT** |  | **IAM** | **HAR** | **DFT** |
| **Bond lengths (Å)** | | | | | | | |
| O1-C7 | 1.220(3) | 1.2210(19) | 1.211 | C3-H3A | 0.94(5) | 1.16(3) | 1.094 |
| O2-C6 | 1.449(3) | 1.4422(17) | 1.447 | C3-H3B | 0.96(5) | 1.08(3) | 1.093 |
| O2-C13 | 1.460(2) | 1.4535(15) | 1.456 | C4-H4A | 0.93 (4) | 1.15(2) | 1.092 |
| C1-C2 | 1.538(4) | 1.538(2) | 1.555 | C4-H4B | 0.99(3) | 1.11(2) | 1.094 |
| C1-C5 | 1.533(3) | 1.5327(19) | 1.541 | C5-H5 | 1.01(3) | 1.09(2) | 1.099 |
| C1-C10 | 1.530(3) | 1.5282(19) | 1.533 | C8-H8A | 1.03(3) | 1.13(2) | 1.095 |
| C2-C3 | 1.551(4) | 1.553(3) | 1.564 | C8-H8B | 0.99(3) | 1.11(2) | 1.092 |
| C2-C11 | 1.521(4) | 1.522(3) | 1.534 | C9-H9 | 1.01(3) | 1.112(19) | 1.095 |
| C3-C4 | 1.528(5) | 1.534(3) | 1.547 | C10-H10A | 1.00(3) | 1.11(2) | 1.096 |
| C4-C5 | 1.533(3) | 1.535(2) | 1.540 | C10-H10B | 0.99(4) | 1.12(2) | 1.095 |
| C5-C6 | 1.561(3) | 1.562(2) | 1.570 | C11-H11A | 0.94(7) | 1.05(3) | 1.093 |
| C6-C7 | 1.527(3) | 1.530(2) | 1.541 | C11-H11B | 0.97(5) | 1.06(3) | 1.094 |
| C6-C12 | 1.521(3) | 1.5176(19) | 1.524 | C11-H11C | 0.96(4) | 1.12(4) | 1.095 |
| C7-C8 | 1.503(3) | 1.500(2) | 1.519 | C12-H12A | 0.98(3) | 1.11(2) | 1.091 |
| C8-C9 | 1.538(3) | 1.539(2) | 1.540 | C12-H12B | 0.97(4) | 1.06(3) | 1.091 |
| C9-C10 | 1.535(3) | 1.536(2) | 1.552 | C12-H12C | 1.01(4) | 1.11(3) | 1.091 |
| C9-C13 | 1.542(3) | 1.544(2) | 1.552 | C14-H14A | 0.99(4) | 1.12(2) | 1.091 |
| C13-C14 | 1.519(3) | 1.519(2) | 1.541 | C14-H14B | 0.90(3) | 1.13(2) | 1.092 |
| C13-C15 | 1.526(3) | 1.530(2) | 1.532 | C14-H13C | 1.00(3) | 1.01(2) | 1.094 |
| C1-H1 | 0.96(3) | 1.07(2) | 1.094 | C15-H15A | 0.99(4) | 1.10(2) | 1.090 |
| C2-H2 | 1.00(4) | 1.10(2) | 1.095 | C15-H14C | 1.00(3) | 1.12(2) | 1.092 |
|  |  |  |  | C15-H15B | 0.97(4) | 1.09(2) | 1.094 |
| **Bond angles (°)** | | | | | | | |
| C6-O2-C13 | 117.38(16) | 117.85(10) | 119.99 | C10-C1-C5 | 116.24(19) | 116.30(12) | 117.05 |
| C10-C1-C2 | 116.9(2) | 116.98(13) | 117.68 | C5-C1-C2 | 103.69(18) | 103.73(11) | 104.17 |
| C10-C1-H1 | 105.8(17) | 106.23 (18) | 106.89 | C5-C1-H1 | 105.9(17) | 106.23 (1) | 104.06 |
| C2-C1-H1 | 107.5(18) | 107.27 (18) | 105.67 | C11-C2-C1 | 114.6(2) | 114.61(14) | 115.25 |
| C11-C2-C3 | 112.0(3) | 111.64(16) | 111.76 | C1-C2-C3 | 102.3(2) | 102.40(14) | 103.41 |
| C11-C2-H2 | 107.(2) | 108.10 (2) | 107.48 | C1-C2-H2 | 108.(2) | 106.43 (1) | 108.86 |
| C3-C2-H2 | 113.(2) | 113.50 (2) | 110.01 | C4-C3-C2 | 107.2(2) | 107.21(15) | 106.89 |
| C4-C3-H3A | 115.(3) | 115.52 (3) | 111.65 | C2-C3-H3A | 106.(3) | 107.40 (2) | 112.01 |
| C4-C3-H3B | 111.(3) | 110.71 (2) | 110.08 | C2-C3-H3B | 109.(3) | 109.67 (2) | 109.68 |
| H3A-C3-H3B | 109.(4) | 106.27 (4) | 106.57 | C3-C4-C5 | 105.7(2) | 105.47(13) | 103.70 |
| C3-C4-H4A | 115.(3) | 114.82 (2) | 110.49 | C5-C4-H4A | 107.(3) | 106.89 (2) | 113.44 |
| C3-C4-H4B | 111.(2) | 109.29 (2) | 112.36 | C5-C4-H4B | 109.(2) | 110.49 (2) | 109.39 |
| H4A-C4-H4B | 109.(3) | 109.43 (3) | 107.45 | C1-C5-C4 | 101.60(19) | 101.85(12) | 101.00 |
| C1-C5-C6 | 113.21(18) | 113.11(11) | 113.35 | C4-C5-C6 | 117.49(19) | 117.11(12) | 117.75 |
| C1-C5-H5 | 107.7(17) | 107.53 (1) | 109.57 | C4-C5-H5 | 108.9(17) | 108.38 (1) | 107.30 |
| C6-C5-H5 | 107.5(17) | 108.10 (1) | 107.52 | O2-C6-C12 | 105.55(19) | 105.98(12) | 105.80 |
| O2-C6-C7 | 110.69(18) | 110.41(11) | 111.14 | C12-C6-C7 | 110.3(2) | 110.20(12) | 110.52 |
| O2-C6-C5 | 110.60(18) | 110.69(11) | 110.67 | C12-C6-C5 | 114.1(2) | 114.11(13) | 113.39 |
| C7-C6-C5 | 105.74(18) | 105.50(11) | 105.42 | O1-C7-C8 | 122.1(2) | 121.96(14) | 121.98 |
| O1-C7-C6 | 122.6(2) | 122.47(13) | 122.56 | C8-C7-C6 | 115.29(19) | 115.54(12) | 115.41 |
| C7-C8-C9 | 111.83(18) | 111.69(12) | 112.62 | C7-C8-H8A | 106.8(16) | 106.68 (1) | 107.16 |
| C9-C8-H8A | 111.1(17) | 111.83 (1) | 112.18 | C7-C8-H8B | 105.1(17) | 106.29 (1) | 107.58 |
| C9-C8-H8B | 112.9(18) | 111.88 (1) | 111.20 | H8A-C8-H8B | 109.(2) | 107.98 (2) | 105.72 |
| C10-C9-C8 | 111.7(2) | 111.77(12) | 111.55 | C10-C9-C13 | 114.28(19) | 114.11(12) | 114.54 |
| C8-C9-C13 | 108.64(18) | 108.61(11) | 108.63 | C10-C9-H9 | 107.5(18) | 108.40 (1) | 107.03 |
| C8-C9-H9 | 109.5(17) | 108.42 (1) | 107.82 | C13-C9-H9 | 104.8(17) | 105.07 (1) | 106.97 |
| C1-C10-C9 | 114.67(18) | 114.70(12) | 115.06 | C1-C10-H10A | 110.4(17) | 109.72 (2) | 108.47 |
| C9-C10-H10A | 105.0(17) | 105.31 (2) | 107.20 | C1-C10-H10B | 106.(2) | 107.62 (2) | 110.65 |
| C9-C10-H10B | 107.(2) | 108.55 (1) | 109.33 | H10A-C10-H10B | 113.(3) | 110.88 (3) | 105.73 |
| C2-C11-H11A | 116.(4) | 112.14 (3) | 112.15 | C2-C11-H11B | 112.(3) | 112.14 (2) | 111.83 |
| H11A-C11-H11B | 101.(4) | 111.16 (3) | 107.26 | C2-C11-H11C | 110.(2) | 119.07 (4) | 110.10 |
| H11A-C11-H11C | 107.(4) | 99.29 (5) | 107.34 | H11B-C11-H11C | 111.(3) | 104.33 (4) | 107.93 |
| C6-C12-H12A | 108.(2) | 106.65 (2) | 109.85 | C6-C12-H12B | 112.(2) | 109.10 (1) | 109.96 |
| H12A-C12-H12B | 112.(3) | 110.69 (2) | 108.13 | C6-C12-H12C | 110.(2) | 109.66 (2) | 110.90 |
| H12A-C12-H12C | 108.(3) | 108.04 (3) | 108.66 | H12B-C12-H12C | 108.(3) | 112.52 (2) | 109.29 |
| O2-C13-C14 | 106.12(18) | 106.56(12) | 107.56 | O2-C13-C15 | 107.29(18) | 107.54(12) | 106.20 |
| C14-C13-C15 | 109.2(2) | 108.95(13) | 108.24 | O2-C13-C9 | 111.27(17) | 111.23(11) | 110.51 |
| C14-C13-C9 | 111.9(2) | 111.78(12) | 111.52 | C15-C13-C9 | 110.80(19) | 110.60(12) | 112.54 |
| C13-C14-H13C | 110.2(19) | 114.11 (2) | 112.36 | C13-C14-H14A | 108.(2) | 110.20 (2) | 109.20 |
| H14C-C14-H14A | 112.(3) | 105.90 (3) | 107.37 | C13-C14-H14B | 115.4(19) | 109.07 (2) | 111.14 |
| H14C-C14-H14B | 105.(3) | 104.86 (3) | 108.35 | H14A-C14-H14B | 106.(3) | 112.67 (3) | 108.35 |
| C13-C15-H14C | 109.(2) | 107.24 (3) | 108.27 | C13-C15-H15A | 113.(2) | 108.35 (2) | 110.26 |
| H15C-C15-H15A | 110.(3) | 109.77 (2) | 108.22 | C13-C15-H15B | 107.(2) | 111.67 (3) | 112.48 |
| H15C-C15-H15B | 106.(3) | 110.26 (3) | 107.96 | H15A-C15-H15B | 111.(3) | 109.77 (3) | 108.39 |
| **Torsion angles (°)** | | | | | | | |
| C10-C1-C2-C11 | -46.3(3) | -46.55 (3) | -39.59 | C5-C1-C2-C11 | 83.0(3) | 82.92 (2) | 91.86 |
| C10-C1-C2-C3 | -167.8(2) | -167.79 (2) | -161.86 | C5-C1-C2-C3 | -38.4(2) | -38.31 (2) | -30.40 |
| C11-C2-C3-C4 | -105.3(3) | -105.33 (3) | -120.30 | C1-C2-C3-C4 | 17.9(3) | 17.82 (3) | 4.26 |
| C2-C3-C4-C5 | 9.2(3) | 9.25(16) | 23.32 | C10-C1-C5-C4 | 174.1(2) | 174.13 (2) | 176.88 |
| C2-C1-C5-C4 | 44.4(2) | 44.28 (2) | 45.06 | C10-C1-C5-C6 | -59.0(3) | -58.96 (2) | -56.20 |
| C2-C1-C5-C6 | 171.26(18) | 171.18 (2) | 171.97 | C3-C4-C5-C1 | -32.6(3) | -32.55 (2) | -41.68 |
| C3-C4-C5-C6 | -156.6(2) | -156.50(13) | -165.63 | C13-O2-C6-C12 | -149.4(2) | -149.21 (1) | -150.99 |
| C13-O2-C6-C7 | -30.1(3) | -30.10 (2) | -30.98 | C13-O2-C6-C5 | 86.7(2) | 86.74 (2) | 85.79 |
| C1-C5-C6-O2 | -23.7(2) | -23.25(13) | -26.37 | C4-C5-C6-O2 | 94.3(2) | 94.73(12) | 91.14 |
| C1-C5-C6-C12 | -142.5(2) | -142.69(12) | -145.08 | C4-C5-C6-C12 | -24.5(3) | -24.71(15) | -27.56 |
| C1-C5-C6-C7 | 96.2(2) | 96.19(12) | 93.88 | C4-C5-C6-C7 | -145.79(19) | -145.83(13) | -148.60 |
| O2-C6-C7-O1 | -126.5(2) | -126.87(16) | -133.89 | C12-C6-C7-O1 | -10.1(3) | -10.13(18) | -16.73 |
| C5-C6-C7-O1 | 113.6(3) | 113.50(16) | 106.15 | O2-C6-C7-C8 | 54.9(3) | 54.76(14) | 48.71 |
| C12-C6-C7-C8 | 171.3(2) | 171.24 (2) | 165.87 | C5-C6-C7-C8 | -64.9(2) | -64.87(12) | -71.23 |
| O1-C7-C8-C9 | 163.5(2) | 163.69(16) | 172.76 | C6-C7-C8-C9 | -17.9(3) | -17.93(14) | -9.82 |
| C7-C8-C9-C10 | 88.7(2) | 88.66(13) | 83.69 | C7-C8-C9-C13 | -38.3(3) | -38.11(14) | -43.48 |
| C5-C1-C10-C9 | 42.8(3) | 42.61 (2) | 44.24 | C2-C1-C10-C9 | 165.9(2) | 165.80 (2) | 169.56 |
| C8-C9-C10-C1 | -77.0(2) | -76.89(13) | -79.33 | C13-C9-C10-C1 | 46.9(3) | 46.83(14) | 44.56 |
| C6-O2-C13-C14 | -148.8(2) | -148.73 (2) | -145.40 | C6-O2-C13-C15 | 94.5(2) | 94.63 (2) | 98.88 |
| C6-O2-C13-C9 | -26.9(3) | -26.92 (2) | -23.07 | C10-C9-C13-O2 | -62.4(2) | -62.40(12) | -63.72 |
| C8-C9-C13-O2 | 63.1(2) | 63.01(13) | 61.72 | C10-C9-C13-C14 | 56.1(3) | 56.01 (2) | 54.81 |
| C8-C9-C13-C14 | -178.3(2) | -178.01(12) | -179.73 | C10-C9-C13-C15 | 178.33(19) | 178.20 (2) | 176.67 |
| C8-C9-C13-C15 | -56.1(2) | -56.43(12) | -57.87 |  |  |  |  |

**Table S5.** Interaction Energies (kJ/mol), R is the distance between molecular centroids (mean atomic position) in Å.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | N | Symop | R | Electron Density | E\_ele | E\_pol | E\_dis | E\_rep | E\_tot |
|  | 2 | -x+1/2, -y, z+1/2 | 8.17 | B3LYP/6-31G(d,p) | -9.4 | -3.8 | -16.3 | 13.4 | -18.7 |
|  | 2 | -x, y+1/2, -z+1/2 | 5.86 | B3LYP/6-31G(d,p) | -10.7 | -2.5 | -42.8 | 25.6 | -34.6 |
|  | 2 | x, y, z | 9.12 | B3LYP/6-31G(d,p) | -3.6 | -0.7 | -19.1 | 12.3 | -13.3 |
|  | 2 | x+1/2, -y+1/2, -z | 8.77 | B3LYP/6-31G(d,p) | -1.1 | -0.1 | -11.4 | 4.9 | -8.1 |
|  | 2 | -x+1/2, -y, z+1/2 | 7.87 | B3LYP/6-31G(d,p) | -1.7 | -0.3 | -20.0 | 9.1 | -13.8 |
|  | 2 | -x, y+1/2, -z+1/2 | 10.61 | B3LYP/6-31G(d,p) | -0.1 | -0.0 | -3.6 | 0.4 | -3.0 |
|  | 2 | -x, y+1/2, -z+1/2 | 11.05 | B3LYP/6-31G(d,p) | -0.8 | -0.1 | -1.1 | 0.0 | -1.9 |
|  | 2 | x+1/2, -y+1/2, -z | 11.08 | B3LYP/6-31G(d,p) | 0.1 | -0.1 | -0.7 | 0.0 | -0.5 |
|  | 2 | x+1/2, -y+1/2, -z | 8.61 | B3LYP/6-31G(d,p) | -0.9 | -0.2 | -14.0 | 5.8 | -9.7 |
|  | 2 | x+1/2, -y+1/2, -z | 10.96 | B3LYP/6-31G(d,p) | 0.0 | -0.0 | -0.9 | 0.0 | -0.8 |
|  | 2 | -x+1/2, -y, z+1/2 | 12.56 | B3LYP/6-31G(d,p) | -0.0 | -0.0 | -0.4 | 0.0 | -0.4 |
|  | 2 | -x+1/2, -y, z+1/2 | 12.36 | B3LYP/6-31G(d,p) | -0.0 | -0.0 | -0.4 | 0.0 | -0.3 |
|  | 2 | x, y, z | 11.70 | B3LYP/6-31G(d,p) | 0.3 | -0.0 | -0.4 | 0.0 | -0.0 |
|  | 2 | x, y, z | 12.58 | B3LYP/6-31G(d,p) | -0.3 | -0.0 | -0.4 | 0.0 | -0.7 |
|  | 2 | -x+1/2, -y, z+1/2 | 15.41 | B3LYP/6-31G(d,p) | 0.1 | -0.0 | -0.1 | 0.0 | 0.0 |
|  | 2 | x+1/2, -y+1/2, -z | 15.59 | B3LYP/6-31G(d,p) | -0.2 | -0.0 | -0.1 | 0.0 | -0.3 |
|  | 2 | -x, y+1/2, -z+1/2 | 13.98 | B3LYP/6-31G(d,p) | -0.1 | -0.0 | -0.2 | 0.0 | -0.2 |
|  | 2 | -x, y+1/2, -z+1/2 | 16.83 | B3LYP/6-31G(d,p) | 0.3 | -0.0 | -0.0 | 0.0 | 0.2 |
|  | 2 | x, y, z | 18.23 | B3LYP/6-31G(d,p) | -0.0 | -0.0 | -0.0 | 0.0 | -0.1 |
|  | 2 | x, y, z | 15.54 | B3LYP/6-31G(d,p) | -0.3 | -0.0 | -0.1 | 0.0 | -0.4 |
|  | 2 | -x+1/2, -y, z+1/2 | 14.94 | B3LYP/6-31G(d,p) | 0.1 | -0.0 | -0.2 | 0.0 | -0.1 |
|  | 2 | -x, y+1/2, -z+1/2 | 16.54 | B3LYP/6-31G(d,p) | -0.1 | -0.0 | -0.1 | 0.0 | -0.2 |
|  | 2 | x, y, z | 15.54 | B3LYP/6-31G(d,p) | 0.1 | -0.0 | -0.1 | 0.0 | -0.0 |

**Table S6.** Calculated global reactivity properties of the molecule.

|  |  |
| --- | --- |
| **Global Reactivity**  **Descriptors** | **DFT**  Energy (eV) |
| **Compound 1** |
| Band Gap | 5.65 |
| HOMO Energy | -6.56 |
| LUMO Energy | -0.91 |
| Ionization Potential  I= -EHOMO | 5.65 |
| Electron Affinity  A= -ELUMO | 0.91 |
| Global Hardness  η= (I-A)/2 | 2.83 |
| Electronegativity  χ= (I+A)/2 | 3.74 |
| Electrophilicity  ω=μ2/2η, μ= -χ | 2.47 |

**Table S7.** Dipole moment (µ) in Debye (D), polarizability (α), and hyperpolarizability (β) of the titled compound using the base level of DFT/B3LYP 6-311G\*\* method

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | esu (×10-24) |  |  | esu (×10-33) |
| αXX | -15.61 |  | βXXX | -131.59 |
| αXY | 0.966 |  | βXXY | -62.25 |
| αYY | -16.44 |  | βXYY | 56.27 |
| αXZ | 0.103 |  | βYYY | -106.52 |
| αZZ | -0.188 |  | βXXZ | -32.32 |
| αYZ | -0.804 |  | βXYZ | 93.82 |
| αTotal | -10.748 |  | βYYZ | -140.92 |
| ∆α | 15.856 |  | βXZZ | 26.39 |
| µx | 1.046 D |  | βYZZ | -90.12 |
| µy | -3.053 D |  | βZZZ | -29.46 |
| µz | -0.301 D |  | βtotal | 332.44 |
| µtotal | 3.241 D |  |  |  |

**Table S8.** NBO analysis of natural compound

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Donor (i)** | **ED(i)** |  | **Acceptor (j)** | **ED(j)** |  | **E(2)a** | **Ej-Eib** | **F(i,j)c** |
| LP (2) O1 | 1.88297 | s( 0.01%)p99.99( 99.92%)d 5.09( 0.06%) | BD\*(1) C6 – C7 | 0.08537 | s( 25.15%)p 2.97( 74.77%)d 0.00( 0.07%) | 21.39 | 0.64 | 0.105 |
| LP (2) O1 | 1.88297 | s( 0.01%)p99.99( 99.92%)d 5.09( 0.06%) | BD\*(1) C7 – C8 | 0.06095 | s( 34.48%)p 1.90( 65.48%)d 0.00( 0.04%) | 19.87 | 0.66 | 0.104 |
| LP (1) O2 | 1.95837 | s( 39.70%)p 1.52( 60.28%)d 0.00( 0.02%) | BD\*(1) C 15 – C16 | 0.08537 | s( 25.15%)p 2.97( 74.77%)d 0.00( 0.07%) | 2.6 | 0.9 | 0.044 |
| LP (1) O2 | 1.95837 | s( 39.70%)p 1.52( 60.28%)d 0.00( 0.02%) | BD\*(1) C9 – C13 | 0.04248 | s( 26.70%)p 2.74( 73.25%)d 0.00( 0.04%) | 3.84 | 0.89 | 0.052 |
| LP (1) O2 | 1.95837 | s( 39.70%)p 1.52( 60.28%)d 0.00( 0.02%) | BD\*(1) C12 – H12B | 0.00507 | s( 23.46%)p 3.26( 76.48%)d 0.00( 0.06%) | 0.58 | 0.96 | 0.021 |
| LP (2) O2 | 1.92575 | s( 0.50%)p99.99( 99.46%)d 0.06( 0.03%) | BD\*(1) C5 – C6 | 0.04745 | s( 26.86%)p 2.72( 73.10%)d 0.00( 0.05%) | 6.62 | 0.65 | 0.059 |
| LP (2) O2 | 1.92575 | s( 0.50%)p99.99( 99.46%)d 0.06( 0.03%) | BD\*(1) C6 – C7 | 0.08537 | s( 25.15%)p 2.97( 74.77%)d 0.00( 0.07%) | 3.28 | 0.66 | 0.042 |
| LP (2) O2 | 1.92575 | s( 0.50%)p99.99( 99.46%)d 0.06( 0.03%) | BD\*(1) C13-C15 | 0.02509 | s( 27.14%)p 2.68( 72.81%)d 0.00( 0.05%) | 2.23 | 0.67 | 0.035 |
| LP (2) O2 | 1.92575 | s( 0.50%)p99.99( 99.46%)d 0.06( 0.03%) | BD\*(1) C13 – C14 | 0.03104 | s( 26.80%)p 2.73( 73.15%)d 0.00( 0.05%) | 6.34 | 0.66 | 0.058 |
| LP (2) O2 | 1.92575 | s( 0.50%)p99.99( 99.46%)d 0.06( 0.03%) | BD\*(1) C14 – H14A | 0.00689 | s( 23.05%)p 3.34( 76.88%)d 0.00( 0.07%) | 0.89 | 0.7 | 0.023 |

aE(2) means stabilization energy

bEnergy difference between donor i and acceptor j NBO orbitals

cFock matrix element between i and j NBO orbitals

**Table S9.** Binding free energies of the docked complex.

|  |  |
| --- | --- |
| **Binding Energy Component** | **Compound** |
| ∆Evdw | -42.41 |
| ∆Eele | -14.36 |
| Htot,GB | -48.76 |
| ∆Gsolv,GB | 8.01 |
| ∆Egas | -56.77 |
| ∆Gsolv, PB | 12.12 |
| Htot, PB | -44.65 |