Supplementary Material for

In silico identification and experimental validation of (−)-Muqubilin A, a marine norterpene peroxide, as PPARα/γ-RXRα agonist and RARα positive allosteric modulator.

Enrico D’Aniello1,2, Fabio Arturo Iannotti3,4, Lauren G. Falkenberg5, Andrea Martella6, Alessandra Gentile7, Fabrizia De Maio8, Maria Letizia Ciavatta9, Margherita Gavagnin10, Joshua S. Waxman11, Vincenzo Di Marzo12,13,14, Pietro Amodeo15* and Rosa Maria Vitale16*

1 Department of Biology and Evolution of Marine Organisms, Stazione Zoologica “Anton Dohrn”, 80121, Naples, Italy; enrico.daniello@szn.it
2 Endocannabinoid Research Group (ERG), Institute of Biomolecular Chemistry, National Research Council (ICB-CNR), Via Campi Flegrei 34, 80078, Pozzuoli (NA), Italy; enrico.daniello@szn.it
3 Endocannabinoid Research Group (ERG), Institute of Biomolecular Chemistry, National Research Council (ICB-CNR), Via Campi Flegrei 34, 80078, Pozzuoli (NA), Italy; fabio.iannotti@icb.cnr.it
4 Institute of Biomolecular Chemistry, National Research Council (ICB-CNR), Via Campi Flegrei 34, 80078, Pozzuoli, (NA), Italy; fabio.iannotti@icb.cnr.it
5 Molecular Cardiovascular Biology Division, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA; lauren.falkenberg@cchmc.org
6 Institute of Biomolecular Chemistry, National Research Council (ICB-CNR), Via Campi Flegrei 34, 80078, Pozzuoli, (NA), Italy; a.martella@lacdr.leidenuniv.nl
7 Institute of Biomolecular Chemistry, National Research Council (ICB-CNR), Via Campi Flegrei 34, 80078, Pozzuoli, (NA), Italy; alessandra.gentile@mpi-bn.mpg.de
8 Institute of Biomolecular Chemistry, National Research Council (ICB-CNR), Via Campi Flegrei 34, 80078, Pozzuoli, (NA), Italy; fabriziamedaio@yahoo.it
9 Institute of Biomolecular Chemistry, National Research Council (ICB-CNR), Via Campi Flegrei 34, 80078, Pozzuoli, (NA), Italy; lciavatta@icb.cnr.it
10 Institute of Biomolecular Chemistry, National Research Council (ICB-CNR), Via Campi Flegrei 34, 80078, Pozzuoli, (NA), Italy; mgavagnin@icb.cnr.it
11 Molecular Cardiovascular Biology Division, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA; Joshua.Waxman@cchmc.org
12 Institute of Biomolecular Chemistry, National Research Council (ICB-CNR), Via Campi Flegrei 34, 80078, Pozzuoli, (NA), Italy; vdimarzo@icb.cnr.it
13 Endocannabinoid Research Group (ERG), Institute of Biomolecular Chemistry, National Research Council (ICB-CNR), Via Campi Flegrei 34, 80078, Pozzuoli (NA); vdimarzo@icb.cnr.it
14 Canada Excellence Research Chair on the Microbiome-Endocannabinoidome Axis in Metabolic Health (CERC-MEND)-Université Laval, Quebec City, Canada; vdimarzo@icb.cnr.it
S1: Effect of Muqubilin on the viability of COS-7 cells.
Cell viability was assessed using the MTT assay. Statistical analysis was performed comparing each compound to the DMSO group using the Student t-test. Statistically significant differences were accepted when the p-value was at least ≤ 0.05. Data are expressed as means ± SEM, (n=3). *p ≤ 0.05.

Figure S2: Evaluation of stability of the ligand binding mode during the last 30ns of MD. Rmsd plots of Muq in PPARs (A) and retinoids receptors (B) complexes after protein backbone best-fit.