The study of mechanisms and therapeutic potential of innate immune receptors is an increasingly explored research field in cancer and inflammatory diseases. In this scenario, targeting immune receptors with small molecules, able to activate and modulate downstream signalling pathways, represents an ambitious and promising line of investigation opening the way towards new therapeutic applications. The design of this proposal starts from our identification of a nature-inspired sulfoglicolipid, named Sulfavant A, as prototype of new class of immunomodulatory molecules, able to activate innate immune system by binding with triggering receptor express on myeloid cells (TREM2). TREM2 is a receptor of the Ig-superfamily mainly expressed in microglia, in dendritic cells and macrophages, that has been correlated to neurodegenerative, inflammatory and tumor pathologies. In this regard, our recent investigation on this receptor has revealed a new homeostasis-determining mechanism of regulation of the immune response following cellular dysfunctions and/or alterations. Before Sulfavant A characterization, no specific TREM2 ligands were reported and several aspects of TREM2 signalling, from the molecular receptor-ligand interaction to the cell pathway, remained poorly understood. In this frame this substance represents the first synthetic small molecule selectively targeting this receptor and a crucial tool to fully elucidate the TREM2-ligand interaction and the downstream biochemical activation steps, main topics of this proposal. This project aims to delineate the receptor signalling following TREM2-ligand binding by the construction of a four components fluorescence resonance energy transfer (FRET) system and a second two components FRET system to measure the effect of the binding on cell membranes biophysics. The structure of the receptor-ligand interaction will be also defined by integration of Cellular Thermal Shift Assay (CeTSA) and mass spectrometry methods. Each study will be performed with Sulfavant A and its structural analogues synthetized in this project, to define how chemical modifications on TREM2 ligands could impact on the receptor binding and subsequent signal transduction.