GS04-3 Novel Rhodopsin Ligands that Promote Proper Folding of the Misfolding-prone Rhodopsin Mutant Responsible for Retinitis Pigmentosa

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Structural development studies for creating potent small molecules which correct trafficking defect of rhodopsin mutants responsible for retinitis pigmentosa, presumably by binding to and promoting proper folding of the mutant rhodopsin, will be presented. Although the endogenous ligands (11-*cis*-retinal and its isomer 9-*cis*-retinal) have been reported to promote proper folding of rhodopsin mutant, these retinals possess drawbacks, including chemical instability, high toxicity and potential action on nuclear receptors (RAR and RXR). To overcome these drawbacks, we set out to design novel rhodopsin ligands that improve folding efficiency of rhodopsin mutants. To attain this goal, we employed plasma membrane expression level of rhodopsin mutant as a surrogate for folding efficiency. “Misfolded” rhodopsin does not pass the quality control checkpoints in the ER, and therefore they are not transported to the plasma membrane. Induction of proper folding of the mutated rhodopsin results in its translocation to the plasma membrane. Based on this assay system, we successfully identified a series of non-polyene type compounds which are superior in the efficacy of proper folding-inducing activity on the rhodopsin mutant. This class of compounds may have potential in the treatment of retinitis pigmentosa caused by rhodopsin mutations associated with folding/trafficking defect.