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Development of a pharmacorphore model for pharmacological chaperones targeting mutant trafficking-deficient CNG channels

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Complete colorblindness (achromatopsia) is caused by autosomal recessively inherited mutations in the retinal phototransduction pathway, predominantly in the CNGA3- and CNGB3-subunit of the cyclic nucleotide-gated (CNG) channels in cone photoreceptors. CNGA3, which is mutated in about 25% of the achromatopsia patients, mainly harbors missense mutations which frequently impair the folding and/or trafficking of the mutant CNGA3-channels [1].

Pharmacological chaperones stabilizing the folding of the mutant protein may be used to overcome this folding-/trafficking-deficiency. More than 50 compounds were evaluated in their ability to restore signal transduction using a calcium imaging-based bioassay utilizing the CNGA3-mutant E228K [2]. With this data we created several pharmacophore models using Schrödinger Phase [3], which describe the chemical features of potential pharmacological chaperones targeting achromatopsia.

We used several approaches leading to different pharmacophore hypotheses:

a) Training with the complete set of experimental data (see Figure 1)

b) Training with only dihydropyridines since this group showed the highest experimental activity, and

c) Training with a data set excluding dihydropyridines.

Our in-house database TueScreen, which includes ZINC12 [4], was screened to identify potentially active compounds. As a result, several potential molecule classes could be found that may be useful as pharmacological chaperones to improve folding/trafficking of mutant CNG-channels. We will experimentally validate these predictions in a calcium imaging-based bioassay.

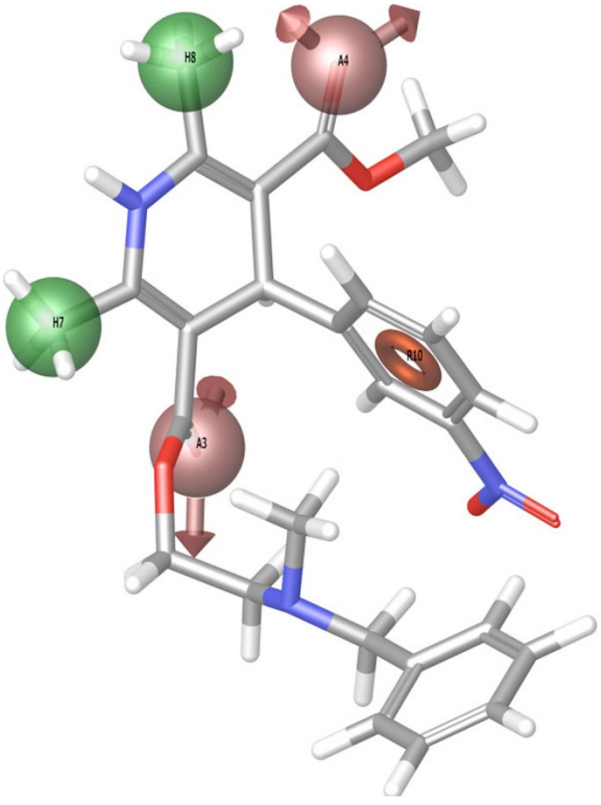

Figure 1 Pharmacophore depicting potential features of CNG channel-chaperones.

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