Small molecules to treat diabetic retinopathy: structure based in-silico approach for discovery of HuR inhibitors.

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Diabetic retinopathy (DR) is an inflammatory and microvascular disease. The ELAVL-1 (HuR) RNA binding protein is able to stabilize the mRNA of TNF-alpha and VEGFA (1), whose corresponding proteins play a key role in DR-associated inflammation and angiogenesis, respectively. Inhibition of HuR-mRNA binding can represent a novel approach towards DR treatment. To this aim, we searched for novel compounds able to interfere with the HuR-mRNA complex. Crystal structure of HuR (PDB:4EGL) and HuR-mRNA (PDB:4ED5) have been used for molecular docking of HuR inhibitors and inactive compounds. Compounds to be docked were selected from a proprietary database by means of Tanimoto similarity search between caffeic acid phenethyl ester (CAPE) and database entries. Therefore, twelve CAPE and twenty indole derivatives have been docked at 4EGL and 4ED5. Docking was carried out with the Schrodinger® package. Docking results have been re-scored with MM-GBSA calculations. Structural interaction fingerprints (SIFts) have been calculated for further analysis of docking results.

Active compounds dihydrotanshinone I (2) okicenone (3), dehydromutactin, MS444, quercetin (4) clustered together with best docking score based on SIFts calculations. MM-GBSA calculations revealed that inactive compounds are characterized by high negative coulomb contribution to dG binding energy and more positive lipofilic energy, in comparison to active compounds. Based on these characteristics, two indole compounds VP12_14 and VP12_110 clustered with dihydrotanshinone I and MS444. Hybrid esters of CAPE bearing aspirin and indomethacin moieties (5) showed high negative lipofilic energy and more positive coulomb energy, like known HuR inhibitors.

The results indicate that VP12_14, VP12_110, and hybrid esters of CAPE could interfere with HuR-mRNA complex. Considering the crucial implication of TNF-alpha and VEGFA in DR development, these compounds can be potentially useful in inhibiting inflammation and angiogenesis processes.

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References

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