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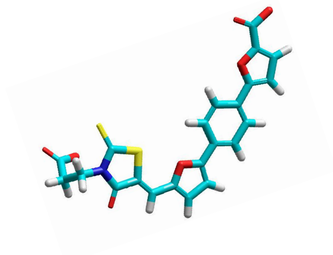
INTEGRATIVE MODEL OF RHODANINE DERIVATIVES AS TAU AGGREGATION INHIBITORS IN ALZHEIMER'S DISEASE

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ABSTRACT

Tau aggregation is responsible for the formation of neurofibrillary tangles which is one hallmark of Alzheimer's disease. Short hexapeptides of Tau (PHF6) are known to be responsible for the formation of aggregates. Rhodanine-based compounds are known as Tau anti-aggregation inhibitors. However, their precise mode of action on Tau is still undefined, e.g. the binding site(s), binding mode(s), or stoichiometry remain undefined. To date, there is no structural data on Tau complex with any Rhodanine derivatives, and there is no rationale for their activity or toxicity. Three computational modelling approaches have been used to propose an integrative model for the mode of action of Rhodanine derivatives. First, QSAR studies were used to identify and quantify the molecular properties relevant to their activity and toxicity. The more active and less active compounds were then used in docking simulation to identify the possible binding modes and the contacts specific to the more active compounds. Finally, molecular dynamics simulations were performed to validate the 3D models of interaction between Tau (PHF6) and the more active Rhodanine compound and determine the more probable stoichiometry. Possible pathways for their insertion into the aggregated PHF6 peptides are also identified suggesting how they may act as Tau anti-aggregation inhibitors.



5-(4-(5-((Z)-3-(2-carboxy-ethyl)-4-oxo-2-thioxo-thiazolidin-5-ylidene methyl)-furan-2-yl)-phenyl)-furan-2-carboxylic acid.

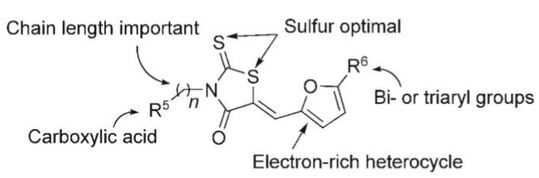
Most active compound (Ligand 20)

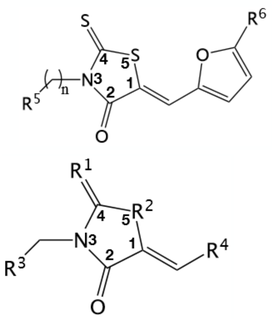
INTRODUCTION

In recent years, tau proteins has received wide attention as a promising target for Alzheimer's disease. The tau protein is microtubule-associated and mainly found in the axon of mature neurons. Tau protein dysfunction is sufficient to cause neurodegeneration. Its aggregation characterizes cases of Alzheimer's disease as well as a group of other neurodegenerative diseases known as tauopathies. In the microtubule-binding region of tau, the hexapeptide motif (306VQIVYK311) can form intermolecular β-sheet structures. This hexapeptide might be an excellent molecular target for new treatments of Alzheimer's disease. Indeed, many tau aggregation inhibitors are small compounds capable of disrupting the β-sheet structure of 306VQIVYK311, such as rhodanines. However, little is known so far about how these compounds interact with ^{306}VQIVYK^{311}. It largely hinders rational design of new, more effective tau inhibitors. The objectives of the present study are: (1) To obtain a predictive QSAR models for the anti-Alzheimer activity of 46 rhodanine derivatives; (2) docking predictions of 46 AAC for obtaining the best conformation ad helps to interpret already elucidated structure-activity relationships in this chemical series, in terms of predicted interactions with tau proteins; (3) to confirm the results obtained from docking analyses, and to achieve a better understanding about the molecular mechanisms and atomic interactions involved in ligand-complex formation and stability by means of molecular dynamics simulations for the most active compound (ligand **20**).

RESULTS AND DISCUSSION

QSAR MODEL OF RHODANINE DERIVATIVES





Global – steric : low value of molar refractivity (**MR**)

Global –electronic : high value of **HOMO** and dipolar moment (μ)

Local – electronic : negative charge on C3, C4 and C5

QSAR MODELS FOR INHIBITORY POTENCY (PIC50)

pIC50 = -1.14MR +45.43HOMO +0.14μ -3.24q4 +16.58 (1)
n=35; R^2= 0.81; s=0.33; F=15.99; q^2 =0.60; p<0.01
Test set: n=9; R^2= 0.60; s=0.57; F=5.86

QSAR MODEL FOR CYTOTOXICITY (LOG LDH), LACTATE DEHYDROGENASE (LDH) ENZIME VALUE

LOG (LDH) = -2.28MR -3.21q3 -3.88q4 -3.72q5 + 2.05 (2)
n= 35; R^2 = 0.84; s=0.41; F= 27.36; q2 = 0.70
Test set: n=9; R^2= 0.55; s=0.56; F=8.94

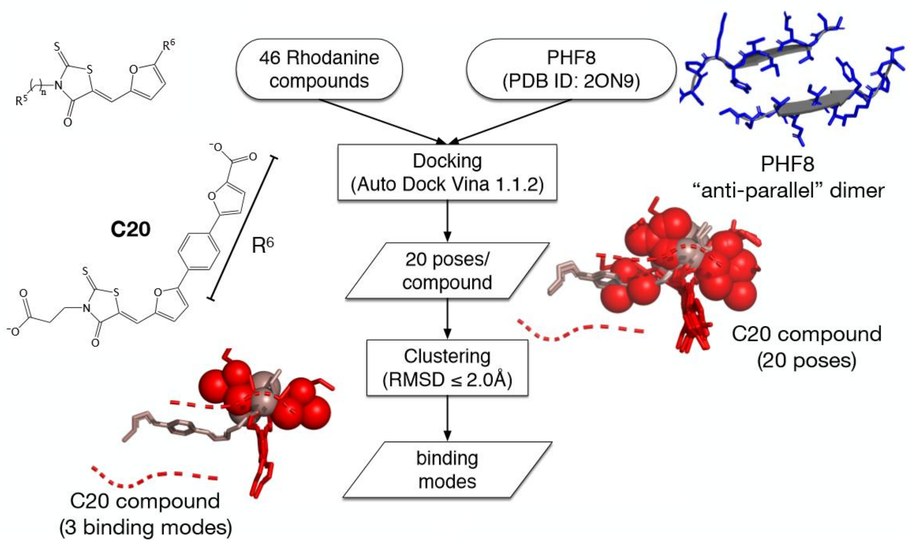


Figure 1. Docking protocol of Rhodanine compounds.

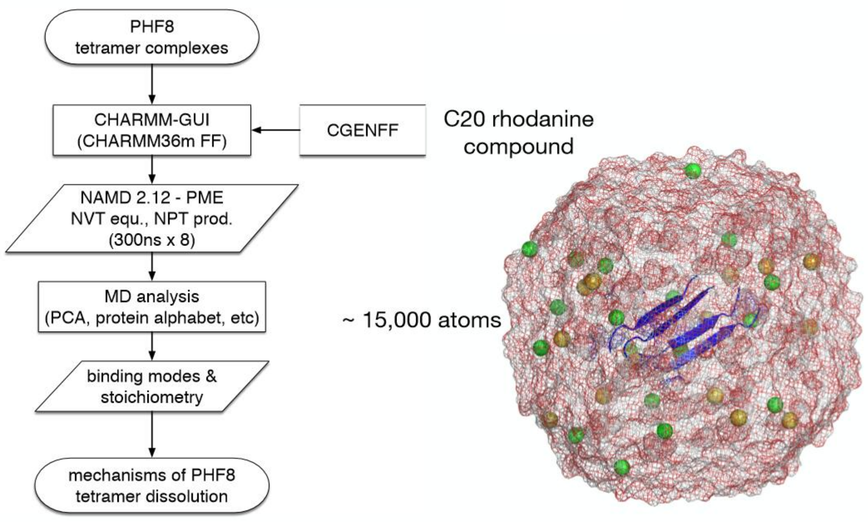


Figure 2. Molecular dynamics protocol of PHF8 tetramers complexes.

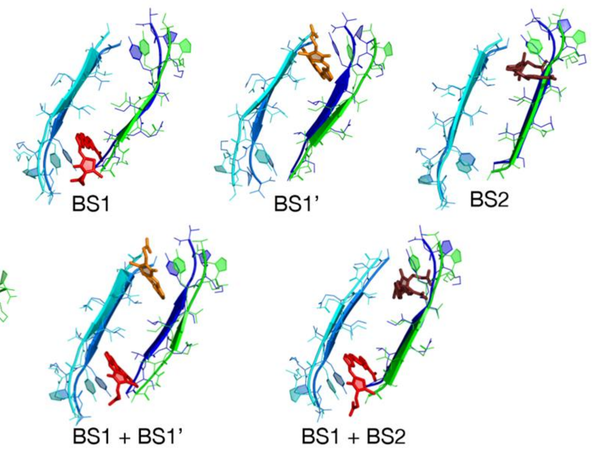


Figure 3. Ligand 20 positions before 300 ns MD simulation. *inicial

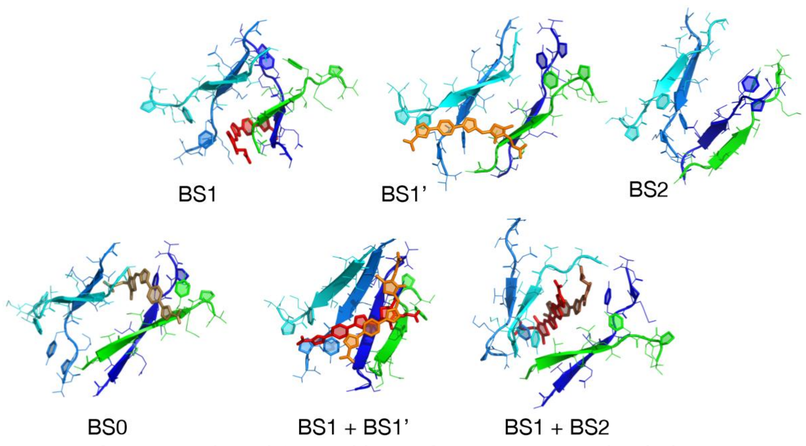


Figure 4. Ligand 20 positions after 300 ns MD simulation.

CONCLUSIONS

The QSAR models should help to explain the structural features in the Rhodanines molecules that contribute to the affinity with the tau proteins in the human organism. Two dimensional QSAR models were obtained using multiple linear regression analysis. Compound´s inhibitory potency (pIC50) is correlated with: high molar refractivity value (MR), a steric molecular descriptors (MD), showed a negative contribution in the inhibitory potency; a negative charge on atom C4, a electronic MD, increases the inhibitory potency and the high HOMO and dipolar moment (μ) values, as electronics MD, showed a positive contribution in the inhibitory potency. Lactate dehydrogenase (LDH) enzyme value describes the cytotoxicity of the compounds and according the QSAR model is expressed as: high molar refractivity value, a steric MD, showed a negative contribution in the cytotoxicity and negative charges on atoms C3, C4 and C5, electronics MD, that increases the cytotoxicity. Seven compounds were identified as leading. The most potent was the 5-(4-(5-((Z)-3-(2-carboxy-ethyl)-4-oxo-2-thioxo-thiazolidin-5-ylidene methyl)-furan-2-yl)-phenyl)-furan-2-carboxylic acid (ligand **20**). Important conclusions have been also deduced from structure-activity studies using docking analyses, and molecular dynamics simulations for the most active compound. It was concluded that the inhibitors of the Rhodanine destabilizes the tetramer of the hexapeptide ^{306}VQIVYK^{311} through of loss of native contacts, destabilization of C-terminus, transitions with increase of radius of gyration, sizzling motion in anti-parallel dimers, binding modes with shifting one parallel (parallel) β-strand dimer, stoichiometry 2:1 may facilitate inter-dimer insertion.