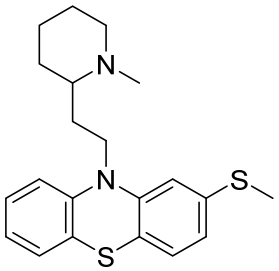
SYNTHESIS AND OPTIMIZATION OF 10*H*-PHENOTHIAZINE ANALOGUES FOR THE INHIBITION OF AUTOPHAGY

Eirin Alme, Lukas Petersen, and Hans-Renè Bjørsvik*

Department of Chemistry, University of Bergen, Allègaten 41, 5007 Bergen, Norway

A lysosomal degradation process called autophagy is receiving attention due to its ability to influence anticancer drugs [1]. Autophagy is also called cellular self-digestion and is primarily a protective process of the cell [2]. It can be activated as a response to adverse microenvironmental stresses, and chemotherapeutics are known to cause metabolic stress. Autophagy has been observed to have a resistance mechanism against anticancer drugs, reducing their efficiency [1]. In our work we are looking at the drug-repurposing of phenothiazine antipsychotics. Phenothiazine analogues will be used to develop a way to treat cancer via autophagy inhibition. In our research we are particularly looking at thioridazine, a drug that has been used for the treatment of schizophrenia. Quantitative Structure-Activity Relationship (QSAR) multivariate analysis can be used to identify and quantify the physiochemical properties of a drug and to see if these properties have an effect on the drug's biological activity. If there is a relationship between the properties and the activity an equation can be calculated which quantifies the relationship and makes it possible to predict which properties have an important role in the mechanism of action in the drug [3]. QSAR can therefore be used to help identify which physiochemical properties causes the inhibition of autophagy. The first step for the prediction of QSAR involves the principal component analysis (PCA)[4] method, which will be used on a series of commercially available phenothiazine derivatives. Based on the results, interesting phenothiazine analogues will be synthesized for future biological investigations.



Thioridazine

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