Quantitative Analysis of Structure–Activity Relationships of Tetrahydro-2H-isoindole Cyclooxygenase-2 Inhibitors

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Abstract—Using the GUSAR program, structure–activity relationships on inhibition of cyclooxygenase-2 (COX-2) catalytic activity were quantitatively analyzed for twenty-six derivatives of 4,5,6,7-tetrahydro-2H-isoindole, 2,3-dihydro-1H-pyrrolyzine, and benzothiophene in the concentration range of 0.6-700 nmol/liter IC_{50} values. Six statistically significant consensus QSAR models for prediction of IC_{50} values were designed based on MNA- and QNA-descriptors and their combinations. These models demonstrated high accuracy in the prediction of IC_{50} values for structures of both training and test sets. Structural fragments of the COX-2 inhibitors capable of strengthening or weakening the desired property were determined using the same program. This information can be taken into consideration on molecular design of new COX-2 inhibitors. It was shown that in most cases, the influence of structural fragments on the inhibitory activity of the studied compounds revealed with the GUSAR program coincided with the results of expert evaluation of their effects based on known experimental data, and this can be used for optimization of structures to change the value of their biological activity.

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