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Purposeful Synthesis of 4-Thiazolidinones with High Levels of Predicted Anticancer Activity

Використовуючи раніше розроблені QSAR-моделі, проведено віртуальний скринінг бібліотеки похідних 4-тіазолідинонів. Вибрано та в подальшому отримано синтетично 14 нових 4-тіазолідинонів з піразоліновим та ізатиновим фрагментами у структурі молекул та значним рівнем прогнозованої протипухлинної активності. Успішність такої стратегії підтверджена біологічними дослідженнями, згідно яких синтезовані сполуки здатні інгібувати ріст ракових клітин в мікромолярних концентраціях.

Using previously obtained QSAR models, the virtual screening of 4-thiazolidinones library has been carried out. 14 new 4-thiazolidinones containing pyrazoline and isatin fragments with high levels of predicted anticancer activity have been selected and further synthesized. The success of the directed synthesis strategy has been confirmed by biological assays, according to which the synthesized compounds can inhibit cancer cells growth in micromolar concentrations.

4-Thiazolidinone is a promising core structure for the search of new biologically active and especially anticancer agents. Significant amount of efforts in the medicinal chemistry of 4-thiazolidinones have been dedicated to the discovery of quantitative relationships between molecular structure and anticancer activity, resulting in several successful QSAR models, developed with Random Forest algorithm, Gaussian processes regression and pharmacophore modeling. Using obtained models, the virtual screening of 4-thiazolidinone derivatives library has been carried out, and 14 novel 4-thiazolidinones with pyrazoline and isatin fragments in molecular structure were selected. The synthesis has been carried out in two stages with initial formation of 3,5-diaryl-1-thiocarbamoyl-2-pyrazolines *via* condensation of thiosemicarbazide and appropirate chalcones in ethanol medium. Following further one-pot reaction of obtained pyrazoline derivative with chloroacetic acid and appropriate isatin in the presence of sodium acetate in boiling acetic acid target 3-[2-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-ylidene]-2,3-dihydro-1H-indol-2-ones were synthesized. Structures of synthesized compounds were confirmed by NMR spectra. The success of the purposeful synthesis strategy has been confirmed by biological assays, according to which the synthesized compounds can inhibit cancer cells growth in micromolar concentrations. The four most potent synthesized compounds show IC_{50} values between 0,16-10μM under MTT assays of rat glioma cells *C6*, *Mino* cells, *Jurkat* and *L1210* cells growth inhibition. Additionally, it has been discovered that the immobilization of compounds on the oligoelectrolite polymeric carrier significantly increases the activity.