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New N-aryl- 4-methysulfonylaminobenzenesulfonamides as selective COX-2 inhibitors

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Introduction: A group of N-aryl- 4-methylsulfonylaminobenzenesulfonamides, possessing a methylsulfonyl amino pharmacophore at the para-position of the one phenyl ring, in conjunction with a another substituted-phenyl ring (4-F, 4-H, 4-Me, 4-OMe), was evaluated as selective cyclooxygenase-2 (COX-2) inhibitors.

Materials and methods: Interaction of test compounds with COX-2 was investigated in silico. The ability of the test compounds 6a-e to inhibit ovine COX-1 and COX-2 was determined using a colorimetric COX (ovine) inhibitor screening assay which utilizes the peroxidase component of cyclooxygenase. The peroxidase activity is assayed colorimetrically by monitoring the appearance of oxidized N,N,N′,N′-tetramethyl-p-phenylenediamine (TMPD) at 590 nm.

Results: *In silico* studies showed the best results for 6e. In vitro COX-2 isozyme inhibition structure–activity studies identified 6e with 4-OMe substituent as a potent COX-2 inhibitor (IC50 = 1. 59 m M) with a high COX-2 selectivity index (SI = 51.7) comparable to the reference drug celecoxib (COX-2 IC50 = 9. 59 m M; COX-2 SI = 25.62).

Conclusion: The structure–activity data acquired indicate that the sulfonamido moiety constitutes a suitable scaffold to design new acyclic – N- aryl- 4-methysulfonylaminobenzenesulfonamides derivatives with selective COX-2 inhibitory activity.

Keywords: Sulfonylaminobenzenesulfonamides, COX, Inhibition, Novel scafold

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Kinetic modeling and sensitivity analysis of elongation cycle in protein synthesis

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Introduction: One of the famous processes that in many research studied kinetically in vitro, is the elongation process. Elongation is meddle step in translation of proteins, during which peptide chain is made and elongated using some factors names 'elongation factors'. In this work, detailed kinetics of the elongation cycle has been modeled.

Material and methods: Kinetic simulations of the model were performed in ODEs form with Matlab simbiology Toolbox.

Results: Using ordinary differential equations (ODEs) kinetics of the model was simulated. After simulation, various quasi-steady states were observed for the intermediate complexes that they have different amplitudes and times. During formation of the activated elongation factor Tu, some parameters have more effects than others; these parameters were assigned by sensitivity analysis and the mechanistic results were discussed. By incrementing Ts concentration production of Tu.GTP and also the rate of process are increased. Formation of pre translocation complex is sensitive to initial concentrations of the ribosome that were used during simulations. Finally effects of elongation factors concentration on the formation of post translocation complex were determined qualitatively by parameter scan.

Conclusion: Here complete detailed model of elongation cycle has been established. The current model stems from in vitro measurements of elongation kinetics. The results are in agreement with experimental works.

Keywords: Elongation, Modeling, kinetics, Systems biology, Quasi-steady state, Sensitivity analysis, Parameter scan

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2D and 3D Quantitative Structure Activity Relationship studies of Human Microsomal Epoxide Hydrolase Inhibitors

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Introduction: Human microsomal epoxide hydrolase (hmEH) is an enzyme involved in biotransformation of epoxides to their vicinal diols and plays a key role in detoxification of wide range of xenobiotics such as anticonvulsant drugs. The aim of this study is to develop 2D- and 3D QSAR models to predict the biological activity of hmEH inhibitors.

Materials and methods: The molecular descriptors were calculated for the studied inhibitors and then genetic algorithm coupled partial least square (GA-PLS) method and multiple linear regression (MLR) were used to develop 2D-QSAR models. HASL technique was used to perform 3D-QSAR studies.

Results: The 2D and 3D-QSAR models developed in this study were able to predict the binding affinities of the inhibitors based on the different electronic and topological molecular descriptors. The squared correlation coefficients (r2) between the predicted and observed potency (pKi) values for the test compounds are in the range of 0.78 to 0.85 with the mean absolute percentage errors of 6.8 to 9.0 for different 2D and 3D-QSAR models.

Conclusion: The results of the current study can be used in drug development where hmEH system is involved, such as virtual evaluation for possible drug interactions.

Keywords: 2D-QSAR, 3D-QSAR, Epoxide hydrolase, Biotransformation, Genetic algorithm, MLR

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Study of engineered Taka Alpha Amylase by means of molecular dynamics simulation and docking

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