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Lead generation of cysteine based mesenchymal epithelial transition (c-Met) kinas inhibitors: Using structure-based scaffold hopping, 3D-QSAR pharmacophore modeling, virtual screening, molecular docking and molecular dynamics simulation

Asmaa Raafat
Misr International University, Egypt

The Cysteine-based mesenchymal–epithelial transition (c-Met) is a receptor tyrosine kinase that plays a definitive role during cancer progression and was identified as a possible target for antiangiogenisis drugs. In the present study, different protocols of computer-based drug design were performed.

Construction of predictive pharmacophore model using HypoGen algorithm resulted in a validated model of four features of positive ionizable, hydrogen bond acceptor, hydrophobic and ring aromatic features with a correlation coefficient of 0.87, a configuration cost of 14.95 and a cost difference of 357.92. The model revealed a promising predictive power and had >90% probability of representing true correlation with the activity data. The model was established using Fisher's validation test at the 95% confidence level and test set prediction (r = 0.96), furthermore, the model was validated by mapping of set of compounds undergoing clinical trials as class c-met inhibitors. The generated valid pharmacophore model was then anticipated for virtual screening of three data bases. Moreover, scaffold hopping using replace fragments protocol was implemented. Hits generated were filtered according to Lipinski's rule; 510 selected hits were anatomized and subjected to molecular docking studies into the crystal structure of c-Met kinase. The good correlation between docking scores and ligand pharmacophore mapping fit values provided a reliable foundation for designing new potentially active candidates that may target c- Met kinase. Eventually, eight hits were selected as potential leads. Subsequently, seven (Hits) have displayed a higher dock score and demonstrated key residue interactions with stable molecular dynamics simulation. Therefore, these c-Met kinase inhibitors may further serve as new chemical spaces in designing new compounds.

Biography

Asmaa Raafat, Master's, Assistant lecturer in Arab Academy for Science Technology and Maritime Transport (AASTMT), Alexandria., I was born in Alexandria. I started out in education for cancer research since 2018 Bachelor's degree, Pharmacy (Clinical Pharmacy) 2017. I finished out master's degree, pharmaceutical sciences. Faculty of Pharmacy, Misr International University, Cairo, Egypt 2022. I worked as research chemist at Misr International University, Cairo, Egypt since 2018 till now.

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