Med Chem 2019, Volume 09
DOI: 10.4172/2161-0444-C1-049

Anti-proliferative effect of potential LSD1/CoREST inhibitors based on molecular dynamics model derived from its interaction with tetrahydrofolate cofactor

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Targeting cancer through epigenetics is a recent era, where a specific gene is manipulated without destroying it. Lysine-specific demethylase 1 (LSD1) is one of the enzymes that are associated with chromatin for post-translational modifications, where it demethylates lysine amino acid in the chromatin H3 tail. LSD1 is associated with its corepressor protein CoREST, and utilizes tetrahydrofolate as a cofactor to accept CH2 from the demethylation process. Many studies showed that inhibiting LSD1 could potentially be used to treat cancer epigenetically. The fact that the cofactor is best bound to the active site inspired us to explore its interactions to LSD1/CoREST enzyme complex utilizing molecular dynamics simulation, which aids designing novel and potent inhibitors. Also, the conformational existence of the enzyme complex bound to the cofactor has been investigated. According to the molecular dynamics simulation study, LSD1/CoREST complex is present in open and closed conformations. Furthermore, tetrahydrofolate was found to bind to two binding sub-sites with different binding modes. The model derived from the molecular dynamics simulation study and the key contacts to the active site were used in the subsequent structure based drug design and *in-silico* screening, which revealed a number of new chemical entities with a potential inhibitory effect of LSD1/CoREST complex. *in-silico* mining on National Cancer Institute (NCI) database identified 60 promising and structurally diverse inhibitors. The cytotoxic activities of these compounds were tested against different cancer cell lines with different expression modes of LSD1/CoREST complex such as leukaemia K562, prostate cancer PC3 and neuroblastoma SH-SY5Y. All compounds were also tested against normal fibroblast cells to study their selectivity against cancer cells. Applying the above mentioned molecular modeling procedure, yielded array of LSD1/CoREST inhibiters with IC^{50}<5 μM, when tested against different cancer cell lines. Three compounds inhibited the growth of PC3 prostate cells with IC50=(2.68, 2.08 and 2.95 μM). Four of them inhibited the growth of K562 leukaemia cells with IC50=(1.20, 1.92, 2.70, and 1.20 μM) and three of them inhibited the growth of SH-SY5Y neuroblastoma cells with IC50=(0.27, 0.83 and 4.28 μM). These compounds are excellent candidates for further optimization.

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