Perancangan De Novo dan identifikasi kemo-bioinformatika senyawa derivat 2-oxo-1,3-Thiazolidine sebagai inhibitor potensial Histone Deacetylase (HDAC) Kelas II pada terapi kanker serviks= De Novo design and chemo bioinformatics identification of 2-oxo-1,3 Thiazolidine derivatives as novel potential inhibitors of class II histone deacetylase (HDAC) in cervical cancer treatment

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Abstrak

Kanker serviks berada di peringkat ketiga sebagai kanker yang paling banyak menyebabkan kematian wanita di seluruh dunia dan menempati peringkat pertama di negara berkembang. Kanker ini disebabkan oleh infeksi human papilloma virus (HPV) yang memiliki onkoprotein E6 dan E7 yang mempengaruhi regulasi epigenetik termasuk overekspresi gen histone deacetylase (HDAC) yang menyebabkan karsinogenesis serviks. Sehingga HDAC menjadi target inhibisi yang potensial untuk terapi kanker serviks. Pada penelitian ini, suatu seri terbaru senyawa turunan 4-[(2-okso-1,3-thiazolidin-3-yl)karbonil]anilin dirancang sebagai inhibitor HDAC (HDACI) terbaru berdasarkan pendekatan de novo. Aktivitas inhibisi dari ligan rancangan ini terhadap HDAC kelas II Homo sapiens ditentukan melalui simulasi molecular docking. Analisis docking menghasilkan delapan ligan terbaik (F, Ib14, O38, Kb17, Gd40, Aa50, Gc42, dan Bb38) yang memiliki afinitas pengikatan lebih baik dibandingkan standar. Kemudian analisis interaksi mengindikasikan bahwa seluruh ligan terbaik membentuk koordinasi dengan kofaktor zinc pada charge-relay system HDAC, juga ikatan hidrogen dan interaksi hidrofobik yang penting pada aktivitas inhibisi dari inhibitor HDAC.
Analisis QSAR (quantitative structure-activity relationship) dari senyawa ini, termasuk karakter farmakologi, bioaktivitas, mutagenisitas-karsinogenisitas, dan karakter ADMET (absorpsi, distribusi, metabolisme, ekskresi, dan toksisitas) dilakukan secara in silico. Melalui analisis ini, kedelapan ligan terbaik memenuhi Lipinski’s rule of five, memiliki drug score yang lebih baik dibanding standar, dan juga menunjukkan bioaktivitas, bioavailabilitas oral, dan karakter ADMET yang baik. Seluruh ligan terbaik juga mudah disintesis serta terbukti sebagai senyawa baru yang belum pernah disintesis sebelumnya. Kestabilan kompleks HDAC-ligan pada pengaruh pelarut dikalkulasi melalui simulasi molecular dynamics (MD). Berdasarkan simulasi ini, ligan terbaik yang membentuk kompleks dengan HDAC memiliki stabilitas yang baik berdasarkan RMSD (root mean square deviation) dan analisis interaksi. Ligan terbaik ini dapat disintesis untuk pengujian klinis lebih lanjut. Penelitian ini diharapkan dapat menghasilkan inhibitor HDAC yang lebih potensial sebagai obat terbaru untuk terapi kanker serviks.
.....Cervical cancer ranks third as the most common deadly cancer in women worldwide and ranks first in developing countries. It is caused by human papillomavirus (HPV) infection which has E6 and E7 oncoproteins that induce epigenetic regulation including overexpression of histone deacetylases (HDACs) gene leading to cervical carcinogenesis. Thus HDACs becomes potential inhibition target for cervical cancer treatment.
In this study, a novel series of 4-[(2-oxo-1,3-thiazolidin-3-yl)carbonyl]aniline derivatives were designed as novel HDAC inhibitors (HDACIs) based on de novo approach. The inhibitory activity of these new

designed ligands against Homo sapiens class II HDAC was determined by molecular docking simulation. Docking analysis has yielded eight best ligands (F, Ib14, O38, Kb17, Gd40, Aa50, Gc42, and Bb38) which have better binding affinity than the standards. Therefore, interaction analysis indicated that all best ligands were formed coordination with zinc cofactor in HDAC charge-relay system, also hydrogen bond and hydrophobic interaction which are essential for the HDAC inhibitory activities of these inhibitors.
QSAR (quantitative structure-activity relationship) analysis of these compounds including pharmacology properties, bioactivity, mutagenicity-carcinogenicity, and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties were done in silico. Through this analysis, all eight best ligands meet Lipinski's rule of five, have a better drug score than standards, and shows good bioactivity, oral bioavailability and ADMET properties. All best ligands also have a good synthetic accessibility and were proved to be new compounds that never been synthesized before. Stability of HDAC-ligand complexes in the presence of solvent were also calculated through molecular dynamics (MD) simulation.
Based on this simulation, all best ligands complex with corresponding HDAC have a good stability based on RMSD (root mean square deviation) and interaction analysis. The best ligands can be synthesized for further clinical testing. This study is expected to produce more potent HDAC inhibitors as novel drugs for cervical cancer treatment.