A THEORETICAL APPROACH: QSAR ANALYSIS OF COUMARIN COMPOUNDS AS ANTI ACETYLCHOLINESTERASE (AChE) AGENT FOR ALZHEIMER'S DISEASES

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ABSTRACT

Twenty-six derivatives of coumarin compounds were optimized as anti-acetylcholinesterase (AChE) agents for Alzheimer's diseases, using a theoretical approach of Quantitative Structure-Activity Relationship (QSAR) prediction. The DFT/B3LYP method and basis set 6-31G was selected to validate this method for computing electronic and molecular descriptors. This research attempts to create a novel drug design based on an analysis of QSAR. A genetic algorithm was used in internal validation to solve the optimization problems based on a natural selection process. Twenty-one training set compounds were developed for internal validation with r^2 tranning = 0.916 and SEE 0.219. The best QSAR model was chosen by external validation using five test set compounds. The optimal equation of the QSAR model was developed by Log IC50 = (-1,868068 x qC6) + (-48,4806 X qC16) + (0,0272 x surface area) + (-0,0185 x volume) + 17,27 with statistical parameters r^2 test 0.897 and PRESS 1.120. Lipinski's rule was utilized to describe a physicochemical property of a compound that modified a hydroxy group in substituents for design compounds. The highest biological activity with the lowest IC_{50} resulted from compound N-(4-(7,8-dihydroxy-2-oxo-2H-chromen-3-yl) phenyl)-1-naphthamide.

Keywords: Alzheimer, anti-AChE, coumarin, DFT, QSAR

PENDEKATAN TEORITIS: ANALISIS QSAR SENYAWA KUMARIN SEBAGAI AGEN ANTI ACETYLCHOLINESTERASE (AChE) PADA PENYAKIT ALZHEIMER

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INTISARI

Dua puluh enam turunan senyawa kumarin dioptimalkan sebagai agen anti-asetilkolinesterase (AChE) pada penyakit Alzheimer, menggunakan pendekatan teoritis Quantitative Structure-Activity Relationship (QSAR). Metode DFT/B3LYP dan basis set 6-31G dipilih untuk untuk menghitung deskriptor elektronik dan molekuler. Penelitian ini bertujuan untuk mendesain obat baru berdasarkan analisis QSAR. Algoritma Genetika digunakan saat validasi internal untuk menyelesaikan masalah optimasi berdasarkan proses seleksi alam. Dua puluh satu senyawa set pelatihan dikembangkan untuk validasi internal dan diiperoleh *tranning* set r^2 = 0,916 dan SEE 0,219. Model QSAR terbaik dipilih dengan validasi eksternal menggunakan lima senyawa *test set*. Persamaan optimal model QSAR adalah Log IC50 = (-1,868068 x qC6) + (-48,4806 X qC16) + (0,0272 x surface area) + (-0,0185 x volume) + 17,27 dengan parameter statistik uji r^2 0,897 dan PRESS 1,120. Aturan Lipinski digunakan ketika memodifikasi gugus asam karboksilat pada senyawa desain. Aktivitas biologis tertinggi dengan IC_{50} terendah dihasilkan dari senyawa N-(4-(7,8-dihydroxy-2-oxo-2H-chromen-3-yl) phenyl)-1-naphthamide.

Keywords: Alzheimer, anti-AChE, coumarin, DFT, QSAR