Sintesis, penambatan molekuler, dan uji in vitro senyawa benzimidazolvanilin dan turunan basa Mannich-nya sebagai antioksidan dan antiinflamasi = Synthesis, molecular docking, and in vitro testing of Benzimidazolvanillin compounds and their Mannich base derivatives as antioxidants and anti-inflammatories

Inas Priasti Siwi, author

Abstrak

Obat antiinflamasi non-steroid (OAINS) adalah salah satu obat antiinflamasi yang paling sering digunakan. Namun, OAINS menghambat enzim COX-1 dan COX-2 sekaligus sehingga memiliki efek samping yang cukup serius jika digunakan jangka panjang, seperti gastrointestinal dan gangguan ginjal. Studi melaporkan benzimidazol dan vanilin memiliki aktivitas antioksidan dan antiinflamasi namun potensi dari kedua senyawa ini masih rendah. Modifikasi struktur benzimidazol pada posisi 2 dan substitusi basa C-Mannich diharapkan dapat memberikan peningkatan aktivitas antioksidan dan antiinflamasi serta bioavailibiltas yang lebih baik. Dengan demikian, dilakukan sintesis, uji in vitro antioksidan dan antiinflamasi serta studi penambatan molekuler senyawa turunan basa Mannich dari benzimidazolvanilin. Sintesis dilakukan dalam dua tahapan, yaitu sintesis benzimidazolvanilin melalui reaksi siklokondensasi antara o-fenilendiamin dengan vanilin. Dilanjutkan dengan sintesis tahap 2, yaitu reaksi basa Mannich yang terdiri dari reaksi kondensasi, dehidrasi, dan adisi nukelofilik antara senyawa benzimidazolvanilin dengan formaldehid dan amina sekunder. Telah berhasil disintesis 4 senyawa turunan benzimidazolvanilin yang merupakan senyawa benzimidazol tersubstitusi vanilin pada posisi 2 dan tersubstitusi basa C-Mannich pada posisi orto pada fenolik yaitu; benzimidazolvanilin-morfolin (2a), benzimidazolvanilin-pirolidin (2b), benzimidazolvanilin-dietilamina (2c), danbenzimidazolvanilin-dimetilamina (2d) dengan persen rendemen sebesar (%) 82,51 (2a); 43,74 (2b); 47,78 (2c); 51,12 (2d). Senyawa yang terbentuk dikarakterisasi strukturnya menggunakan FTIR, 1H-NMR, dan 13C-NMR. Senyawa-senyawa tersebut dilakukan uji aktivitas antioksidan dengan metode DPPH, hasil menunjukkan IC50 (M) sebesar 59,63 (2a); 76,33 (2b); 70,00 (2c); 76,24 (2d). Selanjutnya dilakukan uji aktivitas antiinflamasi dengan metode penghambatan denaturasi protein, menunjukkan IC50 (M) sebesar 231,06 (2a); 210,43 (2b); 229,55 (2c) dan 243,74 (2d). Pengujian in-silico dilakukan dengan penambatan molekuler antara senyawa 2a-2d terhadap protein COX-2 dan COX-1 menggunakan program Autodock. Hasil penambatan molekuler didapatkan senyawa 2b merupakan senyawa dengan indeks selektivitas terbaik sebesar 23,32 dan binding affinity sebesar -9,09 kkal/mol. Dari data tersebut menunjukkan senyawa hasil sintesis bukan merupakan inhibitor COX-2 selektif.

.....Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used anti-inflammatory drugs. However, NSAIDs inhibit COX-1 and COX-2 enzymes at the same time and have serious side effects if used long-term, such as gastrointestinal and renal disorders. Studies report benzimidazole and vanillin have antioxidant and anti-inflammatory activities but the potency of these two compounds is still low. Modification of the benzimidazole structure at position 2 and C-Mannich base substitution are expected to provide increased antioxidant and anti-inflammatory activity and better bioavailability. Thus, the synthesis, antioxidant and anti-inflammatory in vitro tests and molecular tethering studies of Mannich base derivative compounds of benzimidazolvaniline were carried out. The synthesis was carried out in two stages, namely

the synthesis of benzimidazolvaniline through a cyclocondensation reaction between o-phenylenediamine and vanillin. Followed by stage 2 synthesis, which is a Mannich base reaction consisting of condensation, dehydration, and nucleophilic addition reactions between benzimidazolvaniline compounds with formaldehyde and secondary amines. Four benzimidazolvanillin-derived compounds have been successfully synthesized which are vanillin-substituted benzimidazole compounds at position 2 and C-Mannich base substituted at the ortho position on phenolics, namely; benzimidazolvanillin-morpholine (2a), benzimidazolvaniline-pyrrolidine (2b), benzimidazolvaniline-diethylamine (2c), and benzimidazolvaniline-dimethylamine (2d) with percent yields of (%) 82.51 (2a); 43.74 (2b); 47.78 (2c); 51.12 (2d). The formed compounds were characterized using FTIR, 1H-NMR, and 13C-NMR. The compounds were tested for antioxidant activity using the DPPH method, the results showed IC50 (M) of 59.63 (2a); 76.33 (2b); 70.00 (2c); 76.24 (2d). Furthermore, the anti-inflammatory activity was tested using protein denaturation inhibition method, showing IC50 (M) of 231.06 (2a); 210.43 (2b); 229.55 (2c) and 243.74 (2d). In-silico testing was carried out by molecular docking between compounds 2a-2d against COX-2 and COX-1 proteins using the Autodock program. The results of molecular docking showed that compound 2b is the compound with the best selectivity index of 23.32 and binding affinity of -9.09 kcal/mol. The data shows that the synthesized compound is not a selective COX-2 inhibitor.