Studi in silico, sintesis dan aktivitas biologi senyawa turunan eugenol sebagai penghambat pertumbuhan kanker kolorektal = In silico study synthesis and biological activity of eugenol derivatives compounds as a colorectal cancer growth inhibitor

Fadilah, author

Abstrak

ABSTRAK
Senyawa turunan eugenol diduga dapat menginhibisi Bcl-2 pada sel kanker kolorektal HT29. Penelitian ini bertujuan untuk memperoleh senyawa baru turunan eugenol yang dapat menghambat sel kanker kolorektal HT29 secara in vitro dan menurunkan ekspresi Bcl-2 pada mencit yang mengalami pre-klamsia terhadap kolon secara in vivo. Penelitian ini diawali dengan melakukan desain senyawa turunan secara in silico. Hasil senyawa hit disintesis di laboratorium. Uji secara in vitro, uji apoptosis dan uji in vivo dilakukan berturut-turut pada hasil senyawa sintesis. Hasil in silico, dari skrining secara farmakofor dengan rancangan acak lengkap menggunakan 220 senyawa desain. Berdasarkan fitur farmakofor dengan cut off 5 fitur dihasilkan 23 senyawa. Hasil skrining farmakofor dilakukan docking menghasilkan delapan senyawa yaitu senyawa 4 rsquo;- 2-kloro-3-hidroksipropil -2 rsquo;-metoksifenil 2-hidroksibenzoat 57, 4 rsquo;- 2-kloro-3-hidroksi-propil -2 rsquo;-hidroksifenil 2-hidroksibenzoat 167, S -4 rsquo;- 2,3-dihidroksipropil -2 rsquo;-metoksifenil 2-hidroksibenzoat 59, R -4 rsquo;- 2,3-dihidroksipropil -2 rsquo;-metoksifenil 2-hidroksibenzoat 60, 4 rsquo;-alil-2 rsquo;-metoksifenil 4-amino-2-hidroksibenzoat 71, 4 rsquo;-alil-2 rsquo;-hidroksifenil 4-amino-2-hidroksibenzoat 181, 4 rsquo;-alil-2 rsquo;-metoksifenil 3,4,5-trihidroksibenzoat 86 dan 4 rsquo;-alil-2 rsquo;-metoksifenil 3,5-diihidroksi-4-metoksibenzoat 91 dengan energi ikatan lebih negatif dari standar. Delapan senyawa hasil skrining disintesis melalui reaksi esterifikasi, adisi halogen, hidroksilasi dan demetilasi. Hasil sintesis diuji aktivitas penghambatannya secara in vitro terhadap sel HT29 kanker kolon. Aktivitas penghambatan terhadap sel HT29 menunjukkan nilai IC50 antara 82.98 g/mL - 8.455 g/mL. Nilai IC50 tersebut lebih negatif dibandingkan senyawa penuntun eugenol. Hubungan Kuantitatif Struktur Aktivitas terhadap sel line HT29 menghasilkan persamaan Log 1/IC50 = -0.865-0.210 LogP 2 1.264 logP - 0.994CMR n=10; r=0.706; SE:0.21; F=0.497, sig=7.86 . Persamaan menunjukkan variabel log P dan CMR berpengaruh terhadap IC50. Sifat hidrofobisitas log P lebih berperan dibandingkan dengan sifat sterik CMR . Hasil uji in vivo terhadap mencit Mus musculus menunjukkan senyawa turunan 59 memiliki nilai HE dan IHK mendekati kontrol positif. Peningkatan dosis pemberian menyebabkan peningkatan degradasi Bcl-2 pada jaringan mendekati kontrol normal. Hasil penelitian menunjukkan bahwa senyawa baru turunan eugenol 59 yang diperoleh dapat menghambat kanker kolorektal secara in vitro dan in vivo.
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ABSTRACT
Compounds derived from eugenol are thought to inhibit Bcl 2 in HT29 colorectal cancer cells. The aim of this study was to obtain new compounds of eugenol derivatives that could inhibit in HT29 cell invitro test and decrease of Bcl 2 expression in mice pre clammed on colon with invivo test. This research begins by designing in silico derivative compounds. The result of the hit compound is synthesized in the laboratory. In vitro tests, apoptotic test and in vivo test were performed successively on the result of the synthesis

compound. In silico yield, from a complete randomized pharmacophore screening using 220 design compounds. Based on the pharmacophore features with cut off 5 features produced 23 compounds. The results of pharmacophore screening conducted docking which yielded eight compounds of compound 4 rsquo 2 chloro 3 hydroxypropyl 2 rsquo metohoxyphenyl 2 hydroxybenzoat 57, 4 rsquo 2 chloro 3 hidroxy propyl 2 rsquo hydroxyphenyl 2 hydroxybenzoat 167, S 4 rsquo 2,3 dihydroxypropyl 2 rsquo methoxyphenyl 2 hydroxybenzoat 59, R 4 rsquo 2,3 dihydroxypropyl 2 rsquo methoxyphenyl 2 hydroxybenzoat 60, 4 rsquo allyl 2 rsquo methoxyphenyl 4 amino 2 hydroxybenzoat 71, 4 rsquo allyl 2 rsquo hydroxyphenyl 4 amino 2 hydroxybenzoat 181, 4 rsquo allyl 2 rsquo methoxyphenyl 3,4,5 trihydroxybenzoat 86 dan 4 rsquo allyl 2 rsquo methoxyphenyl 3,5 dihydroxy 4 methoxybenzoat 91 with energy binding more negative than standard. The eight compounds of the screening are synthesized by esterification reaction, addition with halogen, hydroxylation. And demetylation The synthesis results were tested in vitro inhibitory activity against HT29 colon cancer cells. The inhibitory activity against HT29 cells shows an IC50 value between 82.98 g mL 8,455 g mL. The value of IC50 is better than the eugenol guiding compound. Quantitative Relation of Structure Activity against cell line HT29 with equation Log 1 IC50 0.865 0.210 LogP 2 1.264 logP 0.994CMR n 10 r 0.706 SE 0.21 F 0.497, sig 7.86 . This equation showed that log P and CMR have effect with IC50. Hydrophobicity log P more of effect compared than steric parameters CMR . In vivo test of Mus musculus that showed compound derivative 59 based on HE and IHK values approaching positive control. Increased dosage of administration leads to an increase in Bcl 2 degradation in tissues near normal control. The results showed that the new compound derived eugenol 59 obtained can inhibit colorectal cancer in vitro and in vivo.