Sintesis dan Karakterisasi Senyawa 4-(3-nitrofenil)-1,2,3,4,5,6,7,8-oktahidrokuinazolin-2-on = Synthesis and Characterization of 4-(3-nitrophenyl) -1,2,3,4,5,6,7,8-octahydroquinazoline-2-one

Agnes Tanubrata, author

Abstrak

Inhibitor Dipeptidil Peptidase-4 (DPP-4) merupakan terapi oral baru untuk pasien diabetes tipe 2 (T2DM). Inhibitor DPP-4 sebagai terapi pilihan karena dapat menurunkan kadar HbA1c secara signifikan, meregenerasi dan diferensiasi sel- pankreas, serta menurunkan risiko hipoglikemia. Vildagliptin merupakan inhibitor DPP-4 peptidomimetik dengan gugus farmakoforik, 2-sianopirolidin, yang berikatan kovalen dengan residu Ser630 pada situs S1 DPP-4. Namun vildagliptin tidak selektif, karena dapat menginhibisi DPP-8 dan DPP-9 yang dapat menimbulkan efek toksik. Senyawa dengan struktur inti kuinazolinon telah terbukti berpotensi sangat baik terhadap DPP-4 (IC50=7 nM) dan selektif (DPP-8, IC50>10 M; DPP-9, IC50>10 M). Sintesis hibrid antara derivat kuinazolinon dengan fragmen farmakoforik inhibitor DPP-4 vildagliptin diharapkan dapat menghasilkan inhibitor DPP-4 yang poten dan selektif. Berdasarkan pemaparan tersebut, dilakukan sintesis senyawa baru “4-(3-nitrofenil)-1,2,3,4,5,6,7,8-oktahidrokuinazolin-2-on” sebagai derivat kuinazolinon. Sintesis senyawa tersebut memerlukan dua tahapan. Tahap 1 melalui reaksi kondensasi aldol silang antara 3-nitrobenzaldehida dengan sikloheksanon. Tahap 2 melalui reaksi adisi Michael antara produk tahap 1 dengan urea, dilanjutkan siklokondensasi, dan eliminasi. Kedua senyawa hasil sintesis diuji kemurniannya menggunakan KLT dan penetapan jarak lebur. Nilai rendemen senyawa hasil sintesis tahap 1 dan tahap 2 secara berturut-turut adalah 77,78% dan 51,63%. FTIR produk tahap 1 memperlihatkan adanya ikatan =CH alkena ulur dan tekuk luar bidang, =CH alkana ulur, CH2 tekuk, C=O keton, dan C=C alkena yang menunjukkan produk tahap 1 telah terbentuk. FTIR produk tahap 2 memperlihatkan adanya ikatan C=O amida serta N-H ulur dan tekuk. Namun pada 1H-NMR selain memperlihatkan proton-proton yang sesuai dengan senyawa target sintesis masih teramati adanya proton-proton dari pengotor, sehingga disimpulkan bahwa senyawa 4-(3-nitrofenil)-1,2,3,4,5,6,7,8-oktahidrokuinazolin-2-on telah terbentuk, namun belum murni.

.....Dipeptidyl Peptidase-4 (DPP-4) inhibitor is a new oral therapy for type 2 diabetes (T2DM). DPP-4 inhibitors are the best treatment because as it can significantly reduce HbA1c level, regenerated and differentiated cell- pancreas, and reduced the risk of hypoglycemia. Vildagliptin is a peptidomimetic DPP-4 inhibitor with a pharmacophoric group, 2-cyanopyrolidine, which binds covalently to Ser630 residue at the S1 site of DPP-4. However, vildagliptin is not selective because it can also inhibit DPP-8 and DPP-9, causing toxic effect. Hybrid synthesis between quinazolinone derivatives and the pharmacophoric fragment of DPP-4 inhibitor vildagliptin is expected to produce a potent and selective DPP-4 inhibitor. Compound with a quinazolinone core structure have been shown to be highly potent against DPP-4 (IC50=7nM) and selective (DPP-8, IC50>10 M; DPP-9, IC50>10 M). Based on this explanation, a new compound was synthesized “4-(3-nitrophenyl)-1,2,3,4,5,6,7,8-octahydroquininazoline-2-one” as quinazolinone derivative. There are two steps required for synthesis of this compound. The first step is a crossed aldol condensation reaction between 3-nitrobenzaldehyde and cyclohexanone. The second step is Michael addition reaction between product of step 1 with urea, followed by cyclocondensation, and elimination. The two synthesized

compounds were tested for purity using TLC and melting point determination. The yield of compound synthesized in step 1 and 2 were 77,78% and 51,63%, respectively. FTIR of synthesized product of step 1 showed the presence of =CH stretching and out-of-plane bending alkenes, =CH stretching alkanes, CH2 bending, C=O ketones, and C=C alkenes bonds which indicate the product of step 1 has been formed. FTIR of synthesized product of step 2 showed the presence of C=O amides, N-H stretching and bending bonds. However, 1H-NMR spectrum, besides from showing protons appropriate to the target compound, protons from impurities were still observed, so it was concluded that 4-(3-nitrophenyl)-1,2,3,4,5,6,7 ,8-octahydroquinazoline-2-one has been formed, but not pure.