Modifikasi struktur senyawa 1,4- naftokuinon dan 2- hidroksi 1, 4-naftokuinon serta uji aktivitas sitotoksik terhadap sel kanker payudara dan sel kanker hati secara in vitro = Structure modification of 1, 4-naphthoquinone and 2- hydroxy 1- 4 -naphthoquinone and cytotoxicity against breast carcinoma cell line mcf7 and hepatocarcinoma cell line hepg2

Susi Kusumaningrum, author

Abstrak

Naftokuinon dan turunannya dilaporkan mempunyai aktivitas multipotensi. Hasil skrining aktivitas sitotoksik 5 senyawa turunan naftokuinon terhadap sel kanker payudara MCF7 dan sel kanker hati HEPG2, menunjukkan bahwa senyawa 1,4 naftokuinon (N) dan senyawa 2-hidroksi-1,4-naftokuinon(2HN) mempunyai aktivitas sitotoksik yang kuat. Sebagai upaya optimisasi aktivitas sitotoksik selektif terhadap kedua senyawa tersebut dilakukan rancangan modifikasi strukturnya sehingga diperoleh 30 senyawa turunan. Senyawa turunan tersebut selanjutnya dilakukan skrining secara virtual terhadap reseptor target Polo like kinase 1 (Plk-1) dengan perangkat lunak Molegro Virtual Docker. PLk-1 adalah target potensial generasi terbaru dalam terapi kanker, proteinnya terekspresikan secra bermakna dalam beberapa jenis kanker. Hasil skrining virtual menunjukan bahwa senyawa hasil rancangan mempunyai afinitas pengikatan lebih tinggi dibandingkan senyawa induk, ligan acuan benzolaktam serta doxorubicin. Senyawa yang mempunyai nilai afinitas lebih baik dari senyawa induk dan nilai clogp<5 disintesis. Hasil modifikasi senyawa N diperoleh 3 senyawa yaitu senyawa 4-oksim-naftalen-1-on (NO-1); senyawa 4-((benzoiloksi)imino)naftalen-1(4h)-on (NO-2) dan senyawa (E)-4-(asetoxiimino) naftalen-1(4H)-on (NO-6). Sedangkan modifikasi senyawa 2HN diperoleh 4 senyawa yaitu 1,4-diokso-1,4-dihidronaftalen-2il-benzoat (2HN-13), 1,4-diokso-1,4-dihidronaftalen-2-il 4- metilbenzoat (2HN-14); 1,4-diokso-1,4-dihidronaftalen-2il-3-metilbenzoat (2HN-15), dan 1,4-diokso1,4-dihidro-naftalen-2-il 2-metilbenzoat (2HN-16). Struktur senyawa hasil modifikasi dikonfirmasi dengan FTIR, LCMS, 1H-NMR dan 13C-NMR serta aktivitas sitotoksik selektif terhadap sel kanker payudara MCF7, sel kanker hati HEPG2 dan sel normal CHO menggunakan metode MTT. Senyawa yang paling poten dilakukan analisis siklus sel dengan flowcytometry. Hasil penelitian menunjukkan senyawa N, NO-1, NO-2 dan NO-6 mampu menginhibisi proliferasi sel kanker payudara MCF7 dengan masing-masing nilai IC50 20,63 μM, 11,23; 48,18 μM.μM dan 3,24 μM. Senyawa NO-1 dan NO-6 mempunyai aktivitas sitotoksik selektif terhadap sel kanker MCF7 dan tidak selektif sitotoksik terhadap sel kanker hati HepG2. Mekanisme penghambatan proliferasi sel kanker MCF7 oleh senyawa NO-1 dan NO-2 diduga kuat melalui penghambatan plk-1 yang selanjutnya menginduksi apoptosis dan menekan mitosis sel. Hasil analisa HKSA menunjukkan bahwa efek hidrofobik khususnya log p senyawa turunan 1,4 naftokuinon menunjang aktivitas sitotoksik terhadap sel kanker payudara MCF7, namun tidak demikian terhadap sel kanker hati HEPG2. Sedangkan efek sterik dan elektronik tidak memberikan pengaruh yang signifikan.
<hr>
Naphthoquinone and its derivatives have been reported to have multipotent activity. Results from cytotoxic screening against breast carcinoma cell line (MCF7) and hepatocarcinoma cell line (HepG2) showed that

1.4-naphthoquinone and 2-hydroxy-1.4-naphthoquinone compounds had the highest cytotoxic activity. In this study, the selective cytotoxic activity was optimized, 30-naphthoquinone derivatives from 1,4-naphthoquinone and 2-hydroxy-1,4-naphthoquinone were designed and virtually screened using Molegro Virtual Docker software. Those compounds were adhered to targeted receptor, which is Polo-like kinase 1 (Plk-1). Plk 1 is one of the potential targets for cancer therapy because it is expressed on several types of cancer cells. Result of the study demonstrated that naphthoquinone derivatives had more potent bonding activity compared to ligand references, i.e. benzolactam and doxorubicin. Modification of 1.4-naftokuinon to oxyme structure had been performed and resulted in NO-1 (4-oxime-naphtalene-1-on), NO-6 ((E)-4-(acetoxyimino) naphtalen-1(4H)-on) and NO-2 (4-((benzoyloxy)imino)naftalen-1(4h)-on). Furthermore, 2-hydroxy-1,4-naphtho- quinone had been modified and the synthesized compounds were 1,4-dioxo-1,4-dihydronaphtalen-2yl-benzoate (2HN-13), 1,4-dioxo-1,4-dihydronaphthalen-2-yl 4-methylbenzoate (2HN-14) 1,4-dioxo-1,4-dihydronaphtalen-2yl-3-metilbenzoate (2HN-15), and 1,4-dioxo-1,4-dihydronaphthalen-2-yl 2-methylbenzoate (2HN-16). Modified compounds had been confirmed using FTIR, LCMS, 1H-NMR and 13C-NMR. MTT assay was performed to study the selective cytotoxic activity. Flow cytometry was also being used to observe the cell cycles of cell after treated with the potent compounds. In this present study, it was observed that the compound N, NO-1, NO 2 and NO-6 inhibited the proliferation of MCF7 breast carcinoma cell line with IC50 20.63 μM, 11.23.μM, 48.18 μM and 3.24 μM respectively. NO-1 and NO-6 had selective cytotoxic activity against breast carcinoma cell line, MCF7 and had no selective cytotoxic activity against hepatocarcinoma cell line, HepG2. Mechanism of proliferation inhibited breast carcinoma cell line (MCF7) of NO-1 and NO-6 compounds were estimated by Plk-1 inhibition which further induced apoptotic and suppressed mitotic. QSAR analysis presented the hydrophobic effect of oxyme derivatives, particularly log p, played a role to breast carcinoma cell line (MCF7) on cytotoxic effect, but not to hepatocarcinoma cell line (HEPG2). However, the steric and electronic effects did not significantly contribute to the activity.