

DESIGN AND SYNTHESIS OF RECEPTOR TYROSINE KINASE INHIBITORS FOR ANTICANCER TREATMENT

CHAWANNUCH MUDJUPA 5136796 PYPP/D

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THESIS ADVISORY COMMITTEE: OPA VAJRAGUPTA, Ph.D., JUTARAT PIMTHON,
Dr. rer. nat., JIRAPHUN JITTIKOON, Ph.D.

ABSTRACT

A novel tyrosine kinase inhibitors targeting epidermal growth factor receptor (EGFR) were developed in this study based on the core structure of major component in medicinal plants. In searching for the core structure, chlorogenic acid was identified from virtual screening of 2,666 compounds in Thai herbal database. The caffeic motif in the structure of chlorogenic acid was used as core structure for the design. The design strategy composed of (i) extension of molecular structure *via* urea and amide linkers (ii) optimization of the extended structure to enhance EGFR-binding affinity and (iii) modification of phenoxy groups in caffeic motif to avoid ionization. Two series of compounds classified by the linker which are urea series (CIU series) and amide series (CAD series) were designed, synthesized and evaluated for their anti-proliferative activities on a panel of cancer cell lines. CIU1, the most promising compound in urea series, inhibited the growth of EGFR-overexpressing MDA-MB-468 triple-negative breast cancer cells and wild-type non-small-cell lung cancer H460 cells with IC_{50} values of 8.96 μ M and 12.98 μ M, respectively, these anti-proliferative effects of CIU1 were comparable to gefitinib and lapatinib. CIU1 also effectively inhibited the invasive hormone-dependent MCF-7 cancer cells with an IC_{50} 2.34 μ M. The immunoblot analyses revealed that CIU1 induced apoptosis and suppressed EGFR expression in breast cancer MDA-MB468 and lung cancer PC-9 cells. Among compounds in amide series, CAD1, CAD6 and CAD12 were more potent against MCF-7 with IC_{50} of 8.02, 13.69 and 13.66 respectively. CAD1 also showed the inhibition activity against Hela cell line (IC_{50} = 12.55 μ M). The cytotoxicities of all designed compounds on the normal kidney MDCK cells were not observed at 100 μ M. The findings substantiated the design strategy and demonstrated the potential of CIU1 as new lead for further optimization in the development of anticancer drugs against advanced solid tumors. Moreover, the scaffold from natural product was proved to be valuable sources for the success in drug design.

KEY WORDS: EGFR INHIBITOR / KINASE INHIBITOR/ ANTICANCER

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