PP-09

Rational Design of Novel EGFR Kinase Inhibitors as Anticancer Agents

Chia-Hsien Wu (吳佳憲)[1], Wen-Hsing Lin (林文星)[1], John T.A. Hsu (徐祖安)[1], Chun-Chen Liao (廖俊臣)[2], Yu-Sheng Chao (趙宇生)[1], Hsing-Pang Hsieh (謝興邦)[1*]

[1] *Institute of Biotechnology and Pharmaceutical Research,National Health Research Institutes, Miaoli, Taiwan.*
[2]*Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan.*

Lung cancer is the first leading cause of death in human carcinoma, with 80-85% being non-small cell lung cancer (NSCLC). Over-expression of epidermal growth factor receptors (EGFR) is in 40-80% of NSCLC. Gefitinib (Iressa®) and erlotinib (Tarceva®) were approved by FDA as EGFR inhibitors for the treatment of adenocarcinoma (subtype of NSCLC). Gefitinib and erlotinib competitively bind to the ATP binding pocket of EGFR kinase domain and inhibit its activity. These two drugs showed high response rates in Asian NSCLC patients, but patients became resistant to treatment with gefitinib or erlotinib after 6-12 months. Drug resistance occurs as a result of secondary mutation such as T790M mutation. We designed and synthesized novel EGFR- tyrosine kinase inhibitors, which expect to overcome the resistance issues for potential NSCLC therapy.

Through hybrid design and knowledge-based design concepts to obtain compounds **4**, **5**, **6** and **7** with 1-9 nM inhibition against wild type EGFR and HCC827 cell-line (EGFR E746-A750 deletion). This series also showed 10-305 nM inhibition against gefitinib-resistant mutant of EGFR (T790M/L858R). More than 200 analogues were synthesized, and the presence of (*S*)-phenyl-glycinol and Michael acceptor groups are essential for activity in the series of inhibitors.