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Synthesis of Erlotinib Analogues, Conjugation of BSA to Erlotinib Alcohol and Their Anti-Cancer Activity against NSCLC

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Abstract : A series of erlotinib analogues that have structural modification at 6,7-alkoxyl positions is efficiently synthesized. The key reactions that involved in synthesis are one-pot oxime formation-dehydration for the formation of nitrile, quinazoline ring formation reaction between aniline and o-cyanoaniline via formamidine intermediate, Fe/NH4Cl catalyzed reduction-hetereocyclization-reductive ring opening reaction for the formation of o-aminobenzamide, high yielding seal tube reactions for O-demethylation, sodium iodide substitution, ammonia substitution. The in vitro anti-tumor activity of synthesized compounds is studied in two non-small cell lung cancer (NSCLC) cell lines (A549 and H1975). Among the synthesized compounds, the iodo compound 6 (ETN-6) exhibits higher anti-cancer activity compared to erlotinib. An efficient method is developed for the conjugation of erlotinib analogue-4, alcohol compound, with protein, bovine serum albumin (BSA), via succinic acid linker. The in vitro anti-tumor activity of the protein attached erlotinib analogue, 8 (ETN-4-Suc-BSA), showed stronger inhibitory activity in both A549 and H1975 NSCLC cell lines.

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