

MODIFICATION OF IRINOTECAN WITH 4-CYCLOHEXYLPHENYL 2-CHLOROACETATE

N.U. Gafforov¹, A.U. Choriev¹, A.K. Abdushukurov²

¹*Karshi State University, 17 Kuchabog street, 180103 Karshi city, Republic of Uzbekistan, azimjon-organik@mail*

²*National University of Uzbekistan named after Mirzo Ulugbek, 4 Universitetskaya street, 100174 Tashkent, Republic of Uzbekistan, abdushukurov-ximik@mail.ru*

Irinotecan was invented in Japan by Yakult Honsha Company and Daiichi Pharmaceutical Company. The drug is a water-soluble derivative of camptothecin (a substance that blocks topoisomerase I). Camptothecin was isolated from the *Camptotheca acuminata* plant [1]. Y. Shimada et al. published a phase II clinical trial that studied the treatment of metastatic colorectal cancer. The drug was shown to be effective as a single-component therapy, with an objective clinical response rate of 27%. The rights to clinical trials and commercial use in the United States, Canada, Australia, New Zealand, and Latin America were acquired by Pharmacia & Upjohn (P&U), and in Europe, Asia, and Africa by Rhône-Poulenc Rorer (now Aventis) [2], after which clinical trials of the drug began in the United States and Europe. Irinotecan is used both alone and in combination with other antitumor agents. The active form of the drug is the metabolite SN-38, which is produced by the action of the enzyme carboxylesterase on irinotecan. This enzyme has several isoforms. For example, CES1 is expressed to a greater extent in the liver. Interestingly, CES2, which is expressed in the intestine and kidneys, has a higher affinity and rate of conversion of irinotecan to SN-38, but does not affect the pharmacokinetics of irinotecan [3]. Currently, irinotecan is not used as a drug for neoadjuvant therapy of colorectal cancer, but there are a number of studies that raise the question of the effectiveness of combining irinotecan with 5-fluorouracil or its derivatives during preoperative radiation therapy.

In order to increase the retention of irinotecan, it was modified with 4-cyclohexylphenyl 2-chloroacetate. Further studies examined the salt-forming properties of O-chloroacetylphenol derivatives. These studies showed that, due to the low basicity of the nitrogen of the irinotecan ring, they do not form hydrochlorides. However, when heating an alcoholic solution of irinotecan in an excess of 4-cyclohexylphenyl 2-chloroacetate, quaternary salts are formed in good yields. Thus, it was established that the optimal condition for obtaining quaternary salts is boiling an alcohol solution of the initial reagents at a temperature of 85°C for 6-10 hours. Currently, work is underway to determine the biological activity of the obtained compound using the in silico method.

References:

1. Wulaningsih W., Wardhana A., Watkins J. et al. Irinotecan chemo therapy combined with fluoropyrimidines versus irinotecan alone for overall survival and progression free survival in patients with advanced and/or metastatic colorectal cancer. *Cochrane Database Syst Rev* 2016;2: CD008593.
2. Miller L. L., Locker P. K., Schaaf L. J. et al. Irinotecan hydrochloride (CPT-11, CAMPTOSAR), oncologic drugs advisory committee brochure. New York: Pharmacia & Upjohn, 2000. P. 38.
3. Hosokawa M. Structure and catalytic properties of carboxylesterase isozymes involved in metabolic activation of prodrugs. *Molecules* 2008;13(2):412–31.