Секция «Экспериментальные исследования»

Looking beyond epidermoid carcinoma cells for effective combinations of novel photoswitchable combretastatin A-4 derivatives with metformin and chemotherapeutics

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Cancer is the first target for photopharmacology due to its high localization and severe side effects of the existing drugs. Combretastatin A-4 (CA-4) is of a family of stilbenes and is isolated from Combretum caffrum. It inhibits tubulin polymerization and has significant cytotoxic effects on tumour cells. The study was aimed to find effective combinations of CA-4 analogues with cisplatin, 5-fluorouracil and metformin**.**

Materials and methods. The epidermoid carcinoma cell line A-431 was received from ATCC. The antineoplastic agents and metformin were acquired from Cayman Chemical. The Wittig reaction was used for the synthesis of CA-4 analogues based on quinazoline stilbenes. The corresponding aldehydes were condensed with quinazoline phosphorus ylides, and the yield was 65-80%. Phosphorus ylides based on quinazoline were produced via reaction of quinazoline chloromethyl derivatives with triethyl phosphite. All quinazoline analogues of CA-4 were synthesized in the E-form. The constant of the spin-spin bond of olefinic protons was 15.8-16.2 Hz. The MTT test was used to assess the cell viability.

Results. Research of cytotoxic activity of novel CA-4 derivatives showed that the lead compounds could decrease the survival rate for A-431 cells, and the IC_{50} was less than 10 μM. MA-6595, or (E)-2-(3,4,5-trimethoxystyryl)quinazolin-4(3H)-one, showed the highest cytotoxic effect. This derivative underwent isomerization by irradiation at λ=365 nm. The relation between E and Z isomers was 1.25:1. The antiproliferative effect of MA-6595 photoproduct exceeded the activity of the initial compound by 5.4 times. MA-6595 photoproduct was investigated in combinations with cisplatin, 5-fluorouracil and metformin. The photoproduct increased the influence of cisplatin and 5-fluorouracil on epidermoid carcinoma cells. The combination of 5 mM metformin with 1 μM MA-6595 photoproduct revealed the highest synergistic effect on cell viability. The combination index was less than 1.

Conclusions. Novel CA-4 derivatives with high antiproliferative activity were synthesized. The cytotoxic action of the lead compound on epidermoid carcinoma cell culture was highly increased by the irradiation. The hit analogue enhanced the antiproliferative activity of cisplatin and 5-fluorouracil on A-431 skin cancer cells. The combination of the CA-4 derivative with metformin showed high results. Novel CA-4 derivatives can be included in further combination therapies reducing the prescribed dose of the chemotherapy drug.

Funding. The Russian Science Foundation (project 18-13-00308, chemistry) and the Ministry of Education and Science of Russia (project 075-15-2020-789, cisplatin experiments).