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Conjugates containing homing peptide, cell penetrating peptide and a cytostatic or marker potentially useful in the diagnosis or treatment of lung cancer diseases

Piotr Jedrzejczak[a], Anna Gajda[a], Justyna Fraczyk[a], Beata Kolesinska[a]

[a]*Institute of Organic Chemistry, Łódź University of Technology, Żeromskiego 116, 90-924 Lodz, Poland*

Introduction

Lung cancer causes 23% of total cancer deaths worldwide. It is the most deadly cancer, with minimal survival. There are two known forms: non-small cell lung cancer (NSCLC) (85% of cases) and small cell lung cancer (SCLC). NSCLC is sensitive to chemotherapy; however, response varies depending on the specific therapy [1]. Oral administration of anticancer chemotherapeutic agents is often limited by first-pass metabolism. Furthermore, due to their non-targeted nature, most chemotherapeutic agents act on normal tissues, leading to adverse effects. Despite this, classical chemotherapy is used in more than 70% of patients [2]. The chemotherapy drugs used are [3]: antimetabolites (capecitabine, floxuridine, methotrexate), alkylating agents (cisplatin, carboplatin), mechlorethamine, cyclophosphamide or mitomycin C), anitimicrotubule drugs (vinca alkaloids and taxanes), topoisomerase inhibitors (etoposide, doxorubicin, mitoxantrone, novobiocin). In recent years, two groups of drugs have been introduced to the treatment of lung cancer: molecularly targeted and immunotherapy drugs. Most clinically approved therapeutic mAbs are molecularly targeted therapies, they act passively by blocking the activity of receptors or activating the immune system [4]. mAbs have limitations such as nonspecific clearance of antibodies by the reticuloendothelial system which may lead to accumulation of antibody-conjugated drugs or toxins in undesirable sites [5]. Several types of tumor-targeting ligands have been developed, including antibodies, antibody fragments, polypeptides, small molecules, and others [6]. Peptides are an attractive alternative to antibody-based targeted therapies. Unlike antibodies, peptides are easy to synthesize in large quantities [7], and their smaller size improves tissue penetration while preventing nonspecific uptake by the reticuloendothelial system. In addition, peptides can be chemically modified to alter affinity, charge, hydrophobicity, stability, and solubility, and can be optimized for in vivo use through modification. Importantly, peptides can exhibit antibody-like affinity for receptors. The aim of the research is to develop methods for the synthesis of peptide conjugates that determine selective interaction with improve transport to the cell, as well as a compound with anticancer activity.

Results and discussion

Altretamine, a derivative of 1,3,5-triazine, is an anticancer drug. The structure of altreamine was modified by using other secondary amines and by adding a peptide that penetrates cell membranes. The syntheses began with obtaining penetrating peptides using the solid-phase synthesis strategy and obtaining monosubstituted dichlorotriazine derivatives. A quaternary N-triazinylammonium salt was used as the coupling reagent [8]. Then, monosubstituted

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dichlorotriazine derivatives (substituted with a methoxy group or an appropriate amino group) were attached to the obtained peptides on the solid phase.

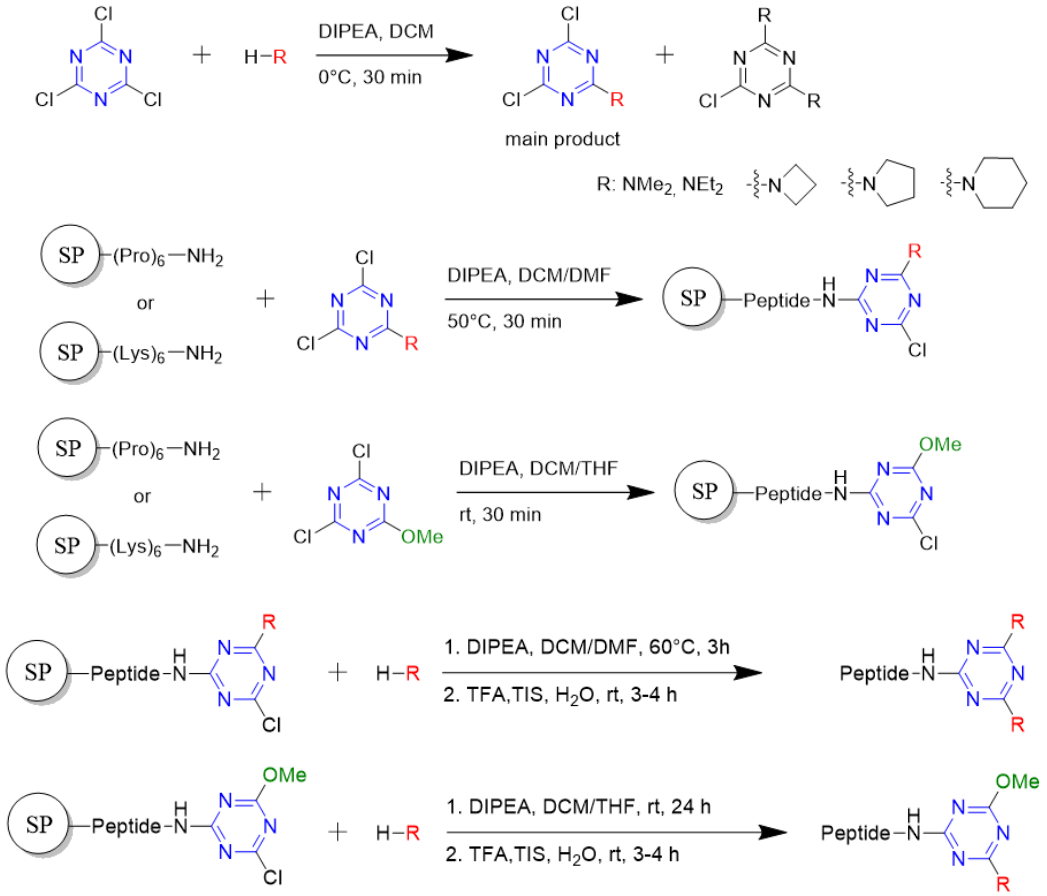

Fig. 1 Scheme for the synthesis of 1,3,5-triazine derivatives containing CPP attached to the triazine ring.

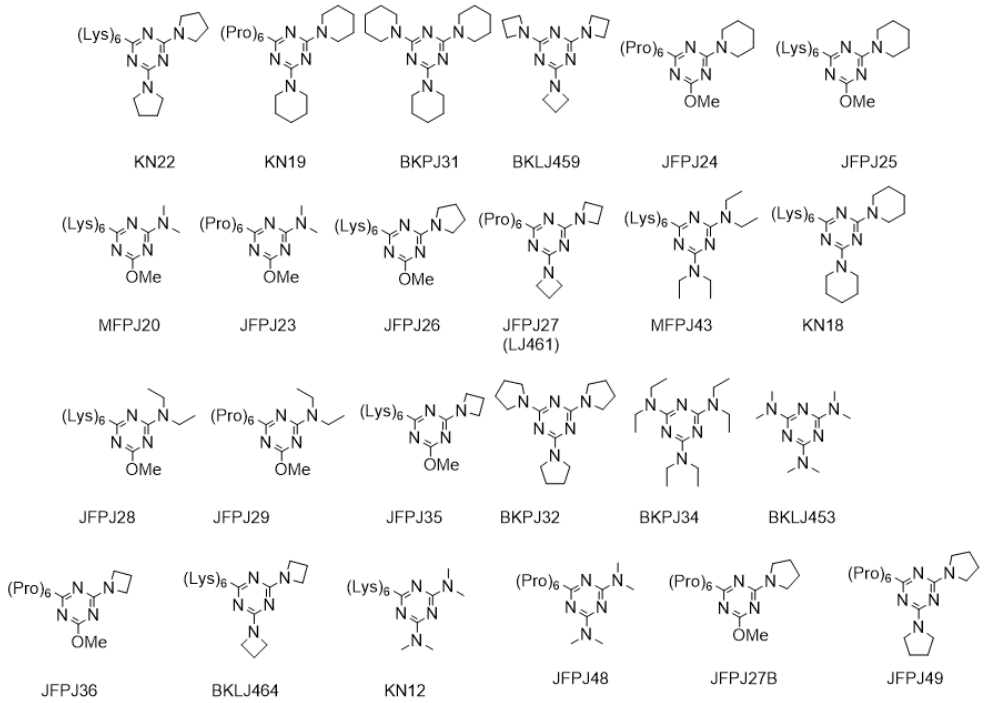

Fig. 2 Structures of the obtained 1,3,5-triazine derivatives (altretamine analogues) with CPP attached to the triazine ring.

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The final stage of the synthesis was the substitution of the last chlorine atom with an amino group and the cleavage of the compound from the solid phase. In total, 19 new compounds and aminoalkyl derivatives of 1,3,5-triazine were obtained, including altretamine as a standard.
In the final stage, the effect of the obtained compounds on A549 cells (non-small cell lung cancer, NSCLC) was assessed and the energy of interaction of the compounds with the EGF receptor was determined.

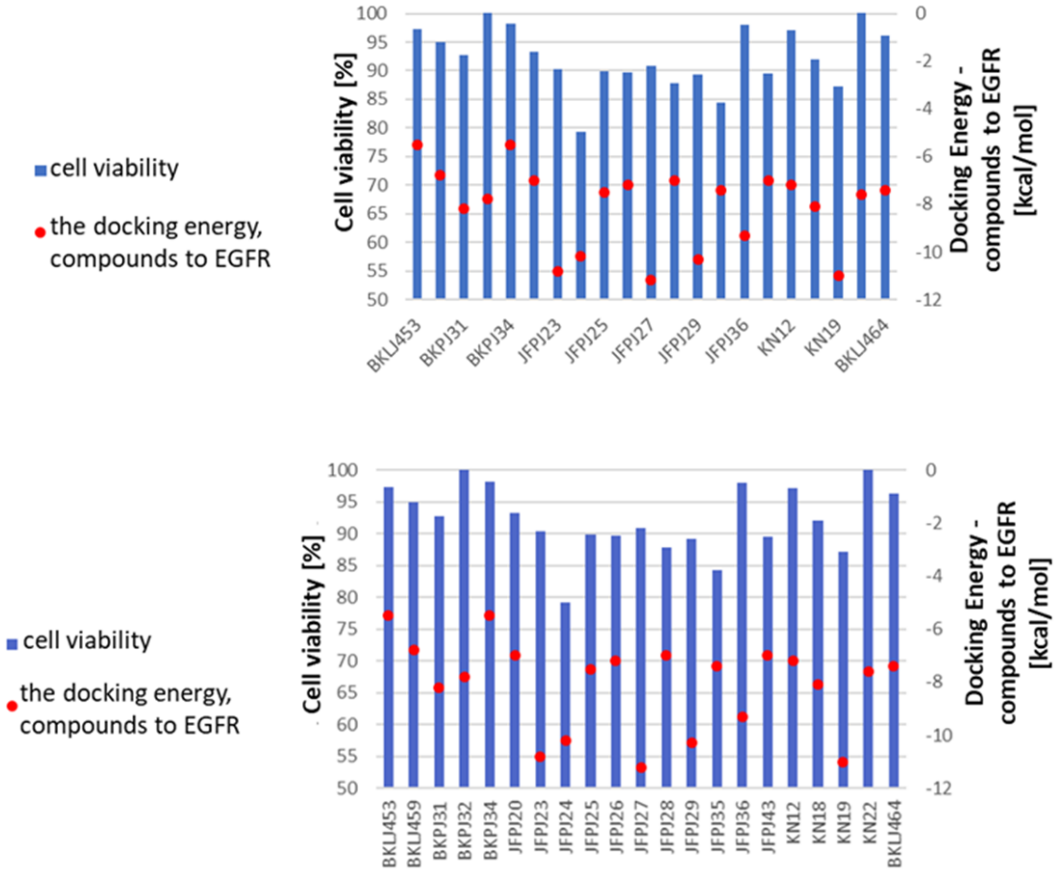

Fig. 3 The results of biological tests on the A549 cell line (NSCLC) and the calculated energy of interaction of compounds with the EGF receptor.

The biological studies carried out indicate the potential of the obtained compounds. However, due to the lack of specificity of CPP, it will be necessary to introduce an additional peptide fragment increasing the specificity towards cancer cells.

Conclusions

The results from first biological tests show increase in activity compared to control (altretamine). Further biological studies are carried out now to better characterize the obtained compounds.

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