CHEMTECH LIFE SCIENCE

TECHNOLOGY OFFER

PELOFEN, A NOVEL PELORUSIDE ANALOGUE WITH MICROTUBULE-STABILIZING ACTIVITY, ENABLING THE TREATMENT OF RESISTANT CANCERS

We are seeking partners interested in the further development of the biological evaluation of Pelofen, a simplified analogue of Peloruside with antitumor activity.

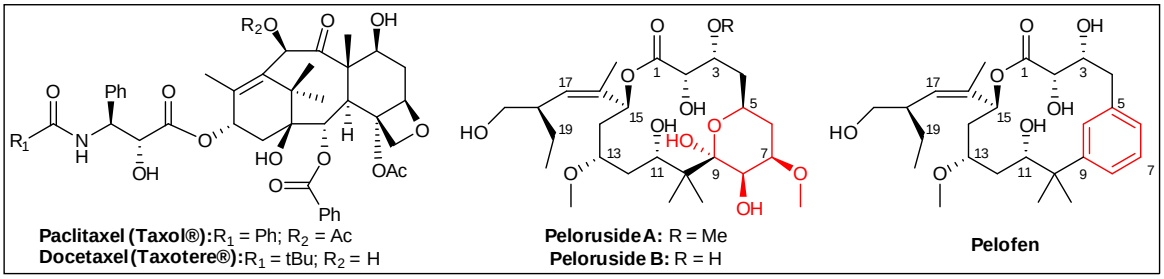
INTRODUCTION

The current broad spectrum antitumor drugs, paclitaxel (Taxol ®) and docetaxel (Taxotere ®), are chemotherapeutics that stabilise the microtubules. As they interfere with the dynamics of the microtubules, they inhibit the formation of the mitotic spindle and consequently arrest the proliferation of fast dividing cells, such as cancer cells. However multidrug resistance, complex pharmaceutical formulations and toxicity limit their pharmaceutical use.

Peloruside A and B, secondary metabolites isolated from a marine sponge, were also identified as a microtubule-stabilizing agent (MSA) and consequently as a mitotic inhibitor. They possess several therapeutic advantages over the current chemotherapeutics, like a unique binding site on tubulin, rendering it highly interesting as a promising anticancer drug. Because of its broad range therapeutic profile and the low bioavailability of peloruside, there is an urge for the development of novel, simplified analogues, that are synthetically more accessible.

TECHNOLOGY

Researchers at Ghent University in the research group of Prof. Johan Van der Eycken have designed a novel simplified peloruside analogue, nicknamed Pelofen, by replacing the pyranose moiety by a phenyl moiety. Despite its simplified structure, biological screening in collaboration with Prof. Marc Bracke showed a pronounced microtubule-stabilizing activity of Pelofen. Moreover, cancer cells obtaining resistance during long treatments with paclitaxel are still vulnerable towards Pelofen. In our endeavour to discover more potent analogues, a flexible, modular synthesis of a broad range of Pelofen analogues was designed.



APPLICATIONS

Pelofen is an attractive therapeutic candidate since it is a potent microtubule-stabilizing agent what makes it especially promising as an anticancer chemotherapeutic drug. Preliminary results with Peloruside encourage the apllication of Pelofen in the treatment of neurodegeneration, autoimmune and inflammation diseases.

ADVANTAGES

- Novel peloruside analogue with a unique binding site on tubulin maintains its activity in paclitaxel-resistant cancers
- Unique binding site on tubulin allows combination therapies with current chemotherapeutics which suppresses development resistance upon treatment of cancer cells (Table 1)
- Synergetic effect with paclitaxel permits lower doses of chemotherapeutics during treatment and consequently reduces side effects
- Hydrophilic nature of Pelofen makes it less susceptible for multidrug resistance via overexpression of the P-gp efflux system and allows easy formulations of the drug
- Simplified structure of Pelofen allows shorter synthesis and makes it more economically feasible as synthetic drug
- Modular synthesis makes a broad range of diverse Pelofen analogues accessible

STATUS OF DEVELOPMENT

Different synthetic routes towards Pelofen were designed and evaluated. Pelofen was fully characterised and evaluated in in vitro assays (MTT, SRB, collagen invasion, chicken heart invasion and CAM). The flexible routes also allowed the synthesis of a serie of Pelofen analogues

MSA	IC_{50} 1A9 (µg/ml) *Parent cell line*	IC_{50} PTX22 (µg/ml) *Mutant cell line*	Resistance Ratio
Genexol-PM (Paclitaxel)	0,0635	1,08	**17,0**
Pelofen	0,527	0,440	**0,835**

Table 1. IC_{50} values Genexol-PM and Pelofen on 1A9 and PTX22

PARTNERSSHIP

Ghent University is searching partners for further evaluation of Pelofen (and its analogues) in cancer treatment, neurodegeneration, inflammation or autoimmune diseases

INTELLECTUAL PROPERTY

An international patent was filed: 'Peloruside analogs', WO2015/079009

KEYWORDS

Peloruside, broad spectrum anticancer drug, resistant cancer, oncology, chemotherapy

REFERENCES

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