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Ornithine Derivatives of Salicylamide with Cytotoxic Potential against A549 Human Lung Carcinoma Cells

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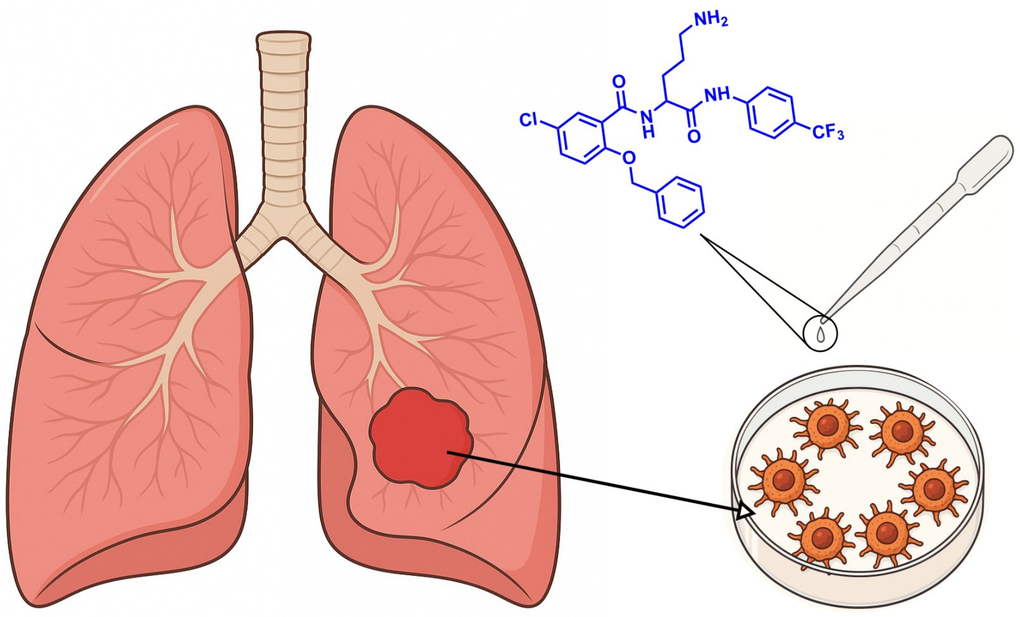
INTRODUCTION & AIM

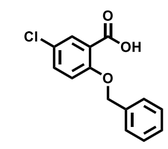
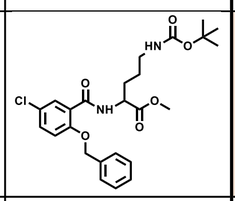
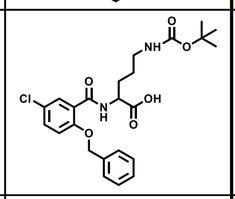
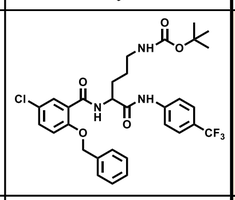
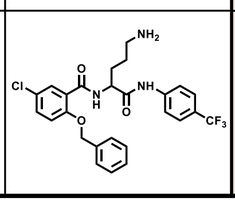
Peptidomimetics represent a promising group of biologically active compounds with broad therapeutic potential that mimic naturally occurring peptides while overcoming their limitations [1]. This study focuses on the synthesis and cytotoxic properties of short original ornithine-based peptidomimetics derived from substituted *O*-benzyl-protected salicylic acid (salicylamide), where L-ornithine is further modified with various aromatic amines, and on the evaluation of their biological activity against the A549 human lung carcinoma cell line. Salicylic acid–based peptidomimetics have previously been synthesized by our research group, demonstrating both anticancer and antimicrobial activity [2–4]. Ornithine-containing peptidomimetics represent synthetic precursors leading to arginine-based peptidomimetics. Arginine peptidomimetics exhibit a wide range of biological activities, such as antimicrobial, antiviral and anticancer effects [5–7].



From the perspective of biological activity, the A549 cell line is a standard *in vitro* model for testing novel candidate anticancer agents against non-small cell lung carcinoma (NSCLC), the most prevalent clinical form of lung cancer. As a control, newly established expandable lung epithelial (ELEP) cells derived form human embryonic stem cells were used as the non-cancer control [8]. While the A549 cell line is derived from lung adenocarcinoma, the ELEP represent a population of immature alveolar type II epithelia.

Figure 1. Illustrative representation of the biological activity testing of the presented ornithine peptidomimetic on the A549 cancer cell line.

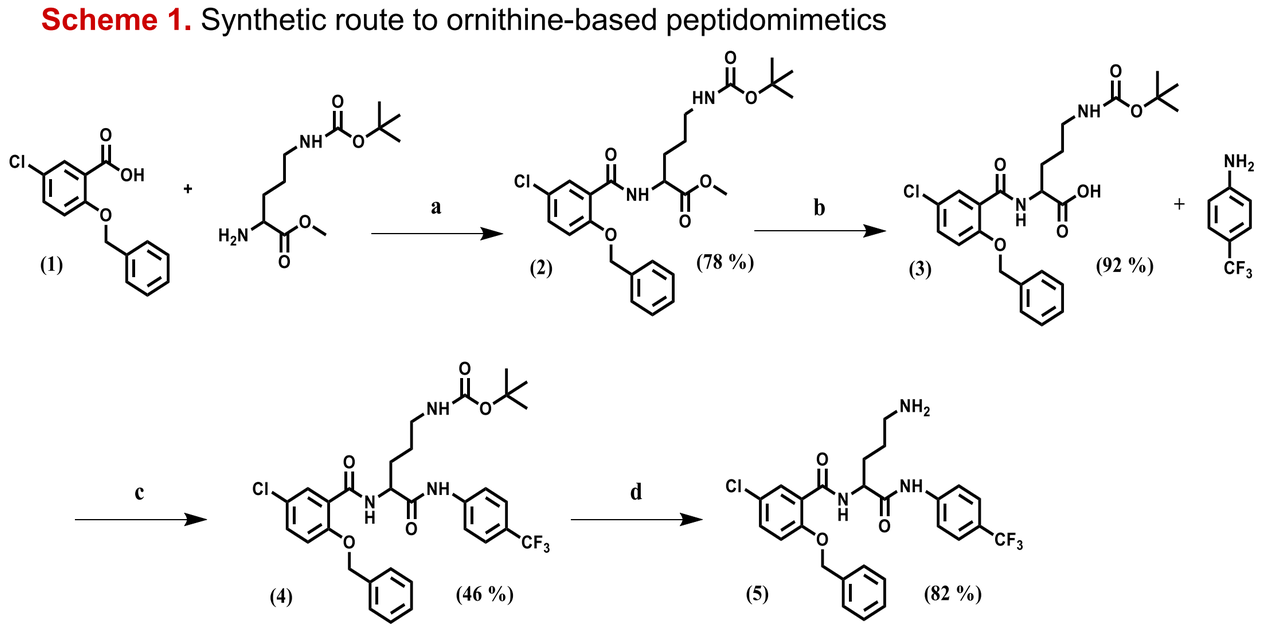
Table 1. Anticancer activity of ornithine-based peptidomimetics and their derivatives

Code	Molecules	IC50 [μM]	
		A549	ELEP
(1)		>38.1	-
(2)		**1.5**	-
(3)		>21	-
(4)		**>1.6**	-
(5)		**1.0**	**1.6**

RESULTS & DISCUSSION

From a synthetic perspective, the peptidomimetic scaffold was synthesized *via* Steglich amidation, and the side chain was modified. A series of novel intermediates and final ornithine-derived peptidomimetic were synthesized following a four-step synthetic route (**Scheme 1**), each of which was repeatedly verified.

Scheme 1. Synthetic route to ornithine-based peptidomimetics



a) EDCI.HCl, HOBt, DCM, RT, 1,5h; b) LiOH, H_2O:1,4-dioxan (1:3), 50 °C, 1h; c) EDCI.HCl, HOBt, TEA, DCM, RT, 16h; d) TFA (80 ekv.), DCM, RT, 2,5h

The synthesis commenced from *O*-benzyl-protected 5-chlorosalicylic acid **(1)**. The corresponding methyl ester **(2)** was obtained *via* Steglich amidation, followed by basic hydrolysis to yield the carboxylic acid intermediate **(3)**. Subsequent Steglich amidation with 4-(trifluoromethyl)aniline provided intermediate **(4)**, and final Boc deprotection afforded the target ornithine-based peptidomimetic **(5)**.

METHOD

All compounds were fully characterized by means of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, HRMS, and elemental analysis. The proposed synthetic route was consistently validated, and the compounds were obtained in a quality suitable for biological testing. A549 cells were cultured in high glucose (4.5 g/L) Dulbecco's Modified Eagle Medium (DMEM) enriched with 10% fetal calf serum (FCS), 50 U/mL penicillin G, and 50 mg/mL streptomycin sulfate at 37°C in a humidified atmosphere with 5% CO_2. Cell viability was measured using MTT assay as described elsewhere [9].

CONCLUSION

In this study, short ornithine-derived derivatives with potential biological activity against the A549 cell line were prepared. The anticancer activity of the synthesized compounds was determined *in vitro* against the A549 cell line, and the activity was confirmed for compounds **(2)**, **(4)** and **(5)**. However, compound **(5)** exhibits high toxicity against ELEP cells, which are commonly used as a standard model of healthy cells. For these reasons, compound **(2)** appears to be more promising for further study.

REFERENCES

[1] Lee, Y. S. *Biomolecules* **2022**, 12 (9), 1241.
[2] Jorda, R.; Imramovský, A.; *et al*. *Eur. J. Med. Chem.* **2017**, 135, 142–158.
[3] Jorda, R.; Imramovský, A.; *et al*. *Eur. J. Med. Chem.* **2020**, 188, 112036.
[4] Jorda, R.; Imramovský, A.; *et al. Bioorg. Chem.* **2021**, 115, 105228.
[5] Baldassarre, L.; *et al. J. Pept. Sci.* **2012**, 18 (9), 567–578.
[6] Nitsche, C.; *et al. J. Med. Chem.* **2017**, 60 (1), 511–516.
[7] Colombo, R.; *et al. J. Med. Chem*. **2012**, 55 (23), 10460–10474.
[8] Kotasová, H.; Vaňhara, P.; *et al. Tissue Eng. Regen. Med.* **2022**, 19(5):1033-1050.
[9] Moráň, L.; Vaňhara, P.; *et al. Metallomics* **2019**, 11(9):1481-1489.