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Anticancer *Vinca* Hybrids: An Overview

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1. Abstract

The research field of our research group is the synthesis and investigation of hybrid molecules with anticancer effects. One of these components is a *Vinca* alkaloid, which was coupled with various pharmacophores.

2. Introduction

Vinblastine (**1**) and vincristine (**2**) are well-known anticancer molecules [1] used in chemotherapy, as very effective agents, however, having some serious side effects [2]. So thus, in most cases, vinblastine is administered in a mixture (cocktail). Vinblastine is a dimeric alkaloid consisting of two components, vindoline (red structure) and catharanthine (black structure), which are ineffective by themselves (Figure 1). However, **vindoline**, when derivatized in various ways, shows significant antiproliferative activity [3, 4].

Molecular hybridization [5, 6] means two distinct pharmacophores which coupled covalently with or without linkers, allowing a non-rigid connection between the structures and providing beneficial changes in the pharmacological effects.x

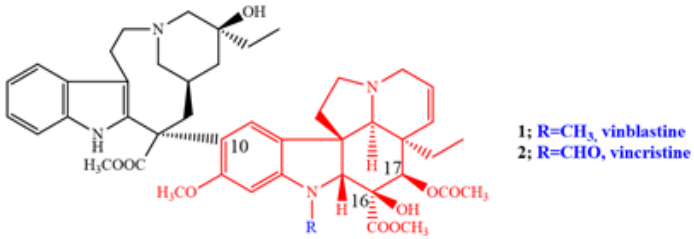

Figure 1: The structure of vinblastine (**1**) and vincristine (**2**).

3. Results and Discussion

First vinblastine (**1**) was coupled with tryptophan methyl ester at position 16, while the 17-OH was desacetylated. Then the molecule was coupled with octaarginine carrier peptide chain resulting in the two tryptophan epimers separated. The antiproliferative activity of the compounds was investigated on HL-60 leukemia and HeLa cells. The activities of conjugates (IC_{50}:1-1.3 μ*M*) were comparable with those of vinblastine sulfate control (IC_{50}: 1.2 μ*M*), furthermore they were effective also on resistant cells [7].

In the following, the **vindoline** monomer analogue alone was investigated. On cell lines HL-60, MDA-MB-231 (IC_{50}: 10-15.1 μ*M*), and MCF-7 (IC_{50}: 5.1-6.4 μ*M*) the effect of the two epimers was almost the same, on C26 and P388 tumor cell lines the epimer (*S*) proved to be more effective. The effect of conjugates on tumor growth was studied *in vivo* on mice by using P388 and C26 cells. Epimers showed remarkable activity on several models [8].

Based on the above results, we developed a number of vindoline hybrids (**3**) taking into account the known hybrid model (Figure 2).

So thus, vindoline was coupled with (D)- and (L)-tryptophan methyl esters in 10 and 17 positions *via* different linkers resulted in hybrids [9] to be more effective than vinblastine on SiHa cells (IC_{50}: 6.0 μ*M*). *Vinca* hybrids with the known (substituted) benzyl-1,2,3 -triazole pharmacophores were, however, ineffective [9].

Similarly, vindoline hybrids with 5α-dihydrotestosterone and 19-nortestosterone showed the highest cell number decreasing activity on COLO 205, SK-MEL-2, and SKMEL-5 cells [10].

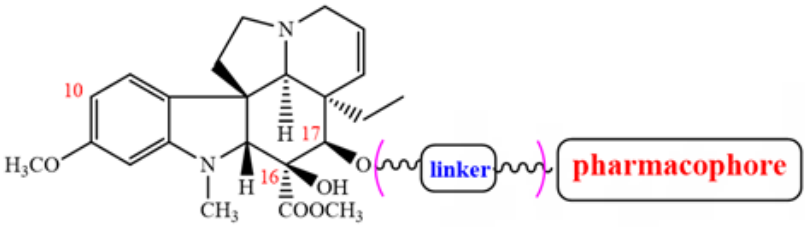

Figure 2: Representative structure of vindoline hybrids (**3**).

Triphenylphosphine-containing hybrids [11, 12] are very effective on colon, melanoma, ovarian, and breast cancer (GI_{50}<0.5 μ*M*), and one of the compounds has an outstanding activity (GI_{50}=0.07 μ*M*) on cell line HOP-92.

A special group of hybrids formed with flavones [13] in the 10 and/or 17-position of vindoline, across the 7-hydroxy group of chrysin with or without spacer. One of the compounds proved to be effective: GI_{50}<1.5 μ*M* on cell lines HOP-92, SNB-75, LOX IMVI, A498, CAKI-1, PC-3, and MCF7.

4. Conclusion

Considering the results presented, the synthesis and testing of hybrids based on *Vinca* alkaloids seem to be far more important. Further toxicity and *in vivo* investigations can decide the future course of the hybrid project.

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