EVALUATION OF CYTOTOXIC POTENTIAL OF N-ACYLHIDRAZONES DERIVATES AGAINST HUMAN CANCER CELL LINES

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Abstract

LASSBio-1920 is ananomolar cytotoxic agent against HL-60, OVCAR-8 and HCT-8, with moderate activity on MDR cancer cell line LUCENA.

Introduction

Cancer is the second most common cause of death in the USA. Among the known classes of anticancer agents, the microtubule-targeted antimitotic drugs are considered to be one of the most important. LASSBio-1586, designed as a new analogue of combretastatin A-4 (CA4), emerged as a simple antitumor drug candidate, which was capable of inhibit microtubule polymerization and showed a broad *in vitro* and *in vivo* cytotoxicprofile[1]. In this study, several newLASSBio-1586 analogueswere evaluated for their activity against human tumor cell lines.

Results and Discussion

The compounds have been evaluated using MTT cell proliferation assay. Cells lines used were: HL-60 (leukemia-human), OVCAR-8 (ovary-human), HCT8 (colon-human) and LUCENA (MDR-leukemia-human). We also determined the cytotoxic activity against human lymphocytes.

The results indicated thatcytotoxic activity against the tumor cell lines is increased with the presence of more lipophilic aromatic substituents linked to imine subunit of the *N*-acylhydrazone framework (Table 1). Contribution of trimethoxyl group to cytotoxic activity was initially evaluated removing one methoxyl group from LASSBio-1586. The resulting compound (i.e. LASSBio-1770), having the 3,5-dimethoxyphenyl group instead of 3,4,5-trimethoxyphenyl subunit presented in CA4 and LASSBio-1586, was significantly less cytotoxic. Based on that, we decided to explore different isostericaromatic substituents on *N*-acyl hydrazone imine moiety maintaining the 3,4,5-trimethoxyphenyl groups. Among the evaluated compounds, LASSBio-1920can be highlighted, with cytotoxic potency in nanomolar range (Table 1). This compound was demonstrated to be a tubulin polymerization inhibitor and was selected to be evaluated on MDR tumor cell line LUCENA. In this cell, this compound showed a modest IC_{50} of 80uM.

Table 1. Cytotoxic potency of LASSBio-1586 and CA4 analogues against tumor cell lines, using MTT assay.

Compound	HL-60 IC_{50} (uM) CI	OVCAR-8 IC_{50}(uM) CI	HCT-8 IC_{50}(uM) CI	Lymphocytes IC_{50}(uM) CI
LASSBio 1914	0.0038 0.00078-0.101868	0.107 0.0560-0.2045	0.0143 0.0047-0.04326	0.015 0.003 – 0.07
LASSBio 1917	0.0871 0.059-0.1270	1.3511 0.7649-2.388	1.4398 0.9126-2.2719	1.35 1.00 - 1.83
LASSBio 1918	2.1531 1.8569-2.4863	11.86 7.5674-18.6052	11.63 9.4340-14.3439	5.21 3.79 – 7.15
LASSBio 1919	0.1941 0.1528-0.2466	0.6787 0.2856-1.1985	0.9309 0.5979-1.4494	0.517 0.44 – 0.60
LASSBio 1920	**0.00075 0.00028-0.0020**	**0.0082 0.0011-0.059**	**0.01149 0.0044-0.0298**	**0.14 0.060 – 0.35**
LASSBio 1770	1.0221 0.7685-1.3594	2.0252 1.7934-2.2865	3.3287 2.2918-4.8362	4.38 3.38 – 5.68
CA-4	0.0021	0.00037	0.0053	0.0032
LASSBio 1586	0.29	0.29	0.45	1.34

Conclusion

LASSBio-1920 is a tubulin polymerization inhibitor, with potent cytotoxic activity against HL-60, OVCAR-8 and HCT-8. However, this compound was significantly less potent against MDR cell LUCENA.

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[1]AMARAL, D. N. et al., Docking, Synthesis and Antiproliferative Activity of N-Acylhydrazone Derivatives Designed as Combretastatin A4 Analogues. Plos One, v. 9, 2014.