Cemtirestat disulfide
a new prodrug of an aldo-keto reductases inhibitor

SUMMARY

Cemtirestat has been designed and patented as a highly efficient and selective inhibitor of aldose reductase with antioxidant properties. Although cemtirestat exhibits effective inhibition of aldo-keto reductases AKR1B1 and AKR1B10, it would be advantageous to improve its pharmacokinetic properties when administered orally and parenterally.
Cemtirestat disulfide was synthesized and tested to obtain a prodrug of the effective aldose reductase inhibitor cemtirestat. Given the key role of aldo-keto reductases AKR1B1 and AKR1B10 in the etiology of several types of cancer associated with chronic inflammation, it is assumed that the release of cemtirestat within tumor cells by reduction of its prodrug cemtirestat disulfide would increase the efficiency and especially the selectivity of this drug.

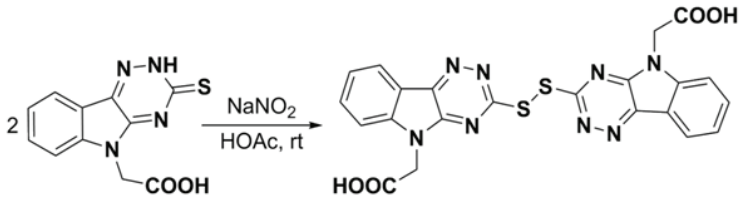
COMPETITIVE ADVANTAGE

- targeted distribution of effective drug into cancer cells, which can lead to higher efficiency and reduced side effects (compared to cemtirestat);
- expected higher efficiency also with respect to the symmetry of cemtirestat disulfide and the provision of two molecules of effective AR inhibitor (cemtirestat) at once;
- increased selectivity of action, thanks to the effective conversion of the prodrug to cemtirestat bound to the naturally increased reducing environment of tumors;
- expected better absorbability of cemtirestat disulfide in the acidic environment of tumors (compared to cemtirestat), thanks to its higher lipophilicity.

INDUSTRIAL APPLICABILITY

- in the field of treatment of cancer originating in chronic inflammation, namely cancer of colon, lung, breast, liver, prostate, pancreas, endometrium and cervix;
- for the treatment of cancer as an adjuvant therapeutic in combination with clinically used chemotherapeutics that are substrates of aldo-keto reductases.

PREPARATION



cemtirestat — cemtirestat disulfide

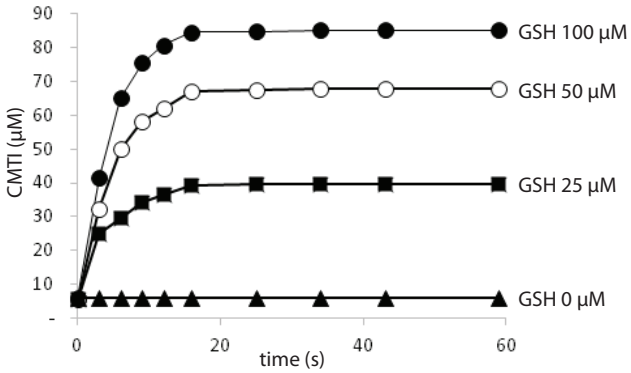
ALDOSE REDUCTASE INHIBITION

Added GSH (μM)	0	5	10	20	40	100	1000	5000
Inhibition I (%)	< 1%	<1%	8,9 ±0,6	12,4 ±1,4	16,1 ±6,9	72,6 ±9,1	94,0 ±1,6	91,1 ±1,5

The natural content of GSH in the used ALR2 preparations was < 0,1 nmol / ml. Cemtirestat disulfide was used in the experiment at a concentration of 100 μM. Enzyme activity was measured 2 min after the addition of GSH to the reaction mixture.

CLEAVAGE KINETICS

Cemtirestat disulfide (50 μM) cleavage kinetics due to increasing concentrations of GSH to form cemtirestat



STAGE OF PROTECTION AND DEVELOPMENT

- priority SK patent application PP 50074-2020;
- TRL 3 – experimental proof of concept.

THE INVENTORS ARE LOOKING FOR AN INDUSTRIAL PARTNER FOR LICENSING THE TECHNOLOGY.

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