Chemosensitizing activity of histone deacetylases inhibitory cyclic hydroxamic acids for combination chemotherapy of lymphatic leukemia

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Background: Anti-tumor effect of hydroxamic acid derivatives is largely connected with its properties as efficient inhibitors of histone deacetylases, and other metalloenzymes involved in carcinogenesis. Objective: The work was aimed to (i) determine the anti-tumor and chemosensitizing activity of the novel racemic spirocyclic hydroxamic acids using experimental drug sensitive leukemia P388 of mice, and (ii) determine the structure-activity relationships as metal chelating and HDAC inhibitory agents. Method: Outbreed male rat of 200-220 g weights were used in biochemical experiments. In vivo experiments were performed using the BDF1 hybrid male mice of 22-24 g weight. Lipid peroxidation, Fe (II) -chelating activity, HDAC fluorescent activity, anti-tumor and anti-metastatic activity, acute toxicity techniques were used in this study. Results: Chemosensitizing properties of water soluble cyclic hydroxamic acids (CHA) are evaluated using in vitro activities and in vivo

methods and found significant results. These compounds possess iron (II) chelating properties, and slightly inhibit lipid peroxidation. CHA prepared from triacetonamine (1a-e) are more effective Fe (II) ions cheaters, as compared to CHA prepared from 1- methylpiperidone (2a-e). The histone deacetylase (HDAC) inhibitory activity, lipophilicity and acute toxicity were influenced by the length amino acids (size) (Glycine<Alanine<Valine<Leucine <Phenylalanine). All compounds bearing spiro-N-methylpiperidine ring (2a-e) are non-toxic up to 1250 mg/kg dose, while compounds bearing spiro-tetramethylpiperidine ring (1a-e) exhibit moderate toxicity which increases with increasing lipophility, but not excite at 400 mg/kg. Conclusion: It was shown that the use of combination of non-toxic doses of cisplatin (cPt) or cyclophosphamide with CHA in most cases result in the appearance of a considerable anti-tumor effect of cytostatics. The highest chemosensitizing activity with respect to leukemia ?388 is demonstrated by the CHA derivatives of Valine 1c or 2c.

Chemosensitizing property

Combination chemotherapy

HDAC inhibitory activity

Histone deacetylases

Hydroxamic acid

Lymphatic leukemia

cyclophosphamide

ferrozine

histone deacetylase inhibitor

hydroxamic acid

trichostatin A

antineoplastic agent

histone deacetylase inhibitor

hydroxamic acid

acute toxicity

animal experiment

antineoplastic activity

Article

chemosensitivity

controlled study

drug structure

drug therapy

iron chelation

LD50

lipid peroxidation

lipophilicity

lymphatic leukemia

male

metastasis inhibition

nonhuman

oxidative stress

rat

animal

chemistry

HeLa cell line

human

lymphatic leukemia

metabolism

mouse

pathology

Animals

Antineoplastic Combined Chemotherapy Protocols

HeLa Cells

Histone Deacetylase Inhibitors

Humans

Hydroxamic Acids

Leukemia, Lymphoid

Male

Mice

Rats