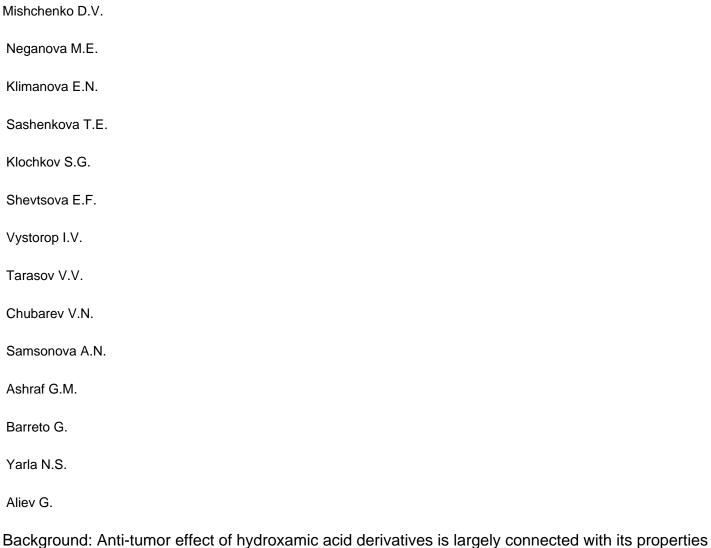
Chemosensitizing activity of histone deacetylases inhibitory cyclic hydroxamic acids for combination chemotherapy of lymphatic leukemia



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. © 2018 Bentham Science Publishers.

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