ISSN 3009-3848
ISSNe 3009-383X

Oncology Insights

Official Journal of the Serbian Association for Cancer Research

SDCR

Year 2023/No. 1

ISSN 3009-3848
ISSNe 3009-383X

ONCOLOGY INSIGHTS

Official Journal of
the Serbian Association for Cancer Research

Belgrade, Serbia
October, 2023

ONCOLOGY INSIGHTS
Official Journal of the Serbian Association for Cancer Research
Publishing annually

Publisher
Serbian Association for Cancer Research
Belgrade, Serbia

Printed by:
Connect Online Studio
Ćirila i Metodija 2a
Belgrade, Serbia

CIP - Каталогизација у публикацији
Народна библиотека Србије, Београд

616-006-08

ONCOLOGY Insights : official Journal of the Serbian Associaton for Cancer Research / editor in chief Milena Čavić. - [Štampano izd.]. - 2023, no. 1- . - Belgrade : Serbian Associaton for Cancer Research, 2023- (Belgrade : Connect Online Studio). - 30 cm

Godišnje. - Drugo izdanje na drugom medijumu:
Oncology Insights (Online) = ISSN 3009-383X
ISSN 3009-3848 = Oncology Insights (Štampano izd.)
COBISS.SR-ID 125366281

INVITED LECTURES

L01

Discovery of novel HDAC inhibitors for therapy of triple-negative breast cancer – preclinical study

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Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer that has poor survival rates due to the absence of specific molecular markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). In the era of precision oncology, it is recognized that an imbalance in post-translational modifications of histones, such as histone lysine acetylation and deacetylation, is closely linked to tumor initiation and progression. Two groups of enzymes control the reversible nature of histone post-translational acetylation: histone acetyltransferases (HATs) and histone deacetylases (HDACs). Isoform-specific targeting of HDACs is considered a rational strategy to develop safe anticancer therapeutics compared to non-selective HDAC inhibitors. However, non-selective HDAC inhibitors have been more extensively studied in clinical trials. This work presents the design and discovery of potent HDAC inhibitors that selectively target HDAC6 isozyme, using 1-benzhydryl piperazine as a surface recognition group with different hydrocarbon linkers. Through in vitro screening, two HDAC6-selective inhibitors with nanomolar IC50 values and two non-selective HDAC inhibitors were identified. Structure-based molecular modelling was utilized to investigate the impact of linker chemistry on the potency of synthesized inhibitors against HDAC6. The anti-cancer, anti-migratory, and anti-invasive activities of these compounds were evaluated using breast cancer cell lines (MDA-MB-231 and MCF-7). Experiments on a zebrafish MDA-MB-231 xenograft model demonstrated that a novel non-selective HDAC inhibitor (compound 8b) with a seven-carbon-atom linker exhibited potent effects against tumor growth, metastasis, and angiogenesis at low micromolar concentrations.
Keywords: anticancer drug, breast cancer, histone deacetylases,hydroxamic acid

L02

Estrogen Receptor Beta promoter methylation as a possible biomarker in breast cancer

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Since the estrogen receptor alpha (ERα), together with the progesterone receptor (PR) and the herceptin receptor 2 (HER-2), are the dominant factors determining the groups of breast cancer (BC) patients, breast cancer treatment depends on the presence or absence of these three molecules. Approximately 70% of patients receive hormone treatment targeting the estrogen receptor alfa, with tamoxifen (selective oestrogen receptor modulator) being the first choice as it inhibits further proliferation of cancer cells. However, 30% of patients do not respond to existing hormone therapy, raising the question of new targets and treatment options. Non-responders include patients who have acquired resistance to standard treatment and triple-negative breast cancer patients (TNBC), characterized by the absence of ERα, PR and HER-2. One of the unexplored potentials for treatment is a protein homologue of ERα, estrogen receptor beta (ERβ), as many studies show ERβ expression in ERα-negative patients. The estrogen receptors alpha and beta belong to the superfamily of nuclear receptors, and their dominant ligand is estrogen. When estrogen binds to estrogen receptors, they form dimers (homo or heterodimers) and bind ERE sequences of target genes (estrogen receptor elements). In a heterodimeric state, ERβ can inhibit ERα transactivation and thus influence the signalling pathways. ERα and ERβ are encoded by highly homologous genes (ESR1 and ESR2), resulting in two highly homologous