BENZO[D]ISOTHIAZOL-3(2H)-ONE-1,1-DIOXIDE CORE DERIVATIVES AND THEIR USE IN THE TREATMENT OF CANCER

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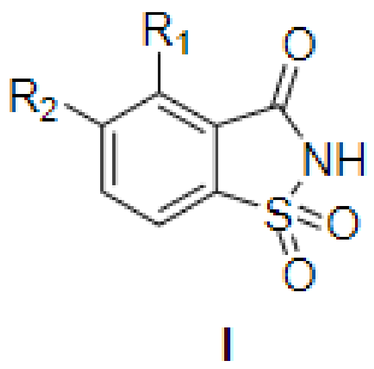
Invention

The present invention relates to novel benzo[d]isothiazolic-3(2H)-one-1,1-dioxide core compounds able to **effectively and selectively inhibiting the IX and XII isoforms of the enzyme carbonic anhydrase (CA)**, which are predominantly **expressed in hypoxic and metastatic tumors**. The invention also relates to synthetic processes for the preparation of novel benzo[d]isothiazolic-3(2H)-one-1,1-dioxide core derivatives, as well as their use in obtaining pharmaceutical compositions for use in the treatment of hypoxic and metastatic tumors.

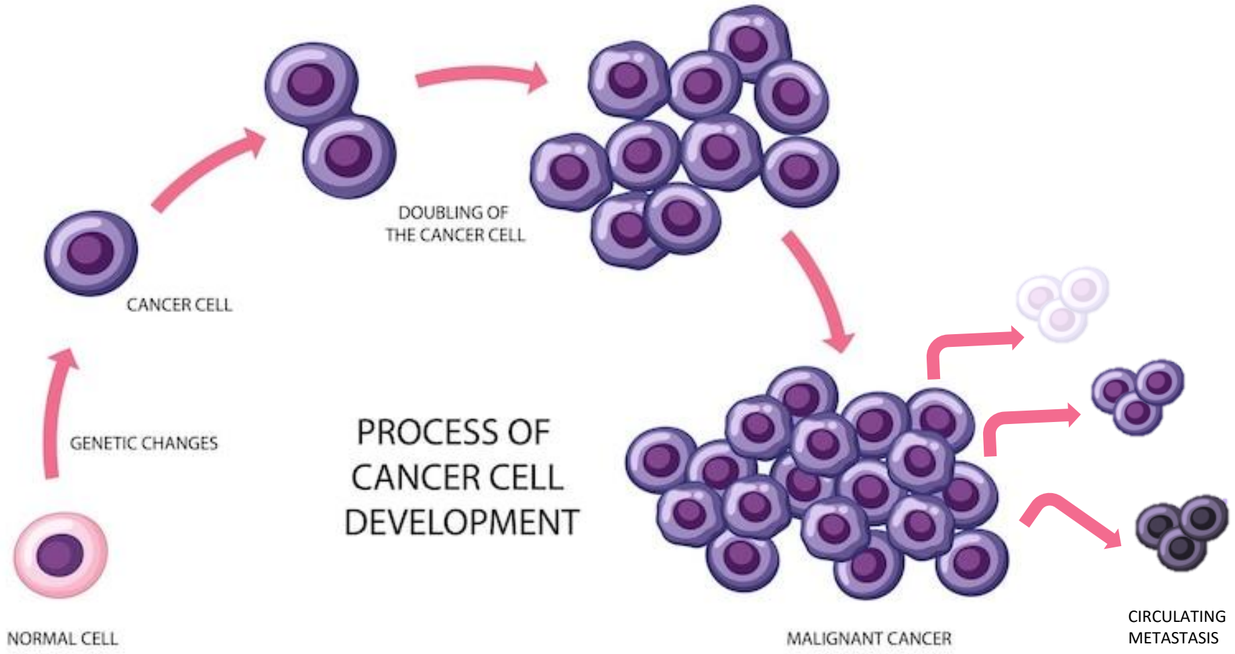
The presence of areas of hypoxia, characterized by low pH and glucose values, is a common feature of most malignant solid tumors with poor prognosis. Hypoxia creates a particular microenvironment capable of influencing gene expression, phenotype, and functional responses of tumor cells, which thus acquire greater aggressiveness, increasing their metastatic potential and being more resistant to radio- and chemotherapy. The main molecular response to hypoxia is the accumulation of HIF-1 (Hypoxia Inducible Factor-1), a heterodimeric transcription factor that activates target genes involved in cellular adaptation and neoplastic progression. These include, in particular, those encoding for isoforms IX and XII of the carbonic anhydrase enzyme (CA9 and CA12), which promote proliferation, survival, and invasiveness of cancer cells. Therefore, specific inhibition of CA9 and CA12, which are predominantly expressed in tumor tissue and generally absent in healthy tissue, represents a valuable therapeutic approach for targeted and selective treatment of hypoxic and metastatic tumors.

Drawings & pictures



I

General formula **I**
of a benzo[d]isothiazol-3(2h)-one-
1,1-dioxide scaffold



Industrial applications

To date, numerous heterocyclic derivatives, mainly sulfonamide and sulfamic, are known to effectively inhibit different isoforms of carbonic anhydrase (CA). Some of them are commonly used in therapy as diuretic and anti-glaucoma drugs but, as broad-spectrum carbonic anhydrase inhibitors, they **lack selectivity** of action against the target isoforms, CA9 and CA12, and cannot be usefully employed as anti-tumor drugs because of **undesirable effects on healthy tissues**.

In contrast, the patented **benzo[d]isothiazole derivatives show specificity of action toward the enzymes** of interest, offering a novel and effective therapeutic opportunity for the treatment of hypoxic and metastatic tumors, when administered alone or in combination with chemotherapeutics or other target therapies.

Possible developments

The synthesized benzo[d]isothiazole derivatives were identified and characterized by physicochemical and spectroscopic data. Their functional efficacy was evaluated by *in vitro* enzyme inhibition assays, conducted on the isolated target enzymes. All tested compounds were shown to inhibit CA9 and CA12, exhibiting **IC_{50} values in the nanomolar range**. In addition, they were **selective against carbonic anhydrase isoforms I, II and VII**. The efficacy of the novel products was further investigated by means of a pre-clinical cell pharmacology study, carried out using the colon adenocarcinoma cell line HT29, which overexpresses CA9 under normoxic and hypoxic conditions. One of the new compounds significantly inhibited HT29 cell proliferation under hypoxic conditions compared to the control (cells treated with vehicle alone and under hypoxia) in a concentration-dependent manner.

The inventors are interested to undertake future collaborations to increase the technological readiness level of the patented invention and expand innovative drug opportunities for target therapy development, considering licensing or transferring possibilities versus interested companies.

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