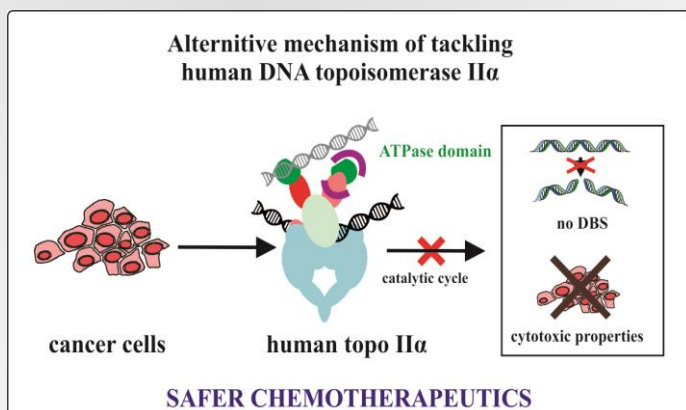


SUBSTITUTED BITHIAZOLES FOR THE TREATMENT OF CANCER



Cancer is one of the most widespread diseases and the second leading cause of death, with WHO reporting almost 10 million deaths annually. Human DNA topoisomerase II α is a well-known and validated anticancer target for chemotherapy, catalyzing topological changes of the DNA molecule.

Current topoisomerase II inhibitors in clinical practice, topo II poisons, suffer from several side effects such as cardiotoxicity and induction of secondary malignancies. This is attributed to the induction of double strand breaks (DBS) in the DNA molecule.

Additionally emerging resistance to existing chemotherapeutics further fuels the need to develop new anticancer drugs. Our goal is to increase the safety profile of this proven chemotherapy approach and discover effective chemotherapeutic agents that inhibit the human DNA topoisomerase II α . To this end, we take advantage of an alternative inhibition mechanism of its complex catalytic cycle and develop molecules that bind to the ATP pocket thus avoiding the DNA damage and lowering the chances of side effects associated with current topo II drugs.

TYPE OF COOPERATION

Technology licensing opportunities

INTELLECTUAL PROPERTY

LU101453

DEVELOPED BY

Laboratory of Computational
Biochemistry and Drug Design
Theory Department

CONTACT

Knowledge Transfer Office
P: 00386 1 4760 529
E: knowledge.transfer@ki.si

MORE INFORMATION ABOUT THE INVENTION



Technology

Using computer-aided drug design we discovered a new class of substituted bithiazoles, acting as catalytic inhibitors of human DNA topoisomerase II α . Through extensive biochemical evaluation we then determined the mechanism of action and level of activity. Bithiazoles bind to the topo II α ATPase domain and inhibit the enzyme via an ATP competitive mechanism. *In vitro*, the investigated compounds inhibit the human topoisomerase II α in a superior fashion compared to some of the clinical topo II poisons. On a cellular level they exhibit cytotoxicity comparable to topo II agents used in chemotherapy but show no induction of DNA double-strand breaks (DBS). Additional assays reveal they reduce the cell proliferation and stop the cell cycle mainly in the G1 phase, all in accordance with a mechanism of action distinct from topo II poisons.

Main advantages

- Potential novel chemotherapeutics with comparable anticancer activity as topo II poisons
- Compounds with a promise of an improved safety profile in chemotherapy by mechanistically avoiding topo II-related side effects
- Compounds that can be applied as a standalone chemotherapy or in combination with several other established anticancer drugs

Key words

oncology, cancer, chemotherapy, anticancer agents, human DNA topoisomerase II α , catalytic inhibitors