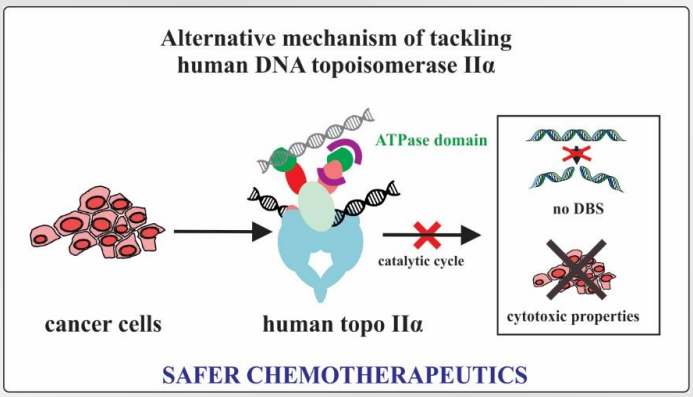
NATIONAL INSTITUTE OF CHEMISTRY

RESEARCH DOMAINS: Life Sciences, Medicine, Drug discovery

INDUSTRIES: Pharmaceutical industry

SUBSTITUTED BITHIAZOLES FOR SAFER COMBINATIONAL CHEMOTHERAPY TREATMENTS



Cancer is one of the most widespread diseases and the second leading cause of death, with WHO reporting almost 10 million deaths annually. The human DNA topoisomerase IIα 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 permanent double strand breaks (DSB) 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 IIα and that could be efficiently incorporated into existing chemotherapy regimens. 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 topo II poisons.

TYPE OF COOPERATION
Technology licensing opportunities, R&D cooperation

INTELLECTUAL PROPERTY
EP3811940 (A1)

DEVELOPED BY
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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 IIα. Through extensive biochemical evaluation we then determined the mechanism of action and level of activity. Bithiazoles bind to the topo IIα ATPase domain and inhibit the enzyme via an ATP competitive mechanism. *In vitro*, the investigated compounds inhibit the human topoisomerase IIα in a superior fashion compared to some of the clinical topo II poisons. On a cellular level they exhibit cytotoxicity on cancer cells comparable to topo II agents used in chemotherapy but show no induction of permanent DNA double-strand breaks (DSB). 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. Currently, we are beginning *in vivo* preclinical testing to obtain further information about their safety and efficacy.

Main advantages

- Potential novel chemotherapeutics with comparable anticancer activity to 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 easily be integrated into existing chemotherapy regimens with several other established anticancer drugs

Key words
oncology, cancer, chemotherapy, anticancer agents, human DNA topoisomerase IIα, catalytic inhibitors

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