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Profiling a multiactions folic acid-octapeptide conjugate to gain anticancer selectivity

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Abstract

Bio A rational design of lead compounds that takes into account their cellular internalization and paths to the targets increases the probability of success in the pharmacokinetic tests to be run in the following stages of lead optimization. In our approach we demonstrate how a computational and chemical-biological integrated approach may yield conjugates of drug leads with improved selectivity. Folic acid is present in human body and physiologically enter the cells through a few different transporters such as folate receptors and reduced folate carriers. These transporters are differentially expressed in normal and cancer cells, therefore characterizing sub-populations that may be subjected to personalized therapy. To take advantage of the mentioned cell specificities, we have designed and synthesized the conjugates of folic acid (FA) with two anticancer octapeptides with the goal of building molecular entities that, on one hand, would exploit the FA moiety to enter cancer cells through the folate receptor α (FRα) or other FA-based transporters and, on the other hand, would employ the peptidic moiety to inhibit intracellular human thymidylate synthase (hTS) by an unconventional mechanism that, not inducing over-expression of the enzyme, helps in avoiding the onset of drug resistance. In one single molecular entity we combine high value biological effects such as selective targeting, innovative on-target mechanism of action and drug resistance decreases. In our studies molecular modeling simulations have shown that, consistently with their difunctional nature, these conjugates feature a complex hTS inhibition mechanism, by binding at the monomer-monomer interface of this dimeric protein through their peptidic moieties. The two bioconjugates have shown cellular growth inhibition levels similar to those of known TS-targeted drugs and were also active towards cisplatin-resistant ovarian cancer cells that overexpress FR□Biological markers indicate their cellular mechanism of action to be different from that of classical TS inhibitors.

Biography

Maria Paola Costi has completed her PhD at the age of 29 years from the University of Modena and Reggio Emilia (UniMORE), Italy. She is Professor of Medicinal Chemistry and Biotechnology at UniMORE. She has over 150 publications that have been cited over 2200 (Scopus)/2670 (G+) times, and her publication H-index is 28 (G+)/ 25(Scopus) and has been serving as an editorial board member of ACS Medicinal Chemistry Letters, Mini Reviews in medicinal Chemistry (MRMC), Current Medicinal Chemistry, Arkivoc, others.

Publications

1. Comprehensive Mechanistic Analysis of Hits from High-Throughput and Docking Screens against β-Lactamase
2. Discovery of potent pteridine reductase inhibitors to guide antiparasite drug development
3. Discovery of highly potent acid ceramidase inhibitors with in vitro tumor chemosensitizing activity
4. Thymidylate synthase structure, function and implication in drug discovery
5. Structure-based discovery and in-parallel optimization of novel competitive inhibitors of thymidylate synthase
6. Optimizing cell permeation of an antibiotic resistance inhibitor for improved efficacy
7. Targeting Class A and C Serine beta-Lactamases with a Broad-Spectrum Boronic Acid Derivative
8. Combination of suboptimal doses of inhibitors targeting different domains of LtrMDR1 efficiently overcomes resistance of Leishmania spp. to miltefosine by inhibiting drug efflux
9. Structure-based studies on species-specific inhibition of thymidylate synthase
10. Homodimeric Enzymes as Drug Targets
11. Novel Approaches for Targeting Thymidylate Synthase To Overcome the Resistance and Toxicity of Anticancer Drugs
12. Inhibitor Specificity via Protein Dynamics
13. Structural study of phenyl boronic acid derivatives as AmpC beta-lactamase inhibitors

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