Lipophilic conjugates of methotrexate with short-chain alkylamino acids as DHFR inhibitors. Synthesis, biological evaluation, and molecular modeling

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"...Calculated apparent partition coefficient at pH 7.4 (Pallas software, Compudrug)…"

Abstract

Pursuing previous researches on lipophilic conjugates of methotrexate, aimed at over-crossing a form of transport resistance shown by some tumor cell lines toward the drug, a new series of derivatives is described in which the drug - and -carboxyl groups have been linked through amide bonds to short-chain -alkylamino acids (4–6 carbon atoms). A specific NMR study was performed to delineate the stereochemistry of the conjugates. The inhibitory activity of these compounds against the target enzyme, (bovine liver) dihydrofolate reductase, and a sensitive (CCRF-CEM) and a transport-resistant tumor cell subline (CEM-MTX) were assessed. The conjugates showed the ability of retaining the same inhibitory activity also against the resistant cell subline, against which the parent drug was much less active than against the wild one; the ,-bis(hexyl) derivative was the most active term of the series. Docking studies are in agreement with the proposed mode of interaction of these conjugates with the human DHFR.

Graphical Abstract

A new series of lipophilic ,-bis(amide) conjugates of the anticancer drug methotrexate (MTX) with short-chain 2-alkylamino acids (4–6 carbon atoms) was described.
The aim of these derivatives was to increase the uptake of the drug into transport-resistant tumor cell lines toward the uptake of MTX. The inhibitory activity of these compounds against the target enzyme, dihydrofolate reductase (DHFR), and a sensitive (CCRF-CEM) and a transport-resistant tumor cell subline (CEM-MTX) was

assessed. The ,-bis(hexyl) derivative was the most active term of the series, showing the ability of retaining the same inhibitory activity also against the resistant cell subline, against which the parent drug was much less active than against the wild one. Docking studies combined with a conformational NMR analysis of MTX conjugates in solution are in agreement with the experimental biological data and the proposed binding mode.

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