Synthesis and biological evaluation of α-methoxylated acetylenic fatty acids

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Abstract: The cytotoxicity, antimicrobial and parasiticidal properties of Δ^6 alkynoic fatty acids are well established. The activity of these fatty acids is associated with the chain length and the position of the triple bond.[1] It has been recently demonstrated that methoxylated acetylenic fatty acids display antiprotozoal and cytotoxic properties. An example is the (±)-2-methoxy-6-icosynoic acid, which displayed cytotoxicity against the human SH-SY5Y neuroblastoma cell line with a half maximal effective concentration (EC_{50}) of 23 ± 1 μM, and against the human adenocarcinoma cervix cell line (HeLa) with an EC_{50} = 26 ± 1 μM.[2] Moreover, the C_{17} methoxylated Δ^6 acetylenic and olefinic fatty acids display inhibitory activity against the leishmania DNA topoisomerase IB (*Ld*TopIB) enzyme, a validated target for the treatment of leishmaniasis.[3] In this work we present the synthesis of (±)-2-methoxy-6-hexadecynoic acid (2-OMe-6-HDA) and demonstrate that it displays cytotoxicity against the human A549 lung carcinoma cell line with an EC_{50}= 32± 8 μM; while the natural compound 6-hexadecynoic acid (6-HDA) displays an EC_{50}= 65± 7 μM against the same cell line. Herein we also demonstrate that the 6-HDA displays inhibitory activity towards *Ld*TopIB (EC_{50}=61±3 μM), but previous studies

have shown that the 2-methoxylated acetylenic and olefinic counterparts should present better *Ld*TopIB inhibition.[4] The total syntheses of 6-HDA, 2-OMe-6-HDA, and other analogs was achieved in 4 to 10 steps, with overall yields between 26% to 76%. We are still studying the bioactivity and biomedical applications of these unusual fatty acids.

References:

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