

Azacarbazole n-3 and n-6 polyunsaturated fatty acids ethyl esters nanoemulsion with enhanced efficacy against *Plasmodium falciparum*

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Streszczenie

Alternative therapies are necessary for the treatment of malaria due to emerging drug resistance. However, many promising antimalarial compounds have poor water solubility and suffer from the lack of suitable delivery systems, which seriously limits their activity. To address this problem, we synthesized a series of azacarbazoles that were evaluated for antimalarial activity against D10 (chloroquine-sensitive) and W2 (chloroquine-resistant) strains of *P. falciparum*. The most active compound, 9*H*-3-azacarbazole (**3**), was encapsulated in a novel o/w nanoemulsion consisting of ethyl esters of polyunsaturated fatty acids n-3 and n-6 obtained from flax oil as the oil phase, S_{mix} (Tween 80 and Transcutol HP) and water. This formulation was further analyzed using transmission electron microscopy, dynamic light scattering and *in vitro* and *in vivo* studies. It was shown that droplets of the **3**-loaded nanosystem were spherical, with satisfactory stability, without cytotoxicity towards fibroblasts and intestinal cell lines at concentrations corresponding to twice the IC₅₀ for *P. falciparum*. Moreover, the nanoemulsion with this type of oil phase was internalized by Caco-2 cells. Additionally, pharmacokinetics demonstrated rapid absorption of compound **3** (t_{max} = 5.0 min) after intragastric administration of **3**-encapsulated nanoemulsion at a dose of 0.02 mg/kg in mice, with penetration of compound **3** to deep compartments. The **3**-encapsulated nanoemulsion was found to be 2.8 and 4.2 times more effective in inhibiting the D10 and W2 strains of the parasite, respectively, compared to non-encapsulated **3**. Our findings support a role for novel o/w nanoemulsions as delivery vehicles for antimalarial drugs.

Słowa kluczowe

Azacarbazoles, Flax oil, n-3 and n-6 polyunsaturated fatty acids ethyl esters, Nanoemulsion, *P. falciparum*, Malaria

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