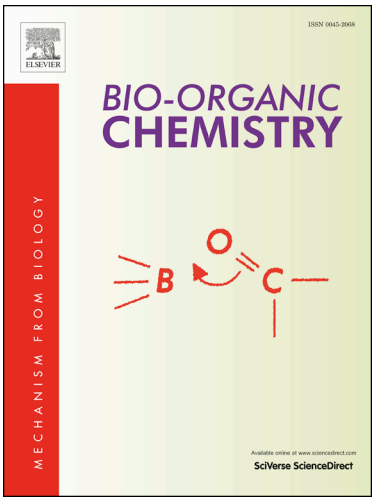

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Tarek Aboul-Fadl, Soliman A. Al-Hamad, Ehab A. Fouad

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Pharmacokinetic studies of naproxen amides of some amino acid esters with promising colorectal cancer chemopreventive activity

Tarek Aboul-Fadl[a,#,*], Soliman A. Al-Hamad[b], Ehab A. Fouad[c,•]

[a] Dept. Med. Chem, Faculty of Pharmacy, Assiut University, Assiut 71526 – Egypt.

[b] Dept. Pharm. Chem, College of Pharmacy, King Saud University, P.O. Box 2457 - Riyadh 11451 Saudi Arabia

[c] Dept. Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut 71526 – Egypt.

*Corresponding author.

E-mail address: fadl@aun.edu.eg

[#]Former Address: College of Pharmacy , King Saud University, P.O. Box 2457 - Riyadh 11451 Saudi Arabia

• Current Address: Department of Pharmaceutics, Almaarefa Colleges for Science and Technology, P.O Box 71666, Riyadh 11597, Saudi Arabia

Abstract

Naproxen (nap) is belonging to Non-steriodal anti-inflammatory drugs (NSAIDs) group of drugs that characterized by their free carboxylic group. The therapeutic activity of nap is usually accompanied by GI untoward side effects. Recently synthesized naproxen amides of some amino acid esters prodrugs to mask the free carboxylic group were reported. Those prodrugs showed a promising colorectal cancer chemopreventive activity. The current study aims to investigate the fate and hydrolysis of the prodrugs kinetically in different pH conditions, simulated gastric and intestinal fluids with pHs of 1.2, 5.5 and 7.4 *in vitro* at 37°C. The effect of enzymes on the hydrolysis of prodrugs was also studied through incubation of these prodrugs at 37°C in human plasma and rat liver homogenates. The pharmacokinetic parameters of selected prodrugs and the liberated nap were studied after oral and intraperitoneal administration in male wistar rats. The results showed the hydrolysis of naproxen amides of amino acid esters to nap through two steps first by degradation of the ester moiety to form the amide of nap with amino acid and the second was through the degradation of the amide link to liberate nap. The two reactions were followed and studied kinetically where K_1 and K_2 (rate constants of degradation) is reported. The hydrolysis of prodrugs was faster in liver homogenates than in plasma. The relative bioavailability of the liberated nap *in vivo* was higher in case of prodrug containing ethyl glycinate moiety than that occupied L-valine ethyl ester moiety. Each of nap. prodrugs containing ethyl glycinate and L-valine ethyl ester moieties appears promising in