Estimation of passive gastrointestinal absorption of novel thiourea derivatives of naproxen using PAMPA technique

Nikola Nedeljković [1], Miloš Nikolić [1], Jelena Bošković [2], Marina Vesović [1], Zorica Vujić [2], Vladimir Dobričić [2*]

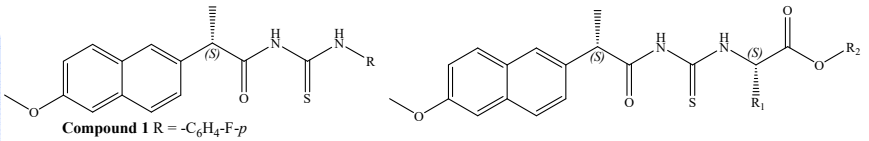
[1] *University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Pharmacy;*
[2] *Department of Pharmaceutical Chemistry, University of Belgrade – Faculty of Pharmacy, Belgrade, Serbia;*
**Correspondence: vladimir@pharmacy.bg.ac.rs*

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in the treatment of pain and inflammation and represent the most popular group of over-the-counter medications. Free carboxyl group of naproxen may induce its local erosive effect on the gastric mucosa. Masking of this functional group could be a promising strategy for the synthesis of new compounds that are more potent and less ulcerotoxic anti-inflammatory agents. The thiourea derivatives of naproxen showed pronounced anti-inflammatory activity in some previous studies. Thiourea moiety has been described as an important pharmacophore in a variety of pharmacologically active compounds such as anti-inflammatory, anti-cancer, and antimicrobial agents. Parallel artificial membrane permeability assay (PAMPA) is a screening tool for the estimation of drug permeability across various biological membrane. We evaluated passive gastrointestinal absorption of fourteen new thiourea derivatives of naproxen using PAMPA test.

Material and methods

Diffusion through artificial membranes that were composed of a mixture of hexadecane and hexane (the first PAMPA model) and of the solution of egg lecithin in dodecane (the second PAMPA model) was tested for the set of seven compounds (derivatives **2-7** and **11**) and parent drug naproxen. The starting solutions were prepared by dissolving tested compounds in a phosphate buffer (pH 5.5), with the addition of DMSO (1%) and TWEEN80 (0.2%). These solutions were transferred into the donor PAMPA plates (300 µl) in triplicates. The acceptor solution (phosphate buffer (pH 7.4) and the same percentage content of DMSO and TWEEN as in the starting solutions) was transferred into the acceptor PAMPA plate (300 µl). Concentrations of analyzed compounds in the starting solutions, as well as in the donor and acceptor solutions after incubation were determined using an HPLC method.



Compound 1 R = -C_6H_4-F-*p*
Compound 2 R = -C_6H_4-OCH_3-*p*
Compound 3 R = -C_6H_4-OCH_2CH_3-*p*
Compound 4 R = -C_6H_4-OCH_3-*m*
Compound 5 R = -C_6H_4-C(=O)CH_3-*p*
Compound 8 R = -C_6H_5
Compound 9 R = -C_6H_4-CH_3-*p*
Compound 10 R = -C_6H_4-CH_3-*o*
Compound 11 R = -C_6H_4-OCH_3-*o*
Compound 12 R = -C_6H_4-F-*o*

Compound 6 R_1 = -CH_2-C_6H_5; R_2 = -CH_2-CH_3
Compound 7 R_1 = -CH_2-(*N*-methyl-1*H*-indol-3-yl); R_2 = -CH_3
Compound 13 R_1 = -CH_2-C_6H_5; R_2 = -CH_3
Compound 14 R_1 = -CH_2-(1*H*-indol-3-yl); R_2 = -CH_3

Figure 1. Chemical structures of tested compounds

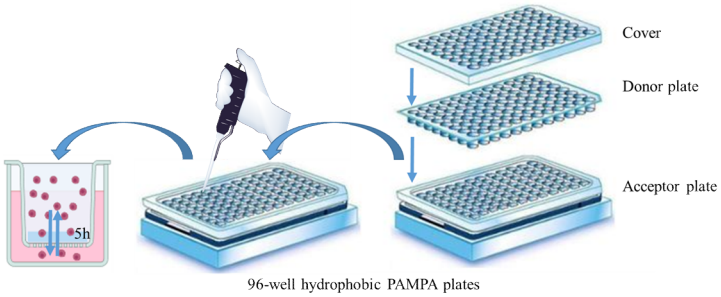


Figure 2. Schematic representation of the first PAMPA model's principle

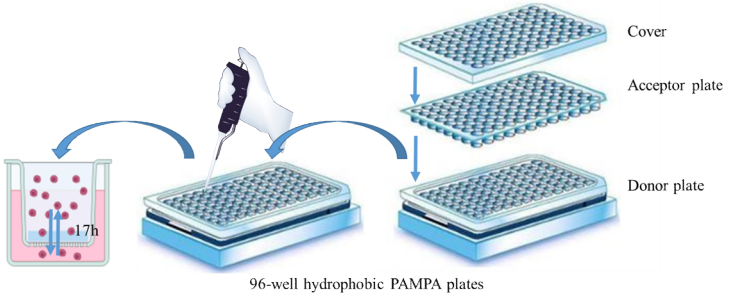


Figure 3. Schematic representation of the second PAMPA model's principle

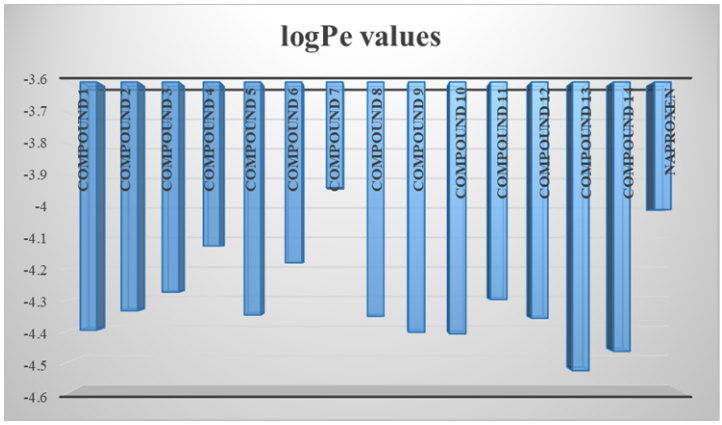


Figure 4. logPe values of tested compounds obtained using the first PAMPA model

Results

Based on the results obtained for the first seven tested compounds, the first PAMPA model was selected for the estimation of passive gastrointestinal absorption of the remaining seven compounds. The model with solution of egg lecithin in dodecane as an artificial membrane did not show any advantage compared to the first model, and requires a significantly longer period of time for its execution. Derivatives **13** and **14** showed the lowest permeability coefficients (logPe values were -4.53 and -4.4, respectively). On the other hand, the highest permeability was determined for derivative **7** (logPe = -3.94). The highest membrane retention was observed for compound **6** (34%) and compound **3** (24%). This could explain lower permeability of these compounds than expected based on their lipophilicity.

Conclusions

According to obtained results, it can be concluded that the lipophilicity of compounds significantly influences their absorption from the gastrointestinal tract. However, certain compounds that did not achieve the expected degree of permeability are subject to the phenomenon of retention in the membrane, which significantly slows down their absorption.