1st International Conference
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ICCBIKG 2021

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1st International Conference on
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BOOK OF PROCEEDINGS

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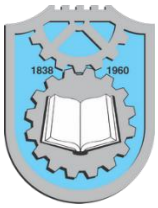

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IN SILICO PREDICTION OF PHARMACOKINETIC PROPERTIES AND DRUGLIKENESS OF NOVEL THIOUREA DERIVATIVES OF NAPROXEN

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Abstract

Masking the carboxyl group of naproxen with other functional groups may be a promising strategy to decrease its gastrointestinal toxicity. Thiourea moiety has been described as an important pharmacophore in a variety of pharmacologically active compounds, including anti-inflammatory, antiviral, anticancer, hypoglycemic and antimicrobial agents. Our research group has previously designed twenty novel thiourea derivatives of naproxen, containing amino acids (glycine, *L*-alanine, β-alanine, *L*-valine and *L*-phenylalanine - compounds **1**,**2**,**3**,**4** and **5**, respectively), their methyl (**6**-**10**) and ethyl esters (**11**-**15**), as well as aromatic amines (**16**-**20**). Pharmacokinetic properties and druglikeness of these compounds were predicted using SwissADME web tool (http://www.swissadme.ch/). Predicted pharmacokinetic properties include potential for gastrointestinal absorption, blood-brain barrier permeability, skin permeability, transport mediated by P-glycoproteins and enzyme inhibitory potential. Druglikeness was evaluated using Lipinski's, Ghose's, Veber's, Egan's and Muegge's rules, as well as on the basis of bioavailability score. All tested compounds had high-predicted gastrointestinal absorption and low blood-brain barrier permeability. Also, derivatives **2**, **4**, **7**, **9**, **10**, **12**, **14**, **15** and **18** were predicted to be substrates for P-glycoprotein. Derivatives with aromatic amines (**16**-**20**) showed inhibitory potential against all tested CYP isoforms. Derivative **19** had the highest, while derivative **13** demonstrated the lowest predicted skin permeability. Finally, derivatives **1**-**12**, except **5** and **10**, have druglike structures, since they obey to all imposed rules.

Key words: naproxen, thiourea derivatives, pharmacokinetic properties, druglikeness, SwissADME.

1. Introduction

Naproxen is one of the most used propionic acid derivatives in the treatment of pain, symptoms of arthritis and joint swelling. It is a non-selective cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitor and its use is associated with some gastrointestinal side effects caused by free carboxyl group. Masking of this group may be a promising strategy to decrease gastrointestinal toxicity [1]. The thiourea moiety is an important pharmacophore in a variety of pharmacologically active compounds, such as antiviral [2], anticancer [3], hypoglycemic [4], antimicrobial [5] and anti-inflammatory agents [6].

ADME (absorption, distribution, metabolism and excretion) properties play significant role in drug discovery. Early estimation of ADME in drug development phase reduces pharmacokinetics-related failure in the clinical phases [7]. The aim of this study was to estimate

ADME properties and druglikeness of newly designed thiourea derivatives of naproxen with potential biological activity using SwissADME predictor (http://www.swissadme.ch/).

2. Methods and Results

Compounds designed and tested in this study (**1-20,** Fig. 1) are thiourea derivatives of naproxen, containing amino acids glycine, *L*-alanine, β-alanine, *L*-valine and *L*-phenylalanine (**1-5**), their methyl (**6-10**) and ethyl (**11-15**) esters, as well as thiourea derivatives of naproxen containing aromatic amines (**16-20**). The ADME study was carried out using SwissADME predictor. SwissADME is freely available web tool used to predict physicochemical, pharmacokinetic properties and druglikeness of molecules based on their SMILES codes.

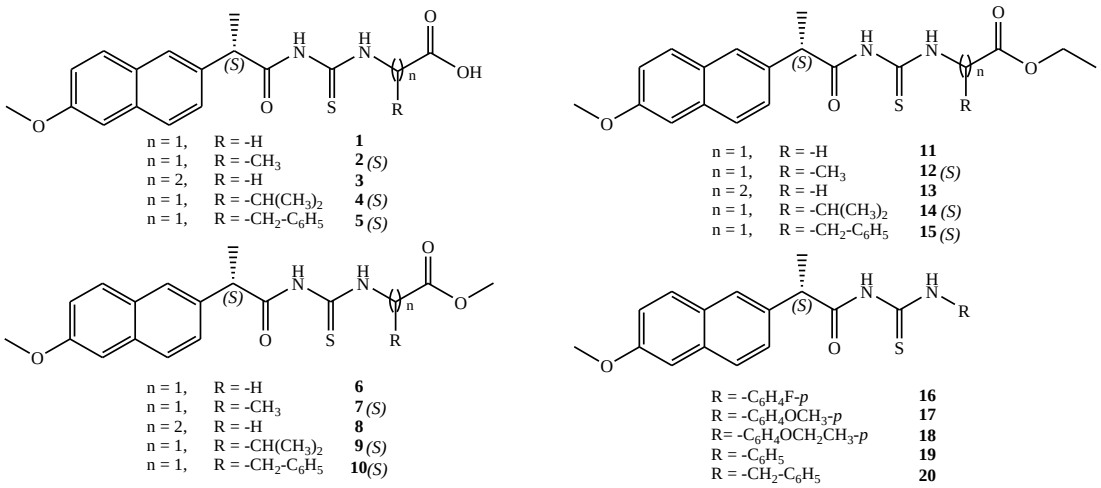

Fig. 1. Chemical structures of tested compounds (**1-20**)

2.1. Pharmacokinetic properties

Predicted pharmacokinetic properties include potential for gastrointestinal absorption, blood-brain barrier permeability, skin permeability, transport mediated by P-glycoproteins and enzyme inhibitiory potential. The predictions of passive human gastrointestinal absorption and blood-brain barrier permeability are based on BOILED-Egg model [8]. The knowledge about compounds being substrates of the P-glycoprotein is crucial to predict active efflux through biological membranes, such as gastrointestinal membrane and blood-brain barrier [9]. CYP450 superfamily of isoenzymes plays vital role in drug biotransformation. The potential of analyzed molecules to be substrates of five major isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4) was also estimated using SwissADME web tool [10].

Based on the results presented in Table 1, all tested compounds had high-predicted gastrointestinal absorption and low blood-brain barrier permeability. Derivatives with aromatic amines (**16-20**) showed inhibitory potential against all tested CYP isoforms. All analyzed molecules had inhibitory potential towards CYP2C9 isoform and only derivatives **2** and **4** did not have the same potential towards CYP2C19. All amino acid and some amino acid methyl ester derivatives had no inhibitory potential towards CYP2D6 and CYP3A4 isoforms. In addition, derivatives **2**, **4**, **7**, **9**, **10**, **12**, **14**, **15** and **18** were predicted to be P-glycoprotein substrates. Derivative **19** had the highest, while derivative **13** demonstrated the lowest predicted skin permeability. In general, amino acid and amino acid ester derivatives showed lower skin permeability than derivatives with aromatic amines.

Table 1. Pharmacokinetic properties of tested compounds

Compound	GA	Bbbp	LogKp	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor

1	High	No	-5.96	No	No	Yes	Yes	No	No
2	High	No	-5.77	Yes	No	No	Yes	No	No
3	High	No	-6.12	No	No	Yes	Yes	No	No
4	High	No	-5.37	Yes	No	No	Yes	No	No
5	High	No	-5.22	No	No	Yes	Yes	No	No
6	High	No	-5.82	No	Yes	Yes	Yes	No	No
7	High	No	-5.74	Yes	Yes	Yes	Yes	No	No
8	High	No	-5.97	No	Yes	Yes	Yes	No	Yes
9	High	No	-5.22	Yes	No	Yes	Yes	No	Yes
10	High	No	-5.07	Yes	No	Yes	Yes	Yes	Yes
11	High	No	-6.01	No	Yes	Yes	Yes	No	Yes
12	High	No	-5.82	Yes	Yes	Yes	Yes	No	Yes
13	High	No	-6.17	No	Yes	Yes	Yes	Yes	Yes
14	High	No	-5.31	Yes	No	Yes	Yes	No	Yes
15	High	No	-4.90	Yes	No	Yes	Yes	Yes	Yes
16	High	No	-4.72	No	Yes	Yes	Yes	Yes	Yes
17	High	No	-4.89	No	Yes	Yes	Yes	Yes	Yes
18	High	No	-4.71	Yes	Yes	Yes	Yes	Yes	Yes
19	High	No	-4.68	No	Yes	Yes	Yes	Yes	Yes
20	High	No	-4.81	No	Yes	Yes	Yes	Yes	Yes

GA – *Gastrointestinal absorption*; Bbbp – *Blood-brain barrier permeant*; LogKp – *Skin permeation* (cm/s); P-gp – *P-glycoprotein*

2.2. Druglikeness properties

Druglikeness was evaluated using Lipinski's [11], Ghose's [12], Egan's [13], Veber's [14] and Muegge's [15] rules, as well as on the basis of bioavailability score (BS).

All analyzed compounds met Lipinski's, Egan's and Ghose's rules, with exception of compound **15**. Derivatives **1-4**, **6-9** and **11-14** fulfilled the Muegge's rule. All derivatives except **10** and **13-15** met Veber's rule. Based on before mentioned, we concluded that derivatives **1-12**, except **5** and **10**, fulfilled all of the imposed druglikeness criteria and could be considered druglike structures. In addition, evaluation was also carried out using BS criteria [16]. These criteria are based on the probability value of a compound to possess optimum profile of bioavailability and permeability, where value of 0.55 implies the obedience of Lipinski rule of five [11] and 55% probability of rat bioavailability value higher than 10%. Amino acid derivatives (**1-5**) showed bioavailability score 0.56, while the other tested compounds had a BS value 0.55.

3. Conclusions

SwissADME web tool enables the estimation of key physicochemical and pharmacokinetic parameters, as well as druglikeness of biologically active molecules. According to conducted research, it could be expected that all designed compounds have high level of gastrointestinal absorption without the possibility of passing through the blood-brain barrier. Derivatives **2**, **4**, **7**, **9**, **10**, **12**, **14**, **15** and **18** were predicted to be P-glycoprotein substrates. Derivative **19** had the highest, while derivative **13** demonstrated the lowest predicted skin permeability. It was also estimated which of designed compounds have potential to inhibit CYP enzymes. Finally, almost all amino acid and their methyl ester derivatives have druglike structures, since they obey to all imposed rules.

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