Molecular docking analysis of novel thiourea derivatives of naproxen with potential anti-inflammatory activity

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Introduction

Administration of current non-steroidal anti-inflammatory drugs is often associated with serious adverse effects. Therefore, there is a constant need to develop new molecules with anti-inflammatory activity. On the other hand, thiourea derivatives of non-steroidal anti-inflammatory drugs demonstrated significant anti-inflammatory activity in numerous studies. To clarify anti-inflammatory mechanism of action, *in silico* study was performed on four thiourea derivatives of naproxen that were docked into the active sites of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX).

Material and methods

Tested compounds contain *p*-fluoroaniline (**16**), *p*-methoxyaniline (**17**), *p*-ethoxyaniline (**18**) and aniline (**19**) in the side chains (Figure 1). Selected 3D structures of enzymes COX-2 (3NT1) and 5-LOX (6NCF) were taken from PDB database (Figure 2). MAKE Receptor 3.2.0.2 software was used for preparation of enzymes' active sites, while ligands were prepared in OMEGA 2.5.1.4. FRED 3.2.0.2 software was employed for the analysis of binding poses into enzymes' active sites [1-3].

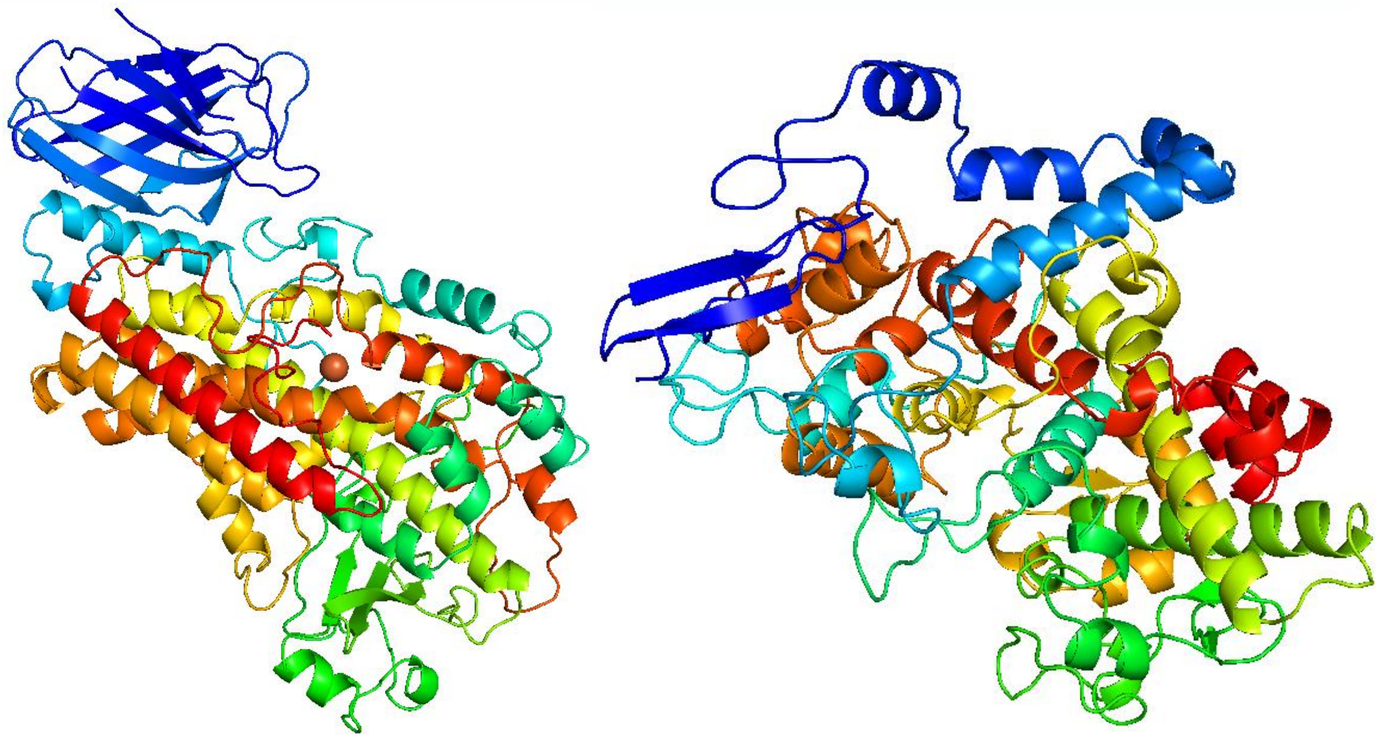

Figure 2. Molecular structures of 5-LOX (left) and COX-2 (right)

Figure 1. Chemical structures of tested compounds

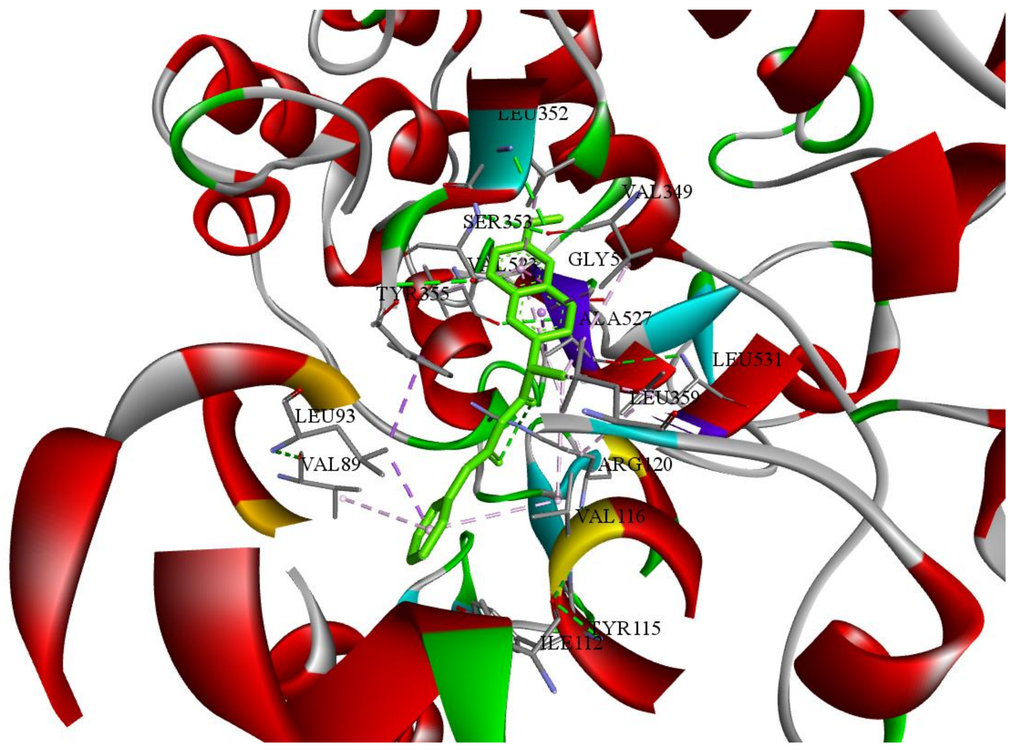

Figure 3. Binding interactions of derivative **19** into the active site of COX-2

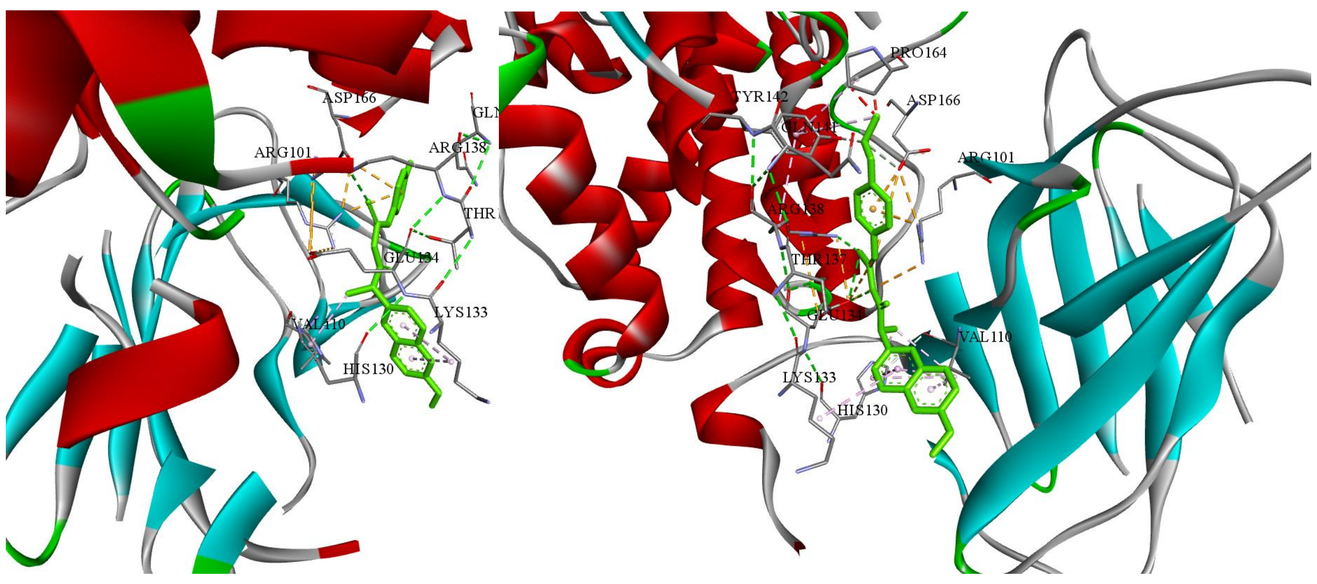

Figure 4. Binding interactions of derivatives **16** (left) and **18** (right) into the active site of 5-LOX

Results

Dual inhibitory potential was defined according three criteria: total number of non-covalent interactions, their type and free binding energies of the best ligand's poses. The highest number of key binding interactions was observed during molecular fitting of derivative **19** into the active site of COX-2 (Figure 3) and derivatives **16** and **18** into the 5-LOX (Figure 4). Derivative **17** had the lowest value of free binding energy for both target enzymes, -14.90 kcal/mol for COX-2 and -9.57 kcal/mol for 5-LOX (Figure 5).

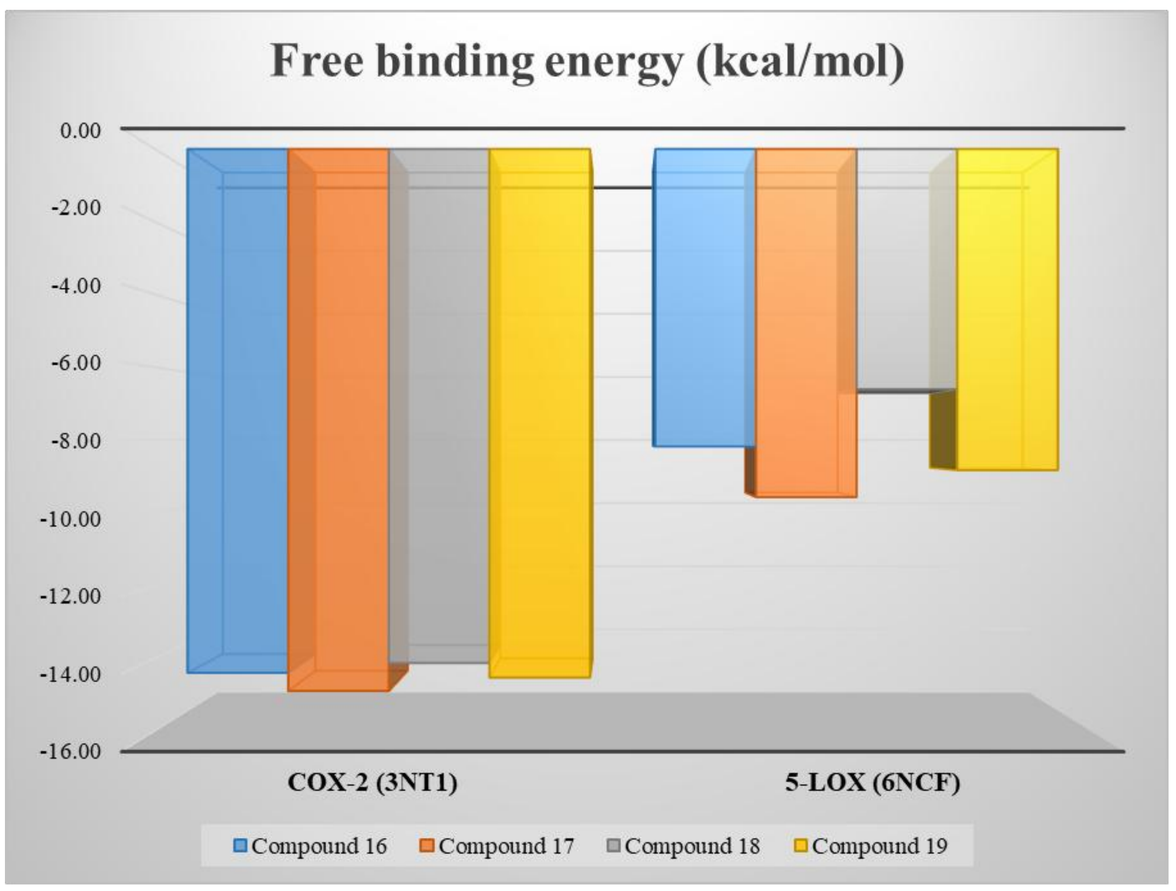

Figure 5. The free binding energy diagram of analyzed compounds

Conclusion

All analyzed compounds represent potential candidates for dual inhibition of mentioned enzymes, which can be a background for further biological research.

References:

[1] FRED 3.2.0.2: OpenEye Scientific Software, Santa Fe, NM, USA; http://www.eyesopen.com.
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[3] McGann M (2012). J Comput Aid Mol Des 26: 897-906.

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