Professor Jurij Svete
University of Ljubljana
Faculty of Chemistry and Chemical Technology
Aškerčeva 5
1000 Ljubljana
Slovenia

Ljubljana, April 10, 2017

Professor Aleksander Pavko
Editor-in-Chief
Acta Chimica Slovenica

Dear Professor Pavko,

I would appreciate if you would consider the manuscript:

Synthesis of novel 5-(N-Boc-N-benzyl-2-aminoethyl)-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidin-3-carboxamides and their inhibition of Cathepsins B and K
by
Branislav Lukić, Uroš Grošelj, Marko Novinec, and Jurij Svete

for publication in **a special issue** of Acta Chimica Slovenica dedicated to professor emeritus **Miha Tišler** on the occasion of his 90th anniversary.

The manuscript describes the synthesis of eight novel 5-(*N*-Boc-*N*-benzyl-2-aminoethyl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-3-carboxamides and their biological evaluation for inhibition of Cathepsins. Pyrazolo[1,5-*a*]pyrimidine is important heterocyclic scaffold, which found use in many different applications, mostly in medicinal chemistry, with sedative agents zaleplon and indiplon and the anxiolytic agent ocinaplon as the most prominent examples. Since inhibition of cathepsin K could prevent bone resorption, it may provide a promising approach for the treatment of osteoporosis, cancer and other diseases. Title compounds were prepared in three steps from methyl 3-amino-1*H*-pyrazole-4-carboxylate and methyl 5-(benzyl(*tert*-butoxycarbonyl)amino)-3-oxopentanoate. The synthetic procedure comprises cyclocondensation of the above starting

compounds, hydrolysis of the ester, and bis(pentafluorophenyl) carbonate (BPC)-mediated amidation. Testing of the final products for inhibition of cathepsins K and B revealed that *N*-butylcarboxamide **5a** exhibited appreciable inhibition of cathepsin K (IC_{50} ~ 25 μM), while the strongest inhibition of cathepsin B was achieved with *N*-(2-picolyl)carboxamide **5c** (IC_{50} ~ 45 μM). Most of other compounds were weak inhibitors at 100 μM concentration. Inhibitory activities of compounds **5a** and **5c** against cysteine peptidases cathepsins B and K identify them as potential leads for drug development. The synthetic method allows for a simple preparation of libraries of title compounds that could be useful for medicinal and pharmaceutical applications.

I hope that you will also find this manuscript interesting and that the reasons stated above justify consideration for publication of this manuscript in a dedicated issue of Acta Chimica Slovenica.

With best regards,

Yours sincerely,

Jurij Svete