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"Cardionephrology Up To Date"

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2-Imino-benzimidazoles and 1,3-thiazolo[3,2-a]benzimidazolones as xanthine oxidase inhibitors

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Xanthine oxidase is flavoprotein enzyme that catalyzes oxidation of hypoxanthine to xanthine, and then xanthine to uric acid. The concentration of xanthine oxidase in serum is increased in pathological conditions such as hepatitis, inflammation, ischemia-reperfusion injury, carcinogenesis and aging. Allopurinol is a known competitive inhibitor of xanthine oxidase widely used in the therapy of gout. There is a need for new xanthine oxidase inhibitors, which would be approximately as efficient as allopurinol, and thereby show fewer side effects. Benzimidazole heterocycle system is an important pharmacophore in medicinal chemistry. Its derivatives show different biological activity.

In this study, five 2-imino-benzimidazoles and four 1,3-thiazolo[3,2-a]benzimidazolones were evaluated for inhibitory activity against commercial enzyme xanthine oxidase. Additionally, an *in silico* study of pharmacokinetic and toxicological properties of the most potent inhibitors was performed.

Commercial bovine milk xanthine oxidase was used for *in vitro* test of enzyme inhibition which was based on the spectrophotometric determination of uric acid formation at 293 nm. Allopurinol was used as a positive control. Pharmacokinetic and toxicological properties of studied benzimidazoles were calculated using OSIRIS Property Explorer, admetSAR and Toxtree.

Four of nine examined benzimidazoles showed an inhibitory effect on xanthine oxidase with an IC_{50} value below 150 μM. The highest inhibitory effect on xanthine oxidase showed compound 5-methyl-1,3-bis(3-phenylpropyl)-1*H*-benzo[d]imidazol-2(3*H*)-imine hydrobromide.

2-Imino-benzimidazoles and 1,3-thiazolo[3,2-a]benzimidazolones are novel non-purine inhibitors of xanthine oxidase.

Inhibicija ksantin-oksidaze 2-imino-benzimidazolima i 1,3-tiazolo[3,2-a]benzimidazolonima

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Ksantin-oksidaza je flavoproteinski enzim koji katalizuje oksidaciju hipoksantina u ksantin, a zatim ksantina u mokraćnu kiselinu. Koncentracija ksantin-oksidaze u serumu povećana je u patološkim stanjima kao što su hepatitis, zapaljenje, ishemija-reperfuzija, karcinogeneza i starenje. Alopurinol je poznati kompetitivni inhibitor ksantin-oksidaze široko zastupljen u terapiji gihta. Postoji potreba za novim inhibitorima ksantin-oksidaze koji bi bili približno efikasni kao alopurinol, a pritom pokazivali manje sporednih efekata od njega. Benzimidazolni heterociklusni sistem je važna farmakofora u farmaceutskoj hemiji. Derivati benzimidazola pokazuju različitu biološku aktivnost.

U ovom radu je ispitan uticaj pet 2-imino-benzimidazola i četiri 1,3-tiazolo[3,2-a]benzimidazolona na aktivnosti komercijalnog enzima ksantin-oksidaze. Takođe, *in silico* metodama je izvršeno predviđanje farmakokinetičkih i toksikoloških parametara najefikasnijih inhibitora.

In vitro test inhibicije komercijalne ksantin-oksidaze, izolovane iz goveđeg mleka, se zasniva na spektrofotometrijskom određivanju dobijene mokraćne kiseline na 293 nm. Alopurinol je korišćen kao pozitivna kontrola. Farmakološki i toksikološki parametri ispitivanih benzimidazola su predviđani kompjuterskim programima OSIRIS Property Explorer, admetSAR i Toxtree.

Četiri od devet ispitivanih benzimidazola je pokazalo inhibitorni efekat na komercijalnoj ksantin-oksidazi sa IC_{50} vrednošću manjom od 150 μM. Najjači inhibitorni efekat na ksantin-oksidazu pokazao je 5-metil-1,3-bis(3-fenilpropil)-1*H*-benzo[d]imidazol-2(3*H*)-imin hidrobromid.

2-Imino-benzimidazoli i 1,3-tiazolo[3,2-a]benzimidazoloni predstavljaju nove nepurinske inibitore ksantin-oksidaze.