SYNTHESIS AND PHYSICOCHEMICAL CHARACTERIZATION OF THREE NEWLY SYNTHESIZED SULFHYDROXAMIC ACID DERIVATIVES AS POTENTIAL DUAL INHIBITORS OF CYCLOOXYGENASE-2 AND 5-LIPOXYGENASE ENZYMES

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Inflammatory mediators derived from arachidonic acid by the enzymes cyclooxygenase (COX) and lipoxygenase (LOX) are involved in the pathogenesis of various inflammatory diseases. Inhibition of the COX pathway is thought to lead to potentiation of the LOX pathway, and inhibition of both pathways represents a rational approach to the design and development of more effective and safer anti-inflammatory drugs (1). The aim of this study was the synthesis and physico-chemical characterization of 1f, 1g and 1h derivatives derived from a previously conducted 3D-QSAR study and molecular docking (2). The sulfhydroxamic acid derivative 1f was synthesized in a two-step process. Sulfonyl chloride was synthesized from commercially available sulfonic acid and thionyl chloride in the presence of a catalytic amount of DMF. Sulfhydroxamic acid was further obtained from previously synthesized sulfonyl chloride and hydroxylamine hydrochloride in the presence of 10% $NaHCO_3$ solution. Sulfhydroxamic acid derivatives, 1g and 1h were synthesized from commercially available sulfonyl chlorides and hydroxylamine hydrochloride in the presence of 10% $NaHCO_3$ solution. The reaction mixtures were purified by liquid-liquid extraction and preparative TLC to give derivatives 1f, 1g, 1h in yields: 26%, 53% and 63%. The structure and purity of the synthesized compounds were confirmed by determination of the melting points and spectroscopic techniques (ATR-FTIR, 1H-NMR, 13C-NMR, MS/MS). Based on a previously conducted *in silico* study, the voluminous sulfhydroxamic group is responsible for iron chelation within 5-LOX active center and for COX-2 selectivity, as COX-2 has wider side pocket, so potent inhibition of COX-2 and 5-LOX enzymes is expected.

References

1. P J.J., Manju S.L., Ethiraj K.R., Elias G. Safer anti-inflammatory therapy through dual COX-2/5-LOX inhibitors: A structure-based approach. Eur. J. Pharm. Sci. 2018; 121: 356-381.
2. Bošković J., Ružić D., Čudina O., Nikolic K., Dobričić V. Design of dual COX-2 and 5-LOX inhibitors with iron-chelating propertiesusing structure-based and ligand-based methods. Lett. Drug Des. Discov. 2022; 19: 279-292.

Acknowledgements

This research was funded by the Ministry of Education, Science and Technological Development, Republic of Serbia through Grant Agreement with University of Belgrade – Faculty of Pharmacy No: 451-03-68/2022-14/200161.

SINTEZA I FIZIČKO-HEMIJSKA KARAKTERIZACIJA TRI NOVOSINTETISANA DERIVATA SULFHIDROKSAMSKE KISELINE KAO POTENCIJALNIH DUALNIH INHIBITORA ENZIMA CIKLOOKSIGENAZE-2 I 5-LIPOOKSIGENAZE

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Inflamatorni medijatori koji nastaju iz arahidonske kiseline posredstvom enzima ciklooksigenaze (COX) i lipooksigenaze (LOX) učestvuju u patogenezi brojnih inflamatornih oboljenja. Smatra se da inhibicija COX puta dovodi do potenciranja LOX puta, te inhibicija oba puta predstavlja racionalan pristup dizajniranja i razvoja novih, efikasnijih i bezbednijih antiinflamatornih lekova (1). Cilj rada je bila sinteza i fizičko-hemijska karakterizacija derivata 1f, 1g i 1h proisteklih iz prethodno sprovedene 3D-QSAR studije i molekulskog *docking*-a (2). Derivat sulfhidroksamske kiseline 1f je sintetisan u dvostepenom postupku pri čemu se najpre iz komercijalno dostupne sulfonske kiseline i tionil hlorida u prisustvu katalitičke količine DMF dobija odgovarajući sulfonil hlorid. Odgovarajuća sulfhidroksamska kiselina (1f) se dobija u drugom koraku iz prethodno sintetisanog sulfonil hlorida i hidroksilamin-hidrohlorida u prisustvu 10% rastvora $NaHCO_3$. Derivati sulfhidroksamske kiseline, 1g i 1h su sintetisani jednostepenim postupkom iz komercijalno dostupnih sulfonil hlorida i hidroksilamin-hidrohlorida u prisustvu 10% rastvora $NaHCO_3$. Nakon postupka sinteze jedinjenja su prečišćena tečno-tečnom ekstrakcijom i preparativnom TLC pri čemu se dobijaju derivati 1f, 1g, 1h u prinosima 26%, 53% i 63%. Struktura i čistoća sintetisanih jedinjenja je potvrđena određivanjem temperature topljenja i spektroskopskim (ATR-FTIR, ^{1}H-NMR, ^{13}C-NMR, MS/MS) tehnikama. Na osnovu prethodno sprovedene *in silico* studije, voluminozni centar i sulfhidroksamska grupa sintetisanih derivata su odgovorni za COX-2 selektivnost zbog prisustva šireg vezivnog mesta unutar COX-2 enzima, dok sulfhidroksamska grupa unutar 5-LOX enzima helira gvožđe aktivnog centra i inhibira enzim, te se očekuje potentna dualna COX-2 i 5-LOX inhibitorna aktivnost sintetisanih derivata.

Literatura

1. P J.J., Manju S.L., Ethiraj K.R., Elias G. Safer anti-inflammatory therapy through dual COX-2/5-LOX inhibitors: A structure-based approach. Eur. J. Pharm. Sci. 2018; 121: 356-381.
2. Bošković J., Ružić D., Čudina O., Nikolic K., Dobričić V. Design of dual COX-2 and 5-LOX inhibitors with iron-chelating propertiesusing structure-based and ligand-based methods. Lett. Drug Des. Discov. 2022; 19: 279-292.

Zahvalnica

Ovo istraživanje finansirano je od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije kroz Ugovor sa Univerzitetom u Beogradu – Farmaceutskim fakultetom broj: 451-03-68/2022-14/200161.