

## POTENTIAL DUAL MECHANISM OF HYPOURICEMIC ACTIVITY OF DPP-4 INHIBITORS WITH PURINE-BASED SCAFFOLD

Katarina Tomović<sup>1</sup>, Gordana Kocić<sup>2</sup>, Andrija Šmelcerović<sup>3</sup>

Dipeptidyl peptidase-4 (DPP-4) binds to adenosine deaminase (ADA) and form a complex which catalyzes an irreversible deamination of extracellular adenosine to inosine, what leads to the generation of hypoxanthine, xanthine and finally uric acid by xanthine oxidase (XO) in purine catabolism with the production of reactive oxygen species. Xanthine-based DPP-4 inhibitor linagliptin showed inhibitory potential on XO. It exerts a hypouricemic effect by inhibiting DPP-4 activity and its binding to ADA, what causes the increase of adenosine and decrease of XO substrates levels, as well as by inhibiting XO activity. Based on the evidenced dual mechanism of hypouricemic activity of linagliptin, the possibility of other DPP-4 inhibitors with the purine-based scaffold to act in the same manner exists.

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**Key words:** dipeptidyl peptidase-4, xanthine oxidase, adenosine deaminase

<sup>1</sup>University of Niš, Faculty of Medicine, Department of Pharmacy, Niš, Serbia

<sup>2</sup>University of Niš, Faculty of Medicine, Institute of Biochemistry, Niš, Serbia

<sup>3</sup>University of Niš, Faculty of Medicine, Department of Chemistry, Niš, Serbia

Contact: Andrija Šmelcerović  
Bulevard dr Zoran Djindjić 81, 18000, Niš, Serbia  
E-mail: a.smelcerovic@yahoo.com

### Introduction

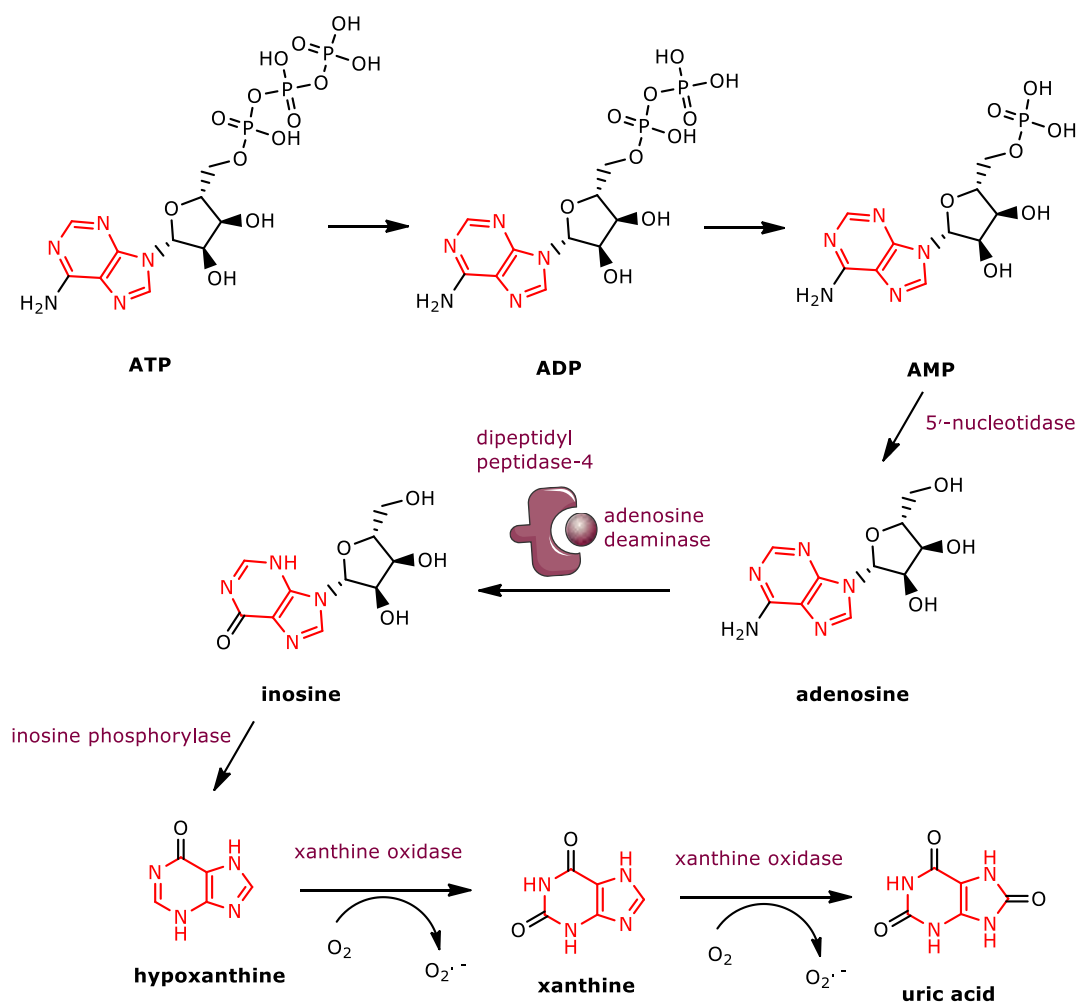
Chronic hyperuricemia represents a risk factor for metabolic syndrome, cardiovascular and renal disorders (1-6). Although the elevation of uric acid levels acts as a risk factor and contributes to the development of mentioned disorders, it also represents a marker and consequence in cardiovascular and renal pathology (7). Hyperuricemia and oxidative stress generated via xanthine oxidase (XO) activity promote endothelial dysfunction. Uric acid stimulates proliferation of vascular smooth muscle cells, elevates levels of inflammatory markers including C-reactive protein and tumor necrosis factor- $\alpha$ , nuclear factor kappa B, monocyte chemoattractant protein-1, interleukin-1 $\beta$  and -6. Improvement might be associated with the administration of urate-lowering agents such as XO inhibitors (1, 3-6).

It has been shown in isolated postischemic rat heart that XO mediated generation of free radicals upon reperfusion is triggered by enhancement of for-

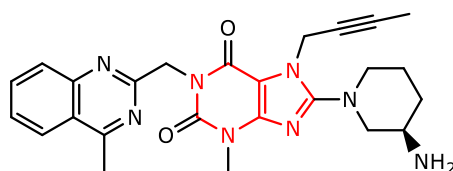
mation of its substrates, hypoxanthine, and xanthine, during ischemia, while alterations in the enzyme activity are not sufficient as major limiting factor. During ischemia, the accumulation of hypoxanthine and xanthine occurs via degradation of adenosine triphosphate (ATP) to adenosine monophosphate (AMP), adenosine and inosine. Since substrates availability is significant in the production of free radicals and consequently in the determination of severity in postischemic injury, the decrease of their formation might offer novel therapeutic approach besides the inhibition of XO activity, with beneficial effect in terms of the increase of adenosine levels as well as the preservation of high energy phosphates (8). Moreover, it has been shown in postischemic rat heart that reduction of XO substrate generation by inhibition of adenosine deaminase (ADA) activity can prevent the production of free radicals and contractile dysfunction (9).

Dipeptidyl peptidase-4 (DPP-4) is ADA binding protein, with which in complex it contributes to T-cell stimulation and proliferation (10, 11). Bimolecular complex of DPP-4 and ADA catalyzes irreversible deamination of extracellular adenosine to inosine, than to hypoxanthine and xanthine finally oxidized to uric acid by xanthine oxidase (XO) in purine catabolic pathway, with generation of superoxide anions (Figure 1). If deamination is absent adenosine is rephosphorylated to 5'-AMP and ATP by adenosine kinase (12).

Therefore, compounds with XO and DPP-4 inhibitory potential will at the same time reduce XO activity, as well as its substrates generation by suppressing formation of the complex between DPP-4 and ADA.



**Figure 1.** Schematic diagram of the irreversible deamination of adenosine to inosine, hypoxanthine and xanthine oxidized to uric acid (adapted from Lee et al. (12) and Xia et al. (9))



**Figure 2.** Chemical structure of linagliptin

### Linagliptin, dipeptidyl peptidase-4 and xanthine oxidase inhibitor

It has been shown that linagliptin, DPP-4 inhibitor with xanthine-based structure (Figure 2) and reported  $IC_{50}$  value of  $\sim 1$  nM (13-16), at the oral dose of 5 mg/kg for 7 days normalized increased serum XO activity in septic rats (17). Additionally,

linagliptin exerted an inhibitory effect on the activity of XO *in vitro* and in human serum derived from the healthy volunteer in a concentration-dependent manner up to 1 mM, as well as lowered uric acid levels in plasma of diabetic patients at the oral dose of 5 mg once daily for 24 weeks (18).

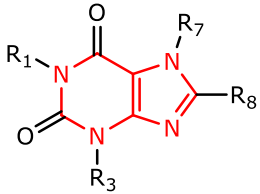
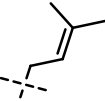
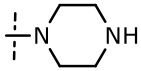
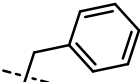
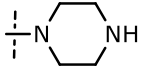
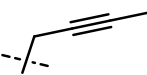
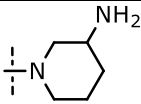
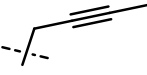
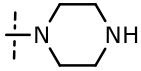
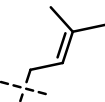
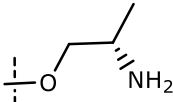
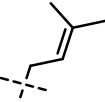

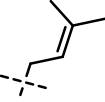
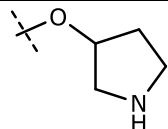
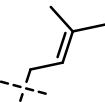
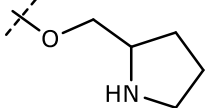
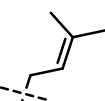
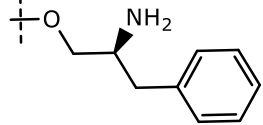
Generally, based on linagliptin as representative, DPP-4 inhibitors with purine-based scaffold may

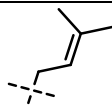
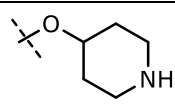
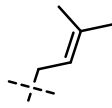
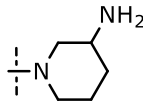
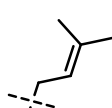
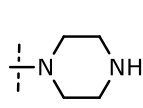
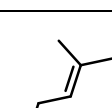
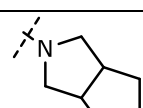
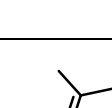
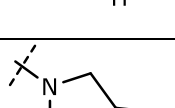
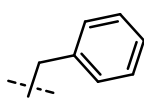
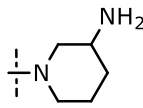
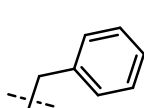
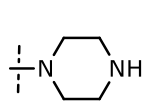
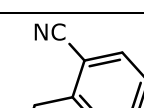
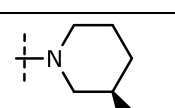
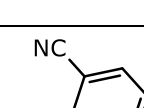
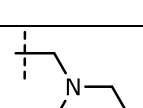
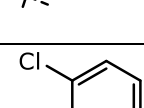
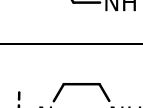
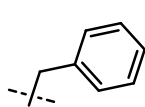
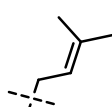
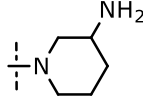
be hypothesized to exert hypouricemic effect via dual mechanism, inhibiting the activity of DPP-4 and its binding to ADA with subsequent increase of adenosine levels and decrease of availability of substrates for XO, as well as inhibiting XO activity, with finally reduced production of uric acid.

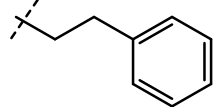
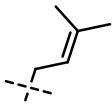
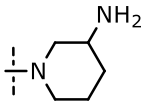
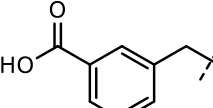
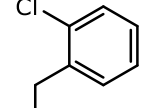
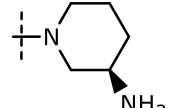
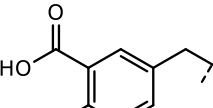
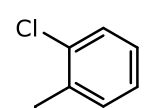
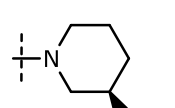
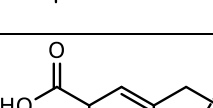
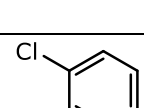
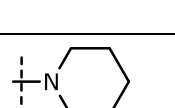
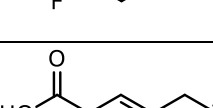
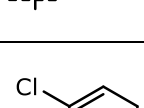
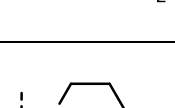
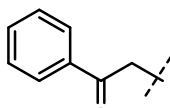
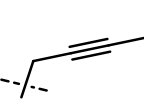
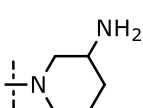
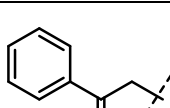
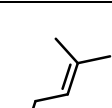
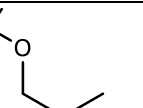
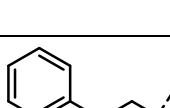
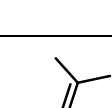
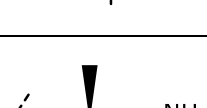
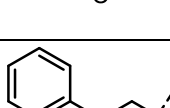
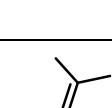
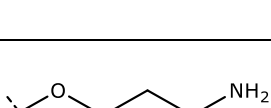
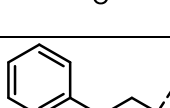
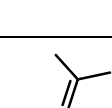
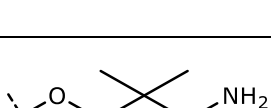
### Overview of purine-based DPP-4 inhibitors

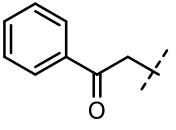
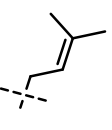
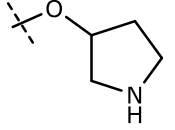
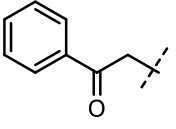
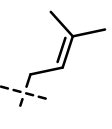
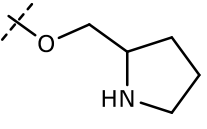
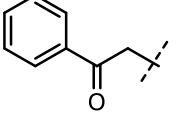
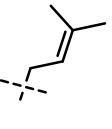
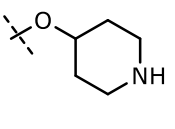
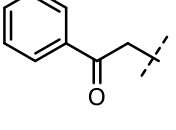
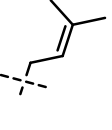
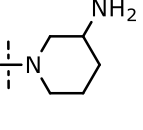
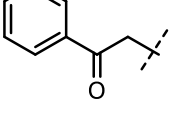
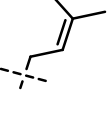
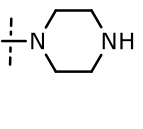
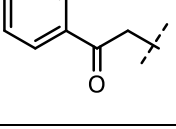
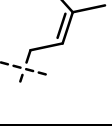
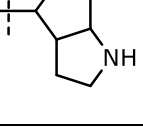
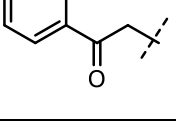
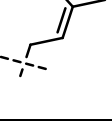
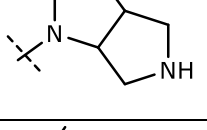
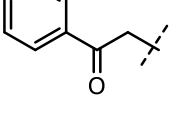
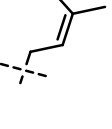
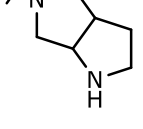
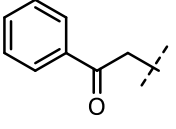
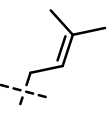
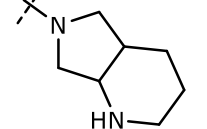
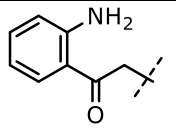
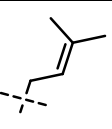
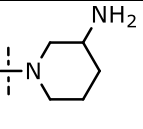
Some DPP-4 inhibitors (13-16, 19-28) have been derived from a xanthine scaffold, similar to the structure of linagliptin (Table 1, Figure 3).

**Table 1.** DPP-4 inhibitors derived from purine scaffold with determined IC<sub>50</sub> values from 0.05 nM to > 24.50 μM (13-16, 19-23, 25-27)

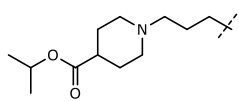
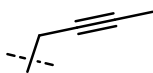
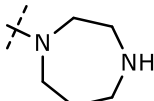
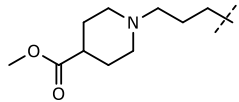
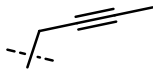
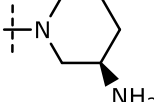
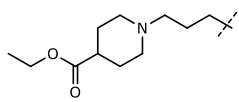
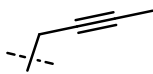
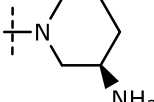
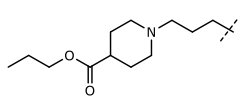
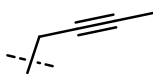
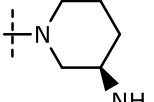
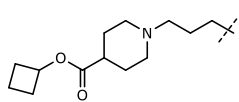

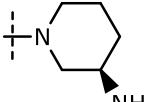
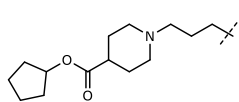
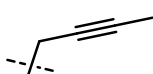
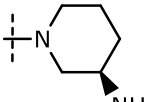
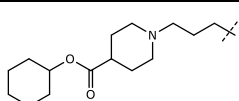
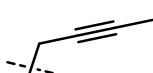
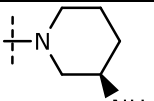
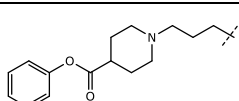
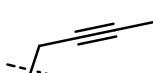
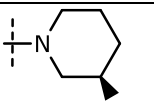
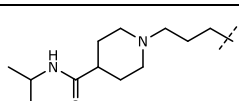
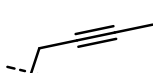
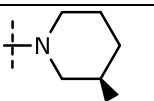
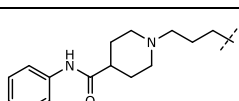
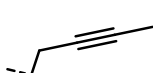
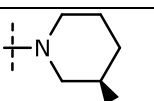
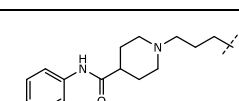
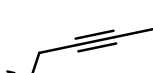
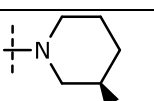
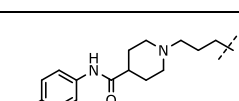
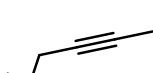
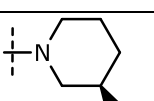
				
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2	H	CH <sub>3</sub>		
3	CH <sub>3</sub>	CH <sub>3</sub>		
4	CH <sub>3</sub>	CH <sub>3</sub>		
5	CH <sub>3</sub>	CH <sub>3</sub>		
6	CH <sub>3</sub>	CH <sub>3</sub>		
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8	CH <sub>3</sub>	CH <sub>3</sub>		
9	CH <sub>3</sub>	CH <sub>3</sub>		

<b>10</b>	CH <sub>3</sub>	CH <sub>3</sub>		
<b>11</b>	CH <sub>3</sub>	CH <sub>3</sub>		
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<b>13</b>	CH <sub>3</sub>	CH <sub>3</sub>		
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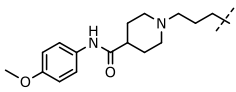
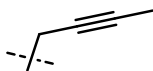
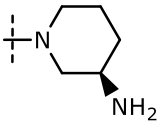
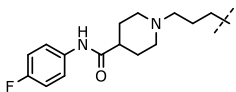
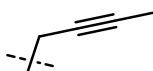
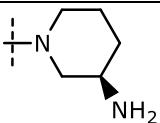
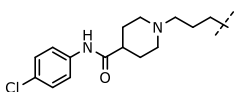
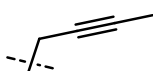
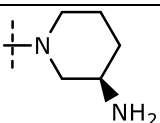
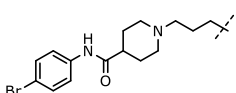
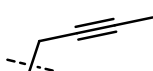
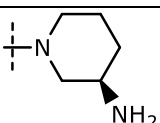
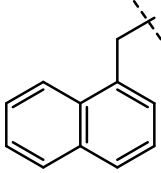

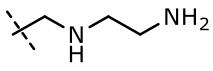
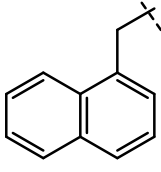
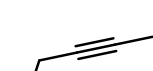
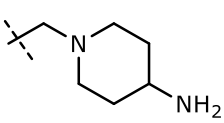
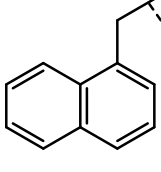
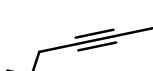
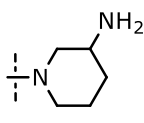
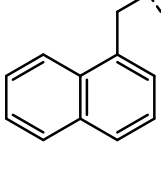
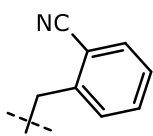
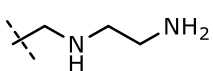
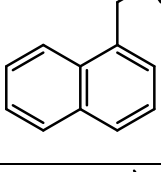
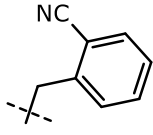
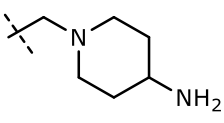
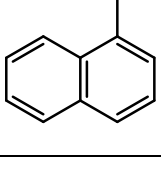
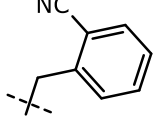
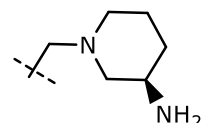
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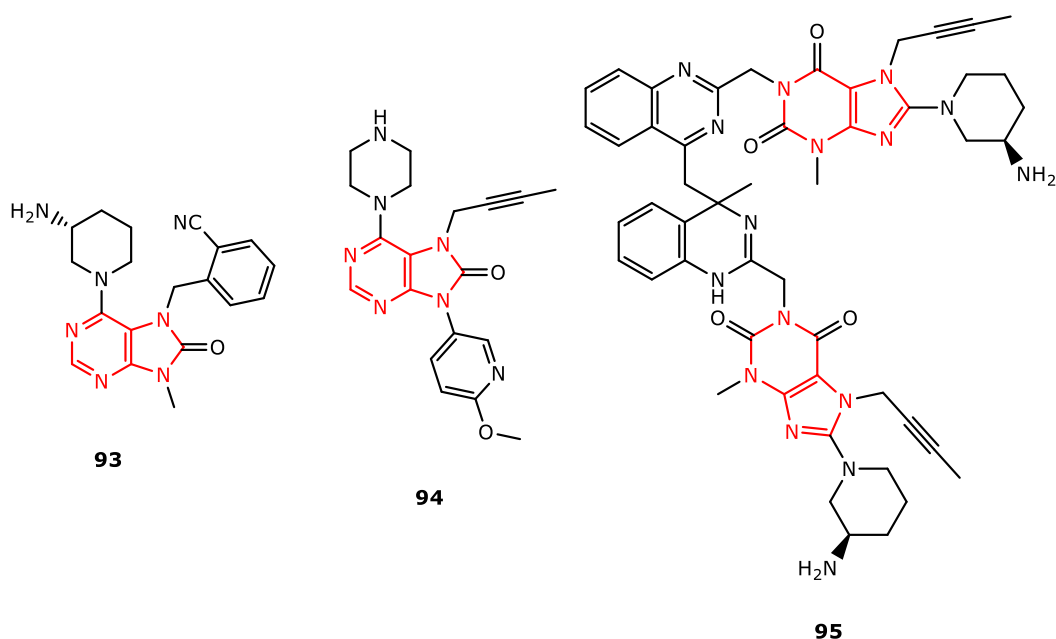
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**Figure 3.** DPP-4 inhibitors with purine scaffold structurally little different from the above listed representatives with reported  $IC_{50}$  values of 10 nM, 89 nM and 6 pM, respectively (21, 24, 28)

## Conclusion

Besides XO activity, the availability of its substrates, affected by modulation of ADA activity, determine production of uric acid, and potential multitarget hypouricemic agents might offer a beneficial therapeutic approach. Based on evidenced linagliptin inhibitory potential on DPP-4 and XO, the possibility of DPP-4 inhibitors with the purine-based scaffold to exert hypouricemic effect via the same dual mechanism like linagliptin exists. Although structures possess the same scaffold, position and type of substituents affect and determine the structure-activity relationship, and inhibitory potential of other purine-

based DPP-4 inhibitors on XO remains to be experimentally assayed.

## Acknowledgments

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Revijalni rad

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doi:10.5633/amm.2019.0109**POTENCIJALNO DUALNI MEHANIZAM HIPOURIKEMIJSKE AKTIVNOSTI  
DPP-4 INHIBITORA PURINSKE STRUKTURE***Katarina Tomović<sup>1</sup>, Gordana Kocić<sup>2</sup>, Andrija Šmelcerović<sup>3</sup>*<sup>1</sup>Univerzitet u Nišu, Medicinski fakultet, Katedra za farmaciju, Niš, Srbija<sup>2</sup>Univerzitet u Nišu, Medicinski fakultet, Katedra za biohemiju, Niš, Srbija<sup>3</sup>Univerzitet u Nišu, Medicinski fakultet, Katedra za hemiju, Niš, Srbija

*Kontakt:* Andrija Šmelcerović  
Bulevar dr Zorana Đinđića 81, 18000, Niš, Srbija  
E-mail: a.smelcerovic@yahoo.com

Dipeptidil peptidaza-4 vezuje adenzin deaminazu, pri čemu nastaje kompleks koji katalizuje ireverzibilnu deaminaciju ekstracelularnog adenzina u inozin, što vodi generisanju hipoksantina i ksantina do mokraćne kiseline ksantin-oksidadom u katabolizmu purina uz produkciju reaktivnih kiseoničnih vrsta. Inhibitor dipeptidil peptidaze-4 ksantinske strukturne osnove, linagliptin, pokazao je inhibitorni potencijal na ksantin-oksidazi. Linagliptin pokazuje hipourikemijski efekat inhibiranjem aktivnosti dipeptidil peptidaze-4 i formiranja kompleksa ove proteaze i adenzin deaminaze, što uzrokuje porast sadržaja adenzina i smanjenu raspoloživosti supstrata ksantin-oksidade, kao i inhibiranjem aktivnosti ksantin-oksidade. Usled dokaza o dualnom mehanizmu hipourikemijske aktivnosti linagliptina, postoji mogućnost da drugi inhibitori dipeptidil peptidaze-4 purinske strukture pokazuju istu aktivnost.

*Acta Medica Medianae 2019;58(1):50-63.****Ključne reči:*** dipeptidil peptidaza-4, ksantin-oksidaza, adenzin deaminaza

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