proceedings

MDPI

Extended Abstract

Mechanisms of Inhibitory Effects of Polysubstituted Pyrimidines on Prostaglandin E_2 Production †

Zdeněk Zídek [1,*], Viktor Kolman [2], Ondřej Baszczyňski [2], Filip Kalčic [2], Daniel Board [2] and Zlatko Janeba [2]

[1] Institute of Experimental Medicine, The Czech Academy of Sciences, 142 20 Prague, Czech Republic
[2] Institute of Organic Chemistry and Biochemistry, The Czech Academy of Sciences, 166 10 Prague, Czech Republic
* Correspondence: zdenek.zidek@iem.cas.cz
† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Received: 7 August 2019

Keywords: pyrimidine analogues; prostaglandin E_2; prostaglandin E_2 synthase-1 inhibitors; anti-inflammatory activity

---

The pyrimidine heterocycle represents an elemental structural motif of numerous drugs. We have synthesized a large series of original derivatives possessing different substituents at C-2, C-4, C-5, and C-6 positions of the pyrimidine ring. The vast majority of prepared pyrimidines inhibit prostaglandin E_2 (PGE_2) production as revealed in vitro in the lipopolysaccharide (LPS)-stimulated mouse macrophages [1,2]. A number of them are effective at sub-micromolar concentration. The compounds are devoid of cytotoxic effects. They do not inhibit activities of phospholipase A2 (sPLA2), cyclooxygenases COX-1 and COX-2, and important enzymes in the PGE_2 biosynthesis pathway. A plausible explanation for the mechanism of PGE_2-inhibitory effects of pyrimidines is provided by findings showing substantial inhibition of activity of the terminal enzyme in PGE_2 formation, i.e., microsomal prostaglandin E_2 synthase-1 (mPGES-1). The IC_{50}s characterizing the potential of compounds to reduce mPGES-1 activity on one site and LPS-induced PGE_2 production on the other one are statistically significantly correlated.

Pyrimidine derivatives exhibit anti-inflammatory activity in vivo, as demonstrated by the significant reduction of carrageenan-induced paw oedema in rats. The findings suggest that pyrimidine inhibitors of mPGES-1 activity and consequent PGE_2 production may be considered as promising candidates for further preclinical research and development of novel non-steroidal anti-inflammatory drugs.

Acknowledgments: The research was supported by grant TE01020028 from the Technology Agency of the Czech Republic.

References

1 Zídek, Z.; Kverka, M.; Dusilová, A.; Kmoníčková, E.; Jansa, P. Dual inhibition of nitric oxide and prostaglandin E_2 production by polysubstituted 2-aminopyrimidines. *Nitric Oxide* **2016**, *57*, 48–56.
2 Kolman, V.; Kalčic, F.; Jansa, P.; Zídek, Z.; Janeba, Z. Influence of the C-5 substitution in polysubstituted pyrimidines on inhibition of prostaglandin E_2 production. *Eur. J. Med. Chem.* **2018**, *156*, 295–301.