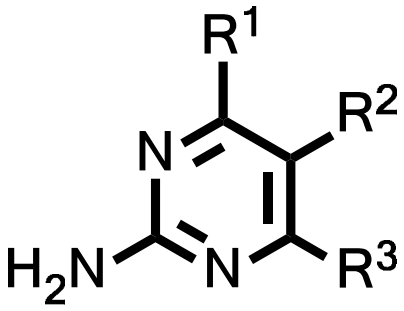
Pyrimidine based receptor for advanced glycation end-products (RAGE) inhibitors as an anti-inflammatory compounds

Introduction:
The interaction between RAGE and its ligands is thought to result in pro-inflammatory gene activation. RAGE has been linked to several chronic diseases, which are thought to result from vascular damage. The pathogenesis is hypothesized to include ligand binding upon which RAGE signals activation of the nuclear factor kappa B (NF-κB). NF-κB controls several genes which are involved in inflammation. Interestingly, RAGE itself will also be up-regulated by NF-κB. Given a condition in which there is a large amount of RAGE ligands (e.g. AGE in diabetes or Amyloid-β-protein in Alzheimer's Disease) this establishes a positive feed-back cycle, which leads to chronic inflammation. This chronic condition is then believed to alter the micro- and macrovasculature in a fatal way which ends in organ damage or even organ failure. Diseases that have been linked to RAGE are: atherosclerosis, peripheral vascular disease, myocardial infarction, congestive heart failure, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, Alzheimer's disease, psoriasis.



Technology description:
Receptor for advanced glycation end-products plays an important role in many pathological processes and thus represents potential for research and development of diagnostic and therapeutic strategies. Although there were several small molecular RAGE inhibitors described in the literature, they mostly have not shown proof-of-concept therapeutic potential, and thus, there is still potential for future developments in the field.

Advantages:
We have discovered a group of pyrimidine derivatives with proprietary structure and ability to inhibit RAGE receptor (low micromolar concentrations). The effects were described under *in vitro* conditions using RAGE ligand (β-amyloid, S-100 protein and glycated albumin) dependent activation of NF-κB, MAPK/JNK (AP-1) and JAK/STAT (STATJ) signaling. The binding was further confirmed and SAR elucidated by docking against the crystal structure of the RAGE. *In vitro* validation experiments have also demonstrated inhibition of RAGE ligand dependent activation of NO production in macrophages co-stimulated with IFN-γ. The compounds have reasonable toxicity, regiments with 50 mg/kg (2-3x daily) orally were well tolerated in rat model of rheumatoid arthritis and inflammatory bowel diseases (IBDs). The model compound was significantly active in IBD (comparable efficacy to sulfasalazine), but not in RA, which seems to be in agreement with published data on RAGE role in IBD versus RA.

Development status:
Laboratory scale, data on cell lines, structural data from receptor docking, limited ADME/Tox data, *in vivo* pharmacology and pharmacodynamics.

IP protection:
Patent protection scheduled for 2019. For more details a CDA/NDA is required

Commercial offer:
Exclusive/non-exclusive license to the know-how and data

Ownership:
Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague
Institute of Experimental Medicine, Czech Academy of Sciences, Prague
Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University, Olomouc

Contact:
More information is available upon signing a CDA/NDA. Please contact IMTM´s director (director@imtm.upol.cz) or the technology transfer office (tto@imtm.upol.cz)