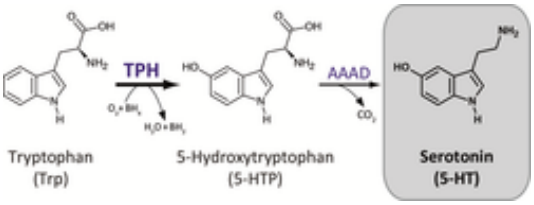
Technology Offer

Novel TPH inhibitors for the treatment of fibrotic diseases and pulmonary arterial hypertension (PAH)

Reference Number 03-00393

Challenge

Serotonin (5-hydroxytryptamine, 5-HT) is a signaling molecule, which is often associated with its function in the CNS. However, more than 90% of the human body's 5-HT is produced in the gut, mainly in enterochromaffin cells, and acts as peripheral 5-HT. 5-HT which is secreted in the gut is taken up by platelets acting as storage and is thus distributed via the circulatory system. Due to its multiple roles acting as a paracrine factor, endocrine hormone, neurotransmitter and growth factor, it is involved in various diseases and disorders. 5-HT is synthesized in a rate-limiting step from tryptophan catalysed by the enzyme tryptophan hydroxylase (TPH), which is present in the two isoforms TPH1 and TPH2. Whereas in the brain only TPH2 is present, TPH1 is responsible for the synthesis of peripheral 5-HT. Since 5-HT can not cross the blood-brain barrier, inhibiting peripheral 5-HT allows to address various disorders without affecting the function of 5-HT in the brain.



Biosynthesis of serotonin (5-HT)

Technology

A novel series of potent TPH small molecule inhibitors is provided which are directed to block the synthesis of peripheral 5-HT. Apart from a pro-inflammatory effect in the intestine, 5-HT is also known to stimulate tissue fibrosis and its function in lung fibrosis is well-known. Several chronic respiratory diseases such as COPD are characterised by fibrosis and remodelling of pulmonary arteries is a key feature in pulmonary arterial hypertension (PAH). Due to the multifactorial causes of PAH, there is still no optimal treatment available and TPH inhibitors are emerging as an attractive approach.

The present series of novel compounds has been identified in a HTS campaign and is based upon a scaffold, which has not yet been linked to TPH. The compounds show potent inhibition of TPH1 and are further developed in respect of favourable drug like properties. The combination of in vitro activity assessment and high-resolution X-ray co-crystalization with TPH1 represents the basis of a lead-driven structure-activity analysis, which lead to the synthesis of potent inhibitors in the nm range.

In addition to the above mentioned indications, TPH1 inhibitors are also suggested for the treatment of irritable bowel syndrome, carcinoid syndrome and osteoporosis. Recent publications do also reveal the role of 5-HT in metabolic homeostasis. Thus, the present inhibitors may have the potential to treat a variety of disorders with aberrant signalling of peripheral 5-HT as a key component.

Commercial Opportunity

Available for licensing or co-development

Patent Situation

EP3262044 and US2018051025 (priority date: 24. February 2015)
WO2018019917 (priority date: 28.July 2016)

Further Reading

Walther, D.J. et al., Science 2003, 299, 76

MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT

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