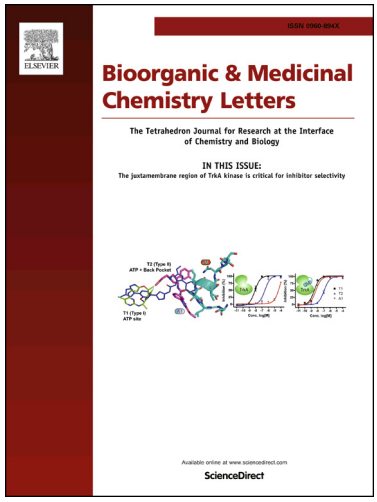
Accepted Manuscript



4-Anilino-pyrimidine, Novel Aldosterone Synthase (CYP11B2) Inhibitors Bearing Pyrimidine Structures

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PII: S0960-894X(17)30271-8
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.03.034
Reference: BMCL 24786

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 27 January 2017
Revised Date: 14 March 2017
Accepted Date: 16 March 2017

Please cite this article as: Meguro, M., Miyauchi, S., Kanao, Y., Naito, S., Suzuki, K., Inoue, S., Yamada, K., Homma, T., Chiba, K., Nara, F., Furuzono, S., 4-Anilino-pyrimidine, Novel Aldosterone Synthase (CYP11B2) Inhibitors Bearing Pyrimidine Structures, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.03.034

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

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Shinagawa R&D Center, Daiichi-Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo, 140-8110, Japan

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Aldosterone,
CYP11B2,
CYP11B1,
Aldosterone synthase inhibitor,
Amino-pyrimidine

ABSTRACT

2,2,2-trifluoro-1-{4-[(4-fluorophenyl)amino]pyrimidin-5-yl}-1-[1-(methylsulfonyl)piperidin-4-yl]ethanol **1** was identified as a novel potent aldosterone synthase inhibitor. Despite large species differences, compound **1** inhibits both human and rodent CYP11B2 in a nano-molar range.

Aldosterone is the major mineralocorticoid hormone, produced in the adrenal cortex by aldosterone synthase, and is known to regulate homeostasis of electrolytes and blood volumes. Aldosterone binds to mineralocorticoid receptors (MRs) and translocates to the cell nucleus. This MR/aldosterone complex then binds to aldosterone-responsive genes that activate or repress gene transcription.[1] Recent studies suggest that aldosterone plays important patho-physiological roles.[2] A chronically high blood aldosterone level leads to blood-pressure independent pro-inflammatory and pro-fibrotic effects resulting in end-organ damage, such as atherosclerosis, myocardial infarction, congestive heart failure, resistant hypertension and diabetic nephropathy. Therefore suppression of the blood aldosterone level is an attractive approach for treatment of cardiovascular disease.

Aldosterone synthase (CYP11B2) catalyzes the final three steps of the biosynthetic pathway of aldosterone. CYP11B2 is a mitochondrial cytochrome P450 (CYP), which is mainly located in the *zona glomerulosa* in the adrenal cortex. Steroid 11β-hydroxygenase (CYP11B1), another isoform of CYP11B, oxidizes 11-deoxycortisol to cortisol, and has approximately 93% homology with the sequence of CYP11B2.[3, 4] Human and rodent (rat, mouse) CYP11B2 have sequences only 68% to one anothor.[3, 4] Inhibition of aldosterone synthase has been recognized as a way for lowering inappropriately high plasma aldosterone concentration.[5]

FAD-286 (*R*-enantiomer of fadrozole) has been identified as an early aldosterone synthase inhibitor (ASI) and examined with double transgenic rats (dTGR rats) overexpressing both human renin and angiotensinogen. This study revealed that FAD-286 diminished plasma aldosterone concentration and reduced mortality and morbidity.[6] LCI-699 (Novartis), structurally related to FAD-286, has had its efficacy clinically evaluated in patients with primary aldosteronism, primary hypertension and resistant hypertension. In the clinical studies, a higher dose of LCI-699 led to suppression of blood cortisol level and increases in both plasma adrenocorticotropic hormone (ACTH) and 11-deoxycortisol (11-DC, precursor of cortisol synthesis) due to strong inhibition of CYP11B1.[7] Since cortisol, a major glucocorticoid, is a vital hormone, significant suppression of plasma cortisol concentration should be avoided. To date, several groups have reported a variety of ASIs[4, 8] to attempt to improve CYP11B2/11B1 selectivity. Most of them have imidazole,[4, 8, 9] pyridine[10-14] and isoquinoline[4, 8] structures (Figure 1).

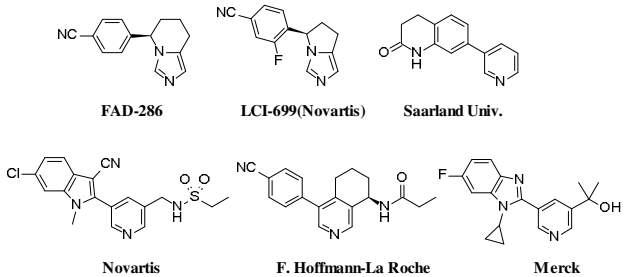

Figure 1. Representative Aldosterone Synthase Inhibitors (ASIs).

* Corresponding author. Tel.: +81-3-3492-3131; fax: +81-3-5740-3643; e-mail: meguro.masaki.i2@daiichisankyo.co.jp