Bioorganic & Medicinal Chemistry Letters 23 (2013) 3051–3058

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

The design and synthesis of a potent glucagon receptor antagonist with favorable physicochemical and pharmacokinetic properties as a candidate for the treatment of type 2 diabetes mellitus

Angel Guzman-Perez *, Jeffrey A. Pfefferkorn, Esther C. Y. Lee, Benjamin D. Stevens, Gary E. Aspnes, Jianwei Bian, Mary T. Didiuk, Kevin J. Filipski, Dianna Moore, Christian Perreault, Matthew F. Sammons, Meihua Tu, Janice Brown, Karen Atkinson, John Litchfield, Beijing Tan, Brian Samas, William J. Zavadoski, Christopher T. Salatto, Judith Treadway

Pfizer Wordwide Research and Development, Eastern Point Road, Groton, CT 06442, USA

ARTICLE INFO

Article history:
Received 8 January 2013
Revised 26 February 2013
Accepted 4 March 2013
Available online 13 March 2013

Keywords:
Glucagon receptor antagonist
Diabetes mellitus
Physicochemical properties

ABSTRACT

A novel and potent small molecule glucagon receptor antagonist for the treatment of diabetes mellitus is reported. This candidate, (*S*)-3-[4-(1-{3,5-dimethyl-4-[4-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenoxy}butyl)benzamido]propanoic acid, has lower molecular weight and lipophilicity than historical glucagon receptor antagonists, resulting in excellent selectivity in broad-panel screening, lower cytotoxicity, and excellent overall in vivo safety in early pre-clinical testing. Additionally, it displays low in vivo clearance and excellent oral bioavailability in both rats and dogs. In a rat glucagon challenge model, it was shown to reduce the glucagon-elicited glucose excursion in a dose-dependent manner and at a concentration consistent with its rat in vitro potency. Its properties make it an excellent candidate for further investigation.

Diabetes mellitus is a rapidly expanding public health problem affecting approximately 347 million people worldwide.[1] Type 2 diabetes mellitus is a metabolic disease in which fasting and postprandial plasma glucose is elevated due to abnormally high hepatic glucose production, reduced glucose-stimulated insulin secretion and insulin resistance.[2] Despite there being several classes of drugs in common clinical use, there is a significant need for new therapies with improved safety and efficacy, in order to help patients achieve appropriate glycemic control and avoid the long term complications associated with the disease.[3]

Glucagon is a polypeptide hormone produced and secreted by α-cells located in the endocrine portion of the pancreas. In the liver, glucagon binding to the glucagon receptor triggers a signal transduction cascade resulting in the stimulation of hepatic glucose production through glycogenolysis and gluconeogenesis. In type 2 diabetic patients, glucagon levels are inappropriately elevated in the fasted state and not adequately suppressed in the postprandial state, which contributes to the elevated hepatic glucose production and plasma glucose levels seen in these patients.[4] Consequently, it has been postulated that a reduction in glucagon action in the liver, brought about by a glucagon receptor antagonist, could reduce hepatic glucose production in type 2 diabetics, resulting in improved glycemic control. This hypothesis is supported by both preclinical and clinical data.[5]

The identification of clinically useful small molecule glucagon receptor antagonists for this class B G-protein coupled receptor has been very difficult. Recently, Merck reported the discovery of MK-0893 (**1**) as a clinical candidate, and several other related series also containing a β-alanine side chain such as compound **2**.[6] Lilly has also recently presented phase 1 data for LY2409021, a glucagon receptor antagonist of undisclosed structure.[7] Most of the reported glucagon receptor antagonists are lipophilic molecules with relatively high molecular weight as exemplified by **1** and **2** (Fig. 1).[8] In order to improve safety and biopharmaceutical properties, we focused our efforts on identifying a series of small molecule glucagon receptor antagonists with reduced lipophilicity ($\log D$ <3) and molecular weight (⩽500).[9]

Previously, we described the identification of a series of pyrazole ethers and amino pyrazoles, exemplified by compound **3**, with low molecular weight and $\log D$.[10] Unfortunately, despite their low dog plasma clearance, these compounds suffered from high rat plasma clearance which complicated rat toxicology studies and reduced the confidence in predictions of human pharmacokinetics. Further, it was discovered that some of the favored compounds from this series had undesired PPAR-δ agonist activity (for example, the PPAR-δ EC_{50} for **3** is 440 nM). Consequently, we explored

* Corresponding author at present address: Therapeutic Discovery, Amgen Inc., 360 Binney St., Cambridge, MA 02142, USA. Tel.: +1 617 444 5070.
E-mail address: aguzmanp@amgen.com (A. Guzman-Perez).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.03.014

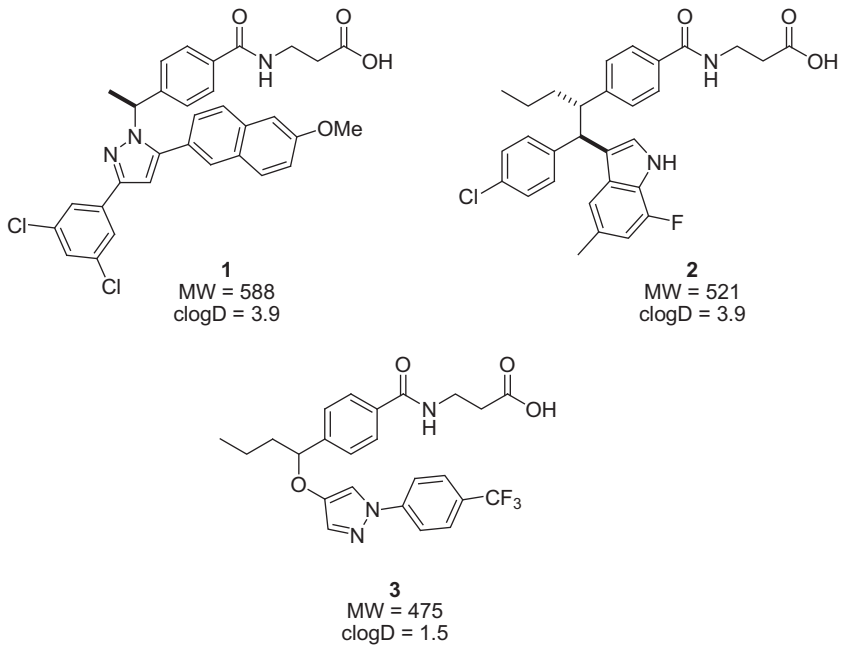
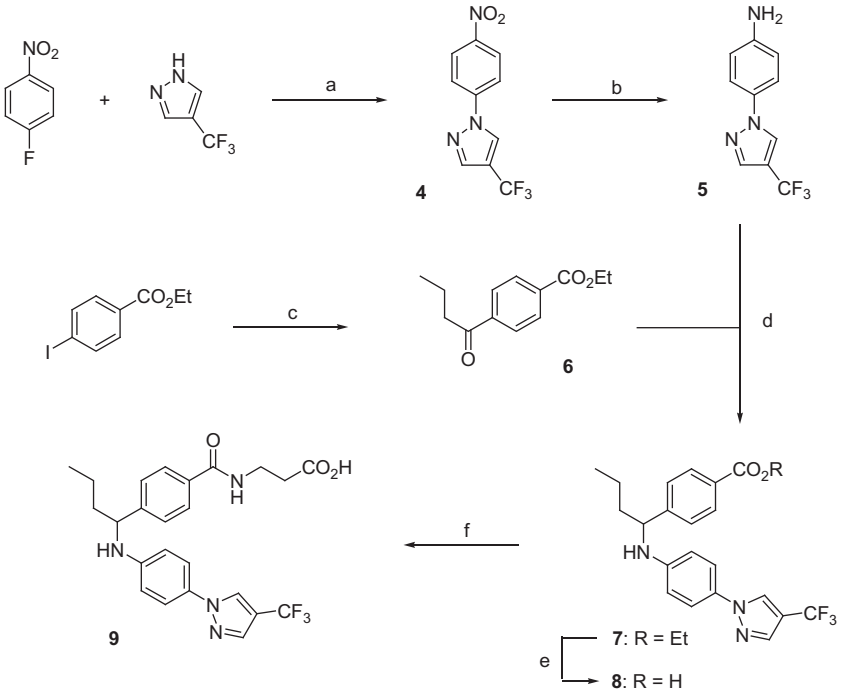


Figure 1. Structures of glucagon receptor antagonists **1**–**3**.

whether polarity could be transposed to the aromatic ring most distal from the acid. This led to the discovery of a new series of polar and low molecular weight glucagon receptor antagonists with improved properties.

The synthesis of the nitrogen-linked versions of these compounds was accomplished as exemplified in Scheme 1. Aniline **5** was prepared in two steps starting from 4-fluoronitrobenzene and 4-trifluoromethylpyrazole, which were coupled to afford intermediate **4**. The nitro functionality in **4** was reduced under transfer hydrogenation conditions to provide **5** in quantitative yield. Butyryl benzoate **6** was synthesized by reacting the Knochel-type Grignard reagent prepared from ethyl-4-iodobenzoate with butyraldehyde to afford the corresponding benzylic alcohol,[11] which was subsequently oxidized under Parikh–Doering conditions. Ketone **6** was an effective substrate for a reductive amination with *N*-heterocyclic aniline **5** using decaborane to afford ester **7**. It is worth noting that decaborane consistently proved superior to other reductive amination reagents for related transformations



Scheme 1. Synthetic method for the synthesis of nitrogen-linked analogs. Reagents and conditions: (a) K_2CO_3, MeCN, 80 °C, 70%; (b) 10% Pd/C, EtOH, THF, $NH_4{\cdot}HCO_2$, quant.; (c) (i) *i*PrMgCl·LiCl, butyraldehyde, THF, −40 °C, (ii) TEA, $SO_3{\cdot}$Pyr., DMSO, CH_2Cl_2, 0 °C, quant.; (d) decaborane, MeOH, 0 °C; (e) 2:1 MeOH: 2.0 M aq LiOH, 66% for two steps; and (f) (i) ethyl-β-alanine·HCl, EDCI, DIPEA, HOBt, THF, (ii) 2:1 MeOH: 2.0 M aq LiOH, 56%.