Bioorganic & Medicinal Chemistry Letters 23 (2013) 6588–6592

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

# Discovery of an intravenous hepatoselective glucokinase activator for the treatment of inpatient hyperglycemia

Benjamin D. Stevens [a,*], John Litchfield [a], Jeffrey A. Pfefferkorn [a], Karen Atkinson [b], Christian Perreault [b], Paul Amor [a], Kevin Bahnck [b], Martin A. Berliner [b], Jessica Calloway [a], Anthony Carlo [b], David R. Derksen [b], Kevin J. Filipski [a], Mike Gumkowski [b], Charanjeet Jassal [b], Margit MacDougall [b], Brendan Murphy [b], Paul Nkansah [b], John Pettersen [b], Charles Rotter [b], Yan Zhang [b]

[a] Cambridge Laboratories, Pfizer Worldwide Research & Development, 620 Memorial Drive, Cambridge, MA 02139, United States
[b] Groton Laboratories, Pfizer Worldwide Research & Development, Eastern Point Road, Groton, CT 06340, United States

ARTICLE INFO

*Article history:*
Received 24 September 2013
Revised 26 October 2013
Accepted 28 October 2013
Available online 4 November 2013

*Keywords:*
Glucokinase
Hepatoselective
Allosteric
OATP
Diabetes

ABSTRACT

Glucokinase (hexokinase IV) continues to be a compelling target for the treatment of type 2 diabetes given the wealth of supporting human genetics data and numerous reports of robust clinical glucose lowering in patients treated with small molecule allosteric activators. Recent work has demonstrated the ability of hepatoselective activators to deliver glucose lowering efficacy with minimal risk of hypoglycemia. While orally administered agents require a considerable degree of passive permeability to promote suitable exposures, there is no such restriction on intravenously delivered drugs. Therefore, minimization of membrane diffusion in the context of an intravenously agent should ensure optimal hepatic targeting and therapeutic index. This work details the identification a hepatoselective GKA exhibiting the aforementioned properties.

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Type 2 Diabetes Mellitus (T2DM) represents one the most significant healthcare challenges facing modern society. It is currently estimated that over 300 million individuals suffer from diabetes worldwide, the majority of these cases being type 2.[1–4] While there have been enormous resources invested in the development of effective oral treatments for T2DM in the outpatient setting, there has been a lack of emphasis on novel agents designed for inpatient glucose control despite the fact that achieving safe and effective inpatient glucose control is an important challenge for healthcare practitioners.[5–12] Preoperative T2DM patients are frequently required to discontinue oral therapies and are generally placed on modified diets or parenteral nutrition leading to considerable variability in glucose levels.[5] It has been demonstrated in observational studies and retrospective analyses that glucose variability including incidents of both hyperglycemia and hypoglycemia in critical care patients correlate with poorer patient outcomes as quantified by such markers as length of stay (LOS), secondary infections, and mortality.[13–20] The current treatment paradigm for inpatient hyperglycemia relies exclusively on intravenous (IV) insulin or complex basal/bolus insulin protocols to control glucose levels. Insulin is highly effective in these settings due to its rapid onset of action and efficacy, but it suffers from a narrow therapeutic index against hypoglycemia. Without the utilization of continuous glucose monitoring (CGM), frequent finger stick tests are necessary to optimize insulin delivery rates and minimize hypoglycemic episodes. Achieving and maintaining effective control in a medically dynamic inpatient setting requires a significant investment in skilled nursing resources and access to glycemic control teams to help prevent the negative outcomes associated with hypo *or* hyperglycemic episodes. Hence, the development of novel therapeutic agents, suitable for inpatient glucose control, with an improved therapeutic index for hypoglycemia could represent an important advance for both patient care and health economics.

The glucokinase enzyme represents one of the most thoroughly studied targets for the treatment of T2DM within the pharmaceutical field. The function of glucokinase (GK) is to convert glucose into glucose 6-phosphate (G-6-P), the key precursor to glycolysis or entry into the pentose phosphate pathway. Although GK plays numerous roles in vivo, it is perhaps most well known for its important function as a 'glucostat' in the β-cells of the pancreas, consequently leading to downstream regulation of glucose-stimulated insulin secretion (GSIS).[21–25,26] The enzyme has clearly evolved to serve in this unique role given that it has low affinity for glucose ($K_m \approx 8$ mM), while it exhibits positive substrate cooperativity and lacks the capacity to be inhibited by G-6-P. Glucokinase also

* Corresponding author. Tel.: +1 4124019375.
*E-mail address:* bdsteven@gmail.com (B.D. Stevens).

0960-894X/$ - see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.bmcl.2013.10.057

plays a key role in the liver where it closely regulates hepatic glucose uptake, glycogen synthesis, and gluconeogenesis.

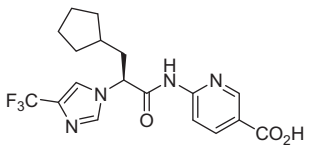
Given the overwhelming body of supporting human genetic data and the repeated demonstration of glucose lowering efficacy with small molecule allosteric activators, it is notable that GK remains as of yet an undrugged target.[27] Induction of clinical hypoglycemia remains a key hurdle that has led to attrition of numerous GK activators.[28] As such, several groups have proposed novel strategies for enhancing the therapeutic index of these compounds. One such strategy has involved the preferential activation of GK within the liver, which can be accomplished by chemically targeting compounds for uptake via OATP transporters that are expressed constitutively in human hepatocytes.[29,30] Simultaneously, the passive permeability of these compounds must be minimized in order to limit exposures within peripheral tissues, thereby effectively eliminating the potentiation of GSIS mediated via activating GK in the pancreas.

For an orally (PO) dosed therapeutic relying on a liver targeting strategy, a key balance between oral bioavailability versus peripheral exposure must be achieved. We recently demonstrated this approach with the discovery of PF-04991532 (**1**, Fig. 1) as an orally administered liver selective glucokinase activator, which advanced to Phase 2 clinical studies for the treatment of T2DM.[29,30] In Wistar rats, PF-04991532 was shown to have enhanced liver to plasma (8.8:1) and impaired pancreas to plasma (0.12:1) distribution affording a substantial differential between liver and pancreas exposure (75:1). This candidate was efficacious in various preclinical models of diabetes and was recently shown to be efficacious in T2DM patients with low hypoglycemia risk.[30]

In this study, sought to evaluate whether this liver targeting approach could be further extended to the targeting of intravenously administered therapeutics. In particular, because intravenously administered therapeutics do not rely on oral absorption, we sought to explore whether even greater hepatic targeting might be realized by further restricting passive permeability to an extent not compatible with oral delivery. Herein we describe the identification and optimization of an IV deliverable hepatoselective glucokinase activator for the potential treatment of in-patient hyperglycemia.

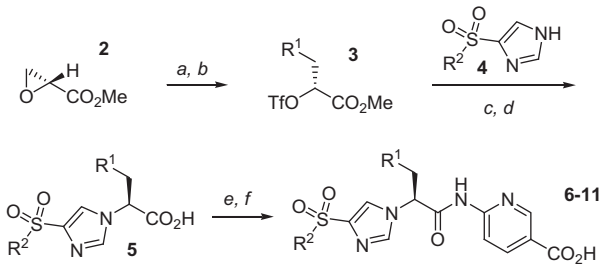
The synthesis of sulfonyl imidazole analogs of **1** generally followed previously reported routes (Scheme 1).[29] Various alkyl Grignard reagents were reacted with commercially available methyl (2*R*)-glycidate **2** to yield the corresponding free alcohols which were readily converted into the intermediate triflates **3**. Nucleophilic inversion of the chiral triflates using sulfonyl imidazoles **4** followed by acidic hydrolysis of the methyl ester afforded carboxylic acid **5**. Subsequent amidation of the free acids with *O*-benzyl-6-aminonicotinate and hydrogenolysis of the protecting group followed by chiral purification gave the final products **6–11** (Table 1).[a]Biochemical assay values reported as the geometric mean of $n$ >2 independent determinations.

The activity of activators prepared in these studies was evaluated in a biochemical assay using human recombinant glucokinase as previously described.[31] In this assay, determination of an activator's maximum fold effect on reducing the glucokinase $K_m$



**1**

**Figure 1.** Structure of Hepatoselective GKA PF-04991532 (1).



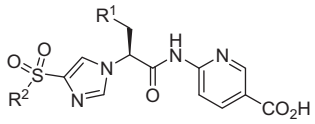
**Scheme 1.** General synthesis of sulfonyl imidazole derivatives. Reagents and conditions: (a) $R^1$-MgBr, $Li_2CuCl_2$, $Et_2O$, THF, −50 → −78 °C; (b) $Tf_2O$, 2,6-lutidine, heptane, $CH_2Cl_2$, −10 °C; (c) $K_2CO_3$, EtOAc, 23 °C; (d) aq 6 N HCl, 100 °C; (e) benzyl 6-aminonicotinate, T3P, 2,6-lutidine, EtOAc, 10 → 23 °C; (f) $H_2$, Pd/C, $^i$PrOH.

for glucose was defined as α and the maximum fold effect on altering the enzyme's $V_{max}$ was defined as β. Values of α ranged from 0–1 with lower values of α representing more substantial reductions $K_m$ and increases in the enzyme's glucose affinity for glucose. Values of β >1 represented activator induced increases in the enzyme's $V_{max}$. An activator's potency or $EC_{50}$ was defined as the concentration affording a half maximal reduction in $K_m$.

From a structure activity perspective, previous work in the hepatoselective cycloalkyl propionate GKAs revealed a tolerance of various R groups in the 4-imidazolyl position. Although lipophilic groups generally led to optimal potency, the pancreatic permeability of these compounds could be reduced by two to threefold by introduction of a polar sulfonyl group (Table 1). Targets **6** and **7** containing a cyclopentyl group at $R^1$ exhibited comparable potency to the corresponding cyclohexyl derivatives **8** and **9**, but led to reduced maximal enzyme activation (β). In addition, the aqueous kinetic solubility of cyclohexyl propionates proved inferior (e.g., **7** = 428 μM vs **9** = 198 μM at pH 6.5), thus rendering them less attractive for IV use. Interestingly, attempts to increase polar surface area and further reduce passive permeability through incorporation of a pyranyl moiety (i.e., **10** and **11**) resulted in substantial loss of activation potency. Both cyclopropyl and cyclobutyl substituents were effective at $R^2$, with cyclopropyl possessing a small advantage in potency, α, and β values.

Of the profiled compounds, **6** and **7** were selected for further study based on their balance of physical properties and enzyme activation profile. Previous work has highlighted the ratio of functional effect in INS-1 cell lines vs $EC_{50}$ in the biochemical glucokinase enzyme assay as an effective gauge of pancreatic impairment; hence, the dose response effect of activators **6** and **7** on glucose-stimulated insulin secretion in INS-1 cells cultured in 5 mM glucose.[29] In this system, activator **6** exhibited an $EC_{50}$ = 26 μM and compound **7** had $EC_{50}$ = 174 μM highlighting the functional impairment of these activators in a pancreatic cell line. By comparison reference compound **1** had $EC_{50}$ = 6.9 μM in the INS-1 assay. Given the enhanced functional impairment for compound **7**, relative to **6**, in the INS-1 assay, this particular compound was selected for further profiling. We next sought to evaluate the effect of **7** in primary rat hepatocytes (expressing organic anion transporters) in order to compare its activity in these cells relative to the INS-1 cells. As previously described, glucokinase activity in hepatocytes is regulated though an interaction with glucokinase regulatory protein (GKRP) which, during conditions of low glucose, binds the inactive conformation of glucokinase and sequesters the enzyme to the nucleus.[29] As glucose concentrations increase, glucokinase dissociates from GKRP and enters the cytoplasm. Glucokinase activators have been previously shown to disrupt this glucokinase-GKRP interaction; thus to characterize the effects of compound **7** on the glucokinase-GKRP interaction, a dose response evaluation was conducted in freshly isolated Wistar rat hepatocytes at

**Table 1**
Structure–activity relationships for glucokinase activators **6–11**[a]




| | $R^1$ | $R^2$ | Human GK activation | | | Permeability RRCK $P_{app}$ ($10^{-6}$ cm/s) | Log*D* (pH 7.4) | tPSA |
|---|---|---|---|---|---|---|---|---|
| | | | $Ec_{50}$ (nM) | α | β | | | |
| **1** | (Fig. 1) | | 90 | 0.03 | 1.65 | 1.0 | 0.68 | 97 |
| **6** | c-pentyl | c-propyl | 137 | 0.05 | 1.68 | 0.6 | −0.20 | 131 |
| **7** | c-pentyl | c-butyl | 201 | 0.06 | 1.35 | 0.5 | −0.10 | 131 |
| **8** | c-hexyl | c-propyl | 113 | 0.08 | 1.50 | 0.5 | −0.25 | 0.5 |
| **9** | c-hexyl | c-butyl | 227 | 0.08 | 1.25 | 0.3 | 0.15 | 131 |
| **10** | 4-Pyranyl | c-propyl | 1350 | 0.11 | 1.21 | 0.9 | −1.85 | 140 |
| **11** | 4-Pyranyl | c-butyl | >10,000 | — | — | 0.9 | −1.55 | 140 |

[a] Biochemical assay values reported as the geometric mean of n > 2 independent determinations.

8.9 mM glucose. Activator induced translocation of glucokinase in the hepatocytes was determined by indirect immunofluoresence which measures the relative staining intensities of glucokinase in the cytoplasm and nucleus. In this assay system, compound **7** was found to have an $IC_{50}$ = 1.7 μM for the nuclear to cyctosolic translocation of glucokinase. The contrast in activity of compound **7** between rat INS-1 cells ($IC_{50}$ = 174 μM) and rat hepatocytes ($IC_{50}$ = 1.7 μM) further illustrates how transporter-mediated uptake of **7** into hepatocytes enhances its activity in these liver cells relative to other cell types that lack organic anion transporter expression.

Transporter-mediated uptake of **7** in comparison to reference compound **1** was also evaluated in sandwich cultured rat hepatocytes, revealing that both compounds were comparable substrates for hepatic transporters as shown in Table 2. In addition, compound **7** was tested in OATP1B1- or OATP1B3-transfected HEK cells for transporter-mediated uptake relative to mock-transfected HEK cells and was found to be a substrate for both 1B1 and 1B3 with uptake ratios of 4.1 and 2.3, respectively.[32] Taken together, this profile would suggest that compound **7** would achieve increased free tissue concentrations within the liver relative to plasma. Therefore, the reduced functional response of **7** in β-cell model systems in addition to in vitro active uptake into hepatocytes illustrated the potential of this compound to provide optimal liver-to-pancreas exposures in vivo which should provide an enhancement in therapeutic index against hypoglycemia.

To complement this functional data in INS-1 cells and hepatocytes, a direct comparison of diffusion rates through RRCK cell monolayers reinforced the overall lower permeability of compound **7** versus **1**, particularly at low pH (Fig. 2). Notably, the passive permeability of **7** remained low across the pH range whereas at lower pH values the passive permeability of reference compound **1** increased consistent with its oral absorption profile.[29]

While compound **7**, as the free carboxylic acid, exhibited moderate aqueous solubility, it presented limitations for the evaluation of higher doses in IV preclinical bolus or infusion efficacy and safety studies. Hence, the corresponding sodium carboxylate salt of compound **7** was prepared and found to have enhanced aqueous solubility (approx. 41 mM, final pH 8.5) thereby enabling a full evaluation of in vivo activity in rodents and dogs. Unfortunately, the heteroaryl amide linkage in **7** proved to be moderately sensitive to hydrolysis under even weakly basic conditions. Thus, for clinical applications, it was necessary to evaluate the stability of the parent acid in various non-aqueous delivery vehicles. Accelerated stability studies suggested that acceptable profiles could be identified; however, as summarized in Table 3, limited impurities derived from the amide hydrolysis would continue to form even given optimal formulations.

Given the encouraging body of in vitro data, compound **7** was evaluated for rodent and dog pharmacokinetics (Table 4). In both species, compound **7** exhibited rapid systemic clearance. Intrinsic microsomal clearance of **7** (<8.0 ml/min/kg) was identical to that

**Table 2**
Active uptake of compounds **7** and **1** in sandwich cultured rat hepatocytes

| | Total uptake (μL/min/mg protein) | Passive uptake (μL/min/mg protein) | Active uptake (%) |
|---|---|---|---|
| **7** | 22 | 12 | 55 |
| **1** | 26 | 11 | 58 |
| Rosuvastatin | 158–271 | 5.8–12 | 91–96 |

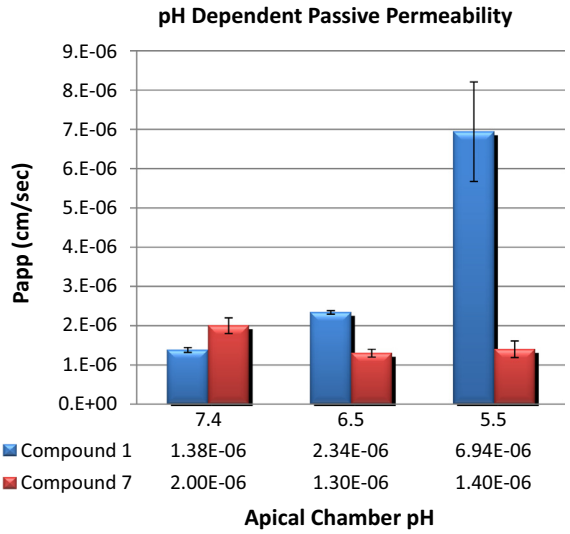



**Figure 2.** pH dependent passive permeability through RRCK cell monolayer.

**Table 3**
Accelerated stability studies of compound **7** in non-aqueous vehicles

| | Storage condition (°C) | Predicted increase of main degradant following 1 week |
|---|---|---|
| PEG 400 | 5 | 0.03 |
| | 25 | 0.29 |
| Propylene glycol | 5 | 0.17 |
| | 25 | 1.41 |
| EtOH/$H_2O$ (8:2) | 5 | 0.03 |
| | 25 | 0.33 |

**Table 4**
Preclinical pharmacokinetics of glucokinase activator **7**

| | Dose (mg/kg) | $AUC_{(0\text{-}24)}$ (ng h/ml) | $C_{max}$ (ng/ml) | Cl (ml $min^{-1}$ $kg^{-1}$) | $T_{1/2}$ (h) | $Vd_{ss}$(L/kg) | F (%) |
|---|---|---|---|---|---|---|---|
| Rat iv | 1 | 176 | 1400 | 96 | 0.2 | 0.8 | |
| Rat po | 5 | 3.4 | 2.5 | | | | <1 |
| Rat iv | 1 | 932 | 6350 | 18 | 0.7 | 0.4 | |
| Dog po | 5 | 36.6 | 12.8 | | | | <5 |

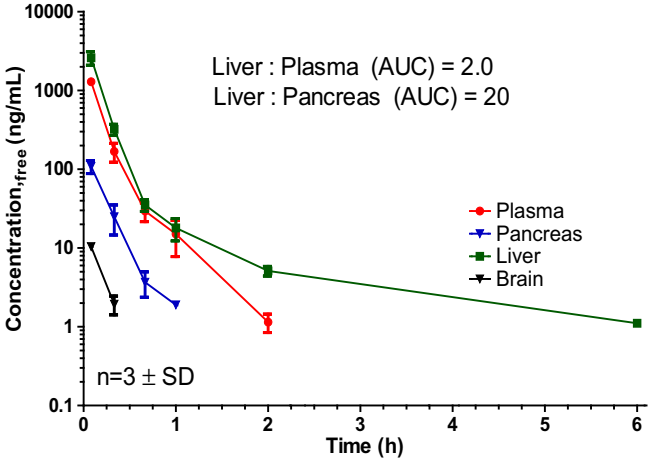



**Figure 3.** IV bolus rat tissue distribution data for compound **7** (5 mg/kg dose).

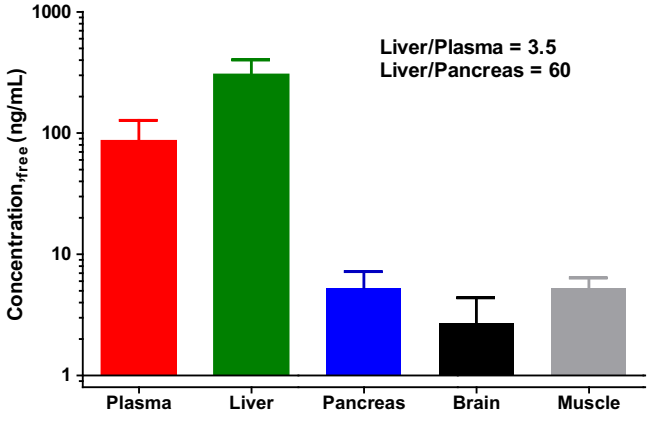



**Figure 4.** IV infusion rat tissue distribution data for compound **7**.

reported for **1**, reflective of a negligible contribution of oxidative metabolism. While the reported oral bioavailability compound **1** was 18% in both rat and dog, negligible exposures were recorded for compound **7** following oral dosing in both species.

Ideal inpatient injectible antiglycemic agents require the capacity for both infusion and bolus administration. As such, tissue distribution under both dosing paradigms was evaluated preclinically in rodents. Following a 5 mg/kg bolus administration to rats, liver-to-pancreas AUC ratio of compound **7** was approximately 20:1 while the liver-to-plasma ratio was 1:2 as shown in Fig. 3. Slightly enhanced liver exposure levels (60:1 liver-to-pancreas, 3.5:1 liver-to-plasma) were observed during a continuous 4 day IV infusion of compound **7** at doses approximating the in vitro $EC_{50}$ (Fig. 4).

To access the glucose lowering efficacy of **7**, we conducted a comparative experiment with PF-04991532 (**1**). This study utilized diabetic Goto-Kakizaki rats which were either administered **1** by oral gavage or **7** via IV infusion. Specifically, compound **7** was delivered as an infusion (IV) at 24 mg/kg/h for a 4 h period while reference compound **1** was delivered as a bolus (PO) at 100 mg/kg, a dose offering plasma exposures comparable levels where clinical efficacy was previously reported in T2DM subjects.[30,33] The corresponding vehicle controls for both compounds were also included. An oral glucose tolerance test (OGTT) was performed 2 h following initiation of the IV infusion of compound **7** and 1 h following the PO dosing of **1**. At these doses, compound **7** lowered glucose excursion AUC by 15.4% while compound **1** afforded a 17.7% reduction suggesting that IV delivery of glucokinase activator **7** offered comparable preclinical efficacy to that observed with oral dosing of PF-04991532 (**1**). No hypoglycemia was observed in this study. Given the previously reported clinical efficacy of reference compound **1**, the comparable efficacy of **7** in this experiment was viewed as a promising indication of its therapeutic potential.

Management of inpatient glucose levels is an important aspect of hospital cost and quality of patient care. In this report, we have identified a new class of hepatic targeted glucokinase activators that may offer the potential for IV delivery. Compound **7** exhibits promising efficacy in preclinical animal models without incurring a risk of hypoglycemia. Given this favorable profile, compound **7** could be administered as a part of a standard admission protocol for inpatient diabetics in cases where oral medications must be discontinued.

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