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Discovery of an Orally Efficacious Positive Allosteric Modulator of the Glucagon-like Peptide-1 Receptor

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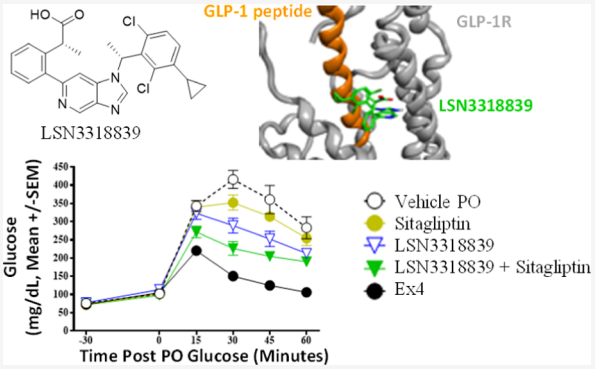
ABSTRACT: The identification of LSN3318839, a positive allosteric modulator of the glucagon-like peptide-1 receptor (GLP-1R), is described. LSN3318839 increases the potency and efficacy of the weak metabolite GLP-1(9-36)NH_2 to become a full agonist at the GLP-1R and modestly potentiates the activity of the highly potent full-length ligand, GLP-1(7-36)NH_2. LSN3318839 preferentially enhances G protein-coupled signaling by the GLP-1R over β-arrestin recruitment. *Ex vivo* experiments show that the combination of GLP-1(9-36)NH_2 and LSN3318839 produces glucose-dependent insulin secretion similar to that of GLP-1(7-36)NH_2. Under nutrient-stimulated conditions that release GLP-1, LSN3318839 demonstrates robust glucose lowering in animal models alone or in treatment combination with sitagliptin. From a therapeutic perspective, the biological properties of LSN3318839 support the concept that GLP-1R potentiation is sufficient for reducing hyperglycemia.



INTRODUCTION

Activation of the glucagon-like peptide-1 receptor (GLP-1R) is a validated mechanism for the treatment of type 2 diabetes mellitus (T2DM). The GLP-1R is a member of the peptide hormone class B G protein-coupled receptors (GPCRs) and is activated by the peptide GLP-1(7-36)NH_2 [hereafter referred to as GLP-1(7−36)], which is secreted by the gut upon nutrient consumption. GLP-1(7−36) binds to the GLP-1R in pancreatic beta cells, activating Gαs to stimulate cAMP production, which ultimately enhances glucose-dependent insulin secretion. The GLP-1R is also expressed in areas of the gastrointestinal tract and in the central and peripheral nervous systems, where it helps regulate energy metabolism.[1] GLP-1(7−36) is rapidly inactivated ($t_{1/2} \approx 1-2$ min) by the ubiquitous enzyme dipeptidylpeptidase 4 (DPP4), which cleaves the first two amino acids of the peptide to yield the metabolite GLP-1(9−36)NH_2 [hereafter referred to as GLP-1(9−36)].

To date, only peptide agonists of the GLP-1R are marketed for the treatment of T2DM,[2] but several small-molecule agonists have entered clinical testing, including TTP273 (presumably OAD2),[3] PF-06882961,[4] PF-07081532,[5] and LY3502970.[6] Small-molecule positive allosteric modulators (PAMs) of the GLP-1R could also offer a pharmacological strategy for this proven therapeutic target.[7,8] Allosteric modulators would only enhance receptor signaling when the endogenous ligand is present, thereby providing an opportunity to selectively enhance the normal GLP-1 response during nutrient consumption. Several small molecules have been described that potentiate the actions of GLP-1(7−36) at the GLP-1R;[9−11] however, less information exists on the potentiation of GLP-1(9−36).[12,13] We recently reported a cryoEM structure of LSN3160440 in complex with the GLP-1R, full-length GLP-1, and the Gs protein.[14] LSN3160440 acts as an uncompetitive activator of the GLP-1R that potentiates the activity of GLP-1(9−36) by interacting with both the peptide and the receptor.

We now present the discovery and large-scale synthesis of the compound LSN3318839, a biased PAM of GLP-1(9−36) and GLP-1(7−36) at the GLP-1R with optimized pharmacokinetic properties. Molecular modeling predicts that the compound interacts simultaneously with the GLP-1R and the

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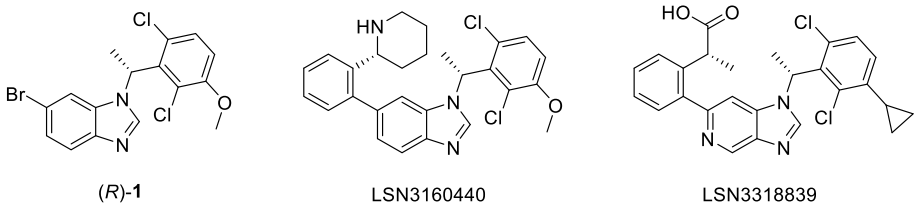

Figure 1. Previously described GLP-1R PAMs (*R*)-**1** and LSN3160440 and the orally efficacious analogue LSN3318839.

peptide acting as a molecular glue, a mechanism similar to that described for LSN3160440. We present *in vivo* studies demonstrating that this compound is an orally efficacious glucose lowering agent.

RESULTS AND DISCUSSION

The discovery of LSN3160440 and its precursor (*R*)-**1** as GLP-1R potentiators was described recently (Figure 1).[14] Poor pharmacokinetic properties in rodents were observed for LSN3160440, particularly high clearance (Cl = 78 ± 10 mL/min/kg) and high volume of distribution (V_{dss} = 18 ± 1 L/kg) in rats, and therefore did not allow advancement of this compound. LSN3160440 was discovered by optimization of the core (*R*)-**1**, and during this process, we found that core (*R*)-7, containing two structural changes relative to (*R*)-**1**, resulted in a threefold improvement in potency (Table 1). In

Table 1. *In vitro* Pharmacology of GLP-1(9−36) Potentiators

	shift of GLP-1 (9−36)		CRC of compound at EC20 of GLP-1(9−36)	
compound	GLP-1(9−36)-fold shift (SE)	E_{MAX} % (SE)	EC_{50} nM (SE)	E_{MAX} % (SE)
(*R*)-**1**	250 (20)	115 (3)	800 (100)	102 (6)
LSN3160440	15000 (2000)	88 (3)	24 (4)	120 (8)
(*R*)-7	830 (50)	102 (3)	270 (40)	98 (6)
8	300 (40)	110 (6)	1800 (400)	113 (5)
LSN3318839	7300 (1000)	103 (3)	14 (2)	104 (2)

an aim to improve the pharmacokinetic properties of the series, a thorough structure−activity relationship campaign on (*R*)-7 substitution at the 6 position of the core led to the identification of LSN3318839, a compound with similar potency but improved pharmacokinetic properties compared to those of LSN3160440. The ability of **8**, diastereomer of LSN3318839 at the new chiral center, to potentiate GLP-1(9−36) was 20-fold worse.

Synthesis. Enantiomerically pure amine (*R*)-**4** was synthesized in five steps starting from 2,4-dichloro-1-bromobenzene **2**. Palladium-catalyzed coupling of **2** with potassium cyclopropyl trifluoroborate followed by lithiation−carbonylation provided aldehyde **3** (Scheme 1). Installation of the chiral amine relied on the Ellman sulfinimide approach.[15] Compound (*R*)-**4** was obtained in three steps in a 78% overall yield and 95% ee. Reaction of amine (*R*)-**4** with 2,4-dibromo-5-nitropyridine followed by reduction of the nitro group with Fe and *in situ* cyclization provided imidazopyridine (*R*)-7 in a 45% yield and 94% ee. Palladium-catalyzed coupling with boronate (±)-**6**, obtained by standard methods from ester **5** in a 79% yield, followed by hydrolysis of the ester and chiral separation of the two diastereomers provided compounds LSN3318839 and **8** in 36 and 39% yield, respectively, and >98% ee.

Pharmacokinetic Properties of LSN3318839. Pharmacokinetic studies were conducted in CD1 mice, SD rats, and beagle dogs to assess the oral and intravenous exposure for compound LSN3318839. Other pharmacokinetic parameters were also determined and are summarized in Table 2. Low to moderate intravenous clearance was observed (Cl 9, 42, and 19 ml/min/kg for mice, rats, and dogs, respectively). The oral bioavailability for mice and rats was calculated to be 67% ± 19 and 45% ± 14, respectively, and rapid absorption was observed in mice (T_{max} = 0.58 h). The V_{dss} was determined to be similar in both rodent species (1.6 L/kg in each) and comparatively lower in dogs (0.3 L/kg). Both clearance and volume of distribution were improved in LSN3318839 versus LSN3160440. Diastereomer **8** was detected in plasma following intravenous and oral administration of LSN3318839 in rats, suggesting partial epimerization of the chiral center alpha to the carboxylic acid. The extent of interconversion appeared to be greater following oral (24% metabolite/parent ratio) than following intravenous administration (8%). The formation of compound **8** was not measured in mice or dogs.

Compound Binding Mode. LSN3318839 was docked into the cryoEM structure of LSN3160440 in complex with the GLP-1R, GLP-1(7-37), and Gs protein (PDB ID: 6VCB). Both molecules occupy a pocket formed by TM1, TM2, and the peptide agonist, showing interactions with each. Similar to LSN3160440, LSN3318839 also has a key $\pi-\pi$ interaction with Tyr145 and several van der Waals interactions with the receptor and with the GLP-1 peptide, through Val16, Leu20, and Phe12 of the peptide ligand (Figure 2A). Although the cyclopropane was identified as a replacement of the OMe group of LSN3160440, the docking model suggested that it could be occupying a buried small lipophilic pocket formed between the stalk region of the GLP-1R, and the peptide with Leu141 of the receptor and Val16 of the peptide at the bottom of the pocket, instead of exposing to the solvent and pointing toward TM2 like the OMe group. The pocket is also surrounded by three other lipophilic residues, Leu142 of the receptor and Leu20 and Tyr19 of the peptide, with Glu138 of the receptor on top of the pocket. There are two reasons for why the OMe group does not occupy the pocket: (1) occupying the pocket would require the OMe group to become perpendicular to the dichlorophenyl ring, which is energetically unfavorable, and (2) the OMe group is too small to fill the pocket completely. This may explain the improvement in potency obtained with the cyclopropane replacement (Figure 2B). The 2-phenylpropionate is exposed to the solvent, with the carboxylic acid forming a salt bridge with Lys202, possibly further stabilizing the complex. Similar to the assessment of LSN3160440,[14] the model predicts that LSN3318839 interacts with Leu12 of GLP-1(9-36) to stabilize

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Scheme 1. Reagents and Conditions: (a) Potassium Cyclopropyl Trifluoroborate, $Pd(OAc)_2$, XPhos, K_2CO_3, Toluene/Water, 85 °C; (b) LDA, DMF, THF, −70 °C, 71%, Two Steps; (c) (*S*)-2-Methyl-2-Propanesulfinamide, Cs_2CO_3, DCM, 40 °C, 99%; (d) MeMgBr, $CuBr_2$, DCM, 5−7 °C, 96%; (e) HCl, MeOH, rt, 83, 95% ee; (f) LHMDS, MeI, THF, −78 °C to −20 °C, Quant.; (g) Bis(pinacolato)diboron, $Pd(dppf)Cl_2$, KOAc, 1,4-Dioxane, 90 °C, 79%; (h) 2,4-Dibromo-5-nitropyridine, Et_3N, K_2CO_3, 2-MeTHF, 70 °C, 88%; (i) Fe, $HC(MeO)_3$, AcOH, 80 °C, 72%; (j) (±)-6, cataCXium A Pd G3, Na_2CO_3, Toluene, 90 °C, 83%, 1:1 Mixture of Isomers; and (k) NaOH, *i*-PrOH/Water, 80 °C, SFC Chiral Separation, 36% for LSN3318839, 39% for 8

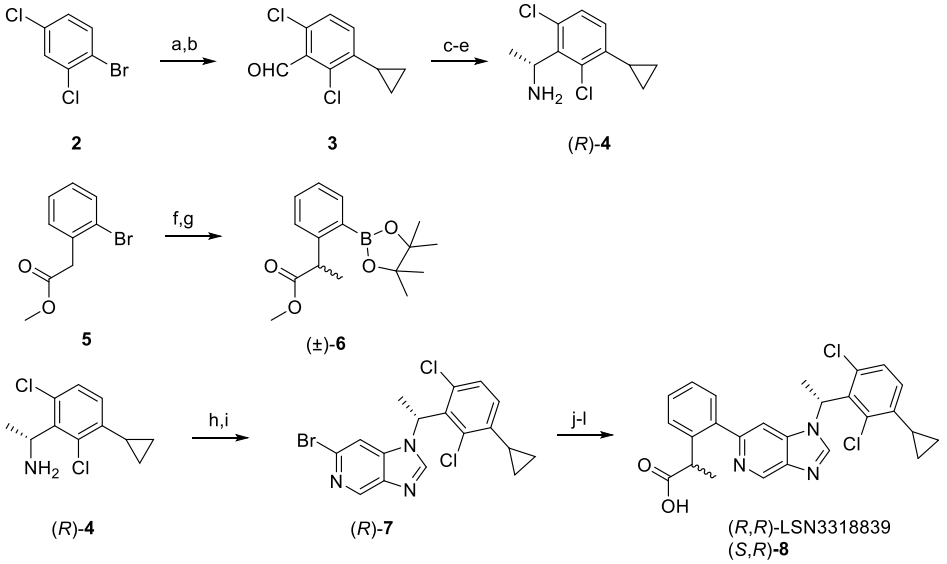

Table 2. Summary of Pharmacokinetic Parameters of LSN3318839 in Mice, Rats, and Dogs (Mean ± SD, N = 3)

	mouse		rat		dog
	1 mg/kg (iv)	3 mg/kg (po)	1 mg/kg (iv)	3 mg/kg (po)	1 mg/kg (iv)
AUC (nM × hour)	3640 ± 393	7300 ± 2060	859 ± 197	1160 ± 359	1880 ± 41
C_{max} (nM)	1430 ± 499	2040 ± 889	1420 ± 72	183 ± 39	6870 ± 230
$T_{1/2}$ (h)	2.1 ± 0.4	1.6 ± 0.4	0.6 ± 0.04	2.9 ± 0	0.6 ± 0.04
V_{dss} (L/kg)	1.6 ± 0.2		1.6 ± 0.2		0.3 ± 0
Cl (mL/min/kg)	9.0 ± 0.9		41.9 ± 9.4		18.5 ± 0.4
T_{max} (h)		0.58 ± 0.14		1.8 ± 1.9	
% F		67 ± 19		45 ± 14	

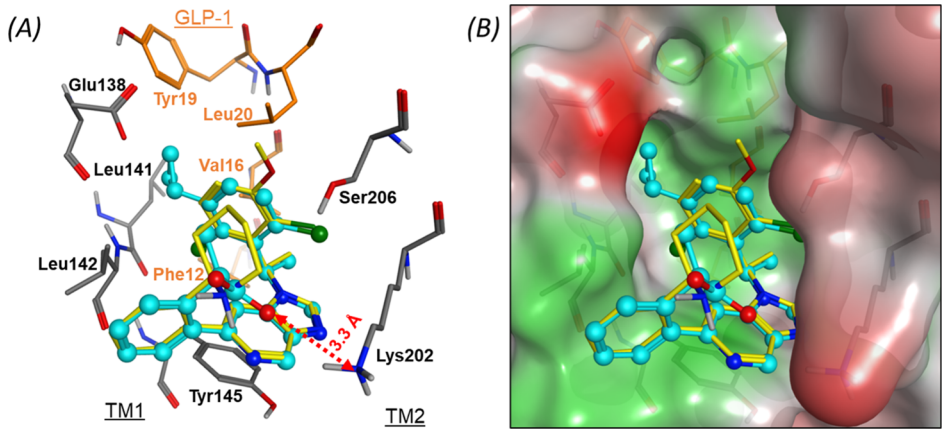

Figure 2. (A) Binding model of LSN3318839 (cyan) in the LSN3160440 pocket based on the cryo-EM structure of LSN3160440 (yellow), GLP-1R (dark grey), GLP-1(7-37) (orange), and the Gs protein (not shown) complex (PDB ID: 6VCB). (B) Molecular surface of the binding pocket colored by hydrophobicity with hydrophilic in red and lipophilic in green. The binding model of LSN3318839 was built by editing LSN3160440 in the GLP-1R/GLP-1 complex, followed by energy minimization in MOE2019 (Chemical Computing Group) and MD simulation refinement using Desmond in Maestro 2019.4 (Schrödinger Release 2019-4) as described previously for LSN3160440.[14] The molecular graphs were generated using MOE2019.

it in the bound conformation, thus enhancing affinity for the active state of the receptor.

***In Vitro* Pharmacology.** We quantified the ability of LSN3318839 to potentiate GLP-1R-stimulated cAMP accu-

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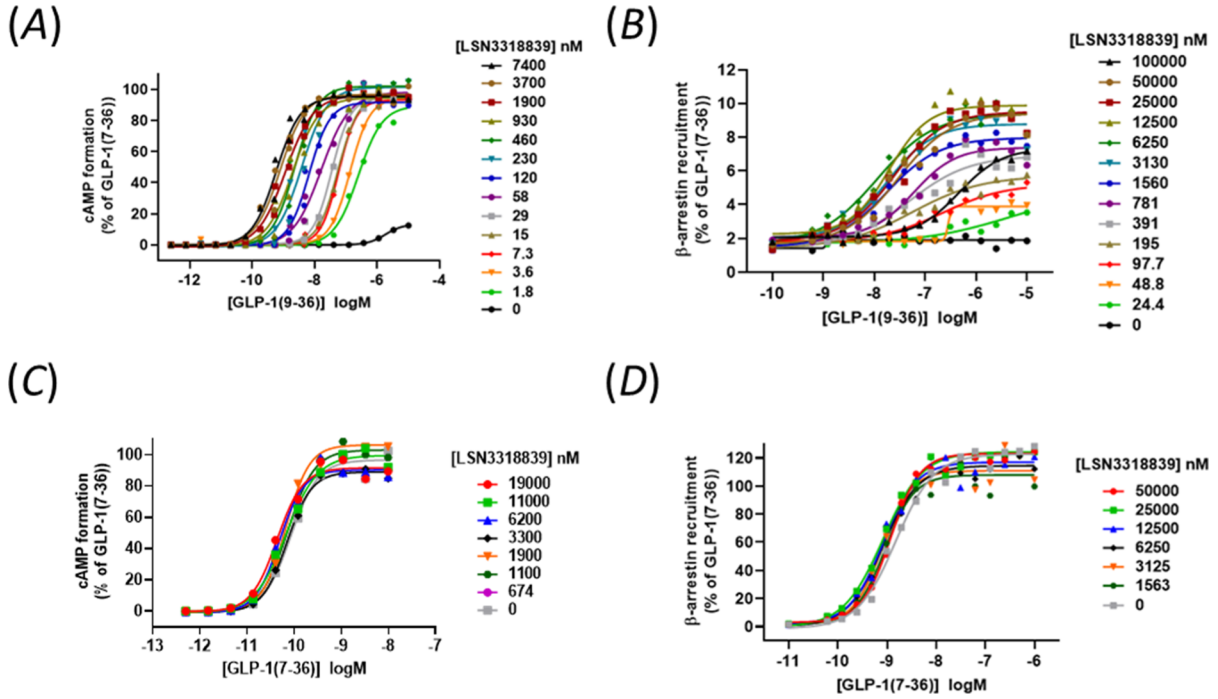

Figure 3. cAMP accumulation in GLP-1R-expressing HEK293 cells produced in the presence of various concentrations of LSN3318839 in combination with GLP-1(9−36) (A) or GLP-1(7−36) (C). *β*-Arrestin recruitment measured in GLP-1R-expressing CHO-K1 cells in the presence of various concentrations of LSN3318839 in combination with GLP-1(9−36) (B) or GLP-1(7−36) (D).

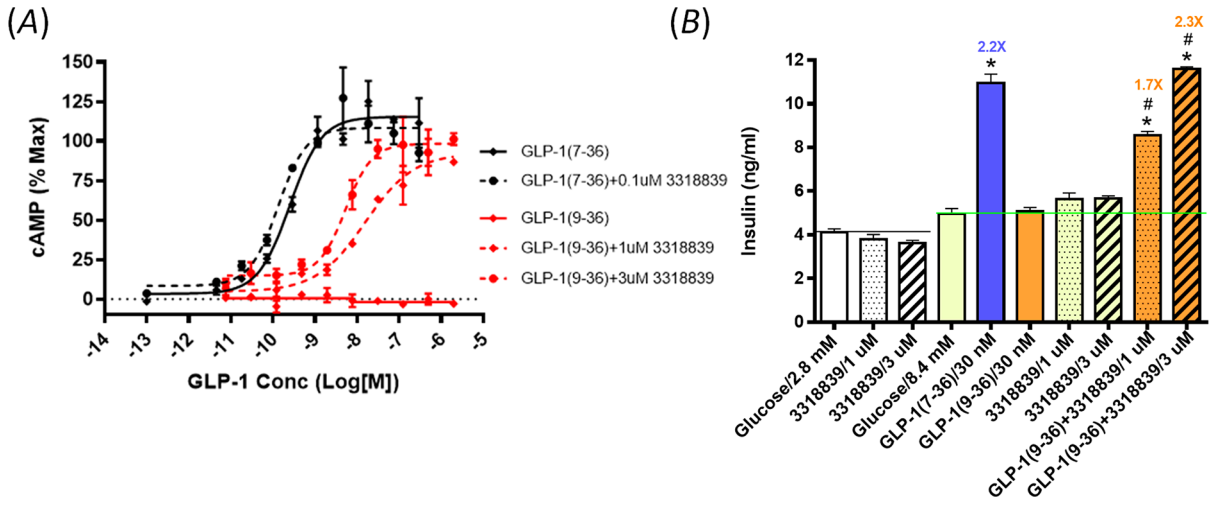

Figure 4. (A) cAMP accumulation in INS-1 832-3 cells produced by LSN3318839 in combination with GLP-1(9−36) or GLP-1(7−36). (B) Insulin levels in media from INS-1 832-3 cells at high glucose. *, $p < 0.05$; #, $p < 0.05$; using one-way ANOVA followed by Dunnett's comparison versus vehicle treatment or GLP-1(9−36) at 30 nM.

mulation using a heterologous cellular system (Figure 3A,C). Experiments consisted of concentration responses of the corresponding peptide [GLP-1(9−36) in panel A and GLP-1(7−36) in panel C], at several concentrations of LSN3318839. In GLP-1R-expressing HEK293 cells, GLP-1(7-36) is a highly potent full agonist (EC_{50} = 85 pM) and GLP-1(9−36) is a low-efficacy partial agonist (EC_{50} = 1.8 μM, E_{MAX} = 13%).[16] In the presence of a submaximal concentration of LSN3318839 (0.12 μM), the potency of GLP-1(9−36) improved to 7 nM and achieved full agonism (E_{MAX} = 92%). Given that both the potency and efficacy of GLP-1(9−36) are enhanced by LSN3318839, it is apparent that the mechanism of action of the PAM likely involves modulation of orthosteric ligand affinity and efficacy. This is consistent with the mechanism of action of LSN3160440, for which was demonstrated using radioligand binding approaches.[14] In contrast, LSN3318839 did not affect the efficacy of GLP-1(7−36), but an increase in the potency of the peptide by twofold at maximally effective concentrations was observed (Figure 3C).

To determine the effect of the PAM on a different signaling pathway, we studied the activity of LSN3318839 on *β*-arrestin recruitment by both peptide ligands (Figure 3B,D). LSN3318839 had a marginal effect on the EC_{50} of GLP-1(7−36) (1.9 fold), consistent with the cAMP accumulation data. In contrast, the PAM produced a low-efficacy, albeit

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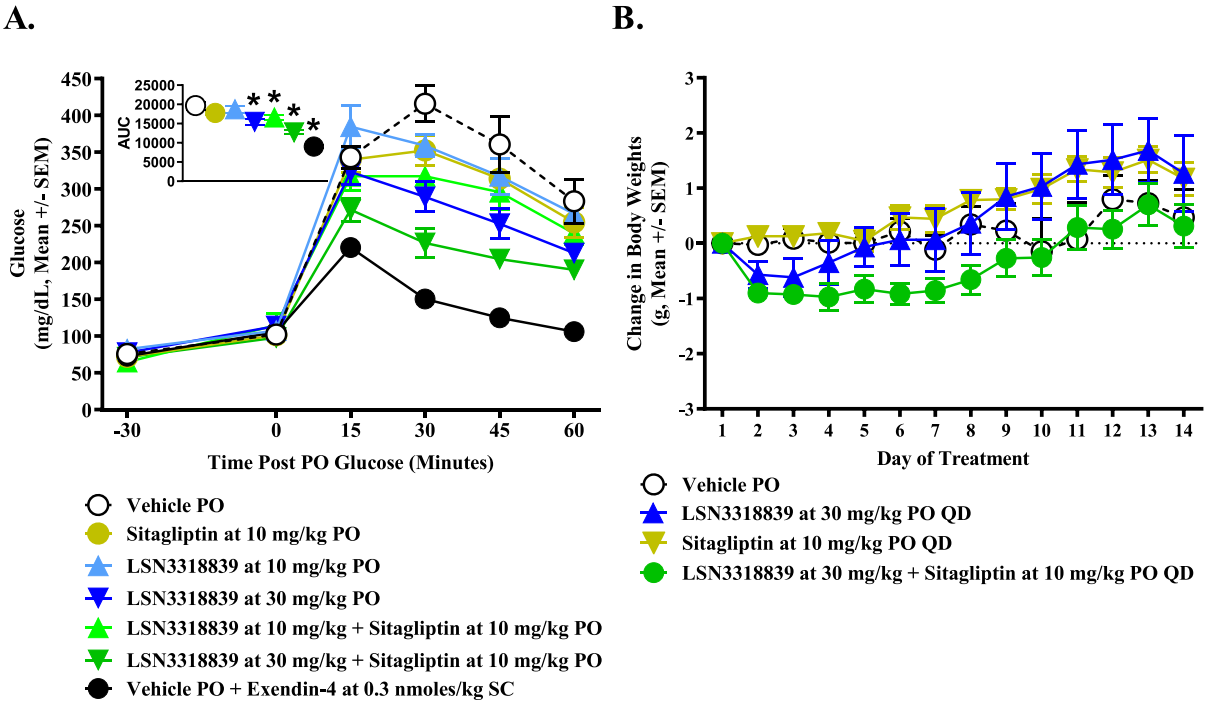

Figure 5. (A) Time course of glucose levels in overnight-fasted GIPR KO mice treated orally with LSN3318839 alone or LSN3318839 + sitagliptin followed 30 min later by an oral dose of dextrose (3 g/kg). Oral sitagliptin and subcutaneous exenatide were used as controls in the study. The inset shows the area under the curve (AUC). (B) Change in nonfasted body weights of DIO mice with daily treatment of LSN3318839, sitagliptin, or combination of LSN3318839 and sitagliptin for 2 weeks. Results are expressed as mean ± S.E.M. Analysis of variance was used to assess statistical significance: $*p < 0.05$, versus vehicle.

measurable, increase in β-arrestin recruitment by GLP-1(9−36). Although enhancement of efficacy was low (10% E_{MAX}), the effect was highly potent (e.g., EC_{50} of GLP-1(9−36) with 6 μM of LSN3318839 was 12 nM) and saturable, indicating a high receptor occupancy. These data suggest that the potentiation of GLP-1(9−36) and GLP-1(7−36) by LSN3318839 is predominantly biased toward G protein signaling. Together, the concentration response studies of LSN3318839 in the cAMP and β-arrestin recruitment assays provide a quantitative assessment of the pharmacological properties of the compound.

Next, we investigated whether LSN3318839 could induce GLP-1R activity in native systems (Figure 4). Thus, cAMP accumulation produced by GLP-1(9−36) or GLP-1(7−36) in the presence of LSN3318839 was measured in INS-1 832-3 cells.[17] Similar to the results obtained in the HEK293 cells, the combination of GLP-1(7−36) with 0.1 μM LSN3318839 produced a 2.7-fold improvement of the potency of the peptide, while the combination of GLP-1(9−36) with 3 μM LSN3318839 increased the potency of the peptide to 7 nM and the efficacy to 87% E_{MAX} (Figure 4A). Next, insulin secretion was measured in the INS-1 832-3 cells (Figure 4B).[18] In cultures of INS-1 832-3 cells, the combination of LSN3318839 (at 1 and 3 μM) and GLP-1(9−36) in the presence of high glucose profoundly increased insulin levels in the media. The effect on insulin secretion of GLP-1(9−36) in combination with 3 μM LSN3318839 was comparable to that produced by GLP-1(7−36). These results are in line with previous insulin secretion experiments using LSN3160440.[14] Together, the INS-1 832-3 cell studies demonstrate the anticipated PAM/GLP-1 activation mechanism of LSN3318839, which requires the presence of high glucose and GLP-1(9−36) to enhance insulin secretion.

***In Vivo* Pharmacology.** To investigate whether the insulinotropic effects observed in INS-1 832-3 cells extend to the *in vivo* setting, we performed oral glucose tolerance tests (oGTTs). Since the control of glucose homeostasis mediated by the incretin response is driven by both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), we utilized GIPR KO mice as a model to focus assessment of GLP-1R-mediated control of a glucose excursion (Figure 5A).[19] A glucose bolus (3 g/kg) was administered orally to animals pretreated with an oral dose of LSN3318839 of 10 or 30 mg/kg, alone or in combination with sitagliptin, a DPP4 inhibitor that prevents the degradation of GLP-1(7−36) to GLP-1(9−36).[20] Blood samples were taken in intervals of 15 min during a 60 min period. Exenatide was used as a positive control in this experiment as this peptide is fully efficacious in these mice.[19]

No clear effect on hyperglycemia was observed when LSN3318839 was administered at 10 mg/kg (9% nonstatistically significant glucose lowering AUC, $p > 0.05$), but a significant reduction in glucose excursion occurred following treatment with the 30 mg/kg dose (40% glucose lowering AUC, $p < 0.05$). Interestingly, an additive glucose lowering effect was observed when LSN3318839 was coadministered with 10 mg/kg sitagliptin (which alone produced 18% nonstatistically significant glucose lowering AUC, $p > 0.05$), producing a significant 29% ($p < 0.05$) and 65% ($p < 0.05$) glucose lowering AUC at 10 and 30 mg/kg LSN3318839, respectively.

Taking into account that the circulating levels of GLP-1(9−36) are negligible in animals treated with sitagliptin, our *in vivo* data suggest that at least in the studies where LSN3318839 was combined with the DPP4 inhibitor, the efficacy of the potentiator was likely due to activation of the GLP-1R by the combined effect of PAM and only GLP-1(7−36) [i.e., not

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by potentiation of GLP-1(9−36)]. Additionally, these data suggest that the β-arrestin pathway is not essential for the insulinotropic effects and the glucose lowering ability of GLP-1R activation shown above, as LSN3318839 is biased toward G protein signaling. Furthermore, the glucose lowering effect produced by LSN3318839 in GIPR KO mice was GLP-1R-dependent, as glucose lowering was negligible in oGTT experiments performed in mice where this receptor has been deleted (Supporting Information, Figure S1). Of note, the results of these studies support the requirement of the GLP-1R for compound activity but do not inform on the endogenous peptide working in concert with LSN3318839 for efficacy.

In addition to glucose lowering, GLP-1R agonist peptides are known to produce a reduction in body weight after chronic treatment.[21,22] To determine whether potentiation of endogenous GLP-1 peptides could have a beneficial effect on body weight control, diet-induced obese (DIO) mice were treated with a daily dose of 30 mg/kg LSN3318839 for 14 days, alone or in combination with 10 mg/kg sitagliptin, and the change in body weight was measured daily (Figure 5B). No effect was observed in any of the groups compared to untreated animals (nonstatistically significant, $p > 0.05$).

Taken together, these experiments show that the combination of endogenous levels of the GLP-1 peptides and orally administered LSN3318839 is sufficient to produce a therapeutic effect in glucose control but not on body weight reduction. It remains unclear whether the latter could be achieved with PAMs possessing pharmacological characteristics superior to those of LSN3318839.

CONCLUSIONS

In summary, we describe the identification of LSN3318839, a biased GLP-1R modulator that potentiates activity of GLP-1(7−36) and the low-affinity metabolite GLP-1(9−36). Although the compound was developed as a GLP-1(9−36) PAM, a small but measurable potentiation of GLP-1(7−36) was observed in several assays. LSN3318839 produces glucose lowering that requires the GLP-1R, and the efficacy is additive to that of the DPP4 inhibitor sitagliptin. However, no effect on body weight was observed during chronic treatment of the compound alone or in combination with sitagliptin. To our knowledge, LSN3318839 is the first GLP-1R PAM to produce GLP-1R-dependent glucose lowering by potentiating endogenous concentrations of peptide. Molecules previously reported in the field, such as LSN3160440[14] or "compound **19**" from Méndez et al.,[13] apparently required the injection of exogenous GLP-1(9−36) to produce an effect on glucose excursion.

Although our findings indicate that the PAM approach could be suitable for developing GLP-1R potentiators as oral drugs, clinical data generated with long-acting peptides such as dulaglutide or semaglutide versus short-acting analogues, such as exenatide (which have intermittent periods of low GLP-1R occupancy), suggest that constant activation of the GLP-1R produces higher efficacy. Therefore, GLP-1R agonists would be predicted to be more efficacious in T2DM and obesity than potentiators, which would only offer significant activity during or shortly after meals when endogenous levels of GLP-1 are increased. Our results in DIO mice suggest that transient activation of the receptor is likely insufficient for GLP-1R-related body weight reduction.

The implications of our findings for small-molecule class B GPCRs, particularly challenging targets for the identification of agonists, are manifold. For instance, our results support the concept that potentiation of a peptide is a functional approach that can be exploited for identifying oral drugs to activate these receptors.[23,24] Finally, LSN3318839 represents the first molecular glue for GPCRs that has in vivo efficacy, thereby demonstrating the proof of concept for a new modality for targeting this class of receptors.

EXPERIMENTAL SECTION

Chemistry. *General.* All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. All solvents were of ACS grade. Reactions were performed under an air atmosphere unless otherwise indicated. ^{1}H NMR and ^{13}C NMR data for characterization of compounds were recorded on a Bruker AM-400 (400 MHz) or a Bruker AM-300 (300 MHz). Nuclear magnetic resonance (NMR) experiments were acquired at 25 °C in DMSO-d_6 referencing all the NMR spectra to the residual solvent signals at 2.50 and 39.5 ppm, for the proton and carbon, respectively. One-dimensional spectra were acquired using 16 K data points and zero filled to 32 K. Analytical high-performance liquid chromatography (HPLC) was carried out on an Agilent 1260 liquid chromatography (LC) system equipped with a solvent degasser, quaternary pump, auto sampler, column compartment, and a diode array detector (Agilent Technologies, Waldbronn, Germany). The ultraviolet (UV) wavelength was set at 214 nm. Electrospray mass spectrometry (MS) measurements were performed on a MSD quadrupole mass spectrometer (Agilent Technologies, Palo Alto, CA, USA) interface to the Agilent HPLC system. MS measurements were acquired simultaneously in both positive and negative ionization modes. Data acquisition and integration for LC−UV and MS detection were collected using Chemstation software (Agilent Technologies). Analytical conditions: Method A: Column Gemini NX C18 (3 μm, 2 × 50 mm); UV: 214 and 300 nm; MS ESI(±) 150−700. (A) H_2O + 0.1% formic acid; (B) CH_3CN + 0.1% formic acid. Flow rate: 1.2 mL/min; column T 50 °C; gradient mode: from 5 to 95% B in 1.5 min; hold 0.5 min at 95% B. Method B: Column XBridge C18 (3.5 μm, 2.1 × 50 mm); UV: 214 and 300 nm; MS−ESI 100−800. (A) 10 mM ammonium bicarbonate pH 9.0; (B) CH_3CN. Flow rate: 1.2 mL/min; column T 50 °C; gradient mode: from 5 to 95% B in 1.5 min, hold 0.5 min at 95% B. Key compounds [(*R*)-7, LSN3318839, **8**] had ≥95% purity by both methods. Optical rotations were measured with an Anton Paar MCP 500. Flash chromatography was performed in silica gel. Eluents are indicated in parenthesis.

*2,6-Dichloro-3-cyclopropylbenzaldehyde (**3**).* 1-Bromo-2,4-dichloro-benzene (182 g, 805 mmol), potassium cyclopropyltrifluoroborate (155 g, 1046 mmol), XPhos (36.5 g, 77 mmol), and potassium carbonate (327 g, 3 equiv) were combined in a mixture of toluene (2.8 L) and water (0.9 L) at 25 °C. Stirring was started, while the mixture was bubbled with N2 for 20 min. Palladium acetate (9 g, 0.05 equiv) was added, and the mixture was stirred under reflux for 16 h under N_2. The reaction was cooled to rt, filtered through a pad of Celite, and rinsed with MTBE (2 L). The aqueous layer was discarded, and the organic layer was washed with aq. 1 M HCl (1 L) and brine (2 × 1 L), dried over anhydrous sodium sulfate, filtered, and concentrated to afford 2,4-dichloro-1-cyclopropyl-benzene as yellow oil. Purification by flash chromatography (petroleum ether) provided 138 g of the desired product at 77% purity, which was used in the next step without further purification. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 7.54 (d, J = 2.2 Hz, 1H), 7.30 (dd, J = 8.4 and 2.1, 1H), 7.04 (d, J = 8.5 Hz, 1H), 2.10 (m, 1H), 1.00 (m, 2H), 0.69 (m, 2H).

To a solution of diisopropylamine (131.1 mL, 935 mmol) in tetrahydrofuran (THF) at −70 °C was added *n*-buLi (2.5 M in hexanes, 362 mL, 905 mmol) dropwise during 25 min, keeping internal temperature at −65 ∼ −70 °C. The solution was stirred at −70 °C for 1 h, and then, a solution of 2,4-dichloro-1-cyclopropyl-benzene (138 g, 77% pure) in THF (650 mL) was added dropwise during 30 min (slight exotherm was observed). After stirring at −65 ∼ −70 °C for 1 h, dimethylformamide (DMF) (93 mL, 1249 mmol) was added dropwise during 30 min, keeping at −65 ∼ −70 °C (slight

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exotherm was observed). The mixture was stirred at −70 °C for 2 h, and then, it was poured into 1 L of MTBE and 1 L of aq. 1 M HCl slowly at 0−10 °C. The material was extracted with EtOAc (2 × 2 L), and the combined organic layers were washed with water (2 L), aq. 1 M HCl (2 L), and brine (2 × 2 L), dried over Na_2SO_4, filtered, and concentrated to dryness. Purification by flash chromatography [gradient of petroleum ether/EtOAc (100:0 to 50:1)] afforded 106 g of **3** as yellow oil (71% yield, two steps). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm): 10.37 (s, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 2.22−2.13 (m, 1H), 1.08−1.02 (m, 2H), 0.77−0.71 (m, 2H).

*(R)-1-(2,6-Dichloro-3-cyclopropyl-phenyl)ethanamine [(R)-**4**].* (*S*)-(−)-2-Methylpropanesulfinamide (27.3 g, 225.5 mmol) and cesium carbonate (73.5 g, 225.5 mmol) were added to a stirred solution of **3** (50.0 g, 225.5 mmol) in DCM (0.5 L). A condenser with a nitrogen inlet was fitted, and the mixture refluxed for 1.5 h. The mixture was cooled and then filtered through a silica pad (1 cm depth), rinsing with DCM (1.5 L). The filtrate was concentrated under reduced pressure to afford (*S*,*E*)-*N*-[(2,6-dichloro-3-cyclopropyl-phenyl)methylene]-2-methyl-propane-2-sulfinamide as yellow oil which solidified slowly upon standing (72.5 g, 99% yield). MS(ESI) m/z (^{35}Cl/^{37}Cl): 318/320/322 [M + H]$^+$; ^{1}H NMR (400.15 MHz, $CDCl_3$): δ 8.91 (s, 1H), 7.29 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 2.22−2.13 (m, 1H), 1.32 (s, 9H), 1.09−1.02 (m, 2H), 0.71−0.64 (m, 2H).

(*S*,*E*)-*N*-[(2,6-Dichloro-3-cyclopropyl-phenyl)methylene]-2-methyl-propane-2-sulfinamide (58.0 g, 178.6 mmol) and cupric bromide (2.0 g, 8.9 mmol, 5 mol %) were combined in DCM (0.6 L) under nitrogen and cooled to 5 °C (internal). Methylmagnesium bromide (3.0 M in diethyl ether, 87.0 mL, 261.0 mmol) was added using a syringe pump at a rate of 1 mL/min. After 2 h, 1 M aq. hydrochloric acid (0.3 L) was added slowly, and the mixture was stirred vigorously for 10 min. The phases were separated, and the organic phase was filtered, washed with water (0.12 L) and brine (0.12 L), dried over $MgSO_4$, and filtered. The filtrate was concentrated by approx. half under reduced pressure and then eluted through a silica pad (2 cm depth), rinsing with 1:4 MTBE/DCM. The filtrate was concentrated under reduced pressure to afford crude (*S*)-*N*-[(1*R*)-1-(2,6-dichloro-3-cyclopropyl-phenyl)ethyl]-2-methyl-propane-2-sulfinamide (96% de, 58.5 g, 96% yield), which was used without further purification. MS(ESI) m/z: (^{35}Cl/^{37}Cl): 334/336/338 [M + H]$^+$; ^{1}H NMR (400.21 MHz, $CDCl_3$): δ 7.25−7.09 (m, 1H), 6.88−6.76 (m, 1H), 5.63−5.35 (m, 1H), 4.47−4.26 (m, 1H), 2.22−2.04 (m, 1H), 1.79−1.63 (m, 3H), 1.15 (br s, 9H), 1.07−0.94 (m, 2H), 0.71−0.56 (m, 2H).

A stirred solution of this compound (45.0 g, 131.9 mmol) in methanol (67.5 mL) was cooled in an ice-water bath. HCl (4 M in dioxane, 67.5 mL, 270 mmol) was added over a period of 10 min. Stirring was continued for 15 min in the ice bath and then for 30 min at room temperature. The mixture was concentrated under reduced pressure, and the residue partitioned between MTBE (0.25 L) and water (0.25 L). The phases were separated, and the organic phase was extracted with water (2 × 50 mL). The aqueous portions were combined and washed with MTBE (2 × 0.1 L); the MTBE portions were discarded. The aqueous was stirred with a fresh portion of MTBE (0.25 L) and treated with 2 M aq. NaOH to pH 10. The phases were separated, and the aqueous was discarded. The MTBE extract was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (1*R*)-1-(2,6-dichloro-3-cyclopropyl-phenyl)ethanamine [(*R*)-**4**] as pale brown oil (95% ee, 5.9 g, 83% yield). Chiral CE method used to determine ee: 50 μM × 30 cm capillary, −15 kV, 20 °C; running buffer 5% beta−HS−CD, 25 mM phosphate, retention time of 3.69 min for (*R*)-**4**, 3.86 min for (*S*)-**4**. MS(ESI) m/z: (^{35}Cl/^{37}Cl): 230/232/234 [M + H]$^+$; ^{1}H NMR (400.21 MHz, $CDCl_3$): δ 7.16 (d, J = 11.2 Hz, 1H), 6.79 (d, J = 10.8 Hz, 1H), 5.09−4.83 (m, 1H), 2.21−2.06 (m, 1H), 2.00 (br s, 2H), 1.55 (d, J = 9.2 Hz, 3 H), 1.04−0.95 (m, 2H), 0.67−0.59 (m, 2H).

*Methyl 2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]propanoate [(±)-**6**].* Methyl 2-(2-bromophenyl)acetate (**5**) (22 g, 96 mmol) was dissolved in anhydrous THF (330 mL) under a nitrogen atmosphere. The solution was cooled at −78 °C. 1 M lithium bis(trimethylsilyl)amide in THF (100 mL) was added dropwise over a period of 15 min. The reaction mixture was stirred at −78 °C for 1 h. Iodomethane (7.7 mL, 120 mmol) was added to the reaction mixture at −78 °C, and the reaction mixture was allowed to warm slowly to −20 °C. The reaction was quenched by the addition of saturated NH_4Cl (100 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (250 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to afford (±)-methyl 2-(2-bromophenyl)-propanoate (24.9 g, quant.) as orange oil. ^{1}H NMR (300.16 MHz, DMSO-d_6): 7.62 (dd, J = 8.0 and 1.1 Hz, 1H), 7.41−7.32 (m, 2H), 7.24−7.19 (m, 1H), 4.13 (q, J = 7.2 Hz, 1H), 3.60 (s, 3H), 1.40 (d, J = 7.1 Hz, 3H).

A round-bottomed flask was charged with potassium acetate (1.25 g, 12.7 mmol), 1,1′-bis(diphenylphosphino)ferrocene-palladium(ii)-dichloride dichloromethane complex (260 mg, 0.32 mmol), and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.43 g, 9.57 mmol). After 3 cycles of vacuum/nitrogen, a solution of (±)-methyl 2-(2-bromophenyl)propanoate (1.55 g, 6.38 mmol) in anhydrous 1,4 dioxane (16 mL) was added. The reaction mixture was stirred and heated at 90 °C overnight. The reaction mixture was cooled to rt, diluted with ethyl acetate (50 mL), and washed with water (25 mL) and brine (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to afford black oil (3.43 g). The residue was loaded onto an 80 g silica gel column and purified by flash chromatography eluting with a gradient of hexane/EtOAc 3%−10% (in 10 CV) to provide (±)-**6** (1.46 g, 79% yield) as colorless oil. MS(ESI) m/z: 291 [M + H]$^+$; ^{1}H NMR (400.13 MHz, $CDCl_3$): 7.81 (d, J = 7.4 Hz, 1H), 7.42−7.36 (m, 1H), 7.30−7.20 (m, 2H), 4.67 (q, J = 7.0 Hz, 1H), 3.64 (d, J = 2.0 Hz, 3H), 1.47 (d, J = 7.0 Hz, 3H), 1.35 (s, 12H).

*6-Bromo-1-[(1R)-1-(2,6-dichloro-3-Cyclopropyl-phenyl)ethyl]-imidazo[4,5-c]pyridine [(R)-**7**)].* A solution of (1*R*)-1-(2,6-dichloro-3-cyclopropyl-phenyl)ethanamine [(*R*)-**4**] (20.0 g, 86.9 mmol) in 2-methyltetrahydrofuran (50 mL) was added to a stirred mixture of 2,4-dibromo-5-nitropyridine (25.0 g, 86.9 mmol) and potassium carbonate (25.0 g, 180.9 mmol) in 2-methyltetrahydrofuran (100 mL). Triethylamine (25.0 mL, 179.4 mmol) was added, and the mixture was stirred at 70 °C for 20 min. The mixture was cooled and washed with water, half-saturated brine, and brine (each 100 mL). The organics were passed and eluted through a 4 cm pad of silica under suction, eluting with further 2-methyltetrahydrofuran. The eluate was concentrated under reduced pressure to afford crude 2-bromo-*N*-[(1*R*)-1-(2,6-dichloro-3-cyclopropyl-phenyl)ethyl]-5-nitro-pyridin-4-amine (38.9 g, 76.7 mmol, 88%) as a thick orange gum. LCMS purity 92% (3% regioisomer). MS(ESI) m/z: (^{35}Cl/^{37}Cl): 430/432/434 [M + H]$^+$; ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 8.85 (s, 1H), 8.82 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.82 (s, 1 H), 5.68−5.51 (m, 1H), 2.22−2.06 (m, 1H), 1.73 (d, J = 6.9 Hz, 3H), 1.08−0.93 (m, 2H), 0.77−0.60 (m, 2H).

A solution of crude 2-bromo-*N*-[(1*R*)-1-(2,6-dichloro-3-cyclopropyl-phenyl)ethyl]-5-nitro-pyridin-4-amine (37.0 g, 85.8 mmol) and trimethyl orthoformate (74 mL, 676.4 mmol) and acetic acid (0.37 L) was prepared in a round-bottomed flask with a mechanical stirrer. The mixture was heated in an 80 °C block and treated with iron powder (37.0 g, 662.5 mmol). After the initial exotherm subsided, the heating block temperature was increased to 90 °C. After a total of 3 h, heating was stopped, and diatomaceous earth and ethanol (0.5 L) were added. The cooled mixture was filtered through a pad of diatomaceous earth, and the pad was rinsed with further ethanol. The filtrate was concentrated under reduced pressure, and the residue partitioned between isopropyl acetate (0.5 L) and 1 M aq. HCl (0.3 L). The phases were separated, and the organics were washed with 0.1 L portions of 1 M aq. HCl, 1 M aq. NaOH (×4), and brine and then eluted through a 3 cm silica pad under suction, rinsing with ethyl acetate. The eluate was concentrated under reduced pressure, taken up in MTBE (70 mL), and stirred overnight. The resulting thick slurry was diluted with further MTBE, and the solid

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was collected by filtration. The filter cake was dried to afford (*R*)-7 (22.35 g, 54.36 mmol, 63, 96% ee) as white powder. A second crop (3.16 g, 7.69 mmol, 9, 94% ee) was obtained similarly from mother liquors. MS(ESI) *m/z*: ($^{35}Cl/^{37}Cl$): 410/412/414 $[M + H]^+$; $[\alpha]20^D$ −96 (*c* 0.7, MeOH); ^1H NMR (400.21 MHz, DMSO-d_6): δ 8.83 (s, 1H), 8.78 (d, *J* = 0.7 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.89 (d, *J* = 0.7 Hz, 1H), 6.39 (q, *J* = 7.2 Hz, 1H), 2.16−2.09 (m, 4H), 1.06−0.94 (m, 2H), 0.72−0.66 (m, 2H); ^{13}C NMR (100.63 MHz, DMSO-d_6): δ 147.2, 142.5, 142.3, 141.4, 141.2, 135.3, 133.5, 132.3, 131.1, 130.1, 128.0, 109.2, 53.5, 16.9, 14.1, 8.9, 8.7.

A sample of the title compound was treated with tripotassium phosphate (4 equiv) in DMSO (5 mL/g) at 120 °C overnight to afford a near-racemic sample. The chiral reverse-phase HPLC method was used to determine ee: CHIRALPAK IA-3R column (3 μm, 4.6 × 50 mm), solvent A: NH_4HCO_3 10 mM pH 9/solvent B: CH_3CN, gradient from 70 to 99% B in 3.2 min, retention time of 1.77 min for (*R*)-7 and 2.02 min for (*S*)-7.

2-(2-(1-((*R*)-1-(2,6-Dichloro-3-cyclopropylphenyl)ethyl)-1*H*-imidazo[4,5-*c*]pyridin-6-yl)phenyl)propanoic acid (LSN3318839, **8**). Boronate (±)-**6** (10.1 g, 34.1 mmol) and bromide (*R*)-**7** (13.0 g, 31.0 mmol) were dissolved in toluene (0.3 L). A 1 M solution of sodium carbonate in water (92.9 mL, 92.9 mmol) was added. N_2 was bubbled through the reaction mixture for 5 min. CataCXium A Pd G3 (1.19 g, 1.5 mmol) was added, and the reaction was vigorously stirred at 90 °C under nitrogen for 17 h. The reaction was cooled to room temperature, layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (2-methylhexane/acetone 4:1 to 4:6) provided a 1:1 mixture of esters as yellow foam (13.1 g, 83% yield). MS(ESI) *m/z*: ($^{35}Cl/^{37}Cl$): 494/496/498 $[M + H]^+$.

The esters (14.1 g, 27.7 mmol) were dissolved in *i*-PrOH (140 mL), 1 M NaOH in water (110 mL, 110 mmol) was added, and the reaction was stirred at 80 °C for 3 h. The reaction was allowed to cool to room temperature, and *i*-PrOH was removed under reduced pressure. The aqueous layer was taken to pH 4.5−5 by dropwise addition of 5% citric acid in water. EtOAc was added, and layers were separated. The aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (gradient of DCM/MeOH 98:2 to 94:6) to provide a 1:1 mixture of acids as beige powder (13.8 g, 88% yield). SFC separation of diastereomers was performed in an AD-H column (30.0 × 250 mm, 5 μm).

Separation was carried out on a Chiralpak AD-H (30 × 250 mm, 5 μm) column from Chiral Technologies Europe. The sample was dissolved in 150 mL of methanol, and the resulting solution was filtered prior to injection onto the preparative SFC instrumentation. Elution was performed under isocratic conditions with a mobile phase consisting of 22% methanol with 20 mM ammonia (from 2 M ammonia in methanol). Separation was run at 35 °C at a 110 g min^{-1} flow rate and 105 bar outlet pressure. Stacked injections of 800 μL solution were run every 340 s. Detection UV was at 220 nm; the retention time was 1.84 min for **8** (6.12 g; >98% ee, 43%) and 3.14 min for LSN3318839 (5.80 g; >98% ee, 41%). Fraction collection was triggered by UV detection (220 nm). The chiral HPLC method was used to determine ee: Chiralpak AD-H (4.6 × 100 mm, 5 μm) column from Chiral Technologies Europe. Elution was performed under gradient conditions from 10 to 55% modifier in CO_2 over 2.4 min, and then, conditions were held at 55% modifier for 2.1 min (4.5 min total run time). The modifier consisted of methanol with 1% of 2 M ammonia in methanol. The flow rate was 4 ml min^{-1}. The outlet pressure was set to 100 psi at 35 °C. UV (DAD: 200−300 nm) and MS detection was used for monitoring. The retention time was 1.60 min for **8** and 1.80 min for LSN3318839. **8**: MS(ESI) *m/z*: ($^{35}Cl/^{37}Cl$): 480/482/484 $[M + H]^+$; $[\alpha]^D_{20}$ + 59 (c 0.7, MeOH); ^1H NMR (400.21 MHz, DMSO-d_6): δ 14.1 (br s, 1H), 9.09 (d, *J* = 0.7 Hz, 1H), 8.92 (s, 1H), 7.43−7.37 (m, 3H), 7.30−7.26 (m, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.95−6.94 (m, 2H), 6.50 (q, *J* = 7.0 Hz, 1H), 3.89 (q, *J* = 6.9 Hz, 1H), 2.18 (d, *J* = 7.2 Hz, 3H), 2.15−2.08 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.05−1.00 (m, 2H), 0.72−0.63 (m, 2H); ^{13}C NMR (100.63 MHz, DMSO-d_6): δ 175.1, 150.6, 147.1, 142.2, 140.7, 140.3, 140.2, 139.7, 139.4, 135.4, 133.9, 131.2, 130.6, 130.1, 129.3, 128.0, 127.6, 127.4, 106.6, 53.6, 40.9, 18.3, 16.8, 14.2, 8.9, 8.4; LSN3318839: MS(ESI) *m/z*: ($^{35}Cl/^{37}Cl$): 480/482/484 $[M + H]^+$; $[\alpha]^D_{20}$ −97 (c 0.7, MeOH); ^1H NMR (400.21 MHz, DMSO-d_6): δ 13.54 (br s, 1H), 9.07 (s, 1H), 8.91 (s, 1H), 7.42−7.29 (m, 4H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.01 (s, 1H), 6.50 (q, *J* = 7.2 Hz, 1H), 3.85 (q, *J* = 6.9 Hz, 1H), 2.17 (d, *J* = 7.2 Hz, 3H), 2.12−2.06 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.01−0.95 (m, 2H), 0.67−0.62 (m, 2H); ^{13}C NMR (100.63 MHz, DMSO-d_6): δ 175.3, 150.9, 147.0, 142.2, 140.9, 140.2, 140.1, 139.9, 139.7, 135.3, 133.9, 131.1, 130.6, 130.1, 129.1, 127.8, 127.5, 127.3, 106.4, 53.5, 40.8, 18.6, 17.0, 14.0, 8.8.

The absolute configuration of LSN3318839 was determined to be (*R*,*R*) by VCD of its methyl ester synthesized by standard methods from the acid.

Biology. *General.* All reagents were of the highest quality and purity available from Sigma (St Louis, MO) unless otherwise described. Synthetic peptides were synthesized at Eli Lilly, Bachem (Torrance, CA), or CPC Scientific (Sunnyvale, CA) to >95% purity.

cAMP Accumulation. Cyclic adenosine monophosphate accumulation in the presence of IBMX was quantified in HEK293 cells stably expressing the human GLP-1 receptor or in INS-1 832-2. Methods and data analysis procedures have been previously described.[14,25]

β-Arrestin Recruitment. Beta-arrestin 2 recruitment to the human GLP-1 receptor was quantified in CHO-K1 cells expressing ProLink-tagged GLP-1R and the enzyme acceptor-tagged β-Arrestin (DiscoveRx, Fremont CA). Assays were conducted according to manufacturer's specifications and were conducted as previously described.[25]

Insulin Secretion Assays. The methods and data analysis procedures for the INS-1 832-3 cell insulin secretion assays have been previously described.[14]

Data Analysis. For *in vitro* pharmacology experiments, data were normalized to % stimulation using maximally efficacious concentrations of GLP-1(7-36) unless otherwise specified. Unless otherwise described, curves were fit to the four-parameter logistic equation.[26] Data were graphed and fit to models using PRISM (GraphPAD, San Diego CA). For the data in Table 1, shift experiments were conducted using 10 μM of the compound. All results were calculated using at least six observations in a minimum of 3 runs.

Animal Studies. Animals were studied and maintained in accordance with the Institutional Animal Care and Use Committee of Eli Lilly and Company and the Guide for the Use and Care of Laboratory Animals by the National Institutes of Health. All animal studies described herein were approved by the Institutional Animal Care and Use Committee of Eli Lilly and Company.

Determination of LSN3318839 Pharmacokinetics. The pharmacokinetic parameters of LSN3318839 were determined in CD1 mice, Sprague−Dawley rats, and Beagle dogs. The iv dose (administered at 1 mg/kg) was formulated in a standard captisol 20% w/v in $NaPO_4$ buffer 25 mM, adjusted to pH 8. The oral dose (administered at 3 mg/kg in mice and 5 mg/kg in rats) was formulated with hydroxycellulose (1% w/v), polysorbate 80 (0.25% v/v), and antifoam (0.05% v/v) in purified water. Samples were collected up to 8 h for the iv-dosed groups and up to 16 h for the oral-dosed animals. Samples were processed to plasma and analyzed by LC−MS/MS. Animal studies were conducted at Covance (Greenfield, IN), and bioanalytical measurements were made by IQVIA (Indianapolis, IN). Pharmacokinetic parameters were calculated by Watson LIMS (ThermoFisher, Billerica, MA). Data are the geometric means from three animals in each dose group.

oGTTs and Chronic Studies in DIO Mice. These studies were conducted as previously described.[19,27,28]

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.1c00029.

oGTT of LSN3318839 in GLP-1R KO mice and selectivity data for LSN3318839 (PDF)

Molecular formula strings (CSV)

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Notes

The authors declare the following competing financial interest(s): All the authors of this manuscript are or have been Eli Lilly and Company employees and may own company stock or possess stock options.

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■ ABBREVIATIONS USED

XPhos, 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; CataCXium A Pd G3, [(Di(1-adamantyl)-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate

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