Bioorganic & Medicinal Chemistry Letters xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Discovery of novel spiro[chromane-2,4′-piperidine] derivatives as potent and orally bioavailable G-protein-coupled receptor 119 agonists

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ARTICLE INFO

Keywords:
GPR119 agonists
Type 2 diabetes mellitus
Spiro[chromane-2,4′-piperidine]
Biphenyl

ABSTRACT

Herein, we describe the discovery, synthesis, and evaluation of a novel series of spiro[chromane-2,4′-piperidine] derivatives as G-protein-coupled receptor 119 agonists. Their initial design exploited the conformational restriction in the linker-to-tail moiety, which was a key concept in this study, to give lead compound **11** (EC_{50} = 369 nM, E_{max} = 82%). An extensive structure–activity relationship study resulted in the identification of the optimized drug candidate **(*R*)-29** (EC_{50} = 54 nM, E_{max} = 181%). The defining structural features of the series were a terminal benzyl-type bulky substituent and a methylene linker between the sulfonyl and phenyl groups, both of which were in the head moiety as well as the spiro-type scaffold in the linker-to-tail moiety. An in vivo oral glucose-tolerance test using C57BL/6N mice showed that **(*R*)-29** reduced glucose excursion at a dose of 3 mg/kg in a dose-dependent manner.

Diabetes mellitus (DM) is a chronic condition that, as of 2014, affects approximately 400 million people globally.[1] Type 2 diabetes mellitus (T2DM), which accounts for the majority of DM cases, is a metabolic disorder characterized by relative insulin deficiency and resultant pathologically high blood glucose levels.[2] Although several types of agents that stimulate insulin secretion, such as sulfonylureas, are widely used to treat T2DM,[3] most of these agents cause hypoglycemia and β-cell dysfunction as side effects because they act irrespectively of blood glucose levels.[3] The use of dipeptidyl peptidase-4 (DPP-4) inhibitors, which affect insulin secretion in a blood-glucose-level-dependent manner, has emerged recently as a means of treating T2DM with a reduced risk of hypoglycemia.[4] However, the glucose-lowering activity of DPP-4 inhibitors is mild, necessitating therapeutic strategies that involve a combination with sulfonylureas to maintain and/or optimize their long-term therapeutic effects.[4b] Thus, novel insulin secretagogues that present reduced risk of hypoglycemia and protect β-cell function are required.

G-protein-coupled receptor 119 (GPR119) is predominantly expressed in pancreatic β-cells and gastrointestinal L-cells.[5] The activation of GPR119 both enhances glucose-dependent insulin secretion from pancreatic β-cells and increases the release of gut hormones such as glucagon-like peptide-1 (GLP-1) (which has a significant role in glucose homeostasis) from gastrointestinal L-cells.[5,6] This dual glycemic control mechanism is considered to avoid the risk of hypoglycemia and thus to be highly advantageous for patients with T2DM. Moreover, animal studies with GPR119 agonists have evidenced β-cell preservation,[7] which is assumed to be a critical issue in T2DM treatment. Accordingly, GPR119 agonism has been investigated extensively as a potential strategy for the treatment of T2DM.[8]

GPR119 agonists typically have a three-module structure that comprises head, linker, and tail moieties (Fig. 1).[8] The head moiety has an aromatic ring bearing electron-withdrawing substituents such as a sulfonyl group and/or a fluorine atom, and the tail moiety has a piperidine ring with a bulky alkyl carbamate (or an appropriate bioisostere), and these are recognized as the key pharmacophoric elements for GPR119 activation.[8]

We recently reported the first-generation GPR119 agonist **1**, which contains a bicyclic pyrimidine scaffold as the linker (Fig. 2).[9] During its development, we discovered that conformational restriction of the head moiety is required for potent GPR119 agonism. Subsequently, in an effort to develop a backup series with a novel scaffold, we reasoned that the introduction of conformational constraints between the linker and tail moieties would also benefit potency. In this context, we were drawn to the spiro[chromane-2,4′-piperidine] motif,[10] which is known to be a privileged structure with inherent affinity for diverse biological targets.[11]

Accordingly, in this study we synthesized a series of spiro[chromane-2,4′-piperidine] derivatives and performed a detailed structure–activity

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https://doi.org/10.1016/j.bmcl.2018.08.010
Received 26 June 2018; Received in revised form 10 August 2018; Accepted 11 August 2018

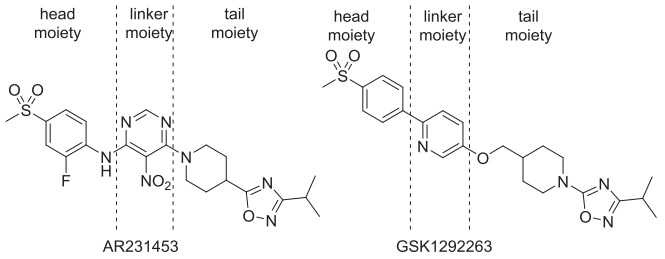


Fig. 1. Representative GPR119 agonists.[8]

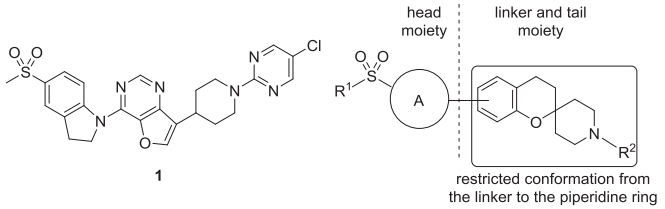
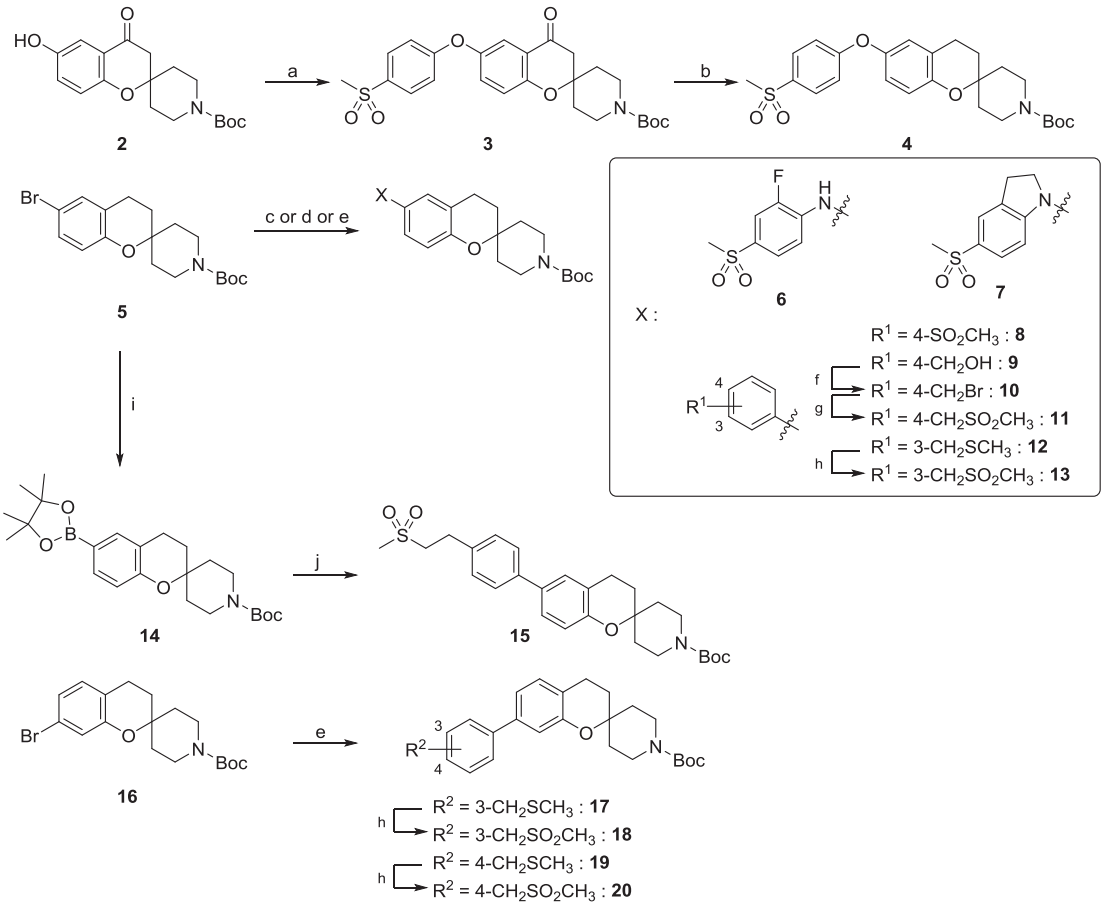


Fig. 2. Our first generation GPR119 agonist **1** and our new scaffold with spiro[chromane-2,4′-piperidine].

relationship (SAR) study to identify the structural features responsible for their activities as novel GPR119 agonists.

The synthesis of spiro[chromane-2,4′-piperidine] compounds for optimization of the head moiety started from 1′-*tert*-butoxycarbonyl-6-hydroxy-4-oxospiro[chromane-2,4′-piperidine] (**2**),[12] 1′-*tert*-butoxycarbonyl-6-bromospiro[chromane-2,4′-piperidine] (**5**),[10,13] or 1′-*tert*-butoxycarbonyl-7-bromospiro[chromane-2,4′-piperidine] (**16**),[14] as summarized in Scheme 1. *O*-Phenylation of phenol **2** by Chan–Lam–Evans coupling[15] with the appropriate boronic acid using copper(II) acetate afforded **3** in 39% yield. Thereafter, **3** was converted to spirochromane derivative **4** in 85% overall yield via a three-step sequence involving reduction of the carbonyl group and reprotection of the nitrogen. Compounds **6** and **7** were synthesized from arylbromide **5** and the corresponding anilines, using Buchwald–Hartwig amination methodology,[16] in 89% and 98% yields, respectively. Compounds **8**, **9**, **12**, **17**, and **19** were prepared using Suzuki–Miyaura coupling[17] of arylbromide **5** or **16** with the corresponding substituted phenyl boronic acid in 46–72% yields. Bromination of benzyl alcohol **9** with carbon tetrabromide afforded benzyl bromide **10**, which was subjected to a substitution reaction with sodium methanesulfinate to afford the desired sulfone **11**. Oxidation of sulfides **12**, **17**, and **19** with 3-chloroperoxybenzoic acid (*m*CPBA) afforded the corresponding sulfones **13**, **18**, and **20** in 30–40% yields. Conversion of arylbromide **5** to sulfone **15** was accomplished by reaction with bis(pinacolato)diboron in the presence of dichlorobis(triphenylphosphine)palladium(II) and Suzuki–Miyaura coupling.

Initially, we used the 1′-*tert*-butoxycarbonyl-spiro[chromane-2,4′-piperidine]-6-yl structure as a tentative linker-to-tail moiety and evaluated its combinations with different head moieties (Table 1).[18]



Scheme 1. Synthesis of spirochromane derivatives **4**, **6**, **7**, **8**, **11**, **13**, **15**, **18**, and **20**. Reagents and conditions: (a) (4-(methylsulfonyl)phenyl)boronic acid, $Cu(OAc)_2$, Et_3N, MS4Å, CH_2Cl_2, rt, 24 h, 39%; (b) (i) $NaBH_4$, EtOH, 50 °C, 1 h; (ii) Et_3SiH, 2,2,2-trifluoroacetic acid, reflux, 8 h; (iii) Boc_2O, K_2CO_3, acetone, rt, 24 h, 85% (3 steps); (c) for **6**: 2-fluoro-4-(methylsulfonyl)aniline, $Pd_2(dba)_3$, P^tBu_3, NaO^tBu, toluene, 90 °C, 6 h, 89%; (d) for **7**: 5-(methylsulfonyl)indoline, $Pd(P^tBu_3)_2$, NaO^tBu, toluene, 100 °C, 6.5 h, 98%; (e) for **8**, **9**, **12**, **17**, and **19**: $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, 90–95 °C, 9–18 h, 46–72%; (f) CBr_4, PPh_3, CH_2Cl_2, rt, 1 h, 92%; (g) $NaSO_2CH_3$, DMSO, 120 °C, 30 min, 100%; (h) *m*CPBA, CH_2Cl_2, rt, 2–4 h, 30–40%; (i) bis(pinacolato)diboron, $PdCl_2(PPh_3)_2$, KOAc, 1,4-dioxane, 90 °C, 10 h, 78%; (j) 1-bromo-4-(2-(methylsulfonyl)ethyl)benzene, $Pd(PPh_3)_4$, K_2CO_3, DME–H_2O, 90 °C, 18 h, 62%.