Bioorganic & Medicinal Chemistry Letters 19 (2009) 2400–2403

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and SAR of 1,2,3,4-tetrahydroisoquinolin-1-ones as novel G-protein-coupled receptor 40 (GPR40) antagonists

Paul S. Humphries *, John W. Benbow, Paul D. Bonin, David Boyer, Shawn D. Doran, Richard K. Frisbie, David W. Piotrowski, Gayatri Balan, Bruce M. Bechle, Edward L. Conn, Kenneth J. Dirico, Robert M. Oliver, Walter C. Soeller, James A. Southers, Xiaojing Yang

Pfizer Global R&D, Eastern Point Road, Groton, CT 06340, USA

ARTICLE INFO

Article history:
Received 4 February 2009
Revised 16 March 2009
Accepted 20 March 2009
Available online 25 March 2009

Keywords:
Diabetes
GPR40
Tetrahydroisoquinolinones
Ligand efficiency

ABSTRACT

The development of a series of novel 1,2,3,4-tetrahydroisoquinolin-1-ones as antagonists of G protein-coupled receptor 40 (GPR40) is described. The synthesis, in vitro inhibitory values for GPR40, in vitro microsomal clearance and rat in vivo clearance data are discussed. Initial hits displayed high rat in vivo clearances that were higher than liver blood flow. Optimization of rat in vivo clearance was achieved and led to the identification of **15i**, whose rat oral pharmacokinetic data is reported.

Type 2 diabetes (T2D), the most commonly occurring form of diabetes, is a condition in which the body resists the insulin that is produced by the pancreas and may fail to make enough insulin to maintain normal glucose levels.[1] The incidence of T2D has increased worldwide in recent years, largely because of growing rates of obesity, and is likely to grow to greater than 366 million by the year 2030.[2]

One of the recently characterized G-protein-coupled receptor (GPCR) families is the GPR40–43 family,[3] comprising GPR40, 41 and 43.[4] These three family members share ~30–40% sequence identity. Three independent groups have identified GPR40 as a receptor for medium- (C6–C12) and long-chain (C14–C24) fatty acids (FAs).[5] GPR40 is preferentially expressed in the pancreas with elevated levels reported in the islets and also in the pancreatic β-cell lines.[6] GPR40-deficient β-cells secrete less insulin in response to FAs, and loss of GPR40 protects mice from obesity-induced hyperinsulinemia, increased hepatic glucose output, yperglycemia and glucose intolerance.[7] Conversely, overexpression of GPR40 in β-cells of mice leads to impaired cell function, hypoinsulinemia and diabetes. These results suggest that GPR40 plays a critical role in linking obesity and T2D.

Efforts toward the identification of 1,2,3,4-tetrahydroisoquinolin-1-ones as novel GPR40 antagonists are reported here. A high-throughput screen (HTS) of the Pfizer compound collection identified compounds **1** and **2** (Fig. 1) as antagonists of GPR40. These hits were extremely attractive based on their high ligand efficiency,[8] low human liver microsomal (HLM) clearance and promising selectivity in an initial selectivity panel. The above properties motivated an initiation of hit-to-lead chemistry to explore the activity of this class of compounds as GPR40 antagonists.

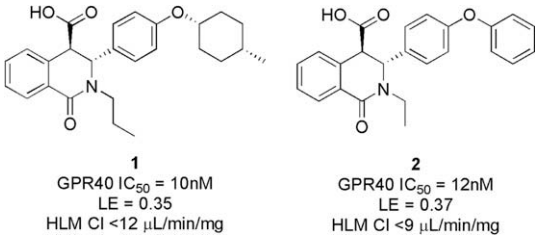


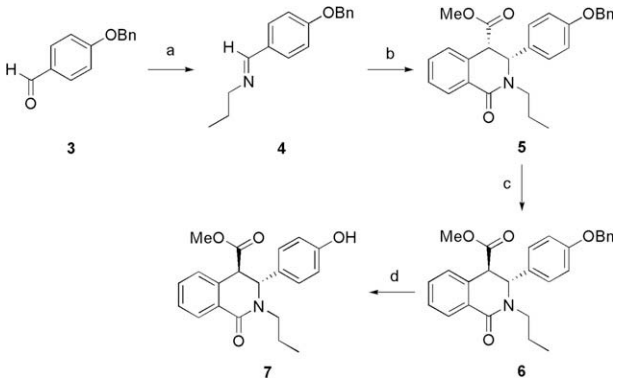
Figure 1. Initial hits from high-throughput screening.

Initial efforts involved exploration of the SAR of the terminal cyclohexyl and phenyl moieties of **1** and **2**. In order to do this in an efficient manner, a concise synthesis of phenol intermediate **7** was required. Intermediate **7** could then be utilized for late stage diversification and efficient SAR exploration of this region of the molecule.

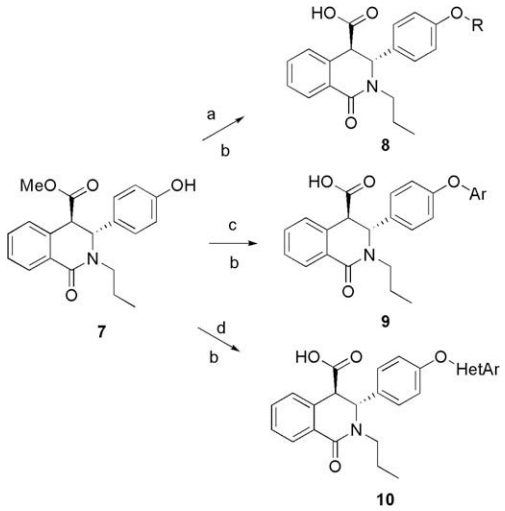
Phenol **7** was accessed in a straightforward fashion following the five step protocol below (Scheme 1). 4-Benzyloxybenzaldehyde **3** was condensed with propylamine to afford imine **4** in excellent yield. Treatment of imine **4** with homophthalic anhydride resulted in the formation of *cis*-lactam **5** in moderate yield along with minor

* Corresponding author. Tel.: +1 860 705 0559.
E-mail address: phumphri@gmail.com (P.S. Humphries).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.03.082



Scheme 1. Reagents and conditions: (a) $C_3H_7NH_2$, 4 Å MS, CH_2Cl_2, rt, 16 h, 100%; (b) homophthalic anhydride, CH_3CN, 60 °C, 16 h, 50%; (c) AcOH, 120 °C, 16 h, 95%; (d) MeI, K_2CO_3, Me_2CO, rt, 16 h, 90%; (e) BBr_3, CH_2Cl_2, rt, 16 h, 90%.



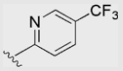
Scheme 2. Reagents and conditions: (a) ROH, PPh_3, DIAD, THF, DMF, 80 °C, 16 h. (b) LiOH, THF, MeOH, H_2O, rt, 16 h; (c) $ArB(OH)_2$, Et_3N, $Cu(OAc)_2$, Py, 1,2-DCE, DMF, 4 Å MS, air, 50 °C, 16 h; (d) 2-Br-HetAr, CuI (cat.), ligand 1 from ref.14 (cat.), K_3PO_4, MeCN, 100 °C, 16 h.

amounts of *trans*-lactam **6**.[9] The thermodynamically less stable isomer **5** could be epimerized under acidic conditions, resulting in the exclusive formation of *trans*-lactam **6** in excellent yield.[10] Esterification of acid **6** with iodomethane afforded the intermediate methyl ester, which was subsequently debenzylated utilizing boron tribromide to yield the required phenol intermediate **7**.[11]

Phenol **7** underwent a Mitsunobu reaction, followed by saponification, to afford required products **8** in a parallel fashion (Scheme 2).[12] Diaryl ethers **9** were also accessed from phenol **7** utilizing elegant methodology developed by Evans.[13] S_NAr reaction of phenol **7** with 2-bromoheteroaryls yielded products **10** via a copper-catalyzed Ullman-type coupling.[14]

All the compounds were tested in a GPR40 FLIPR calcium mobilization assay.[5] Simultaneously, compounds were screened in human (HLM) and rat liver microsome (RLM) assays. The effect of different terminal substitution (e.g., replacements for cyclohexyl and phenyl moieties in **1** and **2**) was studied first, and these results are summarized in Table 1. Both compounds **1** and **2** have good GPR40 activity and low human microsomal clearance, but high rat microsomal clearance. Knowing that the desired pre-clinical diabetic model study would be in a rat, improvements in the rodent in vitro clearance of this series was required, while maintaining our GPR40 potency and excellent human in vitro clearance. Significant reduction in MW (e.g., **8a**) resulted in a concomitant drop-off in potency, but interestingly this compound possessed low rat microsomal clearance. Benzyl substitution (e.g., **8b**) resulted in a compound with moderate GPR40 activity and low human and rat in vitro clearance. Biaryl ethers (e.g., **9b** and **10a**) also provided excellent potency and in vitro clearance.

Table 1
GPR40 activity, human and rat liver microsome data for antagonists **1**, **2** and **8**–**10**

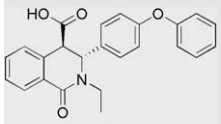
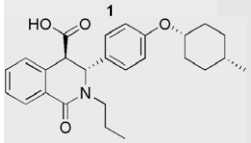
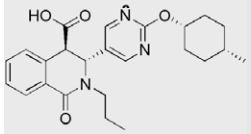
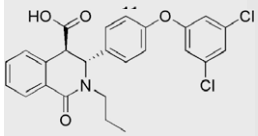
Compound	R/Ar/HetAr	GPR40 IC_{50} (nM)[a]	HLM Cl (μL/min/kg)	RLM Cl (μL/min/kg)
1	—	10	<12	274
2	—	12	<9	97
8a	Me	2100	<8	<14
8b	CH_2Ph	96	<8	<16
9a	3,5-Di-Me–Ph	2	21	46
9b	3,4-Di-Me–Ph	3	<8	<14
10a		29	<8	<14

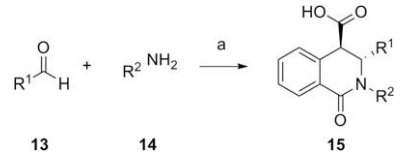
[a] Values are means of two or more independent experiments.

Compound **8b** was then selected for rat pharmacokinetic (PK) studies.[15] Administration to male Sprague–Dawley (SD) rats surprisingly resulted in iv clearance that was greater than liver blood flow (82.8 mL/min/kg). In order to see whether this high rat iv clearance held true across the series, a number of other compounds were tested and all possessed high rat in vivo clearance.

In an effort to better understand the reason for the higher than predicted in vivo rat clearance, four compounds were cassette

Table 2
Rat in vivo clearance and biliary excretion results

Structure	Rat iv Cl (mL/min/kg)	Percent dose in bile (%)
 **1**	111	13.9
	84.5	22.9
	136	69.9
 **12**	32.7	64.6



Scheme 3. Reagents and conditions: (a) MeOH, rt, 16 h then DMF, homophthalic anhydride, rt, 16 h then 1 N aq NaOH, rt, 16 h.