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Discovery of dimethyl pent-4-ynoic acid derivatives, as potent and orally bioavailable DGAT1 inhibitors that suppress body weight in diet-induced mouse obesity model

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ABSTRACT

Diacylglycerol acyltransferase (DGAT) is expressed abundantly in intestine, liver, and adipose tissues. DGAT1 is the crucial and rate-limiting enzyme that mediates the final step in triacylglycerol (TAG) resynthesis during dietary fat absorption. However, too much triacylglycerol (TAG) reserve will lead to genetic obesity (Hubert et al., 2000). DGAT1 knockout mice could survive and displayed a reduction in the postprandial rise of plasma TG, and increased sensitivity of insulin and leptin. Here we report the discovery and characterization of a novel selective DGAT1 inhibitor **29** to potentially treat obesity. Compound **29** showed lipid lowering effect in mouse lipid tolerance test (LTT) and also reduced body weight in DIO mice without observable liver damage.

Diacylglycerol acyltransferase (DGAT) is a microsomal enzyme that plays a central role in the metabolism of cellular glycerolipids. DGAT catalyzes the final step in triacylglycerol (TAG) biosynthesis by converting diacylgycerol and fatty acyl-coenzyme A into triacylglycerol. DGAT plays a fundamental role in the metabolism of cellular diacylglycerol and is important in higher eukaryotes for physiologic processes involving triacylglycerol metabolism such as intestinal absorption, lipoprotein assembly, adipose tissue formation, and lactation. Triacylglycerol (TAG) is the essential material for mammal to maintain normal physiological function. However, too much triacylglycerol (TAG) reserve will lead to genetic obesity.[1] While DGAT-2 is essential for survival in mice,[2] Dgat-1$^{-/-}$ mice had normal basal levels of plasma glucose and insulin. When subjected to a glucose load, Dgat-1$^{-/-}$ mice tended to have lower glucose and insulin levels than wild-type mice, suggesting improved glucose metabolism in DGAT deficiency. Consequently, DGAT-1 represents an attractive target for the treatment of obesity.

In the past decade, Several research groups have disclosed potent and selective DGAT1 inhibitors from several distinct chemical series, including the most advanced compound **1** (**LCQ-908**) which is in phase 3 clinical study for treatment of FCS, HCV, NAFLD.[3–5] Other compounds in clinical or discovery stage include **2** (**PF-04620110**),[6] **3** (**AZD-7687**),[7] **4** (**A-922500**),[8] compound **5**[9] and compound **6**[10] as shown in Fig. 1.

Based on the extensive work on DGAT1 inhibitors of many pharmaceutical companies, a well-defined pharmacophore has emerged for high activity. Most reported DGAT1 inhibitors contain an H-bond donor/acceptor pair in or with aromatic system, a central phenyl ring, a linker, and a right hand side carboxylic acid. The spacer is typically aromatic or aliphatic ring system which ensures right distance and optimal orientation.[11,12]

We sought to explore the possibility of employing substituted acetylene novel space. The structure of alkyne is more rigid and straight, along with the adjacent quaternary carbon will be likely to help maintain the spatial distance and optimal orientation between the two pharmacophores. Furthermore, replacing cyclohexane or phenyl ring with alkyne can decrease MW and LogP value. Alkyne group was used in many drugs such as Ponatinib (cancer), Apatinib (cancer), erlotinib (cancer), pralatrexate (cancer), Efavirenz (HIV), rasagiline (Parkinsons disease), bosentan (PAH), Regadenoson (Coronary artery disease), linagliptin (diabetes). Herein we describe the identification of a promising candidate 5-(4-(4-amino-5-oxo-7,8-dihydropyrimido[5,4*f*][1,4]oxazepin-6(5*H*)-yl)-2,6-dimethylphenyl)-3,3-dimethylpent-4-ynoic acid (**29**), an effective compound in LTT (Lipid tolerance test)[13] and DIO (diet induced obesity)[10] model. Meanwhile, the

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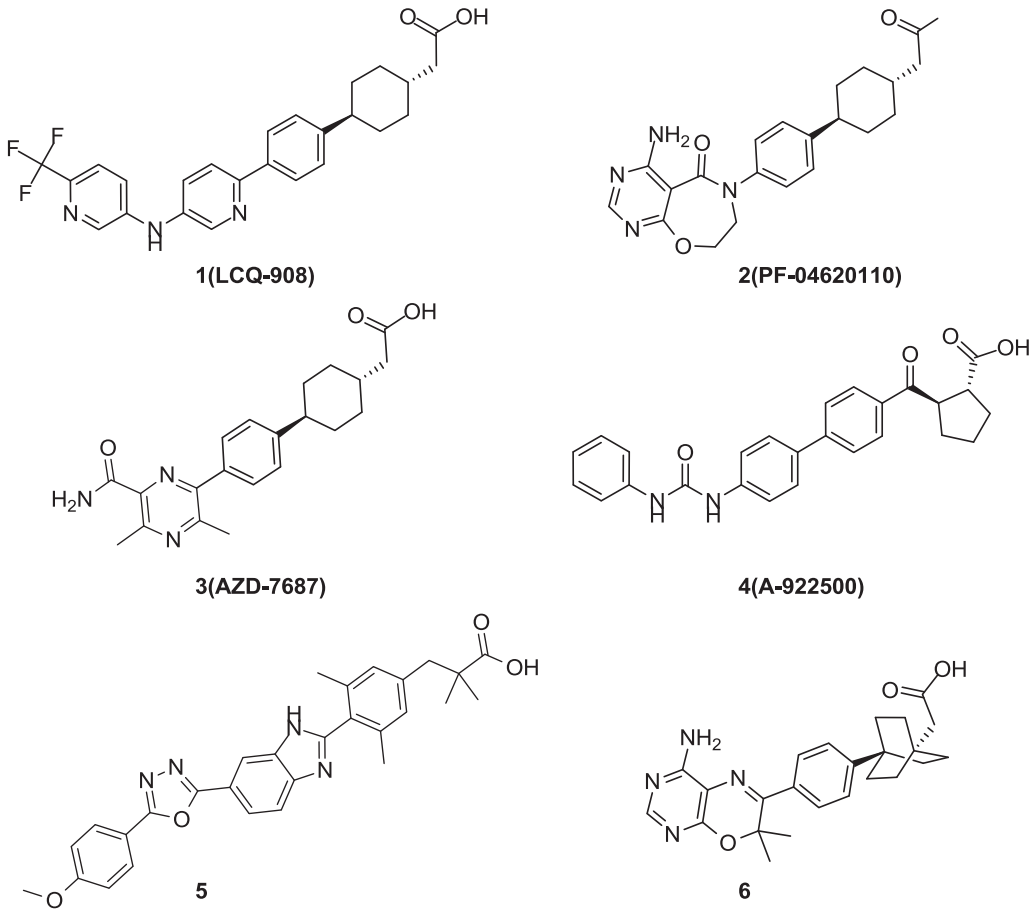

Fig. 1. Selected examples of DGAT1 inhibitors from literature.

extensive structure-activity relationship (SAR) of this series was revealed here.

Target compounds **7a**–**7k** were synthesized as shown in Scheme 1. Commercially available 1-bromo-4-nitrobenzene **8**, 4-iodobenzoic acid **10** or benzene halide **12**, **14**, **16** were used as starting materials for desired compounds. The key intermediates **9**, **11**, **13** were synthesized from starting materials **8**, **10**, **12** by Sonogashira coupling reaction with alkyne which were prepared by the reported procedure by literature.[14] The intermediate **9** was hydrogenation followed by reacted with corresponding isocyanate or Boc_2O to afforded compound **7a**, **7b**, **7c** (route A). Condensation reaction carried out from intermediate **11** to afford compound **7d** (route B). The intermediate **13** was reacted with bis(pinacolato)diboron and then treated with different bromide by Suzuki coupling reaction to obtain compound **7e**, **7f**, **7g** (route C). Compound **7h**, **7j** were prepared by route D. 4-Iodobenzoyl chloride as starting material was reacted with isopropylmagnesium chloride in the presence of $Fe(acac)_3$ to afford 1-(4-iodophenyl)-2-methylpropan-1-one, which was treated with Br_2 followed by cyclization to afford the intermediate **15**. Compound **7h** was obtained from intermediate **15** by Sonogashira coupling reaction and subsequent hydrolysis. Compound **7j** was obtained from compound **7h** with $NaBH_4$ treatment. Compound **7k** was synthesized in similar manner according to published procedures.[11] The synthetic route is described in route E of Scheme 1.

Compound **7m**, **25**–**41** ware synthesized according to published procedures[15] or in a similar manner as shown in Scheme 2. The synthesis of these compounds were initiated from commercially available substituted benzene halide, which reacted with ethyl 3,3-dimethylpent-4-ynoate[14] in presence of $Pd(dppf)Cl_2$/CuI at reflux and further reacted with 2-((*tert*-butyldimethylsilyl)oxy) ethanamine in presence of x-phos/$Pd_2(dba)_3$ utilizing Buchwald conditions. 21 analogs were obtained form **20** analogs with 4,6-dichloropyrimidine-5-carbonyl chloride by acylation reactions. Further, de-protection using HCl/ethanol and cyclization in the presence of Et_3N conditions afforded **23** analogs. The desired compounds **25**–**41** were obtained from **23** analogs by amination and subsequent hydrolysis.

Compounds were evaluated for their activity in hDGAT1 enzyme assay.[16] Firstly, these compounds were tested under single concentration. Those compounds with over 50% inhibition activity against hDGAT1 enzyme were further evaluated in multiple concentrations to generate IC_{50} value. A variety of literatures documented left hand side pharmacophoric groups were combined with the pentynoic acid through a phenyl group (Table 1). Compounds **7a**–**7d**, **7f**, **7g** are all inactive, while compounds **7j**, **7k** have modest activity (5.5 μM and 1.9 μM respectively). Compounds **7e**, **7h**, **7m** are more potent with IC_{50} of 281–468 nM. We decided to optimized **7m** because 1) It's the most active in this series; 2) It's relatively easier to make than **7h**; 3) It has lower clogP value vs **7e**.

We first evaluate pharmacokinetic properties of **7m** in SD rat (Table 5). It is orally bioavailable (42%) with oral exposure of 4105 ng.h/mL when dosed at 10 mg/kg and a moderate clearance of 14.8 mL/min/kg. Overall, it was explored as a lead compound.

We next sought to improve potency by substituting the phenyl ring of linker moiety. Compounds with different substituents at phenyl ring were designed, synthesized and evaluated (Table 2). Small 2-substituents such as Me (**25**), F (**27**), Cl (**28**), CF_3 (**34**) all