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Discovery of novel quinoline carboxylic acid series as DGAT1 inhibitors

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ABSTRACT

Herein we report the design and synthesis of a series of novel bicyclic DGAT1 inhibitors with a carboxylic acid moiety. The optimization of the initial lead compound **7** based on in vitro and in vivo activity led to the discovery of potent indoline and quinoline classes of DGAT1 inhibitors. The structure–activity relationship studies of these novel series of bicyclic carboxylic acid derivatives as DGAT1 inhibitors are described.

Excess accumulation of triglycerides (TG) is often associated with health risk and can lead to a number of additional conditions including obesity, type 2 diabetes, atherosclerosis, hypertension, and cardiovascular disease.[1] Current drugs available to treat diabetes and obesity have limitations in terms of long term efficacy and/or side effects. The unmet need prompts significant research efforts in this area.[2]

Dietary TGs are broken down in the gut to monoacylglycerol and then absorbed in the small intestines. TGs are then reassembled with the sequential addition of two acyl chains. Acyl CoA:diacylglycerol acyltransferase (DGAT) catalyzes the formation of TG from diacylglycerol and acyl-CoA, the terminal and committed step in TG synthesis.[3] Although both DGAT1 and DGAT2 are transmembrane proteins found in white adipose tissue, small intestine, liver, and mammary gland, they are from different gene families with distinctive functions. DGAT1 has more sequence homology to acyl CoA:cholesterol acyltransferase (ACAT1 and ACAT2), which plays an important role in cholesterol homeostasis.[4] DGAT1 knockout mice exhibit resistance to weight gain when fed a high-fat diet, have increased insulin sensitivity, and have increased leptin sensitivity.[5] In contrast, DGAT2 is critical to survival due to lipopenia and skin homeostasis abnormalities.[6] DGAT1 knock-out mouse phenotyping studies has shown that inhibition of DGAT1 could be a potential mechanism for the treatment of T2DM and obesity.

Over the last decade, genetic evidence in this area has inspired major efforts in identifying small molecule DGAT1 inhibitors for potential treatment of diabetes and obesity. The discovery of selective DGAT1 inhibitors has been disclosed in a number of recent reviews and publications from Japan Tobacco, Pfizer, Bayer, and Abbott, etc.[7] A number of drug candidates have been advanced into clinical trials.[8] Most discovered DGAT1 inhibitor (Fig. 1) have a terminal carboxylic acid moiety which mimics the fatty acid substrate of DGAT1.[7,9]

Pharmacophore modelling around carboxylic acid containing DGAT1 inhibitors **3** (Bayer), **5** (Abbott), **6** (Astrazeneca) was conducted using full conformational analysis to identify a low energy conformation starting point. All these ligands overlaid to each other fairly well in superposition. Key elements of the plausible pharmacophore-based binding area are illustrated in Figure 2.

This pharmacophore modeling inspired us to utilize Abbott ligand **5**[24] (green color) and AstraZeneca ligand **6** (shown in pink colour, lit.[25] IC_{50} = 2.5 nM) as the starting point for our ligand design (Fig. 3). Through ring constraining strategy and hybridization of fragment from Abbott and AstraZeneca DGAT1 ligands (in the

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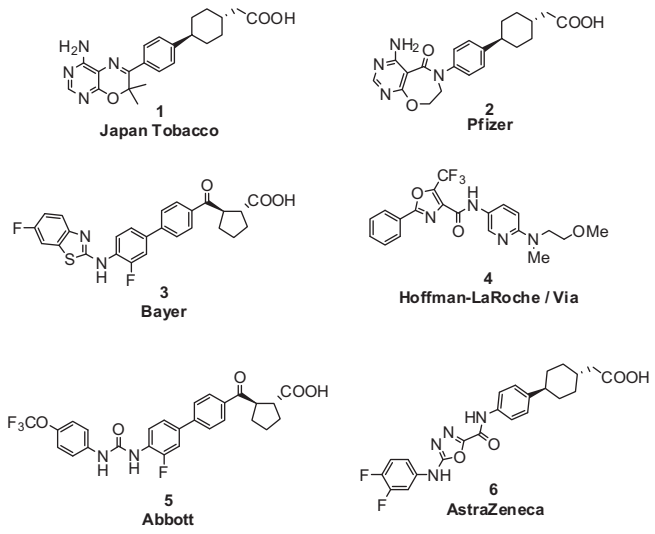

Figure 1. Selected examples of literature inhibitors for DGAT1.

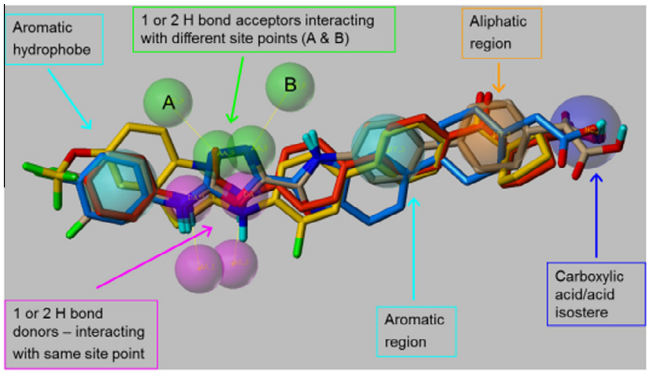

Figure 2. Pharmocophore model of Abbott (red), Bayer (yellow), AstraZeneca (blue) DGAT1 inhibitors.

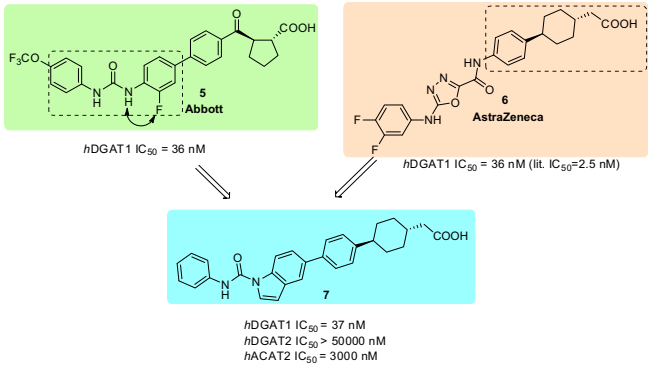

Figure 3. Lead structure design based on Abbott and AstraZeneca DGAT1 inhibitors.

box region), indole compound **7** (cyan color) was initially proposed to probe the effects of torsional constraints on the urea motif by formation of an additional ring. This modification appeared structurally well tolerated as good alignment of the urea hydrogen bond donor and acceptor features was observed for compounds **5** and **7**. This initial proposal has led to the identification of the lead compound **7** with reasonable in vitro DGAT1 inhibitory activity and good selectivity over DGAT2 and ACAT, as well as moderate efficacy measured by triacylglyceride reduction in our in vivo mouse postprandial triglyceridemia (PPTG)[10] assay (−45% at 10 mg/kg @ 2 h). Stability issue was a concern with decomposition of indole **7** in both human and mouse plasma (~40% loss of parent compound measured in ex vivo human plasma at 25 °C after 12 h). SAR has been focused on improving in vitro and in vivo potency while increasing stability properties.

Following up the lead compound **7**, initial investigations were carried out by alternating bicyclic indole ring. Representative examples (**8**–**20**) of bicyclic core modification (boxed) are summarized in Table 1. Despite good fit with the consensus pharmacophore obtained from overlaying the Abbott and AstraZeneca reported inhibitors, benzooxazole **8**, quinazoline **9**, benzimidazole **10** and indazole **11** showed poor DGAT1 enzyme activity. Changing the indole substitution pattern as shown in compounds **12** and **13** resulted in a several fold loss in DGAT1 binding potency. Compound **13** which has different substitution pattern and free NH group, still maintains certain degree of activity against mouse DGAT1 enzyme, and it is interesting to see how it behaves in vivo. To our surprise, compound **13** induced an increase in triacylglycerides levels comparing to vehicle control in mouse PPTG assay at 10 mg/kg. Replacement of the indole core with tetrahydroquinoline **14**, tetrahydroquinolinone **15**, tetrahydroquinoxaline **16** or tetrahydrobenzodiazepine **17** resulted in reduced in vitro affinity and in vivo efficacy.

An important breakthrough came with the design of indoline compound **18**, which displayed very good in vitro inhibition of the human DGAT1 enzyme and improved ex vivo plasma stability properties (~20% loss of parent compound measured in ex vivo human plasma at 25 °C after 12 h). However, compound **18** showed low triacylglyceride reduction (−15% at 10 mg/kg) in our mouse PPTG assay. In contrast, the ring-expanded benzooxazine **19** retained the good in vitro potency profile of indoline **18** as well as desirable plasma stability (~80% recovery of parent compound measured in ex vivo human plasma at 25 °C after 6 days) and molecular properties while dramatically improving in vivo efficacy. Triglyceride levels in the PPTG assay were decreased by 52% at 10 mg/kg in comparison to the vehicle-treated group. Interestingly, the pharmacokinetic properties for both compounds **18** and **19** were dramatically increased (rat AUC = 17 μM h, PPB = 99.8% for **18** and AUC = 58 μM h, PPB = 99.8% for **19**, respectively, at 10 mg/kg) due to improved solubility (50, 100 μM for **18** and **19**, respectively), Caco2 permeability (170 and 448 nm/s for **18** and **19**, respectively), low clearance ($Cl_{rat/hu}$ = 13:3 μl/min/Mcells for **18**, $Cl_{rat/hu}$ = 9:11 μl/min/Mcells for **19**), good rat oral bioavailability (>90%) and half-life ($T_{1/2}$ = 3 h for **18** and 4 h for **19**), and better plasma stability. Compound **19** also demonstrated acceptable selectivity over *h*DGAT2 (IC_{50} > 10 μM), *h*ACAT2 (IC_{50} = 9.7 μM) and clean ancillary profile except CYP 1A1 induction (3-fold for **18** and 10-fold for **19** at 30 μM). It is worth noting that the design of indoline **18** and benzomorpholine **19** were driven in large part by the desire to break the aromaticity of the second ring in indole structure, seeking improvement in physical properties and the potential for novel substitution patterns.

Cold metabolite identification studies of compound **19** confirmed that cleavage of the urea group is the major pathway in plasma. Therefore another strategy to reduce plasma stability issues and concomitant formation of aniline-type by-products is to modify the dihydrobenzoxazine core, replacing the urea moiety with a less labile amide. We were able to replace the benzomorpholine ring with a naphthalene ring, which featured a more stable amide moiety (compound **20**). Unfortunately, lipophilicity increase due to the presence of the bicyclic aromatic naphthalene in **20** resulted in extremely low permeability (Caco2 = 0 nm/s) and low pH 7 solubility (10 μM). This could explain the lack of in vivo efficacy for **20** (absence of plasma TG reduction in mice in PPTG assay), in spite of excellent potency against DGAT1 enzyme.