Accepted Manuscript

Accelerating the discovery of DGAT1 inhibitors through the application of parallel medicinal chemistry (PMC)

Yang Yu, Zhicai Wu, Zhi-Cai Shi, Shuwen He, Zhong Lai, Timothy A. Cernak, Petr Vachal, Liu Min, Jian Liu, Qingmei Hong, Tianying Jian, Deodial Guiadeen, Arto Krikorian, Donald M. Sperbeck, Andreas Verras, Lisa M. Sonatore, Beth A. Murphy, Judyann Wiltsie, Christine C. Chung, Judith N. Gorski, Jinqi Liu, Jianying Xiao, Michael Wolff, Sharon X. Tong, Maria Madeira, Bindhu V. Karanam, Dong-Ming Shen, James M. Balkovec, Robert J. De Vita, Shirly Pinto, Ravi P. Nargund

PII: S0960-894X(19)30177-5
DOI: https://doi.org/10.1016/j.bmcl.2019.03.039
Reference: BMCL 26353

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 28 January 2019
Revised Date: 19 March 2019
Accepted Date: 25 March 2019

Please cite this article as: Yu, Y., Wu, Z., Shi, Z-C., He, S., Lai, Z., Cernak, T.A., Vachal, P., Min, L., Liu, J., Hong, Q., Jian, T., Guiadeen, D., Krikorian, A., Sperbeck, D.M., Verras, A., Sonatore, L.M., Murphy, B.A., Wiltsie, J., Chung, C.C., Gorski, J.N., Liu, J., Xiao, J., Wolff, M., Tong, S.X., Madeira, M., Karanam, B.V., Shen, D-M., Balkovec, J.M., De Vita, R.J., Pinto, S., Nargund, R.P., Accelerating the discovery of DGAT1 inhibitors through the application of parallel medicinal chemistry (PMC), *Bioorganic & Medicinal Chemistry Letters* (2019), doi: https://doi.org/10.1016/j.bmcl.2019.03.039

Accelerating the Discovery of DGAT1 Inhibitors through the Application of Parallel Medicinal Chemistry (PMC)

Yang Yu*, Zhicai Wu, Zhi-Cai Shi, Shuwen He, Zhong Lai, Timothy A. Cernak, Petr Vachal, Liu Min, Jian Liu, Qingmei Hong, Tianying Jian, Deodial Guiadeen, Arto Krikorian, Donald M. Sperbeck, Andreas Verras, Lisa M. Sonatore, Beth A. Murphy, Judyann Wiltsie, Christine C. Chung, Judith N. Gorski, Jinqi Liu, Jianying Xiao, Michael Wolff, Sharon X. Tong, Maria Madeira, Bindhu V. Karanam, Dong-Ming Shen, James M. Balkovec, Robert J. DeVita, Shirly Pinto and Ravi P. Nargund

Discovery and Preclinical Sciences, Merck & Co. Inc., 2000 Galloping Hill Road, Kenilworth, New Jersey 07033, United States

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Parallel medicinal chemistry
High throughput purification
DGAT1 inhibitor
Triglyceride
Benzimidazole
ACAT1
A_{2A} receptor
Cyclohexane acetic acid
Lipid tolerance test
Pharmacokinetics

ABSTRACT

The parallel medicinal chemistry (PMC) was effectively applied to accelerate the optimization of diacylglycerol O-acyltransferase I (DGAT-1) inhibitors. Through a highly collaborative and iterative library design, synthesis and testing, a benzimidazole lead was rapidly and systematically advanced to a highly potent, selective and bioavailable DGAT1 inhibitor with the potential for further development.

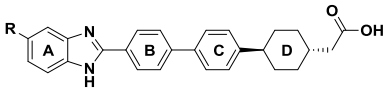
The pharmaceutical industry has been under increased pressure to deliver drug candidates in a more cost-effective and timely manner.[1] Pharma companies are increasingly developing and applying innovative capabilities to make better molecules faster. Many enabling chemistries and technologies were developed to improve the access to target molecules with expanded chemical diversity. Parallel medicinal chemistry (PMC) and high throughput purification are also routinely applied to reduce the design-make-test cycle time.[2]

We have effectively applied a highly collaborative PMC model to champion the design, synthesis and purification of target molecules to accelerate drug discovery programs.[3] As a case study, here we describe how we accelerated the optimization of diacylglycerol O-acyltransferase I (DGAT1) inhibitors via the application of PMC from a benzimidazole lead to a promising candidate with the potential for further development in less than one and half years.

Obesity and diabetes have become perceivable threats to public health and national interest.[4] Over accumulation of triglycerides (TG) is one of the main causes of obesity

and diabetes.[5, 6] During dietary fat absorption, dietary TG are digested to monoacylglycerols in the gut and absorbed in small intestines. DGAT1, a transmembrane protein, catalyzes the final step wherein TG are re-assembled from monoacylglycerols.[7] Multiple pharmaceutical companies had executed DGAT1 projects intending to develop novel small molecule drugs targeting human metabolic diseases.[8 – 14] Some of those inhibitors entered clinical trials for the treatment of obesity or type II diabetes.[15]

Most of the disclosed DGAT1 inhibitors contained a phenyl-cyclohexane acetic acid moiety that is apparently critical for DGAT1 potency. Our DGAT-1 team developed a benzimidazole lead series as exemplified by **1** and **2** in Figure 1. The representative compounds **1** and **2** displayed strong potency against human and mouse DGAT1 isoforms, but with poor selectivity against ACAT1 (ACAT1 IC_{50} = 325 nM for **1** and 485 nM for **2**) which could cause adrenocortical toxicities.[16]

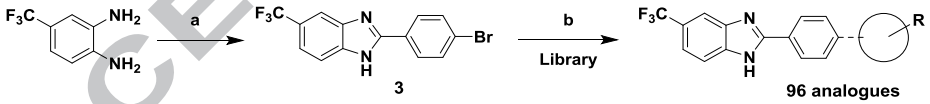


	1 (R=CF_3)	2 (R=Cl)
hDGAT1 IC_{50} (nM)	2.3	1.7
mDGAT1 IC_{50} (nM)	1.8	1.7
hACAT1 IC_{50} (nM)	325	485
HPLC LogD	2.31	2.08

Figure 1. Benzimidazole lead series

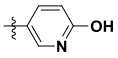
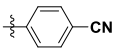
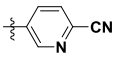
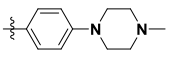
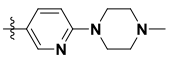
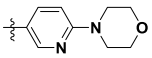
To address the ACAT1 selectivity issue, we systematically studied each structural component of the lead class. Lead Optimization (LO) team explored the structure-activity-relationship (SAR) of B-ring through traditional singleton synthesis. PMC focused on investigating A, C and D rings by library screening. One of the diversified libraries to explore the SAR of C-ring was exemplified in Scheme 1. The library was synthesized by Suzuki coupling intermediate **3** with a variety of boronic acids or boronates.

Scheme 1. Exploration of C-ring SAR [a]



[a] Reagents of condition: (a) 6-bromophenylaldehyde, potassium peroxymonosulfate, DMF-water, 72%; (b) Boronic acids / pinacol boronates, Na_2CO_3, $PdCl_2$(dppf), dioxane-water, 90°C, 16 h.

Table 1. Selected examples of the C-ring library shown in Scheme 1

Compound					
	4	**5**	**6**	**7**	**8**
hDGAT1 IC_{50}	1327 nM	127 nM	6.4 nM	98 nM	38 nM
hACAT1 IC_{50}	NT	NT	3784 nM	1402 nM	> 10000 nM
hEGR *Ki*	2314 nM	1427 nM	2250 nM	616 nM	> 60000 nM
Compound					
	9	**10**	**11**	**12**	
hDGAT1 IC_{50}	451 nM	66 nM	70 nM	65 nM	
hACAT1 IC_{50}	NT	1352 nM	2717 nM	1325 nM	
hEGR *Ki*	1641 nM	820 nM	426 nM	13040 nM	

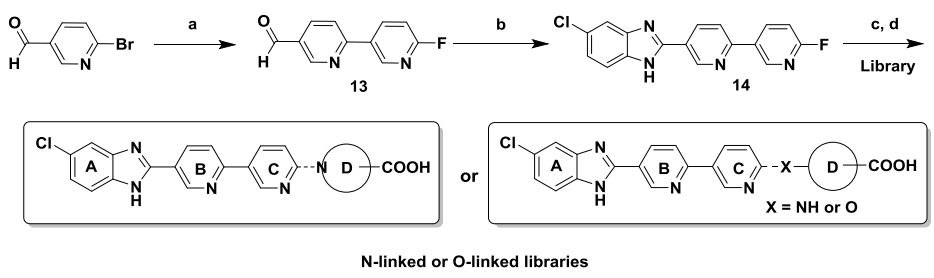
NT = Not tested due to low DGAT1 potency

Selected analogues in Table 1 showed that replacing the C-ring with pyridine not only significantly improved DGAT1 potency (Compound **4** vs. **5** and Compound **9** vs. **6**) but also increased the ACAT1 selectivity (Compound **7** vs. **8** and compound **10** vs. **11**). Among these compounds, the IC_{50} ratio of human ACAT1 versus DGAT1 of compound **6** was > 500 folds. Compounds **6**, **10**, **11** and **12** with oxygen or nitrogen substitution at the 2-position of the pyridine retained good human DGAT1 inhibiting activities. We hypothesized that lowering LogD and increasing flexibility of the lead compound could improve the selectivity against ACAT1 while maintaining good DGAT1 potency. Moreover, compared with those with phenyl ring as C-ring, compounds with pyridine as the C-ring had comparable selectivity against hERG channel.

Meanwhile, B-ring SAR explored by LO team showed that compounds with pyridine as the B-ring had comparable profiles as phenyl ring, but exhibited superior bioavailability. Thus, benzimidazole pyridyl-pyridyl N- and O-linked libraries were designed and synthesized to explore the feasibility (Scheme 2).

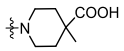
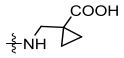
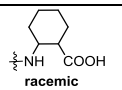
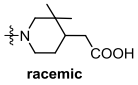
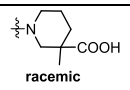
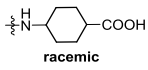
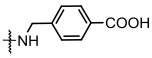
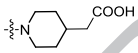
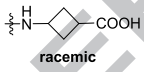
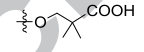
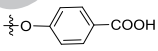
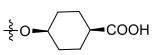
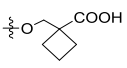
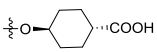
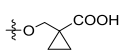
To substitute the fluoro group on pyridyl-pyridyl scaffold, intermediate **14** was reacted with 24 amino carboxylic acids or carboxylates via S_NAr reaction. The resulting carboxylate intermediates were hydrolyzed to furnish the N-linked analogues. Compound **14** was also used to produce the O-linked library by substituting the fluoro group with 20 diverse ester-containing alcohols or phenols and then hydrolyzing the ester to acid to yield the products.

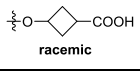
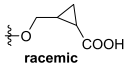
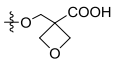
Scheme 2. Design and synthesis of benzimidazole pyridyl-pyridyl N- and O-linked libraries [a]



[a] Reagents and conditions: (a) (6-fluoropyridin-3-yl)boronic acid, Na_2CO_3, $PdCl_2$(dppf), DMF-water, 80°C, 16 h, 69%; (b) 4-chlorobenzene-1,2-diamine, potassium peroxymonosulfate, DMA-Water, 16 h, 70%; (c) For amino building blocks with carboxylic acids or carboxylates, $NaHCO_3$, NMP, 110°C, 16 h; For phenols, K_2CO_3, NMP, 110°C, 20 h; For alcohols with carboxylates, NaH, NMP, 110°C, 20 h; (d) For N-linked analogues with carboxylates, LiOH-H_2O, MeOH-THF (1:1), 50°C, 2 h; For O-linked analogues with carboxylates, one-pot, MeOH, ambient temperature, 2 h.

Table 2. Profile of representative compounds of benzimidazole N-linked and O-linked pyridyl-pyridyl libraries, N-linked analogues **15 – 23**, O-linked analogues **24 - 32**

Comp	D-ring	Human DGAT1 IC_{50} (nM)	Mouse DGAT1 IC_{50} (nM)	LogD (HPLC)	Human ACAT1 IC_{50} (nM)	hERG binding (K_i, μM)	Mouse LTT
15		2.5	20	1.45	> 10000	4.8	-96%
16		2.9	20	1.33	> 10000	12.12	0%
17	 racemic	4.2	21	1.51	> 10000	3.56	0%
18	 racemic	4.5	33	1.56	> 2000	1.74	-66%
19	 racemic	4.5	36	1.43	> 2000	1.98	-63%
20	 racemic	5.4	48	1.37	> 2000	3.75	-70%
21		9.6	84	1.30	> 10000	11.89	NT
22		10.2	108	1.48	> 2000	5.22	-62%
23	 racemic	22.0	247	1.29	> 2000	> 60	NT
24		0.7	1.4	1.44	971	8.14	NT
25		1.3	4.4	1.49	1940	1.36	NT
26		1.5	2.8	1.42	>2000	5.39	-144%
27		1.7	5.0	1.24	1718	20.05	-89%
28		2.6	6.3	1.39	1967	3.52	-83%
29		3.1	11	1.35	1652	10.75	-50%

30	 racemic	3.5	24	1.16	>2000	20.23	-54%
31	 racemic	3.6	30	1.19	>2000	18.98	-91%
32		5.3	36	1.16	>10000	6.54	-87%

NT = Not tested; Mouse lipid tolerance test (LTT) was measured after 18 hours at 10 mg/kg single oral dosing.

Table 2 summarizes the representative compounds from these two libraries. N-linked compounds **15** – **23** showed potent inhibition of human and mouse DGAT1. These compounds generally have a clean off-target profile. All compounds had > 2000 nM ACAT1 IC_{50} and some of them exhibited > 10000 nM ACAT1 IC_{50}. Thus, the N-linked pyridyl-pyridyl series substantially improved the selectivity against ACAT1.

Compound **15** had the best human DGAT1 potency (IC_{50} = 2.5 nM) and the best selectivity against ACAT1 (> 4000-fold) in the N-linked series. An *in-vivo* mouse lipid tolerance test (LTT) was utilized to evaluate pharmacodynamics efficacies by comparing the reduction of lipid excursions of the synthesized compounds with vehicle and a positive control compound.[17] Compound **15** displayed an excellent *in-vivo* efficacy in mouse LTT with 96% reduction of lipid excursion after 18 hours at 10 mg/kg single oral dose. Compounds **18**, **19**, **20** and **22** had modest lipid excursion reductions (> 60% after 18 hours at 10 mg/kg single oral dosing) in mouse LTT. In addition, compounds **16** and **17** did not show any mouse LTT efficacy and compound **21** had high CYP 2C8 inhibition (IC_{50} = 2.5 nM). Unfortunately, none of these analogues met the desired selectivity against the hERG channel (*Ki* > 30 μM) except for compound **23,** which lacked strong mouse DGAT1 potency and was not tested in mouse LTT. Many follow-up analogues were synthesized and tested in singleton or library format. However, it was challenging to identify compounds that balanced DGAT1 potency and hERG selectivity.

On the other hand, compounds **27**, **30** and **31** in the O-linked library showed improved selectivity against hERG channel. By calculating the basicity of the most basic group of the O-linked scaffold (calculated pKa ~ 3.0) versus that of the N-linked scaffold (calculated pKa > 5.0), we arrived at the hypothesis that the low basicity of the O-linked analogues contributed to this improvement.

Moreover, the O-linked pyridyl-pyridyl analogues generally show better human and mouse DGAT1 inhibitory activity than the N-linked analogues. HPLC measured LogDs of the O-linked pyridyl-pyridyl analogues were comparable with those of the N-linked compounds. Among these selected O-linked analogues, compound **24** had poor ACAT1 selectivity (IC_{50} =971 nM), in spite of potent human DGAT1 inhibition (IC_{50} < 1 nM). Compound **25** had unacceptable solubility (<1 μM at pH = 7). Compounds **26**, **28** and **32** demonstrated robust lipid excursion reductions in the mouse LTT but had poor hERG selectivity. Compounds **27** and **31** showed strong *in-vivo* efficacy and improved hERG selectivity (both had > 89% lipid excursion reductions after 18 hours at 10 mg/kg single

oral dosing in mouse LTT). Compounds **29** and **30** displayed acceptable selectivity against ACAT1 and hERG with modest lipid excursion reductions in mouse LTT.

In an effort to address these issues, we fixed the D-ring pharmacophores of these analogues (**26**, **27**, **28**, **29**, **30**, **31** and **32**) and explored the A-ring SAR through seven individual libraries (Figure 2) with a similar set of substituted benzimidazoles or azabenzimidazoles as exhibited in Table 3.

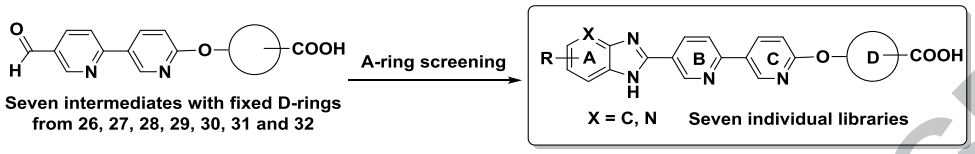


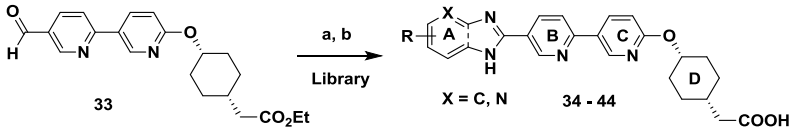
Figure 2. A-ring screening of pyridyl-pyridyl series

Libraries with D-ring pharmacophores from compounds **27**, **29**, **30**, **31** and **32** did not result in compounds with good *in-vivo* efficacies and improved hERG selectivity. In contrast, screening the A-ring with *cis*- and *trans*-oxy-cyclohexane carboxylic acids derived from compounds **26** and **28** as the D-ring resulted in several good compounds with balanced selectivity, off-target-activities and *in-vivo* efficacy in mouse LTT. Unfortunately, we found that the carboxylic acid on the cyclohexane ring of those compounds can undergo a *cis*/*trans* epimerization *in-vivo*.[18]

One plausible explanation for such isomerization is that the acyl-CoA covalently interacts with the carboxylic acid group and causes the *cis*/*trans* isomerization through a cyclohexylidene (acyl-CoA) methanolate intermediate.[19] We devised several strategies to address this issue. First, we substituted the hydrogen at the α-position of the carboxylic acid on the cyclohexane ring with a methyl group, which blocks the epimerization. Second, we replaced carboxylic acid with acetic acid on the cyclohexane ring to eliminate the epimerization.

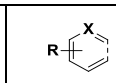
While keeping the oxy-cyclohexane α-methyl carboxylic acid or oxy-cyclohexane acetic acid as the D-ring, we applied focused libraries to rapidly evaluate these two strategies. Gratifyingly, we did not observe isomerization during *in-vitro* hepatocyte incubation study or *in-vivo* mouse LTT study. The compounds with the oxy-cyclohexane α-methyl carboxylic acid (both *cis* and *trans*), however, had lower *in-vivo* efficacy in mouse LTT than that of the corresponding oxy-cyclohexane acetic acid analogues. Profile of the focused library of *cis* oxy-cyclohexane acetic acid analogues is summarized in Table 3 due to their overall superior *in-vitro* and *in-vivo* experimental data to the corresponding *trans* isomers.

Scheme 3. Synthesis of pyridyl-pyridyl *cis* oxy-cyclohexane acetic acid library [a]



[a] Reagents and conditions: (a) substituted benzene or pyridine diamines, potassium peroxymonosulfate, 3% HOAc/DMF, 100°C, overnight; (b) LiOH-H_2O, DMF, ambient temperature, overnight.

Table 3. Profile of A-ring pyridyl-pyridyl *cis* oxy-cyclohexane acetic acid library, compounds **34** – **44**

Comp		Human DGAT1 IC_{50} (nM)	Mouse DGAT1 IC_{50} (nM)	Human ACAT1 IC_{50} (nM)	hERG binding (K_i, μM)	Human A_{2A} cAMP IC_{50} (μM)	Mouse LTT
34		1.3	1.7	942	3.0	NT	NT
35		1.6	1.5	970	4.1	NT	NT
36		1.7	2.6	> 2000	19.0	NT	NT
37		2.1	2.3	606	3.8	NT	NT
38		2.4	3.2	> 2000	8.2	0.42	-109%
39		3.2	5.9	1629	8.6	NT	NT
40		3.6	17.8	> 10000	2.7	0.43	-63%
41		5.2	5.2	> 2000	26.9	0.45	-92%
42		7.0	9.5	> 2000	23.4	0.97	-92%
43		11.6	9.8	> 2000	37.7	1.20	-96%
44		30.8	38.1	> 10000	> 60	0.49	NT

NT = Not tested; Mouse LTT was measured after 18 hours at 3 mg/kg single oral dosing.

Although most of the analogues had IC_{50} < 10 nM against human or mouse DGAT1, only compounds **41**, **42** and **43** had acceptable selectivity against both human ACAT1 (IC_{50} > 2000 nM) and the hERG channel (*Ki* ~ 30 μM). These three compounds significantly reduced lipid excursion (> 90%) in the mouse LTT after 18 hours at 3 mg/kg single oral dose. We advanced them to an *in-vitro* safety pharmacology screening against a panel of known biological targets to identify off-target liabilities. Unfortunately, all of them showed unacceptable activity against human Adenosine IIa (A_{2A}) receptors. We then tested 30 representative compounds from the O- or N-linked benzimidazole pyridyl-pyridyl series in an A_{2A} cAMP functional assay. All of them showed activity against the human A_{2A} receptor.

Collaborating with Computational Modeling and Informatics (CM&I) group, we studied the binding model of benzimidazole pyridyl-pyridyl molecules with A_{2A} receptors and found that the C-ring played a critical role in the binding interaction. The docking model indicated that the nitrogen on the pyridine formed a hydrogen bond with amino acid residue Tyr 271 of the A_{2A} receptor, as well as the aromatic pyridine ring interacted with Leu 167 of the A_{2A} receptor through hydrophobic interactions.

We therefore designed and synthesized libraries and singletons, which used a variety of piperidine or spiropiperidine derivatives to replace the C-ring pyridine in an effort to improve the A_{2A} selectivity.[20, 21] Several representative compounds were tested in the A_{2A} binding assay. The results showed that these compounds (e.g. **45** and **46**) not only had high selectivity against A_{2A} and ACAT1, but also exhibited strong DGAT1 inhibitory potency (Figure 3).

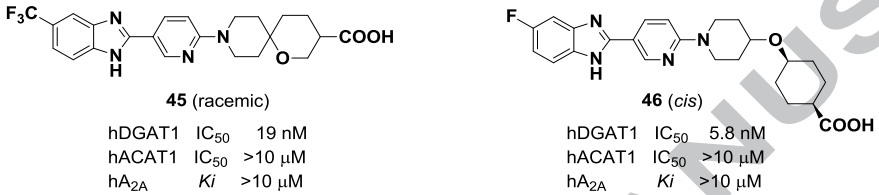
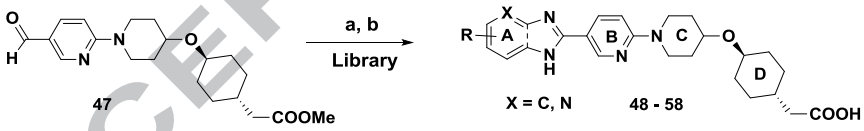


Figure 3. Profile of spiropiperidine or piperidine as the C-ring of benzimidazole series

Encouraged by such a profile, we designed a focused library to explore the A-ring SAR with piperidine as the C-ring and oxy-cyclohexane acetic acid as the D-ring (Scheme 4). Both *cis* and *trans* oxy-cyclohexane acetic acid libraries were synthesized and tested. Only the profile of *trans* isomers is summarized in Table 4 for their overall better *in-vitro* and *in-vivo* experimental data than those of the corresponding *cis* isomers.

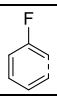
Scheme 4. Synthesis of A-ring pyridyl-piperidinyl *trans* oxy-cyclohexane acetic acid library



[a] Reagents and conditions: (a) substituted benzene or pyridine diamines, potassium peroxymonosulfate, 3% HOAc/DMF, 80°C, overnight; (b) LiOH-H_2O, MeOH - THF (1:1), ambient temperature, 3 h.

Table 4. Profile of A-ring pyridyl-piperidinyl *trans* oxy-cyclohexane acetic acid library, compounds **48 - 58**

Comp	R	Human DGAT1 IC_{50} (nM)	Mouse DGAT1 IC_{50} (nM)	Human ACAT1 IC_{50} (nM)	hERG binding (K_i, μM)	Human A_{2A} cAMP IC_{50} (μM)	Mouse LTT
48		2.0	4.6	> 10000	4.9	1.80	-57%

49		3.1	22.0	> 10000	4.5	0.68	NT
50		4.1	11.0	> 10000	4.1	0.52	-65%
51		6.5	46.0	> 10000	40.7	3.48	-84%
52		8.0	21.4	>10000	10.7	0.91	-92%
53		15.2	42.1	> 10000	25.7	> 10.0	-85%
54		23.6	125	> 10000	12.0	NT	NT
55		26.1	528	> 10000	3.0	NT	NT
56		50.5	78	> 10000	20.5	NT	NT
57		61.3	271	> 10000	NT	NT	NT
58		442.5	1908	NT	NT	NT	NT

NT = Not tested; Mouse LTT was measured after 18 hours at 3 mg/kg single oral dosing.

Analogues **48** – **58** had excellent selectivity against human ACAT1 (IC_{50} > 10000 nM). Compounds **48**, **49**, **50** and **52**, however, failed to meet the hERG and A_{2A} selectivity criteria (*Ki* > 30 µM for hERG channel and IC_{50} > 2 µM for A_{2A} receptor). Compounds **51** and **53** displayed acceptable DGAT1 activity, selectivity and *in-vivo* efficacy. Therefore, we advanced them to genetic toxicology studies. Compound **53** failed in a 3-strain (TA1525, TA98, and TA100) microbial mutagenesis assay. Compound **51** passed the Ames test over a concentration range of 30 to 5000 µg / plate.

Further *in-vivo* efficacy assessment showed that compound **51** significantly reduced lipid excursion in dog LTT (100% at 1 mg/kg oral dosing). In pharmacokinetic studies, compound **51** displayed good data in rat and dog (Table 5).

Table 5. Pharmacokinetic data of compound **51** in rat and dog [a, b]

PK parameters	**rat**	**dog**
F (%)	17	40
Cl (mL min^{-1} kg^{-1})	17.0	3.4
Vdss (L kg^{-1})	1.08	0.81
$t_{½}$ (h)	1.0	3.2
C_{max} (µM)	0.23	2.4
T_{max} (h)	1.0	0.50
AUCn (µM·h/(mg/kg))	0.3	4.1

[a] Compound dosed in Sprague-Dawley rats as a solution in EtOH/PEG400/H_2O (10:50:40) at 1 mg/kg i.v. and 2 mg/kg p.o. [b] Compound dosed in beagles as a solution in EtOH/PEG400/water (10:50:40) at 1 mg/kg, i.v., and as solution in 0.5% methylcellulose at 2 mg/kg, p.o.

In summary, parallel medicinal chemistry was effectively applied on a DGAT1 program to expedite the SAR exploration and address program issues. Lowering LogD and increasing flexibility of the benzimidazole scaffold solved the ACAT1 selectivity issue; decreasing basicity of the molecule improved the selectivity against hERG channel; replacing the aromatic C-ring with piperidine improved the A_{2A} receptor selectivity; substituting carboxylic acid on D-ring cyclohexane with acetic acid eliminated the *cis*/*trans* isomerization problem. Through a highly collaborative and iterative library design, synthesis and testing, we were able to efficiently discover highly potent and selective DGAT1 inhibitors with the potential for further development.

Reference and notes

1. Paul, S. M.; Mytelka, D. S.; Dunwiddie, C. T.; Persinger C. C.; Munos, B. H.; Lindborg, S. R.; Schacht, A. L. *Nat. Rev. Drug Discov.* **2010**, 9, 203.
2. Nettekoven, M.; Thomas, A. W. *Curr. Med. Chem.* **2002**, 9, 2179.
3. Liu, M.; Chen, K. C.; Christian, D.; Fatima, T.; Pissarnitski, N.; Streckfuss, E.; Zhang, C. W.; Xia, L.; Borges, S.; Shi, Z. C.; Vachal, P.; Tata, J.; Athanasopoulos, J. *ACS Comb. Sci.* **2012**, 14, 51.
4. Ogden, C. L.; Carroll, M. D.; Fryar, C. D.; Flegal, K. M. *CDC National Center for Health Statistics (NCHS) Data Brief* **2015**, 219.
5. Eckel, R. H. *Obesity and Heart Disease: Circulation*, **1997**, 96, 3248.
6. Grundy, S. M.; Benjamin, I. J.; Burke, G. L.; Chait, A.; Eckel, R. H.; Howard, B. V.; Mitch, W.; Smith, S. C.; Sowers, J. R. *Diabetes and cardiovascular disease: Circulation* **1999**, 100, 1134.
7. Cases, S.; Stone, S. J.; Zhou, P.; Yen, E.; Tow, B.; Lardizabal, K. D.; Farese, R. V. Jr. *J. Biol. Chem.* **2001**, 276, 38870.
8. Ohshiro, T.; Tomoda, H. *Expert Opin. Ther. Pat.* **2015**, 25, 145.
9. King, A. J.; Judd, A. S.; Souers, A. J. *Expert Opin. Ther. Pat.* **2010**, 20, 19.
10. Yeh, V. S.; Beno, D. W.; Brodjian, S.; Brune, M. E.; Cullen, S. C.; Dayton, B. D.; Dhaon, M. K.; Falls, H. D.; Gao, J.; Grihalde, N.; Hajduk, P.; Hansen, T. M.; Judd, A. S.; King, A. J.; Klix, R. C.; Larson, K. J.; Lau, Y. Y.; Marsh, K. C.; Mittelstadt, S. W.; Plata, D.; Rozema, M. J.; Segreti, J. A.; Stoner, E. J.;Voorbach, M. J.; Wang, X.; Xin, X.; Zhao, G.; Collins, C. A.; Cox, B. F.; Reilly, R. M.; Kym, P. R.; Souers, A. J. *J. Med. Chem.* **2012**, 55, 1751.
11. Fox, B. M.; Furukawa, N.; Hao, X.; Iio, K.; Inaba, T.; Jackson, S. M.; Kayser, F.; Labelle, M.; Li, K.; Matsui, T.; McMinn, D. L.; Ogawa, N.; Rubenstein, S. M.; Sagawa, S.; Sugimoto, K.; Suzuki, M.; Tanaka, M.; Ye, G.; Yoshida, A.; Zhang, J. WO2004/047755A2.
12. Dow, R. L.; Li, J. C.; Pence, M. P.; Gibbs, E. M.; LaPerle, J. L.; Litchfield, J.; Piotrowski, D. W.; Munchhof, M. J.; Manion, T. B.; Zavadoski, W. J.; Walker, G. S.; McPherson, R. K.; Tapley, S.; Sugarman, E.; Guzman-Perez, A.; DaSilva-Jardine, P. *ACS Med. Chem. Lett.* **2011**, 2, 407.

13. Serrano-Wu, M. H.; Coppola, G.; Gong, Y.; Neubert, A.; Chatelain, R.; Clairmont, K. B.; Commerford, R.; Cosker, T.; Daniels, T.; Hou, Y.; Jain, M.; Juedes, M.; Li, L.; Mullarkey, T.; Rocheford, E.; Sung, M. J.; Tyler, A.; Yang, Q.; Yoon, T.; Hubbard, B. K. *ACS Med. Chem. Lett.* **2012**, 3, 411.
14. Barlind, J. G.; Bauer, U. A.; Birch, A. M.; Birtles, S.; Buckett, L. K.; Butlin, R. J.; Davies, R. D. M.; Eriksson, J. W.; Hammond, C. D.; Hovland, R.; Johannesson, P.; Johanson, M. J.; Kemmitt, P. D.; Lindmark, B. T.; Gutierrez, P. M.; Noeske, T. A.; Nordin, A.; O'Donnell, C. J.; Petersson, A. U.; Redzic, A.; Turnbull, A. V.; Vinblad, J. *J. Med. Chem.* **2012**, 55, 10610.
15. DeVita, R. J.; Pinto, S. *J. Med. Chem.* **2013**, 56, 9820.
16. Floettmann, J. E.; Buckett, L. K. Turnbull, A. V.; Smith, T.; Hallberg, C.; Birch, A.; Lees, D.; Jones, H. B. *Toxicol. Pathol.* **2013**, 41, 941.
17. Liu, J.; Gorski, J.; Gold, S. J.; Chen, D.; Chen, S.; Forrest, G.; Itoh, Y.; Marsh, D. J.; McLaren, D. J.; Shen, Z.; Sonatore, L.; Carballo-Jane, E.; Craw, S.; Guan, X.; Karanam, B.; Sakaki, J.; Szeto, D.; Tong, X.; Xiao, J.; Yoshimoto, R.; Yu, H.; Balkovec, J.; Pinto, S. *Obesity* **2013**, 21, 1406.
18. He, S. W.; Hong, Q. M.; Lai, Z.; Wu, Z. C.; Yu, Y.; Kim, D. W.; Ting, P. C.; Kuethe, J. T.; Yang, G. X.; Jian, T. Y.; Liu, J.; Guiadeen, D.; Krikorian, A. D.; Sperbeck, D. M.; Sonatore, L. M.; Wiltsie, J.; Chung, C. C.; Gibson, J. T.; Lisnock, J. M.; Murphy, B. A.; Gorski, J. N.; Liu, J. Q.; Chen, D. L.; Chen, X. L.; Wolff, M.; Tong, S. X.; Madeira, M.; Karanam, B. V.; Shen, D. M.; Balkovec, J. M.; Pinto, S.; Nargund, R. P.; DeVita, R. J. *ACS Med. Chem. Lett.* **2013**, 4, 773.
19. Sanins, S. M.; Adams, W. J.; Kaiser, D. G.; Halstead, G. W.; Hosley, J.; Barnes, H.; Baillie, T. A. *Drug Metab. Dispos.* **1991**, 19, 405.
20. Cernak, A. T.; Gesmundo, N.; Dykstra, K.; Yu, Y.; Wu, Z. C.; Shi, Z. C.; Vachal, P.; Sperbeck, D. M.; He, S. W.; Murphy, B.; Sonatore, L. M.; Williams, S.; Madeira, M.; Verras, A.; Reiter, M.; Lee, C.; Cuff, J.; Sherer, E.; Kuethe, J.; Goble, S.; Perrotto, N.; Pinto, S.; Shen, D. M.; Balkovec, J. M.; Nargund, R.; DeVita, R. J.; Dreher, S. D. *J. Med. Chem.* **2017**, 60, 3594.
21. He, S. W.; Hong, Q. M.; Lai, Z.; Yang, D. X.; Ting, P. C.; Kuethe, J. T.; Cernak, T. A.; Dykstra, K. D.; Sperbeck, D. M.; Wu, Z. C.; Yu, Y.; Yang, G. X.; Jian, T. Y.; Liu, J.; Guiadeen, D.; Krikorian, A. D.; Sonatore, L. M.; Wiltsie, J.; Liu, J. Q.; Gorski, J. N.; Chung, C. C.; Gibson, J. T.; Lisnock, J. M.; Xiao, J. Y.; Wolff, M.; Tong, S. X.; Madeira, M.; Karanam, B. V.; Shen, D. M.; Balkovec, J. M.; Pinto, S.; Nargund, R. P.; DeVita, R. J. *ACS Med. Chem. Lett.* **2014**, 5, 1082.

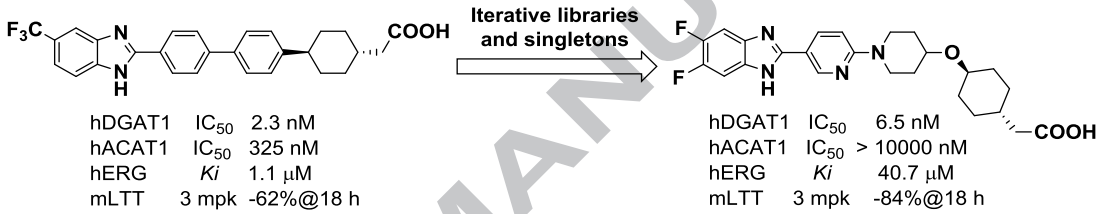
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Accelerating the Discovery of DGAT1 Inhibitors through the Application of Parallel Medicinal Chemistry (PMC)

Leave this area blank for abstract info.

Yang Yu*, Zhicai Wu, Zhi-Cai Shi, Shuwen He, Zhong Lai, Timothy A. Cernak, Petr Vachal, Min Liu, Jian Liu, Qingmei Hong, Tianying Jian, Deodial Guiadeen, Arto Krikorian, Donald M. Sperbeck, Andreas Verras, Lisa M. Sonatore, Beth A. Murphy, Judyann Wiltsie, Christine C. Chung, Judith N. Gorski, Jinqi Liu, Jianying Xiao, Michael Wolff, Sharon X. Tong, Maria Madeira, Bindhu V. Karanam, Dong-Ming Shen, James M. Balkovec, Robert J. DeVita, Shirly Pinto and Ravi P. Nargund



hDGAT1	IC_{50}	2.3 nM
hACAT1	IC_{50}	325 nM
hERG	*Ki*	1.1 μM
mLTT	3 mpk	-62%@18 h

hDGAT1	IC_{50}	6.5 nM
hACAT1	IC_{50}	> 10000 nM
hERG	*Ki*	40.7 μM
mLTT	3 mpk	-84%@18 h