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Article

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Keywords: MGAT2 inhibitor, acyltransferase, triacylglycerol, obesity, metabolic disease, indoline, conformation

ABSTRACT. Acyl CoA:monoacylglycerol acyltransferase-2 (MGAT2) has attracted interest as a novel target for the treatment of obesity and metabolic diseases. Starting from a *N*-phenylbenzenesulfonamide derivative **1** with moderate potency for MGAT2 inhibition, we explored an effective location of the hydrophobic group at the 1-position to enhance MGAT2

inhibitory activity. Shifting the hydrophobic group to the adjacent position followed by introduction of a bicyclic central core to restrict the substituent orientation produced a *N*-phenylindoline-5-sulfonamide derivative **10b**, which displayed much improved potency, with an IC_{50} value of 1.0 nM. This compound also exhibited excellent selectivity (greater than 30,000-fold) against related acyltransferases (MGAT3, DGAT1, DGAT2, and ACAT1). Subsequent optimization efforts were directed toward improving pharmacokinetic profiles, which resulted in the identification of 5-[(2,4-difluorophenyl)sulfamoyl]-7-(2-oxopyrrolidin-1-yl)-*N*-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1*H*-indole-1-carboxamide (**24d**) endowed with potent MGAT2 inhibitory activity (IC_{50} = 3.4 nM) and high oral bioavailability (F = 52%, mouse). In a mouse oral fat tolerance test, oral administration of this compound effectively suppressed the elevation of plasma triacylglycerol levels.

INTRODUCTION

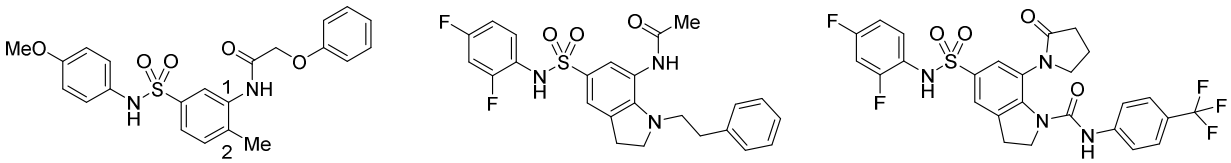
Dietary fat mainly consists of triacylglycerol (TG), and it is one of the important sources of energy for our body. Fat absorption includes multiple steps, namely hydrolysis of TG by gastric and pancreatic lipases to fatty acids and monoacylglycerol (MG), uptake of the cleaved products in the enterocytes, resynthesis of TG from MG, incorporation of TG in chylomicrons, and entrance of chylomicrons into the systemic circulation.[1-3] Acyl CoA:monoacylglycerol acyltransferases (MGATs) are enzymes that catalyze the synthesis of diacylglycerol (DG) from MG and fatty acyl CoA, which is a crucial step in TG synthesis by the MGAT pathway. MGATs belong to the DGAT2 gene family of enzymes, and three isoforms (MGAT1, MGAT2, and MGAT3) have been identified till date.[4, 5] Among them, MGAT2 is highly expressed in the small intestine, and it is considered to play an important role in dietary fat absorption.

Recently, independent research groups reported that MGAT2-deficient mice were protected from high-fat diet-induced obesity and exhibited improved insulin sensitivity and glucose tolerance.[6-8] Interestingly, the MGAT2-deficient mice displayed increased oxygen consumption in comparison with the wild-type mice. The anti-obesity phenotype of the MGAT2-deficinet mice is likely associated with enhanced energy expenditure, although the precise pharmacological basis remains to be elucidated. Furthermore, in the MGAT2-deficient mice, fatty and oily stool was not observed, whereas orlistat, a pancreatic lipase inhibitor, exerted these types of gastrointestinal adverse effects.[9] These preclinical data strongly suggested that MGAT2 inhibitors can serve as novel anti-obesity and anti-diabetic agents.

Despite the potential pharmacological benefits, only a few reports of MGAT2 inhibitors have been reported,[10, 11] and there is no clinical information regarding MGAT2 inhibitors. We initiated a program to develop MGAT2 inhibitors as a novel treatment for obesity and metabolic diseases. Because the substrates of MGAT2, MG and fatty acyl CoA, contain long fatty acyl chains, it is assumed that the high lipophilicity of compounds may lead to a high affinity for MGAT2. However, it is of considerable importance to produce a drug candidate molecule with low lipophilicity from the viewpoint of a better chance of successful drug development, and it is proposed that the optimal range of lipophilicity (LogD or LogP) lies between 1 and 3.[12] Therefore, our goal was to deliver a clinical candidate of MGAT2 inhibitor with desirable lipophilicity.

Novel series of MGAT2 inhibitors were identified from high-throughput screening of our chemical library. Among several hit chemotypes, we selected a sulfonamide derivative **1** with an IC_{50} value of 130 nM as a starting point on the basis of its low lipophilicity as well as moderate potency (Figure 1). An initial structure–activity relationship (SAR) study revealed that the

$ArNHSO_2Ar$ structure was indispensable for MGAT2 inhibitory activity, and even slight structural modification on this motif led to an abrupt decline in potency. In contrast, the modification of the phenoxyacetamide moiety at the 1-position was tolerated, although hydrophobic groups such as a phenyl ring were required for MGAT2 inhibition. We hypothesized that optimal arrangement of the hydrophobic group could lead to enhanced MGAT2 inhibitory activity. On the basis of this concept, rearrangement of the hydrophobic group to the adjacent position and introduction of a bicyclic central core to restrict the orientation of the substituent were implemented, leading to the discovery of an indoline-5-sulfonamide derivative **10b** with potent and highly selective MGAT2 inhibitory activity and desired lipophilicity as a promising lead compound. Our subsequent optimization efforts were directed to improve the pharmacokinetic profiles of the lead compound **10b**. This resulted in the identification of a compound **24d**, which suppressed the elevation of plasma TG levels in an oral fat tolerance test (OFTT) in mice after oral administration. Here we report the design, synthesis, and biological activity of *N*-phenylindoline-5-sulfonamide derivatives as a novel series of MGAT2 inhibitors. The relationship between MGAT2 potency and electron density on the carbonyl group at the indoline 7-position, one of the important pharmacophoric elements, is also discussed.



1
hMGAT2 IC_{50} = 130 nM

10b
hMGAT2 IC_{50} = 1.0 nM

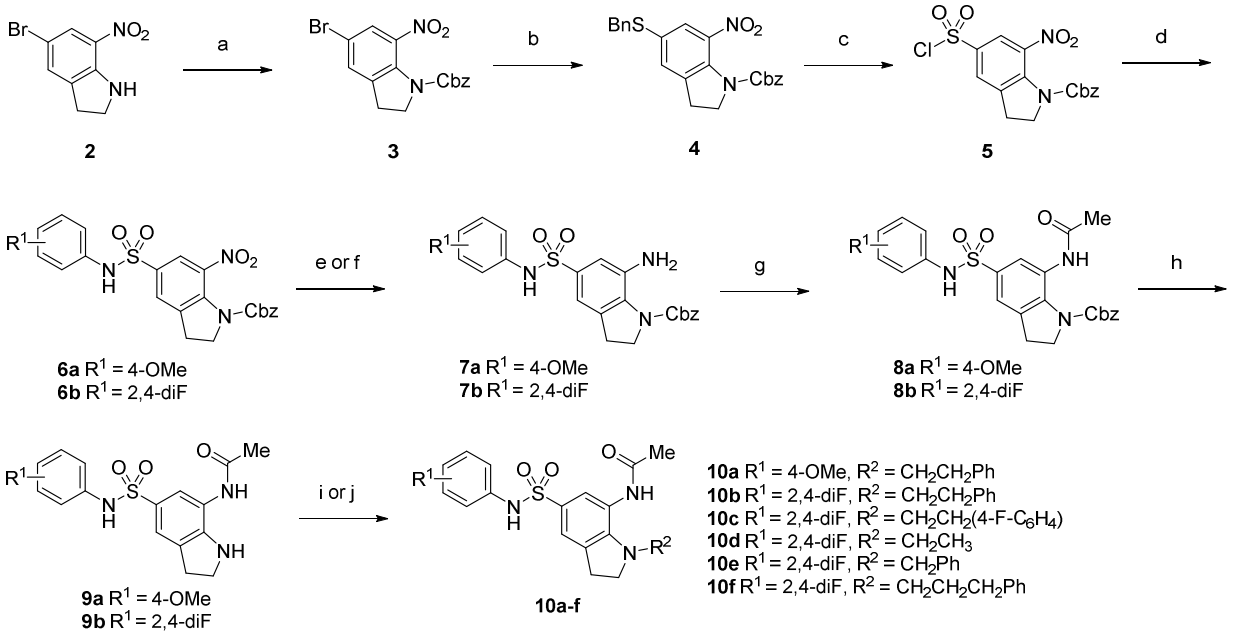
24d
hMGAT2 IC_{50} = 3.4 nM

Figure 1. *N*-Phenylbenzenesulfonamide- and *N*-phenylindoline-5-sulfonamide-based MGAT2 inhibitors.

CHEMISTRY

Scheme 1 describes the steps to synthesize indoline-5-sulfonamide derivatives **10a**–**f**. The synthesis started from protection of the nitrogen atom of 5-bromo-7-nitroindoline (**2**) with a benzyloxycarbonyl (Cbz) group, followed by palladium-catalyzed coupling with benzyl mercaptan to give benzyl sulfide **4**. To prepare sulfonyl chloride **5**, oxidative chlorination of **4** using *N*-chlorosuccinimide (NCS) in aqueous acetic acid was employed according to a method reported for aryl methoxymethyl sulfides.[13] Sulfonamidation of **5** with anilines smoothly proceeded in *N*,*N*-dimethylacetamide (DMA) without the addition of a base to furnish **6a** and **6b** in good yields. Reduction of the nitro group of **6a** or **6b** and subsequent N-acetylation of the resulting aniline afforded **8a** or **8b**, respectively. After removal of the Cbz groups of **8a** and **8b**, variations on the substituent at the indoline 1-position were achieved by reductive amination with aldehydes under a sodium triacetoxyborohydride or 2-picoline borane complex condition to deliver the final products **10a**–**f**.

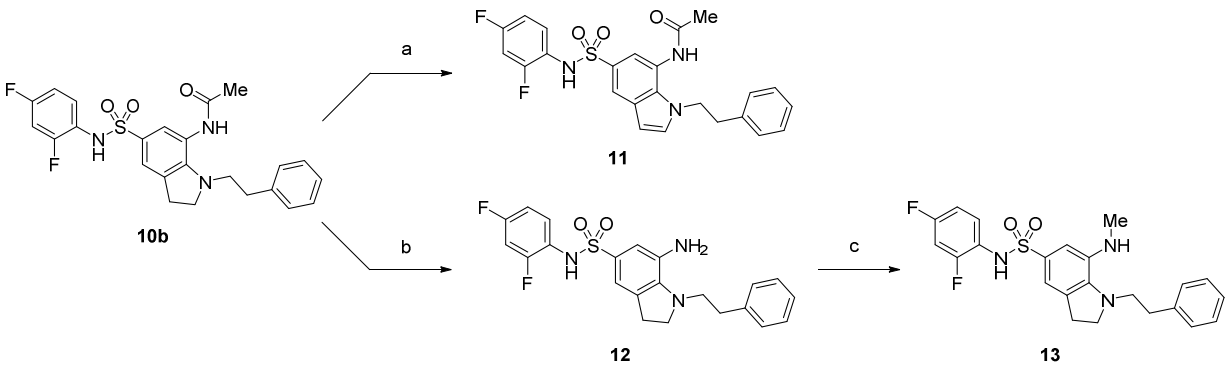
Scheme 1. Synthesis of indoline-5-sulfonamide derivatives **10a**–**f**[a]



[a]Reagents and conditions: (a) NaH, CbzCl, THF, 0 °C to rt, 84%; (b) BnSH, $Pd_2(dba)_3$, Xantphos, DIEA, toluene, reflux, 73%; (c) NCS, AcOH, H_2O, 0 °C to rt, 97%; (d) 4-methoxyaniline or 2,4-difluoroaniline, DMA, rt, 86–96%; (e) Fe, $CaCl_2$, EtOH, H_2O, reflux, 66% (for **7a**); (f) Zn, AcOH, rt, 94% (for **7b**); (g) AcCl, DMA, 0 °C to rt, 89–94%; (h) H_2 (1 atm), Pd on carbon, THF, MeOH, rt, 92–99%; (i) aldehyde, $NaBH(OAc)_3$, AcOH, CH_3CN, rt, 27–68% (for **10a**–**e**); (j) $PhCH_2CH_2CHO$, 2-picoline-borane complex, MeOH, AcOH, rt, 93% (for **10f**).

Further derivatizations from **10b** are described in Scheme 2. The indoline ring of **10b** was efficiently oxidized to an indole ring by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to afford the corresponding indole derivative **11**. N-Deacetylation of **10b** by acidic alcoholysis afforded aniline **12**, which was then subjected to reductive amination with formaldehyde to give a *N*-methyl analog **13**.

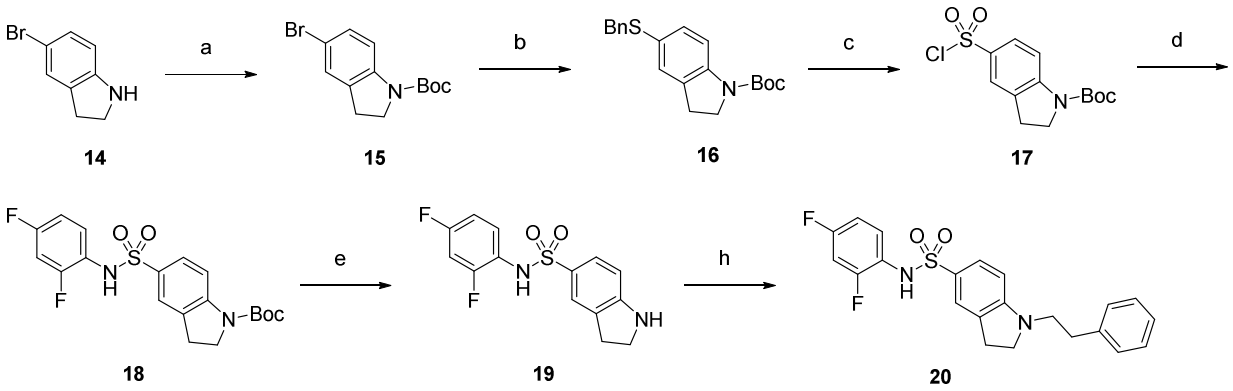
Scheme 2. Synthesis of indoline-5-sulfonamide derivatives **11** and **13**[a]



[a]Reagents and conditions: (a) DDQ, THF, rt, 54%; (b) HCl, MeOH, 80 °C, 58%; (c) formaldehyde, $NaBH(OAc)_3$, AcOH, THF, rt, 29%.

Scheme 3 outlines the synthesis of an analog bearing no substituent at the indoline 7-position. The desired compound **20** was prepared from Boc-protected 5-bromoindoline (**15**) in a manner analogous to that described in Scheme 1.

Scheme 3. Synthesis of indoline-5-sulfonamide derivative **20**[a]

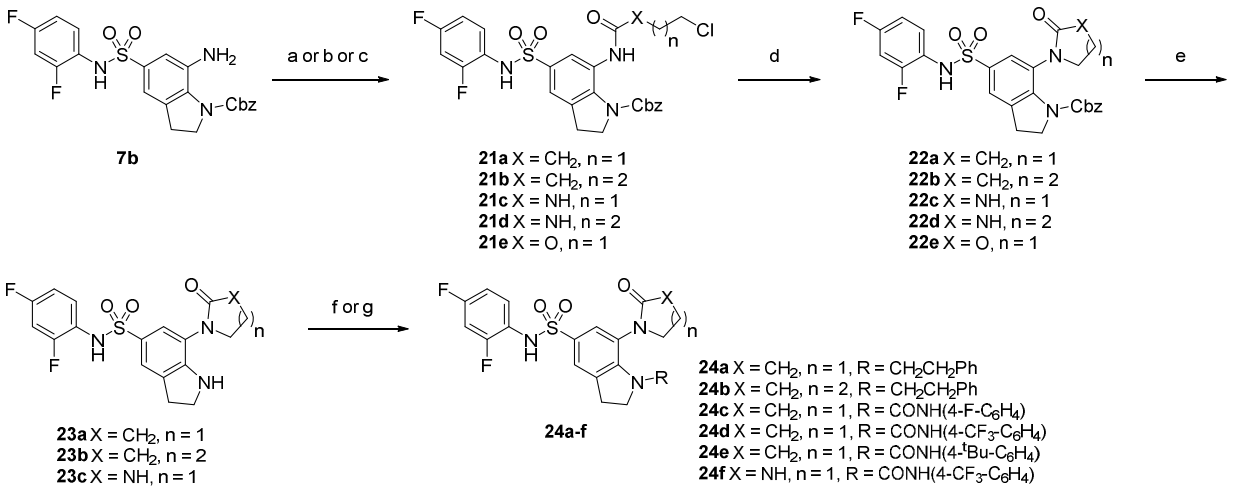


[a]Reagents and conditions: (a) Boc_2O, THF, rt, 95%; (b) BnSH, $Pd_2(dba)_3$, Xantphos, DIEA, toluene, reflux, 100%; (c) NCS, AcOH, H_2O, 0 °C to rt, 63%; (d) 2,4-difluoroaniline, pyridine, 0 °C to rt, 87%; (e) HCl, AcOEt, rt, 86%; (f) $PhCH_2CHO$, $NaBH(OAc)_3$, AcOH, CH_3CN, rt, 70%.

Compounds with a heterocycle at the indoline 7-position were synthesized by the method presented in Scheme 4. The lactam rings of **22a** and **22b** and a cyclic carbamate of **22e** were

constructed by intramolecular cyclization of **21a**, **21b**, and **21e**, which were prepared by the acylation of **7b** with appropriate acyl chlorides. In an analogous manner, urea formation of **7b** with isocyanates and subsequent intramolecular cyclization gave cyclic urea derivatives **22c** and **22d** in good yields. Removal of the Cbz groups of **22a**–**c** was followed by modification of the nitrogen atom at the indoline 1-position. For reductive amination of **23a** or **23b** with phenylacetaldehyde, the hydrogenation condition in the presence of platinum oxide was more effective than that in the presence of sodium triacetoxyborohydride, which afforded the desired products **24a** and **24b**. Compounds **24c**–**f** were obtained by urea formation of **23a** or **23c** with anilines using triphosgene as a carbonyl source.

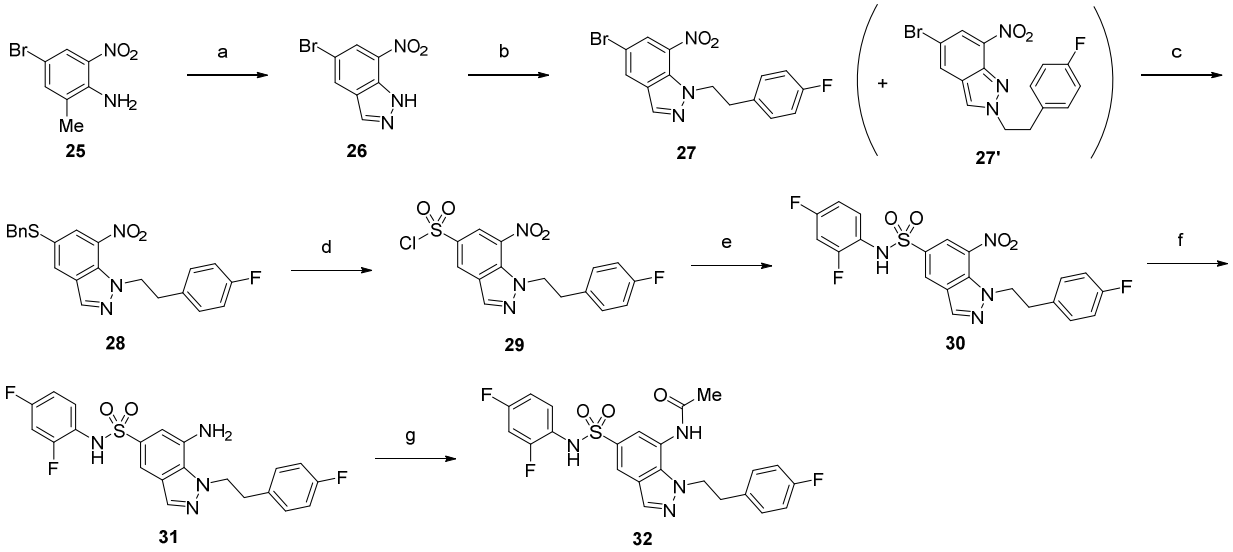
Scheme 4. Synthesis of indoline-5-sulfonamide derivatives **24a**–**f**[a]



[a]Reagents and conditions: (a) 4-chlorobutyryl chloride or 5-chlorovaleryl chloride, DMA, 0 °C to rt; (b) 2-chloroethyl isocyanate or 3-chloropropyl isocyanate, THF, 60–70 °C; (c) 2-chloroethyl chloroformate, TEA, THF, 0 °C to rt; (d) NaH, DMF, 0 °C to rt, 59–92% over 2 steps (for **22a** and **22b**), 64–74% over 2 steps (for **22c** and **22d**), 11% over 2 steps (for **22e**); (e) H_2 (1 atm), Pd on carbon, THF, MeOH, rt, 94–99%; (f) $PhCH_2CHO$, H_2 (1 atm), PtO_2, THF, EtOH, rt, 41-62% (for **24a** and **24b**); (g) 4-substituted aniline, triphosgene, pyridine, TEA, THF, 0 °C to rt, 62–92% (for **24c**–**f**).

A synthetic route to the indazole derivative **32** is depicted in Scheme 5. The requisite 5-bromo-7-nitroindazole (**26**) was synthesized by diazotization of *o*-toluidine **25** and following self-cyclization.[14] Regioselectivity for N-alkylation of **26** with 2-(4-fluorophenyl)ethyl bromide was not observed, and the desired compound **27** was obtained in a yield of 42% after separation. The structures of **27** and the regioisomer **27′** were determined by NMR experiments.[15] Compound **27** was converted to the final product **32** through structural modifications at the 5- and 7-positions on the indazole ring by methods similar to those described in Scheme 1.

Scheme 5. Synthesis of 1*H*-indazole-5-sulfonamide derivative **32**[a]

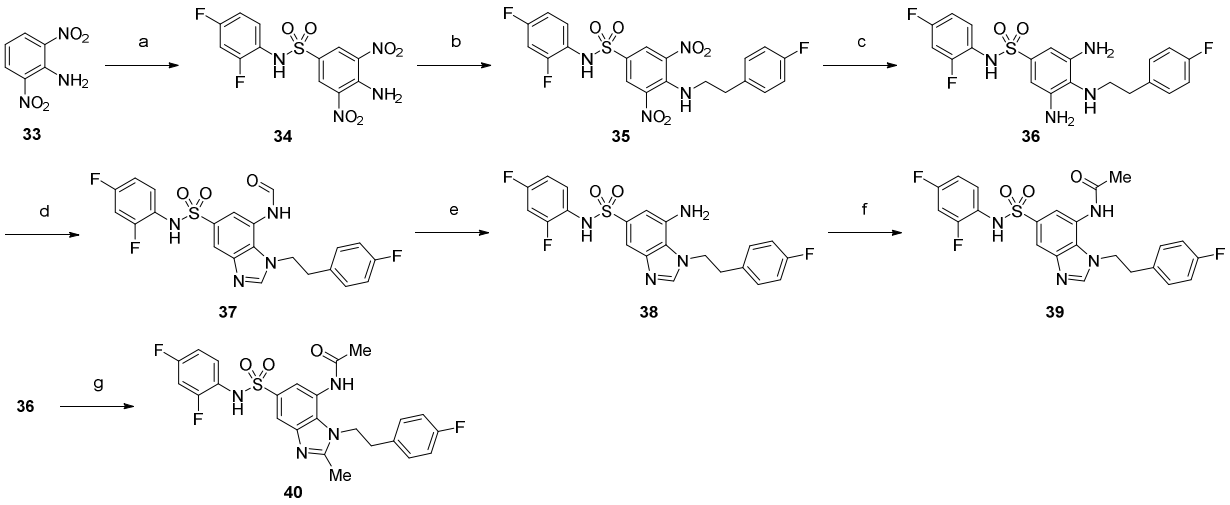


[a]Reagents and conditions: (a) $NaNO_2$, AcOH, H_2O, rt, 56%; (b) 2-(4-fluorophenyl)ethyl bromide, Cs_2CO_3, DMF, rt, 42%; (c) BnSH, $Pd_2(dba)_3$, Xantphos, DIEA, toluene, reflux, 92%; (d) NCS, AcOH, H_2O, 0 °C to rt, 92%; (e) 2,4-difluoroaniline, DMA, rt, 87%; (f) H_2 (1 atm), Pd on carbon, THF, MeOH, rt, 95%; (g) AcCl, DMA, rt, 46%.

To access the benzimidazole derivatives **39** and **40**, the synthetic procedures described in Scheme 6 were employed. Direct chlorosulfonylation of 2,6-dinitroaniline (**33**) with chlorosulfonic acid was achieved under a previously reported condition,[16] and the obtained

sulfonyl chloride was subjected to sulfonamidation with 2,4-difluoroaniline to yield **34**. Sandmeyer reaction of **34** followed by nucleophilic substitution with 4-fluorophenethylamine furnished **35**, which underwent hydrogenation to provide 3,4,5-triaminobenzenesulfonamide **36**. Upon treatment of **36** with formic acid, N-formylation of the amino groups was accompanied by construction of a benzimidazole ring to yield **37**. Compound **37** was transformed to the final product **39** by deformylation and N-acetylation. In contrast, refluxing of compound **36** in acetic acid afforded 2-methylbenzimidazole **40** after acetylation of the remaining amino group.

Scheme 6. Synthesis of 1*H*-benzimidazole-5-sulfonamide derivatives **39** and **40**[a]

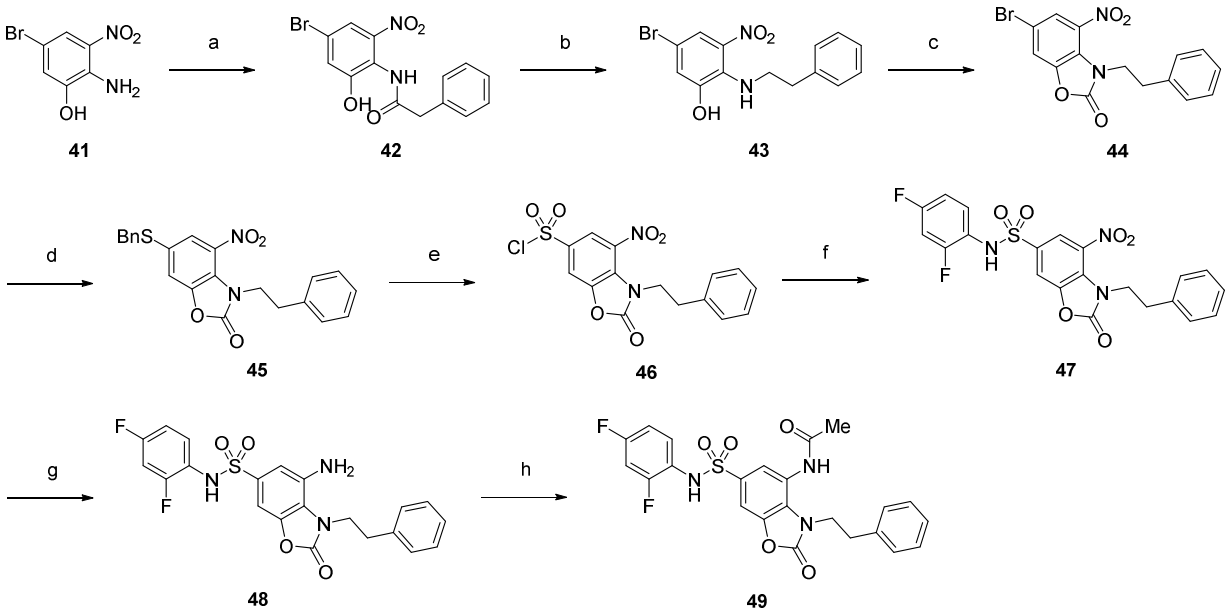


[a]Reagents and conditions: (a) (1) $ClSO_3H$, 100 °C, (2) 2,4-difluoroaniline, DMA, rt, 72%; (b) (1) $NaNO_2$, $CuCl_2$, H_2SO_4, HCl, AcOH, rt to 70 °C, (2) 4-fluorophenethylamine, THF, rt, 58%; (c) H_2 (1 atm), Pd on carbon, THF, rt, 76%; (d) formic acid, reflux, 96%; (e) HCl, MeOH, H_2O, rt to 60 °C, 97%; (f) AcCl, DMA, rt, 91%; (g) (1) AcOH, reflux, (2) AcCl, DMA, rt, 70%.

Synthesis of a 1,3-benzoxazolone derivative **49** was achieved by the route illustrated in Scheme 7. Compound **43** was synthesized from 2-aminophenol **41**[17] by a two-step sequence consisting of N-acylation and subsequent borane reduction. Reaction of **43** with 1,1′-

carbonyldiimidazole constructed a 1,3-benzoxazolone scaffold to yield **44**, which was elaborated to the final compound **49** in a manner similar to the method detailed in Scheme 1.

Scheme 7. Synthesis of 2-oxo-2,3-dihydro-1,3-benzoxazole-6-sulfonamide derivative **49**[a]

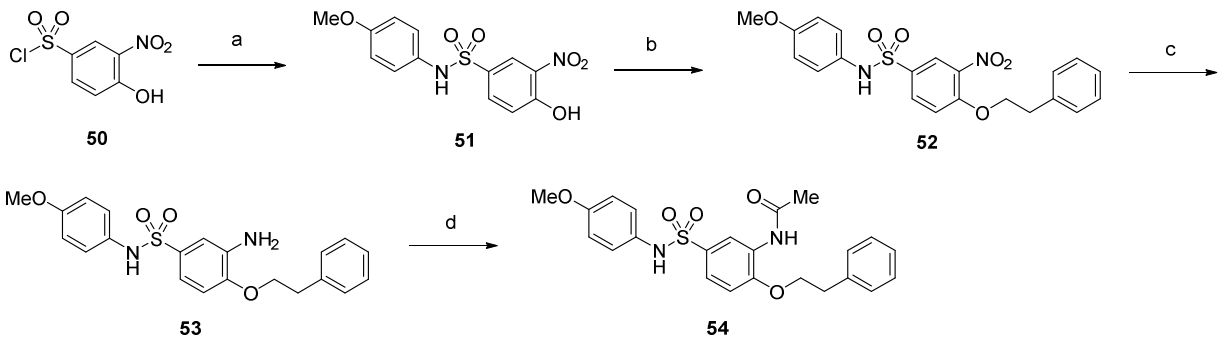


41 42 43 44 45 46 47 48 49

[a]Reagents and conditions: (a) phenylacetyl chloride, NaH, THF, rt, 42%; (b) borane-THF complex, THF, rt to 50 °C, 72%; (c) CDI, THF, rt, 81%; (d) BnSH, $Pd_2(dba)_3$, Xantphos, DIEA, toluene, reflux, 91%; (e) NCS, AcOH, H_2O, 0 °C to rt, 74%; (f) 2,4-difluoroaniline, DMA, rt, 73%; (g) Zn, AcOH, 0 °C to rt; (h) AcCl, DMA, rt, 35% over 2 steps.

Scheme 8 describes the synthetic steps to 4-(2-phenylethoxy)benzenesulfonamide **54**. Sulfonamidation of a commercially available sulfonyl chloride **50** with *p*-anisidine afforded **51**, which was subjected to Mitsunobu reaction with 2-phenylethanol to give **52**. After reduction of the nitro group of **52**, acetylation of the resulting amine produced the final compound **54**.

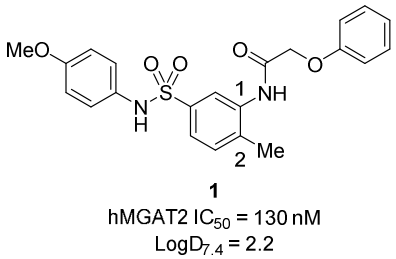
Scheme 8. Synthesis of 4-(2-phenylethoxy)benzenesulfonamide derivative **54**[a]



[a]Reagents and conditions: (a) 4-methoxyaniline, DMA, rt, 89%; (b) 2-phenylethanol, DIAD, PPh_3, 0 °C, 71%; (c) H_2 (1 atm), Pd on carbon, THF, MeOH, rt, 91%; (d) Ac_2O, pyridine, rt, 37%.

RESULTS AND DISCUSSION

The newly synthesized compounds were tested for MGAT2 inhibitory activity using membrane fractions from the MGAT2 expression. A sulfonamide derivative **1** was identified as an initial lead compound with moderate MGAT2 inhibitory activity (EC_{50} = 130 nM) via high-throughput screening in our library (Figure 2). The initial SAR study revealed that the *N*-arylbenzenesulfonamide motif was essential for MGAT2 inhibitory activity, and potency for MGAT2 inhibition was not retained after structural conversion of the sulfonamide linkage. In contrast, the phenoxyacetyl moiety at the 1-position was tolerated for structural modification. Simple amidation reactions with various carboxylic acids allowed us to comprehend SAR at the 1-position promptly, and several derivatives containing a hydrophobic group such as a phenyl ring displayed a similar level of MGAT inhibitory activity to **1**, although notable enhancement of potency was not observed (data not shown).



1

hMGAT2 IC_{50} = 130 nM

$LogD_{7.4}$ = 2.2

Figure 2. Structure of an initial lead compound **1**.

Given the tolerability for structural modification of the substituent at the 1-position, we attempted to rearrange the hydrophobic group from the 1-position to the 2-position in order to expand the chemical series (Figure 3A, **II**). Consequently, we identified compound **54**, which displayed comparable potency to **1**, with an IC_{50} value of 130 nM. We assumed that the benzene ring at the 1-position of **1** or the 2-position of **54** would occupy the same binding site during its interaction with MGAT2. Figure 4 shows a result of flexible alignment of compounds **1** and **54** using Molecular Operating Environment software (MOE).[18] Namely, we hypothesized that MGAT2 would have a hydrophobic space between the 1- and 2-positions of this series of compounds in interaction (Figure 3B), which could be approached by both series **I** and **II**. Meanwhile, the orientation of the phenethyloxy group of **54** likely prefers conformation **IIIa** to **IIIb** because of steric hindrance with the substituent at the 1-position (Figure 5A). This concept was supported by calculation of a stable conformation of **54** using MOE. For the aforementioned interaction with the putative hydrophobic site, compound **54** needs to adopt an energetically unfavorable conformation similar to **IIIb**. Based on this hypothesis, we designed a series of compounds with a bicyclic core (**IV**), which enables efficient orientation of a hydrophobic substituent in the desired position (Figure 5B). We anticipated that this conformational

restriction could reduce the entropic cost on binding and should lead to the enhancement of MGAT2 inhibition potency.

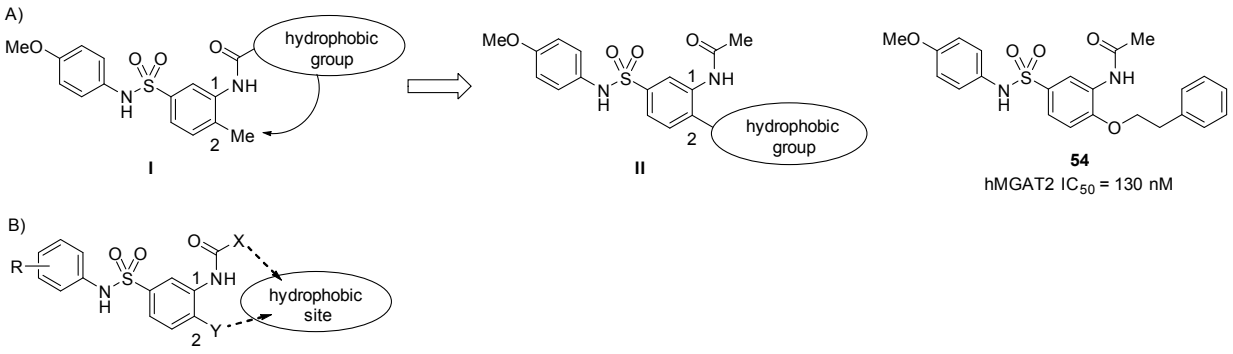


Figure 3. A) Repositioning of a hydrophobic group from the 1-position to the 2-position. B) Presumed hydrophobic space between the 1- and 2-positions.

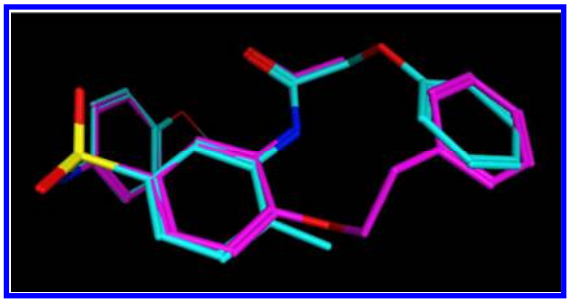


Figure 4. Flexible alignment of compounds **1** (cyan) and **54** (magenta) using MOE.

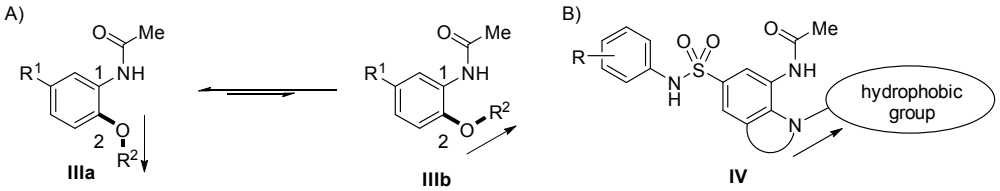
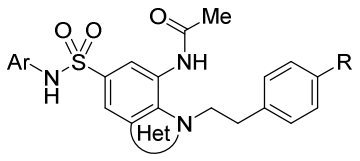
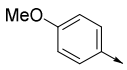
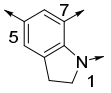
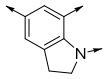
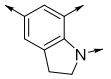
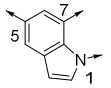
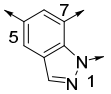
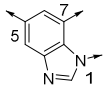
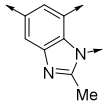
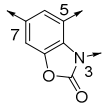


Figure 5. A) Conformational preference of the alkoxy (OR^2) moiety. B) Design of orienting a substituent to a presumed hydrophobic site by introduction of bicyclic core systems.

Table 1 summarizes the MGAT2 inhibitory activity of compounds with various bicyclic core systems. Gratifyingly, an indoline derivative **10a** exhibited a 60-fold improvement in potency in comparison with the parent **54** despite the lowered lipophilicity. This result highlighted that conformational constraints on the phenethyl group had a significant impact on potency as expected, presumably due to efficient interaction with the putative hydrophobic site of MGAT2. The electron density of the aniline moiety had no effect on MGAT2 inhibitory activity. Indeed, the 4-methoxyaniline of **10a** could be transformed to 2,4-difluoroaniline, an electron-deficient aniline, to yield **10b** without compromising potency. Introduction of a fluorine atom on the benzene ring of the phenethyl group also resulted in potent MGAT2 inhibitory activity (**10c**). Although desaturation of the central indoline ring to the corresponding indole ring was tolerated (**11**), conversion to an indazole derivative **32** or benzimidazole derivative **39** resulted in a more than 10-fold decrease in potency. In addition, installation of a methyl group at the 2-position of the benzimidazole ring of **39** led to a profound loss of potency (**40**). These data indicated that the central bicyclic core of **10a**–**c** or **11** would efficiently occupy a hydrophobic and size-limited pocket of MGAT2 during binding. This speculation was consistent with the fact that the benzoxazolone derivative **49** displayed only weak MGAT2 inhibitory activity. Through these explorations, the indoline or indole ring was found to serve as a scaffold to optimally orient the phenethyl group to the presumed hydrophobic site in MGAT2 and confer greatly enhanced MGAT2 inhibitory activity. In terms of synthetic accessibility, the indoline core was selected for further exploration of structural requirements at the 1- and 7-positions on the central core.

Table 1. MGAT2 inhibitory activity: SAR of central bicyclic systems



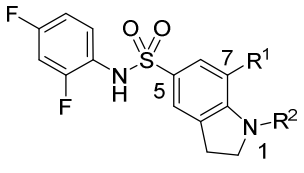
Compound	Ar	Het	R	hMGAT2[a] IC_{50} (nM)	$LogD_{7.4}$[b]
10a			H	2.2 (2.0–2.4)	2.2
10b			H	1.0 (0.89–1.2)	2.5
10c			F	1.2 (1.0–1.3)	2.5
11			H	2.1 (1.8–2.3)	2.3
32			F	41 (36–48)	2.2
39			F	170 (130–210)	1.5
40			F	3300 (3000–3600)	1.6
49			H	2100 (1700–2600)	2.0

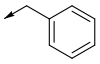
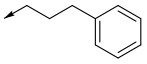
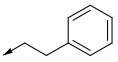
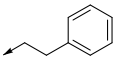
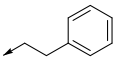
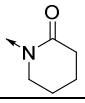
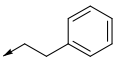
[a]Inhibitory activity against human MGAT2. IC_{50} values are presented as means of duplicate experiments with their 95% confidence intervals in parentheses. [b]LogD value at pH 7.4.[19]

The results from a representative selection of compounds with various substituents at the indoline 1- and 7-positions are presented in Table 2. Deletion of the phenyl ring of the 1-phenethyl group of **10b** resulted in more than 100-fold decline in potency (**10d**), demonstrating the importance of the terminal hydrophobic group at the 1-position in driving MGAT2 inhibition. The observation that the 1-phenylpropyl analog **10f** was equipotent to the phenethyl analog **10b** indicated that the presumed hydrophobic site of MGAT2 could accommodate an extended or

larger substituent. In contrast, the benzyl analog **10e** displayed a 10-fold reduction in potency in comparison with **10b**. This was likely the result of the phenyl group at the 1-position of **10e** being unable to reach the best hydrophobic site.

Table 2. MGAT2 inhibitory activity: SAR at the 1- and 7-positions of the indoline ring



Compound	R^1	R^2	hMGAT2[a] IC_{50} (nM)	$LogD_{7.4}$[b]
10d			220 (180–260)	1.4
10e			23 (18–31)	2.2
10f			3.7 (3.0–4.6)	2.8
20			270 (200–380)	3.7
13			130 (99–180)	3.7
24a			6.7 (4.9–9.1)	2.9
24b			7.3 (6.5–8.2)	3.1

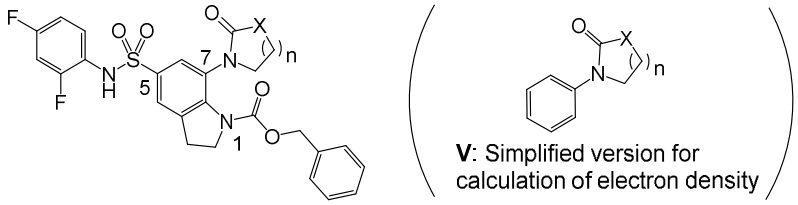
[a]Inhibitory activity against human MGAT2. IC_{50} values are presented as means of duplicate experiments with their 95% confidence intervals in parentheses. [b]LogD value at pH 7.4.[19]

We also found that the acetylamino group at the indoline 7-position had a significant contribution to MGAT2 inhibitory activity. Removal of the acetylamino or carbonyl group induced an abrupt loss of potency (**20** or **13**), despite their increases of lipophilicity in

comparison with **10b**. In contrast, incorporation of a lactam ring resulted in the maintenance of potent MGAT2 inhibitory activity, as illustrated by **24a** and **24b**. Based on these results, we hypothesized that the carbonyl oxygen atom at the 7-position could have a critical interaction with MGAT2 as a hydrogen bond acceptor (HBA).

To examine the influence of electron density at the carbonyl oxygen on potency, we prepared and compared lactam, cyclic urea, and cyclic carbamate derivatives, which have different electron densities at the carbonyl oxygen with a similar size and shape of molecules (Table 3). The electron density at the carbonyl oxygen of each simplified version **V** shown in Table 3 was calculated using the semiempirical PM3 (MOPAC) method[20] in Molecular Operating Environment software.[18] The cyclic urea **22c** displayed more potent inhibitory activity than the lactam **22a**, whereas the cyclic carbamate **22e** had attenuated potency in comparison with **22a**. Interestingly, a good correlation between MGAT2 inhibitory activity and electron density at the carbonyl oxygen was observed. According to the calculation, the electron density increases in the order of cyclic urea **22c** > lactam **22a** > cyclic carbamate **22e**. It was reported that cyclic ureas have stronger hydrogen bond basicity than the corresponding lactams,[21] which is consistent with this calculated result. The lower electron density of the cyclic carbamate was presumably driven by the electron withdrawing nature of the oxygen atom adjacent to the carbonyl group. Potency enhancement by conversion of a lactam to the corresponding cyclic urea was also observed for six-membered rings, as illustrated by the comparison of **22b** and **22d**. These results suggested that the carbonyl oxygen at the 7-position should participate in an interaction with MGAT2 as HBA and that MGAT2 inhibitory activity could be enhanced by increasing the electron density.

Table 3. MGAT2 inhibitory activity: SAR at the 7-position of the indoline ring



Compound	X	n	hMGAT2[a] IC_{50} (nM)	Electron charge on the carbonyl oxygen of **V**[b]	$LogD_{7.4}$[c]
22a	CH_2	1	14 (10–19)	−0.353	2.8
22c	NH	1	3.4 (2.9–3.9)	−0.394	2.3
22e	O	1	43 (33–56)	−0.334	2.3
22b	CH_2	2	10 (8.3–13)	−0.353	3.2
22d	NH	2	2.2 (1.8–2.7)	−0.399	2.6

[a]Inhibitory activity against human MGAT2. IC_{50} values are presented as means of duplicate experiments with their 95% confidence intervals in parentheses. [b]Electron density on the carbonyl oxygen of **V** was calculated by MOPAC using PM3 method. [c]LogD value at pH 7.4.[19]

Following this, we examined the selectivity against other related acyltransferases of a representative compound of this novel series of *N*-phenylindoline-5-sulfonamide derivatives (Table 4). Compound **10b** exhibited more than 30,000-fold selectivity over MGAT3, DGAT1, DGAT2, and ACAT1. In addition to the aforementioned potent MGAT2 inhibitory activity and tolerability for structural modification at the 1- and 7-positions of this series of compounds, the excellent selectivity of **10b** made this compound a promising lead compound of novel MGAT2 inhibitors. In contrast, DMPK assessment revealed that compound **10b** was rapidly cleared by liver microsomes both in humans and mice, which was reflected in its high in vivo clearance and low plasma concentrations after oral administration in mice (Table 5; CL_{total} = 4977 mL/h/kg, *F*

= 4.6%). Accordingly, further structural modification focused on the improvement of its pharmacokinetic profiles.

Table 4. Selectivity of **10b** over other acyltransferases

Compound	hMGAT3[a] IC_{50} (nM)	hDGAT1[a] IC_{50} (nM)	hDGAT2[a] IC_{50} (nM)	hACAT1[a] IC_{50} (nM)
10b	> 30000	> 30000	> 30000	35000

[a] IC_{50} values are presented as means of duplicate experiments.

Table 5. Microsomal clearances and pharmacokinetic profiles of compound **10b**

Compound	in vitro CL_{int}[a] (μL/min/mg)		Pharmacokinetic profiles in mice[b, c]		
	HLM	MLM	CL_{total}[b] (mL/h/kg)	AUC_{0-8h}[c] (ng·h/mL)	F[c] (%)
10b	101	220	4977	9.2	4.6

[a]Human/mouse liver microsomal clearance. [b]0.1 mg/kg, iv. [c]1 mg/kg, po.

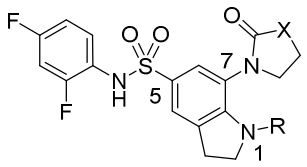
In the initial optimization step, we explored functionalized benzene rings connected through an alkyl linkage to the indoline 1-position, which afforded several analogs with potent MGAT2 inhibitory activity such as a difluorophenyl, (trifluoromethyl)phenyl, or (alkoxycarbonyl)phenyl derivative; however, no appreciable improvement in microsomal stability was detected in comparison with **10b** (data not shown). From these results, we presumed that the poor metabolic stability of **10b** should be attributed to the vulnerability to oxidative metabolism of the alkylene spacer at the indoline 1-position. Based on this assumption, compounds with an *N*-acyl-type substituent at the 1-position were designed to improve metabolic stability. In addition, in vitro

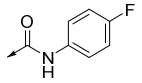
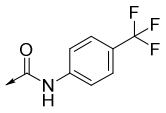
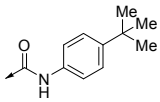
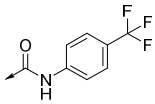
metabolite analysis of related analogs suggested that the *N*-acetyl group at the 7-position of **10b** would be easily hydrolyzed, presumably being associated in part with the high in vivo clearance. This guided us to employ a lactam or cyclic urea at the 7-position, which was expected to be more resistant to hydrolysis, instead of the *N*-acetyl group.

MGAT2 inhibitory activities, microsomal clearances, and plasma concentration after oral administration of compounds with structural modifications at the indoline 1- and 7-positions are presented in Table 6. Introduction of a urea-type linkage at the 1-position provided compound **24c** with an IC_{50} value of 28 nM, which expectedly displayed a significant beneficial improvement in microsomal stability in comparison with the phenethyl analog **10b** or **24a** (CL_{int} (HLM/MLM) = 112/248 μL/min/mg). Although the potency of **24c** was weaker than that of the corresponding phenethyl analog **24a**, their ligand lipophilicity efficiency (LLE) values[22] were equivalent (LLE = 5.3 (**24a**) and 5.4 (**24c**)). We surmised that increasing lipophilicity of the substituent at the 1-position would enhance MGAT2 inhibitory activity because this position is possibly located in a hydrophobic site of MGAT2 during interaction. Indeed, the addition of a hydrophobic substituent on the terminal benzene ring resulted in increased potency. The 4-(trifluoromethyl)phenyl derivative **24d** exhibited potent MGAT2 inhibitory activity with an IC_{50} value of 3.4 nM and an LLE value of 5.4, which was comparable with that of the phenethyl derivative **24a**, while maintaining improved microsomal stability. Introduction of a *tert*-butyl group also enhanced MGAT2 inhibitory activity to a similar level as that of **24d** (**24e**: IC_{50} = 3.1 nM). However, **24e** displayed inferior metabolic stability to the trifluoromethyl derivative **24d**. This may be caused by the higher elevation of lipophilicity of **24e** than that of **24d** ($LogD_{7.4}$ = 3.1 (**24d**) and 3.6 (**24e**)). In terms of lipophilicity efficiency, the trifluoromethyl group could

more effectively achieve an interaction with the putative hydrophobic site of MGAT2 than the *tert*-butyl group.

Table 6. MGAT2 inhibitory activity, microsomal clearances, and plasma concentration



Compound	R	X	hMGAT2[a] IC_{50} (nM)	$LogD_{7.4}$[b]	in vitro CL_{int}[c] (μL/min/mg)		AUC_{0-8h}[d] (ng·h/mL)
					HLM	MLM	
24c		CH_2	28 (26–31)	2.2	30	143	NT
24d		CH_2	3.4 (3.0–3.9)	3.1	36	84	842
24e		CH_2	3.1 (2.7–3.5)	3.6	66	146	15
24f		NH	1.8 (1.3–2.4)	2.5	63	82	87

[a]Inhibitory activity against human MGAT2. IC_{50} values are presented as means of duplicate experiments with their 95% confidence intervals in parentheses. [b]LogD value at pH 7.4.[19] [c]Human/mouse liver microsomal clearance. [d]Mice. 1 mg/kg, po. NT = not tested.

To further enhance MGAT2 inhibitory activity, a cyclic urea motif was embedded at the 7-position with the aim of increasing electron density at the carbonyl oxygen, as mentioned above. As anticipated, compound **24f** displayed more potent activity and lower lipophilicity than **24d**, resulting in a much higher LLE value (LLE = 6.2). Compound **24f** also exhibited improved microsomal stability to a level similar to that of **24d**.

Given several compounds endowed with potent MGAT2 inhibitory activity and improved metabolic stability such as **24d** and **24f**, we next investigated pharmacokinetic profiles when compounds were orally administered to mice at a dose of 1 mg/kg. Pharmacokinetic studies revealed that compound **24d** displayed a high plasma concentration ($AUC_{0–8h}$ = 842 ng·h/mL) and favorable oral bioavailability (*F* = 52%), which were probably driven by the improved stability against oxidative metabolism and hydrolysis. In contrast, the *tert*-butyl analog **24e** did not display improved bioavailability. We assume that the poor bioavailability of **24e** is due to the insufficient metabolic stability and/or deteriorated aqueous solubility in comparison with compound **24d** (4.8 μg/mL (**24e**) vs 12 μg/mL (**24d**) at pH 6.8). Interestingly, it was found that transformation of the lactam ring to a cyclic urea at the 7-position negatively affected pharmacokinetic profiles. The AUC level of compound **24f** was approximately one-tenth that of compound **24d**, whereas the two compounds exhibited similar in vitro microsomal stabilities and volumes of distribution (Vdss = 732 and 872 mL/h/kg for **24d** and **24f**, respectively). This unexpected result may be because of deterioration of membrane permeability owing to an additional hydrogen bond donor (PAMPA permeability[23]: 396 nm/sec (**24d**) vs 94 nm/sec (**24f**) at pH 7.4). Consequently, compound **24d** was selected for further in vivo evaluation on the basis of its potent MGAT2 inhibitory activity and desirable pharmacokinetic profiles.

For evaluating the in vivo efficacy, compound **24d** was examined for its effect on hypertriglyceridemia during OFTT using C57BL/6J mice. To inhibit the hydrolysis of plasma TG by lipoprotein lipase (LPL), mice were pretreated with an LPL inhibitor, Pluronic F127 (Poloxamer 407),[24] permitting measurement of the accumulation of plasma TG following olive oil administration. Compound **24d** and vehicle were administered 6 h before the oral olive oil load, and plasma chylomicron TG concentrations were monitored for 4 h. As shown in Figure 6,

compound **24d** effectively and dose-dependently suppressed plasma TG elevation after olive oil challenge. The TG-lowering effect of **24d** was significant ($p < 0.025$) at doses of 10 and 30 mg/kg. A similar effect of reducing the rate of fat entrance into the circulation was observed in MGAT2 gene knockout mice.[6] Accordingly, this result indicated that compound **24d** suppressed plasma TG elevation via MGAT2 inhibition in vivo.

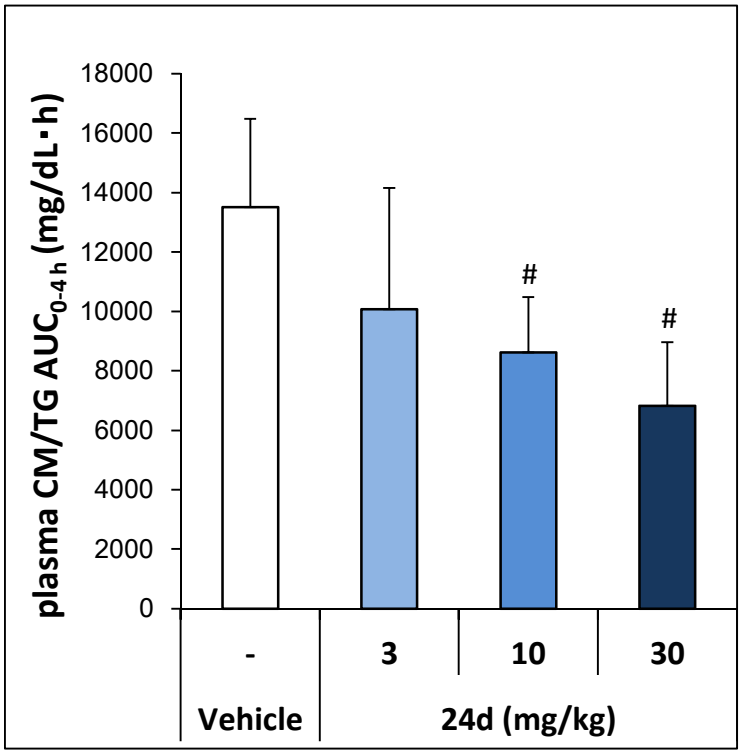


Figure 6. Effect of **24d** on plasma TG elevation during oral fat tolerance test in C57BL/6J mice. **24d** (3, 10, 30 mg/kg) was orally administered 6 h prior to oil challenge. Figure shows area under the curve (AUC) of plasma chylomicron/TG (CM/TG) levels during 4 h after oil challenge. Data are the mean + SD (n = 5). #, $p \leq 0.025$ versus vehicle by William's test.

CONCLUSION

We identified a novel series of *N*-phenyl-indoline-5-sulfonamide derivatives as potent, selective, and orally bioavailable MGAT2 inhibitors. Starting from the sulfonamide derivative **1**, we explored an optimal arrangement of the hydrophobic group as a key pharmacophoric motif. Conformational restriction by employing a bicyclic central core was useful to orient the substituents for effective interaction with MGAT2. Consequently, the indoline derivative **10b** served as an attractive lead compound with potent MGAT2 inhibitory activity and high selectivity over related acyltransferases. We also demonstrated that the carbonyl group at the indoline 7-position was crucial for MGAT2 inhibition and that electron density on the carbonyl group was correlated with potency. Subsequent optimization efforts were conducted to address the poor DMPK issues of **10b**. Structural modification to the presumed metabolically vulnerable moieties significantly improved oral bioavailability in mice, resulting in the identification of **24d**. Compound **24d** effectively suppressed post olive oil-loaded TG excursion after oral administration. These results indicated that this series of MGAT2 inhibitors could have therapeutic potential for the treatment of metabolic disorders. Further optimization efforts and pharmacological effects of this series will be described in due course.

EXPERIMENTAL SECTION

Chemistry general method. Melting points were determined in open capillary tubes on a Büchi melting point apparatus B545 and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE III (300 MHz) or Bruker Advance III plus (400 MHz) spectrometer. Chemical shifts are given in parts per million (ppm) downfield from tetramethysilane (δ) as the internal standard in deuterated solvent and coupling constants (*J*) are in Hertz (Hz). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d

= doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, bs = broad signal), and coupling constants. All solvents and reagents were obtained from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was performed on Merck silica gel plates $60F_{254}$. Silica gel column chromatography was performed on Purif-Pack (SI or NH, SHOKO SCIENTIFIC). LC–MS analysis was performed on a Shimadzu Liquid Chromatography–Mass Spectrometer System, operating in APCI (+ or −) or ESI (+ or −) ionization mode. Analytes were eluted using a linear gradient of 0.05% TFA containing water/acetonitrile or 5 mM ammonium acetate containing water/acetonitrile mobile phase, and detected at 220 nm. The purities of compounds submitted for biological evaluation were > 95% as determined by elemental analyses within ±0.4% of the calculated values. The purities of intermediates were determined by LC–MS analysis (detection at 220 nm). Yields are not optimized.

Benzyl 5-bromo-7-nitro-2,3-dihydro-1*H*-indole-1-carboxylate (3).[25] To a mixture of 5-bromo-7-nitro-2,3-dihydro-1*H*-indole (61.7 g, 254 mmol, commercially available (purchased from Small Molecules, Inc.)) and THF (1.6 L) was added sodium hydride (60% oil dispersion, 15.2 g, 380 mmol) at 0 °C. The mixture was stirred at rt under N_2 atmosphere for 3 h. CbzCl (47.1 mL, 330 mmol) was added to the mixture at 0 °C, and the resulting mixture was stirred at rt for 3 days. The mixture was quenched with crushed ice at 0 °C and THF was removed under reduced pressure. To the residue was added a mixed solvent of AcOEt/hexane/water (1:3:3 v/v, 700 mL) under stirring. The precipitated solid was collected by filtration to give the title compound as a yellow solid (80.4 g, 213 mmol, 84%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20 (2H, t, J = 8.3 Hz), 4.19 (2H, t, J = 8.3 Hz), 5.16 (2H, s), 7.30-7.44 (5H, m), 7.77-7.82 (1H, m), 7.83-7.89 (1H, m). Purity 95.8% (LC–MS).

Benzyl 5-(benzylsulfanyl)-7-nitro-2,3-dihydro-1*H*-indole-1-carboxylate (4). A mixture of compound **3** (20.9 g, 55.4 mmol), phenylmethanethiol (7.14 mL, 61.0 mmol), $Pd_2(dba)_3$ (5.07 g, 5.54 mmol), Xantphos (6.41 g, 11.1 mmmol), and DIEA (29.0 mL, 166 mmol) in toluene (250 mL) was refluxed under N_2 atmosphere for 5 h. After cooling to rt, AcOEt (250 mL) and H_2O (250 mL) were added to the mixture, and insoluble materials were removed by filtration. The filtrate was diluted with AcOEt (250 mL) and successively washed water, 0.2 M hydrochloric acid, aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was crystallized from AcOEt–$^{i}Pr_2O$ to give the title compound as a yellow solid (17.0 g, 40.4 mmol, 73%). MS (ESI/APCI) *m/z* 421.3 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.14 (2H, t, J = 8.3 Hz), 4.16 (2H, t, J = 8.3 Hz), 4.28 (2H, s), 5.14 (2H, s), 7.20-7.42 (10H, m), 7.55 (2H, dd, J = 8.2, 1.8 Hz). Purity 98.1% (LC–MS).

Benzyl 5-(chlorosulfonyl)-7-nitro-2,3-dihydro-1*H*-indole-1-carboxylate (5). To a mixture of compound **4** (130 g, 309 mmol), acetic acid (960 mL), and water (320 mL) was added portionwise *N*-chlorosuccinimide (165 g, 1.24 mol) at 0 °C. The mixture was stirred at rt for 4 h. Precipitated solid was collected by filtration, successively washed with water and $^{i}Pr_2O$, and dried to give the title compound as a pale yellow solid (119 g, 300 mmol, 97%). This compound was used for the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20 (2H, t, *J* = 8.3 Hz), 4.20 (2H, t, *J* = 8.3 Hz), 5.16 (2H, s), 7.33–7.42 (5H, m), 7.73 (1H, d, *J* = 1.4 Hz), 7.77 (1H, d, *J* = 1.4 Hz). Purity 92.7% (LC–MS).

Benzyl 5-[(4-methoxyphenyl)sulfamoyl]-7-nitro-2,3-dihydro-1*H*-indole-1-carboxylate (6a). A mixture of compound **5** (2.82 g, 7.11 mmol) and 4-methoxyaniline (1.05 g, 8.53 mmol) in DMA (30 mL) was stirred at rt overnight. The mixture was quenched with iced water and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$,

and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt = 90/10 to 50/50) to give the title compound as a yellow amorphous solid (3.31 g, 6.85 mmol, 96%). MS (ESI/APCI) *m/z* 482.1 $[M - H]^-$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.22 (2H, t, *J* = 8.1 Hz), 3.67 (3H, s), 4.22 (2H, t, *J* = 8.5 Hz), 5.17 (2H, s), 6.78–6.88 (2H, m), 6.95–7.06 (2H, m), 7.30–7.46 (5H, m), 7.77 (1H, d, *J* = 1.1 Hz), 7.91 (1H, d, *J* = 1.5 Hz), 10.04 (1H, s). Purity 99.8% (LC–MS).

Benzyl 5-[(2,4-difluorophenyl)sulfamoyl]-7-nitro-2,3-dihydro-1*H*-indole-1-carboxylate (6b). Compound **5** (77.5 g, 195 mmol) was added portionwise to a solution of 2,4-difluoroaniline (23.9 mL, 234 mmol) in DMA (750 mL) at 0 °C. The mixture was stirred at rt overnight. The mixture was quenched with water at 0 °C and extracted with AcOEt. The organic layer was washed with water (3 times) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was crystallized from AcOEt–^{i}Pr$_2$O to give the title compound as a pale yellow solid (82.0 g, 167 mmol, 86%). MS (ESI/APCI) *m/z* 488.1 $[M - H]^-$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.24 (2H, t, *J* = 8.3 Hz), 4.25 (2H, t, *J* = 8.4 Hz), 5.19 (2H, s), 7.00–7.12 (1H, m), 7.18–7.48 (7H, m), 7.81 (1H, d, *J* = 1.7 Hz), 7.93 (1H, d, *J* = 1.8 Hz), 10.30 (1H, s). Purity 94.9% (LC–MS).

Benzyl 7-amino-5-[(4-methoxyphenyl)sulfamoyl]-2,3-dihydro-1*H*-indole-1-carboxylate (7a). A mixture of compound **6a** (2.45 g, 5.07 mmol), iron powder (1.42 g, 25.3 mmol), and calcium chloride (0.562 g, 5.07 mmol) in a mixed solvent of EtOH (20 mL) and water (5 mL) was refluxed overnight. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was extracted with AcOEt. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. To the residue was added AcOEt and ^{i}Pr$_2$O. The precipitated solid was collected to give the title

compound as a light brown solid (1.52 g, 3.35 mmol, 66%). MS (ESI/APCI) *m/z* 454.4 $[M + H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 2.96 (2H, t, *J* = 8.2 Hz), 3.76 (3H, s), 4.11 (2H, t, *J* = 8.3 Hz), 4.95 (2H, br s), 5.23 (2H, s), 6.17 (1H, s), 6.77 (2H, d, *J* = 8.8 Hz), 6.86–6.92 (2H, m), 6.98 (2H, d, *J* = 8.8 Hz), 7.31–7.44 (5H, m). Mp 127–129 °C. Purity 96.0% (LC–MS).

Benzyl 7-amino-5-[(2,4-difluorophenyl)sulfamoyl]-2,3-dihydro-1*H*-indole-1-carboxylate (7b). A mixture of compound **6b** (81.9 g, 167 mmol) and zinc powder (109 g, 1.67 mol) in acetic acid (800 mL) was stirred at rt overnight. The mixture was diluted with THF and filtered through a pad of Celite. The filtrate was concentrated and the residue was suspended in $^iPr_2O$. The precipitated solid was collected and washed with $^iPr_2O$ to give the title compound as a beige solid (72.6 g, 158 mmol, 94%). MS (ESI/APCI) *m/z* 460.3 $[M + H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.98 (2H, t, *J* = 8.1 Hz), 4.07 (2H, t, *J* = 8.2 Hz), 5.21 (2H, s), 5.68 (2H, br s), 6.82 (1H, s), 6.90–7.06 (2H, m), 7.13–7.27 (2H, m), 7.29–7.48 (5H, m), 9.88 (1H, br s). Purity 97.9% (LC–MS).

Benzyl 7-(acetylamino)-5-[(4-methoxyphenyl)sulfamoyl]-2,3-dihydro-1*H*-indole-1-carboxylate (8a). Compound **8a** was prepared from compound **7a** in a manner similar to that described for compound **8b** (Purification: silica gel column chromatography (hexane/AcOEt = 90/10 to 50/50)). White amorphous solid. Yield 89%. MS (ESI/APCI) *m/z* 496.4 $[M + H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (3H, s), 2.99 (2H, t, *J* = 8.3 Hz), 3.74 (3H, s), 4.06–4.21 (2H, m), 5.28 (2H, s), 6.70 (1H, s), 6.75 (2H, d, *J* = 8.8 Hz), 7.09 (2H, d, *J* = 8.8 Hz), 7.18 (1H, s), 7.33–7.46 (5H, m), 8.49 (1H, s), 10.38 (1H, br s). Purity 100% (LC–MS).

Benzyl 7-(acetylamino)-5-[(2,4-difluorophenyl)sulfamoyl]-2,3-dihydro-1*H*-indole-1-carboxylate (8b). To a solution of compound **7b** (18.0 g, 39.1 mmol) in DMA (200 mL) was added acetyl chloride (3.62 mL, 50.9 mmol) at 0 °C. The mixture was stirred at rt overnight. The

reaction mixture was quenched with water at 0 °C and extracted with AcOEt. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. To the residue was added EtOH. The precipitated solid was collected to give the title compound as a white solid (18.4 g, 36.6 mmol, 94%). MS (ESI/APCI) *m/z* 502.4 $[M + H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 1.97 (3H, s), 3.08 (2H, t, *J* = 8.0 Hz), 4.13 (2H, t, *J* = 8.1 Hz), 5.24 (2H, s), 7.01 (1H, t, *J* = 8.3 Hz), 7.16–7.55 (8H, m), 8.16 (1H, s), 9.88–10.17 (2H, m). Purity 100% (LC–MS).

***N*-{5-[(4-Methoxyphenyl)sulfamoyl]-2,3-dihydro-1*H*-indol-7-yl}acetamide (9a).** Compound **9a** was prepared from compound **8a** in a manner similar to that described for compound **9b**. White amorphous solid. Yield 99%. MS (ESI/APCI) *m/z* 362.3 $[M + H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.02 (3H, s), 2.97 (2H, t, *J* = 8.7 Hz), 3.54 (2H, t, *J* = 8.7 Hz), 3.66 (3H, s), 5.77 (1H, s), 6.78 (2H, d, *J* = 8.9 Hz), 6.97 (2H, d, *J* = 8.8 Hz), 7.14 (1H, s), 7.63 (1H, s), 9.37 (1H, s), 9.59 (1H, br s). Purity 98.6% (LC–MS).

***N*-{5-[(2,4-Difluorophenyl)sulfamoyl]-2,3-dihydro-1*H*-indol-7-yl}acetamide (9b).** A mixture of compound **8b** (18.4 g, 36.7 mmol) and 10% palladium on carbon (2.0 g) in a mixed solvent of MeOH (150 mL) and THF (150 mL) was stirred under H_2 atmosphere (1 atm, balloon) at rt for 4 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give the title compound as a white amorphous solid (12.3 g, 33.6 mmol, 92%). MS (ESI/APCI) *m/z* 368.2 $[M + H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.02 (3H, s), 2.99 (2H, t, *J* = 8.7 Hz), 3.57 (2H, t, *J* = 8.7 Hz), 5.84 (1H, br s), 6.94–7.05 (1H, m), 7.13 (1H, s), 7.16–7.27 (2H, m), 7.61 (1H, s), 9.37 (1H, s), 9.69 (1H, s). Purity 95.2% (LC–MS).

***N*-{5-[(4-Methoxyphenyl)sulfamoyl]-1-(2-phenylethyl)-2,3-dihydro-1*H*-indol-7-yl}acetamide (10a).** To a mixture of compound **9a** (150 mg, 0.415 mmol), 2-phenylacetaldehyde

(0.093 mL, 0.83 mmol), and acetic acid (0.119 mL, 2.08 mmol) in CH_3CN (4 mL) was added sodium triacetoxyborohydride (264 mg, 1.25 mmol) at rt. The mixture was stirred at rt under N_2 atmosphere overnight. Saturated aqueous $NaHCO_3$ solution was added to the reaction mixture. The resulting mixture was extracted with AcOEt, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 80/20 to 40/60) to give the title compound as a white solid (131 mg, 0.282 mmol, 68%). MS (ESI/APCI) *m/z* 466.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.96 (3H, s), 2.63–2.76 (2H, m), 2.91 (2H, t, *J* = 8.7 Hz), 3.36–3.47 (2H, m), 3.54 (2H, t, *J* = 8.8 Hz), 3.66 (3H, s), 6.79 (2H, d, *J* = 8.7 Hz), 6.99 (2H, d, *J* = 8.8 Hz), 7.12–7.34 (7H, m), 9.51 (1H, s), 9.60 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.8, 27.0, 32.7, 49.5, 52.8, 55.1, 114.2, 117.2, 120.6, 122.6, 126.1, 126.6, 128.4, 128.5, 130.9, 132.6, 139.2, 149.1, 156.0, 169.0. Mp 140–142 °C. Anal. Calcd for $C_{25}H_{27}N_3O_4S$: C, 64.50; H, 5.85; N, 9.03. Found: C, 64.43; H, 5.86; N, 8.98.

***N*-{5-[(2,4-Difluorophenyl)sulfamoyl]-1-(2-phenylethyl)-2,3-dihydro-1*H*-indol-7-yl}acetamide (10b).** To a mixture of compound **9b** (16.7 g, 45.4 mmol), 2-phenylacetaldehyde (25.5 mL, 227 mmol), and acetic acid (13.0 mL, 227 mmol) in CH_3CN (500 mL) was added portionwise sodium triacetoxyborohydride (28.8 g, 136 mmol) at rt. The mixture was stirred at rt overnight. Saturated aqueous $NaHCO_3$ solution was added to the reaction mixture. The resulting mixture was extracted with AcOEt, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was triturated with AcOEt–^{i}Pr$_2$O to give a white solid, which was recrystallized from EtOH–water to give the title compound as a white solid (12.2 g, 25.9 mmol, 57%). MS (ESI/APCI) *m/z* 472.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.96 (3H, s), 2.62–2.77 (2H, m), 2.93 (2H, t, *J* = 8.7 Hz), 3.39–3.50 (2H, m), 3.56

(2H, t, *J* = 8.7 Hz), 7.00 (1H, t, *J* = 7.7 Hz), 7.06–7.37 (9H, m), 9.52 (1H, s), 9.71 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.8, 26.9, 32.7, 49.4, 52.8, 104.5 (dd, *J* = 26.8, 24.6 Hz), 111.4 (dd, *J* = 22.0, 3.7 Hz), 117.1, 120.5, 121.5 (dd, *J* = 13.2, 3.7 Hz), 126.1, 126.4, 127.7 (d, *J* = 10.3 Hz), 128.4, 128.5, 132.8, 139.2, 149.4, 155.9 (dd, *J* = 250.2, 12.5 Hz), 159.5 (dd, *J* = 245.0, 11.0 Hz), 169.0. Mp 169–170 °C. Anal. Calcd for $C_{24}H_{23}F_2N_3O_3S$: C, 61.13; H, 4.92; F, 8.06; N, 8.91; S, 6.80. Found: C, 61.16; H, 4.98; F, 8.02; N, 8.91; S, 6.83.

***N*-{5-[(2,4-Difluorophenyl)sulfamoyl]-1-[2-(4-fluorophenyl)ethyl]-2,3-dihydro-1*H*-indol-7-yl}acetamide (10c).** Compound **10c** was prepared from compound **9b** and 2-(4-fluorophenyl)acetaldehyde in a manner similar to that described for compound **10a** (Purification: silica gel column chromatography (hexane/AcOEt = 90/10 to 40/60)). White solid. Yield 27%. MS (ESI/APCI) *m/z* 490.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.95 (3H, s), 2.60–2.79 (2H, m), 2.93 (2H, t, *J* = 8.8 Hz), 3.36–3.50 (2H, m), 3.55 (2H, t, *J* = 8.9 Hz), 7.00 (1H, t, *J* = 7.4 Hz), 7.05–7.33 (8H, m), 9.52 (1H, s), 9.73 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.8, 26.9, 31.8, 49.4, 52.8, 104.5 (d, *J* = 26.4, 24.2 Hz), 111.4 (d, *J* = 22.0, 3.7 Hz), 115.1 (d, *J* = 21.3 Hz), 117.1, 120.5, 121.6 (d, *J* = 13.9 Hz), 126.5, 127.7 (dd, *J* = 9.9, 1.8 Hz), 128.4, 130.3 (d, *J* = 8.1 Hz), 132.8, 135.3 (d, *J* = 2.9 Hz), 149.4, 155.9 (dd, *J* = 250.2, 12.5 Hz), 159.5 (dd, *J* = 244.5, 11.0 Hz), 160.8 (d, *J* = 242.1 Hz), 169.1. Mp 180–182 °C. Anal. Calcd for $C_{24}H_{22}F_3N_3O_3S$: C, 58.89; H, 4.53; N, 8.58. Found: C, 58.86; H, 4.66; N, 8.54.

***N*-{5-[(2,4-Difluorophenyl)sulfamoyl]-1-ethyl-2,3-dihydro-1*H*-indol-7-yl}acetamide (10d).** Compound **10d** was prepared from compound **9b** and acetaldehyde in a manner similar to that described for compound **10a** (Purification: silica gel column chromatography (hexane/AcOEt = 60/40 to 25/75)). White solid. Yield 37%. MS (ESI/APCI) *m/z* 396.1 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98 (3H, t, *J* = 7.0 Hz), 1.97 (3H, s), 2.92 (2H, t, *J* = 8.7 Hz), 3.26–3.37 (2H,

m), 3.50 (2H, t, J = 8.9 Hz), 6.94–7.04 (1H, m), 7.07–7.27 (4H, m), 9.42 (1H, s), 9.71 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 11.7, 22.6, 26.9, 41.9, 52.0, 104.4 (dd, J = 26.4, 24.2 Hz), 111.4 (dd, J = 22.7, 3.7 Hz), 117.1, 120.4, 121.6 (dd, J = 12.8, 3.3 Hz), 126.2, 127.6 (dd, J = 9.9, 1.8 Hz), 128.4, 132.8, 149.6, 155.9 (dd, J = 250.2, 12.5 Hz), 159.4 (dd, J = 245.0, 11.7 Hz), 168.9. Mp 152–153 °C. Anal. Calcd for $C_{18}H_{19}F_2N_3O_3S$: C, 54.67; H, 4.84; N, 10.63. Found: C, 54.76; H, 4.90; N, 10.48.

***N*-{1-Benzyl-5-[(2,4-difluorophenyl)sulfamoyl]-2,3-dihydro-1*H*-indol-7-yl}acetamide (10e).** Compound **10e** was prepared from compound **9b** and benzaldehyde in a manner similar to that described for compound **10a** (Purification: silica gel column chromatography (hexane/AcOEt = 90/10 to 40/60)). White solid. Yield 67%. MS (ESI/APCI) *m/z* 458.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (3H, s), 2.93 (2H, t, J = 8.8 Hz), 3.40 (2H, t, J = 8.7 Hz), 4.51 (2H, s), 7.00 (1H, t, J = 8.1 Hz), 7.11 (1H, s), 7.15–7.40 (8H, m), 9.46 (1H, s), 9.73 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.6, 26.8, 51.2, 52.6, 104.5 (dd, J = 26.4, 24.2 Hz), 111.4 (dd, J = 22.0, 3.7 Hz), 117.4, 120.6, 121.4 (dd, J = 13.2, 3.7 Hz), 126.6, 127.0, 127.5, 127.8 (dd, J = 9.9, 1.8 Hz), 128.3, 128.4, 132.5, 138.1, 149.9, 156.0 (dd, J = 250.5, 12.8 Hz), 159.5 (dd, J = 245.0, 11.0 Hz), 169.0. Mp 150–152 °C. Anal. Calcd for $C_{23}H_{21}F_2N_3O_3S$: C, 60.38; H, 4.63; N, 9.18. Found: C, 60.41; H, 4.77; N, 9.10.

***N*-{5-[(2,4-Difluorophenyl)sulfamoyl]-1-(3-phenylpropyl)-2,3-dihydro-1*H*-indol-7-yl}acetamide (10f).** To a suspension of compound **9b** (200 mg, 0.544 mmol) and 3-phenylpropanal (0.143 mL, 1.09 mmol) in a mixed solvent of MeOH (5 mL) and acetic acid (0.5 mL) was added 2-picoline borane complex (69.9 mg, 0.654 mmol) at rt. The mixture was stirred at rt under N_2 atmosphere for 4 h. After the reaction mixture was concentrated under reduced pressure, 3 N hydrochloric acid (10 mL) was added to the residue followed by stirring for 30

min. The mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 90/10 to 40/60) to give the title compound as a white solid (246 mg, 0.506 mmol, 93%). MS (ESI/APCI) *m/z* 486.4 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.73 (2H, quint, *J* = 7.8 Hz), 1.91 (3H, s), 2.42–2.61 (2H, m), 2.92 (2H, t, *J* = 8.7 Hz), 3.20–3.37 (2H, m), 3.53 (2H, t, *J* = 8.9 Hz), 6.92–7.04 (1H, m), 7.07 (1H, d, *J* = 1.9 Hz), 7.11–7.32 (8H, m), 9.41 (1H, s), 9.70 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.6, 26.9, 28.5, 32.8, 47.6, 52.8, 104.4 (dd, *J* = 26.8, 24.6 Hz), 111.4 (dd, *J* = 22.4, 4.0 Hz), 116.9, 120.4, 121.5 (dd, *J* = 12.5, 3.7 Hz), 125.7, 126.1, 127.6 (dd, *J* = 10.3, 2.2 Hz), 128.1, 128.2, 128.5, 132.6, 141.5, 149.9, 155.9 (dd, *J* = 250.2, 12.5 Hz), 159.4 (dd, *J* = 245.0, 11.0 Hz), 169.0. Mp 153–155 °C. Anal. Calcd for $C_{25}H_{25}F_2N_3O_3S$: C, 61.84; H, 5.19; N, 8.65. Found: C, 61.76; H, 5.27; N, 8.52.

***N*-{5-[(2,4-Difluorophenyl)sulfamoyl]-1-(2-phenylethyl)-1*H*-indol-7-yl}acetamide (11).** A mixture of compound **10b** (300 mg, 0.636 mmol) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (173 mg, 0.762 mmol) in THF (10 mL) was stirred at rt for 15 h. The mixture was diluted with AcOEt, washed with saturated aqueous $NaHCO_3$ solution and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt = 47/53 to 15/85) and crystallized from AcOEt–hexane to give the title compound as a white solid (160 mg, 0.341 mmol, 54%). MS (ESI/APCI) *m/z* 470.2 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 2.09 (3H, s), 2.89–2.99 (2H, m), 4.41–4.51 (2H, m), 6.59 (1H, d, *J* = 3.0 Hz), 6.93–7.03 (1H, m), 7.12–7.33 (8H, m), 7.40 (1H, d, *J* = 3.1 Hz), 7.84 (1H, d, *J* = 1.4 Hz), 9.94 (1H, s), 10.04 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 23.0, 37.4, 48.9, 102.6, 104.5 (dd, *J* = 26.8, 24.6 Hz), 111.4 (dd, *J* = 22.0, 3.7 Hz), 118.8, 119.5, 121.3 (dd, *J* = 12.8, 3.3 Hz),

122.2, 126.4, 127.9 (d, J = 9.5 Hz), 128.4, 128.5, 130.0, 130.4, 132.5, 133.1, 138.1, 156.1 (dd, J = 250.5, 12.8 Hz), 159.6 (dd, J = 245.4, 10.6 Hz), 169.8. Mp 148–150 °C. Anal. Calcd for $C_{24}H_{21}F_2N_3O_3S$: C, 61.40; H, 4.51; N, 8.95. Found: C, 61.26; H, 4.54; N, 8.89.

7-Amino-*N*-(2,4-difluorophenyl)-1-(2-phenylethyl)-2,3-dihydro-1*H*-indole-5-sulfonamide (12). A mixture of compound **11** (3.35 g, 7.10 mmol), 6 M hydrochloric acid (35 mL), and MeOH (35 mL) was stirred at 80 °C for 2.5 h. The reaction mixture was basified with saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 100/0 to 70/30) to give the title compound as an off-white solid (1.77 g, 4.12 mmol, 58%). MS (ESI/APCI) *m/z* 430.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.74 (2H, t, J = 7.7 Hz), 2.86 (2H, t, J = 8.8 Hz), 3.36–3.54 (4H, m), 4.65 (2H, s), 6.77 (1H, s), 6.84 (1H, s), 7.00 (1H, t, J = 8.4 Hz), 7.12–7.35 (7H, m), 9.60 (1H, br s). Mp 96–98 °C. Purity 100% (LC–MS).

***N*-(2,4-Difluorophenyl)-7-(methylamino)-1-(2-phenylethyl)-2,3-dihydro-1*H*-indole-5-sulfonamide (13).** A mixture of compound **12** (500 mg, 1.16 mmol), formaldehyde solution (37%, 0.095 mL, 1.3 mmol), and acetic acid (0.133 mL, 2.33 mmol) in THF (10 mL) was stirred at rt for 2 h. Sodium triacetoxyborohydride (370 mg, 1.75 mmol) was added to the mixture, and the mixture was stirred at rt overnight. Formaldehyde solution (37%, 0.043 mL, 0.58 mmol) and sodium triacetoxyborohydride (370 mg, 1.75 mmol) was added again to the mixture, and the resulting mixture was stirred at rt overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 95/5 to 60/40) to give the title compound as a

white solid (149 mg, 0.336 mmol, 29%). MS (ESI/APCI) *m/z* 444.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.57 (3H, d, *J* = 4.9 Hz), 2.71 (2H, t, *J* = 7.7 Hz), 2.88 (2H, t, *J* = 8.7 Hz), 3.33–3.42 (2H, m), 3.49 (2H, t, *J* = 8.8 Hz), 4.64 (1H, d, *J* = 4.9 Hz), 6.63 (1H, s), 6.83 (1H, s), 7.01 (1H, t, *J* = 7.8 Hz), 7.10–7.36 (7H, m), 9.67 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 28.4, 30.5, 33.4, 51.7, 53.5, 104.3 (dd, *J* = 26.4, 24.2 Hz), 108.6, 111.3 (dd, *J* = 22.0, 3.7 Hz), 112.9, 121.8 (dd, *J* = 13.2, 3.7 Hz), 126.0, 127.7 (dd, *J* = 9.5, 2.2 Hz), 128.2, 128.8, 130.6, 131.1, 136.3, 139.8, 143.0, 155.9 (dd, *J* = 250.2, 12.5 Hz), 159.4 (dd, *J* = 245.0, 11.0 Hz). Mp 119–120 °C. Anal. Calcd for $C_{23}H_{23}F_2N_3O_2S$: C, 62.29; H, 5.23; N, 9.47. Found: C, 62.32; H, 5.27; N, 9.38.

***N*-(2,4-Difluorophenyl)-1-(2-phenylethyl)-2,3-dihydro-1*H*-indole-5-sulfonamide (20).** Compound **20** was prepared from compound **19** in a manner similar to that described for compound **10a** (Purification: silica gel column chromatography (hexane/AcOEt = 90/10 to 40/60)). White solid. Yield 70%. MS (ESI/APCI) *m/z* 415.1 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (2H, t, *J* = 7.5 Hz), 2.95 (2H, t, *J* = 8.7 Hz), 3.39 (2H, t, *J* = 7.5 Hz), 3.51 (2H, t, *J* = 8.7 Hz), 6.18 (1H, d, *J* = 8.5 Hz), 6.43 (1H, br s), 6.67–6.77 (1H, m), 6.83 (1H, t, *J* = 8.4 Hz), 7.13–7.34 (6H, m), 7.39 (1H, d, *J* = 8.3 Hz), 7.54 (1H, td, *J* = 8.9, 6.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 26.9, 32.3, 48.2, 51.5, 104.1, 104.4 (dd, *J* = 27.1, 24.9 Hz), 111.3 (dd, *J* = 22.7, 3.7 Hz), 121.7 (dd, *J* = 13.2, 3.7 Hz), 122.5, 125.6, 126.1, 127.7 (dd, *J* = 9.5, 2.2 Hz), 128.0, 128.3, 128.7, 129.7, 139.3, 155.0, 155.8 (dd, *J* = 250.2, 12.5 Hz), 159.4 (dd, *J* = 245.0, 11.0 Hz). Mp 111–113 °C. Anal. Calcd for $C_{22}H_{20}F_2N_2O_2S$: C, 63.75; H, 4.86; N, 6.76. Found: C, 63.48; H, 4.81; N, 6.75.

Benzyl 5-[(2,4-difluorophenyl)sulfamoyl]-7-(2-oxopyrrolidin-1-yl)-2,3-dihydro-1*H*-indole-1-carboxylate (22a). Step A. To a solution of compound **7b** (15.0 g, 32.7 mmol) in DMA (200 mL) was added 4-chlorobutyryl chloride (3.83 mL, 35.9 mmol) at 0 °C. The mixture was stirred

at rt overnight. The mixture was quenched with water at 0 °C and extracted with AcOEt. The organic layer was separated, washed with water and brine, dried over $MgSO_4$. After removal of the solvent, the residue was passed through a short pad of silica gel to give benzyl 7-[(4-chlorobutanoyl)amino]-5-[(2,4-difluorophenyl)sulfamoyl]-2,3-dihydro-1*H*-indole-1-carboxylate as a brown amorphous solid (**21a**, 15.6 g, 27.6 mmol, 85%). MS (ESI/APCI) *m/z* 564.4 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.91–2.06 (2H, m), 2.41 (2H, t, *J* = 7.3 Hz), 3.08 (2H, t, *J* = 8.1 Hz), 3.66 (2H, t, *J* = 6.6 Hz), 4.14 (2H, t, *J* = 8.2 Hz), 5.24 (2H, s), 6.92–7.10 (1H, m), 7.13–7.51 (8H, m), 8.14 (1H, d, *J* = 1.7 Hz), 9.97–10.19 (2H, m). Purity 94.2% (LC–MS).

Step B. To a mixture of compound **21a** (10.0 g, 17.7 mmol) in DMF (100 mL) was added sodium hydride (60% oil dispersion, 1.56 g, 39.0 mmol) at 0 °C. The mixture was stirred at rt overnight. The mixture was quenched with water at 0 °C and extracted with AcOEt. The organic layer was separated, successively washed with water, 0.1 N hydrochloric acid, aqueous $NaHCO_3$ solution, and brine, and then dried over $MgSO_4$. and concentrated under reduced pressure. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt = 70/30 to 20/80) and recrystallized from EtOH–acetone–water to give the title compound as a white solid (6.43 g, 12.2 mmol, 69%). MS (ESI/APCI) *m/z* 528.5 $[M + H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 1.90–2.07 (2H, m), 2.11–2.25 (2H, m), 3.11 (2H, t, *J* = 8.1 Hz), 3.65 (2H, t, *J* = 6.9 Hz), 4.11 (2H, t, *J* = 8.2 Hz), 5.15 (2H, s), 6.97–7.11 (1H, m), 7.17–7.49 (9H, m), 10.05 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 18.2, 27.6, 30.0, 48.8, 49.7, 66.9, 104.6 (dd, *J* = 26.8, 24.6 Hz), 111.6 (dd, *J* = 22.4, 3.3 Hz), 120.3, 120.9 (dd, *J* = 13.2, 3.7 Hz), 124.3, 126.1, 127.5, 127.9, 128.3, 128.5 (dd, *J* = 9.9, 1.8 Hz), 134.9, 136.3, 137.2, 140.0, 151.6, 156.3 (dd, *J* = 250.5, 12.8 Hz), 159.9 (dd, *J* = 245.8, 11.0 Hz), 171.9. Mp 181–183 °C. Anal. Calcd for $C_{26}H_{23}F_2N_3O_5S$: C, 59.20; H, 4.39; N, 7.97. Found: C, 59.26; H, 4.47; N, 7.92.

Benzyl 5-[(2,4-difluorophenyl)sulfamoyl]-7-(2-oxopiperidin-1-yl)-2,3-dihydro-1*H*-indole-1-carboxylate (22b). To a mixture of compound **7b** (500 mg, 1.09 mmol) in DMA (10 mL) was added 5-chlorovaleryl chloride (0.169 mL, 1.31 mmol) at rt. The mixture was stirred at rt for 10 h. The reaction mixture was diluted with AcOEt, successively washed with water, aqueous $NaHCO_3$ solution, and brine, and then dried over Na_2SO_4. The solvent was removed by evaporation to give benzyl 7-[(5-chloropentanoyl)amino]-5-[(2,4-difluorophenyl)sulfamoyl]-2,3-dihydro-1*H*-indole-1-carboxylate (**21b**) as a pale yellow oil. The oil was dissolved in DMF (20 mL) and sodium hydride (60% oil dispersion, 109 mg, 2.72 mmol) was added to the mixture at rt. The mixture was stirred at rt for 3 h. The reaction mixture was quenched with water at rt and extracted with AcOEt. The organic layer was washed with water and brine, and then dried over Na_2SO_4. After removal of the solvent, the residue was crystallized from AcOEt–$^{i}Pr_2O$ to give the title compound as a white solid (540 mg, 0.997 mmol, 92% over 2 steps). MS (ESI/APCI) *m/z* 542.4 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.65–1.88 (4H, m), 2.02–2.20 (2H, m), 2.96–3.21 (2H, m), 3.43–3.62 (2H, m), 3.85–4.03 (1H, m), 4.13–4.30 (1H, m), 5.16 (2H, d, J = 6.0 Hz), 6.99–7.09 (1H, m), 7.18–7.46 (9H, m), 9.99 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 20.4, 22.7, 27.5, 31.8, 49.7, 50.4, 66.8, 104.6 (dd, J = 26.8, 24.6 Hz), 111.6 (dd, J = 22.7, 3.7 Hz), 120.7, 120.9 (dd, J = 12.8, 3.3 Hz), 126.0, 127.6, 127.9, 128.3, 128.5 (dd, J = 9.9, 1.8 Hz), 130.1, 134.7, 136.4, 136.6, 141.2, 151.4, 156.3 (dd, J = 250.5, 12.8 Hz), 159.9 (dd, J = 245.8, 11.0 Hz), 166.9. Mp 161–163 °C. Anal. Calcd for $C_{27}H_{25}F_2N_3O_5S$: C, 59.88; H, 4.65; N, 7.76. Found: C, 59.87; H, 4.72; N, 7.64.

Benzyl 5-[(2,4-difluorophenyl)sulfamoyl]-7-(2-oxoimidazolidin-1-yl)-2,3-dihydro-1*H*-indole-1-carboxylate (22c). A mixture of compound **7b** (4.00 g, 8.71 mmol) and 2-chloroethyl isocyanate (1.12 mL, 13.1 mmol) in THF (40 mL) was stirred at 60 °C for 3.5 h. The mixture

was quenched with 0.02 N hydrochloric acid and extracted with AcOEt. The organic layer was separated, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was dissolved in DMF (150 mL) and sodium hydride (60% oil dispersion, 1.05 g, 26.1 mmol) was added to the mixture at 0 °C. The mixture was stirred at rt for 6 h. The reaction mixture was quenched with water and acidified with 1 N hydrochloric acid to pH3. The resulting mixture was extracted with AcOEt, washed with water and brine, and dried over $MgSO_4$. The solvent was removed by evaporation and the residue was triturated with AcOEt–$^{i}Pr_2O$ to give the title compound as a white solid (3.40 g, 6.43 mmol, 74% over 2 steps). MS (ESI/APCI) *m/z* 529.4 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.06 (2H, t, *J* = 7.9 Hz), 3.23–3.29 (2H, m), 3.57–3.70 (2H, m), 4.08 (2H, t, *J* = 8.1 Hz), 5.15 (2H, s), 6.57 (1H, s), 6.97–7.08 (1H, m), 7.18–7.43 (8H, m), 7.49 (1H, d, *J* = 1.8 Hz), 10.03 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 27.9, 37.6, 45.2, 49.8, 67.0, 104.6 (dd, *J* = 27.1, 24.2 Hz), 111.6 (dd, *J* = 22.4, 4.0 Hz), 118.8, 120.9 (dd, *J* = 12.8, 4.0 Hz), 123.5, 127.7, 127.8, 127.9, 128.3 (dd, *J* = 9.9, 1.8 Hz), 128.4, 135.1, 136.3, 137.2, 139.2, 152.1, 156.2 (dd, *J* = 250.5, 12.8 Hz), 158.2, 159.9 (dd, *J* = 245.8, 11.0 Hz). Mp 185–187 °C. Anal. Calcd for $C_{25}H_{22}F_2N_4O_5S$: C, 56.81; H, 4.20; N, 10.60. Found: C, 56.51; H, 4.25; N, 10.47.

Benzyl 5-[(2,4-difluorophenyl)sulfamoyl]-7-(2-oxotetrahydropyrimidin-1(2*H*)-yl)-2,3-dihydro-1*H*-indole-1-carboxylate (22d). Compound **22d** was prepared from compound **7b** and 3-chloropropyl isocyanate in a manner similar to that described for compound **22c** (Purification: crystallization from AcOEt–$^{i}Pr_2O$). White solid. Yield 64% over 2 steps. MS (ESI/APCI) *m/z* 543.4 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.84–1.94 (2H, m), 3.02–3.15 (4H, m), 3.47 (2H, t, *J* = 5.6 Hz), 3.97–4.15 (2H, m), 5.17 (2H, s), 6.36 (1H, s), 6.99–7.07 (1H, m), 7.21–7.44 (9H, m), 9.99 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 21.9, 27.8, 47.8, 49.7, 66.8, 104.6 (dd, *J* = 26.8, 24.6 Hz), 111.6 (dd, *J* = 22.0, 3.7 Hz), 119.7, 121.1 (dd, *J* = 13.9, 4.4 Hz), 126.7, 127.6,

127.9, 128.3, 128.4, 131.6, 134.7, 136.4, 136.6, 141.5, 151.8, 153.0, 156.2 (dd, J = 250.5, 12.8 Hz), 159.8 (dd, J = 246.5, 11.7 Hz). Mp 174–176 °C. Anal. Calcd for $C_{26}H_{24}F_2N_4O_5S$: C, 57.56; H, 4.46; N, 10.33. Found: C, 57.53; H, 4.47; N, 10.29.

Benzyl 5-[(2,4-difluorophenyl)sulfamoyl]-7-(2-oxo-1,3-oxazolidin-3-yl)-2,3-dihydro-1*H*-indole-1-carboxylate (22e). To a mixture of compound **7b** (200 mg, 0.435 mmol) and triethylamine (0.079 mL, 0.57 mmol) in THF (4 mL) was added 2-chloroethyl chloroformate (0.049 mL, 0.48 mmol) at 0 °C. The mixture was stirred at rt overnight. The reaction mixture was quenched with water and extracted with AcOEt. The organic layer was separated, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was dissolved in DMF (5 mL) and sodium hydride (60% oil dispersion, 23 mg, 0.57 mmol) was added to the mixture. The mixture was stirred at rt for 2.5 h. The reaction mixture was quenched with 0.1 N hydrochloric acid and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 90/10 to 50/50) to give the title compound as a light brown solid (15.6 mg, 0.0295 mmol, 11% over 2 steps). MS (ESI/APCI) *m/z* 530.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.12 (2H, t, J = 7.8 Hz), 3.87 (2H, t, J = 7.8 Hz), 4.12 (2H, t, J = 8.2 Hz), 4.32 (2H, t, J = 7.7 Hz), 5.18 (2H, s), 6.97–7.08 (1H, m), 7.18–7.29 (2H, m), 7.30–7.56 (7H, m), 10.08 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 27.7, 46.0, 49.8, 62.5, 67.1, 104.6 (dd, J = 26.4, 24.2 Hz), 111.7 (dd, J = 22.7, 3.7 Hz), 120.7, 120.8, 124.6, 125.0, 127.7, 128.0, 128.4, 128.6 (dd, J = 9.5, 2.2 Hz), 135.3, 136.1, 137.6, 139.9, 152.0, 154.6, 156.3 (dd, J = 250.5, 12.8 Hz), 160.0 (dd, J = 245.8, 11.7 Hz). Mp 170–172 °C. Anal. Calcd for $C_{25}H_{21}F_2N_3O_6S$: C, 56.71; H, 4.00; N, 7.94. Found: C, 56.73; H, 4.03; N, 7.91.

***N*-(2,4-Difluorophenyl)-7-(2-oxopyrrolidin-1-yl)-2,3-dihydro-1*H*-indole-5-sulfonamide (23a).** Compound **23a** was prepared from compound **22a** in a manner similar to that described for compound **9b**. Pale yellow amorphous solid. Yield 99%. MS (ESI/APCI) *m/z* 394.1 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.07 (2H, quint, J = 7.4 Hz), 2.38 (2H, t, J = 8.0 Hz), 3.01 (2H, t, J = 8.7 Hz), 3.51–3.65 (4H, m), 6.05 (1H, s), 6.94–7.06 (1H, m), 7.12–7.30 (4H, m), 9.67 (1H, s). Purity 94.5% (LC–MS).

***N*-(2,4-Difluorophenyl)-7-(2-oxopiperidin-1-yl)-2,3-dihydro-1*H*-indole-5-sulfonamide (23b).** Compound **23b** was prepared from compound **22b** in a manner similar to that described for compound **9b**. Colorless amorphous solid. Yield 97%. MS (ESI/APCI) *m/z* 408.3 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.75–1.88 (4H, m), 2.28–2.39 (2H, m), 3.01 (2H, t, J = 8.7 Hz), 3.27–3.37 (2H, m), 3.56 (2H, t, J = 8.7 Hz), 6.14 (1H, s), 6.95–7.04 (1H, m), 7.08 (1H, d, J = 1.8 Hz), 7.15–7.28 (3H, m), 9.62 (1H, br s). Purity 100% (LC–MS).

***N*-(2,4-Difluorophenyl)-7-(2-oxoimidazolidin-1-yl)-2,3-dihydro-1*H*-indole-5-sulfonamide (23c).** Compound **23c** was prepared from compound **22c** in a manner similar to that described for compound **9b** (Purification: trituration with EtOH–AcOEt–^{i}Pr$_2$O). White solid. Yield 94%. MS (ESI/APCI) *m/z* 395.2 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.99 (2H, t, J = 8.6 Hz), 3.34–3.45 (2H, m), 3.55 (2H, t, J = 8.8 Hz), 3.60–3.70 (2H, m), 6.09 (1H, s), 6.87 (1H, s), 6.94–7.06 (1H, m), 7.10–7.30 (4H, m), 9.67 (1H, s). Mp 180–182 °C. Purity 99.7% (LC–MS).

***N*-(2,4-Difluorophenyl)-7-(2-oxopyrrolidin-1-yl)-1-(2-phenylethyl)-2,3-dihydro-1*H*-indole-5-sulfonamide (24a).** Compound **24a** was prepared from compound **23a** in a manner similar to that described for compound **24b** (Purification: silica gel column chromatography (hexane/AcOEt = 40/60 to 20/80)). White solid. Yield 41%. MS (ESI/APCI) *m/z* 498.4 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86–2.02 (2H, m), 2.34 (2H, t, J = 7.7 Hz), 2.75 (2H, t, J =

7.7 Hz), 2.97 (2H, t, *J* = 8.8 Hz), 3.23–3.44 (4H, m), 3.60 (2H, t, *J* = 8.8 Hz), 7.00 (1H, br s), 7.12 (1H, s), 7.15–7.38 (8H, m), 9.72 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 18.1, 26.8, 30.4, 32.6, 49.5, 50.0, 52.6, 104.5 (dd, *J* = 26.4, 24.2 Hz), 111.4 (dd, *J* = 22.4, 4.0 Hz), 118.5, 121.3 (dd, *J* = 13.2, 4.4 Hz), 121.4, 126.2, 126.9, 128.1 (dd, *J* = 10.3, 2.2 Hz), 128.2, 128.4, 128.5, 133.3, 139.2, 150.2, 156.2 (dd, *J* = 250.5, 12.8 Hz), 159.7 (dd, *J* = 245.0, 11.0 Hz), 175.0. Mp 160–162 °C. Anal. Calcd for $C_{26}H_{25}F_2N_3O_3S \cdot 0.1H_2O$: C, 62.54; H, 5.09; N, 8.41. Found: C, 62.30; H, 5.19; N, 8.24.

***N*-(2,4-Difluorophenyl)-7-(2-oxopiperidin-1-yl)-1-(2-phenylethyl)-2,3-dihydro-1*H*-indole-5-sulfonamide (24b).** A mixture of compound **23b** (135 mg, 0.331 mmol), phenylacetaldehyde (0.078 mL, 0.66 mmol), and platinum(IV) oxide (30 mg) in a mixed solvent of THF (5 mL) and EtOH (5 mL) was stirred at rt for 15 h under H_2 atmosphere (1 atm, balloon). The catalyst was removed by filtration through a PTFE membrane filter and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 35/65 to 20/80) to give the title compound as a colorless amorphous solid (105 mg, 0.205 mmol, 62%). MS (ESI/APCI) *m/z* 512.5 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56–1.87 (4H, m), 2.13–2.28 (1H, m), 2.31–2.44 (1H, m), 2.65–3.07 (4H, m), 3.22 (2H, t, *J* = 5.5 Hz), 3.39 (2H, t, *J* = 7.7 Hz), 3.46–3.68 (2H, m), 6.95–7.04 (1H, m), 7.07 (1H, d, *J* = 1.9 Hz), 7.15–7.35 (8H, m), 9.68 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 20.6, 22.5, 26.8, 32.5, 32.9, 49.1, 50.8, 52.4, 104.5(dd, *J* = 26.8, 24.6 Hz), 111.4 (dd, *J* = 22.0, 3.7 Hz), 121.1, 121.4 (dd, *J* = 12.8, 4.0 Hz), 122.8, 126.2, 126.8, 128.1 (dd, *J* = 9.5, 2.2 Hz), 128.4, 128.5, 128.9, 133.2, 139.2, 149.5, 156.1 (dd, *J* = 250.5, 12.8 Hz), 159.6 (dd, *J* = 245.0, 11.0 Hz), 169.4. Anal. Calcd for $C_{27}H_{27}F_2N_3O_3S$: C, 63.39; H, 5.32; N, 8.21. Found: C, 63.20; H, 5.28; N, 8.08.

5-[(2,4-Difluorophenyl)sulfamoyl]-*N*-(4-fluorophenyl)-7-(2-oxopyrrolidin-1-yl)-2,3-dihydro-1*H*-indole-1-carboxamide (24c). To a mixture of 4-fluoroaniline (0.097 mL, 1.0 mmol) and pyridine (0.082 mL, 1.0 mmol) in THF (6 mL) was added triphosgene (106 mg, 0.357 mmol) at 0 °C. After stirring at 0 °C for 1 h, the mixture was added to a mixture of compound **23a** (200 mg, 0.508 mmol) and triethylamine (0.142 mL, 1.02 mmol) in THF (3 mL) at 0 °C. The resulting mixture was stirred at rt for 15 h. The reaction mixture was diluted with AcOEt, successively washed with water, 0.1 N hydrochloric acid and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 35/65 to 10/90) to give the title compound as a white solid (180 mg, 0.339 mmol, 67%). MS (ESI/APCI) *m/z* 531.3 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91–2.05 (2H, m), 2.13–2.23 (2H, m), 3.15 (2H, t, *J* = 8.2 Hz), 3.71 (2H, t, *J* = 6.8 Hz), 4.16 (2H, t, *J* = 8.4 Hz), 7.00–7.18 (3H, m), 7.21–7.33 (2H, m), 7.40–7.45 (2H, m), 7.47–7.55 (2H, m), 9.18 (1H, s), 10.02 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 18.5, 27.9, 30.3, 48.5, 50.8, 104.6 (dd, *J* = 26.4, 24.2 Hz), 111.6 (dd, *J* = 22.0, 3.7 Hz), 115.1 (d, *J* = 22.7 Hz), 120.2, 121.0 (d, *J* = 7.3 Hz), 121.1, 124.3, 125.6, 128.2 (dd, *J* = 9.9, 1.8 Hz), 133.4, 135.9 (d, *J* = 2.2 Hz), 136.5, 141.5, 151.8, 156.1 (dd, *J* = 250.5, 12.8 Hz), 157.6 (d, *J* = 239.2 Hz), 159.8 (dd, *J* = 245.4, 11.4 Hz), 171.8. Mp 211–213 °C. Anal. Calcd for $C_{25}H_{21}F_3N_4O_4S$: C, 56.60; H, 3.99; N, 10.56. Found: C, 56.46; H, 4.04; N, 10.44.

5-[(2,4-Difluorophenyl)sulfamoyl]-7-(2-oxopyrrolidin-1-yl)-*N*-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1*H*-indole-1-carboxamide (24d). Compound **24d** was prepared from compound **23a** and 4-(trifluoromethyl)aniline in a manner similar to that described for compound **24c** (Purification: silica gel column chromatography (hexane/AcOEt = 80/20 to 40/60) and recrystallization from AcOEt–THF–^{i}Pr$_2$O). White solid. Yield 62%. MS

(ESI/APCI) *m/z* 581.3 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.90–2.07 (2H, m), 2.11–2.23 (2H, m), 3.16 (2H, t, *J* = 8.2 Hz), 3.73 (2H, t, *J* = 6.9 Hz), 4.19 (2H, t, *J* = 8.4 Hz), 6.98–7.13 (1H, m), 7.19–7.36 (2H, m), 7.40–7.52 (2H, m), 7.58–7.83 (4H, m), 9.54 (1H, s), 10.03 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 18.5, 28.0, 30.3, 48.6, 50.8, 104.6 (dd, *J* = 26.8, 24.6 Hz), 111.6 (dd, *J* = 22.0, 3.7 Hz), 118.7, 120.2, 121.1 (dd, *J* = 13.2, 2.9 Hz), 122.2 (q, *J* = 32.0 Hz), 124.1, 124.5 (q, *J* = 272.9 Hz), 125.8, 125.9, 128.2 (dd, *J* = 10.3, 1.5 Hz), 133.9, 136.8, 141.1, 143.5, 151.5, 156.1 (dd, *J* = 250.5, 12.8 Hz), 159.8 (dd, *J* = 245.4, 11.4 Hz), 171.8. Mp 206–208 °C. Anal. Calcd for $C_{26}H_{21}F_5N_4O_4S$: C, 53.79; H, 3.65; F, 16.36; N, 9.65; S, 5.52. Found: C, 53.96; H, 3.81; F, 16.42; N, 9.65; S, 5.57.

***N*-(4-*tert*-Butylphenyl)-5-[(2,4-difluorophenyl)sulfamoyl]-7-(2-oxopyrrolidin-1-yl)-2,3-dihydro-1*H*-indole-1-carboxamide (24e).** Compound **24e** was prepared from compound **23a** and 4-(*tert*-butyl)aniline in a manner similar to that described for compound **24c** (Purification: silica gel column chromatography (hexane/AcOEt = 80/20 to 40/60) and crystallization from AcOEt–^{i}Pr$_2$O). White solid. Yield 64%. MS (ESI/APCI) *m/z* 567.3 $[M - H]^-$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26 (9H, s), 1.91–2.07 (2H, m), 2.12–2.25 (2H, m), 3.15 (2H, t, *J* = 8.3 Hz), 3.70 (2H, t, *J* = 6.9 Hz), 4.15 (2H, t, *J* = 8.5 Hz), 6.96–7.11 (1H, m), 7.18–7.35 (4H, m), 7.36–7.49 (4H, m), 9.07 (1H, s), 10.00 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 18.5, 27.9, 30.4, 31.2, 33.9, 48.5, 50.8, 104.6 (dd, *J* = 27.1, 24.2 Hz), 111.6 (dd, *J* = 22.4, 4.0 Hz), 119.0, 120.2, 121.1 (dd, *J* = 12.5, 3.7 Hz), 124.5, 125.1, 125.6, 128.2 (dd, *J* = 10.3, 1.5 Hz), 133.3, 136.4, 137.0, 141.8, 144.7, 151.8, 156.1 (dd, *J* = 250.2, 12.5 Hz), 159.8 (dd, *J* = 245.8, 11.0 Hz), 171.8. Mp 224–226 °C. Anal. Calcd for $C_{29}H_{30}F_2N_4O_4S$: C, 61.25; H, 5.32; N, 9.85. Found: C, 61.09; H, 5.46; N, 9.67.

5-[(2,4-Difluorophenyl)sulfamoyl]-7-(2-oxoimidazolidin-1-yl)-*N*-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1*H*-indole-1-carboxamide (24f). Compound **24f** was prepared from compound **23a** and 4-(trifluoromethyl)aniline in a manner similar to that described for compound **24c** (Purification: silica gel column chromatography (hexane/AcOEt = 80/20 to 40/60)). White solid. Yield 92%. MS (ESI/APCI) *m/z* 582.4 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.12 (2H, t, *J* = 7.9 Hz), 3.23 (2H, t, *J* = 8.0 Hz), 3.66–3.81 (2H, m), 4.14 (2H, t, *J* = 8.2 Hz), 6.49 (1H, s), 6.97–7.10 (1H, m), 7.19–7.33 (2H, m), 7.36 (1H, d, *J* = 1.7 Hz), 7.48 (1H, d, *J* = 1.8 Hz), 7.54–7.66 (2H, m), 7.67–7.79 (2H, m), 9.52 (1H, s), 10.03 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 28.2, 37.9, 45.1, 50.9, 104.6 (dd, *J* = 26.8, 24.6 Hz), 111.6 (dd, *J* = 22.7, 3.7 Hz), 118.6, 118.9, 121.2 (dd, *J* = 13.2, 3.7 Hz), 122.0 (q, *J* = 31.5 Hz), 123.2, 124.5 (q, *J* = 270.7 Hz), 125.7 (q, *J* = 3.7 Hz),127.4, 128.0 (dd, *J* = 10.3, 1.5 Hz), 134.2, 136.7, 140.7, 143.6, 151.7, 156.0 (dd, *J* = 250.2, 13.2 Hz), 158.1, 159.7 (dd, *J* = 245.0, 11.0 Hz). Mp 132–135 °C. Anal. Calcd for $C_{25}H_{20}F_5N_5O_4S$: C, 51.64; H, 3.47; N, 12.04. Found: C, 51.64; H, 3.65; N, 11.75.

***N*-{5-[(2,4-Difluorophenyl)sulfamoyl]-1-[2-(4-fluorophenyl)ethyl]-1*H*-indazol-7-yl}acetamide (32).** Compound **32** was prepared from compound **31** in a manner similar to that described for compound **8b** (Purification: crystallization from AcOEt). White solid. Yield 46%. MS (ESI/APCI) *m/z* 489.1 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.12 (3H, s), 3.02 (2H, t, *J* = 7.7 Hz), 4.59–4.70 (2H, m), 6.94–7.27 (7H, m), 7.51 (1H, d, *J* = 1.4 Hz), 8.04 (1H, d, *J* = 1.5 Hz), 8.27 (1H, s), 10.08 (1H, s), 10.13 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.9, 35.7, 51.5, 104.6 (dd, *J* = 26.8, 24.6 Hz), 111.6 (dd, *J* = 22.0, 3.7 Hz), 115.1 (d, *J* = 20.5 Hz), 119.7, 120.9 (dd, *J* = 11.7, 3.7 Hz), 121.9, 122.5, 124.9, 128.5 (d, *J* = 10.3 Hz), 130.3 (d, *J* = 8.1 Hz), 132.2, 134.0 (d, *J* = 2.9 Hz), 135.1, 136.2, 156.4 (dd, *J* = 250.9, 13.2 Hz), 159.9 (dd, *J* = 245.8,

11.7 Hz), 160.9 (d, *J* = 242.1 Hz), 169.9. Mp 195–197 °C. Anal. Calcd for $C_{23}H_{19}F_3N_4O_3S$: C, 56.55; H, 3.92; N, 11.47. Found: C, 56.49; H, 4.01; N, 11.39.

***N*-{5-[(2,4-Difluorophenyl)sulfamoyl]-1-[2-(4-fluorophenyl)ethyl]-1*H*-benzimidazol-7-yl}acetamide (39).** Compound **39** was prepared from compound **38** in a manner similar to that described for compound **8b** (Purification: crystallization from AcOEt). White solid. Yield 91%. MS (ESI/APCI) *m/z* 489.4 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.12 (3H, s), 2.99 (2H, t, *J* = 7.4 Hz), 4.50 (2H, t, *J* = 7.4 Hz), 6.95–7.30 (7H, m), 7.44 (1H, d, *J* = 1.1 Hz), 7.83 (1H, d, *J* = 1.3 Hz), 8.16 (1H, s), 10.09 (1H, s), 10.15 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.9, 36.0, 46.7, 104.6 (dd, *J* = 26.8, 24.6 Hz), 111.6 (dd, *J* = 22.0, 3.7 Hz), 115.2 (d, *J* = 21.3 Hz), 116.9, 120.1, 121.0 (dd, *J* = 13.2, 2.9 Hz), 122.9, 128.3 (d, *J* = 10.3 Hz), 130.3 (d, *J* = 8.1 Hz), 131.9, 133.1, 133.6 (d, *J* = 2.9 Hz), 144.6, 147.9, 156.2 (dd, *J* = 250.9, 12.5 Hz), 159.8 (dd, *J* = 245.8, 11.0 Hz), 161.0 (d, *J* = 242.1 Hz), 170.0. Mp 262–264 °C. Anal. Calcd for $C_{23}H_{19}F_3N_4O_3S$: C, 56.55; H, 3.92; N, 11.47. Found: C, 56.56; H, 3.99; N, 11.38.

***N*-{5-[(2,4-Difluorophenyl)sulfamoyl]-1-[2-(4-fluorophenyl)ethyl]-2-methyl-1*H*-benzimidazol-7-yl}acetamide (40).** A mixture of compound **36** (100 mg, 0.229 mmol) and acetic acid (5 mL) was refluxed for 5 h. After the mixture was concentrated under reduced pressure, the residue was dissolved in DMA (3 mL). Acetyl chloride (0.033 mL, 0.46 mmol) was added to the mixture followed by stirring at rt for 30 min. The reaction mixture was diluted with AcOEt, washed with water (3 times) and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was crystallized from AcOEt–^{i}Pr$_2$O to give the title compound as a white solid (80 mg, 0.16 mmol, 70%). MS (ESI/APCI) *m/z* 503.1 $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.10 (3H, s), 2.30 (3H, s), 2.92 (2H, t, *J* = 7.4 Hz), 4.38 (2H, t, *J* = 7.3 Hz), 6.93–7.29 (8H, m), 7.36 (1H, d, *J* = 1.2 Hz), 7.73 (1H, d, *J* = 1.4 Hz), 10.07 (1H, d, *J* = 9.5 Hz). ^{13}C

NMR (101 MHz, DMSO-d_6) δ 13.4, 22.8, 35.4, 45.5, 104.5 (dd, J = 26.8, 24.6 Hz), 111.5 (dd, J = 22.7, 3.7 Hz), 115.2 (d, J = 21.3 Hz), 115.7, 120.2, 121.1 (dd, J = 13.9, 2.9 Hz), 121.9, 128.3 (d, J = 9.5 Hz), 130.4 (d, J = 8.1 Hz), 132.7, 133.0, 133.7 (d, J = 2.9 Hz), 143.4, 155.7, 156.2 (dd, J = 250.9, 12.5 Hz), 159.8 (dd, J = 245.8, 11.0 Hz), 161.1 (d, J = 242.8 Hz), 170.1. Mp 142–144 °C. Anal. Calcd for $C_{24}H_{21}F_3N_4O_3S \cdot 0.2{}^{i}Pr_2O$: C, 57.88; H, 4.59; N, 10.71. Found: C, 57.97; H, 4.62; N, 10.50.

***N*-{6-[(2,4-Difluorophenyl)sulfamoyl]-2-oxo-3-(2-phenylethyl)-2,3-dihydro-1,3-benzoxazol-4-yl}acetamide (49).** Compound **49** was prepared from compound **47** in a manner similar to that described for compound **7b** and **8b**. Yellow solid. Yield 35% over 2 steps. MS (ESI/APCI) *m/z* 488.3 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.10 (3H, s), 2.89 (2H, t, J = 7.2 Hz), 4.06 (2H, t, J = 7.4 Hz), 6.97–7.14 (3H, m), 7.18–7.33 (5H, m), 7.42 (1H, s), 7.53 (1H, s), 10.10 (1H, s), 10.18 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.8, 34.5, 43.9, 104.7 (dd, J = 27.1, 24.2 Hz), 106.0, 111.7 (dd, J = 22.0, 3.7 Hz), 120.6, 120.7, 123.1, 126.7, 128.5, 128.5, 128.7 (dd, J = 10.3, 1.5 Hz), 129.8, 133.4, 137.2, 142.5, 153.4, 156.4 (dd, J = 250.9, 12.5 Hz), 160.0 (dd, J = 245.8, 11.7 Hz), 170.1. Mp 163–165 °C. Anal. Calcd for $C_{23}H_{19}F_2N_3O_5S$: C, 56.67; H, 3.93; N, 8.62. Found: C, 56.58; H, 4.07; N, 8.45.

***N*-{5-[(4-Methoxyphenyl)sulfamoyl]-2-(2-phenylethoxy)phenyl}acetamide (54).** To a solution of compound **53** (250 mg, 0.627 mmol) in pyridine (3.0 mL) was added acetic anhydride (0.118 mL, 1.25 mmol) at rt. The mixture was stirred at rt for 2 h. The reaction mixture was diluted with AcOEt, successively washed with H_2O, 1 N hydrochloric acid and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt = 70/30 to 30/70) to give a solid, which was washed with ${}^{i}Pr_2O$ and dried under reduced pressure to give the title compound as a white solid (101 mg, 0.229

mmol, 37%). MS (ESI/APCI) *m/z* 441.1 $[M + H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (3H, s), 3.13 (2H, t, *J* = 6.6 Hz), 3.73 (3H, s), 4.29 (2H, t, *J* = 6.5 Hz), 6.39 (1H, s), 6.73 (2H, d, *J* = 8.9 Hz), 6.79 (1H, d, *J* = 8.5 Hz), 7.00 (2H, d, *J* = 8.9 Hz), 7.21–7.39 (5H, m), 7.50 (1H, br s.), 8.82 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.7, 35.4, 55.4, 69.3, 110.3, 114.3, 118.2, 123.9, 125.2, 126.9, 128.3, 128.8, 129.2, 131.4, 137.5, 149.7, 157.6, 168.4. Mp 144–146 °C. Anal. Calcd for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36. Found: C, 62.57; H, 5.55; N, 6.21.

In vitro inhibitory activity against MGAT2. Protein preparation. The full-length coding sequence of human MGAT2 is identical to NCBI accession number NM_025098.[4] The gene of interests was subcloned with FLAG tag in the N-terminal region into pcDNA3.3 vector (Life Technologies, Carlsbad, CA). The expression vector was transfected into FreeStyle293 cells (Life Technologies, Carlsbad, CA) for human MGAT2 expression. After 2-days-culture, cells were homogenized in ice-cold 20 mM Tris-HCl buffer (pH 7.5 at 25 °C) containing 1 mM EDTA and 300 mM sucrose. Total membrane fractions were isolated by ultracentrifugation. Pellets were re-suspended in the same buffer and stored at −80 °C. The protein concentration was determined with the BCA Protein Assay Kit (Pierce Biotechnology, Inc., IL) according to the instruction manual.

RapidFire/MS assay. The test compounds were dissolved in 5 μL of an assay buffer, which consisted of 100 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 200 mM sucrose, 0.01% Tween 20, 2 mM DTT, 0.01% BSA, and 5% DMSO and incubated with 10 μL of 0.6 μg/mL MGAT2 enzyme for 60 min. The reaction was started with the addition of 5 μL of ^{13}C×18 oleoyl-CoA (Sigma-Aldrich, St. Lois, Missouri) and 2-oleoyl-glycerol (Sigma-Aldrich, St. Lois, Missouri) at 20 μM each. After incubation at rt for 30 min, the reaction was stopped with acetonitrile containing 0.88% formic acid and 1.3 μM 1,2-dioleoyl-glycerol (Sigma-Aldrich, St. Lois, Missouri) as an

internal standard. High-throughput online solid phase extraction was performed using a RapidFire® 300 (Agilent Technologies, Santa Clara, CA). Mass spectrometric analysis was performed using an API-4000^{TM} triple quadrupole mass spectrometer (AB SCIEX, Framingham, MA) in positive SRM mode. The SRM transitions for $^{13}C\times18$ dioleoylglycerol as a reaction product and dioleoylglycerol were set as 656.6/339.2 and 638.5/339.2, respectively. Analytical data was acquired using Analyst software version 1.5.0 (AB SCIEX, Framingham, MA) and 656.6/339.2 was divided by 638.5/339.2 for calibration. The IC_{50} values for test compounds were calculated using XLfit software (IDBS, London, UK).

In vitro inhibitory activity against MGAT3, DGAT1, DGAT2, and ACAT1. Protein preparation. The full-length coding sequences of human MGAT3 is identical to NCBI accession number NM_178176.[26] The gene of interests was subcloned with FLAG tag in the N-terminal region into pcDNA3.3 vector (Life Technologies, Carlsbad, CA). The expression vector was transfected into FreeStyle293 cells (Life Technologies, Carlsbad, CA) for human MGAT3 expression. After 2-days-culture, cells were homogenized in ice-cold 20 mM Tris-HCl buffer (pH 7.5 at 25 °C) containing 1 mM EDTA and 300 mM sucrose. The full-length coding sequences of human DGAT1, DGAT2, and ACAT1 are identical to NCBI accession numbers AB057815,[27] NM_032564,[28] and NM_003101,[29] respectively. All genes of interests were subcloned with FLAG tag in the N-terminal region to make expression vectors. Recombinant baculoviruses were prepared according to the procedure of the Bac-to-Bac baculovirus expression system (Life Technologies, Carlsbad, CA). After infection with recombinant baculoviruses, Sf-21 insect cells were homogenized in an ice-cold Buffer (100 mM sucrose, 50 mM KCl, and 40 mM KH_2PO_4/K_2HPO_4 at pH 7.4). Total membrane fractions were isolated by ultracentrifugation. Pellets were re-suspended in the same buffer for each homogenization and

stored at −80 °C. The protein concentration was determined with the BCA Protein Assay Kit (Pierce Biotechnology, Inc., IL) according to the instruction manual.

Thin Layer Chromatography (TLC) assay. The assays with human MGAT3, human ACAT1, human DGAT1, and human DGAT2 were performed by TLC assay. For human MGAT3 assay, the reaction was run in an assay buffer, which consisted of 100 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 200 mM sucrose, 2 mM DTT, 0.01% BSA, 0.01% Tween 20, and 5% DMSO, supplemented with 5 μM [1-^{14}C]-oleoyl-CoA (PerkinElmer, Waltham, MA), 5 μM 2-oleoyl-glycerol, and 30 μg/mL MGAT3 enzyme for 30 min at rt. For human ACAT1 assay, 5 μM [1-14C]-oleoyl-CoA and 100 μM cholesterol were reacted with 30 μg/mL human ACAT1 enzyme for 40 min at 32 °C. For human DGAT1 and DGAT2 assays, 5 μM [1-^{14}C]-oleoyl-CoA and 40 μM 1,2-dioleoyl-glycerol were reacted with 30 μg/mL human DGAT1 and DGAT2 enzyme, respectively, for 40 min at 32 °C. The modified Bligh & Dyer method was applied to the sample preparations. Organic phase was applied onto a silica TLC plate (Merck KGaA, Darmstadt, Germany) and separated with a solvent system of hexane, ethyl ether, and acetic acid. The radioactivities incorporated into lipids were measured with Typhoon FLA 7000 (GE Healthcare UK Ltd, Buckinghamshire, England) and analyzed with Image Quant TL (GE Healthcare UK Ltd, Buckinghamshire, England).

Estimation of LogD at pH 7.4. $LogD_{7.4}$, which is a partition coefficient between 1-octanol and aqueous buffer pH 7.4, of the compounds was measured on the chromatographic procedure whose condition was developed based on a published method.[30] The instruments were Waters Alliance 2795 HPLC system with 2996 UV-vis detector (Milford, MA, USA).

In vitro metabolic clearance in human and mouse hepatic microsomes. Human and mouse liver microsomes were purchased from Xenotech, LLC (Lenexa, KS). An incubation mixture

consisted of microsomal protein in 50 mM KH_2PO_4–K_2HPO_4 phosphate buffer (pH 7.4) and 1 μM test compound. The concentration of microsomal protein was 0.2 mg/mL. An NADPH-generating system containing 5 mM $MgCl_2$, 5 mM glucose-6-phosphate, 0.5 mM β-$NADP^+$, and 1.5 units/mL glucose-6-phosphate dehydrogenase was added to the incubation mixture to initiate the enzyme reaction. The reaction was terminated 15 and 30 min after the initiation of the reaction by mixing the reaction mixture with acetonitrile, followed by centrifugation. The supernatant was subjected to LC/MS/MS analysis. The metabolic velocity was calculated as the slope of the concentration-time plot.

Pharmacokinetic analysis in mouse cassette dosing. Test compounds were administered intravenously (0.1 mg/kg) or orally (1 mg/kg, suspended in 0.5% methylcellulose aqueous solution) by cassette dosing to non-fasted mice. After administration, blood samples were collected and centrifuged to obtain the plasma fraction. The plasma samples were deproteinized by mixing with acetonitrile followed by centrifugation. The compound concentrations in the supernatant were measured by LC/MS/MS.

Oral fat tolerance test (OFTT). Male C57BL/6J mice (20–25 g, Charles River Laboratories Japan, Inc.) were used in the OFTT study. The animals were fed with standard chow and tap water ad libitum, maintained at 23 ± 3 °C with a constant humidity of 40–70%, and acclimated with a cycle of 12 h of light and 12 h of darkness. All animal experiments were performed according to the guidelines of the Institutional Animal Care and Use Committee in Takeda Pharmaceutical Company Ltd. Overnight fasted mice were orally treated with a single dose of 3, 10, and 30 mg/kg body weight of compound **24d**. At 6 h after the treatment of **24d**, mice were orally given 8 mL/kg olive oil or water. To inhibit the hydrolysis of plasma TG by lipoprotein lipase (LPL), mice were treated with a LPL inhibitor, Pluronic F127 (Poloxamer 407, i.p., 500

mg/kg) 30 min prior to olive oil load. Blood samples were collected via tail vein at 0, 2, and 4 h after the olive oil load. Plasma fractions were obtained by centrifugation at 11,100 G for 5 min at 4 °C. Plasma TG concentration was determined using a 7180 biochemistry automatic analyzer (Hitachi high-Tech, Japan). Chylomicron TG (CM/TG), a triacylglycerol derived from small intestine, was calculated by subtracting the plasma TG concentration of water-treated group from the plasma TG concentration of each olive oil-treated group.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures for the synthesis of intermediates **15**–**19**, **26**–**31**, **34**–**38**, **42**–**47**, and **51**–**53**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

ACAT, acyl CoA:cholesterol acyltransferase; APCI, atomospheric pressure cheimcal ionization; CDI, carbonyldiimidazole; CM, chylomicron; dba, dibenzylideneacetone; DG, diacylglycerol; DGAT, acyl CoA:diacylglycerol acyltransferase; DIAD, diisopropyl azodicarboxylate; DIEA, *N*,*N*-diisopropylethylamine; DMPK, drug metabolism and pharmacokinetics; HLM, human liver microsome; LPL, lipoprotein lipase; MG, monoacylglycerol; MLM, mouse liver microsome; OFTT, oral fat tolerance test; PTFE, polytetrafluoroethylene; TEA, triethylamine; TG, triacylglycerol.

REFERENCES

1. Mansbach, C. M.; Siddiqi, S. A. The Biogenesis of Chylomicrons. *Annu. Rev. Physiol.* **2010,** *72*, 315-333.

2. Lehner, R.; Kuksis, A. Biosynthesis of triacylglycerols. *Prog. Lipid Res.* **1996,** *35*, 169-201.

3. Coleman, R. A.; Mashek, D. G. Mammalian Triacylglycerol Metabolism: Synthesis, Lipolysis, and Signaling. *Chem. Rev.* **2011,** *111*, 6359-6386.

4. Yen, C. L.; Farese, R. V., Jr. MGAT2, a monoacylglycerol acyltransferase expressed in the small intestine. *J. Biol. Chem.* **2003,** *278*, 18532-18537.

5. Cao, J.; Cheng, L.; Shi, Y. Catalytic properties of MGAT3, a putative triacylgycerol synthase. *J. Lipid Res.* **2007,** *48*, 583-591.

6. Yen, C. L.; Cheong, M. L.; Grueter, C.; Zhou, P.; Moriwaki, J.; Wong, J. S.; Hubbard, B.; Marmor, S.; Farese, R. V., Jr. Deficiency of the intestinal enzyme acyl CoA:monoacylglycerol acyltransferase-2 protects mice from metabolic disorders induced by high-fat feeding. *Nat. Med.* **2009,** *15*, 442-446.

7. Nelson, D. W.; Gao, Y.; Spencer, N. M.; Banh, T.; Yen, C. L. Deficiency of MGAT2 increases energy expenditure without high-fat feeding and protects genetically obese mice from excessive weight gain. *J. Lipid Res.* **2011,** *52*, 1723-1732.

8. Tsuchida, T.; Fukuda, S.; Aoyama, H.; Taniuchi, N.; Ishihara, T.; Ohashi, N.; Sato, H.; Wakimoto, K.; Shiotani, M.; Oku, A. MGAT2 deficiency ameliorates high-fat diet-induced obesity and insulin resistance by inhibiting intestinal fat absorption in mice. *Lipids Health Dis.* **2012,** *11*, 75.

9. Guerciolini, R.; Radu-Radulescu, L.; Boldrin, M.; Dallas, J.; Moore, R. Comparative evaluation of fecal fat excretion induced by orlistat and chitosan. *Obes. Res.* **2001,** *9*, 364-367.

10. Barlind, J. G.; Buckett, L. K.; Crosby, S. G.; Davidsson, O.; Emtenas, H.; Ertan, A.; Jurva, U.; Lemurell, M.; Gutierrez, P. M.; Nilsson, K.; O'Mahony, G.; Petersson, A. U.; Redzic, A.; Wagberg, F.; Yuan, Z. Q. Identification and design of a novel series of MGAT2 inhibitors. *Bioorg. Med. Chem. Lett.* **2013,** *23*, 2721-2726.

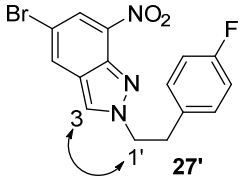
11. Scott, J. S.; Berry, D. J.; Brown, H. S.; Buckett, L.; Clarke, D. S.; Goldberg, K.; Hudson, J. A.; Leach, A. G.; MacFaul, P. A.; Raubo, P.; Robb, G. Achieving improved permeability by hydrogen bond donor modulation in a series of MGAT2 inhibitors. *Med. Chem. Commun.* **2013,** *4*, 1305-1311.

12. Waring, M. J. Lipophilicity in drug discovery. *Expert Opin. Drug Discov.* **2010,** *5*, 235-248.

13. Kim, D.-W.; Ko, Y. K.; Kim, S. H. A New and Facile Synthesis of Sulfonyl Chlorides. *Synthesis* **1992,** *1992*, 1203-1204.

14. Cottyn, B.; Vichard, D.; Terrier, F. o.; Nioche, P.; Raman, C. S. Efficient Synthesis of 7-Substituted or 3,7-Disubstituted 1H-Indazoles. *Synlett* **2007**, 1203-1206.

15. The isomer for which NOE cross peaks were observed between H-3 on the indazole ring and the H-1' of the phenethyl moiety was determined as **27'**.



27'

16. Buhr, W.; Zimmermann, P. J.; Chiesa, V.; Palmer, A.; Brehm, C.; Grundler, G.; Senn-Bilfinger, J.; Simon, W.-A.; Postius, S.; Kromer, W. 4-Substituted benzimidazoles and their use as inhibitors of gastric secretion. WO2004/054984.

17. Charifson, P. S.; Grillot, A.-L.; Grossman, T. H.; Parsons, J. D.; Badia, M.; Bellon, S.; Deininger, D. D.; Drumm, J. E.; Gross, C. H.; LeTiran, A.; Liao, Y.; Mani, N.; Nicolau, D. P.; Perola, E.; Ronkin, S.; Shannon, D.; Swenson, L. L.; Tang, Q.; Tessier, P. R.; Tian, S.-K.; Trudeau, M.; Wang, T.; Wei, Y.; Zhang, H.; Stamos, D. Novel Dual-Targeting Benzimidazole Urea Inhibitors of DNA Gyrase and Topoisomerase IV Possessing Potent Antibacterial Activity: Intelligent Design and Evolution through the Judicious Use of Structure-Guided Design and Stucture−Activity Relationships. *J. Med. Chem.* **2008,** *51*, 5243-5263.

18. Molecular Operating Environment (MOE), C. C. G. I., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, 2012. Molecular Operating Environment (MOE), 2012.10; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, 2012.

19. Nakashima, S.; Yamamoto, K.; Arai, Y.; Ikeda, Y. Impact of Physicochemical Profiling for Rational Approach on Drug Discovery. *Chem. Pharm. Bull. (Tokyo).* **2013,** *61*, 1228-1238.

20. Stewart, J. P. Optimization of parameters for semiempirical methods IV: extension of MNDO, AM1, and PM3 to more main group elements. *J. Mol. Model.* **2004,** *10*, 155-164.

21. Laurence, C.; Brameld, K. A.; Graton, J. r. m.; Le Questel, J.-Y.; Renault, E. The pKBHX Database: Toward a Better Understanding of Hydrogen-Bond Basicity for Medicinal Chemists. *J. Med. Chem.* **2009,** *52*, 4073-4086.

22. Leeson, P. D.; Springthorpe, B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat. Rev. Drug Discov.* **2007,** *6*, 881-890.

23. Avdeef, A.; Strafford, M.; Block, E.; Balogh, M. P.; Chambliss, W.; Khan, I. Drug absorption in vitro model: filter-immobilized artificial membranes: 2. Studies of the permeability properties of lactones in Piper methysticum Forst. *Eur. J. Pharm. Sci.* **2001,** *14*, 271-280.

24. Millar, J. S.; Cromley, D. A.; McCoy, M. G.; Rader, D. J.; Billheimer, J. T. Determining hepatic triglyceride production in mice: comparison of poloxamer 407 with Triton WR-1339. *J. Lipid Res.* **2005,** *46*, 2023-2028.

25. Hassner, A.; Yagudayev, D.; Pradhan, T. K.; Nudelman, A.; Amit, B. Light-Sensitive Protecting Groups for Amines and Alcohols: The Photosolvolysis of N-Substituted 7-Nitroindolines. *Synlett* **2007,** *15*, 2405-2409.

26. Cheng, D.; Nelson, T. C.; Chen, J.; Walker, S. G.; Wardwell-Swanson, J.; Meegalla, R.; Taub, R.; Billheimer, J. T.; Ramaker, M.; Feder, J. N. Identification of Acyl Coenzyme A:Monoacylglycerol Acyltransferase 3, an Intestinal Specific Enzyme Implicated in Dietary Fat Absorption. *J. Biol. Chem.* **2003,** *278*, 13611-13614.

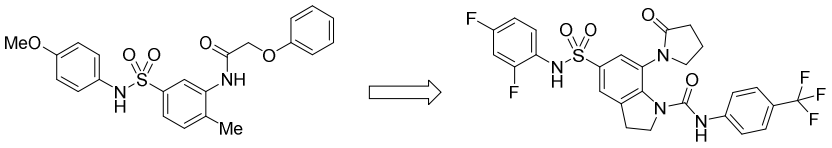
27. Oelkers, P.; Behari, A.; Cromley, D.; Billheimer, J. T.; Sturley, S. L. Characterization of Two Human Genes Encoding Acyl Coenzyme A:Cholesterol Acyltransferase-related Enzymes. *J. Biol. Chem.* **1998,** *273*, 26765-26771.

28. Cases, S.; Stone, S. J.; Zhou, P.; Yen, E.; Tow, B.; Lardizabal, K. D.; Voelker, T.; Farese, R. V. Cloning of DGAT2, a Second Mammalian Diacylglycerol Acyltransferase, and Related Family Members. *J. Biol. Chem.* **2001,** *276*, 38870-38876.

29. Chang, C. C.; Huh, H. Y.; Cadigan, K. M.; Chang, T. Y. Molecular cloning and functional expression of human acyl-coenzyme A:cholesterol acyltransferase cDNA in mutant Chinese hamster ovary cells. *J. Biol. Chem.* **1993,** *268*, 20747-55.

30. Masumoto, K.; Takeyasu, A.; Oizumi, K.; Kobayashi, T. Studies of novel 1,4-dihydropyridine Ca antagonist CS-905. I. Measurement of partition coefficient (log P) by high performance liquid chromatography (HPLC). *Yakugaku Zasshi.* **1995,** *115*, 213-220.

Table of Contents Graphic



1
hMGAT2 IC_{50} = 130 nM

24d
hMGAT2 IC_{50} = 3.4 nM
BA 52% (mouse, 1 mg/kg)