Regular Article

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Discovery and Biological Evaluation of Potent and Orally Active Human 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors for the Treatment of Type 2 Diabetes Mellitus

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We synthesized and evaluated novel 5-[2-(thiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole derivatives as 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors. Optimization of the thiophene ring and the substituents on the 1,2,4-triazole ring produced 3,4-dicyclopropyl-5-{2-[3-fluoro-5-(trifluoromethyl)thiophen-2-yl]propan-2-yl}-4*H*-1,2,4-triazole monohydrochloride (9a), which showed potent and selective inhibitory activity against human 11β-HSD1. Compound 9a was also metabolically stable against human and mouse liver microsomes. Oral administration of 9a to diabetic ob/ob mice lowered corticosterone levels in adipose tissue, and thereby reduced plasma glucose and insulin levels in a dose-dependent manner.

Key words type II diabetes mellitus; 11β-hydroxysteroid dehydrogenase type 1; liver microsomal stability

Introduction

Diabetes mellitus is a metabolic disease in which hyperglycemia persists chronically as a result of deficient insulin action due to failed insulin secretion in the pancreas or insulin resistance in peripheral tissues.[1] Diabetes mellitus is divided into two types according to the cause[2]: type 1 diabetes is caused by insulin deficiency due to destruction of pancreatic β cells; and type 2 diabetes is caused by environmental factors such as genetic factors, obesity, binge eating, lack of exercise and a high fat diet. Numerous therapeutic agents for type 2 diabetes have been studied,[3] and insulin secretagogues and insulin sensitizers have been developed. However, owing to limited pharmacological effects and harmful side effects, glycemic control in many type 2 diabetic patients remains insufficient. Therefore, development of drugs with new mechanisms of action is warranted.

11β-Hydroxysteroid dehydrogenase is an enzyme that catalyzes the conversion of glucocorticoids. Two isozymes have been identified (Fig. 1): 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) converts inactive glucocorticoids into active glucocorticoids in the liver and adipose tissue, while 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts active glucocorticoids into inactive glucocorticoids in the kidney. Reports have identified a relationship between abnormal activation of glucocorticoids in adipose tissue and diabetes.[4] Reports have also demonstrated increased 11β-HSD1 activity in the adipose tissue of obese patients,[5] and a correlation between 11β-HSD1 activity and body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-IR) and fasting blood glucose level.[6] In addition, a transgenic mouse selectively overexpressing 11β-HSD1 in adipose tissue had raise glucocorticoids levels in adipose tissue and insulin resistance and hyperlipidemia.[7,8] Therefore, an 11β-HSD1 selective inhibitor is expected to suppress glucocorticoid action by inhibiting the conversion of inactive glucocorticoids to active glucocorticoids, and improve metabolic abnormalities caused by glucocorticoids such as hyperglycemia, insulin resistance and hyperlipidemia. However, inhibition of 11β-HSD2 in the kidney is also known to induce hypertension,[9] making selectivity for 11β-HSD1 over 11β-HSD2 of paramount importance. Various 11β-HSD1 inhibitors have been reported to date,[10] and clinical trials of several compounds[11–16] have been conducted (Fig. 2), but none of the compounds have been launched yet. Therefore, we conceptualized that the discovery of a new type of 11β-HSD1 inhibitor is necessary to overcome the current stagnation in clinical trials and initiated research from ground up.

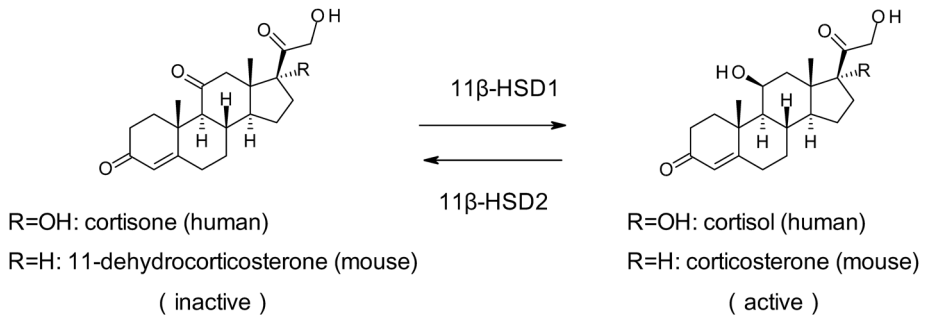

Fig. 1. Interconversion of Glucocorticoids in Humans and Mice

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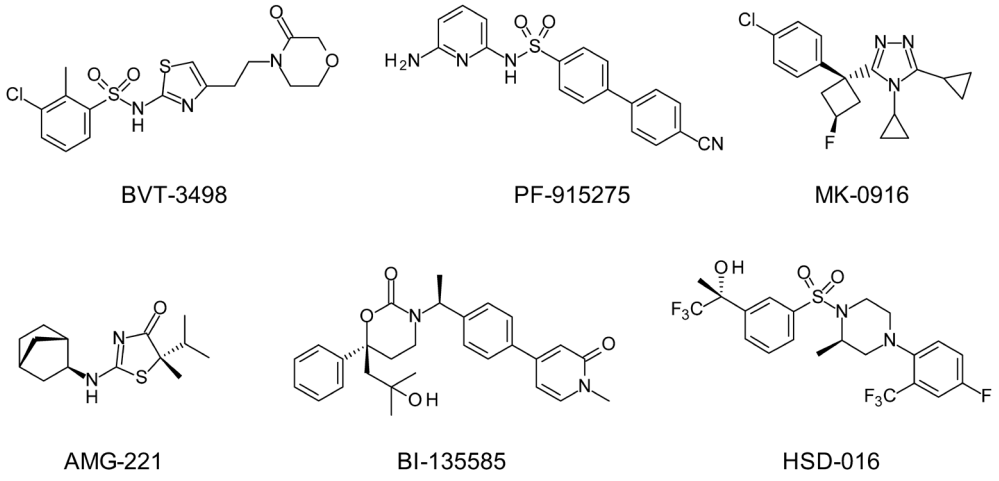


Fig. 2. Structure of 11β-HSD1 Inhibitors

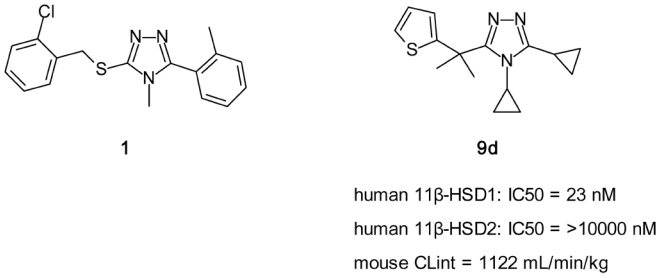


Fig. 3. Structure of **1** and **9d**

We have been focusing on developing novel 11β-HSD1 inhibitors as a new class of drugs for type 2 diabetes. High throughput screening (HTS) of the Astellas compound library identified compound **1** as a novel 11β-HSD1 inhibitor. In our initial study, to find patentable compounds, we converted the linker moiety, chlorobenzene moiety and the substituents at the 3 and 4 positions on the triazole ring of compound **1** to produce lead compound **9d** (unpublished data; Fig. 3). Compound **9d** had no inhibitory activity against human 11β-HSD2, but showed moderate inhibitory activity against human 11β-HSD1 ($IC_{50} = 23$ nM) and insufficient metabolic stability in mice ($CL_{int} = 1122$ mL/min/kg).

Therefore, we aimed to further improve the inhibitory activity of compound **9d** against human 11β-HSD1 and its metabolic stability in mice for testing in a diabetes mouse model. Here, we describe further optimization of **9d** as a novel 11β-HSD1 inhibitor, including structure–activity relationship (SAR) studies and evaluation of its *in vivo* efficacy.

Results and Discussion

Chemistry Synthesis of compounds **9a**–**p** is shown in Chart 1. Esterification of carboxylic acid **2** followed by heating of **3a** and **3b** with hydrazine monohydrate in ethanol (EtOH) yielded acylhydrazine **4a** and **4b**. Compound **5** was converted to **6**, which was hydrolyzed to **7**. Condensation of **7** and hydrazine monohydrate, followed by cyclization of acylhydrazine and *N*-cyclopropylcyclopropanecarboxamide (**8a**) using methyl trifluoromethanesulfonate yielded triazole **9c**. Compounds **9a**, **9b**, and **9d**–**p** were synthesized in a similar manner to **9c**.

Chart 2 shows the synthesis of **10c**, **10d**, **10o**, **11**, **13** and **15**. Chlorination of **9c**, **9d** and **9o** with *N*-chlorosuccinimide gave **10c**, **10d** and **10o**. Compound **9d** was also brominated with *N*-bromosuccinimide to yield **11**, which was treated with *n*-butyl lithium and *N*,*N*-dimethylformamide (DMF) to give aldehyde **12**. Compound **12** was converted to **13** using Wolff–Kishner reduction. Iodization of **9d** and subsequent cyanation with copper(I) cyanide gave nitrile **15**.

Synthesis of **19** is depicted in Chart 3. Cyclization of **16** and **8a** using methyl trifluoromethanesulfonate followed by removal of the *tert*-butoxycarbonyl (Boc) group from **17** with hydrochloric acid yielded amine **18**. Treatment of **18** with 2,5-dimethoxytetrahydrofuran gave pyrrole **19**.

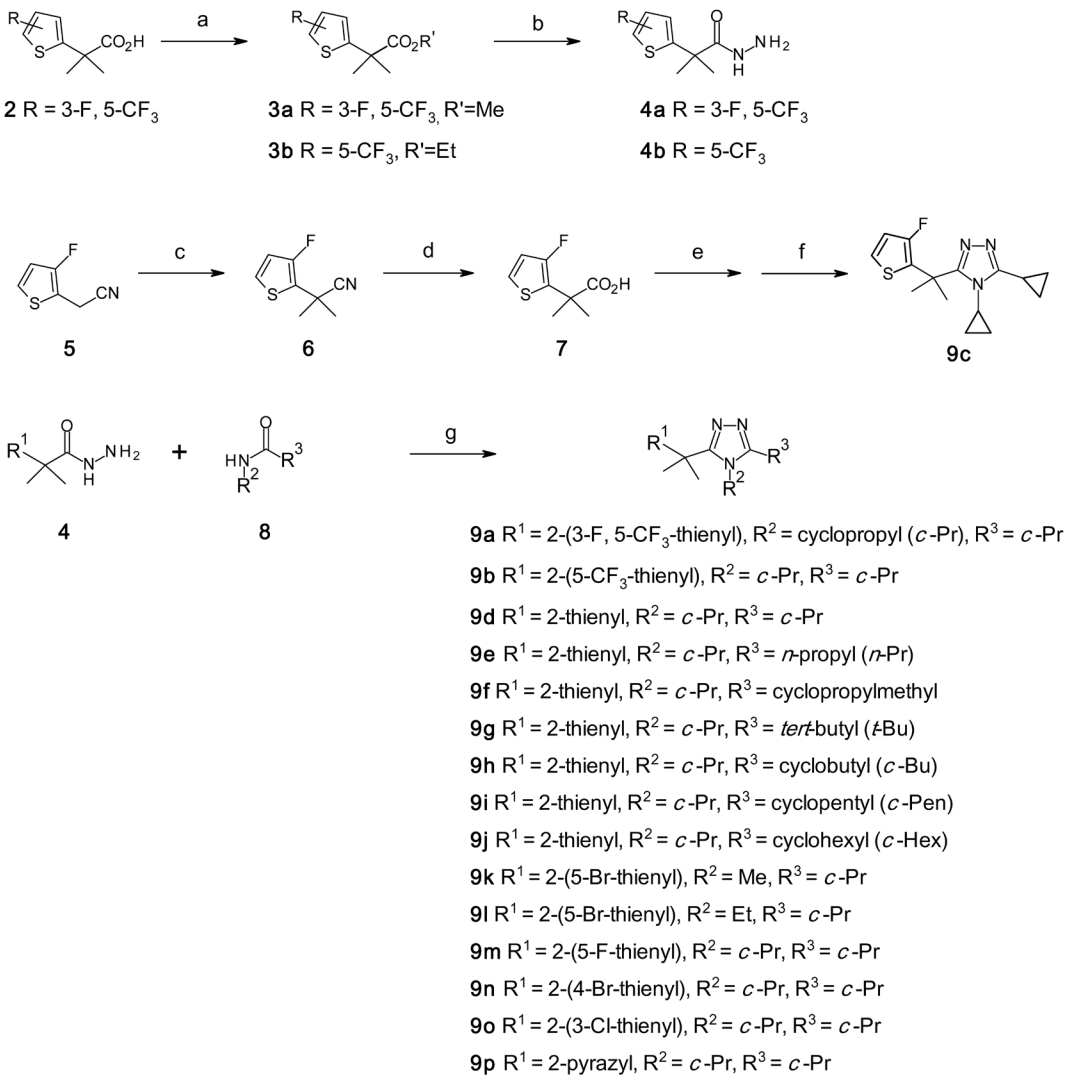
Preparation of **21** is shown in Chart 4. Treatment of **20** with thionyl chloride and subsequent cyclization with formyl hydrazine yielded **21**.

Compounds **25a**–**e** were synthesized as shown in Chart 5. Compound **4d** was condensed with cyclopropanecarbonyl chloride to give **22**, which was cyclized with trifluoromethanesulfonic anhydride to give oxadiazole **23**. Compound **24** was prepared by bromination of **23**, and **24** was reacted with several amines by microwave irradiation to give **25a**–**e**.

Chart 6 shows the synthesis of **29a** and **29b**. Condensation of **26a** and **26b** with cyclopropanecarbonyl chloride followed by cyclization of **27a** and **27b** by treatment with phosphorus oxychloride gave **28a** and **28b**. Reaction of **28a** and **28b** with cyclopropylamine by microwave irradiation yielded **29a** and **29b**.

Biological Evaluation The compounds' enzymatic inhibitory activity against human 11β-HSD1, 11β-HSD2 and mouse 11β-HSD1 was determined by using a homogeneous time-resolved fluorescence method (HTRF®). Truncated recombinant human and mouse 11β-HSD1 proteins (residues 24–292 with His-tag at N-terminal) were produced from *Escherichia coli* (*E. coli*), and full length recombinant human 11β-HSD2 protein was produced from HEK-293. Selected compounds were measured for metabolic stability against mouse and human hepatic CYPs. *C*Log*P* values were calculated using ACD Log*P* prediction software (ACD/Percepta).[17]

The effect of the conversion of the thienyl moiety is shown in Table 1, along with the corresponding data for **9d** for comparison. Pyridine derivatives **29a** and **29b** showed lower inhibitory activity against human 11β-HSD1 than **9d**, and pyrazine derivative **9p** showed a dramatic loss in activity. Replacement with pyrrole (**19**) resulted in a moderate decrease



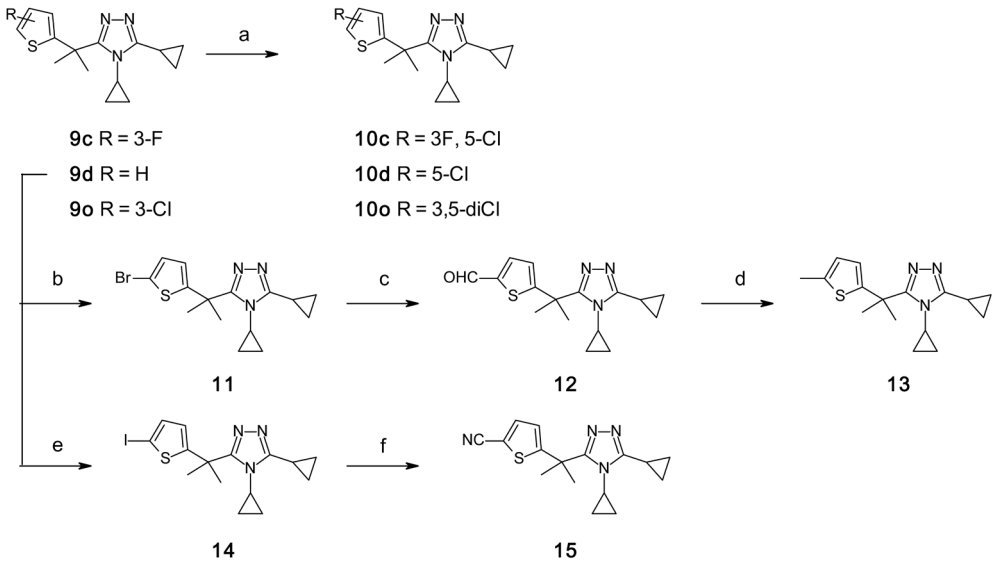
Reagents and conditions: (a) iodomethane, K_2CO_3, DMF (*N*,*N*-dimethylformamide), room temperature (r.t.), 15 h; (b) hydrazine monohydrate, EtOH, 80°C, 24 h; (c) iodomethane, NaH, DMF, r.t., 20 min; (d) KOH, ethylene glycol, 190°C, 2.5 h; (e) hydrazine monohydrate, WSCD (water-soluble carbodiimide)·HCl, HOBt·H_2O (1-hydroxybenzotriazole hydrate), CH_2Cl_2, r.t., overnight; (f) **8a**, methyl trifluoromethanesulfonate, triethylamine (Et_3N), toluene, 60°C, 2 d, 100°C, 2 h; (g) methyl trifluoromethanesulfonate, Et_3N, toluene, 60 to 110°C.

Chart 1. Synthesis of **9a**–**p**

in inhibitory activity against human 11β-HSD1. These results suggest that nitrogen-containing heteroaromatics may be unfavorable at the terminal thiophene ring position. Meanwhile, compound **19** showed improved mouse liver microsomal (MLM) stability. The difference in *C*Log*P* values between **9d** and **19** indicated that the improved MLM stability was due to the decrease in lipophilicity. On the basis of these results, we concluded that the thiophene ring was the most suitable substituent at the R position.

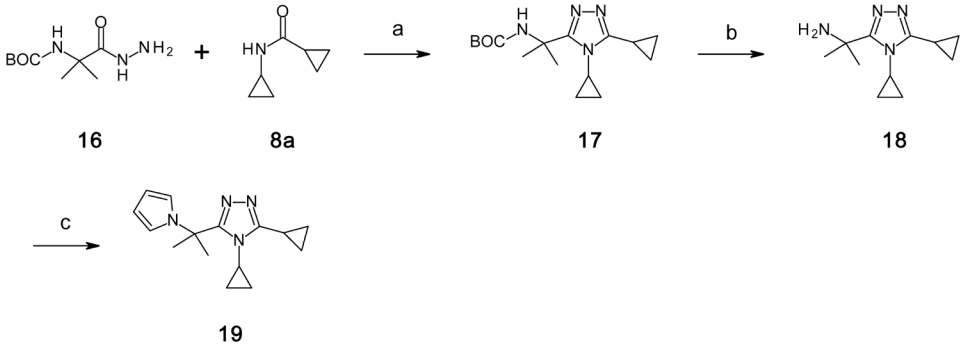
Table 2 summarizes the effects of substituents at the 3-position of the triazole ring. Removal of the 3-position substituent (**21**) resulted in loss of inhibitory activity against human 11β-HSD1, suggesting that substituents are necessary at the 3-position of the triazole ring. Substitution of the cyclopropyl group with an *n*-propyl (**9e**) or cyclopropylmethyl (**9f**) group decreased inhibitory activity against human 11β-HSD1 by about 2-fold. *tert*-Butyl (**9g**), cyclobutyl (**9h**), cyclopentyl (**9i**) and cyclohexyl (**9j**) derivatives showed a slight improvement in inhibitory activity, indicating that bulky substituents are preferable at the 3-position of the triazole ring. Compounds **9e**–**j** showed decreased MLM stability, possibly due to the high lipophilicity compared to **9d**. In contrast, neither group of compounds showed inhibitory activity against human 11β-HSD2. These results indicate that the cyclopropyl group was the most suitable substituent at the 3-position of the triazole ring.

To suppress oxidative metabolism of the thiophene ring, we studied the effects of substituent groups such as electron withdrawing groups on the thiophene ring of compound **9d** (Table 3). Substitution with a halogen atom, such as fluorine (**9m**), chlorine (**10d**) and bromine (**11**), at the 5-position of the thiophene ring increased inhibitory activity against human 11β-HSD1, but was ineffective in improving MLM stability. A 5-methyl derivative (**13**) showed comparable activity to **9d**, but had 2-fold lower MLM stability. Meanwhile, substitution with a 5-cyano group (**15**) resulted in about a 4-fold reduction in inhibitory activity, but 3-fold increase in MLM stability compared to **9d**. This improvement in MLM stability was probably due to a decrease in lipophilicity. Substitution with a 5-trifluoromethyl group (**9b**) resulted in activity equivalent



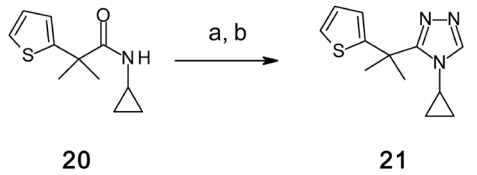
Reagents and conditions: (a) *N*-chlorosuccinimide, acetic acid (AcOH), 50–80°C, 2 h–3 d; (b) *N*-bromosuccinimide, AcOH, 80°C, 2 h; (c) *n*-butyl lithium, *N*,*N*,*N*′,*N*′-tetramethyl ethylenediamine, DMF, tetrahydrofuran (THF), −78°C, 45 min; (d) hydrazine monohydrate, KOH, diethylene glycol, 170°C, 4 h; (e) *N*-iodosuccinimide, AcOH, r.t., overnight; (f) CuCN, pyridine, 115°C, 11.5 h.

Chart 2. Synthesis of **10c**, **10d**, **10o**, **11**, **13** and **15**



Reagents and conditions: (a) methyl trifluoromethanesulfonate, Et_3N, toluene, 60 to 100°C, 3 h; (b) 4 M HCl/EtOAc, EtOH, 50°C, 8 h; (c) 2,5-dimethoxytetrahydrofuran, AcOH, $CHCl_3$, 70°C, 24 h.

Chart 3. Synthesis of **19**

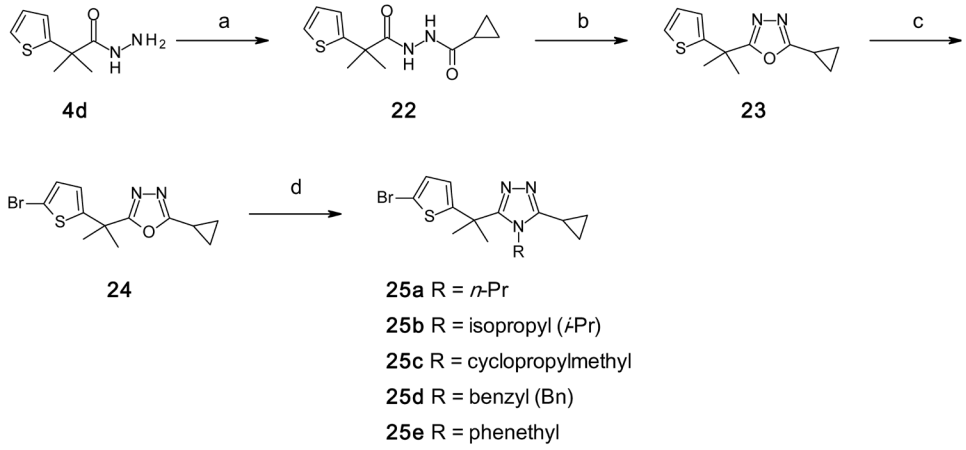


Reagents and conditions: (a) $SOCl_2$, DMF, $CHCl_3$, 60°C, 1 h; (b) formyl hydrazine, toluene, 70°C, 20 h.

Chart 4. Synthesis of **21**

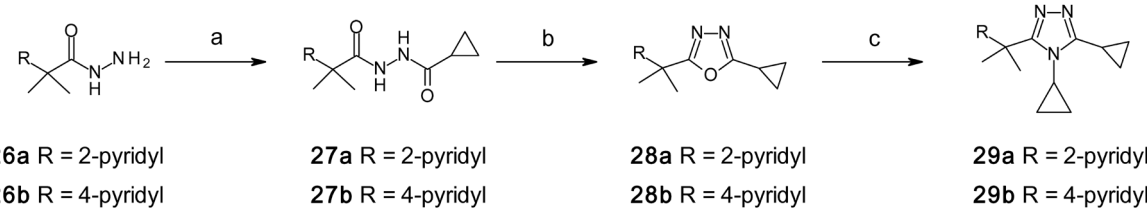
to that of **9d**. Interestingly, compound **9b** had about 3-fold higher MLM stability, despite an increased *C*Log*P* value. This suggests that the improved MLM stability may be due to suppression of oxidative metabolism of the thiophene ring. 3-Fluoro (**9c**), 4-bromo (**9n**) and 3-chloro (**9o**) analogues had increased inhibitory activity against human 11β-HSD1 but no improvement MLM stability. In particular, the 3-chloro derivative showed a significant decrease in MLM stability, indicating that substitution with a chloro group is unfavorable at the 3-position of the thiophene ring. Next, we investigated 3,5-disubstituted derivatives. A 3-fluoro-5-chloro derivative (**10c**) and 3,5-dichloro derivative (**10o**) showed improved inhibitory activity compared to **9d**. However, they had deteriorated MLM stability, especially **10o**, which showed a dramatic decrease similar to **9o**. Interestingly, a 3-fluoro-5-trifluoromethyl derivative (**9a**) was the most potent human 11β-HSD1 inhibitor generated in this series ($IC_{50} = 4.8$ nM), and had enhanced MLM stability (mouse $CL_{int} = 578$ mL/min/kg). Results from compounds **9c**, **10c** and **9a** suggested the fluoro group was the most suitable substituent at the 3-position of the thiophene ring for increasing inhibitory activity against human 11β-HSD1. In addition, results from compounds **9a** and **9b** indicated that substitution of a trifluoromethyl group at the 5-position of the thiophen ring was most effective for improving MLM stability. Neither group of compounds had inhibitory activity against human 11β-HSD2. The above results suggest that the 3-fluoro-5-trifluoromethyl group was the most suitable substituent for the thiophene ring.

The effect of substituents at the 4-position of the triazole ring is shown in Table 4. To improve efficiency for SAR studies, we converted 5-bromothiophene derivatives, which were easier to synthesize than 3-fluoro-5-trifluoromethylthiophene derivatives. The corresponding data for **11** are also shown



Reagents and conditions: (a) cyclopropanecarbonyl chloride, Et_3N, CH_2Cl_2, r.t., overnight; (b) trifluoromethanesulfonic anhydride, pyridine, CH_2Cl_2, r.t., 3 d; (c) *N*-bromosuccinimide, AcOH, r.t.; (d) amine, AcOH, 170°C, 40–60 min (microwave).

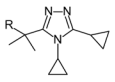
Chart 5. Synthesis of **25a**–**e**



Reagents and conditions: (a) cyclopropanecarbonyl chloride, Et_3N, CH_2Cl_2, 0°C to r.t., 3–14 h; (b) phosphorus oxychloride, reflux, 2–8 h; (c) cyclopropylamine, AcOH, 175°C, 40 min (microwave).

Chart 6. Synthesis of **29a** and **29b**

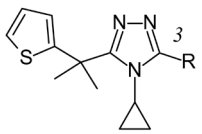
Table 1. Conversion of the Thienyl Moiety



Compound	R	Human 11β-HSD1 IC_{50} (nM)	Human 11β-HSD2 IC_{50} (nM)	Mouse CL_{int} (mL/min/kg)	C Log*P*
9d		23	>10000	1122	2.95
29a[a]		591	NT[b]	NT[b]	2.08
29b[a]		343	NT[b]	NT[b]	2.08
9p		>3000	NT[b]	NT[b]	1.52
19[a]		134	>30000	368	2.39

a) Hydrochloride salt.
b) Not tested.

Table 2. Conversion of the 3-Position Substituent of 1,2,4-Triazole



Compound	R	Human 11*β*-HSD1 IC_{50} (nM)	Human 11*β*-HSD2 IC_{50} (nM)	Mouse CL_{int} (mL/min/kg)	*C*Log*P*
9d	*c*-Pr	23	>10000	1122	2.95
21	H	>3000	NT[b)]	NT[b)]	2.46
9e[a)]	*n*-Pr	51	>10000	1705	3.53
9f	Cyclopropyl methyl	51	>10000	2313	3.38
9g	*t*-Bu	16	>3000	2578	4.05
9h	*c*-Bu	13	>3000	1460	3.42
9i	*c*-Pen	14	>3000	3024	3.99
9j	*c*-Hex	10	>3000	5862	4.37

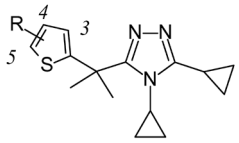
a) Hydrochloride salt. *b*) Not tested.

in Table 4 for comparison. Replacement of the cyclopropyl group with a methyl group (**9k**) resulted in a slight attenuation of inhibitory activity, indicating that a certain bulkiness was required at the 4-position of the thiophen ring. The alkyl derivatives **9l** and **25a**–**c** showed inhibitory activity equivalent to **11**, but **25a**–**c** had decreased MLM stability. Substitution with benzyl (**25d**) and phenethyl (**25e**) groups resulted in a decrease in inhibitory activity against human 11*β*-HSD1, indicating that an alkyl group at the R position may be more suitable than a benzene ring. Neither group of compounds showed inhibitory activity against human 11*β*-HSD2. On the basis of these results, we concluded that a cyclopropyl group was the most suitable substituent at the 4-position of the triazole ring.

Among the aforementioned thiophene derivatives, compound **9a** was chosen for further evaluation. We also evalu-

ated and showed the inhibitory activity of compound **9d** against mouse 11β-HSD1 for comparison. Although compound **9a** showed only moderate inhibitory activity against mouse 11β-HSD1, it had potent inhibitory activity against human 11β-HSD1 and was metabolically stable against human liver microsomes (Table 5). As shown in Fig. 4, we further tested compound **9a** to determine its activity after oral administration. Seven-week-old male diabetic ob/ob mice were treated twice daily with 0.3, 1, 3 and 10 mg/kg of **9a** for four weeks. At 12 h after the final administration, plasma and retroperitoneal adipose tissue samples were collected, and plasma glucose, plasma insulin and corticosterone levels in retroperitoneal adipose tissue were measured. Compound **9a** dose-dependently reduced plasma glucose and insulin levels, and decreased corticosterone levels in adipose tissue. Although compound **9a** showed only moderate inhibitory activity against mouse 11β-HSD1 *in vitro*, its activity was sufficient to lower corticosterone levels in adipose tissue, resulting in a decrease in plasma glucose and insulin levels *in vivo*.

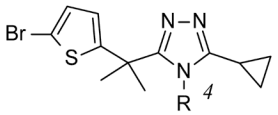
Table 3. Conversion of Substituent on the Thiophene Ring



Compound	R	Human 11β-HSD1 IC_{50} (nM)	Human 11β-HSD2 IC_{50} (nM)	Mouse CL_{int} (mL/min/kg)	$C\log P$
9d	H	23	>10000	1122	2.95
9m[a]	5-F	11	>3000	1461	3.00
10d	5-Cl	15	>10000	1494	3.34
11	5-Br	7.9	>3000	1445	3.54
13	5-Me	19	>10000	1983	3.06
15	5-CN	95	>30000	385	2.49
9b	5-CF_3	24	>10000	423	3.59
9n	4-Br	12	>10000	1674	3.50
9c	3-F	12	>10000	1666	2.90
9o	3-Cl	14	>10000	6791	3.34
10c	3-F, 5-Cl	8.7	>3000	2116	3.06
10o	3,5-diCl	13	>10000	>9066	3.71
9a[a]	3-F, 5-CF_3	4.8	>3000	578[b]	3.53

a) Hydrochloride salt. *b*) Evaluated with free form.

Table 4. Conversion of the 4-Position Substituent of 1,2,4-Triazole



Compound	R	Human 11β-HSD1 IC_{50} (nM)	Human 11β-HSD2 IC_{50} (nM)	Mouse CL_{int} (mL/min/kg)	$C\log P$
11	*c*-Pr	7.9	>3000	1445	3.54
9k[a]	Me	26	NT[b]	NT[b]	3.30
9l[a]	Et	9.6	>3000	1298	3.62
25a[a]	*n*-Pr	8.6	>3000	2771	4.12
25b[a]	*i*-Pr	14	>10000	5746	4.07
25c	Cyclopropyl methyl	12	>10000	4190	4.03
25d[a]	Bn	22	NT[b]	NT[b]	5.16
25e	Phenethyl	43	>10000	NT[b]	5.39

a) Hydrochloride salt. *b*) Not tested.

Table 5. Profile of Compound **9a**

Compound	Human 11β-HSD1 IC_{50} (nM)	Mouse 11β-HSD1 IC_{50} (nM)	Human 11β-HSD2 IC_{50} (nM)	Human CL_{int} (mL/min/kg)	Mouse CL_{int} (mL/min/kg)
9d	23	20	>10000	NT[b]	1122
9a[a]	4.8	189	>3000	27[c]	578[c]

a) Hydrochloride salt. *b*) Not tested. *c*) Evaluated with the free form.

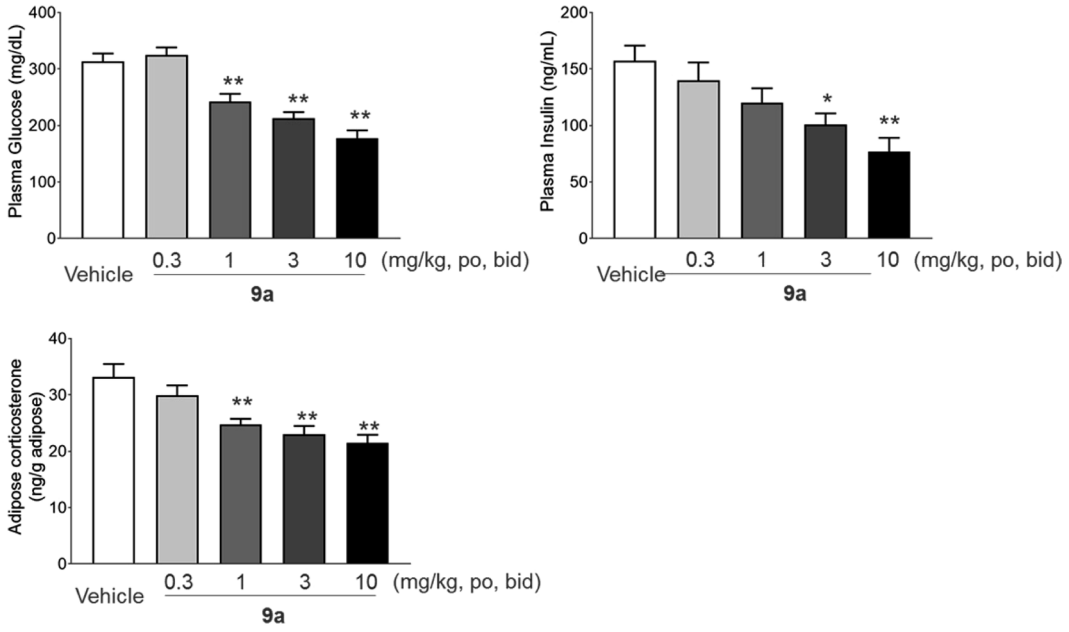


Fig. 4. Effects of Repeated Administration of **9a** in Male ob/ob Mice (0.3–10 mg/kg, Twice Daily for 4 Weeks, $n = 7$–8)

Values are presented as the mean ± standard error (S.E.). $*p < 0.05$, $**p < 0.01$ *versus* vehicle-treated group, using the Dunnett's multiple comparisons test.

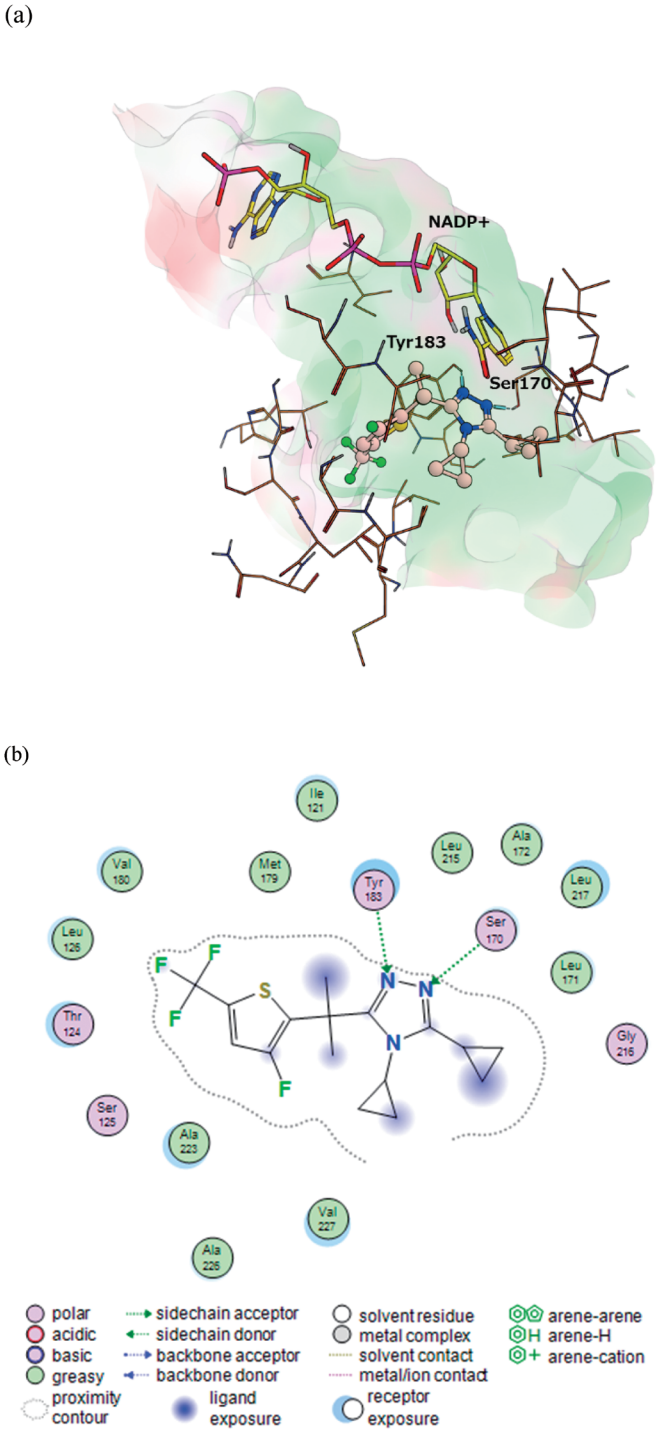


Fig. 5. (a) Molecular Modeling of the Interaction between **9a** (as a Free Base) and Human 11β-HSD1

Best docking solution (lowest binding energy) was calculated using GOLD version 5.5.1[19–21] for compound **9a** (ball and stick diagram: blue is nitrogen, yellow is sulfur, green is fluorine and pale pink is carbon) when surrounded by human 11β-HSD1 active site residues. (b) Two-dimensional diagram prepared using the ligand interactions application in MOE.[22]

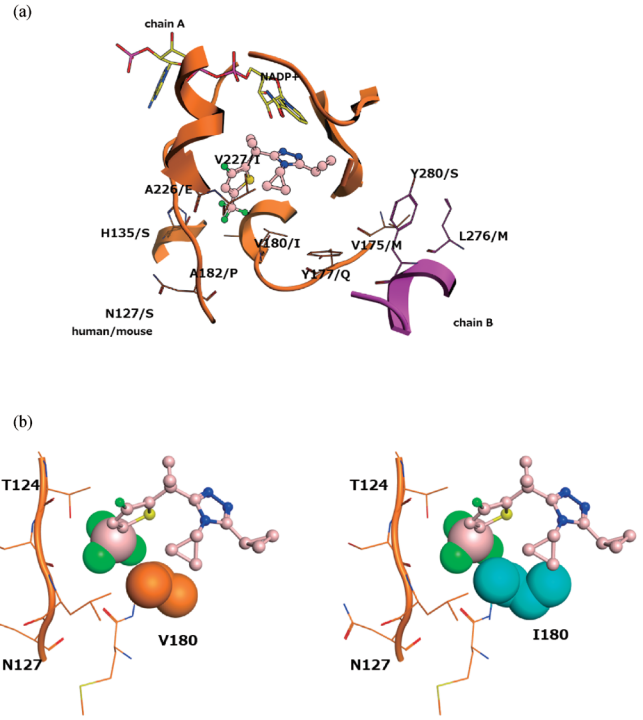


Fig. 6. (a) Molecular Modeling of the Interaction between Compound **9a** (Ball and Stick Diagram: Blue Is Nitrogen, Yellow Is Sulfur, Green Is Fluorine and Pale Pink Is Carbon) and Human 11β-HSD1

The depicted residues are those that differ between human and mouse 11β-HSD1. For example, Val180 in human, Ile in mouse. (b) Simplified view of (a) focusing on the difference between human Val180 and mouse Ile180. Atoms relevant for the discrepancy in interactions are shown in Space-filling spheres. Mouse Ile180 is colored cyan.

Finally, to explore the reason behind the very potent inhibitory activity of **9a** against human 11β-HSD1, we performed a docking analysis of the interaction between **9a** and human 11β-HSD1. The human 11β-HSD1 model was created based on the crystal structure of human 11β-HSD1 in a complex with a triazole inhibitor (PDB code 3D5Q).[18] Compound **9a** was docked using GOLD version 5.5.1,[19–21] as shown in Fig. 5. The docking study suggested that **9a** was positioned in the steroid substrate binding site and that the nitrogen atom at the 1-position of the triazole ring interacted with Tyr183, while the nitrogen atom at the 2-position of the triazole ring interacted with Ser170. In addition, this model indicated that the thiophene moiety of **9a** fit into the hydrophobic pocket of human 11β-HSD1. These findings may form the basis for the potent inhibitory activity of **9a** against human 11β-HSD1. To analyze the species difference in the *in vitro* activity of **9a** against human and mouse 11β-HSD1, we also examined the sequence homology of 11β-HSD1 in humans and mice. We found differences in several amino acid residues around the ligand binding site of 11β-HSD1 between humans and mice, as shown Fig. 6a. Docking analysis of the interaction between **9a** and human 11β-HSD1 suggests that the trifluoromethyl moiety of compound **9a** fit into the hydrophobic pocket, which contained Val180. The corresponding residue to Val180 in mice was isoleucine (Ile), which is more sterically bulky than Val as shown in Fig. 6b. Therefore the trifluoromethyl moiety of **9a** cannot exist at this position in mouse 11β-HSD1 due to steric hindrance, and this may be an explanation for the attenuated inhibitory activity of **9a** against mouse 11β-HSD1 compared to human 11β-HSD1.

Conclusion

In our investigation of novel 11β-HSD1 inhibitors, optimization of **9d** resulted in the discovery of compound **9a**, 3,4-dicyclopropyl-5-{2-[3-fluoro-5-(trifluoromethyl)-thiophen-2-yl]propan-2-yl}-4*H*-1,2,4-triazole monohydrochlo-

ride, which showed potent and selective inhibitory activity against human 11β-HSD1, and good human and mouse liver microsomal stability. Oral administration of compound **9a** reduced corticosterone levels in adipose tissue, resulting in reduced plasma glucose and insulin levels in diabetic ob/ob mice. Therefore, **9a** may be a new type of insulin sensitizer with the potential to be an effective treatment for type II diabetes.

Experimental

Chemistry Starting materials and reagents are commercially available. ^{1}H-NMR spectra were recorded on Varian 300-MR, Varian 400-MR, Varian VNS-400 or JEOL LAMBDA and chemical shifts were expressed in δ (ppm) values with trimethylsilane as an internal reference (s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, q = quartet, m = multiplet, br = broad and brs = broad singlet). MS were recorded on JEOL JMS-LX2000, Waters ZQ2000, Thermo Electron TRACE DSQ, Thermo Electron LCQ Advantage or Thermo Scientific Exactive Plus. Elemental analyses were performed with Elementar Vario EL III (C, H, N) and DIONEX ICS-5000 (S, halogen) instruments, and results were within $\pm$0.4% of theoretical values. All reactions were carried out using commercially available reagents and solvents without further purification. The following abbreviations are used: AcOH, acetic acid; DMF, *N*,*N*-dimethylformamide; DMSO, *N*,*N*-dimethylsulfoxide; Et_2O, diethyl ether; EtOAc, ethyl acetate; EtOH, ethanol; Et_3N, triethylamine; HOBt, 1-hydroxybenzotriazole; MeOH, methanol; THF, tetrahydrofuran; WSCD, water-soluble carbodiimide; CAS No., Chemical Abstracts Service Registry Number.

Methyl 2-[3-Fluoro-5-(trifluoromethyl)thiophen-2-yl]-2-methylpropanoate (3a) Dipotassium carbonate (6.20 g, 44.9 mmol) and iodomethane (2.27 mL, 36.5 mmol) were added to an ice-cooled solution of 2-[3-fluoro-5-(trifluoromethyl)-thiophen-2-yl]-2-methyl propanoic acid (**2**, 7.67 g, 29.9 mmol, CAS No.; 950604-93-0) in DMF (30 mL), and the mixture was stirred at r.t. for 15 h. The reaction mixture was diluted with water (60 mL) and extracted with Et_2O. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (hexane–Et_2O) to give the title compound **3a** (6.81 g, 25.2 mmol, 84%) as a pale yellow syrup. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.65 (6H, s), 3.73 (3H, s), 7.12–7.13 (1H, m).

2-[3-Fluoro-5-(trifluoromethyl)thiophen-2-yl]-2-methylpropanehydrazide (4a) Hydrazine monohydrate (1.0 mL, 21 mmol) was added to a solution of **3a** (322 mg, 1.19 mmol) in EtOH (2 mL) and the mixture was stirred at 80°C for 24 h. The reaction mixture was concentrated *in vacuo*. The resulting residue was diluted with saturated aqueous sodium hydrogen carbonate solution and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH) to give the title compound **4a** (286 mg, 1.06 mmol, 89%) as a pale yellow syrup. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.66 (6H, s), 2.10–3.90 (2H, br), 6.80–7.04 (1H, m), 7.17 (1H, s). Chemical ionization mass spectrometry (CI-MS) *m/z*: 271 $[M+H]^+$.

2-Methyl-2-[5-(trifluoromethyl)thiophen-2-yl]propanehydrazide (4b) The title compound was prepared in a similar manner to that described for **4a** from ethyl 2-methyl-2-[5-(trifluoromethyl)thiophen-2-yl]propanoate (**3b**, 1.51 g, 5.67 mmol, CAS No.; 950604-90-7) at 89% yield (1.27 g, 5.03 mmol). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.56 (6H, s), 4.27 (2H, brs), 7.04–7.07 (1H, m), 7.51–7.55 (1H, m), 9.09 (1H, brs). Electrospray ionization (ESI)-MS *m/z*: 253 $[M+H]^+$.

2-(3-Fluorothiophen-2-yl)-2-methylpropanenitrile (6) A mixture of iodomethane (2.14 mL, 34.4 mmol) and (3-fluorothiophen-2-yl)acetonitrile (**5**, 1.62 g, 11.5 mmol, CAS No.; 950604-64-5) in DMF (15 mL) was slowly added to an ice-cooled mixture of sodium hydride (NaH) (60% in mineral oil; 1.19 g, 29.8 mmol) in DMF (25 mL), and the mixture was stirred at r.t. for 20 min. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (EtOAc–hexane) to give the title compound **6** (1.75 g, 10.3 mmol, 90%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.81 (6H, s), 6.81 (1H, d, J = 5.6 Hz), 7.08–7.13 (1H, m).

2-(3-Fluorothiophen-2-yl)-2-methylpropanoic Acid (7) Potassium hydroxide (1.74 g, 31.0 mmol) was added to a solution of **6** (1.75 g, 10.3 mmol) in ethylene glycol (17.5 mL) and the mixture was stirred at 190°C for 2.5 h. The reaction mixture was cooled to r.t. and water was added to the mixture. The mixture was washed with Et_2O and the aqueous layer was cooled in an ice bath, and conc. hydrochloric acid (*ca.* 30 mL) was added. The mixture was extracted with Et_2O and washed with 1 M hydrochloric acid and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, then dried to give the title compound **7** (1.91 g, 10.1 mmol, 98%) as an ochre solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.67 (6H, s), 6.76 (1H, d, J = 5.6 Hz), 7.04 (1H, dd, J = 3.7, 5.6 Hz).

3,4-Dicyclopropyl-5-[2-(3-fluorothiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (9c) WSCD·HCl (2.41 g, 12.6 mmol) was added to an ice-cooled solution of **7** (2.15 g, 11.4 mmol), hydrazine monohydrate (1.11 mL, 22.9 mmol) and HOBt·H_2O (1.84 g, 12.0 mmol) in CH_2Cl_2 (21.5 mL), and the mixture was stirred at r.t. overnight. WSCD·HCl (240 mg, 1.25 mmol) was added and the reaction mixture was stirred at r.t. for 2 h. Saturated aqueous sodium hydrogen carbonate solution was added and the reaction mixture was extracted with $CHCl_3$, and washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, then dried to give a pale yellow solid (2.10 g, 10.4 mmol). A mixture of *N*-cyclopropylcyclopropanecarboxamide (**8a**, 1.56 g, 12.5 mmol) and methyl trifluoromethanesulfonate (1.59 mL, 13.5 mmol) was stirred at 60°C for 30 min. Toluene (26 mL), Et_3N (1.88 mL, 13.5 mmol) and the obtained solid described above (2.10 g, 10.4 mmol) were added and the mixture was stirred at 60°C for 2 d and 100°C for 2 h. $CHCl_3$ and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the organic layer was separated. The organic layer was washed with brine, dried and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (EtOAc–MeOH) to give a pale yellow solid. $CHCl_3$ was added to the resulting solid and the precipitated solid was filtered off. Diisopropyl ether was added to the resulting residue and solidified. The obtained solid was washed with a solvent comprising hexane, EtOAc and Et_2O, followed

by washing with diisopropyl ether to give the title compound **9c** (878 mg, 3.01 mmol, 26%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.79–1.05 (6H, m), 1.15–1.22 (2H, m), 1.88–2.00 (1H, m), 1.93 (6H, s), 2.70–2.79 (1H, m), 6.71 (1H, d, J = 5.6 Hz), 7.01–7.05 (1H, m). ESI-MS m/z: 292 $[M+H]^+$. High resolution (HR)-MS (ESI) m/z: 292.1276 $[M+H]^+$ (Calcd for $C_{15}H_{19}N_3FS$: 292.1278).

3,4-Dicyclopropyl-5-{2-[3-fluoro-5-(trifluoromethyl)thiophen-2-yl]propan-2-yl}-4*H*-1,2,4-triazole Monohydrochloride (9a) A mixture of **8a** (220 mg, 1.76 mmol) and methyl trifluoromethanesulfonate (200 μL, 1.77 mmol) was stirred at 60°C for 30 min and diluted with toluene (4 mL). A solution of Et_3N (500 μL, 3.59 mmol) and **4a** (279 mg, 1.03 mmol) in toluene (6 mL) was added and the mixture was stirred at 60°C for 24 h, 90°C for 9 h and 110°C for 15 h. The reaction mixture was concentrated *in vacuo*, diluted with water (20 mL) and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH) to give a colorless syrup. The syrup was diluted with EtOAc (5 mL), and 4 M HCl solution in EtOAc (0.3 mL, 1.2 mmol) was added to the mixture. The reaction mixture was stirred at r.t. for 30 min and concentrated *in vacuo*. The resulting solid was washed with diisopropyl ether, collected by filtration and dried to give the title compound **9a** (166 mg, 0.419 mmol, 41%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.78–0.84 (2H, m), 0.98–1.05 (2H, m), 1.14–1.20 (4H, m), 1.91 (6H, s), 2.19–2.28 (1H, m), 3.15–3.22 (1H, m), 7.80 (1H, d, J = 1.0 Hz). FAB-MS m/z: 360 $[M+H]^+$. HR-MS (ESI) m/z: 360.1151 $[M+H]^+$ (Calcd for $C_{16}H_{18}N_3F_4S$: 360.1152). *Anal.* Calcd for $C_{16}H_{17}F_4N_3S$.HCl: C, 48.55; H, 4.58; N, 10.62; S, 8.10; Cl, 8.96; F, 19.20. Found: C, 48.95; H, 4.82; N, 10.60; S, 8.06; Cl, 8.85; F, 19.10.

3,4-Dicyclopropyl-5-{2-[5-(trifluoromethyl)thiophen-2-yl]-propan-2-yl}-4*H*-1,2,4-triazole (9b) The title compound was prepared in a similar manner to that described for **9a**, except for the salt-forming procedure, from **4b** (1.00 g, 3.96 mmol) and **8a** (843 mg, 6.73 mmol) at 34% yield (456 mg, 1.34 mmol). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.48–0.53 (2H, m), 0.88–1.02 (6H, m), 1.89 (6H, s), 2.00–2.07 (1H, m), 3.02–3.09 (1H, m), 6.92–6.95 (1H, m), 7.55–7.58 (1H, m). ESI-MS m/z: 342 $[M+H]^+$. HR-MS (ESI) m/z: 342.1243 $[M+H]^+$ (Calcd for $C_{16}H_{19}N_3F_3S$: 342.1246).

3,4-Dicyclopropyl-5-[2-(thiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (9d) The title compound was prepared in a similar manner to that described for **9a**, except for the salt-forming procedure, from 2-methyl-2-(thiophen-2-yl)-propanehydrazide (**4d**, 1.00 g, 5.43 mmol, CAS No.; 880166-34-7) and **8a** (1.02 g, 8.14 mmol) at 29% yield (425 mg, 1.55 mmol) as a solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.45–0.50 (2H, m), 0.83–0.89 (2H, m), 0.92–1.03 (4H, m), 1.85 (6H, s), 2.01–2.08 (1H, m), 2.96–3.03 (1H, m), 6.81 (1H, dd, J = 1.2, 3.6 Hz), 6.95 (1H, dd, J = 3.5, 5.0 Hz), 7.39 (1H, dd, J = 1.2, 5.2 Hz). FAB-MS m/z: 274 $[M+H]^+$. HR-MS (ESI) m/z: 274.1366 $[M+H]^+$ (Calcd for $C_{15}H_{20}N_3S$: 274.1372).

4-Cyclopropyl-3-propyl-5-[2-(thiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole Monohydrochloride (9e) The title compound was prepared in a similar manner to that described for **9a** from **4d** (449 mg, 2.44 mmol) and *N*-cyclopropylbutanamide (310 mg, 2.44 mmol) at 11% yield (80 mg, 0.26 mmol) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.72–0.78 (2H, m), 1.01–1.11 (5H, m), 1.87–2.03 (2H, m), 2.00 (6H, s), 2.95–3.02 (1H, m), 3.10–3.18 (2H, m), 6.80 (1H, dd, J = 1.2, 3.6 Hz), 6.97 (1H, dd, J = 3.5, 5.3 Hz), 7.23–7.28 (1H, m). FAB-MS m/z: 276 $[M+H]^+$. HR-MS (ESI) m/z: 276.1524 $[M+H]^+$ (Calcd for $C_{15}H_{22}N_3S$: 276.1529).

4-Cyclopropyl-3-(cyclopropylmethyl)-5-[2-(thiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (9f) The title compound was prepared in a similar manner to that described for **9a**, except for the salt-forming procedure, from **4d** (883 mg, 4.79 mmol) and *N*,2-dicyclopropylacetamide (1.00 g, 7.18 mmol) at 51% yield (709 mg, 2.47 mmol) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.23–0.29 (2H, m), 0.48–0.60 (4H, m), 0.80–0.87 (2H, m), 1.15–1.24 (1H, m), 1.96 (6H, s), 2.71–2.78 (3H, m), 6.73 (1H, dd, J = 1.2, 3.6 Hz), 6.90 (1H, dd, J = 3.5, 5.1 Hz), 7.15 (1H, dd, J = 1.1, 5.1 Hz). FAB-MS m/z: 288 $[M+H]^+$. HR-MS (ESI) m/z: 288.1527 $[M+H]^+$ (Calcd for $C_{16}H_{22}N_3S$: 288.1529).

3-*tert*-Butyl-4-cyclopropyl-5-[2-(thiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (9g) The title compound was prepared in a similar manner to that described for **9a**, except for the salt-forming procedure, from **4d** (814 mg, 4.42 mmol) and *N*-cyclopropyl-2,2-dimethylpropanamide (2.50 g, 17.7 mmol) at 6.5% yield (83.0 mg, 0.287 mmol) as a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.44–0.51 (2H, m), 0.86–0.94 (2H, m), 1.44 (9H, s), 1.85 (6H, s), 3.09–3.19 (1H, m), 6.76 (1H, dd, J = 1.1, 3.5 Hz), 6.95 (1H, dd, J = 3.5, 5.1 Hz), 7.37 (1H, dd, J = 1.1, 5.1 Hz). ESI-MS m/z: 290 $[M+H]^+$. HR-MS (ESI) m/z: 290.1690 $[M+H]^+$ (Calcd for $C_{16}H_{24}N_3S$: 290.1685).

3-Cyclobutyl-4-cyclopropyl-5-[2-(thiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (9h) The title compound was prepared in a similar manner to that described for **9a**, except for the salt-forming procedure, from **4d** (1.32 g, 7.18 mmol) and *N*-cyclopropylcyclobutanecarboxamide (1.00 g, 7.18 mmol) at 29% yield (590 mg, 2.05 mmol) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.27–0.33 (2H, m), 0.74–0.81 (2H, m), 1.80–1.92 (1H, m), 1.85 (6H, s), 1.95–2.08 (1H, m), 2.25–2.41 (4H, m), 2.80–2.87 (1H, m) 3.63–3.73 (1H, m) 6.77 (1H, dd, J = 1.1, 3.6 Hz), 6.94 (1H, dd, J = 3.5, 5.1 Hz), 7.37 (1H, dd, J = 1.1, 5.1 Hz). FAB-MS m/z: 288 $[M+H]^+$. HR-MS (ESI) m/z: 288.1534 $[M+H]^+$ (Calcd for $C_{16}H_{22}N_3S$: 288.1529).

3-Cyclopentyl-4-cyclopropyl-5-[2-(thiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (9i) The title compound was prepared in a similar manner to that described for **9a**, except for the salt-forming procedure, from **4d** (1.00 g, 5.43 mmol) and *N*-cyclopropylcyclopentanecarboxamide (1.25 g, 8.14 mmol) at 37% yield (611 mg, 2.03 mmol) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.51–0.57 (2H, m), 0.84–0.91 (2H, m), 1.59–1.72 (2H, m), 1.84–2.15 (6H, m), 1.96 (6H, s), 2.71–2.78 (1H, m), 3.21–3.32 (1H, m), 6.72–6.75 (1H, m), 6.91 (1H, dd, J = 3.8, 4.8 Hz), 7.15–7.19 (1H, m). ESI-MS m/z: 302 $[M+H]^+$. HR-MS (ESI) m/z: 302.1682 $[M+H]^+$ (Calcd for $C_{17}H_{24}N_3S$: 302.1685).

3-Cyclohexyl-4-cyclopropyl-5-[2-(thiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (9j) The title compound was prepared in a similar manner to that described for **9a**, except for the salt-forming procedure, from **4d** (1.00 g, 5.43 mmol) and *N*-cyclopropylcyclohexanecarboxamide (1.18 g, 7.06 mmol) at 40% yield (687 mg, 2.18 mmol) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.50–0.55 (2H, m), 0.84–0.90 (2H, m), 1.27–1.43 (3H, m), 1.71–2.01 (7H, m), 1.95 (6H, s), 2.68–2.76 (1H, m), 2.82–2.92 (1H, m), 6.73 (1H, dd, J = 1.2, 3.6 Hz), 6.90

(1H, dd, $J = 3.6$, 5.1 Hz), 7.16 (1H, dd, $J = 1.1$, 5.1 Hz). ESI-MS m/z: 316 $[M + H]^+$. HR-MS (ESI) m/z: 316.1843 $[M + H]^+$ (Calcd for $C_{18}H_{26}N_3S$: 316.1842).

3-[2-(5-Bromothiophen-2-yl)propan-2-yl]-5-cyclopropyl-4-methyl-4*H*-1,2,4-triazole Monohydrochloride (9k) The title compound was prepared in a similar manner to that described for **9a** from 2-(5-bromothiophen-2-yl)-2-methylpropanehydrazide (690 mg, 2.62 mmol, CAS No.; 950604-87-2) and *N*-methylcyclopropanecarboxamide (390 mg, 3.93 mmol) at 13% yield (127 mg, 0.350 mmol) as a solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.16–1.21 (4H, m), 1.78 (6H, s), 2.13–2.21 (1H, m), 3.45 (3H, s), 6.88 (1H, d, $J = 3.9$ Hz), 7.16 (1H, d, $J = 3.9$ Hz). ESI-MS m/z: 326 $[M + H]^+$. HR-MS (ESI) m/z: 326.0324 $[M + H]^+$ (Calcd for $C_{13}H_{17}N_3BrS$: 326.0321).

3-[2-(5-Bromothiophen-2-yl)propan-2-yl]-5-cyclopropyl-4-ethyl-4*H*-1,2,4-triazole Monohydrochloride (9l) The title compound was prepared in a similar manner to that described for **9a** from 2-(5-bromothiophen-2-yl)-2-methylpropanehydrazide (500 mg, 1.90 mmol) and *N*-ethylcyclopropanecarboxamide (323 mg, 2.85 mmol) at 16% yield (111 mg, 0.295 mmol) as a solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.20 (3H, t, $J = 7.2$ Hz), 1.39–1.46 (2H, m), 1.87–1.94 (3H, m), 1.89 (6H, s), 4.02 (2H, q, $J = 7.3$ Hz), 6.67 (1H, d, $J = 3.8$ Hz), 6.97 (1H, d, $J = 3.8$ Hz). ESI-MS m/z: 340 $[M + H]^+$. HR-MS (ESI) m/z: 340.0479 $[M + H]^+$ (Calcd for $C_{14}H_{19}N_3BrS$: 340.0478).

3,4-Dicyclopropyl-5-[2-(5-fluorothiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole Monohydrochloride (9m) The title compound was prepared in a similar manner to that described for **9a** from 2-(5-fluorothiophen-2-yl)-2-methylpropanehydrazide (515 mg, 2.55 mmol CAS No.; 950604-98-5) and **8a** (637 mg, 5.09 mmol) at 19% yield (161 mg, 0.491 mmol) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.74–0.80 (2H, m), 1.00–1.07 (2H, m), 1.19–1.31 (4H, m), 1.85 (6H, s), 2.23–2.32 (1H, m), 3.21–3.28 (1H, m), 6.60–6.63 (2H., m). FAB-MS m/z: 292 $[M + H]^+$. HR-MS (ESI) m/z: 292.1276 $[M + H]^+$ (Calcd for $C_{15}H_{19}N_3FS$: 292.1278).

3-[2-(4-Bromothiophen-2-yl)propan-2-yl]-4,5-dicyclopropyl-4*H*-1,2,4-triazole (9n) The title compound was prepared in a similar manner to that described for **9a**, except for the salt-forming procedure, from 2-(4-bromothiophen-2-yl)-2-methylpropanehydrazide (7.4 g, 28 mmol, CAS No.; 950604-78-1) and **8a** (4.58 g, 36.6 mmol) at 41% yield (4.07 g, 11.6 mmol) as a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.47–0.55 (2H, m), 0.87–1.02 (6H, m), 1.84 (6H, s), 1.98–2.08 (1H, m), 2.98–3.08 (1H, m), 6.88 (1H, d, $J = 1.5$ Hz), 7.54 (1H, d, $J = 1.4$ Hz). ESI-MS m/z: 352 $[M + H]^+$. HR-MS (ESI) m/z: 352.0478 $[M + H]^+$ (Calcd for $C_{15}H_{19}N_3BrS$: 352.0478).

3-[2-(3-Chlorothiophen-2-yl)propan-2-yl]-4,5-dicyclopropyl-4*H*-1,2,4-triazole (9o) The title compound was prepared in a similar manner to that described for **9a**, except for the salt-forming procedure, from 2-(3-chlorothiophen-2-yl)-2-methylpropanehydrazide (8.32 g, 38.0 mmol, CAS No.; 950604-75-8) and **8a** (5.71 g, 45.7 mmol) at 18% yield (2.10 g, 6.82 mmol) as a pale yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.76–0.93 (4H, m), 0.95–1.04 (2H, m), 1.12–1.19 (2H, m), 1.85–1.97 (1H, m), 1.93 (6H, s), 2.48–2.58 (1H, m), 6.85 (1H, d, $J = 5.3$ Hz), 7.16 (1H, d, $J = 5.4$ Hz). ESI-MS m/z: 308 $[M + H]^+$. HR-MS (ESI) m/z: 308.0983 $[M + H]^+$ (Calcd for $C_{15}H_{19}N_3ClS$: 308.0983).

2-[2-(4,5-Dicyclopropyl-4*H*-1,2,4-triazol-3-yl)propan-2-yl]pyrazine (9p) The title compound was prepared in a similar manner to that described for **9a**, except for the salt-forming procedure, from 2-methyl-2-(pyrazin-2-yl)-propanehydrazide (800 mg, 4.44 mmol, CAS No.; 950604-81-6) and **8a** (885 mg, 7.07 mmol) at 43% yield (513 mg, 1.90 mmol) as a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.28–0.35 (2H, m), 0.61–0.69 (2H, m), 0.89–1.00 (4H, m), 1.82 (6H, s), 1.94–2.05 (1H, m), 2.71–2.80 (1H, m), 8.55–8.57 (2H, m), 8.59–8.61 (1H, m). ESI-MS m/z: 270 $[M + H]^+$. HR-MS (ESI) m/z: 270.1712 $[M + H]^+$ (Calcd for $C_{15}H_{20}N_5$: 270.1713).

3-[2-(5-Chlorothiophen-2-yl)propan-2-yl]-4,5-dicyclopropyl-4*H*-1,2,4-triazole (10d) *N*-Chlorosuccinimide (51.3 mg, 0.384 mmol) was added to a solution of **9d** (100 mg, 0.366 mmol) in AcOH (3 mL) and the mixture was stirred at 80°C for 2 h. The reaction mixture was concentrated *in vacuo* and diluted with $CHCl_3$. One molecule aqueous sodium hydroxide solution was added and the reaction mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH). The obtained product was washed with Et_2O, and dried to give the title compound **10d** (66.7 mg, 0.217 mmol, 59%) as a light pink solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.56–0.61 (2H, m), 0.90–1.01 (6H, m), 1.83 (6H, s), 1.98–2.07 (1H, m), 3.00–3.07 (1H, m), 6.70 (1H, d, $J = 3.7$ Hz), 6.96 (1H, d, $J = 3.9$ Hz). FAB-MS m/z: 308 $[M + H]^+$. HR-MS (ESI) m/z: 308.0984 $[M + H]^+$ (Calcd for $C_{15}H_{19}N_3ClS$: 308.0983).

3-[2-(5-Chloro-3-fluorothiophen-2-yl)propan-2-yl]-4,5-dicyclopropyl-4*H*-1,2,4-triazole (10c) The title compound was prepared in a similar manner to that described for **10d** from **9c** (150 mg, 0.515 mmol) at 63% yield (106 mg, 0.325 mmol) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87–0.96 (2H, m), 0.97–1.07 (4H, m), 1.14–1.22 (2H, m), 1.85–1.99 (1H, m), 1.91 (6H, s), 2.77–2.88 (1H, m), 6.61 (1H, s). ESI-MS m/z: 326 $[M + H]^+$. HR-MS (ESI) m/z: 326.0888 $[M + H]^+$ (Calcd for $C_{15}H_{18}N_3ClFS$: 326.0889).

3,4-Dicyclopropyl-5-[2-(3,5-dichlorothiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (10o) The title compound was prepared in a similar manner to that described for **10d** from **9o** (100 mg, 0.325 mmol) at 51% yield (56.8 mg, 0.166 mmol) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89–1.05 (6H, m), 1.13–1.20 (2H, m), 1.87–1.98 (1H, m), 1.90 (6H, s), 2.57–2.66 (1H, m), 6.71 (1H, s). ESI-MS m/z: 342 $[M + H]^+$. HR-MS (ESI) m/z: 342.0596 $[M + H]^+$ (Calcd for $C_{15}H_{18}N_3Cl_2S$: 342.0593).

3-[2-(5-Bromothiophen-2-yl)propan-2-yl]-4,5-dicyclopropyl-4*H*-1,2,4-triazole (11) *N*-Bromosuccinimide (68 mg, 0.38 mmol) was added to a solution of **9d** (100 mg, 0.366 mmol) in AcOH (3 mL) and the mixture was stirred at 80°C for 2 h. The reaction mixture was concentrated *in vacuo* and diluted with $CHCl_3$. One molar aqueous sodium hydroxide solution was added and the reaction mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH). The obtained product was washed with Et_2O, and dried to give the title compound **11** (72.8 mg, 0.207 mmol, 57%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.54–0.60 (2H, m), 0.89–1.01 (6H, m), 1.83 (6H, s), 1.99–2.07 (1H, m), 3.00–3.06 (1H, m), 6.67 (1H, d, $J = 3.6$ Hz), 7.06 (1H, d, $J = 3.9$ Hz). FAB-MS m/z: 354 $[M + H]^+$. HR-MS (ESI) m/z:

352.0477 $[M+H]^+$ (Calcd for $C_{15}H_{19}N_3BrS$: 352.0478).

5-[2-(4,5-Dicyclopropyl-4*H*-1,2,4-triazol-3-yl)propan-2-yl]thiophene-2-carbaldehyde (12) *N*,*N*,*N*′,*N*′-Tetramethyl ethylenediamine (1.64 mL, 10.9 mmol) was added to a solution of **11** (1.92 g, 5.45 mmol) in THF (40 mL) and the mixture was cooled to −78°C. *n*-Butyl lithium (1.6 M in hexane; 5.1 mL, 8.2 mmol) was added and the mixture was stirred at −78°C for 45 min. A solution of DMF (1.27 mL, 16.4 mmol) in THF (10 mL) was added and the mixture was stirred at −78°C for 30 min. The reaction mixture was poured into water and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH). The obtained product was washed with diisopropyl ether, and dried to give the title compound **12** (950 mg, 3.15 mmol, 58%) as a pale yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.47–0.53 (2H, m), 0.86–1.01 (6H, m), 1.89 (6H, s), 1.99–2.07 (1H, m), 3.00–3.07 (1H, m), 7.03 (1H, d, $J=3.9$ Hz), 7.89 (1H, d, $J=3.9$ Hz), 9.85 (1H, s). ESI-MS *m*/*z*: 302 $[M+H]^+$.

3,4-Dicyclopropyl-5-[2-(5-methylthiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (13) A mixture of **12** (300 mg, 0.995 mmol), diethylene glycol (10 mL) and hydrazine monohydrate (121 μL, 2.49 mmol) was stirred at 130°C for 3 h. Potassium hydroxide (140 mg, 2.49 mmol) was added and the mixture was stirred at 170°C for 4 h. The reaction mixture was cooled and water was added. The reaction mixture was extracted with $CHCl_3$ and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH). The obtained product was washed with diisopropyl ether and dried to give the title compound **13** (54.9 mg, 0.191 mmol, 19%) as a pale yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.52–0.57 (2H, m), 0.85–1.01 (6H, m), 1.80 (6H, s), 1.98–2.06 (1H, m), 2.36 (3H, s), 2.95–3.01 (1H, m), 6.56–6.62 (2H, m). ESI-MS *m*/*z*: 288 $[M+H]^+$. HR-MS (ESI) *m*/*z*: 288.1529 $[M+H]^+$ (Calcd for $C_{16}H_{22}N_3S$: 288.1529).

3,4-Dicyclopropyl-5-[2-(5-iodothiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (14) *N*-Iodosuccinimide (286 mg, 1.27 mmol) was added to a solution of **9d** (331 mg, 1.21 mmol) in AcOH (5 mL) and the mixture was stirred overnight at r.t. $CHCl_3$ and water were added, and the mixture was extracted with $CHCl_3$. The organic layer was washed with 1 M aqueous sodium hydroxide solution and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH) to give the title compound **14** (437 mg, 1.09 mmol, 90%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.51–0.57 (2H, m), 0.87–1.00 (6H, m), 1.82 (6H, s), 1.97–2.06 (1H, m), 2.97–3.04 (1H, m), 6.54 (1H, d, $J=3.5$ Hz), 7.16 (1H, d, $J=3.6$ Hz). FAB-MS *m*/*z*: 400 $[M+H]^+$.

5-[2-(4,5-Dicyclopropyl-4*H*-1,2,4-triazol-3-yl)propan-2-yl]thiophene-2-carbonitrile (15) Copper cyanide (196 mg, 2.19 mmol) was added to a solution of **14** (437 mg, 1.09 mmol) in pyridine (10 mL) and the mixture was stirred at 115°C for 11.5 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH) and the resulting solid was washed with Et_2O and recrystallized from toluene to give the title compound **15** (170 mg, 0.568 mmol, 52%) as a pale yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.48–0.54 (2H, m), 0.88–1.02 (6H, m), 1.89 (6H, s), 1.99–2.07 (1H, m), 3.01–3.07 (1H, m), 7.02 (1H, d, $J=3.9$ Hz), 7.84 (1H, d, $J=3.9$ Hz). FAB-MS *m*/*z*: 299 $[M+H]^+$. HR-MS (ESI) *m*/*z*: 299.1324 $[M+H]^+$ (Calcd for $C_{16}H_{19}N_4S$: 299.1325).

***tert*-Butyl [2-(4,5-Dicyclopropyl-4*H*-1,2,4-triazol-3-yl)-propan-2-yl]carbamate (17)** A mixture of **8a** (500 mg, 3.99 mmol) and methyl trifluoromethanesulfonate (452 μL, 3.99 mmol) was stirred at 60°C for 30 min. Toluene (9 mL), Et_3N (557 μL, 3.99 mmol) and *tert*-butyl (1-hydrazinyl-2-methyl-1-oxopropan-2-yl)carbamate (**16**, 723 mg, 3.33 mmol, CAS No.; 184002-61-7) were added and the reaction mixture was stirred at 60°C for 2 h and 100°C for 1 h. $CHCl_3$ and saturated aqueous sodium hydrogen carbonate solution were added to the mixture, and the organic layer was separated and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH) to give the title compound **17** (464 mg, 1.51 mmol, 46%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.94–1.24 (8H, m), 1.35 (9H, br s), 1.78 (6H, s), 1.88–2.01 (1H, m), 3.00–3.13 (1H, m), 5.28 (1H, br s). ESI-MS *m*/*z*: 307 $[M+H]^+$.

2-(4,5-Dicyclopropyl-4*H*-1,2,4-triazol-3-yl)propan-2-amine (18) A mixture of **17** (480 mg, 1.57 mmol), 4 M HCl solution in EtOAc (1.96 mL, 7.83 mmol) and EtOH (10 mL) was stirred at 50°C for 8 h. $CHCl_3$, 1 M aqueous sodium hydroxide solution and water were added to the mixture. The organic layer was separated and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*, then dried to give the title compound **18** (320 mg, 1.55 mmol, 99%) as a pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.98–1.06 (2H, m), 1.12–1.27 (4H, m), 1.33–1.41 (2H, m), 1.67 (6H, s), 1.89–2.01 (1H, m), 3.17–3.26 (1H, m). ESI-MS *m*/*z*: 207 $[M+H]^+$.

3,4-Dicyclopropyl-5-[2-(1*H*-pyrrol-1-yl)propan-2-yl]-4*H*-1,2,4-triazole Monohydrochloride (19) A mixture of **18** (500 mg, 2.42 mmol), 2,5-dimethoxytetrahydrofuran (373 μL, 2.91 mmol), AcOH (5 mL) and $CHCl_3$ (5 mL) was stirred at 70°C for 24 h. $CHCl_3$, 1 M aqueous sodium hydroxide solution and water were added to the mixture. The organic layer was separated and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH). The obtained product was dissolved in Et_2O (20 mL), and 4 M HCl solution in EtOAc (606 μL, 2.42 mmol) was added to the mixture. The reaction mixture was stirred at r.t. for 30 min and the solid was precipitated. The precipitate was collected by filtration and dried to give the title compound **19** (590 mg, 2.02 mmol, 83%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.38–0.43 (2H, m), 0.87–0.94 (2H, m), 1.21–1.35 (4H, m), 1.99 (6H, s), 2.24–2.31 (1H, m), 3.07–3.13 (1H, m), 6.08 (2H, t, $J=2.2$ Hz), 6.75 (2H, t, $J=2.2$ Hz). FAB-MS *m*/*z*: 257 $[M+H]^+$. HR-MS (ESI) *m*/*z*: 257.1755 $[M+H]^+$ (Calcd for $C_{15}H_{21}N_4$: 257.1761).

4-Cyclopropyl-3-[2-(thiophen-2-yl)propan-2-yl]-4*H*-1,2,4-triazole (21) Thionyl chloride (3.49 mL, 47.8 mmol) and DMF (74 μL, 0.96 mmol) were added to a solution of *N*-cyclopropyl-2-methyl-2-(thiophen-2-yl)propanamide (**20**, 2.00 g, 9.56 mmol, CAS No.; 950604-59-8) in $CHCl_3$ (30 mL), and the mixture was stirred at 60°C for 1 h. The reaction mixture was concentrated *in vacuo*, and toluene (40 mL) and formyl hydrazine (631 mg, 10.5 mmol) were added to the resulting

mixture. The mixture was stirred at 70°C for 20 h, and $CHCl_3$ and 1 M aqueous sodium hydroxide solution were added. The organic layer was separated and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH). The obtained product was washed with hexane and dried to give the title compound **21** (565 mg, 2.42 mmol, 25%) as a colorless solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.74–0.80 (4H, m), 1.86 (6H, s), 2.75–2.81 (1H, m), 6.89 (1H, dd, J = 1.1, 3.5 Hz), 6.97 (1H, dd, J = 3.5, 5.3 Hz), 7.42 (1H, dd, J = 1.2, 5.1 Hz), 8.37 (1H, s). EI-MS m/z: 233 $[M]^+$. HR-MS (ESI) m/z: 234.1053 $[M+H]^+$ (Calcd for $C_{12}H_{16}N_3S$: 234.1059).

***N′*-[2-Methyl-2-(thiophen-2-yl)propanoyl]cyclopropanecarbohydrazide (22)** Et_3N (15 mL, 108 mmol) was added to a solution of **4d** (19.0 g, 103 mmol) in dichloromethane (150 mL) and the mixture was cooled in an ice bath. A solution of cyclopropanecarbonyl chloride (9.80 mL, 109 mmol) in dichloromethane (50 mL) was added and the mixture stirred overnight at r.t. Water was added, and the mixture was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained solid was washed with Et_2O and dried to give the title compound **22** (24.0 g, 95.1 mmol, 92%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.66–0.75 (4H, m), 1.53–1.62 (1H, m), 1.56 (6H, s), 6.94 (1H, dd, J = 3.5, 5.1 Hz), 7.07 (1H, dd, J = 1.0, 3.5 Hz), 7.37 (1H, dd, J = 1.1, 5.2 Hz), 9.41 (1H, br s), 9.87 (1H, br s). EI-MS m/z: 252 $[M]^+$.

2-Cyclopropyl-5-[2-(thiophen-2-yl)propan-2-yl]-1,3,4-oxadiazole (23) Pyridine (16.9 mL, 209 mmol) was added to a solution of **22** (24.0 g, 95.1 mmol) in dichloromethane (480 mL) and the mixture was cooled in an ice bath. Trifluoromethanesulfonic anhydride (21.8 mL, 133 mmol) was added and the mixture was stirred at r.t. for 3 d. Saturated aqueous sodium hydrogen carbonate solution was added and the mixture was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc). The obtained solid was washed with hexane and dried to give the title compound **23** (6.34 g, 27.1 mmol, 28%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.06–1.11 (4H, m), 1.86 (6H, s), 2.05–2.13 (1H, m), 6.89 (1H, dd, J = 1.2, 3.6 Hz), 6.94 (1H, dd, J = 3.6, 5.1 Hz), 7.20 (1H, dd, J = 1.2, 5.1 Hz). EI-MS m/z: 234 $[M]^+$.

2-[2-(5-Bromothiophen-2-yl)propan-2-yl]-5-cyclopropyl-1,3,4-oxadiazole (24) *N*-Bromosuccinimide (5.28 g, 29.7 mmol) was added to a solution of **23** (6.32 g, 27.0 mmol) in AcOH (95 mL) and the mixture was stirred at r.t. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc and washed with 1 M aqueous sodium hydroxide solution. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc). The obtained solid was washed with hexane and dried to give the title compound **24** (6.32 g, 20.2 mmol, 75%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.07–1.13 (4H, m), 1.82 (6H, s), 2.06–2.13 (1H, m), 6.65 (1H, d, J = 3.9 Hz), 6.88 (1H, d, J = 3.9 Hz). FAB-MS m/z: 315 $[M+H]^+$.

3-[2-(5-Bromothiophen-2-yl)propan-2-yl]-5-cyclopropyl-4-propyl-4*H*-1,2,4-triazole Monohydrochloride (25a) *n*-Propylamine (1.37 mL, 16.7 mmol) was added to a solution of **24** (500 mg, 1.60 mmol) in AcOH (5 mL) and reacted at 170°C for 60 min using a microwave reaction device. The reaction mixture was cooled to r.t. Toluene was added and the mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc and the mixture was washed with H_2O. The organic layer was dried over $MgSO_4$ and filtered. 4 M HCl solution in EtOAc (1 mL, 4 mmol) was added and the mixture was concentrated *in vacuo*. The residue was washed with EtOAc and diisopropyl ether, then dried to give the title compound **25a** (231 mg, 0.591 mmol, 37%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, t, J = 7.4 Hz), 1.37–1.53 (4H, m), 1.84–2.00 (3H, m), 1.90 (6H, s), 3.86–3.93 (2H, m), 6.70 (1H, d, J = 3.9 Hz), 6.98 (1H, d, J = 3.8 Hz). FAB-MS m/z: 356 $[M+H]^+$. HR-MS (ESI) m/z: 354.0634 $[M+H]^+$ (Calcd for $C_{15}H_{21}N_3BrS$: 354.0634).

3-[2-(5-Bromothiophen-2-yl)propan-2-yl]-5-cyclopropyl-4-(propan-2-yl)-4*H*-1,2,4-triazole Monohydrochloride (25b) The title compound was prepared in a similar manner to that described for **25a** from **24** (500 mg, 1.60 mmol) and isopropylamine (1.37 mL, 16.7 mmol) at 12% yield (74 mg, 0.19 mmol) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.41–1.48 (8H, m), 1.87 (6H, s), 1.96–2.08 (3H, m), 4.52–4.63 (1H, m), 6.62 (1H, d, J = 3.9 Hz), 6.97 (1H, d, J = 3.9 Hz). FAB-MS m/z: 356 $[M+H]^+$. HR-MS (ESI) m/z: 354.0635 $[M+H]^+$ (Calcd for $C_{15}H_{21}N_3BrS$: 354.0634).

3-[2-(5-Bromothiophen-2-yl)propan-2-yl]-5-cyclopropyl-4-(cyclopropylmethyl)-4*H*-1,2,4-triazole (25c) Cyclopropanemethylamine (568 mg, 7.99 mmol) was added to a solution of **24** (500 mg, 1.60 mmol) in AcOH (5 mL) and reacted at 170°C for 40 min using a microwave reaction device. The reaction mixture was cooled to r.t. and concentrated *in vacuo*. The residue was dissolved in EtOAc and extracted with 1 M hydrochloric acid. The aqueous layer was neutralized with 1 M aqueous sodium hydroxide solution and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained syrup was dissolved in EtOAc, and 4 M HCl solution in EtOAc (1 mL, 4 mmol) was added and the mixture was concentrated *in vacuo*. The obtained solid was washed with diisopropyl ether to give a white solid. The solid was mixed with 1 M aqueous sodium hydroxide solution and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained solid was washed with diisopropyl ether, then dried to give the title compound **25c** (92 mg, 0.25 mmol, 16%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.17–0.22 (2H, m), 0.52–0.58 (2H, m), 0.77–0.87 (1H, m), 0.96–1.03 (2H, m), 1.14–1.20 (2H, m), 1.71–1.79 (1H, m), 1.86 (6H, s), 3.61 (2H, d, J = 6.2 Hz), 6.55 (1H, d, J = 3.7 Hz), 6.88 (1H, d, J = 3.9 Hz). FAB-MS m/z: 368 $[M+H]^+$. HR-MS (ESI) m/z: 366.0635 $[M+H]^+$ (Calcd for $C_{16}H_{21}N_3BrS$: 366.0634).

4-Benzyl-3-[2-(5-bromothiophen-2-yl)propan-2-yl]-5-cyclopropyl-4*H*-1,2,4-triazole Monohydrochloride (25d) The title compound was prepared in a similar manner to that described for **25a** from **24** (500 mg, 1.60 mmol) and benzylamine (1.74 mL, 15.9 mmol) at 33% yield (231 mg, 0.526 mmol) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.14–1.21 (2H, m), 1.62–1.70 (1H, m), 1.77–1.85 (2H, m), 1.83 (6H, s), 5.20 (2H, s), 6.64 (1H, d, J = 3.9 Hz), 6.80–6.87 (2H, m), 6.86 (1H, d, J = 3.9 Hz), 7.34–7.38 (3H, m). FAB-MS m/z: 404 $[M+H]^+$. HR-MS (ESI) m/z: 402.0634 $[M+H]^+$ (Calcd for $C_{19}H_{21}N_3BrS$: 402.0634).

3-[2-(5-Bromothiophen-2-yl)propan-2-yl]-5-cyclopropyl-

4-(2-phenylethyl)-4*H*-1,2,4-triazole (25e) The title compound was prepared in a similar manner to that described for **25a**, except for the salt-forming procedure, from **24** (500 mg, 1.60 mmol) and 2-phenylethylamine (2.00 mL, 15.8 mmol) at 20% yield (131 mg, 0.314 mmol) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.03–1.09 (2H, m), 1.19–1.24 (2H, m), 1.64–1.73 (1H, m), 1.85 (6H, s), 2.63–2.70 (2H, m), 3.88–3.94 (2H, m), 6.64 (1H, d, J = 3.7 Hz), 6.95 (1H, d, J = 3.8 Hz), 6.96–7.00 (2H, m), 7.22–7.33 (3H, m). FAB-MS m/z: 416 $[M+H]^+$.

***N*′-[2-Methyl-2-(pyridin-2-yl)propanoyl]cyclopropanecarbohydrazide (27a)** Et_3N (3.42 mL, 24.6 mmol) was added to a solution of 2-methyl-2-(pyridin-2-yl)propanehydrazide (**26a**, 4.00 g, 22.3 mmol, CAS No.; 880166-60-9) in dichloromethane (20 mL), and then a solution of cyclopropanecarbonyl chloride (2.11 mL, 23.4 mmol) in dichloromethane (20 mL) was added dropwise to the mixture at 0°C. The reaction mixture was stirred at 3 h and saturated aqueous sodium hydrogen carbonate solution was added. The mixture was extracted with $CHCl_3$, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH) to give the title compound **27a** (5.25 g, 21.2 mmol, 95%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.75–0.82 (2H, m), 0.97–1.03 (2H, m), 1.51–1.59 (1H, m), 1.68 (6H, s), 7.23 (1H, dd, J = 5.0, 7.3 Hz), 7.44 (1H, d, J = 8.0 Hz), 7.72 (1H, ddd, J = 1.7, 7.8, 7.8 Hz), 8.63 (1H, d, J = 4.0 Hz), 8.93–9.02 (1H, m), 10.06–10.18 (1H, m).

***N*′-[2-Methyl-2-(pyridin-4-yl)propanoyl]cyclopropanecarbohydrazide (27b)** The title compound was prepared in a similar manner to that described for **27a** from 2-methyl-2-(pyridin-4-yl)propanehydrazide (**26b**, 166 mg, 0.926 mmol, CAS No.; 950604-79-2) at 45% yield (103 mg, 0.418 mmol) as a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.68–0.76 (4H, m), 1.45–1.63 (1H, m), 1.47 (6H, s), 7.38–7.42 (2H, m), 8.47–8.51 (2H, m), 9.47 (1H, br s), 9.87 (1H, br s). ESI-MS m/z: 248 $[M+H]^+$.

2-[2-(5-Cyclopropyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine (28a) A mixture of **27a** (10.1 g, 40.8 mmol) and phosphorus oxychloride (76 mL, 0.82 mol) was stirred at reflux temperature for 8 h and poured into ice water. The reaction mixture was neutralized with 4 M aqueous sodium hydroxide solution and extracted with EtOAc. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH) to give the title compound **28a** (5.81 g, 25.3 mmol, 62%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.03–1.11 (4H, m), 1.83 (6H, s), 2.03–2.16 (1H, m), 7.12–7.21 (2H, m), 7.60–7.68 (1H, m), 8.53–8.59 (1H, m). ESI-MS m/z: 230 $[M+H]^+$.

4-[2-(5-Cyclopropyl-1,3,4-oxadiazol-2-yl)propan-2-yl]pyridine (28b) The title compound was prepared in a similar manner to that described for **28a** from **27b** (100 mg, 0.404 mmol) at 45% yield (41.7 mg, 0.182 mmol) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.03–1.14 (4H, m), 1.79 (6H, s), 2.03–2.14 (1H, m), 7.15–7.19 (2H, m), 8.54–8.60 (2H, m). ESI-MS m/z: 230 $[M+H]^+$.

2-[2-(4,5-Dicyclopropyl-4*H*-1,2,4-triazol-3-yl)propan-2-yl]pyridine Monohydrochloride (29a) Cyclopropyl amine (900 μL, 13.1 mmol) was slowly added to a solution of **28a** (300 mg, 1.31 mmol) in AcOH (3 mL) at 0°C, and the mixture was reacted at 175°C for 40 min using a microwave reaction device. The reaction mixture was neutralized with 1 M aqueous sodium hydroxide solution and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc–MeOH then $CHCl_3$–MeOH) to give 2-[2-(4,5-dicyclopropyl-4*H*-1,2,4-triazol-3-yl)propan-2-yl]pyridine (200 mg, 0.746 mmol, 57%) as a pale yellow oil. Four molar HCl solution in 1,4-dioxane (169 μL, 0.677 mmol) was added to a solution of 2-[2-(4,5-dicyclopropyl-4*H*-1,2,4-triazol-3-yl)propan-2-yl]-pyridine (182 mg, 0.677 mmol) in EtOAc (2 mL). The mixture was stirred at r.t. for 1 h and the solid was precipitated. The precipitate was collected by filtration, washed with EtOAc, and dried to give the title compound **29a** (158 mg, 0.518 mmol, 76%) as a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.40–0.47 (2H, m), 0.74–0.82 (2H, m), 1.23–1.30 (4H, m), 1.85 (6H, s), 2.26–2.36 (1H, m), 3.05–3.14 (1H, m), 7.35–7.40 (1H, m), 7.53 (1H, d, J = 8.0 Hz), 7.90 (1H, ddd, J = 1.8, 7.8, 7.8 Hz), 8.47–8.51 (1H, m). ESI-MS m/z: 269 $[M+H]^+$. HR-MS (ESI) m/z: 269.1759 $[M+H]^+$ (Calcd for $C_{16}H_{21}N_4$: 269.1761).

4-[2-(4,5-Dicyclopropyl-4*H*-1,2,4-triazol-3-yl)propan-2-yl]pyridine Monohydrochloride (29b) The title compound was prepared in a similar manner to that described for **29a** from **28b** (36.4 mg, 0.159 mmol) at 22% yield (10.5 mg, 0.0344 mmol) as a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.53–0.60 (2H, m), 0.81–0.89 (2H, m), 1.18–1.26 (4H, m), 1.86 (6H, s), 2.17–2.28 (1H, m), 3.03–3.12 (1H, m), 7.74 (2H, d, J = 6.5 Hz), 8.82 (2H, d, J = 6.4 Hz). ESI-MS m/z: 269 $[M+H]^+$. HR-MS (ESI) m/z: 269.1759 $[M+H]^+$ (Calcd for $C_{16}H_{21}N_4$: 269.1761).

11β-HSD1 and 11β-HSD2 Assay Recombinant human and mouse 11β-HSD1 enzymes were prepared in accordance with a previous study.[23] Test compounds were dissolved in DMSO and diluted to the desired concentrations. The reaction was initiated by adding the compound to a reaction mixture containing 10 mM phosphate buffer (pH 6.6), 200 nM cortisone, 40 μM reduced nicotinamide adenine dinucleotide phosphate (NADPH) and the 11β-HSD1 enzyme, and incubating at r.t. for 1 h.

The 11β-HSD2 assay was conducted using the same method as that used for the 11β-HSD1 assay, except for the enzyme reaction conditions. The human 11β-HSD2 enzyme was produced in HEK293 cells transfected with an expression vector (pcDNA3.1, Invitrogen) encoding human 11β-HSD2. The crude extract from HEK293 cell homogenates was used as the enzyme source for the human 11β-HSD2 assay. The enzyme reaction was initiated by adding the compound to a reaction mixture containing 40 mM Tris–HCl buffer (pH 8.0), 200 nM cortisol, 200 μM nicotinamide adenine dinucleotide (NAD) and the 11β-HSD2 enzyme, and incubating at 37°C for 2 h.

After the enzymatic reaction, the enzymatic inhibitory activity was measured by detecting cortisol using a HTRF®. Each of the XL-665-labeled cortisol containing 400 μM carbenoxolone and cryptate-labeled cortisol antibody (Cisbio Bioassays, Codolet, France) was added and incubated at r.t. for 2 h, and the fluorescence intensity was measured using a fluorophotometer (ARVO HTS, PerkinElmer, Inc., Waltham, MA, U.S.A.). The enzymatic inhibitory activity was calculated from the fluorescence intensity ratio at two wavelengths

(665 nm/620 nm). The ratio when DMSO was added instead of the compound was regarded as 0% and the ratio when neither 11β-HSD1 nor 11β-HSD2 was added was regarded as 100%.

Effect of Repeated Administration in ob/ob Mice All experiments were performed in accordance with the regulation of the Animal Ethics Committee of Astellas Pharma Inc.

Male diabetic ob/ob mice were purchased from Charles River Laboratories Japan (Kanagawa, Japan). Compound **9a** was dissolved in 6% 2-hydroxypropyl-β-cyclodextrin (Sigma-Aldrich Co. LLC., St. Louis, MO, U.S.A.). Seven-week-old male ob/ob mice ($n = 7$–8) were orally administered vehicle or 0.3–10 mg/kg of **9a** twice daily for four weeks. At 12 h after the final administration, plasma and retroperitoneal adipose tissue samples were collected. Plasma glucose levels were determined using the Glucose CII test (Wako, Osaka, Japan). Plasma insulin levels were determined using the Insulin enzyme-linked immunosorbent assay (ELISA) kit (Shibayagi, Gunma, Japan). Corticosterone levels in retroperitoneal adipose tissue were determined using the Corticosterone ELISA kit (Enzo Life Sciences, Farmingdale, NY, U.S.A.).

***In Vitro* Intrinsic Clearance with Mouse and Human Liver Microsomes** To estimate the metabolic stability of compounds against mouse or human hepatic CYPs, the test compound (0.2 μM) was incubated with pooled male CD1 mouse or human liver microsomes (0.2 mg protein/mL), NADPH (1 mM) and ethylenediaminetetraacetic acid (EDTA) (0.1 mM) in pH 7.4 Na+–K+ phosphate buffer (100 mM) at 37°C. Incubations were conducted for 0, 15, 30, and 45 min. The peak area of the compound and internal standard was measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and analyzed to calculate CL_{int} (mL/min/kg).[24]

Molecular Modeling

Human 11β-HSD1 Model

The crystal structure of human 11β-HSD1 was obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB code: 3D5Q).[25] After deleting C and D chains, hydrogen atoms were added to the protein using the Protonate3D module with the Amber10EHT force field in MOE.[22]

Docking Study

The ligand molecule was prepared using LigPrep[26] and MacroModel[27] and energy-minimized conformation was used to input molecules. Compounds were docked to the human 11β-HSD1 model using the docking program GOLD version 5.5.1. The ligand molecule was docked 10 times. The top scoring position, as assessed by GoldScore, was employed for discussion.

Sequence Homology between Human and Mouse

The crystal structure of mouse 11β-HSD1 was downloaded from RCSB (PDB code: 4K26[28]). The homology between human 11β-HSD1(PDB code: 3D5Q) and mouse 11β-HSD1(PDB code: 4K26) sequences was evaluated using MOE.

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Conflict of Interest The authors declare no conflict of interest.

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