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# Discovery of triazolone derivatives as novel, potent stearoyl-CoA desaturase-1 (SCD1) inhibitors

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ABSTRACT

Stearoyl-CoA desaturase-1 (SCD1) plays an important role in lipid metabolism. Inhibition of SCD1 activity represents a potential novel approach for the treatment of metabolic diseases such as obesity, type 2 diabetes and dyslipidemia, as well as skin diseases, acne and cancer. Herein, we report the synthesis and structure–activity relationships (SAR) of a series of novel triazolone derivatives, culminating in the identification of pyrazolyltriazolone **17a**, a potent SCD1 inhibitor, which reduced plasma C16:1/C16:0 triglycerides desaturation index (DI) in an acute Lewis rat model in a dose dependent manner, with an $ED_{50}$ of 4.6 mg/kg. In preliminary safety studies, compound **17a** did not demonstrate adverse effects related to SCD1 inhibition after repeat dosing at 100 mg/kg. Together, these data suggest that sufficient safety margins can be achieved with certain SCD1 inhibitors, thus allowing exploration of clinical utility in metabolic disease settings.



## 1. Introduction

It has been well established that lipids play a crucial role in the etiology of metabolic diseases, therefore, several enzymes regulating lipid metabolism have recently been proposed as therapeutic targets.[1,2] One such target is stearoyl-CoA desaturase-1 (SCD1). SCD1, also known as delta-9 desaturase (D9D), is a microsomal enzyme that catalyzes the de novo synthesis of monounsaturated fatty acids (MUFA) from saturated fatty acids by introducing a *cis*-double bond between carbons 9 and 10. The products, mainly oleate and palmitoleate, are key substrates for synthesis of triglycerides, wax esters, cholesterol esters and phospholipids.[3] To date, four SCD isoforms (SCD1–4) have been characterized in rodents,[4–7] and two SCD isoforms (SCD1 and SCD5) in humans. SCD1, with 85% identity across species, is the predominant isoform expressed in lipogenic tissues including liver and adipose.[8,9] SCD1 knockout mice display a beneficial metabolic phenotype characterized by increased energy expenditure, reduced adiposity, improved insulin sensitivity and resistance to high fat diet-induced obesity.[10–12] Similar beneficial effects are observed in high fat diet-induced obese (DIO) mice treated with SCD1 antisense oligonucleotides.[13,14] In humans, elevated SCD1 activity is positively correlated with high triglyceride levels in familial hypertriglyceridemia subjects,[15] increased body mass index (BMI) and high plasma insulin levels.[16] Cross species studies provide evidence to support the view that SCD1 is a critical player in the regulation of skeletal muscle and fat metabolism.[17] In addition to the beneficial metabolic effects associated with SCD1 inhibition, studies in mice further suggested that SCD1 activity is important to maintaining the normal functioning of the skin as a result of its important role in lipid synthesis within sebaceous glands. Mouse strains deficient in the enzyme SCD1 exhibit severe hypoplasia of sebaceous glands.[18,19] Small molecule SCD1 inhibition has shown to reduce sebaceous size and number in animal models.[20] SCD1 is also involved in the regulation of cell proliferation, growth and apoptosis. A couple of studies have implicated SCD1 expression and activity in the pathogenesis of cancer.[21–24] Therefore inhibition of SCD1 represents a potential novel approach for the treatment of metabolic diseases such as obesity, type 2 diabetes and dyslipidemia, as well as skin diseases, acne, and cancer.

Small molecule SCD1 inhibitors have been reviewed,[25–27] with several new structures reported recently.[28,29] Our efforts continue to focus on the identification of novel scaffolds, with differing properties, as SCD1 inhibitors.[30–32] We previously described the

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0968-0896/

application of bioisostere strategies in the replacement of the amide bond at the C2-position of compound **1**.[31] These studies led us to identify a series of novel thiazolylimidazolidinone SCD1 inhibitors. The advantages of this chemical series are improved inhibitory potency and metabolic stability, as exemplified by XEN723 (Fig. 1). This compound is a potent SCD1 inhibitor with an enzymatic $IC_{50}$ of 6 nM in mouse SCD1 assay, and good in vivo efficacy in an acute Lewis rat model with $ED_{50}$ of 4.5 mg/kg. Similar to other systemic SCD1 inhibitors,[30] undesired skin and eye adverse effects were observed in XEN723 treated rats in chronic studies. These adverse events (AEs) are believed to be due to mechanism-based depletion of essential SCD-derived lubricating lipids.[18,19] We wished to identify potent SCD1 inhibitors with desirable physiochemical properties in alternative chemical space to mitigate mechanism-related AEs. In this report, we describe the synthesis and structure–activity relationships (SAR) of a series of novel triazolone-based SCD1 inhibitors. This work led to the discovery of the pyrazolyltriazolone analogue **17a**, an efficacious SCD1 inhibitor with an improved AEs profile.

## 2. Chemistry

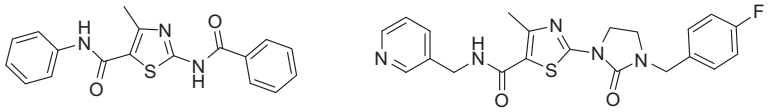
The synthesis of thiazolyltriazolone analogues **7a–7w** is outlined in Scheme 1. Ethyl 2-amino-4-methylthiazole-5-carboxylate **2** was treated with 4-nitrophenyl chloroformate in the presence of pyridine in THF to provide the corresponding nitrophenyl carbamate, which was converted to **3** by in situ cleavage with hydrazine. Upon heating with trimethyl orthoformate in ethanol, **3** was converted to the key triazolone intermediate **4**. Alkylation of **4** with various alkyl halides and subsequent hydrolysis of the ester **5a–5i** gave the corresponding acids **6a–6i**. Amide formation of **6a–6i** under standard amide formation conditions with select amines produced amides **7a–7dd** and **7e–7w**. The piperidinyl analogue **7d** was obtained upon removal of the Boc protecting group of **7dd**.

Synthesis of pyrazolyltriazolone analogues **17a–17f** (Scheme 2) started from commercially available 3-nitro-1*H*-pyrazole-5-carboxylic acid **8**, which was treated with thionyl chloride in methanol, resulting in methyl ester **9**. Subsequent alkylation of **9** with 4-methoxybenzyl bromide afforded the Pmb-protected intermediate **10**. Reduction of the nitro group in **10** by hydrogenolysis yielded **11**. The amine intermediate **11** was then converted into amides **16a–16f** in a similar manner as described above for preparation of **7a–7w**. The 5-step sequence to reach **16a–16f** was followed by Pmb deprotection to finally provide the desired products **17a–17f**.

## 3. Results and discussion

The potency of the prepared compounds was first assessed in a primary SCD1 biochemical assay, using mouse liver microsomes. Compounds with significant SCD1 inhibition in this assay were then advanced for further characterization in a human liver hepatocellular carcinoma (HepG2) cell-based assay. In the mouse liver microsomal assay, the SCD1 activity was determined by measuring the decreased production of tritiated water released from (9,10-$^3$H)-labeled stearoyl coenzyme A substrate mediated by SCD1.[30,33] In the human HepG2 cell-based assay, SCD1 activity was assessed by determination of the amount of $^{14}$C-oleic acid product formed from $^{14}$C stearate substrate.[30,34] Besides SCDs, there are two other fatty acid desaturases in humans: delta-5 desaturases (D5D) and delta-6 desaturases (D6D). These related enzymes are required for the synthesis of highly unsaturated fatty acids (HUFAs), which are mainly esterified into phospholipids and contribute to maintaining membrane fluidity. Therefore, achieving selectivity against D5D and D6D is essential to avoid undesirable toxicities.[35] Compounds with good potency against SCD1 were also screened for their selectivity against D5D and D6D. None of the compounds evaluated (all with $IC_{50}$ <100 nM in SCD1 mouse liver microsomes) demonstrated significant reduction in D5D and D6D activity when tested at a concentration of 10 μM.[30,34] Based on their in vitro potencies, as well as their overall properties, several potent SCD1 inhibitors were selected for evaluation of their in vivo effects on the plasma C16:1n7/C16:0 triglycerides (TG) desaturation index (DI) in an acute Lewis rat model.[31] C16 and C18 DI have been well-documented as biomarkers for SCD1 target engagement.[14,18]

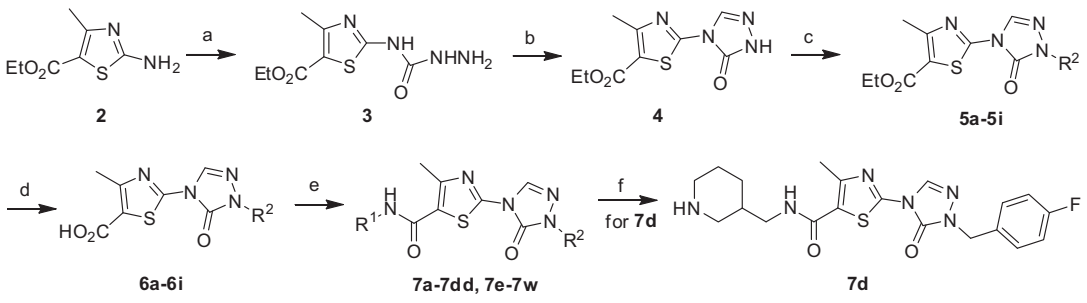
Using XEN723 as the starting point, we replaced the imidazolidinone ring with a triazolone moiety, while keeping the



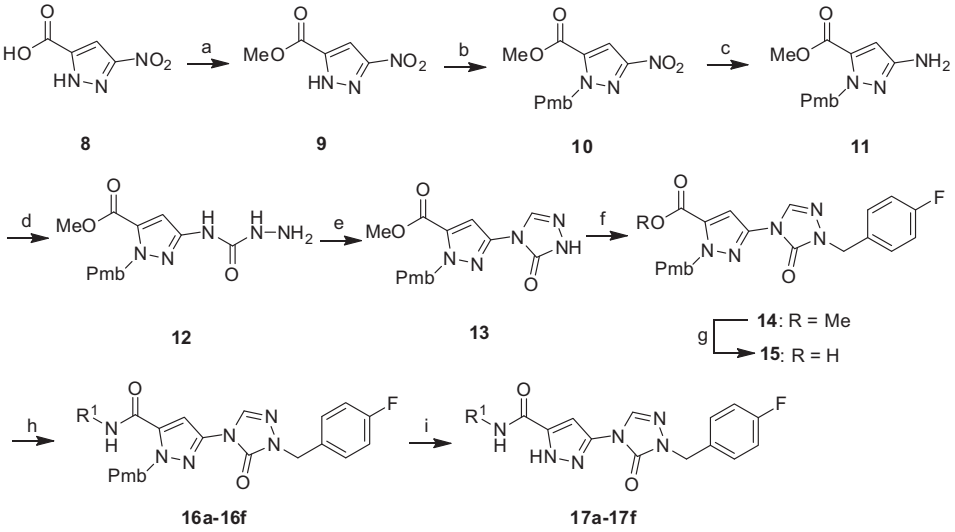
**1**
Mouse SCD1 $IC_{50}$: 3400 nM

**XEN723**
Mouse SCD1 $IC_{50}$: 6 nM

**Figure 1.** Aminothiazole-based SCD inhibitors.

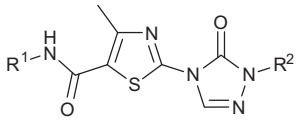


**Scheme 1.** Reagents and conditions: (a) 4-nitrophenyl chloroformate, pyridine, THF, rt, then $NH_2NH_2{\cdot}H_2O$, rt; (b) $HC(OMe)_3$, $TsOH{\cdot}H_2O$, ethanol, reflux; (c) $R^2X$, $K_2CO_3$, acetone, reflux; (d) NaOH, ethanol, $H_2O$, reflux; (e) $R^1NH_2$, EDCI or TBTU, HOBt, $^iPr_2NEt$, DMF, rt; (f) $CF_3CO_2H$, $CH_2Cl_2$, rt.




**Scheme 2.** Reagents and conditions: (a) methanol, $SOCl_2$, reflux; (b) 4-methoxybenzyl bromide, $K_2CO_3$, DMF, 60 °C; (c) $H_2$, 10% Pd-C, methanol; (d) 4-nitrophenyl chloroformate, pyridine, THF, rt, then $NH_2NH_2{\cdot}H_2O$, rt; (e) $HC(OMe)_3$, $TsOH{\cdot}H_2O$, ethanol, reflux; (f) 4-fluorobenzyl chloride, $K_2CO_3$, acetone, reflux; (g) NaOH, ethanol, $H_2O$, reflux; (h) $R^1NH_2$, TBTU, HOBt, $^iPr_2NEt$, DMF, rt; (i) $CF_3SO_3H$, $CF_3CO_2H$, $CH_2Cl_2$, rt.

**Table 1**
SAR of thiazolyltriazolones



| Compound | $R^1$ | $R^2$ | Mouse SCD1 $IC_{50}$[a] (nM) | HepG2 SCD1 $IC_{50}$[a] (nM) | Metabolic stability[b] | Permeability[c] ($\times10^{-6}$ cm/s) |
|---|---|---|---|---|---|---|
| **7a** | Pyridin-3-ylmethyl | 4-Fluorobenzyl | 20 | 268 | 65 | 22/19 |
| **7b** | Pyridin-2-ylmethyl | 4-Fluorobenzyl | 22 | 67 | 68 | 35/30 |
| **7c** | 6-(Trifluoromethyl)pyridin-3-yl)methyl | 4-Fluorobenzyl | 1722 | nd | nd | nd |
| **7d** | Piperidin-3-ylmethyl | 4-Fluorobenzyl | >10,000 | nd | nd | nd |
| **7e** | (5-Methylpyrazin-2-yl)methyl | 4-Fluorobenzyl | 15 | 194 | 75 | 36/28 |
| **7f** | Oxazol-4-ylmethyl | 4-Fluorobenzyl | 12 | 39 | 76 | 32/27 |
| **7g** | Oxazol-2-ylmethyl | 4-Fluorobenzyl | 22 | 214 | 90 | 24/23 |
| **7h** | Thiazol-2-ylmethyl | 4-Fluorobenzyl | 12 | 9 | 71 | 24/20 |
| **7i** | (2-Methylthiazol-4-yl)methyl | 4-Fluorobenzyl | 24 | 32 | 51 | 25/19 |
| **7j** | (1*H*-Pyrazol-3-yl)methyl | 4-Fluorobenzyl | 46 | 105 | 83 | 25/25 |
| **7k** | (5-Methyl-1*H*-pyrazol-3-yl)methyl | 4-Fluorobenzyl | 9 | 280 | 66 | 21/20 |
| **7l** | 1-Methyl-1*H*-pyrazol-4-yl)methyl | 4-Fluorobenzyl | 19 | 477 | 90 | 32/27 |
| **7m** | (1-Methyl-1*H*-imidazol-4-yl)methyl | 4-Fluorobenzyl | 27 | 504 | 96 | 41/33 |
| **7n** | H | 4-Fluorobenzyl | 65 | 945 | nd | nd |
| **7o** | Pyridin-3-ylmethyl | (4-Trifluoromethyl)-benzyl | 16 | 46 | 80 | 15/15 |
| **7p** | Pyridin-3-ylmethyl | 3,5-Difluorobenzyl | 19 | 125 | 51 | 28/22 |
| **7q** | Pyridin-3-ylmethyl | 5-(Trifluoromethyl)-furan-2-yl | 7 | 8 | 45 | 39/31 |
| **7r** | Pyridin-3-ylmethyl | (4-Fluorophenoxy)ethyl | 15 | 9 | 22 | 40/33 |
| **7s** | Pyridin-3-ylmethyl | Cyclopropylmethyl | 98 | 140 | 85 | 23/22 |
| **7t** | Pyridin-3-ylmethyl | (2,2-Difluorocyclopropyl)-methyl | 55 | 306 | 91 | 34/33 |
| **7u** | Pyridin-3-ylmethyl | 4,4,4-Trifluorobutyl | 21 | 398 | 76 | 26/20 |
| **7v** | Pyridin-2-ylmethyl | (4-Trifluoromethyl)-benzyl | 14 | 227 | 100 | 26/23 |
| **7w** | Pyridin-2-ylmethyl | 1-(4-Fluorophenyl)ethyl) | 30 | 66 | 71 | 27/25 |

nd: not determined.
[a] $IC_{50}$s are an average of at least two independent determinations; nd: not determined.
[b] Expressed as % of compound remaining after a 30 min incubation with 0.5 mg/mL rat liver microsomes.
[c] Permeability was determined using Caco-2 cells. Data are expressed as $P_{app}$ (a to b)/$P_{app}$ (b to a).

remaining structural elements unchanged. This modification (**7a**) resulted in decrease in potency in both assays with an enzymatic $IC_{50}$ of 20 nM in mouse liver microsomal assay, and a cellular $IC_{50}$ of 268 nM in human HepG2 cell assay. Despite the significant loss in cellular potency, compound **7a**, at 5 mg/kg, demonstrated potent in vivo efficacy in an acute Lewis rat model with 54% plasma C16:1/C16:0 TG DI reduction 4 h post oral administration.

Based on the encouraging results observed with **7a**, we proceeded with a systematic SAR investigation of the thiazolyltriazolone core. Initially, we modified the left-hand side changing the $R^1$ group, while keeping the right hand side of the molecule, $R^2$, constant with the 4-fluorobenzyl group. The results of in vitro activity, metabolic stability and permeability are summarized in Table 1. In general, the modifications at $R^1$ were well tolerated. Both six-membered heterocycle analogues **7b**, **7e**, and five-membered heterocycle analogues **7f**, **7g**, **7h** and **7i** demonstrated better or comparable inhibitory activity against SCD1. However, the five-membered analogs **7g**, **7h** and **7i** displayed undesired activity against P450 CYP3A4 with more than 50% inhibition at 10 μM. A $CF_3$ substitution at the 6-position on pyridinyl ring was found to be detrimental to SCD1 inhibition, as the activity of **7c** dropped by almost 80-fold in mouse SCD1 assay. Replacement of the pyridinyl ring with a saturated piperidinyl moiety abolished the activity, as observed in **7d**. Truncation to the primary amide provided **7n** which was only about 3-fold less potent in the mouse SCD1 assay, however a much more significant loss was observed in the HepG2 assay.

The in vivo efficacy of compounds **7b**, **7e**, **7f**, and **7k** on the plasma C16:1/C16:0 TG DI reductions are shown in Figure 2. Consistent with the potency in both in vitro assays, **7b** and **7f** were the most efficacious compounds tested, as they reduced plasma C16:1/C16:0 TG DI by more than 70% at 5 mg/kg, 4 h post oral administration. It was later found that **7f** displayed undesired activity toward pregnane X receptor (PXR), which induced CYP3A4 mRNA expression level in human hepatocytes by almost 10-fold at 50 μM.

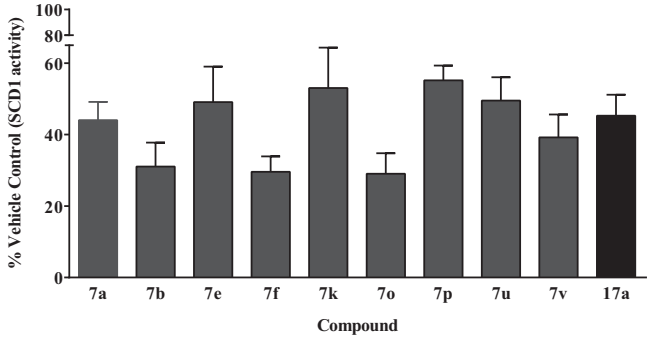



**Figure 2.** Effects of compounds on plasma C16:1/C16:0 TG desaturation index 4 h after a 5 mg/kg oral dose in Lewis rats. Each bar represents the mean ± SEM ($n = 4$), and the error bars represent standard errors of the mean.

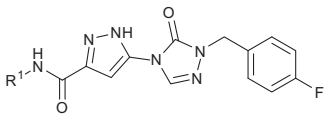
Based on potency and favorable overall properties, the $R^1$ pyridyl substituents as found in compounds **7a** and **7b** were held constant while modifications to the right hand side, $R^2$, where explored. $R^2$ analogues with modified benzyl groups (**7o**, **7p**) and the 5-(trifluoromethyl)-furan-2-yl group (**7q**) displayed good potency. The longer chain, (4-fluorophenoxy)ethyl in **7r** was also tolerated, but was less metabolically stable. Replacement of 4-fluorobenzyl with 1-(4-fluorophenyl)ethyl) group (**7w**) was also well tolerated and retained good metabolic stability. Replacement of the aryl group with an alkyl or a cycloalkyl group at $R^2$, as in compounds **7s**, **7t** and **7u**, retained good inhibitory potency in both assay systems. **7u** was evaluated in the acute Lewis rat model and demonstrated 50% plasma C16:1/C16:0 TG DI reduction at 5 mg/kg, 4 h post oral administration. Compound **7o**, one of the most potent compound $R^2$ modifications, demonstrated similar in vivo efficacy as compared to **7b**, reducing plasma C16:1/C16:0 TG DI by 71% at 5 mg/kg, 4 h post oral administration.

To explore additional scaffold modifications, we replaced the thiazole core with a pyrazole group. The pyrazolyl core introduces a hydrogen bond donor, lowers *c*log*P* by 1.76 units (1.47 of **17a** vs 3.23 of **7a**), and increases tPSA to 102 from 90 of **7a**, results in decreased permeability. However, despite the low permeability as assessed by a Caco2 assay, **17a** displayed good in vitro potency, and demonstrated reduction of the plasma C16:1/C16:0 TG DI by 54% at 5 mg/kg, 4 h post oral administration in Lewis rats. PK analysis indicated that compound **17a** had good plasma exposure ($AUC_{0-24\ h}$ = 6.0 μM h). **17a** was readily absorbed in Lewis rats with a $C_{max}$ of 2.2 μM. The oral terminal half-life of **17a** was 4.0 h. Following intravenously administration with 1 mg/kg of **17a** in Lewis rats, the plasma concentration of **17a** appeared to decline rapidly with $t_{½}$ of 1.3 h, and the plasma exposure was 2.3 μM h. As a result, the oral bioavailability of **17a** is 52% at 5 mg/kg in Lewis rats (Tables 2 and 3).

Disappointingly, modifications of the left-hand side pyridin-4-ylmethyl $R^1$ of **17a** with other heteroaryl groups resulted in significant loss in potency. For example, the pyridin-2-ylmethyl analogue **17b** is 3-fold less potent against mouse SCD1 enzyme and 7-fold less potent in human HepG2 cellular assay, while pyridin-4-ylmethyl analogue **17c** was more than 380-fold less potent against mouse SCD1 enzyme. Other analogues generated from replacement of pyridin-3-ylmethyl at $R^1$ such as oxazol-4-ylmethyl (**17d**), 1-methyl-1*H*-pyrazol-4-yl)methyl (**17e**), and methyl (**17f**) were all less potent against mouse SCD1 enzyme. Thus, the pyridin-3-ylmethyl group appears to be essential for maintaining the in vitro activity in this sub-series.

To evaluate the mechanism-based AEs associated with SCD1 deficiency of SCD1 inhibitors, we developed a preclinical safety

**Table 2**
SAR of pyrazolyltriazolones




| Compound | $R^1$ | Mouse SCD1 $IC_{50}$[a] (nM) | HepG2 SCD1 $IC_{50}$[a] (nM) | Metabolic stability[b] | Permeability[c] ($\times 10^{-6}$ cm/s) |
|---|---|---|---|---|---|
| **17a** | Pyridin-3-ylmethyl | 7 | 103 | 66 | 12/19 |
| **17b** | Pyridin-2-ylmethyl | 23 | 720 | 58 | nd |
| **17c** | Pyridin-4-ylmethyl | 2673 | nd | nd | nd |
| **17d** | Oxazol-4-ylmethyl | 165 | nd | nd | nd |
| **17e** | 1-Methyl-1*H*-pyrazol-4-yl)methyl | 147 | nd | nd | nd |
| **17f** | Methyl | 385 | nd | nd | nd |

nd: not determined.
[a] $IC_{50}$s are an average of at least two independent determinations; nd: not determined.
[b] Expressed as % of compound remaining after a 30 minute incubation with 0.5 mg/mL rat liver microsomes.
[c] Permeability was determined using Caco-2 cells. Data are expressed as $P_{app}$ (a to b)/$P_{app}$ (b to a).

**Table 3**
Rat PK profiles for compound **17a**

| Parameter | IV[a] (1 mg/kg) | P.O.[b] (5 mg/kg) |
|---|---|---|
| Cl (L/h/kg) | 1.1 | |
| $t_{½}$ (h) | 1.3 | 4.0 |
| $C_{max}$ (μM) | 3.3 | 2.3 |
| $T_{max}$ (h) | | 0.50 |
| $V_{ss}$ (L/kg) | 1.2 | |
| $AUC_{0-24\ h}$ (μM h) | 2.3 | 6.0 |
| $F$ (%) | | 52 |

[a] Average of two Lewis rats, intravenously dosed with **17a** in 10% DMA, 10% solutol, 50% PG and 30% water.
[b] Average of four Lewis rats, orally dosed with **17a** in 1% carboxymethyl cellulose (low viscosity), 0.2% Tween 20 and 98.8% water.

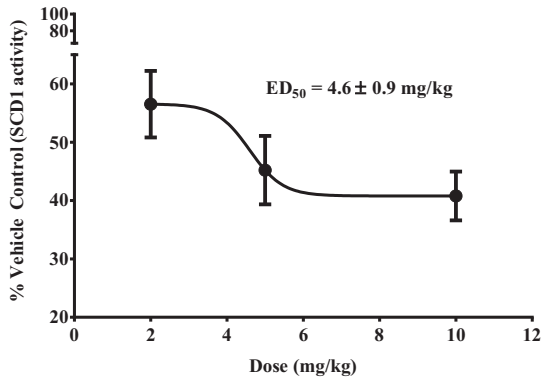



**Figure 3.** Dose response of compound **17a** on plasma C16:1/C16:0 TG desaturation index 4 h after oral dosing in Lewis rats. Each data point represents the mean ± SEM ($n$ = 4), and the error bars represent standard errors of the mean.

assessment screening model in rats.[30] This model provides an efficient means to assess the mechanism-based toxicity of SCD1 inhibitors at an early stage. Compounds **7a**, **7b 7e**, **7f**, **7o**, **7u**, **7v**, and **17a** were selected for evaluation in this model. Female Sprague-Dawley rats, which were found to be particularly sensitive to SCD1 AEs, were administered SCD1 inhibitors orally, once daily at 100 mg/kg (~20-fold of the efficacious dose) for 10 consecutive days. Rats were examined daily for general health and the specific observations on eyes and skin. Most inhibitors manifested mechanism-based toxicities, such as red eye, dry skin and hair loss as early as day 3 of dosing with symptoms. We were encouraged by the observation that **17a** did not elicit any abnormalities related to SCD inhibition or any other general health issue over the course of this study. The plasma exposure ($AUC_{0-24\ h}$) of compound **17a** on Day 11 was 207 μM h. Comparing this value to the exposure obtained in the Lewis rat model (5 mg/kg, $AUC_{0-24\ h}$ = 6.0 μM h), a greater than 34-fold window exists between efficacy and adverse effects due to SCD1 inhibition in these models. Though sebaceous and meibomian glands levels of **17a** was not determined, the improved AEs profile might indicate low exposure in these tissues due to its favorable physicochemical properties.

Compound **17a** was evaluated in the acute Lewis rat DI model in a dose–responsive manner, using doses from 2 mg/kg to 10 mg/kg and measuring effects at the 4 hour time point. The results indicated a dose–responsive reduction of plasma TG DI with an $ED_{50}$ estimated to be about 4.6 mg/kg (Fig. 3).

## 4. Conclusion

In summary, we discovered a series of novel, potent triazolone-based SCD1 inhibitors. SAR investigations addressing potency, metabolic stability and permeability led to the identification of **17a**, a potent, orally active SCD1 inhibitor, which demonstrated good in vivo efficacy reducing plasma C16:1/C16:0 TG DI in an acute Lewis rat model in a dose dependent manner, with an $ED_{50}$ of 4.6 mg/kg. In preliminary safety studies, compound **17a** did not demonstrate adverse effects related to SCD1 inhibition, suggesting that a safety margin was achieved as compared to previously identified SCD1 inhibitors. Further work including efforts toward optimization of in vivo efficacy and safety, as well as pharmacological evaluation in obesity and type 2 diabetes diseases models, will be reported in due course.

## 5. Experimental section

### 5.1. General method

Chemicals, reagents and solvents were purchased from commercial sources and were either used as supplied or purified using reported methods. Final compounds reported herein exhibited spectral data consistent with their proposed structure by nuclear magnetic resonance spectra ($^1$H NMR and $^{13}$C NMR) and mass spectra data. NMR spectra were recorded on a Bruker Avance 300 spectrometer with chemical shifts ($\delta$) reported in parts-per-million (ppm) relative to the residual signal of the deuterated solvent. $^1$H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), coupling constants in Hertz and number of protons. Mass spectra were obtained using a Waters 2795/ZQ LC/MS system (Waters Corporation, Milford, MA). Final compounds were greater than 95% pure as determined by analytical HPLC on Agilent 1200 systems (Agilent Technologies, Santa Clara, CA) using an EMD Chromolith SpeedROD RP-18e column (4.6 mm i.d. × 50 mm length) (Merck KGaA, Darmstadt, Germany). The mobile phase consisted of a gradient of component 'A' (0.1% v/v aqueous trifluoroacetic acid) and component 'B' (acetonitrile) at a flow rate of 1 mL/min. The gradient program used was as follows: initial conditions 5% B, hold at 5% B for 1 min., linear ramp from 5% to 95% B over 5 min., 100% B for 3 min., return to initial conditions for 1 min. Peaks were detected at a wavelength of 254 nm with an Agilent photodiode array detector. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Chemical names were generated using ChemBioDraw version 12.0 (CambridgeSoft, Cambridge, MA.).

#### 5.1.1. Ethyl 2-(hydrazinecarboxamido)-4-methylthiazole-5-carboxylate (3)

To a solution of **2** (100.0 g, 0.537 mol) and pyridine (74.0 mL, 0.913 mol) in anhydrous tetrahydrofuran (2.5 L) was added 4-nitrophenyl chloroformate (140.7 g, 0.698 mol) in anhydrous tetrahydrofuran (0.5 L) dropwise at 0 °C over 40 min. The reaction mixture was stirred for 2 h at 0 °C, then a solution of hydrazine monohydrate (156 mL, 0.322 mol) in anhydrous tetrahydrofuran (0.5 L) was added to the reaction mixture dropwise at 0 °C over 30 min. The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 2 h, then cooled to 0 °C. The solid was collected by filtration, rinsed with methanol (200 mL) and dried to afford **3** as a pale yellow solid (108.0 g, 82%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.24 (br s, 4H), 4.21 (t, $J$ = 7.1 Hz, 2H), 2.48 (s, 3H), 1.26 (t, $J$ = 7.1 Hz, 3H); MS (ES+) $m/z$ 245.0 (M+1).

#### 5.1.2. Ethyl 4-methyl-2-(5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)thiazole-5-carboxylate (4)

To a suspension of **3** (115.0 g, 0.471 mol) and trimethyl orthoformate (155.0 mL, 1.412 mol) in anhydrous ethanol (2.5 L) was

added $TsOH{\cdot}H_2O$ (1.0 g, 0.005 mol). The reaction mixture was heated at reflux for 2 h, then cooled to 0 °C. The solid was collected by filtration, rinsed with methanol (200 mL), and dried to afford **4** as an off-white solid (110.0 g, 91%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 12.94 (br s, 1H), 9.09 (s, 1H), 4.64 (t, $J$ = 7.1 Hz, 2H), 2.98 (s, 3H), 1.67 (t, $J$ = 7.1 Hz, 3H); MS (ES+) $m/z$ 255.0 (M+1).

#### 5.1.3. Ethyl 2-(1-(4-fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylate (5a)

To a solution of **4** (25.0 g, 98.4 mmol) and $K_2CO_3$ (20.4 g, 147.6 mmol) in acetone (800 mL) was added 4-fluorobenzyl benzyl bromide (15.7 mL, 126.0 mmol). The reaction mixture was heated at reflux for 5 h, then cooled to ambient temperature and filtered. The filtrate was concentrated in vacuo and the residue was triturated in hexanes (200 mL). The solid was collected by filtration, rinsed with water, and dried to afford **5a** as an off-white solid (30.0 g, 84%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.27 (s, 1H), 7.47–7.30 (m, 2H), 7.11–6.97 (m, 2H), 4.98 (s, 2H), 4.32 (q, $J$ = 7.1 Hz, 2H), 2.65 (s, 3H), 1.34 (t, $J$ = 7.1 Hz, 3H); MS (ES+) $m/z$ 363.1 (M+1).

#### 5.1.4. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylic acid (6a)

To a solution of **5** (30.0 g, 82.85 mmol) in ethanol (330 mL), and water (170 mL) was added NaOH (6.96 g, 174.0 mmol) at ambient temperature. The resulting reaction mixture was heated at reflux for 1 h, and then concentrated in vacuo to remove most of the organic volatiles. The residue was neutralized to pH 4–5 with 10% hydrochloric acid, and the resulting precipitate was collected by filtration, rinsed with water then diethyl ether and dried to afford **6a** as an off-white solid (20.21 g, 73%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.40 (br s, 1H), 8.74 (s, 1H), 7.37–7.31 (m, 2H), 7.19–7.11 (m, 2H), 4.96 (s, 2H), 2.57 (s, 3H); MS (ES−) $m/z$ 333.0 (M−1).

#### 5.1.5. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(pyridin-3-ylmethyl)thiazole-5-carboxamide (7a)

To a solution of **6a** (2.00 g, 5.98 mmol), EDCI (1.50 g, 7.82 mmol) and $^i$Pr$_2$NEt (2.67 mL, 15.64 mmol) in *N*,*N*-dimethylformamide (80 mL) was added HOBt (1.00 g, 7.40 mmol). The reaction mixture was stirred at ambient temperature for 15 min, followed by addition of 3-(aminomethyl)pyridine (0.73 mL, 7.16 mmol). After stirring for 17 h at ambient temperature, the reaction mixture was diluted with ethyl acetate (300 mL) and sequentially washed with water, saturated $NaHCO_3$ solution, water and brine. The organic solution was dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated in vacuo, and the residue was crystallized from ethyl acetate and hexanes to yield **7a** as an off-white solid (1.93 g, 76%), mp 178–180 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.59 (br s, 2H), 8.23 (s, 1H), 7.80–7.71 (m, 1H), 7.44–7.27 (m, 2H), 7.08–6.96 (m, 2H), 6.42 (t, $J$ = 5.8 Hz, 1H), 6.46 (t, $J$ = 7.4 Hz, 1H), 4.96 (s, 2H), 4.62 (d, $J$ = 5.8 Hz, 2H), 2.64 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 162.7 (d, $J_{CF}$ = 244 Hz), 161.7, 161.0, 159.6, 153.4, 151.0, 149.9, 136.1, 131.0, 130.8 (d, $J_{CF}$ = 3 Hz), 130.3 (d, $J_{CF}$ = 8 Hz), 121.6, 119.1, 115.8 (d, $J_{CF}$ = 22 Hz), 48.9, 41.6, 17.2; MS (ES+) $m/z$ 425.3 (M+1). Anal. Calcd for $C_{20}H_{17}FN6O_2S$: C, 56.59; H, 4.04; N, 19.80. Found: C, 56.24; H, 4.01; N, 19.55.

#### 5.1.6. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(pyridin-2-ylmethyl)thiazole-5-carboxamide (7b)

By a similar procedure described for **7a**, **7b** was obtained as an off-white solid (2.36 g, 46%). Mp 174–175 °C (ethanol); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.89 (t, $J$ = 5.8 Hz, 1H), 8.78 (s, 1H), 8.53–8.51 (m, 1H), 7.80–7.75 (m, 1H), 7.41–7.16 (m, 6H), 5.01 (s, 2H), 4.53 (d, $J$ = 5.8 Hz, 2H), 2.59 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.7 (d, $J_{CF}$ = 244 Hz), 161.1, 158.2, 151.4, 151.1, 149.7, 148.8, 136.7, 132.2 (d, $J_{CF}$ = 3 Hz), 132.0, 130.0 (d, $J_{CF}$ = 8 Hz), 122.4, 122.1, 120.9, 115.4 (d, $J_{CF}$ = 21 Hz), 47.7, 44.7, 16.9; MS (ES+) $m/z$ 424.9 (M+1). Anal. Calcd for $C_{20}H_{17}FN_6O_2S$: C, 56.59; H, 4.04; N, 19.80. Found: C, 56.24; H, 4.09; N, 19.74.

#### 5.1.7. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-((6-(trifluoromethyl)pyridin-3-yl)methyl)-thiazole-5-carboxamide (7c)

To a solution of **6** (0.33 g, 1.00 mmol) and $^i$Pr$_2$NEt (0.1 mL, 5.55 mmol) in anhydrous tetrahydrofuran (15 mL) was added TBTU (0.64 g, 1.99 mmol) and HOBt (0.27 g, 1.99 mmol). After stirring for 15 min at ambient temperature, a solution of 3-aminomethyl-6-(trifluoromethyl)pyridine (0.53 g, 3.00 mmol) in anhydrous tetrahydrofuran (10 mL) was added to the reaction mixture. After stirring at ambient temperature for 16 h, the reaction mixture was quenched with a saturated $NaHCO_3$ solution (20 mL), and extracted with ethyl acetate (30 mL × 3). The combined organic layers were dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography eluting with 5% methanol in dichloromethane to afford **7c** as an off-white solid (0.17 g, 34%). Mp 168–170 °C (dichloromethane/methanol); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.97 (t, $J$ = 5.8 Hz, 1H), 8.78 (s, 1H), 8.74 (d, $J$ = 1.3 Hz, 1H), 8.01 (dd, $J$ = 8.1, 1.3 Hz, 1H), 7.90 (d, $J$ = 8.1 Hz, 1H), 7.41–7.36 (m, 2H), 7.21–7.17 (m, 2H), 5.00 (s, 2H), 4.56–4.52 (m, 2H), 2.57 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 162.2 (d, $J_{CF}$ = 240 Hz), 161.7, 152.1, 152.0, 150.2, 149.9, 145.3 (t, $J_{CF}$ = 38 Hz), 139.4, 137.6, 132.7 (d, $J_{CF}$ = 8 Hz), 132.5, 130.5 (d, $J_{CF}$ = 8 Hz), 124.0, 122.3, 121.1, 115.9 (d, $J_{CF}$ = 23 Hz), 50.7, 48.2, 17.5; MS (ES+) $m/z$ 492.9 (M+1).

#### 5.1.8. *tert*-Butyl 3-((2-(1-(4-fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxamido)methyl)-piperidine-1-carboxylate (7dd)

By a similar procedure as described for **7c**, **7dd** was obtained as an off-white solid (0.82 g, 77%), which was used for next step without further purification. MS (ES+) $m/z$ 531.1 (M+1), 431.1 (M−100).

#### 5.1.9. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(piperidin-3-ylmethyl)thiazole-5-carboxamide trifluoroacetic acid salt (7d)

To a solution of **7dd** (0.82 g, 1.55 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (4.0 mL). The reaction mixture was stirred at ambient temperature for 16 h, then concentrated in vacuo. The residue was crystallized from ethanol and diethyl ether to yield **7d** as an off-white solid (0.43 g, 65%). Mp 137–138 °C (ethanol/diethyl ether); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.96–8.77 (m, 1H), 8.72 (s, 1H), 8.64–8.46 (m, 1H), 8.41 (t, $J$ = 5.7 Hz, 1H), 7.37–7.31 (m, 2H), 7.18–7.12 (m, 2H), 4.97 (s, 2H), 3.27–3.03 (m, 4H), 2.64–2.42 (m, 5H), 2.04–1.84 (m, 1H), 1.79–1.71 (m, 2H), 1.62–1.45 (m, 1H), 1.24–1.11 (m, 1H); MS (ES+) $m/z$ 431.1 (M+1).

#### 5.1.10. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-((5-methylpyrazin-2-yl)methyl)thiazole-5-carboxamide (7e)

By a similar procedure as described for **7a**, **7e** was obtained as an off-white solid (1.90 g, 58%). Mp 188–189 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.92 (t, $J$ = 5.7 Hz, 1H), 8.77 (s, 1H), 8.50–8.49 (m, 2H), 7.41–7.36 (m, 2H), 7.22–7.16 (m, 2H), 5.00 (s, 2H), 4.53 (d, $J$ = 5.7 Hz, 2H), 2.57 (s, 3H), 2.47 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.7 (d, $J_{CF}$ = 244 Hz), 161.1, 151.8, 151.4, 151.3, 150.5, 149.7, 143.3, 142.1, 132.2 (d, $J_{CF}$ = 3 Hz), 132.0, 130.0 (d, $J_{CF}$ = 8 Hz), 122.2, 115.5, 115.2, 47.7, 42.5, 20.7, 16.9; MS (ES+) $m/z$ 440.2 (M+1). Anal. Calcd for $C_{20}H_{18}FN_7O_2S$: C, 54.66; H, 4.13; N, 22.31. Found: C, 54.47; H, 4.11; N, 22.33.

#### 5.1.11. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(oxazol-4-ylmethyl)thiazole-5-carboxamide (7f)

By a similar procedure as described for **7a**, **7f** was obtained as an off-white solid (1.98 g, 51%). Mp 183–184 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.79–8.76 (m, 2H), 8.34 (s, 1H), 7.98 (s, 1H), 7.41–7.36 (m, 2H), 7.22–7.17 (m, 2H), 5.00 (s, 2H), 4.33 (d, $J$ = 5.4 Hz, 2H), 2.55 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 162.1 (d, $J_{CF}$ = 243 Hz), 160.9, 152.0, 151.3, 151.0, 149.7, 137.4, 136.1, 132.2 (d, $J_{CF}$ = 3 Hz), 132.0, 129.9 (d, $J_{CF}$ = 8 Hz), 122.4, 115.4 (d, $J_{CF}$ = 21 Hz), 47.7, 35.2, 16.9; MS (ES+) $m/z$ 415.3 (M+1). Anal. Calcd for $C_{18}H_{15}FN_6O_3S$: C, 52.17; H, 3.65; N, 20.28. Found: C, 52.12; H, 3.60; N, 20.54.

#### 5.1.12. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(oxazol-2-ylmethyl)thiazole-5-carboxamide (7g)

By a similar procedure as described for **7a**, **7g** was obtained as an off-white solid (0.14 g, 57%). Mp 152–153 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.26 (s, 1H), 7.65 (s, 1H), 7.41–7.32 (m, 2H), 7.09 (s, 1H), 7.07–6.98 (m, 2H), 6.54 (t, $J$ = 5.2 Hz, 1H), 4.98 (s, 2H), 4.73 (d, $J$ = 5.2 Hz, 2H), 2.67 (s, 3H); MS (ES+) $m/z$ 415.1 (M+1).

#### 5.1.13. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(thiazol-2-ylmethyl)thiazole-5-carboxamide (7h)

By a similar procedure as described for **7a**, **7h** was obtained as an off-white solid (0.17 g, 66%). Mp 189–190 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.25 (s, 1H), 7.74 (br s, 1H), 7.40–7.31 (m, 3H), 7.06–6.97 (m, 2H), 6.78 (t, $J$ = 5.4 Hz, 1H), 4.97 (s, 2H), 4.92 (d, $J$ = 5.4 Hz, 2H), 2.67 (s, 3H); MS (ES+) $m/z$ 431.1 (M+1).

#### 5.1.14. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-((2-methylthiazol-5-yl)methyl)thiazole-5-carboxamide (7i)

By a similar procedure as described for **7a**, **7i** was obtained as an off-white solid (0.18 g, 68%). Mp 176–177 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.25 (s, 1H), 7.41–7.31 (m, 2H), 7.07–6.97 (m, 3H), 6.49 (t, $J$ = 5.3 Hz, 1H), 4.97 (s, 2H), 4.62 (d, $J$ = 5.3 Hz, 2H), 2.70 (s, 3H), 2.64 (s, 3H); MS (ES+) $m/z$ 445.1 (M+1).

#### 5.1.15. *N*-((1*H*-Pyrazol-3-yl)methyl)-2-(1-(4-fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxamide (7j)

By a similar procedure as described for **7a**, **7j** was obtained as an off-white solid (1.77 g, 31%). Mp 181–182 °C (ethyl acetate); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 12.63 (br s, 1H), 8.76–8.72 (m, 2H), 7.62 (s, 1H), 7.41–7.36 (m, 2H), 7.22–7.17 (m, 2H), 6.17 (d, $J$ = 1.8 Hz, 1H), 5.00 (s, 2H), 4.42 (d, $J$ = 5.6 Hz, 2H), 2.56 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.7 (d, $J_{CF}$ = 244 Hz), 160.8, 151.3, 150.7, 149.7, 132.2 (d, $J_{CF}$ = 3 Hz), 132.1, 130.0 (d, $J_{CF}$ = 8 Hz), 129.1, 122.8, 115.4 (d, $J_{CF}$ = 22 Hz), 103.1, 47.7, 37.1, 16.9; MS (ES+) $m/z$ 413.8 (M+1); Anal. Calcd for $C_{18}H_{16}FN_7O_2S$: C, 52.29; H, 3.90; N, 23.72. Found: C, 51.78; H, 3.94; N, 23.23.

#### 5.1.16. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-((3-methyl-1*H*-pyrazol-5-yl)methyl)-thiazole-5-carboxamide (7k)

By a similar procedure as described for **7a**, **7k** was obtained as an off-white solid (1.90 g, 35%). Mp 237–238 °C (*N*,*N*-dimethylformamide/water); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 12.25 (br s, 1H), 8.76 (s, 1H), 8.67 (t, $J$ = 5.5 Hz, 1H), 7.41–7.16 (m, 4H), 5.91 (s, 1H), 5.00 (s, 2H), 4.33 (d, $J$ = 5.5 Hz, 2H), 2.55 (s, 3H), 2.17 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.7 (d, $J_{CF}$ = 244 Hz), 160.7, 151.2, 150.5, 149.7, 149.6, 138.7, 132.2 (d, $J_{CF}$ = 3 Hz), 132.1, 130.0 (d, $J_{CF}$ = 8 Hz), 122.9, 115.4 (d, $J_{CF}$ = 22 Hz), 102.3, 47.7, 37.3, 16.9, 10.4; MS (ES+) $m/z$ 428.0 (M+1); Anal. Calcd for $C_{19}H_{18}FN_7O_2S$: C, 53.39; H, 4.24; N, 22.94. Found: C, 53.47; H, 4.28; N, 22.82.

#### 5.1.17. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-((1-methyl-1*H*-pyrazol-4-yl)methyl)thiazole-5-carboxamide (7l)

By a similar procedure as described for **7a**, **7l** was obtained as an off-white solid (2.55 g, 62%). Mp 205–206 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.76 (s, 1H), 8.66 (t, $J$ = 5.6 Hz, 1H), 7.60 (s, 1H), 7.40–7.45 (m, 3H), 7.22–7.17 (m, 2H), 5.00 (s, 2H), 4.23 (d, $J$ = 5.6 Hz, 2H), 3.78 (s, 3H), 2.55 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.7 (d, $J_{CF}$ = 244 Hz), 160.6, 151.2, 150.7, 149.7, 138.0, 132.2 (d, $J_{CF}$ = 3 Hz), 132.0, 130.0 (d, $J_{CF}$ = 8 Hz), 129.5, 122.6, 118.6, 115.4 (d, $J_{CF}$ = 21 Hz), 47.7, 38.4, 33.6, 16.9; MS (ES+) $m/z$ 428.1 (M+1); Anal. Calcd for $C_{19}H_{18}FN_7O_2S$: C, 53.39; H, 4.24; N, 22.94. Found: C, 53.41; H, 4.26; N, 23.28.

#### 5.1.18. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-((1-methyl-1*H*-imidazol-4-yl)methyl)thiazole-5-carboxamide (7m)

By a similar procedure as described for **7a**, **7m** was obtained as an off-white solid (2.01 g, 57%). Mp 225–226 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.76 (s, 1H), 8.65–8.60 (m, 1H), 7.49 (s, 1H), 7.41–7.35 (m, 2H), 7.22–7.17 (m, 2H), 6.96 (s, 1H), 5.00 (s, 2H), 4.27 (d, $J$ = 5.6 Hz, 2H), 3.60 (s, 3H), 2.55 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.7 (d, $J_{CF}$ = 244 Hz), 160.7, 151.2, 150.4, 149.7, 138.9, 137.2, 132.2 (d, $J_{CF}$ = 3 Hz), 132.0, 130.0 (d, $J_{CF}$ = 84 Hz), 122.9, 117.6, 115.4 (d, $J_{CF}$ = 22 Hz), 47.7, 37.4, 32.8, 16.9; MS (ES+) $m/z$ 428.2 (M+1). Anal. Calcd for $C_{19}H_{18}FN_7O_2S$: C, 53.39; H, 4.24; N, 22.94. Found: C, 53.50; H, 4.11; N, 22.89.

#### 5.1.19. 2-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxamide (7n)

To a solution of **6** (0.35 g, 1.05 mmol) and $^i$Pr$_2$NEt (1.09 mL, 6.28 mmol) in anhydrous *N*,*N*-dimethylformamide (10 mL) was added HOBt (0.28 g, 2.09 mmol), HATU (0.80 g, 2.09 mmol), and $NH_4Cl$ (0.22 g, 4.19 mmol). The resulting reaction mixture was stirred at ambient temperature for 72 h then concentrated in vacuo. The residue was triturated with saturated $NaHCO_3$ solution (100 mL). The crude product was collected by filtration, rinsed with water and then recrystallization in ethanol to afford **7n** as an off-white solid (0.27 g, 73%). Mp 232–233 °C (ethanol); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.75 (s, 1H), 7.64 (br s, 2H), 7.40–7.36 (m, 2H), 7.22–7.16 (m, 2H), 5.00 (s, 2H), 2.55 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 162.7, 161.69 (d, $J_{CF}$ = 244 Hz), 151.3, 150.9, 149.7, 132.2 (d, $J_{CF}$ = 3 Hz), 132.0, 129.9 (d, $J_{CF}$ = 8 Hz), 123.0, 115.4 (d, $J_{CF}$ = 22 Hz), 47.7, 16.8; MS (ES+) $m/z$ 334.3 (M+1).

#### 5.1.20. Ethyl 4-methyl-2-(5-oxo-1-(4-(trifluoromethyl)-benzyl)-1*H*-1,2,4-triazol-4(5*H*)-yl)thiazole-5-carboxylate (5b)

By a similar procedure as described for **5a**, **5b** was obtained as an off-white solid (16.0 g, 99%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.29 (s, 1H), 7.61 (d, $J$ = 8.3 Hz, 2H), 7.50 (d, $J$ = 8.3 Hz, 2H), 5.07 (s, 2H), 4.32 (q, $J$ = 7.1 Hz, 2H), 2.67 (s, 3H), 1.35 (t, $J$ = 7.1 Hz, 3H); MS (ES+) $m/z$ 413.2 (M+1).

#### 5.1.21. 4-Methyl-2-(5-oxo-1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,4-triazol-4(5*H*)-yl)thiazole-5-carboxylic acid (6b)

By a similar procedure as described for **6a**, **6b** was obtained as an off-white solid (11.8 g, 80%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.43 (br s, 1H), 8.82 (s, 1H), 7.75–7.72 (m, 2H), 7.57–7.54 (m, 2H), 5.13 (s, 2H), 2.61 (s, 3H); MS (ES+) $m/z$ 385.2 (M+1).

#### 5.1.22. 4-Methyl-2-(5-oxo-1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,4-triazol-4(5*H*)-yl)-*N*-(pyridin-3-ylmethyl)thiazole-5-carboxamide (7o)

By a similar procedure as described for **7a**, **7o** was obtained as an off-white solid (2.95 g, 79%). Mp 168–169 °C (ethyl acetate/hexanes). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.58 (s, 1H), 8.55 (s, 1H), 8.30–8.27 (m, 1H), 7.73–7.68 (m, 1H), 7.65–7.58 (m, 2H), 7.53–7.46 (m, 2H), 7.42–7.23 (m, 1H), 6.21 (s, 1H), 5.07 (s, 2H), 4.63–4.60 (m, 2H), 2.65 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.6, 153.3, 151.0, 149.9, 149.3, 138.9, 135.7, 131.2, 128.7, 125.9 (q, $J_{CF}$ = 112 Hz), 125.7, 123.9 (d, $J_{CF}$ = 271 Hz), 123.8, 122.9, 121.8, 49.1, 41.6, 17.2; MS (ES+) *m*/*z* 475.3 (M+1). Anal. Calcd for $C_{21}H_{17}F_3N_6O_2S$: C, 53.16; H, 3.61; N, 17.71. Found: C, 52.94; H, 3.71; N, 17.52.

#### 5.1.23. Ethyl 2-(1-(3,5-difluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylate (5c)

By a similar procedure as described for **5a**, **5c** was obtained as an off-white solid (7.0 g, 93%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.82 (s, 1H), 7.23–7.16 (m, 1H), 7.12–7.05 (m, 2H), 5.06 (s, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.64 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

#### 5.1.24. 2-(1-(3,5-Difluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylic acid (6c)

By a similar procedure as described for **6a**, **6c** was obtained as an off-white solid (4.66 g, 73%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.42 (br s, 1H), 8.79 (s, 1H), 7.22–7.06 (m, 3H), 5.06 (s, 2H), 2.61 (s, 3H).

#### 5.1.25. 2-(1-(3,5-Difluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(pyridin-3-ylmethyl)thiazole-5-carboxamide (7p)

By a similar procedure as described for **7a**, **7p** was obtained as an off-white solid (0.10 g, 80%). Mp 194–196 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.91 (t, *J* = 5.8 Hz, 1H), 8.79 (s, 1H), 8.55 (d, *J* = 1.9 Hz, 1H), 8.41–8.38 (m, 1H), 7.76–7.70 (m, 1H), 7.42–7.35 (m, 1H), 7.23–7.07 (m, 3H), 5.06 (s, 2H), 4.44 (d, *J* = 5.8 Hz, 2H), 2.58 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 162.4 (dd, $J_{CF}$ = 246 Hz, 13 Hz), 161.1, 151.5, 151.3, 149.9, 148.9, 148.1, 140.5 (dd, $J_{CF}$ = 9 Hz, 9 Hz), 135.2, 134.7, 132.4, 123.5, 122.0, 110.9–110.6 (m), 103.2 (dd, $J_{CF}$ = 26 Hz, 26 Hz), 47.4, 40.5, 16.9; MS (ES+) *m*/*z* 442.8 (M+1).

#### 5.1.26. Ethyl 4-methyl-2-(5-oxo-1-((5-(trifluoromethyl)-furan-2-yl)methyl)-1*H*-1,2,4-triazol-4(5*H*)-yl)thiazole-5-carboxylate (5d)

By a similar procedure as described for **5a**, **5d** was obtained as an off-white solid (0.31 g, 56%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.26 (s, 1H), 6.69–6.62 (m, 1H), 6.29–6.20 (m, 1H), 5.03 (s, 2H), 4.32 (q, *J* = 7.0 Hz, 2H), 2.64 (s, 3H), 1.35 (t, *J* = 7.0 Hz, 3H); MS (ES+) *m*/*z* 403.3 (M+1).

#### 5.1.27. 4-Methyl-2-(5-oxo-1-((5-(trifluoromethyl)-furan-2-yl)methyl)-1*H*-1,2,4-triazol-4(5*H*)-yl)thiazole-5-carboxylic acid (6d)

By a similar procedure as described for **6a**, **6d** was obtained as an off-white solid (0.2 g, 84%). MS (ES−) *m*/*z* 373.0 (M−1).

#### 5.1.28. 4-Methyl-2-(5-oxo-1-((5-(trifluoromethyl)furan-2-yl)methyl)-1*H*-1,2,4-triazol-4(5*H*)-yl)-*N*-(pyridin-3-ylmethyl)thiazole-5-carboxamide (7q)

By a similar procedure as described for **7a**, **7q** was obtained as an off-white solid (0.16 g, 57%). Mp 124–125 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.63 (s, 2H), 8.28 (s, 1H), 7.82–7.75 (m, 1H), 7.36 (s, 1H), 6.77–6.72 (m, 1H), 6.52 (t, *J* = 5.5 Hz, 1H), 6.47–6.42 (m, 1H), 5.04 (s, 2H), 4.66–4.60 (m, 2H), 2.64 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.6, 153.3, 150.8 (d, $J_{CF}$ = 28 Hz), 149.2 (d, $J_{CF}$ = 41 Hz), 135.7, 131.4, 123.7 (q, $J_{CF}$ = 2 Hz), 122.1(d, $J_{CF}$ = 244 Hz), 116.9, 122.5 (q, $J_{CF}$ = 3 Hz), 110.4, 42.1, 41.6, 17.2; MS (ES+) *m*/*z* 465.3 (M+1).

#### 5.1.29. Ethyl 2-(1-(2-(4-fluorophenoxy)ethyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylate (5e)

By a similar procedure as described for **5a**, **5e** was obtained as an off-white solid (0.11 g, 48%) by column chromatography eluting with 10–50% a gradient ethyl acetate in hexanes. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.26 (s, 1H), 6.93–6.84 (m, 2H), 6.81–6.75 (m, 2H), 4.32–4.15 (m, 6H), 2.62 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); MS (ES+) *m*/*z* 393.3 (M+1).

#### 5.1.30. 2-(1-(2-(4-Fluorophenoxy)ethyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylic acid (6e)

By a similar procedure as described for **6a**, **6e** was obtained as an off-white solid (0.08 g, 78%). MS (ES−) *m*/*z* 363.1 (M−1).

#### 5.1.31. 2-(1-(2-(4-Fluorophenoxy)ethyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(pyridin-3-ylmethyl)thiazole-5-carboxamide (7r)

By a similar procedure as described for **7a**, **7r** was obtained as an off-white solid (0.03 g, 45%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.58 (br s, 1H), 8.53–8.45 (m, 1H), 8.26 (s, 1H), 7.72–7.65 (m, 1H), 7.30–7.21 (m, 1H), 6.98–6.86 (m, 2H), 6.85–6.75 (m, 2H), 6.61 (t, *J* = 5.8 Hz, 1H), 4.59 (d, *J* = 5.8 Hz, 2H), 4.28–4.15 (m, 4H), 2.63 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.7, 157.6 (d, $J_{CF}$ = 239 Hz), 154.2, 153.3, 150.6 (d, $J_{CF}$ = 59 Hz), 149.2 (d, $J_{CF}$ = 16 Hz), 135.8, 133.6, 131.0, 123.7, 121.6, 116.0, 115.9, 115.8, 115.7, 65.5, 45.3, 41.6, 17.2; MS (ES+) *m*/*z* 455.3 (M+1).

#### 5.1.32. Ethyl 2-(1-(cyclopropylmethyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylate (5f)

By a similar procedure as described for **5a**, **5f** was obtained as a off-white solid (2.47 g, 99%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.27 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.63 (d, *J* = 7.1 Hz, 2H), 2.64 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.19–1.04 (m, 1H), 0.53–0.42 (m, 2H), 0.36–0.27 (m, 2H); MS (ES+) *m*/*z* 309.2 (M+1).

#### 5.1.33. 2-(1-(Cyclopropylmethyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylic acid (6f)

By a similar procedure as described for **6a**, **6f** was obtained as a off-white solid (2.1 g, 95%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.39 (br s, 1H), 8.72 (s, 1H), 3.63 (d, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 1.19–1.04 (m, 1H), 0.53–0.42 (m, 2H), 0.36–0.27 (m, 2H); MS (ES−) *m*/*z* 279.0 (M−1).

#### 5.1.34. 2-(1-(Cyclopropylmethyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(pyridin-3-ylmethyl)thiazole-5-carboxamide (7s)

By a similar procedure as described for **7a**, **7s** was obtained as an off-white solid (2.38 g, 89%). Mp 136–137 °C (ethyl acetate/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.57 (br s, 1H), 8.47 (br s, 1H), 8.24 (s, 1H), 7.79–7.71 (m, 1H), 7.44–7.27 (m, 1H), 6.38 (t, *J* = 5.8 Hz, 1H), 4.62 (d, *J* = 5.8 Hz, 2H), 3.70 (d, *J* = 7.2 Hz, 2H), 2.65 (s, 3H), 1.34–1.14 (m, 1H), 0.63–0.52 (m, 2H), 0.46–0.31 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.8, 153.4, 151.2, 149.9, 149.2, 148.9, 135.8, 133.7, 130.5, 123.8, 121.4, 117.9, 50.6, 41.6, 17.2, 10.2, 3.7; MS (ES+) *m*/*z* 371.3 (M+1). Anal. Calcd for $C_{17}H_{18}N_6O_2S$: C, 55.12; H, 4.90; N, 22.69. Found: C, 55.05; H, 4.90; N, 22.99.

#### 5.1.35. Ethyl 2-(1-((2,2-difluorocyclopropyl)methyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylate (5g)

By a similar procedure as described for **5a**, **5g** was obtained as an off-white solid (10.8 g, 98%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.74 (s, 1H), 4.23 (t, *J* = 7.1 Hz, 2H), 3.97–3.77 (m, 2H), 2.54 (s,

3H), 2.20–2.04 (m, 1H), 1.73–1.60 (m, 1H), 1.48–1.37 (m, 1H), 1.26 (t, $J$ = 7.1 Hz, 3H); MS (ES+) $m/z$ 344.9 (M+1).

#### 5.1.36. 2-(1-((2,2-Difluorocyclopropyl)methyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylic acid (6g)

By a similar procedure as described for **6a**, **6g** was obtained as an off-white solid (1.21 g, 80%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.43 (br s, 1H), 8.74 (s, 1H), 3.97–3.77 (m, 2H), 2.54 (s, 3H), 2.20–2.04 (m, 1H), 1.73–1.60 (m, 1H), 1.48–1.37 (m, 1H); MS (ES+) $m/z$ 317.1 (M+1).

#### 5.1.37. 2-(1-((2,2-Difluorocyclopropyl)methyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(pyridin-3-ylmethyl)thiazole-5-carboxamide (7t)

By a similar procedure as described for **7a**, **7t** was obtained as an off-white solid (2.90 g, 90%). Mp 120–122 °C (ethanol/diethyl ether); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.87 (t, $J$ = 5.8 Hz, 1H), 8.75 (s, 1H), 8.51 (s, 1H), 8.43 (d, $J$ = 3.7 Hz, 1H), 7.69 (d, $J$ = 7.9 Hz, 1H), 7.33 (dd, $J$ = 7.8, 4.8 Hz, 1H), 4.44 (d, $J$ = 5.8 Hz, 2H), 4.01–3.83 (m, 2H), 2.57 (s, 3H), 2.24–2.08 (m, 1H), 1.77–1.63 (m, 1H), 1.52–1.40 (m, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 160.9, 151.3, 151.2, 149.4, 148.8, 148.0, 135.1, 131.8, 123.4, 122.0, 113.9 (t, $J_{CF}$ = 285 Hz), 42.2, 42.1, 20.2 (t, $J_{CF}$ = 8 Hz), 16.8, 14.4 (t, $J_{CF}$ = 8 Hz); MS (ES+) $m/z$ 406.8 (M+1); Anal. Calcd for $C_{17}H_{16}F_2N_6O_2S$: C, 50.24; H, 3.97; N, 20.68. Found: C, 50.41; H, 4.03; N, 20.44.

#### 5.1.38. Ethyl 4-methyl-2-(5-oxo-1-(4,4,4-trifluorobutyl)-1*H*-1,2,4-triazol-4(5*H*)-yl)thiazole-5-carboxylate (5h)

By a similar procedure as described for **5a**, **5h** was obtained as an off-white solid (0.09 g, 32%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.28 (s, 1H), 4.29 (q, $J$ = 7.1 Hz, 2H), 3.92 (t, $J$ = 6.6 Hz, 2H), 2.64 (s, 3H), 2.99–1.96 (m, 4H), 1.35 (t, $J$ = 7.1 Hz, 3H); MS (ES+) $m/z$ 365.3 (M+1).

#### 5.1.39. 4-Methyl-2-(5-oxo-1-(4,4,4-trifluorobutyl)-1*H*-1,2,4-triazol-4(5*H*)-yl)thiazole-5-carboxylic acid (6h)

By a similar procedure as described for **6a**, **6h** was obtained as an off-white solid (0.07 g, 84%). MS (ES−) $m/z$ 335.2 (M−1).

#### 5.1.40. 4-Methyl-2-(5-oxo-1-(4,4,4-trifluorobutyl)-1*H*-1,2,4-triazol-4(5*H*)-yl)-*N*-(pyridin-3-ylmethyl)thiazole-5-carboxamide (7u)

By a similar procedure as described for **7a**, **7u** was obtained as an off-white solid (0.04 g, 45%). Mp 192–195 °C (ethyl acetate/hexane); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.87 (s, 1H), 8.71 (s, 1H), 8.51 (d, $J$ = 1.7 Hz, 1H), 8.43 (dd, $J$ = 4.7, 1.4 Hz, 1H), 7.69 (d, $J$ = 8.4 Hz, 1H), 7.33 (dd, $J$ = 7.8, 4.7 Hz, 1H), 4.40 (s, 2H), 3.84 (t, $J$ = 6.7 Hz, 2H), 2.53 (s, 3H), 2.41–2.24 (m, 2H), 1.93–1.83 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.5, 151.9, 151.8, 150.2, 149.3, 148.6, 135.6, 135.2, 132.3, 129.8, 124.0, 122.4, 44.1, 41.0, 30.2 (q, $J_{CF}$ = 120 Hz), 21.2, 17.4; MS (ES+) $m/z$ 427.2 (M+1).

#### 5.1.41. 4-Methyl-2-(5-oxo-1-(4-(trifluoromethyl)benzyl)-1*H*-1,2,4-triazol-4(5*H*)-yl)-*N*-(pyridin-2-ylmethyl)thiazole-5-carboxamide (7v)

By a similar procedure as described for **7a**, **7v** was obtained as an off-white solid (4.80 g, 77%). Mp 168–169 °C (ethanol/water); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.89 (t, $J$ = 5.8 Hz, 1H), 8.82 (s, 1H), 8.53–8.51 (m, 1H), 7.80–7.72 (m, 3H), 7.56 (d, $J$ = 8.1 Hz, 2H), 7.34 (d, $J$ = 8.1 Hz, 1H), 7.29–7.25 (m, 1H), 5.14 (s, 2H), 4.53 (d, $J$ = 5.8 Hz, 2H), 2.60 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.1, 158.2, 151.4, 151.1, 149.8, 148.8, 140.7, 136.7, 132.3, 128.5, 128.4 (q, $J_{CF}$ = 32 Hz), 125.5 (q, $J_{CF}$ = 4 Hz), 124.2 (d, $J_{CF}$ = 272 Hz), 122.5, 122.1, 120.9, 47.9, 44.7, 16.9; MS (ES+) $m/z$ 474.8 (M+1). Anal. Calcd for $C_{21}H_{17}F_3N_6O_2S$: C, 53.16; H, 3.61; N, 17.71. Found: C, 53.19; H, 3.66; N, 17.67.

#### 5.1.42. Ethyl 2-(1-(1-(4-fluorophenyl)ethyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylate (5i)

By a similar procedure as described for **5a**, **5i** was obtained as an off-white solid (6.30 g, 69%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.81 (s, 1H), 7.45–7.40 (m, 2H), 7.21–7.16 (m, 2H), 5.49 (q, $J$ = 7.1 Hz, 1H), 4.28 (q, $J$ = 7.1 Hz, 2H), 2.61 (s, 3H), 1.71 (d, $J$ = 7.1 Hz, 3H), 1.29 (t, $J$ = 7.1 Hz, 3H); MS (ES+) $m/z$ 377.1 (M+1).

#### 5.1.43. 2-(1-(1-(4-Fluorophenyl)ethyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methylthiazole-5-carboxylic acid (6i)

By a similar procedure as described for **6a**, **6i** was obtained as an off-white solid (0.56 g, 78%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.43 (br s, 1H), 8.80 (s, 1H), 7.45–7.40 (m, 2H), 7.21–7.16 (m, 2H), 5.49 (q, $J$ = 7.1 Hz, 1H), 2.60 (s, 3H), 1.70 (d, $J$ = 7.1 Hz, 3H); MS (ES+) $m/z$ 349.0 (M+1).

#### 5.1.44. 2-(1-(1-(4-Fluorophenyl)ethyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-4-methyl-*N*-(pyridin-2-ylmethyl)thiazole-5-carboxamide (7w)

By a similar procedure as described for **7a**, **7w** was obtained as an off-white solid (2.35 g, 75%). Mp 169–170 °C (tetrahedrofuran/diethyl ether); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.87 (t, $J$ = 5.8 Hz, 1H), 8.80 (s, 1H), 8.50 (d, $J$ = 4.7 Hz, 1H), 7.81–7.75 (m, 1H), 7.45–7.40 (m, 2H), 7.33 (d, $J$ = 7.9 Hz, 1H), 7.27 (dd, $J$ = 7.2, 5.0 Hz, 1H), 7.22–7.17 (m, 2H), 5.50 (q, $J$ = 6.9 Hz, 1H), 4.52 (d, $J$ = 5.8 Hz, 2H), 2.59 (s, 3H), 1.70 (d, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.4 (d, $J_{CF}$ = 244 Hz), 161.0, 158.1, 151.2, 150.9, 149.1, 148.7, 136.9 (d, $J_{CF}$ = 3 Hz), 136.6, 131.8, 128.6 (d, $J_{CF}$ = 8 Hz), 122.4, 115.2 (d, $J_{CF}$ = 21 Hz), 120.8, 52.9, 44.6, 19.8, 16.8; MS (ES+) $m/z$ 439.1 (M+1).

#### 5.1.45. Methyl 3-nitro-1*H*-pyrazole-5-carboxylate (9)

To a solution of **8** (20.0 g, 127.32 mmol) in anhydrous methanol (70 mL) was added $SOCl_2$ (10.2 mL, 140.11 mmol) dropwise at 0 °C. The resulting mixture was heated at reflux for 16 h, and then concentrated in vacuo. The residue was dissolved in ethyl acetate (200 mL) and washed with saturated $NaHCO_3$ solution (40 mL × 2), water (40 mL), and brine (40 mL), dried over anhydrous $Na_2SO_4$, and filtered. The filtrate was concentrated in vacuo, and the residue was crystallized from ethyl acetate/hexane to afford **9** as an off-white solid (15.0 g, 69%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 11.52 (br s, 1H), 7.41 (s, 1H), 4.01 (s, 3H); MS (ES−) $m/z$ 170.0 (M−1).

#### 5.1.46. Methyl 1-(4-methoxybenzyl)-3-nitro-1*H*-pyrazole-5-carboxylate (10)

To a mixture of **9** (13.00 g, 76.02 mmol) and $K_2CO_3$ (18.30 g, 132.40 mmol) in anhydrous *N*,*N*-dimethylformamide (350 mL) was added 4-methoxybenzyl bromide (15.0 mL, 120.38 mmol). The resulting mixture was heated at 60 °C for 5 h. The solid was filtered off and the filtrate was concentrated under reduced pressure at a temperature below 80 °C. The residue was dissolved in ethyl acetate (500 mL), washed with 10% aqueous $NH_4Cl$ solution (100 mL × 2) and brine (100 mL), dried over anhydrous $Na_2SO_4$, and filtered. The filtrate was concentrated in vacuo, and the residue was crystallized from methanol to afford crude **10** as an off-white solid (23.0 g), which was used in the next step without further purification. For an analytical sample, a small amount of crude material was purified by column chromatography eluted with a gradient of 50–80% dichloromethane in hexanes to afford **10** as an off-white solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.39 (s, 1H), 7.34

(d, $J$ = 8.6 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 5.76 (s, 2H), 3.92 (s, 3H), 3.78 (s, 3H).

#### 5.1.47. Methyl 3-amino-1-(4-methoxybenzyl)-1*H*-pyrazole-5-carboxylate (11)

To a solution of crude **10** (23.0 g, 78.96 mmol) in methanol (500 mL) and tetrahydrofuran (100 mL) was added palladium (10% Pd on carbon). The reaction mixture was stirred under hydrogen atmosphere at ambient temperature for 48 h, then filtered through a pad of celite. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography eluted using a gradient of 3–10% methanol in dichloromethane to afford **11** as a pale yellow solid (17.0 g, 82%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.21–7.18 (m, 2H), 6.82–6.79 (m, 2H), 6.15 (s, 1H), 5.48 (s, 2H), 5.28 (s, 2H), 3.81 (s, 3H), 3.75 (s, 3H); MS (ES+) $m/z$ 283.8 (M+23).

#### 5.1.48. Methyl 3-(hydrazinecarboxamido)-1-(4-methoxybenzyl)-1*H*-pyrazole-5-carboxylate (12)

To a solution of **11** (6.90 g, 26.41 mmol) and pyridine (2.57 mL, 31.77 mmol) in dichloromethane (80 mL) and tetrahydrofuran (80 mL) was added 4-nitrophenyl chloroformate in dichloromethane (20 mL) dropwise at 0 °C. The reaction mixture was stirred at ambient temperature for 2.5 h. Hydrazine monohydrate (7.68 mL, 158.32 mmol) was added and stirring was continued for 3 h, then the mixture was concentrated in vacuo. The residue was triturated in dichloromethane (100 mL). The solid was collected by filtration, rinsed with water (100 mL) and dried to give **12** as an off-white solid (5.90 g, 70%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.45 (br s, 1H), 7.21–7.18 (m, 2H), 6.96 (br s, 2H), 6.84–6.81 (m, 2H), 5.57 (s, 2H), 5.28 (s, 2H), 3.84 (s, 3H), 3.76 (s, 3H); MS (ES+) $m/z$ 319.8 (M+1).

#### 5.1.49. Methyl 1-(4-methoxybenzyl)-3-(5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-1*H*-pyrazole-5-carboxylate (13)

To a suspension of **12** (5.20 g, 16.28 mmol) and trimethyl orthoformate (5.18 g, 48.90 mmol) in ethanol (160 mL) was added $TsOH{\cdot}H_2O$ (0.50 g, 2.60 mmol). The reaction mixture was heated at reflux for 2.5 h then cooled to 0 °C. The solid was recovered by filtration, rinsed with diethyl ether and dried to afford **13** as an off-white solid (3.81 g, 71%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 12.07 (br s, 1H), 8.30 (d, $J$ = 1.2 Hz, 1H), 7.17–7.12 (m, 3H), 6.86–6.83 (m, 2H), 5.59 (s, 2H), 3.82 (s, 3H), 3.68 (s, 3H); MS (ES+) $m/z$ 351.7 (M+23).

#### 5.1.50. Methyl 3-(1-(4-fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-1-(4-methoxybenzyl)-1*H*-pyrazole-5-carboxylate (14)

To a mixture of **13** (4.48 g, 13.60 mmol) and $K_2CO_3$ (2.82 g, 20.40 mmol) in acetone (450 mL) was added 4-fluorobenzyl bromide (2.1 mL, 16.85 mmol). The reaction mixture was heated at reflux for 3.5 h. The hot reaction mixture was filtered and washed with acetone. The filtrate was concentrated in vacuo, and the residue was crystallized from acetone and diethyl ether to afford **14** as an off-white solid (5.90 g, 98%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.79 (s, 1H), 7.33–7.29 (m, 2H), 7.20–7.17 (m, 3H), 6.99–6.94 (m, 2H), 6.78–6.75 (m, 2H), 5.58 (s, 2H), 4.91 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H); MS (ES+) $m/z$ 459.9 (M+23).

#### 5.1.51. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-1-(4-methoxybenzyl)-1*H*-pyrazole-5-carboxylic acid (15)

To a solution of **14** (3.80 g, 8.69 mmol) in ethanol (100 mL) and water (20 mL) was added NaOH (0.728 g, 18.20 mmol). The reaction mixture was heated at reflux for 2 h, then concentrated in vacuo to remove most of the organic volatiles. The residue was neutralized to pH 4 ~ 5 with 10% hydrochloric acid solution. The solid was collected by filtration, rinsed with water and diethyl ether, then dried to afford **15** as an off-white solid (3.50 g, 95%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.83 (br s, 1H), 8.44 (s, 1H), 7.38–7.23 (m, 2H), 7.21–7.16 (m, 4H), 7.11 (s, 1H), 6.89–6.86 (m, 2H), 5.64 (s, 2H), 4.94 (s, 2H), 3.71 (s, 3H); MS (ES+) $m/z$ 445.9 (M+23).

#### 5.1.52. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-1-(4-methoxybenzyl)-*N*-(pyridin-3-ylmethyl)-1*H*-pyrazole-5-carboxamide (16a)

To a solution of **15** (2.00 g, 4.72 mmol) and $^i$Pr$_2$NEt (5.0 mL 28.70 mmol) in anhydrous tetrahydrofuran (110 mL) was added HOBt (1.28 g, 9.45 mmol), TBTU (3.03 g, 9.43 mmol), and 3-(aminomethyl)pyridine (0.73 mL, 7.16 mmol). The reaction mixture was stirred at ambient temperature for 3 h, then concentrated in vacuo. The residue was triturated in saturated $NaHCO_3$ solution (400 mL). The solid was collected by filtration, rinsed with water and dried to afford **16a** as an off-white solid (2.30 g, 95%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.37 (t, $J$ = 5.9 Hz, 1H), 8.53–8.43 (m, 2H), 8.44 (s, 1H), 7.68–7.64 (m, 1H), 7.37–7.32 (m, 4H), 7.21–7.14 (m, 4H), 6.85–6.82 (m, 2H), 5.65 (s, 2H), 4.95 (s, 2H), 4.45 (d, $J$ = 5.9 Hz, 2H), 3.71 (s, 3H); MS (ES+) $m/z$ 514.0 (M+1).

#### 5.1.53. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-*N*-(pyridin-3-ylmethyl)-1*H*-pyrazole-5-carboxamide (17a)

To a solution of **16a** (3.50 g, 6.82 mmol) in dichloromethane (100 mL) was added trifluoroacetic acid (100 mL) and trifluoromethanesulfonic acid (5.30 g, 35.31 mmol). The dark purple reaction mixture was stirred at ambient temperature for 1.5 h and concentrated in vacuo. The residue was triturated in methanol (30 mL) and saturated aqueous $NaHCO_3$ solution (100 mL). The solid was collected by filtration and rinsed with water. The crude product was then purified by column chromatography eluting with a gradient of 2–10% methanol in $CH_2Cl_2$ then recrystallization from ethanol to afford **17** as an off-white solid (1.72 g, 64%). Mp 235–236 °C (ethanol); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.84 (br s, 1H), 9.31 (t, $J$ = 5.8 Hz, 1H), 8.56 (d, $J$ = 1.7 Hz, 1H), 8.48 (dd, $J$ = 4.7, 1.3 Hz, 1H), 8.45 (s, 1H), 7.72 (ddd, $J$ = 7.8, 1.7, 1.7 Hz, 1H), 7.39–7.31 (m, 4H), 7.21–7.16 (m, 2H), 4.96 (s, 2H), 4.49 (d, $J$ = 5.8 Hz, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.6 (d, $J_{CF}$ = 243 Hz), 158.1, 150.4, 148.9, 148.2, 142.5, 138.0, 135.2, 134.4, 133.5, 133.0 (d, $J_{CF}$ = 3 Hz), 129.8 (d, $J_{CF}$ = 8 Hz), 123.6, 115.4 (d, $J_{CF}$ = 21 Hz), 95.7, 47.5, 39.9; MS (ES+) $m/z$ 394.1 (M+1); Anal. Calcd for $C_{19}H_{16}FN_7O_2$ 1.5$H_2O$: C, 54.28; H, 4.56; N, 23.32. Found: C, 54.20; H, 4.19; N, 23.24.

#### 5.1.54. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-1-(4-methoxybenzyl)-*N*-(pyridin-2-ylmethyl)-1*H*-pyrazole-5-carboxamide (16b)

By a similar procedure as described for **16a**, **16b** was obtained as an off-white solid (0.11 g, 51%). MS (ES+) $m/z$ 513.7 (M+1).

#### 5.1.55. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-*N*-(pyridin-2-ylmethyl)-1*H*-pyrazole-5-carboxamide (17b)

By a similar procedure as described for **17a**, **17b** was obtained as an off-white solid (0.09 g, 58%). Mp 224–225 °C (*N*,*N*-dimethylformamide/water); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.83 (br s, 1H), 9.36 (t, $J$ = 5.8 Hz, 1H), 8.52 (d, $J$ = 4.2 Hz, 1H), 8.46 (s, 1H), 7.77 (ddd, $J$ = 7.7, 7.7, 1.6 Hz, 1H), 7.38–7.26 (m, 5H), 7.22–7.16 (m, 2H), 4.97 (s, 2H), 4.56 (d, $J$ = 5.8 Hz, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.6 (d, $J_{CF}$ = 243 Hz), 158.2, 158.1, 150.4, 148.9, 142.4, 138.1, 136.8, 133.6, 132.9 (d, $J_{CF}$ = 3 Hz), 129.8 (d, $J_{CF}$ = 8 Hz), 122.2, 121.1, 115.4 (d, $J_{CF}$ = 21 Hz), 95.9, 47.5, 44.1; MS (ES+) $m/z$ 393.8 (M+1).

#### 5.1.56. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-1-(4-methoxybenzyl)-*N*-(pyridin-4-ylmethyl)-1*H*-pyrazole-5-carboxamide (16c)

By a similar procedure as described for **16a**, **16c** was obtained as an off-white solid (0.14 g, 63%). MS (ES+) $m/z$ 513.7 (M+1).

#### 5.1.57. 3-(1-(4-fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-*N*-(pyridin-4-ylmethyl)-1*H*-pyrazole-5-carboxamide (17c)

By a similar procedure as described for **17a**, **17c** was obtained as an off-white solid (0.10 g, 77%). Mp 262–263 °C (*N*,*N*-dimethylformamide/water); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.86 (br s, 1H), 9.36 (t, $J$ = 5.8 Hz, 1H), 8.53–8.51 (m, 2H), 8.46 (s, 1H), 7.38–7.30 (m, 5H), 7.22–7.16 (m, 2H), 4.97 (s, 2H), 4.49 (d, $J$ = 5.8 Hz, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.6 (d, $J_{CF}$ = 243 Hz), 158.3, 150.4, 149.6, 147.9, 133.6, 132.9 (d, $J_{CF}$ = 3 Hz), 129.8 (d, $J_{CF}$ = 8 Hz), 122.1, 115.4 (d, $J_{CF}$ = 21 Hz), 95.8, 47.5, 41.2; MS (ES+) $m/z$ 393.8 (M+1).

#### 5.1.58. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-1-(4-methoxybenzyl)-*N*-(oxazol-4-ylmethyl)-1*H*-pyrazole-5-carboxamide (16d)

By a similar procedure as described for **16a**, **16d** was obtained as an off-white solid (0.09 g, 39%). MS (ES+) $m/z$ 503.9 (M+1).

#### 5.1.59. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-*N*-(oxazol-4-ylmethyl)-1*H*-pyrazole-5-carboxamide (17d)

By a similar procedure as described for **17a**, **17d** was obtained as an off-white solid (0.06 g, 66%). Mp 267–268 °C (*N*,*N*-dimethylformamide/water); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.80 (br s, 1H), 9.18 (t, $J$ = 5.6 Hz, 1H), 8.44 (s, 1H), 8.34 (s, 1H), 8.00 (s, 1H), 7.38–7.32 (m, 3H), 7.22–7.16 (m, 2H), 4.96 (s, 2H), 4.36 (d, $J$ = 5.6 Hz, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.6 (d, $J_{CF}$ = 243 Hz), 158.0, 152.1, 150.4, 142.4, 138.0, 137.1, 136.2, 133.6, 132.9 (d, $J_{CF}$ = 3 Hz), 129.8 (d, $J_{CF}$ = 8 Hz), 115.4 (d, $J_{CF}$ = 21 Hz), 95.9, 47.5, 34.6; MS (ES+) $m/z$ 383.8 (M+1).

#### 5.1.60. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-1-(4-methoxybenzyl)-*N*-((1-methyl-1*H*-pyrazol-4-yl)methyl)-1*H*-pyrazole-5-carboxamide (16e)

By a similar procedure as described for **16a**, **16e** was obtained as an off-white solid (0.15 g, 68%). MS (ES+) $m/z$ 516.9 (M+1).

#### 5.1.61. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-*N*-((1-methyl-1*H*-pyrazol-4-yl)methyl)-1*H*-pyrazole-5-carboxamide (17e)

By a similar procedure as described for **17a**, **17e** was obtained as an off-white solid (0.10 g, 53%). Mp 239–241 °C (*N*,*N*-dimethylformamide/water); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.77 (br s, 1H), 9.04 (t, $J$ = 5.6 Hz, 1H), 8.44 (s, 1H), 7.61 (s, 1H), 7.37–7.27 (m, 4H), 7.22–7.16 (m, 2H), 4.95 (s, 2H), 4.27 (d, $J$ = 5.6 Hz, 2H), 3.78 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 161.6 (d, $J_{CF}$ = 243 Hz), 157.7, 150.4, 142.4, 138.3, 138.0, 133.6, 132.9 (d, $J_{CF}$ = 3 Hz), 129.8 (d, $J_{CF}$ = 8 Hz), 129.5, 118.2, 115.4 (d, $J_{CF}$ = 21 Hz), 95.7, 47.5, 38.3, 33.0; MS (ES+) $m/z$ 396.9 (M+1).

#### 5.1.62. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-5-carboxamide (16f)

By a similar procedure as described for **16a**, **16g** was obtained as an off-white solid (0.2 g, 99%). MS (ES+) $m/z$ 437.3 (M+1).

#### 5.1.63. 3-(1-(4-Fluorobenzyl)-5-oxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-*N*-methyl-1*H*-pyrazole-5-carboxamide (17f)

By a similar procedure as described for **17a**, **17f** was obtained as an off-white solid (0.04 g, 29%). Mp 268–269 °C (ethanol); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.72 (br s, 1H), 8.63 (t, $J$ = 4.6 Hz, 1H), 8.40 (s, 1H), 7.36–7.28 (m, 2H), 7.21–7.10 (m, 3H), 4.92 (s, 2H), 2.73 (d, $J$ = 4.6 Hz, 3H); MS (ES+) $m/z$ 317.1 (M+1).

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