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Identification and Structure–Activity Relationship (SAR) of potent and selective oxadiazole-based agonists of sphingosine-1-phosphate receptor ($S1P_1$)

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ABSTRACT

Agonism of $S1P_1$ receptor has been proven to be responsible for peripheral blood lymphopenia and elicts the identification of various $S1P_1$ modulators. In this paper we described a series of oxadiazole-based $S1P_1$ direct-acting agonists disubstituted on terminal benzene ring, with high potency for $S1P_1$ receptor and favorable selectivity against $S1P_3$ receptor. In addition, two representative agents named **16-3b** and **16-3g** demonstrated impressive efficacy in lymphocyte reduction along with reduced effect on heart rate when orally administered. Furthermore, these compounds have been shown to possess desired pharmacokinetic (PK) and physicochemical profiles. The binding mode between **16-3b** and the activated $S1P_1$ model was also studied.

1. Introduction

Sphingolipids are important plasma-membrane lipids, where sphingosine-1 phosphate (S1P, Fig. 1) is the endogenous ligand for a family of five G-protein coupled receptors known as $S1PR_{1\text{-}5}$, regulating a variety of physiological processes including cell differentiation, vascular stabilization, inflammation, endothelium integrity and angiogenesis [1–5]. In recent studies, $S1P_1$ receptor has become an attractive drug target, involved in occurrence and development of many diseases, especially for immune-mediated diseases [6,7]. Notably, sustained activation of $S1P_1$ receptor by the synthetic modulators instead of S1P results in the internalization and degradation of $S1P_1$ receptors, thereby lymphocytes are sequestrated in the lymph nodes and secondary lymphoid organs, restricting the auto immune reactivity, which is mechanistically identified as “functional antagonism” [8–12].

Along with the research for the mechanism of $S1P_1$ receptor toward lymphocyte migration, a great deal of effort has been devoted to the discovery of potent $S1P_1$ agonists, including FTY720 (**2**), BAF312, ACT-12800, ONO-4641 (**3**), RPC1063 (**4**), etc. [13–16]. In 2010, Fingolimod (FTY720, Fig. 1) is the first oral drug approved for the treatment of relapsing remitting multiple sclerosis (RRMS) [17]. As a pro-drug, FTY720 can be phosphorylated to (S)-FTY720-P, which exhibits affinity for 4 of the 5 S1P receptors ($S1P_{1,3,4,5}$) [18–21]. During the clinical trial of FTY720, several researches reveal that there exist some potential side effects which are related to the activation of $S1P_3$ receptor in rodent, such as the risk of cardiovascular effects [22,23]. On the other hand, the overlong half-life of FTY720 raises some concerns about the prognosis after the drug administration is ceased. As a result, more potent $S1P_3$-sparing $S1P_1$ direct-acting agonists with improved pharmacokinetic profile remain to be the focus in drug discovery.

Despite structural diversity of $S1P_1$ agonists, the key features can be generally divided into three parts: polar head, aromatic region, and lipophilic tail. In our previous study, highly predictive 3D QSAR pharmacophore model of $S1P_1$ agonists has been constructed, which indicated that properly rigid hydrophobic region was favorable for $S1P_1/S1P_3$ receptor selectivity [24]. Moreover, in 2012 Stevens’s group disclosed the crystal structure of the $S1P_1$ receptor fused to T4-lysozyme ($S1P_1$-T4L) in complex with an antagonist ML056, which suggested that binding pocket appeared to be amphiphilic and significant π-π stacking was observed between Phe125 and aromatic heterocyclic region [25].

Inspired by the valuable results above, we intended to employ diphenyl ether scaffold to maintain the rigidity of hydrophobic tail, which

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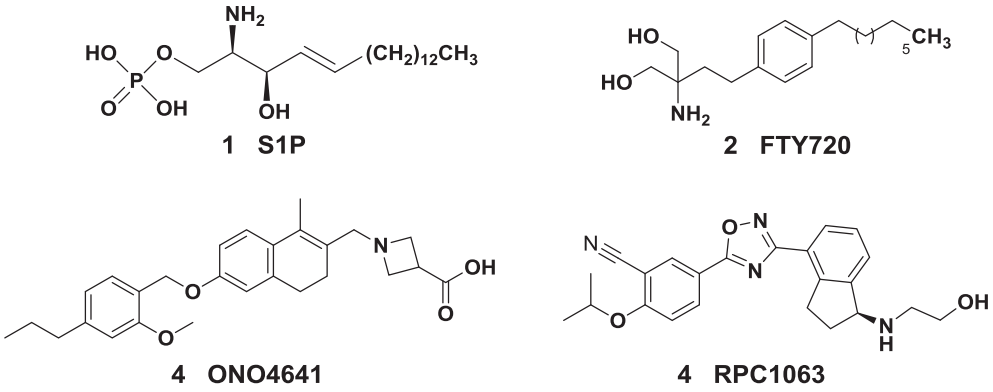


Fig. 1. Structures of sphingosine, Fingolimod (FTY720), and their phosphates.

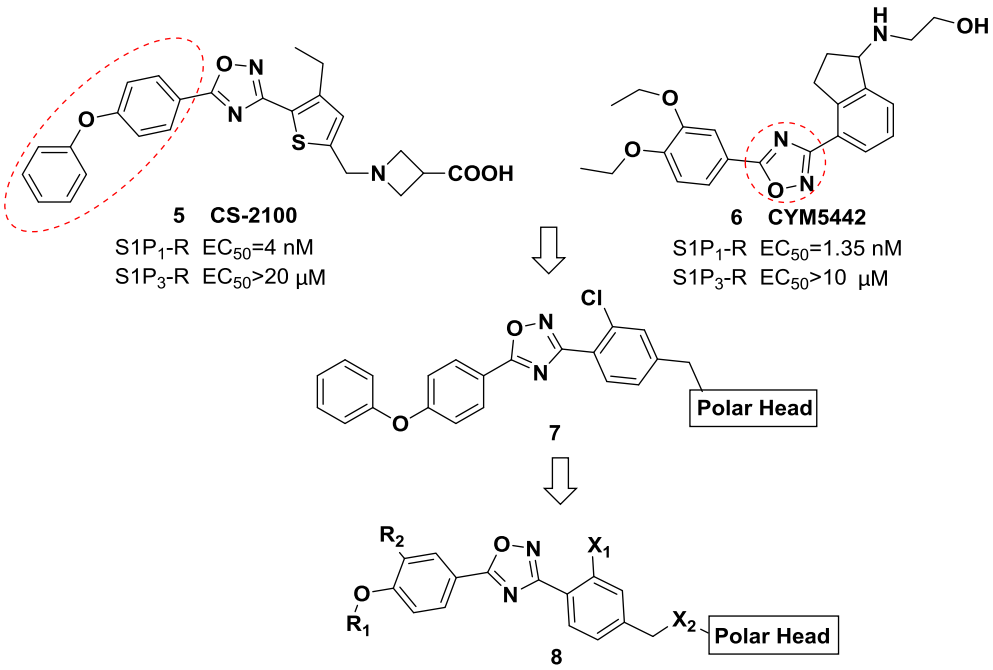


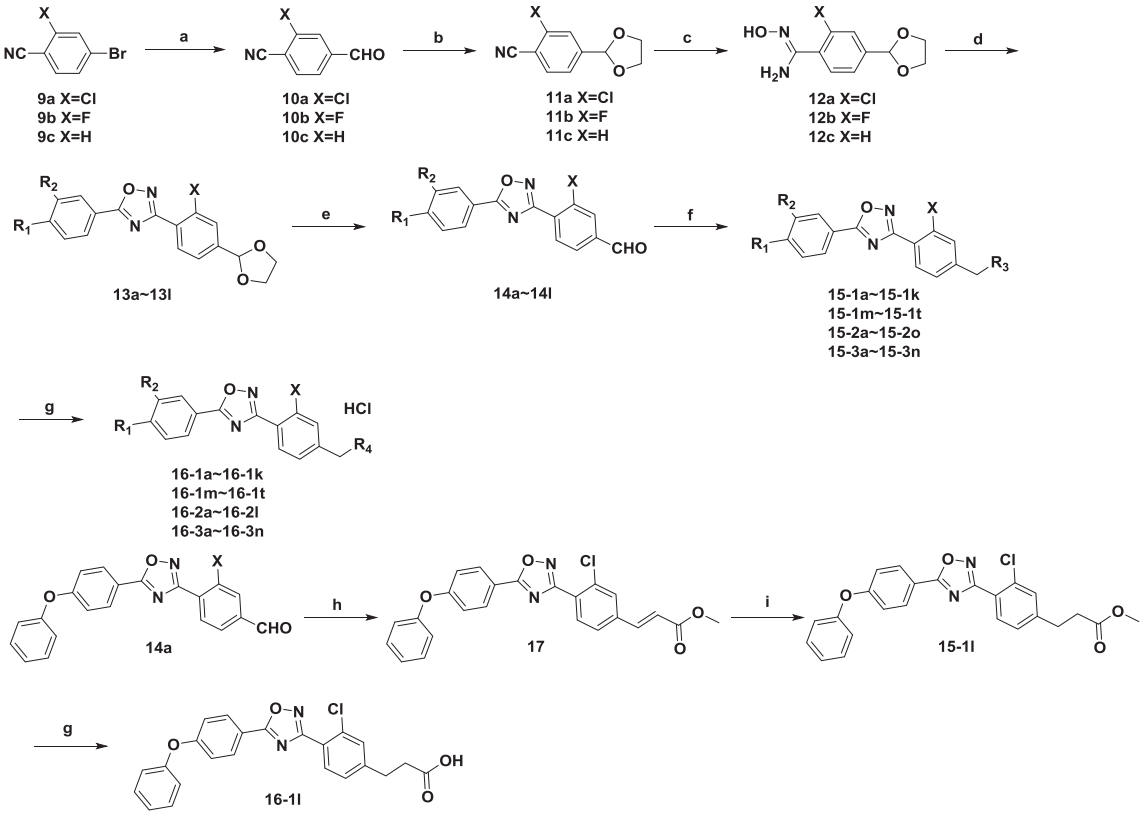
Fig. 2. Design of oxadiazole-based $S1P_1$ modulators.

is derived from CS2100 (**5,** Fig. 2), a potent $S1P_1$ agonist with 5000-fold selectivity against $S1P_3$ receptor reported by Nakamura et al. [26] Meanwhile, in order to further decrease the electricity of aromatic region, the oxadiazole group derived from CYM5442 and CS-2100 was also adopted as part of the linker to enhance its interaction with $S1P_1$ receptor [27]. As illustrated in Fig. 2, selective $S1P_1$ modulators were synthesized on the basis of rational design. After several rounds of cascade modification, highly potent oxadiazole-based $S1P_1$ agonists (structures 8) were identified, where terminal phenyl ring was disubstituted, represented by compound **16-3b** and **16-3g**. In addition to the exploration of structure–activity relationship (SAR) *in vitro*, effects on lymphocyte reduction and heart rate, pharmacokinetic and physicochemical profiles, in silico docking results were fully evaluated and analyzed in detail.

2. Results and discussion

2.1. Chemistry

The synthetic pathway utilized in the preparation of oxadiazole-based derivatives is outlined in Scheme 1. Polysubstituted aromatic aldehydes (**10**) were either commercially available or easily prepared from aryl halides (**9**) by using isopropylmagnesium chloride and 1-formylpiperidine [28]. Initially, aromatic aldehydes (**10**) were converted to acetals (**11**) under the catalysis of PTSA to protect the formyl group in advance [29]. Subsequent addition reaction was performed between **11** and hydroxylamine hydrochloride to provide N'-hydroxybenzimidamides (**12**) [30]. Intermediates **12** were then coupled with different substituted benzoic acids, which were commercially available or prepared according to literature in two steps, employing HOBt and EDCI·HCl as activating reagents to afford 1,2,4-oxadiazoles **13** [31]. After deprotection of **13** with hydrochloric acid, the corresponding aldehydes **14** were then reacted with amino carboxylic ester or alkamine through reductive amination, using either sodium cyanoborohydride or sodium triacetoxyborohydride as the reducing agent to give corresponding intermediates **15** or alkamine end-products [32,33]. Finally, hydrolysis of amino carboxylic esters **15** with lithium hydroxide followed by hydrochloric acid treatment afforded the desired hydrochloride of oxadiazole-based derivatives **16**. Besides, wittig reaction of **14a** with Methyl (triphenylphosphoranylidene) acetate was carried out to prepare substituted α, β-unsaturated ester **17** [34]. Reduction of **17** was performed with Pd/C and H_2, subsequent hydrolysis of the reduction product furnished phenylpropionic acid derivative **16-11**.



Scheme 1. Synthesis of 1,2,4-oxadiazole derivatives. Reagents and Conditions: (a) *N*-Formylpiperidine, i-PrMgCl, THF, 0 °C, 2 h; (b) Ethylene glycol, PTSA, Toluene, reflux; (c) NH_2OH-HCl, $NaHCO_3$, MeOH, reflux; (d) Substituted benzoic acid, HOBt, EDCI, K_2CO_3, DMF, 110 °C; (e) 2 mol/L HCl, Acetone, 55 °C; (f) Amino acid ester (hydrochloride) or alkamine, DIPEA, AcOH, Sodium cyanoborohydride, DCM + MeOH; (g) 0.5 mol/L LiOH, MeOH, Acidification; (h) Methyl (triphenylphosphoranylidene)acetate, DMF; (i) H_2, Pd/C, EA. For the structure of compounds 13a ~ 13 l, 14a ~ 14 l, 15-1a ~ 15-3n and 16-1a ~ 16-3n see Tables 1–3 and Supplementary Material.

2.2. Biological evaluation

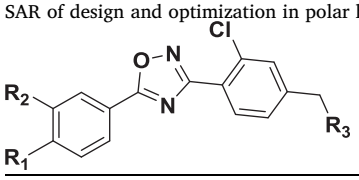
All compounds were evaluated for affinity and selectivity against the $S1P_1$ receptor in an HTRF-IP1 functional assay [35,36]. As illustrated in Table 1, phenoxy on the 4-position of terminal benzene was selected as the lipophilic tail, various polar groups were screened for human $S1P_1$ and $S1P_3$ receptor agonism at first. Among the selected groups, glycine (**16-1a**), pyrrolidine-3-carboxylic acid (**16-1d**), sarcosine (**16-1f**), aspartic acid (**16-1j**) and 2-(piperidin-4-yl) acetic acid (**16-1k**) exhibited moderate nanomolar $S1P_1$ agonistic activities in the same order of magnitude. However, in the case of pyrrolidine-3-carboxylic acid functioned as the polar head, a relative loss in $S1P_1$/$S1P_3$ selectivity was observed. Additionally, proline and 2-amino-2-methylpropanoic acid displayed poor potency for $S1P_1$ receptor, which indicated that steric hindrance and high rigidity in polar head are disadvantageous for affinity. To keep proper rigidity and O/W partition coefficient, glycine was chosen for next investigation.

Thus, we extended our studies to compounds wherein glycine was maintained as the polar head, evaluating the influence of substitution on the benzene ring of lipophilic tail. It was found that replacing the phenoxy by bulk group led to no measurable agonist activity against $S1P_1$ receptor, exemplified by phenyl or tertiary butyl monosubstituted compounds **16-1m** and **16-1n**. Interestingly, potency was regained when terminal phenyl ring was disubstituted with isopropoxy and other specific groups (**16-1q** ~ **16-1s**), which proved to be important factors contributing to favorable $S1P_1$ agonistic activity. Compared the obvious difference of $S1P_1$ agonistic activity between **16-1p** and **16-1q**, this was might due to the electric distinction of aromatic region as well as the necessity of proper steric effect on terminal benzene ring, further analysis of binding mode between compounds and the activated $S1P_1$ model would be discussed in later docking studies. Compounds **16-1q** ~ **16-1s** showed almost equipotent to $S1P_1$ receptor, while the solubility of **16-1q** appeared to be much better than **16-1r**. 3-cyano-4-isopropoxy was then determined to be the optimized piece for the SAR exploration of the rest scaffold.

As described in Table 2, with terminal phenyl ring disubstituted with isopropoxy and nitrile group, a number of compounds listed below exhibited satisfied EC_{50} (< 10 nM) and selectivity at $S1P_1$ receptor, demonstrating that with the suitable lipophilic tail, the $S1P_1$ receptor can accommodate various moieties in the polar head. Meanwhile, in comparison with other derivatives, compounds **16-2f** and **16-2i** were relative less potent on $S1P_1$ receptor. The former might due to the absence of carboxyl or alcoholic hydroxyl group in polar motif, which resulted in scarcely any electrostatic interaction *vs* $S1P_1$ receptor. In terms of the later, the inappropriate length and rigidity of 4-aminocyclohexane-1-carboxylic acid should be accounted for the decrease of potency on $S1P_1$ receptor. On the basis of the SAR analysis, five approving polar head groups were selected for subsequent optimization, including glycine, sarcosine, pyrrolidine-3-carboxylic acid, aspartic acid and 2-(piperidin-4-yl) acetic acid.

Since the polar head has been investigated in detail, a particular attention was focused on exploring substitution at the phenyl ring of aromatic region. As shown with examples in Table 3, the disubstituted pattern of terminal benzene ring with 3-cyano-4-isopropoxy was maintained, when fluorine was introduced in the aromatic ring, most compounds displayed fairly high potency for $S1P_1$ receptor, especially for compound **16-3b** with an EC_{50} of 0.46 nM. Besides, it was worth noting that removing halogen at the phenyl ring furnished compounds with considerable $S1P_1$ agonist activities and good $S1P_1$ selectivity over $S1P_3$ receptor, which suggested that halogen is not indispensable for the

Table 1
SAR of design and optimization in polar head and lipophilic tail.[a]



No	R_1	R_2	R_3	EC_{50} (nM)	
				$hS1P_1$	$hS1P_3$
16-1a	phenoxy	H	Glycine	39.5	> 10,000
16-1b	phenoxy	H	Alanine	111	4610
16-1c	phenoxy	H	3-Aminopropanoic acid	204	> 10,000
16-1d	phenoxy	H	pyrrolidine-3-carboxylic acid	59.2	671
16-1e	phenoxy	H	Proline	415	> 10,000
16-1f	phenoxy	H	Sarcosine	52.9	> 10,000
16-1g	phenoxy	H	Azetidine-3-carboxylic acid	> 10,000	> 10,000
16-1h	phenoxy	H	2-Amino-2-methylpropanoic acid	368	2919
16-1i	phenoxy	H	Piperidine-4-carboxylic acid	472	> 10,000
16-1j	phenoxy	H	Aspartic acid	18.3	> 10,000
16-1k	phenoxy	H	2-(Piperidin-4-yl) acetic acid	18.2	> 10,000
16-1l	phenoxy	H	Acetic acid	99.8	> 10,000
16-1m	phenyl	H	Glycine	> 10,000	> 10,000
16-1n	*tert*-butyl	H	Glycine	> 10,000	> 10,000
16-1o	isopropyl	H	Glycine	824	> 10,000
16-1p	isopropoxy	H	Glycine	> 10,000	> 10,000
16-1q	isopropoxy	cyano	Glycine	26.2	> 10,000
16-1r	isopropoxy	trifluoromethyl	Glycine	17.1	> 10,000
16-1s	isopropoxy	chlorine	Glycine	26.2	> 10,000
16-1t	isopropoxy	methyl	Glycine	53.6	> 10,000

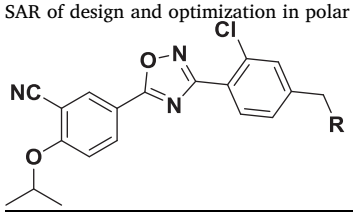
[a] EC_{50} is the mean of three experimental determinations.

interaction between $S1P_1$ receptor and agonists. Remarkably, compound **16-3g** was very efficacious as well, similar in potency to compound **16-3b** with an EC_{50} of 0.47 nM, which spurred interest in further research.

In the last series, we intended to replace isopropoxy by cyclopentyl to evaluate the influence of rigidity of hydrophobic region, while keeping the cyano group to retain its electric and steric function on aromatic region. Apparently, under this circumstance, increasing the size of lipophilic tail left the affinity and selectivity for $S1P_1$ receptor largely unchanged. Nevertheless, the substitution of aspartic acid and 2-(piperidin-4-yl) acetic acid led to slight reduction in potency, which confirmed that the $S1P_1$ binding pocket applied restriction on the shape and size of agonists to some extent, supporting our initial assumption about the significance of proper rigidity in $S1P_1$ agonistic activity and selectivity.

In general, the cascade optimization afforded a relatively elaborate SAR study, coming up with several compounds which performed

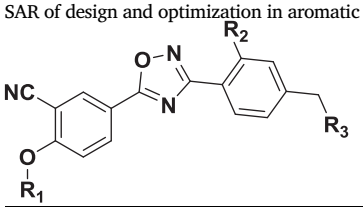
Table 2
SAR of design and optimization in polar head.[a]



No	R	EC_{50} (nM)	
		$hS1P_1$	$hS1P_3$
16-2a	Sarcosine	6.2	> 10,000
16-2b	Azetidine-3-carboxylic acid	4.8	> 10,000
16-2c	Aspartic acid	1.71	4737
16-2d	Pyrrolidine-3-carboxylic acid	1.1	> 10,000
16-2e	2-(Piperidin-4-yl) acetic acid	2.9	> 10,000
16-2f	Pyrrolidin-2-one	70	> 10,000
16-2g	3-(Methylamino)propanoic acid	4.1	> 10,000
16-2h	Piperidine-3-carboxylic acid	1.7	> 10,000
16-2i	4-Aminocyclohexane-1-carboxylic acid	121	> 10,000
16-2j	Serine	1.46	> 10,000
16-2k	Homoserine	8.3	> 10,000
16-2l	Glutamic acid	3.4	> 10,000
15-2m	2-Aminopropane-1,3-diol	6.6	> 10,000
15-2n	2-Aminoethan-1-ol	1.0	> 10,000
15-2o	1-Aminopropan-2-ol	1.0	> 10,000

[a] EC_{50} is the mean of three experimental determinations.

Table 3
SAR of design and optimization in aromatic region, lipophilic tail and polar head.[a]



No	R_1	R_2	R_3	EC_{50} (nM)	
				$hS1P_1$	$hS1P_3$
16-3a	Isopropyl	F	Glycine	1.37	> 10,000
16-3b	Isopropyl	F	Sarcosine	0.46	> 10,000
16-3c	Isopropyl	F	Aspartic acid	1.2	> 10,000
16-3d	Isopropyl	F	2-(Piperidin-4-yl) acetic acid	33	> 10,000
16-3e	Isopropyl	H	Glycine	4.7	> 10,000
16-3f	Isopropyl	H	Sarcosine	1.3	> 10,000
16-3g	Isopropyl	H	Pyrrolidine-3-carboxylic acid	0.47	> 10,000
16-3h	Isopropyl	H	Aspartic acid	2.5	> 10,000
16-3i	Isopropyl	H	2-(Piperidin-4-yl) acetic acid	21	> 10,000
16-3j	Cyclopentyl	H	Glycine	8.7	> 10,000
16-3k	Cyclopentyl	H	Sarcosine	6.4	> 10,000
16-3l	Cyclopentyl	H	Pyrrolidine-3-carboxylic acid	3.6	> 10,000
16-3m	Cyclopentyl	H	Aspartic acid	31	1940
16-3*n*	Cyclopentyl	H	2-(Piperidin-4-yl) acetic acid	123	> 10,000

[a] EC_{50} is the mean of three experimental determinations.

Table 4
Lymphocyte count, plasma concentrations of compounds **16-2d**, **16-2e**, **16-3b**, **16-3g** and **16-3l** after 3 mg/kg oral administration to SD rats.[a]

No	LC reduction (%)				Plasma concentration (ng/mL)			
	4 h	8 h	12 h	24 h	4 h	8 h	12 h	24 h
RPC1063	−5	−30	−80	−35	23.98	15.2	13.36	2.4
16-2d	−54	−38	−38	131	97.24	4.38	1.83	BLQ
16-2e	−27	+36	−36	154	673.8	424	251.98	11.25
16-3b	−74	−82	−91	−47	44.46	11.59	5.28	BLQ
16-3g	−52	−90	−83	−64	153.2	35.19	9.14	2.34
16-3l	−23	−73	53	7	54.54	9.98	3.04	BLQ

[a] Data are expressed as mean ± SD of three animals.

superior in selective $S1P_1$ receptor agonism. Hence, 5 compounds with excellent functional potency for $S1P_1$ receptor and desirable selectivity profile for $S1P_3$ receptor were advanced to mice models for evaluating their ability in lymphocytes reduction, including **16-2d**, **16-2e**, **16-3b**, **16-3g** and **16-3l**.

As outlined in Table 4, blood lymphocyte reduction along with plasma exposure was measured at multiple time points, after oral administration of the compounds discussed above at dose of 3 mg/kg. As expected, in comparison with positive control RPC1063, most compounds displayed delightful levels of lymphopenia in *vivo* efficacy, especially for compound **16-3b** and **16-3g**, which provided around 90% decrease of lymphocyte counts. In addition, the largest lymphocyte reduction occurred at 8–12 h, which was generally consistent with the agonist activity trends observed before (Fig. 3). Overall, the lymphocyte reduction usually recovered to baseline 24 h after administration. In the meantime, the plasma concentration almost vanished thoroughly, indicating the relative rapid onset of function as well as complete recovery of lymphopenia.

To gain insight into the metabolic feature *in vivo*, pharmacokinetics studies in mice were subsequently assessed at dose of 3 mg/kg, with RPC1063 as the positive control. It was of note that compound **16-2e** exhibited rather high blood concentration (C_{max}) and area under the curve ($AUC_{(0-t)}$) in oral administration, which was likely due to lower plasma clearance. On the other hand, other compounds possessed moderate C_{max}, differences in C_{max} and clearance might be ascribed to plasma protein binding and tissue distribution. Besides, as depicted in Table 5, all these compounds showed relatively short $t_{1/2}$, which achieved our previous goal of properly curtailing $t_{1/2}$ to improve prognosis. In light of outstanding $S1P_1$ agonist activity and lymphopenia of compound **16-3b** and **16-3g**, they were further progressed to intravenous administration, where **16-3g** was observed for favorable oral bioavailability of 50.31%.

Moreover, it is recognized that both pharmacological activity and druggability are essential elements in drug discovery. Ligand lipophilicity efficiency (LLE) calculated by both the activity and lipophilicity of compound, was basically recommended over 6 to maintain proper druggability for oral drugs. Therefore, LogD at pH 7.4 and LLE were also measured to evaluate the lipophilicity and efficiency comprehensively on a Gemini Profiler instrument (pION) by potentiometric titration method. To our delight, the whole compounds exhibited log D (pH 7.4) < 3 and LLE > 6, which provided satisfying balance of $S1P_1$ potency and druglike properties, indicating promising prospect of the following modification.

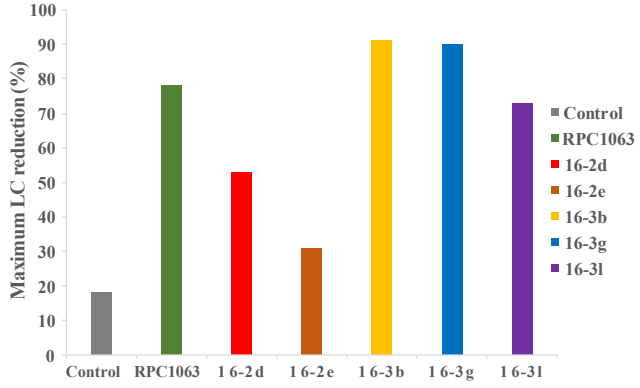


Fig. 3. Maximum LC reduction of compounds **16-2d**, **16-2e**, **16-3b**, **16-3g** and **16-3l** in SD rats.

It is well established from the profiles above that compound **16-3b** and **16-3g** are promising in pharmacodynamics and pharmacokinetics studies. In consequence, they were further tested for effect on heart rate at dose of 10 mg/kg oral administration to rats. As summarized in Fig. 4, compared with marketed drug FTY720, neither of these two compounds had obvious influence on heart rate, let alone induced bradycardia. Additionally, the apparent decrease in the risk of cardiovascular side effect appeared to be driven by improvement in selectivity against $S1P_3$ receptor, which confirmed the importance of developing selective $S1P_1/S1P_3$ modulators.

2.3. Molecular docking

To rationalize the structure activity relationships (SARs) in this study, compound **16-3b** and **16-3g** were evaluated by docking studies in order to better understand the ligand-protein interactions. The active state of $S1P_1$ model was induced by Gaussian accelerated molecular dynamics, which was used as receptor for docking study. The binding mode analysis was then performed by Schrödinger and PyMOL [37]. As is evident from Fig. 5, the docking result of **16-3b** in binding pocket was presented in 3D diagram (Fig. 5a). The charged carboxyl group in polar head strongly contacted with Arg120 via salt bridge and established an H-bond with Tyr29, while α-amino group linked to Glu121 by electronic interaction as well. Phenyl moiety in lipophilic tail was adjacent to Phe125, a π-π stacking interaction was found for both compounds, which was enhanced by electron-withdrawing effect of nitrile group and proved to be obligatory for $S1P_1$ agonist activity. In addition, isopropoxy group and nitrile group of terminal benzene ring were involved in hydrophobic interaction with some lipophilic amino acid residues, such as Phe210, Trp269, Leu272, Phe273 and Leu276. Besides, comparing the binding mode of **16-3b** and **16-3g** (Fig. 5a), they behaved similar in the cavity of $S1P_1$ receptor, where all the significant contacts mentioned above could be observed. Moreover, in terms of the docking result between compound **16-3g** and **16-3i** (Fig. 5b), nearly every bond length of important contacts attached to **16-3g** was shorter than that of **16-3i**, which further proved the reasonability of high efficiency in **16-3g**. Hence, the computational assay depicted a general binding mode along with key interactions, which elucidated high $S1P_1$ potency of **16-3b** and **16-3g** primarily.

3. Conclusion

In summary, a series of potent oxadiazole-based $S1P_1$ direct-acting agonists possessing specific disubstitution on terminal benzene ring was identified with favorable selectivity against $S1P_3$ receptor. Taking multiple pharmacological parameters into consideration, cascade and targeted structural modification led to elaborate SAR study of $S1P_1$ selective modulators. Moreover, most compounds demonstrated impressive efficacy *in vitro*, while two representative compounds **16-3b** and **16-3g** (EC_{50} < 1 nM) displayed satisfied lymphopenia activities *in vivo* and exhibited reduced effect on heart rate. Apart from the improvement in pharmacokinetics properties, the two compounds also possessed desired physicochemical features. As a consequence, further optimization and evaluation of this scaffold is ongoing to provide more potent and selective $S1P_1$ agonists with superior pharmacokinetic profiles.

Table 5
Pharmacokinetic parameters after 3 mg/kg oral administration in SD rats and physicochemical profiles of compounds **16-2d**, **16-2e**, **16-3b**, **16-3g** and **16-3l**.[a,b]

No	C_{max} (ng/ml)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-t} (ng·h/mL)	CLz (ml/(h·kg))	Vz (ml/kg)	log D (pH 7.4)	LLE[c]
RPC1063	26.4	3.5	5.95	306.87	9709.98	77503.5	–	–
16-2d	895	1	1.75	3998.89	1612.01	2981.2	1.79	7.17
16-2e	1419	1.4	2.66	9434.1	329.46	1261.34	1.38	7.16
16-3b	86.32	1.8	1.71	388.133	8373.71	20719.15	1.76	7.58
16-3g	232.8	2.8	1.98	1053.88	2946.96	8144.34	1.49	7.84
16-3l	74.32	2.2	1.73	367.98	8381.94	19620.8	2.19	6.25

[a] Data are expressed as mean ± SD of three animals.
[b] Data are expressed as mean of three measurements.
[c] LLE = pIC_{50} − Clog*P*.

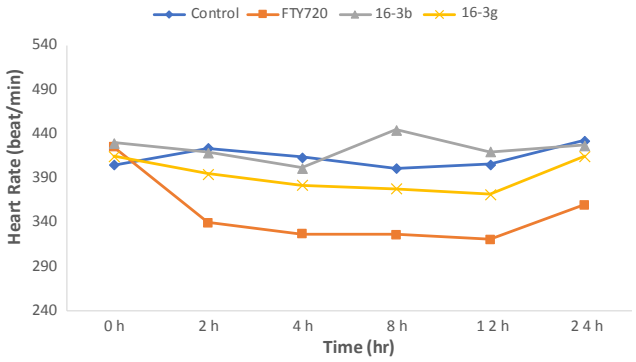


Fig. 4. Effect on heart rate after 10 mg/kg oral administration of compound **16-3b** and **16-3g** to SD rats.

4. Experimental

4.1. Chemistry

4.1.1. General experimental information

All reagents and solvents were obtained from commercial sources and used without further purification. Melting points were determined on Yanaco MP-J3 microscope melting point apparatus. NMR spectra were recorded on Mercury-400, Mercury-500, and Mercury-600 spectrometers. Chemical shifts are referenced to the residual solvent peak and reported in ppm (δ scale) and all coupling constant (J) values are given in Hz. ESI-HRMS data were measured on Thermo Exactive Orbitrap plus spectrometer. Flash column chromatography was performed on Biotage Isolera one. All the solvents and chemicals were obtained from commercial sources and used without further purification.

4.1.2. General procedure for the synthesis of 2-halogen-4-formylbenzonitrile (*10a ~ b*)

To a solution of 4-halogen-2-chlorobenzonitrile (23.10 mmol) in dry THF under Argon at 0 °C was added isopropyl magnesium chloride (30.03 mmol, 2 M solution in ether) dropwise during 20 min, and the reaction mixture was stirred for 2 h, keeping the temperature around 0 °C. Then 1-formyl piperidine (30.03 mmol) was added dropwise at 0 °C and stirred for additional 2 h at 0 °C. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, then filtered and concentrated. The residue was purified by silica gel flash column chromatography (PE/EtOAc = 3:1) to afford compound **10a** and **10b**.

*4.1.2.1. 2-Chloro-4-formylbenzonitrile (**10a**).* Yield:65.9%; White solid; Mp: 114–115 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.23–8.22 (m, 2H), 8.02 (d, J = 7.6 Hz, 1H); MS (ESI) m/z 166.0 $(M+H)^+$.

*4.1.2.2. 2-Fluoro-4-formylbenzonitrile (**10b**).* Yield: 53.1%; White solid; Mp: 87–88 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.20 (dd, J = 8.0, 6.4 Hz, 1H), 7.99 (dd, J = 9.2, 1.2 Hz, 1H), 7.94 (dd, J = 7.8, 1.2 Hz, 1H); MS (ESI) m/z 150.0 $(M+H)^+$.

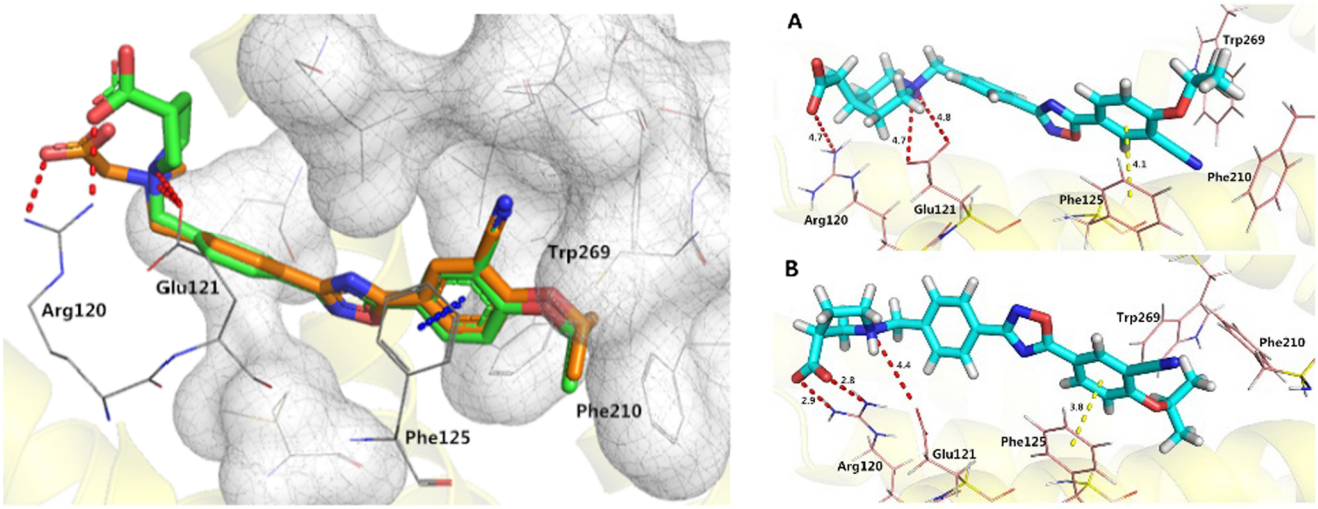


Fig. 5. Docking poses of compound **16-3b, 16-3g** and **16-3i** within $S1P_1$ binding pocket. (5-1) 3D binding modes of compound **16-3b** (orange sticks) and **16-3g** (green sticks). Ionic bonds are reported as dotted red lines, π-π stacking is reported as dotted blue lines. (5-2) 3D binding modes of compound **16-3i** (A) and **16-3g** (B). Ionic bonds are reported as dotted red lines, π-π stacking is reported as dotted yellow lines.

*4.1.3. General procedure for the synthesis of 4-(1,3-dioxolan-2-yl) benzonitrile (**11a**∼**c**)*

In a round flask was placed 4-formylbenzonitrile (15.10 mmol), ethane-1,2-diol (60.39 mmol) and *p*-toluenesulfonic acid (1.2 mmol) as catalyst. The mixture was dissolved in dry toluene and stirred for 18 h under reflux, with the continuous removal of H_2O in a Dean–Stark apparatus. The solvent was removed by distillation, the residue was redissolved in EtOAc (15 mL) and then neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, then filtered and concentrated. The residue was purified by silica gel flash column chromatography (PE/Acetone/DCM = 24:4:3) to afford compound **11a**∼**c**.

*4.1.3.1. 2-Chloro-4-(1,3-dioxolan-2-yl)benzonitrile (**11a**)*. Yield: 74.2%; White solid; Mp: 60–61 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 5.86 (s, 1H), 4.09–3.94 (m, 4H); MS (ESI) m/z 210.0 $(M+H)^+$.

*4.1.3.2. 4-(1,3-Dioxolan-2-yl)-2-fluorobenzonitrile (**11b**)*. Yield: 78.4%; Colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (dd, J = 8.0, 6.4 Hz, 1H), 7.54 (dd, J = 10.0, 1.2 Hz, 1H), 7.48–7.46 (m, 1H), 5.86 (s, 1H), 4.08–3.94 (m, 4H); MS (ESI) m/z 194.1 $(M+H)^+$.

*4.1.3.3. 4-(1,3-Dioxolan-2-yl)benzonitrile (**11c**)*. Yield: 72.5%; White solid; Mp: 32–35 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 5.83 (s, 1H), 4.08–3.94 (m, 4H); MS (ESI) m/z 176.1 $(M+H)^+$.

*4.1.4. General procedure for the synthesis of 4-(1,3-dioxolan-2-yl)-N′-hydroxybenzimidamide (**12a**∼**c**)*.

To a solution of 4-(1,3-dioxolan-2-yl) benzonitrile (10.97 mmol) in MeOH was added hydroxyamine hydrochloride (38.40 mmol) and $NaHCO_3$ (43.89 mmol) and heated to reflux for 5 h. The reaction mixture was then cooled to rt, then filtered and concentrated. The filtrate was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (DCM / MeOH = 20:1) to afford compound **12a**∼**c**.

*4.1.4.1. 2-Chloro-4-(1,3-dioxolan-2-yl)-N′-hydroxybenzimidamide (**12a**)*. Yield: 79.1%; White solid; Mp: 110–113 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 1H), 7.50 (s, 1H), 7.45–7.39 (m, 2H), 5.84 (s, 2H), 5.77 (s, 1H), 4.09–3.92 (m, 4H); MS (ESI) m/z 243.0 $(M+H)^+$.

*4.1.4.2. 4-(1,3-Dioxolan-2-yl)-2-fluoro-N′-hydroxybenzimidamide (**12b**)*. Yield: 76.9%; White solid; Mp: 87–88 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.54–7.50 (m, 1H), 7.28–7.24 (m, 2H), 5.83 (s, 2H), 5.77 (s, 1H), 4.08–3.92 (m, 4H); MS (ESI) m/z 227.1 $(M+H)^+$.

*4.1.4.3. 4-(1,3-Dioxolan-2-yl)-N′-hydroxybenzimidamide (**12c**)*. Yield: 81.2%; White solid; Mp: 135–136 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.69–7.67 (m, 2H), 7.43–7.41 (m, 2H), 5.82 (s, 2H), 5.74 (s, 1H), 4.07–3.93 (m, 4H); MS (ESI) m/z 209.1 $(M+H)^+$.

*4.1.5. General procedure for the synthesis of 3-(4-(1,3-dioxolan-2-yl) phenyl)-5-(substituted phenyl)-1,2,4-oxadiazole (**13a**∼**l**)*.

A solution of substituted benzoic acid (8.61 mmol), 1-Hydroxybenzotriazole (7.83 mmol), 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (7.83 mmol) and K_2CO_3 (11.74 mmol) in DMF was stirred at rt for 30 min. 4-(1,3-dioxolan-2-yl)-N′-hydroxybenzimidamide (7.83 mmol) was then added to the reaction mixture at rt and the resulting slurry was stirred under Argon at 110 °C for additional 2 h. The reaction mixture was then cooled to rt, then filtered and concentrated. The filtrate was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (PE/EtOAc = 3:1) to afford compound **13a**∼**l**.

*4.1.5.1. 3-(2-Chloro-4-(1,3-dioxolan-2-yl)phenyl)-5-(4-phenoxyphenyl)-1,2,4-oxadiazole (**13a**)*. Yield: 64.7%; White solid; Mp: 79–81 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20 (d, J = 6.8 Hz, 2H), 8.04 (d, J = 6.0 Hz, 1H), 7.72 (s, 1H), 7.62 (d, J = 6.0 Hz, 1H), 7.50 (t, J = 6.2 Hz, 2H), 7.29 (t, J = 6.0 Hz, 1H), 7.21–7.18 (m, 4H), 5.87 (s, 1H), 4.12–3.97 (m, 4H); MS (ESI) m/z 421.1 $(M+H)^+$.

*4.1.5.2. 5-([1,1′-Biphenyl]-4-yl)-3-(2-chloro-4-(1,3-dioxolan-2-yl) phenyl)-1,2,4-oxadiazole (**13b**)*. Yield: 61.8%; White solid; Mp: 134–137 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (d, J = 8.0 Hz, 2H), 8.11 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 7.5 Hz, 2H), 7.76 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.5 Hz, 2H), 7.49 (t, J = 7.5 Hz, 1H), 5.91 (s, 1H), 4.12–4.03 (m, 4H); MS (ESI) m/z 405.1 $(M+H)^+$.

*4.1.5.3. 5-(4-(tert-Butyl)phenyl)-3-(2-chloro-4-(1,3-dioxolan-2-yl) phenyl)-1,2,4-oxadiazole (**13c**)*. Yield: 62.2%; White solid; Mp: 77–79 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.72–7.67 (m, 3H), 7.62 (d, J = 8.0 Hz, 1H), 5.87 (s, 1H), 4.12–3.96 (m, 4H), 1.33 (s, 9H); MS (ESI) m/z 385.1 $(M+H)^+$.

*4.1.5.4. 3-(2-Chloro-4-(1,3-dioxolan-2-yl)phenyl)-5-(4-isopropylphenyl)-1,2,4-oxadiazole (**13d**)*. Yield: 47.5%; White solid; Mp: 53–55 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 5.87 (s, 1H), 4.10–3.98 (m, 4H), 3.02 (hept, J = 7.0 Hz, 1H), 1.25 (d, J = 7.0 Hz, 6H); MS (ESI) m/z 371.1 $(M+H)^+$.

*4.1.5.5. 3-(2-Chloro-4-(1,3-dioxolan-2-yl)phenyl)-5-(4-isopropoxyphenyl)-1,2,4-oxadiazole (**13e**)*. Yield: 42.3%; White solid; Mp: 88–90 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12–8.09 (m, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.62 (dd, J = 7.8, 1.4 Hz, 1H), 7.19–7.15 (m, 2H), 5.87 (s, 1H), 4.79 (hept, J = 6.0 Hz, 1H), 4.11–3.98 (m, 4H), 1.32 (d, J = 6.4 Hz, 6H); MS (ESI) m/z 387.1 $(M+H)^+$.

*4.1.5.6. 5-(3-(2-Chloro-4-(1,3-dioxolan-2-yl)phenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitri-le (**13f**)*. Yield: 87.0%; White solid; Mp: 153–155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.62 (dd, J = 8.0, 1.2 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 5.87 (s, 1H), 4.98 (hept, J = 6.0 Hz, 1H), 4.13–3.96 (m, 4H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 412.1 $(M+H)^+$.

*4.1.5.7. 3-(2-Chloro-4-(1,3-dioxolan-2-yl)phenyl)-5-(4-isopropoxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (**13g**)*. Yield: 72.3%; White solid; Mp: 131–134 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (dd, J = 8.8, 2.4 Hz, 1H), 8.29 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.62 (dd, J = 8.4, 1.6 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 5.87 (s, 1H), 4.97 (hept, J = 6.0 Hz, 1H), 4.12–3.96 (m, 4H), 1.35 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 455.1 $(M+H)^+$.

*4.1.5.8. 3-(2-Chloro-4-(1,3-dioxolan-2-yl)phenyl)-5-(3-chloro-4-isopropoxyphenyl)-1,2,4-oxadiazole (**13h**)*. Yield: 71.7%; White solid; Mp: 130–133 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (dd, J = 2.4, 0.8 Hz, 1H), 8.11 (ddd, J = 8.7, 2.2, 0.7 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.72 (m, 1H), 7.63–7.61 (m, 1H), 7.44 (d, J = 8.4 Hz, 1H), 5.87 (s, 1H), 4.88 (hept, J = 6.1 Hz, 1H), 4.13–3.98 (m, 4H), 1.36 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 421.1 $(M+H)^+$.

*4.1.5.9. 3-(2-Chloro-4-(1,3-dioxolan-2-yl)phenyl)-5-(4-isopropoxy-3-methylphenyl)-1,2,4-oxadiazole (**13i**)*. Yield: 64.9%; White solid; Mp: 71–74 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 8.0 Hz, 1H), 8.00–7.97 (m, 2H), 7.71 (d, J = 1.6 Hz, 1H), 7.61 (dd, J = 8.0, 1.6 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 5.87 (s, 1H), 4.78 (hept, J = 6.1 Hz, 1H), 4.12–3.96 (m, 4H), 2.23 (s, 3H), 1.33 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 401.1 $(M+H)^+$.

*4.1.5.10. 5-(3-(4-(1,3-Dioxolan-2-yl)-2-fluorophenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile (**13j**)*. Yield: 81.7%; White solid; Mp: 148–150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 2.4 Hz, 1H), 8.41 (dd, J = 9.2, 2.4 Hz, 1H), 8.18–8.14 (m, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.53–7.49 (m, 2H), 5.87 (s, 1H), 4.98 (hept, J = 5.9 Hz, 1H), 4.12–3.96 (m, 4H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 396.1 $(M+H)^+$.

*4.1.5.11. 5-(3-(4-(1,3-Dioxolan-2-yl)phenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile (**13k**)*. Yield: 59.7%; White solid; Mp: 119–120 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.37 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 9.2 Hz, 1H), 5.82 (s, 1H), 4.96 (hept, J = 6.0 Hz, 1H), 4.10–3.95 (m, 4H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 378.1 $(M+H)^+$.

*4.1.5.12. 5-(3-(4-(1,3-Dioxolan-2-yl)phenyl)-1,2,4-oxadiazol-5-yl)-2-(cyclopentyloxy)benzonitrile (**13l**)*. Yield: 72.9%; White solid; Mp: 147–148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.4 Hz, 1H), 8.41 (dd, J = 9.0, 2.2 Hz, 1H), 8.12–8.10 (m, 2H), 7.67–7.65 (m, 2H), 7.52 (d, J = 8.8 Hz, 1H), 5.84 (s, 1H), 5.18–5.14 (m, 1H), 4.12–3.96 (m, 4H), 2.06–1.99 (m, 2H), 1.82–1.63 (m, 6H); MS (ESI) m/z 404.2 $(M+H)^+$.

*4.1.6. General procedure for the synthesis of 4-(5-(substituted phenyl)-1,2,4-oxadiazol-3-yl)benzaldehyde (**14a**∼**l**)*

To a stirred suspension of 3-(4-(1,3-dioxolan-2-yl)phenyl)-5-(substituted phenyl)-1,2,4-oxadiazole (4.75 mmol) in acetone was added 2 N aqueous hydrochloric acid (38.00 mmol), and the resulting mixture was stirred at 55 °C for 5 h. The reaction mixture was cooled to room temperature, the precipitated solid was filtered and then dried in vacuo to afford compound **14a**∼**l**.

*4.1.6.1. 3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzaldehyde (**14a**)*. Yield: 94.4%; White solid; Mp: 191–193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.25–8.20 (m, 4H), 8.06 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.22–7.19 (m, 4H); MS (ESI) m/z 377.1 $(M+H)^+$.

*4.1.6.2. 4-(5-([1,1′-Biphenyl]-4-yl)-1,2,4-oxadiazol-3-yl)-3-chlorobenzaldehyde (**14b**)*. Yield: 94.8%; White solid; Mp: 193–195 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.30–8.27 (m, 3H), 8.22 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 7.5 Hz, 2H), 7.47 (t, J = 7.5 Hz, 1H); MS (ESI) m/z 361.1 $(M+H)^+$.

*4.1.6.3. 4-(5-(4-(tert-Butyl)phenyl)-1,2,4-oxadiazol-3-yl)-3-chlorobenzaldehyde (**14c**)*. Yield: 88.0%; White solid; Mp: 132–135 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.21 (s, 1H), 8.13 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.5 Hz, 2H), 1.34 (s, 9H); MS (ESI) m/z 341.1 $(M+H)^+$.

*4.1.6.4. 3-Chloro-4-(5-(4-isopropylphenyl)-1,2,4-oxadiazol-3-yl) benzaldehyde (**14d**)*. Yield: 89.0%; White solid; Mp: 119–121 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 1.6 Hz, 1H), 8.14 (dt, J = 8.4, 1.9 Hz, 2H), 8.07 (dd, J = 7.8, 1.4 Hz, 1H), 7.58–7.55 (m, 2H), 3.04 (hept, J = 6.9 Hz, 1H), 1.27 (d, J = 6.8 Hz, 6H); MS (ESI) m/z 327.1 $(M+H)^+$.

*4.1.6.5. 3-Chloro-4-(5-(4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl) benzaldehyde (**14e**)*. Yield: 73.2%; White solid; Mp: 107–109 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 1.2 Hz, 1H), 8.14–8.10 (m, 2H), 8.06 (dd, J = 7.8, 1.4 Hz, 1H), 7.20–7.16 (m, 2H), 4.80 (hept, J = 6.1 Hz, 1H), 1.32 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 343.1 $(M+H)^+$.

*4.1.6.6. 5-(3-(2-Chloro-4-formylphenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile (**14f**)*. Yield: 76.9%; White solid; Mp: 177–179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.41 (dd, J = 9.0, 2.2 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 1.2 Hz, 1H), 8.08–8.05 (m, 1H), 7.56 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 5.9 Hz, 1H), 1.39 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 368.1 $(M+H)^+$.

*4.1.6.7. 3-Chloro-4-(5-(4-isopropoxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)benzaldehyde (**14g**)*. Yield: 70.9%; White solid; Mp: 121–124 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 8.8 Hz, 1H), 8.31 (m, 1H), 8.26 (dd, J = 7.8, 1.4 Hz, 1H), 8.20 (m, 1H), 8.07–8.05 (m, 1H), 7.59 (d, J = 8.8 Hz, 1H), 4.98 (hept, J = 6.0 Hz, 1H), 1.36 (dd, J = 6.0, 1.6 Hz, 6H); MS (ESI) m/z 411.1 $(M+H)^+$.

*4.1.6.8. 3-Chloro-4-(5-(3-chloro-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzaldehyde (**14h**)*. Yield: 86.8%; White solid; Mp: 136–138 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.21–8.19 (m, 2H), 8.12 (dd, J = 8.8, 2.4 Hz, 1H), 8.06 (dd, J = 8.0, 1.6 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 4.89 (hept, J = 5.9 Hz, 1H), 1.36 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 377.0 $(M+H)^+$.

*4.1.6.9. 3-Chloro-4-(5-(4-isopropoxy-3-methylphenyl)-1,2,4-oxadiazol-3-yl)benzaldehyde (**14i**)*. Yield: 83.1%; White solid; Mp: 107–109 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 8.05 (dd, J = 8.0, 1.6 Hz, 1H), 8.02–7.98 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H), 4.78 (hept, J = 6.1 Hz, 1H), 2.23 (s, 3H), 1.34 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 357.1 $(M+H)^+$.

*4.1.6.10. 5-(3-(2-Fluoro-4-formylphenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile (**14j**)*. Yield: 63.2%; White solid; Mp: 184–185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (d, J = 1.2 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 8.8, 2.4 Hz, 1H), 8.36–8.32 (m, 1H), 7.99–7.94 (m, 2H), 7.56 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 6.1 Hz, 1H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 352.1 $(M+H)^+$.

*4.1.6.11. 5-(3-(4-Formylphenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile (**14k**)*. Yield: 82.6%; White solid; Mp: 160–161 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 8.28 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 9.2 Hz, 1H), 4.97 (hept, J = 6.0 Hz, 1H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 334.1 $(M+H)^+$.

*4.1.6.12. 2-(Cyclopentyloxy)-5-(3-(4-formylphenyl)-1,2,4-oxadiazol-5-yl)benzonitrile (**14l**)*. Yield: 64.4%; White solid; Mp: 160–161 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.42 (dd, J = 8.8, 2.4 Hz, 1H), 8.32–8.29 (m, 2H), 8.14–8.10 (m, 2H), 7.53 (d, J = 9.2 Hz, 1H), 5.19–5.15 (m, 1H), 2.07–1.98 (m, 2H), 1.83–1.63 (m, 6H); MS (ESI) m/z 360.1 $(M+H)^+$.

*4.1.7. General procedure for the synthesis of (4-(5-(substituted phenyl)-1,2,4-oxadiazol-3-yl)benzyl) carboxylic ester or alkamine (**15-1a**∼**15-3n**)*

To a solution of 4-(5-(substituted phenyl)-1,2,4-oxadiazol-3-yl)benzaldehyde (0.53 mmol)in 10 mL DCM was added methyl glycinate hydrochloride (0.80 mmol), acetic acid (2.12 mmol), and N,*N*-diisopropylethylamine (0.80 mmol), and 10 mL MeOH. After the reaction was stirred

for 3 h, sodium cyanoborohydride (0.53 mmol) was added. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, then filtered and concentrated. The residue was purified by silica gel flash column chromatography (DCM:MeOH = 20:1) to afford compound **15-1a**～**15-3n** (except for **15-1l**).

*4.1.7.1. Methyl (3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)glycinate (**15-1a**)*. Yield: 80.5%; White solid; Mp: 62–65 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 7.6 Hz, 1H), 7.57 (s, 1H), 7.41 (q, J = 8.5 Hz, 3H), 7.22 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 8.0 Hz, 4H), 3.88 (s, 2H), 3.75 (s, 3H), 3.44 (s, 2H), 1.92 (s, 1H); MS (ESI) m/z 450.1 $(M+H)^+$.

*4.1.7.2. Methyl (3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)alaninate (**15-1b**)*. Yield: 74.1%; White solid; Mp: 77–79 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.41 (q, J = 8.0 Hz, 3H), 7.22 (t, J = 7.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 4H), 3.90 (d, J = 13.6 Hz, 1H), 3.75 (m, 3H), 3.71 (s, 1H), 3.40 (q, J = 6.9 Hz, 1H), 2.22 (s, 1H), 1.36 (d, J = 7.2 Hz, 3H); MS (ESI) m/z 464.1 $(M+H)^+$.

*4.1.7.3. Methyl 3-((3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)amino)propanoate (**15-1c**)*. Yield: 79.6%; White solid; Mp: 60–63 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.55 (s, 1H), 7.44–7.36 (m, 3H), 7.22 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 8.0 Hz, 4H), 3.87 (s, 2H), 3.71 (s, 3H), 2.91 (t, J = 6.4 Hz, 2H), 2.56 (t, J = 6.4 Hz, 2H); MS (ESI) m/z 464.1 $(M+H)^+$.

*4.1.7.4. Methyl 1-(3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)pyrrolidine-3-carboxylate (**15-1d**)*. Yield: 70.8%; White solid; Mp: 78–79 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.44–7.36 (m, 3H), 7.22 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 8.0 Hz, 4H), 3.70 (s, 3H), 3.68–3.63 (m, 2H), 3.10–3.02 (m, 1H), 2.88 (t, J = 8.6 Hz, 1H), 2.72–2.68 (m, 2H), 2.58 (q, J = 8.0 Hz, 1H), 2.16–2.10 (m, 2H); MS (ESI) m/z 490.2 $(M+H)^+$.

*4.1.7.5. Methyl (3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)prolinate (**15-1e**)*. Yield: 73.2%; White solid; Mp: 52–54 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.56 (s, 1H), 7.41 (q, J = 8.0 Hz, 3H), 7.22 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 8.0 Hz, 4H), 3.99 (d, J = 13.2 Hz, 1H), 3.70 (s, 3H), 3.59 (d, J = 13.4 Hz, 1H), 3.33 (t, J = 7.4 Hz, 1H), 3.08–3.03 (m, 1H), 2.43 (q, J = 8.3 Hz, 1H), 2.22–2.12 (m, 1H), 2.04–1.89 (m, 2H), 1.86–1.82 (m, 1H); MS (ESI) m/z 490.2 $(M+H)^+$.

*4.1.7.6. Ethyl N-(3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)-N-methylglycinate (**15-1f**)*. Yield: 57.5%; White solid; Mp: 58–60 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.42 (t, J = 7.6 Hz, 3H), 7.22 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 8.4 Hz, 4H), 4.20 (q, J = 7.1 Hz, 2H), 3.77 (s, 2H), 3.32 (s, 2H), 2.43 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H); MS (ESI) m/z 478.2 $(M+H)^+$.

*4.1.7.7. Methyl 1-(3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)azetidine-3-carboxylate (**15-1g**)*. Yield: 73.5%; White solid; Mp: 73–76 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.50 (s, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 8.4 Hz, 4H), 3.72 (s, 3H), 3.66 (s, 2H), 3.58–3.54 (m, 2H), 3.36 (m, 3H); MS (ESI) m/z 476.1 $(M+H)^+$.

*4.1.7.8. Methyl 2-((3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)amino)-2-methylpropanoate (**15-1h**)*. Yield: 71.6%; White solid; Mp: 96–98 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.50 (t, J = 7.4 Hz, 3H), 7.28 (t, J = 7.4 Hz, 1H), 7.21–7.18 (m, 4H), 3.70 (d, J = 6.8 Hz, 2H), 3.64 (s, 3H), 2.78 (t, J = 7.4 Hz, 1H), 1.28 (s, 6H); MS (ESI) m/z 478.2 $(M+H)^+$.

*4.1.7.9. Ethyl 1-(3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)piperidine-4-carboxylate (**15-1i**)*. Yield: 68.9%; White solid; Mp: 93–95 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.51 (t, J = 7.8 Hz, 3H), 7.30 (t, J = 7.4 Hz, 1H), 7.23–7.20 (m, 3H), 5.77 (s, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.57 (s, 2H), 2.78 (d, J = 11.2 Hz, 2H), 2.36–2.30 (m, 1H), 2.08 (t, J = 11.2 Hz, 2H), 1.83 (d, J = 12.8 Hz, 2H), 1.66–1.56 (m, 2H), 1.19 (t, J = 7.0 Hz, 3H); MS (ESI) m/z 518.2 $(M+H)^+$.

*4.1.7.10. Dimethyl (3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)aspartate (**15-1j**)*. Yield: 74.9%; White solid; Mp: 62–63 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.49 (q, J = 8.0 Hz, 3H), 7.28 (t, J = 7.4 Hz, 1H), 7.21–7.18 (m, 4H), 3.90 (dd, J = 15.0, 6.0 Hz, 1H), 3.73 (dd, J = 15.0, 6.0 Hz, 1H), 3.64 (s, 3H), 3.61 (s, 3H), 3.58–3.54 (m, 1H), 3.02–2.96 (m, 1H), 2.73 (dd, J = 16.0, 6.4 Hz, 1H), 2.64 (dd, J = 16.0, 7.2 Hz, 1H); MS (ESI) m/z 522.1 $(M+H)^+$.

*4.1.7.11. Methyl 2-(1-(3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)acetate (**15-1k**)*. Yield: 69.3%; White solid; Mp: 109–112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 7.6 Hz, 1H), 7.59 (s, 1H), 7.51–7.46 (m, 3H), 7.28 (t, J = 7.4 Hz, 1H), 7.20–7.18 (m, 4H), 3.58 (s, 3H), 3.54 (s, 2H), 2.78 (d, J = 11.2 Hz, 2H), 2.24 (d, J = 6.4 Hz, 2H), 1.98 (t, J = 11.4 Hz, 2H), 1.70–1.60 (m, 3H), 1.27–1.18 (m, 2H); MS (ESI) m/z 518.2 $(M+H)^+$.

*4.1.7.12. Methyl (4-(5-([1,1′-biphenyl]-4-yl)-1,2,4-oxadiazol-3-yl)-3-chlorobenzyl)glycinate (**15-1m**)*. Yield: 72.5%; White solid; Mp: 88–90 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (d, J = 8.5 Hz, 2H), 7.98 (dd, J = 8.0, 2.0 Hz, 3H), 7.80 (d, J = 7.5 Hz, 2H), 7.67 (s, 1H), 7.56–7.50 (m, 3H), 7.46 (t, J = 7.2 Hz, 1H), 3.84 (s, 2H), 3.64 (s, 3H), 3.37 (s, 2H), 2.77 (s, 1H); MS (ESI) m/z 434.1 $(M+H)^+$.

*4.1.7.13. Methyl (4-(5-(4-(tert-butyl)phenyl)-1,2,4-oxadiazol-3-yl)-3-chlorobenzyl)glycinate (**15-1n**)*. Yield: 57.7%; White solid; Mp: 79–82 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.65 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 3.82 (s, 2H), 3.63 (s, 3H), 3.37 (s, 2H), 2.76 (s, 1H), 1.34 (s, 9H); MS (ESI) m/z 414.2 $(M+H)^+$.

*4.1.7.14. Methyl (3-chloro-4-(5-(4-isopropylphenyl)-1,2,4-oxadiazol-3-yl) benzyl)glycinate (**15-1o**)*. Yield: 70.7%; White solid; Mp: 68–70 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12–8.10 (m, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 1.2 Hz, 1H), 7.56–7.54 (m, 2H), 7.50 (dd, J = 8.0, 1.2 Hz, 1H), 3.83 (s, 2H), 3.63 (s, 3H), 3.37 (s, 2H), 3.03 (hept, J = 6.9 Hz, 1H), 2.78 (s, 1H), 1.26 (d, J = 6.8 Hz, 6H); MS (ESI) m/z 400.1 $(M+H)^+$.

*4.1.7.15. Methyl (3-chloro-4-(5-(4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)glycinate (**15-1p**)*. Yield: 86.6%; White solid; Mp: 59–60 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.18–7.16 (m, 2H), 4.80 (hept, J = 6.1 Hz, 1H), 3.82 (s, 2H), 3.63 (s, 3H), 3.36 (s, 2H), 2.76 (s, 1H), 1.32 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 416.1 $(M+H)^+$.

*4.1.7.16. Methyl (3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)glycinate (**15-1q**)*. Yield: 88.3%; White solid; Mp: 107–110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.4 Hz, 1H), 8.39 (dd, J = 9.2, 2.4 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 1.2 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.50 (dd, J = 8.0, 1.6 Hz,

1H), 4.98 (hept, J = 6.1 Hz, 1H), 3.82 (s, 2H), 3.63 (s, 3H), 3.37 (s, 2H), 2.77 (s, 1H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 441.1 $(M+H)^+$.

4.1.7.17. Methyl (3-chloro-4-(5-(4-isopropoxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)benzyl)glycinate ***(15-1r)***. Yield: 73.5%; White solid; Mp: 88–90 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (dd, J = 8.8, 2.0 Hz, 1H), 8.30 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.50 (dd, J = 8.0, 1.6 Hz, 1H), 4.98 (hept, J = 6.0 Hz, 1H), 3.83 (s, 2H), 3.63 (s, 3H), 3.37 (s, 2H), 2.77 (s, 1H), 1.35 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 484.1 $(M+H)^+$.

4.1.7.18. Methyl (3-chloro-4-(5-(3-chloro-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)glycinate ***(15-1s)***. Yield: 82.5%; White solid; Mp: 83–86 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 2.0 Hz, 1H), 8.09 (dd, J = 8.6, 2.2 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 1.2 Hz, 1H), 7.48 (dd, J = 8.0, 1.6 Hz, 1H), 7.43 (d, J = 9.2 Hz, 1H), 4.87 (hept, J = 6.1 Hz, 1H), 3.82 (s, 2H), 3.63 (s, 3H), 3.36 (s, 2H), 2.76 (s, 1H), 1.36 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 450.1 $(M+H)^+$.

4.1.7.19. Methyl (3-chloro-4-(5-(4-isopropoxy-3-methylphenyl)-1,2,4-oxadiazol-3-yl)benzyl)glycinate ***(15-1t)***. Yield: 77.7%; White solid; Mp: 83–85 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99–7.96 (m, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 1.6 Hz, 1H), 7.48 (dd, J = 8.0, 1.6 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 4.77 (hept, J = 6.1 Hz, 1H), 3.82 (s, 2H), 3.63 (s, 3H), 3.36 (s, 2H), 2.76 (s, 1H), 2.22 (s, 3H), 1.33 (d, J = 6.4 Hz, 6H); MS (ESI) m/z 430.2 $(M+H)^+$.

4.1.7.20. Ethyl N-(3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-N-methylglycinate ***(15-2a)***. Yield: 62.5%; White solid; Mp: 68–69 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.4 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.64 (m, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.51–7.49 (m, 1H), 4.98 (hept, J = 6.1 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.75 (s, 2H), 3.36 (s, 2H), 2.30 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H), 1.21 (t, J = 7.0 Hz, 3H); MS (ESI) m/z 469.2 $(M+H)^+$.

4.1.7.21. Methyl 1-(3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-azetidin-e-3-carboxylate ***(15-2b)***. Yield: 72.8%; White solid; Mp: 110–111 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 9.2, 2.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.57–7.54 (m, 2H), 7.45 (d, J = 7.6 Hz, 1H), 4.98 (hept, J = 6.0 Hz, 1H), 3.66 (s, 2H), 3.64 (s, 3H), 3.47 (t, J = 7.0 Hz, 2H), 3.39–3.34 (m, 1H), 3.27 (t, J = 6.6 Hz, 2H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 467.1 $(M+H)^+$.

4.1.7.22. Dimethyl (3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-aspartate ***(15-2c)***. Yield: 78.1%; White solid; Mp: 89–90 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.4 Hz, 1H), 8.39 (dd, J = 8.8, 2.4 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 0.8 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.47 (dd, J = 8.0, 1.2 Hz, 1H), 4.98 (hept, J = 6.1 Hz, 1H), 3.93–3.72 (m, 2H), 3.64 (s, 3H), 3.61 (s, 3H), 3.57 (s, 1H), 3.00 (s, 1H), 2.76–2.61 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 513.2 $(M+H)^+$.

4.1.7.23. Methyl 1-(3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-pyrrolidine-3-carboxylate ***(15-2d)***. Yield: 69.1%; White solid; Mp: 111–113 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.4 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 1.6 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.49 (dd, J = 8.0, 1.6 Hz, 1H), 4.98 (h, J = 6.1 Hz, 1H), 3.73–3.64 (m, 2H), 3.61 (s, 3H), 3.11–3.03 (m, 1H), 2.76–2.67 (m, 2H), 2.56 (t, J = 6.8 Hz, 2H), 2.05–1.95 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 481.2 $(M+H)^+$.

4.1.7.24. Methyl 2-(1-(3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-piperidin-4-yl)acetate ***(15-2e)***. Yield: 69.1%; White solid; Mp: 130–132 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 8.8, 2.4 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.59 (s, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 4.98 (hept, J = 6.1 Hz, 1H), 3.58 (s, 3H), 3.54 (s, 2H), 2.78 (d, J = 11.2 Hz, 2H), 2.25 (d, J = 6.8 Hz, 2H), 1.98 (t, J = 11.0 Hz, 2H), 1.72–1.61 (m, 3H), 1.38 (d, J = 6.0 Hz, 6H), 1.28–1.18 (m, 2H); MS (ESI) m/z 509.2 $(M+H)^+$.

4.1.7.25. Methyl 4-((3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-amino)butanoate ***(15-2f)***. Yield: 58.2%; White solid; Mp: 115–116 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 2.0 Hz, 1H), 8.51 (dd, J = 9.2, 2.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.68 (d, J = 9.2 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 5.10 (hept, J = 5.9 Hz, 1H), 3.89 (s, 2H), 3.71 (s, 3H), 3.45 (s, 1H), 2.63–2.61 (m, 4H), 1.82 (quint, J = 7.0 Hz, 2H), 1.51 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 469.2 $(M+H)^+$.

4.1.7.26. Methyl 3-((3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-(methyl)amino)propanoate ***(15-2g)***. Yield: 54.0%; White solid; Mp: 80–81 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 2.4 Hz, 1H), 8.38 (dd, J = 8.8, 2.4 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 1.2 Hz, 1H), 7.54 (d, J = 9.2 Hz, 1H), 7.45 (dd, J = 8.0, 1.2 Hz, 1H), 4.97 (hept, J = 6.1 Hz, 1H), 3.60 (s, 3H), 3.57 (s, 2H), 2.66 (t, J = 6.8 Hz, 2H), 2.53 (t, J = 6.6 Hz, 2H), 2.17 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 469.2 $(M+H)^+$.

4.1.7.27. Methyl 1-(3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-piperidine-3-carboxylate ***(15-2h)***. Yield: 54.0%; White solid; Mp: 102–103 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 9.2, 2.4 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 1.2 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.48 (dd, J = 8.0, 1.6 Hz, 1H), 4.98 (hept, J = 6.0 Hz, 1H), 3.63–3.53 (m, 5H), 2.77–2.74 (m, 1H), 2.67–2.56 (m, 2H), 2.34–2.15 (m, 2H), 1.80–1.66 (m, 2H), 1.53–1.48 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 495.2 $(M+H)^+$.

4.1.7.28. Methyl 4-((3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-amino)cyclohexane-1-carboxylate ***(15-2i)***. Yield: 69.0%; White solid; Mp: 126–127 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 1.2 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.50 (d, J = 8.0, 1.2 Hz, 1H), 4.98 (hept, J = 6.0 Hz, 1H), 3.76 (s, 2H), 3.58 (m, 3H), 2.32 (d, J = 6.8 Hz, 2H), 2.23 (tt, J = 12.2, 3.4 Hz, 1H), 1.91–1.82 (m, 4H), 1.38 (d, J = 6.0 Hz, 6H), 1.36–1.26 (m, 2H), 0.96–0.86 (m, 2H); MS (ESI) m/z 509.2 $(M+H)^+$.

4.1.7.29. Methyl (3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-serinate ***(15-2j)***. Yield: 64.2%; White solid; Mp: 109–110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.4 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 0.8 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.50 (dd, J = 8.0, 1.2 Hz, 1H), 4.97 (hept, J = 6.1 Hz, 1H), 4.88 (t, J = 5.8 Hz, 1H), 3.92–3.71 (m, 2H), 3.63–3.60 (m, 5H), 3.30 (t, J = 5.2 Hz, 1H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 471.1 $(M+H)^+$.

4.1.7.30. 5-(3-(2-chloro-4-(((2-oxotetrahydrofuran-3-yl)amino)methyl) phenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile ***(15-2k)***. Yield: 62.5%; White solid; Mp: 134–136 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.4 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 1.2 Hz, 1H), 7.56–7.52 (m, 2H), 4.97 (hept, J = 5.9 Hz, 1H), 4.32 (td, J = 8.5, 2.7 Hz, 1H), 4.18–4.12 (m, 1H), 4.00–3.89 (m, 2H), 3.58–3.53 (m, 1H), 3.03–3.01 (m, 1H), 2.44–2.37 (m, 1H), 2.03–1.95 (m, 1H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 453.1 $(M+H)^+$.

*4.1.7.31. Dimethyl (3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-glutamate (**15-2l**)*. Yield: 67.3%; White solid; Mp: 91–93 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.47 (dd, J = 8.0, 1.6 Hz, 1H), 4.98 (hept, J = 6.0 Hz, 1H), 3.88–3.84 (m, 1H), 3.66–3.61 (m, 4H), 3.57 (s, 3H), 3.25–3.19 (m, 1H), 2.81–2.75 (m, 1H), 2.47–2.42 (m, 2H), 1.92–1.74 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 527.2 $(M+H)^+$.

*4.1.7.32. 5-(3-(2-Chloro-4-(((1,3-dihydroxypropan-2-yl)amino)methyl) phenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile hydrochloride (**15-2m**)*. Yield: 63.5%; White solid; Mp: 134–136 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.4 Hz, 1H), 8.38 (dd, J = 9.0, 2.2 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 7.53 (t, J = 8.0 Hz, 2H), 4.97 (hept, J = 6.0 Hz, 1H), 4.47 (s, 2H), 3.88 (s, 2H), 3.42 (s, 2H), 3.38 (s, 2H), 2.54 (q, J = 5.6 Hz, 1H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.21, 167.06, 162.56, 147.10, 134.63, 133.82, 131.92, 131.47, 129.89, 126.97, 123.26, 115.80, 115.24, 114.91, 102.50, 72.56, 61.10, 60.33, 49.67, 21.49; HRMS (ESI) m/z calcd. For $C_{22}H_{24}ClN_4O_4$ $(M+H)^+$ 443.1481, found 443.1480.

*4.1.7.33. 5-(3-(2-Chloro-4-(((2-hydroxyethyl)amino)methyl)phenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile hydrochloride (**15-2n**)*. Yield: 70.2%; White solid; Mp: 132–135 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.62–7.59 (m, 1H), 7.56 (d, J = 9.2 Hz, 1H), 5.76 (s, 1H), 4.98 (hept, J = 6.0 Hz, 1H), 4.86 (s, 1H), 4.02 (s, 2H), 3.57 (s, 2H), 2.77 (t, J = 5.6 Hz, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.32, 166.92, 162.59, 142.74, 134.64, 133.85, 132.01, 131.66, 130.88, 127.96, 124.23, 115.74, 115.22, 114.93, 102.50, 72.57, 58.75, 50.54, 50.07, 21.48; HRMS (ESI) m/z calcd. For $C_{21}H_{22}ClN_4O_3$ $(M+H)^+$ 413.1375, found 413.1376.

*4.1.7.34. 5-(3-(2-Chloro-4-(((2-hydroxypropyl)amino)methyl)phenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile hydrochloride (**15-2o**)*. Yield: 58.4%; White solid; Mp: 172–175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 2.0 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.82 (s, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 6.1 Hz, 2H), 4.05–4.00 (m, 2H), 3.47–3.44 (m, 2H), 2.90 (s, 1H), 1.38 (d, J = 6.0 Hz, 6H), 1.10 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.30, 166.91, 162.58, 143.05, 134.63, 133.84, 131.98, 131.63, 130.92, 127.97, 124.19, 115.74, 115.22, 114.92, 102.49, 72.56, 63.52, 54.27, 48.00, 21.48, 15.55; HRMS (ESI) m/z calcd. For $C_{22}H_{24}ClN_4O_3$ $(M+H)^+$ 427.1531, found 427.1531.

*4.1.7.35. Methyl (4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-glycinate (**15-3a**)*. Yield: 92.1%; White solid; Mp: 150–151 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.2 Hz, 1H), 8.39 (dd, J = 8.8, 2.4 Hz, 1H), 8.05 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.43–7.38 (m, 2H), 4.98 (hept, J = 6.1 Hz, 1H), 3.84 (s, 2H), 3.63 (s, 3H), 3.37 (s, 2H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 425.1 $(M+H)^+$.

*4.1.7.36. Ethyl N-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-N-methylglycinate (**15-3b**)*. Yield: 58.9%; White solid; Mp: 101–102 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 2.4 Hz, 1H), 8.38 (dd, J = 8.8, 2.4 Hz, 1H), 8.06 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 9.2 Hz, 1H), 7.40–7.37 (m, 2H), 4.97 (hept, J = 6.1 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.75 (s, 2H), 3.36 (s, 2H), 2.30 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H), 1.21 (t, J = 7.0 Hz, 3H); MS (ESI) m/z 453.2 $(M+H)^+$.

*4.1.7.37. Dimethyl (4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-aspartate (**15-3c**)*. Yield: 73.7%; White solid; Mp: 87–89 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.04 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 11.2 Hz, 2H), 5.00–4.94 (m, 1H), 3.92 (dd, J = 15, 2.2 Hz, 1H), 3.75 (dd, J = 15.8, 3.4 Hz, 1H), 3.64–3.56 (m, 7H), 2.99 (s, 1H), 2.76–2.61 (m, 2H), 1.38 (d, J = 5.9 Hz, 6H); MS (ESI) m/z 497.2 $(M+H)^+$.

*4.1.7.38. Methyl 2-(1-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-piperidin-4-yl)acetate (**15-3d**)*. Yield: 53.4%; White solid; Mp: 110–111 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.39 (d, J = 8.8 Hz, 1H), 8.05 (t, J = 7.8 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.36 (d, J = 9.6 Hz, 2H), 5.00–4.94 (m, 1H), 3.58 (s, 3H), 3.54 (s, 2H), 2.78 (d, J = 10.0 Hz, 2H), 2.25 (d, J = 6.4 Hz, 2H), 1.98 (t, J = 11.2 Hz, 2H), 1.64–1.61 (m, 3H), 1.38 (d, J = 6.0 Hz, 6H), 1.28–1.19 (m, 2H); MS (ESI) m/z 493.2 $(M+H)^+$.

*4.1.7.39. Methyl (4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)glycinate (**15-3e**)*. Yield: 78.7%; White solid; Mp: 122–124 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (m, 1H), 8.39 (dt, J = 9.2, 1.7 Hz, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.56–7.53 (m, 3H), 4.97 (hept, J = 5.9 Hz, 1H), 3.81 (s, 2H), 3.63 (s, 3H), 3.36 (s, 2H), 2.73 (s, 1H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 407.2 $(M+H)^+$.

*4.1.7.40. Ethyl N-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-N-methyl-glycinate (**15-3f**)*. Yield: 68.8%; White solid; Mp: 93–94 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 2.0 Hz, 1H), 8.38 (dd, J = 9.0, 1.8 Hz, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.53 (t, J = 7.8 Hz, 3H), 4.97 (hept, J = 5.8 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.73 (s, 2H), 3.33 (s, 2H), 2.28 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H), 1.20 (t, J = 7.0 Hz, 3H); MS (ESI) m/z 435.2 $(M+H)^+$.

*4.1.7.41. Methyl 1-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)pyrrolidine-3-carboxylate (**15-3g**)*. Yield: 68.8%; White solid; Mp: 94–95 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 8.8, 2.4 Hz, 1H), 8.04–8.02 (m, 2H), 7.56–7.51 (m, 3H), 4.97 (hept, J = 6.0 Hz, 1H), 3.70–3.63 (m, 2H), 3.61 (s, 3H), 3.10–3.02 (m, 1H), 2.75 (t, J = 8.6 Hz, 1H), 2.68–2.64 (m, 1H), 2.56–2.53 (m, 2H), 2.07–1.94 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 447.2 $(M+H)^+$.

*4.1.7.42. Dimethyl (4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)aspartate (**15-3h**)*. Yield: 71.3%; White solid; Mp: 75–76 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 8.03–8.01 (m, 2H), 7.56–7.50 (m, 3H), 4.97 (hept, J = 6.1 Hz, 1H), 3.91–3.71 (m, 2H), 3.64 (s, 3H), 3.60 (s, 3H), 3.57 (m, 1H), 2.87 (s, 1H), 2.76–2.61 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 479.2 $(M+H)^+$.

*4.1.7.43. Methyl 2-(1-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)acetate (**15-3i**)*. Yield: 74.8%; White solid; Mp: 122–123 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.4 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 8.04–8.02 (m, 2H), 7.55 (d, J = 9.2 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.97 (hept, J = 6.1 Hz, 1H), 3.58 (s, 3H), 3.52 (s, 2H), 2.78 (d, J = 11.6 Hz, 2H), 2.24 (d, J = 6.8 Hz, 2H), 1.99–1.93 (m, 2H), 1.63–1.60 (m, 3H), 1.38 (d, J = 6.0 Hz, 6H), 1.27–1.17 (m, 2H); MS (ESI) m/z 475.2 $(M+H)^+$.

*4.1.7.44. Methyl (4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-glycinate (**15-3j**)*. Yield: 92.1%; White solid; Mp: 150–151 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.2 Hz, 1H), 8.39 (dd, J = 8.8, 2.4 Hz, 1H), 8.05 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.43–7.38 (m, 2H), 4.98 (hept, J = 6.1 Hz, 1H), 3.84 (s, 2H), 3.63 (s, 3H), 3.37 (s, 2H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 425.1 $(M+H)^+$.

*4.1.7.45. Ethyl N-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-N-methylglycinate (**15-3k**)*. Yield: 58.9%; White

solid; Mp: 101–102 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 2.4 Hz, 1H), 8.38 (dd, J = 8.8, 2.4 Hz, 1H), 8.06 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 9.2 Hz, 1H), 7.40–7.37 (m, 2H), 4.97 (hept, J = 6.1 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.75 (s, 2H), 3.36 (s, 2H), 2.30 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H), 1.21 (t, J = 7.0 Hz, 3H); MS (ESI) m/z 453.2 $(M+H)^+$.

4.1.7.46. Methyl 1-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-pyrrolidine-3-carboxylate ***(15-3l)***. Yield: 66.7%; White solid; Mp: 96–98 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 8.06 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.39 (m, 1H), 7.37 (m, 1H), 4.98 (p, J = 6.1 Hz, 1H), 3.73–3.65 (m, 2H), 3.61 (s, 3H), 3.11–3.03 (m, 1H), 2.77–2.66 (m, 2H), 2.56 (t, J = 7.0 Hz, 2H), 2.08–1.95 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); MS (ESI) m/z 465.2 $(M+H)^+$.

4.1.7.47. Dimethyl (4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-aspartate ***(15-3m)***. Yield: 73.7%; White solid; Mp: 87–89 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.04 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 11.2 Hz, 2H), 5.00–4.94 (m, 1H), 3.92 (dd, J = 15, 2.2 Hz, 1H), 3.75 (dd, J = 15.8, 3.4 Hz, 1H), 3.64–3.56 (m, 7H), 2.99 (s, 1H), 2.76–2.61 (m, 2H), 1.38 (d, J = 5.9 Hz, 6H); MS (ESI) m/z 497.2 $(M+H)^+$.

4.1.7.48. Methyl 2-(1-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-piperidin-4-yl)acetate ***(15-3n)***. Yield: 53.4%; White solid; Mp: 110–111 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.39 (d, J = 8.8 Hz, 1H), 8.05 (t, J = 7.8 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.36 (d, J = 9.6 Hz, 2H), 5.00–4.94 (m, 1H), 3.58 (s, 3H), 3.54 (s, 2H), 2.78 (d, J = 10.0 Hz, 2H), 2.25 (d, J = 6.4 Hz, 2H), 1.98 (t, J = 11.2 Hz, 2H), 1.64–1.61 (m, 3H), 1.38 (d, J = 6.0 Hz, 6H), 1.28–1.19 (m, 2H); MS (ESI) m/z 493.2 $(M+H)^+$.

4.1.8. General procedure for the synthesis of (3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl) carboxylic acid ***(16-1a ~ 16-3n)***

To a solution of (4-(5-(substituted phenyl)-1,2,4-oxadiazol-3-yl) benzyl) carboxylic ester (0.43 mmol) in 15 mL MeOH was added 0.5 N aqueous lithium hydroxide solution (3.41 mmol) and heated to 45 °C for 3 h. The reaction mixture was cooled to rt and then added 2 N aqueous hydrochloric acid to adjust the PH to 2–3. The solvent was evaporated and 25 mL H_2O was added. The precipitated solid was filtered, washed with ether, and then dried in vacuo to afford compound **16-1a ~ 16-3n**.

4.1.8.1. (3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl) glycine hydrochloride ***(16-1a)***. Yield: 75.3%; White solid; Mp: 220–223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 2H), 8.19 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.4 Hz, 4H), 4.24 (s, 2H), 3.82 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.61, 167.88, 166.75, 161.53, 154.68, 136.52, 132.46, 132.09, 131.86, 130.46, 130.42, 129.45, 125.87, 125.07, 120.22, 118.12, 117.45, 48.69, 46.58; HRMS (ESI) m/z calcd. For $C_{23}H_{19}ClN_3O_4$ $(M+H)^+$ 436.1059, found 436.1057.

4.1.8.2. 3-((3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)amino)propanoic acid hydrochloride ***(16-1b)***. Yield: 69.5%; White solid; Mp: 232–235 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 2H), 8.20 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.0 Hz, 1H), 7.93 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.8 Hz, 4H), 4.29 (q, J = 13.5 Hz, 2H), 4.06 (q, J = 7.1 Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.62, 170.80, 166.75, 161.53, 154.69, 136.74, 132.40, 132.08, 131.86, 130.46, 130.43, 129.41, 125.83, 125.07, 120.22, 118.12, 117.46, 54.54, 47.37, 14.59; HRMS (ESI) m/z calcd. For $C_{24}H_{21}ClN_3O_4$ $(M+H)^+$ 450.1215, found 450.1206.

4.1.8.3. 3-((3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)amino)propanoic acid hydrochloride ***(16-1c)***. Yield: 68.4%; White solid; Mp: 218–219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (s, 1H), 9.32 (s, 2H), 8.20 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.0 Hz, 1H), 7.94 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.6 Hz, 4H), 4.29 (s, 2H), 3.16 (t, J = 7.2 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.61, 171.55, 166.74, 161.53, 154.69, 136.86, 132.23, 132.15, 131.88, 130.45, 130.42, 129.26, 125.80, 125.06, 120.21, 118.11, 117.45, 48.77, 42.25, 30.28; HRMS (ESI) m/z calcd. For $C_{24}H_{21}ClN_3O_4$ $(M+H)^+$ 450.1215, found 450.1206.

4.1.8.4. 1-(3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)pyrrolidine-3-carboxylic acid hydrochloride ***(16-1d)***. Yield: 59.7%; White solid; Mp: 228–231 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 11.71 (s, 1H), 8.20 (d, J = 8.4 Hz, 2H), 8.07–8.03 (m, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.2 Hz, 4H), 4.47 (s, 2H), 3.34 (m, 5H), 2.33–2.08 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.62, 173.05, 166.74, 161.53, 154.70, 136.25, 132.76, 132.30, 131.99, 130.46, 130.43, 129.75, 126.14, 125.06, 120.21, 118.13, 117.46, 55.40, 53.71, 52.59, 40.74, 26.64; HRMS (ESI) m/z calcd. For $C_{26}H_{23}ClN_3O_4$ $(M+H)^+$ 476.1372, found 476.1363.

4.1.8.5. (3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl) proline hydrochloride ***(16-1e)***. Yield: 54.1%; White solid; Mp: 200–202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 8.19 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 7.6 Hz, 1H), 7.82 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.21–7.18 (m, 4H), 4.35 (d, J = 13.2 Hz, 1H), 4.14 (d, J = 13.6 Hz, 1H), 3.94 (s, 1H), 3.30 (s, 1H), 2.95 (s, 1H), 2.35–2.30 (m, 1H), 2.01–1.92 (m, 2H), 1.85–1.82 (m, 1H); ^{3}C NMR (151 MHz, DMSO-d_6) δ 174.59, 166.77, 161.54, 154.68, 132.21, 132.13, 131.92, 130.46, 130.43, 129.26, 125.63, 125.08, 120.23, 118.12, 117.46, 65.39, 56.35, 54.11, 28.36, 22.43; HRMS (ESI) m/z calcd. For $C_{26}H_{23}ClN_3O_4$ $(M+H)^+$ 476.1372, found 476.1368.

4.1.8.6. N-(3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)-N-methylglycine Hydrochloride ***(16-1f)***. Yield: 76.3%; White solid; Mp: 189–191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (s, 1H), 8.20 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.22–7.18 (m, 4H), 4.09 (s, 2H), 3.67 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.52, 169.74, 166.85, 161.50, 154.69, 139.86, 132.16, 131.91, 131.82, 130.44, 130.40, 129.01, 125.19, 125.05, 120.20, 118.11, 117.49, 58.39, 56.18, 41.02; HRMS (ESI) m/z calcd. For $C_{24}H_{21}ClN_3O_4$ $(M+H)^+$ 450.1215, found 450.1206.

4.1.8.7. 1-(3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)azetidine-3-carboxylic acid hydrochloride ***(16-1g)***. Yield: 63.4%; White solid; Mp: 183–185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1H), 11.49 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.2 Hz, 4H), 4.49 (s, 2H), 4.20 (d, J = 8.4 Hz, 4H), 3.68–3.62 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.61, 171.52, 166.69, 161.53, 154.68, 135.33, 132.36, 132.31, 132.08, 130.45, 130.42, 129.30, 126.18, 125.06, 120.21, 118.11, 117.44, 55.61, 54.60, 32.04; HRMS (ESI) m/z calcd. For $C_{25}H_{21}ClN_3O_4$ $(M+H)^+$ 462.1215, found 462.1206.

4.1.8.8. 2-((3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)amino)-2-methylpropanoic acid hydrochloride ***(16-1h)***. Yield: 59.4%; White solid; Mp: 230–233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 2H), 8.20 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.0 Hz, 1H), 7.93 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.8 Hz, 4H), 4.25 (s, 2H), 1.61 (s, 6H);

^{13}C NMR (151 MHz, DMSO-d_6) δ 174.64, 172.48, 166.76, 161.54, 154.68, 137.13, 132.46, 132.00, 131.86, 130.45, 129.53, 125.81, 125.07, 120.21, 118.13, 117.45, 61.77, 45.34, 21.72; HRMS (ESI) *m/z* calcd. For $C_{25}H_{23}ClN_3O_4$ $(M+H)^+$ 464.1372, found 464.1364.

*4.1.8.9. 1-(3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)piperidine-4-carboxylic acid hydrochloride (**16-1i**).* Yield: 48.3%; White solid; Mp: 233–235 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 8.19 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.50 (t, J = 7.6 Hz, 3H), 7.28 (t, J = 7.4 Hz, 1H), 7.21–7.18 (m, 4H), 3.55 (s, 2H), 2.76 (d, J = 11.2 Hz, 2H), 2.22 (m, 1H), 2.05 (t, J = 11.4 Hz, 2H), 1.80 (d, J = 12.8 Hz, 2H), 1.59 (t, J = 11.8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.63, 174.59, 166.73, 161.54, 154.68, 134.45, 133.66, 132.28, 131.92, 130.73, 130.45, 130.42, 126.39, 125.06, 120.21, 118.12, 117.44, 57.51, 50.73, 37.94, 24.99; HRMS (ESI) *m/z* calcd; For $C_{27}H_{25}ClN_3O_4$ $(M+H)^+$ 490.1528, found 490.1524.

*4.1.8.10. (3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl) aspartic acid hydrochloride (**16-1j**).* Yield: 48.3%; White solid; Mp: 212–214 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 2H), 8.19 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 7.6 Hz, 1H), 7.89 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.19 (dd, J = 8.4, 4.8 Hz, 4H), 4.22 (q, J = 12.9 Hz, 2H), 3.98 (t, J = 6.0 Hz, 1H), 3.38 (q, J = 7.1 Hz, 1H), 2.97–2.85 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.54, 171.22, 171.04, 166.86, 161.51, 154.71, 139.84, 132.02, 131.70, 131.61, 130.46, 130.42, 128.63, 125.09, 125.06, 120.22, 118.12, 117.51, 55.71, 48.80, 35.40; HRMS (ESI) *m/z* calcd. For $C_{25}H_{21}ClN_3O_6$ $(M+H)^+$ 494.1113, found 494.1104.

*4.1.8.11. 2-(1-(3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)piperidin-4-yl)acetic acid hydrochloride (**16-1k**).* Yield: 61.4%; White solid; Mp: 234–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 10.84 (s, 1H), 8.20–8.04 (m, 4H), 7.79 (m, 2H), 7.49 (m, 2H), 7.40–6.97 (m, 5H), 4.47–4.36 (m, 2H), 3.14 (s, 1H), 2.97–2.95 (m, 3H), 2.41 (s, 1H), 2.19 (m, 2H), 2.05–1.39 (m, 5H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.62, 172.97, 166.73, 161.53, 154.68, 134.62, 133.61, 132.26, 131.89, 130.67, 130.45, 130.42, 126.33, 125.06, 120.21, 118.12, 117.44, 57.63, 51.42, 30.18, 28.27; HRMS (ESI) *m/z* calcd. For $C_{28}H_{27}ClN_3O_4$ $(M+H)^+$ 504.1685, found 504.1686.

*4.1.8.12. 3-(3-Chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl) phenyl)propanoic acid (**16-1l**).* Yield: 63.5%; White solid; Mp: 137–139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 8.18 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.59 (s, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H), 7.20–7.18 (m, 4H), 2.92 (t, J = 7.6 Hz, 2H), 2.63 (t, J = 7.4 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.36, 173.47, 166.99, 161.43, 154.72, 146.29, 131.92, 131.59, 130.57, 130.43, 130.36, 127.67, 125.01, 123.17, 120.18, 118.09, 117.57, 34.44, 29.73; HRMS (ESI) *m/z* calcd. For $C_{23}H_{18}ClN_2O_4$ $(M+H)^+$ 421.0950, found 421.0942.

*4.1.8.13. (4-(5-([1,1′-biphenyl]-4-yl)-1,2,4-oxadiazol-3-yl)-3-chlorobenzyl)glycine hydrochloride (**16-1m**).* Yield: 64.7%; White solid; Mp: 248–250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1H), 8.28 (d, J = 8.5 Hz, 2H), 8.10 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.93 (s, 1H), 7.81 (d, J = 7.5 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.48–7.46 (m, 1H), 4.29 (s, 2H), 3.91 (s, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.86, 167.83,166.85, 144.84, 138.52, 136.46, 132.53, 132.12, 131.91, 129.51, 129.20, 128.65, 127.76, 127.00, 125.85, 121.93, 48.68, 46.52; HRMS (ESI) *m/z* calcd. For $C_{23}H_{19}ClN_3O_3$ $(M+H)^+$ 420.1109, found 420.1107.

*4.1.8.14. (4-(5-(4-(tert-Butyl)phenyl)-1,2,4-oxadiazol-3-yl)-3-chlorobenzyl)glycine hydrochloride (**16-1n**).* Yield: 71.4%; White solid; Mp: 212–215 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 1H), 4.06 (s, 2H), 3.47 (s, 2H), 1.35 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.99, 169.04, 166.81, 156.70, 132.10, 131.87, 131.76, 131.71, 128.77, 127.88, 126.53, 125.35, 120.44, 49.34, 47.69, 35.05, 30.76; HRMS (ESI) *m/z* calcd. For $C_{21}H_{23}ClN_3O_3$ $(M+H)^+$ 400.1422, found 400.1427.

*4.1.8.15. (3-Chloro-4-(5-(4-isopropylphenyl)-1,2,4-oxadiazol-3-yl) benzyl)glycine hydrochloride (**16-1o**).* Yield: 64.2%; White solid; Mp: 117–119 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H), 8.11 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 1.2 Hz, 1H), 7.72 (dd, J = 8.2, 1.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 4.27 (s, 2H), 3.87 (s, 2H), 3.03 (hept, J = 6.8 Hz, 1H), 1.26 (d, J = 6.8 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 175.07, 167.85, 166.75, 154.51, 136.52, 132.49, 132.09, 131.85, 129.47, 128.14, 127.64, 125.87, 120.76, 48.68, 46.58, 33.61, 23.44; HRMS (ESI) *m/z* calcd. For $C_{20}H_{21}ClN_3O_3$ $(M+H)^+$ 386.1266, found 386.1269.

*4.1.8.16. (3-Chloro-4-(5-(4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl) benzyl)glycine hydrochloride (**16-1p**).* Yield: 65.6%; White solid; Mp: 204–207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.10 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 4.80 (hept, J = 6.1 Hz, 1H), 4.15 (s, 2H), 3.64 (s, 2H), 1.32 (d, J = 6.0 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.91, 167.95, 166.65, 161.64, 136.54, 132.39, 132.09, 131.84, 130.08, 129.39, 126.00, 116.24, 114.95, 69.95, 48.73, 46.66, 21.66; HRMS (ESI) *m/z* calcd. For $C_{20}H_{21}ClN_3O_4$ $(M+H)^+$ 402.1215, found 402.1216.

*4.1.8.17. (3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)glycine hydrochloride (**16-1q**).* Yield: 62.3%; White solid; Mp: 198–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.50 (m, 1H), 8.40 (m, 1H), 8.04 (m, 1H), 7.83 (s, 1H), 7.65–7.57 (m, 2H), 4.98 (s, 1H), 4.13 (s, 2H), 3.61 (s, 2H), 1.39 (m, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.46, 167.98, 166.75, 162.63, 136.73, 134.66, 133.89, 132.44, 132.10, 131.91, 129.41, 125.65, 115.68, 115.22, 114.96, 102.51, 72.59, 48.75, 46.69, 21.49; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}ClN_4O_4$ $(M+H)^+$ 427.1168, found 427.1166.

*4.1.8.18. (3-Chloro-4-(5-(4-isopropoxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)benzyl)-glycine hydrochloride (**16-1r**).* Yield: 68.3%; White solid; Mp: 202–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 8.4 Hz, 1H), 8.30 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.72 (s, 1H), 7.60–7.54 (m, 2H), 5.01–4.95 (m, 1H), 3.94 (s, 2H), 3.23 (s, 2H), 1.35 (d, J = 5.6 Hz, 6H); ^{13}C NMR (101 MHz, CF_3COOD-*d*) δ 178.57, 172.27, 167.72, 164.20, 137.62, 136.14, 134.96, 134.61, 131.02, 130.56 (q, J = 5.4 Hz), 128.46, 124.88 (q, J = 272.6 Hz), 124.03 (q, J = 32.3 Hz), 116.82, 114.44, 75.48, 53.74, 49.42, 22.28; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}ClF_3N_3O_4$ $(M+H)^+$ 470.1089, found 470.1091.

*4.1.8.19. (3-Chloro-4-(5-(3-chloro-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)glycine hydrochloride (**16-1s**).* Yield: 64.5%; White solid; Mp: 217–220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 2.4 Hz, 1H), 8.09 (dd, J = 8.6, 2.2 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 1.6 Hz, 1H), 7.61 (dd, J = 8.0, 1.6 Hz, 1H), 7.44 (d, J = 9.2 Hz, 1H), 4.88 (hept, J = 5.9 Hz, 1H), 4.09 (s, 2H), 3.49 (s, 2H), 1.36 (d, J = 6.4 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.87, 168.06, 166.72, 156.93, 136.84, 132.38, 132.08, 131.90, 129.49, 129.35, 128.69, 125.72, 122.99, 115.82, 115.35, 71.81, 48.78, 46.80, 21.63; HRMS (ESI) *m/z* calcd. For $C_{20}H_{20}Cl_2N_3O_4$ $(M+H)^+$ 436.0825, found 436.0827.

*4.1.8.20. (3-Chloro-4-(5-(4-isopropoxy-3-methylphenyl)-1,2,4-oxadiazol-3-yl)benzyl)glycine hydrochloride (**16-1t**).* Yield: 61.2%; White solid; Mp: 212–214 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00–7.97 (m, 3H),

7.77 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 4.78 (hept, J = 5.9 Hz, 1H), 4.05 (s, 2H), 3.41 (s, 2H), 2.23 (s, 3H), 1.33 (d, J = 6.0 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 175.05, 168.31, 166.62, 159.89, 137.24, 132.14, 132.08, 131.85, 130.14, 129.15, 127.91, 127.81, 125.87, 114.46, 112.89, 70.10, 48.92, 47.08, 21.84, 16.04; HRMS (ESI) *m/z* calcd. For $C_{21}H_{23}ClN_3O_4$ $(M+H)^+$ 416.1372, found 416.1369.

4.1.8.21. N-(3-chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-N-methyl-glycine Hydrochloride ***(16-2a)***. Yield: 64.1%; White solid; Mp: 152–155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 1.2 Hz, 1H), 7.70 (dd, J = 8.2, 1.4 Hz, 1H), 7.57 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 6.1 Hz, 1H), 4.34 (s, 2H), 3.97 (s, 2H), 2.73 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.45, 168.08, 166.75, 162.63, 136.40, 134.66, 133.86, 133.08, 132.27, 132.00, 130.10, 125.88, 115.67, 115.22, 114.97, 102.51, 72.59, 57.84, 55.06, 40.67, 21.48; HRMS (ESI) *m/z* calcd. For $C_{22}H_{22}ClN_4O_4$ $(M+H)^+$ 441.1324, found 441.1326.

4.1.8.22. 1-(3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)azetidine-3-carboxylic acid hydrochloride ***(16-2b)***. Yield: 69.3%; White solid; Mp: 145–147 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.88 (s, 1H), 7.68 (dd, J = 7.8, 2.0 Hz, 1H), 7.57 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 6.2 Hz, 1H), 4.38 (s, 2H), 4.11–4.09 (m, 4H), 3.59 (quint, J = 8.2 Hz, 1H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.33, 172.72, 166.79, 162.59, 139.00, 134.61, 133.81, 132.21, 131.92, 131.41, 128.42, 124.98, 115.68, 115.20, 114.92, 102.49, 72.57, 58.05, 55.46, 32.73, 21.48; HRMS (ESI) *m/z* calcd. For $C_{23}H_{22}ClN_4O_4$ $(M+H)^+$ 453.1324, found 453.1326.

4.1.8.23. (3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)aspartic acid hydrochloride ***(16-2c)***. Yield: 67.2%; White solid; Mp: 165–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.50 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.58–7.54 (m, 2H), 4.97 (hept, J = 6.0 Hz, 1H), 4.09–3.93 (m, 2H), 3.62 (t, J = 6.6 Hz, 1H), 2.74–2.59 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.28, 172.35, 171.69, 166.91, 162.59, 142.27, 134.63, 133.82, 132.04, 131.67, 130.94, 127.94, 124.32, 115.74, 115.24, 114.92, 102.50, 72.59, 56.25, 49.03, 36.51, 21.51; HRMS (ESI) *m/z* calcd. For $C_{23}H_{22}ClN_4O_6$ $(M+H)^+$ 485.1222, found 485.1226.

4.1.8.24. 1-(3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)pyrrolidine-3-carboxylic acid hydrochloride ***(16-2d)***. Yield: 58.3%; White solid; Mp: 212–214 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 11.76–11.40 (m, 1H), 8.50 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 8.08–8.01 (m, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 5.9 Hz, 1H), 4.50 (s, 2H), 3.44–3.36 (m, 5H), 2.22 (s, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.40, 173.00, 166.69, 162.62, 136.04, 134.62, 133.81, 132.89, 132.32, 132.03, 129.81, 125.98, 115.63, 115.20, 114.94, 102.49, 72.60, 55.37, 53.73, 52.18, 40.70, 26.60, 21.49; HRMS (ESI) *m/z* calcd. For $C_{24}H_{24}ClN_4O_4$ $(M+H)^+$ 467.1481, found 467.1487.

4.1.8.25. 2-(1-(3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)acetic acid hydrochloride ***(16-2e)***. Yield: 58.3%; White solid; Mp: 205–207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 10.43 (s, 1H), 8.52 (d, J = 2.0 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.11–8.08 (m, 1H), 8.00 (s, 1H), 7.77–7.75 (m, 1H), 7.57 (d, J = 9.2 Hz, 1H), 4.99 (hept, J = 6.1 Hz, 1H), 4.37–4.36 (m, 2H), 3.41 (m, 2H), 3.02–2.93 (m, 2H), 2.20 (d, J = 6.8 Hz, 2H), 1.87–1.84 (m, 3H), 1.58–1.48 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.48, 172.99, 166.74, 162.64, 134.70, 134.67, 133.86, 133.65, 132.27, 131.94, 130.68,126.13, 115.66, 115.22, 114.97, 102.51, 72.60, 57.68, 51.48, 30.17, 28.29, 21.49; HRMS (ESI) *m/z* calcd. For $C_{26}H_{28}ClN_4O_4$ $(M+H)^+$ 495.1794, found 495.1794.

4.1.8.26. 5-(3-(2-Chloro-4-((2-oxopyrrolidin-1-yl)methyl)phenyl)-1,2,4-oxadiazol-5-yl)-2-isopropoxybenzonitrile hydrochloride ***(16-2f)***. Yield: 60.5%; White solid; Mp: 107–109 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.57–7.55 (m, 2H), 7.41 (d, J = 8.4 Hz, 1H), 4.98 (hept, J = 6.1 Hz, 1H), 4.48 (s, 2H), 3.32–3.28 (m, 2H), 2.33 (t, J = 8.2 Hz, 2H), 1.97 (quint, J = 7.5 Hz, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.38, 173.31, 166.88, 162.58, 142.54, 134.63, 133.82, 132.28, 132.01, 129.70, 126.72, 124.10, 115.73, 115.21, 114.92, 102.49, 72.55, 46.35, 44.73, 30.10, 21.47, 17.47; HRMS (ESI) *m/z* calcd. For $C_{23}H_{22}ClN_4O_3$ $(M+H)^+$ 437.1375, found 437.1376.

4.1.8.27. 3-((3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)(methyl)-amino)propanoic acid hydrochloride ***(16-2g)***. Yield: 62.8%; White solid; Mp: 194–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 9.2, 2.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 6.0 Hz, 1H), 4.41 (s, 2H), 3.30–3.28 (m, 2H), 2.87 (t, J = 7.6 Hz, 2H), 2.67 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.46, 171.60, 166.71, 162.63, 135.46, 134.65, 133.87, 133.29, 132.32, 132.01, 130.32, 126.06, 115.66, 115.21, 114.96, 102.51, 72.59, 57.24, 50.59, 39.02, 28.68, 21.48; HRMS (ESI) *m/z* calcd. For $C_{23}H_{24}ClN_4O_4$ $(M+H)^+$ 455.1481, found 455.1484.

4.1.8.28. 1-(3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)piperidine-3-carboxylic acid hydrochloride ***(16-2h)***. Yield: 55.1%; White solid; Mp: 212–215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 11.00 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 8.00 (s, 1H), 7.77 (m, 1H), 7.57 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 5.9 Hz, 1H), 4.40 (s, 2H), 3.47 (s 2H), 2.92 (s, 3H), 2.01 (s, 1H), 1.84 (s, 2H), 1.47 (s, 1H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.46, 173.03, 166.75, 162.64, 134.66, 133.86, 133.29, 132.29, 131.98, 130.41, 125.96, 115.67, 115.22, 114.96, 102.51, 72.59, 58.05, 51.98, 51.39, 38.48, 24.94, 21.65, 21.49; HRMS (ESI) *m/z* calcd. For $C_{25}H_{26}ClN_4O_4$ $(M+H)^+$ 481.1637, found 481.1640.

4.1.8.29. 4-((3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)amino)-cyclohexane-1-carboxylic acid hydrochloride ***(16-2i)***. Yield: 71.3%; White solid; Mp: 149–151 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 9.28 (s, 2H), 8.51 (d, J = 2.0 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 1.6 Hz, 1H), 7.76 (dd, J = 8.0, 1.6 Hz, 1H), 7.57 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 6.1 Hz, 1H), 4.24 (s, 2H), 2.79 (d, J = 6.4 Hz, 2H), 2.15 (tt, J = 12.2, 3.3 Hz, 1H), 1.94–1.85 (m, 4H), 1.38 (d, J = 6.0 Hz, 6H), 1.35–1.24 (m, 3H), 1.04–0.94 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.52, 173.44, 166.77, 162.63, 136.99, 134.66, 133.88, 132.45, 131.80, 129.45, 125.52, 115.69, 115.22, 114.96, 102.51, 72.59, 52.37, 49.29, 41.98, 33.88, 29.14, 27.93, 26.72, 25.24, 21.49; HRMS (ESI) *m/z* calcd. For $C_{26}H_{28}ClN_4O_4$ $(M+H)^+$ 485.1794, found 495.1779.

4.1.8.30. (3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)serine hydro-chloride ***(16-2j)***. Yield: 61.9%; White solid; Mp: 219–222 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.39 (d, J = 9.6 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 7.83 (s, 1H), 7.64–7.54 (m, 2H), 4.98 (m, 1H), 4.17–4.07 (m, 2H), 3.84–3.75 (m, 2H), 3.58 (s, 1H), 1.39–1.38 (m, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.44,

169.36, 166.82, 162.65, 137.80, 134.68, 133.89, 132.35, 132.01, 131.78, 129.32, 125.35, 115.72, 115.25, 114.98, 102.53, 72.63, 61.26, 59.10, 48.27, 21.51; HRMS (ESI) *m/z* calcd. For $C_{22}H_{22}ClN_4O_5$ $(M+H)^+$ 457.1273, found 457.1277.

*4.1.8.31. (3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)homoserine hydrochloride (**16-2k**)*. Yield: 59.0%; White solid; Mp: 189–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.40 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 7.55 (t, J = 7.2 Hz, 2H), 4.98 (hept, J = 6.0 Hz, 1H), 3.99–3.77 (m, 2H), 3.60–3.49 (m, 2H), 3.59–3.50 (m, 2H), 3.24 (t, J = 6.4 Hz, 1H), 1.83–1.68 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.49, 173.31, 167.00, 162.60, 144.36, 134.68, 133.88, 131.97, 131.62, 130.33, 127.40, 123.85, 115.80, 115.25, 114.95, 102.51, 72.58, 58.20, 58.14, 49.57, 35.06, 21.50; HRMS (ESI) *m/z* calcd. For $C_{23}H_{24}ClN_4O_5$ $(M+H)^+$ 471.1430, found 471.1430.

*4.1.8.32. (3-Chloro-4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)glutamic acid hydrochloride (**16-2l**)*. Yield: 57.6%; White solid; Mp: 147–149 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.0 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 7.57–7.53 (m, 2H), 4.98 (hept, J = 6.0 Hz, 1H), 3.99–3.78 (m, 2H), 3.22 (t, J = 6.6 Hz, 1H), 2.43–2.33 (m, 2H), 1.92–1.79 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.96, 173.30, 166.91, 162.58, 142.17, 134.63, 133.82, 132.17, 131.84, 129.93, 126.91, 124.10, 115.75, 115.23, 114.91, 102.50, 72.57, 58.94, 44.28, 28.84, 22.67, 21.49; HRMS (ESI) *m/z* calcd. For $C_{24}H_{24}ClN_4O_6$ $(M+H)^+$ 499.1379, found 499.1375.

*4.1.8.33. (4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)glycine hydrochloride (**16-3a**)*. Yield: 72.5%; White solid; Mp: 212–214 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 2.4 Hz, 1H), 8.39 (dd, J = 8.8, 2.0 Hz, 1H), 8.15 (t, J = 7.8 Hz, 1H), 7.62 (d, J = 11.2 Hz, 1H), 7.55 (t, J = 9.4 Hz, 2H), 4.98 (hept, J = 6.1 Hz, 1H), 4.18 (s, 2H), 3.67 (s, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.49, 167.93, 164.74 (d, J = 5.4 Hz), 162.61, 159.44 (d, J = 256.5 Hz), 137.80 (d, J = 8.0 Hz), 134.64, 133.88, 130.80, 126.86, 118.54 (d, J = 22.0 Hz), 115.70, 115.21, 114.94, 114.56 (d, J = 12.4 Hz), 102.48, 72.59, 48.83, 46.59, 21.49; HRMS (ESI) *m/z* calcd. For $C_{21}H_{20}N_4O_4$ $(M+H)^+$ 411.1463, found 411.1461.

*4.1.8.34. N-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)-N-methylglycine hydrochloride (**16-3b**)*. Yield: 61.4%; White solid; Mp: 208–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 9.0, 2.2 Hz, 1H), 8.08 (t, J = 7.8 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.42 (t, J = 9.4 Hz, 2H), 4.97 (hept, J = 5.9 Hz, 1H), 3.84 (s, 2H), 3.36 (s, 2H), 2.35 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.44, 169.21, 164.83 (d, J = 5.4 Hz), 162.60, 159.64 (d, J = 256.7 Hz), 139.9, 134.64, 133.86, 130.79, 126.81, 118.40 (d, J = 21.4 Hz), 115.73, 115.22, 114.93, 114.19 (d, J = 11.6 Hz), 102.49, 72.59, 58.38, 55.82, 40.96, 21.49; HRMS (ESI) *m/z* calcd. For $C_{22}H_{22}FN_4O_4$ $(M+H)^+$ 415.1620, found 415.1615.

*4.1.8.35. (4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)aspartic acid hydrochloride (**16-3c**)*. Yield: 68.8%; White solid; Mp: 223–225 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.37 (dd, J = 9.0, 2.2 Hz, 1H), 8.08 (t, J = 7.8 Hz, 1H), 7.56–7.52 (m, 2H), 7.46 (d, J = 8.0 Hz, 1H), 4.97 (hept, J = 5.9 Hz, 1H), 4.14–3.98 (m, 2H), 3.68 (t, J = 6.4 Hz, 1H), 2.77–2.63 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.29, 172.28, 171.65, 164.90 (d, J = 5.6 Hz), 162.55, 159.70 (d, J = 256.1 Hz), 143.45 (d, J = 5.3 Hz), 134.58, 133.79, 130.48, 125.31, 116.90 (d, J = 21.6 Hz), 115.74, 115.21, 114.87, 113.24 (d, J = 12.5 Hz), 102.47, 72.58, 56.18, 49.17, 36.37, 21.50; HRMS (ESI) *m/z* calcd. For $C_{23}H_{22}FN_4O_6$ $(M+H)^+$ 469.1518, found 469.1514.

*4.1.8.36. 2-(1-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-fluorobenzyl)piperidin-4-yl)acetic acid hydrochloride (**16-3d**)*. Yield: 65.9%; White solid; Mp: 199–201 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 11.06–10.91 (m, 1H), 8.50 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.18 (t, J = 7.6 Hz, 1H), 7.85 (d, J = 11.2 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 6.1 Hz, 1H), 4.37–4.36 (m, 2H), 3.36 (s, 2H), 2.96 (q, J = 11.3 Hz, 2H), 2.19 (d, J = 6.4 Hz, 2H), 1.90–1.83 (m, 3H), 1.64–1.55 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.47, 172.98, 164.70 (d, J = 5.6 Hz), 162.60, 159.42 (d, J = 257.0 Hz), 135.80, 134.61, 133.82, 130.83, 128.14, 119.82 (d, J = 21.4 Hz), 115.66, 115.19, 115.04, 114.93, 102.47, 72.59, 57.78, 51.43, 30.20, 28.27, 21.48; HRMS (ESI) *m/z* calcd. For $C_{26}H_{28}FN_4O_4$ $(M+H)^+$ 479.2089, found 479.2087.

*4.1.8.37. (4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)glycine hydrochloride (**16-3e**)*. Yield: 70.6%; White solid; Mp: 212–215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 8.8, 2.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 5.9 Hz, 1H), 4.18 (s, 2H), 3.66 (s, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.94, 167.97, 167.85, 162.54, 135.53, 134.58, 133.79, 131.04, 127.30, 126.43, 115.87, 115.23, 114.91, 102.45, 72.58, 49.44, 46.77, 21.51; HRMS (ESI) *m/z* calcd. For $C_{21}H_{21}N_4O_4$ $(M+H)^+$ 393.1557, found 393.1555.

*4.1.8.38. N-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)-N-methylglycine hydrochloride (**16-3f**)*. Yield: 75.5%; White solid; Mp: 199–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.16 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 6.1 Hz, 1H), 4.45 (s, 2H), 4.07 (s, 2H), 2.79 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.98, 167.79, 167.29, 162.55, 134.57, 133.76, 133.62, 132.28, 127.46, 127.01, 115.83, 115.21, 114.92, 102.45, 72.58, 58.18, 54.31, 40.29, 21.50; HRMS (ESI) *m/z* calcd. For $C_{22}H_{23}N_4O_4$ $(M+H)^+$ 407.1714, found 407.1712.

*4.1.8.39. 1-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)pyrrolidine-3-carboxylic acid hydrochloride (**16-3g**)*. Yield: 75.5%; White solid; Mp: 187–189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 0H), 8.50 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 9.0, 2.2 Hz, 1H), 8.13 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 9.2 Hz, 1H), 4.98 (hept, J = 6.0 Hz, 1H), 4.34 (s, 2H), 3.26–3.16 (m, 5H), 2.29–2.10 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.94, 173.54, 167.86, 162.54, 136.25, 134.58, 133.79, 131.11, 127.40, 126.41, 115.88, 115.22, 114.91, 102.46, 72.56, 56.65, 54.15, 52.80, 40.79, 26.65, 21.49; HRMS (ESI) *m/z* calcd. For $C_{22}H_{23}N_4O_4$ $(M+H)^+$ 433.1870, found 433.1873.

*4.1.8.40. (4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)aspartic acid hydrochloride (**16-3h**)*. Yield: 67.5%; White solid; Mp: 216–219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 2H), 8.48 (d, J = 2.4 Hz, 1H), 8.38 (dd, J = 9.0, 2.2 Hz, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 9.2 Hz, 1H), 4.97 (hept, J = 6.0 Hz, 1H), 4.15–4.01 (m, 2H), 3.69 (dd, J = 7.6, 5.2 Hz, 1H), 2.77–2.62 (m, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.89, 171.26, 171.20, 167.96, 162.53, 138.74, 134.59, 133.82, 130.18, 127.21, 125.71, 115.93, 115.24, 114.90, 102.46, 72.56, 55.72, 49.44, 35.76, 21.50; HRMS (ESI) *m/z* calcd. For $C_{23}H_{23}N_4O_6$ $(M+H)^+$ 451.1612, found 451.1607.

*4.1.8.41. 2-(1-(4-(5-(3-cyano-4-isopropoxyphenyl)-1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)acetic acid hydrochloride (**16-3i**)*. Yield: 69.2%; White solid; Mp: 252–256 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 10.78 (s, 1H), 8.50 (d, J = 2.3 Hz, 1H), 8.40 (dd, J = 9.0,

2.3 Hz, 1H), 8.14 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 9.3 Hz, 1H), 4.98 (p, J = 6.1 Hz, 1H), 4.35 (d, J = 4.1 Hz, 2H), 3.31 (s, 2H), 3.04–2.89 (m, 2H), 2.18 (d, J = 6.6 Hz, 2H), 1.86 (t, J = 15.1 Hz, 3H), 1.58 (q, J = 13.0, 12.2 Hz, 2H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.92, 172.96, 167.79, 162.52, 134.53, 133.72, 133.45, 132.38, 127.30, 126.80, 115.81, 115.19, 114.89, 102.43, 72.55, 58.43, 51.30, 30.25, 28.26, 21.48; HRMS (ESI) m/z calcd. For $C_{26}H_{29}N_4O_4$ $(M+H)^+$ 461.2183, found 461.2182.

*4.1.8.42. (4-(5-(3-cyano-4-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl) benzyl)glycine hydrochloride (**16-3j**)*. Yield: 71.3%; White solid; Mp: 209–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.48 (s, 1H), 8.39 (dd, J = 9.2, 2.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 9.2 Hz, 1H), 5.17–5.14 (m, 1H), 4.19 (s, 2H), 3.69 (s, 2H), 2.06–1.97 (m, 2H), 1.80–1.64 (m, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.00, 167.90, 167.85, 162.60, 135.32, 134.50, 133.73, 131.08, 127.31, 126.49, 115.93, 115.13, 102.49, 81.74, 49.43, 46.57, 32.20, 23.53; HRMS (ESI) m/z calcd. For $C_{23}H_{23}N_4O_4$ $(M+H)^+$ 419.1714, found 419.1771.

*4.1.8.43. N-(4-(5-(3-cyano-4-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)benzyl)-N-methylglycine hydrochloride (**16-3k**)*. Yield: 70.9%; White solid; Mp: 193–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 6.8 Hz, 2H), 7.58 (d, J = 6.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 1H), 5.14 (s, 1H), 3.91 (s, 2H), 3.42 (s, 2H), 2.41 (s, 3H), 2.00 (m, 2H), 1.80–1.65 (m, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.95, 168.61, 167.90, 162.59, 134.49, 133.71, 131.52, 131.35, 127.36, 126.30, 115.12, 115.12, 102.49, 81.72, 58.83, 55.55, 40.77, 32.19, 23.52; HRMS (ESI) m/z calcd. For $C_{24}H_{25}N_4O_4$ $(M+H)^+$ 433.1870, found 433.1868.

*4.1.8.44. 1-(4-(5-(3-cyano-4-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)benzyl)pyrrolidine-3-carboxylic acid hydrochloride (**16-3l**)*. Yield: 64.1%; White solid; Mp: 229–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94–11.36 (m, 1H), 8.51 (d, J = 2.0 Hz, 1H), 8.41 (dd, J = 9.0, 2.2 Hz, 1H), 8.15 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 9.2 Hz, 1H), 5.18–5.15 (m, 1H), 4.46 (s, 2H), 3.35 (s, 5H), 2.33–2.16 (m, 2H), 2.06–1.97 (m, 2H), 1.82–1.61 (m, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.97, 173.09, 167.79, 162.59, 134.95, 134.47, 133.69, 131.46, 127.43, 126.72, 115.89, 115.11, 102.48, 81.73, 56.21, 53.69, 52.63, 40.66, 32.19, 26.55, 23.52; HRMS (ESI) m/z calcd. For $C_{26}H_{27}N_4O_4$ $(M+H)^+$ 459.2027, found 459.2024.

*4.1.8.45. (4-(5-(3-cyano-4-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl) benzyl)aspartic acid hydrochloride (**16-3m**)*. Yield: 64.1%; White solid; Mp: 229–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 2H), 8.48 (d, J = 2.4 Hz, 1H), 8.38 (dd, J = 9.0, 2.2 Hz, 1H), 8.08 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 9.2 Hz, 1H), 5.17–5.14 (m, 1H), 4.15–4.01 (m, 2H), 3.73–3.69 (m, 1H), 2.78–2.63 (m, 2H), 2.06–1.97 (m, 2H), 1.81–1.63 (m, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.99, 170.88, 169.99, 167.90, 162.61, 136.51, 134.52, 133.77, 130.88, 127.28, 126.26, 115.96, 115.13, 102.50, 81.74, 64.92, 55.26, 49.34, 34.59, 32.19, 23.52, 15.18; HRMS (ESI) m/z calcd. For $C_{25}H_{25}N_4O_6$ $(M+H)^+$ 477.1769, found 477.1766.

*4.1.8.46. 2-(1-(4-(5-(3-cyano-4-(cyclopentyloxy)phenyl)-1,2,4-oxadiazol-3-yl)benzyl)piperidin-4-yl)acetic acid hydrochloride (**16-3n**)*. Yield: 65.0%; White solid; Mp: 244–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 10.58–10.43 (m, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.37 (dd, J = 9.0, 2.2 Hz, 1H), 8.12 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 9.2 Hz, 1H), 5.15–5.11 (m, 1H), 4.32–4.31 (m, 2H), 3.32 (s, 2H), 2.98–2.88 (m, 2H), 2.15 (d, J = 6.8 Hz, 2H), 2.03–1.94 (m, 2H), 1.83–1.45 (m, 11H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.01, 173.00, 167.84, 162.61, 134.51, 133.73, 133.39, 132.38, 127.36, 126.87, 115.92, 115.14, 102.50, 81.74, 58.49, 51.42, 32.19, 30.29, 28.31, 23.53; HRMS (ESI) m/z calcd. For $C_{28}H_{31}N_4O_4$ $(M+H)^+$ 487.2340, found 487.2335.

*4.1.9. Synthesis of methyl 3-(3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)acrylate (**17**)*

To a solution of 3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)benzaldehyde (200 mg, 0.53 mmol) under Argon in DMF was added Methyl (triphenylphosphoranylidene)acetate (212.96 mg, 0.64 mmol), and stirred at rt for 3 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, then filtered and concentrated. The residue was purified by silica gel flash column chromatography (PE/EtOAc = 3:1) to afford compound **17** (160 mg, 69.7% yield) as white solid. Mp: 124–126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 8.4 Hz, 2H), 8.12 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 16.0 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.21–7.18 (m, 4H), 6.89 (d, J = 16.0 Hz, 1H), 3.76 (s, 3H); MS (ESI) m/z 433.1 $(M+H)^+$.

*4.1.10. Synthesis of methyl 3-(3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)propanoate (**15-1l**)*

To a solution of methyl 3-(3-chloro-4-(5-(4-phenoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)acrylate (150 mg, 0.35 mmol) in ethyl acetate was added Pd/C (15 mg) in batches. The mixture was stirred under H_2 at rt for 4 h, then filtered via celite and concentrated. The filtrate was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash column chromatography (PE/EtOAc = 3:1) to afford compound **15–1l** (119 mg, 52.1% yield) as white solid. Mp: 88–90 °C; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.17 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.44–7.41 (m, 3H), 7.24–7.20 (m, 2H), 7.10 (d, J = 8.4 Hz, 4H), 3.69 (s, 3H), 3.01 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H), MS (ESI) m/z 435.1 $(M+H)^+$.

4.2. Biological evaluation

4.2.1. IP_1 functional assay

The Homogeneous Time Resolved Fluorescence-IP One (HTRF-IP1) assay was performed by IP-One Tb kit purchased from Cisbio (Cisbio Bioassays). The CHO-$S1P_1$ and CHO-$S1P_3$ cells were prepared in suspension in stimulation buffer containing LiCl and 7 μl of suspension was distributed in 384-well plates with density of 7×10^4 cells/well. Then, 7 μl different concentrations of test agonists were added and the cells were incubated at 37 °C with 5% CO_2 for 2 h. Meanwhile, a standard curve was also built according to the protocol. Subsequently, 3 μl IP1-d2 and Ab-Cryp diluted by Lysis Buffer were added into each well in succession and incubated at room temperature for 1 h at 25 °C. Plates were then read in EnVision reader (PE Company), ratio of 665 nm/615 nm fluorescence was calculated and corrected by standard curve. EC_{50} values are calculated by Graph pad software 5.0.

4.2.2. Blood lymphocyte reduction assay

Male Sprague-Dawley rats (200–220 g) were dosed through intragastric administration with test agonists (as a solution in double distilled water), positive control and vehicle. Blood was drawn at the time 0 h, 4 h, 8 h, 12 h and 48 h after administration via tail vein and peripheral blood lymphocyte counts were assessed using MEK-7222K hematology analyzer.

4.2.3. Heart rate assay

Male SD rats (200–220 g) were dosed orally with 10 mg/kg of test agonists, positive control and vehicle. The heart rate at the time 0 h, 2 h, 4 h, 8 h, 12 h and 24 h after administration were assessed using intelligent non-invasive blood pressure measurement meter.

4.2.4. In vivo pharmacokinetic assay

Blood samples of male SD rats were obtained at 0.08, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 36 and 48 h postdose. The blood was prepared by centrifugation and the plasma samples were analyzed using liquid chromatography coupled to mass spectrometry (LC-MS/MS) after protein precipitation. Data fitting and pharmacokinetic parameter estimates were carried out using WinNonLin Software.

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Appendix A. Supplementary material

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