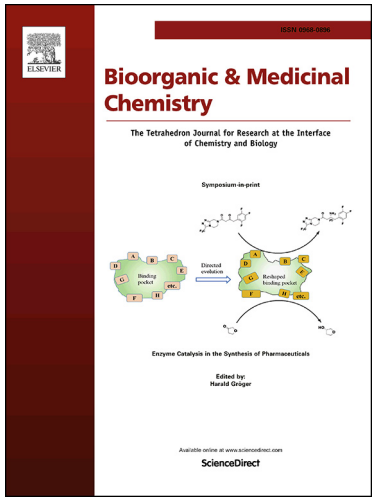
Accepted Manuscript



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PII: S0968-0896(18)30517-0
DOI: https://doi.org/10.1016/j.bmc.2018.04.059
Reference: BMC 14342

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 12 March 2018
Revised Date: 25 April 2018
Accepted Date: 30 April 2018

Please cite this article as: Wu, G., Wang, H., Zhou, W., Zeng, B., Mo, W., Zhu, K., Liu, R., Zhou, J., Chen, C., Chen, H., Synthesis and Structure–Activity Relationship Studies of MI-2 Analogues as MALT1 Inhibitors, *Bioorganic & Medicinal Chemistry* (2018), doi: https://doi.org/10.1016/j.bmc.2018.04.059

Synthesis and Structure–Activity Relationship Studies of MI-2 Analogues as MALT1 Inhibitors

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Highlights

- Various MI-2 analogues have been designed and synthesized.
- Systematic SARs of the MI-2 were investigated.
- The side chain of 2-methoxyethoxy is flexible and tolerable for modifications.
- **81-83** with terminal hydroxyl group show enhanced activities against MALT1.

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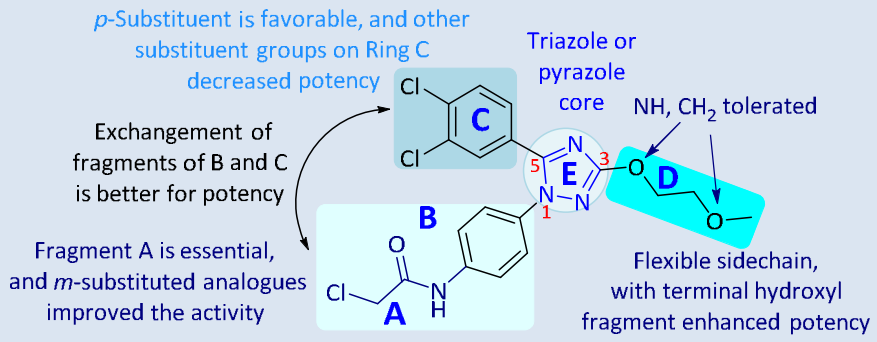


ABSTRACT

Recent studies revealed that MALT1 is a promising therapeutic target for the treatment of ABC-DLBCL. Among several reported MALT1 inhibitors, MI-2 as an irreversible inhibitor represents a new class of ABC-DLBCL therapeutics. Due to its inherent potential cross-reactivity, further structure–activity relationship (SAR) study is imperative. In this work, five focused compound libraries based on the chemical structure of MI-2 are designed and synthesized. The systematic SARs revealed that the side chain of 2-methoxyethoxy has little impact on the activity and can be replaced by other functionalized groups, providing new MI-2 analogues with retained or enhanced potency. Compounds **81-83** with terminal hydroxyl group as side chain displayed enhanced activities against MALT1. Replacement of triazole core with pyrazole is also tolerant, while structural modifications on other sites are detrimental. These findings will facilitate further development of small-molecule MALT1 inhibitors.

Keywords: MALT1; MI-2 analogues; Structure–activity relationships; Cancer Therapeutics

1. INTRODUCTION

Lymphomas are one class of the most common cancers, while non-Hodgkin lymphoma (NHL) accounts for 90% of all lymphomas.[1] Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, representing about a third of cases.[2,3] Among all cases of DLBCL, the activated B cell-like (ABC) DLBCL is the most dangerous one, with the highest rate of complications and mortality.[4-7] Patients with ABC-DLBCL often experience a rapid disease progression and most of them survive less than five years due to the lethal combination of resistance.[8,9]

Accumulating evidence demonstrates that mucosa-associated lymphoid tissue protein-1 (MALT1) plays a key role in maintaining proliferation of ABC-DLBCL cells *via* activating NF-κB signaling.[10-12] Upon antigen receptor stimulation, MALT1 paracaspase forms part of CARMA1-BCL10-MALT1 (CBM) complex, which serves as a signaling scaffold that recruits and activates the IκB kinase b (IKKb) and stimulates NF-κB.[13-16] MALT1 protease activity potentiates NF-κB signaling by cleaving and inactivating negative regulators such as IKK, A20 (TNFAIP3) and CYLD.[17-20] All these findings suggest that the activity of MALT1 is required for survival of ABC-DLBCL.[21] Thus, inhibition of MALT1 proteolytic activity is considered as a promising and powerful therapeutic approach for the treatment of ABC-DLBCL.[21,22]

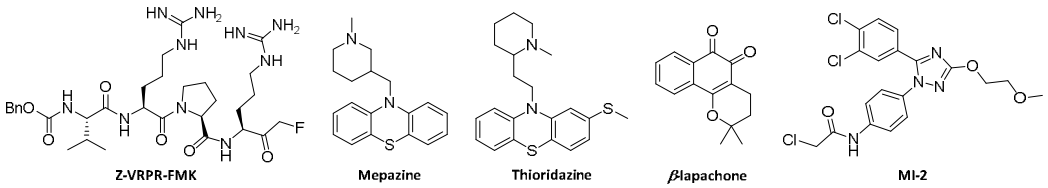


Figure 1. Chemical structures of recently reported MALT1 inhibitors.

The peptide Z-VRPR-FMK is the first reported MALT1 inhibitor that is proven to be effective for interfering with survival of ABC-DLBCL cells *in vitro*.[19,23] However, Z-VRPR-FMK is not an ideal lead compound due to its poor pharmacologic properties such as high molecular weight, relatively poor cell permeability, and potential metabolic instability.[23,24] Recently, several small-molecule MALT1 inhibitors showed apparent anticancer activity *in vitro* and *in vivo*.[25,26] For example, some phenothiazines such as mepazine and thioridazine were identified as selective MALT1 inhibitors *via* mediating reversible MALT1 cleavage inhibition.[24,27] *β*-Lapachone-based scaffold was identified as an irreversible, covalent MALT1 inhibitor.[28] MI-2 is another irreversible MALT1 inhibitor featuring direct binding to MALT1 and suppression of its protease function.[29] Although traditional drug development has shied away from irreversible inhibitors owing to the safety concerns, the resurgence of covalent drugs with outstanding phamacodynamic properties of MI-2 continues to drive medicinal chemists to discover more effective leads through comprehensive SARs.[30] For example, Overkleeft and coworkers explored the effect of different substituents on *C*5-phenyl ring of MI-2 and found that *para*-substituent is of influence on inhibitory potency, whereas *meta*-substituent is preferably avoided.[31] Furthermore, recent findings show that MI-2 is effective against ibrutinib-resistant

chronic lymphocytic leukemia (CLL) and inflammation diseases.[32-34] Those studies greatly expand the potential application of MI-2. In order to determine more detailed structural features which contribute to potency, we generated a focused set of 70 analogues to systematically explore the SARs of MI-2. The structural modification directions of MI-2 were focused on five chemical sites (**Figure 2**): chloromethyl amide moiety (site A), *N*-phenyl group (site B), *C*5-aryl moiety (site C), the side chain of 2-methoxyethoxy (site D), the key core of 1*H*-1,2,4-triazole (site E). Herein, we report the synthesis, pharmacological evaluation, and SARs of MI-2 analogues as MALT1 inhibitors.

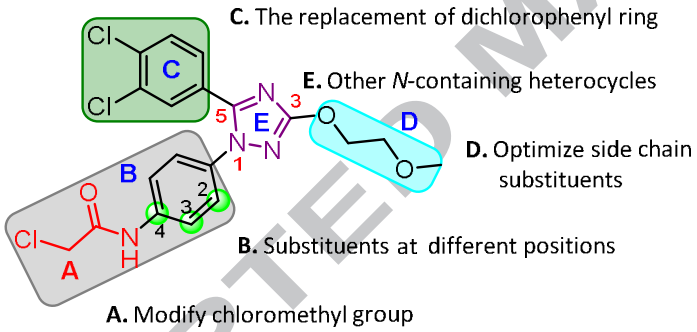


Figure 2. Five structural modification sites based on the chemical structure of MI-2.

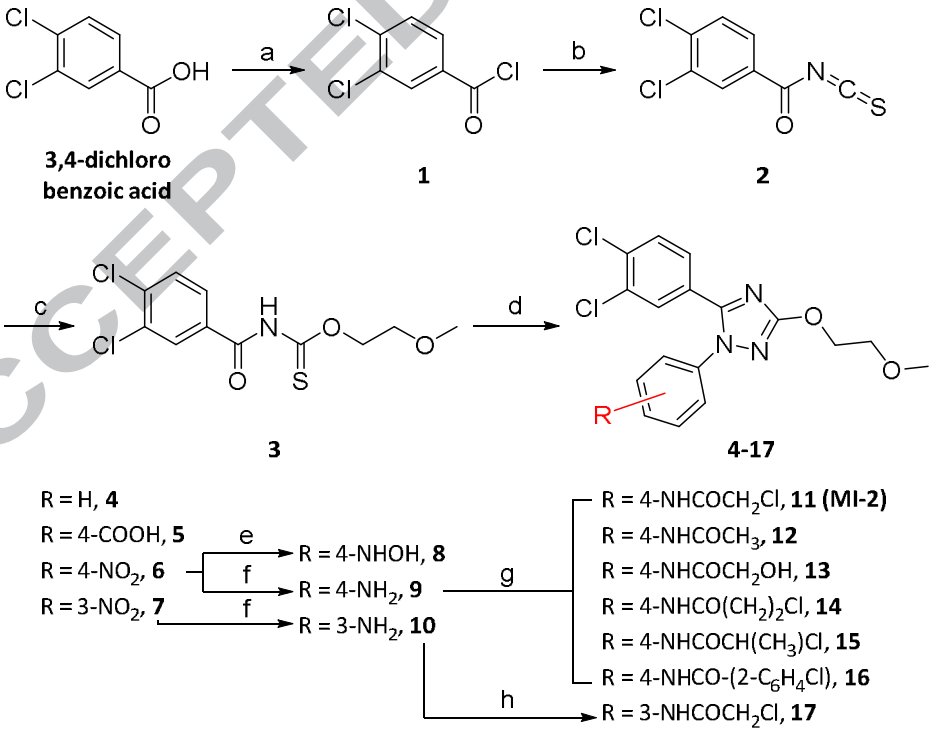
2. RESULTS AND DISCUSSION

2.1. Chemistry

The first library was designed to explore the Site A and Site B. As shown in **Scheme 1**, 3,4-dichlorobenzoic acid was reacted with oxalyl dichloride in CH_2Cl_2 at 0 °C to give the corresponding benzoyl chloride in quantitative yield. Compound **1** was then reacted with potassium thiocyanate (KSCN) in acetone to afford benzoyl

isothiocyanate (**2**). The intermediate **2** was treated with 2-methoxyethan-1-ol at 60 °C to provide *O*-(2-methoxyethyl) benzoylcarbamothioate (**3**). Compound **3** was then treated with substituted phenylhydrazine in ethanol to give the cyclized products **4-7**. The nitro containing **6** was reduced to phenylhydroxylamine **8** in Zn/NH_4Cl system, then converted to aniline **9** in Zn/AcOH/MeOH system. MI-2 (**11**) and its analogues (**12-16**) were obtained by employing a conventional amide coupling protocol. As MI-2 contained the *para*-substituted moiety, MI-2 analogues with other positions (*meta or ortho*) were designed. However, only compound **17** with *meta*-position was obtained, the synthesis of MI-2 analogues with *ortho*-position was unsuccessful due to its steric hindrance.

Scheme 1. Design and synthesis of two focused compound libraries **A** and **B**.[a]

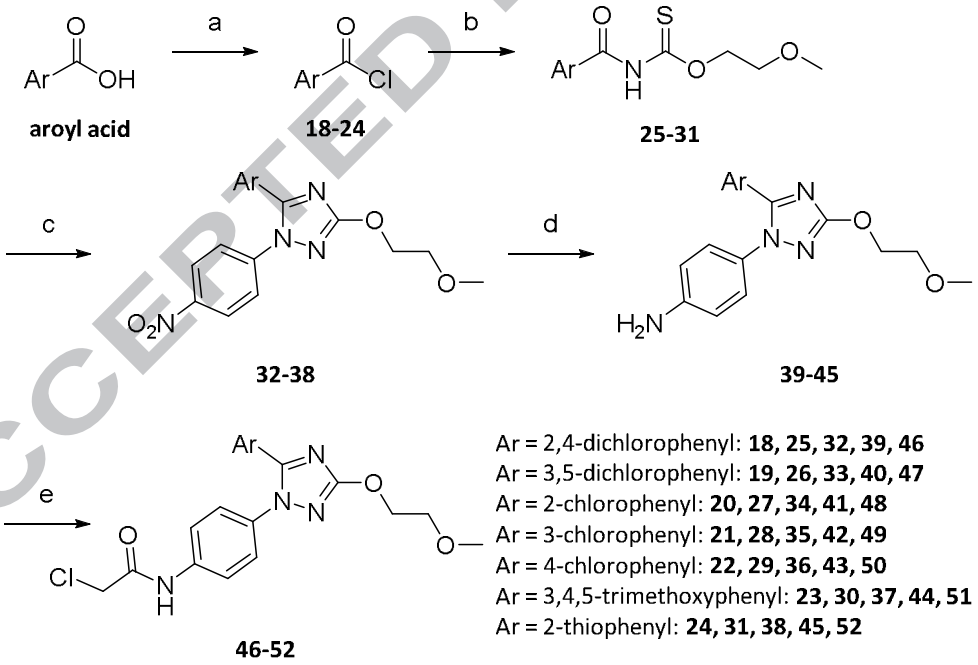


[a]Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, cat. DMF, r.t. 12 h, 100%; (b) KSCN,

acetone, 60 °C, 1 h, 83%; (c) 2-methoxyethan-1-ol, acetone, 60 °C, 3 h, 45%; (d) substituted phenylhydrazine, EtOH, 90 °C, 6-12 h, 42-74%; (e) Zn, NH_4Cl, MeOH, r.t., 1 h, 77%; (f) Zn, AcOH, MeOH, r.t., 12 h, 79-98%; (g) R'COOH, CH_2Cl_2, EDCI, r.t., 0.5-12 h, 42-99%; (h) $ClCH_2COOH$, CH_2Cl_2, EDCI, r.t., 5 h, 58%.

To explore dichlorophenyl ring C, a series of aroyl acids were reacted in the same reaction conditions as described in **Scheme 1**, including chloroformylation, followed by condensation with KSCN and 2-methoxyethan-1-ol, subsequently ring closure with 4-nitrophenylhydrazine. The nitro-containing derivatives were reduced to afford the corresponding anilines, followed by final coupling with 2-chloroacetic acid to produce compounds **46-52** (**Scheme 2**).

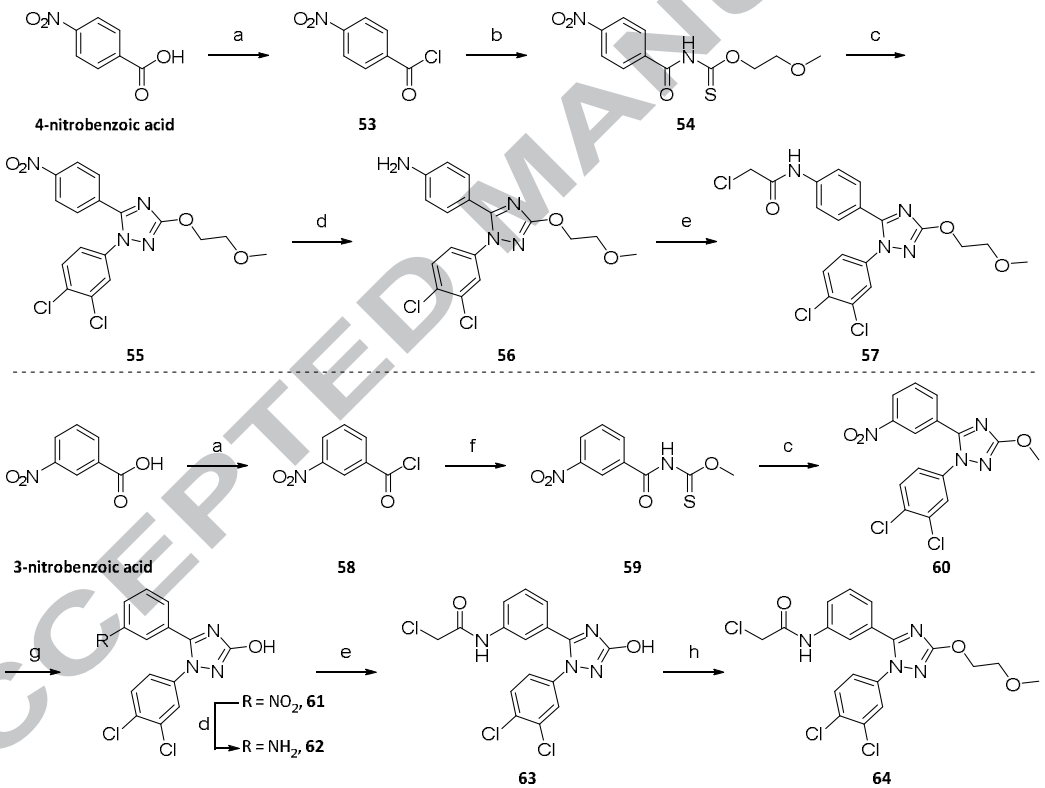
Scheme 2. Design and synthesis of the focused compound library **C**.[a]



[a]Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, cat. DMF, r.t., 2-12 h, 100%; (b) KSCN, acetone, 60 °C, 1-3 h; then 2-methoxyethan-1-ol, 3-8 h, 43%; (c) 4-nitrophenylhydrazine, EtOH, 90 °C, 6-12 h, 38-72%; (d) Zn, AcOH, MeOH, r.t., 12 h, 49-98%; (e) $ClCH_2COOH$, CH_2Cl_2, EDCI, r.t., 2-6 h, 60-96%.

The synthesis of MI-2 analogues with exchange of ring B and ring C was described in **scheme 3** according to the similar reaction conditions. Nitro-substituted benzoic acids were reacted with sulfurous dichloride to provide the corresponding benzoic chlorides. Benzoic chlorides were subjected to two different routes to afford compounds **57** and **64**.

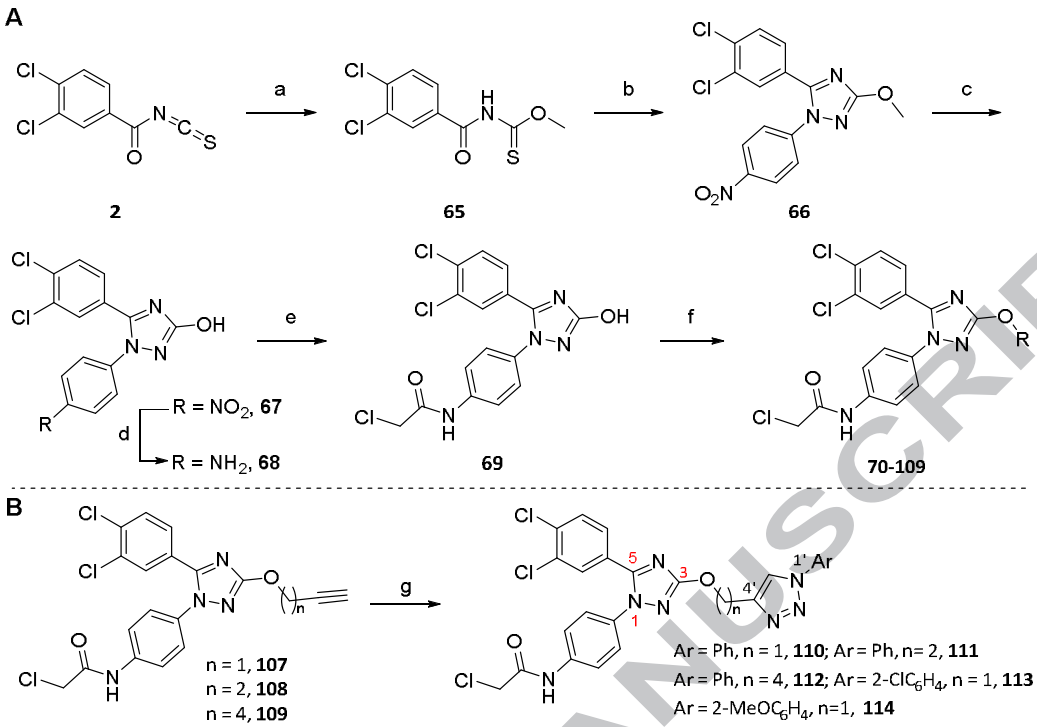
Scheme 3. The exchange of ring **B** and ring **C**.[a]



[a]Reagents and conditions: (a) $SOCl_2$, 80 °C, 2 h; (b) KSCN, acetone, 60 °C, 1 h; then 2-methoxyethan-1-ol, 5 h, 19%; (c) 3,4-dichlorophenylhydrazine, EtOH, 90 °C, 12-18 h, 70-73%; (d) Zn, AcOH, MeOH, r.t., 12 h, 29%; (e) $ClCH_2COOH$, CH_2Cl_2, EDCI, r.t., 16 h, 13-62%. (f) KSCN, acetone, 60 °C, 1 h; then MeOH, 3 h, 61%; (g) 33% HBr/AcOH, 100 °C, 12 h, 80%; (h) 2-methoxyethan-1-ol, PPh_3, DIAD, THF, 0 °C to r.t., 2 h, 50%.

Synthesis of the focused compound library D was followed the expedient route shown in **Scheme 4A**. The key intermediate **69** was obtained in five steps from benzoyl isothiocyanate **2**. This route included methyl substitution, cyclocondensation, demethylation, reduction, coupling reaction and last-stage diversification. MI-2 analogues **70-109** were conveniently prepared by Mitsunobu reaction.[35] Click chemistry is frequently employed in drug discovery and greatly helps advance research programs in the pharmaceutical industry.[36,37] In this work, a series of 3-(1-aryl-1*H*-1,2,3-triazol-4-yl)alkoxy-1,2,4-triazoles have been designed and synthesized *via* click reaction (**Scheme 4B**). The aryl azides were synthesized from the commercially available corresponding arylamine treated with $NaNO_2$ and NaN_3. All azides were directly used in the next step without further purification. Click reaction was performed with an excess of azides to give compounds **110-114**.

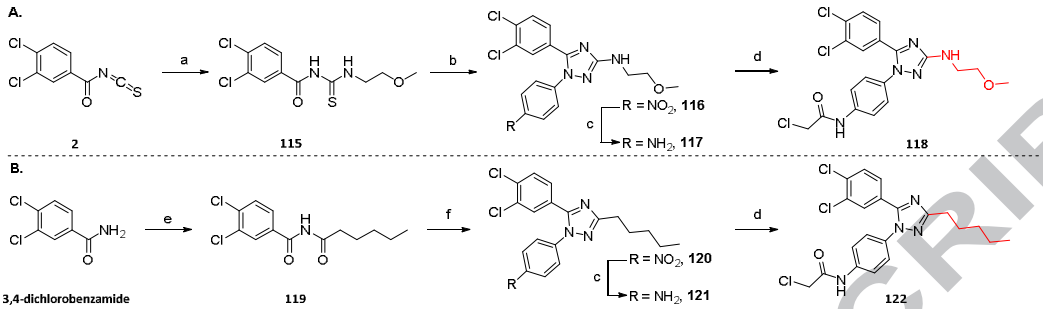
Scheme 4. Design and synthesis of the focused compound library D.[a]



[a](A) Mitsunobu reaction; (B) click reaction. Reagents and conditions: (a) MeOH, acetone, 60 °C, 3 h, 83%; (b) 4-nitrophenylhydrazine, MeOH, 70 °C, 18 h, 89%; (c) 33% HBr/AcOH, 100 °C, 6 h, 99%; (d) Zn, AcOH, r.t., MeOH, 12 h; (e) $ClCH_2COOH$, EDCI, r.t., CH_2Cl_2, 5 h; (f) ROH, PPh_3, DIAD, THF, 0 °C to r.t., 0.5-24 h, 27-96%; (g) Ar-N_3, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, r.t., DMSO, 1 h, 23-60%.

3-(2-Methoxyethyl)amino-1*H*-1,2,4-triazole **118** and 3-pentyl-1*H*-1,2,4-triazole **122** were synthesized according to the similar procedures (**Scheme 1**). Isothiocyanate **2** was condensed with 2-methoxyethan-1-amine in acetone to afford intermediate **115** (**Scheme 5**). In addition, compound **119** was synthesized from the 3,4-dichlorobenzamide according to a reported procedure with minor modifications.[38,39] Compounds **115** and **119** were cyclized with 4-nitrophenylhydrazine in different solvent (DMF for **115**, pyridine for **119**), followed by two general final steps to yield compounds **118** and **122**.

Scheme 5. Design and synthesis of 3-(2-methoxyethyl)amino-1*H*-1,2,4-triazole (**118**) and 3-pentyl -1*H*-1,2,4-triazole (**122**).[a]

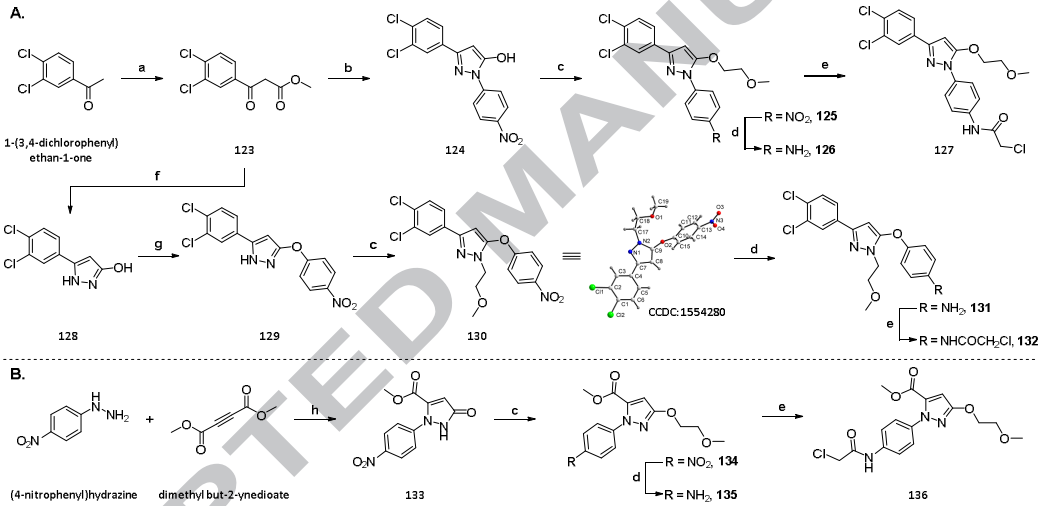


[a]Reagents and conditions: (a) 2-methoxyethan-1-amine, acetone, 60 °C, 4.5 h, 46%; (b) 4-nitrophenylhydrazine, DMF, 135 °C, 13 h, 37%; (c) Zn, AcOH, MeOH, r.t., 12 h, 73%; (d) $ClCH_2COOH$, CH_2Cl_2, EDCI, r.t., 2 h, 64-68%. (e) hexanoic anhydride, H_2SO_4, 100 °C, 2 h, 55%; (f) 4-nitrophenylhydrazine hydrochloride, pyridine, 120 °C, 2 h, 11%.

Scheme 6 depicts the structural modification of site E (the core) in which 1*H*-1,2,4-triazole moiety is replaced with 1*H*-pyrazole core in the light of the high-impact of nitrogen atom.[40] The starting material **123** was prepared from the phenylethanone according to a reported procedure.[41] The subsequent compound library was established by two different facile routes allowing for comprehensive explorations of the SARs. Firstly, phenyl *β*-ketoester **123** reacted with the 4-nitrophenylhydrazine to give intermediate **124**. 1*H*-Pyrazol-5-ol **124** was then treated with 2-methoxyethan-1-ol under Mitsunobu reaction condition to afford **125**. After reduction of nitro group and subsequently condensation, compound **127** was obtained in moderate yield. Another route was started from the cyclization of phenyl *β*-ketoester **123** and hydrazine hydrate to give **128**, which was coupled with 1-bromo-4-nitrobenzene to afford **129**.[42] Compound **129** was subjected to Mitsunobu reaction with 2-methoxyethan-1-ol to afford **130**, the structure of which was further

confirmed by X-ray crystallographic analysis.[43] As shown in **Scheme 6B**, **133** was prepared according to the method described in the literature,[44] and then reacted with 2-methoxyethan-1-ol to afford compound **134**. Finally, the nitro-containing products **130** and **134** were reduced to corresponding anilines, which were coupled with 2-chloroacetic acid to give compounds **132** and **136**, respectively.

Scheme 6. Design and synthesis of the focused compound library E with *N*,3,5-trisubstituted pyrazole scaffold.[a]



[a]Reagents and conditions: (a) Me_2CO_3, NaH, THF, r.t., 2.5 h, 85%; (b) 4-nitrophenylhydrazine, EtOH, 90 °C, 3.5 h, 86%; (c) 2-methoxyethan-1-ol, PPh_3, DIAD, THF, r.t., 1 h, 47-80%; (d) Zn, AcOH, MeOH, r.t., 12 h, 83-98%; (e) $ClCH_2COOH$, EDCI, CH_2Cl_2, r.t., 1 h, 69-80%; (f) $N_2H_4 \cdot H_2O$, EtOH, 90 °C, 0.5 h, 85%; (g) 1-bromo-4-nitrobenzene, *L*-proline, CuI, Cs_2CO_3, DMSO, 90 °C, 2.5 h, 59%; (h) AcOH, toluene, 0 °C for 1 h, then stirred at 100 °C for 4 h, 65%.

2.2. Antiproliferative activity against ABC-DLBCL cell line

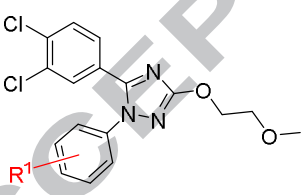
We first evaluated the antiproliferative activity of all MI-2 analogues on the proliferation of Toledo (ABC-DLBCL cell line, T-cell lymphoma) by employing a

CCK-8 (cell counting kit-8) assay. The experimental results were presented as IC_{50} values (μM) and summarized in **Table 1-4**.

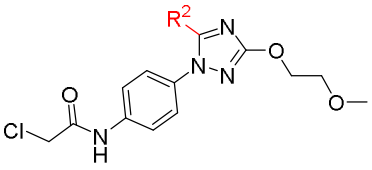
2.2.1. Effect of modification on site A and B

The previous studies indicated that MI-2 covalently binds to MALT1 with its chloromethyl amide group and acts as an irreversible inhibitor.[29] To determine the importance of each portion of the compound for potency, the focused compound library A was firstly synthesized and evaluated (**Table 1**). Compound **4** without chloromethyl amide group was inactive. Similarly, replacement of chloromethyl amide with other related functional group (**5**, **6**, **8**, **12**-**16**) led to a significant loss of antiproliferative activity. Notably, compound **17** with *meta*-position of chloromethyl amide displayed 2-fold higher potency than MI-2. The results further suggest that chloromethyl amide moiety on *C*1-phenyl is crucial for potency.

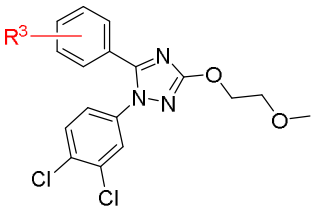
Table 1. Antiproliferative activity of the focused compound libraries A, B and C.



4-6, 8, 11-17



46-52



57, 64

Compd	R	IC_{50} (μM)	Compd	R	IC_{50} (μM)
4	R^1 = H	>160	**17**	R^1 = 3-$NHCOCH_2Cl$	0.40
5	R^1 = 4-COOH	>160	**46**	R^2 = 2,4-dichlorophenyl	2.71
6	R^1 = 4-NO_2	>5.0	**47**	R^2 = 3,5-dichlorophenyl	1.47
8	R^1 = 4-NHOH	24.5	**48**	R^2 = 2-chlorophenyl	3.26
11 (MI-2)	R^1 = 4-$NHCOCH_2Cl$	0.80	**49**	R^2 = 3-chlorophenyl	2.76
12	R^1 = 4-$NHCOCH_3$	>5	**50**	R^2 = 4-chlorophenyl	1.72

13	R^1 = 4-NHCOCH$_2$OH	>5	**51**	R^2 = 3,4,5-trimethoxyphenyl	3.13
14	R^1 = 4-NHCO(CH$_2$)$_2$Cl	>3.2	**52**	R^2 = 2-thiophenyl	2.97
15	R^1 = 4-NHCOCH(CH$_3$)Cl	54.5	**57**	R^3 = 4-(2-chloroacetamido)	0.59
16	R^1 = 4-NHCO-(2-C$_6$H$_4$Cl)	>160	**64**	R^3 = 3-(2-chloroacetamido)	0.98

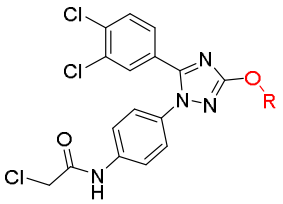
2.2.2. Effect of modification on site C

Previous studies on site C suggest that *para*-substituted phenyl group show much better inhibitory activities than the corresponding *meta*-substituted analogues.[31] Thus, our modifications of this region were aimed to explore the SARs using more typical analogues. We obtained a series of MI-2 analogues bearing general moieties at various positions (**46-52, Table 1**). Among this focused compound library, the potency decreases in the order of **47** > **50** > **46** ≈ **49** > **52** > **51** > **48**. Both chloro-containing compounds and trimethoxy substituted analogue displayed moderate potency. Compound **52** with thiophene ring suffered a significant loss in potency. Our work also showed that compounds with *para*-chlorophenyl substituent exhibited better inhibitory activities than *ortho*- and/or *meta*-substituents. To further investigate the position impact of site B and C, we synthesized two MI-2 analogues with *N*-1 dichlorophenyl substituent on 1*H*-1,2,4-triazole (**57**, **64**). Notably, compound **57** with 4-(2-chloroacetamido)phenyl substituted on *C*-5 exhibited better inhibitory activity than MI-2, while compound **64** with 3-(2-chloroacetamido)phenyl moiety was equipotent to MI-2.

2.2.3. Effect of modification on site D

A comprehensive series of analogues with *O*-substituent sidechain focused on the site D have been prepared *via* Mitsunobu reaction (**Scheme 4**). We initially focused on the introduction of alkyl moieties such as aliphatic chains (**70-77**) or cyclic alkyl fragments (**78-80**), and the results revealed that almost all compounds displayed comparable potency. Compounds **81-83** with hydroxyl moiety at terminal showed a slightly improved potency. Notably, compounds **84-87** with ether chain are approximately two-fold more potent. Additionally, introduction of sulfide (**88**), fluorine atom (**89**) and heterocyclic (**90-91**) also led to nearly two-fold increased activity. In particular, compound **93** with ethyl acetate moiety exhibits improved activity, while acetylation of 1*H*-1,2,4-triazol-3-ol ring (**92**) dramatically reduced potency. Following this trend, unsaturated hydrocarbon substituted analogues (**94-107**) also showed improved activity with IC_{50} values ranging from 0.30 μM to 0.72 μM. Moreover, compound **106**, which was linked with the functional group tryptamine, displayed the similar potency. To further confirm the impact of the replacement of the drug-like fragment on site D, a series of analogues possessing 1,2,3-triazole moiety through click reactions were synthesized (**Table 3**).[45,46] The results showed that almost all compounds (**110-114**) displayed a slightly improved potency. The effect of oxygen element linkage between 1,2,4-triazole and D site chain was also examined.[47,48] The replacement of oxygen with nitrogen (**118**) or methylene group (**122**) did not affect the potency, further indicating that this region can be combined with other functional groups to provide practical probes for further biological mechanism investigation.

Table 2. Antiproliferative activity of the focused compound library D (**part 1**).



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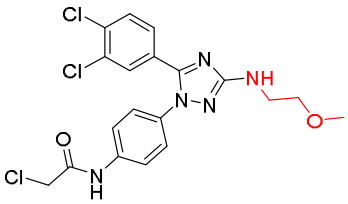
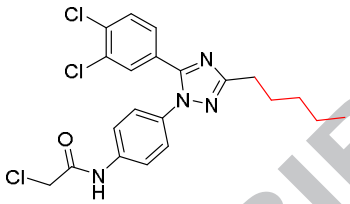
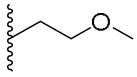
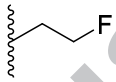
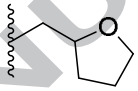
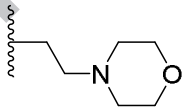
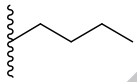
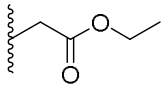
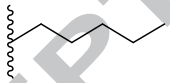
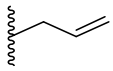
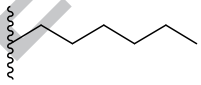
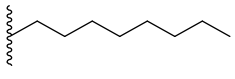
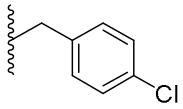
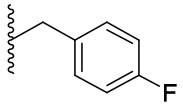
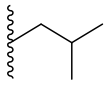
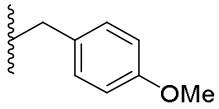


118



122

Compd	R	IC_{50} (μM)	Compd	R	IC_{50} (μM)
11 (MI-2)		0.80	**89**		0.37
69	H	>5	**90**		0.46
70	Me	0.51	**91**		0.47
71	Et	0.81	**92**		>2
72		0.34	**93**		0.50
73		0.61	**94**		0.40
74		0.69	**95**		0.30
75		0.77	**96**		0.38
76		1.56	**97**		0.41
77		1.69	**98**		0.39

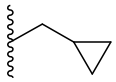
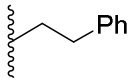
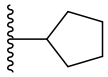
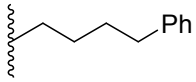
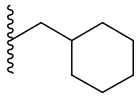
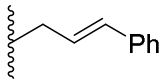
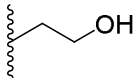
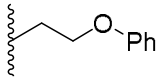
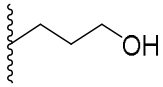
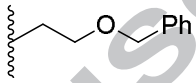
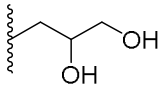
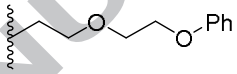
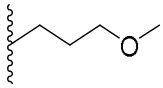
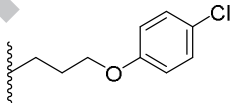
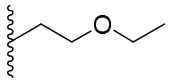
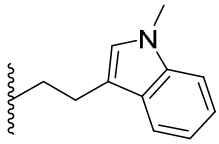
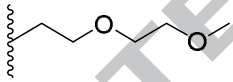
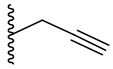
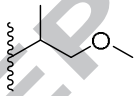
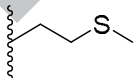
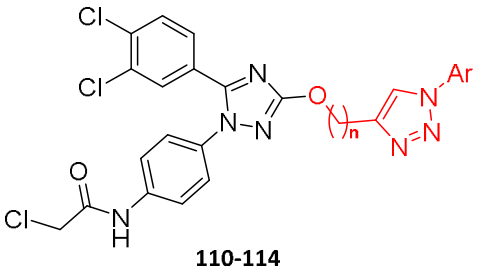
78		0.47	**99**		0.32
79		0.49	**100**		0.43
80		0.69	**101**		0.72
81		0.43	**102**		0.37
82		0.53	**103**		0.34
83		0.75	**104**		0.39
84		0.43	**105**		0.44
85		0.43	**106**		0.38
86		0.40	**107**		0.45
87		0.46	**118**	/	0.75
88		0.42	**122**	/	0.96

Table 3. Antiproliferative activity of the focused compound library D (**part 2**).



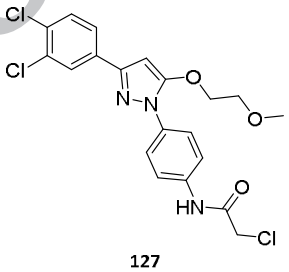
110-114

Compd	n	Ar	IC_{50} (μM)	Compd	n	Ar	IC_{50} (μM)
11 (MI-2)	/	/	0.80	**112**	4	Ph	0.60
110	1	Ph	0.40	**113**	1	2-ClC_6H_4	0.31
111	2	Ph	0.38	**114**	1	2-$MeOC_6H_4$	0.40

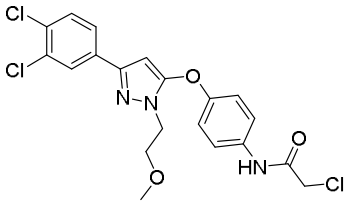
2.2.4. Effect of modification on site E

Further investigation on the role of 1*H*-1,2,4-triazole core were carried out to explore the key core for potency. Analogues **127**, **132** and **136** with 1*H*-pyrazole core were prepared from phenyl *β*-ketoester (**123**) or 4-nitrophenylhydrazine as outlined in **Scheme 6**. As shown in **Table 4**, compounds **127** and **132** exhibited a nearly equipotent antiproliferative effect and compound **136** without dichlorophenyl substituent at *C*5 position displayed a slightly lower potency. Our work indicated that the triazole ring is not indispensable.

Table 4. Antiproliferative activity of the focused compound library E.



127



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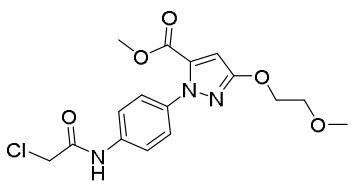

136

Compd	11 (MI-2)	127	132	136
IC_{50} (μM)	0.80	1.11	0.86	7.61

2.3. MI-2 analogues inhibit MALT1 activity determined by western blot assay

Previous findings supported that cleavage of RelB could reflect the activity of MALT1 *via* Western blot assay.[49] To confirm that these new MI-2 analogues might inhibit the functions of MALT1 in ABC-DLBCL cells, several notable compounds were selected for further evaluation. As shown in **Figure 3** and **Figure S1** (see Supporting Information), compounds such as **57**, **81-83**, **86**, **87**, **111**, especially compounds **81-83** with terminal hydroxyl moiety as side chain exhibited better inhibitory activity against MALT1.

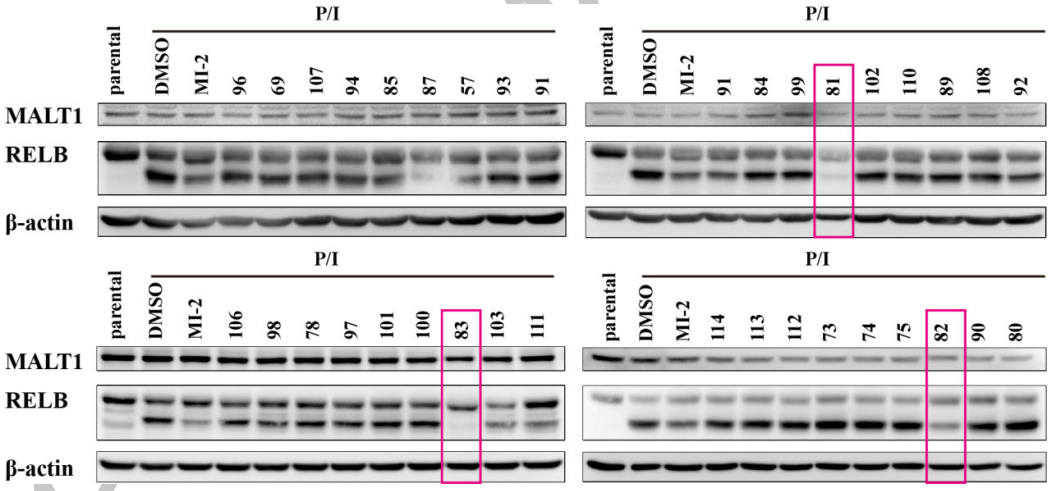

Figure 3. Western blot analysis of RELB cleavage product after Jurkat T cells were treated with MI-2 analogues (2 μM) (See **Figure S1** in the Supporting Information for more details) .

2.4. SARs

The SARs of MI-2 analogous as MALT1 inhibitors are summarized in **Figure 4**. Firstly, both sites A and B are essential fragments to maintain the inhibitory potency,

while changing site C might slightly decrease the activity. In addition, the side chain of 2-methoxyethoxy is more flexible and can be replaced by many functionalized groups, suggesting that MI-2 can assembly combine with other drugs *via* different linker to produce new compounds with more potent pharmacological effects. Furthermore, MI-2 analogues with terminal hydroxyl moiety on site D exhibit better inhibitory activity against MALT1. While, replacement of triazole core with pyrazole moiety is also tolerated, more extensive chemical modifications on this core are needed.

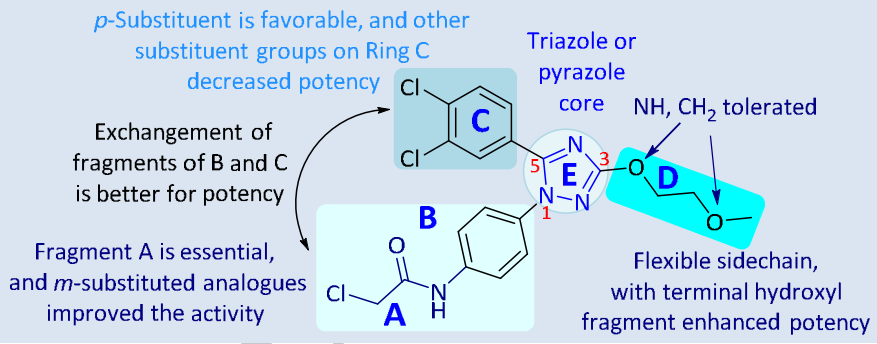

Figure 4. SARs of MI-2 analogous as MALT1 inhibitors.

3. CONCLUSIONS

In summary, our systematic SAR studies identified multiple structural features that affect the potency of MI-2 analogues. We found that analogues with chloromethethyl amide substituent on *C*1-phenyl are important to maintain efficacy of MI-2, and replacement of the *C*5-aryl ring may slightly decrease the activity. Additionally, modifications of the 2-methoxyethoxy chain and triazole core often lead to comparable or enhanced potency against MALT1. This work will facilitate further

development of new small-molecule MALT1 inhibitors.

4. EXPERIMENTAL SECTION

4.1. Chemistry

4.1.1. General Experimental

All reagents were purchased from commercial sources and used without further purification. Thin layer chromatography (TLC) on precoated aluminum plates (silica gel 60 F254, Merck, Darmstadt) was used to monitor reaction progress. Visualization of the developed chromatograms was detected by UV (254 nm and 365 nm). Preparative column chromatography was performed using silica gel (300–400 mesh, flash). Preparative thin layer chromatography (PTLC) separations were carried out on 0.20 mm Yantai Jiangyou silica gel plates (HSGF254). Proton Nuclear Magnetic Resonance NMR (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker-400 (^{1}H, 400 MHz; ^{13}C, 101 MHz) spectrometer. Chemical shifts for protons are reported in parts per million and referenced to the NMR solvent peak ($CDCl_3$: δ 7.26; DMSO-d_6: δ 2.50; CD_3OD: δ 3.31). Chemical shifts for carbons are reported in parts per million and referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ77.16; DMSO-d_6: δ 39.52; CD_3OD: δ 49.00). Signals are listed in ppm, and multiplicity identified as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Chemical shifts were expressed in ppm, and *J* values were given in Hz. High resolution mass spectra (HRMS) were obtained from Thermo Fisher Scientific Exactive Plus mass spectrometer. Melting

point was determined using the X-4A melting point apparatus (Shanghai Yidian Co., Ltd.) and uncorrected.

General procedure A *(synthesis of aroyl chloride from aroyl acid).* To a solution of aroyl acid (1.0 eq) in CH_2Cl_2 was added oxalyl dichloride (1.1 eq) and DMF (2-5 drops) at 0 ^oC. The mixture was allowed to stir at room temperature for 2-12 h. Then the mixture was concentrated to give compounds **1**, **18-24**. The products were used directly in the next reaction.

General procedure B *(Synthesis of O-alkyl aroylcarbamothioate from aroyl chloride).* To a solution of aroyl chloride (1.0 eq) in acetone was added KSCN (1.0 eq). The mixture was stirred at 60 ^oC for 1-3 h until the starting material was completely consumed. The reaction mixture was then cooled to room temperature and ROH (2.5 eq) in acetone was added to the reaction mixture. After stirring at 60 ^oC for another 3-8 h, the reaction mixture was cooled to room temperature and removed the solvent in vacuo. The crude product was dissolved with EtOAc and extracted with H_2O. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated to give crude product under reduced pressure. The residue was purified by silica gel chromatography to give compounds **25-31**, **54** and **59**.

General procedure C *(Synthesis of 1,5-diaryl-1H-1,2,4-triazole).* To a solution of *O*-alkyl aroylcarbamothioate (1.0 eq) in EtOH was added substituted phenylhydrazine (1.0 eq). The mixture was stirred at 90 ^oC for 8-24 h, and then the solvent was removed in vacuo. The crude product was dissolved with EtOAc and washed with portions of H_2O. The organic layer was dried over anhydrous Na_2SO_4, and then

concentrated to give crude product under reduced pressure. The residue was purified by silica gel chromatography to give the desired product.

General procedure D *(Reduction of nitroarenes)*. To a solution of nitro-containing derivatives (1.0 eq) in MeOH was added AcOH and Zn (5.0-10.0 eq). The mixture was stirred at r.t. for 12-24 h. The mixture was diluted with EtOAc and washed with sat. $NaHCO_3$, H_2O and brine, respectively. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated to give crude product under reduced pressure. The residue was purified by silica gel chromatography to give the desired product.

General procedure E *(Coupling reaction of aniline with carboxylic acid)*. To a solution of arylamine (1.0 eq) in CH_2Cl_2 was added the appropriate carboxylic acid (1.5 eq) and EDCI (2.0 eq). The mixture was stirred at r.t. for 5-12 h. The mixture was diluted with EtOAc, washed with H_2O, sat. $NaHCO_3$, brine, respectively. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated to give crude product under reduced pressure. The residue was purified by silica gel chromatography to give the desired product.

General procedure F *(Mitsunobu reaction)*. To a solution of nucleophile (1.0 eq), PPh_3 (1.5-3.0 eq) in THF was added ROH (2.0-5.0 eq) and DIAD (1.5-3.0 eq) dropwise at 0 °C. Then the mixture was allowed to warm to room temperature and stirred for 0.5-24 h. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give the

desired product.

General procedure G *(Click reaction)*. To a solution of terminal alkynes (1.0 eq), azides (6.0 eq) and sodium ascorbate (0.5 eq) in DMSO/H_2O (5/1, *v*/*v*) was added $CuSO_4 \cdot 5H_2O$ (0.5 eq). The mixture was stirred at r.t. for 0.5-3 h. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give the desired product.

*4.1.2. 3,4-Dichlorobenzoyl isothiocyanate (**2**)*. To a solution of **1** (12.9 g, 60 mmol) in acetone (50 mL) was added KSCN (5.8 g, 60 mmol). The mixture was stirred at 60 ^oC for 2 h. Then the solvent was evaporated under vacuum. The resulting residue was dissolved EtOAc (50 mL), washed with H_2O (2 × 20 mL) and brine (20 mL), respectively. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The crude product was purified by silica gel chromatography (PE/EtOAc = 4:1) to give the desired product (11.9 g, 83%) as a white solid. Melting point: 42.4-43.3 ^oC. TLC: R_f = 0.78 (PE). ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.1 Hz, 1H), 7.88 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 150.2, 140.1, 133.8, 132.2, 131.2, 130.7, 129.3. HRMS (ESI): calcd for $C_8H_3Cl_2NOS$ $[M + H]^+$ *m/z* 233.0855, found 233.0860.

*4.1.3. O-(2-Methoxyethyl) (3,4-dichlorobenzoyl)carbamothioate (**3**)***.*** To a solution of **2** (11.6 g, 50 mmol) in acetone (30 mL) was added 2-methoxyethan-1-ol (9.5 g, 125 mmol). The mixture was stirred at 60 ^oC for 5 h. The reaction was diluted with EtOAc (50 mL) and washed with portions of H_2O (3 × 20 mL). The organic layer was dried

over anhydrous Na_2SO_4, and then concentrated to give crude product under reduced pressure. The residue was purified by silica gel chromatography (PE/EtOAc = 8:1) to give the desired product (6.9 g, 45%) as a pale yellow oil. Physical state: pale yellow oil. TLC: R_f = 0.67 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 4.76 – 4.66 (m, 2H), 3.79 – 3.70 (m, 2H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.0, 161.2, 137.9, 133.8, 132.9, 131.1, 130.0, 126.8, 100.1, 71.8, 69.7, 59.3. HRMS (ESI): calcd for $C_{11}H_{11}Cl_2NO_3S$ $[M + H]^+$ *m/z* 307.9909, found 307.9912.

*4.1.4. 5-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1-phenyl-1H-1,2,4-triazole (**4**).* Following the general procedure C, the reaction was conducted from the starting material (81 mg, 0.26 mmol) and phenylhydrazine (34 mg, 0.32 mmol) to give the desired product (71 mg, 74%). Physical state: yellow oil. TLC: R_f = 0.38 (PE/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.49 – 7.37 (m, 3H), 7.37 – 7.27 (m, 3H), 7.18 (d, *J* = 8.8 Hz, 1H), 4.56 – 4.40 (m, 2H), 3.85 – 3.69 (m, 2H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 150.8, 137.7, 134.5, 133.0, 130.7, 130.5, 129.6, 129.3, 127.7, 127.5, 125.5, 70.7, 69.0, 59.2. HRMS (ESI): calcd for $C_{17}H_{15}Cl_2N_3O_2$ $[M + H]^+$ *m/z* 364.0614, found 364.0623.

*4.1.5. 4-(5-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)benzoic acid (**5**).* Following the general procedure C, the reaction was conducted from the starting material (51 mg, 0.16 mmol) and 4-hydrazinylbenzoic acid (30 mg, 0.20 mmol) to give the desired product (28 mg, 42%). Physical state: pale yellow solid; Melting point: 180.6-181.2 ^{o}C. TLC: R_f = 0.34 (CH_2Cl_2/MeOH = 10:1). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.19 – 8.04 (m, 2H), 7.67 (s, 1H), 7.39 (t, *J* = 7.6 Hz, 3H), 7.19 (d, *J* = 8.1 Hz, 1H), 4.56 – 4.48 (m, 2H), 3.84 – 3.76 (m, 2H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 151.3, 141.4, 135.1, 133.4, 131.5, 130.9, 130.8, 127.9, 127.3, 124.8, 70.7, 69.3, 59.2. HRMS (ESI): calcd for $C_{18}H_{15}Cl_2N_3O_4$ $[M + H]^+$ *m/z* 408.0512, found 408.0513.

4.1.6.

5-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1-(4-nitrophenyl)-1H-1,2,4-triazole ***(6).*** Following the general procedure C, the reaction was conducted from the starting material (3.0 g, 10 mmol) and 4-nitrophenylhydrazine (1.5 g, 10 mmol) to give the desired product (2.3 g, 56%). Physical state: yellow oil. TLC: R_f = 0.53 (PE/EtOAc = 2:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.0 Hz, 2H), 7.66 (d, *J* = 1.9 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.20 (dd, *J* = 8.4, 1.9 Hz, 1H), 4.59 – 4.41 (m, 2H), 3.87 – 3.70 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 151.7, 147.1, 142.3, 135.5, 133.6, 131.0, 130.9, 127.9, 127.1, 125.2, 125.0, 70.6, 69.3, 59.2. HRMS (ESI): calcd for $C_{17}H_{14}Cl_2N_4O_4$ $[M + H]^+$ *m/z* 409.0465, found 409.0462.

4.1.7.

*5-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1-(3-nitrophenyl)-1H-1,2,4-triazole (****7****)* . Following the general procedure C, the reaction was conducted from the starting material (200 mg, 0.65 mmol) and 3-nitrophenylhydrazine (119 mg, 0.78 mmol) to give the desired product (179 mg, 67%). Physical state: yellow oil. TLC: R_f = 0.46 (PE/EtOAc = 2:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.29 – 8.23 (m, 1H),

7.69 – 7.65 (m, 1H), 7.60 (d, J = 4.9 Hz, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.23 – 7.18 (m, 1H), 4.55 – 4.47 (m, 2H), 3.81 – 3.75 (m, 2H), 3.48 – 3.40 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 151.5, 148.8, 138.6, 135.4, 133.6, 131.0, 130.9, 130.5, 130.5, 127.7, 126.9, 123.5, 120.3, 70.6, 69.3, 59.2. HRMS (ESI): calcd for $C_{17}H_{14}Cl_2N_4O_4$ $[M + H]^+$ *m/z* 409.0465, found 409.0457.

4.1.8.

*N-(4-(5-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)hydroxylamine (**8**).* To a solution of **6** (2.3 g, 5.6 mmol) in MeOH (80 mL) was added sat. NH_4Cl (20 mL) and Zn (3.68 g, 56 mmol). The mixture was stirred at r.t. for 1 h. The mixture was poured into the cold water to give a brown solid (1.7 g, 77%) without further purification. Physical state: brown solid; Melting point: 147.2-147.8 °C. TLC: R_f = 0.64 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.97 – 6.86 (m, 3H), 4.54 – 4.45 (m, 2H), 3.82 – 3.73 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 151.4, 150.9, 134.5, 133.1, 130.8, 130.5, 127.6, 127.4, 126.6, 114.3, 70.8, 69.1, 59.3. HRMS (ESI): calcd for $C_{17}H_{16}Cl_2N_4O_3$ $[M + H]^+$ *m/z* 395.0672, found 395.0665.

*4.1.9. 4-(5-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)aniline (**9**).* Following the general procedure D, the reduction was conducted from the starting material (137 mg, 0.33 mmol) to give the desired product (124 mg, 98%). Physical state: yellow solid; Melting point: 116.5-117.2 °C. TLC: R_f = 0.22 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.9 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.22

(dd, *J* = 8.4, 2.0 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 4.51 – 4.41 (m, 2H), 4.31 – 3.92 (m, 2H), 3.82 – 3.73 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 167.4, 150.7, 147.6, 134.2, 132.9, 130.7, 130.4, 128.3, 127.6, 127.0, 115.3, 70.7, 69.0, 59.2. HRMS (ESI): calcd for $C_{17}H_{16}Cl_2N_4O_2$ $[M + H]^+$ *m/z* 379.0723, found 379.0719.

*4.1.10. 3-(5-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)aniline (**10**).* Following the general procedure D, the reduction was conducted from the starting material (78 mg, 0.19 mmol) to give the desired product (57 mg, 79%). Physical state: yellow oil. TLC: R_f = 0.56 (CH_2Cl_2/MeOH = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.75 – 6.70 (m, 1H), 6.67 (t, *J* = 2.1 Hz, 1H), 6.63 – 6.58 (m, 1H), 4.52 – 4.45 (m, 2H), 3.80 – 3.76 (m, 2H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 150.6, 147.7, 138.5, 134.3, 132.9, 130.6, 130.3, 130.3, 127.6, 127.5, 115.7, 115.3, 111.6, 70.6, 69.0, 59.1. HRMS (ESI): calcd for $C_{17}H_{16}Cl_2N_4O_2$ $[M + H]^+$ *m/z* 379.0723, found 379.0732.

4.1.11.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**11**) (**MI-2**).* Following the general procedure E, the reaction was conducted from the corresponding aniline (379 mg, 1.0 mmol) and 2-chloroacetic acid (142 mg, 1.5 mmol) to give the desired product (355 mg, 78%). Physical state: white solid; Melting point: 133.7-134.5 ^{o}C. TLC: R_f = 0.46 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.73 – 7.59 (m, 3H), 7.44 – 7.27 (m, 3H), 7.21 –

7.14 (m, 1H), 4.59 – 4.41 (m, 2H), 4.20 (s, 2H), 3.85 – 3.69 (m, 2H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 164.2, 150.9, 137.7, 134.7, 134.1, 133.2, 130.8, 130.6, 127.7, 127.4, 126.3, 120.7, 70.7, 69.1, 59.2, 42.9. HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 455.0439, found 455.0427.

4.1.12.

*N-(4-(5-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**12**).* Following the general procedure E, the reaction was conducted from the corresponding aniline (30 mg, 0.08 mmol) and acetic acid (10 mg, 0.16 mmol) to give the desired product (33 mg, 99%). Physical state: pale yellow solid; Melting point: 178.5-179.5 °C. TLC: R_f = 0.47 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.67 (d, *J* = 2.1 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.19 – 7.14 (m, 1H), 4.55 – 4.44 (m, 2H), 3.81 – 3.72 (m, 2H), 3.44 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 167.8, 150.9, 138.9, 134.7, 133.3, 133.2, 130.8, 130.6, 127.7, 127.5, 126.3, 120.3, 70.8, 69.1, 59.2, 24.7. HRMS (ESI): calcd for $C_{19}H_{18}Cl_2N_4O_3$ $[M + H]^+$ *m/z* 421.0829, found 421.0825.

4.1.13.

*N-(4-(5-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)-2-hydroxyacetamide (**13**).* Following the general procedure E, the reaction was conducted from the corresponding aniline (42 mg, 0.11 mmol) and 2-hydroxyacetic acid (13 mg, 0.17 mmol) to give the desired product (24 mg, 50%). Physical state: colorless oil. TLC: R_f = 0.44 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.66

(d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.16 – 7.12 (m, 1H), 4.58 – 4.44 (m, 3H), 4.17 (s, 2H), 3.80 – 3.75 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 167.7, 151.1, 138.5, 134.9, 133.3, 133.1, 130.8, 130.7, 127.6, 127.1, 126.4, 120.3, 70.7, 69.2, 62.2, 59.2. HRMS (ESI): calcd for $C_{19}H_{18}Cl_2N_4O_4$ $[M + H]^+$ *m/z* 437.0778, found 437.0776.

4.1.14.

*3-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)propanamide (**14**).* Following the general procedure E, the reaction was conducted from the corresponding aniline (80 mg, 0.21 mmol) and 3-chloropropanoic acid (35 mg, 0.32mmol) to give the desired product (43 mg, 43%). Physical state: pale yellow solid; Melting point: 119.2-120.5 ^{o}C. TLC: R_f = 0.31 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.14 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.53 – 4.47 (m, 2H), 3.85 (t, *J* = 6.4 Hz, 2H), 3.80 – 3.76 (m, 2H), 3.43 (s, 3H), 2.84 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 167.7, 150.9, 138.7, 134.7, 133.3, 133.2, 130.7, 130.6, 127.7, 127.3, 126.2, 120.7, 70.7, 69.0, 59.1, 40.3, 39.8. HRMS (ESI): calcd for $C_{20}H_{19}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 469.0596, found 469.0593.

4.1.15.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)propanamide (**15**).* Following the general procedure E, the reaction was conducted from the corresponding aniline (46 mg, 0.12 mmol) and 2-chloropropanoic acid (20 mg, 0.18 mmol) to give the desired product (35 mg, 61%). Physical state:

pale yellow solid; Melting point: 70.9-72.1 °C. TLC: R_f = 0.64 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.19 – 7.14 (m, 1H), 4.56 (q, *J* = 7.0 Hz, 1H), 4.51 – 4.46 (m, 2H), 3.80 – 3.73 (m, 2H), 3.43 (s, 3H), 1.81 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 167.7, 150.9, 137.9, 134.7, 134.0, 133.2, 130.8, 130.6, 127.7, 127.5, 126.3, 120.7, 70.7, 69.1, 59.2, 56.0, 22.5. HRMS (ESI): calcd for $C_{20}H_{19}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 469.0596, found 469.0596.

4.1.16.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)benzamide (**16**).* Following the general procedure E, the reaction was conducted from the corresponding aniline (40 mg, 0.11 mmol) and 2-chlorobenzoic acid (18 mg, 0.12 mmol) to give the desired product (23 mg, 42%). Physical state: yellow solid; Melting point: 74.8-76.2 °C. TLC: R_f = 0.61 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.81 – 7.69 (m, 4H), 7.53 – 7.42 (m, 2H), 7.41 – 7.35 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 1H), 4.52 – 4.46 (m, 2H), 3.80 – 3.75 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 164.7, 150.9, 138.4, 134.7, 134.7, 133.9, 133.2, 132.1, 130.9, 130.7, 130.7, 130.6, 130.6, 127.7, 127.5, 127.5, 126.3, 120.7, 70.8, 69.1, 59.3. HRMS (ESI): calcd for $C_{24}H_{19}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 517.0596, found 517.0591.

4.1.17.

*2-Chloro-N-(3-(5-(3,4-dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**17**).* Following the general procedure E, the reaction was conducted

from the corresponding aniline (13 mg, 0.03 mmol) and 2-chloroacetic acid (4 mg, 0.05 mmol) to give the desired product (9 mg, 58%). Physical state: colorless oil. TLC: R_f = 0.22 (CH_2Cl_2/EtOAc = 6:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.75 (s, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.43 – 7.35 (m, 2H), 7.25 – 7.21 (m, 1H), 7.07 – 7.02 (m, 1H), 4.54 – 4.46 (m, 2H), 4.19 (s, 2H), 3.82 – 3.74 (m, 2H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.1, 151.1, 138.4, 138.2, 134.8, 133.2, 130.9, 130.7, 130.3, 127.8, 127.4, 122.0, 120.4, 117.1, 70.8, 69.2, 59.3, 42.9. HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 455.0439, found 455.0438.

4.1.18.

*5-(2,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1-(4-nitrophenyl)-1H-1,2,4-triazole (**32**).* Following the general procedure C, the reaction was conducted from compound **25** (200 mg, 0.65 mmol) and 4-nitrophenylhydrazine (100 mg, 0.65 mmol) to give the desired product (101 mg, 38%). Physical state: brown oil. TLC: R_f = 0.51 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.0 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.48 – 7.35 (m, 4H), 4.59 – 4.49 (m, 2H), 3.86 – 3.75 (m, 2H), 3.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 150.6, 146.5, 142.4, 138.1, 134.4, 132.6, 130.5, 128.2, 126.4, 125.0, 122.8, 70.6, 69.4, 59.3. HRMS (ESI): calcd for $C_{17}H_{14}Cl_2N_4O_4$ $[M + H]^+$ *m/z* 409.0465, found 409.0465.

4.1.19.

*5-(3,5-Dichlorophenyl)-3-(2-methoxyethoxy)-1-(4-nitrophenyl)-1H-1,2,4-triazole (**33**).* Following the general procedure C, the reaction was conducted from compound **26** (394 mg, 1.3 mmol) and 4-nitrophenylhydrazine (196 mg, 1.3 mmol) to give the

desired product (254 mg, 48%). Physical state: yellow oil. TLC: R_f = 0.68 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.47 (s, 1H), 7.36 (s, 2H), 4.55 – 4.49 (m, 2H), 3.82 – 3.77 (m, 2H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 151.3, 147.2, 142.2, 135.9, 131.0, 130.2, 127.3, 125.1, 125.1, 70.7, 69.5, 59.3. HRMS (ESI): calcd for $C_{17}H_{14}Cl_2N_4O_4$ $[M + H]^+$ *m/z* 409.0465, found 409.0460.

*4.1.20. 5-(2-Chlorophenyl)-3-(2-methoxyethoxy)-1-(4-nitrophenyl)-1H-1,2,4-triazole (**34**).* Following the general procedure C, the reaction was conducted from compound **27** (95 mg, 0.3 mmol) and 4-nitrophenylhydrazine (61 mg, 0.4 mmol) to give the desired product (71 mg, 55%). Physical state: yellow oil. TLC: R_f = 0.41 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.45 – 7.37 (m, 4H), 4.60 – 4.50 (m, 2H), 3.85 – 3.76 (m, 2H), 3.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 151.5, 146.3, 142.6, 133.6, 132.4, 131.7, 130.5, 127.9, 127.7, 124.8, 122.7, 70.7, 69.4, 59.3. HRMS (ESI): calcd for $C_{17}H_{15}ClN_4O_4$ $[M + H]^+$ *m/z* 375.0855, found 375.0848.

*4.1.21. 5-(3-Chlorophenyl)-3-(2-methoxyethoxy)-1-(4-nitrophenyl)-1H-1,2,4-triazole (**35**).* Following the general procedure C, the reaction was conducted from compound **28** (467 mg, 1.9 mmol) and 4-nitrophenylhydrazine (296 mg, 1.9 mmol) to give the desired product (474 mg, 64%). Physical state: pale yellow solid; Melting point: 102.1-103.2 ^{o}C. TLC: R_f = 0.54 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.9 Hz, 2H), 7.56 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 4.56 – 4.49 (m, 2H), 3.83 –

3.75 (m, 2H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 152.6, 146.9, 142.5, 135.2, 131.0, 130.30, 129.2, 129.1, 127.0, 125.1, 125.0, 70.7, 69.3, 59.3. HRMS (ESI): calcd for $C_{17}H_{15}ClN_4O_4$ $[M + H]^+$ *m/z* 375.0855, found 375.0851.

*4.1.22. 5-(4-Chlorophenyl)-3-(2-methoxyethoxy)-1-(4-nitrophenyl)-1H-1,2,4-triazole (**36**).* Following the general procedure C, the reaction was conducted from compound **29** (250 mg, 0.91 mmol) and 4-nitrophenylhydrazine (139 mg, 0.91 mmol) to give the desired product (202 mg, 57%). Physical state: brown oil. TLC: R_f = 0.53 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.42 – 7.35 (m, 4H), 4.54 – 4.49 (m, 2H), 3.81 – 3.76 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 153.0, 146.9, 142.6, 137.2, 130.3, 129.4, 125.8, 125.1, 124.9, 70.6, 69.3, 59.3. HRMS (ESI): calcd for $C_{17}H_{15}ClN_4O_4$ $[M + H]^+$ *m/z* 375.0855, found 375.0858.

*4.1.23. 3-(2-Methoxyethoxy)-1-(4-nitrophenyl)-5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (**37**).* Following the general procedure C, the reaction was conducted from compound **30** (165 mg, 0.5 mmol) and 4-nitrophenylhydrazine (77 mg, 0.5 mmol) to give the desired product (146 mg, 68%). Physical state: brown oil. TLC: R_f = 0.15 (CH_2Cl_2/MeOH = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 6.64 (s, 2H), 4.53 – 4.43 (m, 2H), 3.84 (s, 3H), 3.78 – 3.73 (m, 2H), 3.67 (s, 6H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 153.9, 153.4, 146.5, 142.8, 140.1, 125.1, 124.6, 122.2, 106.3, 70.6, 69.1, 61.0, 59.1, 56.2. HRMS (ESI): calculated for $C_{20}H_{22}N_4O_7$ $[M + H]^+$ *m/z* 431.1561, found 431.1561.

*4.1.24. 3-(2-Methoxyethoxy)-1-(4-nitrophenyl)-5-(thiophen-2-yl)-1H-1,2,4-triazole (**38**).* Following the general procedure C, the reaction was conducted from compound **31** (356 mg, 1.5 mmol) and 4-nitrophenylhydrazine (230 mg, 1.5 mmol) to give the desired product (372 mg, 72%). Physical state: brown oil. TLC: R_f = 0.28 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 9.1 Hz, 2H), 7.46 – 7.38 (m, 1H), 7.11 – 7.04 (m, 1H), 6.99 – 6.92 (m, 1H), 4.48 – 4.41 (m, 2H), 3.77 – 3.70 (m, 2H), 3.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 148.7, 147.3, 142.5, 129.7, 129.6, 128.2, 127.8, 126.4, 124.8, 70.5, 69.1, 59.0. HRMS (ESI): calcd for $C_{15}H_{14}N_4O_4S$ $[M + H]^+$ *m/z* 347.0809, found 347.0798.

*4.1.25. 4-(5-(2,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)aniline (**39**).* Following the general procedure D, the reduction was conducted from compound **32** (72 mg, 0.18 mmol) to give the desired product (66 mg, 97%). Physical State: yellow solid; Melting point: 126.1-127.7 ^{o}C. TLC: R_f = 0.45 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 2H), 7.27 (d, *J* = 6.9 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.54 (d, *J* = 8.3 Hz, 2H), 4.58 – 4.43 (m, 2H), 3.81 – 3.74 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 149.4, 146.7, 136.9, 134.8, 132.7, 130.0, 128.5, 127.4, 127.0, 125.2, 115.0, 70.8, 69.0, 59.2. HRMS (ESI): calcd for $C_{17}H_{16}Cl_2N_4O_2$ $[M + H]^+$ *m/z* 379.0723, found 379.0721.

*4.1.26. 4-(5-(3,5-Dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)aniline (**40**).* Following the general procedure D, the reduction was conducted from compound **33** (66 mg, 0.16 mmol) to give the desired product (60 mg, 98%). Physical state: yellow oil. TLC: R_f = 0.65 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.37 (d, *J* = 1.7 Hz, 2H), 7.31 (s, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 4.52 – 4.44 (m, 2H), 3.79 – 3.73 (m, 2H), 3.43 (d, *J* = 3.0 Hz, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 150.2, 147.8, 135.1, 130.6, 129.8, 128.1, 127.0, 126.9, 115.3, 70.7, 69.0, 59.2. HRMS (ESI): calcd for $C_{17}H_{16}Cl_2N_4O_2$ $[M + H]^+$ *m/z* 379.0723, found 379.0717.

*4.1.27. 4-(5-(2-Chlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)aniline (**41**).* Following the general procedure D, the reduction was conducted from compound **34** (65 mg, 0.17 mmol) to give the desired product (56 mg, 94%). Physical state: yellow oil. TLC: R_f = 0.30 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 3.8 Hz, 2H), 7.29 (s, 1H), 7.00 (d, *J* = 7.9 Hz, 2H), 6.54 (d, *J* = 7.9 Hz, 2H), 4.59 – 4.46 (m, 2H), 4.05 – 3.57 (m, 4H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 150.4, 146.4, 133.9, 131.9, 131.4, 130.0, 128.8, 128.5, 126.9, 125.2, 115.0, 70.8, 69.0, 59.3. HRMS (ESI): calcd for $C_{17}H_{17}ClN_4O_2$ $[M + H]^+$ *m/z* 345.1113, found 345.1112.

*4.1.28. 4-(5-(3-Chlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)aniline (**42**).* Following the general procedure D, the reduction was conducted from compound **35** (420 mg, 1.1 mmol) to give the desired product (345 mg, 83%). Physical state: yellow solid; Melting point: 101.9-103.2 ^{o}C. TLC: R_f = 0.43 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.31 (t, *J* = 8.8 Hz, 2H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 4.52 – 4.46 (m, 2H), 3.80 – 3.76 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 151.5, 147.4, 134.5, 129.9, 129.7, 129.6, 128.9, 128.8, 127.1, 126.7, 115.3, 70.8, 69.0, 59.2. HRMS (ESI): calcd

for $C_{17}H_{17}ClN_4O_2$ $[M + H]^+$ *m/z* 345.1113, found 345.1108.

*4.1.29. 4-(5-(4-Chlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)aniline (**43**).*

Following the general procedure D, the reduction was conducted from compound **36** (55 mg, 0.15 mmol) to give the desired product (25 mg, 49%). Physical state: brown oil. TLC: R_f = 0.31 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 4.52 – 4.45 (m, 2H), 4.08 – 3.64 (m, 4H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 151.9, 147.3, 140.7, 130.1, 128.9, 128.8, 127.1, 126.4, 115.3, 70.8, 68.9, 59.3. HRMS (ESI): calcd for $C_{17}H_{17}ClN_4O_2$ $[M + H]^+$ *m/z* 345.1113, found 345.1112**.**

4.1.30.

*4-(3-(2-Methoxyethoxy)-5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazol-1-yl)aniline (**44**).*

Following the general procedure D, the reduction was conducted from compound **37** (74 mg, 0.17 mmol) to give the desired product (58 mg, 85%). Physical state: yellow solid; Melting point: 130.1-132.6 °C. TLC: R_f = 0.78 (CH_2Cl_2/MeOH = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.7 Hz, 2H), 6.75 (s, 2H), 6.68 (d, *J* = 7.8 Hz, 2H), 4.52 – 4.43 (m, 2H), 3.82 (s, 4H), 3.79 – 3.74 (m, 2H), 3.65 (s, 6H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 152.9, 152.8, 147.4, 139.3, 129.2, 127.6, 122.9, 115.1, 106.0, 70.8, 68.8, 60.9, 59.2, 56.0. HRMS (ESI): calcd for $C_{20}H_{24}N_4O_5$ $[M + H]^+$ *m/z* 401.1819, found 401.1818.

*4.1.31. 4-(3-(2-Methoxyethoxy)-5-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl)aniline (**45**).*

Following the general procedure D, the reduction was conducted from compound **38**

(121 mg, 0.35 mmol) to give the desired product (74 mg, 67%). Physical state: yellow oil. TLC: R_f = 0.30 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 1H), 7.20 – 7.14 (m, 2H), 7.11 – 7.07 (m, 1H), 6.94 – 6.89 (m, 1H), 6.75 – 6.69 (m, 2H), 4.49 – 4.43 (m, 2H), 4.00 (s, 2H), 3.78 – 3.73 (m, 2H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 148.9, 148.2, 129.5, 128.9, 128.6, 128.3, 128.0, 127.5, 115.2, 70.8, 68.8, 59.1. HRMS (ESI): calcd for $C_{15}H_{16}N_4O_2S$ $[M + H]^+$ *m/z* 317.1067, found 317.1058.

4.1.32.

*2-Chloro-N-(4-(5-(2,4-dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**46**)*. Following the general procedure E, the reaction was conducted from the corresponding aniline (35 mg, 0.09 mmol) and 2-chloroacetic acid (19 mg, 0.14 mmol) to give the desired product (26 mg, 63%). Physical state: yellow oil. TLC: R_f = 0.35 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.54 (d, *J* = 8.9 Hz, 2H), 7.43 – 7.38 (m, 2H), 7.32 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.22 – 7.18 (m, 2H), 4.55 – 4.50 (m, 2H), 4.17 (s, 2H), 3.81 – 3.77 (m, 2H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.0, 149.7, 137.4, 136.7, 134.6, 134.2, 132.7, 130.2, 127.7, 126.7, 124.2, 120.4, 70.7, 69.2, 59.3, 42.9. HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 455.0439, found 455.0429.

4.1.33.

*2-Chloro-N-(4-(5-(3,5-dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**47**)*. Following the general procedure E, the reaction was conducted from the corresponding aniline (60 mg, 0.11 mmol) and 2-chloroacetic acid (23 mg,

0.24 mmol) to give the desired product (64 mg, 88%). Physical state: yellow oil. TLC: R_f = 0.65 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.38 – 7.32 (m, 3H), 7.29 (d, *J* = 8.7 Hz, 2H), 4.51 – 4.46 (m, 2H), 4.19 (s, 2H), 3.80 – 3.74 (m, 2H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 164.3, 150.4, 137.7, 135.4, 133.8, 130.2, 130.2, 127.1, 126.2, 120.7, 70.7, 69.1, 59.2, 42.9. HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 455.0439, found 455.0438.

4.1.34.

*2-Chloro-N-(4-(5-(2-chlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**48**).* Following the general procedure E, the reaction was conducted from the corresponding aniline (41 mg, 0.12 mmol) and 2-chloroacetic acid (17 mg, 0.18 mmol) to give the desired product (48 mg, 96%). Physical state: yellow oil. TLC: R_f = 0.32 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.40 – 7.30 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 2H), 4.55 – 4.50 (m, 2H), 4.14 (s, 2H), 3.81 – 3.76 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 164.1, 150.6, 136.6, 134.2, 133.7, 131.8, 131.8, 130.2, 128.1, 127.2, 124.0, 120.3, 70.7, 69.1, 59.2, 42.9. HRMS (ESI): calcd for $C_{19}H_{18}Cl_2N_4O_3$ $[M + H]^+$ *m/z* 421.0829, found 421.0827.

4.1.35.

*2-Chloro-N-(4-(5-(3-chlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**49**).* Following the general procedure E, the reaction was conducted from the corresponding aniline (46 mg, 0.12 mmol) and 2-chloroacetic acid (17 mg, 0.18 mmol) to give the desired product (46 mg, 91%). Physical state: yellow solid; Melting

point: 121.4-121.7 °C. TLC: R_f = 0.64 (CH_2Cl_2/MeOH = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.56 (s, 1H), 7.37 – 7.33 (m, 1H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.24 – 7.18 (m, 2H), 4.54 – 4.47 (m, 2H), 4.20 (s, 2H), 3.81 – 3.75 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 164.2, 151.8, 137.4, 134.8, 134.3, 130.3, 129.9, 129.3, 129.0, 126.8, 126.2, 120.6, 70.7, 69.1, 59.2, 42.9. HRMS (ESI): calcd for $C_{19}H_{18}Cl_2N_4O_3$ $[M + H]^+$ *m/z* 421.0829, found 421.0822.

4.1.36.

*2-Chloro-N-(4-(5-(4-chlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**50**)*. Following the general procedure E, the reaction was conducted from the corresponding aniline (25 mg, 0.07 mmol) and 2-chloroacetic acid (10 mg, 0.11 mmol) to give the desired product (15 mg, 60%). Physical state: yellow solid; Melting point: 138.8-139.1 °C. TLC: R_f = 0.26 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.34 – 7.27 (m, 4H), 4.54 – 4.47 (m, 2H), 4.21 (s, 2H), 3.81 – 3.74 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.1, 152.2, 137.3, 136.5, 134.6, 130.2, 129.0, 126.3, 126.1, 120.7, 70.8, 69.1, 59.3, 42.9. HRMS (ESI): calcd for $C_{19}H_{18}Cl_2N_4O_3$ $[M + H]^+$ *m/z* 421.0829, found 421.0827.

4.1.37.

*2-Chloro-N-(4-(3-(2-methoxyethoxy)-5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**51**)*. Following the general procedure E, the reaction was conducted from the corresponding aniline (33 mg, 0.08 mmol) and 2-chloroacetic acid (11 mg, 0.12 mmol) to give the desired product (23 mg, 61%). Physical state: yellow

oil. TLC: R_f = 0.26 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.69 (s, 2H), 4.49 (t, *J* = 4.7 Hz, 2H), 4.20 (s, 2H), 3.84 (s, 3H), 3.78 (t, *J* = 4.8 Hz, 2H), 3.65 (s, 6H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 167.7, 164.1, 153.1, 139.7, 137.2, 134.9, 126.6, 122.6, 120.6, 106.2, 70.8, 69.0, 61.0, 59.2, 56.1, 42.9. HRMS (ESI): calcd for $C_{22}H_{25}ClN_4O_6$ $[M + H]^+$ *m/z* 477.1535, found 477.1534.

4.1.38.

*2-Chloro-N-(4-(3-(2-methoxyethoxy)-5-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**52**).* Following the general procedure E, the reaction was conducted from the corresponding aniline (40 mg, 0.13 mmol) and 2-chloroacetic acid (19 mg, 0.20 mmol) to give the desired product (33 mg, 65%). Physical state: yellow oil. TLC: R_f = 0.16 (PE/EtOAc/CH_2Cl_2 = 2:1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 5.2 Hz, 1H), 7.04 (d, *J* = 3.8 Hz, 1H), 6.94 – 6.89 (m, 1H), 4.49 – 4.44 (m, 2H), 4.21 (s, 2H), 3.78 – 3.74 (m, 2H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 164.3, 148.8, 138.3, 134.0, 129.2, 129.0, 129.0, 127.7, 127.7, 120.7, 70.7, 69.0, 59.2, 43.0. HRMS (ESI): calcd for $C_{17}H_{17}N_4O_3S$ $[M + H]^+$ *m/z* 345.1112, found 345.1092.

*4.1.39. 4-Nitrobenzoyl chloride (**53**).* This compound was synthesized according to the reported procedures with slight modifications.[50] $SOCl_2$ (1.3 mL, 18.0 mmol) was added dropwise to 4-nitrobenzoic acid (1.0 g, 6.0 mmol), and the mixture was stirred at 80 ^{o}C for 2 h, and then concentrated in vacuo. The crude product was used immediately without further purification or characterization.

4.1.40.

*1-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-5-(4-nitrophenyl)-1H-1,2,4-triazole (**55**).* Following the general procedure C, the reaction was conducted from compound **54** (126 mg, 0.44 mmol) and (3,4-dichlorophenyl)hydrazine (78 mg, 0.44 mmol) to give the desired product (131 mg, 73%). Physical state: yellow oil. TLC: R_f = 0.68 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 2H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.14 – 7.08 (m, 1H), 4.55 – 4.48 (m, 2H), 3.83 – 3.76 (m, 2H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 151.3, 148.8, 136.7, 134.1, 133.8, 133.1, 131.3, 129.9, 127.3, 124.4, 124.1, 70.7, 69.4, 59.3. HRMS (ESI): calcd for $C_{17}H_{14}Cl_2N_4O_4$ $[M + H]^+$ *m/z* 409.0465, found 409.0486.

*4.1.41. 4-(1-(3,4-Dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-5-yl)aniline (**56**).* Following the general procedure D, the reduction was conducted from compound **55** (79 mg, 0.19 mmol) to give the desired product (21 mg, 29%). Physical state: pale yellow oil. TLC: R_f = 0.36 (PE/CH_2Cl_2/EtOAc = 1:2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 2.5 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.17 – 7.13 (m, 1H), 6.59 (d, *J* = 8.7 Hz, 2H), 4.49 – 4.46 (m, 2H), 3.95 (s, 2H), 3.78 – 3.75 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 154.1, 148.7, 137.8, 133.3, 132.3, 130.8, 130.3, 127.1, 124.4, 116.7, 114.6, 70.8, 68.9, 59.2. HRMS (ESI): calcd for $C_{17}H_{16}Cl_2N_4O_2$ $[M + H]^+$ *m/z* 379.0723, found 379.0718.

4.1.42.

2-Chloro-N-(4-(1-(3,4-dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-5-yl)ph

*enyl)acetamide (**57**)*. Following the general procedure E, the reaction was conducted from compound **56** (14 mg, 0.037 mmol) and 2-chloroacetic acid (3.5 mg, 0.037 mmol) to give the desired product (10 mg, 62%). Physical state: pale yellow oil. TLC: R_f = 0.34 (PE/CH_2Cl_2/EtOAc = 1:2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.63 – 7.53 (m, 3H), 7.50 – 7.41 (m, 3H), 7.15 – 7.08 (m, 1H), 4.53 – 4.46 (m, 2H), 4.19 (s, 2H), 3.81 – 3.75 (m, 2H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 164.1, 152.9, 138.8, 137.3, 133.6, 133.0, 131.0, 129.9, 127.1, 124.4, 123.7, 119.8, 70.7, 69.1, 59.3, 42.9. HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 455.0439, found 455.0434.

*4.1.43. 3-Nitrobenzoyl chloride (**58**).* The title compound was obtained from 3-nitrobenzoic acid in the same conditions described above to prepare compound **53**.

*4.1.44. 1-(3,4-Dichlorophenyl)-3-methoxy-5-(3-nitrophenyl)-1H-1,2,4-triazole (**60**).* Following the general procedure C, the reaction was conducted from compound **59** (817 mg, 3.4 mmol) and (3,4-dichlorophenyl)hydrazine (598 mg, 3.4 mmol) to give the desired product (863 mg, 70%). Physical state: yellow oil. TLC: R_f = 0.61 (PE/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (t, *J* = 2.1 Hz, 1H), 8.32 – 8.25 (m, 1H), 7.79 – 7.72 (m, 1H), 7.61 – 7.53 (m, 2H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.17 – 7.11 (m, 1H), 4.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 151.2, 148.4, 136.7, 134.3, 134.0, 133.7, 131.3, 130.0, 129.0, 127.2, 125.2, 124.3, 124.0, 57.3. HRMS (ESI): calcd for $C_{15}H_{10}Cl_2N_4O_3$ $[M + H]^+$ *m/z* 365.0203, found 365.0206.

*4.1.45. 1-(3,4-Dichlorophenyl)-5-(3-nitrophenyl)-1H-1,2,4-triazol-3-ol (**61**).* To a solution of **60** (710 mg, 1.95 mmol) in 10 mL AcOH was added 33 wt.% HBr (5 mL,

19.5 mmol). The resulting mixture was stirred at 100 °C for 12 h. After cooling, 50 mL of ice water was added to the mixture. After vigorous shaking, an insoluble material was isolated by filtration and dried in vacuo (552 mg, 80%). Physical state: white solid; Melting point: 241.3-241.9 °C. TLC: R_f = 0.58 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.38 – 8.25 (m, 2H), 7.86 – 7.76 (m, 2H), 7.75 – 7.68 (m, 2H), 7.43 – 7.36 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.7, 150.4, 147.7, 137.1, 134.7, 131.8, 131.5, 131.4, 130.4, 128.9, 127.4, 125.7, 124.8, 123.5. HRMS (ESI): calcd for $C_{14}H_8Cl_2N_4O_3$ $[M + H]^+$ *m/z* 351.0046, found 351.0021.

*4.1.46. 5-(3-Aminophenyl)-1-(3,4-dichlorophenyl)-1H-1,2,4-triazol-3-ol (**62**).* Following the general procedure D, the reduction was conducted from compound **61** (542 mg, 1.53 mmol) to give the desired product. Physical state: white solid; Meting point: >300 °C. TLC: R_f = 0.45 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 2.4 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 2.2 Hz, 1H), 6.65 – 6.61 (m, 1H), 6.45 (d, *J* = 7.5 Hz, 1H), 5.31 (s, 2H). HRMS (ESI): calcd for $C_{14}H_{10}Cl_2N_4O$ $[M + H]^+$ *m/z* 321.0304, found 321.0307.

4.1.47.

*2-Chloro-N-(3-(1-(3,4-dichlorophenyl)-3-hydroxy-1H-1,2,4-triazol-5-yl)phenyl)aceta mide (**63**).* Following the general procedure E, the reaction was conducted from compound **62** (80 mg, 0.4 mmol) and 2-chloroacetic acid (57 mg, 0.6 mmol) to give the desired product (20 mg, 13%). Physical state: yellow solid; Melting point:

214.5-215.2 °C. TLC: R_f = 0.52 (CH_2Cl_2/MeOH = 10:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 10.45 (s, 1H), 7.87 (t, *J* = 1.9 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.64 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.09 – 7.02 (m, 1H), 4.23 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.7, 165.0, 152.3, 138.9, 137.5, 131.8, 131.3, 131.1, 129.4, 128.1, 127.1, 125.4, 124.0, 121.0, 119.4, 43.6. HRMS (ESI): calcd for $C_{16}H_{11}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 397.0020, found 397.0023.

4.1.48.

*2-Chloro-N-(3-(1-(3,4-dichlorophenyl)-3-(2-methoxyethoxy)-1H-1,2,4-triazol-5-yl)phenyl)acetamide (**64**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (9 mg, 0.023 mmol) and 2-methoxyethan-1-ol (5 mg, 0.068 mmol) to give the desired product (5 mg, 50%). Physical state: white oil. TLC: R_f = 0.39 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.78 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.17 – 7.09 (m, 2H), 4.55 – 4.47 (m, 2H), 4.18 (s, 2H), 3.82 – 3.76 (m, 2H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 164.0, 152.8, 137.5, 137.1, 133.6, 133.0, 131.0, 129.7, 128.3, 127.1, 125.2, 124.3, 122.1, 120.5, 70.7, 69.2, 59.3, 42.9. HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 455.0439, found 455.0437.

*4.1.49. O-Methyl (3,4-dichlorobenzoyl)carbamothioate (**65**)*. The title compound was obtained from **2** (504 mg, 2.2 mmol) in the same conditions described above to prepare compound **3**. Yield: 83%. Physical state: white solid; Melting point: 129.5-130.4 °C. TLC: R_f = 0.79 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ

9.16 (s, 1H), 7.92 (d, *J* = 2.1 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 4.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 160.8, 138.0, 133.8, 132.7, 131.1, 130.0, 126.8, 59.7. HRMS (ESI): calcd for $C_9H_7Cl_2NO_2S$ $[M + H]^+$ *m/z* 263.9647, found 263.9654.

*4.1.50. 5-(3,4-Dichlorophenyl)-3-methoxy-1-(4-nitrophenyl)-1H-1,2,4-triazole (**66**).* Following the general procedure C, the reaction was conducted from the starting material (432 mg, 1.6 mmol) and 4-nitrophenylhydrazine (250 mg, 1.6 mmol) to give the desired product (517 mg, 89%). Physical state: yellow solid; Melting point: 152.1-152.9 °C. TLC: R_f = 0.37 (PE/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.0 Hz, 2H), 7.69 (d, *J* = 2.1 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.23 – 7.19 (m, 1H), 4.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 151.9, 147.1, 142.4, 135.6, 133.7, 131.1, 131.0, 127.9, 127.2, 125.2, 125.1, 57.3. HRMS (ESI): calcd for $C_{15}H_{10}Cl_2N_4O_3$ $[M + H]^+$ *m/z* 365.0203, found 365.0155.

*4.1.51. 5-(3,4-Dichlorophenyl)-1-(4-nitrophenyl)-1,2-dihydro-3H-1,2,4-triazol-3-one (**67**).* To a solution of **66** (109 mg, 0.30 mmol) in 5 mL of AcOH was added 33% HBr in AcOH (736 mg, 3.0 mmol). The resulting mixture was stirred at 100 °C for 6 h. Then it was poured into iced water (~50 mL). After vigorous shaking, an insoluble material was isolated by filtration and dried in vacuo (104 mg, 99%). Physical state: white solid; Melting point: 259.8-260.4 °C. TLC: R_f = 0.24 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.30 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.38 – 7.32 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 167.0, 150.7, 146.4, 142.2, 133.4, 131.7, 131.1, 130.8, 129.0, 128.1, 125.6, 124.9. HRMS (ESI): calcd for $C_{14}H_8Cl_2N_4O_3$ $[M + H]^+$ *m/z* 351.0046, found 351.0041.

*4.1.52. 1-(4-Aminophenyl)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-3-ol (**68**).* To a solution of **67** (1.4 g, 4.0 mmol) in MeOH (15 mL) was added AcOH (4 mL) and Zn (2.6 g, 40.0 mmol). The mixture was stirred at r.t. for 12 h. The mixture was dispersed into the cold water. After vigorous shaking, a white solid was isolated by filtration and dried in vacuo. Physical state: white solid; Melting point: >300 ^{o}C. TLC: R_f = 0.55 (CH_2Cl_2/MeOH = 10:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 1H), 7.66 – 7.55 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.60 (d, *J* = 8.2 Hz, 2H), 5.50 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.1, 149.6, 149.1, 132.4, 131.3, 130.9, 129.9, 128.5, 128.2, 126.9, 125.9, 113.8. HRMS (ESI): calcd for $C_{14}H_{10}Cl_2N_4O$ $[M + H]^+$ *m/z* 321.0304, found 321.0321.

4.1.53.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-hydroxy-1H-1,2,4-triazol-1-yl)phenyl)aceta mide (**69**).* To a solution of **68** (1.3 g, 4.0 mmol) in CH_2Cl_2 (10 mL) was added EDCI (1.6 g, 8.0 mmol) and 2-chloroacetic acid (574 mg, 6.0 mmol). The mixture was stirred at r.t. for 12 h. The solvent was removed in vacuo to give the crude product. The residue was dispersed into the cold water. After vigorous shaking, a white solid was isolated by filtration and dried in vacuo. Physical state: white solid; Melting point: 238.8-239.6 ^{o}C. TLC: R_f = 0.52 (CH_2Cl_2/MeOH = 10:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (s, 1H), 10.57 (s, 1H), 7.73 – 7.61 (m, 4H), 7.36 (d, *J* = 8.7 Hz,

2H), 7.31 – 7.26 (m, 1H), 4.27 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 165.1, 149.6, 139.0, 133.0, 132.8, 131.5, 131.0, 130.3, 128.5, 128.2, 126.4, 119.9, 43.6. HRMS (ESI): calcd for $C_{16}H_{11}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 397.0020, found 397.0031.

4.1.54.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-methoxy-1H-1,2,4-triazol-1-yl)phenyl)aceta mide (**70**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and MeOH (16 mg, 0.5 mmol) to give the desired product (75 mg, 91%). Physical state: white solid; Melting Point: 170.1-170.8 °C. TLC: R_f = 0.20 (PE/EtOAc =2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 3H), 7.37 – 7.30 (m, 3H), 7.19 – 7.15 (m, 1H), 4.19 (s, 2H), 4.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 164.2, 151.0, 137.6, 134.7, 134.1, 133.2, 130.8, 130.6, 127.74 127.4, 126.3, 120.7, 57.1, 42.9. HRMS (ESI): calcd for $C_{17}H_{13}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 411.0177, found 411.0177.

4.1.55.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-ethoxy-1H-1,2,4-triazol-1-yl)phenyl)acetami de (**71**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and EtOH (23 mg, 0.5 mmol) to give the desired product (79 mg, 93%). Physical state: white solid; Melting point: 188.4-189.7 °C. TLC: R_f = 0.55 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.19 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.20 (s, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 164.1,

150.9, 137.5, 134.7, 134.3, 133.2, 130.8, 130.6, 127.7, 127.5, 126.4, 120.7, 65.8, 42.9, 14.8. HRMS (ESI): calcd for $C_{18}H_{15}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 425.0333, found 425.0334.

4.1.56.

2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-isopropoxy-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**72**). Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (40 mg, 0.1 mmol) and butan-1-ol (15 mg, 0.2 mmol) to give the desired product (38 mg, 79%). Physical state: white solid; Melting point: 182.8-183.3 °C. TLC: R_f = 0.33 (PE/EtOAc/CH_2Cl_2 = 4:1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.71 – 7.63 (m, 3H), 7.38 – 7.31 (m, 3H), 7.19 (d, *J* = 8.4 Hz, 1H), 4.33 (t, *J* = 6.5 Hz, 2H), 4.21 (s, 2H), 1.84 – 1.77 (m, 2H), 1.56 – 1.46 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 164.1, 150.9, 137.5, 134.7, 134.3, 133.2, 130.8, 130.6, 127.7, 127.5, 126.4, 120.7, 69.8, 42.9, 31.2, 19.1, 13.9. HRMS (ESI): calcd for $C_{20}H_{19}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 453.0646, found 453.0643.

4.1.57.

2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(pentyloxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**73**). Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and pentan-1-ol (28 mg, 0.32 mmol) to give the desired product (52 mg, 69%). Physical state: white solid; Melting point: 162.5-163.2 °C. TLC: R_f = 0.33 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.75 – 7.61 (m, 3H), 7.42 – 7.29 (m, 3H), 7.19 (d, *J* = 7.4 Hz, 1H), 4.32 (t, *J* = 6.3 Hz, 3H), 4.21 (s, 2H), 1.88 – 1.76 (m, 2H), 1.51 – 1.33 (m, 4H), 0.92 (t, *J* = 7.1

Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 164.1, 150.9, 137.5, 134.7, 134.3, 133.2, 130.8, 130.6, 127.7, 127.5, 126.4, 120.7, 70.1, 42.9, 28.9, 28.0, 22.5, 14.1. HRMS (ESI): calcd for $C_{21}H_{21}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 467.0803, found 467.0796.

4.1.58.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(hexyloxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**74**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and hexan-1-ol (33 mg, 0.32 mmol) to give the desired product (56 mg, 73%). Physical state: white solid; Melting point: 125.1-125.7 °C. TLC: R_f = 0.52 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.80 – 7.57 (m, 3H), 7.35 (t, *J* = 9.1 Hz, 3H), 7.20 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.33 (t, *J* = 6.5 Hz, 2H), 4.22 (s, 2H), 1.90 – 1.76 (m, 2H), 1.53 – 1.44 (m, 2H), 1.38 – 1.30 (m, 4H), 1.26 – 1.24 (m, 2H), 0.93 – 0.86 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 164.1, 150.9, 137.5, 134.7, 134.3, 133.2, 130.8, 130.6, 127.7, 127.5, 126.4, 120.7, 70.1, 42.9, 31.6, 29.1, 25.6, 22.7, 14.1. HRMS (ESI): calcd for $C_{22}H_{23}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 481.0959, found 481.0953.

4.1.59.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(octyloxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**75**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and octan-1-ol (42 mg, 0.32 mmol) to give the desired product (42 mg, 52%). Physical state: white solid; Melting point: 101.4-103.1 °C. TLC: R_f = 0.54 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.76 – 7.60 (m, 3H), 7.40 – 7.28 (m, 3H), 7.19 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.32

(t, *J* = 6.6 Hz, 2H), 4.21 (s, 2H), 1.87 – 1.77 (m, 2H), 1.52 – 1.43 (m, 2H), 1.36 – 1.22 (m, 8H), 0.87 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 164.1, 150.9, 137.5, 134.7, 134.3, 133.2, 130.8, 130.6, 127.7, 127.5, 126.4, 120.7, 70.1, 42.9, 31.9, 29.3, 29.3, 29.2, 25.9, 22.7, 14.2. HRMS (ESI): calcd for $C_{24}H_{27}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 509.1272, found 509.1266.

4.1.60.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-isopropoxy-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**76**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and propan-2-ol (31 mg, 0.5 mmol) to give the desired product (56 mg, 64%). Physical state: pale yellow solid; Melting point: 184.2-184.7 °C. TLC: R_f = 0.60 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.21 – 7.17 (m, 1H), 5.08 – 4.97 (m, 1H), 4.21 (s, 2H), 1.43 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 164.1, 150.7, 137.4, 134.6, 134.4, 133.2, 130.8, 130.6, 127.7, 127.6, 126.3, 120.7, 73.3, 42.9, 22.1. HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 439.0490, found 439.0491.

4.1.61.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-isobutoxy-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**77**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (40 mg, 0.1 mmol) and 2-methylpropan-1-ol (15 mg, 0.2 mmol) to give the desired product (34 mg, 76%). Physical state: white solid; Melting point: 148.4-150.2 °C. TLC: R_f = 0.51 (PE/EtOAc = 2:1). ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.72 – 7.64 (m, 3H), 7.37 – 7.30 (m, 3H), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.21 (s, 2H), 4.10 (d, *J* = 6.6 Hz, 2H), 2.18 – 2.10 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 164.2, 150.9, 137.6, 134.7, 134.2, 130.8, 130.6, 127.7, 127.5, 126.4, 120.7, 76.2, 43.0, 28.3, 19.1. HRMS (ESI): calcd for $C_{20}H_{19}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 453.0646, found 453.0645.

4.1.62.

*2-Chloro-N-(4-(3-(cyclopropylmethoxy)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-1-yl) phenyl)acetamide (**78**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (105 mg, 0.4 mmol) and cyclopropylmethanol (29 mg, 0.4 mmol) to give the desired product (50 mg, 56%). Physical state: white solid; Melting point: 186.2-186.9 °C. TLC: R_f = 0.42 (PE/EtOAc = 2:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.76 – 7.61 (m, 3H), 7.40 – 7.29 (m, 3H), 7.19 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.21 (s, 2H), 4.17 (d, *J* = 7.2 Hz, 2H), 1.40 – 1.30 (m, 1H), 0.69 – 0.58 (m, 2H), 0.44 – 0.34 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 164.1, 150.9, 137.5, 134.7, 134.3, 133.2, 130.8, 130.6, 127.7, 127.6, 126.4, 120.7, 74.7, 42.9, 10.2, 3.4. HRMS (ESI): calcd for $C_{20}H_{17}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 451.0490, found 451.0482.

4.1.63.

*2-Chloro-N-(4-(3-(cyclopentyloxy)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-1-yl)phen yl)acetamide (**79**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and cyclopentanol (34 mg, 0.4 mmol) to give the desired product (34 mg, 37%). Physical state: white

solid; Melting point: 203.1-203.6 °C. TLC: R_f = 0.51 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.73 – 7.61 (m, 3H), 7.40 – 7.30 (m, 3H), 7.19 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.27 – 5.17 (m, 1H), 4.21 (s, 2H), 2.01 – 1.80 (m, 6H), 1.67 – 1.59 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 164.1, 150.7, 137.4, 134.6, 134.4, 133.2, 130.8, 130.6, 127.7, 127.6, 126.4, 120.7, 82.5, 42.9, 32.9, 23.7. HRMS (ESI): calcd for $C_{21}H_{19}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 465.0646, found 465.0641.

4.1.64.

*2-Chloro-N-(4-(3-(cyclohexylmethoxy)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**80**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and cyclohexylmethanol (46 mg, 0.4 mmol) to give the desired product (55 mg, 56%). Physical state: white solid; Melting point: 152.3-152.9 °C. TLC: R_f = 0.60 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.74 – 7.61 (m, 3H), 7.39 – 7.29 (m, 3H), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.20 (s, 2H), 4.14 (d, *J* = 6.0 Hz, 2H), 1.89 – 1.83 (m, 2H), 1.78 – 1.67 (m, 3H), 1.35 – 1.04 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 164.1, 150.9, 137.5, 134.7, 134.3, 133.2, 130.8, 130.6, 127.7, 127.5, 126.4, 120.7, 75.2, 42.9, 37.6, 29.6, 26.5, 25.8. HRMS (ESI): calcd for $C_{23}H_{23}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 493.0959, found 493.0953.

4.1.65.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-hydroxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**81**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (159 mg, 0.4 mmol) and ethane-1,2-diol

(99 mg, 1.6 mmol) to give the desired product (88 mg, 49%). Physical state: white solid; Melting point: 87.2-88.1 °C. TLC: R_f = 0.42 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 7.79 – 7.60 (m, 4H), 7.46 – 7.24 (m, 3H), 4.99 (s, 1H), 4.35 – 4.20 (m, 4H), 3.73 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.3, 165.2, 150.4, 139.2, 133.1, 132.7, 131.5, 131.0, 130.4, 128.6, 127.9, 126.6, 120.0, 71.2, 59.4, 43.6. HRMS (ESI): calcd for $C_{18}H_{15}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 441.0282, found 441.0275.

4.1.66.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(3-hydroxypropoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**82**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and propan-1,3-diol (30 mg, 0.4 mmol) to give the desired product (23 mg, 27%). Physical state: white solid; Melting point: 136.2-136.9 °C. TLC: R_f = 0.31 (CH_2Cl_2/EtOAc = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.77 – 7.58 (m, 3H), 7.44 – 7.28 (m, 3H), 7.19 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.52 (t, *J* = 5.9 Hz, 2H), 4.21 (s, 2H), 3.83 (t, *J* = 6.0 Hz, 2H), 2.46 (s, 1H), 2.06 (p, *J* = 5.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 164.2, 150.9, 138.1, 137.6, 134.7, 134.1, 133.2, 130.8, 130.6, 128.4, 127.8, 127.7, 127.7, 127.4, 126.3, 120.7, 73.4, 69.3, 68.3, 42.9. HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 455.0439, found 455.0431.

4.1.67.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2,3-dihydroxypropoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**83**).* This compound was synthesized according to the reported

procedures with slight modifications.[51] To a solution of **69** (80 mg, 0.20 mmol) and PPh_3 (105 mg, 0.40 mmol) in THF (2 mL) was added (2,2-dimethyl-1,3-dioxolan-4-yl)methanol (53 mg, 0.40 mmol) and DIAD (81 mg, 0.40 mmol) dropwise at 0 °C. Then the mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was diluted with EtOAc (15 mL) and extracted with H_2O (3 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated to give crude product under reduce pressure. Purification by silica gel chromatography (PE/EtOAc = 2:1) furnished a white solid, which was added to 0.5 N HCl (1.0 mL) in EtOH (5.0 mL). Then the mixture was stirred at r.t. for another 24 h. The mixture was added to the cold water. After vigorous shaking, a white solid was isolated by filtration and dried in vacuo. Physical state: white solid; Melting point: 135.2-135.9 °C. TLC: R_f = 0.53 (CH_2Cl_2/MeOH = 10:1). ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.30 (dd, *J* = 8.5, 2.1 Hz, 1H), 4.46 – 4.41 (m, 1H), 4.37 – 4.32 (m, 1H), 4.21 (s, 2H), 4.05 – 4.00 (m, 1H), 3.72 – 3.63 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 168.9, 167.6, 152.3, 140.6, 135.7, 134.6, 133.8, 131.9, 131.8, 129.4, 128.7, 127.6, 121.8, 72.1, 71.3, 63.9, 44.0. HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_4O_4$ $[M + H]^+$ *m/z* 471.0388, found 471.0382.

4.1.68.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(3-methoxypropoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**84**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and

3-methoxypropan-1-ol (29 mg, 0.32 mmol) to give the desired product (23 mg, 31%). Physical state: white solid; Melting point: 126.3-127.3 °C. TLC: R_f = 0.65 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.71 – 7.64 (m, 3H), 7.38 – 7.29 (m, 3H), 7.21 – 7.15 (m, 1H), 4.42 (t, *J* = 6.3 Hz, 2H), 4.20 (s, 2H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.35 (s, 3H), 2.13 – 2.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 164.1, 150.9, 137.6, 134.7, 134.2, 133.2, 130.8, 130.6, 127.7, 127.5, 126.3, 120.7, 69.0, 67.0, 58.8, 42.9, 29.5. HRMS (ESI): calcd for $C_{20}H_{19}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 469.0596, found 469.0592.

4.1.69.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-ethoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**85**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and 2-ethoxyethan-1-ol (29 mg, 0.32 mmol) to give the desired product (70 mg, 93%). Physical state: white solid; Melting point: 120.3-121.5 °C. TLC: R_f = 0.72 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.71 – 7.62 (m, 3H), 7.37 – 7.28 (m, 3H), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.52 – 4.44 (m, 2H), 4.20 (s, 2H), 3.86 – 3.78 (m, 2H), 3.60 (q, *J* = 7.0 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.1, 150.9, 137.6, 134.7, 134.2, 133.2, 130.8, 130.6, 127.7, 127.5, 126.3, 120.7, 69.3, 68.7, 66.9, 42.9, 15.3. HRMS (ESI): calcd for $C_{20}H_{19}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 469.0596, found 469.0607.

4.1.70.

2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-(2-methoxyethoxy)ethoxy)-1H-1,2,4-triaz

*ol-1-yl)phenyl)acetamide (**86**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and 2-(2-methoxyethoxy)ethan-1-ol (61 mg, 0.4 mmol) to give the desired product (86 mg, 86%). Physical state: yellow oil. TLC: R_f = 0.28 (CH_2Cl_2/EtOAc = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.76 – 7.62 (m, 3H), 7.39 – 7.30 (m, 3H), 7.19 (d, *J* = 8.4 Hz, 1H), 4.51 (t, *J* = 4.8 Hz, 2H), 4.22 (s, 2H), 3.93 – 3.87 (m, 2H), 3.76 – 3.71 (m, 2H), 3.59 – 3.55 (m, 2H), 3.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.1, 151.0, 137.5, 134.7, 134.3, 133.3, 130.8, 130.7, 127.7, 127.5, 126.4, 120.7, 72.1, 70.9, 69.5, 69.4, 59.2, 42.9. HRMS (ESI): calcd for $C_{21}H_{21}Cl_3N_4O_4$ $[M + H]^+$ *m/z* 499.0701, found 499.0703.

4.1.71.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-((1-methoxypropan-2-yl)oxy)-1H-1,2,4-triaz ol-1-yl)phenyl)acetamide (**87**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and 1-methoxypropan-2-ol (29 mg, 0.32 mmol) to give the desired product (40 mg, 53%). Physical state: white solid; Melting point: 87.4-89.8 ^{o}C. TLC: R_f = 0.48 (CH_2Cl_2/EtOAc = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.72 – 7.61 (m, 3H), 7.39 – 7.29 (m, 3H), 7.21 – 7.17 (m, 1H), 5.14 – 5.04 (m, 1H), 4.21 (s, 2H), 3.68 – 3.62 (m, 1H), 3.58 – 3.53 (m, 1H), 3.42 (s, 3H), 1.42 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 164.1, 150.8, 137.5, 134.6, 134.3, 133.2, 130.8, 130.6, 127.7, 127.6, 126.3, 120.7, 75.5, 75.4, 59.4, 42.9, 16.9. HRMS (ESI): calcd for $C_{20}H_{19}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 469.0596, found 469.0592.

4.1.72.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-(methylthio)ethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**88**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (40 mg, 0.10 mmol) and 2-(methylthio)ethan-1-ol (18 mg, 0.20 mmol) to give the desired product (45 mg, 96%). Physical state: white solid; Melting point: 135.2-136.3 ^{o}C. TLC: R_f = 0.36 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.71 – 7.62 (m, 3H), 7.38 – 7.29 (m, 3H), 7.20 – 7.15 (m, 1H), 4.51 (t, *J* = 6.9 Hz, 2H), 4.20 (s, 2H), 2.92 (t, *J* = 6.9 Hz, 2H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 164.1, 150.9, 137.6, 134.7, 134.1, 133.2, 130.8, 130.6, 127.7, 127.4, 126.3, 120.7, 69.0, 42.9, 32.7, 16.1. HRMS (ESI): calcd for $C_{19}H_{17}Cl_3N_4O_2S$ $[M + H]^+$ *m/z* 471.0211 ,found 471.0208.

4.1.73.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-fluoroethoxy)-1H-1,2,4-triazol-1-yl)phen yl)acetamide (**89**).* Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and 2-fluoroethanol (26 mg, 0.4 mmol) to give the desired product (69 mg, 75%). Physical state: white solid; Melting point: 189.2-189.5 ^{o}C. TLC: R_f = 0.29 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.73 – 7.63 (m, 3H), 7.41 – 7.29 (m, 3H), 7.19 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.88 – 4.79 (m, 1H), 4.75 – 4.68 (m, 1H), 4.66 – 4.61 (m, 1H), 4.59 – 4.53 (m, 1H), 4.21 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 164.1, 151.1, 137.7, 134.8, 134.1, 133.3, 130.8, 130.7, 127.7, 127.3, 126.3, 120.7, 82.4, 80.7, 68.9,

68.7, 42.9. HRMS (ESI): calcd for $C_{18}H_{14}Cl_3FN_4O_2$ $[M + H]^+$ *m/z* 443.0239, found 443.0234.

4.1.74.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-((tetrahydrofuran-2-yl)methoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**90**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and (tetrahydrofuran-2-yl)methanol (41 mg, 0.4 mmol) to give the desired product (75 mg, 78%). Physical state: white solid; Melting point: 175.6-176.1 ^oC. TLC: R_f = 0.58 (PE/EtOAc = 1:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.68 – 7.62 (m, 3H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.15 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.35 – 4.31 (m, 2H), 4.18 (s, 2H), 3.94 – 3.88 (m, 1H), 3.83 – 3.77 (m, 1H), 2.11 – 1.77 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.3, 150.9, 137.7, 134.7, 134.0, 133.2, 130.7, 130.6, 127.7, 127.4, 126.2, 120.7, 76.6, 71.7, 68.6, 43.0, 28.0, 25.8. HRMS (ESI): calcd for $C_{21}H_{19}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 481.0596, found 481.0587.

4.1.75.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-morpholinoethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**91**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and 2-morpholinoethan-1-ol (42 mg, 0.32 mmol) to give the desired product (79 mg, 96%). Physical state: yellow solid; Melting point: 160.2-161.6 ^oC. TLC: R_f = 0.66 (CH_2Cl_2/EtOAc = 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.71 – 7.62 (m, 3H), 7.38 – 7.29 (m, 3H), 7.20 – 7.15 (m, 1H), 4.48 (t, *J* = 5.5 Hz, 2H), 4.20 (s, 2H),

3.71 (t, *J* = 4.6 Hz, 4H), 2.84 (t, *J* = 5.6 Hz, 2H), 2.60 (t, *J* = 4.6 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 164.1, 150.9, 137.6, 134.7, 134.1, 133.2, 130.8, 130.6, 127.7, 127.4, 126.3, 120.7, 67.6, 67.0, 57.4, 54.0, 42.9. HRMS (ESI): calcd for $C_{22}H_{22}Cl_3N_5O_3$ $[M + H]^+$ *m/z* 510.0861, found 510.0858.

4.1.76.

*1-(4-(2-Chloroacetamido)phenyl)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-3-yl acetate (**92**)*. To a magnetically stirred solution of **69** (32 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) at 0 ^{o}C was treated with AcCl (8 mg, 0.10) and Et_3N (12 mg, 0.12 mmol). The whole reaction mixture was stirred at r.t. for 5 h. It was then diluted with EtOAc (20 mL), the organic layer was washed with water, dried over anhydrous Na_2SO_4, and then concentrated to give crude product under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeOH = 30:1) to give the desired product (17 mg, 48%) as a yellow solid. Physical state: yellow solid; Melting point: 148.7-150.2 ^{o}C. TLC: R_f = 0.47 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.81 – 7.62 (m, 3H), 7.44 – 7.31 (m, 3H), 7.20 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.22 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 164.0, 161.3, 151.8, 137.9, 135.1, 133.6, 133.3, 130.8, 130.6, 127.6, 126.7, 126.2, 120.6, 42.8, 20.6. HRMS (ESI): calcd for $C_{18}H_{13}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 439.0126, found 439.0118.

*4.1.77. Ethyl 2-((1-(4-(2-chloroacetamido)phenyl)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-3-yl)oxy)acetate (**93**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and ethyl

2-hydroxyacetate (42 mg, 0.4 mmol) to give the desired product (72 mg, 74%). Physical state: pale yellow oil. TLC: R_f = 0.32 (CH_2Cl_2/EtOAc = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.67 – 7.61 (m, 3H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 2H), 7.16 – 7.12 (m, 1H), 4.90 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.18 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 167.1, 164.4, 151.0, 137.9, 134.7, 133.7, 133.1, 130.7, 130.6, 127.7, 127.2, 126.1, 120.7, 65.8, 61.5, 43.0, 14.2. HRMS (ESI): calcd for $C_{20}H_{17}Cl_3N_4O_4$ $[M + H]^+$ *m/z* 483.0388 , found 483.0382.

4.1.78.

*N-(4-(3-(allyloxy)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-1-yl)phenyl)-2-chloroaceta mide (**94**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and prop-2-en-1-ol (19 mg, 0.32 mmol) to give the desired product (47 mg, 67%). Physical state: pale yellow solid; Melting point: 152.8-153.6 °C. TLC: R_f = 0.37 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.76 – 7.58 (m, 3H), 7.42 – 7.27 (m, 3H), 7.21 – 7.15 (m, 1H), 6.22 – 5.95 (m, 1H), 5.45 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.85 (d, *J* = 5.5 Hz, 2H), 4.19 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 164.2, 150.9, 137.6, 134.7, 134.1, 133.2, 132.3, 130.8, 130.6, 127.7, 127.4, 126.3, 120.7, 118.3, 70.4, 42.9. HRMS (ESI): calcd for $C_{19}H_{15}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 437.0333, found 437.0324.

4.1.79.

N-(4-(3-(Benzyloxy)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-1-yl)phenyl)-2-chloroac

*etamide (**95**)*. Following the general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (84 mg, 0.32 mmol) and phenylmethanol (35 mg, 0.32 mmol) to give the desired product (62 mg, 79%). Physical state: white solid; Melting point: 148.7-149.5 ^{o}C. TLC: R_f = 0.24 (PE/CH_2Cl_2/EtOAc = 8:5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.74 – 7.65 (m, 3H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.41 – 7.32 (m, 6H), 7.22 – 7.19 (m, 1H), 5.41 (s, 2H), 4.22 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.1, 151.0, 137.5, 136.2, 134.8, 134.3, 133.3, 130.8, 130.7, 128.5, 128.3, 128.0, 127.7, 127.5, 126.4, 120.7, 71.4, 42.9. HRMS (ESI): calcd for $C_{23}H_{17}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 487.0490, found 487.0488.

4.1.80.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-((4-fluorobenzyl)oxy)-1H-1,2,4-triazol-1-yl) phenyl)acetamide (**96**)*. Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and (4-fluorophenyl)methanol (51 mg, 0.4 mmol) to give the desired product (80 mg, 80%). Physical state: white solid; Melting point: 176.2-177.1 ^{o}C. TLC: R_f = 0.45 (PE/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 3H), 7.55 – 7.42 (m, 2H), 7.41 – 7.28 (m, 3H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.06 (t, *J* = 8.5 Hz, 2H), 5.35 (s, 2H), 4.21 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 164.1, 151.1, 137.6, 134.8, 134.2, 133.3, 130.8, 130.7, 130.1, 130.0, 127.7, 127.4, 126.3, 120.7, 115.6, 115.4, 70.8, 42.9. HRMS (ESI): calcd for $C_{23}H_{16}Cl_3FN_4O_2$ $[M + H]^+$ *m/z* 505.0396, found 505.0382.

4.1.81.

*2-Chloro-N-(4-(3-((4-chlorobenzyl)oxy)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-1-yl) phenyl)acetamide (**97**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and (4-cholrophenyl)methanol (46 mg, 0.32 mmol) to give the desired product (46 mg, 54%). Physical state: white solid; Melting point: 161.8-162.5 ^{o}C. TLC: R_f = 0.56 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.76 – 7.60 (m, 3H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.28 (m, 5H), 7.22 – 7.16 (m, 1H), 5.36 (s, 2H), 4.21 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 164.1, 151.1, 137.6, 134.8, 134.7, 134.2, 134.1, 133.3, 130.8, 130.7, 129.4, 128.7, 127.7, 127.4, 126.3, 120.7, 70.6, 42.9. HRMS (ESI): calcd for $C_{23}H_{16}Cl_4N_4O_2$ $[M + H]^+$ *m/z* 521.0100, found 521.0104.

4.1.82.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-((4-methoxybenzyl)oxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**98**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and (4-methoxyphenyl)methanol (55 mg, 0.4 mmol) to give the desired product (45 mg, 80%). Physical state: pale yellow solid; Melting point: 165.7-166.6 ^{o}C. TLC: R_f = 0.46 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.73 – 7.63 (m, 3H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.40 – 7.32 (m, 3H), 7.20 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.95 – 6.88 (m, 2H), 5.33 (s, 2H), 4.22 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.1, 159.7, 151.0, 137.5, 134.7, 134.4, 133.3, 130.8, 130.7, 130.0, 128.3, 127.7, 127.6, 126.4, 120.7, 113.9, 71.3, 55.4, 42.9. HRMS (ESI): calcd for $C_{24}H_{19}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 517.0596, found 517.0610.

4.1.83.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-phenethoxy-1H-1,2,4-triazol-1-yl)phenyl)ac etamide (**99**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and 2-phenylethan-1-ol (29 mg, 0.24 mmol) to give the desired product (56 mg, 72%). Physical state: yellow solid; Melting point: 143.5-144.5 ^{o}C. TLC: R_f = 0.46 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.76 – 7.60 (m, 3H), 7.44 – 7.27 (m, 7H), 7.25 – 7.21 (m, 1H), 7.20 – 7.16 (m, 1H), 4.55 (t, *J* = 7.0 Hz, 2H), 4.21 (s, 2H), 3.15 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.0, 150.9, 137.9, 137.5, 134.7, 134.3, 133.3, 130.8, 130.7, 129.2, 128.6, 127.7, 127.5, 126.6, 126.3, 120.7, 70.5, 42.9, 35.7. HRMS (ESI): calcd for $C_{24}H_{19}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 501.0646,found 501.0644.

4.1.84.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(4-phenylbutoxy)-1H-1,2,4-triazol-1-yl)phen yl)acetamide (**100**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and 4-phenylbutan-1-ol (60 mg, 0.4 mmol) to give the desired product (72 mg, 68%). Physical state: white solid; Melting point: 135.3-136.0 ^{o}C. TLC: R_f = 0.51 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.76 – 7.58 (m, 3H), 7.38 – 7.16 (m, 9H), 4.36 (t, *J* = 5.9 Hz, 2H), 4.21 (s, 2H), 2.69 (t, *J* = 7.0 Hz, 2H), 1.93 – 1.78 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 164.1, 151.0, 137.5, 136.5, 134.8, 134.3, 133.8, 133.3, 130.9, 130.7, 128.7, 128.1, 127.8, 127.5, 126.7, 126.4, 123.5, 120.7, 70.2, 42.9. HRMS (ESI): calcd for $C_{26}H_{23}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 529.0959, found 529.0952.

4.1.85.

*(E)-2-Chloro-N-(4-(3-(cinnamyloxy)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**101**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and (*E*)-3-phenylprop-2-en-1-ol (54 mg, 0.4 mmol) to give the desired product (82 mg, 80%). Physical state: white solid; Melting point: 126.2-126.8 ^{o}C. TLC: R_f = 0.52 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.74 – 7.64 (m, 3H), 7.45 – 7.40 (m, 2H), 7.39 – 7.30 (m, 5H), 7.29 – 7.26 (m, 1H), 7.21 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.81 (d, *J* = 15.9 Hz, 1H), 6.50 – 6.41 (m, 1H), 5.03 (d, *J* = 6.0, 1.5 Hz, 2H), 4.22 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 164.1, 151.0, 137.5, 136.5, 134.8, 134.3, 133.8, 133.3, 130.9, 130.7, 128.7, 128.1, 127.8, 127.5, 126.7, 126.4, 123.5, 120.7, 70.2, 42.9. HRMS (ESI): calcd for $C_{25}H_{19}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 513.0646, found 513.0641.

4.1.86.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-phenoxyethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**102**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and 2-phenoxyethan-1-ol (55 mg, 0.4 mmol) to give the desired product (77 mg, 74%). Physical state: white solid; Melting point: 128.7-129.5 ^{o}C. TLC: R_f = 0.38 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.72 – 7.64 (m, 3H), 7.38 – 7.26 (m, 5H), 7.19 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.98 – 6.92 (m, 3H), 4.70 (t, *J* = 4.9 Hz, 2H), 4.39 – 4.34 (m, 2H), 4.20 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 164.1, 158.6,

151.0, 137.6, 134.8, 134.1, 133.2, 130.8, 130.7, 129.5, 127.7, 127.4, 126.3, 121.1, 120.7, 114.7, 68.1, 66.0, 42.9. HRMS (ESI): calcd for $C_{24}H_{19}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 517.0596, found 517.0593.

4.1.87.

*N-(4-(3-(2-(benzyloxy)ethoxy)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-1-yl)phenyl)-2-chloroacetamide (**103**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and 2-(benzyloxy)ethan-1-ol (61 mg, 0.4 mmol) to give the desired product (90 mg, 85%). Physical state: white solid; Melting point: 156.1-156.7 ^{o}C. TLC: R_f = 0.42 (PE/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.69 – 7.63 (m, 3H), 7.40 – 7.26 (m, 8H), 7.17 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.63 (s, 2H), 4.56 – 4.51 (m, 2H), 4.19 (s, 2H), 3.90 – 3.84 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 164.2, 150.9, 138.1, 137.6, 134.7, 134.1, 133.2, 130.8, 130.6, 128.4, 127.8, 127.7, 127.7, 127.4, 126.3, 120.7, 73.4, 69.3, 68.3, 42.9. HRMS (ESI): calcd for $C_{25}H_{21}Cl_3N_4O_3$ $[M + H]^+$ *m/z* 531.0752, found 531.0744.

4.1.88.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-(2-phenoxyethoxy)ethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**104**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and 2-(2-phenoxyethoxy)ethan-1-ol (73 mg, 0.4 mmol) to give the desired product (32 mg, 28%). Physical state: yellow oil. TLC: R_f = 0.55 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.70 – 7.60 (m, 3H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J*

= 8.7 Hz, 2H), 7.25 – 7.22 (m, 2H), 7.16 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.96 – 6.85 (m, 3H), 4.56 – 4.48 (m, 2H), 4.18 (s, 2H), 4.15 – 4.11 (m, 2H), 3.98 – 3.89 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 164.1, 158.7, 150.8, 137.6, 134.6, 134.0, 133.1, 130.7, 130.5, 129.4, 127.6, 127.3, 126.2, 120.9, 120.6, 114.6, 69.9, 69.6, 69.2, 67.4, 42.9. HRMS (ESI): calcd for $C_{26}H_{23}Cl_3N_4O_4$ $[M + H]^+$ *m/z* 561.0858, found 561.0852.

4.1.89.

*2-Chloro-N-(4-(3-(3-(4-chlorophenoxy)propoxy)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**105**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and 3-(4-chlorophenoxy)propan-1-ol (75 mg, 0.4 mmol) to give the desired product (30 mg, 27%). Physical state: white solid; Melting point: 109.5-111.2 °C. TLC: R_f = 0.44 (PE/EtOAc =2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.75 – 7.61 (m, 3H), 7.39 – 7.28 (m, 3H), 7.23 – 7.16 (m, 3H), 6.86 – 6.80 (m, 2H), 4.54 (t, *J* = 6.0 Hz, 2H), 4.21 (s, 2H), 4.15 (t, *J* = 6.1 Hz, 2H), 2.36 – 2.24 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.1, 157.5, 151.0, 137.6, 134.8, 134.2, 133.3, 130.8, 130.7, 129.4, 127.7, 127.4, 126.4, 125.6, 120.7, 115.9, 66.4, 64.5, 42.9, 29.2. HRMS (ESI): calcd for $C_{25}H_{20}Cl_4N_4O_3$ $[M + H]^+$ *m/z* 565.0362, found 565.0359.

4.1.90.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-(1-methyl-1H-indol-3-yl)ethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**106**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (80 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)ethan-1-ol (42 mg, 0.24 mmol) to give the desired product

(106 mg, 95%). Physical state: pale yellow oil. TLC: R_f = 0.68 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.76 – 7.58 (m, 4H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.26 (m, 3H), 7.24 – 7.16 (m, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.01 (s, 1H), 4.63 (t, *J* = 7.0 Hz, 2H), 4.15 (s, 2H), 3.72 (s, 3H), 3.31 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 164.2, 150.7, 137.6, 136.9, 134.6, 134.0, 133.1, 130.7, 130.5, 127.8, 127.6, 127.4, 127.3, 126.1, 121.5, 120.6, 118.8, 118.8, 110.2, 109.2, 70.0, 42.9, 32.6, 25.1. HRMS (ESI): calcd for $C_{27}H_{22}Cl_3N_5O_2$ $[M + H]^+$ *m/z* 554.0912, found 554.0908.

4.1.91.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(prop-2-yn-1-yloxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**107**)*. Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and prop-2-yn-1-ol (18 mg, 0.32 mmol) to give the desired product (62 mg, 89%). Physical state: pale yellow solid; Melting point: 111.9-113.1 °C. TLC: R_f = 0.57 (CH_2Cl_2/EtOAc = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.71 – 7.62 (m, 3H), 7.38 – 7.31 (m, 3H), 7.21 – 7.17 (m, 1H), 4.99 (d, *J* = 2.5 Hz, 2H), 4.21 (s, 2H), 2.55 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 164.1, 151.2, 137.6, 134.8, 134.1, 133.3, 130.8, 130.7, 127.7, 127.3, 126.3, 120.7, 77.9, 75.6, 57.4, 42.9. HRMS (ESI): calcd for $C_{19}H_{13}Cl_3N_4O_2$ $[M + H]^+$ *m/z* 435.0177, found 435.0187.

4.1.92.

*N-(4-(3-(but-3-yn-1-yloxy)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazol-1-yl)phenyl)-2-chloroacetamide (**108**)*. Following general procedure F, the reaction was conducted from

the corresponding 1*H*-1,2,4-triazol-3-ol (64 mg, 0.16 mmol) and but-3-yn-1-ol (54 mg, 0.4 mmol) to give the crude product, which was used directly without further purification.

4.1.93.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(4-(1-phenyl-1H-1,2,3-triazol-4-yl)butoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**109**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-1,2,4-triazol-3-ol (40 mg, 0.1 mmol) and hex-5-yn-1-ol (20 mg, 0.2 mmol) to give the crude product, which was used directly without further purification.

4.1.94.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**110**).* Following the general procedure G, the click reaction was conducted from **107** (44 mg, 0.1 mmol) and azidobenzene (71 mg, 0.6 mmol) to give the desired product (53 mg, 60%). Physical state: pale yellow solid; Melting point: 158.2-158.8 ^{o}C. TLC: R_f = 0.35 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.17 (s, 1H), 7.82 – 7.64 (m, 5H), 7.53 (t, *J* = 7.7 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.21 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.63 (s, 2H), 4.22 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 164.2, 151.2, 144.2, 137.7, 137.1, 134.9, 134.2, 133.3, 130.8, 130.7, 129.9, 129.0, 127.8, 127.4, 126.4, 121.6, 120.8, 120.7, 63.4, 43.0. HRMS (ESI): calcd for $C_{25}H_{18}Cl_3N_7O_2$ $[M + H]^+$ *m/z* 554.0660, found 554.0686.

4.1.95.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(2-(1-phenyl-1H-1,2,3-triazol-4-yl)ethoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**111**).* Following general procedure G, the click reaction was conducted from **108** (92 mg, 0.2 mmol) and azidobenzene (142 mg, 1.2 mmol) to give the desired product (20 mg, 30%). Physical state: pale yellow solid; Melting point: 195.2-196.4 ^{o}C. TLC: R_f = 0.72 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.99 (s, 1H), 7.77 – 7.61 (m, 5H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.44 – 7.38 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.16 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.68 (t, *J* = 6.2 Hz, 2H), 4.20 (s, 2H), 3.36 (t, *J* = 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 164.2, 151.0, 145.1, 137.7, 137.2, 134.8, 134.1, 133.3, 130.8, 130.7, 129.8, 128.7, 127.7, 127.4, 126.3, 120.7, 120.6, 120.6, 68.6, 43.0, 26.1. HRMS (ESI): calcd for $C_{26}H_{20}Cl_3N_7O_2$ $[M + H]^+$ *m/z* 568.0817, found 568.0807.

4.1.96.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-(4-(1-phenyl-1H-1,2,3-triazol-4-yl)butoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**112**).* Following general procedure G, the click reaction was conducted from **109** (40 mg, 0.08 mmol) and azidobenzene (57 mg, 0.48 mmol) to give the desired product (11 mg, 23%). Physical state: yellow solid; Melting point: 75.5- 76.5 ^{o}C. TLC: R_f = 0.43 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.81 – 7.60 (m, 6H), 7.52 – 7.30 (m, 6H), 7.20 – 7.15 (m, 1H), 4.40 (d, *J* = 5.7 Hz, 2H), 4.21 (s, 2H), 2.89 (d, *J* = 7.1 Hz, 2H), 2.02 – 1.88 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 164.1, 150.9, 148.7, 137.6, 137.3, 134.7, 134.2, 133.2, 130.8, 130.6, 129.8, 128.6, 127.7, 127.5, 126.3, 120.7, 120.5, 119.1, 69.6, 43.0, 28.6, 25.8, 25.3. HRMS (ESI): calcd for $C_{28}H_{24}Cl_3N_7O_2$ $[M + H]^+$ *m/z* 596.1130,

found 596.1114.

4.1.97.

*2-Chloro-N-(4-(3-((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-(3,4-dichlor ophenyl)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**113**).* Following general procedure G, the click reaction was conducted from **107** (65 mg, 0.15 mmol) and 1-azido-2-chlorobenzene (138 mg, 0.90 mmol) to give the desired product (40 mg, 45%). Physical state: yellow solid; Melting point: 101.3-102.1 ^{o}C. TLC: R_f = 0.37 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.18 (s, 1H), 7.72 – 7.65 (m, 3H), 7.64 – 7.60 (m, 1H), 7.59 – 7.55 (m, 1H), 7.48 – 7.42 (m, 2H), 7.38 – 7.30 (m, 3H), 7.19 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.63 (s, 2H), 4.21 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 164.3, 151.1, 143.1, 137.8, 134.8, 134.0, 133.3, 131.0, 130.9, 130.8, 130.7, 128.6, 128.1, 127.8, 127.7, 127.3, 126.3, 125.7, 120.8, 63.1, 43.0. HRMS (ESI): calcd for $C_{25}H_{17}Cl_4N_7O_2$ $[M + H]^+$ *m/z* 588.0271, found 588.0262.

4.1.98.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**114**).* Following general procedure G, the Click reaction was conducted from **107** (65 mg, 0.15 mmol) (65 mg, 0.15 mmol) and 1-azido-2-methoxybenzene (134 mg, 0.90 mmol) to give the desired product (35 mg, 40%). Physical state: yellow solid; Melting point: 110.3-111.1 ^{o}C. TLC: R_f = 0.65 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.33 (s, 1H), 7.85 – 7.78 (m, 1H), 7.76 – 7.66 (m, 3H), 7.48 – 7.42 (m, 1H), 7.41 – 7.33 (m, 3H), 7.22 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.16 – 7.09 (m, 2H), 5.65 (s, 2H), 4.24 (s, 2H),

3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 164.3, 151.2, 151.1, 142.7, 137.8, 134.8, 134.1, 133.3, 130.8, 130.7, 130.3, 127.7, 127.4, 126.3, 126.3, 125.8, 125.6, 121.3, 120.8, 112.4, 63.4, 56.1, 43.0. HRMS (ESI): calcd for $C_{26}H_{20}Cl_3N_7O_3$ $[M + H]^+$ *m/z* 584.0766, found 584.0749.

*4.1.99. 3,4-Dichloro-N-((2-methoxyethyl)carbamothioyl)benzamide (**115**).* The title compound was obtained from **2** (325 mg, 1.4 mmol) and 2-methoxyethan-1-amine (210 mg, 2.8 mmol) in the same conditions described above to prepare compound **3**. Yield: 46%. Physical state: yellow solid; Melting point: 122.9-123.3 °C. TLC: R_f = 0.59 (PE/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.75 (s, 1H), 9.02 (s, 1H), 7.95 (d, *J* = 2.1 Hz, 1H), 7.65 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 3.90 (q, *J* = 5.2 Hz, 2H), 3.66 – 3.61 (m, 2H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 164.6, 138.4, 134.0, 131.7, 131.2, 129.9, 126.4, 69.6, 59.1, 45.8. HRMS (ESI): calcd for $C_{11}H_{12}Cl_2N_2O_2S$ $[M + H]^+$ *m/z* 307.0069, found 307.0069.

4.1.100.

*5-(3,4-Dichlorophenyl)-N-(2-methoxyethyl)-1-(4-nitrophenyl)-1H-1,2,4-triazol-3-amine (**116**).* Following general procedure C with slight modifications, the reaction was initiated from the **115** (128 mg, 0.42 mmol) and 4-nitrophenylhydrazine (64 mg, 0.42 mmol) in DMF to give the desired product (181 mg, 37%). Physical state: brown oil. TLC: R_f = 0.37 (PE/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.2 Hz, 2H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 9.3 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.20 – 7.16 (m, 1H), 4.81 (t, *J* = 5.9 Hz, 1H), 3.63 – 3.59 (m, 2H), 3.55 – 3.51 (m, 2H), 3.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 151.5, 146.5, 142.7, 135.2, 133.6,

130.9, 130.8, 127.9, 127.7, 124.9, 124.6, 71.2, 58.9, 43.2. HRMS (ESI): calcd for $C_{17}H_{15}Cl_2N_5O_3$ $[M + H]^+$ *m/z* 408.0625, found 408.0625.

4.1.101.

*1-(4-Aminophenyl)-5-(3,4-dichlorophenyl)-N-(2-methoxyethyl)-1H-1,2,4-triazol-3-amine (**117**).* Following the general procedure D, the reduction was conducted from compound **116** (49 mg, 0.12 mmol) to give the desired product (33 mg, 73%). Physical State: yellow solid; Melting point: 134.4-134.6 °C. TLC: R_f = 0.17 (PE/EtOAc/CH_2Cl_2 = 2:1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.1 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 4.60 (s, 1H), 3.87 (s, 2H), 3.62 – 3.58 (m, 2H), 3.54 – 3.49 (m, 2H), 3.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 150.4, 147.2, 133.8, 132.9, 130.6, 130.4, 128.9, 128.2, 127.6, 127.0, 115.3, 71.5, 58.8, 43.4. HRMS (ESI): calcd for $C_{17}H_{17}Cl_2N_5O$ $[M + H]^+$ *m/z* 378.0883, found 378.0883.

4.1.102.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-((2-methoxyethyl)amino)-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**118**).* Following general procedure E, the reaction was conducted from the corresponding aniline (10 mg, 0.03 mmol) and 2-chloroacetic acid (4 mg, 0.04 mmol) to give the desired product (9 mg, 64%). Physical state: yellow solid; Melting point: 198.2-198.4 °C. TLC: R_f = 0.15 (CH_2Cl_2/MeOH = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.18 – 7.14 (m, 1H), 4.66 (t, *J* = 5.9 Hz, 1H), 4.21 (s, 2H), 3.63 – 3.58 (m, 2H), 3.55 – 3.50 (m, 2H), 3.40 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 164.0, 150.8, 137.1, 134.7, 134.4, 133.2, 130.7, 130.6, 128.0, 127.7, 126.2, 120.7, 71.4, 58.9, 43.4, 42.9. HRMS (ESI): calcd for $C_{19}H_{18}Cl_3N_5O_2$ $[M + H]^+$ *m/z* 454.0599, found 454.0599.

*4.1.103. 3,4-Dichloro-N-hexanoylbenzamide (**119**).* This compound was synthesized according to the reported procedures with slight modifications.[38,39] To a solution of the 3,4-dichlorobenzamide (190 mg, 1.0 mmol) in hexanoic anhydride (536 mg, 2.5 mmol) was added conc. H_2SO_4 (2 drops) and the mixture heated to reflux (100 ^oC) for 2 h. The resulting mixture was cooled, quenched with *sat.* aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (PE/EtOAc = 8:1) gave a white semi-solid (680 mg). Then the crude product was recrystallized from PE to give the title compound (158 mg, 55%). Physical state: white solid; Melting point: 121.2-122.3 ^oC. TLC: R_f = 0.43 (PE/EtOAc = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.10 (d, *J* = 2.1 Hz, 1H), 7.85 – 7.72 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 2.99 (t, *J* = 7.4 Hz, 2H), 1.75 – 1.67 (m, 2H), 1.43 – 1.28 (m, 4H), 0.98 – 0.83 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 164.0, 137.9, 133.6, 132.6, 130.9, 130.3, 127.2, 37.8, 31.4, 23.8, 22.6, 14.0. HRMS (ESI): calcd for $C_{13}H_{15}Cl_2NO_2$ $[M + H]^+$ *m/z* 288.0553, found 288.0552.

*4.1.104. 5-(3,4-Dichlorophenyl)-1-(4-nitrophenyl)-3-pentyl-1H-1,2,4-triazole (**120**).* This compound was synthesized according to the reported procedures with slight modifications.[52,53] **119** (58 mg, 0.2 mmol), phenyl hydrazine hydrochloride (45 mg, 0.24 mmol), and pyridine (0.5 mL) were placed in a 10 mL round bottom flask. The

reaction was refluxed (120 ^{o}C) until reaction was finished by TLC monitoring (2 h). Then the mixture was diluted with EtOAc (12 mL) and extracted with H_2O (3 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, and then concentrated to give crude product under reduced pressure. The residue was purified by preparative TLC (PE/EtOAc = 8:1) to give the desired product (9 mg, 11%) as a pale yellow solid. Physical state: pale yellow solid; Melting point: 93.7-94.2 ^{o}C. TLC: R_f = 0.34 (PE/EtOAc = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.25 (m, 2H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.1 Hz, 1H), 2.83 – 2.76 (m, 2H), 1.86 – 1.78 (m, 2H), 1.46 – 1.33 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 152.4, 147.2, 142.5, 135.3, 133.7, 131.0, 130.9, 127.9, 127.5, 125.3, 125.0, 31.7, 28.3, 28.0, 22.5, 14.1. HRMS (ESI): calcd for $C_{19}H_{18}Cl_2N_4O_2$ $[M + H]^+$ *m/z* 405.0880, found 405.0872.

*4.1.105. 4-(5-(3,4-Dichlorophenyl)-3-pentyl-1H-1,2,4-triazol-1-yl)aniline (**121**).* Following the general procedure D, the reduction was conducted from compound **120** (56 mg, 0.14 mmol) to give the desired product (38 mg, 73%). Physical State: pale yellow oil. TLC: R_f = 0.41 (PE/EtOAc/CH_2Cl_2 = 4:1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 2.1 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.11 – 7.03 (m, 2H), 6.71 – 6.64 (m, 2H), 3.71 (s, 2H), 2.80 – 2.75 (m, 2H), 1.86 – 1.78 (m, 2H), 1.43 – 1.34 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 151.6, 147.4, 134.1, 133.0, 130.7, 130.4, 128.6, 128.0, 127.7, 126.8, 115.3, 31.8, 28.4, 28.3, 22.5, 14.1. HRMS (ESI): calcd for $C_{15}H_{11}Cl_2N_4O$ $[M + H]^+$ *m/z* 375.1138, found 375.1136.

4.1.106.

*2-Chloro-N-(4-(5-(3,4-dichlorophenyl)-3-pentyl-1H-1,2,4-triazol-1-yl)phenyl)acetamide (**122**).* Following general procedure E, the reaction was conducted from the corresponding aniline (32 mg, 0.09 mmol) and 2-chloroacetic acid (12 mg, 0.13 mmol) to give the desired product (26 mg, 68%). Physical state: white solid; Melting point: 138.8-139.5 ^{o}C. TLC: R_f = 0.35 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.19 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.21 (s, 2H), 2.83 – 2.76 (m, 2H), 1.87 – 1.78 (m, 2H), 1.43 – 1.35 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 164.1, 151.8, 137.5, 134.6, 134.3, 133.3, 130.8, 130.7, 127.8, 127.7, 126.2, 120.7, 42.9, 31.7, 28.4, 28.2, 22.5, 14.1. HRMS (ESI): calcd for $C_{21}H_{21}Cl_3N_4O$ $[M + H]^+$ *m/z* 451.0854, found 451.0844.

*4.1.107. Methyl 3-(3,4-dichlorophenyl)-3-oxopropanoate (**123**).* This compound was synthesized according to known literatures procedure with slight modifications.[54-56] To a solution of 1-(3,4-dichlorophenyl)ethan-1-one (378 mg, 2 mmol) in THF (5 mL) was treated dropwise with a solution of NaH (160 mg, 4 mmol) in THF (3 mL) at 0 ^{0}C and stirred for 30 min. Then the solution was treated dropwise with dimethylcarbonate (900 mg, 10 mmol) at room temperature. The ensuing exothermic reaction refluxed without additional heat for 10 min, after which reflux was continued 2 h with the aid of an external heat source (60 ^{o}C). The semi-solid mixture was cooled to room temperature, EtOAc (40 mL) added and the organic extracts were washed with saturated aqueous NH_4Cl (3 × 20 mL), brine (40 mL) and dried over anhydrous

Na_2SO_4. Filtration of the drying agent and removal of solvent under vacuum, the residue was purified by silica gel chromatography (PE/CH_2Cl_2 = 2:1) to give the desired product (420 mg, 85%) as a pale yellow solid. Physical state: pale yellow solid; Melting point: 52.3-52.7 ^oC. TLC: R_f = 0.49 (PE/EtOAc = 2:1). ^1H NMR (400 MHz, $CDCl_3$) (2.3:1 keto:enol ratio) δ 12.43 (s, 1H), 7.98 (d, *J* = 2.1 Hz, 2.3H), 7.81 (d, *J* = 2.1 Hz, 1H), 7.73 (dd, 2.3H), 7.56 – 7.50 (m, 3.3H), 7.44 (d, *J* = 8.4 Hz, 1H), 5.61 (s, 1H), 3.95 (s, 4.6H), 3.78 (s, 3H), 3.73 (s, 6.9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 173.2, 168.7, 167.3, 138.5, 135.4, 135.4, 133.6, 133.3, 133.1, 130.9, 130.6, 130.4, 128.0, 127.6, 125.1, 88.1, 52.7, 51.7, 45.5. HRMS (ESI): calcd for $C_{10}H_8Cl_2O_3$ $[M + H]^+$ *m/z* 246.9923, found 246.9939.

*4.1.108. 3-(3,4-Dichlorophenyl)-1-(4-nitrophenyl)-1H-pyrazol-5-ol (**124**).* This compound was synthesized according to the reported procedures with slight modifications.[41] To a solution of **123** (294 mg, 1.2 mmol) in EtOH (3 mL) was added (4-nitrophenyl)hydrazine (183 mg, 1.2 mmol). The mixture was stirred at 90 ^oC for 3.5 h. After cooling, the mixture was poured into water, and the precipitated solid was collected by filtration and washed with water to give a brown solid (360 mg, 86%). The product was used for the subsequent step without further purification. Physical state: brown solid; Melting point: 234.4-235.0 ^oC. TLC: R_f = 0.49 (PE/EtOAc = 2:1). ^1H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 8.37 (d, *J* = 9.3 Hz, 2H), 8.21 (d, *J* = 9.3 Hz, 2H), 8.12 (d, *J* = 2.0 Hz, 1H), 7.89 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 6.23 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.8, 149.5, 144.4, 144.1, 133.8, 132.0, 131.2, 131.1, 127.3, 125.8, 125.2, 120.6, 86.8. HRMS (ESI): calcd for

$C_{15}H_9Cl_2N_3O_3$ $[M + H]^+$ *m/z* 350.0094, found 350.0088.

*4.1.109. 3-(3,4-Dichlorophenyl)-5-(2-methoxyethoxy)-1-(4-nitrophenyl)-1H-pyrazole (**125**).* Following general procedure F, the reaction was conducted from the corresponding 1*H*-pyrazol-5-ol (175 mg, 0.5 mmol) and 2-methoxyethan-1-ol (76 mg, 1.0 mmol) to give the desired product (115 mg, 47%). Physical state: yellow solid; Melting point: 166.6-167.2 °C. TLC: R_f = 0.48 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.2 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.67 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 6.03 (s, 1H), 4.54 – 4.24 (m, 1H), 3.98 – 3.71 (m, 1H), 3.47 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 149.7, 145.0, 143.6, 132.9, 132.7, 132.4, 130.6, 127.4, 124.7, 124.7, 120.9, 85.1, 72.1, 70.3, 59.2. HRMS (ESI): calcd for $C_{18}H_{15}Cl_2N_3O_4$ $[M + H]^+$ *m/z* 408.0512, found 408.0506.

*4.1.110. 4-(3-(3,4-Dichlorophenyl)-5-(2-methoxyethoxy)-1H-pyrazol-1-yl)aniline (**126**).* Following the general procedure D, the reduction was conducted from compound **125** (41 mg, 0.1 mmol) to give the desired product (37 mg, 98%). Physical state: yellow solid; Melting point: 126.5-127.0 °C. TLC: R_f = 0.27 (PE/CH_2Cl_2 = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.0 Hz, 1H), 7.67 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.97 (s, 1H), 4.58 – 4.04 (m, 2H), 3.98 – 3.65 (m, 2H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 147.5, 145.3, 133.8, 132.6, 131.3, 130.4, 129.8, 127.1, 124.5, 124.1, 115.0, 83.8, 71.6, 70.4, 59.2. HRMS (ESI): calcd for $C_{18}H_{17}Cl_2N_3O_2$ $[M + H]^+$ *m/z* 378.0771, found 378.0764.

4.1.111.

*2-Chloro-N-(4-(3-(3,4-dichlorophenyl)-5-(2-methoxyethoxy)-1H-pyrazol-1-yl)phenyl) acetamide (**127**).* Following general procedure E, the reaction was conducted from the corresponding aniline (26 mg, 0.07 mmol) and 2-chloroacetic acid (10 mg, 0.10 mmol) to give the desired product (24 mg, 77%). Physical state: pale yellow solid; Melting point: 120.2-120.9 ^{o}C. TLC: R_f = 0.25 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.78 – 7.53 (m, 3H), 7.45 (d, *J* = 8.4 Hz, 1H), 5.97 (s, 1H), 4.45 – 4.25 (m, 1H), 4.20 (s, 2H), 3.99 – 3.66 (m, 1H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 155.2, 148.2, 135.5, 134.9, 133.4, 132.7, 131.7, 130.5, 127.2, 124.6, 122.6, 120.3, 84.2, 71.8, 70.4, 59.2, 42.8. HRMS (ESI): calcd for $C_{20}H_{18}Cl_3N_3O_3$ $[M + H]^+$ *m/z* 454.0487, found 454.0482.

*4.1.112. 5-(3,4-Dichlorophenyl)-1H-pyrazol-3-ol (**128**).* The title compound was obtained from **123** (490 mg, 2.0 mmol) and hydrazine hydrate (80 w.t%, 188 mg, 3.0 mmol) in the same conditions described above to prepare compound **124**. Yield: 46%. Physical state: white solid; Melting point: 201.9-202.5^{o}C. TLC: R_f = 0.50 (PE/EtOAc = 1:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (d, *J* = 670.7 Hz, 2H), 7.93 (d, *J* = 1.9 Hz, 1H), 7.67 – 7.58 (m, 2H), 5.98 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 131.6, 130.9, 129.8, 126.3, 124.9. HRMS (ESI): calcd for $C_9H_6Cl_2N_2O$ $[M + H]^+$ *m/z* 228.9930, found 228.9925.

*4.1.113. 5-(3,4-Dichlorophenyl)-3-(4-nitrophenoxy)-1H-pyrazole (**129**).* This compound was synthesized according to the reported procedures with slight modifications.[42] To a solution of **128** (115 mg, 0.5 mmol), 1-bromo-4-nitrobenzene (101 mg, 0.5 mmol), *L*-proline (12 mg, 0.1 mmol) in DMSO (2 mL) was added CuI

(10 mg, 0.05 mmol) and Cs_2CO_3 (165 mg, 0.5 mmol) under argon. The mixture was stirred for 2.5 h at 90 °C. Then the mixture was cooled to room temperature, EtOAc (40 mL) added and the organic extracts were acidification with 0.5 mol/L HCl (3 x 20 mL) to pH 1-2, washed with H_2O (1 x 20 mL), brine (1 x 20 mL) and dried over anhydrous Na_2SO_4. Filtration of the drying agents and removal of solvent under vacuum, the residue was purified by silica gel chromatography (CH_2Cl_2/EtOAc = 30:1) to give the desired product (103 mg, 59%) as a pale yellow solid. Physical state: pale yellow solid; Melting point: 170.2 - 171.0 °C. TLC: R_f = 0.60 (CH_2Cl_2/EtOAc = 30:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 8.26 (d, J = 9.2 Hz, 2H), 8.17 – 7.86 (m, 1H), 7.89 – 7.51 (m, 2H), 7.31 (d, J = 9.2 Hz, 2H), 6.73 (d, J = 2.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.9, 159.0, 142.5, 141.4, 131.9, 131.2, 130.9, 129.3, 126.8, 126.0, 125.1, 117.2, 92.7. HRMS (ESI): calcd for $C_{15}H_9Cl_2N_3O_3$ $[M + H]^+$ *m/z* 350.0094, found 350.0077.

*4.1.114. 3-(3,4-Dichlorophenyl)-1-(2-methoxyethyl)-5-(4-nitrophenoxy)-1H-pyrazole (**130**)*. Following general procedure F, the reaction was conducted from the **129** (140 mg, 0.4 mmol) and 2-methoxyethan-1-ol (152 mg, 2.0 mmol) to give the desired product (118 mg, 72%). Physical state: white solid; Melting point: 83.6-84.0 °C. TLC: R_f = 0.45 (PE/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.22 (m, 2H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.56 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.23 (m, 2H), 6.08 (s, 1H), 4.23 (t, *J* = 5.4 Hz, 2H), 3.77 (t, *J* = 5.3 Hz, 2H), 3.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 150.2, 148.1, 144.0, 133.4, 132.9, 131.8,

130.6, 127.1, 126.0, 124.6, 117.3, 89.5, 70.5, 58.8, 47.6. HRMS (ESI): calcd for $C_{18}H_{15}Cl_2N_3O_4$ $[M + H]^+$ *m/z* 408.0512, found 408.0508.

*4.1.115. 4-((3-(3,4-Dichlorophenyl)-1-(2-methoxyethyl)-1H-pyrazol-5-yl)oxy)aniline (**131**).* Following the general procedure D, the reduction was conducted from compound **130** (25 mg, 0.06 mmol) to give the desired product (22 mg, 96%). Physical state: pale yellow oil. TLC: R_f = 0.75 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 2.0 Hz, 1H), 7.51 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 5.70 (s, 1H), 4.27 (t, *J* = 5.8 Hz, 2H), 3.82 (t, *J* = 5.8 Hz, 3H), 3.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 148.8, 147.5, 143.0, 133.9, 132.7, 131.3, 130.5, 127.1, 124.5, 119.9, 116.5, 86.2, 70.7, 58.9, 47.0. HRMS (ESI): calcd for $C_{18}H_{17}Cl_2N_3O_2$ $[M + H]^+$ *m/z* 378.0771, found 378.0782.

4.1.116.

*2-Chloro-N-(4-((3-(3,4-dichlorophenyl)-1-(2-methoxyethyl)-1H-pyrazol-5-yl)oxy)phenyl)acetamide (**132**).* Following general procedure E, the reaction was conducted from the corresponding aniline (17 mg, 0.05 mmol) and 2-chloroacetic acid (9 mg, 0.09 mmol) to give the desired product (16 mg, 80%). Physical state: pale yellow oil. TLC: R_f = 0.45 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.63 – 7.51 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 9.0 Hz, 2H), 5.84 (s, 1H), 4.27 (t, *J* = 5.7 Hz, 2H), 4.21 (s, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 153.3, 152.8, 147.6, 133.6, 133.3, 132.7, 131.4, 130.4, 127.0, 124.4, 121.8, 118.7, 87.3, 70.5, 58.8, 47.1, 42.8. HRMS (ESI): calcd for $C_{20}H_{18}Cl_3N_3O_3$ $[M + H]^+$ *m/z* 454.0487, found 454.0478.

*4.1.117. Methyl 2-(4-nitrophenyl)-5-oxo-2,5-dihydro-1H-pyrazole-3-carboxylate (**133**).* This compound was synthesized according to the reported procedures with slight modifications.[44] To a solution of (4-nitrophenyl)hydrazine (995 mg, 6.5 mmol), dimethyl but-2-ynedioate (1.11 g, 7.8 mmol) in 7 mL toluene was added AcOH (0.5 mL) at 0 °C. After 1 h, the mixture was allowed to react at 100 °C for another 4 h. The resulting precipitate was collected by filtration, and washed with toluene to give the desired product (1.11 g, 65%) as a gray solid. Physical state: gray solid; Melting point: 228.6-229.0 °C. TLC: R_f = 0.76 (CH_2Cl_2/MeOH = 10:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.28 (m, 2H), 8.08 (d, J = 8.7 Hz, 2H), 6.00 (s, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 154.9, 145.2, 143.6, 143.3, 125.0, 121.6, 89.7, 52.0. HRMS (ESI): calcd for $C_{11}H_9N_3O_5$ [M + H] $^+$ *m/z* 264.0615, found 264.0610.

*4.1.118. Methyl 3-(2-methoxyethoxy)-1-(4-nitrophenyl)-1H-pyrazole-5-carboxylate (**134**).* Following general procedure F, the reaction was conducted from **133** (53 mg, 0.2 mmol) and 2-methoxyethan-1-ol (61 mg, 0.8 mmol) to give the desired product (51 mg, 80%). Physical state: white solid; Melting Point: 161.5-162.1 °C. TLC: R_f = 0.57 (PE/EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 9.1 Hz, 2H), 8.05 (d, J = 8.9 Hz, 2H), 6.24 (s, 1H), 4.40 – 4.25 (m, 2H), 3.93 (s, 3H), 3.81 – 3.72 (m, 2H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 155.5, 145.9, 144.0, 143.0, 124.6, 122.3, 89.5, 72.4, 70.2, 59.2, 52.4. HRMS (ESI): calcd for $C_{14}H_{15}N_3O_6$ [M + H]$^+$ *m/z* 322.1034, found 322.1028.

4.1.119. Methyl 1-(4-aminophenyl)-3-(2-methoxyethoxy)-1H-pyrazole-5-carboxylate

*(**135**).* Following the general procedure D, the reduction was conducted from compound **134** (84 mg, 0.26 mmol) to give the desired product (63 mg, 83%). Physical State: yellow oil. TLC: R_f = 0.45 (CH_2Cl_2/MeOH = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 6.17 (s, 1H), 4.20 (t, *J* = 4.6 Hz, 2H), 3.88 (s, 3H), 3.67 (t, *J* = 4.6 Hz, 2H), 3.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 154.3, 146.1, 141.6, 129.0, 124.7, 114.8, 88.5, 71.7, 70.3, 59.1, 52.0. HRMS (ESI): calcd for $C_{14}H_{17}N_3O_4$ $[M + H]^+$ *m/z* 292.1292, found 292.1284.

*4.1.120. Methyl 1-(4-(2-chloroacetamido)phenyl)-3-(2-methoxyethoxy)-1H-pyrazole-5- carboxylate (**136**).* Following general procedure E, the reaction was conducted from the corresponding aniline (46 mg, 0.16 mmol) and 2-chloroacetic acid (23 mg, 0.24 mmol) to give the desired product (40 mg, 69%). Physical state: white solid; Melting point: 134.7-135.2 ^{o}C. TLC: R_f = 0.38 (CH_2Cl_2/MeOH = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.76 – 7.58 (m, 4H), 6.20 (s, 1H), 4.25 (t, *J* = 4.5 Hz, 2H), 4.17 (s, 2H), 3.91 (s, 3H), 3.71 (t, *J* = 4.5 Hz, 2H), 3.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 162.8, 154.7, 142.5, 136.1, 134.6, 123.6, 120.3, 88.9, 72.0, 70.3, 59.2, 52.2, 43.0. HRMS (ESI): calcd for $C_{16}H_{18}ClN_3O_5$ $[M + H]^+$ *m/z* 368.1008, found 368.1000.

4.2. Biology

4.2.1. Cell culture. Toledo (ABC-DLBCL) and Jurkat cells were cultured in RPMI 1640 medium (Invitrogen) supplemented with 10% fetal bovine serum (FBS).

4.2.2. Cell viability CCK-8 assay. Cells were seeded at a density of 2×10^4 cells/well

in 96-well plates and incubated with MI-2 analogous for 48 h. MI-2 was selected as positive control, while DMSO was negative control. After that, 10 μL of CCK-8 solution (Dojindo) was added to each well, and the culture plates were further incubated for additional 3 h at 37 ^{o}C. Optical density (OD) was measured using a scanning multi-well spectrophotometer (BioTek, Winooski, VT, USA) at a wavelength of 450 nm. Each experiment was performed in triplicate and repeated.

4.2.3. Western blot assay. Jurkat T Cells were seeded at a density of 9×10^5 cells/well in 12-well plates and treated with MI-2 analogues or DMSO for 4 h prior to 1 h MG132 (10 μM; Sigma) incubation. After that, stimulation of cells were initiated by the addition of phorbol 12-myristate 13-acetate (PMA; 200 ng/mL; Sigma) and ionomycin (I; 300 ng/mL; Beyotime) for 1 h and harvested for Western blot analysis. Antibodies used were MALT1 (2494S, Cell signaling), RelB (4922S, Cell signaling), β-actin (66009-1-lg; Proteintech).

Appendix A. Supplementary data

Supplementary data related to this article (detailed procedures, ^{1}H and ^{13}C NMR spectra of all new compounds) can be found at http://dx.doi.org/xxx.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This study was supported by grants from "Personalized Medicines – Molecular Signature-based Drug Discovery and Development", a Strategic Priority Research Program of the Chinese Academy of Sciences (XDA12010303 to C. Chen), the National Nature Science Foundation of China (81325016 and U1602221 to C. Chen, 81322038, 81272930 and U1502222 to R. Liu, 81402781 to H. Chen), the Yunnan Applied Basic Research Key Projects (2015FA027 to R. Liu), the West Light Foundation of the Chinese Academy of Sciences (to R. Liu), the Youth Innovation Promotion Association and the Chinese Academy of Sciences (to R. Liu), Scientific Research Foundation for Returned Overseas Chinese Scholars (to H. Chen).

ABBREVIATIONS USED

NHL: non-Hodgkin lymphoma. DLBCL: diffuse large B-cell lymphoma. ABC-DLBCL: the activated B cell-like DLBCL. MALT1: mucosa-associated lymphoid tissue protein-1. NF-κB: nuclear factor κB. CARMA1: CARD-containing MAGUK protein 1 (CARD11, caspase recruitment domain family member 11). BCL10: B-cell lymphoma 10. IKK: IkappaB kinase. A20 (also called TNFAIP3): tumor necrosis factor, α-induced protein 3. CYLD: cylindromatosis. Z-VRPR-FMK: Z, benzyloxycarbonyl; VRPR, tetrapeptide substrate Val-Arg-Pro-Arg; FMK, fluoromethyl ketone. SAR: structure–activity relationships. EDCI: 3-(ethyliminomethylideneamino)-*N*,*N*-dimethylpropan-1-amine,hydrochloride. DIAD: diisopropyl azodicarboxylate.

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