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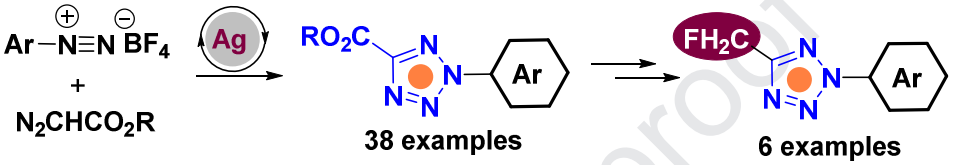

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Regioselective Synthesis of Carboxylic and Fluoromethyl Tetrazoles Enabled by Silver-Catalyzed Cycloaddition of Diazoacetates and Aryl Diazonium Salts

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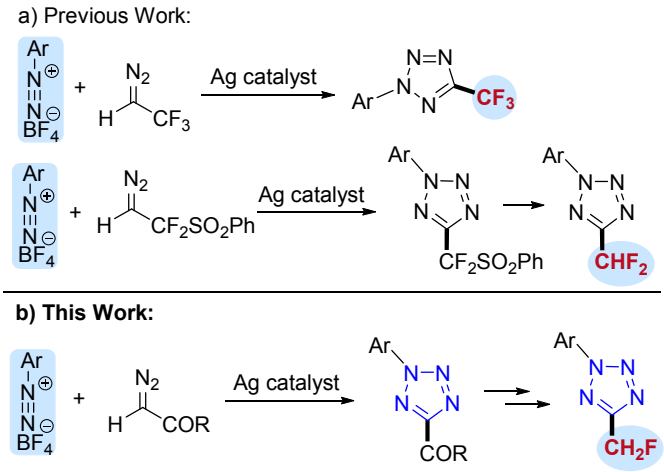
ABSTRACT

Here we present a dipolar [3 + 2] cycloaddition transformation of diazoacetates with arenediazonium salts under silver catalysis, thus offering a straightforward approach for the regioselective construction of carboxylic tetrazoles. Several merits are accompanied with this reaction including readily available starting reagents, broad coupling scope, high yields, and friendly reaction conditions. The synthetic value is further showcased by one-pot conversion of commercially available primary arylamines to tetrazoles and successful transformations of the cycloadducts into valuable 5-fluoromethyltetrazoles and an analogue of P2X3 receptor antagonist.

1. Introduction

Diazoacetates are an important class of building blocks in the realm of synthetic chemistry.[1] By harnessing their versatile reactivity, a large variety of organic transformations have been reported over the past decades, among which are X-Y insertions (X = C, O, N, S, Si etc.; Y = H, O, N, S, etc.),[2] cyclopropanation,[3] migration,[4] ylide rearrangement,[5] and multi-component reactions (MCR).[6] In particular, diazoacetates can also serve as competitive 1,3-dipoles to undergo direct dipolar cycloaddition (DPC) reactions.[7] Notably, such DPC transformations could fully entail the diazo group for the efficient preparation of various pharmaceutically important *N*-containing heterocycles, which is arguably in line with the tenet of atom economy and green chemistry. However, simple hydrocarbon dipolarophiles such as alkenes and alkynes have been extensively studied in most previous reports en route to pyrazolines and pyrazoles, whereas the 1,3-dipolar reactivity of diazoacetates with other hybrid reaction components remains far less investigated. In this context, our group recently demonstrated that aryl diazonium tetrafluoroborate[8] could serve as a feasible dipolarophile to react with trifluorodiazoethane (CF_3CHN_2) and masked difluorodiazoethane ($PhSO_2CF_2CHN_2$) to produce different functionalized tetrazole architectures, respectively (Scheme 1a).[9] From a diversity-oriented synthetic point of view, the development of efficient methods to produce monofluoromethyl tetrazoles by means of this strategy undoubtedly would be equally desirable.[10] More importantly, the



Scheme 1. Synthesis of CF_3-, CHF_2-, and CH_2F-tetrazoles from aryl diazonium salts and diazo compounds.

tetrazole derivatives have been extensively utilized in a wide range of pharmaceuticals, agrochemicals, and materials science at a remarkably increasing level.[11] Therefore, herein we report our exhaustive investigation of the silver-catalyzed [3 + 2] cycloaddition reactions of diazoacetates and α-diazo acetophenones with aryl diazonium salts including optimization of reaction conditions, substrate scope evaluation in terms of both diazocarbonyl compounds and aryl diazonium salts, as well as further synthetic transformations to 5-fluoromethyltetrazoles

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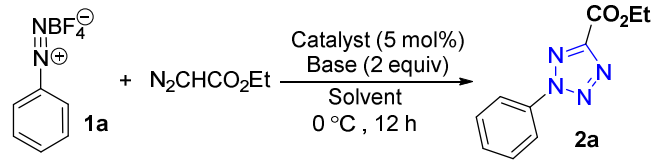
which are otherwise difficult to access via conventional methods (Scheme 1b).

2. Results and discussion

As an outset of this study, we first evaluated the effect of various base on the reactivity of phenyl diazonium tetrafluoroborate **1a** with ethyl diazoacetate under the catalysis of AgOAc (5 mol%) in a co-solvent of THF and DMF (v/v, 20/1) at 0 °C (entries 1–10, Table 1). Compared with Cs_2CO_3, which successfully promoted this reaction to give cycloadduct **2a** in 75% yield in our primary report (entry 1),[9] stronger bases led to significantly decreased yields (entries 2–4), whereas weaker bases brought about comparable or even better results (entries 5–10), and Na_2CO_3 proved to be the optimal choice to deliver the desired 2,5-disubstituted tetrazole **2a** in 82% yield as a single regio-isomer (entry 6). Subsequent catalyst screening indicated that when other silver salts such as $AgNO_3$, AgOTf, $AgSbF_6$, $AgBF_4$, Ag_2CO_3, Ag_3PO_4 and AgF were used, no obvious improvement was observed (entries 11–17). Reducing the loadings of AgOAc or ethyl diazoacetate both resulted in inferior yields (entries 18 and 19), and control experiments revealed that both the silver catalyst and base are pivotal for the success of this reaction (entries 20 and 21). Further examination on the solvent effect (entries 22–26) demonstrated that THF proved to be a better reaction medium and the yield could be finally increased to 86% (entry 22).

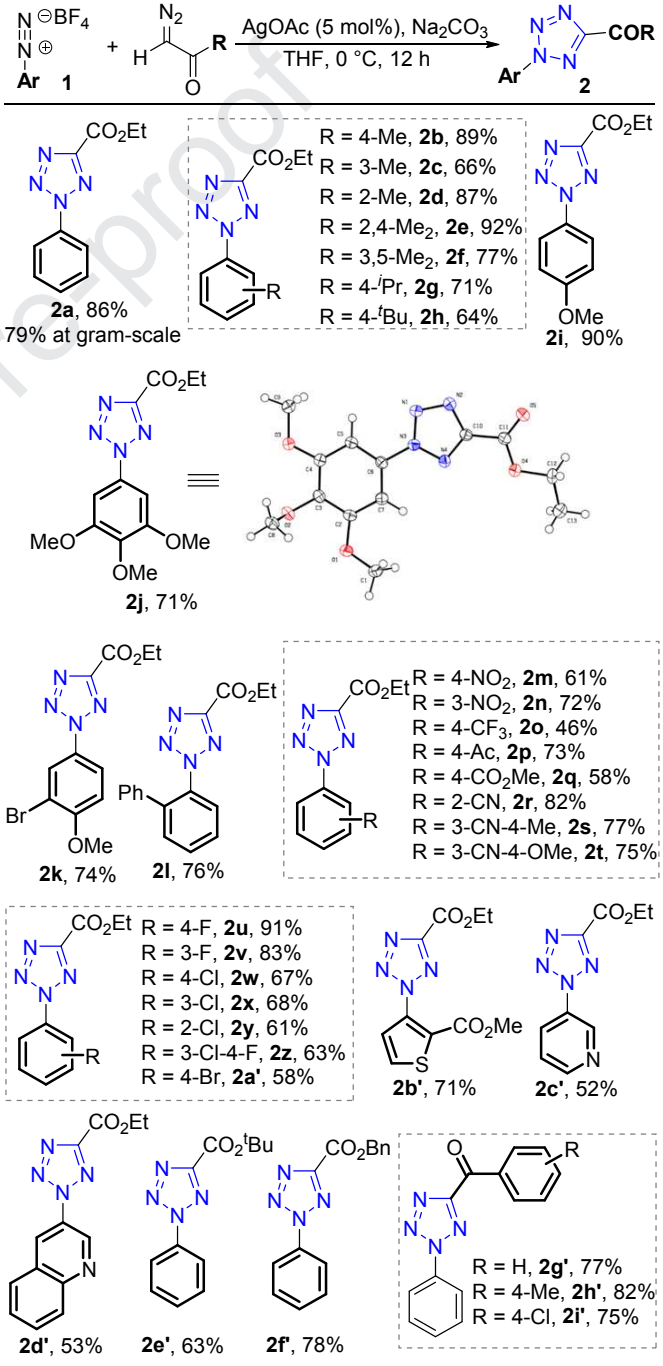
Table 1. Screening studies. [a]



Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	AgOAc	Cs_2CO_3	THF+DMF	75
2	AgOAc	NaOH	THF+DMF	nr
3	AgOAc	EtONa	THF+DMF	62
4	AgOAc	^{t}BuOK	THF+DMF	nr
5	AgOAc	K_2CO_3	THF+DMF	77
6	AgOAc	Na_2CO_3	THF+DMF	82
7	AgOAc	Li_2CO_3	THF+DMF	76
8	AgOAc	$NaHCO_3$	THF+DMF	76
9	AgOAc	NaOAc	THF+DMF	79
10	AgOAc	KOAc	THF+DMF	74
11	$AgNO_3$	Na_2CO_3	THF+DMF	71
12	AgOTf	Na_2CO_3	THF+DMF	64
13	$AgSbF_6$	Na_2CO_3	THF+DMF	63
14	$AgBF_4$	Na_2CO_3	THF+DMF	37
15	Ag_2CO_3	Na_2CO_3	THF+DMF	trace
16	Ag_3PO_4	Na_2CO_3	THF+DMF	trace
17	AgF	Na_2CO_3	THF+DMF	nr
18	AgOAc	Na_2CO_3	THF+DMF	44
19	AgOAc	Na_2CO_3	THF+DMF	60
20	-	Na_2CO_3	THF+DMF	nr
21	AgOAc	-	THF+DMF	nr
22	**AgOAc**	**Na_2CO_3**	**THF**	**86**
23	AgOAc	Na_2CO_3	DMF	67
24	AgOAc	Na_2CO_3	CH_2Cl_2	21
25	AgOAc	Na_2CO_3	MeCN	48
26	AgOAc	Na_2CO_3	toluene	62

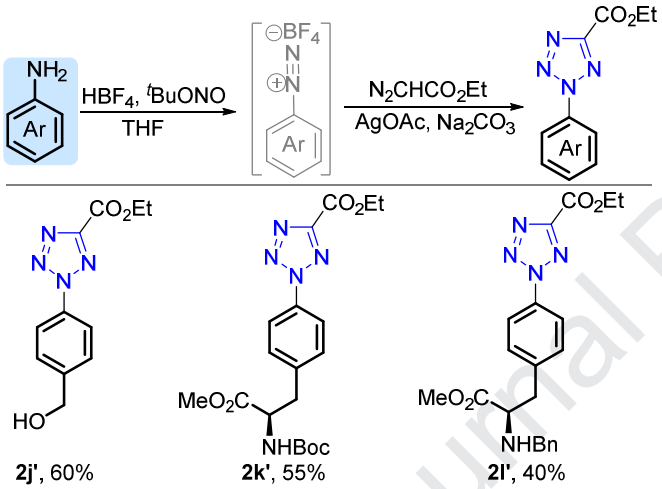
[a] General [3 + 2] DPC conditions: phenyl diazonium tetrafluoroborate **1a** (0.3 mmol), N_2CHCO_2Et (0.6 mmol), silver salt (5 mol%) and base (0.6 mmol) in 3 mL of indicated solvent at 0 °C for 12 h; THF/DMF = 20:1 was used as mixed solvent unless otherwise noted.
[b] Yield of isolated product.
[c] AgOAc (1 mol%).
[d] N_2CHCO_2Et (0.45 mmol).

The substrate scope of arenediazonium salts **1** with ethyl diazoacetate was then investigated under the established conditions. As depicted in Scheme 2, for general phenyl diazonium salts, a broad spectrum of substituents including alkyl (**2a**–**2h**), alkoxyl (**2i**–**2k**), phenyl (**2l**), nitro (**2m** and **2n**), trifluoromethyl (**2o**), acetyl (**2p**), alkoxylcarbonyl (**2q**) and cyano (**2r**–**2t**) were all well tolerated to give the expected di-substituted carboxylic tetrazoles in moderate to high yields (46–92%).



Scheme 2. Regioselective synthesis of carboxylic tetrazoles from arenediazonium salts **1** and diazoacetates.

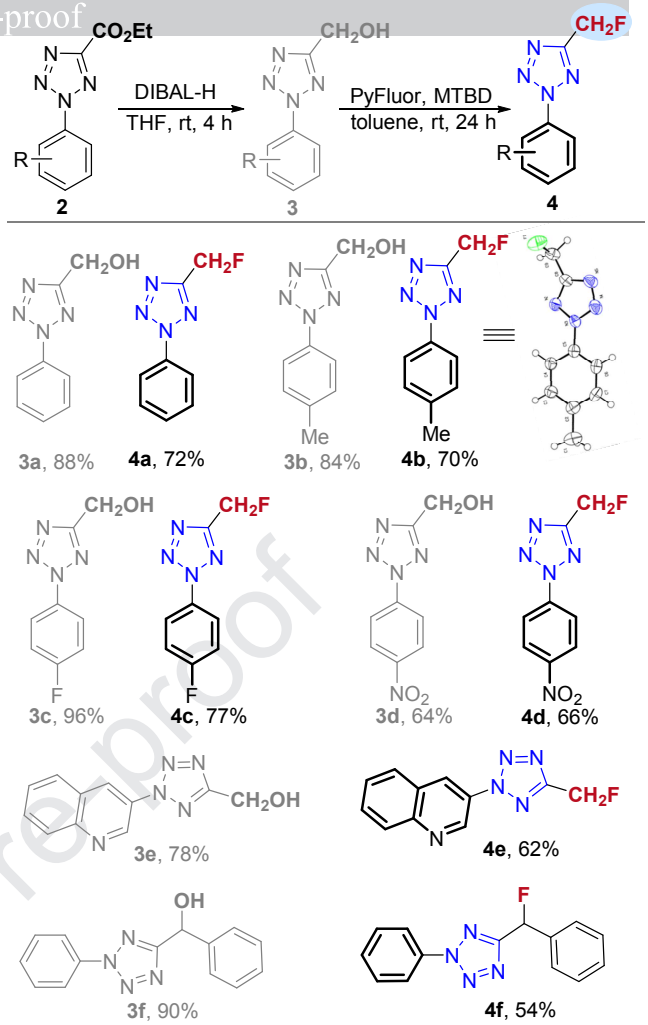
Cycloadduct **2a** could also be prepared in a gram-scale despite with a slightly decreased yield (79%). Notably, various halogen-containing phenyl diazonium salts participated in the [3 + 2] cycloaddition transformation to furnish **2u**–**2a'** in 58–91% yields, which provides new opportunity for further elaborations on these tetrazole derivatives via transition-metal-mediated cross-coupling reactions. In addition, steric effect has no obvious influence on the reaction outcome as evident by the observed high yields for *ortho*-substituted substrates (**2d**, **2e**, **2l**, **2r** and **2y**). Furthermore, hetero-aryl diazonium salts such as 3-thienyl, 3-pyridyl, and 3-quinolyl ones, also proved to be compatible coupling partners, thereby affording the expected products **2b'**–**2d'** in decent yields. As far as diazo compounds are concerned, the substrate scope is not only limited to ethyl diazoacetate. Other diazo reagents such as tert-butyl or benzyl diazo-acetate as well as α-diazo acetophenones also proved to be viable 1,3-dipolar partners, and the corresponding tetrazoles **2e'**–**2i'** were routinely afforded in practical to high yields. It should be noted that exclusive regioselectivity was observed in all cases among the tested substrates. The molecular structure was further unambiguously determined via X-ray analysis of **2j**, and the other compounds are assigned by analogy.[12]



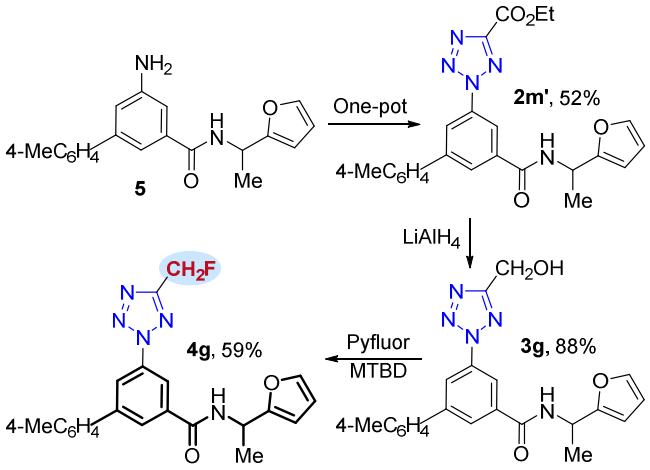
Scheme 3. Regioselective synthesis of free alcohol- or amino acid-containing tetrazoles.

Since arenediazonium salts are not commercially obtainable, and some of them are difficult to separate and purify, we then evaluate the feasibility of performing a one-pot synthesis of 2-aryl tetrazolic esters directly from primary arylamines. As a proof of concept, we chose 4-hydroxylmethylaniline as the starting material, with which we failed to separate the corresponding aryl diazonium salt. To our delight, the tandem diazotization/cycloaddition transformation in one-pot operation readily proceeded to yield the expected cycloadduct **2j'** with good efficiency (Scheme 3). Notably, phenylalanine-derived diazonium salts were also well compatible with the current platform, and the desired amino-acid-containing tetrazoles **2k'** and **2l'** were isolated in 55% and 40% yield, respectively. It should be mentioned that the incorporation of tetrazole motif into amino acids may offer novel bioorthogonal chemical handles for fluorescent labelling in biological studies.[13]

Introducing fluorine atoms into organic small molecules has recognized as a powerful approach to alter physico-chemical and biological properties of parent targets.[14] Compared with the recent progress in accessing trifluoromethyl- and difluoromethyl-tetrazoles,[9] the corresponding monofluoromethyl tetrazole analogues still remain a curiosity. Therefore, we continued our study in transforming cycloadducts **2** to monofluoromethyl tetrazoles. As outlined in Scheme 4, diisobutylaluminum hydride



Scheme 4. Scope of (2-Aryl-2*H*-tetrazol-5-yl)methanol **3** and 5-(Fluoromethyl)-2-aryl-2*H*-tetrazole **4**.



cheme 5. Preparation of CH_2F-functionalized P2X3 receptor antagonist.

(DIBAL-H) readily reduced the cycloadducts **2** into the corresponding tetrazolic alcohols **3** in 64–96% yields under mild conditions, and the hydroxyl moiety could then be successfully converted to fluorine in the presence of 2-pyridinesulfonyl fluoride (PyFluor) and a bicyclic strong guanidine base (MTBD).[15] As a result, a series of 2-aryl-5-fluoromethyltetrazole derivatives **4** were ultimately obtained in 42–74% total yields over two steps. Among them, fluoromethyl tetrazole **4b** was crystallized and analyzed by X-ray diffraction.[12] Ketone-substituted tetrazole **2g'** could also be easily converted to

corresponding α-phenyl fluoromethyl tetrazole **4f** in 49% total yield.

To further showcase the practicality of this protocol, we devoted our attention to the synthesis of CH_2F-functionalized P2X3 receptor antagonist.[16] As depicted in Scheme 5, tetrazole-carboxylate **2m'** could be smoothly prepared in 52% yield by treating easily accessible primary aryl amine **5** under standard one-pot conditions. Subsequently, a reduction/fluorination sequence reaction of **2m'** occurred to deliver the target monofluoromethyltetrazole analogue **4g** in 52% total yield.

In conclusion, a [3 + 2] DPC transformation of arenediazonium salts with diazoacetates and α-diazo acetophenones was established via silver catalysis. Under gentle reaction conditions, a broad array of 2-aryltetrazole-5-carboxylates and 2-aryltetrazole-5-ketones were regioselectively achieved in good to high yields. This protocol's practicality was further highlighted via convenient one-pot protocol directly from primary arylamines, and facile transformation of the cycloadducts into 5-monofluoromethyltetrazoles as well as an analogue of a P2X3 receptor antagonist. Future investigations on the mechanistic elucidation and applications of these functionalized tetrazoles are underway in our laboratory.

3. Experimental section

3.1. Synthesis of tetrazoles 2 from the corresponding arenediazonium salts 1 (Method A).

An oven-dried Schlenk tube equipped with a magnetic stir bar was charged with AgOAc (2.6 mg, 0.015 mmol, 5 mol%) and Na_2CO_3 (63.6 mg, 0.6 mmol, 2 equiv). Then THF (3 mL) and N_2CHCO_2Et (68.5 mg, 0.6 mmol, 2 equiv) were added. The resulting suspension was stirred at 0 °C for 10 minutes before the aryl diazonium salts **1** (0.3 mmol) was added in one portion. The resulting mixture was allowed to stir at 0 °C for 12 hours. Then the mixture was filtered through a Celite plug, rinsed with ethyl acetate. The resulting clear organic solution was concentrated under reduced pressure, and the residue was further purified by a silica gel column chromatography (eluant: petroleum ether/ethyl acetate = 30:1) to yield the corresponding ethyl 2-aryl-2*H*-tetrazole-5-carboxylate **2**.

3.2. Synthesis of tetrazoles 2 from the corresponding aniline derivatives (Method B).

An oven-dried Schlenk tube equipped with a magnetic stir bar was charged with anilines (0.2 mmol), then dry THF (4 mL) were added. To the resulting solution which was precooled to 0 °C, aqueous HBF_4 (30 μL, 50% in water, 0.4 mmol, 2.0 equiv) was added. After 5 minutes, ^{t}BuONO (54 μL, 0.4 mmol, 2.0 equiv) was added subsequently. The mixture was allowed to stir at 0 °C for 15 minutes before N_2CHCO_2Et (45.7 mg, 0.4mmol, 2 equiv.) was added. After that, AgOAc (1.7 mg, 0.01 mmol, 5 mol%) and Na_2CO_3 (63.6 mg, 0.6 mmol, 3 equiv) were added together. After addition was complete, the mixture was stirred at 0 °C for additional 12 hours. Then the mixture was filtered through a Celite plug, rinsed with ethyl acetate. The resulting clear organic solution was concentrated under reduced pressure, and the residue was further purified by a silica gel column chromatography (eluant: petroleum ether/ethyl acetate = 10:1) to yield the corresponding ethyl 2-aryl-2*H*-tetrazole-5-carboxylate **2**.

3.3. Synthesis of fluoromethyl tetrazoles 4 from the corresponding carboxylic tetrazoles 2.

To a solution of compounds **2** (0.2 mmol, 1.0 equiv.) in 3 mL THF was added dropwise DIBAL-H in hexane (0.4 mL, 1.0 N, 0.4 mmol, 2.0 equiv.) at 0 °C. The reaction mixture was allowed to stir at room temperature for 4 hours until completion indicated by TLC. The obtained solution was subsequently quenched with 1N HCl solution at 0 °C, extracted with EtOAc, and the organic phase was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was further purified by a silica gel column chromatography (eluant: petroleum ether/ethyl acetate = 5:1) to afford the expected products **3**. To a solution of **3** (0.3 mmol) in toluene (2 mL) was added Pyfluor (2-pyridinesulfonyl fluoride, CAS 878376-35-3, 0.33 mmol, 1.1 equiv.) and MTBD (7-Methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene, CAS 84030-20-6, 0.45 mmol, 1.5 equiv.) dropwise at room temperature. The resulting mixture was stirred at the same temperature for 24 hours until completion indicated by TLC. The obtained solution was subsequently quenched with saturated sodium bicarbonate solution at 0 °C, extracted with DCM, and the organic phase was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by a silica gel column chromatography (eluant: petroleum ether/ethyl acetate = 30:1) to afford the desired products **4**.

Ethyl 2-phenyl-2H-tetrazole-5-carboxylate (2a). Light yellow solid; (56 mg, 86%); m.p.: 68-69 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 7.5 Hz, 2H), 7.67 – 7.41 (m, 3H), 4.54 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 136.4, 130.7, 129.9, 120.3, 62.8, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{10}H_{11}N_4O_2]^+$ 219.0877; Found 219.0885.

Ethyl 2-(p-tolyl)-2H-tetrazole-5-carboxylate (2b). Yellow solid; (62 mg, 89%); m.p.: 62-63 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.77 (m, 2H), 7.25 (d, J = 8.3 Hz, 2H), 4.45 (q, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 157.7, 141.2, 134.3, 130.4, 120.3, 62.8, 21.4, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_{13}N_4O_2]^+$ 233.1033; Found 233.1035.

Ethyl 2-(m-tolyl)-2H-tetrazole-5-carboxylate (2c). Yellow liquid; (46 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.93 (m, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 4.57 (q, J = 7.2 Hz, 2H), 2.47 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 157.8, 140.6, 136.5, 131.5, 129.7, 120.9, 117.6, 62.9, 21.5, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_{13}N_4O_2]^+$ 233.1033; Found 233.1038.

Ethyl 2-(o-tolyl)-2H-tetrazole-5-carboxylate (2d). Yellow liquid; (60.5 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 8.0, 1.4 Hz, 1H), 7.48 (td, J = 7.5, 1.4 Hz, 1H), 7.43 – 7.34 (m, 2H), 4.56 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 157.8, 136.1, 133.3, 132.1, 131.1, 127.1, 125.6, 62.9, 18.7, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_{13}N_4O_2]^+$ 233.1033; Found 233.1042.

Ethyl 2-(2, 4-dimethylphenyl)-2H-tetrazole-5-carboxylate (2e). Yellow solid; (68 mg, 92%); m.p.: 66-68 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.1 Hz, 1H), 7.23 – 7.14 (m, 2H), 4.56 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 2.32 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 157.7, 141.5, 133.8, 133.0, 132.6, 127.7, 125.4, 62.9, 21.4, 18.6, 14.4. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{12}H_{14}N_4N_aO_2]^+$ 269.1009; Found 269.1008.

Ethyl 2-(3, 5-dimethylphenyl)-2H-tetrazole-5-carboxylate (2f). White solid; (57 mg, 77%); m.p.: 70-71 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 1.6 Hz, 2H), 7.15 (s, 1H), 4.57 (q, J = 7.1 Hz, 2H), 2.42 (s, 6H), 1.49 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 158.0, 157.8, 140.1, 136.4, 132.4, 118.1, 62.9, 21.4, 14.4. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{12}H_{15}N_4O_2]^+$ 247.1190; Found 247.1194.

Ethyl 2-(4-isopropylphenyl)-2H-tetrazole-5-carboxylate (2g). Yellow liquid; (55 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 7.92 (m, 2H), 7.47 – 7.34 (m, 2H), 4.57 (q, *J* = 7.1 Hz, 2H), 3.01 (hept, *J* = 6.9 Hz, 1H), 1.49 (t, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 157.8, 152.1, 134.5, 127.9, 120.5, 62.9, 34.1, 23.9, 14.4. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{13}H_{17}N_4O_2]^+$ 261.1346; Found 261.1351.

Ethyl 2-(4-(tert-butyl)phenyl)-2H-tetrazole-5-carboxylate (2h). Red liquid; (52.5 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.00 (m, 2H), 7.67 – 7.51 (m, 2H), 4.58 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 157.9, 154.4, 134.2, 126.9, 120.2, 62.9, 35.2, 31.4, 14.4. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{14}H_{19}N_4O_2]^+$ 275.1503; Found 275.1510.

Ethyl 2-(4-methoxyphenyl)-2H-tetrazole-5-carboxylate (2i). White solid; (67 mg, 90%); m.p.: 75-76 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.1 Hz, 2H), 4.55 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 158.0, 157.7, 129.9, 122.0, 114.9, 62.8, 55.8, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_{13}N_4O_3]^+$ 249.0982; Found 249.0990.

Ethyl 2-(3,4,5-trimethoxyphenyl)-2H-tetrazole-5-carboxylate (2j). White solid; (65.5 mg, 71%); m.p.: 145-146 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 2H), 4.54 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 6H), 3.87 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 157.7, 154.0, 139.9, 132.0, 97.9, 62.9, 61.1, 56.6, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{13}H_{17}N_4O_5]^+$ 309.1193; Found 309.1202.

Ethyl 2-(3-bromo-4-methoxyphenyl)-2H-tetrazole-5-carboxylate (2k). White solid; (72 mg, 74%); m.p.: 107-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.7 Hz, 1H), 8.12 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 157.7, 157.7, 130.0, 125.4, 120.5, 112.6, 111.9, 62.8, 56.7, 14.2. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_{12}N_4O_3Br]^+$ 327.0093; Found 327.0100.

Ethyl 2-([1,1'-biphenyl]-2-yl)-2H-tetrazole-5-carboxylate (2l). Red liquid; (67 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (ddd, *J* = 16.8, 7.8, 1.5 Hz, 2H), 7.57 (ddd, *J* = 15.0, 7.9, 1.5 Hz, 2H), 7.26 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.14 – 7.02 (m, 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 157.6, 138.7, 136.9, 134.7, 131.6, 131.6, 128.6, 128.4, 128.4, 128.1, 126.6, 62.7, 14.2. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{16}H_{15}N_4O_2]^+$ 295.1195; Found 295.1197.

Ethyl 2-(4-nitrophenyl)-2H-tetrazole-5-carboxylate (2m). Yellow solid; (52 mg, 66%); m.p. 136-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 – 8.40 (m, 4H), 4.57 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 157.4, 148.7, 140.2, 125.7, 121.2, 63.3, 14.3. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{10}H_9N_5NaO_4]^+$ 286.0547; Found 286.0553.

Ethyl 2-(3-nitrophenyl)-2H-tetrazole-5-carboxylate (2n). Red liquid; (57 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (t, *J* = 2.1 Hz, 1H), 8.57 (dd, *J* = 8.1, 2.1 Hz, 1H), 8.41 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.84 (t, *J* = 8.2 Hz, 1H), 4.57 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 157.4, 149.1, 137.0, 131.3, 125.7, 125.2, 115.7, 63.2, 14.3. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{10}H_9N_5NaO_4]^+$ 286.0547; Found 286.0541.

Ethyl 2-(4-(trifluoromethyl)phenyl)-2H-tetrazole-5-carboxylate (2o). Light yellow solid; (39.5 mg, 46%). m.p.: 113-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 – 8.22 (m, 2H), 7.95 – 7.77 (m, 2H), 4.58 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 157.5, 138.6, 132.6 (q, *J* = 33.3 Hz), 127.2 (q, *J* = 3.8 Hz), 123.3 (q, *J* = 272.6 Hz), 120.6, 63.0, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.87. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{11}H_9F_3N_4N_aO_2]^+$ 309.0570; Found 309.0574.

Ethyl 2-(4-acetylphenyl)-2H-tetrazole-5-carboxylate (2p). White solid; (60 mg, 73%). m.p. 95-96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 – 8.23 (m, 2H), 8.22 – 8.01 (m, 2H), 4.55 (q, *J* = 7.1 Hz, 2H), 2.65 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 158.2, 157.6, 139.1, 138.5, 130.1, 120.4, 63.0, 26.8, 14.3. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{12}H_{12}N_4NaO_3]^+$ 283.0802; Found 283.0799.

Ethyl 2-(4-(methoxycarbonyl)phenyl)-2H-tetrazole-5-carboxylate (2q). White solid; (48 mg, 58%). m.p.: 96-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (q, *J* = 8.5 Hz, 4H), 4.57 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 158.2, 157.7, 139.3, 132.2, 131.5, 120.2, 63.1, 52.7, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{12}H_{13}N_4O_4]^+$ 277.0931; Found 277.0942.

Ethyl 2-(2-cyanophenyl)-2H-tetrazole-5-carboxylate (2r). Yellow solid; (60 mg, 82%); m.p. 76-77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.87 (td, *J* = 7.9, 1.5 Hz, 1H), 7.74 (td, *J* = 7.7, 1.2 Hz, 1H), 4.57 (q, *J* = 7.2 Hz, 2H), 1.48 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 157.4, 137.0, 135.3, 134.3, 131.3, 124.8, 114.9, 107.3, 63.2, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_{10}N_5O_2]^+$ 244.0829; Found 244.0830.

Ethyl 2-(3-cyano-4-methylphenyl)-2H-tetrazole-5-carboxylate (2s). White solid; (59 mg, 77%). m.p.: 118-119 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.44 (d, *J* = 2.3 Hz, 1H), 8.32 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 2.65 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 158.1, 157.5, 144.8, 134.6, 132.1, 124.1, 123.9, 116.4, 114.7, 63.1, 20.6, 14.3. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{12}H_{11}N_5NaO_2]^+$ 280.0805; Found 280.0800.

Ethyl 2-(3-cyano-4-methoxyphenyl)-2H-tetrazole-5-carboxylate (2t). Light yellow solid; (61.5 mg, 75%). m.p. 133-134 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.49 – 8.27 (m, 2H), 7.19 (d, *J* = 9.1 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 4.05 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 162.5, 158.1, 157.6, 129.6, 126.3, 125.7, 114.6, 112.6, 103.5, 63.1, 57.0, 14.3. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{12}H_{11}N_5NaO_3]^+$ 296.0754; Found 296.0755.

Ethyl 2-(4-fluorophenyl)-2H-tetrazole-5-carboxylate (2u). White solid; (64 mg, 91%). m.p.: 65-66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.14 (m, 2H), 7.33 – 7.19 (m, 2H), 4.57 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (d, *J* = 252.1 Hz), 158.0, 157.8, 132.8 (d, *J* = 3.0 Hz), 122.6 (d, *J* = 8.8 Hz), 117.1 (d, *J* = 23.5 Hz), 63.0, 14.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.86 (ddd, *J* = 12.5, 8.2, 4.7 Hz). HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{10}H_{10}FN_4O_2]^+$ 237.0782; Found 237.0784.

Ethyl 2-(3-fluorophenyl)-2H-tetrazole-5-carboxylate (2v). Yellow liquid; (59 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.94 (dt, *J* = 9.0, 2.3 Hz, 1H), 7.56 (td, *J* = 8.3, 5.8 Hz, 1H), 7.25 (tdd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 4.56 (q,

J = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (d, *J* = 249.8 Hz), 157.9, 157.6, 137.3 (d, *J* = 10.3 Hz), 131.4 (d, *J* = 8.7 Hz), 117.7 (d, *J* = 21.2 Hz), 115.9 (d, *J* = 3.5 Hz), 108.2 (d, *J* = 27.4 Hz), 62.9, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.93 (td, *J* = 8.6, 5.8 Hz). HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{10}H_9FNaN_4O_2]^+$ 259.0602; Found 259.0607.

Ethyl 2-(4-chlorophenyl)-2H-tetrazole-5-carboxylate (2w). Light yellow solid; (50 mg, 66%). m.p.: 95- 96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 7.94 (m, 2H), 7.75 – 7.48 (m, 2H), 4.56 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 157.7, 136.8, 134.9, 130.2, 121.7, 63.0, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{10}H_{10}ClN_4O_2]^+$ 253.04087; Found 253.04089.

Ethyl 2-(3-chlorophenyl)-2H-tetrazole-5-carboxylate (2x). Yellow solid; (51 mg, 68%). m.p.: 60-61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (t, *J* = 1.5 Hz, 1H), 8.12 (td, *J* = 4.2, 3.6, 2.1 Hz, 1H), 7.58 – 7.46 (m, 2H), 4.57 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 157.7, 137.2, 136.0, 131.1, 130.9, 120.7, 118.5, 63.1, 14.3. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{10}H_9ClN_4NaO_2]^+$ 275.0306; Found 275.0309.

Ethyl 2-(2-chlorophenyl)-2H-tetrazole-5-carboxylate (2y). Yellow liquid; (46 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (ddd, *J* = 7.8, 4.1, 1.6 Hz, 2H), 7.57 (td, *J* = 7.7, 1.7 Hz,1H), 7.48 (td, *J* = 7.7, 1.5 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 157.7, 134.5, 132.6, 131.3, 130.1, 127.9, 127.8, 63.0, 14.3. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{10}H_9ClN_4NaO_2]^+$ 275.0306; Found 275.0302.

Ethyl 2-(3-chloro-4-fluorophenyl)-2H-tetrazole-5-carboxylate (2z). Yellow solid; (49 mg, 61%). m.p.: 69-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 6.2, 2.7 Hz, 1H), 8.12 (dt, *J* = 9.2, 3.3 Hz, 1H), 7.37 (t, *J* = 8.6 Hz, 1H), 4.57 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.94 (td, *J* = 7.2, 6.8, 4.2 Hz). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.4 (d, *J* = 239.7 Hz), 158.0, 157.6, 132.9 (d, *J* = 3.3 Hz), 123.3, 123.1, 120.3 (d, *J* = 7.9 Hz), 118.0 (d, *J* = 23.1 Hz), 63.1, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{10}H_9FClN_4O_2]^+$ 271.9308; Found 271.9303.

Ethyl 2-(4-bromophenyl)-2H-tetrazole-5-carboxylate (2a'). Yellow solid; (47 mg, 53%). m.p.: 92-93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.06 (m, 2H), 7.75 – 7.69 (m, 2H), 4.57 (q, *J* = 7.2 Hz, 2H), 1.48 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 157.6, 135.3, 133.1, 124.8, 121.7, 62.9, 14.2. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{10}H_{10}BrN_4O_2]^+$ 296.9983; Found 296.9987.

Ethyl 2-(2-(methoxycarbonyl)thiophen-3-yl)-2H-tetrazole-5-carboxylate (2b'). Red liquid; (60 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 5.3 Hz, 1H), 7.36 (d, *J* = 5.3 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 157. 7, 157.7, 135.8, 131.1, 128.9, 126.3, 63.0, 52.9, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{10}H_{11}N_4O_4S]^+$ 283.0501; Found 283.0502.

Ethyl 2-(pyridin-3-yl)-2H-tetrazole-5-carboxylate (2c'). Light yellow liquid; (34 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, *J* = 2.5 Hz, 1H), 8.82 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.50 (ddd, *J* = 8.3, 2.6, 1.5 Hz, 1H), 7.57 (ddd, *J* = 8.4, 4.8, 0.8 Hz, 1H), 4.58 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 157.6, 151.8, 141.8, 133.2, 127.8, 124.3, 63.2, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_9H_{10}N_5O_2]^+$ 220.0834; Found 220.0837.

Ethyl 2-(quinolin-3-yl)-2H-tetrazole-5-carboxylate (2d'). White solid; (43 mg, 53%). m.p. 128-129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 2.3 Hz, 1H), 8.93 (d, *J* = 2.0 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.84 (t, *J* = 7.7 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 4.59 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 157.6, 148.6, 142.1, 131.6, 129.9, 129.9, 128.7, 128.7, 127.0, 126.8, 63.1, 14.3. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{13}H_{11}N_5NaO_2]^+$ 292.0805; Found 292.0806.

Tert-butyl 2-phenyl-2H-tetrazole-5-carboxylate (2e'). Yellow solid; (46 mg, 63%). m.p.: 65-66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.16 (m, 2H), 7.61 – 7.51 (m, 3H), 1.68 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 157.0, 136.6, 130.6, 129.9, 120.4, 84.7, 28.2. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{12}H_{15}N_4O_2]^+$ 247.1190; Found 247.1193.

Benzyl 2-phenyl-2H-tetrazole-5-carboxylate (2f'). Yellow solid; (66 mg, 78%). m.p.: 80-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.09 (m, 2H), 7.62 – 7.47 (m, 5H), 7.45 – 7.31 (m, 3H), 5.54 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.8, 157.8, 136.5, 134.8, 130.8, 130.0, 128.9, 128.9, 128.8, 120.5, 68.3. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{15}H_{12}N_4NaO_2]^+$ 303.0852; Found 303.0854.

Phenyl(2-phenyl-2H-tetrazol-5-yl)methanone (2g'). Light yellow solid; (58 mg, 77%). m.p.: 74-75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.37 (m, 2H), 8.28 – 8.20 (m, 2H), 7.72 – 7.66 (m, 1H), 7.63 – 7.51 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.5, 162.6, 136.5, 135.6, 134.5, 130.8, 130.7, 130.0, 128.8, 120.5. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{14}H_{11}N_4O]^+$ 251.0933; Found 251.0937.

(2-phenyl-2H-tetrazol-5-yl)(p-tolyl)methanone (2h'). Yellow solid; (65 mg, 82%). m.p.: 73-74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 – 8.28 (m, 2H), 8.25 – 8.20 (m, 2H), 7.64 – 7.52 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.1, 162.7, 145.7, 136.6, 133.1, 131.0, 130.7, 130.0, 129.6, 120.5, 22.0. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{15}H_{13}N_4O]^+$ 265.1089; Found 265.1083.

(4-chlorophenyl)(2-phenyl-2H-tetrazol-5-yl)methanone (2i'). White solid; (64 mg, 75%). m.p.: 85-86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.38 (m, 2H), 8.29 – 8.19 (m, 2H), 7.65 – 7.49 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.1, 162.4, 141.2, 136.5, 133.9, 132.3, 130.8, 130.0, 129.2, 120.5. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{14}H_{10}N_4OCl]^+$ 285.0543; Found 285.0537.

Ethyl 2-(4-(hydroxymethyl)phenyl)-2H-tetrazole-5-carboxylate (2j'). Yellow solid; (45 mg, 60%). m.p.: 77-78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.10 (m, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 4.82 (s, 2H), 4.57 (q, J = 7.1 Hz, 2H), 2.09 (s, 1H), 1.49 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 157.9, 143.9, 135.7, 128.1, 120.6, 64.4, 63.0, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_{13}N_4O_3]^+$ 249.0988; Found 249.0995.

Ethyl (R)-2-(4-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl)-2H-tetrazole-5-carboxylate (2k'). Yellow solid; (69 mg, 55%). m.p.: 103-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 5.06 (d, *J* = 8.1 Hz, 1H), 4.63 (q, *J* = 5.9 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.24 (dd, *J* = 13.8, 5.9 Hz, 1H), 3.12 (dd, *J* = 13.7, 6.2 Hz, 1H), 1.48 (t, *J* = 7.1 Hz, 3H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 157.9, 155.1, 139.5, 135.4, 130.9, 120.5, 116.4, 80.4, 62.9, 54.4, 52.6, 38.3, 28.4, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{19}H_{26}N_5O_6]^+$ 420.1183; Found 420.1186.

Ethyl (R)-2-(4-(2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl)-2H-tetrazole-5-carboxylate (2l'). Yellow liquid; (49 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 7.97 (m, 2H), 7.45 – 7.34 (m, 2H), 7.30 – 7.24 (m, 2H), 7.21 (q, *J* = 3.9 Hz, 3H), 4.56 (q, *J* = 7.1 Hz, 2H), 3.81 (d, *J* = 13.2 Hz, 1H), 3.67 (s, 3H), 3.63 (d, *J* = 13.2 Hz, 1H), 3.55 (dd, *J* = 7.3, 6.3 Hz, 1H), 3.08 – 2.95 (m, 2H), 1.84 (s, 1H), 1.48 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 157.9, 157.9, 140.8, 139.4, 135.1, 130.8, 128.5, 128.3, 127.3, 120.3, 62.9, 61.7, 52.2, 52.0, 39.4, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{21}H_{24}N_5O_4]^+$ 410.1828; Found 410.1831.

(2-phenyl-2H-tetrazol-5-yl) methanol (3a). White solid; (31 mg, 88%). m.p.: 102-103 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.17 – 7.99 (m, 2H), 7.54 – 7.38 (m, 3H), 5.06 (d, *J* = 6.4 Hz, 2H), 3.66 (td, *J* = 6.7, 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 136.8, 129.9, 129.8, 120.0 56.1. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_8H_9N_4O]^+$ 177.0776; Found 177.0781.

(2-(p-tolyl)-2H-tetrazol-5-yl) methanol (3b). Light yellow solid; (32 mg, 84%). m.p.: 97-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.84 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.05 (d, *J* = 6.3 Hz, 2H), 3.38 (t, *J* = 6.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 140.3, 134.6, 130.3, 119.9, 56.2, 21.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_9H_{11}N_4O]^+$ 191.0933; Found 191.0934.

(2-(4-fluorophenyl)-2H-tetrazol-5-yl) methanol (3c). Light yellow solid; (37 mg, 96%). m.p.: 99-100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 7.98 (m, 2H), 7.27 – 7.16 (m, 2H), 5.05 (d, *J* = 6.2 Hz, 2H), 3.44 (t, *J* = 6.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.24 (tt, *J* = 8.6, 4.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 163.2 (d, *J* = 250.8 Hz), 133.0 (d, *J* = 2.8 Hz), 122.0 (d, *J* = 8.8 Hz), 116.9 (d, *J* = 23.4 Hz), 56.1. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_8H_8FN_4O]^+$ 195.0682; Found 195.0687.

(2-(4-nitrophenyl)-2H-tetrazol-5-yl) methanol (3d). Orange solid; (28 mg, 64%). m.p.: 135-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.40 (m, 2H), 8.36 (d, *J* = 9.2 Hz, 2H), 5.09 (d, *J* = 6.3 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 148.2, 140.6, 125.6, 120.6, 56.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_8H_8N_5O_3]^+$ 222.0627; Found 222.0632.

(2-(quinolin-3-yl)-2H-tetrazol-5-yl) methanol (3e). White solid; (35.5 mg, 78%). m.p.: 177-178 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (d, *J* = 2.5 Hz, 1H), 9.12 (d, *J* = 2.6 Hz, 1H), 8.26 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.91 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.77 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 5.85 (t, *J* = 6.1 Hz, 1H), 4.86 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.0, 147.4, 142.1, 131.2, 129.8, 129.1, 128.9, 128.3, 126.9, 126.3, 54.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_{10}N_5O]^+$ 228.0885; Found 228.0877.

phenyl(2-phenyl-2H-tetrazol-5-yl) methanol (3f). White solid; (45.5 mg, 90%). m.p.: 112-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.01 (m, 2H), 7.58 – 7.53 (m, 2H), 7.53 – 7.42 (m, 3H), 7.39 – 7.28 (m, 3H), 6.26 (d, *J* = 5.5 Hz, 1H), 3.97 (d, *J* = 5.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 140.2, 136.7, 129.9, 129.7, 128.7, 128.5, 126.8, 120.0, 69.1. HR-MS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $[C_{14}H_{12}N_4ONa]^+$ 275.0909; Found 275.0903.

5-(fluoromethyl)-2-phenyl-2H-tetrazole (4a). White solid; (25.5 mg, 72%). m.p.: 68-69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.01 (m, 2H), 7.60 – 7.43 (m, 3H), 5.70 (d, *J* = 47.3 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -217.20 (t, *J* = 47.3 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7 (d, *J* = 20.4 Hz), 136.7, 130.2, 129.8, 120.1, 74.6 (d, *J* = 169.1 Hz). HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_8H_8FN_4]^+$ 179.0733; Found 179.0732.

5-(fluoromethyl)-2-(p-tolyl)-2H-tetrazole (4b). Light yellow solid; (27 mg, 70%). m.p.: 59-60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.90 (m, 2H), 7.41 – 7.31 (m, 2H), 5.70 (d, *J* = 47.4 Hz, 2H), 2.45 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -217.03 (t, *J* = 47.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7 (d, *J* = 20.3 Hz), 140.6, 134.6, 130.4, 120.1, 74.7 (d, *J* = 169.1 Hz), 21.4. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_9H_{10}FN_4]^+$ 193.0889; Found 193.0893.

5-(fluoromethyl)-2-(4-fluorophenyl)-2H-tetrazole (4c). White solid; (30 mg, 70%). m.p.: 50-51 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.09 (m, 2H), 7.33 – 7.18 (m, 2H), 5.70 (d, *J* = 47.3 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.85 (ddd, *J* = 12.7, 8.1, 4.6 Hz), -217.50 (t, *J* = 47.3 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (d, *J* = 251.2 Hz), 161.9 (d, *J* = 20.5 Hz), 133.0 (d, *J* = 3.4 Hz), 122.2 (d, *J* = 8.8 Hz), 117.0 (d, *J* = 23.5 Hz), 74.6 (d, *J* = 169.4 Hz). HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_8H_7F_2N_4]^+$ 197.0639; Found 197.0637.

5-(fluoromethyl)-2-(4-nitrophenyl)-2H-tetrazole (4d). White solid; (29 mg, 66%). m.p.: 114-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.43 (m, 2H), 8.40 – 8.35 (m, 2H), 5.74 (d, *J* = 47.1 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -218.61 (t, *J* = 47.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (d, *J* = 20.4 Hz), 148.4, 140.4, 125.7, 120.7, 74.5 (d, *J* = 170.3 Hz). HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_8H_7FN_5O_2]^+$ 224.0584; Found 224.0585.

3-(5-(fluoromethyl)-2H-tetrazol-2-yl)quinoline (4e). White solid; (28 mg, 62%). m.p.: 140-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 2.5 Hz, 1H), 8.89 (d, *J* = 2.5 Hz, 1H), 8.26 – 8.20 (m, 1H), 8.03 – 7.93 (m, 1H), 7.85 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.70 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 5.77 (d, *J* = 47.2 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -217.96 (t, *J* = 47.3 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (d, *J* = 20.4 Hz), 148.5, 142.2, 131.4, 130.1, 129.9, 128.7, 127.1, 126.3, 74.6 (d, *J* = 169.9 Hz). HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{11}H_9FN_5]^+$ 230.0842; Found 230.0847.

5-(fluoro(phenyl)methyl)-2-phenyl-2H-tetrazole (4f). Light yellow liquid; (27.5 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.04 (m, 2H), 7.61 (dt, *J* = 7.9, 1.5 Hz, 2H), 7.58 – 7.49 (m, 3H), 7.49 – 7.40 (m, 3H), 6.86 (d, *J* = 45.6 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -171.05 (d, *J* = 45.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9 (d, *J* = 26.4 Hz), 136.8, 136.1 (d, *J* = 21.9 Hz), 130.2, 129.8, 129.6 (d, *J* = 2.2 Hz), 128.9, 127.0 (d, *J* = 5.8 Hz), 120.2, 86.8 (d, *J* = 174.1 Hz). HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{14}H_{12}FN_4]^+$ 255.1046; Found 255.1047.

5-amino-N-(1-(furan-2-yl)ethyl)-4'-methyl-[1,1'-biphenyl]-3-carboxamide (5). White solid; (141 mg, 88%). m.p.: 70-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.34 (d, *J* = 1.8 Hz, 1H), 7.28 (t, *J* = 1.6 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.04 (t, *J* = 1.9 Hz, 1H), 6.93 (t, *J* = 1.9 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.31 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 5.42 (p, *J* = 7.1 Hz, 1H), 3.87 (s, 2H), 2.37 (s, 3H), 1.57 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 154.8, 148.8, 143.6, 142.3, 139.3, 136.5, 134.9, 131.8, 130.1, 127.1, 124.2, 119.8, 110.5, 106.3, 44.0, 21.3, 19.6. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{20}H_{21}N_2O_2]^+$ 321.1603; Found 321.1608.

Ethyl 2-(5-((1-(furan-2-yl)ethyl)carbamoyl)-4'-methyl-[1,1'-biphenyl]-3-yl)-2H-tetrazole-5-carboxylate (2m'). Yellow solid; (46 mg, 52%). m.p.: 91-92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (t, *J* = 1.9 Hz, 1H), 8.45 (t, *J* = 1.8 Hz, 1H), 8.22 (t, *J* = 1.7 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.30 (d, *J*

= 7.9 Hz, 2H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.35 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.30 (d, *J* = 3.3 Hz, 1H), 5.49 (p, *J* = 7.1 Hz, 1H), 4.59 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.66 (d, *J* = 6.9 Hz, 3H), 1.50 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 164.9, 158.0, 157.8, 154.9, 143.9, 142.2, 139.0, 137.0, 136.9, 135.4, 130.0, 128.1, 127.1, 121.1, 116.7, 110.4, 106.3, 63.1, 43.9, 21.3, 19.6, 14.3. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{24}H_{24}N_5O_4]^+$ 446.1828; Found 446.1833.

N-(1-(furan-2-yl)eth-yl)-5-(5-(hydroxymethyl)-2H-tetrazol-2-yl)-4'-methyl-[1,1'-biphenyl]-3-carboxamide (3g). Yellow solid; (71 mg, 88%). m.p.: 177-178 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, *J* = 8.2 Hz, 1H), 8.54 (t, *J* = 1.7 Hz, 1H), 8.43 (t, *J* = 1.8 Hz, 1H), 8.37 (t, *J* = 1.6 Hz, 1H), 7.76 (d, *J* = 7.9 Hz, 2H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 6.42 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.35 (d, *J* = 3.3 Hz, 1H), 5.81 (t, *J* = 6.1 Hz, 1H), 5.35 (p, *J* = 7.1 Hz, 1H), 4.83 (d, *J* = 6.0 Hz, 2H), 2.38 (s, 3H), 1.54 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.8, 163.8, 155.8, 142.1, 142.0, 138.2, 136.8, 136.5, 135.1, 129.8, 126.9, 126.4, 119.8, 117.5, 110.3, 105.6, 54.2, 42.7, 20.7, 18.9. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{22}H_{22}N_5O_3]^+$ 404.1723; Found 404.1728.

5-(5-(fluoromethyl)-2H-tetrazol-2-yl)-N-(1-(furan-2-yl)ethyl)-4'-methyl-[1,1'-biphenyl]-3-carboxamide (4g). White solid; (34 mg, 42%). m.p.: 183-184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dt, *J* = 19.5, 1.9 Hz, 2H), 8.16 (d, *J* = 1.7 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 1.9 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.34 (t, *J* = 2.5 Hz, 1H), 6.29 (d, *J* = 3.3 Hz, 1H), 5.72 (d, *J* = 47.2 Hz, 2H), 5.48 (p, *J* = 7.2 Hz, 1H), 2.41 (s, 3H), 1.65 (d, *J* = 7.0 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -217.67 (t, *J* = 47.2 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 162.0 (d, *J* = 20.6 Hz), 154.9, 143.9, 142.3, 139.0, 137.1, 136.9, 135.6, 130.0, 127.5, 127.2, 120.9, 116.5, 110.5, 106.3, 74.6 (d, *J* = 169.5 Hz), 43.9, 21.3, 19.7. HR-MS (ESI-TOF) m/z: $[M + H]^+$ calcd for $[C_{22}H_{21}FN_5O_2]^+$ 406.1679; Found 406.1686.

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Electronic Supplementary Material

See the Supporting Information for detailed experimental procedures and NMR spectra.

Highlights

1, A silver-catalyzed regioselective cycloaddition reaction between diazoacetates with arenediazonium salts has been developed.

2, Expedient access to both carboxylic and fluoromethyl tetrazoles.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: