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Facile diverted synthesis of pyrrolidinyl triazoles using organotrifluoroborate: discovery of potential mPTP blockers†

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This article describes the rapid and diversified synthesis of pyrrolidinyl triazoles for the discovery of mitochondrial permeability transition pore (mPTP) blockers. The 1,3-dipolar cycloaddition of ethynyl trifluoroborate with azidopyrrolidine produced a key intermediate, triazolyl trifluoroborate **4**, which subsequently underwent a Suzuki–Miyaura coupling reaction to afford a series of 1,4-disubstituted triazoles **2**. Subsequent biological evaluation of these derivatives indicated **2ag** and **2aj** as the most potent mPTP blockers exhibiting excellent cytochrome P450 (CYP) stability when compared to the previously reported oxime analogue **1**. The present work clearly demonstrates that a 1,2,3-triazole can be used as a stable oxime surrogate. Furthermore, it suggests that late-stage diversification through coupling reactions of organotrifluoroborates is suitable for the rapid discovery of biologically active molecules.

1. Introduction

1,2,3-Triazoles are an important class of heterocycles in pharmaceutical science, chemical biology, supramolecular chemistry and materials science.[1–5] In particular, various medicinal agents contain triazoles as important pharmacophores, which can be favorable in the binding to biomolecular targets.[6] Triazoles are often used as peptide bond isosteres because of their planarity and enhanced physiochemical properties such as increased metabolic stability and solubility.[7–9] The nitrogen atoms in the triazole rings have hydrogen bonding capabilities and are not protonated at physiological pH because of their low basicity.

The Huisgen 1,3-dipolar cycloaddition of azides and alkynes is widely used for the synthesis of 1,2,3-triazoles.[9–13] The copper(I) catalyzed version of this reaction, using azides and terminal alkynes, provides 1,4-disubstituted 1,2,3-triazoles with high regioselectivity,[14–18] making this reaction a powerful tool in medicinal chemistry for the structural modification of lead compounds.

Recently, we have identified pyrrolidinyl oxime, **1**, as an mPTP (mitochondrial permeability transition pore) blocker, which is a viable therapeutic target for the treatment of Alzheimer's disease (AD).[19] It effectively recovered amyloid beta-induced mitochondrial dysfunction; however, the cytochrome P450 (CYP) enzyme inhibition study revealed that it significantly reduced CYP enzymatic activities, which can cause side effects such as a drug–drug interaction. In this regard, we proposed that the stable 1,2,3-triazole could serve as an effective isostere of oxime to improve the CYP stability without reducing the mPTP inhibitory activity.[20] In addition, incorporation of substituents on the aromatic ring can alter the effect of CYP inhibition. Considering these structural modifications, we propose triazole derivatives **2** as new candidates for mPTP blockers (Fig. 1).

As described in Scheme 1, we designed an efficient, step-economical synthetic approach toward a chemical library of diverse 1,2,3-triazole derivatives. The synthesis of a triazole *via*

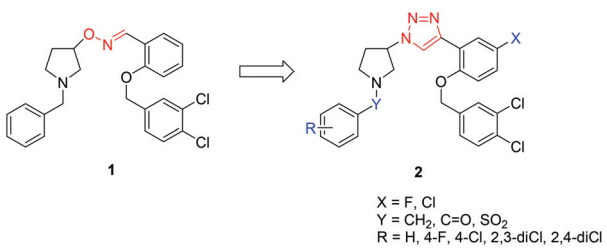

Fig. 1 Structures of pyrrolidinyl oxime **1** and triazole derivatives **2**.

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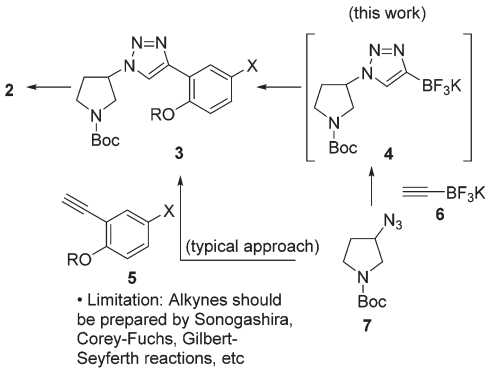


Scheme 1 Proposed synthesis of 1-pyrrolidinyl-1,2,3-triazoles **2**.

a typical 1,3-cycloaddition requires the preparation of a terminal alkyne as a precursor; hence, this strategy is not effective for achieving molecular diversity. Alternatively, we envisioned that triazolyl trifluoroborate **4**, derived from the annulation of ethynyl trifluoroborate **6**[21,22] and azide **7**, can undergo a rapid Suzuki–Miyaura coupling reaction to afford various triazole analogues **3**.[23–25] A recent report showed the transformation of **6** to the corresponding triazolyl trifluoroborates, and subsequent cross-coupling reactions, to afford 1,4-disubstituted 1,2,3-triazoles.[26] However, this protocol was only applied to a limited number of substrates, such as primary or aromatic azides, and no further applications of the synthesized compounds were pursued.

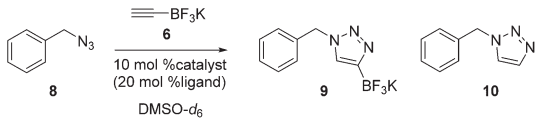
In this paper, we report an efficient and divergent synthesis of various highly functionalized 1-pyrrolidinyl 4-aryl 1,2,3-triazoles **2** *via* triazolyl trifluoroborates for the discovery of mPTP blockers. Furthermore, we investigate the effect of structural modification of oximes into triazoles on the target efficacy and CYP enzyme stability.

2. Results and discussion

As depicted in Table 1, we performed a model study through the cycloaddition of **6**, using benzyl azide **8** as a substrate. Based on the reaction conditions reported in the literature,[27] we employed copper(I) halides as catalysts as well as various bases and additives. Initially, the desired triazole trifluoroborate **9** was obtained in low yields when copper(I) iodide was used (entries 1–3). We explored several bases in order to improve the reaction yield, but the cycloaddition reactions did not afford **9** in any of the cases (entries 4–8). However, **9** was formed in high yield when the reaction with copper(I) bromide and cesium carbonate in the presence of *N*,*N*-dimethylethylenediamine (DMEDA) was performed at 90 °C for 30 min (entry 11).[28,29] The choice of solvent system is crucial to prevent the generation of side product **10**, which is most likely formed by protodeboronation *via* a solvolysis mechanism.[30]

After the optimal reaction conditions were selected, the scope of the cycloaddition reaction of **6** with various substrates was briefly investigated (Table 2). In general, the reactions of

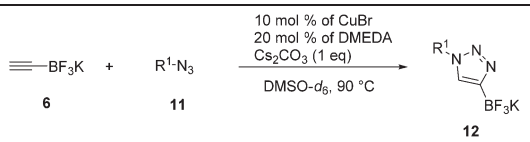
Table 1 Optimization of the cycloaddition reaction conditions



Entry	Conditions	Temp. (°C)	Time (h)	Yield (%)
1	CuI	60	17	24
2[a]	CuI	60	20	40
3	CuI	90	24	28
4	CuI, TEA	50	24	—
5	CuI, K_2CO_3	50	24	—
6	CuI, Cs_2CO_3	50	24	—
7	CuI, iPr_2NEt	50	24	—
8	CuI, iPr_2NH	50	24	—
9[a]	CuBr, Cs_2CO_3	60	15	—[b]
10	CuBr, Cs_2CO_3, DMEDA	60	3	40
11	CuBr, Cs_2CO_3, DMEDA	90	0.5	85
12[a]	CuBr, Cs_2CO_3, DMEDA	60	15	Trace

[a] Reaction was performed in acetone-d_6. [b] The deboronated product **10** was formed exclusively.

Table 2 Cycloaddition reaction of **6** with azides **11** under optimized conditions



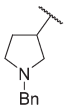
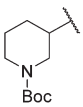
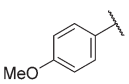
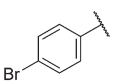
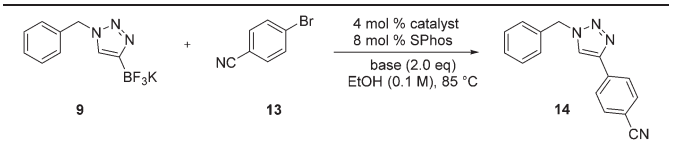
Entry	R^1	Time (h)	Product	Yield (%)
1	$HOCH_2CH_2CH_2$ (**11a**)	0.5	**12a**	72
2	EtO_2CCH_2 (**11b**)	1	**12b**	62
3	$PhCH{=}CHCH_2$ (**11c**)	0.5	**12c**	87
4	 (**11d**)	1.5	**12d**	71
5	 (**11e**)	1.5	**12e**	45
6	 (**11f**)	24	**12f**	No reaction
7	 (**11g**)	0.5	**12g**	90
8	 (**11h**)	1	**12h**	72
9	 (**11i**)	3	**12i**	69

Table 3 Model study of the Suzuki–Miyaura cross-coupling reaction



Entry	Catalyst	Base	Time (h)	Yield (%)
1	$Pd(OAc)_2$	K_2CO_3	3	—
2	$Pd(OAc)_2$	Cs_2CO_3	3	—
3	$Pd(OAc)_2$	K_3PO_4	3	8
4	$Pd(OAc)_2$	Na_2CO_3	18	99
5	$PdCl_2(dppf)\cdot CH_2Cl_2$	Na_2CO_3	12	78
6	$Pd(PPh_3)_4$	Na_2CO_3	18	76
7	$Pd(dba)_2$	Na_2CO_3	7	96
8	$Pd_2(dba)_3$	Na_2CO_3	18	100
9[a]	$Pd_2(dba)_3$	Na_2CO_3	24	9
10[b]	$Pd_2(dba)_3$	Na_2CO_3	18	94
11[c]	$Pd_2(dba)_3$	Na_2CO_3	18	88

[a] No ligand was used. [b] XPhos was used as a ligand. [c] Catalyst (2 mol%), ligand (4 mol%).

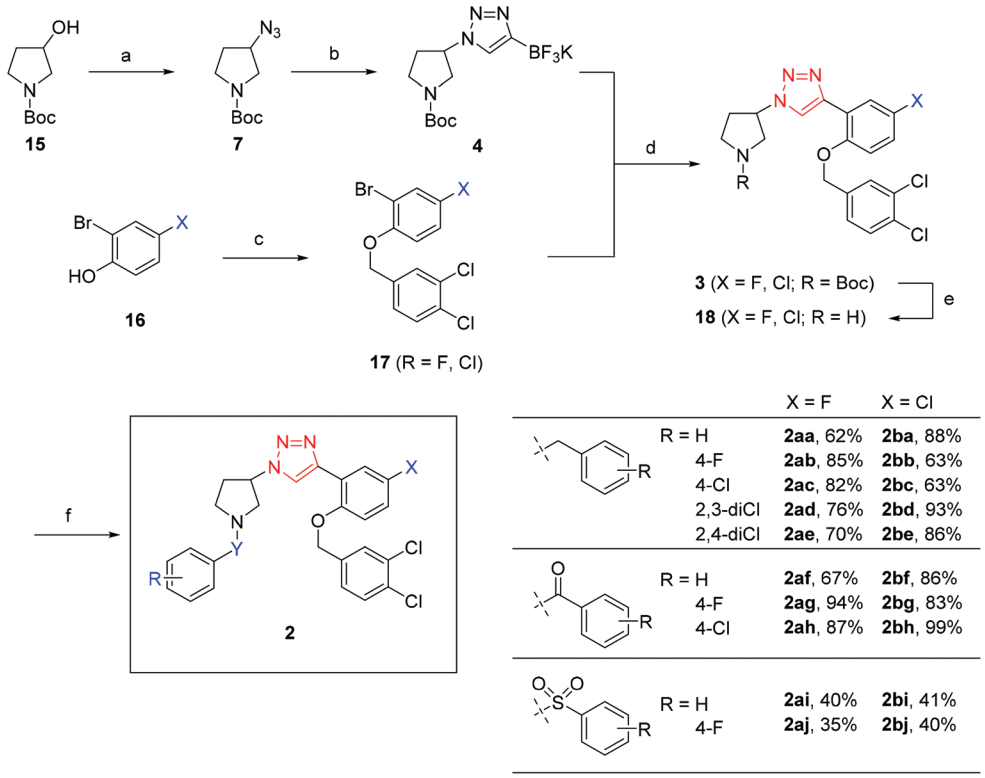
aromatic or aliphatic azides **11** afforded the corresponding triazoles **12** in good to excellent yields. It was found that various functional groups, such as alcohol, ester, allyl, and carbamate, were tolerated under these reaction conditions (entries 1–3, and 5). In particular, secondary pyrrolidine/piperizine azides **11d** and **11e** gave the desired products **12d** and **12e** in good yields (entries 4, 5), which could then be applied to the divergent synthesis of the proposed 1,4-disubstituted triazole library. While the sterically demanding 2,6-dimethylphenyl azide **11i** was readily converted to triazole **12i** within 3 h (entry 9), the use of adamantyl azide **11f** did not provide the desired product **12f** because of the high steric hindrance (entry 6).

The Suzuki–Miyaura coupling reaction was then explored in order to produce a variety of derivatives in the late-stage functionalization, as suggested in Scheme 1. The reaction of **9** with 4-bromobenzonitrile **13** was tested, and the results are summarized in Table 3. Following a literature procedure,[31] the initial reactions were attempted in the presence of $Pd(OAc)_2$ and SPhos using various bases. When K_2CO_3, Cs_2CO_3, and K_3PO_4 were used as bases, **14** was not formed at all, or was obtained in very low yield. However, the use of Na_2CO_3 as a base dramatically increased the yield to up to 99%. A variety of catalysts were also screened in order to optimize the reaction conditions. Among the catalysts tested, $Pd_2(dba)_3$ provided the best results, affording triazole **14** in quantitative yield. Many solvent systems were used, such as DMF/H_2O, DME, THF, and dioxane; however, all these afforded lower yields of the coupled product **14**. Alternatively, ethanol gave higher yields, suggesting that it is a critical component in the reaction efficiency.

Given the positive results from the optimized cycloaddition reaction and the Suzuki–Miyaura coupling reaction in the model study, these reactions were applied to the synthesis of triazole derivatives **2** as mPTP blockers (Scheme 2). Starting from commercially available 3-hydroxy *N*-Boc-pyrrolidine **15**, 3-azidopyrrolidine **7** was easily prepared by mesylation and consecutive S_N2 displacement of the azide. According to the experimental procedure previously established in Table 1, we attempted the 1,3-dipolar cycloaddition of potassium ethynyl trifluoroborate **6** with azide **7**. As anticipated, the desired triazolyl trifluoroborate **4** was obtained in 70% yield. In the meantime, 2-bromo-1-benzyloxybenzenes **17**, containing either a fluoride or chloride substituent at the 4-position, were easily prepared as coupling partners by benzylation of bromophenols **16**. A coupling reaction of **4** and **17** could then be completed under the optimized conditions. This reaction proceeded successfully, giving 1,4-disubstituted triazoles **3** in moderate yields. Removal of the Boc protecting group on **3** using trifluoroacetic acid afforded the secondary amine **18** as a salt. This was then subjected to reductive amination, acylation, and sulfonylation to provide N-functionalized pyrrolidines **2** in good yields. Thus, we obtained a series of twenty new triazole derivatives in this concise and divergent manner using **4** as a key intermediate.

The inhibitory activity of pyrrolidinyl triazoles **2** against amyloid beta-induced mPTP opening was evaluated by a cell-based JC-1 assay (Fig. 2).[32,33] In this assay, the color of the JC-1 dye changed from green to red as the mitochondrial membrane potential increased. Thus, the lower the percent increase of the green/red (g/r) ratio of the compound, the higher is the recovery of mitochondrial function in the cell. Twelve of the triazole derivatives **2** increased the inhibition of mPTP opening with less than 40% increase in the g/r ratio, indicating that the triazole is an effective structural surrogate of oxime. Further consideration of the structure–activity relationship (SAR) demonstrated the **2a** series containing fluorine on the internal phenyl ring (X = F) to be more active than the chlorine-substituted **2b** compounds. Smaller substituents at the *R* position were found to increase the inhibitory activity against mPTP opening. In particular, electron-withdrawing groups, such as carbonyl or sulfonyl, between pyrrolidine and the terminal phenyl ring significantly enhanced the inhibitory activity when compared to the initial lead compound **1**.

In order to determine the effect of triazoles on the CYP stability, the inhibitory activities of selected compounds **2** against five CYP450 isozymes in the human liver were tested. Using the CYP450 screening kits, the percent remaining activity of the CYP enzymes after treatment with **2** was obtained, as shown in Table 4. The selected compounds **2** significantly increased the percent CYP remaining activities in comparison with oxime **1**. In particular, the most active triazole derivatives **2ag** and **2aj**, containing 4-fluorobenzoyl and 4-fluorobenzenesulfonyl groups, exhibited relatively low inhibitory activities against the tested CYP isozymes. This suggested that this triazole-based structural modification played an important role in the stability of the CYP enzymes as well as in blocking the mPTP opening.



Scheme 2 Divergent synthesis of 1-pyrrolidynyl triazoles **2**: (a) (i) MsCl, TEA, CH_2Cl_2, rt, 18 h, (ii) NaN_3, DMF, 80 °C, 3 h, 85%; (b) **6**, CuBr, Cs_2CO_3, DMEDA, DMSO, 90 °C, 1.5 h, 70%; (c) 3,4-dichlorobenzyl chloride, K_2CO_3, KI, acetone, 60 °C, 75% (**17a**), and 95% (**17b**); (d) $Pd_2(dba)_3$, SPhos, Na_2CO_3, 85 °C, 18 h, 54% (**3a**), and 53% (**3b**); (e) TFA, CH_2Cl_2, rt, 0.5 h, 99% (**18a**), and 99% (**18b**); (f) ArCHO, $NaBH(OAc)_3$, AcOH, THF, rt, 24 h (for **2aa–e** and **2ba–e**), or ArCOCl, Et_3N, THF, rt, 24 h (for **2af–h** and **2bf–h**), or $ArSO_2Cl$, Et_3N, THF, rt, 24 h (for **2ai–j** and **2bi–j**).

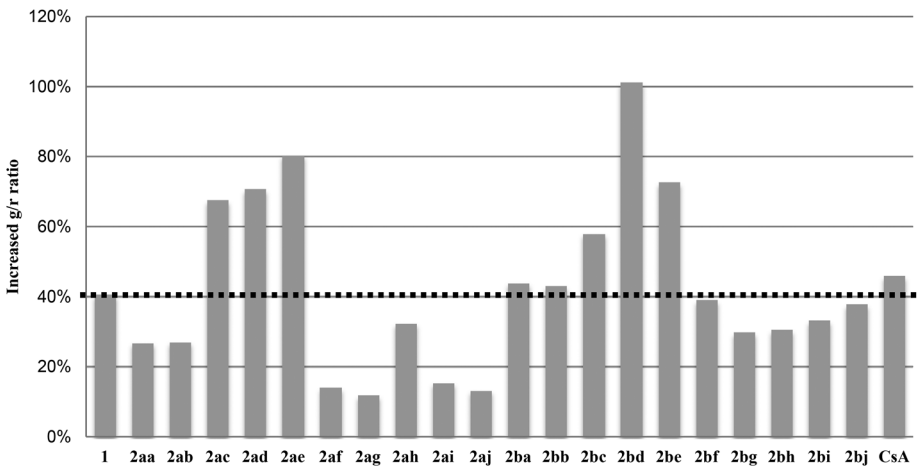


Fig. 2 Inhibitory activity of **2** against amyloid beta-induced mPTP opening. Percent increase in the fluorescence ratio (green/red) after treatment of each compound with amyloid beta with respect to that of amyloid beta alone (100%). Cyclosporin A (CsA) was used as a control.

3. Conclusion

In this study, we have demonstrated the synthesis of twenty pyrrolidinyl triazoles **2** *via* cycloaddition of ethynyl trifluoroborate **6**, followed by the Suzuki–Miyaura coupling reaction of the corresponding cycloadducts. These were then evaluated for their inhibitory activity against amyloid beta-induced mPTP opening. The reaction conditions that were optimized in the model system were successfully applied to the synthesis of key intermediates **4**, which were transformed to a library of N-functionalized pyrrolidinyl triazoles **2** in a divergent manner with high overall yields. Thus, we believe that this methodology is

Table 4 CYP inhibition[a,b] of the selected compounds **2**

	% CYP isozyme remaining activity[c]				
Compds	1A2	2D6	2C9	3A4	2C19
2ab	67.97	47.00	32.74	12.34	11.21
2ag	83.44	102.41	20.66	36.74	20.47
2aj	86.97	137.73	33.77	38.72	13.64
2bb	62.32	44.25	80.28	8.32	14.06
2bg	65.10	78.86	23.30	26.72	20.67
2bj	68.08	37.66	41.60	16.83	5.37
1	3.24	6.25	34.67	−0.06	—
Control[d]	4.27	6.66	10.44	9.85	5.77

[a] Each value represents the mean of triplicate experiments. [b] Each value represents the mean of duplicated experiments. [c] The remaining activity of each isozyme was obtained at a concentration of 10 μM using a fluorogenic Vivid® CYP450 screening kit. [d] The reference compounds for each CYP isozyme assay are as follows: α-naphthoflavone (1A2), quinidine (2D6), sulfaphenazole (2C9), ketoconazole (3A4), and miconazole (2C19).

useful for the rapid preparation of a large number of 1,4-disubstituted 1,2,3-triazole analogs.

Screening of the triazole analogues **2** in the JC-1 assay identified **2ag** and **2aj** as potent mPTP blockers. These also showed excellent CYP stability in comparison with oxime **1**. These findings indicate that the 1,2,3-triazole functional group can be used as a stable isostere of oxime to improve the CYP stability while maintaining the inhibitory activity against a molecular target.

Experimental section

General

All reactions were carried out under dry nitrogen unless otherwise indicated. Commercially available reagents were used without further purification. Solvents and gases were dried according to standard procedures. Organic solvents were evaporated with reduced pressure using a rotary evaporator. Analytical thin layer chromatography (TLC) was performed using glass plates precoated with silica gel (0.25 mm). TLC plates were visualized by exposure to UV light (UV), and then were visualized with a *p*-anisaldehyde stain followed by brief heating on a hot plate. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck) with the indicated solvents. ^{1}H, ^{11}B, ^{13}C and ^{19}F spectra were recorded on Bruker 300, Bruker 400 (376 MHz) or Varian 300 NMR spectrometers. ^{1}H NMR spectra are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (*J*) in hertz (Hz). ^{1}H NMR chemical shifts are reported relative to $CDCl_3$ (7.26 ppm). ^{13}C NMR spectra were recorded relative to the central line of $CDCl_3$ (77.0 ppm). ^{19}F NMR chemical shifts were referenced to external $CFCl_3$ (0.0 ppm). ^{11}B NMR spectra at 128 MHz were obtained on a spectrometer equipped with the appropriate decoupling accessories. All ^{11}B NMR chemical shifts were referenced to external $BF_3{\cdot}OEt_2$ (0.0 ppm) with a negative sign indicating an upfield shift.

Potassium ethynyltrifluoroborate (6).[22] To a solution of ethynylmagnesium bromide in THF (20 mL, 10.0 mmol, 0.5 M in THF solution) was added trimethylborate (1.59 g, 15.3 mmol) at −78 °C. The solution was stirred for 1 h at this temperature, and then warmed up to −20 °C and stirred for 1 h. To the resulting white suspension, a solution of KHF_2 (4.71 g, 60.3 mmol) in distilled water (15 mL) was added at −20 °C and the solution was stirred at this temperature for 1 h and at room temperature for additional 1 h. The obtained reaction mixture was concentrated and the residue was dissolved in hot acetone. The residue was removed by filtration and the filtrate was concentrated to give the title compound **6** (1.05 g, 80%) as a white solid; mp 208.0–211.3 °C (decomp.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.90 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 98.5, 78.9. ^{19}F NMR (DMSO-d_6, 376 MHz) δ −132.2, −132.3, −132.4, 132.5. ^{11}B NMR (DMSO-d_6, 128 MHz) δ −1.87, −2.16, −2.44, −2.72.

Potassium (1-benzyl-1*H*-1,2,3-triazol-4-yl)trifluoroborate (9) (Table 1). To a solution of potassium ethynyltrifluoroborate **6** (21.0 mg, 159 μmol), CuBr (2.30 mg, 15.9 μmol), *N*,*N*-dimethylethylenediamine (3.40 μL, 31.8 μmol) and Cs_2CO_3 (51.0 mg, 159 μmol) in DMSO-d_6 (0.7 mL) in a NMR tube was added benzyl azide **8** (21.2 mg, 159 μmol) at room temperature. The reaction mixture was carried out at 90 °C for 30 min (until the ^{1}H NMR indicated completion of the reaction). Then, the solvent was completely removed under high vacuum. The residual product was dissolved in dry acetone (3 × 5 mL) and the insoluble salts were removed by filtration through Celite® and activated carbon. The solvent was concentrated and the crude solid was purified by dissolution in a minimal amount of dry acetone and precipitation with Et_2O to give the title compound **9** (35.8 mg, 85%) as a white solid; mp 171.9–173.8 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.43 (s, 1H), 7.36–7.23 (m, 5H), 5.46 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 137.6, 128.9, 128.2, 128.1, 126.3, 52.1. ^{19}F NMR (DMSO-d_6, 376 MHz) δ −135.6. ^{11}B NMR (DMSO-d_6, 128 MHz) δ 2.19.

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)benzonitrile (14) (Table 3). A sealed tube was charged with potassium (1-benzyl-1*H*-1,2,3-triazol-4-yl)trifluoroborate **7** (40.0 mg, 150 μmol), 4-bromobenzonitrile (18.0 mg, 98.9 μmol), $Pd_2(dba)_3$ (3.70 mg, 4.04 μmol), SPhos (3.30 mg, 8.03 μmol) and Na_2CO_3 (21.0 mg, 198 μmol). The tube was sealed with a cap and purged with argon gas. Ethanol (1 mL) was added *via* a syringe and the reaction was carried out at 85 °C for 18 h under the protection of argon gas. Then, the reaction mixture was allowed to cool down to room temperature and filtered through a thin pad of silica gel (eluting with EtOAc) and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc–*n*-hexane = 1 : 3) to give the title compound **14** (25.7 mg, 99.9%) as a white solid; mp 140.4–142.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, J = 8.5 Hz, 2H), 7.77 (s, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.38 (m, 3H), 7.31 (m, 2H), 5.58 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.3,

134.9, 134.2, 132.6, 129.2, 129.0, 128.1, 126.0, 120.7, 118.7, 111.4, 54.4.

***tert*-Butyl 3-azidopyrrolidine-1-carboxylate (7).** To a solution of *t*-butyl-3-(methylsulfonyloxy)pyrrolidine-1-carboxylate (0.74 g, 2.78 mmol) in DMF (7 mL) was added NaN_3 (0.45 mg, 6.95 mmol) in DMF (7 mL). The reaction mixture was stirred at 80 °C for 3 h, then cooled to room temperature and diluted with water. The aqueous phase was then extracted with ethyl acetate (3 × 20 mL). The organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (EtOAc–*n*-hexane = 15 : 1) to give the title compound **7** (0.49 mg, 85%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.11 (m, 1H), 3.52–3.42 (m, 4H), 2.12–1.95 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.7, 78.8, 60.1, 59.4, 50.6, 50.3, 43.5, 43.2, 30.9, 30.1, 27.9.

Potassium 1-(1-(*t*-butoxycarbonyl)pyrrolidin-3-yl)-1*H*-1,2,3-triazole-4-yl trifluoroborate (4). Following the same procedure as that used for the synthesis of **9**, the reaction of *tert*-butyl-3-azidopyrrolidine-1-carboxylate **7** (47.9 mg, 225 μmol), potassium ethynyltrifluoroborate **6** (27.0 mg, 207 μmol), CuBr (3.00 mg, 20.7 μmol), *N*,*N*-dimethylethylenediamine (4.40 μL, 40.8 μmol) and Cs_2CO_3 (67.0 mg, 207 μmol) in DMSO-d_6 in an NMR tube gave the title compound **4** (49.2 mg, 70%) as a white solid; mp 200.9–202.0 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.45 (s, 1H), 5.10 (m, 1H), 3.72 (q, J = 9.0 Hz, 1H), 3.54 (d, J = 10.7 Hz, 1H), 3.41 (m, 2H), 2.37–2.24 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 154.0, 125.7, 79.3, 58.1, 57.4, 51.9, 51.6, 44.7, 44.5, 31.8, 31.0, 28.5; ^{19}F NMR (DMSO-d_6, 376 MHz) δ −135.6; ^{11}B NMR (DMSO-d_6, 128 MHz) δ 2.14.

1-Bromo-4-fluoro-2-(3,4-dichlorobenzyloxy)-benzene (17a). To a solution of 2-bromo-4-fluorophenol (1.00 g, 5.26 mmol), 3,4-dichlorobenzylchloride (0.95 mL, 6.84 mmol) and K_2CO_3 (1.10 g, 7.85 mmol) in acetone (35 mL) was added KI (1.40 g, 8.38 mmol). The reaction mixture was stirred at 60 °C for 24 h, then cooled to room temperature and diluted with water. The aqueous phase was then extracted with DCM (3 × 30 mL). The organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (EtOAc–*n*-hexane = 1 : 15) to give the title compound **17a** (1.38 g, 75%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (d, J = 1.9 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.31 (td, J = 2.6, 7.8 Hz, 2H), 7.99–6.93 (m, 1H), 6.84 (q, J = 4.6 Hz, 1H), 4.99 (s, 2H).

1-Bromo-4-chloro-2-(3,4-dichlorobenzyloxy)benzene (17b). Following the same procedure as that used for the synthesis of **17a**, the reaction of 2-bromo-4-chlorophenol (1.12 g, 5.41 mmol), 3,4-dichlorobenzylchloride (1.37 mL, 7.03 mmol), K_2CO_3 (1.12 g, 8.12 mmol) and KI (1.43 g, 8.66 mmol) in acetone (36 mL) gave the title compound **17b** (1.89 g, 95%) as a yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (d, J = 2.3 Hz, 2H), 7.46 (d, J = 8.2 Hz, 1H), 7.29 (dd, J = 1.6, 8.3 Hz, 1H), 7.21 (dd, J = 2.5, 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 5.05 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.4, 136.3, 133.1, 132.8, 132.2, 130.7, 128.9, 128.3, 126.9, 126.2, 114.3, 113.0.

***t*-Butyl-3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidine-1-carboxylate (3a).** Following the same procedure as that used for the synthesis of **14**, the reaction of potassium 1-(1-(*t*-butoxycarbonyl)pyrrolidin-3-yl)-1*H*-1,2,3-triazole-4-yl trifluoroborate **4** (31.4 mg, 116 μmol), 1-bromo-4-fluoro-2-(3,4-dichlorobenzyloxy)-benzene **17a** (21.0 mg, 77.5 μmol), $Pd_2(dba)_3$ (2.20 mg, 3.09 μmol), SPhos (2.00 mg, 6.19 μmol) and Na_2CO_3 (13.0 mg, 155 μmol) in ethanol (1 mL) gave the title compound **3a** (16.3 mg, 54%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (dd, J = 3.1, 9.5 Hz, 1H), 7.93 (s, 1H), 7.53 (d, J = 1.7 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.24 (dd, J = 2.0, 8.2 Hz, 1H), 6.97 (td, J = 3.1, 8.2 Hz, 1H), 6.89 (q, J = 4.4 Hz, 1H), 5.12 (bs, 1H), 5.09 (s, 2H), 3.93 (q, J = 6.2 Hz, 1H), 3.74 (bs, 1H), 3.57 (bs, 2H), 2.46 (bs, 1H), 2.36 (bs, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.6 (d, ^1J = 237.8 Hz), 154.1, 150.5, 142.3, 136.7, 132.9, 132.5, 130.9, 129.3, 126.7, 121.8, 121.2 (d, ^3J = 7.9 Hz), 115.1 (d, ^2J = 23.4 Hz), 114.5 (d, ^2J = 25.0 Hz), 113.4 (d, ^3J = 8.4 Hz), 80.0, 69.8, 59.3, 58.7, 51.4, 44.3, 43.9, 31.9, 31.0, 28.4.

***t*-Butyl-3-(4-(5-chloro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidine-1-carboxylate (3b).** Following the same procedure as that used for the synthesis of **14**, the reaction of potassium 1-(1-(*t*-butoxycarbonyl)pyrrolidin-3-yl)-1*H*-1,2,3-triazole-4-yl trifluoroborate **4** (43.6 mg, 126 μmol), 1-bromo-4-chloro-2-(3,4-dichlorobenzyloxy)benzene **17b** (32.6 mg, 84.6 μmol), $Pd_2(dba)_3$ (3.10 mg, 3.38 μmol), SPhos (2.80 mg, 6.82 μmol) and Na_2CO_3 (18.0 mg, 169 μmol) in ethanol (1 mL) gave the title compound **3b** (23.6 mg, 53%) as a white solid; mp 127.3–129.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (d, J = 2.6 Hz, 1H), 7.91 (s, 1H), 7.53 (d, J = 1.2 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.25–7.21 (m, 2H), 6.88 (d, J = 8.8 Hz, 1H), 5.10 (bs, 3H), 3.93 (q, J = 6.2 Hz, 1H), 3.74 (m, 1H), 3.56 (bs, 2H), 2.46 (bs, 1H), 2.36 (bs, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.1, 152.8, 142.0, 136.5, 132.9, 132.5, 130.9, 129.3, 128.5, 127.6, 126.9, 126.7, 121.9, 121.2, 113.3, 80.0, 69.5, 59.3, 58.7, 51.4, 44.3, 44.0, 31.9, 31.0, 28.4.

3-(4-(5-Fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate (18a). To a solution of *t*-butyl-3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidine-1-carboxylate **17a** (0.52 g, 1.03 mmol) in DCM (5 mL) was added TFA (1.90 mL, 25.7 mmol). The reaction mixture was stirred at room temperature for 0.5 h. The solvent was removed under reduced pressure to give the title compound **18a** (0.57 g, 99%) as a yellowish solid; mp 157.1–159.5 °C; ^{1}H NMR (MeOH-d_4, 400 MHz) δ 8.38 (s, 1H), 7.81 (dd, J = 3.2, 9.6 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 2.0, 8.4 Hz, 1H), 7.08–7.01 (m, 2H), 5.50 (m, 1H), 5.19 (s, 2H), 3.91 (m, 2H), 3.64 (m, 2H), 2.67 (m, 1H), 2.53 (m, 1H); ^{13}C NMR (MeOH-d_4, 100 MHz) δ 157.3 (d, ^1J = 236.0 Hz), 150.7, 142.2, 137.6, 132.1, 131.5, 130.5, 129.3, 127.1, 123.9, 120.6 (d, ^3J = 8.0 Hz), 115.0 (d, ^2J = 24.0 Hz), 114.1 (d, ^3J = 8.0 Hz), 113.3 (d, ^3J = 25.0 Hz).

3-(4-(5-Chloro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate (18b). Following the same procedure as that used for the synthesis of **18a**, the

reaction of *t*-butyl-3-(4-(5-chloro-2-(3,4-dichlorobenzyloxy)-phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidine-1-carboxylate **17b** (180 mg, 343 μmol) and TFA (0.64 mL, 8.58 mmol) in DCM (1.7 mL) gave the title compound **18b** (18.5 mg, 99%) as a yellowish solid; ^{1}H NMR (MeOH-d_4, 400 MHz) δ 8.37 (s, 1H), 8.11 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.39 (dd, J = 2.0, 8.0 Hz, 1H), 7.30 (dd, J = 2.6, 9.0 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 5.49 (m, 1H), 5.26 (s, 2H), 3.94 (dd, J = 1.6, 12.8 Hz, 1H), 3.84 (q, J = 6.5 Hz, 1H), 3.63 (m, 2H), 2.67 (m, 1H), 2.51 (m, 1H); ^{13}C NMR (MeOH-d_4, 100 MHz) δ 153.2, 142.0, 137.5, 132.2, 131.6, 130.5, 129.3, 128.6, 127.1, 126.7, 126.2, 124.0, 120.7, 114.2, 69.0, 58.9, 50.1, 44.6, 31.6.

1-(1-Benzylpyrrolidin-3-yl)-4-(2-(3,4-dichlorobenzyloxy)-5-fluorophenyl)-1*H*-1,2,3-triazole (2aa). To a solution of 3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate **18a** (25.0 mg, 47.9 μmol), CH_3CO_2H (0.55 μL, 9.59 μmol) and $NaBH(OAc)_3$ (30.4 mg, 144 μmol) in THF (0.5 mL) was added benzaldehyde (7.33 μL, 71.9 μmol). The reaction mixture was stirred at room temperature for 24 h, and then diluted with water. The aqueous phase was then extracted with DCM (3 × 3 mL). The organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (EtOAc–*n*-hexane = 1 : 1) to give the title compound **2aa** (14.8 mg, 62%) as a yellow solid; mp 148.6–149.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (s, 1H), 8.07 (dd, J = 3.0, 9.5 Hz, 1H), 7.54 (s, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.25–7.23 (m, 6H), 7.00–6.91 (m, 2H), 5.25 (m, 1H), 5.05 (s, 2H), 3.66 (q, J = 13.1 Hz, 2H), 2.91 (m, 3H), 2.58 (m, 2H), 2.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7 (d, ^1J = 237.8 Hz), 150.6 (d, ^4J = 2.0 Hz), 142.5 (d, ^4J = 2.8 Hz), 136.7, 132.9, 132.5, 130.8, 129.5, 128.9, 128.6, 127.9, 126.8, 122.1, 121.5 (^{3}d, J = 8.7 Hz), 115.0 (d, ^2J = 23.3 Hz), 114.5 (^{2}d, J = 25.0 Hz), 113.4 (d, ^3J = 8.4 Hz), 77.2, 69.9, 59.2, 59.0, 52.6, 32.7; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{26}H_{24}Cl_2FN_4O$ 497.13057, found 497.13019.

1-(1-(4-Fluorobenzyl)pyrrolidin-3-yl)-4-(2-(3,4-dichlorobenzyloxy)-5-fluorophenyl)-1*H*-1,2,3-triazole (2ab). Following the same procedure as that used for the synthesis of **2aa**, the reaction of 3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate **18a** (32.6 mg, 62.5 μmol), 4-fluorobenzaldehyde (13.4 μL, 125 μmol), CH_3CO_2H (1.07 μL, 18.8 μmol) and $NaBH(OAc)_3$ (53.0 mg, 250 μmol) in THF (0.6 mL) gave the title compound **2ab** (27.2 mg, 85%) as a yellow solid; mp 43.2–45.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (s, 1H), 8.07 (dd, J = 3.0, 9.6 Hz, 1H), 7.55 (d, J = 1.7 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.26 (dd, J = 1.8, 8.1 Hz, 1H), 7.13 (bs, 2H), 7.01–6.88 (m, 4H), 5.23 (m, 1H), 5.08 (s, 2H), 3.58 (q, J = 12.6 Hz, 2H), 2.86 (m, 3H), 2.56 (m, 2H), 2.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3 (d, ^1J = 244.6 Hz), 157.7 (d, ^1J = 237.8 Hz), 150.6 (d, ^4J = 1.9 Hz), 142.5 (d, ^4J = 2.0 Hz), 136.7, 132.9, 132.5, 130.8, 130.3, 129.6, 126.9, 121.9, 121.5 (d, ^3J = 8.3 Hz), 115.4 (d, ^2J = 21.2 Hz), 115.0 (d, ^2J = 23.3 Hz), 114.4 (d, ^2J = 25.0 Hz), 113.3 (d, ^3J = 8.3 Hz), 77.2, 69.9, 59.4, 59.1, 58.5, 52.5, 32.7; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{26}H_{23}Cl_2F_2N_4O$ 515.12115, found 515.12072.

1-(1-(4-Chlorobenzyl)pyrrolidin-3-yl)-4-(2-(3,4-dichlorobenzyloxy)-5-fluorophenyl)-1*H*-1,2,3-triazole (2ac). Following the same procedure as that used for the synthesis of **2aa**, the reaction of 3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate **18a** (33.4 mg, 64.1 μmol), 4-chlorobenzaldehyde (18.0 mg, 128 μmol), CH_3CO_2H (1.10 μL, 19.2 μmol) and $NaBH(OAc)_3$ (54.3 mg, 256 μmol) in THF (0.6 mL) gave the title compound **2ac** (27.7 mg, 82%) as a yellow solid; mp 49.6–50.3 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (s, 1H), 8.06 (dd, J = 2.9, 9.6 Hz, 1H), 7.55 (d, J = 1.8 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.25 (dd, J = 1.5, 6.6 Hz, 1H), 7.19 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 6.95 (m, 2H), 5.22 (m, 1H), 5.08 (s, 2H), 3.58 (q, J = 14.1 Hz, 2H), 2.88 (m, 3H), 2.56 (m, 2H), 2.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7 (d, ^1J = 237.9 Hz), 150.6 (d, ^4J = 1.9 Hz), 142.5 (d, ^4J = 2.1 Hz), 136.7, 133.3, 132.9, 132.5, 130.8, 129.9, 129.6, 128.6, 126.9, 121.9, 121.5 (d, ^3J = 8.4 Hz), 115.0 (d, ^2J = 23.4 Hz), 114.4 (d, ^2J = 25.1 Hz), 113.3 (d, ^3J = 8.3 Hz), 77.2, 69.9, 59.5, 59.1, 58.5, 52.5, 32.7; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{26}H_{23}Cl_3FN_4O$ 531.09160, found 531.09110.

1-(1-(2,3-Dichlorobenzyl)pyrrolidin-3-yl)-4-(2-(3,4-dichlorobenzyloxy)-5-fluorophenyl)-1*H*-1,2,3-triazole (2ad). Following the same procedure as that used for the synthesis of **2aa**, the reaction of 3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate **18a** (34.3 mg, 65.8 μmol), 2,3-dichlorobenzaldehyde (23.0 mg, 132 μmol), CH_3CO_2H (1.13 μL, 19.7 μmol) and $NaBH(OAc)_3$ (55.8 mg, 263 μmol) in THF (0.6 mL) gave the title compound **2ad** (28.1 mg, 76%) as a yellow solid; mp 72.4–75.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (s, 1H), 8.06 (dd, J = 3.0, 9.6 Hz, 1H), 7.47 (dd, J = 1.4, 9.7 Hz, 1H), 7.33 (t, J = 7.2 Hz, 2H), 7.22–7.04 (m, 3H), 6.97 (td, J = 3.0, 8.2 Hz, 1H), 6.0 (q, J = 4.6 Hz, 1H), 5.28 (m, 1H), 5.09 (s, 2H), 3.74 (bs, 2H), 3.00 (bs, 2H), 2.86 (bs, 1H), 2.59 (m, 2H), 2.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7 (d, ^1J = 237.8 Hz), 150.6 (d, ^4J = 1.9 Hz), 142.6 (d, ^4J = 2.0 Hz), 136.8, 133.2, 132.8, 132.3, 132.2, 130.6, 129.4, 128.4, 127.2, 126.8, 121.8, 121.6 (d, ^3J = 8.5 Hz), 114.9 (d, ^2J = 23.2 Hz), 114.4 (d, ^2J = 25.1 Hz), 113.3 (d, ^3J = 8.3 Hz), 77.2, 69.8, 60.0, 59.3, 56.7, 52.5, 32.8; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{26}H_{22}Cl_4FN_4O$ 565.05263, found 565.05217.

1-(1-(2,4-Dichlorobenzyl)pyrrolidin-3-yl)-4-(2-(3,4-dichlorobenzyloxy)-5-fluorophenyl)-1*H*-1,2,3-triazole (2ae). Following the same procedure as that used for the synthesis of **2aa**, the reaction of 3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate **18a** (33.3 mg, 63.9 μmol), 2,4-dichlorobenzaldehyde (22.4 mg, 128 μmol), CH_3CO_2H (1.10 μL, 19.2 μmol) and $NaBH(OAc)_3$(54.2 mg, 256 μmol) in THF (0.6 mL) gave the title compound **2ae** (25.3 mg, 70%) as a yellowish solid; mp 120.0–121.3 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (s, 1H), 8.06 (dd, J = 2.9, 9.6 Hz, 1H), 7.50 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.29 (s, 1H), 7.23–7.07 (m, 3H), 6.97 (td, J = 3.0, 8.2 Hz, 1H), 6.91 (q, J = 4.5 Hz, 1H), 5.24 (bs, 1H), 5.08 (s, 2H), 3.68 (bs, 2H), 2.98–2.83 (m, 3H), 2.57 (m, 2H), 2.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7 (d, ^1J = 237.7 Hz), 150.6 (d, ^4J = 2.0 Hz), 142.6 (d, ^4J = 2.9 Hz), 142.5, 136.8, 134.6, 133.6, 132.9,

132.4, 131.1, 130.7, 129.4, 129.3, 127.1, 126.8, 121.7, 121.6 (d, ^3J = 8.2 Hz), 114.9 (d, ^2J = 23.3 Hz), 114.4 (d, ^2J = 25.0 Hz), 113.2 (d, ^3J = 8.4 Hz), 77.2, 69.8, 59.9, 59.3, 55.4, 52.5, 32.7.

(3-(4-(2-(3,4-Dichlorobenzyloxy)-5-fluorophenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidin-1-yl)(phenyl)methanone (2af). To a solution of 3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate **18a** (28.8 mg, 55.2 μmol) and TEA (7.78 μL, 55.8 μmol) was added benzoyl chloride (6.41 μL, 55.2 μmol). The reaction mixture was stirred at room temperature for 24 h, and then diluted with water. The aqueous phase was then extracted with DCM (3 × 3 mL). The organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (EtOAc–*n*-hexane = 1 : 1) to give the title compound **2af** (18.7 mg, 67%) as a white solid; mp 55.4–57.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, J = 7.3 Hz, 1H), 7.90 (s, 1H), 7.52–7.41 (m, 7H), 7.23 (s, 1H), 6.98 (td, J = 3.0, 8.2 Hz, 1H), 6.89 (q, J = 4.4 Hz, 1H), 5.21 (bs, 1H), 5.10 (s, 2H), 4.19–3.65 (m, 4H), 2.51 (bs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1, 157.7 (d, ^1J = 238.0 Hz), 150.5, 142.4, 136.7, 135.9, 133.0, 132.6, 130.9, 130.4, 129.4, 128.4, 127.2, 126.7, 122.3, 120.9 (d, ^3J = 9.2 Hz), 115.3 (d, ^2J = 23.4 Hz), 114.5 (d, ^2J = 25.3 Hz), 113.4 (d, ^3J = 8.3 Hz), 77.2, 69.8, 65.8, 63.7, 59.3, 58.4, 54.2, 51.8, 47.7, 44.3, 32.7, 30.5; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{26}H_{22}Cl_2FN_4O_2$ 511.10984, found 511.10888.

(3-(4-(2-(3,4-Dichlorobenzyloxy)-5-fluorophenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidin-1-yl)(4-fluorophenyl)methanone (2ag). Following the same procedure as that used for the synthesis of **2af**, the reaction of 3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate **18a** (32.7 mg, 62.7 μmol), 4-fluorobenzoyl chloride (7.41 μL, 62.7 μmol) and TEA (11.4 μL, 81.5 μmol) in THF (0.6 mL) gave the title compound **2ag** (31.2 mg, 94%) as a white solid; mp 111.8–113.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, J = 12.3 Hz, 1H), 7.90 (s, 1H), 7.52 (d, J = 1.4 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.22 (bs, 1H), 7.07 (t, J = 7.8 Hz, 2H), 6.97 (td, J = 3.0, 8.2 Hz, 1H), 6.89 (q, J = 4.5 Hz, 1H), 5.19 (bs, 1H), 5.09 (s, 2H), 4.16–4.01 (m, 2H), 3.85 (bs, 1H), 3.65 (bs, 1H), 2.51 (bs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 163.8 (d, ^1J = 249.4 Hz), 157.7 (d, ^1J = 238.2 Hz), 150.5, 142.4, 136.7, 133.0, 132.6, 132.0, 130.9, 129.6 (d, ^3J = 8.5 Hz), 129.4, 126.8, 122.2, 120.9 (d, ^3J = 8.4 Hz), 115.6 (d, ^2J = 19.9 Hz), 115.3 (d, ^2J = 22.9 Hz), 114.5 (d, ^2J = 25.2 Hz), 113.3 (d, ^3J = 8.4 Hz), 77.2, 69.8, 59.3, 58.4, 54.3, 52.0, 47.8, 44.5, 32.7, 30.5; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{26}H_{21}Cl_2F_2N_4O_2$ 529.10041, found 529.09987.

(4-Chlorophenyl)(3-(4-(2-(3,4-dichlorobenzyloxy)-5-fluorophenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidin-1-yl)methanone (2ah). Following the same procedure as that used for the synthesis of **2af**, the reaction of 3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)-phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate **18a** (33.4 mg, 64.1 μmol), 4-chlorobenzoyl chloride (8.21 μL, 64.1 μmol) and TEA (11.6 μL, 83.3 μmol) in THF (0.6 mL) gave the title compound **2ah** (30.5 mg, 87%) as a white solid; mp 137.4–140.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, J = 14.6 Hz, 1H), 7.90 (s, 1H), 7.52–7.37 (m, 6H), 7.26–7.22 (m, 1H), 6.97 (td, J = 3.0, 8.2 Hz, 1H), 6.89 (q, J = 4.4 Hz, 1H), 5.18 (bs, 1H), 5.08 (s, 2H), 4.14–3.99 (m, 2H), 3.85 (bs, 1H), 3.65 (bs, 1H), 2.50 (bs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 157.7 (d, ^1J = 238.1 Hz), 150.6 (d, ^4J = 1.7 Hz), 142.4, 136.7, 136.5, 134.2, 133.0, 132.6, 130.9, 129.4, 128.7, 126.8, 122.3, 120.9 (d, ^3J = 7.7 Hz), 115.3 (d, ^2J = 23.3 Hz), 114.5 (d, ^2J = 25.1 Hz), 113.3 (d, ^3J = 8.3 Hz), 77.2, 69.9, 59.3, 58.3, 54.2, 52.0, 47.7, 44.4, 32.7, 30.5; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{26}H_{21}Cl_3FN_4O_2$ 545.07086, found 545.07018.

4-(2-(3,4-Dichlorobenzyloxy)-5-fluorophenyl)-1-(1-(phenylsulfonyl)pyrrolidin-3-yl)-1*H*-1,2,3-triazole (2ai). Following the same procedure as that used for the synthesis of **2af**, the reaction of 3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate **18a** (25.4 mg, 48.7 μmol), benzenesulfonyl chloride (6.22 μL, 48.7 μmol) and TEA (6.68 μL, 49.2 μmol) in THF (0.5 mL) gave the title compound **2ai** (10.6 mg, 40%) as a white solid; mp 136.3–137.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01 (dd, J = 3.1, 9.5 Hz, 1H), 7.90 (s, 1H), 7.79 (dd, J = 1.5, 8.1 Hz, 2H), 7.56–7.47 (m, 5H), 7.28 (m, 1H), 7.00 (td, J = 2.0, 4.9 Hz, 1H), 6.90 (q, J = 4.5 Hz, 1H), 5.09 (bs, 3H), 3.72 (m, 2H), 3.47 (m, 2H), 2.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7 (d, ^1J = 232.8 Hz), 150.5, 142.5, 136.7, 136.1, 133.1, 133.0, 132.6, 131.0, 129.5, 129.2, 127.4, 126.9, 121.7, 121.0 (d, ^3J = 8.4 Hz), 115.2 (d, ^2J = 23.2 Hz), 114.5 (d, ^2J = 25.2 Hz), 113.3 (d, ^3J = 8.3 Hz), 69.9, 58.8, 53.4, 46.2, 31.5; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{25}H_{22}Cl_2FN_4O_3S$ 547.07682, found 547.07700.

4-(2-(3,4-Dichlorobenzyloxy)-5-fluorophenyl)-1-(1-((4-fluorophenyl)sulfonyl)pyrrolidin-3-yl)-1*H*-1,2,3-triazole (2aj). Following the same procedure as that used for the synthesis of **2af**, the reaction of 3-(4-(5-fluoro-2-(3,4-dichlorobenzyloxy)-phenyl)-1*H*-1,2,3-triazole-1-yl)pyrrolidinium 2,2,2-trifluoroacetate **18a** (32.9 mg, 63.1 μmol), 4-fluorobenzenesulfonyl chloride (12.3 mg, 63.1 μmol) and TEA (11.4 μL, 81.5 μmol) in THF (0.6 mL) gave the title compound **2aj** (12.4 mg, 35%) as a yellowish solid; mp 167.0–168.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (dd, J = 3.1, 9.5 Hz, 1H), 7.89 (s, 1H), 7.79 (m, 2H), 7.54–7.52 (m, 2H), 7.28 (m, 1H), 7.17 (t, J = 8.5 Hz, 2H), 7.00 (td, J = 3.0, 8.2 Hz, 1H), 6.91 (q, J = 4.5 Hz, 1H), 5.09 (bs, 3H), 3.72 (m, 2H), 3.48 (t, J = 7.1 Hz, 2H), 2.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4 (d, ^1J = 254.1 Hz), 157.7 (d, ^1J = 234.5 Hz), 150.5, 142.5, 136.6, 132.8 (d, ^2J = 25.8 Hz), 132.3, 131.0, 130.2 (d, ^3J = 9.3 Hz), 129.5, 126.9, 121.7, 120.9 (d, ^3J = 8.5 Hz), 116.5 (d, ^2J = 22.3 Hz), 115.3 (d, ^2J = 23.1 Hz), 114.5 (d, ^2J = 25.3 Hz), 113.2 (d, ^3J = 8.3 Hz), 69.8, 58.8, 53.5, 46.2, 31.6; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{25}H_{20}Cl_2F_2N_4O_3S$ 565.05263, found 565.05216.

Biological evaluation

JC-1 mitochondrial membrane potential assay

HT-22 cells (30 000 per well) were seeded into a clear 96-well plate (FALCON) at 200 μL per well one day prior to assay.

750 μM of JC-1 (Stratagene) in DMSO stock solution was dissolved in phenol red-free Opti-MEM (GIBCO) medium to make a final concentration of 7.5 μM JC-1 per well. The medium was removed from the plate, and 100 μL per well of JC-1 was added. Plates were incubated for 1 h and 15 min at 37 °C and washed twice with 100 μL per well PBS. Subsequently, cells were treated with 25 μL solution of each compound at 10 μM in Opti-MEM and incubated at 37 °C for 10 min followed by addition of 25 μL of amyloid beta (American peptide, 1–42) solution at 10 μM. Fluorescence was measured at every one hour for three hours at ex/em 530 nm/580 nm ('red') and ex/em 485 nm/530 nm ('green'). The ratio of green to red fluorescence was recorded and the percent changes in the ratio for each compound were calculated and normalized using the vehicle control as 100%.

CYP inhibition assay

The test compound (40 μL of a 25 μM solution of the compound in distilled water) into a 96-well plate and then 50 μL of the Master Pre-Mix (CYP450 BACULOSOMES® Reagent and Regeneration System) were added. The plate was incubated for 20 min at 37 °C to allow the compound to interact with the CYP450. The reaction was initiated by adding Vivid® CYP450 substrate/$NADP^+$ buffer (10 μL). The remaining enzyme activity was measured by reading the amount of fluorescent product using a fluorescence plate reader. The reference inhibitor for each CYP isozyme is indicated in Table 4.

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