Short cut to 1,2,3-triazole-based p38 MAP kinase inhibitors *via* [3 + 2]-cycloaddition chemistry†

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A series of 4,5-substituted 1,2,3-triazoles was synthesised *via* Cu(I)-catalysed azide–alkyne 1,3-dipolar [2 + 3]-cycloaddition reactions followed by a Suzuki coupling. The 1,2,3-triazoles were evaluated as inhibitors of the p38α MAP kinase, showing IC_{50} values in the high nanomolar range.

Introduction

The mitogen-activated protein (MAP) kinases participate in important cellular processes and are potential targets in treatments of inflammation, cancer, and other diseases. The MAP kinase p38 responds to environmental stress (*e.g.* UV radiation, osmotic shock and mechanical stress) and is involved in the production of cytokines (IL-1 and TNFα), both of which are implicated in chronic inflammatory diseases.[1] Consequently, inhibition of the p38 MAP kinase with small organic molecules could provide an effective therapy for the treatment of these chronic autoimmune diseases and, therefore, major efforts have been made in order to synthesise and evaluate different inhibitors of p38 kinase.[2–5]

One class of compounds that have been developed as selective p38 inhibitors are the pyridinylimidazole-based compounds (SB, SmithKline Beecham). Several of these compounds have been shown to be highly potent and to inhibit the p38 kinase at nanomolar concentration (Fig. 1).[6,7]

In our search for new scaffolds that could be used in the development of kinase inhibitors we became interested in 4- and 5-substituted 1,2,3-triazoles. The key step in forming this five-membered ring system would be the Cu(I)-catalysed azide–alkyne 1,3-dipolar [2 + 3]-cycloaddition reaction.[8,9] With the high reaction yield and simple reaction and purification conditions of the "click chemistry", 1,3-dipolar [2 + 3]-cycloaddition has found its use in applications in organic synthesis and drug discovery.[10–13]

The structural similarities between 4- and 5-substituted 1,2,3-triazoles and the pyridinylimidazole-based inhibitors suggest a possible similarity in binding mode to the p38 MAP kinase.

With this strategy, the desired inhibitors could easily be obtained in only two steps, starting with the conversion of the azide into the 4-aryl substituted 5-iodo-1,2,3-triazole *via* cycloaddition (and *in situ* iodination) and followed by the substitution of the iodine for the pyridinyl ring *via* a Suzuki coupling (Scheme 1).

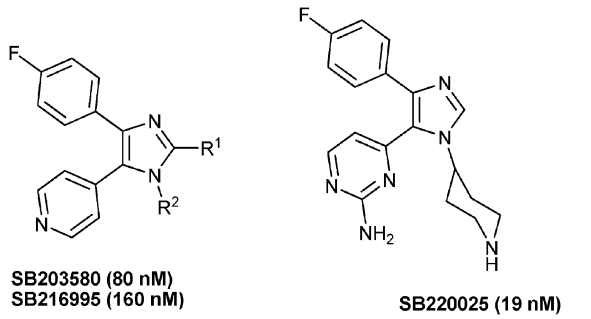
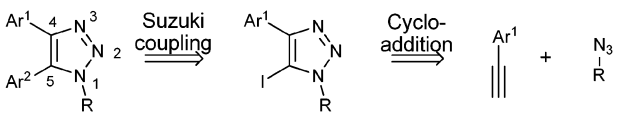


Fig. 1 Examples of the known p38 kinase inhibitors SB203580 (R^1: 4-Ph-$SOCH_3$; R^2: H), SB216995 (R^1: H; R^2: cyclopropylmethyl), and SB220025.



Scheme 1 Retrosynthetic strategy for 4- and 5-substituted 1,2,3-triazoles.

In this paper we wish to present the design, synthesis and biological evaluation of 4,5-substituted 1,2,3-triazoles. The results show that these compounds are potential inhibitors of p38α MAP kinase.

Results and discussion

Design

The design of the inhibitors is based on the docking (Glide, XP mode) of different 1,2,3-triazole based inhibitors into the p38α MAP kinase having the SB220025 inhibitor in the active site (pdb-1BL7).[14–16]

The docking was used in order to evaluate if the triazole-based compounds can mimic the binding modes of the pyridine ring to the hinge region and the 4-fluorophenyl group to the hydrophobic pocket I, as seen for the SB inhibitors

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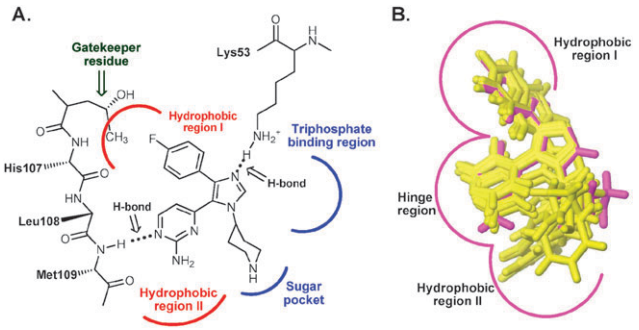

Fig. 2 (A) Important interactions of inhibitor SB220025 in p38α MAP kinase. (B) Superposition of 4,5-substituted 1,2,3-compounds **5a–h** docked into p38α kinase (SB220025: purple; **5a–h**: yellow).

(Fig. 2). Furthermore, the docking was used to guide the design of new compounds in which the R-group interacts with the hydrophobic region II of the ATP binding site (Fig. 3). The docking results show that triazole compound **5a** docks into the ATP binding site in an almost identical way to the SB220025 ligand, *i.e.* the pyridine nitrogen hydrogen bonds to the hinge region and the 4-fluorophenyl group is positioned in the hydrophobic pocket I. The docking results also show that the benzyl group in compound **5a** is positioned in the hydrophobic region II below the pyridine ring.

Compound **5e** was used in order to directly compare the binding of the 1,2,3-triazole scaffold and the imidazole based inhibitor SB216995 to p38α kinase. The only difference between **5e** and SB216995 is that the carbon atom in the 2-position of the imidazole ring has been replaced with a nitrogen atom in the triazole ring of compound **5e** (*cf.* SB216995, Fig. 1). The docking results suggest a binding mode for compound **5e** similar to that for compound **5a**.

Another set of compounds that was found to mimic the binding mode of the SB220025 inhibitor, *i.e.* binds to the hinge region and hydrophobic region I (Fig. 2B), was compounds **5f–h** which are derived from azides of the corresponding amino acid derivatives (such as L-tryptophan, L-phenylalaninol, and L-valinol). The docking of these compounds into the ATP binding site of p38 suggests that the heteroatoms could form hydrogen bonds to the entrance of the ATP pocket and thus bind more strongly to the active site of the kinase.

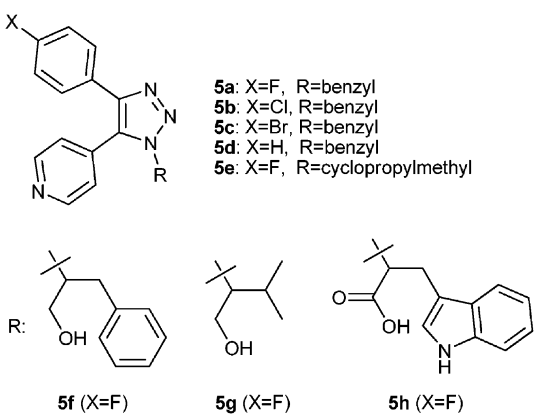

Fig. 3 Potential 4- and 5-substituted 1,2,3-triazoles as inhibitors of p38 MAP kinase.

In order to explore the binding interaction between hydrophobic region I and the aromatic substituent in the 4-position of the triazole ring, the fluorine in **5a** was substituted with chlorine (**5b**), bromine (**5c**) or a hydrogen (**5d**). The substitution generates compounds that also dock into the "preferred" binding mode.

Synthesis

With these promising docking results in hand, we turned to our synthesis route in order to obtain the desired 1,2,3-triazole compounds **5a–h**. The benzyl azide **2a** was easily prepared from benzyl bromide and sodium azide in acetone in good yield (75%) (Fig. 4).[17] For the synthesis of the azido alcohols **2f–g**, the corresponding amino acid derivative was converted to the azide in moderate to good yields (32–84%) using triflyl azide and DMAP in DCM.[18] The L-tryptophan ethyl ester was converted to the corresponding azide **2h** in 51% isolated yield, using triflyl azide, DIPEA, $CuSO_4 \cdot 5H_2O$ and methanol at room temperature for 18 h.[19] The azides **2a** and **2f–h** were converted to the 4-aryl substituted 5-iodo-1,2,3-triazoles (**4a–d** and **4f–h**) *via* the Cu(I)-catalysed [3 + 2] cycloaddition with 4-halogenated ethynylbenzene in THF–DCM and simultaneous iodination with ICl.[20] The reactions proceeded smoothly overnight in good yields (41–67%) considering this is a one-pot two-step reaction with no intermediate purifications.

The syntheses of 4- and 5-substituted 1,2,3-triazole inhibitors **5a–h** were completed *via* a palladium-catalysed Suzuki coupling reaction between the halogenated 4-aryl substituted 5-iodo-1,2,3-triazoles (**4a–d** and **4f–h**) and 4-pyridineboronic acid in the presence of $Pd(PPh_3)_4$ 2 mol% and K_2CO_3 at 150 °C in a microwave reactor. The triazole compounds **5a–d** having a benzyl substituent were obtained in good yields (63–85%) and the amino acid derivatives **5f–h** were obtained in moderate to good yields (35–85%). The lower yield of the tryptophan compound **5h** (35%) could be explained by the fact that the ester functionality was hydrolysed *in situ* to the

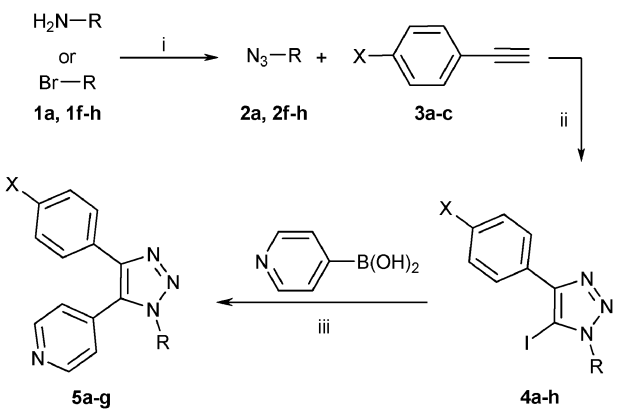

Fig. 4 Synthesis of 4- and 5-substituted 1,2,3-triazoles as potential p38α inhibitors. (i) Amino acid derivatives, TfN_3, CH_2Cl_2–methanol, r.t. or benzyl bromide, NaN_3, acetone–H_2O, r.t., 2 h. (ii) Compounds **2a–d**, CuI, triethylamine (1.2 equiv.), ICl, THF, r.t., overnight. (iii) Compounds **4**, 4-pyridineboronic acid (1.5 equiv.), K_2CO_3 (3 equiv.), $Pd(PPh_3)_4$ (2%), dioxane–H_2O, MW (150 °C, 30 min).

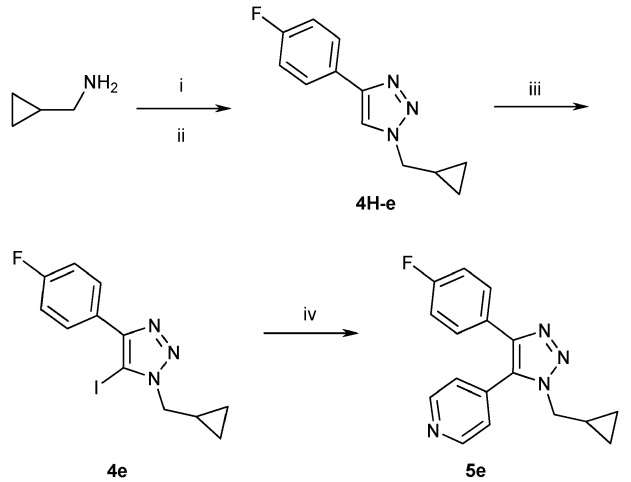

Fig. 5 Synthesis of inhibitor **5e**. (i) TfN_3, $CuSO_4{\cdot}5H_2O$, $NaHCO_3$, DCM–MeOH–H_2O, 30 min, r.t. (ii) 1-Ethynyl-4-fluorobenzene, TBTA, Na ascorbate, 80 °C, MW, 1 h. (iii) *n*-BuLi, THF, −78 °C, 20 min, then add I_2, 2 h. (iv) Compound **4e**, 4-pyridineboronic acid (1.5 equiv.), K_2CO_3 (3 equiv.), $Pd(PPh_3)_4$ (2%), dioxane–H_2O, MW (150 °C, 30 min).

carboxylic acid, thus making it difficult to purify by silica gel chromatography.

Due to the volatility of the cyclopropyl azide, 1,2,3-triazole **4H-e** was formed from the reaction between cyclopropyl azide (prepared *in situ*) and subsequent reaction of the azide with 1-ethynyl-4-fluorobenzene (79% isolated yield) (Fig. 5). The iodine was introduced in the 5-position *via* a deprotonation of the triazole with *n*-butyllithium at −78 °C, followed by addition of iodine. The final compound **5e** was obtained by the Suzuki coupling in 78% yield using the same conditions as previously described.

Biology

The inhibitory potencies of the compounds **5a–h** were evaluated using a commercial radiometric p38 assay.‡ The obtained IC_{50} values for compounds **5a–h** are shown in Table 1. The best inhibition is seen for compounds **5a–c** having a benzyl group in the 1-position of the triazole ring and a fluorine, a chlorine, or a bromine atom in the *para*-position of the phenyl group in the 4-position of the 1,2,3-triazole ring. Surprisingly, *p*-chlorophenyl (**5b**) and *p*-bromophenyl (**5c**) gave a two-fold increase in inhibition compared to the *p*-fluorophenyl derivative **5a**, while the inhibition of compound **5d** (having a phenyl group in the 4-position) decreases two-fold.

Introducing more bulky substituents in the 1-position, such as in compounds **5f–h**, resulted in a reduced inhibitory effect. The decrease in activity was most dramatic for compounds **5h** and **5f**, having a 1*H*-indol-3-ylpropanoic acid group and a phenylpropan-1-ol group in the 1-position, respectively, where the IC_{50} value dropped by a factor of more than a hundred compared to compound **5b**. Furthermore, the results showed

‡ Millipore's KinaseProfiler™ service and protocols available at http://www.millipore.com/drugdiscovery/dd3/KinaseProfiler http://www.millipore.com/drugdiscovery/dd3/brochure

Table 1 IC_{50} values for synthesised compounds **5a–h** in p38α MAP kinase inhibition

Compound	IC_{50}/nM[a]
SB203580	110 (80)
SB220025	19
SB216995	160
5a	807
5b	404
5c	509
5d	2020
5e	961
5f	83 454
5g	3977
5h	> 100 000

[a] Titration curves for the IC_{50} determinations are available in the ESI.†

that introducing a cyclopropylmethyl group in the 1-position (**5e**) leads to a similar inhibition as seen for compound **5a** (*cf.* 961 nM to 807 nM, respectively).

The conclusion is that the 4,5-substituted 1,2,3-triazole ring can be used as a scaffold for synthesising inhibitors of the p38α MAP kinase. However, the results also suggest that the 1,2,3-triazole scaffold binds five times more weakly to the active site of p38α kinase than the imidazole-based scaffold (compound **5e** (807 nM) compared to SB216995 (160 nM)), despite the structural similarity of the scaffolds.

As seen from the binding mode of SB220025 (Fig. 2A), a lysine residue (Lys53) hydrogen bonds to one of the nitrogens in the five-membered ring. A comparison of the pK_{AH} of the protonated nitrogen in the imidazole and in the 1,2,3-triazole (pK_{AH} = 6.95 and pK_{AH} = 1.2, respectively) suggests that the more basic imidazole is a better hydrogen bond acceptor to the lysine than triazole. In order to further investigate the hydrogen bond acceptor capability of imidazole and triazole, we performed a computational study of the electrostatic potential of compound **5e** and the SB216995 inhibitor at the B3LYP/6-31G(d) level of theory.[21–25]

The calculation shows a higher negative potential around the imidazole nitrogen, indicating that the imidazole nitrogen is a better hydrogen acceptor than 1,2,3-triazole (Fig. 6).

In order to quantify the difference in strength of the hydrogen bond to imidazole and 1,2,3-triazole, we optimised the structures of 1-methylimidazole and 1-methyl-1,2,3-triazole in water (continuum model) at the B3LYP/6-31G(d) level of theory. Further we also optimised the 1-methylimidazole and 1-methyl-1,2,3-triazole hydrogen bonded to an ammonium ion in water (continuum model) at the same level of theory. From the energies of the optimised molecules, the isodesmic reaction energy was calculated to be −1.1 kcal mol^{-1} (Fig. 6) in favour of hydrogen bonding to 1-methylimidazole. An isodesmic reaction energy difference of 1.1 kcal mol^{-1} corresponds to a 6.2 times stronger binding of the ammonium ion to 1-methylimidazole compared to 1-methyl-1,2,3-triazole. The isodesmic energy for this reaction was also calculated using explicit solvation of water on the nitrogen in 1-methyl-1,2,3-triazole and 1-methylimidazole and the energy difference of 0.73 kcal mol^{-1} corresponds to a 3.5 times stronger binding of the ammonium ion to 1-methylimidazole compared to 1-methyl-1,2,3-triazole at the same level of theory. These

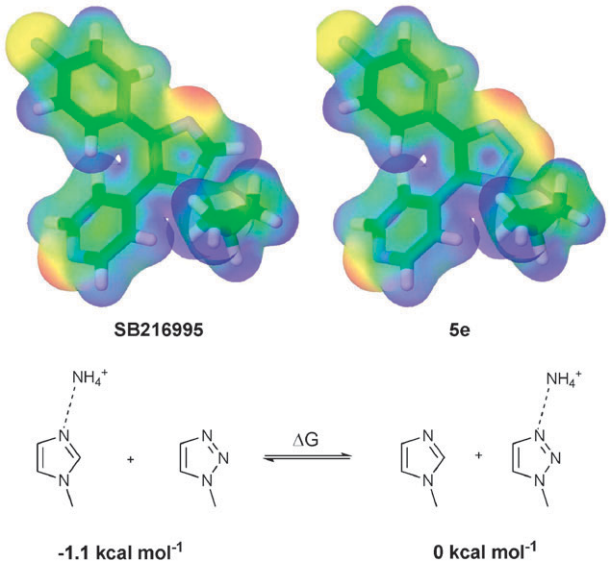

Fig. 6 Electrostatic potential for optimised compounds SB216995 and **5e** at the B3LYP/6-31G(d) level of theory. Isodesmic energy for the hydrogen bonded ammonium ion to 1-methylimidazole in water compared to hydrogen bonded ammonium ion to 1-methyl-1,2,3-triazole in water at the B3LYP/6-31G(d) level of theory.

results are in good agreement with the results obtained experimentally (five times stronger binding). The result suggests that the weaker hydrogen bonding ability of the nitrogen in the 1,2,3-triazole ring is the major reason for the difference in inhibition between **5e** and SB216995.

Conclusions

In summary, we report a fast and efficient synthesis of 4,5-substituted 1,2,3-triazoles using Cu(I)-catalysed azide–alkyne 1,3-dipolar [2 + 3]-cycloadditions and Suzuki coupling chemistry. The obtained compounds show activity as inhibitors of p38α MAP kinase in the high nanomolar range. The best inhibition is seen for compound **5b**, having a benzyl group in the 1-position of the triazole ring and a *p*-chlorophenyl group in the 4-position of the 1,2,3-triazole ring. From the docking results, the benzyl group is suggested to interact with the hydrophobic region II in the active site of p38α MAP kinase (Fig. 7).

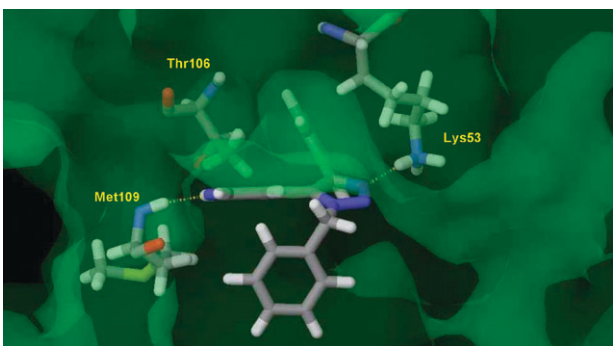

Fig. 7 Suggested binding mode of compound **5b** from Glide docking in XP mode. Compound **5b** hydrogen bonds to Met109 (hinge region) and to Lys53.

The 1,2,3-triazole scaffold gives lower inhibition than can be seen for the imidazole scaffold and the explanation for the lower inhibition is the weaker hydrogen bonding ability of the nitrogen in the 1,2,3-triazole ring. In order to improve the triazole-based inhibitors, future work will focus on investigating the substitution in the 1-, 4-, and 5-position of the scaffold in order to improve potency.

Experimental

General

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were obtained using a JEOL JNM-EX 400 spectrometer. Column chromatography was performed by manual flash chromatography (wet packed silica, 0.04–0.063 mm) or by automated column chromatography on Biotage SP-4 using pre-packed columns. Microwave reactions were performed in a Biotage Initiator reactor with fixed hold time. IR spectra were recorded on a Perkin-Elmer 16 PC spectrometer. Separation of CH_2Cl_2 and H_2O was performed by a phase separator. All azides were prepared according to the literature and products were in accordance with the literature. All comparative kinase assays were conducted using Millipore's KinaseProfiler™ service according to the standard protocols.‡

Computational details

Docking. X-ray structures with inhibitors were used as the starting point for all dockings. The p38 kinase was prepared according to the standard procedure in the Schrödinger package. Docking was performed by using Glide (Schrödinger) with extraprecision (XP) settings and standard parameters for ligand docking.

Quantum chemical calculations. Compounds **5e** and SB216995 were optimised at the B3LYP/6-31G(d) level of theory using Jaguar[26] from Schrödinger Inc. 1-Methylimidazole, 1-methylimidazole*NH_4^+, 1-methyl-1,2,3-triazole, 1-methyl-1,2,3-triazole*NH_4^+ were optimised at the B3LYP/6-31G(d) level of theory using a continuum model in water.

Synthesis

General procedure A for preparation of triazoles. Azide (1 equiv.), alkyne (1 equiv.), Et_3N (1.2 equiv.), dry THF (10 ml), ICl dissolved in CH_2Cl_2 (1 equiv.) and CuI (1 equiv.) were added in that order. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 18 h and concentrated under reduced pressure. The crude product was purified by flash chromatography on a silica gel column using hexane–ethyl acetate as eluent.

1-Benzyl-4-(4-fluorophenyl)-5-iodo-1*H*-1,2,3-triazole (4a). The title compound was prepared according to the general procedure A and was obtained by flash chromatography eluting with hexane–ethyl acetate (11 : 1) to yield a yellow solid (314 mg, 41%). ^{1}H NMR ($CDCl_3$): δ 7.93–7.90 (m, 2H), 7.39–7.13 (m, 7H), 5.67 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 163.3 (d, C–F, J = 247.0), 149.8, 134.6, 129.7 (d, C–F, J = 7.7 Hz), 129.3, 128.9, 128.2, 126.7, 115.9 (d, C–F, J = 22.2 Hz), 76.6,

54.8; IR (KBr, cm^{-1}): 3429, 3031, 2924, 1609, 1542, 1479, 1236, 836, 723. EA($C_{15}H_{11}FIN_3$): Required: 47.51 (C); 2.92 (H); 11.08 (N); Found: 47.43 (C), 2.92 (H), 10.28 (N).

1-Benzyl-4-(4-chlorophenyl)-5-iodo-1*H*-1,2,3-triazole (4b). The title compound was prepared according to the general procedure A and was obtained by flash chromatography eluting with hexane–ethyl acetate (11 : 1) to yield a yellow solid (396 mg, 50%). ^{1}H NMR ($CDCl_3$): δ 7.90 (d, J = 8.8 Hz, 2H), 7.44–7.30 (m, 7H), 5.67 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 149.5, 134.9, 134.5, 129.3, 129.1, 129.0, 129.0, 128.9, 128.2, 76.8, 54.8; IR (KBr, cm^{-1}): 3429, 3030, 2919, 2359, 1463, 1231, 1091, 831, 718. EA($C_{15}H_{11}ClIN_3$): Required: 45.54 (C); 2.80 (H); 10.62 (N); Found: 45.16 (C), 2,62 (H), 10.34 (N).

1-Benzyl-4-(4-bromophenyl)-5-iodo-1*H*-1,2,3-triazole (4c). The title compound was prepared according to the general procedure A and was obtained by flash chromatography eluting with hexane–ethyl acetate (12 : 1) to yield a yellow solid (588 mg, 67%). ^{1}H NMR ($CDCl_3$): δ 8.84 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.39–7.30 (m, 5H), 5.67 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 149.5, 134.5, 132.1, 129.5, 129.3, 129.2, 128.8, 128.2, 123.1, 76.8, 54.8; IR (KBr, cm^{-1}): 3433, 2919, 1454, 1225, 1066, 977, 825, 70. EA($C_{15}H_{11}BrIN_3$): Required: 40.94 (C); 2.52 (H); 9.55 (N); Found: 41.39 (C), 2.41 (H), 9.30 (N).

1-Benzyl-5-iodo-4-phenyl-1*H*-1,2,3-triazole (4d). The title compound was prepared according to the general procedure A and was obtained by flash chromatography eluting with hexane–ethyl acetate (7 : 1) to yield a white solid (408 mg, 57%). ^{1}H NMR ($CDCl_3$): δ 7.94 (d, J = 7.0 Hz, 2H), 7.48–7.41 (m, 8H), 5.68 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 150.5, 134.7, 130.5, 129.2, 128.9, 128.9, 128.8, 128.1, 127.8, 76.7, 54.7; IR (KBr, cm^{-1}): 3423, 3030, 2927, 1606, 1445, 1224, 697. EA($C_{15}H_{12}IN_3$): Required: 49.88 (C); 3.35 (H); 11.63 (N); Found: 49.63 (C), 2.93 (H), 11,27 (N).

1-(Cyclopropylmethyl)-4-(4-fluorophenyl)-1*H*-1,2,3-triazole (4H-e). Cyclopropanemethylamine (129 µl, 1.5 mmol), $CuSO_4 \cdot 5H_2O$ (7.5 mg, 30 µmol) and $NaHCO_3$ (126 mg, 1.5 mmol) were placed in a microvial and dissolved in H_2O (3 ml). Freshly prepared triflyl azide was added, followed by addition of methanol until the solution became homogenous. The reaction mixture was stirred at room temperature until completion of the reaction according to TLC (30 min). 1-Ethynyl-4-fluorobenzene (180 mg, 1.5 mmol), TBTA (40 mg, 75 µmol) and sodium ascorbate (30 mg, 0.15 mmol) were added to the solution and the reaction mixture was heated in the microwave reactor at 80 °C for 1 h. The solvents were removed under reduced pressure and the resulting slurry was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic phases were washed with brine (10 ml) and H_2O (10 ml), the organic and aqueous layers were separated with a phase separator and concentrated under reduced pressure. The title compound was obtained by flash chromatography eluting with hexane–ethyl acetate (4 : 1 v/v) to yield a white solid (258 mg, 79%). ^{1}H NMR ($CDCl_3$): δ 7.83 (s, 1H), 7.77 (m, 2H), 7.09–7.03 (m, 2H), 4.20 (d, J = 7.3 Hz, 2H), 1.29 (m, 1H), 0.67 (m, 2H), 0.42 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 163.1 (d, C–F, J = 245.5 Hz), 146.7, 127.3 (d, C–F, J = 8.4 Hz), 127.0 (d, C–F, J = 3.1 Hz), 118.8, 115.6 (d, C–F, J = 21.4 Hz), 55.0, 10.9, 4.1; IR (KBr, cm^{-1}): 3444, 3100, 1493, 1226, 1067, 829. EA($C_{12}H_{12}FN_3$): Required: 66.34 (C); 5.57 (H); 19.34 (N); Found: 66.07 (C), 6.43 (H), 19.29 (N).

1-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-iodo-1*H*-1,2,3-triazole (4e). *n*-BuLi (616 µl, 1.4 M in hexane, 0.58 mmol) was added to a 0.1 M solution of 1-(cyclopropylmethyl)-4-(4-fluorophenyl)-1*H*-1,2,3-triazole (125 mg, 0.58 mmol) in dry THF (5.8 ml) under nitrogen atmosphere at −78 °C. After 20 min a solution of I_2 (292 mg, 1.15 mmol) in dry THF (1.3 ml) was added and the reaction mixture was allowed to stir at −78 °C for 1 h and was then stirred an additional hour at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic and aqueous layers were separated with a phase separator. The organic layer was concentrated under reduced pressure and the target compound was obtained by flash chromatography eluting with hexane–ethyl acetate (4 : 1) to yield a yellow solid (101 mg, 51%). ^{1}H NMR ($CDCl_3$): δ 7.91 (m, 2H), 7.15 (m, 2H), 4.31 (d, J = 7.0 Hz, 2H), 1.44 (m, 1H), 0.65 (m, 2H), 0.54 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 162.8 (d, C–F, J = 248.3 Hz), 148.9, 129.3 (d, C–F, J = 8.5 Hz), 126.5 (d, C–F, J = 3.1 Hz), 115.5 (d, C–F, J = 22.2 Hz), 75.8, 55.3, 11.2, 4.3; IR (KBr, cm^{-1}): 3433, 2997, 1610, 1479, 1226, 836. EA($C_{12}H_{11}FIN_3$): Required: 42.00 (C); 3.23 (H); 12.25 (N); Found: 41.36 (C), 3.30 (H), 11.90 (N).

2-(4-(4-Fluorophenyl)-5-iodo-1*H*-1,2,3-triazol-1-yl)-3-phenylpropan-1-ol (4f). The title compound was prepared according to the general procedure A and was obtained by flash chromatography eluting with hexane–ethyl acetate (2 : 1) to yield a yellow solid (409 mg, 64%). ^{1}H NMR ($CDCl_3$): δ 7.60 (m, 2H), 7.22–7.03 (m, 7H), 4.88 (m, 1H), 4.74 (s, 1H), 4.47 (m, 1H), 4.11(m, 1H), 3.25 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 162.8 (d, C–F, J = 248.3 Hz), 147.3, 136.1, 129.1 (d, C–F, J = 8.5 Hz), 129.0, 128.5, 127.0, 125.6 (d, C–F, J = 3.1 Hz), 115.4 (d, C–F, J = 21.5 Hz), 79.1, 65.8, 64.3, 37.8; IR (KBr, cm^{-1}): 3295, 2933, 1607, 1473, 1232, 1041, 835. EA($C_{17}H_{15}FIN_3O$): Required: 48.24 (C); 3.57 (H); 9.93 (N); Found: 48.21 (C), 3.61 (H), 9.83 (N).

2-(4-(4-Fluorophenyl)-5-iodo-1*H*-1,2,3-triazol-1-yl)-3-methylbutan-1-ol (4g). The title compound was prepared according to the general procedure A and was obtained by flash chromatography eluting with hexane–ethyl acetate (2 : 1) to yield a yellow solid (236 mg, 47%). ^{1}H NMR ($CDCl_3$): δ 7.82 (m, 2H), 7.13 (m, 2H), 4.39 (m, 2H), 4.06 (m, 1H), 2.53 (m, 1H), 1.12 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 162.9 (d, C–F, J = 248.3 Hz), 147.7, 129.4 (d, C–F, J = 8.5 Hz), 126.0 (d, C–F, J = 3.1 Hz), 115.5 (d, C–F, J = 21.5 Hz), 79.3, 69.7, 63.1, 30.6, 19.5, 19.4; IR (KBr, cm^{-1}): 3416, 2865, 1608, 1475, 1228, 1076, 834; $[\alpha]_D^{25}$ = −5.6 (c = 0.5 in CH_2Cl_2). $[M + 1]^+$ calcd for $C_{13}H_{15}N_3OFI$: 376.0317; found 376.0327.

Ethyl 2-(4-(4-fluorophenyl)-5-iodo-1*H*-1,2,3-triazol-1-yl)-3-(1*H*-indol-3-yl)propanoate (4h). The title compound was prepared according to the general procedure A and was

obtained by flash chromatography eluting with hexane–ethyl acetate (4 : 1) to yield a yellow oil (217 mg, 62%). ^{1}H NMR ($CDCl_3$): δ 8.22 (bs, 1H), 7.82 (m, 2H), 7.59 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.20–7.09 (m, 4H), 6.85 (s, 1H), 5.52 (app. t, J = 7.3, 8.1 Hz, 1H), 4.29 (q, J = 7.0, 7.3 Hz, 2H), 3.96 (d, J = 7.7 Hz, 2H), 1.27 (t, J = 7.0, 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 167.6, 162.8 (d, C–F, J = 247.8 Hz), 148.5, 136.0, 129.4 (d, C–F, J = 7.6 Hz), 126.9, 126.1 (d, C–F, J = 3.1 Hz), 123.7, 122.1, 119.6, 118.0, 115.5 (d, C–F, J = 21.4 Hz), 111.3, 109.4, 79.0, 63.8, 62.5, 27.4, 14.0; IR (KBr, cm^{-1}): 3408, 2927, 1741, 1480, 1230. $[M + 1]^+$ calcd for $C_{21}H_{18}N_4O_3FI$: 505.0531; found 505.0531.

General procedure for B Suzuki coupling reactions

Triazole (1 equiv.) was dissolved in dioxane–H_2O (3 : 1) and boronic acid (1.5 equiv.) and K_2CO_3 (3 equiv.) were added. Nitrogen was bubbled through the reaction mixture for five minutes before $Pd(PPh_3)_4$ (0.02 equiv.) was added. The reaction mixture was irradiated with microwaves for 30 min at 150 °C. The resulting solution was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (3 ml) and filtered through Celite (2 cm). The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography on a silica gel column with hexane–ethyl acetate as eluent.

1-Benzyl-4-(4-fluorophenyl)-5-(pyridin-4-yl)-1*H*-1,2,3-triazole (5a). The title compound was prepared according to the general procedure B and was obtained by flash chromatography eluting with hexane–ethyl acetate (2 : 1) to yield a yellow solid (145 mg, 80%). ^{1}H NMR ($CDCl_3$): δ 8.67 (d, J = 5.7 Hz, 2H), 7.46 (m, 2H), 7.25 (m, 3H), 7.06–6.94 (m, 6H), 5.45 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 163.0 (d, C–F, J = 246.8 Hz), 151.1, 144.8, 136.5, 135.0, 131.2, 129.2, 129.1 (d, C–F, J = 7.7 Hz), 128.8, 127.6, 126.3 (d, C–F, J = 3.1 Hz), 124.7, 116.0 (d, C–F, J = 21.5 Hz), 52.8; IR (KBr, cm^{-1}): 3439, 3054, 1606, 1506, 1220, 833, 721. EA($C_{20}H_{15}FN_4$): Required: 72.71 (C); 4.58 (H); 16.96 (N); Found: 72.38 (C), 4.40 (H), 16.89 (N).

1-Benzyl-4-(4-chlorophenyl)-5-(pyridin-4-yl)-1*H*-1,2,3-triazole (5b). The title compound was prepared according to the general procedure B and was obtained by flash chromatography eluting with hexane–ethyl acetate (2 : 1) to yield a yellow solid (133 mg, 63%). ^{1}H NMR ($CDCl_3$): δ 8.66 (d, J = 5.5 Hz, 2H), 7.41 (d, J = 8.42, 2H), 7.26–7.22 (m, 4H), 7.05–6.98 (m, 5H), 5.43 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 151.1, 144.6, 136.4, 135.0, 134.5, 131.5, 129.3, 129.2, 128.9, 128.8, 128.5, 127.6, 124.7, 52.8; IR (KBr, cm^{-1}): 3440, 3033, 1603, 1494, 836, 720. $[M + 1]^+$ calcd for $C_{20}H_{15}N_4Cl$: 347.1058; found 347.1061.

1-Benzyl-4-(4-bromophenyl)-5-(pyridin-4-yl)-1*H*-1,2,3-triazole (5c). The title compound was prepared according to the general procedure B and was obtained by flash chromatography eluting with hexane–ethyl acetate (1 : 1) to yield a yellow solid (145 mg, 53%). ^{1}H NMR ($CDCl_3$): δ 8.68 (bs, 2H), 7.42–7.24 (m, 7H), 7.05–6.99 (m, 4H), 5.45 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 151.1, 144.7, 136.4, 135.0, 132.2, 131.6, 129.4, 129.3, 128.9, 128.7, 127.6, 124.7, 122.8, 52.9; IR (KBr, cm^{-1}): 3433, 3030, 1600, 1472, 836, 714. EA($C_{20}H_{15}BrN_4$): Required: 61.39 (C); 3.86 (H); 14.32 (N); Found: 61.41 (C), 3.72 (H), 14.38 (N).

1-Benzyl-4-phenyl-5-(pyridin-4-yl)-1*H*-1,2,3-triazole (5d). The title compound was prepared according to the general procedure B and was obtained by flash chromatography eluting with hexane–ethyl acetate (1 : 1) to yield a white solid (30 mg, 85%). ^{1}H NMR ($CDCl_3$): δ 8.6 (s, 2H), 7.50–7.46 (m, 2H), 7.28–7.24 (m, 6H), 7.06–6.99 (m, 4H), 5.45 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 150.0, 145.7, 136.8, 135.1, 131.4, 130.4, 129.2, 129.0, 128.8, 128.6, 127.6, 127.3, 124.8, 52.8; IR (KBr, cm^{-1}): 3416, 3035, 1602, 1219, 835, 751. EA($C_{20}H_{16}N_4$): Required: 76.90 (C); 4.96 (H); 17.94 (N); Found: 76.46 (C), 4.96 (H), 17.73 (N).

1-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-(pyridin-4-yl)-1*H*-1,2,3-triazole (5e). The title compound was prepared according to the general procedure B and was obtained by flash chromatography eluting with hexane–ethyl acetate (1 : 1) to yield a white solid (85 mg, 78%). ^{1}H NMR ($CDCl_3$): δ 8.76 (d, J = 5.1 Hz, 2H), 7.42 (m, 2H), 7.28 (m, 2H), 6.94 (m, 2H), 4.09 (d, J = 7.3 Hz, 2H), 1.07 (m, 1H), 0.51 (m, 2H), 0.22 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 162.8 (d, C–F, J = 246.2 Hz), 151.2, 144.4, 136.9, 130.8, 129.1 (d, C–F, J = 7.6 Hz), 126.7 (d, C–F, J = 3.1 Hz), 124.7, 115.9 (d, C–F, J = 21.4 Hz), 53.6, 11.7, 4.6; IR (KBr, cm^{-1}): 3432, 3068, 3002, 1602, 1503, 1209, 838. EA($C_{17}H_{15}FN_4$): Required: 69.37 (C); 5.14 (H); 19.04 (N); Found: 69.18 (C), 5.08 (H), 18.83 (N).

2-(4-(4-Fluorophenyl)-5-(pyridin-4-yl)-1*H*-1,2,3-triazol-1-yl)-3-phenylpropan-1-ol (5f). The title compound was prepared according to the general procedure B and was obtained by flash chromatography eluting with hexane–ethyl acetate (1 : 2) to yield a white solid (143 mg, 85%). ^{1}H NMR ($CDCl_3$): δ 8.36 (s, 2H), 7.11–6.98 (m, 5H), 6.82 (m, 2H), 6.64 (m, 2H), 6.28 (m, 2H), 5.82 (bs, 1H), 4.70 (m, 1H), 4.22 (m, 1H), 4.08 (m, 1H), 3.24 (m, 1H), 2.98 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 162.4 (d, C–F, J = 249.1 Hz), 150.0, 142.2, 136.4, 135.1, 133.0, 128.7, 128.6, 128.8 (d, C–F, J = 7.4 Hz), 126.8, 125.5 (d, C–F, J = 3.1 Hz), 124.6, 115.5 (d, C–F, J = 21.5 Hz), 65.0, 64.7, 38.2; $[\alpha]_D^{25}$ = −106.1 (c = 0.5 in CH_2Cl_2); IR (KBr, cm^{-1}): 3400, 3168, 2859, 1609, 1510, 1222, 1063, 833. $[M + 1]^+$ calcd for $C_{22}H_{19}N_4OF$: 375.1616; found 375.1630.

2-(4-(4-Fluorophenyl)-5-(pyridin-4-yl)-1*H*-1,2,3-triazol-1-yl)-3-methylbutan-1-ol (5g). The title compound was prepared according to the general procedure B and was obtained by flash chromatography eluting with hexane–ethyl acetate (1 : 2) to yield a white solid (85 mg, 53%). ^{1}H NMR ($CDCl_3$): δ 8.64 (d, J = 5.86 Hz, 2H), 7.15 (m, 2H), 7.09 (d, J = 5.86 Hz), 6.89 (m, 2H), 4.98 (bs, 1H), 4.50 (m, 1H), 4.10 (m, 1H), 3.82 (m, 1H), 2.35 (m, 1H), 0.92 (d, J = 6.59 Hz, 3H), 0.57 (d, J = 6.59 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 162.5 (d, C–F, J = 249.1 Hz), 150.5, 142.3, 135.8, 133.0, 128.6 (d, C–F, J = 8.4 Hz), 125.6 (d, C–F, J = 3.1 Hz), 125.1, 115.5 (d, C–F, J = 21.5 Hz), 68.2, 63.6, 30.7, 19.7, 19.6; $[\alpha]_D^{25}$ = −29.3 (c = 0.32 in CH_2Cl_2); IR (in $CDCl_3$, cm^{-1}): 3298, 2968, 2878, 2240, 1608, 1230, 1058, 910, 733. $[M + 1]^+$ calcd for $C_{13}H_{15}N_3OFI$: 327.1616; found 327.1627.

2-(4-(4-Fluorophenyl)-5-(pyridin-4-yl)-1*H*-1,2,3-triazol-1-yl)-3-(1*H*-indol-3-yl)propanoic acid (5h). The title compound was prepared according to the general procedure B and was obtained by flash chromatography eluting with ethyl acetate–methanol (4 : 1) to yield a yellow solid (85 mg, 35%). ^{1}H NMR ($DMSO_6$): δ 8.45 (d, 2H), 7.34–7.10 (m, 6H), 7.01 (app. t, 1H), 6.86–6.83 (m, 3H), 6.64 (d, 1H), 4.64 (dd, J = 2.93, 11.72 Hz, 1H), 3.71 (dd, J = 2.93, 15.01 Hz, 1H), 3.53 (dd, J = 11.72, 15.01 Hz, 1H); ^{13}C NMR (MeOD): δ 174.8, 163.9 (d, C–F, J = 246.8 Hz), 150.4, 144.1, 137.9, 137.8, 134.6, 130.2 (d, C–F, J = 8.5 Hz), 128.2, 127.7 (d, C–F, J = 3.1 Hz), 126.1, 124.2 122.4, 119.9, 118.7, 116.4 (d, C–F, J = 22.3 Hz), 112.3, 111.6, 66.2, 30.2 ($CHCH_2C$); $[\alpha]_D^{25}$ = −27.7 (c = 0.5 in MeOH); IR (KBr, cm^{-1}): 3404, 1616, 1397, 1227, 832, 744. $[M + 1]^+$ calcd for $C_{24}H_{18}N_5O_2F$: 428.1517; found 428.1503.

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