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Sequential one-pot three-step synthesis of polysubstituted 4-(5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-1,2,3-triazole systems†

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This work reports a successful one-pot three-step protocol for the synthesis of a new series of 15 examples of polysubstituted 4-(5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-1,2,3-triazoles, in which sequential Sonogashira cross-coupling, desilylation, and a copper(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) with an overall yield of up to 72% were used. The presence of a trifluoromethyl substituent attached to the pyrazole moiety made the Sonogashira cross-coupling reaction challenging. Additionally, the selection of the ancillary ligand XPhos was essential and indispensable for the desired heterocyclic construction.

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Introduction

Due to their broad spectrum of biological properties, five-membered nitrogen heterocycles with trifluoromethyl moieties represent sought-after motifs in many fields of medicinal chemistry, biology, materials science, and agriculture.¹ Several trifluoromethylated azole cores are present in many of the prescribed and/or profitable drugs commercialized in the U.S. pharmaceutical market. As an example, sitagliptin is an anti-diabetic drug that was the fifteenth most prescribed drug overall in 2015, generating \$ 2.8 billion; while celecoxib – which is a nonsteroidal anti-inflammatory drug – generated \$ 2.2 billion in the U.S. market in the same year (Fig. 1).²

Notably, 20–30% of approved drugs, and about 40% of the new compounds entering phase III trials, possess at least one fluorine atom in their structure.² This trend is mainly due to the nature of the fluorine atom, which furnishes specific physicochemical properties such as: the introduction of fluorine groups to aromatic compounds, which increases the lipophilicity and metabolic stability of the molecule *in vivo*; and stronger electrostatic interaction with the receptors that bind the compounds more tightly in the active sites of the enzymes.³ The increasing use of fluorine atoms in active pharmaceutical ingredients parallels advances in understanding of physicochemical attributes, and it gives an enhanced appreciation of how these unique properties can be exploited to address the

numerous challenges encountered in pharmaceutical candidate optimization.¹

Given our shared interest in the synthesis of fluorinated nitrogenous heterocycles with potential pharmacological application,⁴ in a recent publication we disclosed cross-coupling reactions involving 4-halo-5-trifluoromethyl-1*H*-pyrazoles, in order to achieve the related tetrasubstituted structures.⁵ Despite such success, cross-coupling reactions of this type involving organometallic reagents derived from nitrogen-containing heterocycles continue to represent a significant challenge.

Given the established anticancer,⁷ antimycobacterial,⁸ CB₁ receptor ligand,^{9,10} antibacterial,¹¹ and nematocidal^{12,13} properties of heterocyclic systems containing pyrazole-1,2,3-triazole

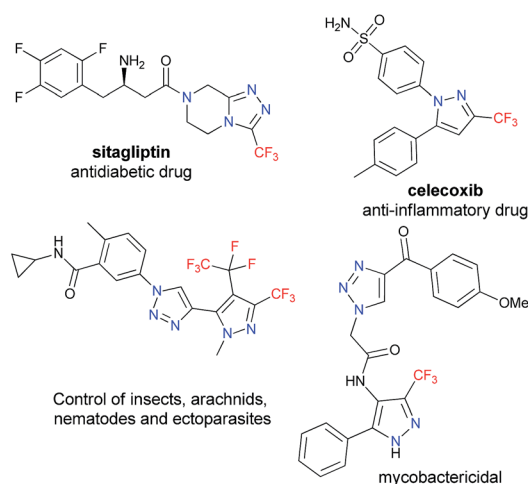
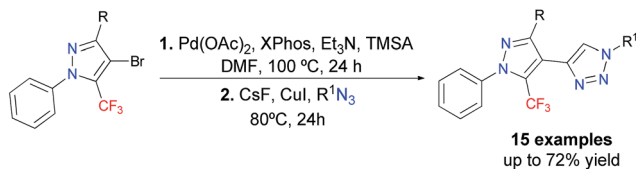


Fig. 1 Some fluorinated azoles and pyrazolyl-1,2,3-triazoles with biological activity.

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Scheme 1 Sequential one-pot, three-step synthesis of 4-(5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazoles.

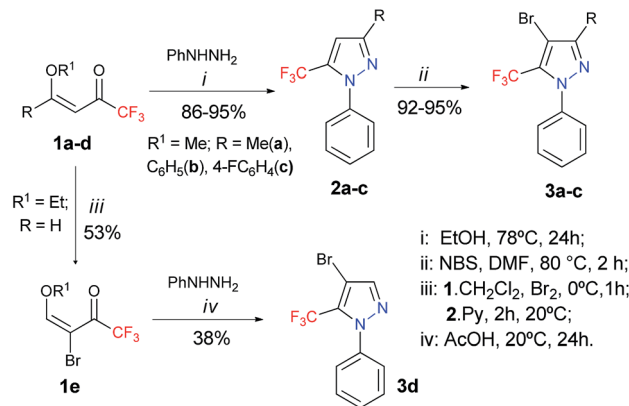
scaffolds (Fig. 1), we were encouraged to develop an efficient and useful protocol for obtaining 4-(pyrazol-4-yl)-1H-1,2,3-triazole systems, seeking to avoid some limitations associated with coupling reactions involving trifluoromethyl-substituted pyrazole precursors.^{5,6}

Thus, we envisioned the possibility of performing Sonogashira coupling and copper(i)-catalyzed azide-alkyne cycloaddition (CuAAC) in a one-pot fashion. The Pd(0) catalyzed cross-coupling reaction of 4-bromo-5-trifluoromethyl-1H-pyrazole with ethynyltrimethylsilane (TMSA) would furnish the alkyne-containing TMSA-5-trifluoromethyl-1H-pyrazoles, which, after *in situ* fluorine deprotection, would give terminal alkyne intermediates. The Cu(i)-catalyzed reaction (CuAAC) is a click reaction, in which the reaction involving an azide and the terminal 4-ethynyl-5-trifluoromethyl-1H-pyrazoles would give direct access to 4-(5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazoles, in a one-pot sequential metal-catalyzed reaction. Selected examples in the literature detail the synthesis of a 4-(1H-pyrazol-4-yl)-1H-1,2,3-triazole by a similar approach; however, this pyrazolyl-triazole did not have a trifluoromethyl group in the pyrazole core.¹⁴ The presence of an electron-withdrawing group like CF₃ would make the Sonogashira cross-coupling difficult, and hinder the synthesis of the compounds proposed herein.

In this work we disclose the Sonogashira cross-coupling, desilylation, and CuAAC in a sequential one-pot three-step reaction – which is summarized in Scheme 1 – for the synthesis of a new series of 15 examples of a polysubstituted 4-(5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole system.

Results and discussion

We commenced our investigations by targeting an expedient route for the synthesis of 4-bromo-5-(trifluoromethyl)-1H-pyrazoles **3a–d**, for use as starting materials for the proposed study (Scheme 2). Compounds **2a–c** were prepared by the cyclocondensation reaction of 1,1,1-trifluoro-4-methoxy-alken-2-ones (**1a–c**) and phenylhydrazine, following procedures found in the literature.¹⁵ The starting materials **3a–d** were obtained by the subsequent bromination reaction of **2a–c** with NBS, following a procedure that we described previously.⁵ Seeking to increase the scope of this reaction, we also tried to expand this bromination methodology to aryl substituents attached to the 3-position of the pyrazole ring. When we used the same reaction condition for a 3-(furan-2-yl)pyrazole, the formation of a non-separable mixture of dibrominated (both rings) and monobrominated products was observed *via* GC. For the 1-(4-



Scheme 2 Synthesis of 4-bromo-5-(trifluoromethyl)-1H-pyrazoles **3a–d**.

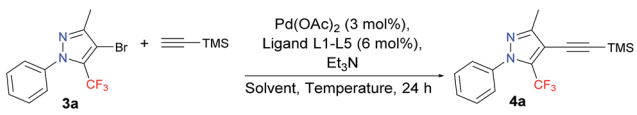
methoxyphenyl)pyrazole, the formation of another non-separable mixture of monobrominated products (both rings) and the starting pyrazole was observed. However, when we applied the same reaction conditions to the 3-(4-fluorophenyl)pyrazole, the formation of the desired monobrominated pyrazole **3c** was observed as a single product in 92% yield. The structurally simple 4-bromo-1-phenylpyrazole **3d** was prepared in 38% yield, from the bromination reaction of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one **1d** *via* a cyclocondensation reaction involving the brominated enone **1e** and phenylhydrazine, in accordance with a procedure described in the literature.^{16,17}

With the starting materials **3a–d** in hand, we turned our attention towards targeting an expedient protocol for the Sonogashira cross-coupling reaction between trimethylsilylacetylene (TMSA) and 4-bromo-5-trifluoromethyl-1H-pyrazole **3a** – see Table 1. The presence of a trifluoromethyl group makes these substrates less reactive, and, consequently, Pd-catalyzed alkyne coupling transformations become a challenge that has to be overcome. However, according to the literature, for the activation of less reactive substrates, the simple PPh₃ or other triarylphosphines have proven to be ineffective.¹⁸ In keeping with this trend, poor results were obtained in an initial test involving the reaction between **3a** and TMSA, following a procedure similar to that in the literature,¹⁹ but using: 3 mol% Pd(OAc)₂, 6 mol% PPh₃, and 6 mol% CuI as the catalyst; Et₃N as the base; and DMF as the solvent, at 100 °C in an argon atmosphere. As expected, this reaction provided a conversion rate of only 18% for **4a**.


To address this difficulty, a screening involving several highly effective, bulky electron-rich dialkylbiarylphosphine ligands (**L1–L5**) – with Pd(OAc)₂ as the catalyst, Et₃N as the base, and MeCN as the solvent, at 110 °C in an argon atmosphere (Table 1, entries 1–5) – was performed. These ligands have been used in a variety of transformations especially in Pd-catalyzed carbon–carbon, carbon–nitrogen, and carbon–oxygen bond-forming processes – for the synthesis of pharmaceuticals, natural products, polymers, and new materials.²⁰

Among the five different phosphine ligands tested, the best conversion was found with 3 mol% of Pd(OAc)₂ and 6 mol% of XPhos (**L4**) – see Table 1, entry 5. XPhos was previously reported



Table 1 Optimization of the Sonogashira coupling of 4-bromo-3-methyl-5-(trifluoromethyl)-1H-pyrazole^a


Entry	Solvent	Ligand	T (°C)	Conversion ^b [%]
1	MeCN	CyJohnPhos (L1)	110	28
2	MeCN	JohnPhos (L2)	110	33
3	MeCN	<i>t</i> BuXPhos (L5)	110	19
4	MeCN	SPhos (L3)	110	77
5	MeCN	XPhos (L4)	110	94
6	THF	XPhos (L4)	65	31
7	DMF	XPhos (L4)	100	98 (83) ^d
8	DMF	XPhos (L4)	25	32
9	DMF	XPhos (L4)	50	81
10 ^c	DMF	XPhos (L4)	100	89



^a Reaction conditions: pyrazole **3a** (0.5 mmol), TMSA (0.75 mmol), Et₃N (1.5 mmol), and solvent (2 mL). ^b Conversion determined by GC. ^c 1.5 mol% of Pd(OAc)₂ and 3 mol% of ligand were used. ^d Isolated yield after column chromatography.

like an active ligand in copper-free Sonogashira coupling reaction with various aryl chlorides and tosylates in the presence of PdCl₂(CH₃CN)₂,¹⁸ or aryl(heteroaryl) halides in combination with precatalyst in continuous-flow²¹ or by copper-free Sonogashira coupling of aryl chlorides on charcoal,²² or by Negishi cross-coupling reaction of trifluoromethylated 1H-pyrazoles.⁵

In light of a previous report stating that copper suppresses the desired transformation,¹⁸ we chose a copper-free version, which, under such conditions, is also known as the Heck alkylation.

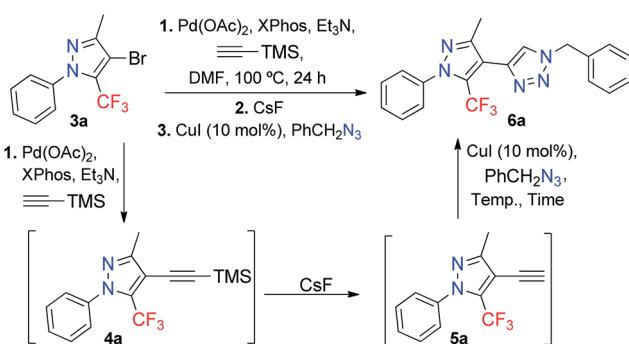
We next focused on studying the effect of solvent on the reaction, including transformations in THF at 65 °C and DMF at 100 °C (Table 1, entries 6–7). The best conversion was observed when the reaction was conducted in DMF at 100 °C. The effects of lowering the reaction temperature were also investigated. We observed that a reduction in reaction temperature from 100 °C to 25 °C and 50 °C significantly decreased the conversion observed, from 98% to 32% and 81%, respectively (Table 1, entries 8–9), which indicates that 100 °C was probably close to the optimal temperature for this reaction. Finally, the effects of lowering the catalyst concentration to 3 mol% of XPhos and 1.5 mol% of Pd(OAc)₂ resulted in low conversion (Table 1, entry 10).

After establishing the best reaction condition for Sonogashira coupling (Table 1, entry 7), we next turned our attention to optimizing the sequential desilylation-CuAAC cycloaddition in a one-pot fashion. It has previously been reported that TMS acetylenes can be deprotected by using several reagents – such

as tetrabutylammonium fluoride (TBAF), fluorine salts,²³ or silver salts²⁴ – to give terminal alkynes. We chose CsF as the reagent for deprotecting TMSA-5-trifluoromethyl-1H-pyrazole **4a** in order to generate the terminal alkyne **5a**, which subsequently reacted with 1.5 equivalents of benzyl azide and 10 mol% of CuI to furnish the 4-(5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole **6a** (Table 2).

In optimizing the temperature we observed that when the reaction was conducted at 25 °C, only the 4-ethynyl-5-trifluoromethyl-1H-pyrazole **5a** was isolated (Table 2, entry 1). However, with an increase in temperature, the formation of the desired product was observed (Table 2, entries 2–4). When the reaction was conducted at 100 °C, decomposition of the product and a lower yield than that obtained at 80 °C was observed. The use of 3 equiv. of CsF was necessary to obtain an optimal yield (Table 2, entry 5). The worst yield resulted when we tried to substitute the use of pre-formed benzyl azide with the *in situ* formation of benzyl azide, by adding equimolar quantities of benzyl chloride and NaN₃ to the reaction (Table 2, entry 6).

Given the optimized reaction conditions (Table 2, entry 5), the scope for the synthesis of 4-(5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazoles was explored – the results are shown in Table 3. We investigated the scope of the azide in this reaction by exploring the reactivity of different benzyl, alkyl, and aryl azides. The best results were obtained for the benzyl azides, while the worst results were noted for the alkyl and aryl azides.

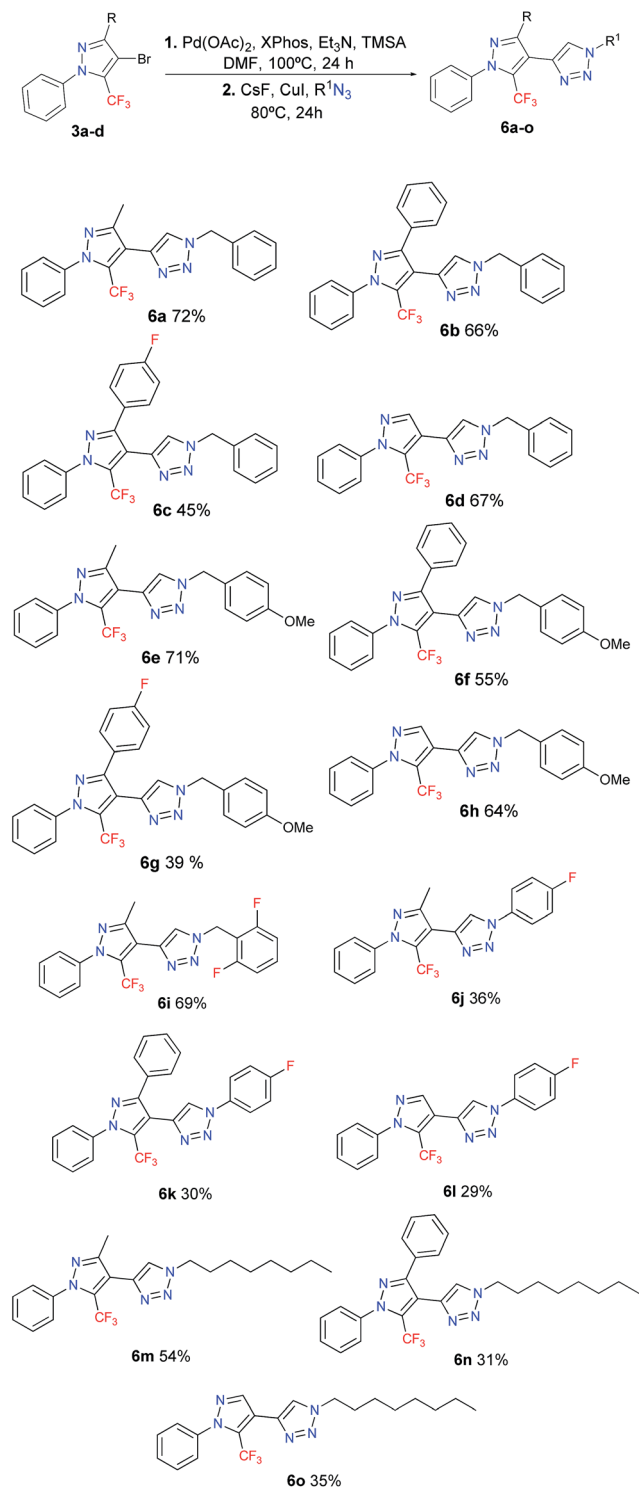
Table 2 One-pot, three-step optimization: Sonogashira coupling, TMS desilylation, and CuAAC^a


Entry	CsF (eq.)	T (°C)	t (h)	Yield ^b [%]
1	2	25	24	0 ^d
2	2	50	24	40
3	2	80	24	58
4	2	100	24	45
5	3	80	24	72
6 ^c	3	80	24	64
7	3	100	24	61
8	3	80	16	64
9	3	60	24	63

^a Reaction conditions: pyrazole **3a** (0.5 mmol), Pd(OAc)₂ (3 mol%), XPhos (6 mol%), TMSA (0.75 mmol), Et₃N (1.5 mmol), DMF (2 mL), CuI (10 mol%), and PhCH₂N₃ (0.75 mmol). ^b Isolated yields after column chromatography. ^c Benzyl chloride (0.75 mmol) and NaN₃ (0.75 mmol) were used instead of benzyl azide. ^d **5a** was isolated.



Table 3 Sequential one-pot three-step synthesis of 4-(5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-1,2,3-triazoles^{a,b}



^a Reaction conditions: pyrazole **3a-d** (0.5 mmol), Pd(OAc)₂ (3 mol%), XPhos (6 mol%), TMSA (0.75 mmol), Et₃N (1.5 mmol), DMF (2 mL), CsF (1.5 mmol), CuI (10 mol%), and R¹N₃ (0.75 mmol). ^b Isolated yields after column chromatography.

We also utilized fluorinated azides, such as 1-azido-4-fluorobenzene and 2-(azidomethyl)-1,3-difluorobenzene, given the biological potential that these compounds may have. Compound **6i** feature the (2,6-difluorobenzyl)-1,2,3-triazole fragment, that is present in the anticonvulsant Rufinamide, a drug which is used in combination with other medication and therapy to treat Lennox-Gastaut syndrome and various other seizure disorders.²⁵ All the new products were fully characterized on the basis of GC-MS and ¹H/¹³C NMR spectroscopic data, as well as elemental analysis or high-resolution mass spectrometric data. For the final compounds **6a-o**, the ¹³C{¹H} NMR spectra recorded in CDCl₃ displayed a through-space ¹³C-¹⁹F spin-spin coupling between the fluorine atoms of the CF₃ group and the C-5 carbon of the triazole. The signal for the hydrogenated C-5 carbon of the triazole was observed in the range of 121.1–123.8 ppm, as a broad singlet or a quartet with a *J*_{CF} between 2–4 Hz. The ¹⁹F NMR spectra were recorded for representative compounds. The CF₃ signals appeared as a singlet, in average at –55.3 ppm because are very little influenced by both electronic and steric effects. Notably, the average yield obtained for **6a-o** (51%) corresponds to an 80% yield across each of the three synthetic steps involved in our one-pot protocol (Sonogashira cross-coupling, desilylation, and copper(i)-catalyzed azide-alkyne cycloaddition).

Conclusions

In summary, we successfully developed a new one-pot, three-step protocol for the synthesis of a series of 15 examples of polysubstituted 4-(5-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-1,2,3-triazoles, by employing a sequential Sonogashira cross-coupling, desilylation, and copper(i)-catalyzed azide-alkyne cycloaddition (CuAAC). The presence of a trifluoromethyl group in the pyrazole core made Sonogashira cross-coupling a challenge, and the selection of ancillary ligand XPhos was indispensable for the desired heterocyclic transformation in search of new bioactive molecules. The new useful method applied successful to pyrazoles in this work creates the possibility also for other azoles containing electron-withdrawing groups.

Experimental section

General considerations

Unless otherwise indicated, all reagents and solvents used were obtained from commercial suppliers and were used without further purification. The THF was purified by refluxing over Na/benzophenone, followed by distillation. The DMF and MeCN were purified and stored over activated 4 Å molecular sieves. Column chromatography was performed on silica gel (230–400 mesh). The melting points were determined using glass capillary tubes in the Electrothermal MEL-TEMP 3.0 apparatus, with uncorrected values. ¹H and ¹³C spectra were acquired on a Bruker DPX 400 (¹H at 400 MHz and ¹³C at 100 MHz) or a Bruker Avance III HD 600 (¹H at 600 MHz and ¹³C at 150 MHz), with 5 mm sample tubes, 298 K, and digital resolution of 0.01 ppm, in CDCl₃ and using TMS as an internal reference. ¹⁹F NMR spectra of selected compounds were registered on



a Bruker Avance III 600 spectrometer (at 565 MHz), in CDCl₃ and using fluorobenzene as external reference with the chemical shifts reported according to the CFCl₃ standard. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (University of São Paulo, SP, Brazil). Gas chromatography was done using an Agilent Technologies 6890N Network GC system, autosampler 7683 series, injector 7683B series, detector 5975 B inert XL EI/CI MSD. High-resolution mass spectra (HRMS) were obtained for all compounds using an LTQ Orbitrap Discovery mass spectrometer (Thermo Fisher Scientific).

General procedure for the synthesis of 3-substituted-1-phenyl-5-(trifluoromethyl)-1H-pyrazoles (2a–c)

The pyrazoles were prepared by following the procedures described in the literature.^{5,15} A solution of phenylhydrazine (5.5 mmol, 0.59 g) in ethanol (20 mL) was added dropwise – *via* a pipette over the course of 5 min – into a 100 mL round bottom flask containing a magnetic stir bar and a solution of the corresponding enone **1a–c** (5 mmol) in ethanol (50 mL), which was kept at 0 °C under magnetic stirring. The system was subsequently left to warm to room temperature over a 1 h period. A reflux condenser was then affixed to the reaction flask, and the flask was submerged in an oil bath, set to 78 °C, that was continually stirred for 24 h. The solvent was removed in a rotary evaporator under reduced pressure, and the residual crude pyrazoles **2a–c** were purified *via* column chromatography, by using 5% ethyl acetate in hexane solution as eluent.

3-Methyl-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (2a). Physical aspect: yellow oil. Yield: 1.07 g, 95%. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.48–7.41 (m, 5H), 6.59 (s, 1H), 2.35 (s, 3H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 148.9, 139.1, 132.9 (q, ²J_{C-F} = 39), 129.0, 198.9, 125.5, 119.8 (q, ¹J_{C-F} = 269), 108.5 (q, ³J_{C-F} = 2), 13.2. Agrees with data previously reported in the literature.⁵

1,3-Diphenyl-5-(trifluoromethyl)-1H-pyrazole (2b). Physical aspect: yellow solid. Yield: 1.32 g, 92%. Melting point: 52–54 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.91–7.88 (m, 2H), 7.60–7.57 (m, 2H), 7.55–7.50 (m, 3H), 7.48–7.44 (m, 2H), 7.42–7.37 (m, 1H), 7.14 (s, 1H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 151.7, 139.3, 134.0 (q, ²J_{C-F} = 39), 131.8, 129.4, 129.2, 128.9, 128.8, 126.0, 125.8, 119.9 (q, ¹J_{C-F} = 269), 106.2. Agrees with data previously reported in the literature.⁵

3-(4-Fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (2c). Physical aspect: yellow solid. Yield: 1.31 g, 86%. Melting point: 57–60 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.85–7.80 (m, 2H), 7.56–7.47 (m, 5H), 7.14–7.08 (m, 2H), 7.05 (s, 1H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 163.2 (d, *J* = 248), 134.1, 150.8, 139.2, 134.1 (q, ²J_{C-F} = 38), 129.5, 129.3, 128.1 (d, *J* = 3), 127.7 (d, *J* = 8), 119.8 (q, ¹J_{C-F} = 269), 115.9 (d, *J* = 22), 106.0 (d, *J* = 2). Agrees with data previously reported in the literature.²⁶

General procedure for the synthesis of 4-bromo-1-phenyl-5-(trifluoromethyl)-1H-pyrazoles (3a–c)

Pyrazoles **3a–c** were prepared by following the procedures described in the literature.⁵ An oven-dried 25 mL round bottom

flask, equipped with a rubber septum and a stirrer bar, was charged with the pyrazole (**2a–c**, 5 mmol) and NBS (12.5 mmol, 2.22 g for **2a**; 15 mmol, 2.67 g for **2b–c**). The system was evacuated and backfilled with argon (operation performed three times in total). Anhydrous DMF (15 mL) was added, and the mixture was stirred at 80 °C for 2 h. Upon cooling to room temperature, the crude reaction mixture was purified *via* column chromatography (without prior removal of the DMF), by using 2% ethyl acetate in hexane solution as eluent.

4-Bromo-3-methyl-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (3a). Physical aspect: yellow oil. Yield: 1.43 g, 94%. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.48–7.44 (m, 3H), 7.43–7.39 (m, 2H), 2.34 (s, 3H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 149.3, 139.6, 130.4 (q, ²J_{C-F} = 38), 129.6, 129.2, 126.0, 119.5 (q, ¹J_{C-F} = 271), 97.7, 12.2. Agrees with data previously reported in the literature.⁵

4-Bromo-1,3-diphenyl-5-(trifluoromethyl)-1H-pyrazole (3b). Physical aspect: white solid. Yield: 1.70 g, 93%. Melting point: 98–100 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.89–7.87 (m, 2H), 7.51–7.48 (m, 5H), 7.48–7.42 (m, 3H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 150.8, 139.7, 131.5 (q, ²J_{C-F} = 38), 130.7, 129.9, 129.3, 129.2, 129.0, 128.5, 126.2, 119.5 (q, ¹J_{C-F} = 271), 95.7. Agrees with data previously reported in the literature.⁵

4-Bromo-3-(4-fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (3c). Physical aspect: white solid. Yield: 1.69 g, 92%. Melting point: 94–97 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.89–7.85 (m, 2H), 7.52–7.46 (m, 5H), 7.17–7.13 (m, 2H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 163.4 (d, *J* = 249), 150.0, 139.6, 131.6 (q, ²J_{C-F} = 38), 130.4 (d, *J* = 8), 130.0, 129.3, 126.9 (d, *J* = 3), 126.2, 119.4 (q, ¹J_{C-F} = 271), 115.7 (d, *J* = 22), 95.6. GC-MS (EI, 70 eV): *m/z* (%) 384 (M⁺, 100), 304 (31), 77 (33). Elemental analysis: C₁₆H₉BrF₄N₂ requires: C 49.89; H 2.36; N 7.27. Found: C 50.15; H 2.38; N 7.25.

General procedure for the synthesis of 4-bromo-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (3d)

This procedure was adapted from the literature.¹⁶ A phenylhydrazine (5.2 mmol, 0.56 g) was slowly added to a stirred solution of the enone **1e** (5.0 mmol, 1.23 g) in AcOH (15 mL), and this was then stirred at 25 °C for 24 h. The reaction was then poured into water and extracted with AcOEt (3 × 20 mL). The combined organic extracts were washed with a solution of NaHCO₃ and water, then dried with Na₂SO₄ and filtered, and the solvent was then removed in a rotary evaporator under reduced pressure. The residual crude pyrazole was purified *via* column chromatography by using 5% ethyl acetate in hexane solution as eluent.

4-Bromo-1-phenyl-5-(trifluoromethyl)-1H-pyrazole (3d). Physical aspect: yellow oil. Yield: 0.99 g, 34%. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.71 (s, 1H), 7.50–7.46 (m, 3H), 7.43–7.39 (m, 2H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 141.9, 139.5, 129.9 (q, ²J_{C-F} = 38), 129.9, 129.3, 126.1, 119.6 (q, ¹J_{C-F} = 271), 97.0. Agrees with data previously reported in the literature.¹⁶

General procedure for the synthesis of azides

The alkyl azides and 1-azido-4-fluorobenzene were prepared by following the procedures described in the literature.²⁷



Alkyl azides. In a round bottom flask, alkyl chloride or alkyl bromide (10 mmol) was dissolved in DMSO (15 mL), and NaN_3 (12 mmol) was added slowly. The reaction was stirred overnight at room temperature until the raw materials were consumed. The mixture was poured into water and extracted with Et_2O (3×20 mL). The combined organic extracts were washed with water (3×20 mL) and then brine (20 mL), then they were dried with Na_2SO_4 , filtered, and concentrated *in vacuo* in order to furnish the azide without further purification.

1-Azido-4-fluorobenzene. In a round bottom flask, 4-fluoroaniline (4 mmol) was dissolved in 10% aqueous HCl (10 mL). NaNO_2 (4 mmol) was added dropwise to the solution at 0°C , and this was then stirred for 10 min, and then NaN_3 (5 mmol) was added portionwise. The solution was allowed 2 h – while being stirred – to warm to room temperature. The reaction was diluted with H_2O , extracted with Et_2O , washed with water and then brine, and the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to furnish the product without further purification.

General procedure for the synthesis of 3-methyl-1-phenyl-5-(trifluoromethyl)-4-((trimethylsilyl)ethynyl)-1H-pyrazole (4a)

An oven-dried 5 mL round bottom flask, equipped with a rubber septum and a stirrer bar, was charged with the 4-bromo-3-methyl-1-phenyl-5-(trifluoromethyl)-1H-pyrazole **3a** (0.5 mmol, 152.5 mg), $\text{Pd}(\text{OAc})_2$ (3 mol%, 3.35 mg), and ligand (**L1–L5**, 6 mol%). The system was evacuated and backfilled with argon (operation performed three times), then Et_3N (1.5 mmol, 0.21 mL), TMSA (0.75 mmol, 0.11 mL), and dry solvent (2 mL) were added successively in an argon atmosphere. The round bottom flask was sealed and the mixture was stirred at the indicated temperature for 24 h. The crude reaction mixture was then cooled to room temperature, filtered through a silica pad with ethyl acetate (60 mL), and the filtrate was concentrated under reduced pressure and the pyrazole **4a** was purified *via* column chromatography, using 2% ethyl acetate in hexane solution as eluent.

3-Methyl-1-phenyl-5-(trifluoromethyl)-4-((trimethylsilyl)ethynyl)-1H-pyrazole (4a). Physical aspect: brown oil. Yield: 134 mg, 83%. NMR: ^1H (400 MHz, CDCl_3 , 25°C) δ = 7.47–7.44 (m, 3H), 7.42–7.40 (m, 2H), 2.38 (s, 3H), 0.26 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ (100 MHz, CDCl_3 , 25°C) δ = 152.5, 139.2, 133.5 (q, $^2J_{\text{C-F}}$ = 38), 129.5, 129.2, 126.1, 119.6 (q, $^1J_{\text{C-F}}$ = 271), 106.39, 102.05, 93.1, 12.2, –0.1. GC-MS (EI, 70 eV): m/z (%) 322 (M^+ , 62), 307 (100), 287 (30), 77 (27). HRMS (ESI-TOF): $\text{C}_{16}\text{H}_{18}\text{F}_3\text{N}_2\text{Si}$ ($\text{M} + \text{H}$) requires 323.1186/found: 323.1190.

General procedure for the synthesis of 4-(5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazoles (6a–o)

An oven-dried 5 mL round bottom flask, equipped with a rubber septum and a stirrer bar, was charged with the 4-bromopyrazoles (**3a–d**, 0.5 mmol), $\text{Pd}(\text{OAc})_2$ (3 mol%, 3.35 mg), and XPhos (6 mol%, 14.3 mg). The system was evacuated and backfilled with argon (operation performed three times), and then Et_3N (1.5 mmol, 0.21 mL), TMSA (0.75 mmol, 0.11 mL), and DMF (2 mL) were added successively in an argon

atmosphere. The round bottom flask was sealed, and the mixture was stirred at 100°C for 24 h. After cooling to room temperature, the system was opened, and CsF (1.5 mmol, 0.227 g), CuI (10 mol%, 10.0 mg), and organic azide (0.75 mmol) were added. The mixture was then stirred at 80°C for 24 h. The crude reaction mixture was then cooled to room temperature, filtered through a silica pad with ethyl acetate (80 mL), and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography furnished the desired product.

1-Benzyl-4-(3-methyl-1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole (6a). Eluted with 25% EtOAc/hexanes. Physical aspect: white solid. Yield: 138 mg, 72%. Melting point: $152\text{--}154^\circ\text{C}$. NMR: ^1H (400 MHz, CDCl_3 , 25°C) δ = 7.57 (s, 1H), 7.49–7.41 (m, 5H), 7.38–7.35 (m, 3H), 7.30–7.28 (m, 2H), 5.59 (s, 2H), 2.42 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ (100 MHz, CDCl_3 , 25°C) δ = 149.4, 139.6, 138.3, 134.7, 129.5 (q, $^2J_{\text{C-F}}$ = 38), 129.3, 129.2, 129.1, 128.8, 127.9, 126.0, 122.9 (q, J = 3), 120.1 (q, $^1J_{\text{C-F}}$ = 271), 113.2, 54.2, 12.82. ^{19}F (565 MHz, CDCl_3 , 25°C): δ = –55.4. GC-MS (EI, 70 eV): m/z (%) 383 (M^+ , 15), 355 (61), 286 (100), 264 (77), 91 (64), 77 (38). Elemental analysis: $\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_5$ requires: C 62.66; H 4.21; N 18.27. Found: C 62.53; H 4.33; N 18.14.

1-Benzyl-4-(1,3-diphenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole (6b). Eluted with 15% EtOAc/hexanes. Physical aspect: white solid. Yield: 147 mg, 66%. Melting point: $214\text{--}215^\circ\text{C}$. NMR: ^1H (600 MHz, CDCl_3 , 25°C) δ = 7.55 (d, J = 5.9, 2H), 7.51–7.48 (m, 5H), 7.40 (s, 1H), 7.36–7.33 (m, 3H), 7.31–7.25 (m, 3H), 7.19 (d, J = 6.5, 2H), 5.58 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ (150 MHz, CDCl_3 , 25°C) δ = 151.6, 139.4, 137.9, 134.7, 131.9 (q, $^2J_{\text{C-F}}$ = 38), 131.3, 129.6, 129.1, 129.1, 128.7, 128.5, 128.3, 128.3, 127.6, 126.1, 123.7, 119.7 (q, $^1J_{\text{C-F}}$ = 271), 112.1, 54.2. ^{19}F (565 MHz, CDCl_3 , 25°C): δ = –55.3. GC-MS (EI, 70 eV): m/z (%) 445 (M^+ , 25), 416 (85), 348 (55), 321 (57), 91 (100), 77 (54). Elemental analysis: $\text{C}_{25}\text{H}_{18}\text{F}_3\text{N}_5$ requires: C, 67.41; H, 4.07; N, 15.72. Found: C, 67.23; H, 4.17; N, 15.34.

1-Benzyl-4-(3-(4-fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole (6c). Eluted with 15% EtOAc/hexanes. Physical aspect: white solid. Yield: 104 mg, 45%. Melting point: $227\text{--}229^\circ\text{C}$. NMR: ^1H (400 MHz, CDCl_3 , 25°C) δ = 7.53–7.46 (m, 7H), 7.40 (s, 1H), 7.38–7.33 (m, 3H), 7.24–7.17 (m, 3H), 6.94 (t, J = 8.7, 2H), 5.58 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ (100 MHz, CDCl_3 , 25°C) δ = 163.1 (d, J = 248), 150.9, 139.4, 137.9, 134.7, 132.0 (q, $^2J_{\text{C-F}}$ = 37), 130.2 (d, J = 9), 129.8, 129.3, 129.0, 127.8, 127.6 (d, J = 3), 126.2, 123.8, 119.7 (q, $^1J_{\text{C-F}}$ = 271), 115.5 (d, J = 23), 112.0, 54.3. ^{19}F (565 MHz, CDCl_3 , 25°C): δ = –55.3, –113.0. GC-MS (EI, 70 eV): m/z (%) 463 (M^+ , 13), 435 (32), 366 (49), 344 (30), 91 (100), 77 (41). HRMS (ESI-TOF): $\text{C}_{25}\text{H}_{17}\text{F}_4\text{N}_5$ ($\text{M} + \text{H}$) requires 464.1493/found: 464.1515.

1-Benzyl-4-(1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole (6d). Eluted with 20% EtOAc/hexanes. Physical aspect: white solid. Yield: 124 mg, 67%. Melting point: $135\text{--}137^\circ\text{C}$. NMR: ^1H (600 MHz, CDCl_3 , 25°C) δ = 8.19 (s, 1H), 7.61 (s, 1H), 7.50–7.45 (m, 5H), 7.41–7.35 (m, 3H), 7.30 (d, J = 6.8, 2H), 5.60 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ (150 MHz, CDCl_3 , 25°C) δ = 140.4, 139.6, 138.3, 134.6, 129.6, 129.3, 129.2, 129.0, 128.1, 127.8 (q, $^2J_{\text{C-F}}$ = 38), 126.1, 122.0 (q, J = 4), 120.27 (q, $^1J_{\text{C-F}}$ = 270), 115.5, 54.4. ^{19}F (565 MHz, CDCl_3 , 25°C): δ = –55.3. GC-MS (EI, 70 eV): m/z (%) 369 (M^+ , 17), 340 (50), 272 (89), 250 (100), 91 (75), 77



(41). Elemental analysis: C₁₉H₁₄F₃N₅ requires: C, 61.79; H, 3.82; N, 18.96. Found: C, 61.90; H, 3.91; N, 18.60.

1-(4-Methoxybenzyl)-4-(3-methyl-1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole (6e). Eluted with 25% EtOAc/hexanes. Physical aspect: white solid. Yield: 147 mg, 71%. Melting point: 136–138 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.51 (s, 1H), 7.48–7.43 (m, 5H), 7.26 (d, *J* = 8.7, 2H), 6.92 (d, *J* = 8.7, 2H), 5.54 (s, 2H), 3.81 (s, 3H), 2.41 (s, 3H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 160.1, 149.5, 139.6, 138.3, 129.7, 129.6 (q, ²*J*_{C-F} = 38), 129.4, 129.1, 126.6, 126.1, 122.7 (q, *J* = 3), 120.1 (q, ¹*J*_{C-F} = 271), 114.7, 113.2, 55.5, 53.9, 12.9. GC-MS (EI, 70 eV): *m/z* (%) 413 (M⁺, 23), 385 (48), 316 (72), 264 (94), 121 (100), 77 (43). HRMS (ESI-TOF): C₂₁H₁₉F₃N₅O (M + H) requires 414.1536/found: 414.1552.

4-(1,3-Diphenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1-(4-methoxybenzyl)-1H-1,2,3-triazole (6f). Eluted with 15% EtOAc/hexanes. Physical aspect: white solid. Yield: 122 mg, 55%. Melting point: 192–194 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.58–7.47 (m, 7H), 7.36 (s, 1H), 7.29–7.23 (m, 3H), 7.15 (d, *J* = 8.6, 2H), 6.87 (d, *J* = 8.6, 2H), 5.50 (s, 2H), 3.79 (s, 3H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 160.0, 151.7, 139.5, 137.8, 131.9 (q, ²*J*_{C-F} = 37), 131.5, 129.6, 129.3, 129.2, 128.6, 128.4, 128.3, 126.8, 126.2, 123.6, 119.8 (q, ¹*J*_{C-F} = 271), 114.6, 112.3, 55.4, 53.8. HRMS (ESI-TOF): C₂₆H₂₁F₃N₅O (M + H) requires 476.1693/found: 476.1699.

4-(3-(4-Fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1-(4-methoxybenzyl)-1H-1,2,3-triazole (6g). Eluted with 15% EtOAc/hexanes. Physical aspect: white solid. Yield: 95 mg, 39%. Melting point: 197–200 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.54–7.46 (m, 7H), 7.37 (s, 1H), 7.18–7.16 (d, 2H), 6.97–6.88 (m, 4H), 5.52 (s, 2H), 3.81 (s, 3H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 163.1 (d, *J* = 248), 160.1, 150.9, 139.4, 137.7, 132.0 (q, ²*J*_{C-F} = 37), 130.2 (d, *J* = 8), 129.7, 129.4, 129.4, 127.6 (d, *J* = 3), 126.6, 126.2, 123.6, 119.7 (q, ¹*J*_{C-F} = 271), 115.5 (d, *J* = 22), 114.6, 112.1, 55.5, 53.9. GC-MS (EI, 70 eV): *m/z* (%) 493 (M⁺, 15), 469 (52), 333 (55), 281 (40), 207 (100), 121 (79), 77 (30). HRMS (ESI-TOF): C₂₆H₂₀F₄N₅O (M + H) requires 494.1598/found: 494.1601.

1-(4-Methoxybenzyl)-4-(1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole (6h). Eluted with 20% EtOAc/hexanes. Physical aspect: white solid. Yield: 129 mg, 64%. Melting point: 127–129 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 8.17 (s, 1H), 7.56 (s, 1H), 7.49–7.42 (m, 5H), 7.26 (d, *J* = 8.5, 2H), 6.91 (d, *J* = 8.6, 2H), 5.52 (s, 2H), 3.81 (s, 3H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 160.2, 140.4, 139.7, 138.2, 129.7, 129.6, 129.2, 127.7 (q, ²*J*_{C-F} = 37), 126.6, 126.2, 121.8 (q, *J* = 4), 120.2 (q, ¹*J*_{C-F} = 270), 115.6, 114.7, 55.5, 54.0. GC-MS (EI, 70 eV): *m/z* (%) 399 (M⁺, 24), 370 (25), 302 (61), 250 (68), 121 (100), 77 (35). HRMS (ESI-TOF): C₂₀H₁₇F₃N₅O (M + H) requires 400.1380/found: 400.1393.

1-(2,6-Difluorobenzyl)-4-(3-methyl-1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole (6i). Eluted with 25% EtOAc/hexanes. Physical aspect: white solid. Yield: 146 mg, 69%. Melting point: 167–169 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.72 (s, 1H), 7.54–7.42 (m, 5H), 7.41–7.34 (m, 1H), 6.98 (t, *J* = 7.9, 2H), 5.70 (s, 2H), 2.42 (s, 3H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 161.4 (dd, *J* = 251, 7), 149.4, 139.5, 138.1, 131.6 (t, *J* = 10), 129.5 (q,

²*J*_{C-F} = 38), 129.3, 129.1, 126.0, 123.1, 120.0 (q, ¹*J*_{C-F} = 271), 113.0, 111.9 (dd, *J* = 19, 6), 110.7 (t, *J* = 19), 41.5 (t, *J* = 4), 12.8. GC-MS (EI, 70 eV): *m/z* (%) 419 (M⁺, 5), 391 (34), 322 (100), 264 (66), 127 (165), 77 (53). HRMS (ESI-TOF): C₂₀H₁₅F₅N₅ (M + H) requires 420.1242/found: 420.1268.

1-(4-Fluorophenyl)-4-(3-methyl-1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole (6j). Eluted with 15% EtOAc/hexanes. Physical aspect: white solid. Yield: 66 mg, 35%. Melting point: 177–180 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 8.01 (s, 1H), 7.80–7.77 (m, 2H), 7.51–7.47 (m, 5H), 7.27–7.23 (m, 2H), 2.50 (s, 3H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 162.7 (d, *J* = 249), 149.6, 139.6, 138.9, 133.3, 129.8 (q, ²*J*_{C-F} = 38), 129.5, 129.2, 126.1, 122.7 (d, *J* = 9), 121.1 (q, *J* = 3), 120.1 (q, ¹*J*_{C-F} = 271), 117.0 (d, *J* = 23.3), 112.7, 13.0. GC-MS (EI, 70 eV): *m/z* (%) 387 (M⁺, <1), 359 (100), 290 (65), 95 (20), 77 (41). HRMS (ESI-TOF): C₁₉H₁₄F₄N₅ (M + H) requires 388.1180/found: 388.1201.

4-(1,3-Diphenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-1H-1,2,3-triazole (6k). Eluted with 15% EtOAc/hexanes. Physical aspect: white solid. Yield: 74 mg, 33%. Melting point: 222–224 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.88 (s, 1H), 7.75–7.72 (m, 2H), 7.60–7.52 (m, 7H), 7.35–7.32 (m, 3H), 7.25–7.20 (m, 2H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 162.6 (d, *J* = 249), 151.9, 139.5, 138.5, 133.2, 132.0 (q, ²*J*_{C-F} = 37), 131.4, 129.8, 129.3, 128.8, 128.6, 128.5, 126.2, 122.6 (d, *J* = 9), 121.7, 120.1 (q, ¹*J*_{C-F} = 271), 117.0 (d, *J* = 23), 111.6. ¹⁹F (565 MHz, CDCl₃, 25 °C): δ = –55.1, –111.8. GC-MS (EI, 70 eV): *m/z* (%) 449 (M⁺, <1), 421 (100), 352 (38), 95 (18), 77 (45). HRMS (ESI-TOF): C₂₄H₁₆F₄N₅ (M + H) requires 450.1336/found: 450.1354.

1-(4-Fluorophenyl)-4-(1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole (6l). Eluted with 15% EtOAc/hexanes. Physical aspect: white solid. Yield: 51 mg, 29%. Melting point: 157–159 °C. NMR: ¹H (600 MHz, CDCl₃, 25 °C) δ = 8.27 (s, 1H), 8.07 (d, *J* = 1), 7.79–7.76 (m, 2H), 7.53–7.50 (m, 5H), 7.27–7.25 (m, 2H). ¹³C{¹H} (150 MHz, CDCl₃, 25 °C) δ = 162.7 (d, *J* = 249), 140.4, 139.5, 138.8, 133.3 (d, *J* = 3), 129.8, 129.3, 128.0 (q, ²*J*_{C-F} = 39), 126.1, 122.8 (d, *J* = 9), 120.3 (q, ¹*J*_{C-F} = 271), 120.2 (q, *J* = 4), 117.0 (q, *J* = 23), 115.0. GC-MS (EI, 70 eV): *m/z* (%) 373 (M⁺, <1), 345 (100), 276 (3), 128 (17), 77 (26). HRMS (ESI-TOF): C₁₈H₁₂F₄N₅ (M + H) requires 374.1023/found: 374.1045.

4-(3-Methyl-1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1-octyl-1H-1,2,3-triazole (6m). Eluted with 15% EtOAc/hexanes. Physical aspect: white solid. Yield: 109 mg, 54%. Melting point: 95–97 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.60 (s, 1H), 7.54–7.43 (m, 5H), 4.42 (t, *J* = 7.2, 2H), 2.44 (s, 3H), 2.02–1.93 (m, 2H), 1.40–1.22 (m, 10H), 0.88 (t, *J* = 6.7, 3H). ¹³C{¹H} (100 MHz, CDCl₃, 25 °C) δ = 149.6, 139.8, 137.9, 129.4, 129.4 (q, ²*J*_{C-F} = 37), 129.2, 126.2, 122.8 (q, *J* = 2), 121.6 (q, ¹*J*_{C-F} = 270), 113.4, 50.6, 31.8, 30.4, 29.2, 29.1, 26.6, 22.7, 14.1, 13.0. ¹⁹F (565 MHz, CDCl₃, 25 °C): δ = –55.4. GC-MS (EI, 70 eV): *m/z* (%) 391 (M⁺, 22), 279 (100), 251 (62), 238 (48), 77 (31). HRMS (ESI-TOF): C₂₁H₂₇F₃N₅ (M + H) requires 406.2213/found: 406.2238.

4-(1,3-Diphenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1-octyl-1H-1,2,3-triazole (6n). Eluted with 15% EtOAc/hexanes. Physical aspect: white solid. Yield: 72 mg, 31%. Melting point: 165–166 °C. NMR: ¹H (400 MHz, CDCl₃, 25 °C) δ = 7.58–7.56 (m, 2H), 7.54–7.50 (m, 5H), 7.44 (s, 1H), 7.32–7.27 (m, 3H), 4.39 (t, *J* = 7.1, 2H), 1.95–1.86 (m, 2H), 1.38–1.20 (m, 10H), 0.88 (t, *J* = 6.8, 3H).



$^{13}\text{C}\{^1\text{H}\}$ (100 MHz, CDCl_3 , 25 °C) δ = 151.7, 139.5, 137.4, 131.9 (q, $^2J_{\text{C-F}}$ = 37), 131.5, 129.6, 129.2, 128.6, 128.4, 128.4, 126.2, 123.5, 119.8 (q, $^1J_{\text{C-F}}$ = 271), 112.3, 50.5, 31.7, 30.3, 29.1, 29.0, 26.4, 22.7, 14.1. GC-MS (EI, 70 eV): m/z (%) 467 (M^+ , 30), 439 (22), 355 (100), 326 (55), 313 (82), 77 (50). HRMS (ESI-TOF): $\text{C}_{26}\text{H}_{29}\text{F}_3\text{N}_5$ ($\text{M} + \text{H}$) requires 468.2370/found: 468.2379.

1-Octyl-4-(1-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1H-1,2,3-triazole (60). Eluted with 15% EtOAc/hexanes. Physical aspect: white solid. Yield: 68 mg, 35%. Melting point: 57–59 °C. NMR: ^1H (400 MHz, CDCl_3 , 25 °C) δ = 8.21 (s, 1H), 7.66 (s, 1H), 7.58–7.40 (m, 5H), 4.40 (t, J = 7.1, 2H), 2.01–1.89 (m, 2H), 1.42–1.19 (m, 10H), 0.88 (t, J = 6.8, 3H). $^{13}\text{C}\{^1\text{H}\}$ (100 MHz, CDCl_3 , 25 °C) δ = 140.4, 139.7, 137.8, 129.6, 129.2, 127.8 (q, $^2J_{\text{C-F}}$ = 38), 126.2, 121.9 (q, J = 4), 120.4 (q, $^1J_{\text{C-F}}$ = 271), 115.7, 50.6, 31.8, 30.4, 29.1, 29.0, 26.6, 22.7, 14.1. GC-MS (EI, 70 eV): m/z (%) 391 (M^+ , 22), 279 (100), 251 (62), 238 (48), 77 (31). HRMS (ESI-TOF): $\text{C}_{20}\text{H}_{25}\text{F}_3\text{N}_5$ ($\text{M} + \text{H}$) requires 392.2057/found: 392.2070.

Conflicts of interest

There are no conflicts to declare.

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