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# Synthesis of some novel 1-aryl-1*H*-1,2,3-triazole-4-carboxamides and ethyl 1-aryl-5-(1,2,3-triazol-1-yl)-1*H*-pyrazole-4-carboxylates

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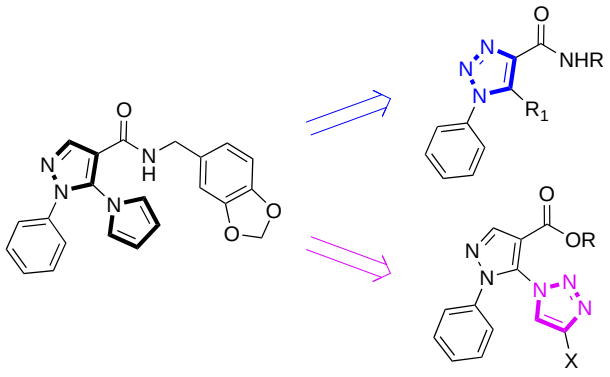
## Abstract

Starting from 5-(pyrrol-1-yl)pyrazole derivatives, the synthesis of triazole-based compounds by isosteric replacement of pyrrole and pyrazole was studied. The amido derivatives were obtained by organocatalyzed cycloaddition reactions between aryl azides and β-ketoamides or β-ketoesters. The synthesis of the second series of compounds, namely 5-(triazol-1-yl)pyrazole derivatives, involved the preparation of 5-azido-1*H*-pyrazole derivatives to be subjected to cycloaddition with alkynes.




**Keywords**: 1,2,3-Triazole derivatives, organocatalyzed cycloaddition, click chemistry, isosteric substitution, scaffold hopping

## Introduction

Over time, interest in the chemistry of pyrazoles and pyrroles has increased considerably, largely due to their occurrence in numerous natural products and the interesting properties of numerous derivatives of these classes of heterocyclic compounds.[1-3] Pyrazoles and pyrroles have become privileged scaffolds in medicinal chemistry due to their demonstrated or potential applications in the pharmaceutical field. Notable contributions in the recent literature have described a large number of drugs or drug candidates (Figure 1) that have pyrazole[4] or pyrrole[5] structures.

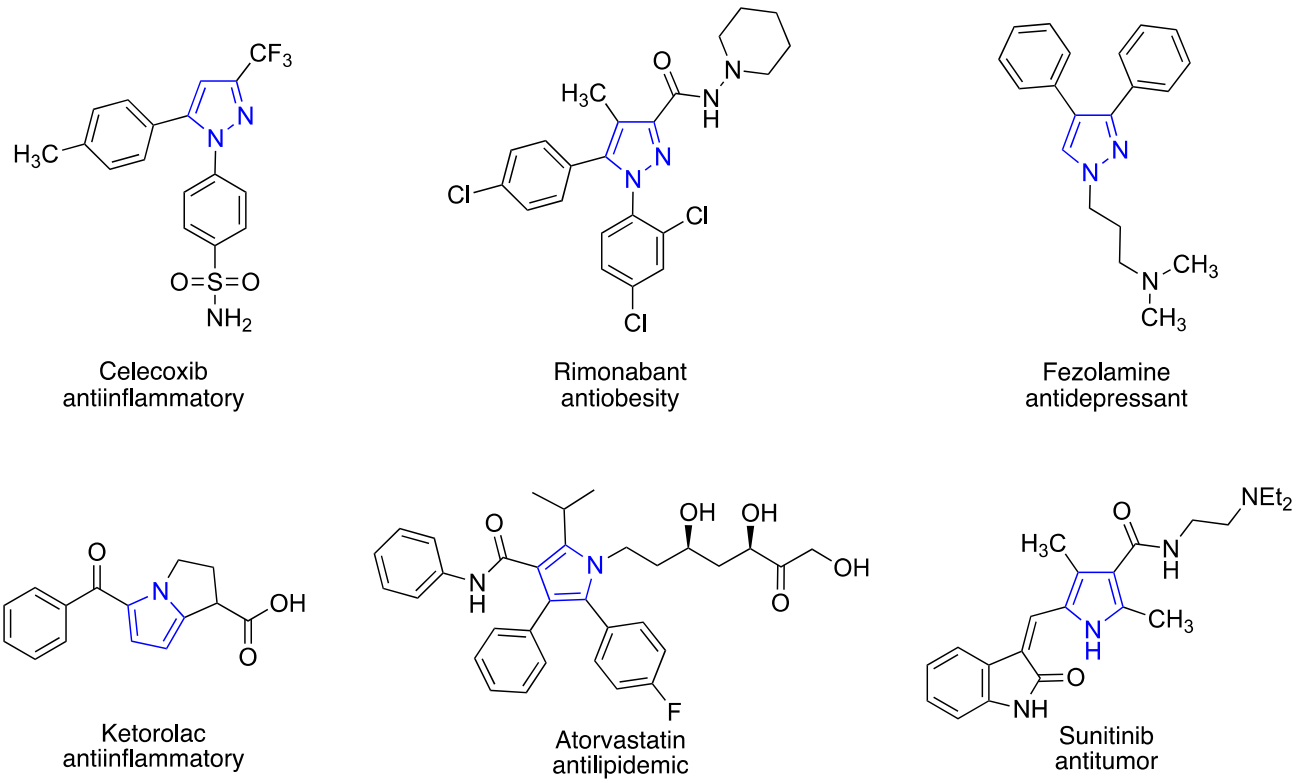



**Figure 1**. Structure of some representative pyrazole and pyrrole drugs.

Over the years, we have extensively studied the synthesis and chemical and pharmacological properties of 3-/5-pyrrolylpyrazoles.[6-9] Recently, a non-targeted screening of an in-house library of pyrazole derivatives with the aim of revealing possible antimicrobial potential has brought to light some derivatives of the series (e.g., **1**, Figure 2) that possess indirect antibacterial activity.[10] This means that although they are not able to inhibit bacterial replication *per se*, they can lower the $IC_{50}$ value of known antibiotics, especially colistin (a mixture of polymyxin E1/E2), by several log units against Gram-negative bacteria of great clinical importance.[11] The significant results prompted us to investigate further structural modifications of **1**.

Thanks to the development of click chemistry for the synthesis of 1,2,3-triazole,[12,13] this structure has become easily accessible synthetically and is attracting increasing interest as an isosteric replacement for trans-amide bond and, more generally, as a metabolically stable scaffold for drug development.[14,15] Accordingly, we wanted to investigate the possibility of a scaffold-hopping approach in which the pyrazole or pyrrole ring can be replaced by the 1,2,3-triazole core to obtain compounds of general structure **2** and **3** (Figure 2).

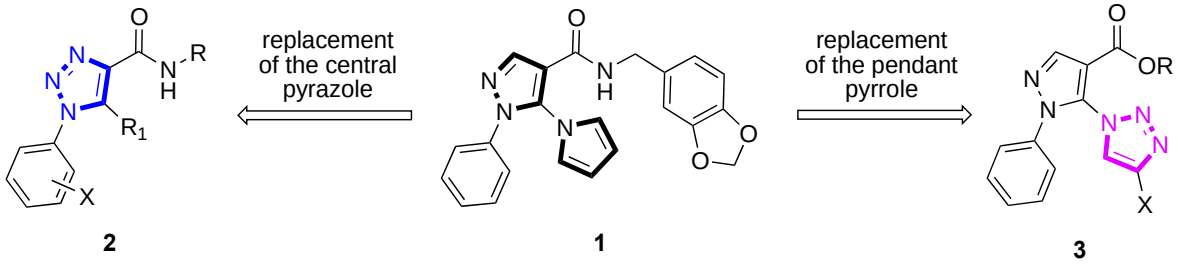
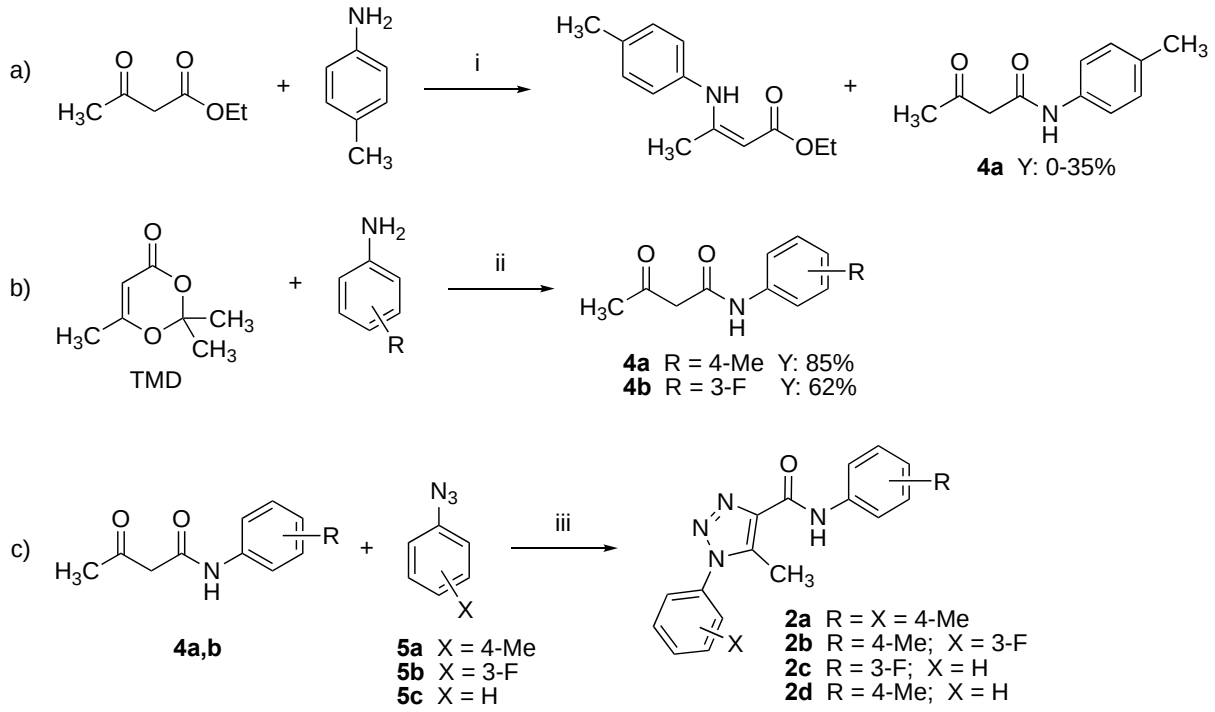



**Figure 2**. The scaffold hopping approach.

Compared to lead compound **1**, this isosteric modification should not alter the three-dimensional structure and general physicochemical properties of the new molecules but should allow them to better associate with biological targets through hydrogen bonding and dipole interactions.[13]

## Results and Discussion

For the synthesis of the compounds of general structure **2**, we aimed to use the 1,3-dipolar cycloaddition reaction between β-ketoamides and aryl azides, which has been recently reported in the literature,[16] since these starting materials can be easily prepared.



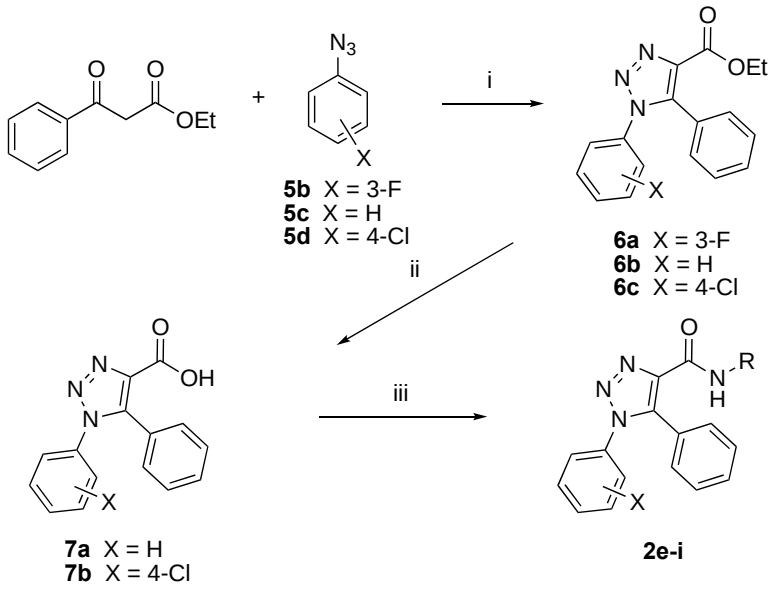

**Scheme 1.** Preparation of β-ketoamides and their use in the synthesis of 1,2,3-triazole compounds. *Reagents and conditions*: (i) silver(I) triflate, nitromethane; (ii) water, reflux; (iii) DBU, chloroform, room temperature.

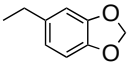
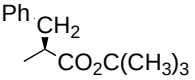
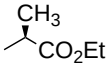
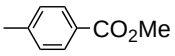
In particular, β-ketoamides were obtained by Vandavasi *et al*. by the reaction of β-ketoesters and anilines in the presence of AgOTf in nitromethane as solvent.[17] To test this procedure, we used ethyl acetoacetate and *p*-toluidine as reactants. However, this reaction did not proceed as we expected, and even when we changed

some experimental conditions (time and/or temperature), we always obtained a mixture of β-enamino ester and β-ketoamide **4a**, the latter being isolated in a yield never exceeding 35% (Scheme 1, Equation a). Therefore, we decided to use an alternative procedure that allowed us to obtain β-ketoamides **4a** and **4b** in satisfactory yields by simply refluxing *p*-toluidine or 3-fluoroaniline with TMD (2,2,6-trimethyl-4*H*-1,3-dioxin-4-one) in water for 4 h (Scheme 1, Equation b). Compounds **4a** and **4b** were then subjected to organocatalyzed cycloaddition with azides **5a-c** (namely *p*-tolyl azide, 3-fluorophenyl azide, and phenyl azide, respectively) to afford triazole derivatives **2a-d** in 61-82% yield (Scheme 1, Equation c).

Although this approach was quite efficient, it suffered from a limitation due to the availability of starting materials such as TMD. Therefore, to increase the possibility of expanding the chemical diversity at position 5 of the triazole ring, a modification was introduced in the synthesis of compounds **2** involving cycloaddition as the first step followed by the amidation reaction. Thus, ethyl benzoylacetate and azides **5b-d** (namely 3-fluorophenyl azide, phenyl azide, and 4-chlorophenyl azide, respectively) were heated in chloroform with DBU as catalyst to afford the triazole derivatives **6a-c** (Scheme 2). Alkaline hydrolysis of **6b,c** led to the corresponding acids **7a,b**, which were then converted to the final amides **2e-i** by coupling reaction with EDC/HOBt, using different amines to test the possibility of accessing compounds with different structural features.



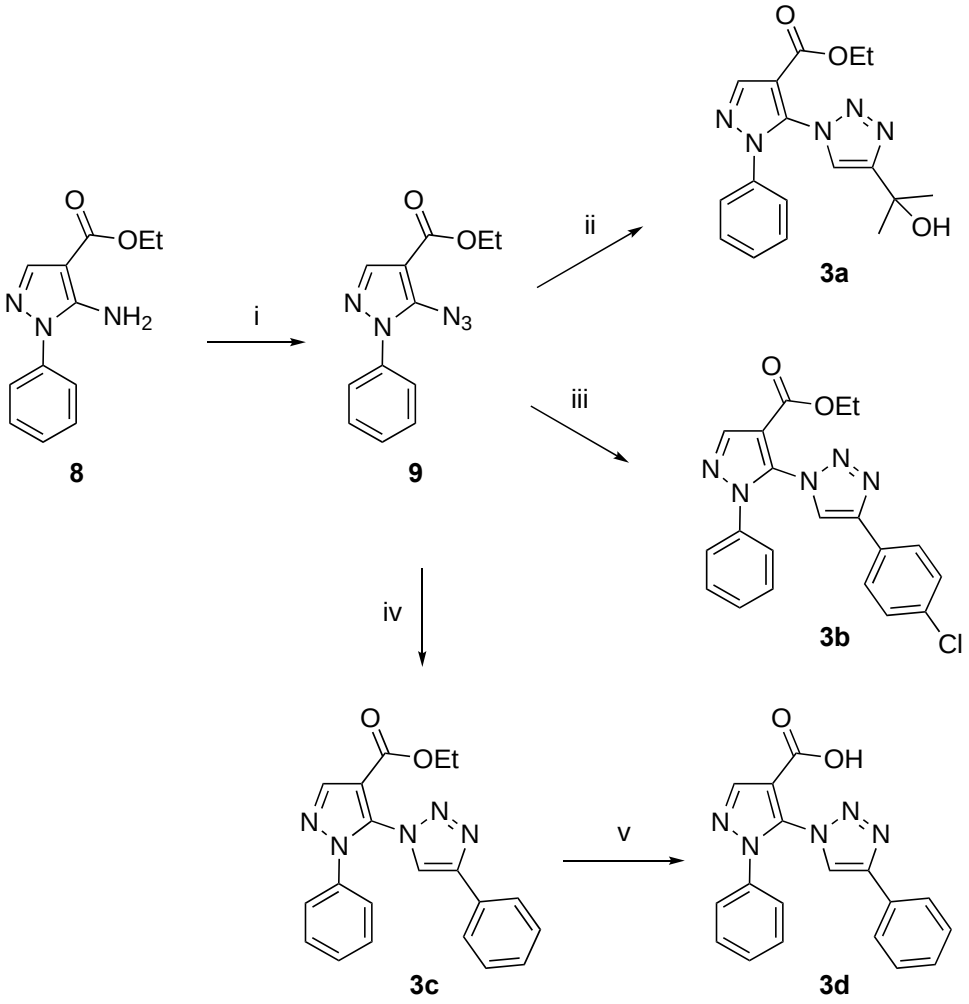

| Compound | X | R | Yield (%) |
|---|---|---|---|
| **2e** | H |  | 81 |
| **2f** | H |  | 88 |
| **2g** | H |  | 56 |
| **2h** | Cl |  | 69 |
| **2i** | Cl |  | 72 |

**Scheme 2.** Alternative approach to 1,2,3-triazole compounds. *Reagents and conditions*: (i) DBU, chloroform, reflux; (ii) NaOH, methanol/water; (iii) *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) hydrochloride, 1-hydroxybenzotriazole (HOBt), dichloromethane.

As for the 5-(1,2,3-triazol-1-yl)pyrazole derivatives of general structure **3**, these new compounds were synthesized starting from ethyl 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylate (**8**) (Scheme 3).[18] This was diazotized with sodium nitrite in TFA to give the diazonium salt, which reacted in situ with sodium azide to give the azide derivative **9** with an overall yield of 89%, compared with the 50% yield reported from a similar procedure.[19] The azide **9** was subjected to cycloaddition with various alkynes to afford the desired compounds **3a-c** with a yield of 20-48%. Compound **3c** was then hydrolyzed with lithium hydroxide to give the corresponding carboxylic acid **3d**, but subsequent attempts to convert **3d** to an amido derivative with L-phenylalanine ethyl ester hydrochloride under standard condensation conditions (EDC, HOBt) were

unsuccessful. Therefore, this procedure for obtaining **3d** from **8** proved to be quite fast and easy to perform, while further work is needed to establish the use of **3d** in subsequent transformations.




**Scheme 3**. Synthesis of 5-(1,2,3-triazol-1-yl)pyrazole compounds. *Reagents and conditions*: sodium nitrite, water, trifluoroacetic acid, then sodium azide, 0-5 °C; (ii) 2-methyl-3-butyn-2-ol, sodium L-ascorbate, copper(II) sulfate, dry DMF; (III) 1-chloro-4-ethynylbenzene, sodium L-ascorbate, copper(II) sulfate, dry DMF; (iv) phenylacetylene, sodium L-ascorbate, copper(II) sulfate, dry DMF; (v) LiOH, methanol/water.

## Conclusions

Different scaffold hopping approaches were evaluated to obtain two small families of isosteric compounds starting from the lead compound **1**. The results obtained show the possibility of expanding each class of these isosteres into larger libraries in view of their possible biological evaluation.

## Experimental Section

**General.** Merck silica gel 60 was used for flash chromatography (23-400 mesh). For thin layer chromatography (TLC), silica-coated aluminum plates (Merck Kieselgel F254) were used. Melting points were determined on a Gallenkamp apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR were recorded on a Bruker Avance DPX400 or Bruker Avance 600 spectrometers operating at 400/100 MHz or 600/150 MHz, respectively. Chemical shifts (d) are in part per million (ppm) relative to TMS as internal standard and coupling constants (*J*) are reported in Hz. Mass spectral (MS) data were obtained using an Agilent 1100 LC/MSD VL system (G1946C) with a 0.4 mL/min flow rate using a binary solvent system of 95:5 methanol/water. UV detection was monitored at 254 nm. Elemental analyses were performed on a Perkin-Elmer PE 2400 elemental analyzer and the data for C, H, and N are within 0.4% of the theoretical values. The chemical purity of the target compounds was determined using an Acquity Waters UPLC-MS system under the following conditions: Waters BEH C18 (2.1 mm x 50 mm, 1.7 µm) reversed phase column; method: gradient elution, solvent A (0.1% formic acid in water), solvent B (0.1% formic acid in acetonitrile) 90:10 to 0:100 over 2.9 min, flow rate of 0.5 mL/min, UV detector, 254 nm. For compound **3b**, the following conditions were used: Symmetry® C18 column (4.6x75 mm, 3.5 µm) with methanol as the mobile phase at a flow rate of 0.5 mL/min, UV detector, 254 nm.

**General procedure for the synthesis of β-oxoamides 4**. 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (TMD) (350 mg, 2.5 mmol) was added to a solution of the appropriate aniline (1.54 mmol) in water (3 mL) preheated at 100 °C. Heating was maintained for 4-6 h with stirring and the progress of the reaction was monitored by TLC (silica, EtOAc/hexane, 1:3). After completion of the reaction, the mixture was cooled and extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography (silica, EtOAc/hexane, 1:4) to give products **4**.
**3-Oxo-*N*-(p-tolyl)butanamide (4a)**. Light yellow solid (250 mg, 85%). Mp 88-90 °C (lit.[17]: 90-91 °C).
**N-(3-Fluorophenyl)-3-oxobutamanide (4b)**. White crystals (216 mg, 62%). Mp 66-67 °C (lit.[20]: 65-67 °C).
**General procedure for the synthesis of 1-aryl-5-methyl-1*H*-1,2,3-triazole-4-carboxamides 2a-d**. A solution of **4a,b** (0.5 mmol), aryl azide **5a-c** (1 mmol), and DBU (0.05 mmol) in chloroform (3-4 mL) was stirred at room temperature for 24 h. After completion of the reaction (TLC, silica, EtOAc/hexane 1:4), solvent was removed under reduced pressure and the residue was triturated with diethyl ether/methanol and then recrystallized from methanol to give the title compound.
**5-Methyl-*N*,1-di-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide (2a)**. Yield: 63%. Colorless needles. Mp 249-251 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.95 (s, 1H, NH), 7.53 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.36-7.26 (m, 4H), 7.12 (d, *J* = 8.1 Hz, 2H, Ar-H), 2.58 (s, 3H, Me), 2.41 (s, 3H, Me), 2.28 (s, 3H, Me). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.2, 140.4, 138.6, 137.3, 135.2, 133.9, 133.1, 130.2 (x2C), 129.6 (x2C), 125.1 (x2C), 119.8 (x2C), 21.3, 20.9, 9.8. MS (ESI): *m/z* 307 $[M + H]^+$. Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.73; H, 5.87; N, 18.02.
**1-(3-Fluorophenyl)-5-methyl-*N*-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide (2b)**. Yield: 61%. Colorless needles. Mp 180-183 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.94 (NH), 7.71-7.46 (m, 3H, Ar-H), 7.31-7.18 (m, 3H, Ar-H), 7.12 (d, *J* = 8.2 Hz, 2H, Ar-H), 2.64 (s, 3H, Me), 2.28 (s, 3H, Me). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.0 and 161.5 (C-F coupling), 158.9, 138.8, 137.3, 136.8 and 136.7 (C-F coupling), 135.1, 134.0, 131.1 and 131.0 (C-F coupling), 129.6 (x2C), 120.9 (C-F coupling), 119.9 (x2C), 117.3 and 117.1 (C-F coupling), 113.2 and 112.9 (C-F coupling), 20.9, 9.8. MS (ESI): *m/z* 311 $[M + H]^+$. Anal. Calcd for $C_{17}H_{15}FN_4O$: C, 65.80; H, 4.87; N, 18.05. Found: C, 65.58; H, 4.78; N, 17.89.
***N*-(3-Fluorophenyl)-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide (2c)**. Yield: 69%. White crystals. Mp 169-171 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H, NH), 7.65 (m, 1H, Ar-H), 7.59-7.49 (m, 3H, Ar-H), 7.46-7.39

(m, 2H, Ar-H), 7.30-7.23 (m, 2H, Ar-H), 6.80 (m, 1H), 2.62 (s, 3H, Me). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.3 and 161.8 (C-F coupling), 159.3, 139.3 and 139.2 (C-F coupling), 138.3, 137.6, 135.4, 130.2 and 130.1 (1C + C-F coupling), 129.7 (x2C), 125.3 (x2C), 115.1 and 115.0 (C-F coupling), 111.1 and 110.9 (C-F coupling), 107.4 and 107.1 (C-F coupling), 9.8. MS (ESI): *m/z* 297 $[M + H]^+$. Anal. Calcd for $C_{16}H_{13}FN_4O$: C, 64.86; H, 4.42; N, 18.91. Found: C, 65.08; H, 4.51; N, 18.70.

**5-Methyl-1-phenyl-*N*-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide (2d)**. Yield: 82%. White crystals. Mp 155-156 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H, NH), 7.53 (m, 5H, Ph), 7.42 (d, *J* = 7.9 Hz, 2H, tolyl), 7.12 (d, *J* = 8.1 Hz, 2H, tolyl), 2.62 (s, 3H, Me), 2.28 (s, 3H, Me). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.1, 138.7, 137.3, 135.6, 135.2, 134.0, 130.1, 129.7(x2C), 129.6(x2C), 125.3(x2C), 119.9(x2C), 20.9, 9.8. MS (ESI): *m/z* 315 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.17. Found: C, 70.13; H, 5.37; N, 18.92.

**General procedure for the synthesis of ethyl 1-aryl-5-phenyl-1*H*-1,2,3-triazole-4-carboxylates 6a-c**. Starting from ethyl benzoylacetate and the appropriate aryl azide **5b-d**, compounds **6a-c** were synthesized by refluxing in chloroform in presence of DBU and then isolated and purified as described above for the synthesis of **2a-d**.

**Ethyl 1-(3-fluorophenyl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate (6a).** Obtained using 3-fluorophenyl azide. Yield: 74%. Colorless needles. Mp 143-145 °C. $^1$H NMR (600 MHz, $CDCl_3$): δ 7.45 (m, 1H, F-Ar-H), 7.40 (t, *J* = 7.4 Hz, 2H, Ar-H), 7.34 (dt, *J* = 8.4 and 6.4 Hz, 1H, F-Ar-H), 7.30 (d, *J* = 7.1 Hz, 2H, Ar-H), 7.12 (t, *J* = 7.1 Hz, 1H, Ar-H), 7.06 (dt, *J* = 8.5 and 4.8 Hz, 2H, F-Ar-H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$): δ 163.3 and 161.7 (C-F coupling), 160.8, 140.9, 137.2, 137.0 and 136.9 (C-F coupling), 130.7 and 130.6 (C-F coupling), 130.2, 130.1(x2C), 128.5(x2C), 125.5, 120.9 and 120.8 (C-F coupling), 116.7 and 116.6 (C-F coupling), 113.0 and 112.8 (C-F coupling), 61.3, 14.1. MS (ESI): *m/z* 334 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{14}FN_3O_2$: C, 65.59; H, 4.53; N, 13.50. Found: C, 65.30; H, 4.61; N, 13.26.

**Ethyl 1,5-diphenyl-1*H*-1,2,3-triazole-4-carboxylate (6b).** Prepared starting from phenyl azide. Yield: 77%. White crystals. Mp 136-137 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 6H), 7.23-7.20 (m, 4H), 4.30 (q, *J* = 7.0 Hz, 2H), 1.25 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 161.0, 140.8, 137.0, 136.0, 130.3, 129.9, 129.5, 129.3, 128.4, 125.8, 125.2, 61.2, 14.2. MS (ESI): *m/z* 316 $[M + Na]^+$. All spectral data are in agreement with those previously reported.[21]

**Ethyl 1-(4-chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate (6c).** Prepared from 4-chlorophenyl azide. Yield: 96%. White needles. Mp 108-110 °C. $^1$H NMR (600 MHz, $CDCl_3$): δ 7.45 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.40 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.7 Hz, 2H, Cl-Ar-H), 7.29 (d, *J* = 7.1 Hz, 2H, Ar-H), 7.22 (d, *J* = 8.7 Hz, 2H, Cl-Ar-H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$): δ 160.8, 140.8, 137.2, 135.6, 134.3, 130.2(x2C), 130.1, 129.6(x2C), 128.6(x2C), 126.3(x2C), 125.5, 61.3, 14.2. MS (ESI): *m/z* 350 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{14}ClN_3O_2$: C, 62.30; H, 4.31; N, 12.82. Found: C, 62.50; H, 4.37; N, 12.65.

**General procedure for the synthesis of 1-aryl-5-phenyl-1*H*-1,2,3-triazole-4-carboxylic acids 7a and 7b**. To a solution of ester **6b** or **6c** (2.4 mmol) in EtOH (9 mL) was added 3.5 N NaOH solution (9 mL, 31.5 mmol) and the mixture was refluxed for 30 min, then concentrated to half volume, cooled in ice bath, and acidified with 3 N HCl. The solid which formed was extracted with EtOAc and the organic layer was washed with brine and dried over sodium sulfate. Evaporation of the solvent left a residue which was recrystallized from EtOH.

**1,5-Diphenyl-1*H*-1,2,3-triazole-4-carboxylic acid (7a).** Prepared starting from **6b** in 96% yield. White solid. Mp 182-184 °C.

**1-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid (7b).** Prepared starting from **6c** in 95% yield. White solid. Mp 165-167 °C.

**General procedure for the synthesis of 1-aryl-5-phenyl-1*H*-1,2,3-triazole-4-carboxamides 2e-i.** To a solution of **7a** or **7b** (2.6 mmol) and the appropriate amine (4.0 mmol) in dry DCM (50 mL), EDC (1.0 g, 5.2 mmol) and HOBt (350 mg, 2.6 mmol) were added and the mixture was stirred at room temperature for 5 h. Then the

reaction mixture was washed with 1 N HCl, 10% $NaHCO_3$ solution, and brine. After drying over sodium sulfate, the organic solution was concentrated in vacuo and the residue was purified as reported below.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1,5-diphenyl-1*H*-1,2,3-triazole-4-carboxamide (2e)**. Synthesized starting from **7c** and piperonylamine. Recrystallized from MeOH. Colorless crystals. Yield: 81%. Mp 198-200 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.58 (t, *J* = 5.0 Hz, 1H, NH), 7.41-7.24 (m, 8H, Ar-H), 7.20 (d, *J* = 8.1 Hz, 2H, Ar-H), 6.79 (s, 1H, piperonyl H-4), 6.76 (d, *J* = 8.1 Hz, 1H, piperonyl H-6), 6.70 (d, *J* = 7.9 Hz, 1H, piperonyl H-7), 5.87 (s, 2H, O-C*H*$_2$-O), 4.46 (d, *J* = 5.9 Hz, 2H, C*H*$_2$-NH). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 160.1, 147.9, 147.0, 139.0, 138.7, 136.0, 132.0, 130.6(x2C), 129.8, 129.5, 129.3(x2C), 128.3(x2C), 125.7, 125.3(x2C), 121.2, 108.6, 108.3, 101.0, 42.9. MS (ESI): *m/z* 421 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{18}N_4O_3$: C, 69.34; H, 4.55; N, 14.06. Found: C, 69.55; H, 4.38; N, 13.85.

***N*-(Adamantan-1-yl)-1,5-diphenyl-1*H*-1,2,3-triazole-4-carboxamide (2f)**. Prepared in 88% yield starting from **7c** and 1-aminoadamantane and purified by recrystallization from MeOH. Colorless crystals. Mp >230 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.41-7.23 (m, 8H), 7.17 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.09 (s, 1H, NH), 2.08 (m, 6H, adamantyl), 2.04 (m, 3H, adamantyl), 1.64 (m, 6H, adamantyl). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.3, 139.6, 138.6, 136.2, 130.6(x2C), 129.6, 129.3, 129.2(x2C), 128.3(x2C), 126.0, 125.3(x2C), 52.1, 41.7(x3C), 36.4(x3C), 29.5(x3C). MS (ESI): *m/z* 421 $[M + Na]^+$. Anal. Calcd for $C_{25}H_{26}N_4O$: C, 75.35; H, 6.58; N, 14.06. Found: C, 75.55; H, 6.43; N, 13.84.

***tert*-Butyl (*S*)-3-Phenyl-2-[[[1,5-diphenyl-1*H*-1,2,3-triazole-4-yl]carbonyl]amino]propanoate (2g).** Prepared in 56% yield starting from **7c** and L-threonine *tert*-butyl ester hydrochloride according to the general procedure reported above by adding also $NEt_3$ (4 mmol). Recrystallized from 70% EtOH. White solid. Mp 74-76 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.3 Hz, 1H, NH), 7.44-7.11 (m, 15H, Ar-H), 4.89 (m, 1H, C*H*-CO), 3.12 (d, *J* = 5.8 Hz, 2H, C*H*$_2$), 1.33 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.3, 159.7, 139.0, 138.5, 136.3, 136.0, 130.5(x2C), 129.8, 129.6(x2C), 129.4, 129.3(x2C), 128.4(x2C), 128.3(x2C), 126.9, 125.7, 125.3(x2C), 82.2, 53.4, 38.6, 28.0(x3C). MS (ESI): *m/z* 491 $[M + Na]^+$. Anal. Calcd for $C_{28}H_{28}N_4O_3$: C, 71.78; H, 6.02; N, 11.96. Found: C, 72.05; H, 5.90; N, 11.74.

**Ethyl (*S*)-2-[[[1-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole-4-yl]carbonyl]amino]propanoate (2h).** Prepared in 69% yield starting from **7d** and L-alanine ethyl ester hydrochloride according to the general procedure reported above by adding also $NEt_3$ (4 mmol) and prolonging the reaction time to 18 h. Purified by trituration with hexane. White solid. Mp 128-131 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.8 Hz, 1H, NH), 7.40-7.22 (m, 7H, Ar-H), 7.15 (d, *J* = 8.7 Hz, 2H, Ar-H), 4.68 (m, 1H, C*H*CO), 4.16 (q, *J* = 7.2 Hz, 2H, C*H*$_2$CH$_3$), 1.46 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 1.22 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 172.5, 159.6, 139.1, 138.5, 135.5, 134.5, 130.4(x2C), 130.0, 129.6(x2C), 128.4(x2C), 126.4(x2C), 125.3, 61.5, 47.8, 18.5, 14.1. MS (ESI): *m/z* 421 $[M + Na]^+$. Anal. Calcd for $C_{20}H_{19}ClN_4O_3$: C, 60.23; H, 4.80; N, 14.05. Found: C, 60.51; H, 4.92; N, 13.80.

**Methyl [[[1-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole-4-yl]carbonyl]amino]benzoate (2i).** Prepared in 72% yield starting from **7d** and methyl 4-aminobenzoate and purified by recrystallization from MeOH. White solid. Mp 229-230 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H, NH), 7.97 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.71 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.42-7.26 (m, 7H, Ar-H), 7.18 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.84 (s, 3H, Me). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.6, 158.0, 141.8, 139.9, 138.6, 135.8, 134.3, 130.9(x2C), 130.4(x2C), 130.3, 129.7(x2C), 128.6(x2C), 126.4(x2C), 125.8, 125.0, 119.0(x2C), 52.0. MS (ESI): *m/z* 455 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{17}ClN_4O_3$: C, 63.82; H, 3.96; N, 12.94. Found: C, 64.10; H, 4.09; N, 12.70.

**Ethyl 5-Azido-1-phenyl-1*H*-pyrazole-4-carboxylate (9).** A solution of sodium nitrite (660 mg, 9.5 mmol) in water (1 mL) was added to a solution of **8** (462 mg, 2 mmol) in TFA (5 mL) cooled in an ice bath. After stirring for 15 min, a solution of sodium azide (1.38 mg, 21 mmol) in water (5 mL) was added and the mixture was stirred at room temperature for 2 h, then extracted with EtOAc. The combined organic layer was dried over

sodium sulfate and evaporated under vacuum to give a residue which was purified by flash chromatography (silica, hexane/EtOAc 5:1) affording **9** (89%) as a brown solid, which was directly used in the next step

**General procedure for the synthesis of ethyl 5-(4-substitued-1*H*-1,2,3-triazole-1-yl)-1-phenyl-1*H*-pyrazole-4-carboxylates 3a-c**. A mixture of the azido derivative **9** (437 mg,1.7 mmol), the appropriate alkyne (1.7 mmol), $CuSO_4$ (26.62 mg, 0.17 mmol), and sodium L-ascorbate (33.68 mg, 0.17 mmol) in dry DMF (4 mL) was stirred at room temperature for 6 h, then diluted with water (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with 5% LiCl aqueous solution (2 x 15 mL), then with brine (3 x 10 mL), and dried over sodium sulfate. Evaporation under reduced pressure gave a solid which was purified as reported below.

**Ethyl 5-[4-(2-Hydroxypropane-2-yl)-1*H*-1,2,3-triazole-1-yl)-1-phenyl-1*H*-pyrazole-4-carboxylate (3a).** Synthesized using 2-methyl-3-butyn-2-ol. Purified by flash chromatography (silica, hexane/AcOEt 5:1). Yellow solid. Yield: 31%. Mp 130-133 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H, triazole-H), 7.64 (s, 1H, pyrazole-H), 7.31-7.26 (m, 3H, Ar-H), 7.18-7.13 (m, 2H, Ar-H), 4.13 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 1.59 (s, 6H), 1.13 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 160.9, 155.9, 141.8, 137.1, 135.3, 129.3(x2C), 129.2, 123.8(x2C), 123.1, 111.7, 68.6, 60.9, 30.4(x2C), 14.0. MS (ESI): *m/z* 342 $[M + H]^+$. Anal. Calcd for $C_{17}H_{19}N_5O_3$: C, 59.81; H, 5.61; N, 20.52. Found: C, 59.58; H, 5.49; N, 20.70.

**Ethyl 5-[4-(4-Chlorophenyl)-1*H*-1,2,3-triazole-1-yl]-1-phenyl-1*H*-pyrazole-4-carboxylate (3b).** Synthesized starting using 4-chlorophenylacetylene. Purified by flash chromatography (silica, hexane/AcOEt 5:1), followed by trituration with hexanes. Light yellow solid. Yield: 43%. Mp 170-173 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H, triazole-H), 7.99 (s, 1H, pyrazole-H), 7.72 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.29 (m, 3H, Ph), 7.26-7.21 (m, 2H, Ph), 4.15 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 1.12 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 160.7, 145.8, 142.0, 137.2, 135.7, 133.6, 130.0(x2C), 129.9, 129.7(x2C), 128.8, 127.6(x2C), 126.3, 124.5(x2C), 111.8, 61.0, 14.2. MS (ESI): *m/z* 394 $[M + H]^+$. Anal. Calcd for $C_{20}H_{16}ClN_5O_2$: C, 61.00; H, 4.10; N, 17.78. Found: C, 61.27; H, 4.19; N, 17.90.

**Ethyl 5-(4-Phenyl-1*H*-1,2,3-triazole-1-yl)-1-phenyl-1*H*-pyrazole-4-carboxylate (3c).** Synthesized using phenylacetylene. Purified by flash chromatography (silica, DCM/hexane 2:1) followed by recrystallization from EtOH. Yield: 20%. Yellow solid. Mp 121-123 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H, triazole-H), 7.99 (s, 1H, pyrazole-H), 7.78 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.37 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.32-7.19 (m, 6H, Ar-H), 4.13 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 1.11 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 161.1, 147.7, 141.8, 137.2, 135.6, 135.2, 129.5(x2C), 129.2, 129.0(x2C), 128.7, 125.9(x2C), 123.9(x2C), 122.9, 111.8, 60.9, 14.0. MS (ESI): *m/z* 382 $[M + Na]^+$. Anal. Calcd for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49. Found: C, 66.60; H, 4.66; N, 19.67.

**5-(4-Phenyl-1*H*-1,2,3-triazole-1-yl)-1-phenyl-1*H*-pyrazole-4-carboxylic acid (3d).** To a solution of **3c** (264 mg, 0.7 mmol) in THF (1.5 mL) and MeOH (0.8 mL) was added a 2 N solution of LiOH (0.8 mL, 1.6 mmol) and the reaction mixture was stirred at room temperature for 3 h. Solvents were removed under reduced pressure and the residue was diluted with water and acidified with conc. HCl. The precipitate was taken up into EtOAc and the organic layer was dried over sodium sulfate. Evaporation of the solvent left a residue which was triturated with hexane and then recrystallized from EtOH to give **3d**. Yield: 85%. Orange crystals. Mp 239-241 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H, triazole-H), 7.98 (s, 2H, pyrazole-H), 7.77 (d, *J* = 7.1 Hz, 2H, Ar-H), 7.36 (t, *J* = 7.2 Hz, 2H, Ar-H), 7.32-7.25 (m, 3H, Ar-H), 7.24-7.17 (m, 3H, Ar-H). $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 162.2, 146.8, 142.3, 137.4(x2C), 135.7, 130.0(x2C), 129.7, 129.6(x2C), 129.0, 125.9, 125.8(x2C), 124.5(x2C), 112.6. MS (ESI): *m/z* 330 $[M - H]^-$. Anal. Calcd for $C_{18}H_{13}N_5O_2$: C, 65.25; H, 3.95; N, 21.14. Found: C, 65.05; H, 4.06; N, 21.40.

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## Supplementary Material

Copies of the $^{1}$H- and $^{13}$C-NMR spectra and HPLC traces of compounds **2** and **3** are given in the Supplementary Material file associated with this manuscript.

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