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# Synthesis of enantiomerically pure α-[4-(1-substituted)-1,2,3-triazol-4-yl]-benzylacetamides via microwave-assisted click chemistry: towards new potential antimicrobial agents

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**Abstract**—Chiral 1-phenyl-2-propynylamines are important building blocks for the synthesis of antifungal and antiaromatase agents related to bifonazole. In this report, a microwave-assisted Cu(I)-catalyzed 'click chemistry' approach has been employed to easily generate a small library of enantiomerically pure α-[4-(1-substituted)-1,2,3-triazol-4-yl]benzylacetamides starting from racemic propargylamines. These compounds could represent easily accessible intermediates for the synthesis of new antimicrobial agents.


## 1. Introduction

Since the identification of clotrimazole **1**[1] in 1972, a number of antifungal azole agents have been studied and are now used in clinical practice. Miconazole **2** and related derivatives, together with bifonazole **3**, belong to the class of imidazoles[2] while fluconazole **4** represents an important example of the triazole family (Fig. 1).[3]

Despite important advances in this field, there is a continuing increase in the incidence of fungal infections, together with a gradual rise in azole resistance. Moreover, further studies have demonstrated that some of these antifungal azoles effectively and rapidly inhibit the growth of chloroquine-resistant strains of *P. falciparum* in vitro.[4]

Our interest in antifungal drugs,[5] together with the experience acquired in the synthesis of chiral azoles and the recent successes in the application of combinatorial techniques and microwave-assisted procedures for the identification of novel lead compounds, brought us to investigate the applicability of the 'click chemistry approach' to generate a small library of novel chiral azole precursors.

In the last few years, click chemistry has emerged as a fast and efficient approach for the synthesis of novel compounds with desired functionality making use of selected

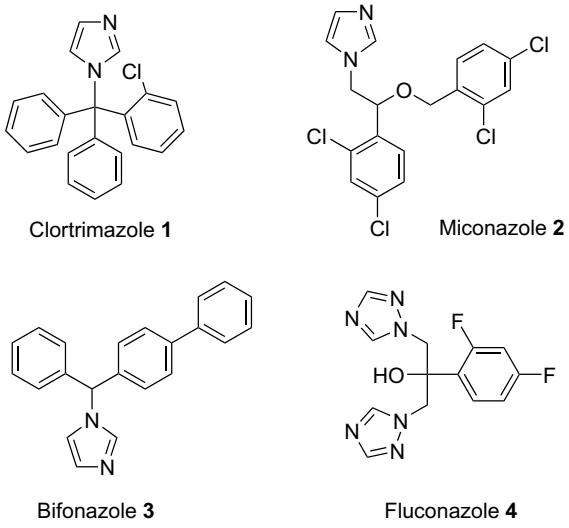


**Figure 1.** Common antifungal agents.

'near perfect' reactions.[6] The concept of click chemistry is experiencing a growing popularity. This term, coined by Sharpless, now refers to reactions yielding the product in high yield without the need for further purification, generating inoffensive by-products, and operating in a benign solvent, usually water. In this way, it is possible to reliably generate a plethora of new compounds and thereby accelerate the process of drug discovery. The most powerful

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click reaction discovered to date is the CuI catalyzed variant of the Huisgen 1,3-dipolar cycloaddition of azides and alkynes to afford 1,2,3-triazoles.[7]

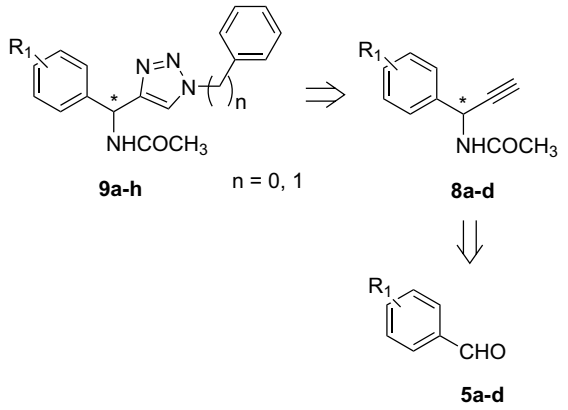
Herein we turned our attention to the synthesis of enantiopure α-[4-(1-substituted)-1,2,3-triazol-4-yl]benzylacetamides **9a**–**h**, using a microwave-assisted copper(I)-catalyzed click chemistry approach. These derivatives could be interesting synthons for the synthesis of new potential antifungal, antiaromatase and antimalarial compounds related to bifonazole or letrazole.

## 2. Results and discussion

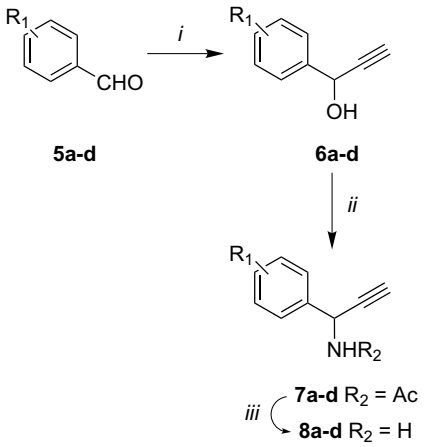
The retrosynthetic approach depicted in Scheme 1 shows that the desired chiral compounds **9a**–**h** could be easily obtained via a 1,3-dipolar cycloaddition (click reaction) from the corresponding propargylamides **8a**–**d**, which could in turn be obtained from the commercial aldehydes **5a**–**d** using an efficient procedure previously reported by us.[5b,8]

Reacting aldehydes **5a**–**d** with the appropriate Grignard reagent at room temperature for 2 h gave the corresponding propargylic alcohols **6a**–**d**. Racemic propargylamines **8a**–**d** were finally achieved in a good overall yield by hydrolysis of acetamides **7a**–**d**, which were in turn obtained from aryl propargylic alcohols **6a**–**d** via a Ritter reaction (acetonitrile/sulfuric acid) (Scheme 2).

The kinetic enzymatic resolution of racemic propargylamines **8a**–**d** with CAL-B as the catalyst gave both (*S*)-amines **8a**–**d** and (*R*)-acetamides **7a**–**d** in good yields and high enantiomeric excess; the absolute configurations were determined by comparison with authentic samples (Scheme 3). The latter compounds (*R*)-**7a**–**d** were then submitted to the microwave-assisted click reaction. In order to prepare the *N*-benzyl triazole derivatives **9e**–**h** ($n = 1$), a three component copper(I)-catalyzed approach[9] was used: alkynes (*R*)-**7a**–**d**, benzyl chloride, and sodium azide were suspended in a 1:1 mixture of *t*-BuOH and water, together with the in situ generated Cu(I) catalyst (sodium ascorbate/$Cu(SO)_4$),[10] in a 10-mL sealed glass vial. After 10 min of irradiation at 125 °C and subsequent cooling to




**Scheme 1.** Retrosynthetic approach.



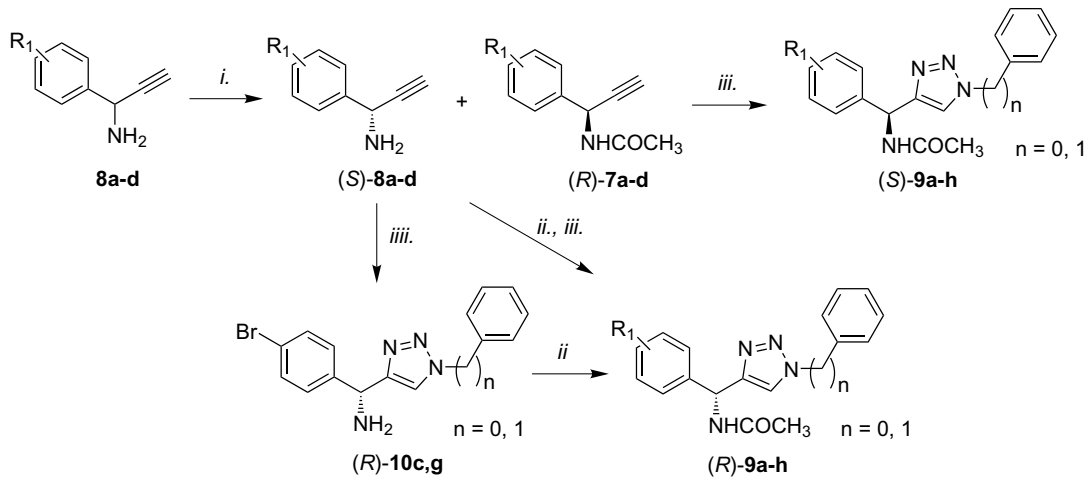

**Scheme 2.** Reagents and conditions: (i) ethynylmagnesium bromide, THF, 2 h, rt; (ii) $H_2SO_4$, $CH_3CN$, rt; (iii) HCl, 70 °C.

room temperature, the triazole products (*S*)-**9e**–**h** were crystallized from the reaction mixture and then isolated by simple filtration. In order to prepare *N*-phenyl triazole derivatives **9a**–**d** ($n = 0$), phenyl azide[11] was used in place of the in situ generated benzyl azide by applying the above described procedure: compounds (*S*)-**9a**–**d** were crystallized from the reaction mixture and then isolated by filtration. (Scheme 3; Table 1).

As expected, the new triazoles (*S*)-**9a**–**h** were formed in a completely regioselective manner, with no contamination by the 1,5-regioisomer as highlighted from NOE experiments (Fig. 2a): in the case of compounds **9e**–**h** ($n = 1$), irradiation of the resonance arising from $H_c$ resulted in the observation of a strong NOE in the resonances arising from $H_b$ and the aromatic *ortho* protons while in the case of compounds **9a**–**d** ($n = 0$), irradiation of the resonance arising from NH resulted in the observation of a strong NOE in the resonances arising from $H_a$ and $H_b$.

Unfortunately, the direct application of the previously described click-chemistry protocol to the amines (*S*)-**8a**–**d** recovered from the CAL-B catalyzed enzymatic resolution never gave the expected triazole derivatives. The presence of the free amino group proved detrimental to the outcome of the 1,3-dipolar cycloaddition reaction most likely as a consequence of the chelation of the copper ions: after filtration of the crude material, the isolated precipitate decomposed in a short time resulting in a complex reaction mixture. Several attempts were made in order to optimize the reaction conditions with compound (*S*)-**8a**; finally it was found that the addition of aqueous ammonia to the crude mixture after the click reaction allowed us to avoid the decomposition of the desired triazole products. Unfortunately, compounds (*R*)-**10c**,**g**, whose structure was confirmed by conversion into the corresponding amides (*R*)-**9c**,**g**, needed to be recovered from the aqueous phase and this procedure was therefore considered impractical for the development of a click library (Scheme 3).

For this reason, in order to obtain the enantiopure triazoles (*R*)-**9a**–**h**, we considered it convenient to transform the




**Scheme 3.** Reagents and conditions: (i) AcOEt, CAL-B, $Et_2O$, rt; (ii) $Ac_2O$, $Et_3N$, $CH_2Cl_2$, rt, 2 h; (iii) (For $n = 1$): $NaN_3$, benzyl chloride, sodium ascorbate/$Cu(SO)_4$, $H_2O$/*t*-ButOH, MW, 125 °C, 10 min; (For $n = 0$): $PhN_3$, sodium ascorbate/$Cu(SO)_4$, $H_2O$/*t*-ButOH, MW, 120 °C, 10 min.

**Table 1.** α-[4-(1-Substituted)-1,2,3-triazol-4-yl]-benzylacetamides **9a**–**h** produced via Scheme 3

| Entry | Compound | | | ee[a] (%) | Yield[b] (%) | $[\alpha]_D^{20}$ [c] |
|---|---|---|---|---|---|---|
| | | R | *n* | | | |
| 1 | (*S*)-**9a** | H | 0 | 95 | 80 | −9.4 (*c* 1.0 $CHCl_3$) |
| 2 | (*S*)-**9b** | 4-F | 0 | 95 | 75 | −6.6 (*c* 0.9 $CHCl_3$) |
| 3 | (*S*)-**9c** | 4-Br | 0 | 89 | 77 | −6.8 (*c* 1.7 $CHCl_3$) |
| 4 | (*S*)-**9d** | 4-Cl | 0 | 79 | 85 | −9.8 (*c* 1.0 $CHCl_3$) |
| 5 | (*S*)-**9e** | H | 1 | 91 | 90 | −9.2 (*c* 0.6 MeOH) |
| 6 | (*S*)-**9f** | 4-F | 1 | 93 | 92 | −7.9 (*c* 1.1 $CHCl_3$) |
| 7 | (*S*)-**9g** | 4-Br | 1 | 95 | 92 | −10.0 (*c* 0.6 $CHCl_3$) |
| 8 | (*S*)-**9h** | 4-Cl | 1 | 99 | 94 | −10.9 (*c* 1.0 $CHCl_3$) |
| 9 | (*R*)-**9a** | H | 0 | 95 | 76 | +9.1 (*c* 1.0 $CHCl_3$) |
| 10 | (*R*)-**9b** | 4-F | 0 | 95 | 78 | +6.9 (*c* 1.0 $CHCl_3$) |
| 11 | (*R*)-**9c** | 4-Br | 0 | 89 | 78 | +6.6 (*c* 1.7 $CHCl_3$) |
| 12 | (*R*)-**9d** | 4-Cl | 0 | 96 | 79 | +9.9 (*c* 1.0 $CHCl_3$) |
| 13 | (*R*)-**9e** | H | 1 | 91 | 92 | +9.4 (*c* 0.6 MeOH) |
| 14 | (*R*)-**9f** | 4-F | 1 | 93 | 89 | +7.8 (*c* 1.1 $CHCl_3$) |
| 15 | (*R*)-**9g** | 4-Br | 1 | 95 | 87 | +9.9 (*c* 0.6 $CHCl_3$) |
| 16 | (*R*)-**9h** | 4-Cl | 1 | 99 | 92 | +10.8 (*c* 1.0 $CHCl_3$) |

[a] Determined by chiral HPLC–MS using an (*S*,*S*)-Whelk-O1 column (methanol/water 95:5, flow rate 0.8 mL/min, UV-254 nm).
[b] Refers to isolated and purified materials.
[c] Measured in $CHCl_3$ solution, except **9e** measured in MeOH.

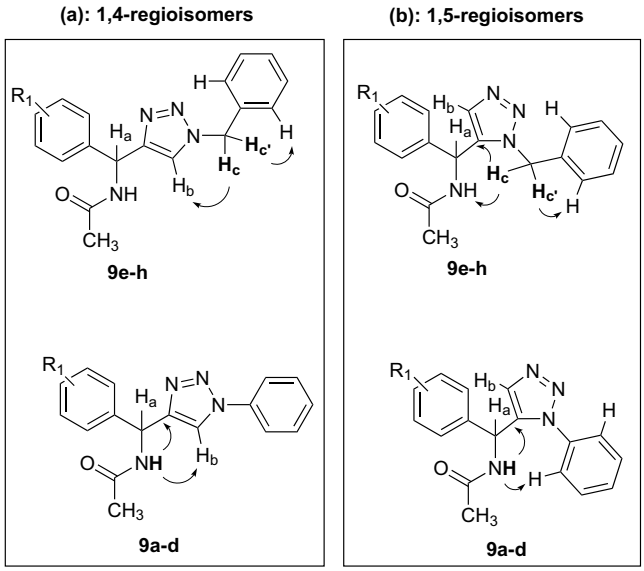



**Figure 2.** (a) Experimentally found NOE correlation for the 1,4-regioisomers, protons in bold represent the irradiated frequency; (b) expected NOE for the 1,5-regioisomers.

amines (*S*)-**8a**–**d** in the corresponding amides (*S*)-**7a**–**d**. The latter compounds were directly submitted to the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction without the need of any purification to give the desired compounds (*R*)-**9a**–**h** as a pure product after simple filtration (Scheme 3, Table 1).

## 3. Conclusion

In conclusion, a microwave-assisted Cu(I)-catalyzed 'click chemistry' approach has been applied to the synthesis of a small library of enantiopure pure α-[4-(1-substituted)-1,2,3-triazol-4-yl]benzylacetamides **9a**–**h**. These triazole derivatives were obtained after a few minutes, in good yields and high enantiomeric excess (Table 1) making them useful and readily accessible intermediates for the synthesis of enantiopure azole analogues as potential antimicrobial agents.

Further studies on the application of the reported intermediate for the synthesis of new potential antimicrobial agents are ongoing and will be published in due course.

## 4. Experimental

Reagents were obtained from commercial suppliers and used without further purification. THF was dried over Na/benzophenone prior to use. Anhydrous reactions were run under a positive pressure of dry $N_2$ or Ar. Merck silica gel 60 was used for flash chromatography (23–400 mesh).

$^1$H NMR and $^{13}$C NMR spectra were measured at 200 MHz on a Brucker AC200F spectrometer and at 400 MHz on a Brucker Avance DPX400. Chemical shifts are reported relative to $CDCl_3$ at $\delta$ 7.24 ppm and tetramethylsilane at $\delta$ 0.00 ppm. Elemental analyses (C, H, N) were performed in-house.

HPLC and MS analyses were performed using a mass spectrometer (Agilent series 1100 LC/MSD) with a UV detector at $\lambda = 254$ nm and an electrospray ionization source (ESI). All solvents were of HPLC grade (Fluka). 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 methyl alcohol/water. UV detection was monitored at 254 nm. Mass spectra were acquired by using electrospray ionization in positive mode scanning over the mass range of 50–1500. The following ion source parameters were used: drying gas flow, 9 mL/min; nebulize pressure, 40 psig; drying gas temperature, 350 °C.

The purity and enantiomeric excess of the compounds were assessed by reverse-phase liquid chromatography (*S*,*S*-Whelk-O1 chiral column) with a mobile phase composed of methanol/water (95:5) and a flow rate of 0.8 mL/min.

Microwave irradiation experiments were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continually focused microwave power delivery system with an operator-selectable power output from 0 to 300 W. The temperature of the contents of the vessels was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All the experiments were performed using a stirring option whereby the contents of the vessel were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

Compounds **7a–d** and **8a–d** have been synthesized following a procedure previously reported by us and fully characterized by comparison with an authentic sample.[5b]

### 4.1. General procedure for the acetylation of propargylamines (*S*)-8a–d

To a stirred solution of (*S*)-1-aryl-2-propynylamines (*S*)-**8a–d** (2 mmol) in dry $CH_2Cl_2$ (4 mL), $Et_3N$ (3 mmol) was added slowly at 0 °C. After 5 min, $(AcO)_2O$ (2.2 mmol) was added dropwise and the reaction was stirred under inert atmosphere at room temperature for 2 h. The mixture was washed with a solution of $NaHCO_3$ ($2 \times 4$ mL) and brine. The organic layer was dried over $Na_2SO_4$, filtered and concentrated. The crude amides (*S*)-**7a–d** were used in the next click reaction without the need for any further purification.

### 4.2. General procedure for the synthesis of triazoles 9a–d

Aniline (2 mmol) was dissolved in HCl and cooled at 0 °C. $NaNO_2$ (2 mmol) was added and the mixture stirred at 0 °C for 10 min. $NaN_3$ was then added and the mixture stirred at room temperature for 2 h. The mixture was diluted with water and extracted with AcOEt two times. The combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered and evaporated to give the crude phenylazide. Then alkyne (1.1 mmol) and freshly synthesized phenylazide (1.1 mmol) were suspended in a 1:1 mixture of water and *tert*-BuOH (1.5 mL each) in a 10 mL glass vial equipped with a small magnetic stirring bar. To this, was added sodium ascorbate (0.1 equiv) and copper(II) sulfate pentahydrate (0.01 equiv), and the vial was tightly sealed with an aluminum/Teflon® crimp top. The mixture was then irradiated for 10 min at 125 °C, using an irradiation power of 100 W. After completion of the reaction, the vial was cooled to 50 °C by gas jet cooling before it was opened. The mixture was then diluted with water (20 mL) and filtered. The residue was washed with cold water (20 mL), 0.1 M NaOH (10 mL) and finally with petroleum ether (50 mL) to furnish triazoles **9a–d** as pure compounds.

**4.2.1. (*S*)-*N*-[Phenyl-(1-phenyl-1*H*-[1,2,3]triazol-4-yl)-methyl]-acetamide 9a.** Yield: 80%. $^1$H NMR ($CDCl_3$): $\delta$ 7.74 (1H, s, CCHNPh), 7.62 (2H, d, $J = 7.9$ Hz, Ph), 7.46–7.22 (8H, m, Ph and CCHNPh), 6.78 (1H, br s, NH), 6.34 (1H, s, CHN), 2.01 (3H, s, $CH_3$). IR (KBr): 1664, 1496 cm$^{-1}$. MS: 293.1 $(M+H)^+$, 315.1 $(M+Na)^+$. $[\alpha]_D^{20} = -9.4$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.17. Found: C, 69.98; H, 5.78; N, 19.43.

**4.2.2. (*R*)-*N*-[Phenyl-(1-phenyl-1*H*-[1,2,3]triazol-4-yl)-methyl]-acetamide 9a.** Yield: 76%. $^1$H NMR ($CDCl_3$): $\delta$ 7.74 (1H, s, CCHNPh), 7.62 (2H, d, $J = 7.9$ Hz, Ph), 7.46–7.22 (8H, m, Ph and CCHNPh), 6.78 (1H, br s, NH), 6.34 (1H, s, CHN), 2.01 (3H, s, $CH_3$). IR (KBr): 1664, 1496 cm$^{-1}$. MS: 293.1 $(M+H)^+$, 315.1 $(M+Na)^+$. $[\alpha]_D^{20} = +9.1$ (*c* 1.0 $CHCl_3$). Anal. Calcd for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.17. Found: C, 69.98; H, 5.78; N, 19.43.

**4.2.3. (*S*)-*N*-[4-Fluorophenyl-(1-phenyl-1*H*-[1,2,3]triazol-4-yl)-methyl]-acetamide 9b.** Yield: 75%. $^1$H NMR ($CDCl_3$): $\delta$ 7.85 (1H, s, CCHNPh), 7.67–6.98 (9H, m, Ph), 6.39 (1H, s, CHN), 2.04 (3H, s, $CH_3$). IR (KBr): 1661, 1494 cm$^{-1}$. MS: 311.1 $(M+H)^+$, 333.1 $(M+Na)^+$. $[\alpha]_D^{20} = -6.6$ (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{17}H_{15}FN_4O$: C, 65.80; H, 4.87; N, 18.05. Found: C, 65.69; H, 4.65; N, 18.34.

**4.2.4. (*R*)-*N*-[4-Fluorophenyl-(1-phenyl-1*H*-[1,2,3]triazol-4-yl)-methyl]-acetamide 9b.** Yield: 78%. $^1$H NMR ($CDCl_3$): $\delta$ 7.85 (1H, s, CCHNPh), 7.67–6.98 (9H, m, Ph), 6.39 (1H, s, CHN), 2.04 (3H, s, $CH_3$). IR (KBr): 1661, 1494 cm$^{-1}$. MS: 311.1 $(M+H)^+$, 333.1 $(M+Na)^+$. $[\alpha]_D^{20} = +6.9$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{15}FN_4O$: C, 65.80; H, 4.87; N, 18.05. Found: C, 65.69; H, 4.65; N, 18.34.

**4.2.5. (*S*)-*N*-[4-Bromophenyl-(1-phenyl-1*H*-[1,2,3]triazol-4-yl)-methyl]-acetamide 9c.** Yield: 77%. $^1$H NMR ($CDCl_3$): $\delta$ 7.87 (1H, s, CCHNPh), 7.63–7.13 (9H, m, Ph), 6.80 (1H, br s, NH), 6.35 (1H, s, CHN), 2.01 (3H, s, $CH_3$). IR (KBr): 1660, 1496 cm$^{-1}$. MS: 371.0 $(M+H)^+$, 393.0 $(M+Na)^+$. $[\alpha]_D^{20} = -6.8$ (*c* 1.7, $CHCl_3$). Anal. Calcd for $C_{17}H_{15}BrN_4O$:

C, 55.00; H, 4.07; N, 15.09. Found: C, 55.32; H, 4.28; N, 15.29.

**4.2.6. (*R*)-*N*-[4-Bromophenyl-(1-phenyl-1*H*-[1,2,3]triazol-4-yl)-methyl]-acetamide 9c.** Yield: 78%. $^1$H NMR ($CDCl_3$): $\delta$ 7.87 (1H, s, CCHNPh), 7.63–7.13 (9H, m, Ph), 6.80 (1H, br s, NH), 6.35 (1H, s, CHN), 2.01 (3H, s, $CH_3$). IR (KBr): 1660, 1496 cm$^{-1}$. MS: 371.0 $(M+H)^+$, 393.0 $(M+Na)^+$. $[\alpha]_D^{20} = +6.6$ ($c$ 1.7, $CHCl_3$). Anal. Calcd for $C_{17}H_{15}BrN_4O$: C, 55.00; H, 4.07; N, 15.09. Found: C, 55.32; H, 4.28; N, 15.29.

**4.2.7. (*S*)-*N*-[(4-Chlorophenyl)(1-phenyl-1*H*-[1,2,3]triazol-4-yl)methyl]acetamide 9d.** Yield: 85%. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.01 (1H, br s, NH), 7.85 (1H, s, CCHN), 7.63–6.97 (9H, m, Ph), 6.38 (1H, s, PhCHC), 2.01 (3H, s, $CH_3$) IR (KBr): 1660, 1496 cm$^{-1}$. MS: 327.1 $(M+H)^+$, 349.1 $(M+Na)^+$. $[\alpha]_D^{20} = -9.8$ ($c$ 1.0 $CHCl_3$). Anal. Calcd for $C_{17}H_{15}BrN_4O$: C, 55.00; H, 4.07; N, 15.09. Found: C, 55.32; H, 4.28; N, 15.29.

**4.2.8. (*R*)-*N*-[(4-Chlorophenyl)(1-phenyl-1*H*-[1,2,3]triazol-4-yl)methyl]acetamide 9d.** Yield: 79%. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.01 (1H, br s, NH), 7.85 (1H, s, CCHN), 7.63–6.97 (9H, m, Ph), 6.38 (1H, s, PhCHC), 2.01 (3H, s, $CH_3$) IR (KBr): 1660, 1496 cm$^{-1}$. MS: 327.1 $(M+H)^+$, 349.1 $(M+Na)^+$. $[\alpha]_D^{20} = +9.9$ ($c$ 1.0 $CHCl_3$). Anal. Calcd for $C_{17}H_{15}BrN_4O$: C, 55.00; H, 4.07; N, 15.09. Found: C, 55.32; H, 4.28; N, 15.29.

### 4.3. General procedure for the synthesis of triazoles 9e–h

Benzyl chloride (1.0 mmol), alkyne (1.1 mmol) and sodium azide (1.1 mmol) were suspended in a 1:1 mixture of water and *tert*-BuOH (1.5 mL each) in a 10 mL glass vial equipped with a small magnetic stirring bar. To this were added sodium ascorbate (0.1 equiv) and copper(II) sulfate pentahydrate (0.01 equiv) and the vial was tightly sealed with an aluminum/Teflon® crimp top. The mixture was then irradiated for 10 min at 125 °C, using an irradiation power of 100 W. After completion of the reaction, the vial was cooled to 50 °C by gas jet cooling before it was opened. The mixture was then diluted with water (20 mL) and filtered. The residue was washed with cold water (20 mL), 0.1 M NaOH (10 mL) and finally with petroleum ether (50 mL) to furnish product triazoles **9e**–**h**.

**4.3.1. (*S*)-*N*-[(1-Benzyl-1*H*-[1,2,3]triazol-4-yl)-phenyl-methyl]-acetamide 9e.** Yield: 90%. $^1$H NMR ($CDCl_3$): $\delta$ 7.33–7.24 (11H, m, Ph and CCHNPh), 6.82 (1H, br s, NH), 6.27 (1H, s, CHN), 5.45 (2H, s, $NCH_2Ph$), 2.00 (3H, s, $CH_3$). IR (KBr): 1666, 1496 cm$^{-1}$. MS: 307.1 $(M+H)^+$, 329.1 $(M+Na)^+$. $[\alpha]_D^{20} = -9.2$ ($c$ 0.6 MeOH). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.68; H, 5.78; N, 18.45.

**4.3.2. (*R*)-*N*-[(1-Benzyl-1*H*-[1,2,3]triazol-4-yl)-phenyl-methyl]-acetamide 9e.** Yield: 92%. $^1$H NMR ($CDCl_3$): $\delta$ 7.33–7.24 (11H, m, Ph and CCHNPh), 6.82 (1H, br s, NH), 6.27 (1H, s, CHN), 5.45 (2H, s, $NCH_2Ph$), 2.00 (3H, s, $CH_3$). IR (KBr): 1666, 1496 cm$^{-1}$. MS: 307.1 $(M+H)^+$, 329.1 $(M+Na)^+$. $[\alpha]_D^{20} = +9.4$ ($c$ 0.6 MeOH). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.68; H, 5.78; N, 18.45.

**4.3.3. (*S*)-*N*-[(1-Benzyl-1*H*-[1,2,3]triazol-4-yl)-(4-fluorophenyl)-methyl]-acetamide 9f.** Yield: 92%. $^1$H NMR ($CDCl_3$): $\delta$ 7.33–6.94 (10H, m, Ph and CCHNPh), 6.90 (1H, br s, NH), 6.30 (1H, s, CHN), 5.46 (2H, s, $NCH_2Ph$), 1.97 (3H, s, $CH_3$). IR (KBr): 1661, 1494 cm$^{-1}$. MS: 325.1 $(M+H)^+$, 347.1 $(M+Na)^+$. $[\alpha]_D^{20} = -7.9$ ($c$ 1.1 $CHCl_3$). Anal. Calcd for $C_{18}H_{17}FN_4O$: C, 66.65; H, 5.28; N, 17.27. Found: C, 66.87; H, 5.46; N, 17.45.

**4.3.4. (*R*)-*N*-[(1-Benzyl-1*H*-[1,2,3]triazol-4-yl)-(4-fluorophenyl)-methyl]-acetamide 9f.** Yield: 89%. $^1$H NMR ($CDCl_3$): $\delta$ 7.33–6.94 (10H, m, Ph and CCHNPh), 6.90 (1H, br s, NH), 6.30 (1H, s, CHN), 5.46 (2H, s, $NCH_2Ph$), 1.97 (3H, s, $CH_3$). IR (KBr): 1661, 1494 cm$^{-1}$. MS: 325.1 $(M+H)^+$, 347.1 $(M+Na)^+$. $[\alpha]_D^{20} = +7.8$ ($c$ 1.1 $CHCl_3$). Anal. Calcd for $C_{18}H_{17}FN_4O$: C, 66.65; H, 5.28; N, 17.27. Found: C, 66.87; H, 5.46; N, 17.45.

**4.3.5. (*S*)-*N*-[(1-Benzyl-1*H*-[1,2,3]triazol-4-yl)-(4-bromophenyl)-methyl]-acetamide 9g.** Yield: 92%. $^1$H NMR ($CDCl_3$): $\delta$ 7.41–7.17 (10H, m, Ph and CCHNPh), 6.21 (1H, s, CHN), 5.46 (2H, s, $NCH_2Ph$), 2.00 (3H, s, $CH_3$). IR (KBr): 1661, 1494 cm$^{-1}$. MS: 385.1 $(M+H)^+$, 407.1 $(M+Na)^+$. $[\alpha]_D^{20} = -10.0$ ($c$ 0.6 $CHCl_3$). Anal. Calcd for $C_{18}H_{17}BrN_4O$: C, 56.12; H, 4.45; N, 14.54. Found: C, 56.34; H, 4.67; N, 14.75.

**4.3.6. (*R*)-*N*-[(1-Benzyl-1*H*-[1,2,3]triazol-4-yl)-(4-bromophenyl)-methyl]-acetamide 9g.** Yield: 87%. $^1$H NMR ($CDCl_3$): $\delta$ 7.41–7.17 (10H, m, Ph and CCHNPh), 6.21 (1H, s, CHN), 5.46 (2H, s, $NCH_2Ph$), 2.00 (3H, s, $CH_3$). IR (KBr): 1661, 1494 cm$^{-1}$. MS: 385.1 $(M+H)^+$, 407.1 $(M+Na)^+$. $[\alpha]_D^{20} = +9.9$ ($c$ 0.6 $CHCl_3$). Anal. Calcd for $C_{18}H_{17}BrN_4O$: C, 56.12; H, 4.45; N, 14.54. Found: C, 56.34; H, 4.67; N, 14.75.

**4.3.7. (*S*)-*N*-[(1-Benzyl-1*H*-[1,2,3]triazol-4-yl)(4-chlorophenyl)methyl]-acetamide 9h.** Yield: 94%. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.70 (1H, br s, NH), 7.32–6.72 (10H, m, Ph and CCHN), 6.19 (1H, s, PhCHC), 5.43 (2H, s, $NCH_2$ Ph), 1.96 (3H, s, $CH_3$) IR (KBr): 1661, 1494 cm$^{-1}$. MS: 341.1 $(M+H)^+$, 363.1 $(M+Na)^+$. $[\alpha]_D^{20} = -10.9$ ($c$ 1.0 $CHCl_3$). Anal. Calcd for $C_{18}H_{17}BrN_4O$: C, 56.12; H, 4.45; N, 14.54. Found: C, 56.34; H, 4.67; N, 14.75.

**4.3.8. (*R*)-*N*-[(1-Benzyl-1*H*-[1,2,3]triazol-4-yl)(4-chlorophenyl)methyl]-acetamide 9h.** Yield: 92%. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.70 (1H, br s, NH), 7.32–6.72 (10H, m, Ph and CCHN), 6.19 (1H, s, PhCHC), 5.43 (2H, s, $NCH_2$ Ph), 1.96 (3H, s, $CH_3$) IR (KBr): 1661, 1494 cm$^{-1}$. MS: 341.1 $(M+H)^+$, 363.1 $(M+Na)^+$. $[\alpha]_D^{20} = +10.8$ ($c$ 1.0 $CHCl_3$). Anal. Calcd for $C_{18}H_{17}BrN_4O$: C, 56.12; H, 4.45; N, 14.54. Found: C, 56.34; H, 4.67; N, 14.75.

### 4.4. (*R*)-*N*-[4-Bromophenyl-(1-phenyl-1*H*-[1,2,3]triazol-4-yl)-methyl]-amine (10c)

Yield: 78%. $^1$H NMR ($CDCl_3$): $\delta$ 7.73–7.07 (10H, m, Ph and CCHNPh), 5.21 (1H, s, PhCHC), 2.27 (2H, br s, $NH_2$). MS: 313.1 $(M-NH_2)^+$, 351.1 $(M+Na)^+$. $[\alpha]_D^{20} = -15.8$ (*c* 1.0 $CHCl_3$). Anal. Calcd for $C_{15}H_{13}BrN_4$: C, 54.73; H, 3.98; N, 17.02. Found: C, 54.68; H, 4.04; N, 17.00.

### 4.5. (*R*)-*N*-[(1-Benzyl-1*H*-[1,2,3]triazol-4-yl)-(4-bromophenyl)-methyl]-amine (10g)

Yield: 75%. $^1$H NMR ($CDCl_3$): $\delta$ 7.37–7.09 (10H, m, Ph and CCHNPh), 5.37 (1H, s, PhCHC), 5.23 (2H, s, $NCH_2Ph$), 2.00 (2H, br s, $NH_2$). MS: 326.2 $(M-NH_2)^+$, 365.1 $(M+Na)^+$. $[\alpha]_D^{20} = -14.5$ (*c* 2.2 $CHCl_3$). Anal. Calcd for $C_{16}H_{15}BrN_4$: C, 55.99; H, 4.41; N, 16.32. Found: C, 55.92; H, 4.40; N, 16.38.

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## References

1. Buchel, K. H.; Draber, W.; Regel, E.; Plempel, M. *Arzneim.-Forsch.* **1972**, *22*, 1260–1272.
2. Heeres, J.; Backx, L. J. J.; Mostmans, J. H.; Van Cutsem, J. *J. Med. Chem.* **1979**, *22*, 1003–1005.
3. Koltin, Y. *Annu. Rep. Med. Chem.* **1990**, *25*, 141–148.
4. Huy, N. T.; Kamei, E.; Kondo, Y.; Serada, S.; Kanaori, K.; Takano, R.; Tajima, K.; Hara, S. *J. Biochem.* **2002**, *131*, 437–444.
5. (a) Corelli, F.; Summa, V.; Brogi, A.; Monteagudo, E.; Botta, M. *J. Org. Chem.* **1995**, *60*, 2008–2015; (b) Messina, F.; Botta, M.; Corelli, F.; Schneider, M. P.; Fazio, F. *J. Org. Chem.* **1999**, *64*, 3767–3769; (c) Botta, M.; Corelli, F.; Gasparrini, F.; Messina, F.; Mugnaini, C. *J. Org. Chem.* **2000**, *65*, 4736–4739; (d) Messina, F.; Botta, M.; Corelli, F.; Paladino, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4895–4901; (e) Tafi, A.; Costi, R.; Botta, M.; Di Santo, R.; Corelli, F.; Massa, S.; Ciacci, A.; Manetti, F.; Artico, M. *J. Med. Chem.* **2002**, *45*, 2720–2732; (f) Di Santo, R.; Tafi, A.; Costi, R.; Botta, M.; Artico, M.; Corelli, F.; Forte, M.; Caporuscio, F.; Angiolella, L.; Palamara, A. T. *J. Med. Chem.* **2005**, *48*, 5140–5153.
6. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021; (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137; (c) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68.
7. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.
8. Castagnolo, D.; Renzulli, M. L.; Galletti, E.; Corelli, F.; Botta, M. *Tetrahedron: Asymmetry* **2005**, *16*, 2893–2896.
9. Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223–4225.
10. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
11. Pagliai, F.; Pirali, T.; Del Grosso, E.; Di Brisco, R.; Tron, G. C.; Sorba, G.; Genazzani, A. A. *J. Med. Chem.* **2006**, *49*, 467–470.