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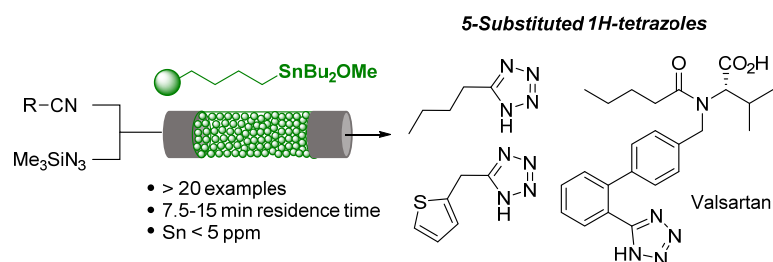
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Synthesis of 5-Substituted 1*H*-tetrazoles from Nitriles by Continuous Flow. Application to the Synthesis of Valsartan.

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ABSTRACT GRAPHIC



ABSTRACT

An efficient continuous flow process for the synthesis of 5-substituted 1*H*-tetrazoles is described. The process involves the reaction between a polymer-supported triorganotin azide and organic nitriles. The polymer-supported organotin azide which is in situ generated with a polystyrene-supported triorganotin alkoxide and trimethylsilylazide, is immobilized in a packed bed reactor. This approach is simple, fast (it takes from 7.5 to 15 min) and guarantees a low concentration of tin residues in the products (< 5 ppm). The process was developed to aryl-, heteroaryl- and also alkylnitriles and was applied for the synthesis of valsartan, an angiotensin II receptor antagonist.

KEYWORDS

continuous-flow, tetrazole, organotin, azide, polymer-supported reagent

■ INTRODUCTION

The tetrazole unit continues to arise a great interest in both academia and industry. Indeed, this heterocycle plays a pivotal role in energetic materials,¹ supramolecular chemistry and coordination chemistry,² organocatalysis³ and medicinal chemistry.^{4,5} This interest is due to their unique structure and properties. In medicinal chemistry, the 5-substituted *1H*-tetrazole unit is frequently used as a carboxylic acid isostere.^{6,7} Generally, the presence of the tetrazole moiety induces an increased activity, a longer biodisponibility and does not enhance the toxicity of the active pharmaceutical ingredient (API). For these reasons, numerous API containing a tetrazole moiety are currently on the pharmaceutical market (Figure 1).

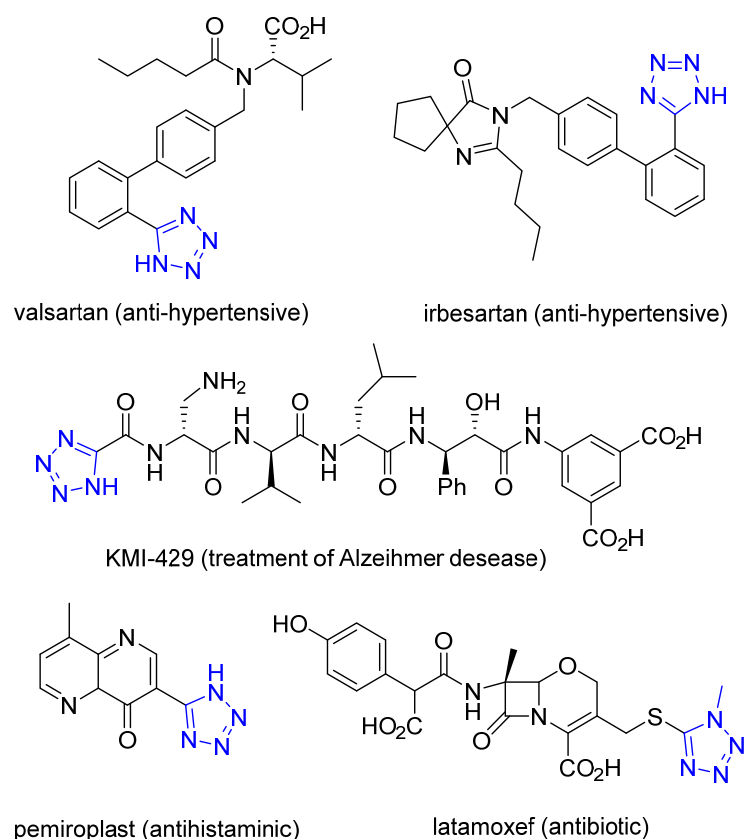


Figure 1: Examples of active pharmaceutical ingredients containing a tetrazole moiety

In this context, there is a continuing interest for the development of efficient procedures for the synthesis of tetrazoles and numerous methodologies have been reported.^{8,9} In addition, there is a growing demand for environmentally friendly, energetically efficient and safe procedures. The search for faster and safer procedures often conduct nowadays to the consideration of the continuous flow technology. The latter enhances mass and heat transfer, reduces cost and time for optimization and facilitates the transition from the R&D to the production. For these reasons

continuous flow chemistry is now recognized as a powerful technology and several contributions related to the synthesis of tetrazoles in flow have already been reported.¹⁰⁻¹²

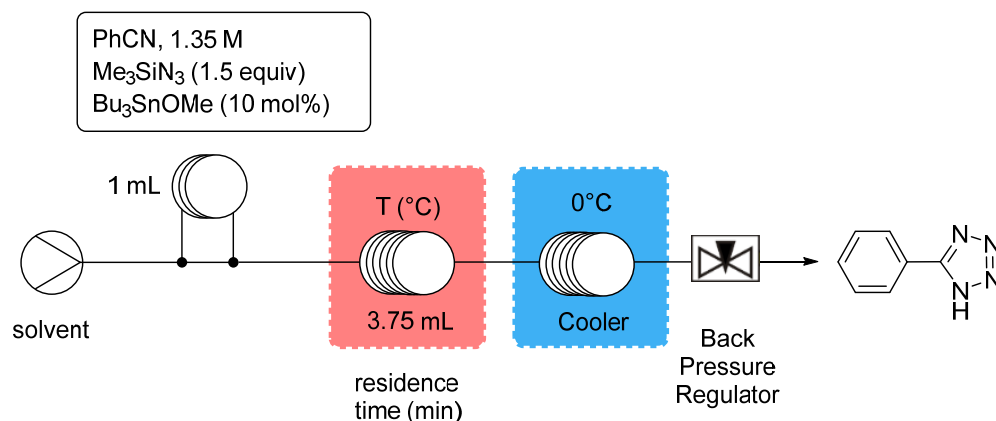
From our side, we have recently reported a versatile synthesis of 5H-substituted 1*H*-tetrazoles **2** through the reaction of trimethylsilylazide with nitriles using a triorganotin alkoxide precatalyst **1**, a strategy which was found to be efficient both for substituted aryl or alkyl tetrazoles.¹³ This procedure involves the in situ generation of a triorganotin azide acting as the effective reaction catalyst. Moreover, a heterogeneous version of the reaction was also developed by using a polystyrene-supported organotin reagent.^{13,14} This methodology limits efficiently the amount of residual tin in the reaction product.^{15,16} The high temperatures required for the preparation of tetrazoles in batch associated to the inherent hazardous nature of azides, prompted us to explore a continuous flow approach of our technology. Here we report our effort toward this end which culminated with the synthesis of valsartan, an angiotensin II receptor antagonist.

■ RESULTS AND DISCUSSION

We began our investigations by studying the synthesis of 5-phenyl 1*H*-tetrazole **2a** as a benchmark transformation. The influence of the temperature, residence time and nature of solvent was considered for the first campaign of runs. The results and a schematic representation of the flow device are reported in Table 1. It consists of a single stream equipped with a 1 mL injection loop (loaded with a preformed solution of benzonitrile, trimethylazide and tributyltin azide), a reactor coil (3.75 mL, 0.76 mm id) placed in an oven for an accurate control of the temperature and a cooler unit (0 °C) to quickly decrease the reaction temperature. In addition, a back pressure regulator was installed to pressurize the flow system (up to 100 bar) and prevent the solvent to vaporize upon high temperature. Therefore, pressurized continuous flow setup offers the opportunity to work with lower boiling point solvents which can be superheated under the processing conditions.^{10,17-21} Initially the flow rate was kept at 0.375 mL/min corresponding to a residence time of 10 min. Our first investigations revealed that neither dibutyl ether nor a mixture of dibutyl ether with THF was compatible with the process due to the precipitation of the reaction product in the cooler device. DMSO was also not compatible, as it solidified in the cooler device, despite the good solubility of tetrazoles in this solvent. We then considered diglyme, THF, DMAc, a mixture of dibutyl ether with DMF (50:50) and acetone and observed that the reaction was rather insensitive to the nature of the solvent (entries 1-5). Therefore, further investigations were pursued in acetone, a solvent having a low boiling point which is not hazardous for health. The influence of the temperature and the

residence time were then evaluated and we concluded that a residence of 20 min (with a flow rate of 0.187 mL/min) and a temperature of 200 °C constituted the best experimental conditions.

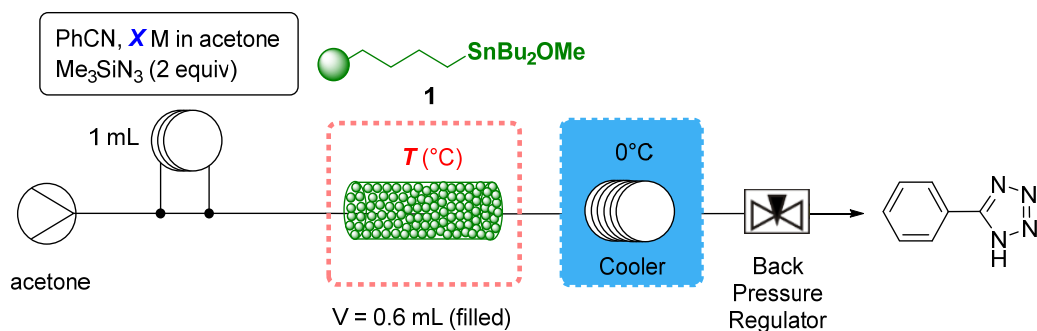
Table 1. Preliminary screening for the continuous-flow tetrazole synthesis.



Entry	Residence time (min)	T(°C)	Solvent	Yield (%)
1	10	200	Diglyme	35
2	10	200	THF	34
3	10	200	DMAc	28
4	10	200	Bu ₂ O:DMF (50:50)	36
5	10	200	Acetone	38
6	10	160	Acetone	14
7	10	180	Acetone	32
8	10	220	Acetone	35
9	20	160	Acetone	25
10	20	180	Acetone	44
11	20	200	Acetone	51
12	20	220	Acetone	33

With this initial screening in hand, we aimed at the development of a more sustainable approach through the use of an immobilized organotin catalyst. The preparation of the latter and its use in batch for the synthesis of 5-substituted *1H*-tetrazole has been recently reported by our group.¹³ We demonstrated that the tin alkoxy moiety grafted on insoluble polystyrene afforded good conversions in batch for a large range of nitrile derivatives and allows a facile procedure to recover the reaction products. However, this procedure suffered from long reaction times (18 h). We reasoned that transferring this technology within a continuous flow system should certainly address this drawback. Indeed, the immobilization of catalysts in cartridges considerably increases their local concentration and significantly speed-up reaction rates.²² Therefore, we considered a stainless steel column (4.6 × 50 mm) filled with the heterogeneous catalyst to perform new runs and optimize the reaction conditions (Table 2).

Table 2. Optimization for the heterogeneous continuous flow tetrazole synthesis in acetone.



Entry	T (°C)	Residence time (min) ^a	Conc. X (mol/L)	Yield (%) ^b
1	160	7.5	0.19	41
2	160	15	0.19	71
3	180	7.5	0.19	63
4	180	15	0.19	79
5	200	7.5	0.19	84
6	200	15	0.19	78
7	220	7.5	0.19	77
8	160	7.5	0.5	21
9	180	7.5	0.5	66
10	200	7.5	1	65
11	180	15	1	39
12	200	15	0.5	80
13	200	15	1	72

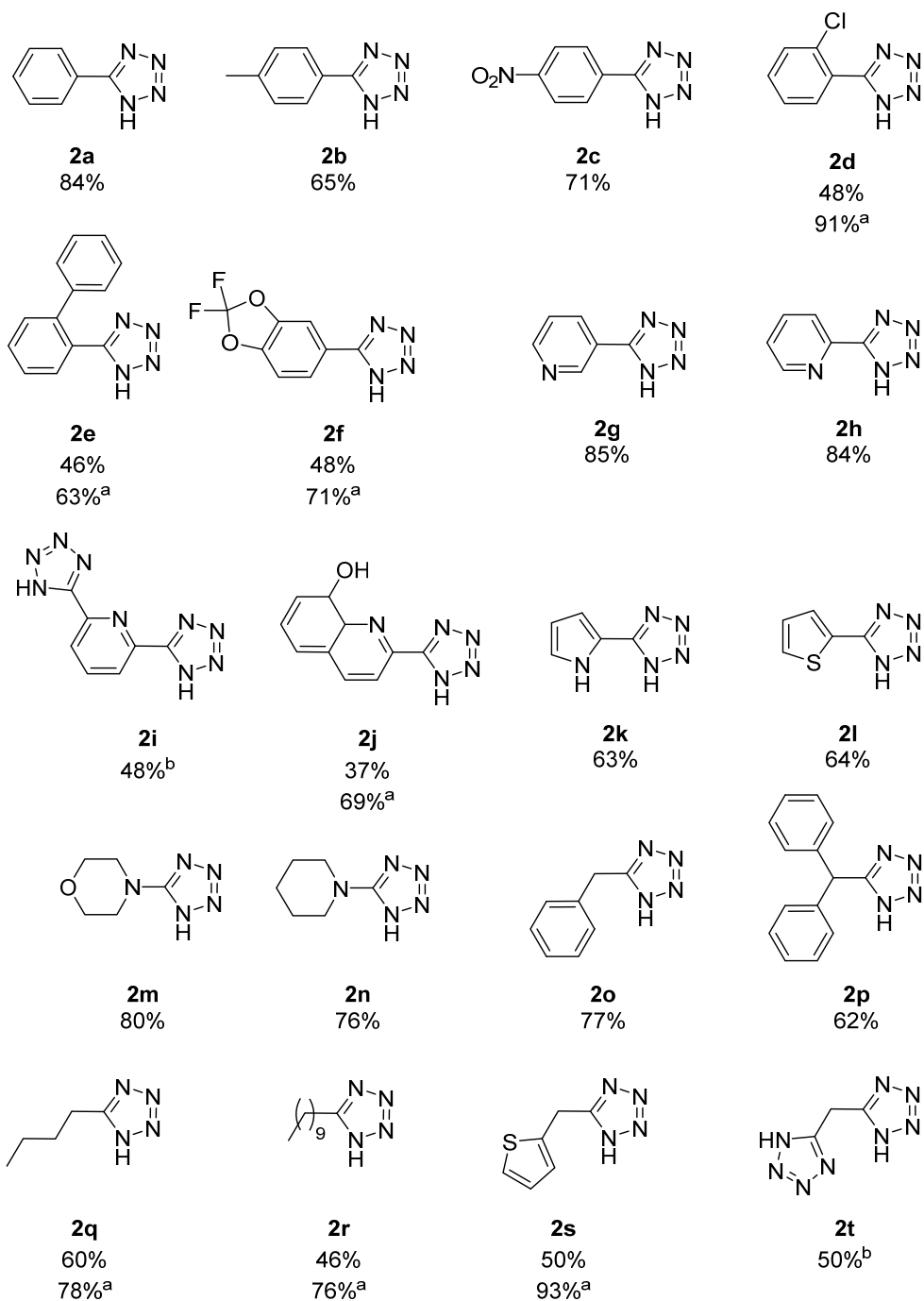
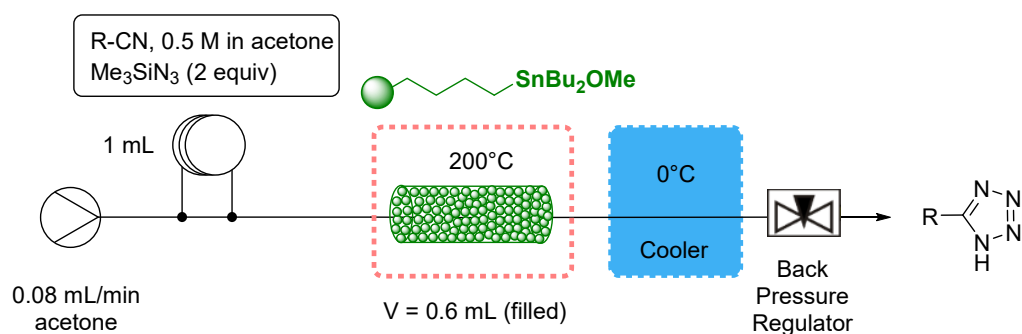
The back pressure regulator was set at 35 bar. a. flow = 0.08 mL/min for a residence of 7.5 min and 0.04 mL/min for 15 min. b NMR yields were determined using trimethylbenzene as internal standard.

Under these conditions, we studied the influence of the temperature, the residence time and the benzonitrile concentration (X) on the reaction yield (entries 1-6). These investigations revealed that a residence time of 7.5 min at 200 °C afforded the best yield when the benzonitrile concentration was set at 0.19 mol/L (84% yield, entry 5). A good yield was also obtained with a more concentrated benzonitrile solution (0.5 mol/L) at 200 °C when the residence time was increased to 15 min (entry 12). Unfortunately, increasing the concentration of benzonitrile to 1 mol/L was detrimental for the yield regardless of the residence time or the reaction temperature (entries 10, 11, 13). These results highlight the advantages of using heterogeneous catalysts in flow; the yields from entries 10, 11 and 13 have to be compared with the 51% yield obtained in 20 min at 200 °C with the homogeneous precatalyst, Bu_3SnOMe (Table 1, entry 11).

With these conditions in hand, we explored the scope of the reaction with a set of 20 aromatic, heteroaromatic and aliphatic nitrile derivatives. The results of our screening are depicted in Table 3. Gratifyingly, the developed flow conditions are robust and tolerate a large range of substrates without issues of clogging. Both aryl and heteroaryl tetrazoles were efficiently prepared in good yields under the optimized conditions. In some cases, the reaction proceeded

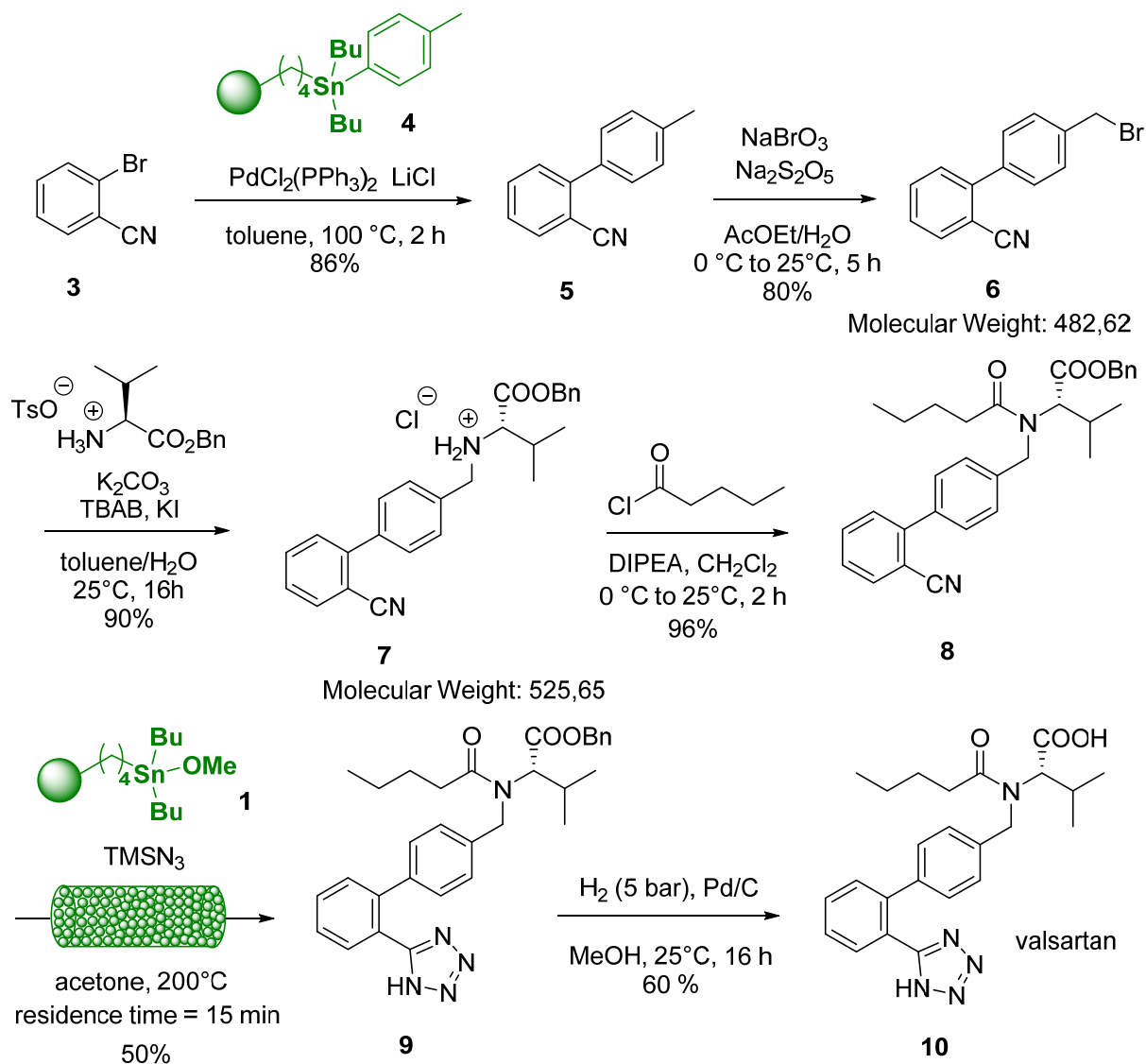
with lower yields due to steric hindrance at the *ortho* positions (compounds **2d**, **2e**, **2j**) but these yields could be improved with a longer residence time (15 min). For derivatives resulting from a double cycloaddition reaction, 4 equiv of Me₃SiN₃ are required to obtain satisfactory yields (**2i**, **2t**). Finally the procedure was also found to be efficient for benzyl **2o**, **2p** and alkyl derivatives **2q**, **2r** even though a residence time of 15 min proved to be necessary to obtain yields above 70%. The space time yields were calculated for each derivatives and for example an 87 mmol/h/L value was found for compound **2a** (see SI for the complete list of space time yields). In addition, upon successive injections, a mass of 1.066 g of compound **2a** could be produced indicating that the process could be scaled up. Finally, it has to be noted that ICP-MS analyses carried out on three compounds (**2a**, **2e** and **2q**) exhibited low concentration of tin residue (less than 5 ppm).

Table 3. Scope of the reaction catalyzed by the heterogeneous catalyst in continuous flow.



Yields refer to isolated products; the back pressure regulator was set at 35 bar. a. Flow = 0.04 mL/min, residence time = 15 min; b. Use of 4 equiv of TMSN₃.

Our technology was applied to the synthesis of valsartan, an angiotensin II receptor blocker, marketed by Novartis company.²³⁻²⁶ The synthesis route we developed, depicted in Scheme 1, is a mix between newly developed steps and literature precedents.²³⁻²⁶ The palladium-catalyzed Stille cross-coupling of 2-bromobenzonitrile **3** and polymer-supported tolyltin **4** performed in batch was adapted from a methodology developed earlier in our laboratory,²⁷⁻³¹ and afforded **5** in 86% yield. Polymer-supported tolyltin **4** was readily prepared by lithiation of 4-bromotoluene with *tert*-butyllithium followed by trapping with the polymer-supported dibutyltin iodide (see Supporting Information for details). Biphenyl **5** derivative was brominated with NaBrO₃ in the presence Na₂S₂O₅ to furnish benzylbromide **6** in 94% yield. This procedure significantly improved the previously described approach using NBS/AIBN which, in our hand, furnished a mixture of mono- and dibromo compounds in a 80/20 ratio.³² The L-valine moiety was installed by substitution of the bromine atom in a biphasic media using TBAB as phase transfer agent and K₂CO₃ as base to give **7** in high yield (90%). Switching K₂CO₃ for *N,N*-diisopropylethylamine as a base and working under anhydrous conditions provided **7**, in our hand, in much lower yield (80%).³² The secondary amine **7** was acylated with pentanoic acid chloride in the presence of *N,N*-diisopropylethylamine in toluene to give compound **8** in 96% yield. Then, the buildup of the tetrazole ring was accomplished following the above-described procedure applied to nitrile **8**. The latter afforded the benzyl valsartan derivative **9** in 50% with a residence time of 15 min. The final hydrogenolysis of the benzyl ester furnished valsartan in 60% yield. An ICP-MS analysis revealed a low residual tin concentration (3 ppm) although two different reactions of this multi-step synthesis were carried out with an organotin reagent. This result demonstrates the efficiency of the polymer-supported strategy applied to organotin chemistry associated to the continuous flow technology and address pharmaceutical requirements, the upper limit of Sn level being ~ 20 ppm.^{33,34} Moreover, this process cannot produce nitrosamines whose presence as byproducts in APIs (in valsartan or sartan-type products notably) has been responsible for recalls recently.³⁵



Scheme 1: Synthesis of valsartan

■ CONCLUSION

An efficient continuous flow process involving a polystyrene-supported organotin reagent was developed for the synthesis of 5-substituted 1*H*-tetrazoles from nitriles. Substituted aryl and alkyl derivatives can be efficiently prepared in a short reaction time (7.5 min or 15 min for the less reactive nitriles) and can be readily isolated in high purity with a low concentration of tin residues (less than 5 ppm). As a testimony for the usefulness of this protocol for the synthesis of 5-Substituted 1*H*-tetrazoles, we realized the synthesis of valsartan, an angiotensin II receptor antagonist.

■ EXPERIMENTAL SECTION

General Methods.

All commercial reagents were used as received. Silica gel (40–63 μm) was used in flash column chromatography. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (TLC silica gel 60 F254), visualized with a UV lamp (254 nm), and stained with a solution of vanillin. Solvent systems and flash column chromatography are reported as percent by volume values. ^1H , ^{13}C and ^{119}Sn NMR spectra were recorded on Bruker Avance 300 or Bruker ARX 400 instruments. Chemical shifts are given in ppm as δ values related to tetramethylsilane (^1H , ^{13}C) and coupling constants are given in Hz. Carbon chemical shifts were internally referenced to the deuterated solvent signals in DMSO (δ 39.52 ppm). Mass spectra were obtained in EI (70 eV) and/or CI mode in direct introduction mode using a HP apparatus (Engine 5989A) or a DSQII (ThermoFisher Scientific). HRMS in ESI mode were recorded on a LTQ-Orbitrap (ThermoFisher Scientific). IR spectra were recorded on a Bruker IFS Vector 22 apparatus in ATR mode. Optical rotations were measured on a Perkin-Elmer 341 apparatus and melting points were determined with a Tottoli SMP3 Stuart apparatus. Sample loops were made out of PEEK with a 0.76 mm internal diameter. The flow rate precision of our pump was less than 0.1 % RSD and the flow accuracy is $\pm 2\mu\text{L}$. ICP analyses were performed at the Institut des Sciences Analytiques in Villeurbanne. Bu_3SnOMe catalyst and polymer-supported organotin alkoxide **1** were prepared according previously described procedures.¹³ TMSN_3 is a flammable and toxic compound which should not be used with strong acids, oxidants and heavy metals. It must be handled with gloves under a well ventilated fume hood.

Procedure for the optimization of homogeneous synthesis of 5-substituted 1*H*-tetrazoles using a flow device:

The reaction was conducted in a stainless steel reactor coil (1/16'' od, 0.75 mm id) with a volume of 3.2 mL. A solution of benzonitrile (1 equiv), tributyltin methoxide (0.1-1 equiv) and TMSN_3 (1.5-2 equiv) in the corresponding solvent (0.3-1.3 mol/L) was loaded in an injection loop (1 mL). The solvent was continuously added with a flow of 160-320 $\mu\text{L}/\text{min}$. The reaction was conducted at the indicated temperature. The reaction mixture was collected and concentrated. Trimethylbenzene was added as an internal standard and a ^1H NMR was recorded in $\text{DMSO}-d_6$ to calculate the NMR yield.

Procedure for the optimization of heterogeneous synthesis of 5-substituted 1*H*-tetrazoles using a flow device.

The reaction was conducted in a stainless steel column (4.6 × 50 mm) filled with 280-340 mg of supported tin catalyst. The residual volume of the column filled was 0.6 mL as measured with a solution of methylene blue. A solution of benzonitrile (1 equiv) and TMSN₃ (2 equiv) in dry acetone (0.2-1 mol/L) was loaded in an injection loop (1 mL). Dry acetone was continuously added with a flow of 40-80 μL/min. The reaction was conducted at the indicated temperature. The reaction mixture was collected and concentrated. The reaction mixture was collected and concentrated. Trimethylbenzene was added as an internal standard and NMR was made in DMSO-*d*₆ to have NMR yield.

General procedure for the heterogeneous synthesis of 5-substituted 1*H*-tetrazoles using a flow device.

The reaction was conducted in a stainless steel column (4.6 × 50 mm) filled with 340 mg of supported tin catalyst **1** (1.13 mmol/g). The residual volume of the column filled was 0.6 mL, as measured with a solution of methylene blue. A solution of nitrile (1 equiv) and TMSN₃ (2 equiv) in dry acetone (0.5 mol/L) was loaded in an injection loop (1 mL). Dry acetone was continuously added with a flow of 80 μL/min unless otherwise indicated. The reaction was conducted at the indicated temperature. The reaction mixture was collected and concentrated. Ethyl acetate and NaOH (1M) was added and stirred during 30 min. The aqueous phase was acidified with HCl until pH 1-2 and then extracted with ethyl acetate. The organic phase was washed with brine and was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the product.

5-phenyl-1*H*-tetrazole, 2a. General procedure afforded compound **2a** as a white solid (61.5 mg, 84%). m.p. 212-214 °C with decomp. [lit.³⁶ 215 °C]. IR (ATR) ν 3200-2400 (br), 1609, 1562, 1485, 1462, 1409, 1162, 989, 785, 682. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.06-8.03 (m, 2H), 7.62-7.58 (m, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 155.33, 131.17, 129.36, 126.92, 124.17. HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₇H₇N₄ 147.0671; Found 147.0665.

5-(4-Tolyl)-1*H*-tetrazole, 2b. General procedure afforded compound **2b** as a white solid (52 mg, 65%). m.p. 249-251 °C with decomp. [lit.³⁷ 246-248 °C with decomp]. IR (ATR) ν 3200-2200 (br), 1615, 1569, 1503, 1437, 1403, 1162, 987, 818, 740, 501. ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.71 (t, *J* = 4.9 Hz, 4H), 3.35 (t, *J* = 4.9 Hz, 4H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 159.79, 65.15, 46.91. HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₈H₉N₄ 161.0822; Found 161.0823.

5-(4-Nitrophenyl)tetrazole, 2c. General procedure afforded compound **2c** as a beige solid (68 mg, 71%). m.p. 219 °C, [lit.³⁶ 220 °C]. IR (ATR) ν 3434, 3370, 3225, 3078, 2900-2100 (br), 1608, 1572, 1524, 1337, 1087, 993, 903, 851, 728, 492. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 (d, *J* = 8.9 Hz, 2H), 8.28 (d, *J* = 8.9 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 155.47, 148.70, 130.65, 128.15, 124.53. HRMS (ASAP⁺) *m/z* [M+H]⁺ Calcd for C₇H₆N₅O₂ 192.0521; Found 192.0521.

5-(2-chlorophenyl)-1H-tetrazole, 2d. General procedure with the flow set at 0.04 mL/min afforded product **2d** as a white solid (82 mg, 91%). m.p. 177 °C [lit.¹⁰ 179-180 °C]. IR (ATR) ν 3100-2200 (br), 1678, 1621, 1560, 1470, 1443, 1159, 1059, 743. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.81 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.70 (dd, *J* = 8, 1.2 Hz, 1H), 7.62 (td, *J* = 5.0, 3.7 Hz, 1H), 7.55 (td, *J* = 5.0, 3.7 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.64, 132.43, 131.94, 131.68, 130.37, 127.69, 124.38. HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₇H₆N₄Cl 181.0276; Found 181.0273.

5-([1,1'-biphenyl]-2-yl)-1H-tetrazole, 2e. General procedure with the flow set at 0.04 mL/min afforded product **2e** as a white solid (71 mg, 63%). m.p. 141 °C [lit.³⁸ 142-144 °C]. IR (ATR) ν 3200-2400 (br), 1599, 1569, 1473, 1388, 1249, 1156, 1114, 1053, 1005, 860, 746, 701. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.70-7.65 (m, 2H), 7.59-7.54 (m, 2H), 7.32-7.29 (m, 3H), 7.11-7.08 (m, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 155.26, 141.44, 139.31, 130.86, 130.53, 128.73, 128.16, 127.64, 127.32, 123.80. HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₁₃H₁₁N₄ 223.0984; Found 223.0984.

5-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-tetrazole, 2f. General procedure with the flow was set at 0.04 mL/min afforded as a beige solid **2f** (80 mg, 71%). m.p. 174 °C. IR (ATR) ν 3100-2200 (br), 1636, 1624, 1579, 1491, 1461, 1428, 1232, 1172, 1126, 1027, 988, 916, 861, 822, 744, 711, 602, 433. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.01 (br. d, *J* = 1.6 Hz, 1H), 7.91 (br. dd, *J* = 8.4, 1.6 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 155.18, 144.43, 143.31, 131.15, 123.91, 121.19, 111.11, 108.72. HRMS (ESI) *m/z* [M+H]⁺ Calcd for C₈H₅N₄O₂F₂ 227.0381; Found 227.0375.

3-(1H-tetrazol-5-yl)pyridine, 2g. General procedure afforded product **2g** as a brown solid (63 mg, 85%). m.p. 235-237 °C with decomp. [lit.¹⁰ 239-240 °C with decomp.]. IR (ATR) ν 3382, 3063, 3000-2200 (br), 1639, 1608, 1578, 1527, 1470, 1331, 999, 818, 676. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.42 (br. s, 1H), 8.89 (br. d, *J* = 4.6 Hz, 1H), 8.79 (br. d, *J* = 8 Hz, 1H), 7.89 (dd,

$J = 7.9, 5.0$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 153.58, 148.48, 144.78, 138.03, 125.72, 122.48. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_6\text{H}_6\text{N}_5$ 148.0618; found 148.0615.

2-(1H-tetrazol-5-yl)pyridine, 2h. General procedure applied afforded compound **2h** as a beige solid (62 mg, 84%). m.p. 213 °C [lit.³⁶ 211 °C]. IR (ATR) ν 3200-2200 (br), 1599, 1557, 1479, 1452, 1156, 1017, 945, 791, 719, 465. ^1H NMR (400 MHz, DMSO- d_6) δ 8.80 (ddd, $J = 4.8, 1.7, 1$ Hz, 1H), 8.23 (dt, $J = 7.8, 1$ Hz, 1H), 8.08 (td, $J = 7.8, 1.7$ Hz, 1H), 7.63 (ddd, $J = 7.8, 4.8, 1.1$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 154.69, 150.04, 143.66, 138.20, 126.06, 122.58. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_6\text{H}_6\text{N}_5$ 148.0618; Found 148.0613.

2,6-di(1H-tetrazol-5-yl)pyridine, 2i. Following the general procedure using 4 equiv of TMSN₃, a flash chromatography (eluent DCM/MeOH 9:1 + 0.1% HCO₂H) afforded product as white solid **2i** (52 mg, 48%). m.p. 280 °C with decomp. [lit.³⁹ < 260 °C]. IR (ATR) ν 3200-2400 (br), 1687, 1602, 1554, 1452, 1180, 1014, 833, 746. ^1H NMR (400 MHz, DMSO- d_6) δ 8.34 (m, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 164.89, 144.53, 140.16, 124.36. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_7\text{H}_6\text{N}_9$ 216.0746; Found 216.0739.

2-(1H-tetrazol-5-yl)quinolin-8-ol, 2j. General procedure with flow set at 0.04 mL/min gave compound **2j** as a beige solid (74 mg, 69%). m.p. 230-234 °C with decomp. IR (ATR) ν 3200-2200 (br), 1602, 1557, 1470, 1440, 1243, 1192, 1140, 1162, 1059, 990, 945, 776, 743. ^1H NMR (300 MHz, DMSO- d_6) δ 9.42 (br. s, 1H), 8.56, 8.29 (AB-system, $^2J_{AB} = 8.6$ Hz, 2H), 7.61-7.51 (m, 2H), 7.22 (dd, $J = 7.4, 1.3$ Hz, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 155.01, 153.12, 140.89, 138.41, 137.46, 129.60, 128.97, 119.18, 117.92, 111.64. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_8\text{N}_5\text{O}$ 214.0723; Found 214.0722.

5-(1H-pyrrol-2-yl)-1H-tetrazole, 2k. General procedure gave compound **2k** as a brown solid (45 mg, 63%). m.p. 225-226 °C [lit.⁴⁰ 226 °C]. IR (ATR) ν 3286, 3150, 3008, 2918, 2900-2100 (br), 1630, 1539, 1464, 1352, 1207, 1053, 888, 734, 583. ^1H NMR (400 MHz, DMSO- d_6) δ 16.30 (br. s, 1H), 11.96 (br. s, 1H), 7.03-7.02 (m, 1H), 6.81-6.79 (m, 1H), 6.26-6.24 (m, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 149.30, 122.52, 115.50, 110.85, 109.60. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_5\text{H}_6\text{N}_5$ 136.0623; Found 136.0620.

5-(thiophen-2-yl)-1H-tetrazole, 2l. General procedure gave compound **2l** as a beige solid (49 mg, 64%). m.p. 209 °C [lit.³⁹ 206-207 °C]. IR (ATR) ν 3105, 3078, 3032, 3000-2200 (br), 1590, 1506, 1406, 1231, 1041, 957, 712. ^1H NMR (400 MHz, DMSO- d_6) δ 7.88 (dd, $J = 5.0, 1.1$ Hz,

1H), 7.80 (dd, $J = 3.7, 1.1$ Hz, 1H), 7.29 (dd, $J = 5.0, 3.7$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 151.39, 130.26, 129.06, 128.53, 125.49. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_5\text{H}_5\text{N}_4\text{S}$ 153.0229; Found 153.0223.

4-(1H-tetrazol-5-yl)morpholine, 2m. General procedure gave compound **2m** as a white solid (63 mg, 80%). m.p. 179 °C [lit.⁴¹ 177 °C]. IR (ATR) ν 3200-2400 (br), 1606, 1450, 1267, 1103, 1021, 923, 735, 557. ^1H NMR (400 MHz, DMSO- d_6) δ 7.93 (d, $J = 8$ Hz, 2H), 7.41 (d, $J = 8$ Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 155.07, 141.17, 129.89, 126.8, 121.26, 20.98. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_5\text{H}_{10}\text{N}_5\text{O}$ 156.0880, Found 156.0875.

1-(1H-tetrazol-5-yl)piperidine, 2n. General procedure gave compound **2n** as a beige solid (58 mg (76%)). m.p. 198 °C [lit.⁴¹ 199 °C]. IR (ATR) ν 3080 (br), 2939, 2856, 2801, 2710, 1611, 1463, 1411, 1011, 912, 735, 678. ^1H NMR (400 MHz, DMSO- d_6) δ 14.85 (br. s, 1H), 3.36 (s, 4H), 1.56 (s, 6H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 159.28, 47.68, 24.27, 23.30; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_6\text{H}_{12}\text{N}_5$ 154.1087; Found 154.1084.

5-benzyl-1H-tetrazole, 2o. General procedure gave compound **2o** as a white solid (56.2 mg, 77%). m.p. 121-122 °C [lit.⁴² 123-124 °C]. IR (ATR) ν 3100-2400 (br), 1530, 1491, 1455, 1427, 1246, 1075, 999, 884, 734, 694. ^1H NMR (400 MHz, DMSO- d_6) δ 7.36-7.24 (m, 5H), 4.28 (s, 2H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 155.21, 135.89, 128.65, 128.59, 126.94, 28.86. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_8\text{H}_9\text{N}_4$ 161.0827; Found 161.0830.

5-benzhydryl-1H-tetrazole, 2p. General procedure gave compound **2p** as a light brown solid (73 mg, 62%). m.p. 164 °C [lit.¹⁰ 165-166 °C]. IR (ATR) ν 3200-2400 (br), 1563, 1524, 1494, 1452, 1243, 1081, 1038, 921, 746, 961. ^1H NMR (400 MHz, DMSO- d_6) δ 7.37-7.25 (m, 10H), 5.95 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 158.10, 140.04, 128.63, 128.38, 127.13, 45.74. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_4$ 237.1140; Found: 237.1129.

5-butyl-1H-tetrazole, 2q. General procedure with flow set at 0.04 mL/min afforded compound **2q** as a beige solid (49 mg, 78%). m.p. 43 °C [lit.⁴² 40-42 °C]. IR (ATR) ν 3200-2200 (br), 2963, 2945, 2872, 1578, 1548, 1578, 1464, 1403, 1259, 1108, 1038, 990, 930, 740. ^1H NMR (400 MHz, DMSO- d_6) δ 2.87 (t, $J = 7.6$ Hz, 2H), 1.67 (quint, $J = 7.5$ Hz, 2H), 1.30 (sext, $J = 7.5$ Hz, 2H), 0.88 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 155.54, 29.07, 22.33, 21.49, 13.45. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_5\text{H}_{11}\text{N}_4$ 127.0978; Found 129.0976.

5-decyl-1H-tetrazole, 2r. General procedure with flow set at 0.04 mL/min afforded compound **2r** as a beige solid (80 mg, 76%). m.p. 58-59 °C. IR (ATR) ν 3153, 3057, 2954, 2918, 2848, 1566, 1464, 1252, 1093, 1071, 767, 722, 691. ^1H NMR (400 MHz, DMSO- d_6) δ 2.85 (t, $J = 7.5$ Hz, 3H), 1.72-1.64 (m, 2H), 1.27-1.24 (m, 14H), 0.87-0.84 (m, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 155.92, 31.21, 28.85, 28.78, 28.60, 28.45, 28.25, 26.93, 22.61, 22.02, 13.87. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{11}\text{H}_{23}\text{N}_4$ 211.1917; Found 211.1915.

5-(thiophen-2-ylmethyl)-1H-tetrazole, 2s. General procedure with flow set at 0.04 mL/min afforded compound **2s** as a beige solid (77 mg, 93%). m.p. 224-226 °C [lit.⁴⁰ 225-230 °C]. IR (ATR) ν 3123, 3000-2400 (br), 1557, 1427, 1237, 1038, 924, 700. ^1H NMR (400 MHz, DMSO- d_6) δ 7.43-7.41 (m, 1H), 7.00-6.97 (m, 2H), 4.52 (s, 2H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 155.03, 137.43, 127.08, 126.62, 125.48, 23.52. HRMS (ASAP⁺) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_6\text{H}_7\text{N}_4\text{S}$ 137.0391; Found 167.0390.

Di(1H-tetrazol-5-yl)methane, 2t. Following the general procedure using 4 equiv of TMSN₃, a flash chromatography (eluent DCM/MeOH 9:1 + 0.1% HCO₂H) afforded **2t** (37 mg, 49%). m.p. 212 °C [lit.⁴³ 210 °C]. IR (ATR) ν 3400-2400 (br), 1669, 1554, 1427, 1406, 1367, 1195, 1141, 1053, 842, 797, 722. ^1H NMR (400 MHz, DMSO- d_6) δ 4.73 (s, 2H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 152.44, 18.97. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_3\text{H}_5\text{N}_8$ 153.0632; Found 153.0630.

4'-methyl-[1,1'-biphenyl]-2-carbonitrile, 5. To a solution of 2-bromobenzonitrile **3** (80 mg, 0.44 mmol) and poly[4-tolyldibutylstannyl]butylstyrene (480 mg, 0.53 mmol) in toluene (5 mL) under argon, was added lithium chloride (55 mg, 1.32 mmol) and Bis(triphenylphosphine)palladium(II) dichloride (16 mg, 0.02 mmol). The resulting mixture was left under orbital stirring for 6 hours at 110 °C. The reaction mixture was extracted with diethyl ether and washed with water. The organic layer was separated, washed with water to obtain a crude product. Purification on silica gel (eluent petroleum ether and ethyl acetate, 95:5) afforded **5** (73 mg, 86%) as a white powder. mp 49-50 °C [lit.^{37,35} 49-51 °C]. IR (ATR) ν 3059, 3022, 2915, 2854, 2225, 1479, 812, 761 cm^{-1} . ^1H NMR (400 MHz, CDCl₃) δ 7.54 (dd, $J = 7.7$ Hz, $J = 0.9$ Hz, 1H), 7.62 (td, $J = 3.8$ Hz, $J = 1.2$ Hz, 1H), 7.51 (br d, $J = 7.7$ Hz, 1H), 7.48, 7.31 (AB-system, $^2J_{AB} = 8$ Hz, 2H), 7.42 (td, $J = 7.7$ Hz, $J = 1.2$ Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, CDCl₃) δ 145.7, 138.8, 135.4, 133.8, 132.9, 130.10, 129.6, 128.7, 127.4, 119.0, 111.3, 21.4; Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{N}$.0.05 $\text{C}_4\text{H}_8\text{O}_2$ C 86.29, H 5.81, N 6.98; found C 86.35, H 5.73, N 6.95. HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{14}\text{H}_{11}\text{NNa}$ 216.0784; Found 216.0777.

4'-(bromomethyl)-[1,1'-biphenyl]-2-carbonitrile, 6. To a solution of sodium bromate (2.71 g, 18 mmol) in H₂O (9 mL), was added a solution of 4'-methyl-[1,1'-biphenyl]-2-carbonitrile (1.16 g, 6 mmol) in ethyl acetate (6 mL). The mixture was cooled to 0 °C and a solution of sodium pyrosulfite (1.82 g, 9.6 mmol) in H₂O (18 mL) was added dropwise. The resulting mixture was stirred at room temperature until the completion of reaction (~ 5-6 h). The precipitate was filtered off, washed with cold ethyl acetate, water and isopropanol. The resulting solid was dried under vacuum at 60 °C to afford **6** (1.30 g, 80%) as a white powder. mp 125-127 °C [lit.⁴⁴ 126-129 °C]. IR (ATR) ν 3055, 3030, 2220, 758 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.77 (br dd, $J = 7.7$ Hz, $J = 0.9$ Hz, 1H), 7.64 (br td, $J = 3.8$ Hz, $J = 1.2$ Hz, 1H), 7.58-7.45 (m, 5H), 7.44 (br td, $J = 3.8$ Hz, $J = 1.2$ Hz, 4.55 (s, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 144.8, 138.4, 138.3, 133.9, 133.0, 130.1, 129.6, 129.3, 127.9, 118.7, 111.4, 32.9. Anal. Calcd for C₁₄H₁₀BrN C 61.79; H 3.70; Br 29.36; N 5.15; found C 62.09; H 3.47; Br 29.45 N 4.99. HRMS (ESI) m/z [M – HCl + H]⁺ Calcd for C₁₄H₁₀NBrNa 293.9889; Found 293.9880.

(S)-N-[(2'-cyanobiphenyl-4-yl)methyl]-(*L*)-valine benzyl ester hydrochloride, 7. To a solution of compound **6** (1.72 g, 6.32 mmol) and *L*-valine benzyl ester tosylate (2 g, 5.27 mmol) in a mixture 1/1 of toluene/ H₂O (12 mL), was added K₂CO₃ (1.4 g, 13.18 mmol), tetrabutyl ammonium bromide (20 mg, 0.062 mmol) and potassium iodide (20 mg, 0.12 mmol). The resulting mixture was left under magnetic stirring for 16 hours at 60 °C. After cooling, the two phases separated. The organic layer was washed with water and acidified with hydrochloric acid to pH 1-2; upon which, the product precipitated which was filtered, washed with toluene and dried to give **7** (2.07 g, 90%) as a white powder. mp 177 °C. $[\alpha]_D^{20} = -28.4$ (c = 1, CHCl₃). IR (ATR) ν 2964, 2698, 2563, 2221, 1739, 1550, 1188, 758, 739 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.76 (dd, $J = 7.7$ Hz, 1H), 7.65-7.58 (m, 3H), 7.53-7.35 (m, 9H), 5.25, 5.20 (AB-system, ² $J_{AB} = 11.9$ Hz, 2H), 4.38, 4.18 (AB-system, ² $J_{AB} = 13.5$ Hz, 2H), 3.47 (d, $J = 3.8$ Hz, 1H), 2.75-2.58 (m, 1H), 1.09 (dd, $J = 10.9$ Hz, $J = 6.9$ Hz). ¹³C NMR (75 MHz, CDCl₃) δ 166.9, 144.4, 139.5, 134.7, 134.0, 133.1, 131.6, 130.3, 130.1, 129.6, 129.5, 129.1, 128.8, 128.1, 118.5, 111.3, 68.1, 63.5, 49.8, 29.8, 19.8, 18.0. HRMS (ESI) m/z [M – HCl + H]⁺ Calcd for C₂₆H₂₇N₂O₂ 399.2063; Found 399.2067.

(S)-N-[(2'-cyanobiphenyl-4-yl)methyl]-*N*-valeroyl-(*L*)-valine benzyl ester, 8: To a solution of compound **7** (1 g, 2.30 mmol) in dichloromethane (10 mL), was added diisopropylethylamine (835 μ L, 4.79 mmol). After cooling at 0 °C, valeroyl chloride (287 μ L, 2.41 mmol) was added

and the mixture was stirred 1 hour between 10-20 °C. Hydrochloric acid 1 N was poured and the resulting solution was stirred during 15 min. The organic layer was separated, washed with hydrochloric acid 1 N, an aqueous solution of 10% NaHCO₃, brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain **8** (1.06 g, 96%) as an orange oil. $[\alpha]_D^{20} = -26.6$ ($c = 1$, CHCl₃). IR (ATR) ν 2964, 2698, 2563, 2221, 1739, 1550, 1188, 758, 739 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.76 (dd, $J = 7.7$ Hz, 1H), 7.65-7.58 (m, 3H), 7.53-7.35 (m, 9H), 5.25, 5.20 (AB-system, $^2J_{AB} = 11.9$ Hz, 2H), 4.38, 4.18 (AB-system, $^2J_{AB} = 13.5$ Hz, 2H), 3.47 (d, $J = 3.8$ Hz, 1H), 2.75-2.58 (m, 1H), 1.09 (dd, $J = 10.9$ Hz, $J = 6.9$ Hz). ¹³C NMR (75 MHz, CDCl₃) δ 166.9, 144.4, 139.5, 134.7, 134.0, 133.1, 131.6, 130.3, 130.1, 129.6, 129.5, 129.1, 128.8, 128.1, 118.5, 111.3, 68.1, 63.5, 49.8, 29.8, 19.8, 18.0. HRMS (ESI) m/z [M + H]⁺ Calcd for C₃₁H₃₅N₂O₃ 483.2643; Found 483.2649.

(S)-N-(1-benzyloxycarbonyl-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine (Benzyl Valsartan), 9: The general procedure described above was applied to compound **8** (400 mg, 0.828 mmol) in the presence of azidotrimethylsilane (448 μ L, 3.312 mmol). The reaction was conducted at 200°C with a residence time of 15 min (flow = 0.04 mL/min). The reaction mixture was collected and concentrated. Ethyl acetate and NaOH (1M) was added and stirred during 30 min. The aqueous phase was acidified with HCl until pH 1-2 and then extracted with ethyl acetate (200 mL). The organic phase was washed with brine and was dried over magnesium sulfate, filtrated and concentrated under reduced pressure. Purification by chromatography on silica gel (eluent petroleum ether, dichloromethane, methanol (7:2.5:0.5) and 0.1% formic acid) afforded benzyl valsartan **9** (217 mg, 50%) as a beige powder. $[\alpha]_D^{20} = -29.8$ ($c = 1$, CHCl₃). IR (ATR) ν 2962, 2933, 2873, 1736, 1604, 1455, 1410, 1200, 1155, 1106, 997, 848, 755, 738, 726, 697, 599 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): (mixture of rotamers) δ 7.8-8.0 (m, 1H), 7.4-7.6 (m, 2H), 7.1-7.4 (m, 6H), 6.8-7.1 (4H), 4.0-5.0 (m, 5H), 2-2.6 (m, 3H), 1.4-1.7 (m, 2H), 1.1-1.4 (m, 2H), 0,7-1 (m, 9H). ¹³C NMR (75 MHz, CDCl₃) (mixture of rotamers) δ 175.16, 175.10, 170.51, 169.73, 155.46, 154.86, 141.19, 141.06, 138.67, 137.99, 137.82, 136.98, 135.38, 134.84, 131,26, 131.20, 130.91, 130.78, 129.40, 128.98, 128.74, 128.59, 128.41, 128.36, 128.10, 127.77, 127.11, 126.57, 123.07, 122.77, 67.27, 66.82, 66.43, 62.87, 49.13, 45.90, 33.55, 33.50, 28.16, 27.98, 27.58, 27.39, 22.47, 20.12, 19.84, 18.95, 18.91, 13.88. HRMS (ESI) m/z [M + Na]⁺ Calcd for C₃₁H₃₅N₅O₃Na 548.2632; Found 548.2636.

(S)-N-(1-Carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amine (Valsartan), 10 : A solution of 200 mg of benzyl valsartan **9** in methanol (5

mL) was hydrogenated at 25°C and 5 bar with Pd(OAc)₂ (9 mg, 0.4 mmol) and charcoal (91 mg) during 16 h. The solution was placed over a pad of Celite and filtrates were collected. A solution of sodium bicarbonate (10% w/v) was added, the mixture was stirred for 20 minutes and the layers were separated. The aqueous layer was washed with ethyl acetate and the pH was adjusted to 1-2 with 2N hydrochloric acid solution and stirred for 15-30 minutes. The aqueous layer was extracted with ethyl acetate, washed with water and brine. The organic layer was dried over magnesium sulfate and dried under vacuum. Ethyl acetate was added to the residue while hot. Stirred for 5 minutes to obtain a clear solution. The residue was recrystallized with ethyl acetate and cyclohexane. The solid was filtered, washed with a mixture of ethyl acetate/cyclohexane (1:9) and dried to give valsartan (100 mg, 60%) as a white powder. m.p. 116 °C [lit⁴⁵ 116-117 °C]. [α]²⁵_D = -65.7 (c = 1, CHCl₃). IR (ATR) ν 3444, 3057, 2962, 2931, 2877, 2741, 2612, 1732, 1608, 1475, 1410, 1273, 1208, 1167, 1128, 1102, 1051, 999, 939, 899, 852, 824, 777, 762, 685, 677, 628, 560 cm⁻¹. ¹H NMR (300 MHz, DMSO-*d*₆) δ 16.25 (br. s, 1H), 12.63 (br. s, 1H), 7.70-7.52 (m, 4H), 7.21-6.96 (m, 4H), 4.67-4.03 (m, 3H), 2.25-1.99 (m, 2H), 1.59-1.11 (m, 5H), 0.94-0.87 (m, 4H), 0.78-0.69 (m, 5H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 206.36, 173.42, 171.83, 171.57, 141.31, 141.18, 138.19, 137.73, 137.10, 131.00, 130.56, 130.49, 128.75, 128.24, 127.65, 127.51, 126.90, 126.24, 65.73, 62.93, 48.69, 45.46, 32.42, 30.62, 27.52, 26.95, 26.76, 21.76, 21.61, 20.09, 19.36, 18.77, 18.46, 13.74, 13.65. HRMS (ESI) *m/z* [M + Na]⁺ Calcd for C₂₄H₂₉N₅O₃Na 458.2163; Found 458.2159.

■ ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the internet at <http://pubs.acs.org>.

Productivities for compounds **2**, procedure for the preparation of polymer **4**, ¹H NMR and ¹³C-NMR spectra of synthesized products.

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Notes

The authors declare no competing financial interest.

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