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Original Research Article

A sustainable and scalable route to 5-substituted 1H-tetrazoles: Application to sartan drug intermediates

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Scalable synthesis.

ABSTRACT
Synthesis of tetrazole process proposes a green and scalable process for the synthesis of 5-substituted 1H-tetrazole derivatives via a one-pot [3+2] cycloaddition strategy. This protocol assisted condensation, cycloaddition, and hydrolysis in a single step under mild thermal conditions (80–100 °C, 2–6 h), by a mixed green solvent system or solvent-free conditions. Copper(II) sulfate pentahydrate (5–10 mol%) was proved as an capable catalyst, assisting high product yields (85–95%) with nominal by-products and removing the need for intermediate purification.The developed methodology demonstrates significant improvements over conventional approaches by reducing reaction steps, avoiding strong bases, and minimizing solvent usage. This Balancing research studies on the base-free conditions and confirm increased reaction efficiency, cut down lengthy work-up, and reduced environmental impact, supporting key green chemistry principles for instance atom economy and waste minimization. To the best of our knowledge, this is the first report integrating one-pot synthesis with base-free conditions for tetrazole derivatives under scalable green conditions. The improved process was suceesfully adopted to the synthesis of critical intermediates for sartan-class antihypertensive drugs, developing scalability to gram-scale reactions without substantial loss of yield or selectivity. This developed protocol proved reproducibility with minimizing the rection workup and time offers for making tetrazole in sartans series active pharma ingradients , which helps to make pharmaceutical manufacturing more efficient and environmental.

1. Introduction

Triazoles and tetrazoles, as nitrogen-rich five-membered heterocyclic systems, constitute an important class of compounds exhibiting diverse biological and pharmacological activities. In particular, triazoles, containing three nitrogen atoms, have been extensively utilized in pharmaceuticals, agrochemicals, and materials science due to their structural versatility and functional relevance. Conventionally, such heterocycles are synthesized via metal-catalyzed approaches, notably the Huisgen 1,3-dipolar cycloaddition. However, these methodologies are often associated with significant limitations, including toxicity of reagents, environmental hazards, elevated costs, and sensitivity toward functional groups. In this context, tetrazole derivatives have gained considerable prominence, especially as key structural motifs in sartan-based antihypertensive drugs. The incorporation of tetrazole rings enhances pharmacokinetic and pharmacodynamic properties by improving binding affinity toward angiotensin II receptors and increasing metabolic stability. Consequently, tetrazoles serve as effective bioisosteres for carboxylic acid functionalities, contributing to improved bioavailability and therapeutic efficacy [1-6].

Recent advancements in green chemistry have facilitated the development of more sustainable and efficient synthetic strategies for tetrazole formation. Among these, the [3+2] cycloaddition of sodium azide with nitriles, catalyzed by copper(II) complexes, has emerged as a highly effective approach. This methodology not only provides high yields of structurally well-defined tetrazoles but also significantly enhances operational safety by minimizing risks associated with nitrogen gas evolution, such as spark discharge and explosion hazards commonly encountered in traditional protocols. The robustness of this catalytic system is further validated through consistent performance across a wide range of substrates, with structural characterization confirming the reliability and reproducibility of the synthesized derivatives [7-11]. The success of this synthetic route underscores the importance of continuous innovation in tetrazole chemistry, particularly for the development of novel active pharmaceutical ingredients (APIs) [12-16].

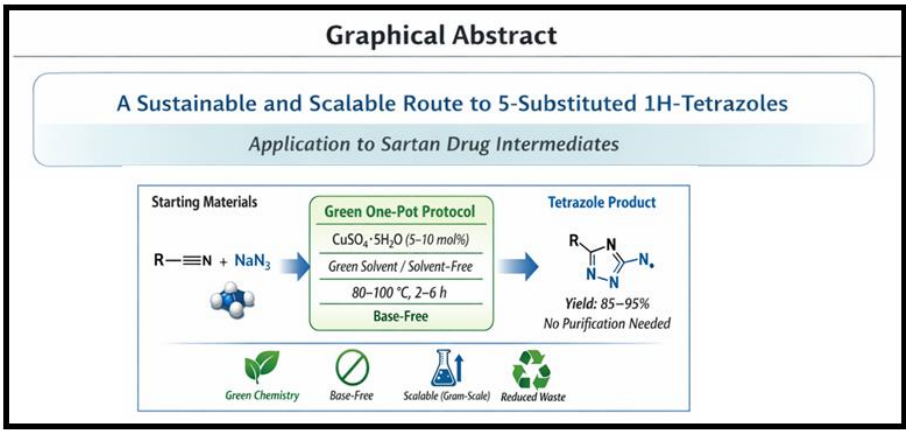


Figure 1: General mechanism of copper-catalyzed [3+2] cycloaddition for tetrazole synthesis sartan drugs containing tetrazole moiety (Valsartan, Losartan, Irbesartan.

Furthermore, the integration of green chemistry principles aligns with global efforts to reduce the environmental footprint of pharmaceutical manufacturing. Eco-friendly synthetic processes not only enhance sustainability but also improve scalability, thereby facilitating industrial implementation and cost-effective production. Tetrazoles are particularly distinguished by their high nitrogen content, which contributes to enhanced biological activity and improved bioavailability. Beyond pharmaceutical applications, these compounds find utility in high-energy materials, coordination chemistry, and as organocatalysts, reflecting their broad functional significance.

Notably, clinically important angiotensin II receptor blockers such as Valsartan, Irbesartan, and Losartan incorporate the (1H-tetrazol-5-yl) biphenyl moiety, which plays a critical role in target protein binding and therapeutic performance. Ongoing research on structurally modified tetrazole derivatives, including benzo-furan analogues, continues to advance the development of more effective, accessible, and affordable treatments for hypertension and cardiovascular diseases [17].

Selection of Green Solvent

The selection of an appropriate green solvent is a critical parameter in sustainable chemical synthesis, requiring careful consideration of safety, environmental impact, renewability, and regulatory compliance. Common green solvent systems include water, supercritical carbon dioxide, ionic liquids, and bio-based or biodegradable solvents such as dimethyl carbonate, ethyl lactate, and propylene carbonate. Dimethyl sulfoxide (DMSO) has emerged as a widely used green solvent due to its low toxicity, biodegradability, and excellent solvating ability for a broad range of organic compounds. However, its limitations, such as incompatibility with certain polymeric materials (e.g., PVC), highlight the need for continued research into more versatile solvent systems. Despite these constraints, DMSO remains a valuable medium in both academic and industrial applications [18-19].

Catalyst Selection and Sustainability

Catalyst design plays a crucial role in achieving efficient and sustainable synthesis. While traditional Lewis acid catalysts such as tributyltin chloride are effective, their toxicity and environmental impact limit their applicability in green chemistry frameworks. In contrast, copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) represents a more sustainable alternative, functioning as an efficient catalytic system for tetrazole synthesis via [3+2] cycloaddition.

The catalytic activity of $CuSO_4 \cdot 5H_2O$ arises from the generation of Cu^{2+} ions, which enhance the electrophilic activation of nitriles and facilitate azide addition. Importantly, this catalyst system aligns with green chemistry principles due to its recyclability and reduced environmental impact. Following tetrazole formation, Cu^{2+} ions can be regenerated and reused in subsequent catalytic cycles, with studies demonstrating minimal loss in catalytic efficiency over multiple iterations. Additionally, residual copper species such as Cu_2O can be effectively converted back to $CuSO_4 \cdot 5H_2O$ using oxidizing agents such as hydrogen peroxide in the presence of sulfuric acid, achieving copper recovery efficiencies of up to 97%. This recyclability further enhances the sustainability and economic viability of the process.

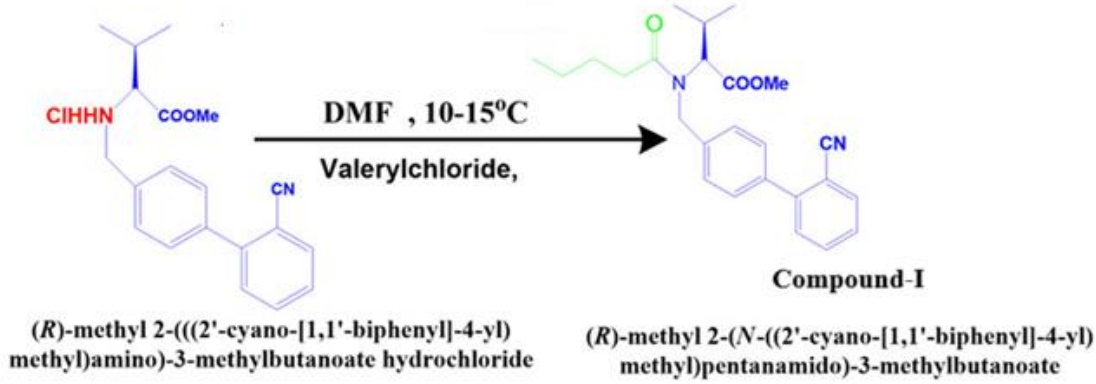
Overall, the utilization of $CuSO_4 \cdot 5H_2O$ as a catalyst provides a mild, efficient, and environmentally benign alternative to conventional systems, reinforcing its suitability for large-scale pharmaceutical synthesis.

2. Experimental Section

2.1 All chemicals were procured from commercial suppliers and used without further purification unless otherwise specified. Reagents were purified by standard distillation methods where necessary. Deuterated solvents for spectroscopic analysis were obtained from Sigma-Aldrich. Thin-layer chromatography (TLC) was carried out on Merck silica gel 1.05554 plates, and spots were visualized under UV light or iodine vapor. Column chromatography was performed using silica gel (60–120 mesh). Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Advance III 400 MHz spectrometer, and chemical shifts were reported in ppm. Electrospray ionization (ESI) mass spectra were obtained using a WATERS XEVO G2-XS QToF instrument. Infrared (IR) and UV–visible spectra were recorded using Thermo Scientific Nicolet iS50 and Agilent Cary 60 spectrophotometers, respectively. In this step, dimethylformamide (DMF) plays a dual role as both solvent and mild organic base, eliminating the need for conventional inorganic bases such as sodium carbonate. This dual functionality enhances the solubility of reactants and promotes efficient condensation. DMF facilitates bond formation between valeryl chloride and the corresponding amine intermediate, leading to improved reaction control and higher

yields. This approach simplifies the reaction system while improving efficiency, demonstrating the advantage of DMF in process optimization. The synthetic route for the preparation of the nitrile intermediate is presented in **Scheme I**.

Scheme-I : DMF plays a dual role as both solvent and mild organic base.



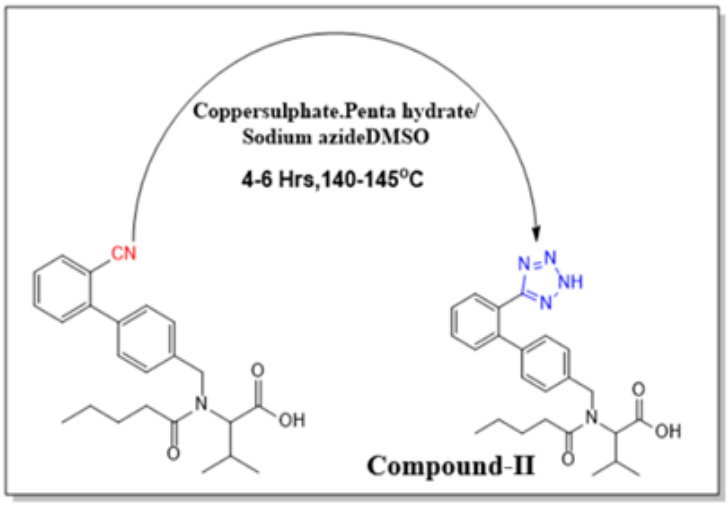
The optimization of reaction conditions with respect to base equivalents and solvent is summarized in Table 1.

Table 1: Optimization of reaction conditions: effect of base equivalents and solvent on yield.

Entry	Solvent	Base (Equiv.)	Temp (°C)	Time (h)	Yield (%)
1	DMF	1	2–4	2	50
2	DMF	2	2–4	2	60
3	DMF	3	2–4	2	70
4	DMF	4	2–4	2	78
5	DMF	5	2–4	2	86
6	DMF	6	2–4	2	96
7	DMSO	3	2–4	2	0
8	DMSO	4	2–4	2	0
9	DMSO	5	2–4	2	0
10	NMP	2	2–4	2	30
11	NMP	3	2–4	2	50
12	NMP	4	2–4	2	50
13	DMF	7	2–4	2	91
14	DMF	8	2–4	2	92
15	DMF	10	2–4	2	92

The copper-catalyzed [3+2] cycloaddition leading to tetrazole formation is depicted in **Scheme II**.

Scheme-II: Copper-catalyzed [3+2] cycloaddition of nitriles with sodium azide for tetrazole formation using catalyst.



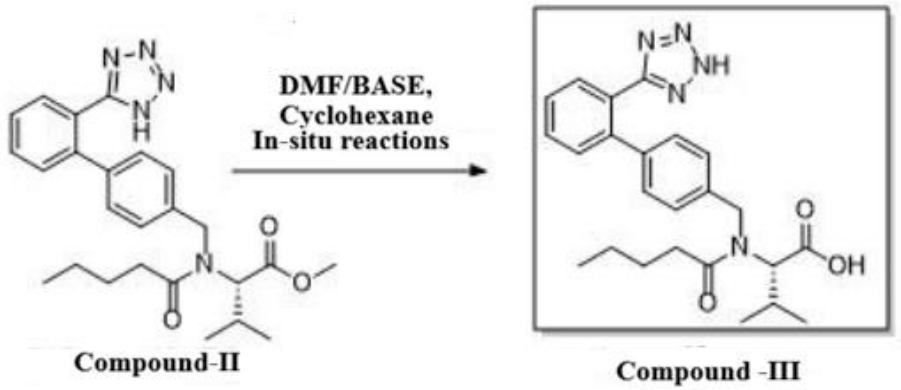
The effect of different catalysts and solvent systems on tetrazole formation is presented in Table 2.

Table 2: Catalyst screening for tetrazole formation under different solvent systems.

Entry	Catalyst	Equiv.	Solvent	Temp (°C)	Time (h)	Yield (%)
1	CC	1	DMSO	140	15	0
2	CC	2	DMF	140	15	0
3	CC	3	DMSO	140	15	0
4	Catalyst	2	Water	140	15	30
5	Catalyst	4	DMSO	140	15	78
6	Catalyst	5	DMF	140	15	86
7	Catalyst	4	DMSO	140	15	95
8	CAC	3	Water	140	15	0
9	CAC	4	Water	140	15	0
10	CAC	5	Water	140	15	0

CC: Copper (II) chloride ($CuCl_2$): **Catalyst:** Copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) **CAC**: Copper (II) acetate ($Cu(C_2H_3O_2)_2$). The overall one-pot synthetic strategy for the preparation of the active compound is illustrated in **Scheme III**.

Scheme III. One-pot synthesis of active compound (Compound-III) via integrated condensation and tetrazole formation.



3. Methods

Synthesis of Compound-I

(R)-Methyl2-(N-((2′-cyano-[1,1′-biphenyl]-4-yl)methyl)pentanamido)-3-methylbutanoate was synthesized via a controlled acylation reaction. A mixture of N-(2-cyanobiphenyl-4-yl)methyl-(L)-valine methyl ester hydrochloride (0.1955 mol), DMF, water (450 mL), and toluene (900 mL) was stirred at 28 °C for 25 min. The reaction mixture was then cooled to 0 °C. Valeryl chloride (0.2932 mol) was added dropwise over 55 min while maintaining the temperature between 0–20 °C. The reaction was further stirred at 2–4 °C for 2 h. Completion of the reaction was confirmed by TLC. The mixture was then allowed to reach room temperature, followed by the addition of water and stirring for 20 min.The organic layer was separated, washed sequentially with sodium bicarbonate solution and water, and concentrated under reduced pressure at 60–68 °C. The desired product was obtained in 96% yield with 99.11% purity (HPLC).

Characterization of (R)-Methyl 2-(N-((2'-cyano-[1, 1'-biphenyl]-4-yl) methyl) pentanamido) - 3-methylbutanoate [Compound-I]: Syrupy mass, Yield: 95%. MS: m/z: 407.3, 406.2, 393.1, 375.2, 323.3, 216.1, 192.4, 130.2 and 102.2. IR data (KBr, ν/cm−1): 3063, 3029, 2960, 2932, 2873, 2734, 2224, 1943, 1740, 1654, 1597, 1517, 1407, 1168,974, 887,765. 1H- NMR (400 MHz, CDCl3): δ7.75 (m,2H), δ7.65 (m,1H), δ7.5 (m,2H), δ7.3 (m,2H),7.18 (m, 1H), 4.7 (s, 2H), 4.30 (m, 1H), 3.75 (s, 3H), 3.4 (m, 1H), 2.33 (t, 2H), 1.60 (m, 2H), 1.35 (m, 2H),0.88(t, 3H). 0.95 (d, 3H) 0.90 (d, 3H).

Synthesis of Compound-II (R)-Methyl 2-(N-((2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)methyl)pentanamido)-3-methylbutanoate was synthesized via tetrazole formation from the corresponding nitrile precursor.A reaction mixture comprising DMSO (510 mL), N-[(2′-cyanobiphenyl-4-yl)methyl]-N-valeryl-(L)-valine methyl ester (0.1819 mol), copper(II) sulfate pentahydrate (0.918 mol), and sodium azide (0.918 mol) was heated under reflux for 14–15 h. Upon completion, the reaction mixture was cooled to 30 °C. An aqueous solution of sodium hydroxide (1.80 mol in 1190 mL water) was then added, and the mixture was stirred for an additional 13 h. The aqueous phase was separated and washed successively with toluene and dichloromethane to remove organic impurities. The pH of the aqueous layer was carefully adjusted to 6.75 using acetic acid, followed by further adjustment to pH 5. The product was then extracted with dichloromethane. The combined organic extracts were washed, concentrated under reduced pressure, and treated with cyclohexane to induce precipitation. The resulting solid was filtered, washed, and dried to afford the desired product in 96% yield with 99.64% purity (HPLC).

Characterization of (R)-methyl 2-(N-((2'-(1H-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl) methyl) pentanamido)-3-methylbutanoate. [Compound-II] : Off white solid, Yield: 96% ,MS : m/z : 450.25, 449.2, 434.1, 418.2, 334.1.1H- NMR (400 MHz, CDCl3): δ7.65 (m,2H), δ7.2 (m,2H), δ7.15 (m,2H), δ7.1 (m,2H), 4.8 (d,2H), 4.5 (s, 2H), 3.30 (s, 3H), 3.25 (m, 1H), 2.1 (t, 2H), 1.6 (m, 2H), 1.35 (m, 2H), 1.0 (t, 3H),0.91(d, 3H), 0.90 (d,3H).

Synthesis of Compound-III : Synthesis of (R)-methyl 2-(N-((2′-(1H-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)methyl)pentanamido)-3-methylbutanoate (Active Compound C) N-(2-cyanobiphenyl-4-yl)methyl-(L)-valine methyl ester hydrochloride (70 g, 0.1955 mol) was dissolved in a mixture of DMF, water, and cyclohexane, and the reaction mixture was cooled to low temperature. Valeryl chloride (0.3925 mol) was added in a controlled manner, and the reaction was stirred until completion, as confirmed by TLC. Without isolation of the intermediate, the reaction mixture was directly subjected to tetrazole formation by the addition of Catalyst (0.4991 mol) and sodium azide (0.4911 mol). The reaction was maintained for 14–15 h, and completion was again confirmed by TLC. The mixture was then cooled to room temperature and treated with aqueous sodium hydroxide, followed by careful pH adjustment using acetic acid to the desired range. The reaction mixture was subsequently extracted and washed with cyclohexane, chloroform, and brine solution to remove impurities. The organic layer was concentrated under reduced pressure, and ethyl acetate was added. The solution was treated with activated charcoal, filtered, and the filtrate was cooled to induce crystallization. The resulting solid was filtered, washed, and dried at 30–35 °C for 14 h to afford the desired product in 79% yield (98 g) with 99.86% purity (HPLC).

Characterization of Compound -III i.e (R)-methyl 2-(N-((2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl) pentanamido)-3-methylbutanoate (Final active compound): white solid, Yield: 97% MS: m/z : 451.2, 450.5, 449.2, 436.4.IR data (KBr, ν/cm−1): 3063, 2745, 2614, 1935, 1513, 1390, 1353, 1240, 1164, 1065, 977, 898,885.1H- NMR (400 MHz, CDCl3): δ8.05 (d,2H), δ7.5 (m,2H), δ7.35 (d,2H), δ7.19 (m,2H), 5.0 (s,2H), 4.55 (d, 1H), 4.03(s, 3H), 3.45 (m, 1H), 2.8 (bs, 1H), 2.45 (t, 2H), 1.75 (m, 2H), 1.45 (m, 2H),1.0(t, 3H), 0.90 (d,6H).13C-NMR (101 MHz, DMSO-d6): δ 177,175, 163,135, 129,128, 127, 75, 57, 51, 35, 28, 27, 23, 19.

4. Results

This study demonstrates a significant advancement in the synthesis of 5-substituted 1H-tetrazoles using copper(II) sulfate pentahydrate as an efficient catalyst (Scheme II). The catalytic role of Catalyst is pivotal in promoting the in-situ generation of copper azide species, which facilitates the [3+2] cycloaddition of nitriles with high selectivity and conversion efficiency. As a result, excellent yields of tetrazole derivatives were obtained, confirming the effectiveness of this catalytic system. A key outcome of this work is the development of a robust one-pot synthetic protocol employing dimethyl sulfoxide (DMSO) as the reaction medium. This approach enhances reaction efficiency while eliminating the need for hazardous reagents such as hydrazoic acid, thereby improving both operational safety and environmental compatibility. The methodology exhibits broad substrate tolerance, accommodating a variety of functional groups and consistently delivering high yields. In parallel, dimethylformamide (DMF) was effectively utilized to facilitate smooth condensation reactions (Scheme I). The presence of DMF improves reaction kinetics and overall yield, enabling efficient formation of key intermediates with minimal side reactions. This highlights its importance in achieving a reliable and high-performing synthetic sequence. Furthermore, the study successfully demonstrates the in situ synthesis of active pharmaceutical ingredients (APIs) through an integrated one-pot strategy (Scheme III). This approach provides near-quantitative yields along with high purity, as confirmed by detailed structural characterization. The in-situ methodology significantly streamlines the synthetic process, reduces intermediate handling, and aligns with green chemistry principles by minimizing waste generation and reagent consumption. A comparative evaluation of the developed methodology with conventional approaches is summarized in Table 3.

Table 3: Comparative analysis of conventional and developed synthetic methods.

Parameter	Conventional	This Work
Process	Multi-step	One-pot
Conditions	Harsh	Mild
Yield (%)	60–80	85–95
Work-up	Complex	Simple
Sustainability	Low	High

5. Discussion

The findings of this study underscore the potential of integrating catalytic efficiency with sustainable synthetic design in pharmaceutical chemistry. The use of Catalyst as a catalyst represents a practical and effective alternative to conventional systems, enabling high-yielding transformations under relatively mild conditions. Importantly, the adoption of one-pot and in situ strategies enhances process efficiency and reduces the environmental footprint by minimizing solvent use, purification steps, and waste generation. While solvents such as DMSO and DMF contribute to reaction efficiency, their environmental impact suggests the need for further research into greener solvent systems without compromising performance. Overall, this work highlights a balanced approach between synthetic efficiency and sustainability. The methodology provides a scalable platform for the preparation of tetrazole-based pharmaceutical intermediates and sets the foundation for future advancements in environmentally responsible process chemistry.

6. Summary and Conclusion

In summary, this study presents a novel and efficient synthetic route for the preparation of 5-substituted 1H-tetrazoles via a copper(II)-mediated [3+2] cycloaddition strategy. The use of copper(II) sulfate pentahydrate catalyst as an effective catalyst enables high conversion and selectivity under optimized conditions. The developed methodology integrates one-pot and in situ strategies, significantly enhancing process efficiency, yield, and scalability. The synthesis of active pharmaceutical intermediates was achieved with high purity and minimal by-product formation, demonstrating the robustness of the protocol. Importantly, this

methodology is readily extendable to other sartan-class drugs, providing an efficient platform for the synthesis of tetrazole-containing intermediates through a one-pot approach. This highlights its broader applicability in the development of angiotensin II receptor blockers. Although solvents such as DMF and DMSO contribute to improved reaction performance, further efforts toward the use of greener solvent systems are desirable to strengthen sustainability. Overall, this work provides a practical, scalable, and versatile approach for tetrazole synthesis, contributing to the advancement of environmentally responsible methodologies in pharmaceutical chemistry.

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Authors' contributions

All authors contributed equally to the conception, design, experimental work, data analysis, interpretation of results, and preparation of the manuscript. All authors reviewed and approved the final version of the manuscript for publication.

Conflicts of interest

The authors declare that there are no conflicts of interest or competing financial interests that could have influenced the outcomes of this study.

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Data availability

No new data were created.

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