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## 2*H*-Thiazolo[4,5-*d*][1,2,3]triazole: synthesis, functionalization, and application in scaffold-hopping†

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This manuscript unveils the synthesis of 2*H*-thiazolo[4,5-*d*][1,2,3]triazole (ThTz), an unprecedented [5-5]-fused heteroaromatic system, and established a scalable synthetic procedure for producing large quantities of the ThTz ring bearing a sulfone group on the thiazole ring. The sulfone moiety proves to be a versatile reactive tag, facilitating diverse transformations such as  $S_NAr$  reactions, metal-catalyzed couplings, and radical-based alkylations. Furthermore, functionalization of the triazole ring highlights the potential of this newly developed heteroaromatic compound as a valuable heteroaryl building block, promoting scaffold hopping strategies in medicinal chemistry.

### Introduction

Heteroarenes have long been celebrated for their pivotal role in synthetic chemistry, serving as the backbone for groundbreaking developments in medicinal, agrochemical, and materials chemistry. Their allure in medicinal chemistry stems from the inclusion of heteroatoms within rigid aromatic rings, which imbue compounds with desirable properties like enhanced hydrophilicity, hydrogen bonding potential, and improved pharmacokinetics.<sup>1</sup> These attributes are crucial for medicinal chemists striving to enhance protein binding, boost target selectivity, and innovate in fragment-based drug design. Additionally, the structural diversity and modifiability of heteroarenes make them invaluable in agrochemical design for developing potent and selective pesticides and fungicides with favorable environmental properties.<sup>2</sup>

Among the diverse landscape of aromatic configurations, [5-5]-bicyclic heteroarenes stand out and have garnered significant attention within the pharmaceutical and agrochemical industries (Fig. 1A). Notable pharmaceutical examples include AstraZeneca's GPI688, which utilizes the 6*H*-thieno[2,3-*b*]

pyrrole scaffold to inhibit glycogen phosphorylase,<sup>3</sup> and Merck's samatasvir, which incorporates thieno[3,2-*b*]thiophene in its quest to inhibit NS5A.<sup>4</sup> Imidazo[2,1-*b*]thiazole has also been embedded in bioactive molecules like PF-5190457<sup>5</sup> and SRT2104,<sup>6</sup> showcasing its utility in drug development. In agrochemistry, these scaffolds are engineered to target specific enzymes or pathways in pests, enhancing the efficacy and prolonging the efficacy offered by agrochemical products.

In this study, we delve into the realm of [5-5]-bicyclic heteroarenes, particularly focusing on thiazole-fused systems, given thiazole's prominence as a privileged structure in medicinal chemistry. Thiazoles are celebrated not only for their pharmacological benefits but also for their robustness and functional versatility, which make them ideal candidates for agrochemical applications where environmental stability and broad-spectrum activity are required.<sup>7</sup>

Our attention is captivated by 2*H*-thiazolo[4,5-*d*][1,2,3]triazole (ThTz), an innovative and previously unexplored aromatic system that brings together the thiazole and triazole rings—both of which are known for their remarkable chemical stability and biological relevance (Fig. 1B). Triazoles are particularly noted for their bioisosteric replacement of amide functionality and their capacity to alter compound architecture through substitution at various nitrogen positions, offering a vast landscape for chemical exploration and optimization. This attribute enables the design of molecules with enhanced metabolic stability and improved binding characteristics, crucial for developing more effective pharmaceuticals and agrochemicals.

The design of ThTz was guided by its potential as a versatile building block, facilitating assembly with various molecular fragments. We introduced a sulfone group on the ThTz scaffold, enhancing its utility as a leaving group and thus increasing its

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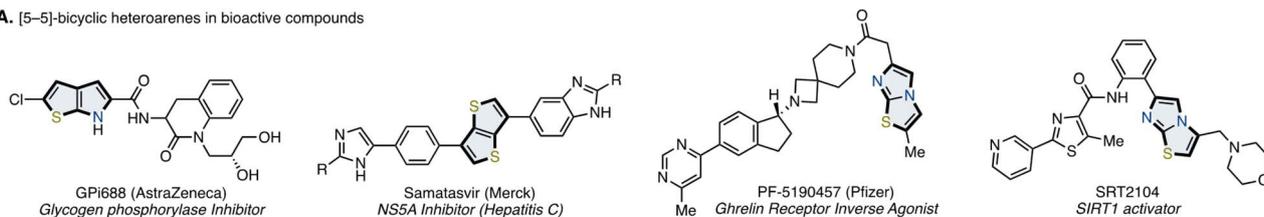
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† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for compounds including <sup>1</sup>H and <sup>13</sup>C NMR spectra. CCDC 2360991 (for 9A) and 2360992 (for 11-N1). For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4sc03874f>

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## A. [5-5]-bicyclic heteroarenes in bioactive compounds



## B. 2H-thiazolo[4,5-d][1,2,3]triazole (ThTz): an innovative and previously unexplored aromatic system

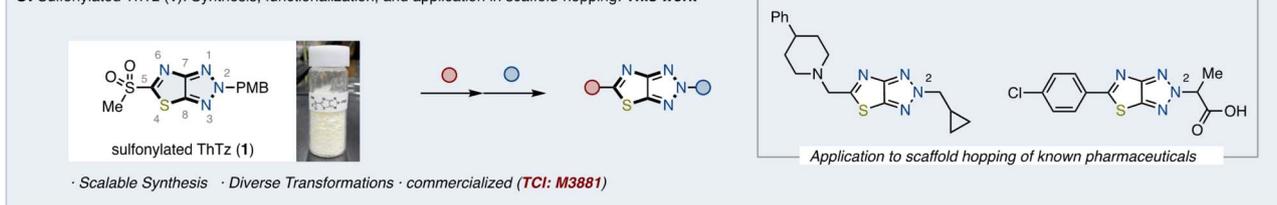
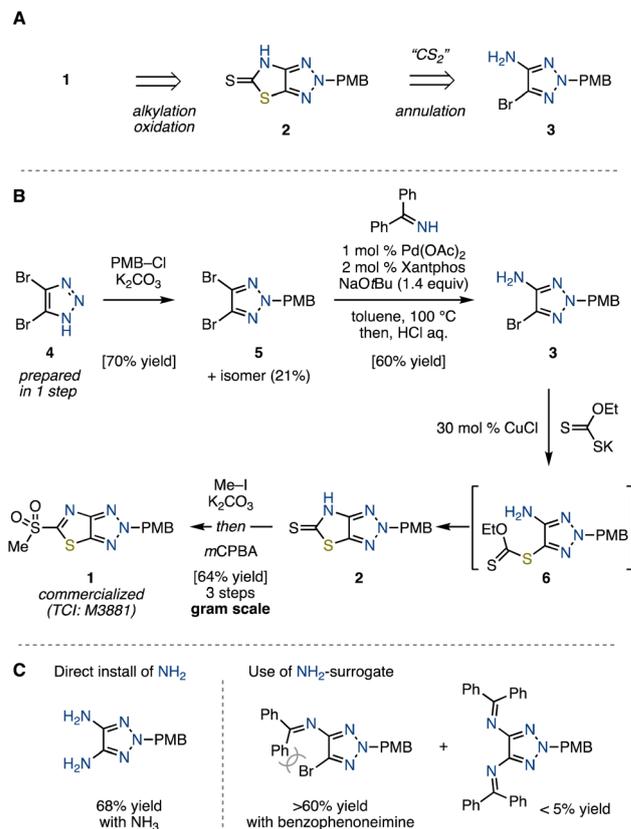
C. Sulfonylated ThTz (1): Synthesis, functionalization, and application in scaffold-hopping: **This work**

Fig. 1 (A) [5-5]-Bicyclic heteroarenes in bioactive compounds. (B) 2H-Thiazolo[4,5-d][1,2,3]triazole (ThTz): an innovative and previously unexplored aromatic system. (C) Sulfonylated ThTz (1): synthesis, functionalization, and application in scaffold-hopping.

versatility in synthetic applications (Fig. 1C).<sup>8</sup> Herein, we report the synthesis of C5-sulfonylated ThTz (1) and its successful deployment as a robust building block. With a high scalability in synthesis and high applicability as a heteroarene building block, 1 has been commercialized through Tokyo Chemical Industry Ltd (TCI: catalogue number M3881).

## Results and discussion

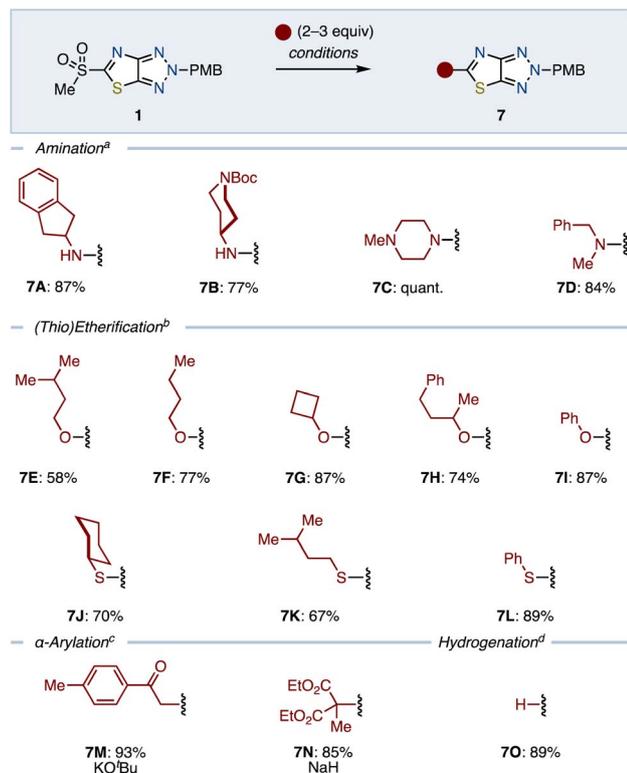
Retro-synthetically, we envisioned that heteroarene 1 could be synthesized through *S*-alkylation and oxidation of thione 2 (Scheme 1A). The synthesis of 2, in turn, was envisaged *via* the annulation of bromoaminotriazole 3 with a CS<sub>2</sub> equivalent. In line with this retro-synthetic analysis, we first embarked on the preparation of bromoaminotriazole 3 (Scheme 1B). The *N*-alkylation of readily prepared dibromotriazole 4<sup>9</sup> with *p*-methoxybenzyl (PMB) chloride afforded PMB-triazole 5 in 70% yield along with its positional isomer in 21% yield, both of which could be separated by silica-gel purification. The reason for the preference for alkylation at the N2 position is the steric hindrance caused by the bromo group.<sup>10</sup> Subsequently, an attempt to directly install an NH<sub>2</sub> group from the obtained 5 using NH<sub>3</sub> under copper-catalyzed conditions led to diamination, proving unsuccessful for our targeted monoamination (Scheme 1C, see the ESI†).<sup>11</sup> We envisaged that the use of a bulky NH<sub>2</sub>-surrogate could suppress the undesired diamination. Pursuing this approach, we employed palladium-catalyzed conditions with benzophenoneimine,<sup>12</sup> followed by an acidic workup to achieve the desired monoamination, delivering bromoaminotriazole 3 in 60% yield with a tiny amount of diamine byproduct (<5% yield). On the other hand, the amination did not proceed at all for the isomer of 5. It is clear that



Scheme 1 (A) Retrosynthetic analysis of sulfonylated ThTz (1). (B) Synthesis of 1. (C) Amination of PMB-triazole 5.

the reactivity of the triazole is significantly influenced by the position of the substituent. With the desired 3 in hand, we next aimed to construct the thiazole ring. Although the utilization of

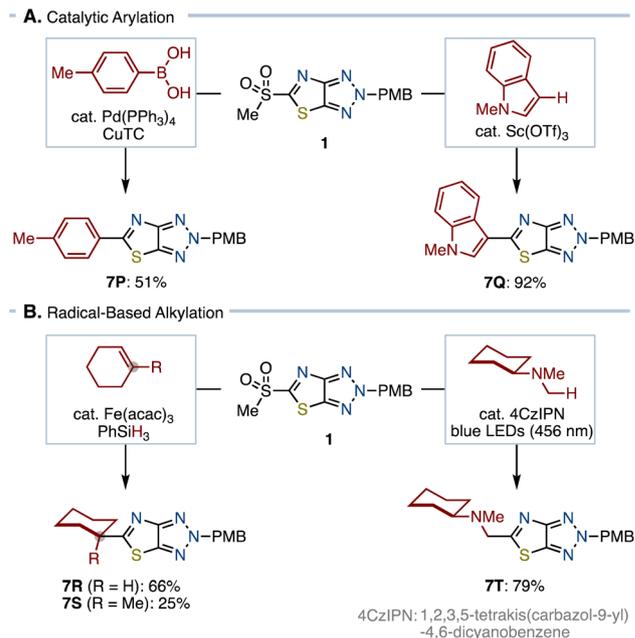




CS<sub>2</sub> as well as isothiourea resulted in failure, potassium ethylxanthate under the influence of a copper catalyst gave thio-carbonyl **2** through a carbonodithioate intermediate **6**, which spontaneously cyclized.<sup>13</sup> The final steps involved *S*-methylation of **2**, followed by oxidation with *m*CPBA, which furnished the desired novel heteroaromatic compound **1** as a stable solid. This synthetic route proved amenable to scale-up, allowing for the production of up to 5.7 g of **1** in a single batch.

To readily introduce a variety of substituents, we next embarked on functionalizing the sulfone moiety of **1** (Scheme 2). We initiated this process by exploring the  $S_NAr$  reaction capabilities with various amines in THF at 60 °C. Amination using both primary and secondary amines proceeded smoothly to give aminated ThTz **7A–7D** generally in good yields. Etherification using alcohol in the presence of NaH in THF was also found to be applicable. The use of primary and secondary alcohols as well as phenol efficiently provided the corresponding heteroaryl ethers (**7E–7I**). However, less nucleophilic tertiary alcohol furnished the product in a low yield (<20%, see the ESI†).

The versatility of the sulfone functionality of **1** was further demonstrated through its reactivity with thiols under the same conditions, leading to a range of thioethers **7J–7L** in moderate to good yields. Enolizable nucleophiles were also accommodated, synthesizing **7M** and **7N** by using the corresponding ketone and ester in the presence of a base. Moreover, removal of the sulfonyl group with NaBH<sub>4</sub> smoothly afforded **7O** in a good yield.



Scheme 3 Arylation and alkylation of **1**.

Further explorations into C–C bond formations such as arylation and alkylation using **1** were conducted. However, attempts using organometallic reagents such as organolithiums and organocuprates unfortunately resulted in failure (see the ESI†). Expecting high reactivity of the sulfone moiety toward transition metal catalysts,<sup>8</sup> we decided to use metal-catalyzed cross-couplings (Scheme 3A). As a result, we found that conditions with the Pd(PPh<sub>3</sub>)<sub>4</sub> catalyst and copper thiophene-2-carboxylate (CuTC)<sup>14</sup> realized cross-coupling between **1** and *p*-tolylboronic acid, furnishing **7P** in 51% yield. Likewise, we uncovered that Sc(OTf)<sub>3</sub><sup>15</sup> can catalyze coupling of **1** with *N*-methylindole, which gave **7Q** in 92% yield. However, these two metal-catalyzed protocols given above were not applicable for alkylations. Focusing on the reactivity of sulfones toward radical *ipso*-substitution, we next explored radical-based reactions (Scheme 3B).<sup>16</sup> Guided by Baran's protocol,<sup>17</sup> we identified that Fe-catalyzed coupling of **1** with alkenes in the presence of silane can provide alkylating products **7R** and **7S**. This protocol allowed for constructing a quaternary carbon center, albeit in a low yield of 25% (**7S**). Furthermore, it was found that photoredox-catalyzed aminoalkylation was possible. Under the photo-irradiated conditions with a photosensitizer,<sup>18</sup> **1** and *N,N*-dimethylcyclohexylamine reacted to provide **7T** in 79% yield.

Overall, the incorporation of a sulfone group on the thiazole moiety of **1** enabled a uniquely diverse range of molecular assemblies in generally good yields. This distinct reactivity, compared to that of other functional groups, highlights the potential of sulfone-functionalized thiazoles as versatile building blocks in synthetic chemistry, offering substantial flexibility for complex molecule construction.

Upon the success in installing a wide range of functional groups on the thiazole moiety, our next interest was aimed at the functionalization of the triazole ring (Scheme 4). Using **7D**

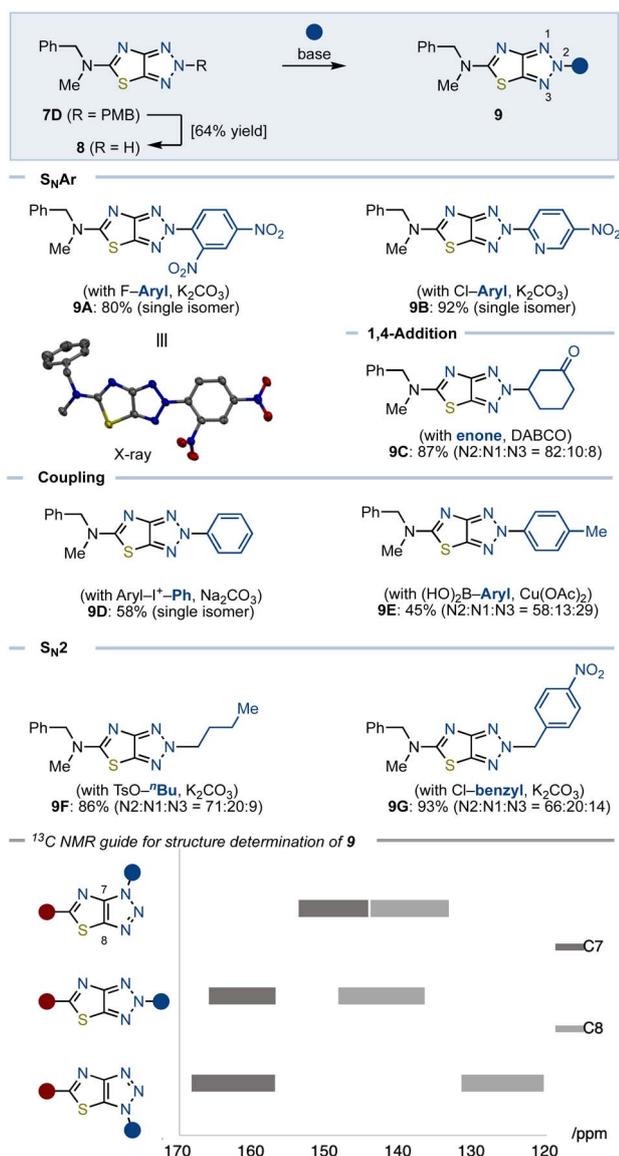


as a representative substrate, we first removed the PMB group using TFA to synthesize unprotected ThTz **8**. Subsequently, the  $S_NAr$  reaction of **8** with an electron-deficient dinitrofluorobenzene delivered heterobiaryl **9A** in 80% yield with a remarkable regioselectivity. X-ray crystallographic analysis of **9A** proved that this  $S_NAr$  reaction proceeded at the N2 position selectively. Similarly, 2-chloropyridine was able to react with **8** to furnish **9B** selectively in an excellent yield. Alkylation of the triazole moiety was also possible by conducting 1,4-addition of cyclohexenone, providing **9C**. In this case, the N2-alkylated product was obtained as a major product, but the other positional isomers were also generated (N2 : N1 : N3 = 82 : 10 : 8). The coupling reaction with aryl halides using a Pd catalyst did not proceed,<sup>19,20</sup> however, the reaction with aryl iodonium salts was successful, yielding **9D** in a moderate yield.<sup>21</sup> Furthermore, the Chan–Lam coupling, although providing **9E** in a low yield and with low regioselectivity, demonstrated that the reaction

could indeed proceed under these conditions.<sup>22</sup> A simple  $S_N2$  reaction using alkyl electrophiles such as butyl tosylate and benzyl chloride delivered the corresponding alkylated products **9F** and **9G**, respectively. We currently assume that this N2-selectivity would be rationalized by the steric factor. Functionalization at the N1 and N3 positions was not preferred due to the steric repulsion between an electrophile and the thiazole ring (nitrogen and sulfur atoms, respectively). Thus, in certain arylation and alkylation reactions of **8**, perfect regioselectivity was not attained. However, from a positive perspective, the generation of these positional isomers is advantageous for the synthesis of diverse derivatives and for scaffold hopping applications. Notably, our preliminary investigations indicate that alkylation under acidic conditions, albeit with low yields, is selective for the N1 position (see the ESI† for details).

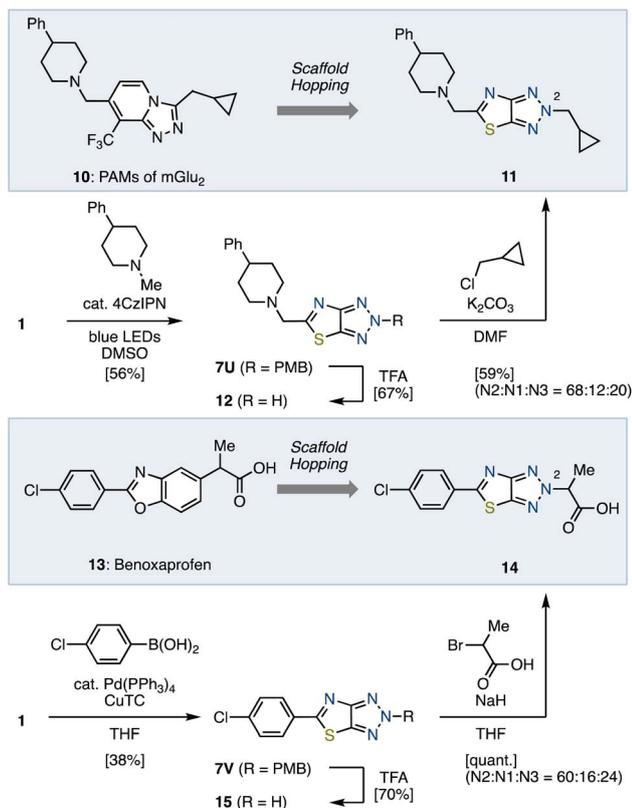
These products **9** pose challenges in structural determination due to the lack of protons on the present heterocycle. In this regard, results from X-ray crystallographic analysis as well as two-dimensional NMR analyses such as HMBC indicated that the <sup>13</sup>C NMR peaks at the C7 and C8 positions of this heterocycle could provide valuable information. As shown in Scheme 4, when the N1 position is functionalized, the <sup>13</sup>C NMR peaks of C7 and C8 appear at 145–153 ppm and 134–143 ppm, respectively. For N2-substituted derivatives, these peaks are observed at 158–167 ppm and 136–149 ppm, while for N3-substituted derivatives, they are found at 158–168 ppm and 120–131 ppm, respectively. It is evident that structural determination *via* <sup>13</sup>C NMR obviates the need for X-ray crystallographic analysis (see the ESI† for details).

Finally, aiming to harness the practical utility of our heteroaryl building block in medicinal chemistry, we explored the replacement of the heteroaromatic ring in known bioactive compounds (Scheme 5). This approach, commonly referred to as scaffold-hopping, is a strategic method used in medicinal chemistry to alter bioactivity, pharmacokinetics, and stability.<sup>23</sup> First, we focused on the triazolopyridine compound **10**, which is known as a positive allosteric modulator (PAM) of the metabotropic glutamate 2 receptor (mGlu<sub>2</sub>).<sup>24</sup> Replacement of the aromatic core of **10** was initiated by photo-irradiated radical alkylation of **1** with *N*-methyl-4-phenylpiperidine, synthesizing aminomethylated product **7U**. Upon removal of the PMB group, we performed *N*-alkylation using cyclopropylmethyl chloride, giving N2-alkylated **11** along with its positional isomers. These were successfully separated by silica-gel chromatography. In another example, we pursued the heteroarene replacement of benoxaprofen (**13**) with anti-inflammatory activity.<sup>25</sup> First, Suzuki–Miyaura-type arylation (**7V**), followed by removal of the PMB group provided heterobiaryl **15**. Subsequent alkylation using 2-bromopropionic acid resulted in the desired benoxaprofen mimic compound **14**. Although for scaffold hopping, the isomer substituted at the N1 position may also be more suitable in these examples, they illustrate the flexibility and potential of our heteroaryl building block for modifying and enhancing the properties of existing pharmacologically active compounds through scaffold-hopping, underscoring its value in the discovery and optimization of new therapeutic agents.



Scheme 4 Functionalization on the triazole ring.





Scheme 5 Heteroarene replacement of bioactive molecules.

## Conclusions

In conclusion, we have developed an unprecedented heteroaromatic system 2*H*-thiazolo[4,5-*d*][1,2,3]triazole (ThTz). Our developed synthesis of sulfonylated ThTz **1** proved to be scalable, enabling extensive functionalization of both the thiazole and triazole moieties. This demonstrates that **1** can serve as a highly versatile building block. The commercialization of our synthesized sulfonylated ThTz **1** paves the way for its use in scaffold-hopping strategies, with practical applications anticipated in medicinal chemistry. We believe that this work will provide a valuable tool for researchers seeking to explore new realms of chemical space in drug development.

## Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for **9A** and **11-N1** have been deposited at the CCDC under CCDC 2360991 and CCDC 2360992. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

## Author contributions

Y. O., M. K., and T. Y. conceived the thiazolotriazole ring. K. M. and J. Y. designed the sulfonylated heterocycle and directed this project. R. M., F. T., and T. K. performed all experiments. K. K.

performed X-ray crystallographic analysis. K. M. and J. Y. wrote the manuscript with feedback from all authors.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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