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Lewis base-catalyzed intermolecular triazene alkyne cycloaddition for late-stage functionalization and scaffold diversification

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3-Trifluoromethylpyrazole and its derivatives are of major interest to both the agrochemical and pharmaceutical industry for their diverse biological activities. Reported routes for the synthesis of 3-trifluoromethylpyrazoles are hindered by poor regioselectivity and limited scope of application. Here we report a directed Lewis base catalyzed intermolecular triazene-alkyne cycloaddition. It is featured that the combination of 1,8-diazabicyclo[5.4.0]undec-7-ene and 2,2,2-trifluorodiazoethane produces reactive triazene intermediates, which readily participate in cycloaddition reactions with terminal/internal alkynes, thus assembling densely substituted 3-trifluoromethylpyrazole scaffolds with environmental friendliness and operational simplicity. Synthetic utility of the protocol is highlighted by late-stage functionalization and scaffolds diversification. The practical value is also emphasized in potential platelet aggregation inhibitor synthesis.

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Pyrazoles are the core scaffolds of numerous biologically active molecules and exhibit innumerable applications in chemistry and biology. Pyrazole derivatives represent one of the most active classes of compounds and possess a broad range of chemical, biological, agrochemical, and pharmacological properties[1,2]. 3-Trifluoromethylpyrazoles, well-known examples of pyrazole derivatives, are key privileged scaffolds widely existed in many important biologically active molecules, agrochemicals, and pharmaceuticals (Fig. 1a)[3–11]. Conventional approaches for the construction of 3-trifluoromethylpyrazoles involve by the condensation of hydrazines with fluoroalkyl 1, 3-dicarbonyl compounds (Fig. 1b)[12–15]. However, these methods are limited by the need for prefunctionalized starting materials and by poor regioselectivities. Notwithstanding recent progress, these specific methods are incompatible with the extreme value of 3-trifluoromethylpyrazoles.

Recently, 2,2,2-trifluorodiazoethane (CF_3CHN_2) has emerged as an attractive synthon and has been extensively studied as a metal carbene precursor, 1,3-dipole, C- nucleophile/electrophile, and N-terminal electrophile[16–40]. Compelling examples have been reported on the utilization of CF_3CHN_2 as a fluorine-containing building block. Considerable efforts have also been expended on the construction of 3-trifluoromethylpyrazoles[25,30]. This has been challenging because the effective documented processes always rely on the use of stoichiometric catalyst or prefunctionalized starting materials and the explored methods are confined to a narrow range of substrates and limited scope of general applications. Due to the explored N-terminal electrophilicity of CF_3CHN_2[34] and triazenes as a versatile tool in organic synthesis[41] together with the convenient methods for the synthesis of CF_3CHN_2 in different solvents reported by Ma's group[42], the applications of the merger of N-terminal electrophilicity of CF_3CHN_2 and Lewis base to form triazene intermediates in organic synthesis and medicinal chemistry have rarely been studied.

Late-stage functionalization (LSF)[43–46], a valuable tool for directly introducing functional groups onto a bioactive compound, has merged as an important strategy for contemporary drug discovery due to enabling rapid structural diversity of drug candidates or drug-like molecules to ultimately affect their physiochemical properties such as ADME (absorption, distribution, metabolism, and excretion)[47]. In support of an on-going drug discovery strategy, novel LSF with high efficiency, selectivity, and operational simplicity is highly desirable. 3-Trifluoromethylpyrazoles, as COXs inhibition pharmacophore[8–10,48], their derivatives have been screened as clinical drug candidates and commercial pharmaceuticals. Drugs aimed at COXs inhibition is a billion opportunity, which has been inspiring medicinal chemists to search constantly for novel COX inhibitors. The attractive transition-metal-free transformation from

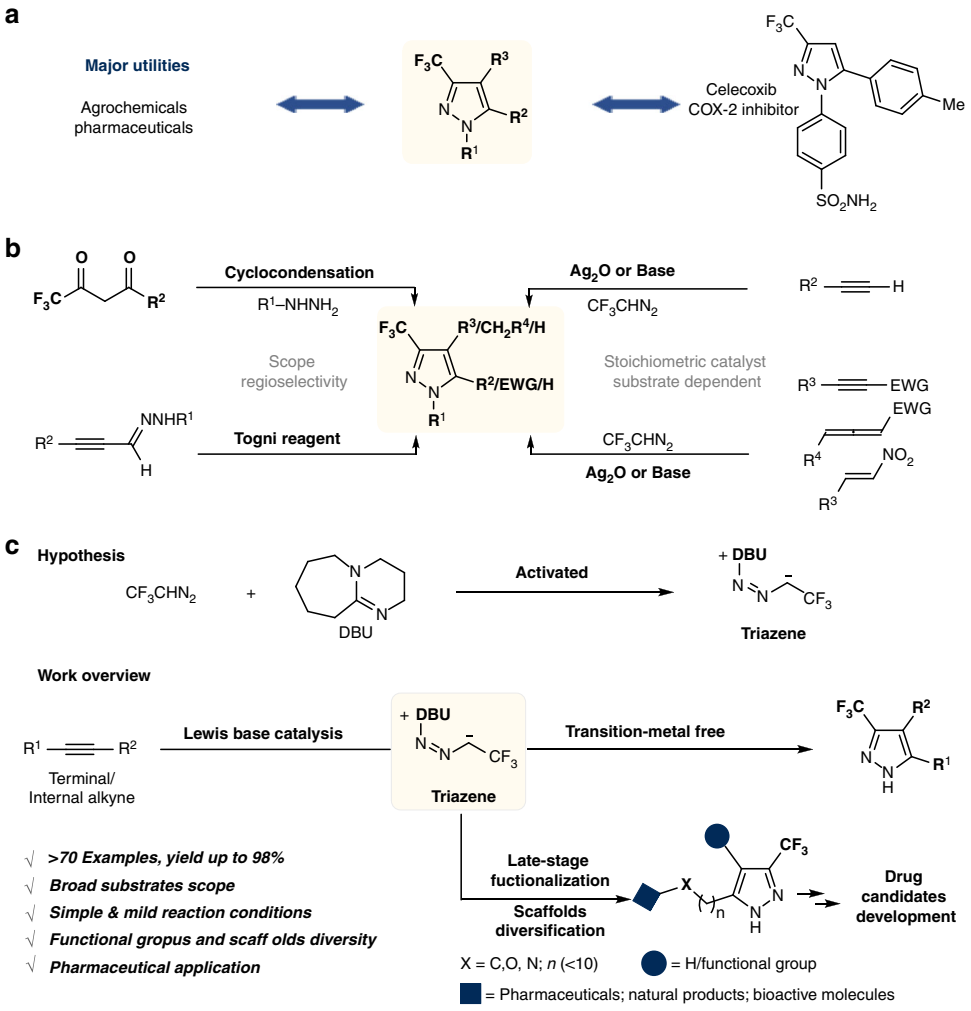
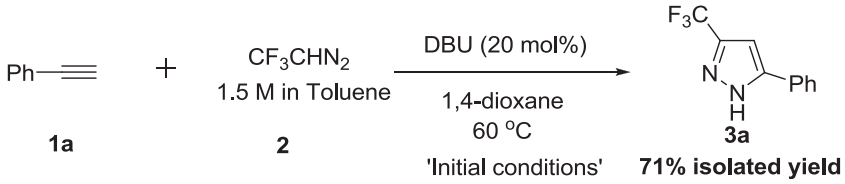


Fig. 1 Recent directions and envisaged approach for 3-trifluoromethylpyrazoles synthesis. **a** Importance of 3-trifluoromethylpyrazoles. **b** Known protocols of 3-trifluoromethylpyrazoles synthesis and limitations. **c** Proposed triazene-alkyne cycloaddition for the direct [3 + 2] assembly of 3-trifluoromethylpyrazoles, late-stage functionalization, and scaffolds diversification

Table 1 Selected optimization of reaction conditions



Entry	Variations from the 'initial conditions'	Yield (%)[a]
1	No DBU	<10
2	1,1,3,3-tetramethylguanidine instead of DBU	57
3	Triethylamine instead of DBU	65
4	4-dimethylaminopyridine instead of DBU	35
5	Tetramethylethylenediamine instead of DBU	51
6	1,4-diazabicyclo[2.2.2]octane instead of DBU	48
7	CF_3CHN_2 in 1,4-dioxane	69
8	CF_3CHN_2 in DCE	22
9	MeCN instead of 1,4-dioxane	14
10	Diethyl ether instead of 1,4-dioxane	31
11	70 °C	79
12	**80 °C**	**97**
13	10 mol% DBU, 80 °C	72

Unless otherwise specified, all reactions were carried out using phenylacetylene **1a** (0.3 mmol, 1.0 equiv.) and CF_3CHN_2 **2** (1.2 mmol, 4.0 equiv., 1.5 M in solvents), 20 mol% base (0.06 mmol, 0.2 equiv.), solvent (0.4 mL), 12 h
[a]Yield of the isolated product 3a after chromatography

the alkyne moiety embedded compounds with known biological properties to the corresponding 3-trifluoromethylpyrazole derivatives via LSF and scaffolds diversification is still rarely explored.

We hypothesized that by the combination of Lewis base catalysis and CF_3CHN_2 to generate reactive triazene intermediates could be employed in cycloaddition reactions with terminal/internal alkynes and open a new avenue for the assembly of densely functionalized 3-trifluoromethylpyrazoles. Also, the newly developed transformations could be hypothetically expanded to enable LSF of pharmaceuticals and diversification of clinical drugs, natural products, and bioactive molecules with 3-trifluoromethylpyrazole scaffold. Currently, there are more than 400 drugs and more than 4000 natural products bearing alkyne moiety (http://dnp.chemnetbase.com). Thus, there is a huge potential demand to develop a facile and generally applicable 3-trifluoromethylpyrazole synthetic procedure for LSF and scaffolds diversification.

Here we show a transition-metal free catalytic intermolecular triazene-alkyne cycloaddition (TAC) procedure for the synthesis of highly substituted 3-trifluoromethylpyrazoles and efficient installation of the title heterocycle into complex bioactive molecules in the context of LSF and scaffold diversification. Considering the important role of COXs inhibition in antiplatelet therapy, we also extend the protocol to assemble drug-like platelet aggregation inhibitors (Fig. 1c).

Results

Screening of reaction conditions. The designed Lewis base catalyzed TAC reaction was evaluated by using the simple terminal alkyne **1a** (1.0 equiv.) and CF_3CHN_2 **2a** (4.0 equiv., 1.5 mol/L in toluene) in the presence of DBU as Lewis bases at 60 °C. We found that the reaction proceeded smoothly and the cycloadduct **3a** was obtained in good yield when 1,4-dioxane was used as the external solvent (71%) (see Supplementary Table 1). Various bases were then evaluated, revealing that DBU was still essential for the high efficiency of this transformation (Table 1, entry 2–6). Further optimizations of reaction conditions indicated that the stock solvents of CF_3CHN_2 could significantly affect the reaction with decreased yield (Table 1, entry 7, 8). Attempts to increase the yield of **3a** were carried out with different reaction temperatures. To our delight, this transformation gave the almost quantitative yield at 80 °C (Table 1, entry 12). It was noted that the erosive yield was observed when the catalyst loading was reduced to 10 mol% (Table 1, entry 13).

Synthesis of 3-trifluormethylpyrazoles. With the established optimal reaction conditions in hand, the generality of this approach to synthesize a range of 3-trifluormethylpyrazoles was evaluated (Fig. 2). Various terminal alkynes **1** bearing electron-neutral, electron-rich, and electron-deficient substituents on the aromatic ring were found to be suitable for this reaction to form the corresponding pyrazoles (**3a–q**) with very good to excellent yields. Notably, heteroaryl terminal alkynes, electron-poor alkyne, and N-protected aliphatic alkyne were also readily converted into the desired products with high efficiency (**3r–x**). However, low yields were obtained when aliphatic alkynes were used in this transformation (**3y**, **3z**).

From the perspective of product diversity, internal alkynes **4** were also explored for this DBU-catalyzed TAC strategy (Fig. 2). The alkyne substrates bearing phenyl, ester, phosphonate diester, aldehyde, halides, indole, N, N-dimethylacetamide, N, N-dimethylethanethioamide, 2-pyridyl, methyl, and trifluoromethyl groups were all compatible, resulting in the synthesis of various desired densely functionalized 3-trifluormethylpyrazoles with moderate to excellent yields (**5a–m**). However, erosive yields were obtained with diphenylacetylene and phenyl

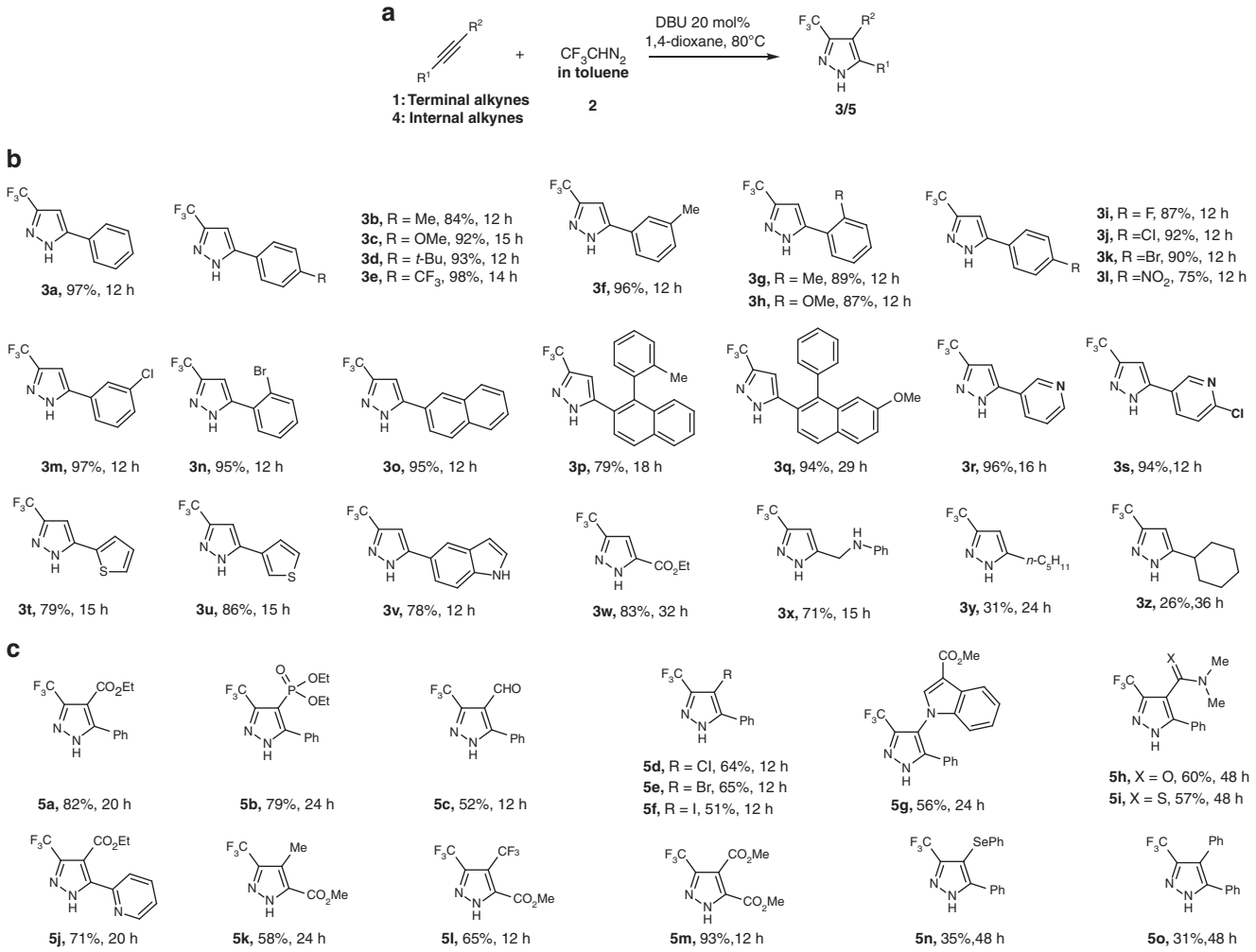


Fig. 2 Scope of terminal and internal alkynes. **a** Reaction scheme. **b** Terminal alkynes. **c** Internal alkynes. Reaction conditions: alkynes **1** or **4** (0.3 mmol, 1.0 equiv.) and CF_3CHN_2 **2** (1.2 mmol, 4 equiv., 1.5 M in toluene), DBU (0.06 mmol, 20 mol%), 1,4-dioxane (0.4 mL), 80 °C, 12–32 h; yields of isolated products **3** or **5** after chromatography

(phenylethynyl) selane as substrates (**5n**, **5o**). Notably, all the internal alkynes afforded densely functionalized 3-trifluormethylpyrazoles with high levels of regioselectivity. Based on the X-ray crystallographic analysis of compounds **5a** and **5k**, the configuration of the functionalized 3-trifluormethylpyrazoles products was assigned (see Supplementary Figs. 230 and 231). However, **5k** and **5l** possessed distinctive substituents compared with others functionalized pyrazoles mainly due to electronic and steric reasons.

Late-stage functionalization. To further indicate the utility of TAC procedures, we set out to perform LSF of pharmaceutically relevant molecules. As indicated in Fig. 3, erlotinib, used to treat nonsmall cell lung cancer and pancreatic cancer, was directly functionalized by our TAC strategy in 49% yield (**7a**). Furthermore, efavirenz, a commercially available anti-HIV drug, was also functionally obtained with product diversity in good yield (**7b**). In addition, the extension of the LSF to pargyline, an antihypertensive drug, was also achieved and formed the corresponding derivative with good yield (**7c**).

Scaffold diversification. To show the generality of TAC procedure, we set out to perform scaffold diversification to embed 3-trifluormethylpyrazole into various kinds of bioactive compounds, ranging from pharmaceutically relevant molecules and natural products to a panel of bioactive heterocycles. As indicated in Fig. 4, paciltaxel, hydroxycamptothecin, and fluorouracil, used to treat different types of cancer, was directly diversified by TAC strategy in very good yield (**9a–d**). Similar method was also directly applied to diversify efavirenz and yielded the product with high efficiency and mono/di selectivity (**9e**, **9f**). Interestingly, penicillin G, a commercially available antibiotic used to treat bacterial infections, was also functionally obtained in good yield. Artemisinin, medication approved for the treatment of malaria, could be varied in a TAC manner and was readily reached in 45% yield after this diversification (**9h**).

The scaffold diversification strategy in terms of various natural products was also explored. As shown in Fig. 4, natural products related with tetracyclic and pentacyclic triterpenes such as cholesterol and oleanolic acid were tolerated for this diversification with high yields (**9i**, **9j**). The variation of scaffold range to flavonoid and coumarin was also successful and assembled the related diversified products with very good yields (**9k**, **9l**). Lignins and alkaloids, such as podophyllotoxin and huperzine A, were also investigated in this TAC

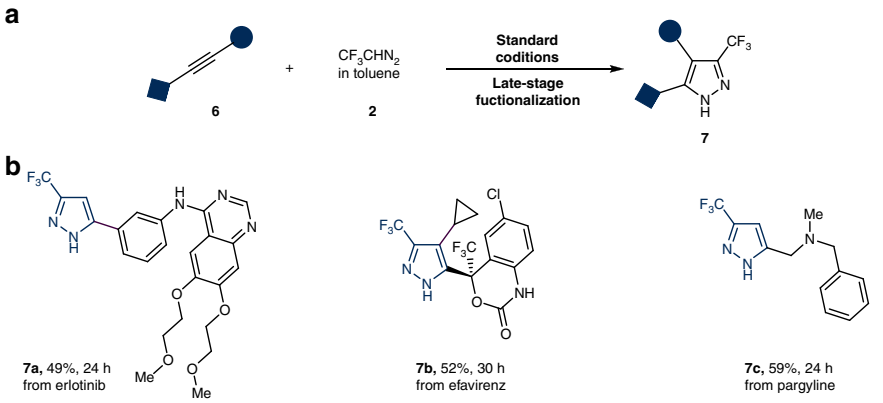


Fig. 3 Late-stage functionalization. **a** Reaction scheme. **b** Late-stage functionalization of marketed drugs. Reaction conditions: **6** (0.3 mmol, 1.0 equiv.) and CF_3CHN_2 **2** (1.2 mmol, 4 equiv., 1.5 M in toluene), DBU (0.06 mmol, 20 mol%), 1,4-dioxane (0.4 mL), 80 °C, 24-30 h; yields of isolated products **7** after chromatography

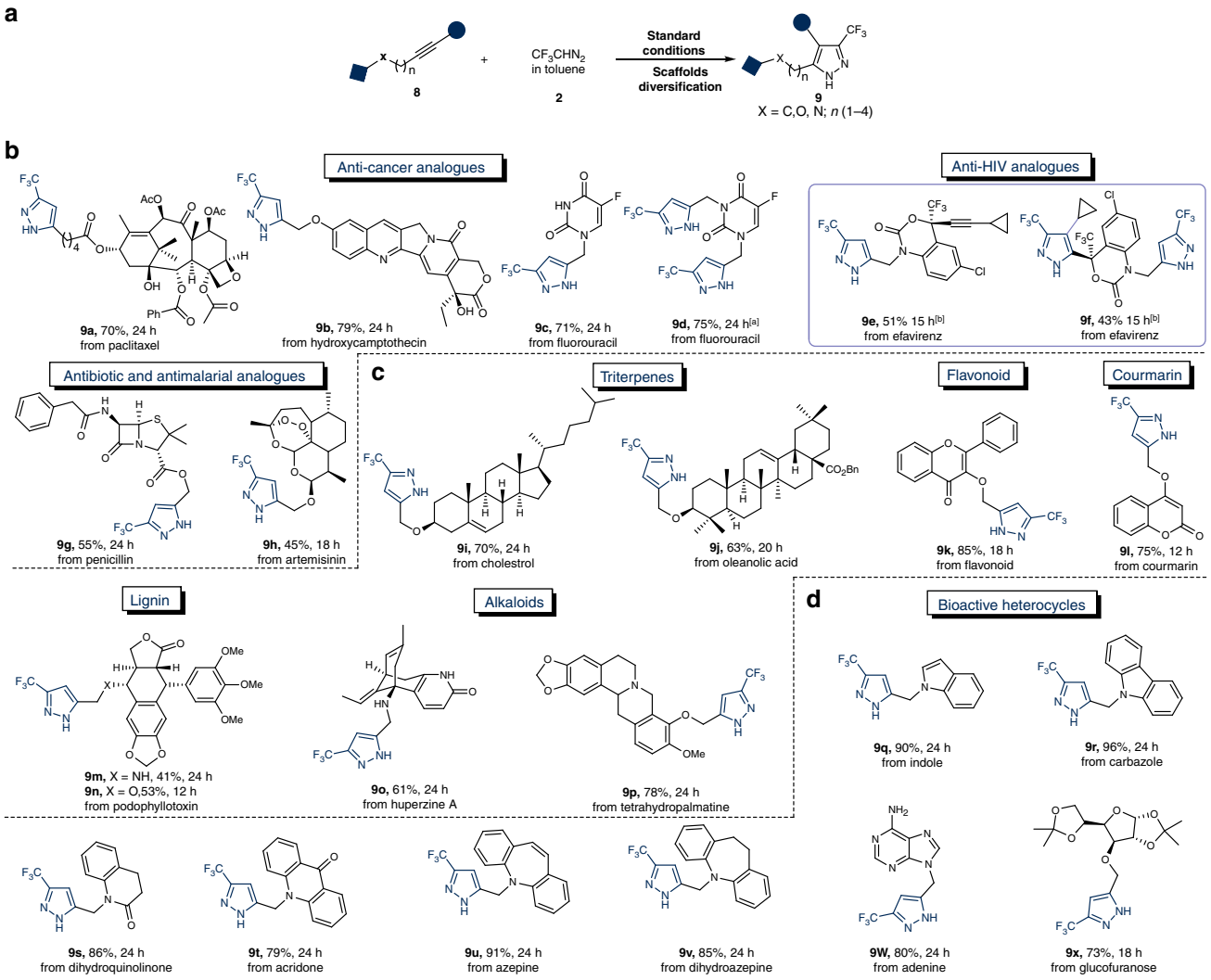


Fig. 4 Scaffold diversification. **a** Reaction scheme. **b** Diversification of related drug analogs. **c** Diversification of related natural products. **d** Diversification of bioactive heterocycles. Reaction conditions: **8** (0.3 mmol, 1.0 equiv.) and CF_3CHN_2 **2** (1.2 mmol, 4 equiv., 1.5 M in toluene), DBU (0.06 mmol, 20 mol%), 1,4-dioxane (0.4 mL), 80 °C, 24–30 h; yields of isolated products **9** after chromatography. [a]CF_3CHN_2 **2** (2.4 mmol, 8 equiv., 1.5 M in toluene). [b]CF_3CHN_2 **2** (2.4 mmol, 8 equiv., 1.5 M in toluene), and mono/di selectivity **(9e, 9f)**

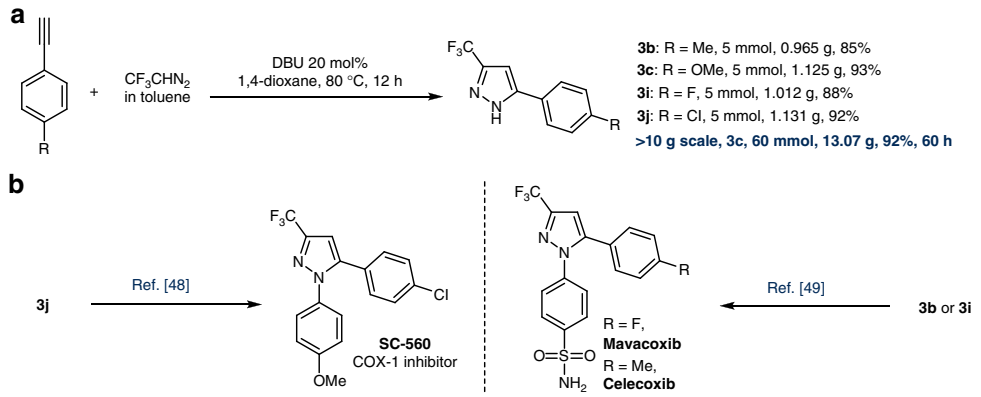


Fig. 5 Synthetic utility of TAC strategy. **a** Gram-scale and 10-g-scale synthesis. **b** Pharmaceuticals synthesis

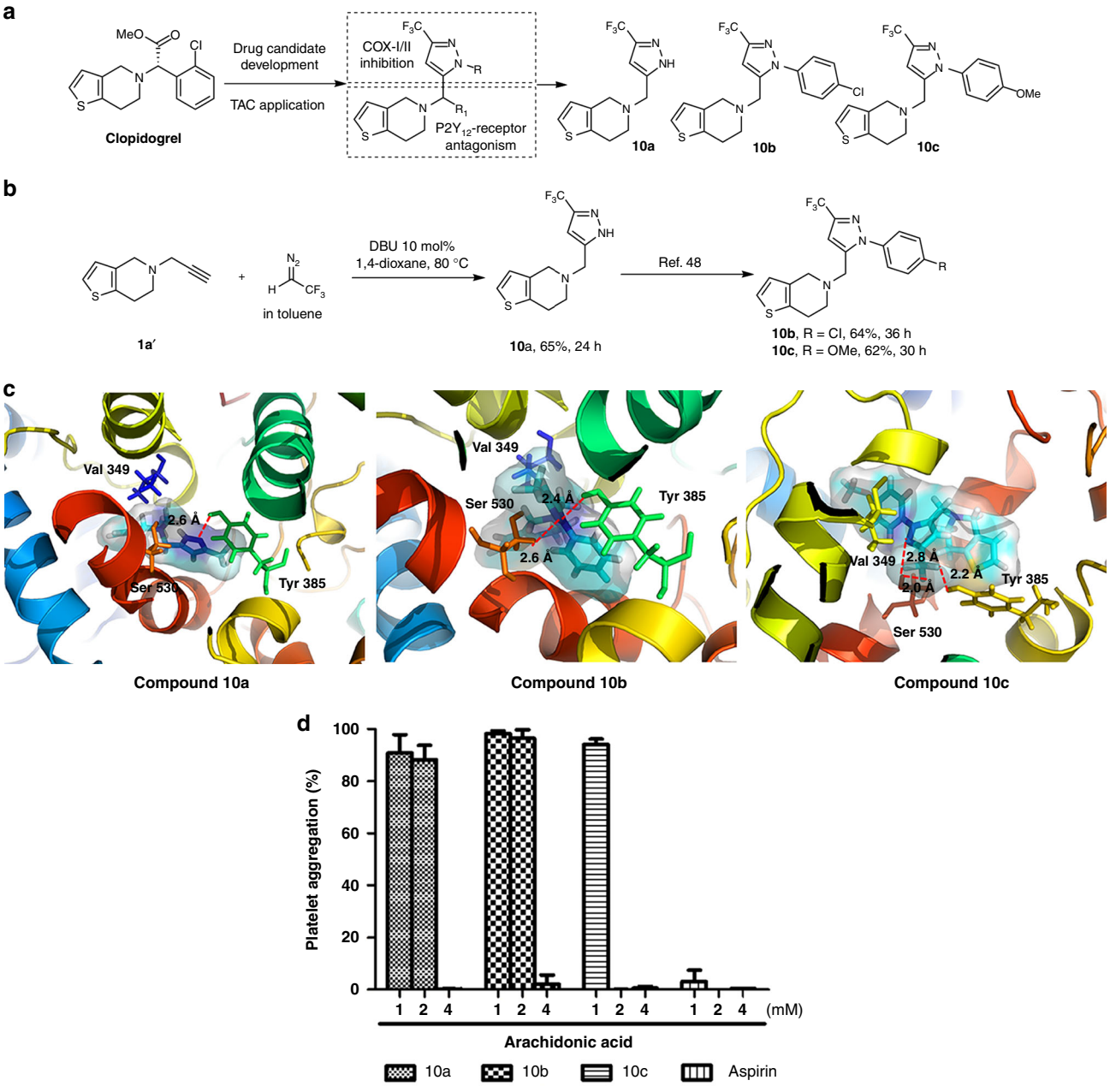


Fig. 6 Application of TAC strategy for drug-like molecule development. **a** Envisaged TAC method for the synthesis of antiplatelet drug-like molecules. **b** Synthesis of target molecules **10a**–**c**. **c** Stereo diagram of binding conformation of novel analogs **10a**–**c** with COX-1 isozyme (PDB:3N8Y). **d** The Platelet aggregation inhibition assay (error bars means ± standard deviation from three independent experiments)

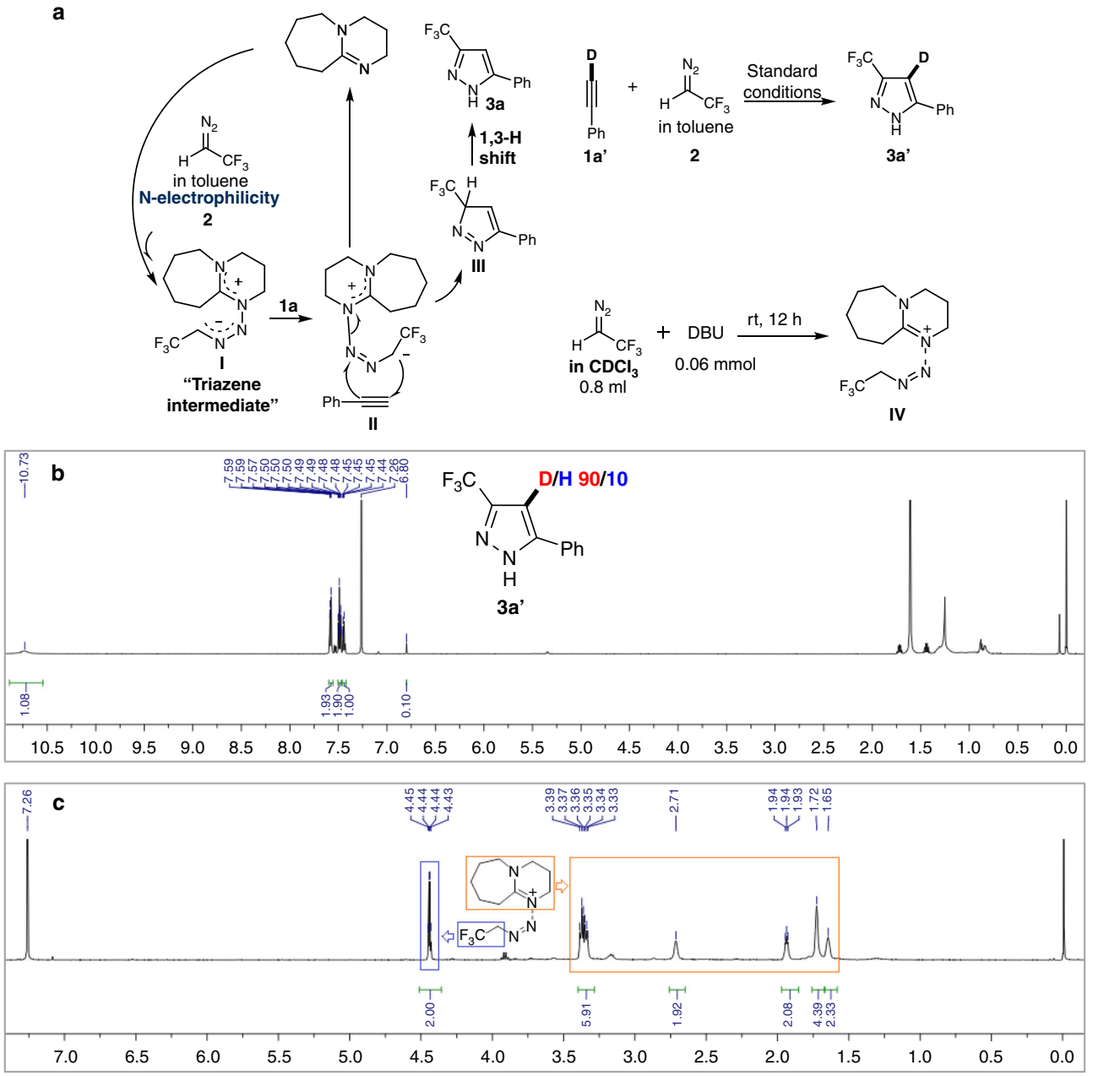


Fig. 7 Postulated mechanism for the TAC reactions. **a** Plausible catalytic cycle. **b** NMR study of deuterium-labeling experiment. **c** NMR study of DBU-CF_3CHN_2 interaction

transformation, giving the corresponding functionalized derivatives with moderate to good yields (**9m–o**). Interestingly, tetrahydropalmatine, applications as an adrenergic agent and a dopaminergic antagonist, was additionally found to be suitable for this diversification in 78% yield (**9p**).

Beyond scaffolds diversification of highly valuable pharmaceuticals and natural products. This TAC strategy also unlocked new pathways for the straightforward and efficient diversification of appealing bioactive molecules. Privileged N-containing heterocycles with various biological activities, such as indole, carbazole, dihydroquinolinone, acridone, azepine, and dihydroazepine were also engaged in this diversification to construct the corresponding functionalized products in high to excellent yields (**9q–v**). Furthermore, adenine, a fundamental component of adenine nucleotides found in both DNA and RNA, was also suitable for this diversification and afforded the functional derivative in very good yield (**9w**). Moreover, we also extended the strategy to protected glucofuranose and provided the diversified product with high efficiency (**9x**).

Applications. Gram-scale synthesis of **3b**, **3c**, **3i**, and **3j** using the established TAC system promoted smoothly without affecting the efficiency outcome of the reactions. To further highlight the potential industrial application of this transformation, a 10-g-scale synthesis of **3c** proceeded smoothly without erosion of the yield but only with increased reaction time (Fig. 5). In addition, the gram-scale products, as crucial intermediates, can be further

used to assemble pharmaceuticals including SC-560, mavacoxib, and celecoxib[49,50].

3-trifluormethylpyrazole synthesis in pharmaceutical applications. To further evaluate the pharmaceutical implication of this TAC protocol, the 3-trifluormethylpyrazole synthesis in drug discovery was also explored. Recently, diaryl-3-trifluormethylpyrazoles have been successfully screened as COXs inhibitor and exerted selectively COX-1 or COX-2 inhibition, such as SC-560 (selective COX-1 inhibitor). Considering the potential combined pharmacological effects of COXs inhibition and P2Y12-receptor antagonism in antiplatelet therapy[51,52], we showcased the structural features of clopidogrel (P2Y12-receptor antagonist) and SC-560 (COX-1 inhibitor) that allow novel analogs to mimic theirs functions and then 3-trifluormethylpyrazole scaffold was embedded onto thienopyridine ring via TAC strategy (Fig. 6a, b) (see Supplementary Methods and Supplementary Fig. 4). Later, we downloaded the crystal structure of COX-1 (3N8Y) from PDB and used Surflex-dock (SYBYL X-2.0) to complete molecular docking[53]. It was found that the N-atom of the pyrazole ring (**10a**, **10b**) showed H-bonding with Tyr385 (distance N–H = 2.6 Å for **10a** and 2.4 Å for **10b**, respectively), while **10c** H-bonded to Tyr385 and Ser530 (key amino-acid residues in COX-1 binding pocket) via the F-atom of the CF_3 group (distance F–H = 2.2 Å for Tyr385 and 2.0 Å for Ser530, respectively). In addition, the N-atom of the pyrazole ring (**10b**, **10c**) also showed H-bonding with Ser530 (distance N–H = 2.6 Å for **10b** and 2.8 Å for **10c**, respectively) (Fig. 6c). These results suggested that the synthetic analogs had potential COX-1 inhibition (see Supplementary Table 2). To prove the reasonable of the docking model and possible pharmacological properties, the platelet aggregation inhibition assay in vitro was evaluated in parallel with aspirin. We found **10c** could dramatically inhibit platelet aggregation which induced by arachidonic acid (Fig. 6d) (see Supplementary Fig. 5). The result indicated the promise of **10c** for future pharmaceutical applications.

Mechanistic proposal. A postulated mechanism for this Lewis base catalysis via the triazene intermediate is proposed (Fig. 7a)[54,55]. A deuterium-labeling experiment was conducted using deuterated alkyne (**1a′**) with CF_3CHN_2. Compound **3a′** with 90% deuterium incorporation onto the pyrazole ring was obtained, which supports our proposed 1,3-H shift. To confirm the DBU activation of CF_3CHN_2 to form triazene intermediate in the cycloaddition reaction, experiments between DBU and CF_3CHN_2 (in $CDCl_3$) were conducted (Fig. 7c). The postulated intermediate **IV** was captured from the crude ^{1}H NMR and LC–MS experiments (see Supplementary Figs. 6 and 7), which further supports the possible mechanism for this Lewis base catalysis.

Discussion

We have developed a TAC reaction to synthesize a series of 3-trifluormethylpyrazole heterocycles in high to excellent yields. In addition, with the newly explored transformation, the cycloaddition strategy is extended to enable LSF of pharmaceuticals and fuse various scaffolds, ranging from clinical drugs and natural products to bioactive heterocycles, which may aid the efficiency of lead compound and drug discovery processes. The protocol, featured in an operationally simple and environmentally friendly manner in comparison to transition-metal catalysis, exhibits a broad, structurally diverse substrate scope (>40 examples), and fused scaffolds scope (>25 examples). Considering the important role of COXs inhibition in antiplatelet therapy, we also developed drug-like platelet aggregation inhibitor synthesis using TAC protocol. Notably, further applications of Lewis base catalysis for the synthesis of related heterocycles will be reported in due course.

Methods

General procedure for the TAC reactions. A dried Schlenk tube is charged with the alkynes **1** (0.30 mmol, 1.0 equiv.), CF_3CHN_2 **2** (1.2 mmol, 4.0 equiv., and1.5 M in toluene), and 0.4 mL 1,4-dioxane. Subsequently, DBU (0.06 mmol, 20 mol%) is successively added. The resulting yellow solution is stirred at room temperature until the reaction is complete (as monitored by TLC). After the solvent is evaporated under reduced pressure, the crude product is purified via flash chromatography (pentane/ethyl acetate 10:1–3:1) to give the 3-trifluormethylpyrazoles **3** as white solids. A similar procedure was used for the synthesis of 3-trifluormethylpyrazole derivatives **5, 7, 9**, and **10**.

Synthetic applications. The procedures for 10-g-scale synthesis, pharmaceuticals synthesis, and drug-like molecules development are available in the Supplementary Methods and Supplementary Figs. 1–4.

Platelet aggregation inhibition assay. Please see Supplementary Methods and Supplementary Fig. 5.

NMR spectra. ^{1}H, ^{13}C, and ^{19}F NMR spectra of purified compounds are available in Supplementary Figs. 8–229.

Crystallography. X-ray crystallographic CIF files for compounds **5a** and **5k** are available in Supplementary Data 1, 2, and Supplementary Figs. 230, 231.

Data availability

The authors declare that all the data supporting the findings of this study are available within the paper and its supplementary information files, or from the corresponding author upon request. The X-ray crystallographic coordinate for structure reported in this article has been deposited at the Cambridge Crystallographic Data Center (CCDC 1886034, CCDC 1907151). These data could be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

S.P.L. and H.Z. performed the experiments and analyzed the experimental data with contributions of X.Y., Y.X., H.J.Z., M.W., and Z.R.D run the molecule docking, H.T.L. and G.B.S. developed the in vitro experiments, X.J.G. carried out the X-ray structure

determinations. L.W. directed the investigations, X.B.S. and L.W. prepared the manuscript with contributions of S.P.L. and H.Z.

Additional information

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