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Traceless solid-phase synthesis of thiazolo[4,5-*b*] pyridin-7(4*H*)-one derivatives

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A traceless and efficient solid-phase synthetic strategy was developed for the construction of thiazolo[4,5-*b*] pyridin-7(4*H*)-one derivatives. The synthesis was initiated on Merrifield resin and proceeded through a five-step sequence, with each transformation monitored in real time using ATR-FTIR spectroscopy. This approach enables controlled and modular introduction of structural diversity. A focused library containing three points of diversification was successfully constructed, affording a total of 60 derivatives. Stepwise yields ranged from 72% to 87%, demonstrating excellent synthetic efficiency and robustness.

Introduction

In recent years, heterocyclic compounds, particularly nitrogen-containing heterocycles—have continued to occupy a central role in medicinal and combinatorial chemistry,[1] owing to their widespread occurrence in natural products and clinically approved pharmaceuticals. With the rapid development of technologies such as DNA-encoded libraries (DELs) and high-throughput screening (HTS), structural diversity has become a critical factor in modern drug discovery.[2] Diverse heterocyclic scaffolds are not only essential for increasing hit rates in screening campaigns but also serve as key intermediates for structure–activity relationship (SAR) studies and lead compound optimization.[3] Therefore, the development of efficient, modular, and structurally diverse synthetic strategies for heterocycles has emerged as a major objective in current combinatorial chemistry. Among these scaffolds, quinolones represent a class of privileged nitrogen-fused scaffolds found in natural products,[4] biologically active molecules,[5] and synthetic intermediates,[6] clinically used 6-fluoro-4-quinolone-3-carboxylic acid derivatives, such as ciprofloxacin, gemifloxacin, and moxifloxacin, exhibit broad-spectrum antibacterial activity and are widely applied in clinical practice.[7] (Fig. 1A) Quinolone derivatives also possess a wide range of biological activities, such as anticancer,[8] anti-inflammatory,[9] and enzyme-inhibitory properties,[10] reinforcing their role as privileged pharmacophore in drug development. Despite their importance, existing synthetic methods for quinolone scaffolds face key limitations. Classical routes such as the Conrad–Limpach condensation,[11] Niementowski synthesis,[12] and Camps cyclization[13] have been developed to synthesize 4-hydroxyquinolines that can be easily transformed into 2-arylquinolin-4(1*H*)-ones *via* tautomerization (Fig. 1B) however, these require high temperatures, involve functional group incompatibility, and offer poor regioselectivity with unsymmetrical substrates. These drawbacks hinder their applicability in diversity-oriented synthesis (DOS) and make them unsuitable for solid-phase synthesis (SPS). Recent strategies employing Pd-catalyzed C–H activation[14] and carbonylation reactions[15] have shown promise yet often rely on high-pressure CO gas or PR functionalized substrates, limiting scalability and functional group tolerance. Hence, there remains a clear need for mild, scalable, and SPS-compatible strategies that can enable the efficient construction of privileged heterocyclic scaffolds. To address this challenge, we report a metal-free, mild, and traceless SPS approach for constructing thiazole[4,5-*b*] pyridin-7(4*H*)-one derivatives. Incorporation of a thiazole unit into the quinolone framework expands chemical space, provides additional derivatization sites, and retains key pharmacophoric features. The thiazole ring is a well-recognized privileged motif in drug design with documented antibacterial,[16] anti-inflammatory,[17] and enzyme-inhibitory properties,[18] and is a privileged motif in drug design (Fig. 1C). Integrating thiazole into a quinolone-like framework expands chemical space and provides a platform for discovering new lead candidates. Building on our prior success with five-membered heterocycle libraries,[19] we developed a parallelizable SPS platform that enabled the synthesis of a structurally diverse library of 60 thiazolo[4,5-*b*]pyridin-7(4*H*)-ones. To our knowledge, this represents the first systematic application of solid-phase methodology to access this fused scaffold. We anticipate that this strategy will provide useful tools for heterocyclic diversification and valuable molecular resources for early-stage drug discovery.

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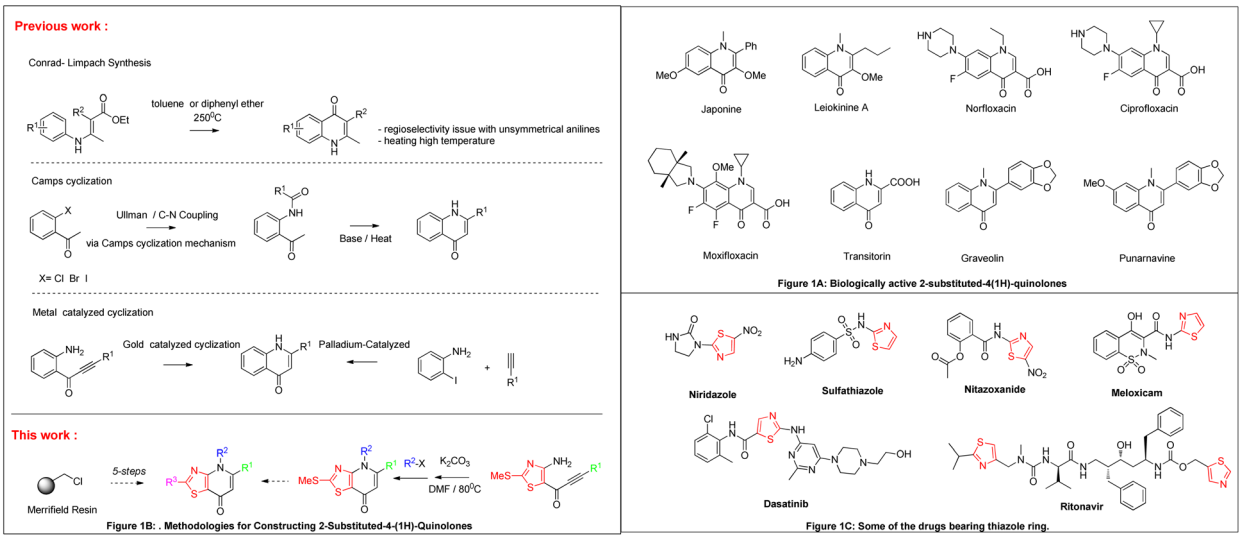
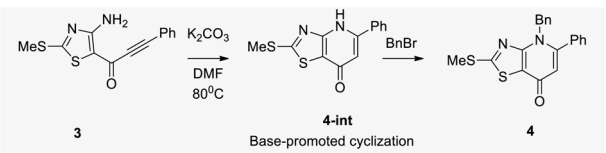


Fig. 1 Methodologies for constructing quinolones from different raw materials.

Results and discussion

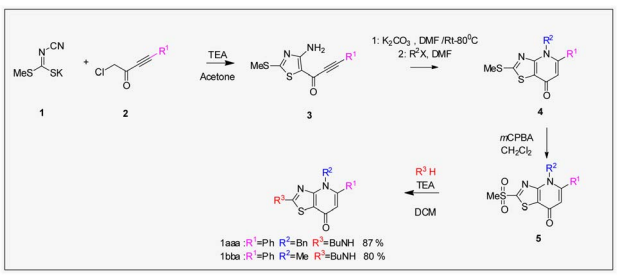
To optimize the cyclization conditions for the target compound 4-benzyl-2-(methylthio)-5-phenylthiazolo[4,5-*b*]pyridin-7(4*H*)-one (**4**), a model study was conducted using intermediate **3** to systematically evaluate the effects of various bases, solvents, and reaction temperatures (Table 1).Under standard conditions using DMF as the solvent, NaH proved to be the most effective base, affording the desired product in 90% isolated yield (entry 1). When K_2CO_3 was used instead, a comparable yield of 88% was obtained (entry 2), indicating its suitability for this transformation. In contrast, the use of Cs_2CO_3 led to a reduced yield of 70% (entry 3). Organic bases were less effective: TEA failed to deliver the cyclized product (entry 4), while DBU gave a moderate yield of 64% with an extended reaction time of 5 hours (entry 5), The effect of temperature was then investigated using K_2CO_3 as the base. At room temperature, the reaction gave only trace amounts of the product (entry 6). Yields improved slightly at 40 °C and 60 °C (entries 7 and 8), but remained lower (74–75%) compared to the optimal temperature of 80 °C, and required longer reaction times (8–10 h), indicating that elevated temperature facilitates this base-promoted cyclization. Solvent

Table 1 Reaction optimizes for synthesis of 4-benzyl-2-(methylthio)-5-phenylthiazolo[4,5-*b*] pyridin-7(4*H*)-one structures

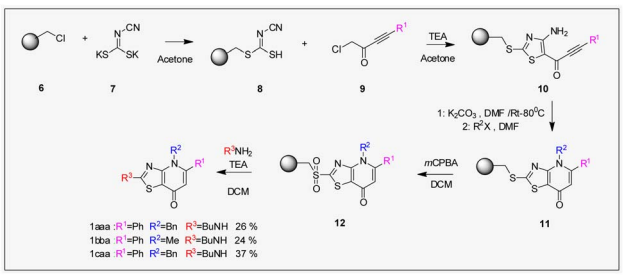


Entry[a]	Base (2 eq)	Solvent (2 ml)	Temp. (°C)	Time (h)	Yield[b d] (%)
1	NaH	DMF	80	2.5	90
2	K_2CO_3	DMF	80	2.5	88
3	CS_2CO_3	DMF	80	2.5	70
4	TEA	DMF	80	5	NR[c]
5	DBU	DMF	80	5	64
6	K_2CO_3	DMF	Rt	10	Trace
7	K_2CO_3	DMF	40	10	74
8	K_2CO_3	DMF	60	8	75
9	K_2CO_3	DMSO	80	8	77
10	K_2CO_3	Dioxane	80	8	NR[c]
11	K_2CO_3	Tol	80	8	NR[c]

[a] All reactions were carried out using intermediate **5** (50 mg). [b] Isolated yield. [c] No reaction. [d] All yields refer to isolated yields of compound **4**.



Scheme 1 Solution-phase of thiazolo[4,5-*b*] pyridin-7(4*H*)-one derivatives.



Scheme 2 Solid-phase synthesis of thiazolo[4,5-*b*] pyridin-7(4*H*)-one derivatives.

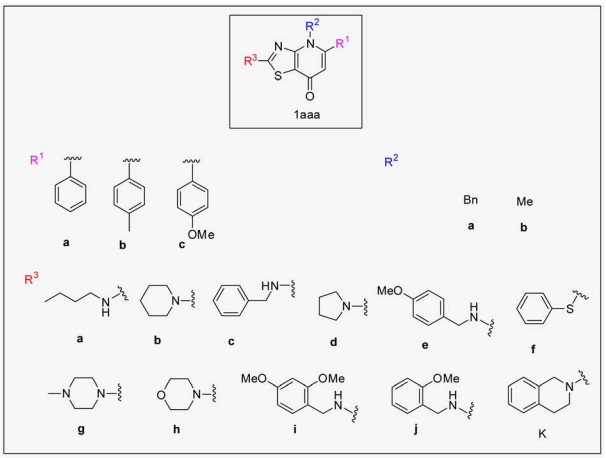
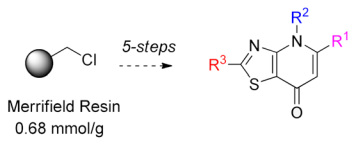


Fig. 2 Diversity elements of thiazolo[4,5-*b*] pyridin-7(4*H*)-one derivatives library.

screening revealed that neither toluene nor 1,4-dioxane supported the reaction under otherwise identical conditions (data not shown). However, switching to DMSO provided a moderate yield of 77% (entry 9), albeit still lower than that obtained in DMF. Taken together, DMF was identified as the optimal solvent, while NaH and K_2CO_3 were found to be the most effective bases. A reaction temperature of 80 °C offered the best balance between reactivity and compatibility. These conditions were thus adopted as the standard protocol for subsequent library construction.

After optimizing the cyclization conditions for compound **4**, the resulting thiazolo[4,5-*b*] pyridine scaffold was further oxidized in CH_2Cl_2 using *m*-chloroperoxybenzoic acid (*m*CPBA) to afford the corresponding sulfone intermediate **5**. Subsequent substitution of the sulfone group in **5** with butylamine ($BuNH_2$) in CH_2Cl_2 led to the formation of the target thiazolo[4,5-*b*] pyridine derivative **1aaa**, with an overall yield of 80% calculated

Table 2 Thiazolo[4,5-*b*] pyridin-7(4*H*)-one derivatives using the solid-phase synthetic



Entry[a]	R^1	R^2	R^3	Yield[b] (%)	Entry[a]	R^1	R^2	R^3	Yield[b] (%)
1	Ph	Bn	a	26	31	PhMe	Me	a	28
2	Ph	Bn	b	29	32	PhMe	Me	b	29
3	Ph	Bn	c	35	33	PhMe	Me	c	26
4	Ph	Bn	d	31	34	PhMe	Me	d	29
5	Ph	Bn	e	21	35	PhMe	Me	e	22
6	Ph	Bn	f	46	36	PhMe	Me	f	24
7	Ph	Bn	g	30	37	PhMe	Me	k	Trace[c]
8	Ph	Bn	h	35	38	PhMe	Me	h	23
9	Ph	Bn	i	40	39	PhMe	Me	i	28
10	Ph	Bn	j	23	40	PhMe	Me	j	23
11	Ph	Me	a	24	41	PhOMe	Bn	a	37
12	Ph	Me	b	26	42	PhOMe	Bn	b	44
13	Ph	Me	c	29	43	PhOMe	Bn	c	33
14	Ph	Me	d	30	44	PhOMe	Bn	d	50
15	Ph	Me	e	20	45	PhOMe	Bn	e	31
16	Ph	Me	f	38	46	PhOMe	Bn	f	56
17	Ph	Me	g	25	47	PhOMe	Bn	k	54
18	Ph	Me	h	21	48	PhOMe	Bn	h	55
19	Ph	Me	i	33	49	PhOMe	Bn	i	33
20	Ph	Me	j	29	50	PhOMe	Bn	j	35
21	PhMe	Bn	a	30	51	PhOMe	Me	a	30
22	PhMe	Bn	b	37	52	PhOMe	Me	b	32
23	PhMe	Bn	c	28	53	PhOMe	Me	c	25
24	PhMe	Bn	d	44	54	PhOMe	Me	d	36
25	PhMe	Bn	e	29	55	PhOMe	Me	e	20
26	PhMe	Bn	f	47	56	PhOMe	Me	f	41
27	PhMe	Bn	k	29	57	PhOMe	Me	k	Trace[c]
28	PhMe	Bn	h	38	58	PhOMe	Me	h	32
29	PhMe	Bn	i	30	59	PhOMe	Me	i	28
30	PhMe	Bn	j	34	60	PhOMe	Me	j	22

[a] Reaction was performed on 0.35 g scale of resin **12**. [b] Overall isolated yields of the final products (five steps). [c] Not isolated.

from compound **4**. The structure of compound **1aaa** (Scheme 1) was confirmed by ^{1}H NMR, and ^{13}C NMR spectroscopy.

Overall, this efficient and practical solution-phase sequence provides a feasible synthetic route and structural foundation for the solid-phase construction of thiazolo[4,5-*b*] pyridin-7(4*H*)-one derivatives to construct thiazolo[4,5-*b*] pyridin-7(4*H*)-one derivatives, a solid-phase synthetic route was developed employing X-substituted phenylpropyl chlorides, alkyl halides, and amines as key building blocks and diversity elements (Scheme 2). The sequence began with the formation of the known solid supported cyanocarbonimidodithioate **8**,[19e,20] generated *via* the reaction of Merrifield resin **6** with potassium cyanocarbonimidodithioate **7**. Following swelling of resin **8** in acetone, it was treated with 1-chloro-4-phenylbut-3-yn-2-one **9**, (the first diversity element) and triethylamine at room temperature. This led to the formation of the thiazole-containing resin **10** *via* Thorpe–Ziegler cyclization. The progress of the reaction was confirmed by FT-IR analysis, which showed characteristic NH_2 stretching vibrations at 3336 and 3480 cm^{-1} and an alkyne C≡C stretching band at 2100 cm^{-1} (see the SI). In parallel with solution-phase conditions, resin **10** was further modified by treatment with K_2CO_3 and (bromomethyl)benzene in DMF, yielding resin **11**. FT-IR analysis revealed the disappearance of NH_2 and alkyne stretching bands, and the appearance of new bands at 1340 cm^{-1} and 1100 cm^{-1}, confirming successful alkylation and structural transformation. Subsequently, oxidation of **11** with *m*CPBA in CH_2Cl_2 afforded sulfone intermediate **12**, as confirmed by the appearance of strong S=O stretching bands at 1342 and 1152 cm^{-1} in the ATR-FTIR spectrum. Finally, nucleophilic substitution with a representative amine such as *n*-butylamine was carried out on sulfone **12**, resulting in desulfonation and resin cleavage to release the target compound **1aaa**. This five-step solid-phase synthesis, starting from Merrifield resin **6**, provided compound **1aaa** in an overall yield of 26.8%. The structure of the purified final product was confirmed by ^{1}H NMR and matched that of the compound synthesized *via* solution-phase methodology, validating the reliability of the synthetic route. Using this solid-phase synthetic strategy, a structurally diverse library of thiazolo[4,5-*b*] pyridin-7(4*H*)-one derivatives was successfully constructed. To introduce molecular diversity, three points of variation were employed: aryl substituents with various functional groups at the R^1 position, methyl (Me) or benzyl (Bn) groups at R^2, and ten different nucleophiles (Fig. 2)—including amines and thiols—at R^3 (Table 2). Analysis of the library yields revealed that substitution at R^1 significantly influenced reaction efficiency. When R^1 was *p*-methoxyphenyl (PhOMe), the resulting compounds exhibited relatively high yields, ranging from 31% to 56% (entries 41–50), In contrast, derivatives bearing unsubstituted phenyl (Ph) or *p*-methylphenyl (PhMe) at R^1 afforded moderate to lower yields, typically ranging from 21% to 46% (entries 1–10) and 29% to 47% (entries 21–30), respectively. Variation at R^2 also affected the overall yields. In general, derivatives containing a benzyl group at R^2 gave higher yields than their methyl-substituted counterparts. For example, when R^1 = PhOMe, compounds with R^2 = Bn (entries 41–50) yielded 31–56%, whereas those with R^2 = Me (entries 51–60) gave lower yields of 20–41%. The nature of the nucleophile at R^3 also contributed to yield variation. Secondary amines, such as those in entries 42, 44, and 48, produced yields in the range of 44–55%. Similarly, primary aims (entries 41, 43, 45) gave comparable results, with yields between 31% and 55%.

Conclusion

In summary, inspired by the pharmacological relevance of the quinolone scaffold, we have established a traceless and modular solid-phase synthetic strategy for the construction of thiazolo[4,5-*b*] pyridin-7(4*H*)-one derivatives. This five-step sequence, initiated from Merrifield resin and monitored by ATR-FTIR spectroscopy, enabled diversification at three positions and afforded a focused library of 60 compounds with Stepwise yields ranged from 72% to 87%, The platform demonstrated robustness and flexibility, highlighting its potential as a general strategy for heterocyclic diversification. Importantly, as thiazolo[4,5-*b*] pyridin-7(4*H*)-ones represent quinolone-derived privileged scaffolds with reported biological activities, the compound library generated here provides a valuable foundation for subsequent structure–activity relationship (SAR) investigations. Future studies will focus on expanding the chemical space by incorporating additional thiazole–aminoamide intermediates, thereby. Further enhancing the applicability of this approach in medicinal chemistry.

Author contributions

S. H., J. M. contributed equally to this work. H. L., E. J. and G. Y. conceived and directed the project, wrote the original draft and revised the manuscript. All authors have approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting the findings of this study are available within the article and its supplementary information file (SI). Supplementary information: FT-IR spectra of solid-phase synthesis, detailed synthetic procedures, and NMR spectra for all new compounds. See DOI: **https://doi.org/10.1039/d5ra05809k**.

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