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Synthesis of thiazolo[4,5-*d*]pyrimidine derivatives based on purine *via* solid-phase synthesis†

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Solid-phase synthesis was employed to construct a library of thiazolo[4,5-*d*]pyrimidine derivatives. The free amide at the 5-position of the thiazole, which was previously difficult to introduce *via* the Thorpe-Ziegler reaction, was successfully optimized in solid-phase synthesis using a 2,4-dimethoxy-substituted scaffold, and using iodine as a catalyst, the reaction with aldehyde successfully synthesized thiazolo-pyrimidinone derivatives. To synthesize thiazolo[4,5-*d*]pyrimidine derivatives, the direct amination reaction using BOP was successfully optimized. By applying the optimized conditions to solid-phase synthesis, a library of 36 derivatives was constructed, achieving average yields of 63–93% over six steps.

Introduction

In drug development, the primary focus in the early stages is identifying potential active compounds through screening various structures, such as High Throughput Screening (HTS) and DNA-Encoded Library Technology (DELT).¹ Building a chemical library with diverse compounds has recently gained increasing attention as an essential aspect of drug development.² Solid-phase synthesis is a common method for building chemical libraries, valued for its simplified purification process. Solid-phase synthesis offers the advantage of reducing synthesis time because purification is carried out after each reaction through washing steps using solvents such as water, DMF, and methanol. Solid-phase synthesis also enables the synthesis of many compounds within a short period of time.³ Therefore, due to the advantages of solid-phase synthesis, research has been conducted not only on peptides but also more recently on the synthesis of heterocycles.⁴ However, solid-phase synthesis has several limitations, including the need to use excess reagents, reaction temperature, and the swelling effect of solvents.⁵ Accordingly, we are focusing on optimizing reactions using solid-phase synthesis to overcome

its synthetic limitations, aiming to synthesize a variety of structurally diverse derivatives. In particular, we are building a chemical library based on various five-membered heterocycles.⁶ Five-membered heterocycles such as thiazole, imidazole, thiophene, and pyrrole have already been shown to have pharmacological activity through extensive research and are used as initial candidates.⁷ In addition, recent drug development research has focused on modifying natural product scaffolds with verified bioactivity to synthesize compounds exhibiting a wide range of biological activities.⁸ This research explores the incorporation of five-membered heterocycles by modifying natural product scaffolds with validated biological activity. Even though purine has a relatively simple structure among natural products, it shows a broad spectrum of pharmacological activities.⁹ Purine has been widely studied by medicinal chemists because of its various biological activities. For instance, purine derivatives are not only a fundamental constituent of nucleic acids in the human body but also exhibit significant potential pharmacological activities in a wide range of therapeutic areas, including anticancer, anti-viral, antioxidant, and antimicrobial applications.¹⁰ Due to the pharmacological activities of these purine derivatives, many have been synthesized and pharmacologically evaluated. Notable examples include olomoucine, a reversible and selective inhibitor of CDKs, istradefylline, which is used alongside levodopa/carbidopa in the treatment of Parkinson's disease, and mercaptopurine, which is used as a chemotherapeutic agent (Fig. 1A).^{11,12} Because of these activities, not only purine derivatives but also various bioisosteres of purine have been synthesized and studied. Notable examples include thiazolo[4,5-*d*]pyrimidine derivatives, where the imidazole of purine is replaced with thiazole. These derivatives are actively

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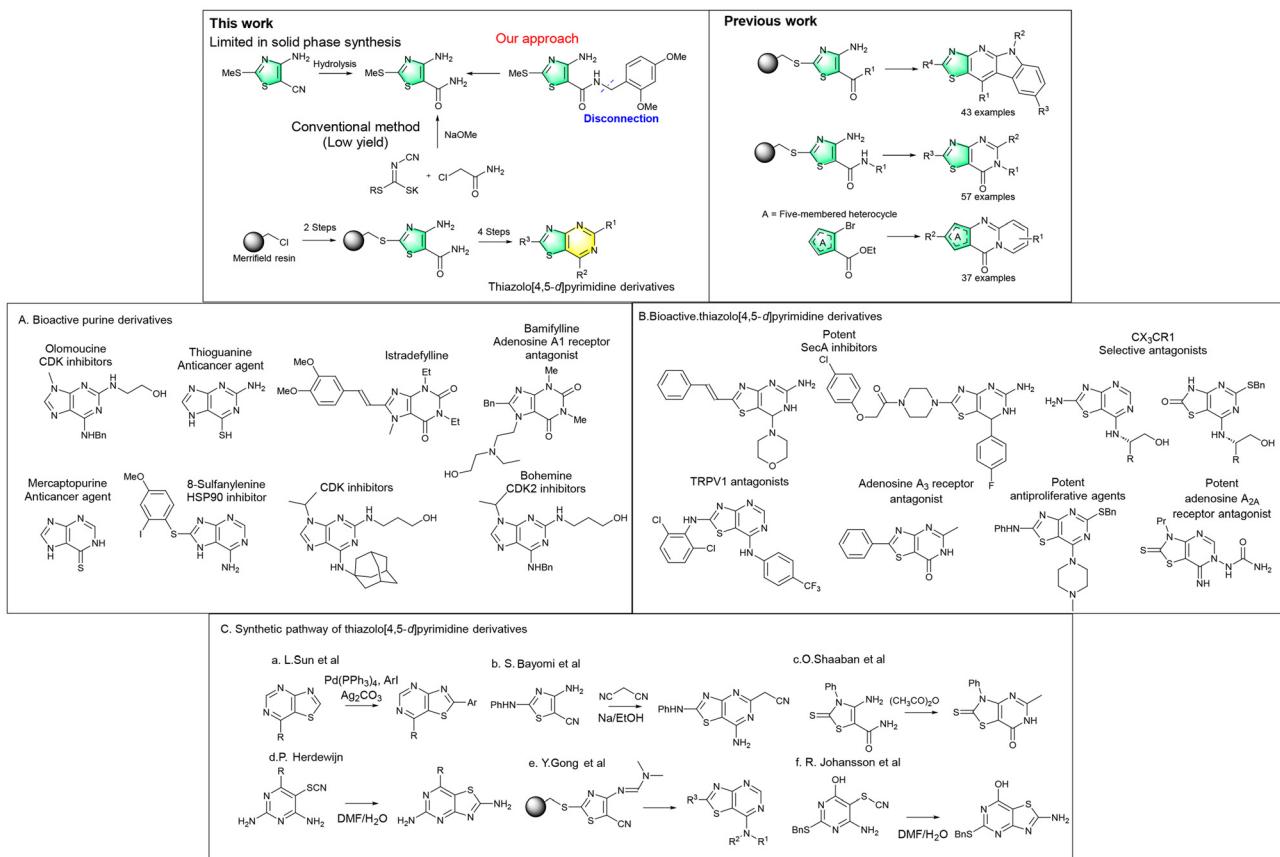


Fig. 1 Bioactive purine or thiazolo[4,5-d]pyrimidine derivatives and the synthetic pathway.

researched as potential inhibitors of SecA,¹³ potent and selective antagonists of the fractalkine receptor (CX₃CR1),¹⁴ potential adenosine A₃ receptor antagonists,¹⁵ TRPV1 antagonists *etc.* (Fig. 1B).^{16–20} Due to the diverse biological activities of thiazolo[4,5-d]pyrimidine derivatives, various synthetic approaches have been developed and reported. Sun's group substituted an aryl group at the C-2 position of thiazole using thiazolo[4,5-d]pyrimidine derivatives and aryl iodides.²¹ Additionally, Bayomi's group synthesized thiazolo[4,5-d]pyrimidine derivatives by reacting thiazolo-aminonitrile with malonitrile.²²

Shaaban's group utilized thiazolo-aminoamide and acetic anhydride to synthesize pyrimidinone structures *via* a cyclization reaction.²³ Furthermore, Herdewijn's group synthesized 2-aminothiazole structures by reacting 5-thiocyanatopyrimidine-2,4-diamine derivatives with DMF and water.¹¹ Recently, Gong's group synthesized thiazolo[4,5-d]pyrimidine derivatives using solid-phase synthesis with Merrifield resin (Fig. 1C).²⁴ In contrast to the previous methods, we introduce a synthesis of thiazolo[4,5-d]pyrimidine derivatives with three diversities. To synthesize the thiazole structure, we primarily use the Thorpe-Ziegler reaction.⁵ However, the Thorpe-Ziegler reaction requires the presence of an electron-withdrawing group (EWG) for the cyclization reaction, which limits the synthesis to EWGs only at the 5-position of the thiazole.²⁵ The amide group, however, is somewhat restricted in the Thorpe-Ziegler reaction, so we have

adopted an alternative method to synthesize thiazole. Building upon our previous work with thiazolo-pyrimidinone derivatives, we now introduce a method for constructing a thiazolo[4,5-d]pyrimidine derivative library through solid-phase synthesis, utilizing thiazolo-aminoamide intermediates.

Table 1 Optimization of the hydrolysis reaction

Entry ^a	Base (eq.)	Solvent	Time (min)	Temp. (°C)	Yield ^c (%)
1	DBU (1.2)	H ₂ O	10	100	65
2	DBU (0.6)	H ₂ O	10	100	39
3	DBU (0.3)	H ₂ O	10	100	22
4	DBU (1.2)	H ₂ O/dioxane	10	100	84
5	DBU (1.2)	H ₂ O	30	100	96
6	DBU (1.2)	H ₂ O	10	150	Quantitative
7	DBU (0.3)	H ₂ O	10	150	91
8 ^b	NaOH (1.2)	NH ₃ ·H ₂ O/DMSO	180	80	84
9 ^b	NaOH (1.2)	H ₂ O/DMSO	180	80	85
10 ^b	NaOH (1.2)	NH ₃ ·H ₂ O	20 h	80	14
11 ^b	DBU (1.2)	H ₂ O/DMSO	120	80	54

^a All reactions were performed on 3 (100 mg) in solvent (2 mL) using MW. ^b Reaction was performed in an oil bath. ^c Isolated yield.

Results and discussion

Two synthetic routes were considered for the synthesis of the thiazolo-aminoamide **4** core intermediate. The first involved reacting potassium-methyl cyanocarbonimidodithioate **2** with bromoacetonitrile to synthesize thiazolo-aminonitrile **3**, followed by hydrolysis of the nitrile to functionalize the compound with an amide group. However, most of the synthesis conditions involved the presence of water, which made it unsuitable for solid-phase synthesis under microwave (MW) conditions. Additionally, the swelling effects of solvents like water or DMSO were not favorable for the reaction (Table 1).

Therefore, a new synthetic route was selected. Using the previously studied method for synthesizing thiazolo-aminoamide, compound **8** was synthesized with an 87% yield. Next, the 2,4-dimethoxy group was removed by reacting with TFA, resulting in the thiazolo-aminoamide core structure **4** with an 81% yield.

To synthesize a thiazolo[4,5-*d*]pyrimidine **5** structure with diversity in *R*¹, iodine was used as a catalyst to react with the aldehyde.²⁶ In the case of direct annulation reactions using iodine, various conditions were tested to optimize the reaction, and an aldehyde scope experiment for solid-phase synthesis was conducted under the optimized conditions (Table S1†).

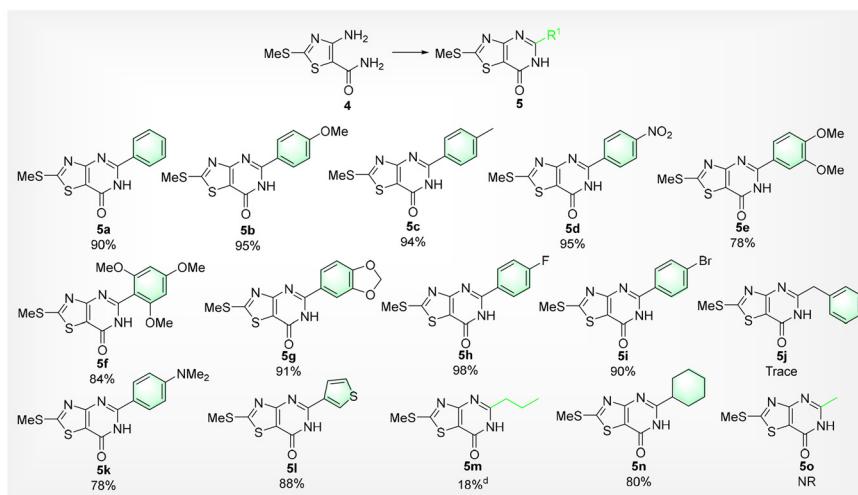
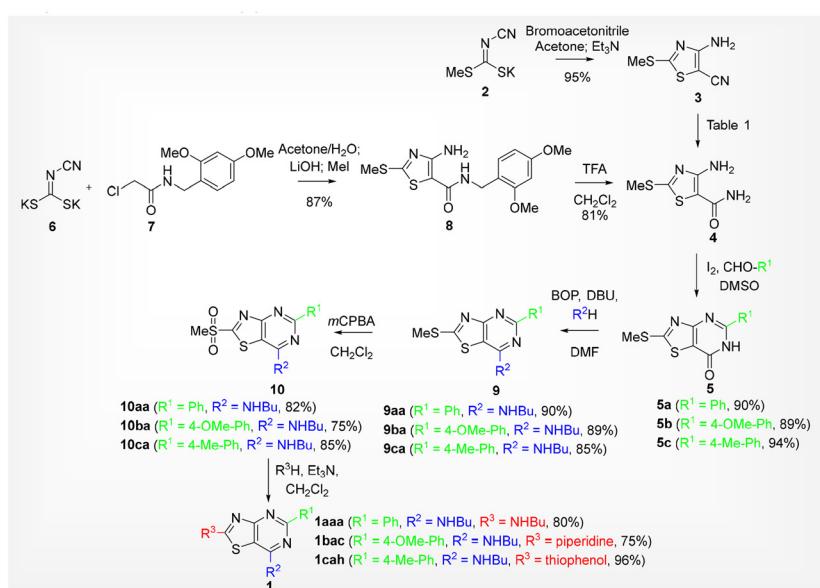
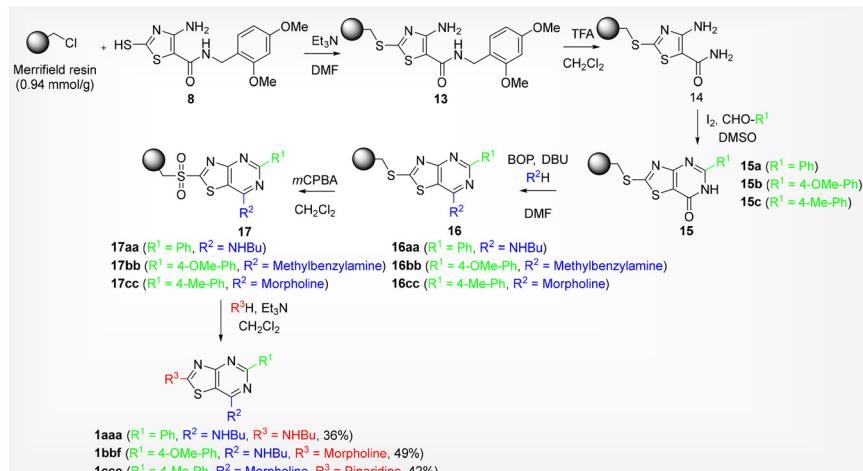


Fig. 2 Oxidative cyclization reaction scope.^{a–c} ^aAll reactions were performed on **4** (0.53 mmol) using iodine (0.053 mmol), aldehyde (0.636 mmol), and DMSO (3 mL) at 100 °C under open air. ^bPurification was carried out by precipitation using water. ^cAll compounds were isolated, and the yields were measured. ^dIsolation was carried out through silica gel column chromatography.



Scheme 1 Synthetic pathway of thiazolo[4,5-*d*]pyrimidine **1** derivatives.





Scheme 2 Solid-phase synthesis of thiazolo[4,5-d]pyrimidine 1 derivatives.

Most compounds were precipitated using water without the need for work-up or column chromatography and were confirmed to have very high purity.

For aldehydes such as benzaldehyde, anisaldehyde, tolualdehyde, and 4-nitrobenzaldehyde, yields of 90–95% were achieved (Fig. 2, **5a**, **5b**, **5c**, and **5d**). Benzaldehydes with methoxy groups, such as 3,4-dimethoxy, 2,4,6-trimethoxy, and piperonal, were obtained with yields from 78 to 91% (**5e**, **5f**, and **5g**). Additionally, when halogen groups like F and Br were present on the phenyl group, the yields remained unchanged (**5h** and **5i**). However, phenylacetaldehyde showed significant impurities when analysed by NMR, suggesting that side reactions occurred. This is presumed to be due to the activation of the benzylic position of the pyrimidine ring, leading to additional reactions (**5j**). Moreover, 4-dimethylaminobenzaldehyde was obtained with a yield of 78% and 3-thiophenecarboxyaldehyde was obtained with a high yield of 88% (**5k** and **5l**). In contrast to aryl aldehydes, aliphatic aldehydes, except for cyclohexanecarboxyaldehyde, could not be precipitated with water and had to be isolated by column chromatography (**5m**, **5n**, and **5o**). Next, to synthesize thiazolo-pyrimidine **9** from thiazolo-pyrimidinone **5**, various conditions were tested to introduce substituents at the R² position (Table S2†). When coupling reagents such as HATU, EDC, DCC, and BOP were used, reactions proceeded only with HATU and BOP. Using these reagents, direct amination with butylamine at the R² position allowed for the synthesis of **9aa** with a yield of 90%.

To substitute various nucleophiles at the R³ position, *m*CPBA was used to oxidize the compound to a sulfone, followed by a desulfonylative nucleophilic substitution reaction to substitute the sulfone with butylamine, resulting in the synthesis of **1aaa** with an 80% yield (Scheme 1). Next, a library of thiazolo[4,5-d]pyrimidine derivatives was constructed using solid-phase synthesis based on the optimized solution-phase synthesis conditions (Scheme 2). The

Merrifield resin and the 4-amino-N-(2,4-dimethoxybenzyl)-2-mercaptopthiazole-5-carboxamide **12** synthesized *via* the Thorpe–Ziegler reaction were shaken in DMF to synthesize resin **13**. Amine and amide bond stretching were observed at 3488, 3428, and 3339 cm^{−1} in the FT-IR spectrum (Fig. 1S†). To remove the 2,4-dimethoxybenzyl group from resin **12**, TFA was used, and the mixture was stirred in CH₂Cl₂. The disappearance of the amine bond stretching at 3428 cm^{−1} and the appearance of a new amide carbonyl stretching at 1649 cm^{−1} were confirmed. Next, thiazolo-pyrimidinone resin **13** was synthesized through an oxidative cyclization reaction using iodine and benzaldehyde. During this process, the carbonyl stretching shifted to 1690 cm^{−1}, and the amine and amide IR peaks disappeared, as observed in the FT-IR spectrum. To substitute butylamine at the R² position of thiazolo-pyrimidinone resin **15**, thiazolo-

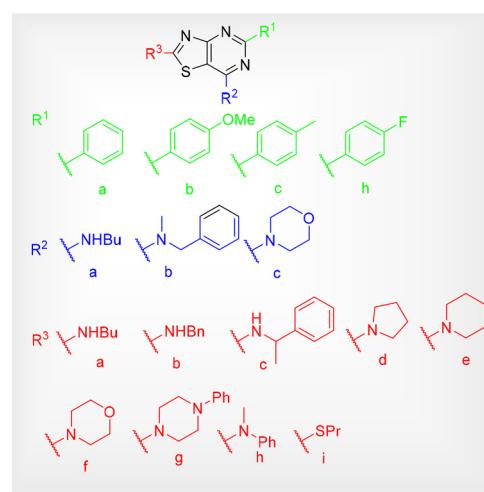


Fig. 3 Diversity elements of thiazolo[4,5-d]pyrimidine 1 derivatives via solid-phase synthesis.



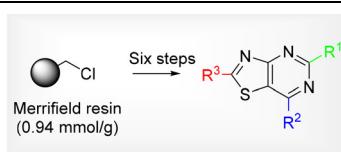
pyrimidine resin **16** was synthesized through a direct amination reaction using BOP. During this process, the carbonyl bond stretching at 1690 cm^{-1} was confirmed to disappear. No significant spectral changes were observed during the sulfone oxidation reaction with *m*CPBA. Compound **1aaa** was synthesized in six steps with a yield of 36% by reacting sulfone resin **17aa** with butylamine (Scheme 2). Using optimized solid-phase synthesis conditions, we selected several building blocks to construct a compound library (Fig. 3). In desulfonyative nucleophilic substitution reactions, secondary amines generally showed higher yields than primary amines. When R^1 was phenyl, no clear trend in yield was

Table 2 Solid-phase synthesis of thiazolo[4,5-*d*]pyrimidine derivatives

Entry ^a	R^1	R^2	R^3	Yield ^b (%)
1	Ph	a	a	36
2	Ph	a	b	19
3	Ph	a	c	Trace
4	Ph	a	f	38
5	Ph	a	g	25
6	Ph	a	h	NR
7	Ph	a	i	34
8	Ph	b	b	16
9	Ph	b	c	Trace
10	Ph	b	d	42
11	Ph	b	e	21
12	Ph	b	f	49
13	Ph	b	g	63
14	Ph	b	h	NR
15	Ph	c	e	42
16	Ph	c	g	59
17	4-OMe-Ph	b	b	10
18	4-OMe-Ph	b	e	33
19	4-OMe-Ph	b	f	36
20	4-OMe-Ph	c	b	7
21	4-OMe-Ph	c	d	10
22	4-OMe-Ph	c	g	38
23	4-Me-Ph	a	e	39
24	4-Me-Ph	a	g	34
25	4-Me-Ph	b	b	6
26	4-Me-Ph	b	e	19
27	4-Me-Ph	b	g	22
28	4-Me-Ph	c	a	Trace
29	4-Me-Ph	c	e	42
30	4-Me-Ph	c	g	42
31	4-F-Ph	a	e	60
32	4-F-Ph	a	f	28
33	4-F-Ph	a	g	74
34	4-F-Ph	b	a	56
35	4-F-Ph	b	b	38
36	4-F-Ph	b	e	66
37	4-F-Ph	b	f	38
38	4-F-Ph	b	g	51
39	4-F-Ph	c	a	17
40	4-F-Ph	c	e	23
41	4-F-Ph	c	g	23

^a All reactions were performed on resin **17** (300 mg) at room temperature. ^b Isolated yield.

observed with respect to the substituents on R^2 (Table 2, entries 1–16). In the case of nucleophiles with low nucleophilicity, such as *N*-methylaniline, the reaction did not proceed (entries 6 and 14). Additionally, in the case of amines with steric hindrance, such as phenylethanamine, the reaction proceeded to a limited extent; however, the desired product was obtained in a very low yield (entries 3 and 9). In contrast to other nucleophiles, benzylamine exhibited poor solubility regardless of the R^1 and R^2 substituents, which made separation difficult and led to a low isolated yield. When R^1 was 4-methoxyphenyl, typical yields were obtained for R^3 groups except for benzylamine (entries 17 and 20). Similarly, when R^1 was 4-methylphenyl, yields comparable to those obtained with phenyl were observed for all R^3 groups except for benzylamine and butylamine (entries 23–30). When R^1 was 4-fluorophenyl, overall yields were found to be higher compared to other R^1 substituents (entries 32–41).



Conclusions

In summary, a library of thiazolo[4,5-*d*]pyrimidine **1** derivatives was constructed through solid-phase synthesis. The compounds in the library exhibited three diversity elements, and the previously limited free-amide at the 5-position of the thiazole, synthesized *via* the Thorpe–Ziegler reaction, was introduced using 2,4-dimethoxybenzylamine. Furthermore, by optimizing the oxidative annulation reaction, which showed high yields when using the iodine catalyst, and applying this method to solid-phase synthesis, a total of 36 thiazolo[4,5-*d*]pyrimidine **1** derivatives were successfully synthesized. This thiazolo[4,5-*d*]pyrimidine library is expected to be useful in the early stages of drug development for identifying hit compounds.

Author contributions

J. M., H. L., and J. K. contributed equally to this work. T. L. and H. L. conceived and directed the project, wrote the original draft and revised the manuscript. J. M., H. L., J. K., S. H., G. Y., H. L., S. S., and Y. J. performed the experiments and collected and analysed the data. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and its ESI.†



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References

- (a) D. G. Brown, *J. Med. Chem.*, 2023, **66**, 7101–7139; (b) Y. Shi, Y. R. Wu, J. Q. Yu, W. N. Zhang and C. L. Zhuang, *RSC Adv.*, 2021, **11**, 2359–2376; (c) R. A. Goodnow Jr., C. E. Dumelin and A. D. Keefe, *Nat. Rev. Drug Discovery*, 2017, **16**, 131–147; (d) R. M. Franzini and C. Randolph, *J. Med. Chem.*, 2016, **59**, 6629–6644.
- D. G. Brown and J. Broström, *J. Med. Chem.*, 2018, **61**, 9422–9468.
- (a) W. A. Warr, *J. Chem. Inf. Comput. Sci.*, 1997, **37**, 134–140; (b) F. Balkenhohl, C. Bussche-Hünnefeld, A. Lansky and C. Zechel, Combinatorial Synthesis of Small Organic Molecules, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2288–2337.
- N. Cankařová, E. Schütznerová and V. Krchňák, *Chem. Rev.*, 2019, **119**(24), 12089–12207.
- (a) Z. S. Alghamdi, M. Klausen, A. Gambardella, A. Lilienkampf and M. Bradley, *Org. Lett.*, 2023, **25**, 3104–3108; (b) C. R. Nakaie, E. Oliveira, E. F. Vicente, G. N. Jubilut, S. E. G. Souza, R. Marchetto and E. M. Cilli, *Bioorg. Chem.*, 2011, **39**, 101–109; (c) J. A. Moss, *Curr. Protoc. Protein Sci.*, 2005, 18.7.1–18.7.19.
- (a) S. Hua, J. Moon and T. Lee, *Molecules*, 2025, **30**, 430; (b) J. Moon, S. Kim, S. Hua, H. Lee, J. Kim and T. Lee, *J. Org. Chem.*, 2025, **90**, 3078–3086; (c) J. Moon, H. Lee and T. Lee, *Asian J. Org. Chem.*, 2025, **14**, e202400795.
- (a) M. L. Fascio, M. I. Errea and N. B. D'Accorso, *Eur. J. Med. Chem.*, 2015, **90**, 666–683; (b) J. Akhtar, A. A. Khan, Z. Ali, R. Haider and M. S. Yar, *Eur. J. Med. Chem.*, 2017, **125**, 143–189; (c) Y. Wang, H. Wang, H. Xu, Z. Zheng, Z. Meng, Z. Xu, J. Li and M. Xue, *Chem. Biol. Drug Des.*, 2022, **100**, 534–552; (d) A. Lauria, R. Delisi, F. Mingoia, A. Terenzi, A. Martorana, G. Barone and A. M. Almerico, *Eur. J. Org. Chem.*, 2014, **16**, 3289–3306; (e) M. T. Chhabria, S. Patel, P. Modi and P. S. Brahmkshatriya, *Curr. Top. Med. Chem.*, 2016, **16**, 2841–2862; (f) A. Rouf and C. Tanyeli, *Eur. J. Med. Chem.*, 2015, **97**, 911–927.
- (a) C. Hui, Z. Wang, S. Wang and C. Xu, *Org. Chem. Front.*, 2022, **9**, 1451–1457; (b) A. G. Atanasov, S. B. Zotchev, V. M. Dirsch, The International Natural Product Sciences Taskforce and C. T. Supuran, *Nat. Rev. Drug. Discovery*, 2021, **20**, 200–216; (c) Z. Guo, *Acta Pharm. Sin. B*, 2017, **7**, 119–136; (d) N. Sabet Mehr, S. Abdolmohammadi and M. Afsharpour, Activated carbon/MoO₃: efficient catalyst for green synthesis of chromeno[d]pyrimidinediones and xanthenones, *Comb. Chem. High Throughput Screening*, 2021, **24**(5), 683–694; (e) S. Abdolmohammadi and M. Afsharpour, An ultrasound assisted cyclocondensation reaction for the efficient synthesis of [1]benzopyranopyrido[d]pyrimidines using porous graphene/MoO₃, *Appl. Organomet. Chem.*, 2021, **35**(1), e6028.
- (a) P. Debnath, *ChemistrySelect*, 2023, **8**, e202300998; (b) M. Rouchal, J. Rudolfova, V. Krystof, V. Vojackova, R. Cmelik and R. Vicha, *Int. J. Mol. Sci.*, 2021, **22**, 12675; (c) M. Otyepka, V. Krystof, L. Havlíček, V. Siglerová, M. Strnad and J. Koca, *J. Med. Chem.*, 2000, **43**, 2506–2513; (d) A. A. Abu-Hashem, O. Hakami, M. El-Shazly, H. A. S. El-Nashar and M. N. M. Yousif, *Chem. Biodivers.*, 2024, **21**, e202400050.
- (a) Y. Deng, M. Chen, J. Yi and Y. Zheng, *Phytochem. Lett.*, 2024, **59**, 10–14; (b) K. Vlkova, T. Gucky, M. Perina, E. Reznickova and V. Krystof, *Bioorg. Med. Chem. Lett.*, 2022, **60**, 128603; (c) J. Peng, S. Gao, J. H. Bi, J. Shi, L. Jia, Q. F. Pang, D. M. Zhao, Y. Fu and F. Ye, *J. Agric. Food Chem.*, 2024, **72**, 8933–8943; (d) A. Chaurasiya, C. Sahu, S. K. Wahan and P. A. Chawla, *J. Mol. Struct.*, 2023, **1280**, 134967; (e) M. D'Hooghe, K. Mollet, R. De Vreese, T. H. Jonckers, G. Dams and N. De Kimpe, *J. Med. Chem.*, 2012, **55**, 5637–5641.
- V. Chaudhary, S. Das, A. Nayak, S. K. Guchhait and C. N. Kundu, *RSC Adv.*, 2015, **5**, 26051–26060.
- S. Yuan, B. Yu and H. M. Liu, *Eur. J. Med. Chem.*, 2020, **205**, 112667.
- M. Y. Jang, S. De Jonghe, K. Segers, J. Anne and P. Herdewijnen, *Bioorg. Med. Chem.*, 2011, **19**, 702–714.
- S. Karlstrom, G. Nordvall, D. Sohn, A. Hettman, D. Turek, K. Ahlin, A. Kers, M. Claesson, C. Slivo, Y. Lo-Alfredsson, C. Petersson, G. Bessidskaia, P. H. Svensson, T. Rein, E. Jerning, A. Malmberg, C. Ahlgen, C. Ray, L. Vares, V. Ivanov and R. Johansson, *J. Med. Chem.*, 2013, **56**, 3177–3190.
- F. Varano, D. Catarzi, L. Squarcialupi, M. Betti, F. Vincenzi, A. Ravani, K. Varani, D. Dal Ben, A. Thomas, R. Volpini and V. Colotta, *Eur. J. Med. Chem.*, 2015, **96**, 105–121.
- A. D. Lebsack, B. J. Branstetter, M. D. Hack, W. Xiao, M. L. Peterson, N. Nasser, M. P. Maher, H. Ao, A. Bhattacharya, M. Kansagara, B. P. Scott, L. Luo, R. Rynberg, M. Rizzolio, S. R. Chapman, A. D. Wickenden and J. Guy Breitenbucher, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 40–46.
- P. M. Luthra, C. B. Mishra, P. K. Jha and S. K. Barodia, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1214–1218.
- Z. H. Li, X. Q. Liu, P. F. Geng, J. L. Ma, T. Q. Zhao, H. M. Wei, B. Yu and H. M. Liu, *MedChemComm*, 2017, **8**, 1655–1658.
- B. Kuppast and H. Fahmy, *Eur. J. Med. Chem.*, 2016, **113**, 198–213.
- F. Varano, D. Catarzi, E. Vigiani, D. Dal Ben, M. Buccioni, G. Marucci, L. D. C. Mannelli, E. Lucarini, C. Ghelardini, R. Volpini and V. Colotta, *Pharmaceuticals*, 2021, **14**, 657.
- Y.-X. Su, Y.-H. Deng, T.-T. Ma, Y.-Y. Li and L.-P. Sun, *Green Chem.*, 2012, **14**, 1979.

22 A. A. Abd Elhameed, N. S. El-Gohary, E. R. El-Bendary, M. I. Shaaban and S. M. Bayomi, *Bioorg. Chem.*, 2018, **81**, 299–310.

23 N. S. Habib, R. Soliman, A. A. El-Tombary, S. A. El-Hawash and O. G. Shaaban, *Arch. Pharmacal Res.*, 2007, **30**, 1511–1520.

24 S. J. Lim, A. Abdildinova and Y. D. Gong, *J. Org. Chem.*, 2021, **86**, 12517–12527.

25 (a) L. Luo, L. Meng, Q. Sun, Z. Ge and R. Li, *Tetrahedron Lett.*, 2014, **55**, 259–263; (b) A. Avadhani, P. Iniyavan, Y. Kumar and H. Ila, *J. Org. Chem.*, 2021, **86**, 8508–8515; (c) K. H. Narasimhamurthy, A. M. Sajith, M. N. Joy and K. S. Rangappa, *ChemistrySelect*, 2020, **5**, 5629–5656.

26 L. Luo, Q. Wang, Y. Xing, X. Peng and C. Hu, *Chem. Heterocycl. Compd.*, 2021, **57**, 1220–1229.