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# A multicomponent reaction for modular assembly of indole-fused heterocycles†

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Indoles are privileged chemical entities in natural products and drug discovery. Indole-fused heterocycles, particularly seven-membered ones, have received increasing attention due to their distinctive chemical characteristics and wide spectrum of bioactivities. However, the synthetic access to these compounds is highly limited. Herein, we report a unique multicomponent reaction (MCR) for modular assembly of indole-fused seven-membered heterocycles. In this process, indole, formaldehyde and amino hydrochloride could assemble rapidly to yield indole-fused oxadiazepines, and another addition of sodium thiosulphate would furnish indole-fused thiadiazepines. The biological evaluation disclosed the promising anticancer activity of these compounds. Furthermore, this MCR could be applicable in the late-stage and selective modifications of peptides. Therefore, this work provides a powerful strategy for indole functionalization and valuable tool for construction of seven-membered heterocycles.

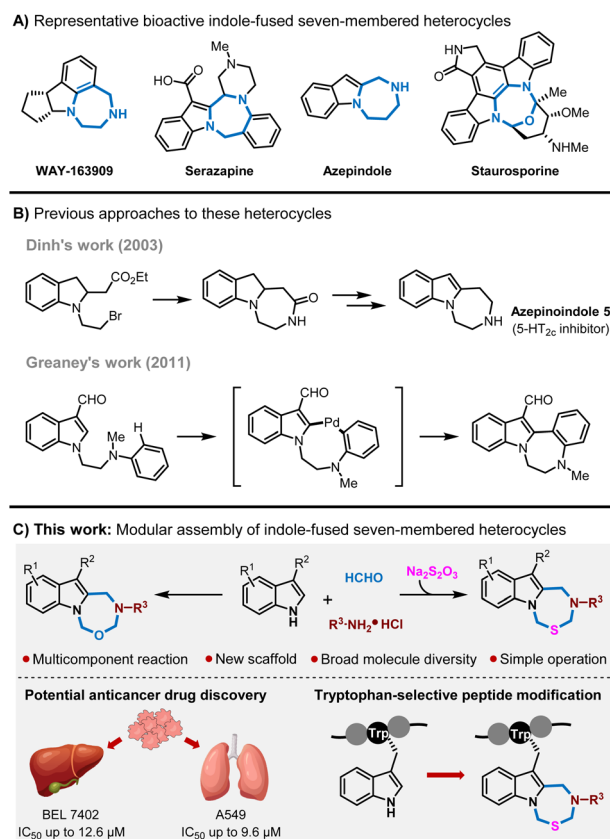
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## Introduction

Indole alkaloids are one of the largest classes of alkaloids in natural products. They possess diverse structural features and exhibit a wide spectrum of biological activities.<sup>1</sup> Moreover, the indole moiety serves as a privileged structure scaffold in pharmaceuticals and is present in a number of approved drugs.<sup>2</sup> Given the prevalence of indole derivatives, the exploration of indole functionalization toward new scaffolds, chemical space expansion and new biological discoveries has gained considerable interest in chemistry and biology.<sup>3</sup> In particular, indole-fused seven-membered heterocycles represent an important subunit of indole derivatives in pharmaceuticals.<sup>4</sup> For instance, indole-fused diazepine acts as a flexible core structure to fit differential targets in drug discovery, and there are a variety of candidates derived from this heterocycle, such as WAY-163909, serazapine, azepindole and staurosporine (Scheme 1A).<sup>5–8</sup> Correspondingly, the synthesis approaches to these compounds attract much attention. Typically, Dinh reported a multi-step synthetic route and Greaney disclosed a Pd-catalyzed oxidative C–H coupling reaction to access these compounds (Scheme 1B).<sup>8,9a</sup> Besides, several alternative methods were also



Scheme 1 Indole-fused seven-membered heterocycles.

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established.<sup>9</sup> However, most of these methods rely on complex starting materials, tedious synthetic procedures and limited structural diversity, which very much hamper the chemical space exploration of indole-fused heterocycles.

Multicomponent reactions (MCRs) are one-pot reactions that employ three or more reactants to form a single product which is incorporated with almost all the atoms from starting materials.<sup>10</sup> MCRs have emerged as a powerful tool in chemistry and biology research, and have also demonstrated success in the construction of new chemical entities.<sup>11</sup> With respect to indoles in MCRs, the current protocols mainly rely on the nucleophilicity of 3-position of indoles, while indole-based MCRs with new functionalization fashions and reaction modes for construction of new scaffolds remain to be investigated.<sup>12</sup> Very recently, our group developed a series of Mannich-like MCRs of benzofurans and indoles, in which the MCR process occurred in both C(sp<sup>2</sup>)-H and benzylic C(sp<sup>3</sup>)-H to achieve an unprecedented alkylaminative cyclization to realize piperidine-fusion on benzofuran and indole frameworks.<sup>11e,12f,13</sup> Inspired by these studies, we envisioned that the MCR process could occur on N-H and the adjacent 2-position of indoles simultaneously, and this might constitute new structured indole-fused heterocycles. Herein, we would like to report a multicomponent reaction for modular assembly of indole-fused seven-membered heterocycles (Scheme 1C).

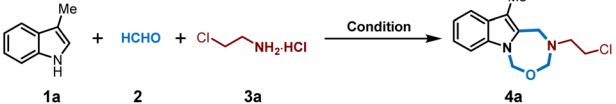
## Results and discussion

Initially, we commenced our investigation by employing 3-methylindole **1a**, formaldehyde **2**, and chloroethylamine hydrochloride **3a** as model substrates. We conducted the reaction by mixing these substrates in one-pot in the solvent of

acetic acid at 45 °C. Interestingly, a new product was formed in 37% yield (Table 1, entry 1) and the characterization identified this product as an intriguing indole-fused oxadiazepine, and this seven-membered heterocycle formation indicated a new multicomponent reaction occurrence. Furthermore, the structure of **4a** was unambiguously confirmed by X-ray analysis. The next screening of solvents showed that the use of DMF, DMSO and MeOH would give low yields (entry 2, entry 5 and entry 7) while THF, CH<sub>3</sub>CN, and DCM were optimal to significantly improve the yield (THF, 75%; CH<sub>3</sub>CN, 63%; DCM, 70%; entries 3–4 and entry 6). The solvent mixture of DMF and CH<sub>3</sub>CN was also effective giving **4a** in 65% yield (entry 8). Increasing the temperature to 60 °C gave a comparable yield (entry 9) while increasing to 70 °C would diminish the yield (entry 10). The following optimization by varying the amounts of **2** and **3a** did not further improve the yields. In addition, conducting this reaction on a gram scale afforded **4a** in 70% yield, thus underscoring the scalability of this process (see the ESI†).

With the optimized reaction conditions in hand, we then investigated the generality of this multicomponent reaction. As shown in Fig. 1, a variety of amino hydrochlorides were varied in this process as amine building blocks, and numerous flexible aliphatic amino hydrochlorides with a diversity of substituents, including chloride, bromide, sulfone, trifluoromethyl, cyano, phthalimide, alkene, alkyne, (hetero)cyclic rings, thiophene and functionalized aryl rings, were found compatible to furnish the corresponding indole-fused oxadiazepines in good to excellent yields (**4a–4t**). Besides, diverse amino acid derivatives have been successfully utilized in this reaction sequence, allowing for seamless integration with 3-methylindoles **1** and formaldehyde **2** to yield the targeted compounds (**4u–4aa**). This process effectively incorporates the chirality and functionality of amino acids directly into products, thereby broadening the chemical diversity of indole-fused heterocycles and offering ample opportunity for biology exploration and lead compound optimization. The use of amino acid derivatives such as glycine, alanine, leucine, and methionine has proven highly effective in this MCR process, consistently producing indole-fused oxadiazepines with good to excellent yields (51–89%). Moreover, the structure of **4s** was confirmed by X-ray analysis wherein the absolute configuration of the chiral center was determined to be identical with the starting amino building block, and it was reasonable that other amino acid derived oxadiazepines retained the same stereochemistry configuration. Aniline hydrochloride was also subjected to these MCRs and was not applicable. On the other hand, the scope of indoles was also investigated. As shown in Fig. 1, various substituted indoles with differential electron-donating and electron-withdrawing profiles and substitution positions were well compatible in this process, and those groups include fluoro, bromo, methoxy, alkene, alkyne, methyl, acetoxyl, ester, *N*-phthalimide, and amide, and this MCR process could convert these indoles to indole-fused oxadiazepines in moderate to good yields (**4ab–4ap**, 41–94%); and there were no significant differences in the yields for differential substitution while the electron-donating methoxy group on the indole ring would lead to slightly low yield probably due to their instability. Moreover, the structure of

Table 1 Reaction optimization<sup>a</sup>



Entry	<b>2</b> (equiv.)	<b>3a</b> (equiv.)	Solvent	Temp.	Yield <sup>b</sup> (%)
1	5	2	AcOH	45 °C	37
2	5	2	DMF	45 °C	32
3	5	2	THF	45 °C	75
4	5	2	CH <sub>3</sub> CN	45 °C	63
5	5	2	DMSO	45 °C	15
6	5	2	DCM	45 °C	70
7	5	2	MeOH	45 °C	Trace
8	5	2	DMF/CH <sub>3</sub> CN (1 : 1)	45 °C	65
9	5	2	THF	60 °C	73
10	5	2	THF	70 °C	54
11	5	4	THF	45 °C	71
12	10	2	THF	45 °C	74

<sup>a</sup> Reaction conditions: the reaction was conducted with **1a** (0.2 mmol, 1 equiv.), formaldehyde **2** (37% in water, 5 or 10 equiv.), **3a** (2 equiv. or 4 equiv.), solvent (2 mL). <sup>b</sup> Yield refers to the isolated product.



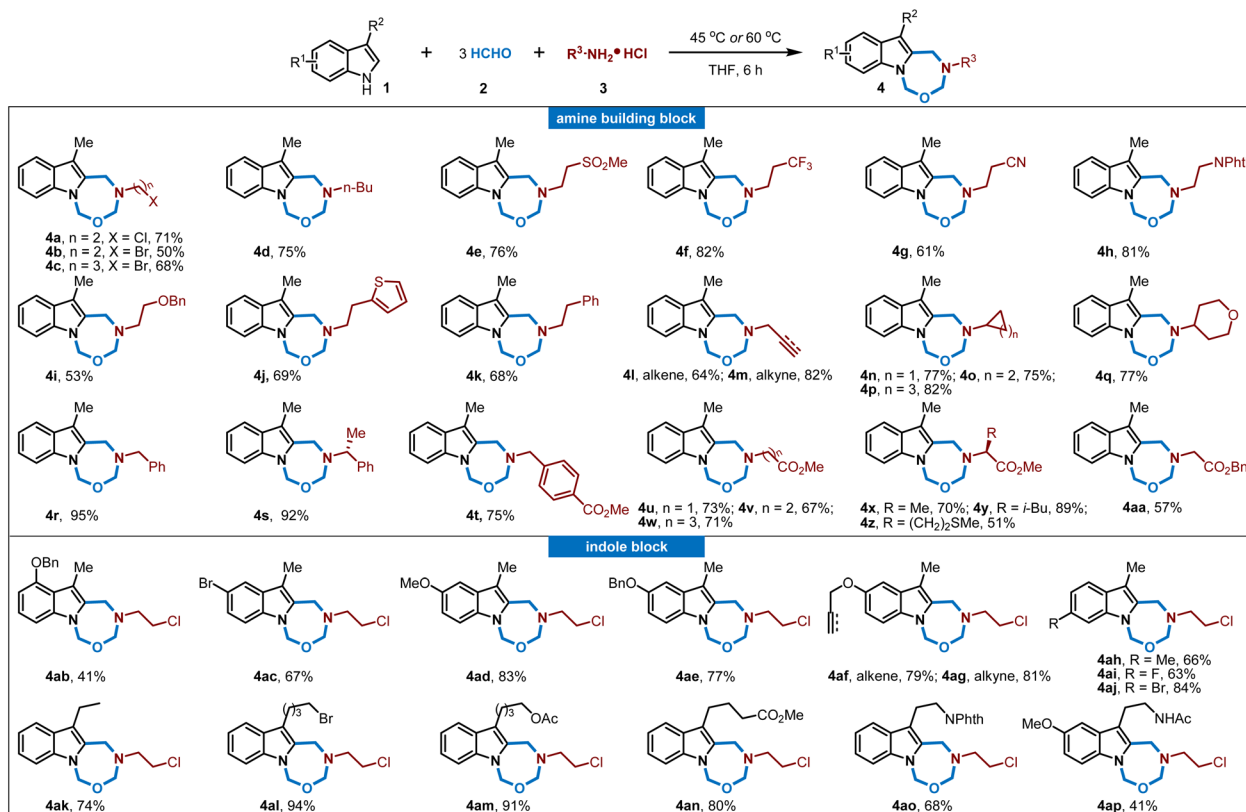


Fig. 1 Scope for the multicomponent synthesis of indole-fused oxadiazepines. Reaction conditions: **1** (0.2 mmol), **2** (1.0 mmol), **3** (0.4 mmol), THF (2 mL), 45 °C or 60 °C, 6 hours. Isolated yields are given. Phth = phthalimide.

compound **4aj** was determined by X-ray analysis. It should be noted that indoles **1o** and **1p** were tryptamine derivatives and melatonin respectively; thus this MCR protocol provides a distinct heterocycle-fused evolution for these bioactive molecules and would definitely be useful in drug discovery.

Encouraged by these results, we wondered whether this MCR strategy could be extended to the facile construction of other new structural indole-fused heterocycles. Based on the reaction mechanism understanding and various experimental attempts (for details, see the ESI<sup>†</sup>), we found that another addition of sodium thiosulfate **5** (Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>) to the mixture of **1**, **2** and **3** with the treatment of aqueous hydrochloride solution would enable a new multicomponent reaction to deliver indole-fused thiazepine. Then the generality of this MCR was explored. As shown in Fig. 2, a wide range of amines bearing diverse functionalities, including flexible aliphatic amines with the substitution of chloro, sulfone, cyano, benzyloxy, heterocyclic rings, alkene, alkyne, cyclobutane and phenyl, were well applicable in this process to furnish the corresponding indole-fused thiazepine products in good to excellent yields (**6a–6j**), and the structure of **6a** was unambiguously confirmed by single-crystal X-ray crystallography. Meanwhile, amino acid derivatives were also compatible in this process and assembled with indole **1**, formaldehyde **2** and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> **5** to rapidly achieve the products in good yields (**6k–6n**). The indole scope was also investigated wherein differential substitution and melatonin were explored,

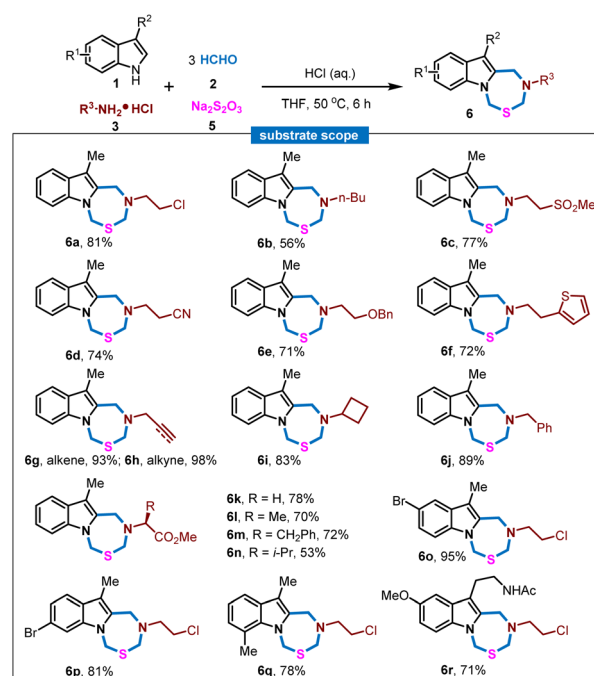


Fig. 2 Scope for the multicomponent synthesis of indole-fused thiazepines. Conditions: **1** (0.2 mmol), **2** (1.0 mmol), **3** (0.4 mmol), Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> **5** (0.4 mmol, 12 N), THF (2 mL), 50 °C, 6 hours. Isolated yields are given.



and the corresponding indole-fused thiadiazepine products were achieved in good to excellent yields (**60–6r**). In addition, a gram-scale synthesis of **6a** was conducted to demonstrate the scalability and practicality of this MCR (see the ESI†).

To further gain insights into the mechanism, a series of control reactions and isotope-labeling reactions were conducted. First, compounds **Int-1** and **Int-2u** were isolated and identified as intermediates. Then, **Int-1**, **Int-2u** and *N*-MOM protected indole **7** were individually subjected to the multi-component reaction with formaldehyde **2** and methyl glycinate hydrochloride **3u**, and the results showed that these MCRs could all furnish the product **4u** in good yields (Fig. 3A). Besides, **1a** was also subjected to a reaction with para-formaldehyde **2** and chloroethylamine hydrochloride **3a** with an addition of  $^{18}\text{O}$ -labelled  $\text{H}_2\text{O}$ , and the result showed that **4a** could be formed in 59% yield coupled with high  $^{18}\text{O}$ -labelled incorporations (Fig. 3B). Based on these results, a plausible mechanism was proposed in Fig. 3C. Initially, indole **1a** could react with formaldehyde **2** to give intermediate **Int-1**, and amino hydrochloride **3** could react with formaldehyde **2** to give iminium intermediate **8**. Afterwards, an alkylation would occur between **Int-1** and **8** to deliver **Int-2**. **Int-2** would further

condense with formaldehyde to give **Int-3**; then water or  $\text{H}_2\text{S}$  (*in situ* generated from  $\text{Na}_2\text{S}_2\text{O}_3$  and aqueous  $\text{HCl}$ ) would undergo a bis-nucleophilic addition to **Int-3** to give indole-fused seven-membered heterocycles, along with the release of **Int-4** which further decomposed to formaldehyde **2** and iminium **8**. When  $\text{Na}_2\text{S}_2\text{O}_3$  was replaced with  $\text{Na}_2\text{S}$ , the MCRs would deliver the same products, thus indicating that  $\text{H}_2\text{S}$  was the real nucleophilic reagent (for details, see the ESI†).<sup>14</sup>

Since indole derivatives were privileged structures in pharmaceuticals, these indole-fused heterocyclic compounds were subsequently subjected to biological evaluation. At the beginning, cytotoxicity evaluation was conducted for these compounds in the GES-1 cell line (human) and 3T3 cell line (mouse) at a concentration of  $10\ \mu\text{M}$  and  $20\ \mu\text{M}$ , and the results revealed their low cytotoxicity (see ESI Fig. S7†). Then, these compounds were subjected to anti-proliferative evaluation against four human cancer cell lines, including A549 (lung cancer cell line), HCT116 (colon cancer cell line), BEL7402 (liver cancer cell line) and MDA-MB-231 (breast cancer cell line). As shown in Fig. 4A (for details, see ESI Fig. S8†), a number of compounds displayed potential inhibitory activities against BEL7402 cells, with  $\text{IC}_{50}$  values ranging from  $12.6\ \mu\text{M}$  to  $23.9\ \mu\text{M}$ . Moreover, compounds **6g** and **6h** exhibited good anti-proliferative activity against A549 cells ( $\text{IC}_{50} = 9.6\ \mu\text{M}$  and  $\text{IC}_{50} = 11.7\ \mu\text{M}$ ). These results indicated that this class of indole-fused heterocycles has potential antitumor activities.

Meanwhile, the synthetic utility of this multicomponent reaction protocol was applied in peptide modification. Because of the natural advantage of mimicking the endogenous portion of the interacting proteins, peptides have gained increased attention.<sup>15</sup> However, their drug discovery was plagued by their particularly poor physicochemical properties and *in vivo* stabilities.<sup>16</sup> Chemical modification has been a robust tool to overcome the intrinsic limitations.<sup>17</sup> In recent decades, the aromatic tryptophan (Trp) side chain has become an attractive target for late-stage modification for its essential role in peptides and proteins.<sup>12k,18</sup> Given the successful implementation of these MCRs on tryptamine and melatonin toward modular assembly of indole-fused seven-membered heterocycles, we hypothesized that this protocol could be a selective and efficient method for tryptophan (Trp) containing peptides. Thus, we used Cbz-Trp-OH as a model substrate to react under standard conditions. As expected, the corresponding product **11a** was obtained in satisfactory yield. The strategy was also tested on the dipeptide substrates Cbz-Ala-Trp-OMe and Cbz-Trp-Phe-OMe, and the results showed that moderate yields could be achieved regardless of whether the Trp residue is located at the C-terminal or N-terminal end (**11b** and **11c**). Furthermore, this multicomponent reaction protocol was capable of tripeptide modification (**11d–11f**), displaying high reaction activity and compatibility with different amino acids. It should be noted that the modified Trp-containing peptides bearing an alkynyl moiety are promising building blocks for click reactions toward diverse derivatization. In addition, we employed Fmoc-Trp-OMe and Fmoc-Lys-OMe as indole and amine building blocks for these MCRs, and gratifyingly, these two peptides could be assembled to form the indole-fused

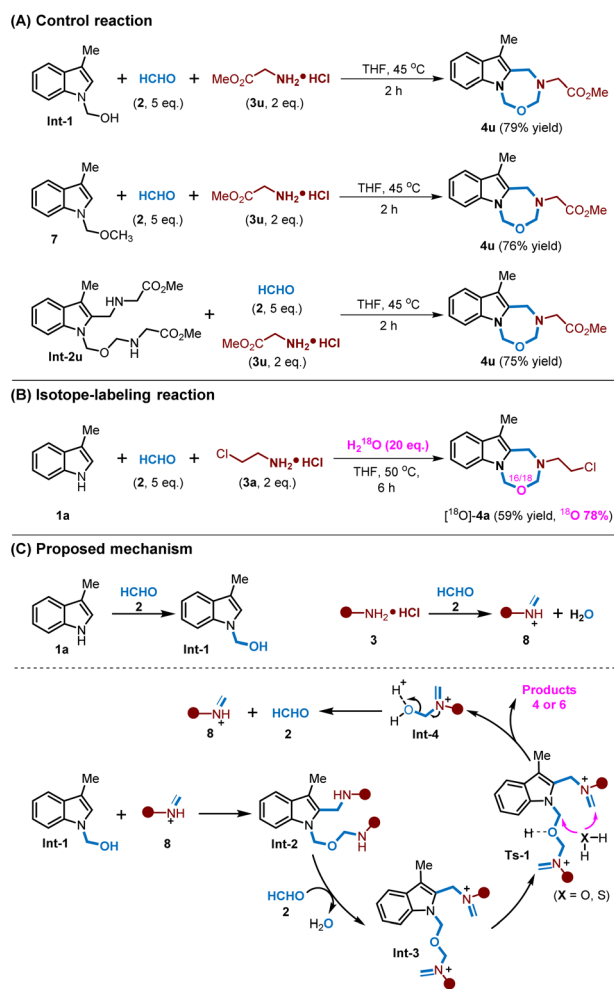


Fig. 3 Mechanism investigation experiments and the proposed mechanism.





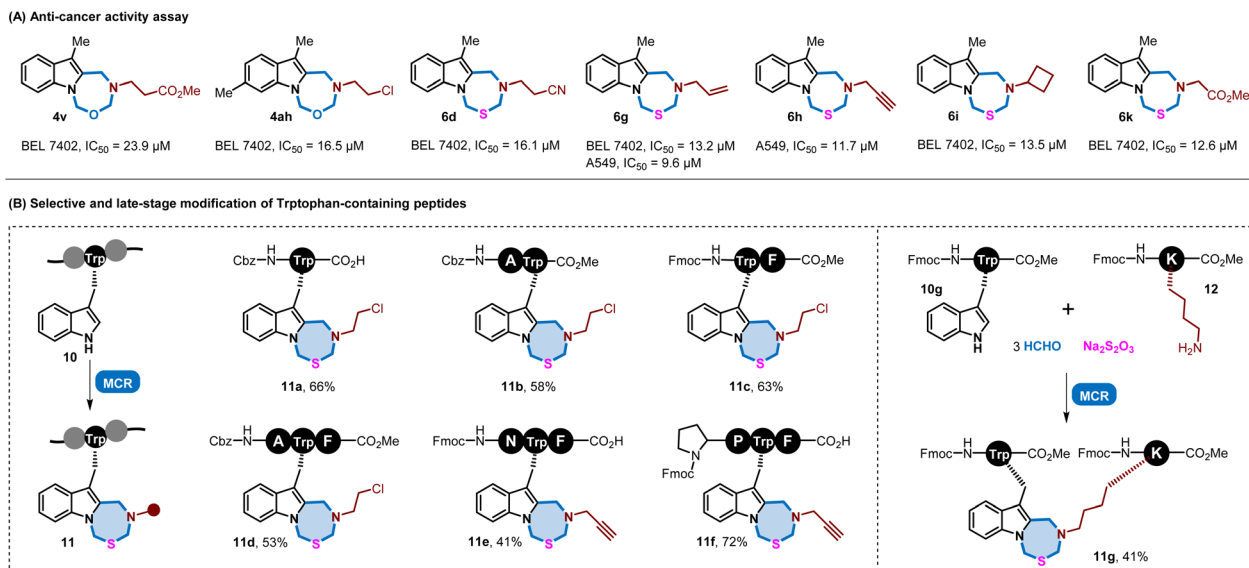


Fig. 4 Application of these MCRs in biological activity assay and peptide chemistry. MCR = multicomponent reaction.

heterocycles **11g** in 41% yield. These results indicated that this multicomponent reaction could be a potent and practical modification strategy for peptides.

## Conclusions

In conclusion, we have developed a modular assembly of indole-fused seven-membered heterocycles through multicomponent reactions. In this process, indole, formaldehyde and amino hydrochloride could assemble rapidly to achieve the construction of indole-fused oxadiazepines, while a further addition of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> would deliver thiadiazepines alternatively, and the reaction process featured mild reaction conditions, broad substrate scope and high efficiency. The control reaction and isotope-labelling reaction revealed an iterative assembly of these building blocks wherein a bis-nucleophilic addition was vital in this process. Biological evaluation disclosed that these compounds exhibit potent anti-proliferative activity, and this protocol could be applicable in the selective and late-stage modification of peptides. Therefore, this protocol provides a distinct and efficient approach for accessing indole-fused heterocycles and serves as an efficient peptide modification strategy and would be useful in organic synthesis, medicinal chemistry and chemical biology.

## Data availability

Detailed synthetic procedures and complete characterization data for all new compounds can be found in the ESI.†

## Author contributions

S. C. conceived and designed the experiments. S. C. and L. Z. directed the project. J. L. performed the experiments. H. N., W. Z., Z. L., and H. J. prepared some starting materials. J. L. and L.

Z. analyzed the data. S. C. and L. Z. wrote the paper. All authors discussed the results and commented on the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- (a) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2005, **22**, 73–103; (b) R. S. Doody, S. I. Gavrillova, M. Sano, R. G. Thomas, P. S. Aisen, S. O. Bachurin, L. Seely and D. Hung, *Lancet*, 2008, **372**, 207–215; (c) E. Stempel and T. Gaich, *Acc. Chem. Res.*, 2016, **49**, 2390–2402; (d) P. T. Singh and M. O. Singh, *Mini-Rev. Med. Chem.*, 2018, **18**, 9–25; (e) Y. Wan, Y. Li, C. Yan, M. Yan and Z. Tang, *Eur. J. Med. Chem.*, 2019, **183**, 111691; (f) J. C. Reisenbauer, O. Green, A. Franchino, P. Finkelstein and B. Morandi, *Science*, 2022, **377**, 1104–



- 1109; (g) J. Woo, A. H. Christian, S. A. Burgess, Y. Jiang, U. F. Mansoor and M. D. Levin, *Science*, 2022, **376**, 527–532.
- 2 (a) J. Sun, H. Lou, S. Dai, H. Xu, F. Zhao and K. Liu, *Phytochemistry*, 2008, **69**, 1405–1410; (b) T. V. Sravanthi and S. L. Manju, *Eur. J. Pharm. Sci.*, 2016, **91**, 1–10; (c) A. Dorababu, *RSC Med. Chem.*, 2020, **11**, 1335–1353; (d) Y. Zhu, J. Zhao, L. Luo, Y. Gao, H. Bao, P. Li and H. Zhang, *Eur. J. Med. Chem.*, 2021, **223**, 113665.
- 3 (a) L. S. Fernandez, M. S. Buchanan, A. R. Carroll, Y. J. Feng, R. J. Quinn and V. M. Avery, *Org. Lett.*, 2009, **11**, 329–332; (b) E. Ascic, J. F. Jensen and T. E. Nielsen, *Angew. Chem., Int. Ed.*, 2011, **50**, 5188–5191; (c) R. Vallakati and J. A. May, *J. Am. Chem. Soc.*, 2012, **134**, 6936–6939; (d) S. G. Dawande, B. S. Lad, S. Prajapati and S. Katukojvala, *Org. Biomol. Chem.*, 2016, **14**, 5569–5573; (e) J. Dai, W. Dan, Y. Zhang and J. Wang, *Eur. J. Med. Chem.*, 2018, **157**, 447–461; (f) Q. Dan, S. A. Newmister, K. R. Klas, A. E. Fraley, T. J. McAfoos, A. D. Somoza, J. D. Sunderhaus, Y. Ye, V. V. Shende, F. Yu, J. N. Sanders, W. C. Brown, L. Zhao, R. S. Paton, K. N. Houk, J. L. Smith, D. H. Sherman and R. M. Williams, *Nat. Chem.*, 2019, **11**, 972–980; (g) X.-Y. Liu and Y. Qin, *Acc. Chem. Res.*, 2019, **52**, 1877–1891; (h) J.-K. Dai, W.-J. Dan and J.-B. Wan, *Eur. J. Med. Chem.*, 2022, **229**, 114057.
- 4 (a) H. Mizoguchi, H. Oikawa and H. Oguri, *Nat. Chem.*, 2014, **6**, 57–64; (b) C. Sherer and T. J. Snape, *Eur. J. Med. Chem.*, 2015, **97**, 552–560; (c) R. Purgatorio, M. de Candia, M. Catto, A. Carrieri, L. Pisani, A. De Palma, M. Toma, O. A. Ivanova, L. G. Voskressensky and C. D. Altomare, *Eur. J. Med. Chem.*, 2019, **177**, 414–424.
- 5 (a) B. E. Maryanoff and D. F. McComsey, *J. Org. Chem.*, 1978, **43**, 2733–2735; (b) B. E. Maryanoff, S. O. Nortey and J. F. Gardocki, *J. Med. Chem.*, 1984, **27**, 1067–1071.
- 6 R. J. Katz, P. S. Landau, M. Lott, A. Bystritsky, B. Diamond, R. Hoehn-Saric, M. Rosenthal and C. Weise, *Biol. Psychiatry*, 1993, **34**, 41–44.
- 7 (a) A. J. M. Disney, B. Kellam and L. V. Dekker, *ChemMedChem*, 2016, **11**, 972–979; (b) K. M. Gayler, K. Kong, K. Reisenauer, J. H. Taube and J. L. Wood, *ACS Med. Chem. Lett.*, 2020, **11**, 2441–2445; (c) J. Zhang, A. Cordshagen, I. Medina, H. G. Nothwang, J. R. Wisniewski, M. Winkhofer and A.-M. Hartmann, *PLoS One*, 2020, **15**, e0232967.
- 8 M. D. Ennis, R. L. Hoffman, N. B. Ghazal, R. M. Olson, C. S. Knauer, C. L. Chio, D. K. Hyslop, J. E. Campbell, L. W. Fitzgerald, N. F. Nichols, K. A. Svensson, R. B. McCall, C. L. Haber, M. L. Kagey and D. M. Dinh, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2369–2372.
- 9 (a) D. G. Pintori and M. F. Greaney, *J. Am. Chem. Soc.*, 2011, **133**, 1209–1211; (b) L. D. Basanagoudar, C. S. Mahajanshetti and S. B. Dambal, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1991, **30**, 1014; (c) Y. Ohta, H. Chiba, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2008, **10**, 3535.
- 10 (a) A. Dömling, W. Wang and K. Wang, *Chem. Rev.*, 2012, **112**, 3083–3135; (b) J. Zhu, *Multicomponent Reactions in Organic Synthesis*, 2015.
- 11 (a) S. J. Zuend, M. P. Coughlin, M. P. Lalonde and E. N. Jacobsen, *Nature*, 2009, **461**, 968–970; (b) E. Ruijter, R. Scheffelaar and R. V. A. Orru, *Angew. Chem., Int. Ed.*, 2011, **50**, 6234–6246; (c) B. Huang, L. Zeng, Y. Shen and S. Cui, *Angew. Chem., Int. Ed.*, 2017, **56**, 4565–4568; (d) C. Wang, Z. Lai, H. Xie and S. Cui, *Angew. Chem., Int. Ed.*, 2021, **60**, 5147–5151; (e) Z. Lai, R. Wu, J. Li, X. Chen, L. Zeng, X. Wang, J. Guo, Z. Zhao, H. Sajiki and S. Cui, *Nat. Commun.*, 2022, **13**, 435; (f) X. Hu, L. Chen, H. Li, Q. Xu, X. Liu and X. Feng, *ACS Catal.*, 2023, **13**, 6675–6682.
- 12 (a) M. Shiri, *Chem. Rev.*, 2012, **112**, 3508–3549; (b) N. Sarkar, A. Banerjee and S. G. Nelson, *J. Am. Chem. Soc.*, 2008, **130**, 9222–9223; (c) T. A. Cernak and T. H. Lambert, *J. Am. Chem. Soc.*, 2009, **131**, 3124–3125; (d) P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7892–7894; (e) M. Terada, K. Machioka and K. Sorimachi, *Angew. Chem., Int. Ed.*, 2009, **48**, 2553–2556; (f) J. S. Alford and H. M. L. Davies, *J. Am. Chem. Soc.*, 2014, **136**, 10266–10269; (g) L. Jiang, W. Jin and W. Hu, *ACS Catal.*, 2016, **6**, 6146–6150; (h) O. Ghashghaei, M. Pedrola, F. Seghetti, V. V. Martin, R. Zavarce, M. Babiak, J. Novacek, F. Hartung, K. M. Rolfes, T. Haarmann-Stemmann and R. Lavilla, *Angew. Chem., Int. Ed.*, 2021, **60**, 2603–2608; (i) S. Yu, W. Chang, R. Hua, X. Jie, M. Zhang, W. Zhao, J. Chen, D. Zhang, H. Qiu, Y. Liang and W. Hu, *Nat. Commun.*, 2022, **13**, 7088; (j) R.-Y. Hua, S.-F. Yu, X.-T. Jie, H. Qiu and W.-H. Hu, *Angew. Chem., Int. Ed.*, 2022, **61**, e202213407; (k) S. Krajcovicova and D. R. Spring, *Angew. Chem., Int. Ed.*, 2023, **62**, e202307782; (l) J. Li, Z. Lai, W. Zhang, L. Zeng and S. Cui, *Nat. Commun.*, 2023, **14**, 4806.
- 13 (a) M. Arend, B. Westermann and N. Risch, *Angew. Chem., Int. Ed.*, 1998, **37**, 1044–1070; (b) M. Yamanaka, J. Itoh, K. Fuchibe and T. Akiyama, *J. Am. Chem. Soc.*, 2007, **129**, 6756–6764; (c) J. M. M. Verkade, L. J. C. v. Hemert, P. J. L. M. Quaedflieg and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29–41; (d) R. G. Arrayás and J. C. Carretero, *Chem. Soc. Rev.*, 2009, **38**, 1940–1948; (e) A. Noble and J. C. Anderson, *Chem. Rev.*, 2013, **113**, 2887–2939; (f) J. Rostoll-Berenguer, G. Blay, J. R. Pedro and C. Vila, *Adv. Synth. Catal.*, 2021, **363**, 602–628; (g) M.-X. Pu, H.-Y. Guo, Z.-S. Quan, X. Li and Q.-K. Shen, *J. Enzyme Inhib. Med. Chem.*, 2023, **38**, 2235095.
- 14 I. Klose, G. Di Mauro, D. Kaldre and N. Maulide, *Nat. Chem.*, 2022, **14**, 1306–1310.
- 15 (a) B. J. Bruno, G. D. Miller and C. S. Lim, *Ther. Delivery*, 2013, **4**, 1443–1467; (b) Q.-S. Du, N.-Z. Xie and R.-B. Huang, *Med. Chem.*, 2015, **11**, 235–247.
- 16 (a) T. Uhlig, T. Kyprianou, F. G. Martinelli, C. A. Oppici, D. Heiligers, D. Hills, X. R. Calvo and P. Verhaert, *EuPa Open Proteomics*, 2014, **4**, 58–69; (b) J. Iegre, J. S. Gaynord, N. S. Robertson, H. F. Sore, M. Hyvönen and D. R. Spring, *Adv. Ther.*, 2018, **1**, 1800052.
- 17 (a) T. A. Hill, N. E. Shepherd, F. Diness and D. P. Fairlie, *Angew. Chem., Int. Ed.*, 2014, **53**, 13020–13041; (b) E. V. Vinogradova, C. Zhang, A. M. Spokoyny, B. L. Pentelute and S. L. Buchwald, *Nature*, 2015, **526**, 687–



- 691; (c) D. S. Nielsen, N. E. Shepherd, W. Xu, A. J. Lucke, M. J. Stoermer and D. P. Fairlie, *Chem. Rev.*, 2017, **117**, 8094–8128; (d) L. Reguera and D. G. Rivera, *Chem. Rev.*, 2019, **119**, 9836–9860.
- 18 (a) K. R. Schramma, L. B. Bushin and M. R. Seyedsayamdost, *Nat. Chem.*, 2015, **7**, 431–437; (b) Z. Bai, C. Cai, W. Sheng, Y. Ren and H. Wang, *Angew. Chem., Int. Ed.*, 2020, **59**, 14686–14692; (c) S. J. Tower, W. J. Hetcher, T. E. Myers, N. J. Kuehl and M. T. Taylor, *J. Am. Chem. Soc.*, 2020, **142**, 9112–9118; (d) R. Mao, S. Xi, S. Shah, M. J. Roy, A. John, J. P. Lingford, G. Gäde, N. E. Scott and E. D. Goddard-Borger, *J. Am. Chem. Soc.*, 2021, **143**, 12699–12707; (e) L. Liu, X. Fan, B. Wang, H. Deng, T. Wang, J. Zheng, J. Chen, Z. Shi and H. Wang, *Angew. Chem., Int. Ed.*, 2022, **61**, e202206177; (f) Y. Weng, X. Xu, H. Chen, Y. Zhang and X. Zhuo, *Angew. Chem., Int. Ed.*, 2022, **61**, e202206308; (g) J. A. C. Delgado, Y.-M. Tian, M. Marcon, B. König and M. W. Paixão, *J. Am. Chem. Soc.*, 2023, **145**, 26452–26462; (h) N. J. Kuehl and M. T. Taylor, *J. Am. Chem. Soc.*, 2023, **145**, 22878–22884.

