RSC Advances



View Article Online **PAPER** View Journal | View Issue



Cite this: RSC Adv., 2025, 15, 46951

One-pot Cul/L-proline-catalysed multicomponent synthesis of pyrido[2',1':2,3]imidazo[4,5-c]quinoline derivatives from 2-(2-bromophenyl) imidazo[1,2-a]pyridines, NH₃ and DMSO under air

Ban Van Phuc,†a Dinh Thi Thuy,†b Phuong Anh Dao,†b Van Loc Nguyen,c Van Ha Nguyen, b Hung Huy Nguyen, b Dang Van Do, b Hien Nguyen, c Tran Quang Hung **D **ad and Tuan Thanh Dang **D **b

Received 9th September 2025 Accepted 14th November 2025

DOI: 10.1039/d5ra06789h

rsc li/rsc-advances

In a new approach, a series of pyrido[2',1':2,3]imidazo[4,5-c]quinoline (PIQ) derivatives were prepared in high yields from 2-(2-bromophenyl)imidazo[1,2-a]pyridines, NH $_3$ and DMSO via a tandem process including Cul/L-proline-catalysed C-N coupling and aerobic oxidative cyclization steps. Consequently, this method could be applied for the synthesis of a series of thiazolo[2',3':2,3]imidazo[4,5-c]quinolines and benzo[4',5']thiazolo[2',3':2,3]imidazo[4,5-c]quinolines in good yields via a similar approach.

Introduction

Fused N-heterocycles have long been acknowledged as crucial targets in the drug discovery process.¹⁻⁴ In particular, imidazo [1,2-a]pyridine derivatives are vital building blocks of several significant drugs and bioactive compounds due to their wide variety of bioactivities.⁵ The imidazo[1,2-a]pyridine core is found in a number of commercial pharmaceuticals, such as the anxiolytics Alpidem, Necopidem, Soraprazan, Saripidem, and Zolimidine, as well as the drug Zolpidem, which is used to address disorders of the brain (Fig. 1).5 Moreover, some novel compounds containing imidazo[1,2-a]pyridine cores have been shown to possess antibacterial, anticancer, anti-inflammatory, antiprotozoal, antiviral, antiparasitic, analgesic, and antipyretic properties.⁶ On the other hand, imidazo[1,2-a]pyridine derivatives have also demonstrated extremely luminescent properties with high quantum yields in addition to pharmacological studies.7

Recently, imidazo[1,2-a]pyridine-fused quinoline(pyridine) derivatives have also found promising applications in the development of medicinal chemistry research such as anticancer, anti-inflammatory, antiplasmodial, antifungal, antibacterial, antiparasitic, antimycobacterial and antileishmanial agents (Fig. 1, compounds A-E).8 Among them, tetracyclic structures, such as pyrido[2',1':2,3]imidazo[4,5-b]quinoline and

fused quinoline derivatives have been reported.8 In general, the standard procedure for the synthesis of this PIQ scaffold included 3 steps: (i) the first formation of imidazopyridine skeleton by the cyclization of 2-aminopyridines and 2-bromo-1-(2-nitrophenyl)ethan-1-one, (ii) the subsequent conversion of nitro-substituted imidazopyridine substrate

Fig. 1 Imidazo[1,2-a]pyridine derivatives with various biological activities.

pyrido[2',1':2,3]imidazo[4,5-c]quinoline (PIQs), are interesting targets because they are similar isosteres of a series of important anticancer compounds such as Ellipticine, Datelliptium, as well as Pazellipticine.9 In fact, many approaches to prepare imidazo[1,2-a]pyridine-

Zolpidem Necopidem Anticancer agent (A) Anticancer agent (B) Anticancer agent (C) Antimycobacterial agent (D) Antileishmanial agent (E)

[&]quot;Institute of Chemistry, Vietnam Academy of Science and Technology, Vietnam. E-mail:

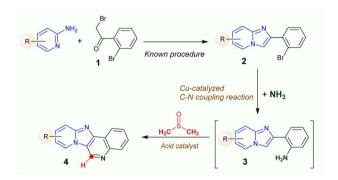
^bFaculty of Chemistry, Hanoi University of Science, Vietnam National University (VNU), Vietnam. E-mail: dangthanhtuan@hus.edu.vn

Faculty of Chemistry, Hanoi National University of Education (HNUE), Vietnam

^dGraduate University of Science and Technology, Vietnam Academy of Science and Technology, Vietnam

[†] These authors equally contributed to this work.

Scheme 1 Several approaches to prepare pyrido[2',1':2,3]imidazo[4,5-c]quinoline (PIQ) derivatives.



Scheme 2 Synthetic route to prepare pyrido[2',1':2,3]imidazo[4,5-c] quinoline derivatives.

corresponding amine-functionalized imidazopyridine and (iii) the acid-catalysed cyclization of its amine with aldehydes to produce imidazo[4,5-c]quinolines via Pictet-Spendler-type reaction (Scheme 1).8 In 2007, Kundu et al. demonstrated the first effort to prepare PIQ molecules through the three step sequence involving the Hantzsch type reaction, nitro group reduction and the Pictet-Spengler cyclization from 2-aminopyridine as starting material. 10 In 2014, Chouhan et al. reported the synthesis of PIQ from imidazo[1,2-a]pyridine amines and aromatic aldehydes in the use of cyanuric chloride as catalyst and TBAB as additive in water. 11 Subsequently, in 2017, Atmakur et al. developed a one-pot protocol from 2-(imidazo[1,2-a] pyridin-2-yl)-aniline and aldehyde using I₂ in DMSO solvent.¹² In 2018, Kamal and coworkers disclosed a one-pot I2-promoted synthesis of PIQs from 2-(imidazo[1,2-a]pyridin-2-yl)aniline and benzylamines.13a Later, the same group also reported I2-catalyzed synthesis of pyridoimidazo[4,5-c]quinolines from 2-(imidazo[1,2-a]pyridin-2-yl)aniline and acetophenone derivatives. 13b In 2022, Jinkala et al. disclosed a modified research for the I2promoted synthesis of PIQs by the cyclization of 2-(imidazo[1,2apyridin-2-yl)aniline with phenylacetic acid via oxidative decarboxylation. 13c Recently, Sun and coworkers reported the preparation of PIQ via metal-free dehydrogenative coupling reaction

of imidazopyridines with cyclic ethers in the presence of hydrogen peroxide.14 In 2025, Chanda et al. reported a one-pot steps-wise microwave-assisted synthesis of PIQ derivatives from simple 2-aminopyridines, 2-bromo-2'-nitroacetophenone and aldehydes in deep eutectic solvents. 15 Notably, Sanz and coworkers reported a novel and sustainable synthesis of a series of N-fused heterocycles including PIGs from easily available nitroaromatics and diols via a Mo-catalysed domino reductionimine formation-intramolecular cyclization-oxidation sequence under microwave heating at 180 °C.16 Even though new pathways for the synthesis of pyridoimidazo [4,5-c] quinolines have advanced significantly, these methods that have been established thus far have certain drawbacks, including the use of hazardous reagents, multi-step synthesis, the requirement for a strong acid medium, high temperature, long reaction times, and a complex workup process. These disadvantages severely restrict the application of pyridoimidazo[4,5-c]quinolines in medicinal chemistry research. Consequently, it may be very advantageous to design quick one-pot synthetic processes that use simpler workup, greener chemicals, and catalysts. Recently, Cu-catalysed C-N coupling reaction in one-pot sequential processes showed effective in forming N-fused heterocycles.17 In 2017, one-pot tandem procedures for the preparation of PIQs including Cu-catalysed C-N coupling from 2-(2-bromophenyl) imidazo[1,2-a]pyridines, azides and aldehydes were reported.18 Recently, several Cu-catalysed methods to access PIQs by direct coupling of 2-(2-bromophenyl)imidazo[1,2-a]pyridines using direct ammonia as the amine source were disclosed.19

In continuation of our efforts on the synthesis of imidazo [1,2-a]pyridine-fused N-heterocycles and other fused N-heterocycles,²⁰ herein, we wish to describe a highly efficient synthesis of PIQ derivatives catalysed by an air-stable and environmentally benign CuI/L-proline catalyst system via a tandem process including: (i) a direct Cu-catalysed coupling of 2-(2-bromophenyl)imidazo[1,2-a]pyridine derivatives using ammonia to form amine intermediates; (ii) the acid-catalysed condensation of these amines with formaldehyde which was in situ-generated from DMSO solvent; (iii) intramolecular oxidative cyclization reaction of in situ-formed imines to afford the PIQ structures. The novelty of our method lies in a practical reaction design, wherein ammonium acetate (NH₄OAc) serves a dual role as both the nitrogen source and a mild base. Most notably, dimethyl sulfoxide (DMSO) is exploited for the first time as both the solvent and the C1 synthon for the quinoline ring formation. This approach not only simplifies the synthetic protocol but also represents a significant advancement in efficiency and atom economy for the synthesis of these complex Nheterocycles.

Results and discussion

In order to develop this synthesis, we used a known method to prepare 2-(2-bromophenyl)imidazo[1,2-a]pyridines 2 by the cyclocondensation of 2-aminopyrines and dibromide compound 1 (Scheme 2). A similar approach was developed by Kumar and coworkers, PIQ derivatives could be prepared in moderate yields (up to 52%) from CuI-catalysed coupling

Table 1 Optimization for the preparation of 2-(imidazo[1,2-a]pyridin-2-yl)aniline 3a^a

Entry	Catalyst	Ligand	Base	Temp. (°C)	Time (h)	$\mathrm{Yield}^{b,c}\left(\%\right)$
1	CuO	L-Proline	K_2CO_3	100	8	40
2	CuCl	L-Proline	K_2CO_3	100	8	60
3	CuI	L-Proline	K_2CO_3	100	8	70
4	$CuCl_2$	L-Proline	K_2CO_3	100	8	55
5	$Cu(OAc)_2$	L-Proline	K_2CO_3	100	8	10
6	CuI	1,10-Phenanthroline	K_2CO_3	100	8	45
7	CuI	<i>N,N</i> -Dimethylglycine	K_2CO_3	100	8	60
8	CuI	Bipyridine	K_2CO_3	100	8	40
9	CuI		K_2CO_3	100	8	35
10	_	_	K_2CO_3	100	8	NR
11	CuI	L-Proline	KOH	100	8	30
12	CuI	L-Proline	KO <i>t</i> Bu	100	8	40
13	CuI	L-Proline	Cs_2CO_3	100	8	68
14	CuI	L-Proline	NH ₄ OAc	100	8	92
15	CuI	L-Proline	NH ₄ OAc	110	8	91
16	CuI	L-Proline	NH ₄ OAc	90	8	90
17	CuI	L-Proline	NH ₄ OAc	100	11	90
18	CuI	L-Proline	NH ₄ OAc	100	6	91
19	CuI	L-Proline	NH ₄ OAc	100	4	80
20	CuI	L-Proline	_	100	6	75

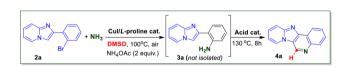
^a Condition: **2a** (0.5 mmol), CuI catalyst (20 mol%), L-proline (20 mol%), DMSO/ammonia solution 25% (1.2 ml/0.8 ml), 110 °C, 4–8 h. ^b Yield of isolated products are given. ^c Reaction was performed in air atmosphere.

reaction of 2-(2-bromophenyl)imidazo[1,2-a]pyridine derivatives with sodium azide (NaN3) in DMAc solvent (Scheme 1).13a In order to improve the yield of desired products, TBHP (2 equiv.) was employed as an oxidant to form quinoline ring easier (Scheme 1).13a To avoid the utilization of toxic, environmentally hazardous and explosive reagents such as NaN3, TBHP and DMAc solvent, we tried to replace them to cheaper, safer and less toxic reagents in this research. In our one-pot synthetic plan, molecular oxygen (in air) was chosen as clean and green oxidant in the last aromatization step. We visualized that the most important step of this route would be the Cu-catalysed C-N bond formation of 2-(2-bromophenyl)imidazo[1,2-a]pyridines 2 with ammonia (Scheme 2). Then, the target PIQ compound 4 could be prepared by the oxidative cyclization of amine intermediate 3 with formaldehyde which could be in situgenerated from dimethyl sulfoxide under acid condition.

With the first purpose of amination of 2-(2-bromophenyl) imidazo[1,2-a]pyridine 2a using direct ammonia as amine source, our attention was solely focused on the investigation of various Cu catalysts with the aim of finding the optimal conditions for this transformation (Table 1). Based on our previous achievements using CuI/L-proline catalyst system for C–N coupling reactions, 20b,l,n,o the common Cu precursors in the combination with K_2CO_3 base were initially examined in DMSO solvent, resulting in a promising 70% yield of the desired amine product 3a (entry 3). The employment of several popular used

Cu(II) salts as catalysts was investigated which resulted in lower yield of **3a** product (entries 4–5). Then, further optimisations using different bidentate amine ligands were carried out (entries 6–8). However, we did not obtain better results. In order

Table 2 Optimization for the synthesis of pyrido[2',1':2,3]imidazo[4,5-c]quinoline $4a^a$



Entry	Catalyst	Temp. (°C)	Time (h)	$\mathrm{Yield}^{b,c}\left(\%\right)$
1	CH_3COOH	130	16	70
2	H_3PO_4	130	16	35
3	TFA	130	16	Trace
4	HCl	130	16	Trace
5 ^b	P-TSA	130	16	Trace
6	CH_3COOH	150	16	58
7	CH_3COOH	120	16	30
8	CH_3COOH	130	24	70
9	CH₃COOH	130	8	68

^a Condition: (i) **2a** (0.5 mmol), CuI catalyst (20 mol%), L-proline (20 mol%), DMSO/ammonia solution 25% (1.2 ml/0.8 ml), 110 °C, 6 h; (ii) acid (0.5 ml) was added. ^b Yield of isolated products are given. ^c Reaction was performed in air atmosphere.

 Table 3
 One-pot tandem synthesis of pyrido[2',1':2,3]imidazo[4,5-c]quinoline 4a–1'

^a Condition: (i) **2a-l** (0.5 mmol), CuI catalyst (20 mol%), L-proline (20 mol%), DMSO/ammonia solution 25% (1.2 ml/0.8 ml), 110 °C, 8 h; (ii) acid (0.5 ml) was added. ^b Yield of isolated products are given. ^c Reaction was performed in air atmosphere.

to understand the effect of Cu catalyst in this reaction, two control experiments were carried out in the absence of either CuI catalyst and/or L-proline ligand. In the absence of any ligands, the PIQ product 3a was only formed in 35% yield (entry 9). Notably, we did not observe the formation of amine product 3a from reaction mixture when this reaction was performed in the absence of CuI/L-proline catalyst (entry 10). In order to understand the effect of bases on this transformation, common bases were investigated in detail. Interestingly, a gently base such as ammonium acetate (NH₄OAc) played a significant role in the improvement of yield of product 3a in 92% (entry 14). In C-N coupling reaction, NH₄OAc may serves a dual role as both the nitrogen source and a mild base. Finally, the other factors such as temperature and reaction time were also examined which did not give us better results (entries 15-20). Obviously, this optimized procedure was chosen for the next cyclization step to give the PIQ product 4a.

Recently, the utilization of *N*,*N*-dimethylformamide (DMF),^{21a} *N*,*N*-dimethylacetamide (DMAc),^{21b} and dimethyl sulfoxide (DMSO)^{21c} as a single carbon source in a variety of chemical transformations under acid conditions has been described.²¹ Relying on these reports, we believe that the target PIQ product **4a** could be prepared by the oxidative cyclization of amine intermediate **3a** with formaldehyde which could be *in situ-*generated from dimethyl sulfoxide solvent. In order to achieve the desired PIQ product **4a**, several acid catalysts were employed for optimization. In the presence of strong acids (HCl, TFA, p-TSA, H₃PO₄) the oxidative cyclization of amine **3a** did not well occur as we expected due to the formation of precipitated amine salts. A weak acid such as acetic acid seems

to be the most suitable catalyst for this transformation (Table 2).

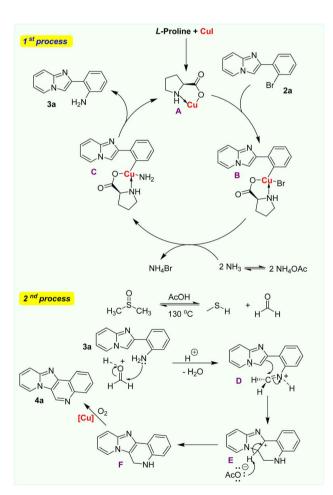
Having the optimised condition in hand, we proceeded to explore the potential application of this one-pot tandem method to prepare PIQ molecules using 2-(2-bromophenyl) imidazo[1,2-a]pyridine derivatives 2a–l and ammonia in DMSO solvent, as depicted in Table 3. In general, the desired PIQ products 4a–l could be successfully prepared, resulting in moderate to good yields. Our method worked very well with 2-(2-bromophenyl)imidazo[1,2-a]pyridines with different functional groups for example, methyl, chloro, fluoro, trifluoro, phenyl ring at C6, C7-positions of imidazo[1,2-a]pyridine ring. In fact, the substituents bearing 2-(2-bromophenyl)imidazo[1,2-a]pyridine skeleton do not make a significant effect on the last yield of PIQ products.

Consequently, we are interested in exploring the scope of substrates applying our method with other imidazole-fused heterocycle derivatives. A series of thiazolo[2',3':2,3]imidazo [4,5-c]quinolines **4m-o** and benzo[4',5']thiazolo[2',3':2,3]imidazo[4,5-c]quinoline **4p-r** were prepared in good yields from the one-pot CuI/L-proline-catalysed tandem reactions of bromides **2m-r** with ammonia and DMSO (Table 4).

In order to confirm the key role of DMSO which can *in situ* generate to formaldehyde under acid condition, DMSO- d_6 was used as the solvent in this transformation. Notably, the desired pyrido[2',1':2,3]imidazo[4,5-c]quinoline-6-d product $4a^{\#}$ was prepared and confirmed by 1 H-NMR spectroscopy. However, a mixture of products 4a and $4a^{\#}$ with a ratio of 1:0.8 was observed due to the deuterium exchange of DMSO- d_6 and acetic acid in reaction mixture (Scheme 4).

Table 4 One-pot tandem synthesis of thiazolo[2',3':2,3]imidazo[4,5-c]quinolines 4m-o and benzo[4',5']thiazolo[2',3':2,3]imidazo[4,5-c]quinolines $4p-r^a$

^a Condition: (i) **2m-r** (0.5 mmol), CuI catalyst (20 mol%), L-proline (20 mol%), DMSO/ammonia solution 25% (1.2 ml/0.8 ml), 110 °C, 8 h; (ii) acid (0.5 ml) was added. ^b Yield of isolated products are given. ^c Reaction was performed in air atmosphere.



Scheme 3 Plausible mechanism for the Cul/L-proline-catalysed formation of pyrido[2',1':2,3]imidazo[4,5-c]quinoline 3 under air atmosphere.

Based on previous research in literature²² and the observed results in control experiments, a plausible mechanism for the CuI/L-proline-catalysed synthesis of PIQs from 2-(imidazo[1,2-a]

Scheme 4 Possible mechanism for deuterium exchange of DMSO- d_6 and the Cul/L-proline-catalysed synthesis of pyrido[2',1':2,3]imidazo [4,5-c]quinoline-6-d 4a[#] under air atmosphere.

pyridin-2-yl)aniline is proposed (Scheme 3). In fact, several reports on the mechanism of Cu-catalysed C-N coupling reactions using amino acids as the ligands were well described.22 Firstly, the oxidative addition of bromide 2a with CuI/L-proline complex A to form a Cu(III) intermediate which subsequently react with ammonia leading to the formation of Cu(III) complex C. The in situ-formed intermediate C would be converted to PIQ product 3a and regenerate the CuI/L-proline catalyst for the next catalytic cycle. Then, in the 2nd process, a formaldehyde molecule was in situ-generated from DMSO solvent in the presence of acid catalyst.21 This reaction was well documented in previous reports.21 Subsequently, the acidcatalysed condensation reaction of amine 3a with formaldehyde afforded to the formation of imine intermediate D. An intramolecular cyclization of intermediate B by Pictet-Spendler type reaction happen to form cyclic amine F via intermediate E. Finally, the last oxidative aromatization of intermediate F in the employment of oxygen molecule (in air) easily occurred to give the desired PIQ product 4a in good yield.

Conclusions

In conclusion, we are reporting a one-pot, practical and convenient method for the CuI/L-proline catalysed synthesis of pyrido[2',1':2,3]imidazo[4,5-c]quinolines from the simple starting materials such as 2-(2-bromophenyl)imidazo[1,2-a] pyridine derivatives and ammonia in DMSO solvent. In our method, with the aim to avoid the utilization of toxic, environmentally hazardous and explosive reagents such as NaN₃, TBHP and DMAc solvent, we tried to replace them with cheaper, safer and less toxic reagents such as NH₃, O₂ (in air) and DMSO, respectively. Indeed, the yield of PIQ products was significantly improved. Then, the application of our method for the synthesis of new quinoline-fused heterocycles, for example, thiazolo [2',3':2,3]imidazo[4,5-c]quinolines and benzo[4',5']thiazolo [2',3':2,3]imidazo[4,5-c]quinolines was successfully explored. In addition, the CuI/L-proline-catalysed synthesis of pyrido [2',1':2,3]imidazo[4,5-c]quinoline-6-d using DMSO-d₆ as solvent was performed to understand insights of the mechanism. Possible reaction pathway for the tandem formation of pyrido [2',1':2,3]imidazo[4,5-c]quinolines involving CuI/L-proline catalysed C-N coupling reaction with ammonia in the first acid-catalysed oxidative cyclization with process and formaldehyde in the second process have been clearly proposed. Furthermore, our method uses cheap and less toxic chemicals which may minimize environmental impact and allow for the smooth synthesis of a library of promising bioactive tetracyclic N-heterocycles with highly functionalized substrates. We anticipate that these findings will provide a valuable contribution to synthetic applications in the fields of medicinal chemistry and materials science. Further investigations into the biological activities and luminescent properties of these newly synthesized compounds are currently underway.

Experimental

General procedure A for synthesis of compound 2a

To a solution of 2-bromo-1-(2-bromophenyl)ethan-1-one 1a (500 mg, 1.8 mmol) and 2-aminopyridine (186 mg, 2 mmol) and sodium bicarbonate (NaHCO₃) (151 mg, 1.8 mmol) in ethanol (4 ml). The resulting mixture was heated at 70 °C and stirred for 6 hours. Upon completion, the mixture was cooled to room temperature, and the solvent was evaporated in vacuo. The residue was partitioned between ethyl acetate and water. The organic phase was separated, dried over anhydrous Na2SO4, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (eluent: hexanes/ethyl acetate = 4:1) afforded 2-(2-bromophenyl)imidazo[1,2-a]pyridine 2a is brown syrup (403 mg, 82%). ¹H NMR (600 MHz, CDCl₃) δ 8.26 (s, 1H), 8.14 (dd, J = 7.82, 1.75 Hz, 1H), 8.10 (dt, J= 6.79, 1.19 Hz, 1H, 7.65 (dd, J = 8.00, 1.26 Hz, 1H), 7.61 (dd, J)= 9.12, 1.03 Hz, 1H), 7.40 (ddd, J = 7.78, 7.27, 1.26 Hz, 1H), 7.18–7.13 (m, 2H), 6.75 (td, J = 6.77, 1.18 Hz, 1H). ¹³C NMR (151 MHz, $CDCl_3$) δ 144.4, 143.1, 134.3, 133.5, 131.5, 128.8, 127.4, 125.6, 124.7, 121.4, 117.5, 112.3, 111.9.

General procedure C for synthesis of compound 4a

The compound 2-(2-bromophenyl)imidazo[1,2-a]pyridine 2a (137 mg, 0.5 mmol), CuI (19 mg, 0.1 mmol), L-proline (12 mg, 0.1 mmol) and NH₄OAc (39 mg, 0.5 mmol) were added into a 25 ml reaction tube. Then, DMSO solvent (1.2 ml) and ammonia solution (0.8 ml) were added. The reaction mixture was then stirred magnetically and heated at 100 °C for 6 h under air atmosphere. Next, the reaction mixture was cooled to 70 °C, the reaction tube was opened for 2 min, and 0.5 ml of AcOH was slowly added. The tube was sealed, and the temperature was raised to 130 °C for 8 h. After cooling, the reaction mixture was extracted with water and ethyl acetate. The organic layer was dried with Na₂SO₄, then filtered and evaporated under reduced pressure to remove the solvent. The brown residue was purified by column chromatography (silica gel, dichloromethane/ethyl acetate 1:1) to obtain pyrido[2',1':2,3]imidazo[4,5-c]quinoline 4a (77 mg, 70%) as a white solid. ¹H NMR (600 MHz, CDCl₃) δ 9.52 (s, 1H), 8.76 (ddt, J = 8.0, 1.7, 0.9 Hz, 2H), 8.29 (ddd, J =8.2, 1.3, 0.6 Hz, 1H), 7.95 (dt, J = 9.2, 1.1 Hz, 1H), 7.80 (ddd, J =8.4, 6.9, 1.6 Hz, 1H), 7.74 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.62 (ddd, J = 9.2, 6.7, 1.3 Hz, 1H), 7.14-7.09 (m, 1H). ¹³C NMR (151) MHz, CDCl₃) δ 149.2, 146.6, 145.9, 135.7, 130.4, 129.8, 128.7, 126.9, 125.3, 122.8, 122.2, 118.3, 112.7.

Conflicts of interest

There are no conflicts to declare.

Data availability

The datasets supporting this article have been uploaded as part of the supplementary information (SI). Data that are reported in this manuscript are available from the authors upon reasonable request. Supplementary information is available. See DOI: https://doi.org/10.1039/d5ra06789h.

Acknowledgements

This research was funded by the research project QG.23.76 of Vietnam National University, Hanoi.

Notes and references

- 1 (a) R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, 57, 5845; (b) A. Gomtsyan, *Chem. Heterocycl. Compd.*, 2012, 48, 7.
- 2 (a) R. Vardanyan, and V. Hruby, *Synthesis of Best-Seller Drugs*, Elsevier Science, 2016, p. 868; (b) J. A. Joule, and K. Mills, *Heterocyclic Chemistry*, Wiley, Chichester, UK, 5th edn, 2010.
- 3 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, 57, 10257.
- 4 (a) M. M. Heravi and V. Zadsirjan, RSC Adv., 2020, 10, 44247;
 (b) R. A. Mekheimer, M. A. Al-Sheikh, H. Y. Medrasi and K. U. Sadek, RSC Adv., 2020, 10, 19867; (c) Z. Zeng, C. Liao and L. Yu, Chin. Chem. Lett., 2024, 35, 109349.

Paper

5 (a) Z. Tashrifi, M. M. Khanaposhtani, B. Larijani and M. Mahdavi, Eur. J. Org. Chem., 2020, 269; (b) V. Kurteva, ACS Omega, 2021, 6, 35173.

- 6 (a) A. Anaflous, N. Benchat, M. Mimouni, S. Abouricha, T. Ben-Hadda, B. El-Bali, A. Hakkou and B. Hacht, *Lett. Drug Des. Discov.*, 2004, **1**, 224; (b) T. H. Al-Tel and R. A. Al-Qawasmeh, *Eur. J. Med. Chem.*, 2010, **45**, 5848; (c) Y. Rival, G. Grassy and G. Michel, *Chem. Pharm. Bull.*, 1992, **40**, 1170; (d) Y. K. Marquez-Flores, M. E. Campos-Aldrete, H. Salgado-Zamora, J. Correa-Basurto and M. E. Melendez-Camargo, *Med. Chem. Res.*, 2011, **21**, 3491; (e) N. Devi, D. Singh, R. K. Rawal, J. Bariwal and V. Singh, *Curr. Top. Med. Chem.*, 2016, **16**, 2963.
- 7 (a) V. Tyagi, S. Khan, V. Bajpai, H. M. Gauniyal, B. Kumar and P. M. S. Chauhan, J. Org. Chem., 2012, 77, 1414; (b) A. El Akkaoui, M. A. Hiebel, A. Mouaddib, S. Berteina-Raboin and G. Guillaumet, Tetrahedron, 2012, 68, 9131; (c) L. Kielesinski, M. Tasior and D. T. Gryko, Org. Chem. Front., 2015, 2, 21; (d) B. Banerji, S. Chatterjee, K. Chandrasekhar, S. Ghosh, K. Mukherjee and C. Mandal, J. Org. Chem., 2018, 83, 13011; (e) Y. Prostota, O. D. Kachkovsky, L. V. Reis and P. F. Santos, Dyes Pigm., 2013, 96, 554; (f) C.-H. Ke, B.-C. Kuo, D. Nandi and H. M. Lee, Organometallics, 2013, 32, 4775; (g) S. Takizawa, J. Nishida, T. Tsuzuki, S. Tokito and Y. Yamashita, Chem. Lett., 2005, 34, 1222.
- 8 (a) W. Jahangir, S. Akram, S. Aslam, M. Ahmad, M. S. Nazir, S. A. Al-Hussain and M. E. A. Zaki, Results Chem., 2025, 15, 102270; (b) S. P. Chowdhuri, S. Dhiman, S. K. Das, N. Meena, S. Das, A. Kumar and B. B. Das, J. Med. Chem., 2023, 66, 3411; (c) B. Boganyi and J. Kaman, J. Heterocycl. Chem., 2009, 46, 33; (d) Z. Tber, M. Loubidi, J. Jouha, I. Hdoufane, M. A. Erdogan, L. Saso, G. Armagan and S. Berteina-Raboin, Pharmaceuticals, 2021, 14, 750; (e) S. Jena, G. Gonzalez, D. Vítek, M. Kvasnicová, S. Štěpánková, M. Strnad, J. Voller and K. Chanda, Eur. J. Med. Chem., 2024, 276, 116592; (f) S. A. Darbandizadeh and S. Balalaie, Asian J. Org. Chem., 2024, 13, e202400041.
- (a) M. Arnould, M.-A. Hiebel, S. Massip, J. M. Léger, C. Jarry, S. Berteina-Raboin and G. Cuillaumet, *Chem. Eur. J.*, 2013, 19, 12249; (b) T. Meng, Z. X. Zhang, D. Y. Hu, L. P. Lin, J. Ding, X. Wang and J. K. Shen, *J. Comb. Chem.*, 2007, 9, 739; (c) K. Pericherla, A. Jha, B. Khungar and A. Kumar, *Org. Lett.*, 2013, 15, 4304; (d) P. Kaswan, K. Pericherla and A. R. Kumar, *Tetrahedron*, 2014, 70, 8539; (e) M. Romero, P. Renard, D.-H. Caignard, G. Atassi, X. Solans, P. Constans, C. Bailly and M. D. Pujol, *J. Med. Chem.*, 2007, 50, 294.
- 10 S. Sharma, B. Saha, D. Sawant and B. Kundu, J. Comb. Chem., 2007, 9, 783.
- 11 A. K. Pandey, R. Sharma, A. Singh, S. Shukla, K. Srivastava, S. K. Puri, B. Kumar and P. M. S. Chauhan, *RSC Adv.*, 2014, 4, 26757.
- 12 A. Kale, C. Bingi, C. N. Ragi, P. Sripadi, R. P. Tadikamalla and K. Atmakur, *Synthesis*, 2017, **49**, 1603.
- 13 (a) S. Satish, P. Siddiq, N. Shaik, K. Hari, K. Bheeshma, A. Abdullah and A. Kamal, *Asian J. Org. Chem.*, 2017, 6,

- 1830; (b) G. S. Mani, A. V. S. Rao, Y. Tangella, S. Sunkari, F. Sultana, H. K. Namballa, N. Shankaraiah and A. Kamal, New J. Chem., 2018, 42, 15820; (c) R. Jinkala, S. K. B. Kumar, V. Rapolua, N. P. Satish, S. R. Jammulaa, S. Vidavalurb, R. Hindupura, K. Tadiparthic and A. Raghunadh, Synth. Commun., 2022, 52, 258.
- 14 L. Guifang, L. Jingyu, L. Ping and P. Sun, J. Org. Chem., 2019, 84, 16346.
- 15 (a) U. Dasmahapatra, B. Choudhury, M. G. Ahmad, B. Maiti and K. Chanda, *Synthesis*, 2025, 57, 1007; (b) R. N. Rao and K. Chanda, *New J. Chem.*, 2021, 45, 3280.
- 16 S. Gomez-Gil, N. Cases, R. Hernandez-Ruiz, R. Rubio-Presa, S. Suarez-Pantiga, M. R. Pedrosa and R. Sanz, *Eur. J. Org. Chem.*, 2024, 27, e202400145.
- 17 (a) S. R. Chemler and P. H. Fuller, Chem. Soc. Rev., 2007, 36, 1153; (b) S. Jena and K. Chanda, ACS Omega, 2023, 8, 23240; (c) H. Xu, Y. Zhang, J. Huang and W. Chen, Org. Lett., 2010, 12(16), 3704; (d) N. K. Nandwana, S. Dhiman, V. N. Shinde, U. Beifuss and A. Kumar, Eur. J. Org. Chem., 2020, 17, 2576.
- 18 (a) N. K. Nandwana, S. Dhiman, H. K. Saini, I. Kumar and A. Kumar, Eur. J. Org. Chem., 2017, 3, 514; (b) G. Pawar, S. M. Ghouse, S. V. Joshi, M. N. Ahmad, A. Dasgupta, Y. V. Madhavi, S. Chopra and S. Nanduri, New J. Chem., 2023, 47, 5961.
- 19 X.-S. Fan, J. Zhang, B. Li and X.-Y. Zhang, *Chem. Asian J.*, 2015, **10**, 1281.
- 20 (a) T. Q. Hung, N. M. Quan, H. V. Dong, T. D. Nguyen, H. L. T. Anh, T. Q. Hung, N. V. Tuyen, N. T. Thuan, T. T. Dang and P. Langer, Synlett, 2019, 30, 303; (b) B. V. Phuc, Q. H. Dinh, N. L. Chi, Q. T. Nguyen, T. T. N. Truong, N. V. Tuyen, H. Nguyen, P. Langer, T. T. Dang and T. Q. Hung, Tetrahedron, 2023, 136, 133360; (c) D. V. Do, H. N. Do, N. K. Nguyen, T. A. Le, T. M. Le, B. V. Phuc, T. S. Le, Q. A. Ngo, H. Nguyen, T. Q. Hung and T. T. Dang, Tetrahedron Lett., 2023, 122, 154504; (d) T. N. Ngo, P. Ehlers, T. T. Dang and P. Langer, Org. Biomol. Chem., 2015, 13, 3321; (e) T. Q. Hung, T. T. Dang, J. Janke, A. Villinger and P. Langer, Org. Biomol. Chem., 2015, 13, 1375; (f) T. N. Ngoc, O. A. Akrawi, T. T. Dang, A. Villinger and P. Langer, Tetrahedron Lett., 2015, 56, 86; (g) T. Q. Hung, A. Villinger, T. T. Dang and P. Langer, Org. Biomol. Chem., 2015, 13, 583; (h) N. N. Pham, T. T. Dang, T. N. Ngo, P. Ehlers and P. Langer, Org. Biomol. Chem., 2015, 13, 6047; (i) T. Q. Hung, N. N. Thang, D. H. Hoang, T. T. Dang, A. Villinger and P. Langer, Org. Biomol. Chem., 2014, 12, 2596; (j) T. Q. Hung, N. N. Thang, D. H. Hoang, T. T. Dang, A. Villinger, K. Ayub, S. Lochbrunner, G. Flechsig and P. Langer, Eur. J. Org. Chem., 2015, 1007; (k) H. N. Do, N. M. Quan, B. V. Phuc, D. V. Tinh, N. Q. Tien, T. T. T. Nga, T. Q. Hung, T. T. Dang and P. Langer, Synlett, 2021, 32, 611; (l) B. V. Phuc, N. T. Nguyen, N. T. H. Van, T. L. Nguyen, V. H. Nguyen, C. M. Tran, H. Nguyen, M. T. Nguyen, T. Q. Hung and T. T. Dang, Chem. Commun., 2023, 59, 1947; (m) T. Q. Hung, B. C. Q. Nguyen, B. V. Phuc, T. D. Dang-Van, C. M. Trang, Q. T. K. Anh, D. V. Do, H. Nguyen, Q. A. Ngo and T. T. Dang, Org. Biomol. Chem., 2023, 21, 8813; (n)

- B. V. Phuc, H. N. Do, N. M. Quan, N. N. Tuan, N. Q. An, N. V. Tuyen, H. L. T. Anh, T. Q. Hung, T. T. Dang and P. Langer, *Synlett*, 2021, 32, 1004; (*o*) T. Q. Hung, B. V. Phuc, M. P. Nguyen, T. L. Tran, D. V. Do, H. T. Nguyen, V. T. Nguyen, H. Nguyen and T. T. Dang, *RSC Adv.*, 2024, 14, 29535.
- 21 (a) Y. Lv, Y. Li, T. Xiong, W. Pu, H. Zhang, K. Sun, Q. Liu and Q. Zhang, *Chem. Commun.*, 2013, 49, 6439; (b) D. Zhao, T. Wang and J.-X. Li, *Chem. Commun.*, 2014, 50, 6471; (c)
- T. Duan, T. Zhai, H. Liu, Z. Yan, Y. Zhao, L. Feng and C. Ma, *Org. Biomol. Chem.*, 2016, **14**, 6561; (*d*) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, 1964, **29**, 221; (*e*) X. Gao, X. Pan, J. Gao, H. Huang, G. Yuan and Y. Li, *Chem. Commun.*, 2015, **51**, 210.
- 22 (a) D. Ma and Y. Jiang, Chimia, 2011, 65, 914; (b) Q. Yang, Y. Zhao and D. Ma, Org. Process Res. Dev., 2022, 26, 1690; (c) J. Wu, Y. Zhang, Q. Hong, H. Yang, L. Zhan, M. Zhan and L. Yu, Chin. Chem. Lett., 2025, 36, 110165.