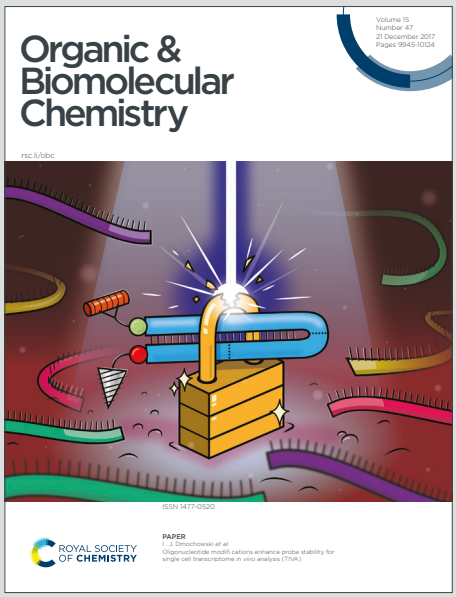
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: X. Feng, R. Fan and Q. He, *Org. Biomol. Chem.*, 2025, DOI: 10.1039/D6OB00390G.



ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

ChemComm

View Article Online
DOI: 10.1039/D6OB00390G

COMMUNICATION

Synthesis of Furoquinolines from 2-Alkenylanilines *via* Anodic Dearomatization and Cascade Cyclization

Xin Feng, [a,b] Renhua Fan, *[a] Qiuqin He *[a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Herein, we report an anodic dearomatization followed by one-pot nucleophilic cycloaddition/Bischler–Napieralski reaction of 2-alkenylanilines for the construction of structurally diverse dihydrofuro[2,3-*g*]quinolinones. These compounds represent an understudied subclass of furoquinoline scaffolds. This metal-free protocol features high atom economy and good functional group tolerance, providing a practical route to dihydrofuro[2,3-*g*]quinolinones. Notably, these products can be readily oxidized to furo[2,3-g]quinolines, which hold potential for the preparation of bioactive compounds.

Furoquinoline derivatives constitute core structural motifs in numerous natural products and other biologically active compounds.[1] Owing to their broad spectrum of biological activities, including antimalarial,[2] anticancer,[3] and antibacterial activities,[4] as well as applications in materials science such as cyanine dyes and metal corrosion inhibitors,[5,6] the efficient construction of furoquinoline frameworks has attracted considerable attention from synthetic chemists. Furoquinoline compounds can be classified into furo[2,3-*b*]quinolines,[7] furo[2,3-*c*]quinolines,[8] and furo[2,3-*g*]quinolines (**Figure 1**).[9] While a variety of synthetic strategies have been developed for the construction of furo[2,3-*b*]- and furo[2,3-*c*]quinoline scaffolds, methods for the synthesis of furo[2,3-*g*]quinoline frameworks remain scarce. In view of their unique structural features and potential biological activities, the development of efficient synthetic methods to further expand the chemical space of furoquinoline derivatives is therefore of significant scientific interest.

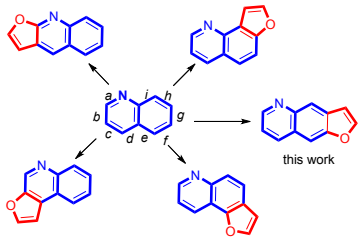
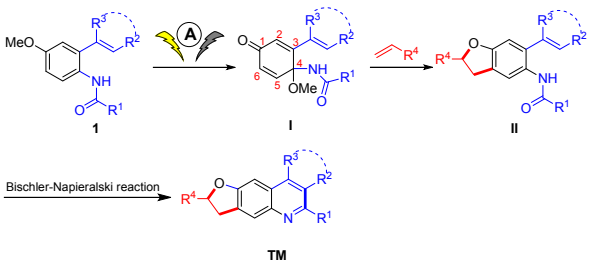


Figure 1. Furoquinoline their skeleton type

Electrochemical reactions represent an emerging and promising technique for sustainable organic synthesis, enabling efficient and green construction of molecular frameworks under mild reaction conditions.[10] Recently, we achieved the anodic dearomatization of 2-alkynylanilines, and the resulting intermediates were converted into a variety of multifunctionalized benzenoid indoles through simple chemical transformations.[11] As illustrated in **Scheme 1**, we envision that the electrochemical oxidative dearomatization of 2-alkenylanilines would generate intermediate **I**, which possesses multiple reactive sites. With an appropriately designed alkene as the nucleophile, nucleophilic attack is anticipated to occur at the C-6 position owing to steric hindrance at the C-4 position, thereby facilitating intramolecular nucleophilic cycloaddition with the alkene to construct a dihydrofuran ring and form intermediate **II**. Additionally, intermediate **II** contains the requisite functional groups for a Bischler–Napieralski reaction,[12] which can undergo cyclization to form a quinoline ring, ultimately affording dihydrofuro[2,3-*g*]quinolinones.



Scheme 1. Construction of dihydrofuro[2,3-g]quinolone from 2-alkenylanilines

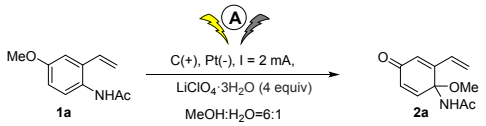
[a] Department of Chemistry, Fudan University, 2005 Songhu Road, Shanghai 200438, China..
[b] Xinjiang College of Science and Technology, Korla, Xinjiang 84100, China.

View Article Online
DOI: 10.1039/D6OB00306C

To commence our study, *N*-(4-methoxy-2-vinylphenyl)acetamide (**1a**) was employed as a model substrate to screen suitable reaction conditions. After systematic screening, the optimal conditions were established as follows: electrolysis was conducted at a constant current of 2 mA using a graphite anode and a platinum cathode in an undivided cell, with 4.0 equiv of $LiClO_4{\cdot}3H_2O$ as the electrolyte in a mixed solvent of MeOH/H_2O (6:1, v/v) for 4 h, affording the desired dearomatized product **2a** in an excellent isolated yield of 92% (**Table 1**, entry **1**).

Increasing the current to 3 mA or decreasing it to 1 mA, even with the reaction time extended to 14 h, resulted in a noticeable decrease in product yield (entries **2–3**). Electrolyte screening experiments demonstrated that ammonium salts and other lithium salts led to diminished yields compared with lithium perchlorate (entries **4–7**). In addition, adjusting the volume ratio of MeOH to H_2O—either increasing or decreasing the proportion of methanol—compromised the reaction yield (entries **8–10**). Moreover, replacing the electrode combination with alternative configurations (e.g., carbon plate anode and cathode, platinum plate anode and cathode, steel anode and platinum cathode, glassy carbon (GC) anode and platinum cathode, or reticulated vitreous carbon (RVC) anode and platinum cathode) failed to improve the yield (entries **11–15**). Notably, the target product **2a** could not be detected in the absence of an applied current (entry **16**).

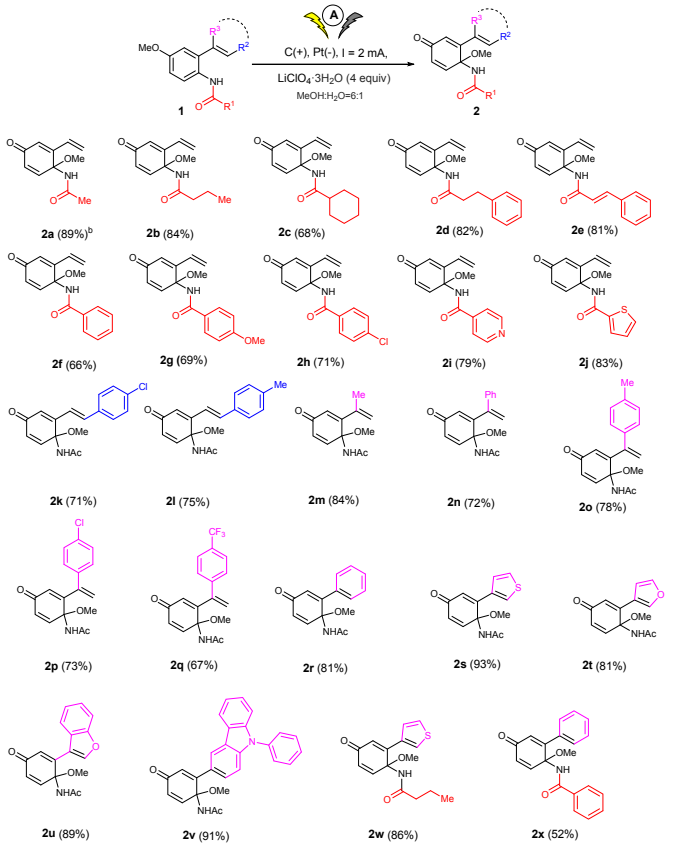
Table 1. Optimization of reaction Conditions[a]



entry	variation from standard conditions	Yield(%)[b]
1	none, 4 h	**92**
2	3 mA	81
3	1 mA, 14 h	85
4	*n*-Bu_4NClO_4 instead of $LiClO_4{\cdot}3H_2O$	81
5	*n*-Bu_4NBF_4 instead of $LiClO_4{\cdot}3H_2O$	71
6	*n*-Bu_4NPF_6 instead of $LiClO_4{\cdot}3H_2O$	64
7	LiCl instead of $LiClO_4{\cdot}3H_2O$	54
8	MeOH: H_2O = 3:1	53
9	MeOH: H_2O = 9:1	72
10	MeOH as solvent	68
11	C (+), C (-)	78
12	Pt (+), Pt (-)	65
13	Steel (+), Pt (-)	60
14	GC (+), Pt (-)	38
15	RVC (+), Pt (-)	58
16	no electric current	0

[a]Standard conditions:**1a** (0.1 mmol, 1.0 equiv), $LiClO_4{\cdot}3H_2O$ (4.0 equiv), MeOH (3 mL), H_2O (0.5 mL), undividedcell equipped with carbon plate anode (0.1 cm^2), platinum plate cathode (0.1 cm^2), 2 mA, rt, 4 h. [b]Isolated yields.

With the optimal reaction conditions in hand, the substrate scope of 2-alkenylanilines was systematically examined (**Scheme 2**). We first assessed the influence of different protecting groups (PGs) on the anodic oxidation process. When the acetyl group was replaced with other protecting groups (**2b–2j**), a decrease in the reaction yield was observed (68–84%). Subsequently, the effect of the R^2 substituent was investigated. When R^2 was a phenyl group, only moderate yields were obtained, irrespective of the presence of electron-donating or electron-withdrawing substituents at the para position (**2k–2l**, 71-75%). In contrast, variation of the R^3 substituent revealed that a methyl group was optimal, affording the highest yield (**2m**, 84%), whereas replacement with a phenyl group or substituted phenyl groups led to diminished yields (**2n–2q**, 67-78%). Furthermore, substrates in which the 2-alkenyl moiety was incorporated into endocyclic double bonds—such as those within phenyl, thiophene, furan, benzofuran, and carbazole frameworks—were also compatible, proceeding smoothly to give the corresponding products in good to excellent yields (**2r–2v**, 81-93%). Similarly, a decrease in yield was also observed when the PG group was replaced with butyryl (**2w**, 86%) or benzoyl groups (**2x**, 52%).

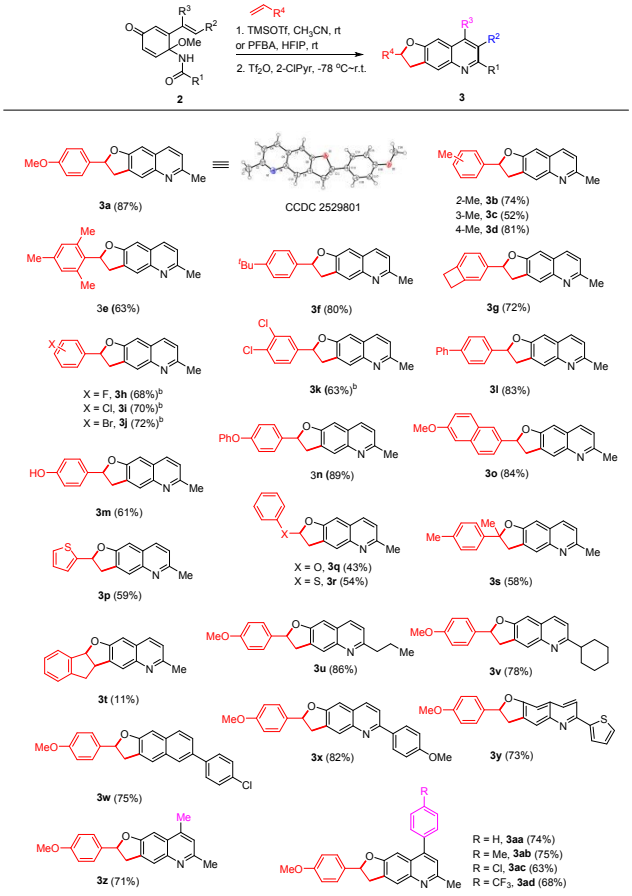


Scheme 2. The scope of 2-alkenylanilines for anodic oxidative dearomatization.[a] [a]Reactions were carried out using standard conditions of Table 1, entry 1. [b]Gram-scale experiment: **1a** (1.0 g).

To explore the nucleophilic cycloaddition reaction, intermediate **2a** was selected as the model substrate, with 4-methoxystyrene employed as the nucleophile. Gratifyingly, the reaction displayed excellent regioselectivity, exclusively delivering the C-6–selective cyclization product as the sole regioisomer. The cyclization proceeded smoothly to generate the corresponding dihydrofuran intermediate. Notably, this

intermediate could be directly subjected to a subsequent transformation without isolation or purification. Treatment with trifluoromethanesulfonic anhydride (Tf_2O) and 2-chloropyridine enabled a Bischler–Napieralski cyclization, efficiently constructing the quinoline ring and affording 2-(4-methoxyphenyl)-6-methyl-2,3-dihydrofuro[2,3-*g*]quinoline (**3a**) in an 87% overall yield over two steps. The structure of **3a** was unambiguously confirmed by single-crystal X-ray diffraction (CCDC: 2529801, SI for details).[13]

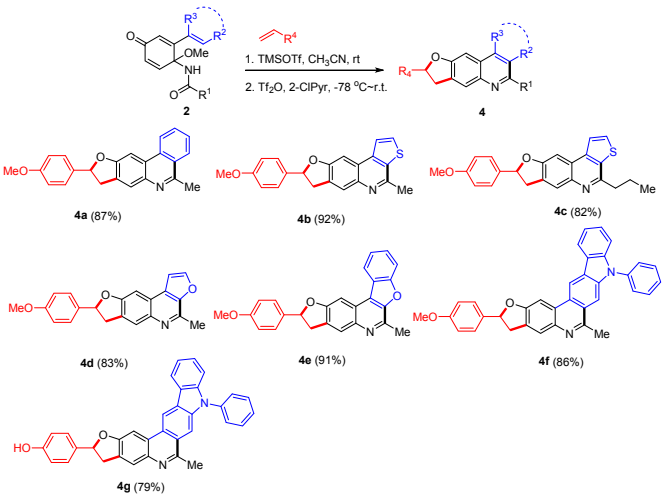
Encouraged by this result, we next systematically examined the substrate scope of the cyclization reaction (**Scheme 3**). Initially, the compatibility of various alkenes with the model substrate **2a** was evaluated. Both monosubstituted alkenes, including styrene, 1-naphthylethylene, and 2-vinylthiophene, as well as sterically hindered gem-disubstituted alkenes, underwent smooth cyclization to furnish the corresponding products **3b–3s** in moderate to good yields. The nature and position of substituents on the styrene ring were found to exert a pronounced influence on the reaction outcome. For example, *p*-methylstyrene (e.g., **3d**) afforded higher yields than its meta- or ortho-substituted counterparts (**3b** and **3c**). Halogen-substituted styrenes (**3h–3k**) were inert in TMSOTf/CH_3CN; instead, the reaction proceeded smoothly only when using the stronger acid pentafluorobenzoic acid in the highly polar solvent hexafluoroisopropanol, affording the corresponding products in moderate yields. Notably, the use of indene as the nucleophile led to the formation of the



Scheme 3. The substrate scope of the cyclization reaction. [a]Isolated yields in two steps. [b]Reactions were performed in pentafluorobenzoic acid and hexafluoroisopropanol at room temperature.

pentacyclic fused-ring system **3t**, albeit in a diminished yield of 11%. Subsequently, using 4-methoxystyrene as the model nucleophile, the generality of the reaction with different dearomatized intermediates **2** was investigated. The nature of the *N*-acyl protecting group was found to have a negligible impact on the reaction efficiency, as substrates bearing either aliphatic or aromatic formyl protecting groups smoothly delivered the desired heterocycles **3u–3y** in yields ranging from 73% to 86%. Furthermore, styrene derivatives bearing a methyl group or substituted phenyl groups at the R^3 position were also well tolerated, affording the corresponding dihydrofuro[2,3-*g*]quinoline products **3z–3ad** in moderate yields (63–75%).

Finally, incorporation of the styrene C=C double bond into cyclic frameworks including benzene, indole, thiophene, and benzofuran moieties allowed for the efficient construction of tetra- to hexacyclic fused furo[2,3-*g*]quinoline architectures **4a-4g** (**Scheme 4**) in 79-92% yields.



Scheme 4. The substrate scope of the cyclization reaction with cyclic frameworks

A plausible mechanism for the overall two-ring construction process is proposed in **Figure 2**. Initially, substrate 1 undergoes single-electron oxidation at the anode to form **Int-1**, which is then subjected to nucleophilic addition with methanol to afford **Int-2**. **Int-2** is further oxidized via single-electron transfer at the anode to generate **Int-3**, followed by hydrolysis to give intermediate 2. Under the promotion of TMSOTf, intermediate 2 undergoes nucleophilic cycloaddition with an alkene to yield **Int-6**. After coordination with TMSOTf, **Int-6** is activated by 2-chloropyridine to form the corresponding onium salt, which finally undergoes intramolecular nucleophilic cycloaddition and aromatization to furnish product **3**.

DOI: 10.1039/D6OB00390G

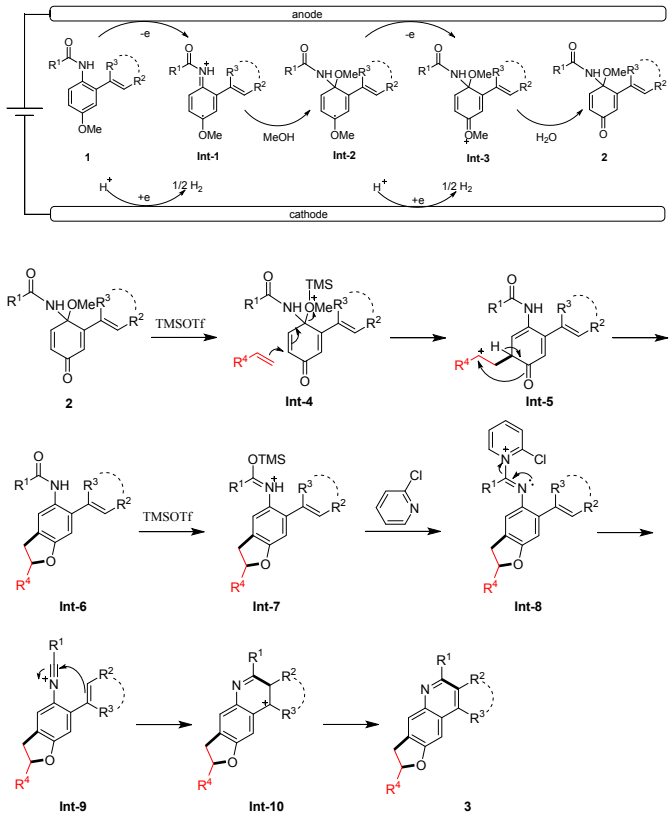


Figure 2. Plausible mechanism

As shown in **Figure 3**, the dihydrofuro[2,3-*g*]quinoline products are readily amenable to oxidation to afford the corresponding furo[2,3-*g*]quinolines.[14] For instance, **3o** and **4f** undergo oxidation upon treatment with DDQ to yield the respective furo[2,3-*g*]quinolones **5a** and **5b** in 89% and 86% yield, respectively.

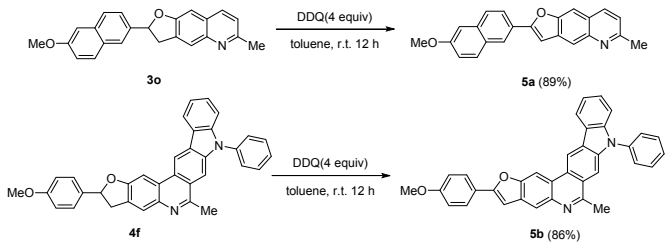


Figure 3. Oxidation of dihydrofuro[2,3-g]quinoline derivatives to the corresponding furo[2,3-*g*]quinolines

In summary, we report a method to synthesize structurally diverse dihydrofuro[2,3-*g*]quinolinones via an anodic dearomatization and one-pot nucleophilic cycloaddition/Bischler–Napieralski reaction of 2-alkenylanilines. Furthermore, the resulting dihydrofuro[2,3-*g*]quinolinone products are readily oxidized to the corresponding furo[2,3-*g*]quinolines, which have potential applications in bioactive molecule synthesis.

Author contributions

X. Feng primarily conducted the experiments. and analyzed the experimental data. R. Fan and Q. He conceived and designed the project and wrote the paper. All authors contributed to the discussion and revision of the paper.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of thesupplementary information (SI). Supplementary information: supplementary figures, synthetic protocols and characterisation data for all compounds. See DOI: CCDC 250708d_a contains the supplementary crystallographic data for this paper

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 22371051) and the Natural Science Foundation of Shanghai Municipality (No. 24ZR1404700) for support of this research.

References

1 (a) J. P. Michael, *Nat. Prod. Rep.*, 2002, **19**, 742–760; (b) J. J. Chen, C. Y. Duh, H. Y. Huang and I. S. Chen, *Planta. Med.*, 2003, **69**, 542-546; (c) C. Ito, M. Itoigawa, A, Sato, C. M. Hasan, M. A. Rashid, H. Tokuda, T. Mukainaka, H. Nishino, and H. Furukawa, *J. Nat. Prod.*, 2004, **67**, 1488-1491; (d) A. R. P. Ambrozina, J. Mafezoli, P. C. Vieira, J. B. Fernandesa, G. F. Silvaa, J. A. Ellenab and S. Albuquerque, *J. Braz. Chem. Soc.*,2005, **16**, 434-439; (e) M. E. Ferreira, A. R. D. Arias, G. Yaluff, N. V. Bilbao, H. Nakayama, S. Torres, A. Schinini, I. Guy, H. Heinzen and A. Fournet, *Phytomedicine.*, 2010, **17**, 375-378; (f) L. P. Sandjo1, V. Kuete, R. S. Tchangna, T. Efferth and B. T. Ngadjui, *Chemistry Central Journal*, 2014, **8**, 61; (g) A. A. Szewczyk, K. Glowniak and T. Baj, *Curr. Issues Pharm. Med. Sci.*, 2016, **29**, 33-38; (h) L. Li, H. H. Zeng, Y. Y. Zhang, J. Y. Liang, X. Z. Zhang and J. B. Peng, *Org. Chem. Front.*, 2022, **9**, 6802; (i) A. Szewczyk and F. Pezek, *Int. J. Mol. Sci.*, 2023, **24**, 12811.

2 (a) L K Basco, S Mitaku, A L Skaltsounis, N Ravelomanantsoa, F. Tillequin, M Koch and J Le Bras, *Antimicrob. Agents Chemother*., 1994, **38**, 1169; (b) J. Li, S. Pei, Y. Zhu, J. Wu , Y. Chen, W. Zhang and Y. Wu, *Letters in Drug Design & Discovery*, 2012, **9**, 379-388; (c) M. Akula, P. Yogeeswari, D. Sriram, M. Jhac and A. Bhattacharya, *RSC Adv.*, 2016, **6**, 46073; (d) V. E. Rasamison, P. J. Brodi, E. F. Merino, M. B. Cassera, M. A. Ratsimbason, S. Rakotonandrasana, A. Rakotondrafara, E. Rafidinarivo, D. G. I. Kingston, H. L. Rakotondraibe, *Nat. Prod. Bioprospect.*, 2016, **6**, 261-265; (e) J. Jampilek, *Curr. Org. Chem.*, 2017, **21**, 1824-1846.

3 (a) M. V. Lohar, R. Mundada, M. Bhonde, A. Padgaonkar, V. Deore, N. Yewalkar, D. Bhatia, M. Rathos, K. Joshi, R. A. Vishwakarma and S. Kumar, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3603-3606; (b) V. Kuetea, H. Fouotsac, A, T. Mbaveng, B. Wiencha, A. E. Nkengfackc and T. Efferth, *Phytomedicine*, 2015, **22**, 946-951; (c) Z. X. Qing, J. L. Huanga, X. Y. Yanga, J. H. Liua, H. L. Caoa, F. Xiang, P. Chenga and J. G. Zeng, *Current Medicinal Chemistry*, 2018, **25**, 5088-5114.

4 (a) A. Dorababu, *Arch Pharm.*, 2021, **354**, e2000232; (b) K. B. Patel and P. Kumari, *J. Mol. Struct*, 2022, **1268**, 133634; (c) S. Dey, A. Patel, N. Haloi, S. Srimayee, S. Paul, G. K. Barik, N. Akhtar, D. Shaw, G. Hazarika, B. M. Prusty, M. Kumar, M. K.

View Article Online
DOI: 10.1039/D6OB00390G

Santra, E. Tajkhorshid, S. Bhattacharjee and D. Manna, *J. Med. Chem.*, 2023, **66**, 11078−11093; (d) P. Luo, X. Feng, S. Liu, Y. Jiang, *DRUG DES DEV THER*, 2024, **18**, 6459-6485.

5 (a) K. Ilina and M. Henary, *Chem. Eur. J.*, 2021, **27**, 4230-4248; (b) R. Y. Balakhonov, E.B. Gaeva, I.S. Mekeda, R.A. Dolotov, A.V. Metelitsa and V.Z. Shirinian, *Dyes and Pigments*, 2024, **225**, 112032.

6 N. O. Eddy, S. R. Stoyanov and E. E. Ebenso, *Int. J. Electrochem. Sci.*, 2010, **5**, 1127-1150.

7 (a) L. Lei, Y. Y. Yao, L. J. Jiang, X. Lu, C. Liang and D. L. Mo, *J. Org. Chem.*, 2020, **85**, 3059−3070; (b) Y. L. Chen, I. L. Chen, T. C. Wang, C. H. Han and C. C. Tzeng, *Eur. J. Med. Chem.*, 2005, **40**, 928-934; (c) C. L. Yang, C. H. Tseng, Y. L. Chen, C. M. Lu, C. L. Kao, M. H. Wu and C. C. Tzeng, *Eur. J. Med. Chem.*, 2010, **45**, 602-607; (d) B. Wang, Q. Q. Li, W, Shi. L. Chen and J. B. Sun, *Chem Biol Drug Des.*, 2018, **91**, 957-961.

8 (a) Y. Kawase, S. Yamaguchi, O. Maeda, A. Hayashi, I. Hayashi, K. Tabata, and M. Kondo, *J. Heterocyclic Chem.*, 1979, **16**, 487; (b) W. Yang, L. Xu, Z. Chen, L. Zhang, M. Miao and H. Ren, *Org. Lett.*, 2013, **15**, 6; (c) R. M. Shanahan, A. Hickey, F. J. Reen, F. O'Gara and G. P. McGlacken, *Eur. J. Org. Chem.*, 2018, 6140-6149; (d) J. P. S. Ferreira, S. M. Cardoso, F. A. A. Paz, A. M. S. Silva and V. L. M. Silva, *New J. Chem.*, 2020, **44**, 6501; (d) K. E. Shepelenko, I. G. Gnatiuk, M. E. Minyaevb and V. M. Chernyshev, *Mendeleev Commun.*, 2024, **34**, 198-200.

9 O. Cherkaoui, P. Nebois and H. Fillion, *Tetrahedron*, 1996, **52**, 9499-9508.

10 (a) M. K. Yadav, S. Chowdhury, *Org. Biomol. Chem.*, 2025, **23**, 506-545; (b) B. Huang, Z. Sun, G. Sun, *eScience*, 2022, **2**, 243-277; (c) S. Lv, G. Zhang, J. Chen, W. Gao, *Adv. Synth. Catal.*, 2020, **362**, 462-477.

11 (a) J. Chen, R. Zhang, C. Ma, P. Zhang, Y. Zhang, B. Wang, F. Xue, W. Jin, Y. Xia and C. Liu, *Green Synthesis and Catalysis*, 2024, **5**, 25-30; (b) A. A. C. Garcia, C. O. Kappe, D. Cantillo and K. Barta, *ChemSusChem*, 2024, **17**, e202301374; (c) Z. Chen, Q. Q. He, H. Guo and R. H. Fan, *Chem. Commun.*, 2022, **58**, 6797, (d)S. Lei, Z. J. Ding, Y. K. Zhao, C. H. Xie, C. Y. Wang, J. Y. Mo M. Zhang, *Org. Lett.*, 2025, **27**, 7858-7862.

12 (a) M. Movassaghi, M. D. Hill and O. K. Ahmad, *J. Am. Chem. Soc.*, 2007, **129**, 10096-10097; (b) M. Movassaghi and M. D. Hill, *Org. Lett.*, 2008, **10**, 3485-3488; (c) L. D. Shan, Y. Y. Weng, H. C. Li, L. Min, X. Y. Wang and Y. F. Hu, *J. Org. Chem.*, 2022, **87**, 4124−4133.

13 CCDC 2529801: Experimental Crystal Structure Determination, DOI: 10.5517/ccdc.csd.cc2qxghm.

14 P. Yamini, B. Duklan, M. Nirmal and D. Yadagiri, *Chem. Commun.*, 2025, **61**, 17017.

View Article Online
DOI: 10.1039/D6OB00390G

Data availability

The data supporting this article have been included as part of thesupplementary information (SI). Supplementary information: supplementary figures, synthetic protocols and characterisation data for all compounds. See DOI: CCDC 250708d_a contains the supplementary crystallographic data for this paper