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Simple and scalable electrosynthesis of 1*H*-1-hydroxy-quinazolin-4-ones†

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Cathodic synthesis provides sustainable access to 1-hydroxy- and 1-oxy-quinazolin-4-ones from easily accessible nitro starting materials. Mild reaction conditions, inexpensive and reusable carbon-based electrode materials, an undivided electrochemical setup, and constant current conditions characterise this method. Sulphuric acid is used as a simple supporting electrolyte as well as a catalyst for cyclisation. The broad applicability of this protocol is demonstrated in 27 differently substituted derivatives in high yields of up to 92%. Moreover, mechanistic studies based on cyclic voltammetry measurements highlight a selective reduction of the nitro substrate to hydroxylamine as a key step. The relevance for preparative applications is demonstrated by a 100-fold scale-up for gram-scale electrolysis.

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Introduction

Nitrogen containing heterocycles are ubiquitous in pharmaceuticals¹ and biomolecules as core motifs.² One particular example is quinazolin-4-ones. Derivatives are present in a variety of drugs and biomolecules with anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive properties.³

Methaqualone (**1**) (Chart 1), known by its brand name Quaalude, is a hypnotic sedative that increases GABA_A receptor activity.⁴ The drug was withdrawn from the U.S. market in 1985, primarily because of its psychologically addictive potential, widespread abuse, and illicit recreational use.⁵ The medication idelalisib (**2**) (Chart 1) is used to treat certain types of blood cancer and acts as a phosphoinositide 3-kinase inhibitor.⁶ This drug alone amounted to a \$72 million annual revenue for Gilead Sciences, Inc.⁷ The naturally occurring plant alkaloid tryptanthrine (**3**) exhibits a broad spectrum of biological and pharmaceutical activity including antimicrobial, antiviral, anticancer, and antiparasitic properties.⁸ In addition, the

AstraZeneca anti-metabolite and cytotoxic drug raltitrexed (**4**) is used in chemotherapy treatments. The folic acid analogue acts as a selective inhibitor of thymidylate synthase.⁹ Notably, *N*-oxides and *N*-hydroxy derivatives of these pharmaceuticals were found to be metabolites of these drugs.^{10,11} However, the therapeutic effects of endocyclic *N*-hydroxy and *N*-oxy compounds have not been researched to the same degree. Considering their metabolic stability and the unique features of the N–O bond, this class of novel compounds are the subject of current pharmaceutical research.¹²

The synthesis of *N*-oxides and *N*-hydroxy derivatives of quinazolin-4-ones is scarce in the literature and the few published examples present various challenges. The synthesis of 1-oxy-2-alkylquinazolin-4-ones was described by Tennant starting from *N*-(1-cyano-alkyl)-2-nitro benzamides (Scheme 1, top).¹³ Its base-catalysed cyclisation approach does not require additional

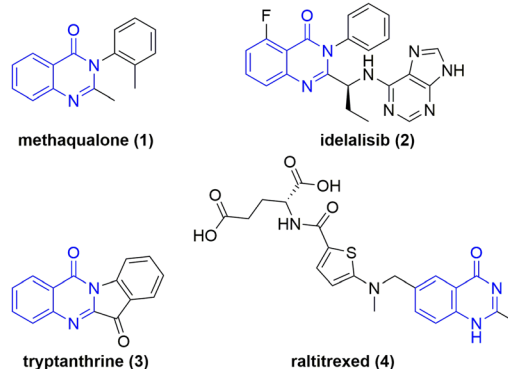


Chart 1 Important biologically active substances with quinazolin-4-one motif.

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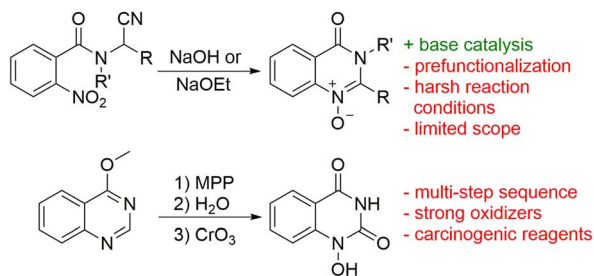
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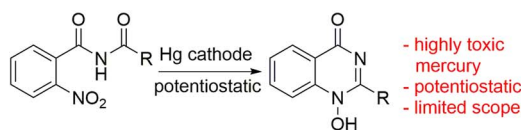
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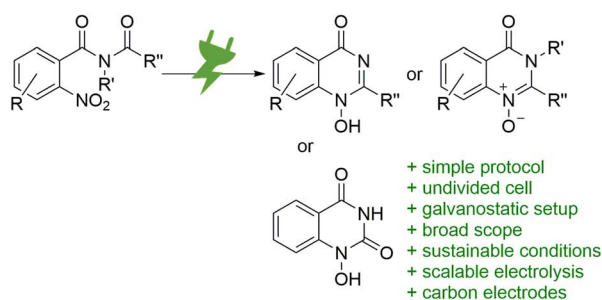
Conventional methods:



Electrochemical approach (Tallec et al.):



This work:



Scheme 1 Synthetic approaches to 1H-1-hydroxy-quinazolin-4-ones. MPP = monoperoxyphthalate.

reagents, but does use harsh reaction conditions.¹³ The synthesis of 1-hydroxyquinazolin-2,4-diones by Yamanaka comprises a multi-step sequence from 4-methoxyquinazoles and involves two oxidizers: hazardous monoperoxyphthalate for the generation of the 1-oxide and highly toxic chromium(vi) oxide for the oxidation of the C-2 (Scheme 1, top).¹⁴ Reductive cyclisation of nitro precursors is also known, typically *via* hydrogenation with expensive palladium catalysts.¹⁵ In addition, Tallec described an electrochemical synthesis within polarographic studies (Scheme 1, middle). However, highly toxic mercury electrodes were required in a sophisticated potentiostatic reaction setup that was run on a small scale with a limited scope.¹⁶

Herein, a versatile, scalable, and high-yielding electrochemical reductive cyclisation of widely available, easy to prepare, and inexpensive nitro arenes¹⁷ into 1-hydroxy-quinazolin-4-ones is presented. The method uses a simple constant current setup and applies conditions that consider sustainable and environmental aspects (Scheme 1, bottom). In particular, this methodology can easily pay off for high value-added products.¹⁸ The field of electrosynthesis is experiencing a renaissance as an alternative to conventional synthesis protocols^{19–21} and is emerging as a key discipline for future synthetic applications.²² The use of electric current as a reagent enables inherently safe processes by precise control of the reaction. Practically, turning off the electricity immediately

stops the conversion and, unlike with traditional reagents, thermal runaway reactions are not possible. The absence of toxic and hazardous reagents and the use of sustainable electricity makes these methods almost waste- and pollutant-free, especially when solvents and supporting electrolytes are reused.^{23,24} However, several parameters and counter reactions seem to play a crucial role for success.^{25,26} Carbon-based electrode materials such as graphite, glassy carbon (GC), and boron-doped diamond (BDD) are sustainable and widely available.²⁷ In particular, these are superior in the synthesis of pharmaceuticals or APIs where trace metal impurities must be avoided.^{22,28}

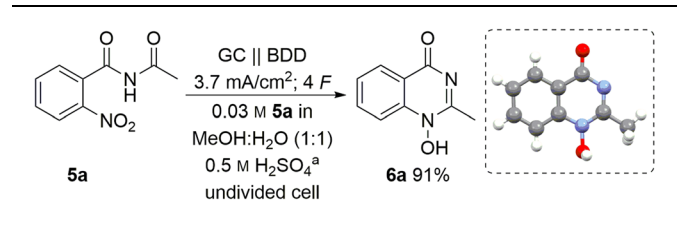
Results and discussion

Optimisation of the electrolysis conditions

Benzamide **5a** was chosen as a test substrate for cathodic reduction of a nitro group, and it was easily synthesised in a single step from commercially available 2-nitrobenzamide by treatment with acetic anhydride in a microwave-assisted acylation reaction or in a pressured vessel approach, both in high yields (see ESI† for detailed description).²⁹ Based on previous work by the Waldvogel lab, a foundation for the electrochemical conditions for nitro reduction were initially tested (Table 1, entry 1).^{30–32}

The starting conditions used a water–methanol mixture (1 : 1 (v/v)) as a green solvent capable of dissolving the nitro compound **5a**. A moderate concentration of sulphuric acid (0.5

Table 1 Screening of electrolysis parameters for the optimisation of the synthesis of 1H-1-hydroxy-2-methyl-quinazolin-4-one (**6a**)



Entry	Deviation from standard conditions	Yield 6a ^b /%
1	None	91% (91%) ^c
2	2.7 mA cm ⁻²	78%
3	5.7 mA cm ⁻²	78%
4	EtOH instead of MeOH	84%
5	MeCN instead of MeOH	71%
6	0.5 M acetate buffer ^d	66%
7	Pb cathode	27%
8	CuSn7Pb15 cathode	0%
9	Pt cathode	0%
10	Graphite cathode	84%
11	GC cathode	90%
12	0.06 M 5a	85%
13	0.10 M 5a	73%

^a Concentration of sulphuric acid in the electrolyte, obtained by using methanol and 1 M aqueous sulphuric acid (1 : 1 (v/v)). ^b Yield of **6a** was determined by ¹H NMR spectroscopy using 2,2-dimethylmalonic acid as internal standard. ^c Isolated yield. ^d 0.5 M AcOH/AcONa was prepared with 90 mmol acetic acid and 10 mmol sodium acetate in 100 mL of distilled water and 100 mL methanol. BDD = boron-doped diamond; GC = glassy carbon.



M) was used as the supporting electrolyte based on previous investigations into the concentration effect of the acidic component on the electrochemical reduction.^{16,33} Moreover, it was envisioned that sulphuric acid may play a dual role in the reaction since acidic media should be beneficial for cyclisation after a nitro group reduction. Taking this into account, we examined constant current electrolysis (3.7 mA cm⁻² current density) of benzamide **5a** in an undivided cell in water-methanol media, using a glassy carbon anode and a boron-doped diamond (BDD) cathode. BDD as a carbon-based material offers unique reactivity towards electrochemical conversion of a multitude of substrates and can be manufactured in a sustainable manner by utilizing methane as carbon source.³⁴

To our delight, the desired 1-hydroxyquinazolinone **6a** was isolated in 91% yield. Furthermore, the theoretical amount of charge required for this process (4 *F*) was applied and the high yield obtained shows that this process has a high current efficiency (Table 1, entry 1). The molecular structure of heterocycle **6a** was confirmed by X-ray analysis of a suitable single crystal.

Deviation from the starting electrolysis conditions obtained by electrochemical screening resulted in lower yields.^{20,21,24,35} Both lower or higher current densities led to a decreased yield of 1-hydroxyquinazolinone **6a** to 78% (Table 1, entries 2 and 3). Replacement of methanol with other solvents such as ethanol and acetonitrile (Table 1, entries 4 and 5) afforded the desired heterocycle **6a** in slightly lower yields of 84% and 71%, respectively. Acetate buffer (Table 1, entry 6) was used as a weaker and biogenic alternative to sulphuric acid; however, the yield of **6a** decreased to 66%. Substitution of BDD as cathode material for lead significantly decreased the yield of **6a** to 27% (Table 1, entry 7). Furthermore, cathodic corrosion was observed resulting in the precipitation of lead salts.

More stable alternatives to lead cathodes such as leaded bronzes³⁶ (Table 1, entry 8) failed entirely in the formation of **6a**. Platinum was equally unsuccessful as cathode material (Table 1, entry 9), completely avoiding the desired reaction likely due to its low overpotential for the hydrogen evolution side-reaction.³⁷

Besides BDD, other carbon-based cathode materials such as graphite and glassy carbon provided product **6a** in comparable yields of 84% and 90% (Table 1, entries 10 and 11). Nevertheless, we decided to proceed with BDD due to its sustainability and chemical durability.³⁸ Electrolysis at higher benzamide **5a** concentrations resulted in lowered yields by up to nearly 20% (Table 1, entries 12 and 13). It is likely that higher concentrations of starting material result in the formation of high molecular weight side products which were observed as a brown plaque after the electrolysis was finished.

Scope of the reductive cyclisation

The broad applicability of the optimised reaction conditions was demonstrated on a versatile scope of substrates (Chart 2). First, we explored the effect of substitution pattern at the C-2 position of quinazolin-4-ones **6b-i** (Chart 2, top). The influence of primary, secondary, and tertiary alkyl substitutions was investigated in the synthesis of heterocycles **6a-c**, resulting in good yields of 78–91%. Here, the *tert*-butyl derivative **6c** with its

sterically demanding substituent gave the lowest yield. Furthermore, 1*H*-2-heptyl-1-hydroxy-quinazolin-4-one (**6d**) with a hydrophobic chain was obtained in a moderate yield of 52%.

Both the 2-unsubstituted quinazolin-4-one **6e** and the 2-phenyl analogue **6h** were obtained in moderate to good yields (65% and 79%, respectively). Alkene as well as a benzylic moieties, usually prone to anodic oxidation, were well tolerated in the electrochemical reduction, and the desired heterocycles **6g** and **6i** were obtained in 67% and 81% yield. Interestingly, even the 2-chloromethyl substituted product **6f** was isolated in 24% yield despite its inherent instability.

Next, various functional groups in the aromatic subunit of 1-hydroxyquinazolin-4-ones **6j-r** were tested (Chart 2, middle). In all cases, the products were obtained in good to excellent yields regardless of the substituent's electronic nature. Benzamides with an electron-donating methoxy group and an electron-withdrawing ester moiety afforded the corresponding heterocycles **6q** and **6r** in comparable yields (77% and 85%, respectively). Likewise, the trifluoromethyl derivative **6n** and methyl quinazolin-4-ones **6o** and **6p** were obtained in 73–92% yield.

The 6-methyl derivative **6o** is an *N*-hydroxy analogue of a precursor to raltitrexed (**4**), thus its successful formation adds industrial relevance to this transformation.³⁹ Halides are redox-active groups in electrochemical reactions. To our delight, fluoro-, chloro- and bromo-substituted quinazolin-4-ones **6j-i** were obtained in 76–85% yield. Moreover, the developed electrochemical method also afforded the iodo-substituted product **6m**, albeit in moderate yield (50%) likely due to its susceptibility to oxidation.

It is noteworthy that heteroaromatic amides such as those derived from pyridines and imidazoles are applicable with the developed conditions (Chart 2, middle left). The pyrido pyrimidinone **6s** was obtained in 82% yield and the bromo substituent offers availability for a variety of post-functionalization reactions. Even the *N*-hydroxy purine **6t** was obtained in a good yield of 57%.

Furthermore, *N*-acetyl-*N*-aryl benzamides were converted into the corresponding *N*-oxy-quinazolin-4-ones **7a** and **7b** in moderate yields, likely due to their tendency to rearrangement reactions (Chart 2, middle right).⁴⁰ Interestingly, **7b** is a reported metabolite of methaqualone (**1**).¹⁰ Furthermore, tertiary amides are also suitable as substrates as exemplified by the synthesis of pyrrolidone-based *N*-oxy-quinazolin-4-one **7c** (72%).

Finally, the presented methodology has also been applied to the synthesis of 1-hydroxy-quinazolin-2,4-diones **8a-d** by electrochemical reduction of methyl-(2-nitrobenzoyl)carbamates, which gave up to 77% yield (Chart 2, bottom). Here, the unsubstituted derivative **8a** had the best yield of 77%. The electron-withdrawing trifluoromethyl- and chloro-substituted products **8b** and **8d** were isolated in 59% and 48% yield. The methyl-substituted derivative **8c** was obtained in moderate yield of 66%.

Scale-up of electrolysis

To demonstrate the synthetic utility and scalability of the developed method, the synthesis of 1*H*-1-hydroxy-2-methyl-



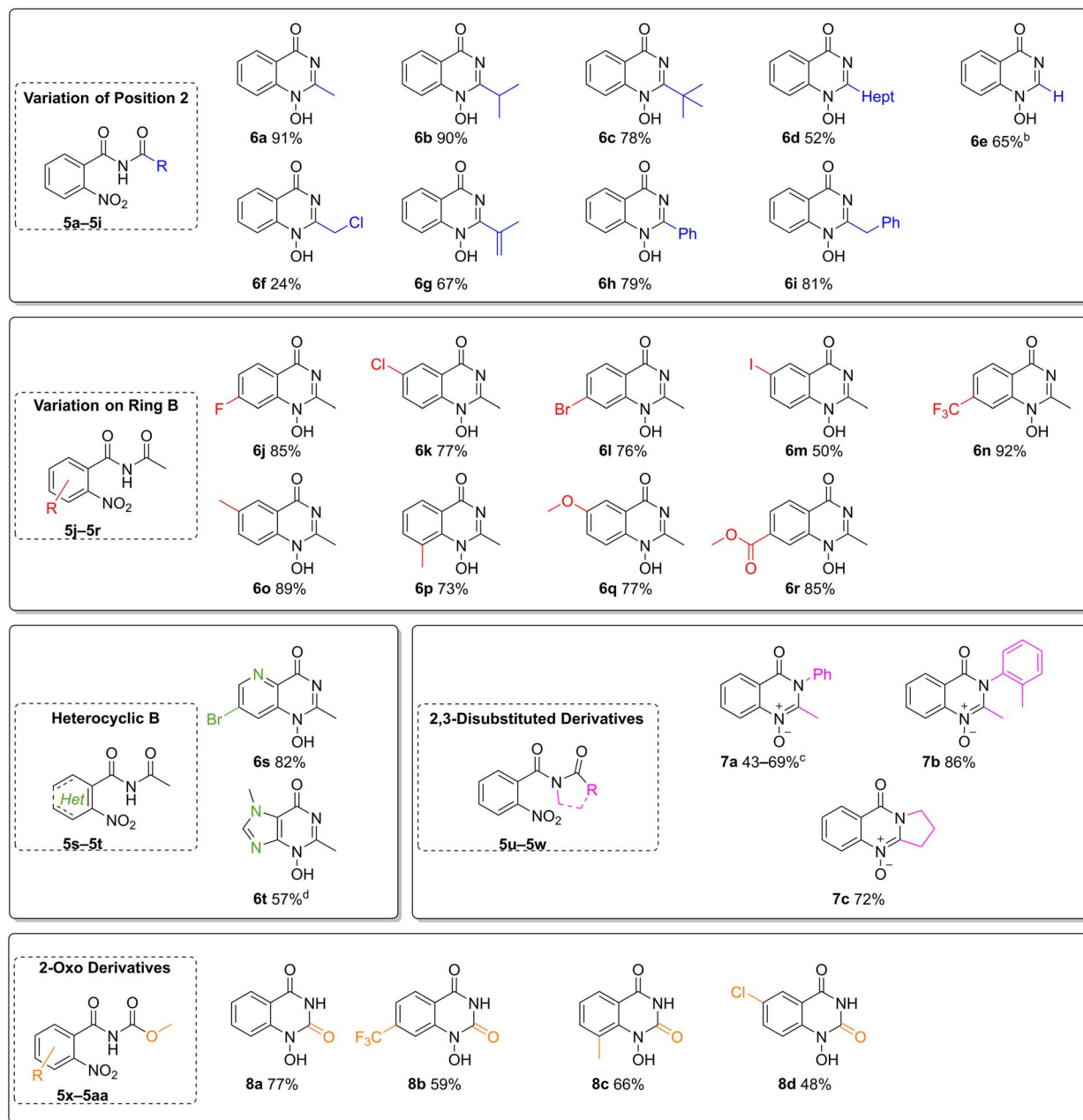
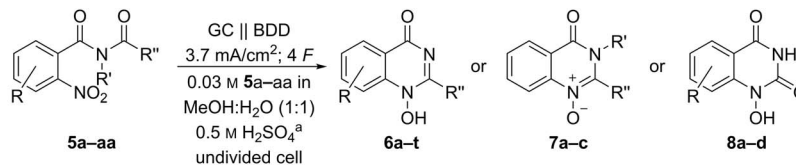






Chart 2 Scope of electrochemical reductive cyclisation and isolated yields. ^a Concentration of sulphuric acid in the electrolyte, obtained by using 12.5 mL methanol and 12.5 mL 1 M aqueous sulphuric acid (1 : 1 (v/v)), undivided 25 mL beaker-type glass cell; ^b isolated yield as formate adduct; ^c variation in yield with repeated electrolysis; ^d isolated yield as acetate adduct.

quinazolin-4-one (**6a**) was successfully scaled up to 15 mmol in a single electrolysis batch (Table 2). The 5-fold scale-up was performed with BDD and GC cathodes to demonstrate the robustness and applicability of the described method. Encouragingly, 20-fold scale-up (3.00 mmol) in a 100 mL electrolysis

cell afforded the desired product **6a** without loss in yield or faradaic efficiency. Gram-scale electrolysis was also performed at 7.5 mmol and 15.0 mmol loading in a 250 mL electrolysis cell, affording 1.13 g and 2.19 g of the desired 1-hydroxy-quinazolin-2-one **6a**, respectively. The trend of decreased yield at higher



Table 2 Scale-up of the electroreduction of 1*H*-1-hydroxy-2-methyl-quinazolin-4-one (**6a**)^a

Electrolysis cell	Scale/mmol	Current (electrolysis time)	Yield 6a
	0.15	5.6 mA (2.9 h)	24 mg (91%)
	0.75 0.75 ^b	22.2 mA (3.6 h)	120 mg (91%) 118 mg (89%)
	3.00	22.2 mA (14.5 h)	481 mg (91%)
	7.50 15.0 ^c	109.9 mA (7.3 h) 109.9 mA (14.6 h)	1.13 g (86%) 2.19 g (83%)

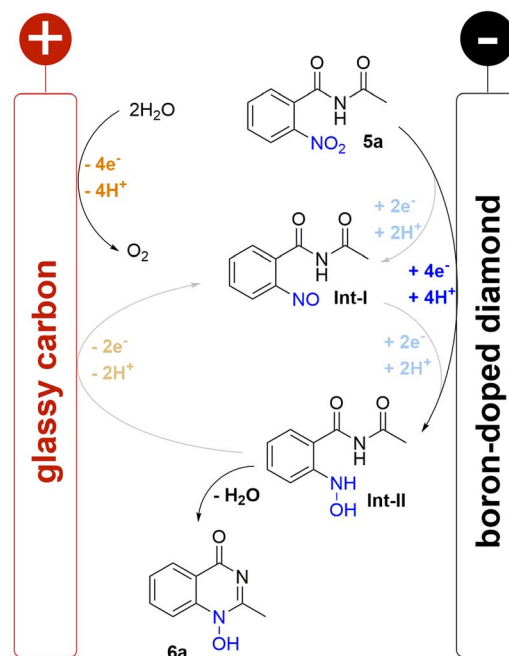
^a Constant current conditions; surface areas of the electrodes: 5 mL Teflon™ cell (1.5 cm²), 25 mL and 100 mL glass cell (6.0 cm²), 250 mL glass cell (29.7 cm²). ^b GC cathode. ^c 0.06 M **5a**.

concentrations was also observed in the optimisation results (Table 1, entries 12 & 13).

Mechanistic studies

A plausible mechanism for the electrochemical cyclisation sequence is proposed based on earlier nitro reduction studies and cyclic voltammetry (CV) measurements of benzamide **5a** (Scheme 2; for detailed information see ESI†).^{16,31–33} Accordingly, the reactions starts with the reduction of the nitro group on the BDD cathode which is evidenced by a single broad, irreversible wave (−0.94 V vs. FcH/FcH⁺) corresponding to the 4e[−]/4H⁺ reduction to the hydroxylamine. It has been previously suggested that the reaction proceeds with two 2e[−] steps *via* intermediates **Int-I** and **Int-II**. However, because only one broad wave was observed rather than two distinct or overlapping waves, this suggests one reduction event occurs and that **5a** is reduced directly to **Int-II**. The irreversible reduction to **Int-II** indicates a fast cyclisation step as no corresponding oxidative wave was observed. Further reduction of the *N*-hydroxy moiety was not observed for non-cyclised **Int-II** or the product **6a**. The impact of the counter reaction on the electrochemical conversion must also be considered; the oxidation of water at the glassy carbon anode is possibly the main counter reaction.²⁵ The corrosion of the glassy carbon anode was not observed after electrolysis. There was no indication of the oxidation of methanol, which was only observed under harsh basic conditions in previous studies.⁴¹ Overall, the high performance of the

reported method was enabled by the electrochemical stability of the product, the selective reduction to the hydroxylamine, and the fast cyclisation process.



Scheme 2 Proposed mechanism for the reductive cyclisation.



Conclusions

In summary, the established method provides simple, direct, and sustainable electrochemical access to *N*-hydroxy- and *N*-oxy-quinazolin-4-ones by a cathodic reduction sequence. The electrolytic conditions allow for a reproducible transformation in commercially available experimental setups. The simplest undivided cell was operated under constant current with widely available and sustainable carbon-based electrodes and a water-methanol mixture as an environmentally benign solvent. The sulphuric acid additive served a dual role as supporting electrolyte and acidic catalyst. The broad applicability of this method was demonstrated by 27 examples with up to 92% isolated yield. The electrolysis tolerates various functional groups, including electron-withdrawing and -donating, sterically demanding, and redox labile moieties such as bromides and iodides. The *N*-hydroxy analogue precursor of the cytotoxic drug raltitrexed was obtained in 89% yield. Selective nitro reduction to the hydroxylamine was confirmed by CV measurements to be a key step in the mechanism. The scalability of this electrochemical protocol was demonstrated by multigram-scale electrolysis.

Data availability

The ESI is available and contains experimental and analytical data.

Author contributions

O. K., T. P. and J. W. contributed equally. T. P. and S. W. conceived the idea of the research. O. K., T. P., J. W. and T. H. designed and carried out the batch electrolysis experiments and analysed the data. M. G. and T. P. designed and analysed the cyclic voltammetry measurements. D. S. performed the X-ray analysis and structural elucidation of the synthesised test substrate. T. P., O. K., J. W., and S. W. wrote the manuscript. S. W. supervised the project and E. S. and S. I. reviewed and edited the manuscript. All authors discussed the results and agreed to the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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References

- 1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
- 2 N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, 2020, **25**, 1909.
- 3 A. Masri, A. Anwar, N. A. Khan, M. S. Shahbaz, K. M. Khan, S. Shahabuddin and R. Siddiqui, *Antibiotics*, 2019, **8**, 179.
- 4 P.-F. Wang, A. A. Jensen and L. Bunch, *ACS Chem. Neurosci.*, 2020, **11**, 4362.
- 5 K. Romanek, H. Fels, T. Dame, G. Skopp, F. Musshoff, H. Eiglmeier and F. Eyer, *Subst. Abuse*, 2021, **42**, 503.
- 6 J. R. Somoza, D. Koditek, A. G. Villaseñor, N. Novikov, M. H. Wong, A. Licican, W. Xing, L. Lagpacan, R. Wang, B. E. Schultz, G. A. Papalia, D. Samuel, L. Lad and M. E. McGrath, *J. Biol. Chem.*, 2015, **290**, 8439.
- 7 San. Franc. Bus. Times, <https://www.bizjournals.com/sanfrancisco/news/2022/01/21/blood-cancer-gilead-sciences-gild-zydelig-fl-sil.html>, accessed January 2023.
- 8 A. M. Tucker and P. Grundt, *Arkivoc*, 2012, 546.
- 9 N. S. Gunasekara and D. Faulds, *Drugs*, 1998, **55**, 423.
- 10 C. N. Reynolds, K. Wilson and D. Burnett, *Xenobiotica*, 1976, **6**, 113.
- 11 M. H. Bickel, *Xenobiotica*, 1971, **1**, 313.
- 12 R. Rani and C. Granchi, *Eur. J. Med. Chem.*, 2015, **97**, 505.
- 13 T. W. M. Spence and G. Tennant, *J. Chem. Soc., Perkin Trans. 1*, 1972, 97.
- 14 H. Yamanaka, *Chem. Pharm. Bull.*, 1959, **7**, 152.
- 15 R. Fielden, O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1973, 702.
- 16 A. Chibani, R. Hazard and A. Tallec, *Bull. Soc. Chim. Fr.*, 1991, **6**, 814.
- 17 A. Z. Halimehjani, I. N. N. Namboothiri and S. E. Hooshmand, *RSC Adv.*, 2014, **4**, 31261.
- 18 (a) J. Seidler, J. Strugatchi, T. Gärtner and S. R. Waldvogel, *MRS Energy Sustain.*, 2020, **7**, 42; (b) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 6018.
- 19 (a) D. Cantillo, *Chem. Commun.*, 2022, **58**, 619; (b) A. Shatskiy, H. Lundberg and M. D. Kärkäs, *ChemElectroChem*, 2019, **6**, 4067; (c) S. R. Waldvogel and B. Janza, *Angew. Chem., Int. Ed.*, 2014, **53**, 7122.
- 20 C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantourout, B. K. Peters, Y. Kawamata and P. S. Baran, *Acc. Chem. Res.*, 2020, **53**, 72.
- 21 M. C. Leech and K. Lam, *Nat. Rev. Chem.*, 2022, **6**, 275.
- 22 D. Pollok and S. R. Waldvogel, *Chem. Sci.*, 2020, **11**, 12386.
- 23 (a) B. A. Frontana-Urbe, R. D. Little, J. G. Ibanez, A. Palma and R. Vasquez-Medrano, *Green Chem.*, 2010, **12**, 2099; (b) M. D. Kärkäs, *Chem. Soc. Rev.*, 2018, **47**, 5786; (c) R. D. Little and K. D. Moeller, *Chem. Rev.*, 2018, **118**, 4483; (d) J. L. Röckl, D. Pollok, R. Franke and S. R. Waldvogel, *Acc. Chem. Res.*, 2020, **53**, 45; (e) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 5594; (f) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl and C. J. Kampf, *Chem. Rev.*, 2018,



- 118, 6706; (g) T. Wirtanen, E. Rodrigo and S. R. Waldvogel, *Adv. Synth. Catal.*, 2020, **362**, 2088.
- 24 M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230.
- 25 M. Klein and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2022, **61**, e202204140.
- 26 S. B. Beil, D. Pollok and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2021, **60**, 14750.
- 27 D. M. Heard and A. J. J. Lennox, *Angew. Chem., Int. Ed.*, 2020, **59**, 18866.
- 28 T. Wirtanen, T. Prenzel, J.-P. Tessonnier and S. R. Waldvogel, *Chem. Rev.*, 2021, **121**, 10241.
- 29 (a) J. Lee, M. Hong, Y. Jung, E. J. Cho and H. Rhee, *Tetrahedron*, 2012, **68**, 2045; (b) X.-G. Yang, K. Zheng and C. Zhang, *Org. Lett.*, 2020, **22**, 2026.
- 30 E. Rodrigo, H. Baunis, E. Suna and S. R. Waldvogel, *Chem. Commun.*, 2019, **55**, 12255.
- 31 E. Rodrigo and S. R. Waldvogel, *Green Chem.*, 2018, **20**, 2013.
- 32 J. Winter, T. Prenzel, T. Wirtanen, D. Schollmeyer and S. R. Waldvogel, *Chem.–Eur. J.*, 2022, e202203319.
- 33 R. Hazard, M. Jubault, C. Mouats and A. Tallec, *Electrochim. Acta*, 1986, **31**, 489.
- 34 S. Lips and S. R. Waldvogel, *ChemElectroChem*, 2019, **6**, 1649.
- 35 (a) C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Cent. Sci.*, 2021, **7**, 415; (b) J. Rein, J. R. Annand, M. K. Wismer, J. Fu, J. C. Siu, A. Klapars, N. A. Strotman, D. Kalyani, D. Lehnher and S. Lin, *ACS Cent. Sci.*, 2021, **7**, 1347; (c) G. Hilt, *ChemElectroChem*, 2020, **7**, 395; (d) M. Dörr, M. M. Hielscher, J. Proppe and S. R. Waldvogel, *ChemElectroChem*, 2021, **8**, 2621; (e) C. Gütz, B. Klöckner and S. R. Waldvogel, *Org. Process Res. Dev.*, 2016, **20**, 26; (f) P. Enders and R. Francke, in *Science of Synthesis*, ed. L. Ackermann, Georg Thieme Verlag KG, Stuttgart, New York, 2022, pp. 67–72.
- 36 C. Gütz, V. Grimaudo, M. Holtkamp, M. Hartmer, J. Werra, L. Frensemeier, A. Kehl, U. Karst, P. Broekmann and S. R. Waldvogel, *ChemElectroChem*, 2018, **5**, 247.
- 37 A. Hickling and F. W. Salt, *Trans. Faraday Soc.*, 1940, **36**, 1226.
- 38 (a) Y. Einaga, *Acc. Chem. Res.*, 2022, **55**, 3605; (b) S. R. Waldvogel, S. Mentizi and A. Kirste, *Top. Curr. Chem.*, 2012, **320**, 1.
- 39 (a) S.-L. Cao, Y.-P. Feng, Y.-Y. Jiang, S.-Y. Liu, G.-Y. Ding and R.-T. Li, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1915; (b) S.-L. Cao, R. Wan and Y.-P. Feng, *Synth. Commun.*, 2003, **33**, 3519.
- 40 F. P. Theil, H. Poehlmann, S. Pfeifer and P. Franke, *Pharmazie*, 1985, **40**, 328.
- 41 T. Wirtanen, E. Rodrigo and S. R. Waldvogel, *Chem.–Eur. J.*, 2020, **26**, 5592.

